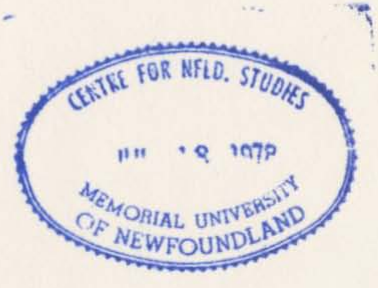
SYNTHESIS OF 1,1,n,n-TETRAMETHYL[n](2,11) TEROPYRENOPHANES - LARGE AND HIGHLY DISTORTED POLYCYCLIC AROMATIC HYDROCARBONS

BRADLEY L. MERNER


CENTRE FOR NFLD. STUDIES
MEMORIAL UNIVERSITY
OF NEWFOUNDLAND

Synthesis of 1,1,*n*,*n*-Tetramethyl[*n*](2,11)teropyrenophanes – Large and Highly Distorted Polycyclic Aromatic Hydrocarbons

by

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To Abby Jayne

Abstract

The synthesis of nonplanar aromatic hydrocarbons has been an area of interest for quite some time now. These distorted π-systems have fascinated the imaginations of organic chemists over the years and through extensive studies and syntheses, many important lessons on the implications of strain and aromaticity have been provided. Moreover, the chemical synthesis of monodisperse single-walled carbon nanotubes (SWCNTs) that does not involve "fullerene surgery" remains a significant challenge. This dissertation involves the synthesis of nonplanar polycyclic aromatic hydrocarbons (PAHs) – namely, 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes, which resemble large segments (about half) of (8,8) armchair SWCNTs. The work described herein focuses on new reactions of the pyrene ring system, the synthesis of new pyrenophane motifs and the exploration of the valence isomerization/dehydrogenation (VID) reaction as a means to synthesizing the most distorted π-systems contained within a cyclophane framework.

Chapter 1: Introduction of underlying concepts involving designed molecule synthesis and seminal work on the synthesis of nonplanar aromatic hydrocarbons. Focus has been placed primarily on the synthesis of nonplanar aromatic systems that are also cyclophanes. Four general strategies towards the synthesis of cyclophanes are highlighted with an emphasis on the most powerful valence isomerization (Strategy D) approach.

Chapter 2: Retrosynthetic analysis of the target 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes and a discussion of the early synthetic efforts to construct the teropyrene system using a four-fold functionalization approach is presented.

Most of the chemistry described in this chapter led to synthetic routes that were incapable of delivering significant quantities of viable advanced intermediates of the designed targets. Also, the attempted synthesis of a modified cyclophane target is described.

Chapter 3: Alternate disconnective analyses of the target 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes, as well as model studies on the 2-*tert*-butylpyrene system and a novel approach to pyrenoid cyclophane systems is discussed. Several new substitution and coupling reactions of substituted pyrene derivatives were discovered during the course of this study and are presented in Chapter 3.

Chapter 4: The synthesis of a series of 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes (*n*=7–9) using two different synthetic routes (Routes A and B) is the main feature of this chapter. Application of a Wurtz-type coupling reaction of 1-(bromomethyl)-7-*tert*-butylpyrene (discovered in Chapter 3) was successful applied in the synthesis of three teropyrenophane targets. As well, the rare use of the McMurry reaction to construct [2.2]metacyclophanediene systems, a structural prerequisite for the pivotal VID reaction, is presented. Interesting structural and spectroscopic properties of 1,1,8,8-tetramethyl[8](2,11)teropyrenophane and future applications of the chemistry developed during the course of this project are also discussed.

Acknowledgments

To Prof. Graham Bodwell, you have been without a doubt the most influential person in my chemistry education. Your pursuit of perfection, attention to detail, relentless enthusiasm, and overall kind-hearted nature has inspired me in so many ways. Everyday I strive to achieve excellence in the highest form in the laboratory, classroom and outside of the academic world. You have been an amazing teacher, advisor, and friend during my time in your group. Studying under your guidance has been a pleasure and an experience that I will cherish forever. I want you to know that the efforts and sacrifices that you have made for the group have not gone unnoticed and I can only hope that others get to experience the true joy of being a "Bod-group" member as I did.

The Bodwell group is well-known for "kicking-but"! The success that has come from inside the doors of our laboratories is in large part due to the outstanding work environment that is provided form Bodwell group members. There has always been a tremendous feeling of family in our group and this speaks directly to the important values of our supervisor. For providing an intellectually stimulating and home away from home atmosphere, I thank you all.

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List of Figures in Order of Appearance

List of Schemes in Order of Appearance

List of Abbreviations and Symbols

Ac	Acetyl
acac	Acetylacetone (or 2,4-pentanedione)
AcOH	Acetic acid
AIBN	2,2′-Azobis(isobutyronitrile)
AM1	Austin Mode 1
APCI	Atmospheric pressure chemical ionization
ASE	Aromatic stabilization energy
B3LYP	Becke 3-Parameter (Exchange), Lee, Yang and Parr
Bpin	Isopropyl pinacol borate
BPO	Dibenzoyl peroxide
Bu	Butyl
°C	Degree(s) Celcius
ca.	Approximately
cgs	Centimeter-gram-second
Cp	Cyclopentadienyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
Dibal-H	diisobutylaluminum hydride
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformaide
DMSO	Dimethyl sulfoxide

DNA	Deoxyribonucleic acid
Et	Ethyl
equiv.	molar equivalents
FVP	Flash vacuum pyrolysis
GIAO	Gauge-including Atomic Orbital
I_h	Icosahedral
h	Planck's constant
K	Kelvin
LDA	Lithium diisopropylamide
LCMS	Liquid chromatography-mass spectrometry
m	Meta
Me	Methyl
MeCN	Acetonitrile
min	Minutes(s)
mmHg	Millimetres of mercury
n	Normal
NBS	*N*-Bromosuccinimide
NICS	Nucleus-independent Chemical Shift
nm	Nanometer
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
Ph	Phenyl
PhH	Benzene

ppm	Parts per million
pyr.	Pyridine
o	Ortho
OAc	Acetate
OTf	Triflate
RCM	Ring-closing metathesis
R_f	Retention factor
rt	Room temperature
s	Secondary
SE	Strain energy
SWCNTs	Single-walled carbon nanotubes
t or *tert*	Tertiary
$t_{1/2}$	Half-life
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
Torr	Torricelli (1 Torr = 1 mmHg)
TPP	5,10,15,20-tetraphenyl-21*H*,23*H*-porphine
Ts	4-Toluenesulfonyl or tosyl
V-65	2,2′-Azobis(2,4-dimethylvaleronitrile)
VID	Valence isomerization / dehydrogenation

VTNMR	Variable temperature nuclear magnetic resonance

CHAPTER 1: Introduction

1.1 Target Oriented Organic Synthesis

1.1.1 Natural Products and Designed Molecules

Target oriented organic synthesis can be subdivided into two areas: (1) total synthesis and (2) the synthesis of designed molecules. The former involves synthetic approaches to natural products that are the results of billions of years of biological evolution and the products of secondary metabolism of living cells, while the latter are often sought-after targets for their applications to other areas of chemistry and science.

Total synthesis has been one of the mainstays in organic chemistry for over 100 years now, and its contribution to the understanding of chemical reactions and enrichment of the minds and abilities of scientists in the field is undeniable. The current rate, at which syntheses of natural products are reported in the literature, is largely due in part to our forefathers' exploration and discovery of chemical transformations. Additionally, some of the best understood concepts and reactions that are used in organic synthesis are a direct result of research programs devoted to total synthesis. During the course of these synthetic endeavours, it is often the case that the development of new reactions,

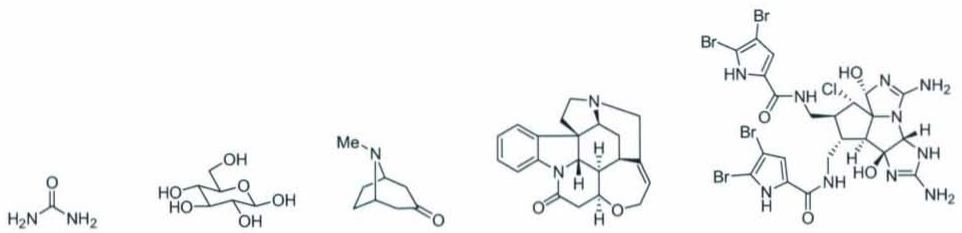


FIGURE 1.1: The evolution of total synthesis (selected natural products)[1]

reagents, or modifications thereof is necessary in order to successfully furnish a synthetic target or intermediate in the synthesis. As such, the pioneering efforts of Nobel laureates Woodward, Barton, and Corey will always be felt in any capacity of organic synthesis as of the field continues to evolve leading to the discovery of new reagents and chemical transformations.

Designed molecule synthesis as a sub-discipline of synthetic organic chemistry (or organic synthesis) can be best described as the pursuit of the synthesis of molecules that are not natural products. The scope of this definition is vast (as is the field) and various sub-divisions within this class exist.[2] Targets are often inspired from the isolation and characterization of natural products, where the modification or derivatization of a

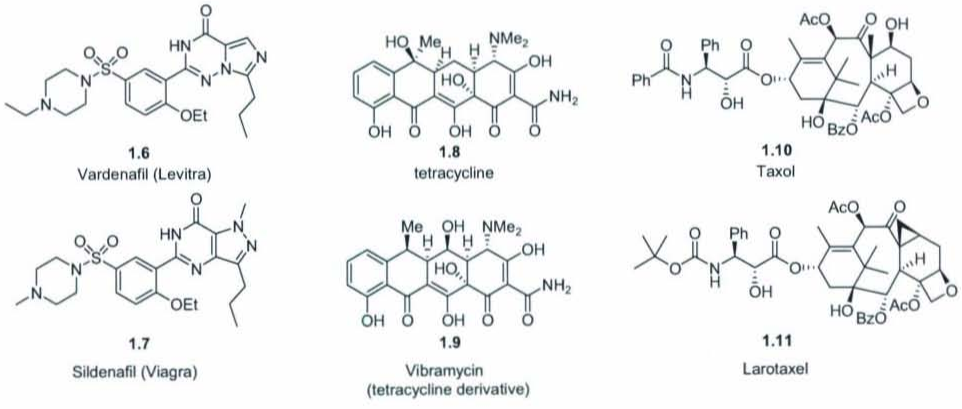
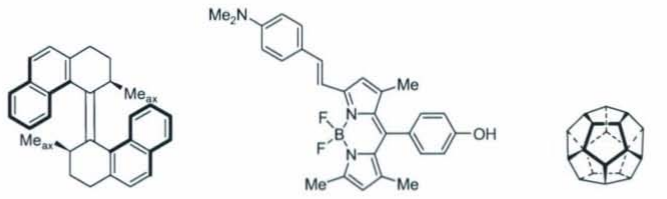


FIGURE 1.2: Natural products (**1.8**, **1.10**) and designed molecules of pharmaceutical interest

particular structural motif of a known natural product is desired to further study its mode of biological action. Such analogs or derivatives form the basis of the pharmaceutical industry and medicinal chemistry programs. Other targets that belong to this class of molecules bear no structural resemblance to natural products or molecules of biological

interest. The synthesis and study of such targets has been engaging the interests of many research groups for decades. Like total synthesis, the pursuit of targets that are purely novel in their design and unrelated to natural products has also made a meaningful contribution to the understanding of chemical reactions and has fostered the current state of the art in organic synthesis.



1.12
Feringa's molecular motor

1.13
molecular calculator

1.14
dodecahedrane

FIGURE 1.3: Designed molecules of theoretical interest[3]

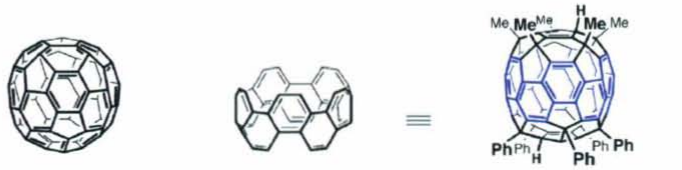
At first glance, from the representative examples illustrated in Figures 1.1–1.3, it would seem that the structural complexity associated with natural products or designed molecules of pharmaceutical interest is far greater than that of the selected designed molecules of theoretical interest. While a contiguous array of stereogenic centers or a complex polycyclic system that has alternating ring sizes and many "unnatural" structural features (such as the anti-Bredt alkene present in Taxol and its derivatives) can present the most formidable synthetic challenge, one must always be cognizant of the fact that there is precedent for these structures through biosynthesis. While the feats of nature may never be entirely matched due to the evolutionary head start that microbes and plants have had, it would be naïve to say that designed molecules are less challenging targets than natural products. When embarking on the synthesis of a designed molecule, one is truly

pursuing a molecule that does not and may never exist. While the application of chemical transformations that are used and have been developed in the arena of total synthesis are inevitably applied in designed molecule construction, the discovery of new reactions and methodologies in this field have benefited organic chemists engaged in total synthesis as well.

One of the major differences between these areas of organic synthesis is that the structures of natural products are often reported as separate communications or reports and the race to become the first to execute a synthesis begins. During the ensuing sprint, communications typically appear from several groups describing either a partial synthesis of the molecule in question or methodologies that have been developed for access to a salient feature of a specific target. For the most part, this direct competition to be first to a particular structure is largely active in the field of designed molecule synthesis. However, it is not with the same tight restrictions as total synthesis. The freedom to slightly alter certain features of an initially designed target is left to the discretion of the scientist and making a slightly modified target that contains all of the key structural details that were initially sought-after, does not weaken the quality of the work.[4] In total synthesis, preparing the wrong stereoisomer of a given target or even a derivative of the target that either lacks a substituent or has an extra substituent can often tie up publication and is generally regarded as not being as significant as a synthesis that is able to secure the correct target with the correct constitution and stereochemistry.

1.1.2 Nonplanar Aromatic Hydrocarbons – Targets in Organic Synthesis

The subject of this dissertation is the synthesis of nonplanar aromatic hydrocarbons, in particular those that have a pyrenoid motif. Further explanation and discussion of the target molecules of this work and their unique structural features will follow in Chapters 2 and 4. Nonplanar aromatic hydrocarbons have been the subjects of intense interest for the last two decades.[5] While research programs directed toward the synthesis of highly deformed or bent benzene rings have been ongoing since the 1950s,[6] it was the landmark discovery of I_h C_{60} fullerene by Kroto, Curl and Smalley[7] that sparked the current surge of activity (which shows no signs of diminishing) in this field. Two of the most noteworthy achievements in this field include a rational laboratory synthesis of I_h C_{60} by Scott and co-workers[8] and the synthesis of a cyclo[10]phenacene (or [10]cyclophenacene)[9] by Nakamura and co-workers[4] – a molecule that maps onto the equator of C_{60} and can also be viewed as an aromatic belt.[10] The pursuit of such molecules predates the genesis of the fullerene allotropes of carbon.[11]



C_{60} fullerene **1.15** | cyclo[10]phenacene **1.16** | Nakamura's cyclo[10]phenacene

FIGURE 1.4: C_{60} fullerene and cyclo[10]phenacene

Nonplanar aromatic hydrocarbons constitute an important class of designed molecules. One of the major difficulties associated with their preparation is the

generation of an innately planar aromatic π-system in a bent form. This major challenge arises from the interplay of two important energetic factors: strain and aromaticity (or rather, aromatic stabilization energy - ASE). Many attempted syntheses of several well-known nonplanar aromatic molecules have failed in the late stages of the synthesis due to the inability of end-game strategies to generate highly strained π-systems by the aromatization of relatively unstrained precursors.[12] The concepts that surround the successful chemical synthesis of highly distorted π-systems and the considerations that one must make in an initial synthesis plan will be discussed in Section 1.2. While nonplanar aromatic hydrocarbons are often devoid of any functional groups (in their final form) the synthetic challenge that is associated with their preparation should not be understated, as many research programs directed toward the synthesis of such compounds never come to fruition.[12]

The interest in synthesizing nonplanar aromatic hydrocarbons stems from the challenge that their structures present. The terms nonplanar and aromatic, may seem somewhat oxymoronic, especially when viewed in the context of traditional or elementary definitions of aromaticity.[13] Most introductory organic chemistry textbooks will list planarity as one of the *criteria* for aromaticity in Hückel aromatic systems. This statement is an oversimplification and neglects other much more important facets of aromaticity. The major criterion for aromaticity that is generally ignored at the introductory level is that of magnetism. Many theoreticians believe that the evaluation of magnetic susceptibility for a π-system is a much more rigorous measure of its aromaticity

and such indices[14] are often invoked in studying the effects on bending the π-system in question. Further discussion of these magnetic criteria will follow in Section 1.4.5.

1.2 The Origin of Nonplanarity in Aromatic and Polycyclic Aromatic Systems

Examples of aromatic and polynuclear aromatic systems that have a nonplanar lowest energy conformation, such as corannulene ([5]Circulene), also predate the discovery of the fullerene allotropes of carbon by nearly 20 years.[15] The distortion or nonplanarity that is present in these systems arises predominately through the application of three different approaches: (1) complete benzannulation of a non-six-membered ring; (2) tethering two nonadjacent positions of an aromatic system (a *cyclophane approach*); and (3) through spatial or non-bonded interactions between neighbouring atoms that arise through angular annulation of aromatic rings (Figure 1.5). In all cases, the lowest energy conformation of the π-system is nonplanar, due primarily to the compromise between the distortion of bond lengths and bond angles.

1.17 [5]circulene **1.18** [6]paracyclophane **1.19** [7]helicene

FIGURE 1.5: Examples of nonplanar aromatic hydrocarbons

Understanding the difference in energetic penalties of these two facets of bonding energy is demonstrated by the two smallest saturated cycloalkanes, cyclopropane and cyclobutane. The overall deviation from the ideal sp^3 hybridized bond angle (109.5°) in

both of these systems is approximately 49° and 21° respectively, while the deviation form the ideal carbon-carbon bond length (1.54 Å) is small at 0.024 Å and 0.020 Å respectively.[16] The large deviation in bonding angles is significant in both molecular geometries and it is clear that bond lengths reside in relatively deep and narrow energy wells (*i.e.* they are relatively hard to distort from ideal values) while bond angles reside in relatively broad and shallow energy wells (*i.e.* they are relatively easy to distort from ideal values).[17] Thus, it quickly becomes evident why the π-systems in question are in fact nonplanar. For each class of nonplanar system, the difference in the ease with which bond angles and lengths can be distorted manifests itself in different ways and these are explained in the following sections.

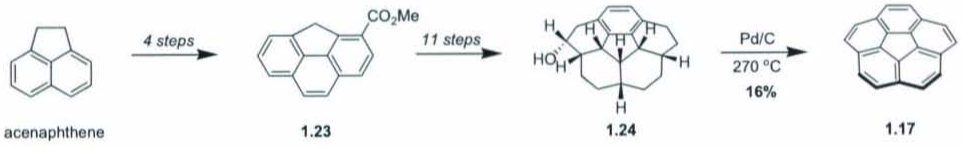
1.2.1 Bowl-shaped and Curved Polycyclic Systems as a Result of Benzannulation

In the case of the [*n*]circulenes[18] (where *n* is not equal to six), the planar (D_{nh}-symmetric) conformations require that the central carbocyclic rings describe polygons that have interior angles that are not equal to 120°. The planar (D_{nh}-symmetric) conformations also cannot maintain ideal carbon-carbon bond lengths. For $n < 6$, bond elongation around the rim and bond contraction around the hub are dictated by the shape

1.20 [4]circulene | **1.17** [5]circulene corannulene | **1.21** [6]circulene coronene | **1.22** [7]circulene pleiadannulene

FIGURE 1.6: Homologous series of [*n*]circulenes

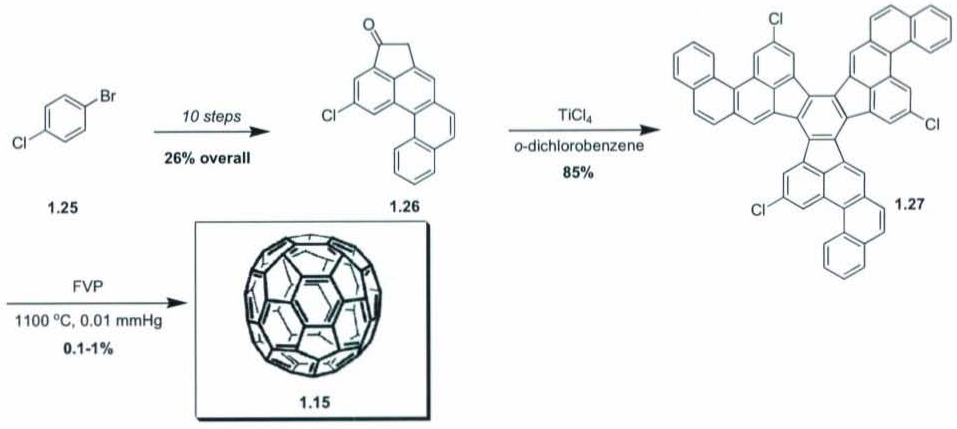
of the hydrocarbons. For $n > 6$, it is the other way around. Either way, it is energetically less costly for the central carbon atoms to undergo pyramidalization than for the bond lengths to deviate significantly from their ideal values (*vide supra*). Consequently, the molecules adopt nonplanar or curved structures. [5]Circulene (**1.17**), or as it is more commonly known – corannulene, is bowl-shaped, while [7]circulene (**1.22**) is saddle-shaped (Figure 1.6). The synthesis of both of these molecules has been achieved,[19] but the syntheses of lower and higher homologs have not been reported.[20] Corannulene has, by far, received the most attention in terms of synthetic investigation of all of the nonplanar [*n*]circulenes, owing to its homology to C_{60} fullerene. However, the first synthesis of [5]Circulene (**1.17**) was reported[15] nearly two decades before the discovery



SCHEME 1.1: The first synthesis of corannulene (**1.17**) by Barth and Lawton

of these fascinating allotropes of carbon.[11] Subsequent studies on the synthesis of this bowl-shaped geodesic structure and structurally related analogs have been ongoing in several research groups since the mid 1980s.[21] The application of high temperature pyrolysis to furnish the nonplanar (and thus strained) polycyclic structures from planar and unstrained hydrocarbons has been a mainstay of this work, although various solution phase methods have been developed recently. The crowning achievement in this area was

the synthesis of C_{60} (**1.15**), which was reported by the Scott group at Boston College in 2002. Their synthesis is summarized in Scheme 1.2.[8]



SCHEME 1.2: Scott and co-workers synthesis of C_{60} in 2002

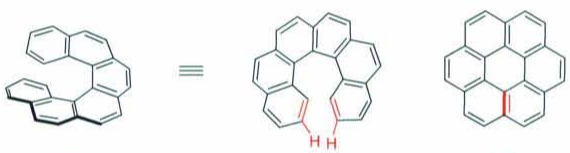
1.2.2 The *Cyclophane Approach* to Bent π-systems

Bridging two non-adjacent positions of an aromatic system gives rise to a cyclophane. Depending upon the nature of the bridging unit, nonplanarity can be enforced in the aromatic unit of the molecule. As such, this approach can be described as a *cyclophane approach* to nonplanar π-systems.[22] Cyclophanes represent a large class of organic compounds that have been well-known now for many years in capacities that include both planar and nonplanar aromatic systems. The introduction of a sufficiently long (aliphatic) bridge to an aromatic system affords an [*n*]cyclophane that is essentially free from strain. In such cases, both the aromatic unit and the bridge can adopt near-ideal conformations. Sequential shortening of this bridge affords a homologous series, in which the amount of strain increases as the length of the bridge decreases. If the aromatic

unit maintains a planar conformation as the bridge becomes shorter, bond length elongation in the bridge and/or bond length contraction in the aromatic unit will be required. However, a less energetically costly form of distortion is for the aromatic unit to bend out of planarity (*vide supra*).[16] This occurs by pyramidalization at the bridgehead positions and bond torsions around the bridged ring(s). By far the most common aromatic unit that has been bridged to form cyclophanes is the quintessential aromatic system, benzene. The benzene rings in these cyclophanes are distorted into boat-shaped conformations, both in the [*n*]meta- and [*n*]paracyclophanes. A discussion of the synthesis of these two classes of cyclophanes and the implications of bending the benzene nucleus (and other aromatic systems) is presented in Sections 1.3–1.5.

1.2.3 Consequences of Angular Annulation of Benzene Rings

Twisted acenes arise due to the non-bonded interactions between neighbouring atoms that would arise if the molecule were to maintain a planar conformation. [6]Helicene (**1.28**) is an example of this class of molecules and, its homology to coronene (**1.21**) speaks to the degree of steric congestion that would otherwise be present in the molecule if it were planar. The colored atoms in [6]helicene (with two *ortho* hydrogens omitted for clarity) are shared as carbon-carbon bonds in planar coronene (Figure 1.7).

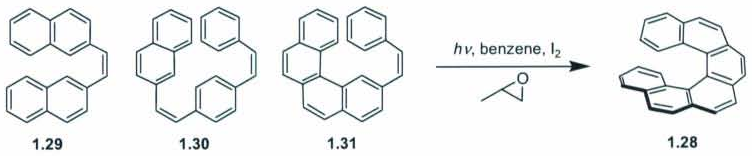


1.28
[6]helicene

1.21
coronene
[6]circulene

FIGURE 1.7: Comparison of nonplanar [6]helicene (**1.28**) and planar coronene (**1.21**)

As such, the two terminal benzene rings are somewhat stacked, and the entire molecule twists out of planarity to give a helical conformation. In general, helical structures of polycyclic aromatic hydrocarbons can be prepared from the photoisomerization of stilbene derivatives such as **1.29–1.31** (Scheme 1.3). However, due to their interesting chirality and potential applications in medicine (due in part to their interactions with DNA) the Collins group has recently reported a very mild and effective synthetic route to helicenes that involves a ring-closing metathesis (RCM) reaction of a biaryl system.[23] Other recent syntheses of helicene and helicene-like molecules have made use of transition metal catalysis via palladium-catalyzed double C–H arylation[24] and nickel or cobalt-catalyzed[25] alkyne cyclotrimerization strategies.



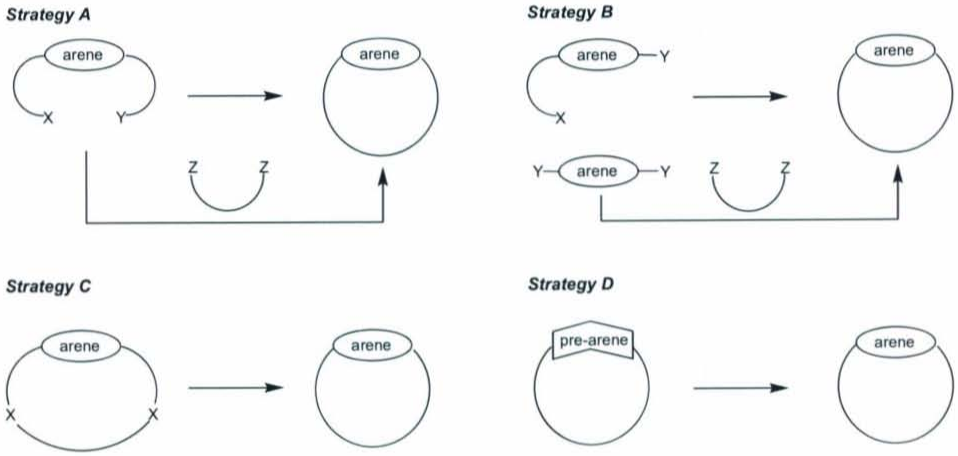
SCHEME 1.3: Synthesis of [6]helicene (**1.28**) through *cis*-stilbene intermediates

1.3 General Strategies for the Synthesis of Cyclophanes Containing Bent Aromatic Systems

The synthesis of cyclophanes containing bent aromatic systems has been accomplished according to four general strategies (A–D), the defining features of which are the ways in which nonplanarity is imparted to the aromatic system (Scheme 1.4). Examples of the most common three of these strategies will be the focus of this section.

Strategy A (Scheme 1.4) involves the formation of a bond between two atoms that comprise part of the bridge. The functional groups X and Y can be identical or different

depending upon the methodology used. Since bond formation is accompanied by bending of the aromatic system out of planarity, the increase in energy associated with bending the arene goes directly to the energy barrier of the bond-forming reaction. If this increase in the energy barrier is significant, the desired intramolecular reaction becomes disfavoured with respect to the corresponding intermolecular reaction and oligomerization reactions



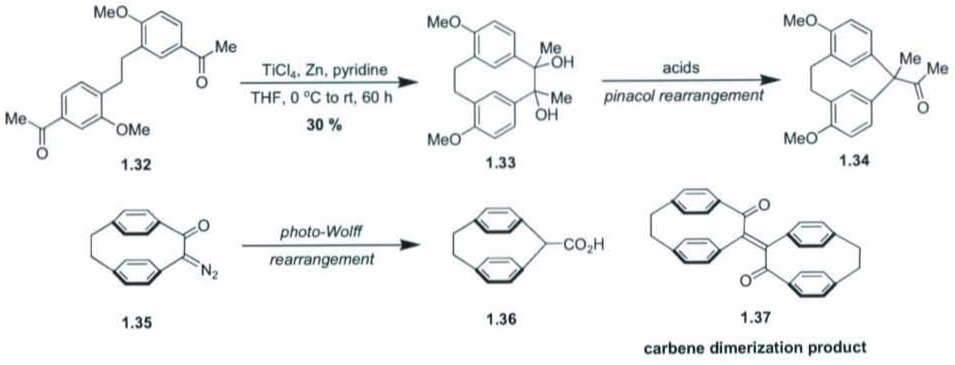
SCHEME 1.4: General strategies for generating cyclophanes containing bent arenes

become possible in such instances. Techniques such as high dilution can help to promote the desired intramolecular reaction, but this is generally an ineffective strategy for the synthesis of cyclophanes with more highly distorted aromatic units. In contrast, it is a very popular and useful strategy for the synthesis of cyclophanes with planar or nearly planar aromatic systems.[6]

Strategy B is similar to Strategy A, but it involves the formation of a bond between an atom of the aromatic system and an atom of the bridge. Like Strategy A, the bending of the arene accompanies the bond formation and it has not proved to be useful

for the formation of cyclophanes with significantly bent π-systems. Strategy B is much less common than Strategy A, even for the formation of unstrained cyclophanes.[26]

Strategy C relies upon the contraction of the bridge(s) of an existing cyclophane. This is a widely used approach, especially for systems where the aromatic unit(s) of the starting cyclophane is/are planar or nearly planar. In such cases, the increase in energy associated with increasing the bend of the aromatic system is relatively small and the energy barrier to the ring contraction reaction does not become prohibitive. However,

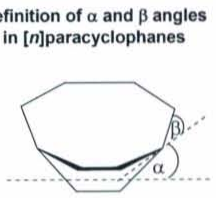


SCHEME 1.5: Attempted synthesis of a [2.1]meta- (**1.34**) and paracyclophane (**1.36**)

when the starting material contains one or more arenes with more pronounced bend, it costs considerably more energy to introduce further bend and the ring contraction can fail. For example, attempted ring contraction of [2.2]metacyclophane **1.33** and [2.2]paracyclophane **1.35** does not afford the desired [2.1]cyclophanes (**1.34** and **1.36**), but rather a carbene dimerization product **1.37** in the case of **1.35** (Scheme 1.5).

Strategy D is overwhelmingly the most powerful strategy for forming cyclophanes with bent aromatic systems and, as the remaining sections of this chapter will describe, is

n	α_{exp}	$\alpha_{calculated}$	SE_{ring} (kcal/mol)	SE_{bridge} (kcal/mol)	SE_{total} (kcal/mol)
3	n/a	42.5	114.2	12.9	127.1
4	n/a	35.5	79.7	7.7	87.4
5	n/a	28.4	50.2	8.3	58.5
6	19.9	22.4	29.1	7.6	36.7
7	15.1	16.4	15.0	6.7	21.7
8	9.1	13.3	10.0	6.0	16.0
9	n/a	8.4	3.9	5.7	9.6
10	n/a	4.9	1.4	7.4	8.8



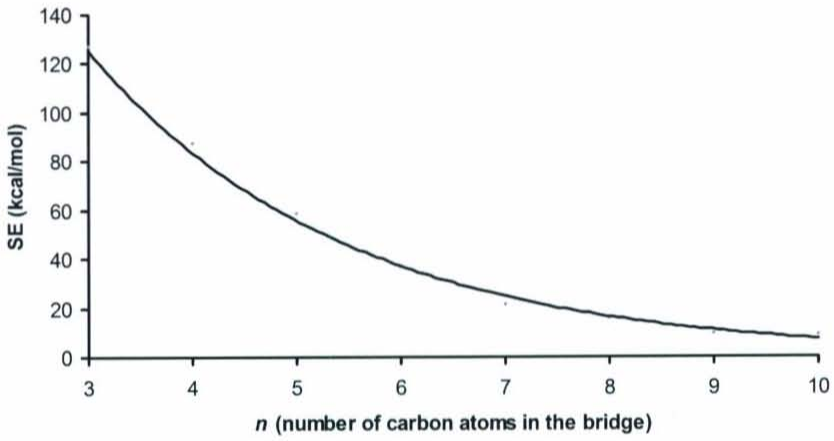


FIGURE 1.8: Strain energies of [*n*]paracylophanes and definition of α and β angles

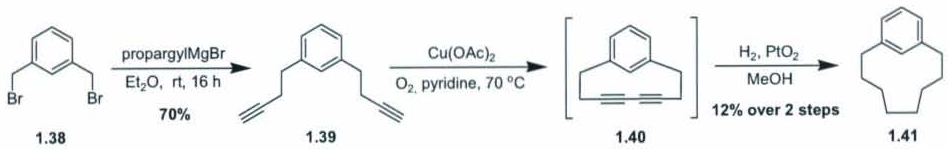
so far the only strategy that can deliver the most highly bent π-systems. The crux of this strategy is to form the aromatic system in its final bent conformation rather than increasing the bend in an existing one. In most cases, this involves the formation of a bridged arene precursor (pre-arene) that can easily accommodate the bridge, followed by the generation of the bent or nonplanar aromatic system. Although the arene is formed in

a nonideal conformation, its formation is nevertheless accompanied by the gain of whatever aromatic stabilization energy (ASE) the bent arene possesses and any strain relief the destruction of the arene precursor provides. Furthermore, competing intermolecular reactions are usually absent. Strategy D has seen applications in the synthesis of nonplanar aromatic systems other than benzene, especially by Bodwell and co-workers in the preparation of several (2,7)pyrenophanes. The work of the Bodwell group in this area will be highlighted in Section 1.5.2 and will serve as a prelude to the new discoveries described in this dissertation. Until then, a discussion of the four strategies and their applications towards the synthesis of bent benzene rings would be instructive.

1.3.1 Synthesis of [*n*]Meta- and [*n*]Paracyclophanes Using Strategies A–C

Hubert and Dale's synthesis of [8]metacyclophane (**1.41**) is an example of Strategy A (Scheme 1.6).[27] It commenced with the alkylation of α,α′-dibromo-*m*-xylene (**1.38**) with the Grignard reagent derived from propargyl bromide to furnish diyne **1.39**. A cyclophanediyne (**1.40**) was then generated by subjection of **1.39** to a Glaser coupling reaction. Finally, hydrogenation of the alkynes afforded [8]metacyclophane (**1.41**). The synthesis is very short (3 steps), but the overall yield is just 8%. It is noteworthy that the majority of the product losses were suffered during the Glaser coupling reaction. Considering that **1.41** is not a particularly strained system (*cf.* [9]paracyclophane, Figure 1.5), the prospects of using a Glaser coupling reaction for the synthesis of lower [*n*]metacyclophanes are bleak. Various other Strategy A approaches have also been

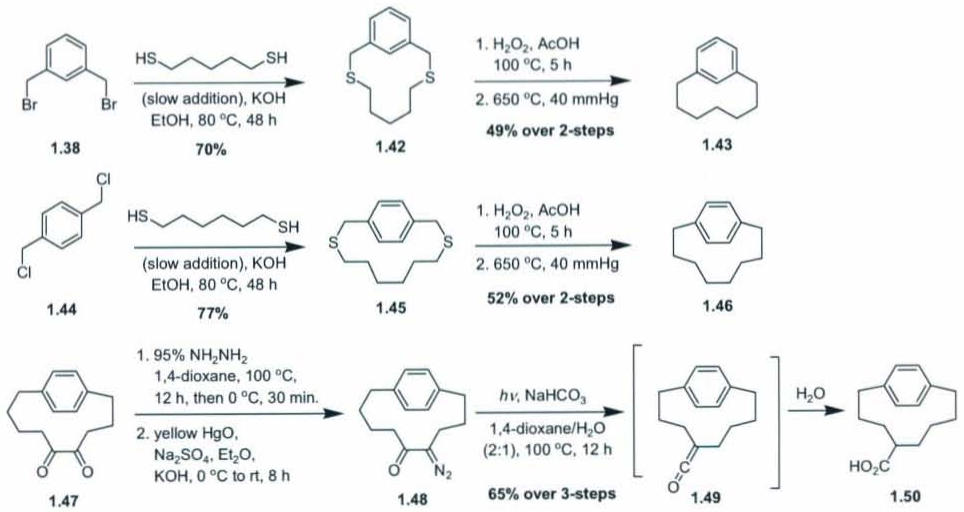
applied, however, only to the synthesis of [*n*]meta and [*n*]paracylophanes that contain very modestly distorted benzenes rings.



SCHEME 1.6: Hubert and Dale's synthesis of [8]metacyclophane (**1.41**) – Strategy A

Strategy C provides a distinct entropic advantage over Strategies A and B and is, in a sense, a more sophisticated method for generating slightly bent arenes. However, all applications of this ring contraction strategy rely on the application of both of these "weaker" concepts in initially generating a cyclophane (*i.e.* forming the initial bridge(s)). *S*-Alkylation of suitable dithiols with bis(halomethyl)benzenes under basic conditions can furnish dithiacylophanes **1.42** and **1.45** in the instances of both [*n*]meta- and [*n*]paracyclophanes (Scheme 1.7).[28] In order to shorten the bridge that connects the aromatic moiety of the cyclophane, extrusion of the sulfur atoms needs to take place. This was achieved by Misumi and co-workers in the synthesis of [7]meta- (**1.43**) and [8]paracyclophane (**1.46**) via oxidation of the sulfides to the corresponding sulfones, which were then extruded as sulfur dioxide upon heating at 650 °C and 40 mmHg. This particular use of Strategy C shortens the alkyl bridge of the cyclophane by two atoms and thus introduces considerably more strain in the π-system than was already present. As such, in instances where $n<7$ or 8 (for meta- and paracyclophanes) respectively the increase in strain energy (*cf.* ΔSE_{total}=0.8 kcal/mol for [10]paracylophane to [9]paracyclophane and ΔSE_{total}=6.4 kcal/mol for [9]paracylophane to [8]paracyclophane,

Figure 1.8) that is associated with bending the aromatic system becomes too large and the extrusion fails. A second example that employs Strategy C is a contribution from Allinger and co-workers, whereby advanced intermediate **1.48** was found to undergo a Wolff rearrangement upon irradiation with light to give [8]paracyclophane derivative **1.50** after ketene intermediate **1.49** was intercepted with water.[29] While the amount of strain that is generated in the ring contraction step is not as large (Figure 1.8) as the sulfur extrusion examples, the use of this methodology was unsuccessful in its application to lower homologs. However, the use of the photo-Wolff rearrangement in the contraction of alkyl bridges will be a recurring theme in the discussion to follow.



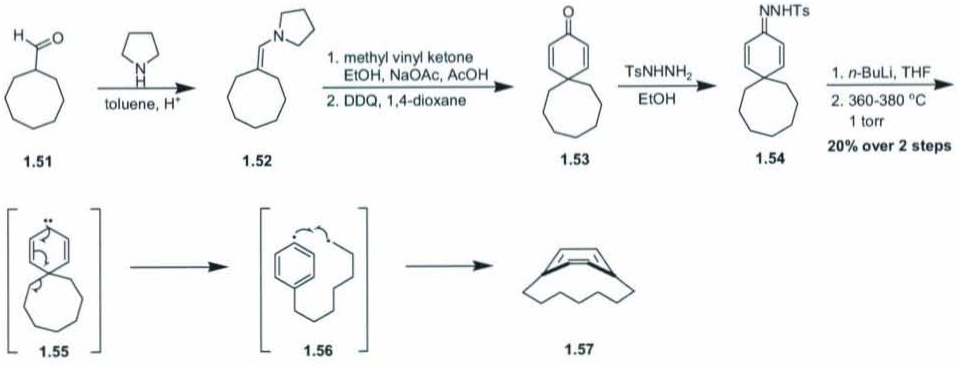
SCHEME 1.7: Application of Strategy C for the synthesis of [7]metacyclophane (**1.43**) and [8]paracyclophanes **1.46** and **1.50**

In general, Strategies A–C are ineffective in synthesizing cyclophanes that contain highly distorted π-systems. While strategy C provides a distinct entropic advantage over strategies A and B, further application towards the synthesis of lower homologs of both

isomeric cyclophanes (other than those highlighted in Scheme 1.7) has never been achieved. Thus, the use of high energy intermediates capable of rearranging to severely strained systems is necessitated.

Along these lines, Jones Jr. and co-workers' unique "Strategy B" syntheses of [7]-(**1.57**) and [6]paracyclophane (**1.58**) rely upon rearrangement of a spirocarbene intermediate (Scheme 1.8).[30] Although a pre-arene can be identified in the starting material (**1.54**), classification of this approach under Strategy D is inappropriate because the pre-arene is not bridged.

Condensation of pyrrolidine and aldehyde **1.51** under Dean-Stark conditions furnished enamine **1.52**, which was reacted further with methyl vinyl ketone under buffered conditions to give a sprirocyclic cyclohexenone via a Robinson



SCHEME 1.8: Jones Jr. and co-workers' synthesis of [7]paracyclophane (**1.57**)

annulation. Dehydrogenation of this enone intermediate with DDQ afforded spirocyclic ketone **1.53**. Formation of the tosyl hydrazone under standard conditions followed by deprotonation with *n*-butyllithium gives a salt that was converted into spirocarbene **1.55**

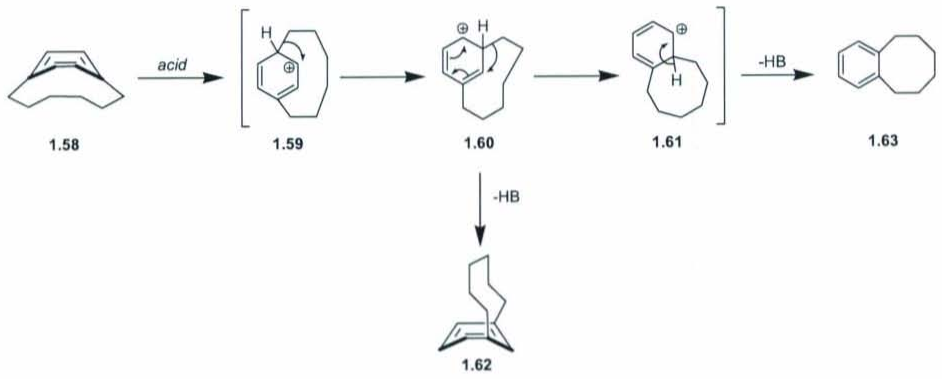
under high temperature and low pressure via a Bamford-Stevens reaction. Driven by the formation of an aromatic sextet, carbene **1.55** underwent C–C bond cleavage to afford diradical **1.56**, which recombined to afford [7]- (**1.57**) and [6]paracyclophane (**1.58**, *vide infra*) in 20% and 2% yields, respectively. An attempt to synthesize [5]paracyclophane (**1.83**, *vide infra*) from a hydrazone akin to **1.54** failed to afford the desired product. This impediment and the low yields of [7]- (**1.57**) and [6]paracyclophane (**1.58**) highlighted the need for more powerful synthetic methods for the generation of the more highly strained systems. Although Jones' approach makes use of high energy intermediates (carbene **1.55** and diradical **1.56**), it suffers entropically from the need to form a new carbon-carbon bond intramolecularly and enthalpically from the need to introduce all of the strain in the product during that bond formation. As such, this method is quite limited.

1. 4 Rearrangements and the Valence Isomerization Approach to Strained Benzene Rings

1. 4. 1 Thermal Rearrangements of Strained Precursors

The synthesis of [*n*]metacyclophanes from [*n*]paracyclophanes via thermal rearrangement of a protonated intermediate was a concept first introduced by Hopf and co-workers.[31] Tobe's group was also able to make use of this strategy in preparing [6]metacyclophane (**1.62**) from [6]paracyclophane (**1.58**) (Scheme 1.9).[32] The rearrangement is driven by the relief of strain that results from protonation of the bridgehead positions of the paracyclophanes. Application of this strategy towards the synthesis of lower homologs in the [*n*]metacyclophane series is not viable since the

preparation of the starting material is much more demanding (synthetically) than the ultimate product. Also, these rearrangements are hampered by the formation of isomeric benzocycloalkanes ("orthocyclophanes") such as **1.63**.



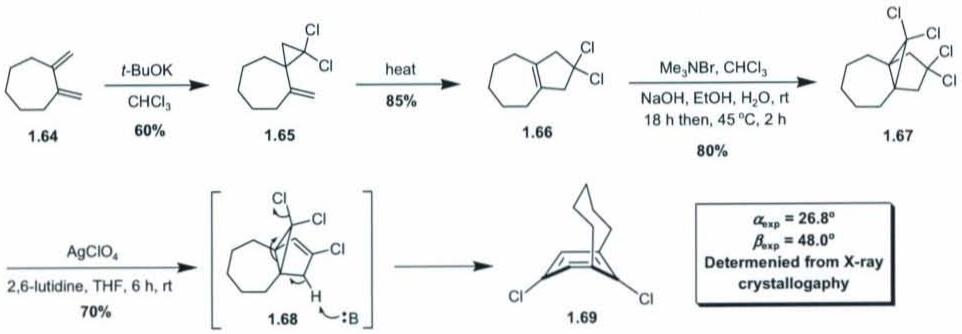
SCHEME 1.9: Acid-catalyzed rearrangement of [6]paracyclophane (**1.58**) to [6]metacyclophane (**1.62**)

Recognizing that major energetic driving forces such as strain relief (of pre-arenes) and the gain of aromatic stabilization energy would be required to overcome the strain energy present in the smaller meta- and paracyclophane homologs, the research groups of Bickelhaupt, Tobe, and Jones developed programs that made use of thermal and photochemical rearrangements to provide entry to some the most strained benzene rings known.

1.4.2 The Synthesis of [5]Metacyclophane 1.69

Bickelhaupt's synthesis of 8,11-dichloro[5]metacyclophane[33] (**1.69**) involved the formation of [5.3.1]propellane **1.67**. Monocyclopropanation of diene **1.64** gave dichloride **1.65**, which upon heating underwent a vinylcyclopropane rearrangement to

furnish bicycle **1.66**. A second cyclopropanation of the alkene in **1.66** gave trichloro[5.3.1]propellane **1.67**. At this juncture, all of the carbon atoms that are present in [5]metacyclophane **1.69** had been installed in the form of this highly strained tricyclic system. Subjection of **1.67** to silver perchlorate and 2,6-lutidine afforded



SCHEME 1.10: Bickelhaupt's synthesis of 8,11-dichloro[5]metacyclophane (**1.69**)

the desired [5]metacyclophane **1.69** via an elimination/fragmentation mechanism. The strain energy inherent in [5.3.1]propellane **1.67** is unveiled at this stage of the synthesis and marks the first example where Strategy D has been employed in this discussion. To date, 8,11-dichloro[5]metacyclophane (**1.69**) still stands as the smallest isolable metacyclophane for which an X-ray crystal structure could be obtained. Other syntheses of [5]metacyclophanes have been reported by Bickelhaupt,[34] but application of this strategy towards the synthesis of [4]metacyclophane furnished only the thermally unstable Dewar benzene isomer.

1.4.3 The Valence Isomerization Approach to Strained [*n*]Paracyclophanes

Dewar benzene, or bicyclo[2.2.0]hexa-2,5-diene, is a valence isomer of benzene. *Valence isomers* are constitutional isomers that are interrelated by pericyclic reactions.[35] The Dewar benzene, and to a lesser extent, the 3,3′-bicyclopropenyl valence isomers of benzene are of significant importance in the synthesis of the most strained paracyclophanes known and will feature prominently in the following discussion.

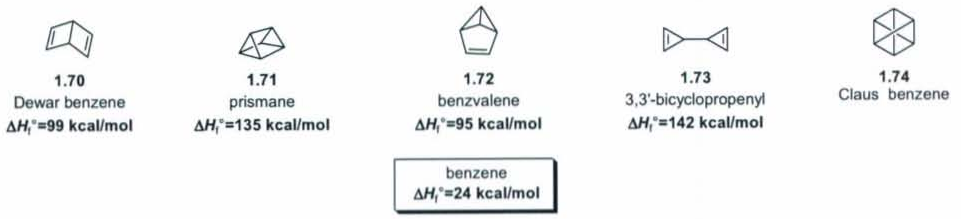


FIGURE 1.9: Valence isomers of benzene and enthalpy of formation values

Sequential reduction of the number of methylene groups (or skeletal atoms) that constitute the bridge of a paracyclophane increases the molecular strain,[36] a major part of which manifests itself in the bending of the benzene nucleus (see Figure 1.8). This is the primary reason why Strategies A–C fail in generating highly distorted benzenes rings (see Section 1.3.1). Thus, as the overall strain energy increases, the relief of strain by way of reorganization of the benzene ring becomes increasingly viable. Thermodynamically, benzene is by far the most stable of all of its valence isomers (*cf.* $\Delta H_f°$=24 kcal/mol) when it is in its native planar conformation. However, leaving the plane causes for an increase in strain energy and, in extreme cases, the once stable aromatic sextet becomes destabilized with respect to other valence isomers (recall the discussion on the interplay of strain and ASE in Section 1.1.2). By the same token, the conversion of a valence

isomer of benzene to benzene in the late stages of a synthesis could provide a gateway to some of the most bent benzene rings known. This is the premise of Strategy D.

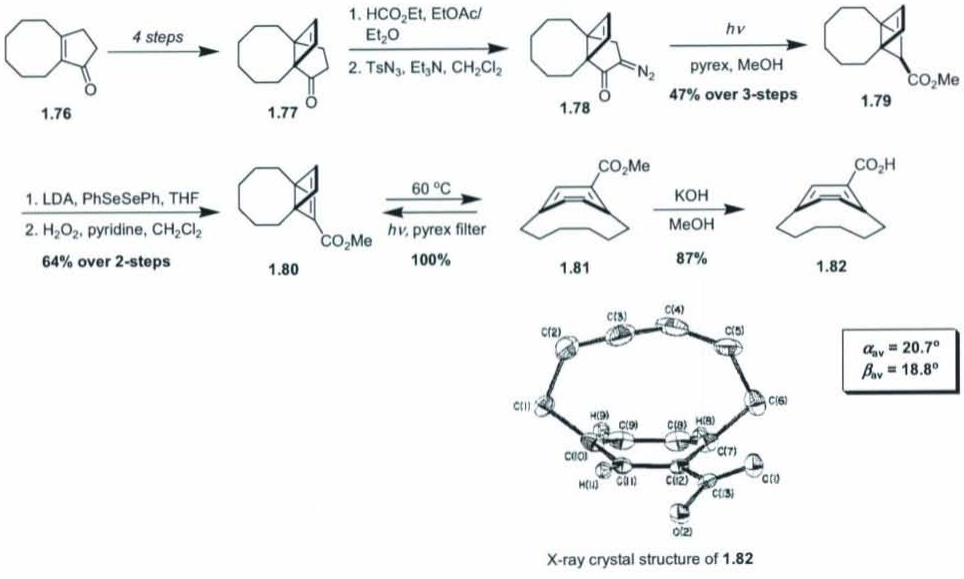
The conversion of Dewar benzene to benzene is a photochemically allowed process under the Woodward-Hoffmann rules on the conservation of symmetry in molecular orbitals.[37] Thermally, the conversion is forbidden as it would necessitate the formation of a *trans*-alkene within the six-membered ring as a result of a conrotatory ring

SCHEME 1.11: Conversion of Dewar benzene to benzene (thermally forbidden)

opening of the cyclobutene portion of **1.70**.[38] In spite of this unfavourable alkene geometry and an activation energy of 37 kcal/mol for the conrotatory ring opening reaction, conversion of hexamethyl Dewar benzene to hexamethyl benzene does take place at 150 °C ($t_{1/2}$ = 3 h) and is exothermic by 60 kcal/mol.[39] Thus, considering the large energy difference between benzene and Dewar benzene (75 kcal/mol, see Figure 1.9), irradiation or gentle heating of an appropriately functionalized Dewar benzene could be a powerful method for generating small [*n*]metacyclophanes or [*n*]paracyclophanes. Furthermore, in cases where the thermal stability of the strained cyclophane targets becomes an issue, photolysis of a Dewar benzene intermediate (at low temperature) may overcome this obstacle. Also, the naturally bent shape of the Dewar benzene valence isomer will aid the aromatization step(s) in the synthesis of the nonplanar target(s).

Tobe and co-workers demonstrated and exploited this concept in their synthesis of 8-carboxy[6]paracyclophane (**1.82**). Conversion of angular propellane **1.77** to

diazoketone **1.78** followed by a photo-Wolff rearrangement gave ester **1.79** in 47% yield over three-steps. Introduction of the necessary unsaturation in **1.79** to furnish Dewar benzene **1.80** was achieved using a two-step sequence. From here, heating **1.80** at 60 °C followed by saponification gave a crystalline sample of [6]paracyclophane **1.82**, which to date remains as the smallest isolable [*n*]paracyclophane known.[40] Interestingly, **1.82** is a chiral compound and the carboxylic acid functionality offers the potential for resolution. However, no work in this area appears to have been done.



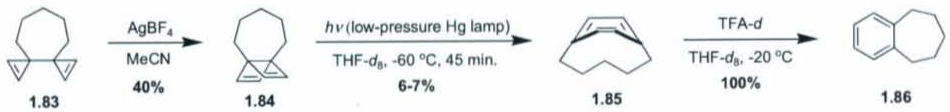
SCHEME 1.12: Tobe's Synthesis of 8-carboxy[6]paracyclophane (**1.82**)

1.4.4 Synthesis of [5]Paracyclophane

The dichotomy of thermal versus photochemical ring opening of a Dewar benzene precursor is illustrated in Bickelhaupt's synthesis of [5]paracyclophane (**1.85**).[42]

Examination of the data presented in Figure 1.8 (*vide supra*) reveals that the remaining homologs in the paracyclophane series are considerably more strained than the previously synthesized system ([6]paracyclophane). The thermal ring opening of a 1,4-bridged Dewar benzene (*cf.* Tobe's synthesis of [6]paracyclophane **1.82**) was ineffective in the synthesis of [5]paracyclophane, owing to the thermal instability of the desired target. However, photochemically the ring opening reaction is allowed and the desired valence isomerization reaction could take place under milder (*i.e.* without heating) conditions to afford the titled target.[41]

One of the advantages of using Dewar benzenes in valence isomerization reactions (Strategy D) to generate nonplanar benzene rings is that they are higher energy intermediates than the corresponding cyclophanes (except in the case where n=4).[48] A similar situation was encountered in Bickelhaupt's study on [1.1]metacyclophane, where the known Dewar isomer was considerably higher in energy (thermodynamically less stable by 24 kcal/mol) than the corresponding aromatized cyclophane.[42] Thus, the strain present in the Dewar isomer can compensate for the considerable amount of strain



SCHEME 1.13: Synthesis of [5]paracyclophane (**1.85**) by Bickelhaupt and co-workers

present in the target (specifically the benzene ring) upon its formation. Analogous to their work on [6]paracyclophane, and with a research program directed towards the synthesis of small cyclophanes using 2,2′-bicyclopropenyl substrates, their synthesis

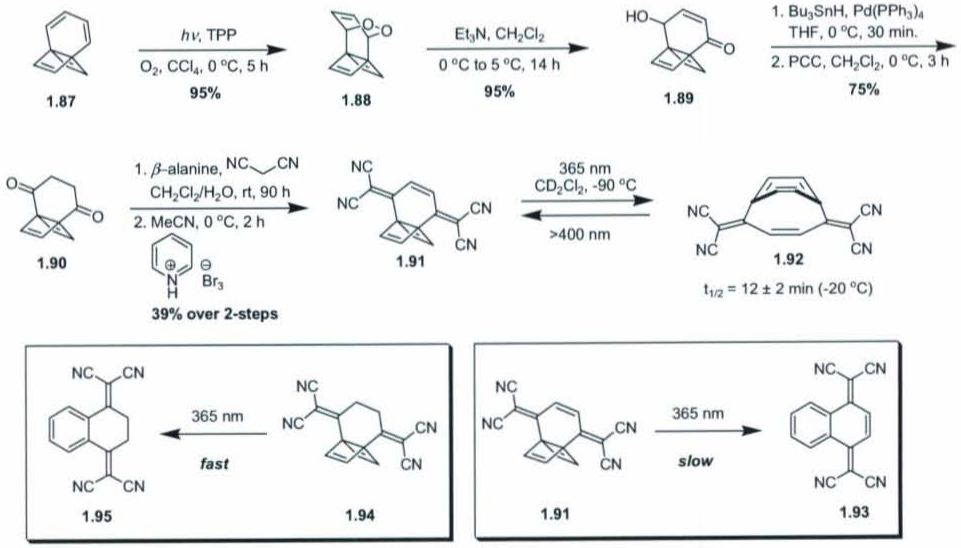
commenced with the silver tetrafluoroborate-catalyzed isomerization of **1.83** to Dewar benzene **1.84**. Subsequent irradiation in an NMR tube at –60 °C furnished the highly strained [5]paracyclophane **1.85**. It is also noteworthy that only the *ortho* isomer **1.86** was obtained when **1.85** was treated with acid, and no [5]metacyclophane was observed (unlike [6]paracylophane, see Scheme 1.9) in this reaction. Both Tobe[43] and Bickelhaupt[44] were also successful in the preparation of substituted derivatives that proved to be more thermally stable. However, to date there has been no report of a [5]paracyclophane that was prepared and isolated to be set on a bench/shelf with an appreciable half-life.

1.4.5 [4]Paracyclophane Derivatives: Synthesis and Properties of Highly Deformed Benzene Rings

Shortening of the bridge by one more atom to yield [4]paracyclophane would seem to be an impossible challenge given what was observed by Bickelhaupt and co-workers in the synthesis of [5]paracyclophane. Initial work aimed toward this goal by Tsuji's group resulted in the observation of the intermediacy of the desired cyclophane in a matrix at 77 K. Contrary to [5]paracyclophane (the Dewar isomer is less stable than the desired target), the benzene ring of [4]paracyclophane is less stable than the corresponding Dewar benzene isomer. Moreover, the calculated strain energy of [4]paracyclophane is estimated to be 91 kcal/mol and, as such, greatly exceeds the resonance energy or ASE which is ~33 kcal/mol based on recent calculations from Schleyer and colleagues.[45] Other than the obvious, the major challenge associated with

isolating or even observation of this highly distorted benzene ring, is its propensity to undergo bridgehead addition to alleviate ring strain.

A clever solution to this bridgehead addition problem was introduced by Tsuji, who rationalized that the introduction of bulky substituents near the bridgehead positions (*e.g.* on the benzylic carbons) could effectively block the addition of electrophiles and facilitate the proper characterization of the deformed aromatic system. To this end, they reported the synthesis of 1,4-bis(dicyanomethylene)[4]paracyclophan-2-ene in 1997 (Scheme 1.14).[46] The synthesis of this [4]paracyclophane derivative was initiated with **1.87**, which had already been reported by Tsuji.[47] Treatment of this advanced intermediate with singlet oxygen furnished endoperoxide **1.88** via a [4+2] cycloaddition. Subsequent treatment with Et_3N delivered enone **1.89**. The alkene was radically reduced



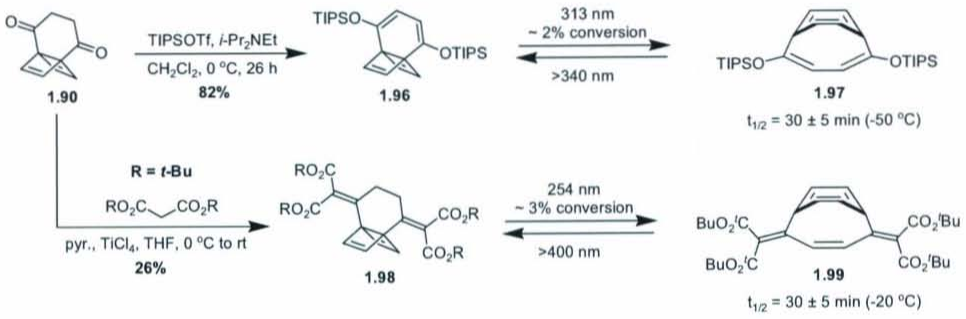
SCHEME 1.14: Tsuji's synthesis of [4]paracyclophane derivative **1.92**

using Bu_3SnH in the presence of $Pd(PPh_3)_4$ and then the alcohol was oxidized with pyridinium chlorochromate (PCC) to give the 1,4-dione **1.90**. Treatment of **1.90** with malononitrile in a Knovenagel condensation under the catalysis of β-alanine furnished a saturated Dewar benzene intermediate, which was further subjected to pyridinium bromide perbromide to install unsaturation at the desired 2-postion of the bridge. During the course of this work it was discovered that installation of an alkene in the bridge of **1.91** thwarted the irreversible photochemical isomerization of the Dewar benzene intermediates to the corresponding naphthalene derivatives (Scheme 1.14), necessitating this structural requirement.[48]

Irradiation of **1.91** at 365 nm as a solution in CD_2Cl_2 at –90 °C led to the development of a broad absorption band between 270 and 420 nm, which is indicative of the formation of a bent benzene ring and signals the disappearance of the strong band between 300 and 390 nm of the Dewar isomer. They also found that only the newly generated species was excited by light of wavelengths of >400 nm and resulted in the reversal of the process (see Scheme 1.14). This product proved to be quite stable (compared to [4]paracyclophane) and remained unchanged at –50 °C in isopentane/ether for ~1 h, long enough for a ^{1}H NMR spectrum to be recorded. The results of the ^{1}H NMR experiment were very encouraging as the original spectrum of **1.91** showed two signals at δ 6.93 and 7.20. Upon irradiation with 365 nm light, a pair of new signals with a 1:2 intensity ratio formed with chemical shifts of δ 5.85 and 7.97. The former spectrum could then be regenerated upon irradiation of **1.92** with 400 nm light. The experimental

values of the chemical shifts and the $\Delta\delta$ values were in good agreement with theoretical calculations.[49]

In an attempt to learn more about the [4]paracyclophane system (especially the bent benzene ring), Tsuji and colleagues recently reported the synthesis of other [4]paracyclophane derivatives that also have large groups shielding the bridgehead positions.[48] The synthesis of these new [4]paracyclophane derivatives is illustrated in Scheme 1.15. Reaction of dione **1.90** with with TIPSOTf and Hünigs base directly afforded bis(silyl enol ether) **1.96**, whereas exposure of **1.90** to di-*tert*-butyl malonate



SCHEME 1.15: Tsuji's synthesis of [4]paracyclophane derivatives **1.97** and **1.99**

under Lewis acidic conditions furnished **1.98**. Irradiation of both of these Dewar benzenes (**1.96** and **1.98**) afforded the corresponding [4]paracyclophane derivatives (**1.97** and **1.99** respectively). However, the most kinetically and thermally stable [4]paracyclophane derivative proved to be tetranitrile **1.92**, which has a half-life of 12 ± 2 min at –20 °C (see Scheme 1.15 for half-lives of **1.97** and **1.99**).

To evaluate the aromatic character of the highly bent benzene rings in their [4]paracyclophane derivatives, Tsuji and co-workers subsequently calculated (GIAO / 6-

31 + G* // B3LYP / 6-31 G*)[45] values for the nucleus-independent chemical shift (NICS) and diamagnetic susceptibility exaltation (Λ). As suggested by Schleyer,[49] these values can be used as indices for aromaticity. For both of these parameters, large negative values are indicative of aromaticity, while positive values suggest antiaromaticity. The NICS value for the distorted benzene ring of **1.92** was calculated to be –8.0, which compares to –9.7 for planar benzene. The value for Λ was computed to be –11.5 ppm cgs for the bent benzene ring in **1.92** versus –15.1 ppm cgs for planar benzene. These relatively large negative values suggest that there is not a major loss of aromaticity in the highly distorted benzene ring of this [4]paracyclophane derivative. This is consistent with the calculated structure of **1.92**, in which very little bond localization (or alternation) was evident. Similarly, in the most recent study of [4]paracyclophane derivatives, the Tsuji group has illustrated that the benzene nucleus of **1.92** exhibits strong diatropicity. However, this is at odds with the suggestions of Schaefer[50] that the severely distorted benzene ring of [4]paracyclophane displays a magnetic susceptibility similar to that of (hypothetical) 1,3,5-cyclohexatriene, which is indicative of a severely diminished ring current.

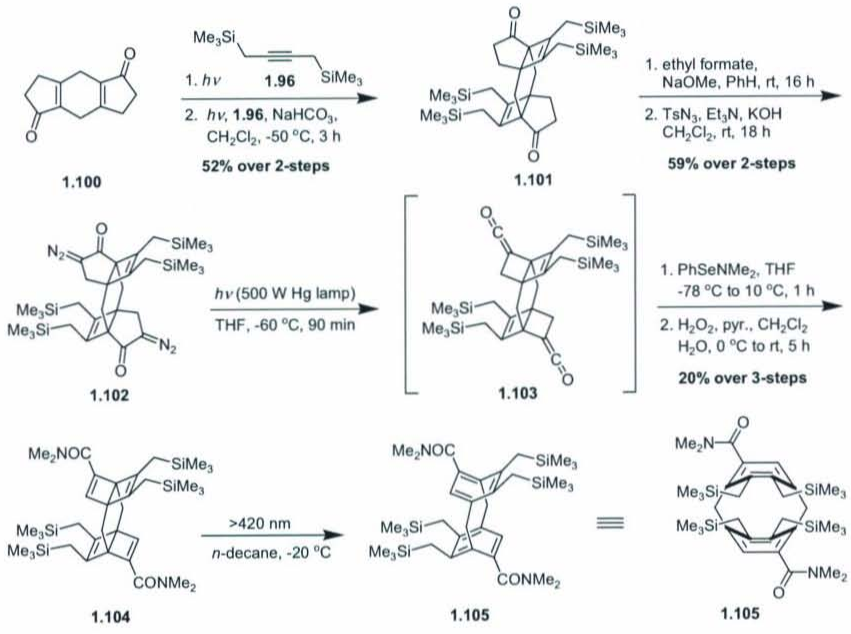
Yet another very interesting result was obtained from the most recent study on [4]paracyclophane by Tsuji.[48] This work provided experimental verification that the Dewar isomer of [4]paracyclophane **1.92** is indeed more stable than the cyclophane itself. Theoretical calculations reported by Grimme[51] suggested that the energy difference between the two isomeric forms is 0 ± 3 kcal/mol, while Schaefer more recently suggested that [4]paracyclophane is 9 ± 4 kcal/mol higher in energy than the Dewar

isomer. In the case of **1.92**, it was found (experimentally) that the free energy of activation for the isomerization of **1.91** to **1.92** is –18.3 ± 0.3 kcal/mol. This is in good agreement with the calculations conducted on this system (–20.3 kcal/mol).[48]

The total amount of bend ($\alpha + \beta$) in the benzene ring of **1.92** is 72.5° ($\alpha = 25.6°$; $\beta = 43.9°$) and, based on a calculations by Dijksha and van Lenthe[52] on bent benzene rings, the aromaticity of the ring should be lost at such a distortion and there should be a transition from a preference for the benzene to the Dewar benzene form. This last facet is indeed the case (as shown by Tsuji), but based on magnetic criteria and NMR evidence, the benzene rings of [4]paracyclophane derivatives are in fact aromatic. However, no X-ray structure has been obtained to date, and we are left with only theoretical calculations of its geometry. For the case of the [*n*]paracyclophanes, the question of how bent can the benzene ring be (and still be considered aromatic) is answered with [4]paracyclophane **1.92** and a calculated bend angle of 72.5°.

It should be noted that the Tsuji group has prepared an isolable paracyclophane derivative for which the distortion of the benzene ring compares to that of the calculated structure for [5]paracyclophane (**1.85**). In order to overcome the high reactivity of this nonplanar system (recall the work of Bickelhaupt and co-workers, Section 1.4.4), Tsuji and co-workers strategically placed bulky substituents near the bridgehead positions of the cyclophane to effectively shield them from addition reactions (and the release of strain). The synthesis of [1.1] paracyclophane **1.105**[53] is summarized in Scheme 1.16 and makes use of well established cyclophane chemistry that has been thoroughly discussed in this chapter. One of the remarkable features of this work is that crystals suitable for X-

ray crystallography were obtained and permitted the complete structural characterization of **1.105**. The total bend angle of 49.8° (α=23°; β=26.8°) constitutes the largest value ever reported (experimentally) for a paracyclophane and is only slightly less than that calculated for [5]paracyclophane.[53b]

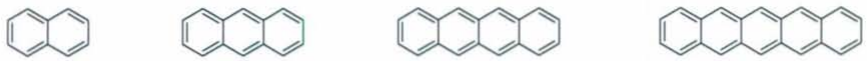


SCHEME 1.16: Tsuji's synthesis of [1.1]paracyclophane **1.105**

1.5 Synthesis of Larger Nonplanar Arenes and Polycyclic Systems

A logical extension of the extensive work that has been conducted on [*n*]metacyclophanes and [*n*]paracyclophanes would be the synthesis of a series of [*n*]naphthalenophanes. While the literature is not devoid of such compounds,[54] nearly all of the [*n*]naphthalenophanes that have been reported to date are simply benzannulated [*n*]meta-[55] and [*n*]paracyclophanes.[56] In all instances, the nonplanarity imposed in the so-

called naphthalenophanes is localized to a single aromatic (or benzene) ring of the acene nucleus and not over the entire π-system. The same is true for the higher acenes, for which very few examples of [*n*]cyclophanes have been reported.[57] If this niche of cyclophane chemistry is to be developed, especially for the more distorted aromatic systems, methodology that enables the generation of a variety nonplanar [*n*]acenes (*i.e.* synthetic approaches which fall under Strategy D) will have to be developed. The inability of current synthetic methods to generate nonplanar acene systems was alluded to in Section 1.1.2.[12]



1.106 naphthalene [2]acene

1.107 anthracene [3]acene

1.108 tetracene [4]acene

1.109 pentacene [5]acene

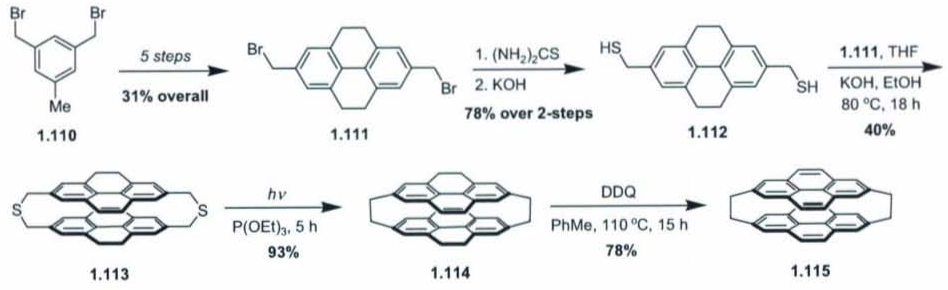
FIGURE 1.10: The [*n*]acenes, $n = 2–5$.

To bend a polynuclear aromatic system out of planarity over the full length of its aromatic framework, the two most distant (or nearly most distant) nonquaternary peripheral positions must be bridged. To study the tolerance of such a system to bending out of planarity and the consequences of this bending necessitates the synthesis of a series of [*n*]cyclophanes, the smallest of which should ideally exhibit significantly lower stability than its higher homologs and atypical reactivity. Until recently, no π-system other than benzene had been subjected to such systematic study. With the maximum bending of the benzene ring in an [*n*]paracylophane having been reached, the synthesis of distorted pyrenes in the form of [*n*](2,7)pyrenophanes has recently emerged as an area of interest. There have been reports on the synthesis of [*n*](2,6)azulenophanes,[58] but the

degree of bend that has been imposed in the π-system is very small and does not warrant further discussion here.

1.5.1 (2,7)Pyrenophanes

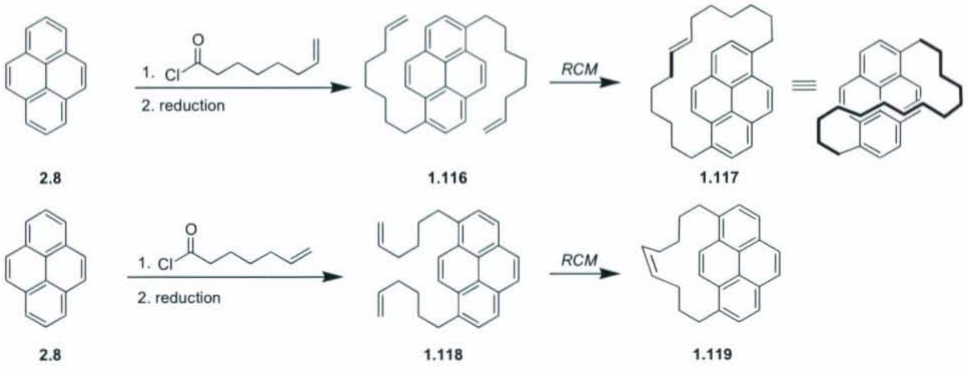
The two most distant positions of pyrene are the 2 and 7 positions, which render the (2,7) bridging motif the one of interest for the investigation of bending out of planarity. Like the bonds emanating from the 1 and 4 positions of benzene, the bonds emanating from the 2 and 7 positions in pyrene are positioned 180°, which renders these two systems structurally homologous, thereby allowing direct comparisons to be made. Due to the greater distance between the 2 and 7 positions of pyrene compared to the 1 and 4 positions of benzene, the application of Strategies A–C to the synthesis of bent pyrenes is not expected to be efficient. In fact, Strategies A and C have been employed in synthesis of various (2,7)pyrenophanes containing this bridging motif, *e.g.* [2.2](2,7)pyrenophane (**1.115**), [59] but the pyrene systems are essentially planar or very gently bent. While there are other bridging motifs that could impart bend on the pyrene system,[60] the (2,7) motif is the most common of these.



SCHEME 1.17: Applications of Strategies A and C in the synthesis of **1.116**

1.5.2 Synthesis of [*n*](2,7)Pyrenophanes

One of the major challenges that is associated with the applications of Strategies A–C in the synthesis of (2,7)pyrenophanes that contain an alkyl bridge is the reluctance of pyrene to undergo substitution at the desired positions (*i.e.* a 10-step synthesis of **1.115**). While substitution of the 2 and 7 positions is possible, it usually only takes place with bulky electrophiles. A more detailed discussion of the substitution chemistry of pyrene will follow in Chapters 2 and 3. In fact the preparation of 2,7-disubstituted pyrenes that do not contain tertiary alkyl substituents requires multistep synthesis that involve the intermediacy of [2.2]metacyclophanes.[59] Despite the difficulty that is associated with the synthesis of 2,7-disubstituted pyrenes, it is quite surprising to find that

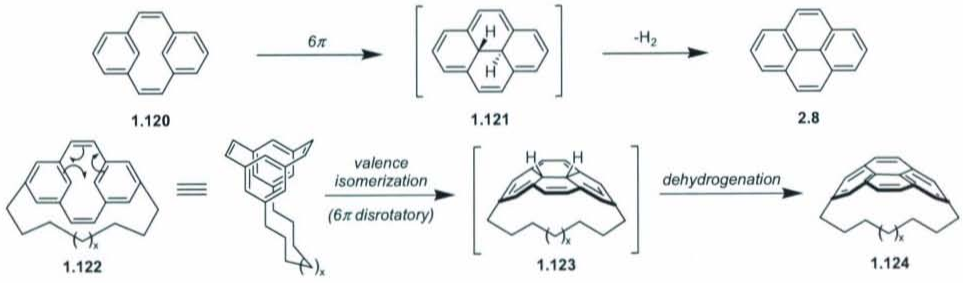


SCHEME 1.18: Potential application of the RCM reaction toward the synthesis of [*n*](1,8)- and (1,6)pyrenophanes

virtually no work has been reported on the synthesis of [*n*](1,6) and (1,8)pyrenophanes, given the ease with which pyrene undergoes substitution at these positions. Admittedly, the preparation of cyclophanes with this bridging motif using the weaker of the four Strategies would be expected to furnish nearly planar pyrenes. Nonetheless, enabling

methodologies, such as the ring-closing metathesis (RCM) reaction, have not featured in the synthesis of such compounds.[61]

The first [*n*](2,7)pyrenophanes appeared in the literature in 1996[62] and reports of several others have appeared since then.[55,63,64,65,66] The lynchpin of all of these syntheses is a pyrene-forming valence isomerization/dehydrogenation (VID) reaction. The adoption of this approach, which falls under Strategy D, was based on an observation by Mitchell and Boekelheide that *trans*-10b,10c-dihydropyrene (**1.121**), the valence isomer of *anti*-[2.2]metacyclophane-1,9-diene (**1.120**), was prone to dehydrogenation to give pyrene.[67] The exploitation of this chemistry to prepare [*n*](2,7)pyrenophanes **1.124** thus requires the synthesis of "tethered" [2.2]metacyclophanedienes **1.122**. The constraints of the tether would be expected to keep the [2.2]metacyclophanediene unit in the *syn* conformation.

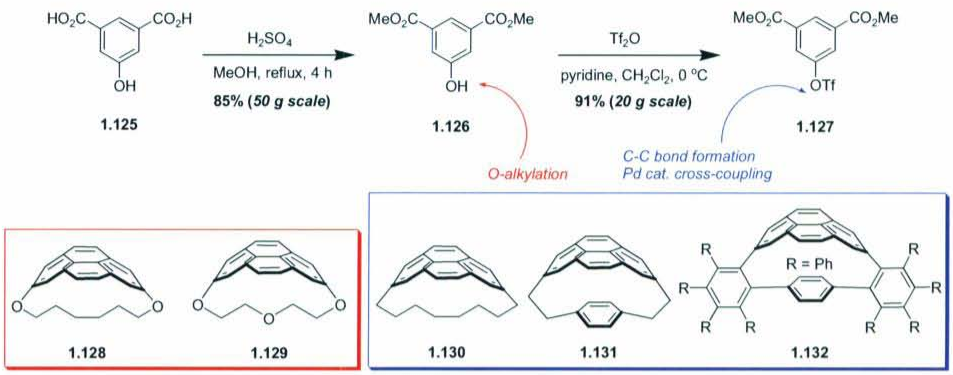


SCHEME 1.19: Strategy for constructing nonplanar (2,7)pyrenophanes

Valence isomerization would then afford *cis*-10b,10c-dihydropyrenophanes **1.123**, dehydrogenation of which would give the desired [*n*](2,7)pyrenophanes **1.124**. Both parts of this reaction contribute to the formation of the nonplanar pyrene system. The valence isomerization step establishes the full connectivity of the pyrene framework, and the

dehydrogenation step fully aromatizes the system. For the smaller values of *n*, the *cis*-10b,10c-dihydropyrenophane **1.123** would be expected to be somewhat distorted from its lowest energy "saucer" shape, but less distorted from its ideal geometry than the corresponding pyrene. The dehydrogenation step would be expected to relieve some torsional strain in the eclipsed central bond of the *cis*-10b,10c-dihydropyrenophane and proceed with the gain of a considerable amount of aromatic stabilization energy.[68] Furthermore, unlike the thermally forbidden valence isomerization of *anti*-[2.2]metacyclophanedienes to *trans*-10b,10c-dihydropyrenes, the valence isomerization of *syn*-[2.2]metacyclophanedienes to *cis*-10b,10c-dihydropyrenophanes is thermally allowed.[26] All in all, the VID approach to making pyrenophanes with severely bent pyrene systems appears to have a lot of advantages, and it has indeed proved to be a very effective reaction in this regard.

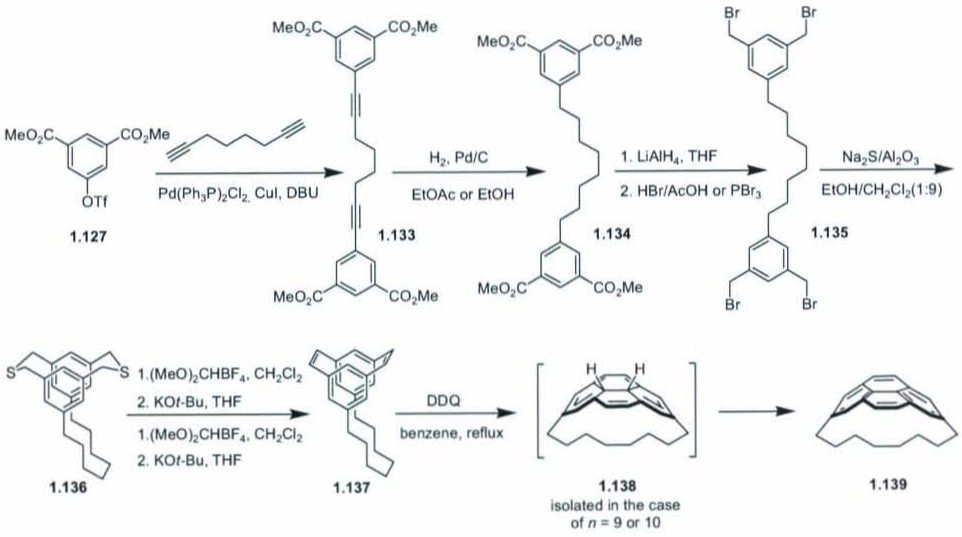
A generalized approach toward the synthesis of (2,7)pyrenophanes that contain a highly distorted pyrene nucleus is illustrated in Scheme 1.21. Bodwell and co-workers have used inexpensive 5-hydroxyisophthalic acid as a starting material in all of their syntheses (with the exception of **1.132**, R = H) of (2,7)pyrenophanes to date. The utility of this starting material comes from the 1,3,5 relationship of the functional groups. Both carboxylic acid groups can be used as building blocks in the construction of a metacyclophane system and the hydroxyl group at the 5-position serves as a handle for the installation of what will become a bridge between the 2 and 7 positions of the pyrene system. Further, due to its amenability to functional group interconversion, this hydroxyl group has enabled the synthesis of various pyrenophanes containing several different bridges.



SCHEME 1.20: Use of 5-hydroxyisophthalic acid derivatives in the synthesis of (2,7)pyrenophanes and the points of synthetic diversity

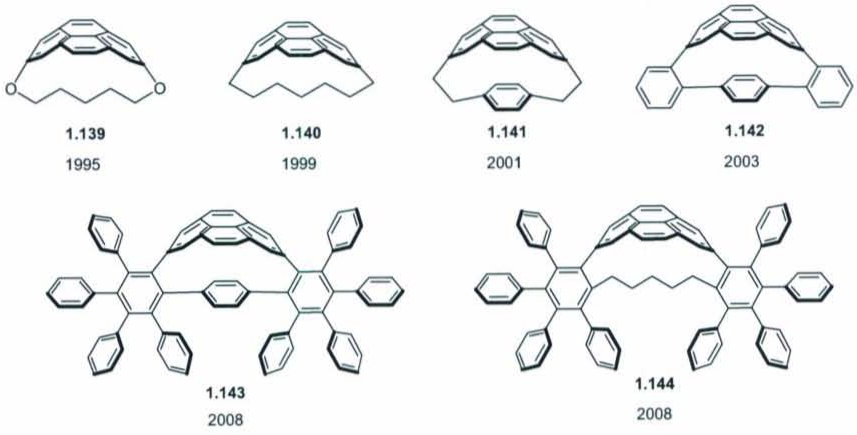
Esterifcation of 5-hydroxyisophthalic acid (**1.125**) gives diester **1.126**. At this point, alkylation of the phenolic oxygen atom can be achieved using Williamson ether synthesis. On the other hand, conversion of the phenol to an aryl triflate makes **1.127** amenable to palladium-catalyzed cross-coupling reactions. While the former approach provided the initial entry point into the field of nonplanar aromatics for the Bodwell group, the latter has served as the workhorse in the synthesis of all other pyrenophanes reported to date. In any case, oxygen-carbon or carbon-carbon bond formation at the 5-position of **1.126** or **1.127** secures what will be the final bridge in the (2,7)pyrenophane target. Once the tether has been converted into its final form, reduction of the esters to the corresponding alcohols, followed by bromination furnishes tetrabromide **1.135** (Scheme 1.21). Treatment of **1.135** with sodium sulfide adsorbed on alumina (Na_2S/Al_2O_3)[69] gives the desired coupling product **1.136**. The assembly of dithia[3.3]cyclophane **1.136** is crucial to the synthesis of (2,7)pyrenophanes as it provides

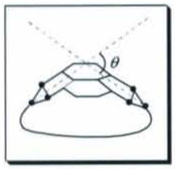
a *syn*-cyclophane system that is relatively unstrained. *S*-Methylation of **1.136** affords a



SCHEME 1.21: Synthesis of [8](2,7)pyrenophane (**1.139**) – a representative example of Bodwell's strategy to (2,7)pyrenophanes

bis(sulfonium tetrafluoroborate) salt, in which bridge contraction is achieved using a thia-Stevens rearrangement. A second *S*-methylation of the newly-generated divalent sulfur atoms, followed by a Hofmann elimination affords the desired [2.2]metacyclophanediene system (**1.137**). For n=6–8 in the [n](2,7)pyrenophane series, the [2.2]metacyclophanediene system is formed cleanly. For n=9, the reaction affords a mixture of the cyclophanediene along with the isomeric [9](2,7)4,5-dihydropyrenophane (**1.138** n=9). For n=10, a mixture of [10](2,7)4,5-dihydropyrenophane (**1.138** n=10) and [10](2,7)pyrenophane is obtained. Whatever the outcome, treatment of the product(s) obtained form the Hoffman elimination reaction with DDQ in benzene at reflux affords the target [n](2,7)pyrenophanes.[70]





Definition of θ angles in [*n*](2,7)pyrenophanes

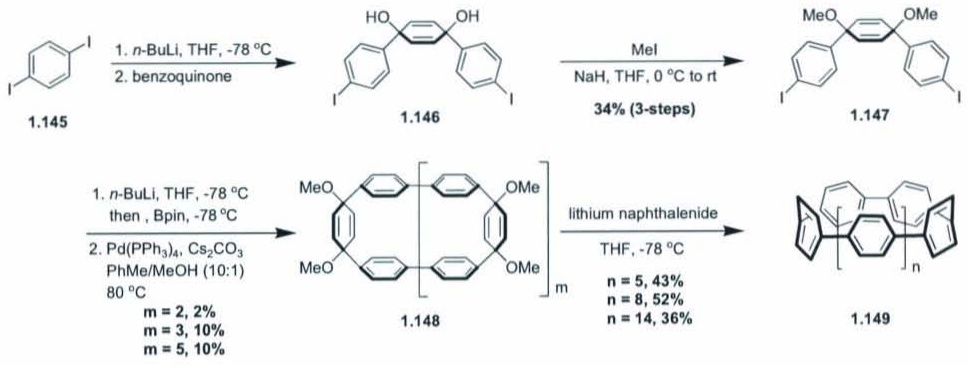
n	θ_{exp}	$\theta_{calculated}$	tether
6	n/a	122.9	
7	n/a	104.6	
8	80.8	87.0	
9	62.4	70.3	
10	46.4	54.4	

FIGURE 1.11: The evolution of (2,7)pyrenophane targets in the Bodwell group and the definition of the angle θ

The first [*n*](2,7)pyrenophanes to be synthesized by the Bodwell group were the 1,*n*-dioxapyrenophanes, *e.g.* **1.139**. These particular pyrenophanes are noteworthy, not only for the seminal nature of the work, but also because this series of cyclophanes contains the most distorted pyrene system to have been isolated to date. 1,7-Dioxa[7](2,7)pyrenophane is the current world record holder when it comes to bending the pyrene nucleus. With a bend angle θ=109.2°, it slightly exceeds the bend angle of the pyrene sub-unit that maps onto the surface of D_{5h} C_{70} which has been estimated to be θ=108°.[63a] The notion that the VID reaction of a tethered[2.2]metacyclophane system can

furnish a nonplanar pyrene system that is slightly more distorted than the pyrene sub-units of fullerenes has been the source of optimism for quite some time now that this methodology could find applications in the synthesis of aromatic belts. These targets, which were briefly alluded to at the beginning of this chapter (Section 1.1.2), have remained as one of the biggest challenges in target-oriented synthesis since they were first proposed by Heilbronner in the 1950s.[11a] Nakamura and co-workers have reported the synthesis of some [10]cyclophenacenes (or cyclo[10]phenacene) derivatives (*e.g.* **1.16**, see Figure 1.4), but these were revealed upon fivefold nucleophilic additions to each of the two polar caps of C_{60}. As such, the synthesis of the aromatic belt was accomplished during the production of C_{60}.

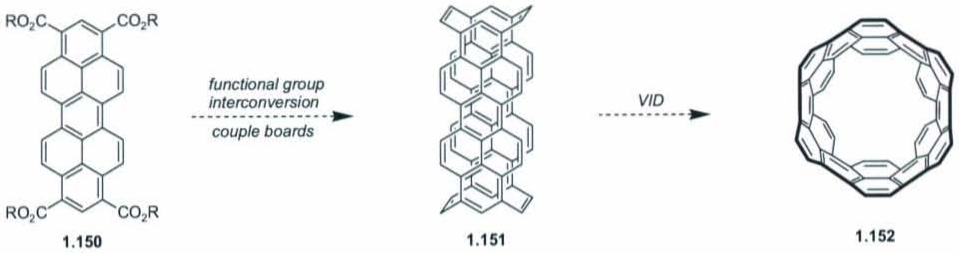
The synthesis of aromatic belts using wet chemical methods has not yet been realized. A recent report from the Bertozzi group on the synthesis of carbon nanohoops[71] (**1.149**) represents the closest example toward the synthesis of these impressive structures.[72] More recently, Itami published a selective synthesis of **1.149** (n=8) using a similar approach. The work by the Bertozzi and Itami groups on the synthesis of these small segments of armchair single-walled carbon nanotubes (SWCNTs) is truly groundbreaking in the field of designed molecule synthesis because it has provided solutions to a nearly 80 year old synthetic problem. The extension of their work to the synthesis of aromatic belts has not yet been reported. Importantly, the synthetic strategy used by both groups involves a last step aromatization of a cyclic precursor such as **1.148**, which categorizes their synthesis under Strategy D.



SCHEME 1.22: Bertozzi's recent synthesis of carbon nanohoops **1.149**

In order to directly apply the Bodwell group's strategy to the synthesis of armchair aromatic belts such as **1.152**, the assembly of appropriately functionalized and larger aromatic building blocks, such as **1.151**, is necessitated. With such intermediates in hand, the application of the cyclophane route to couple two of these "boards" together should be feasible. One potential downfall of this strategy is that in forming the desired belt-shaped macrocycles, the once planar aromatic boards have to adopt a nonplanar conformation in order to accommodate the formation of the *two* central pyrene units of **1.152**. Whether the gain in ASE associated with the formation of the aromatic belt **1.152** is enough to counterbalance the concomitant increase in strain is yet to be established.[73] Thus, in order to garner information as to the viability of the VID reaction in the preparation of aromatic belts, or more specifically monodisperse SWCNTs, such as **1.152**, the preparation of larger nonplanar polycyclic aromatic hydrocarbons contained within a cyclophane motif

would be instructive. While pyrene contains 16 of the 60 carbons of aromatic belt **1.52**,



SCHEME 1.23: Application of the VID reaction towards the synthesis of **1.152**

the synthesis of a larger segment of **1.152** that allows for the distortion of 2 or more pyrene units of **1.152** would really speak to the power of this methodology and provide even further impetus for the application of this strategy in the synthesis of **1.152** and related Vögtle belts (see Figure 2.1, Chapter 2). It was with this in mind that the investigation of the synthesis of 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes was initiated. The remaining chapters of this thesis will describe the experimental work that has been carried out towards synthesizing these large nonplanar polycyclic aromatic hydrocarbons.

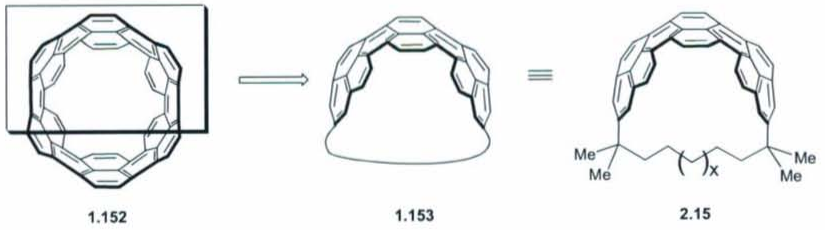


FIGURE 1.12: Proposed synthetic targets **2.15**

1.6 References

[1] *Urea*: Wöhler, F. *Ann. Phys.Chem.* **1828**, *12*, 253-256.

Glucose: Fischer, E. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 799-805.

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Axinellamine A: O'Malley, D. P.; Yamaguchi, J.; Young, I. S.; Seiple, I. B.; Baran, P. S. *Angew. Chem. Int. Ed.* **2008**, *47*, 3581-3583.

[2] Sub-classes of designed molecule synthesis include: medicinal and materials chemistry.

[3] *Feringa's molecular motor*: Koumura, N.; Zijlstra, R. W. J.; van Delden, R. A.; Harada, N.; Feringa, B. L. *Nature* **1999**, *401*, 152-155.

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[4] For example, see Nakamura's synthesis of a [10]cyclophenacene derivative: Nakamura, E.; Tahara, K.; Matsuo, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2834-2835.

[5] For examples see: (a) Wu, Y.-T.; Siegel, J. S.; *Chem. Rev.* **2006**, *106*, 4843-4867; (b) Tsefrikas, V. M.; Scott, L. T. *Chem. Rev.* **2006**, *106*, 4868-4884; (c) references 4, 7, 8, and 12.

[6] For example see: Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1971**, *4*, 204-213.

[7] Kroto, H. W.; Heath, J. R.; O'Brien, S. C.; Curl, R. F.; Smalley, R. E. *Nature* **1985**, *318*, 162-163.

[8] Scott, L. T.; Boorum, M. M.; McMahon, B. J.; Hagen, S.; Mack, J.; Blank, J.; Wegner, H.; de Meijere, A. *Science* **2002**, *295*, 1500-1503.

[9] Both [*n*]cyclophenacene and cyclo[*n*]phenacene have been used to describe this general class of compounds. See: reference 4 and reference 10.

[10] A molecular belt has been defined as: *An object that has two continuous, non-intersecting edges and a width that is small in relation to its circumference.* See: Yao, T.; Yu, H.; Vermeij, R. J.; Bodwell, G. J. *Pure Appl. Chem.* **2008**, *80*, 533-546.

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CHAPTER 2: Toward the Synthesis of [*n*](2,11)Teropyrenophanes: A Tetrafunctionalization Approach and Important Lessons Learned

2. 1. Aromatic Belts: Inspiration for Cyclophane Targets

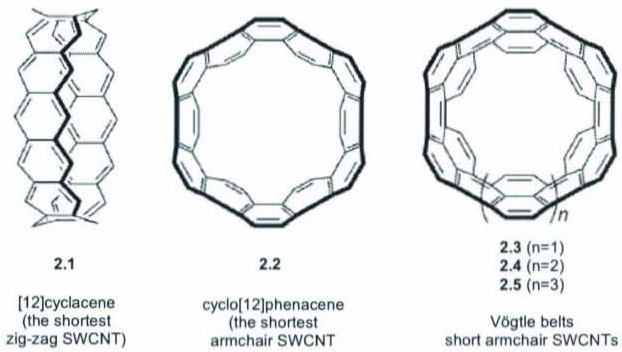


FIGURE 2.1: Zig-zag and armchair single-walled carbon nanotubes (SWCNTs)

One of the longstanding challenges in target-oriented synthesis is the rational laboratory synthesis of fully conjugated molecular belts from simple aromatic building blocks.[1] Such belts (often referred to as "aromatic belts")[2] share structural motifs with the two limiting classes of SWCNTs, zig-zag and armchair. Cyclacenes, *e.g.* [12]cyclacene (**2.1**), correspond to zig-zag SWCNTs and cyclophenacenes, *e.g.* cyclo[12]phenacene (**2.2**), correspond to armchair SWCNTs. As such, aromatic belts can be viewed as "slices" or segments of SWCNTs. Armchair-type belts, especially Vögtle belts (**2.3**–**2.5**),[3] are of interest to the Bodwell group due to the pyrenoid nature of these systems. Interest in synthesizing Vögtle belts was alluded to in Chapter 1. However, to date, all efforts to complete a synthesis of these highly challenging targets have come up short. Currently, the weakness does not appear to lie with the VID methodology, but in the

preparation of synthetically useful amounts of suitable metacyclophanediene-type precursors (see Scheme 1.19, Chapter 1). If true, then the use of the VID reaction in the synthesis of the target teropyrenophanes (**2.15**, Scheme 2.2) will be a valuable test of the methodology – *i.e.* can it deliver a half-belt?

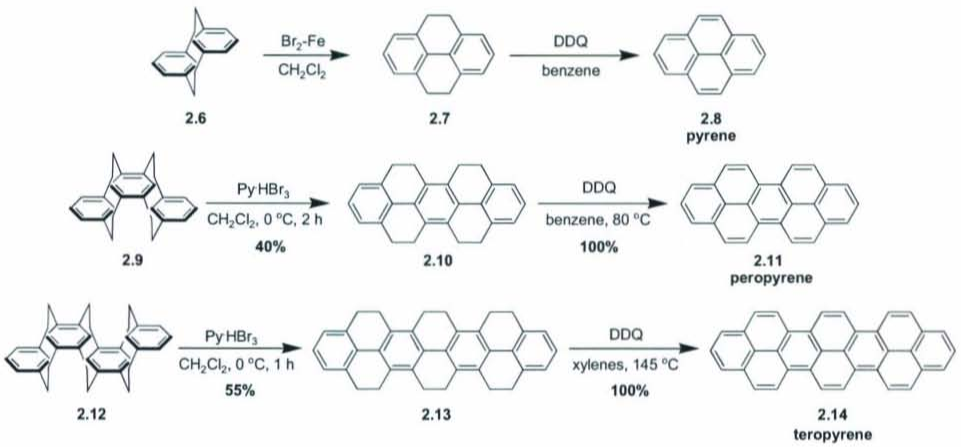
2.1.1 Retrosynthetic Analysis of 1,1,*n*,*n*-Tetramethyl[*n*](2,11)teropyrenophanes

The ability of the VID reaction to generate highly bent pyrenes according to the very powerful Strategy D is discussed at length in the previous chapter. One potential problem that could arise in the application of the VID reaction to the synthesis of larger polycyclic systems is that the pyrene-forming reaction will require the deformation of larger planar building blocks than just benzene rings, and this may bring with it an energetic cost. Another unknown, without embarking on a serious computational project, is whether the energetics of the VID reaction are as favourable for the formation of larger polycyclic systems as they appear to be for pyrene.

Teropyrene was selected as the nonplanar aromatic hydrocarbon to study, since it represents a large portion (about half or 36 carbon atoms) of Vögtle belts **2.3**–**2.5**. Teropyrene is also an interesting system because of the sparse amount of attention that this pyrenoid hydrocarbon has received. In fact, only a single synthesis of the planar parent system has been reported, *i.e.* by Misumi and co-workers in 1975.[4] In the ensuing 35 years, no other work aimed at the synthesis of this or any related system has appeared in the literature. As such, the teropyrene system may provide an opportunity for the discovery of novel cyclophane chemistry. The successful preparation of such large

systems with a high degree of distortion from planarity would be cause for optimism that the VID reaction will be a suitable method for the generation of aromatic belts.

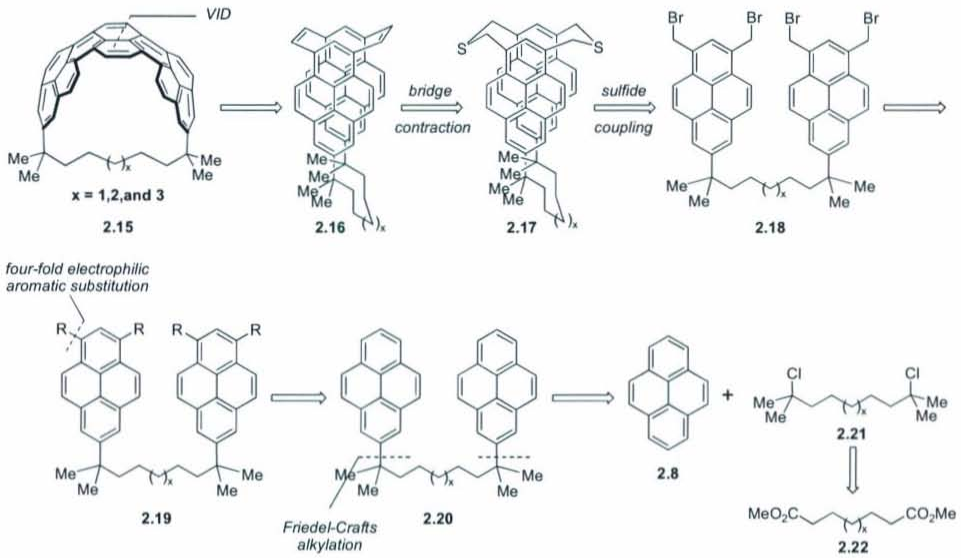
Misumi's synthesis of teropyrene (**2.14**) and that of a smaller PAH, peropyrene (**2.11**), involved the intermediacy of a "layered" [2.2]metacyclophane system. This was followed by a transannular bond formation between neighbouring aromatic rings using a method that has been employed often for the conversion of *anti*-[2.2]metacyclophanes



SCHEME 2.1: Misumi and co-workers' synthesis of peropyrene (**2.11**) and teropyrene (**2.14**)

(such as **2.6**) into 4,5,9,10-tetrahydropyrenes (such as **2.7**).[5] Treatment of **2.9** or **2.12** with pyridinium perbromide brought about the transannular reaction between adjacent benzene rings in both [2.2]metacyclophane systems. Dehydrogenation of the resulting octa- and dodecahydro PAHs furnished the aromatized products in quantitative yields. While this route to teropyrene is both clever and elegant, it is not amenable to the synthesis of the designed targets **2.15** (*vide infra*). As such, a retrosynthetic analysis that incorporates a valence isomerization strategy (Strategy D) was devised.

Three repeating pyrene subunits can be identified in the polycyclic system of teropyrene. Thus, the retrosynthetic analysis of a homologous series of 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes (*n*=7–9) (**2.15**) commenced with the disconnection of the central bond in the central pyrene fragment via a VID transform. Scission of the



SCHEME 2.2: Retrosynthetic analysis of teropyrenophane targets (**2.15**)

indicated bond in **2.15** furnished cyclophanediene(s) **2.16**, which is analogous to the [2.2]metacyclophanediene systems discussed in Section 1.5.2. This also represents a new bridging motif for a pyrenophane, namely an [*n*.2.2](7,1,3)pyrenophane. The key difference between these new systems and the parent [2.2]metacyclophanedienes is the size of the aromatic building blocks (benzene *vs.* pyrene). Further molecular simplification via a bridge-contraction transform reduced the synthetic task to dithiacyclophane(s) **2.17**.

The initial synthetic plan was to make use of well-established cyclophane chemistry, which had already proven its worth in the synthesis of several (2,7)pyrenophanes. As such, dithiacyclophane(s) **2.17** was retrosynthetically reduced to tetrabromide(s) **2.18** using sulfide coupling and then to tetrafunctionalized system(s) **2.19** by way of functional group interconversion. Finally, the four functional groups were disconnected using electrophilic aromatic substitution and disconnection across the indicated bond in bis(2-pyrenyl)-dimethylalkane(s) (**2.20**) brought the retrosynthetic analysis of **2.15** back to two known compounds, pyrene (**2.8**) and diester(s) **2.22**. Both of these materials are available in sufficiently large quantities from commercial sources and the requisite diol or dihalide tethers can be prepared in one or two steps, respectively. With a synthetic plan that relies on pyrene as a key building block in place, it is instructive at this juncture to discuss the reactivity of this polycyclic system.

2.2 The Reactivity of Pyrene: Predictable Substitution Chemistry

The electrophilic aromatic substitution of benzene is one of the very first reactions that students are taught in their undergraduate programs. The importance of aromaticity in causing substitution to occur in preference to addition is introduced and reactions of substituted benzene rings provide a forum for very important lessons about inductive and mesomeric effects, which can be used as predictive tools for the regiochemical outcome of substitution reactions. As the aromatic system in question becomes larger, another issue arises. The initial substitution reaction of the benzene nucleus can only give one substitution product because all 6 positions are equivalent. However, the same does not hold true for many larger systems because not all of the available (nonquaternary) sites

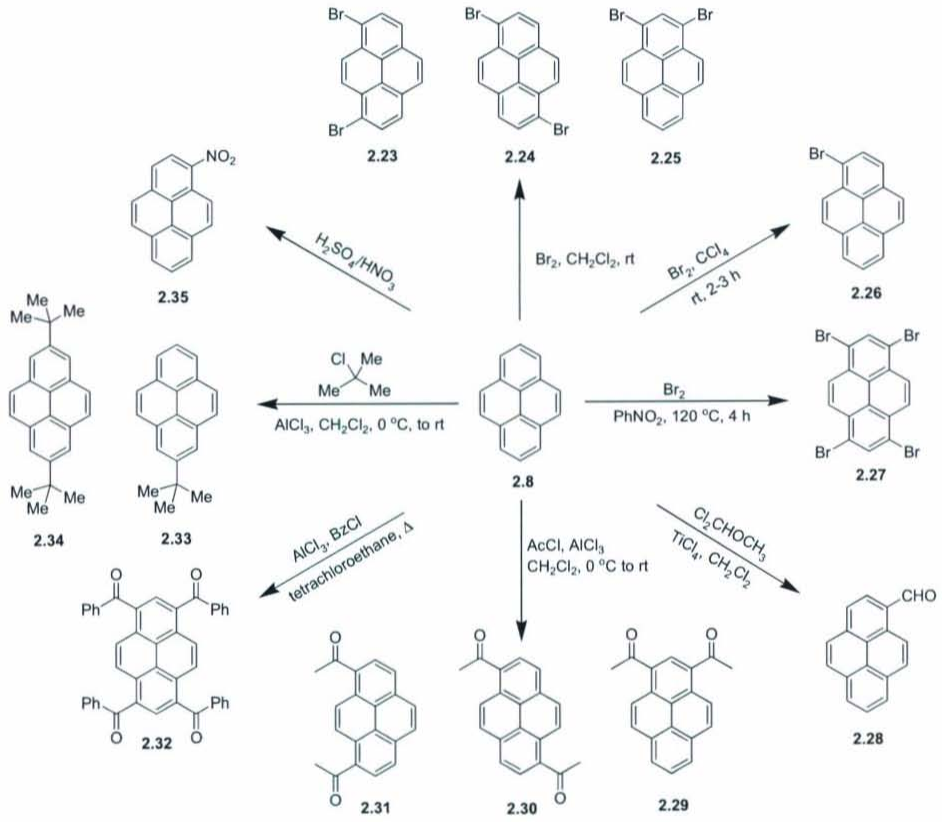
are equivalent. For example, pyrene has three possible positions for an electrophilic aromatic substitution reaction to occur (C-1, C-2 and C-4). Despite this complication, the electrophilic aromatic substitution chemistry of pyrene is well-known and quite predictable (Scheme 2.3).

Pyrene undergoes substitution primarily at the 1, 3, 6 and 8 positions. Selective substitution of the 2 and 7 positions of pyrene is possible when bulky electrophiles (*e.g.* 2-chloro-2-methylpropane) are employed. In such cases, substitution of the neighbouring 1 (or equivalent) position becomes disfavoured due to the steric interaction between the electrophile and the nearby *peri*-proton (10 position) that would arise as the reaction progresses. The 4, 5, 9 and 10 positions of the pyrene ring system are significantly less reactive than the former 6 positions and only undergo substitution in instances where the four reactive (1, 3, 6, and 8) positions are too sterically hindered (*i.e.* the 2 and 7 positions are occupied with large substituents) to participate in further reaction.[6] Knowledge of these changes in reactivity was a key factor in designing the synthetic approach to **2.15** (*vide supra*).

2.2.1 Selective Substitutions of Pyrene

The electrophilic bromination of pyrene is a good example of pyrene's strong preference for reactivity of the 1, 3, 6, and 8 positions. Monobromination of pyrene can be achieved using carefully controlled conditions, however, regioselective dibromination of the pyrene ring system is problematic and mixtures of isomeric dibromides are formed (Scheme 2.3). Complete bromination of the four most reactive positions of pyrene is possible at 120 °C in nitrobenzene to afford **2.27**. Other substitution reactions of pyrene

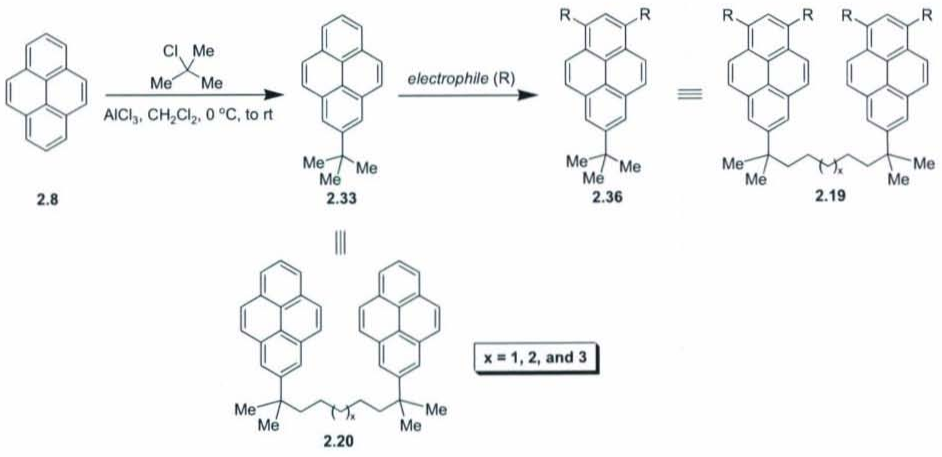
(*i.e.* acylation, nitration, and formylation) proceed in a similar fashion to give either mono, di, or tetrasubstituted systems (*vide infra*). The one clear exception to this reactivity pattern is the reaction of pyrene with 2-chloro-2-methylpropane (*tert*-butyl chloride) under Friedel-Crafts alkylation conditions. Preparation of either 2-*tert*-butyl



SCHEME 2.3: Substitution chemistry of pyrene

(**2.33**) or 2,7-di-*tert*-butylpyrene (**2.34**) is possible under these conditions.[7] This interesting dichotomy in pyrene's substitution chemistry presents the opportunity to solve the problem of regioselectively functionalizing the 1 and 3 positions of the PAH

simultaneously. Introduction of the *tert*-butyl substituent at the 2 position effectively blocks or attenuates the reactivity of the adjacent (1 and 3) positions. Thus, the unsubstituted apical ring of pyrene should undergo substitution in preference to these hindered positions. Despite this seemingly straightforward solution, few examples of the synthesis of 1,3,7-trisubstituted pyrenes in this manner are known.[8]



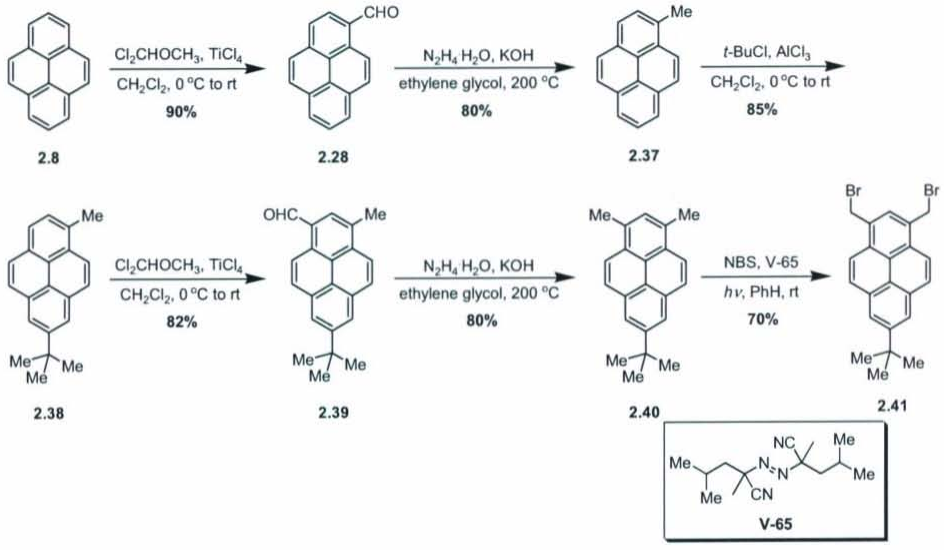
SCHEME 2.4: Possible selective substitution of the 1 and 3 positions of pyrene and **2.20**

2.3 Attempted Synthesis of 1,1,*n*,*n*-Tetramethyl[*n*](2,11)teropyrenophanes

2.3.1 Application of Known Chemistry Towards the Synthesis of Tetrafunctionalized System(s) 2.18

The initial synthetic plan for **2.17** relied upon the reaction of advanced intermediate **2.18** with sodium sulfide (Na_2S/Al_2O_3). The synthesis of such tetrabromides was envisaged to be one of the key stages in the original strategy, so initial work was aimed in this direction. At the time, the only report of a 1,3-bis(bromomethyl)pyrene was by Yamato and co-workers,[9] who described the synthesis of 1,3-bis(bromomethyl)-7-*tert*-

butylpyrene (**2.41**). A notable feature of this work is the use of 1-methylpyrene in the Friedel-Crafts alkylation reaction with 2-chloro-2-methylpropane rather than direct *tert*-butylation of pyrene. As such, the opportunity to capitalize on selectively functionalizing both reactive positions of the unsubstituted apical ring of 2-*tert*-butylpyrene and significantly shorten the synthesis of **2.41** is wasted. Rather, the Yamato group preferred to use a linear six-step synthesis to dibromide **2.41**.



SCHEME 2.5: Yamato's synthesis of 1,3-bis(bromomethyl)-7-*tert*-butyl pyrene (**2.41**)

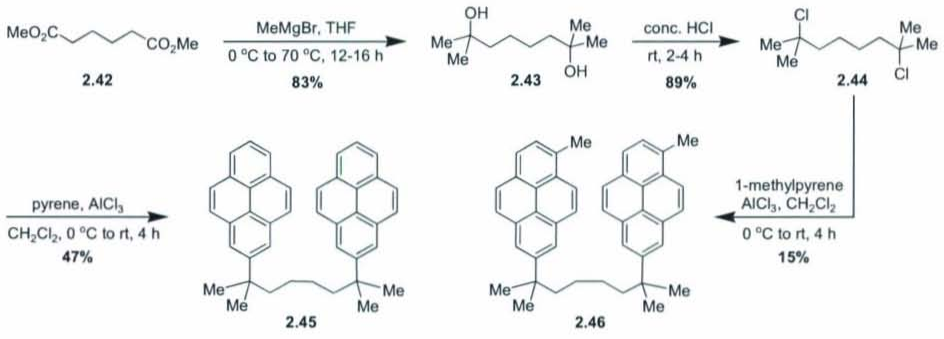
The synthesis of 1-methylpyrene is achieved in two steps. Rieche formylation of pyrene (*ca.* 50 g scale) gave pyrene-1-carbaldehyde (**2.28**) in 90% yield. A straightforward reduction of **2.28** under Wolf-Kishner conditions furnished multi-gram quantities of 1-methylpyrene (**2.37**). Alkylation of **2.37** with 2-chloro-2-methylpropane gave 1,7-disubstituted pyrene **2.39** as the sole product in good yield. A second

formylation/reduction sequence, gave 1,3,7-trisubstituted pyrene **2.40**. Radical bromination of 1,3-dimethyl-7-*tert*-butylpyrene (**2.40**) using rather unconventional conditions (*i.e.* V-65 (2,2′-azobis(2,4-dimethylvaleronitrile) as the radical initiator) was the result of careful inspection. Application of this exotic[13] radical initiator to the synthesis of **2.41** proved to be superior to all other conditions (*i.e.* benzene, carbon tetrachloride, dichloromethane; room temperature, reflux, or *h*ν) and initiators (*i.e.* dibenzoyl peroxide (BPO) and AIBN) screened.

2.3.2 First Generation Synthesis of Advanced Intermediate 2.17: Application of Yamato's Chemistry

The preparation of suitable tether precursors commenced with the Grignard reaction of dimethyl adipate (**2.42**) with methylmagnesium bromide to furnish the requisite diol **2.43** in high yield on a 10 g scale. Treatment of **2.43** with concentrated hydrochloric acid at room temperature for 2 h afforded 2,7-dichloro-2,7-dimethyloctane (**2.44**) in 89% yield. Friedel-Crafts reaction of **2.44** with 1-methylpyrene (**2.37**) using the approach of Yamato and co-workers, never resulted in the complete consumption of starting material and, while separation of the remaining 1-methylpyrene from the product was trivial, the yield of this reaction was low (15%), and the recovery of dichloride **2.44** was not possible. As such, direct alkylation of pyrene with **2.44** proved to be a more suitable means for tethering two pyrene units (see retrosynthetic analysis, Scheme 2.2). Optimization of this reaction required that an excess of pyrene (5 equiv.) be used. This quantity of pyrene proved to be most effective in minimizing the formation of unwanted

disubstituted and oligomeric byproducts.[10] However, the use of excess reagent led to significant challenges with respect to scaling up the reaction. Removal of the excess pyrene from the reaction required careful chromatography and gradient elution that

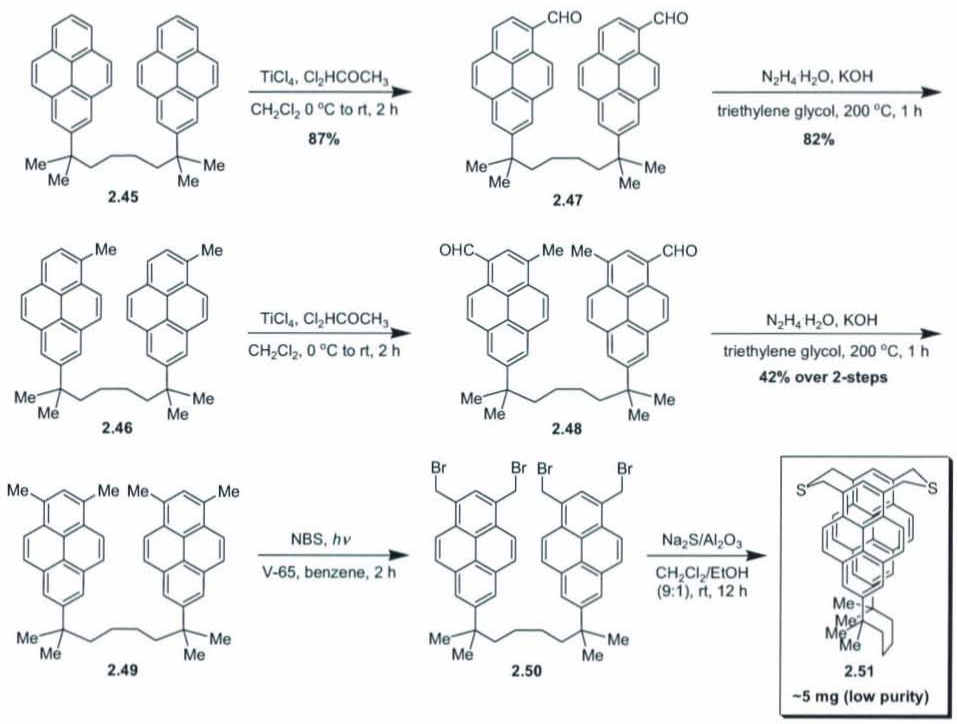


SCHEME 2.6: Friedel-Crafts alkylation of dichloride tether **2.44**

required large volumes of solvent. All attempts to isolate pure **2.45** or to selectively remove pyrene via recrystallization and trituration failed. Nonetheless, 1–3 g of **2.44** could be routinely prepared and the option to explore direct installation of four functional groups in one synthetic operation presented itself. However, at the early stages of this work, it was deemed desirable to follow Yamato's approach to **2.41** for the synthesis of tetrabromide **2.50**.

Rieche formylation[11] of bis(2-pyrenyl)-dimethylalkane **2.45** gave the corresponding dialdehyde **2.47** in good yield. Wolff-Kishner reduction of dialdehyde **2.47** to hydrocarbon **2.46** was achieved using a slight modification of the procedure described by Yamato.[12] A second formylation, followed by immediate Wolff-Kishner reduction of the resulting crude dialdehyde furnished 2,7-bis(6,8-dimethylpyren-2-yl)-

2,7-dimethyloctane (**2.49**) in 42% yield (over 2-steps) and set the stage for a four-fold



SCHEME 2.7: First generation synthesis of dithiacyclophane **2.51**

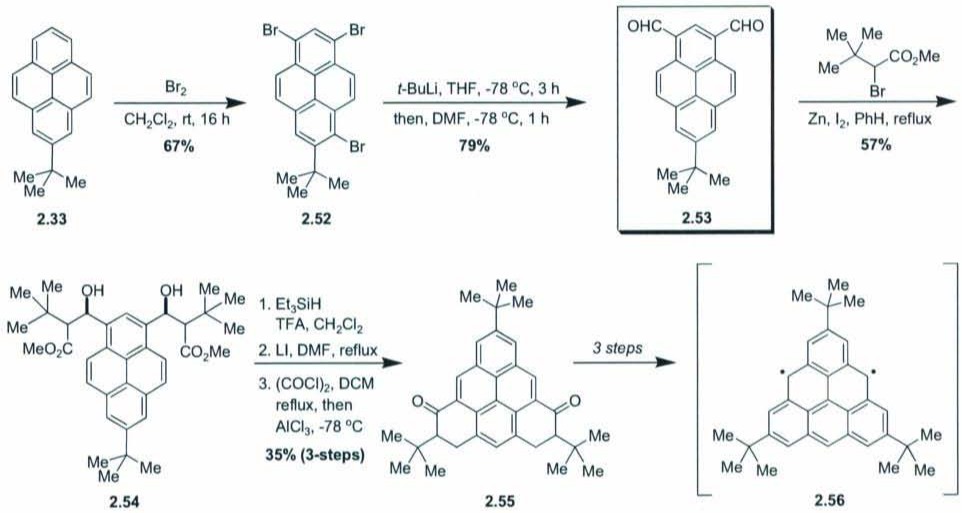
radical bromination reaction. While it was clear from Yamato's work, that the optimal conditions for the radical bromination of a related pyrene species was to use the previously discussed "exotic" conditions, the radical initiator V-65 was not originally available. Attempts to synthesize **2.50** via more conventional radical bromination methods ((BPO or AIBN with dichloromethane, carbon tetrachloride, or benzene), all failed.

A small sample of V-65[13] was obtained from Professor Tsuge's group at the Kyushu Institute of Technology in Japan and this enabled the reaction of **2.49** to proceed under the conditions reported by Yamato.[14] During the course of this reaction, all of the starting martial was consumed and, while only a single mobile spot was observed by TLC analysis, a ^{1}H NMR spectrum of the crude reaction mixture revealed that it was of very low purity. Chromatography and attempted crystallization(s) of the resulting brown mass was unsuccessful in improving the purity of **2.50** and, as such, it was decided to carry the material through to the next step of the synthesis in impure form. This tactic of using a crude (or impure) tetrabromide has precedent in the synthesis of other pyrenophanes[15] in the Bodwell group and it was hoped that its application here would provide entry to pure dithiacyclophane **2.51**. Treatment of crude **2.50** with Na_2S/Al_2O_3 gave the intended sub-target **2.51**, but only material of low purity could be obtained.[16] Moreover, only a very small quantity (*ca.* 5 mg) of dithiacyclophane **2.51** was achievable via this route.[17]

2.3.3 Direct 1,3-Functionalization of Bis(2-pyrenyl)-dimethylalkane(s) (2.20)

In section 2.2.1, the possibility of directly substituting the 1 and 3 positions of pyrene was discussed. This should be achievable if one of the apical rings of the polycyclic system is blocked from further reaction. To this end, Inoue and co-workers were able to synthesize dialdehyde **2.53** from 2-*tert*-butylpyrene (**2.33**) in their synthesis of triangulene (**2.56**) (or Clar's Hydrocarbon).[18] Treatment of **2.33** with an excess of bromine gave 1,3,6-tribromo-7-*tert*-buylpyrene (**2.52**), which was reported to have low solubility in common organic solvents and was thus difficult to characterize. While it would seem that the *tert*-butyl group was not effective in blocking the neighbouring

carbon atoms from further reaction, the next series of synthetic operations benefited from the sterically hindered nature of this position. Halogen-metal exchange of **2.52** with *t*-BuLi, followed by subsequent treatment with *N*,*N*-dimethylformamide (DMF) furnished 1,3-dialdehyde **2.53** in good yield. The somewhat circuitous route to **2.53** was presumably taken because controlling the bromination of 2-*tert*-butylpyrene to

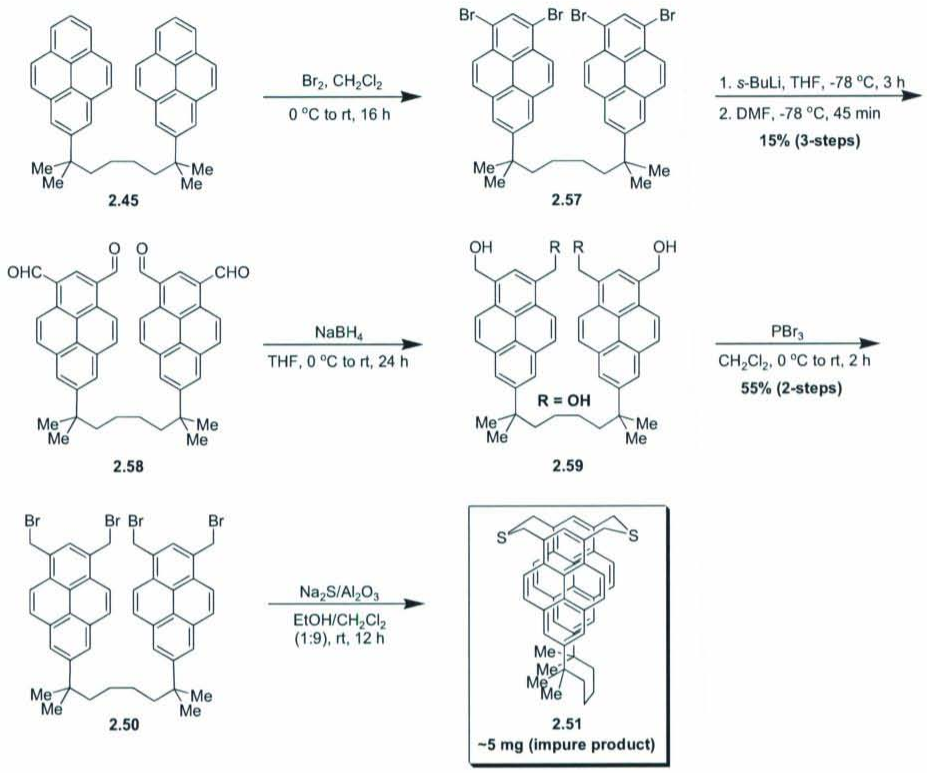


SCHEME 2.8: Inoue's use of dialdehyde **2.53** in their synthesis of triangulene **2.56**

exclusively afford the 1,3-disubstituted system proved to be difficult. However, as discussed in Chapter 3, selective bromination of the 1 and 3 positions can in fact be achieved under appropriate conditions.[19]

Functionalization of **2.45** as a dialdehyde (per pyrene unit) offered the potential to be synthetically valuable in the synthesis of dithiacyclophane **2.51** because it would circumvent the problem of having to use a crude tetrabromide in the pivotal coupling reaction. Applying Inoue and co-workers' bromination conditions to 2,7-dimethyl-2,7-

bis(2-pyrenyl)octane (**2.45**) afforded a poorly soluble white solid, which was presumed to



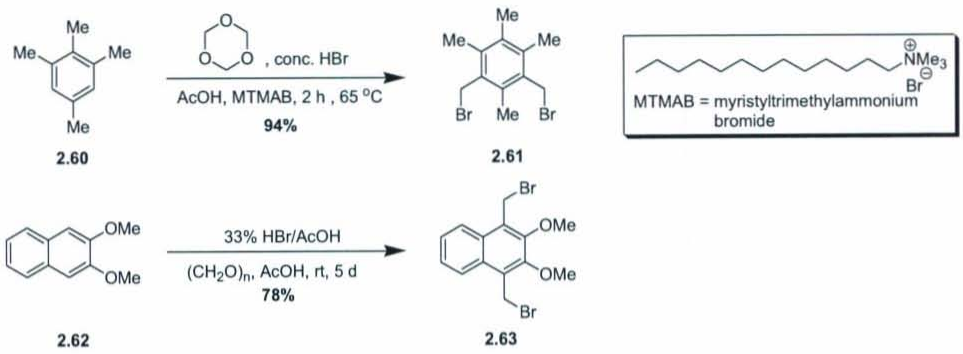
SCHEME 2.9: Second generation synthesis of dithiacyclophane **2.51**

be **2.57**.[20] Characterization of this intermediate was virtually impossible due to its low solubility in common organic solvents. However, subjecting this compound to Inoue's formylation conditions furnished tetraldehyde **2.58**, albeit in 15% yield and *ca.* 70% purity after chromatography and recrystallization. Although **2.58** showed reasonable solubility in common organic solvents, attempts to further purify **2.58** (trituration and further recrystallizations) were futile. However, tetraaldehyde **2.58** did prove to be of considerably higher purity (*c.f.* 70% to <50% purity) than the previously reported

tetrafunctionalized system **2.50** (Scheme 2.8), and the prospects of obtaining pure **2.51** seemed much more likely via this route. In the hope that pure material could be obtained at a later stage, tetraldehyde **2.58** was smoothly reduced with $NaBH_4$ to furnish the corresponding tetraol **2.59**, but purification of this polar intermediate proved to be quite taxing as well. Subjection of **2.59** to PBr_3 furnished tetrabromide **2.50**, once again in an impure (<70 %) form. Like the first-generation synthesis of **2.50**, the coupling of impure material proved to be a problematic approach in acquiring clean **2.51**. Additionally, due to the low yield of the bromination/formylation sequence, only small quantities of **2.51** were obtained. With a recurring theme of low solubility and purity of important synthetic intermediates becoming evident, a better synthetic route to intermediates akin to **2.50** (Scheme 2.2 – retrosynthetic analysis) was necessitated at this juncture.

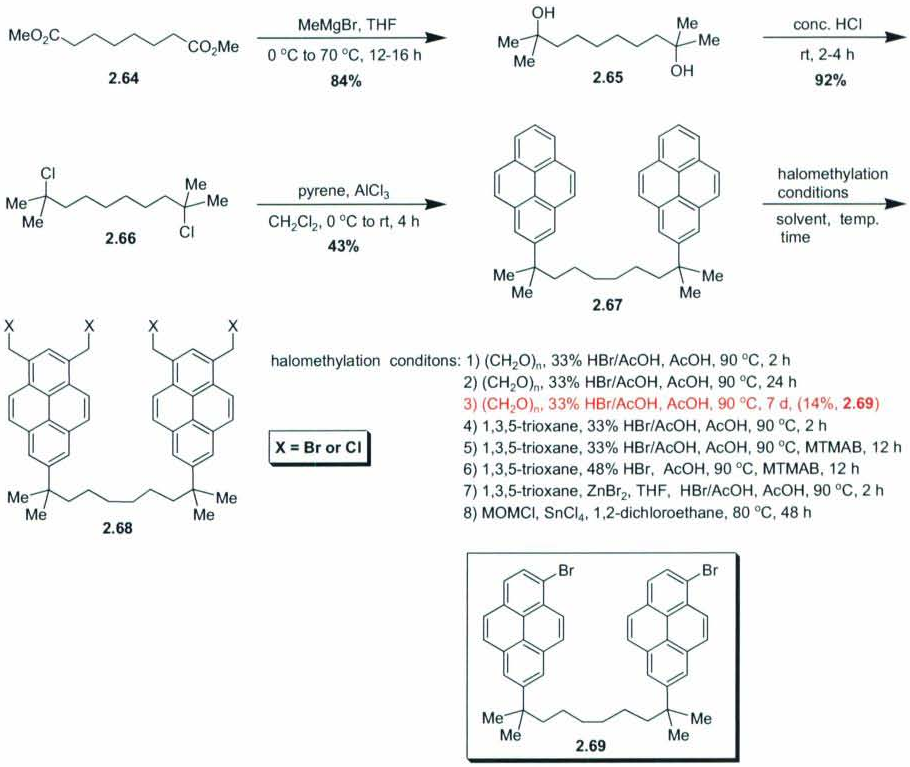
2.3.4 Bromomethylation of 2,9-Dimethyl-2,9-bis(2-pyrenyl)decane (2.67)

The possibility of directly and simultaneously installing four bromomethyl groups into **2.67** using well-known and reliable chemistry presented itself as an attractive approach. The bromomethylation reaction of aromatic compounds has proven to be a very useful reaction and has featured prominently in the preparation of substituted benzene[21] and naphthalene[22] systems (Scheme 2.10) that have served as cyclophane precursors. However, these reactions tend to be much more effective on neat samples, especially those that are available in liquid form. Several variants of the bromomethylation reaction have been reported for application to both less reactive and sensitive systems and, despite **2.67** being a solid, attempts to achieve fourfold bromomethylation were undertaken.



SCHEME 2.10: Bromomethylation of substituted benzene **2.60** and naphthalene **2.62**

The attempts to synthesize tetrabromide (or tetrachloride) **2.68** are summarized in Scheme 2.11.[23] Unfortunately, installation of the requisite bromomethyl or chloromethyl groups proved to be a fruitless endeavour and, in almost all cases, no tractable material could be isolated. The one exception was when ring-brominated product **2.69** was isolated using the conditions shown in Scheme 2.11. Despite the disappointment associated with what seemed to be such a simple and obvious reaction to the synthetic plan, in hindsight it came as no surprise that these reactions would fail. There has not been a single example reported in the literature where a halomethyl group was directly installed onto pyrene. In fact, all reports of bromomethyl-substituted pyrenes involve bromination of a (hydroxymethyl)pyrene (*cf.* **2.70** to **2.71** in Scheme 2.12).[24] This facet of pyrene substitution chemistry was duly noted and played a major role in further synthetic efforts.



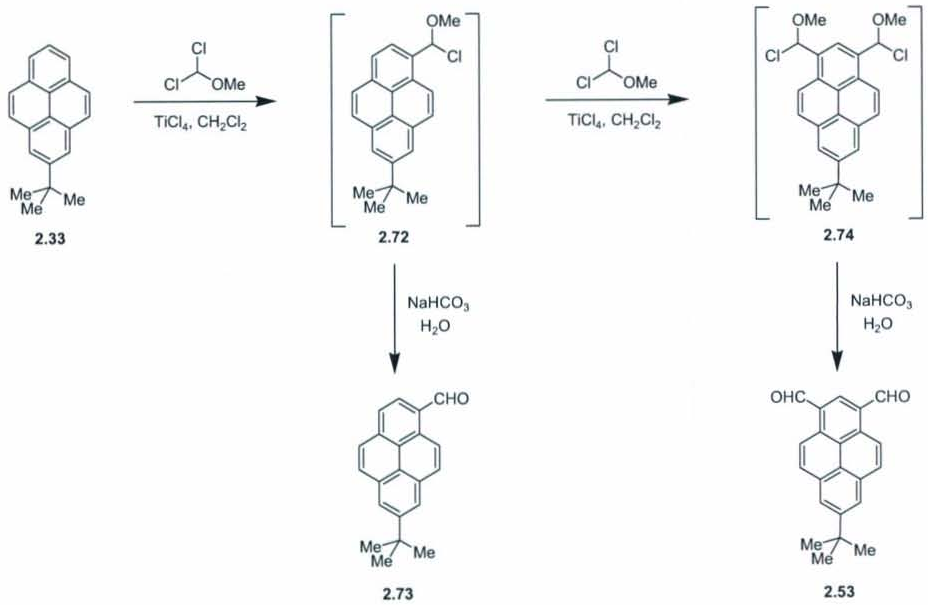
SCHEME 2.11: Attempted halomethylation reactions of **2.67**

SCHEME 2.12: Reliable synthesis of 1-(bromomethyl)pyrene (**2.71**)

2.3.5 Other Attempts to Tetrafunctionalize 2.67

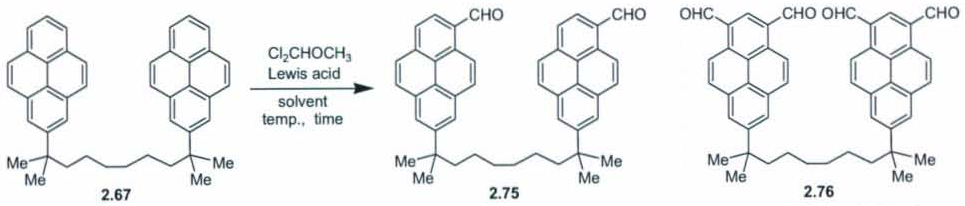
Despite the failure of bromo- and chloromethylation to deliver the desired tetrahalide **2.68**, the possiblility of installing four other functional groups in one synthetic operation was deemed to be a worthwhile endeavour. At this point, the most reliable substitution reaction was the Rieche formylation, which had been found to give synthetically useful quantities of dialdehyde **2.75** in short reaction times. Initially, the synthesis of **2.50** was guided by the literature precedent of Yamato and co-workers and, as such, no work towards exploring the synthetic utility of this reaction towards installing four aldehyde functions was explored. Considering that the reaction is essentially a Friedel-Crafts alkylation, it is reasonable to assume that an intermediate such as **2.72**, which is at the oxidation level of the ensuing aldehyde, is involved. Indeed, the bright yellow color of the aldehyde products obtained from these reactions never manifested itself until aqueous work-up was applied. More importantly, the 1-chloro-1-methoxymethyl substituent was not expected to be sufficiently electron withdrawing to prohibitively deactivate the 3 position of pyrene to further electrophilic substitution. This was critical in rationalizing that a second formylation should be achievable on each pyrene system of **2.67**.

A series of Rieche reactions were performed on **2.67** (Scheme 2.14). In all cases where titanium(IV) chloride was used as the Lewis acid, only dialdehyde **2.75** was obtained. Increasing the temperature and reaction time only served to lower the yields and the reaction products were often isolated in much lower purity (crude form) than in the optimal conditions reported in Scheme 2.14. The use of a much more powerful Lewis acid, aluminium chloride, was then investigated. Although the desired tetraaldehyde



SCHEME 2.13: Stepwise formylation procedure to aldehydes **2.53** and **2.73**

could be obtained in this manner, it was not separable (chromatographically or from recrystallization) from the corresponding trialdehyde byproduct. The reaction was also comparatively low yielding (41–47%) and resulted in the retro-Friedel-Crafts alkylation reaction (tether cleavage) of the starting material. Dealkylation products were evident from LCMS analysis of the crude reaction mixtures and in the instance when the crude material was subjected to chromatography, pyrene-1-carbaldehyde (**2.28**) was indeed isolated. Increasing the temperature and reaction time resulted in more extensive dealkylation.



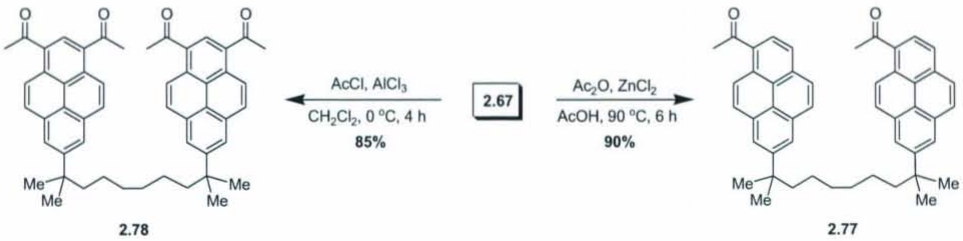
Formylation conditons: 1) $TiCl_4$, CH_2Cl_2, 2 h, 0 °C to rt, **2.75 86%**; **2.76 (0%)**
2) $TiCl_4$, CH_2Cl_2, 14 d, 0 °C to rt, **2.75 (72%)**; **2.76 (0%)**
3) $TiCl_4$, $CHCl_3$, 0 °C to 60 °C, 48 h, **2.75 (69%)**; **2.76 (0%)**
4) $TiCl_4$, 1,2-dichloroethane, 0 °C to 80 °C, 48 h, **2.75 (65%)**; **2.76 (0%)**
5) $AlCl_3$, CH_2Cl_2, 0 °C , 2 h, **2.75 (41%)**; **2.76 (10%)**
6) $AlCl_3$, CH_2Cl_2, 0 °C to rt, 2 h, **2.75 (47%)**; **2.76 (17%)**
7) $AlCl_3$, CH_2Cl_2, 0 °C to 40 °C, 2 h, **complex mixture of multiple formylation and dealkylation products**

SCHEME 2.14: Attempts to tetraformylate **2.67**

2.3.6 Friedel-Crafts Acylation of 2,9-dimethyl-2,9-bis(2-pyrenyl)decane (2.67)

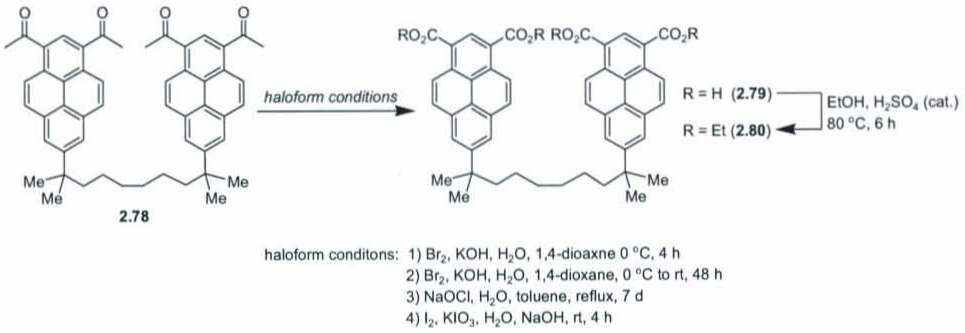
Having observed that exposure of 2,9-dimethyl-2,9-bis(2-pyrenyl)decane (**2.67**) to aluminum chloride for prolonged reaction times and elevated temperatures resulted in extensive retro-Friedel-Crafts alkylation (*vide supra*), it was reasoned that Friedel-Crafts acylation, which can be conducted at low temperatures, might be more successful than Rieche formylation. Indeed, treatment of **2.67** with 4.5 equivalents of acetyl chloride and 9.8 equivalents of $AlCl_3$ at 0 °C for 4 h furnished tetraketone **2.78** in 85% yield. In fact, attempts to furnish a diketone akin to dialdehyde **2.75** using 2.2 equivalents of AcCl and 4.8 equivalents of $AlCl_3$ proved to be difficult, as a mixture of mono-, di- and trisubstitution products was obtained. However, diketone **2.77** could be synthesized upon treatment of **2.67** with $ZnCl_2$, Ac_2O and AcOH.[25] Methyl ketones are rare, but potentially useful, intermediates in the synthesis of cyclophanes (specifically those that contain two or three atom bridges) because they can be converted into carboxylic acids using the haloform reaction.[26] The tetracarboxylic acid derived from **2.78** could be converted to the

corresponding esters or directly reduced to afford a tetraalcohol, the importance of which was discussed in Chapter 1.

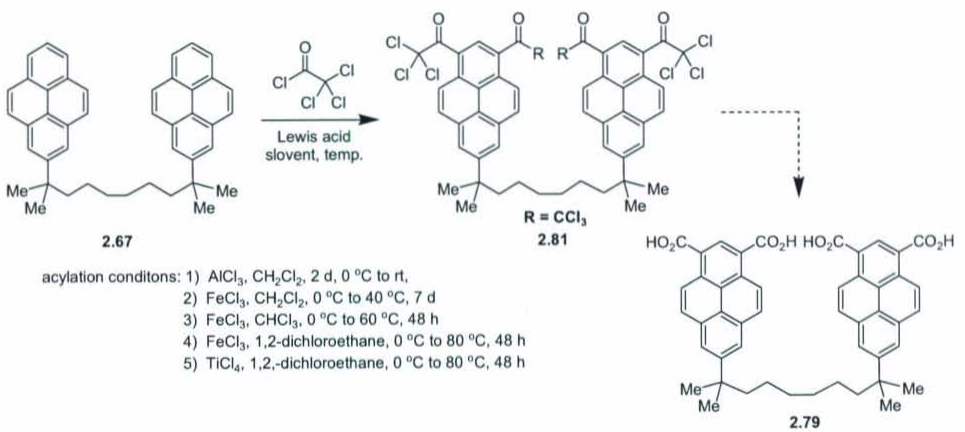


SCHEME 2.15: Synthesis of ketones **2.77** and **2.78**

Tetraketone **2.78** was subjected to several different sets of conditions for the haloform reaction and variants thereof and, in almost all cases, no tractable product was obtained. In the bromoform and chloroform reactions, only starting material was recovered. When the iodoform reaction conditions outlined in Scheme 2.16 were applied, starting material was consumed, but the desired carboxylic acid was not obtained. Attempts to esterify the crude mixture, in hope that the ethyl ester derivative of **2.79** would be isolable, were unsuccessful. Faced with the reluctance of tetraketone **2.78** to undergo a productive haloform reaction, the option to directly install a tricloroacetyl group presented itself as a possible solution to the synthesis of **2.79**. Unfortunately, all attempts to achieve the appropriate Friedel-Crafts acylation reaction under various conditions failed (Scheme 2.17).

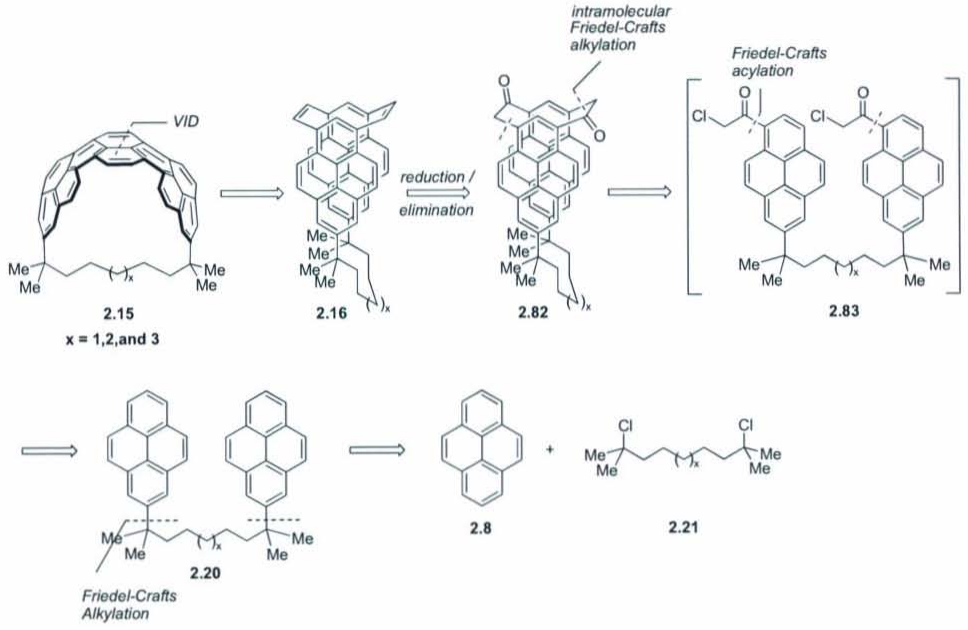


SCHEME 2.16: Attempted haloform reactions of tetraketone **2.78**



SCHEME 2.17: Attempted synthesis of **2.81** via Friedel-Crafts acylation

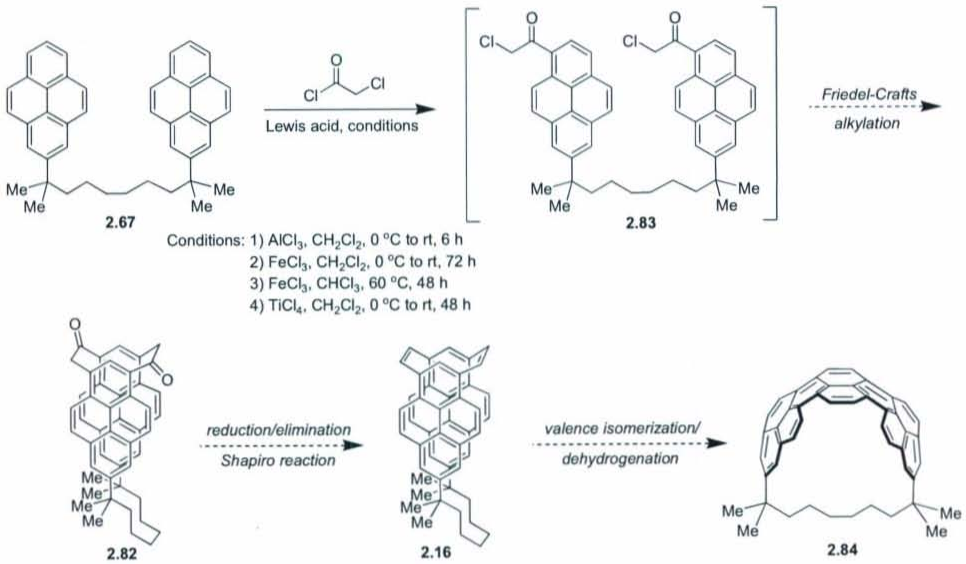
During the retrosynthetic analysis of target **2.15**, the use of chloroacetyl chloride as a bifunctional unit to install the requisite two-atom bridges of precursor **2.82** was considered. The success of the tetraacylation reaction of **2.67** with acetyl chloride was cause for optimism, but, similar to what was observed in the attempted tetraacylation of **2.67** with trichloroacetyl chloride, all attempts to synthesize **2.83** (or **2.82** directly) were unsuccessful. While acylation of **2.67** had proved to be so useful in the synthesis of



SCHEME 2.18: Alternative retrosynthetic analysis of **2.15**

tetraketone **2.78**, all other analogous acylation reactions, with seemingly more useful electrophiles[27] failed to provide entry to the desired synthetic intermediates. A final Friedel-Crafts alkylation-based approach was then attempted. In 1997, Ichihara reported the application of a composite lead(II) fluoride (Pb_2BrF_5) reagent in the Friedel-Crafts alkylation reactions involving allylic chlorides.[28] The advantage of using of this complex over other conventional Lewis acids (such as aluminium chloride) was the absence of a haloacid byproduct, which is capable of adding to the double bond in either the starting allylic chloride or the product. It was envisioned that tetraene **2.85** (Scheme 2.20) would isomerize to isomeric tetraene **2.86** (presumably thermodynamically more stable) upon

treatment with acid and that ozonolytic cleavage of the double bonds in **2.86** would afford aldehyde **2.76**.

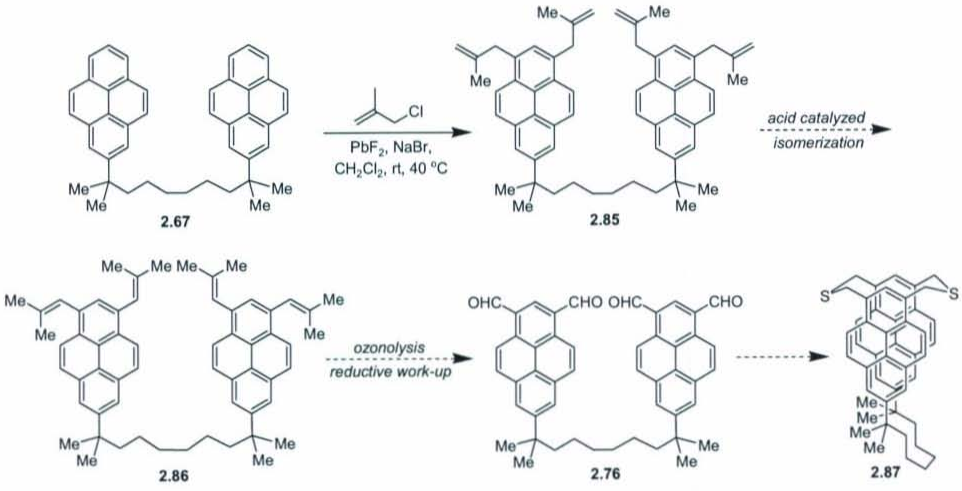


SCHEME 2.19: Attempted synthesis of **2.82** and possible route to **2.84**

Unfortunately, the reaction of **2.67** with methallyl chloride (3-chloro-2-methylprop-1-ene) in the presence of Ichihara's composite PbF_2 reagent did not afford **2.85** (Scheme 2.20).

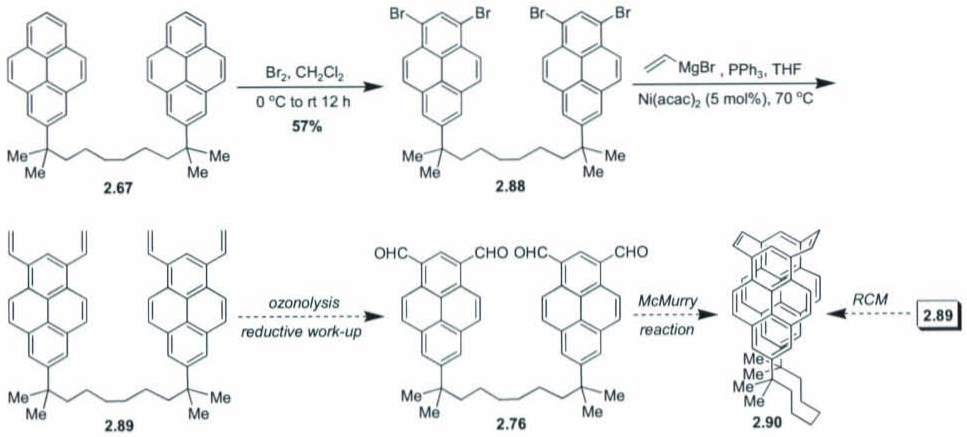
With prospects for the tetrafunctionalization strategy running short, a last-ditch effort to exploit tetrabromide **2.88** was undertaken. This had its foundation in ring-closing metathesis (RCM). With no literature precedent for its use in the construction (or even attempted construction) of a [2.2]metacyclophane system, this was a rather speculative endeavour. However, if it succeeded, it would provide direct access to cyclophanedienes **2.16** and **2.90** (Scheme 2.21). A major concern with this strategy was that if the first metathesis reaction resulted in the formation of a *trans* alkene, then the

second could not take place intramolecularly. Simple inspection of molecular models suggested that the



SCHEME 2.20: Attempted Friedel-Crafts alkylation and envisioned strategy for **2.76**

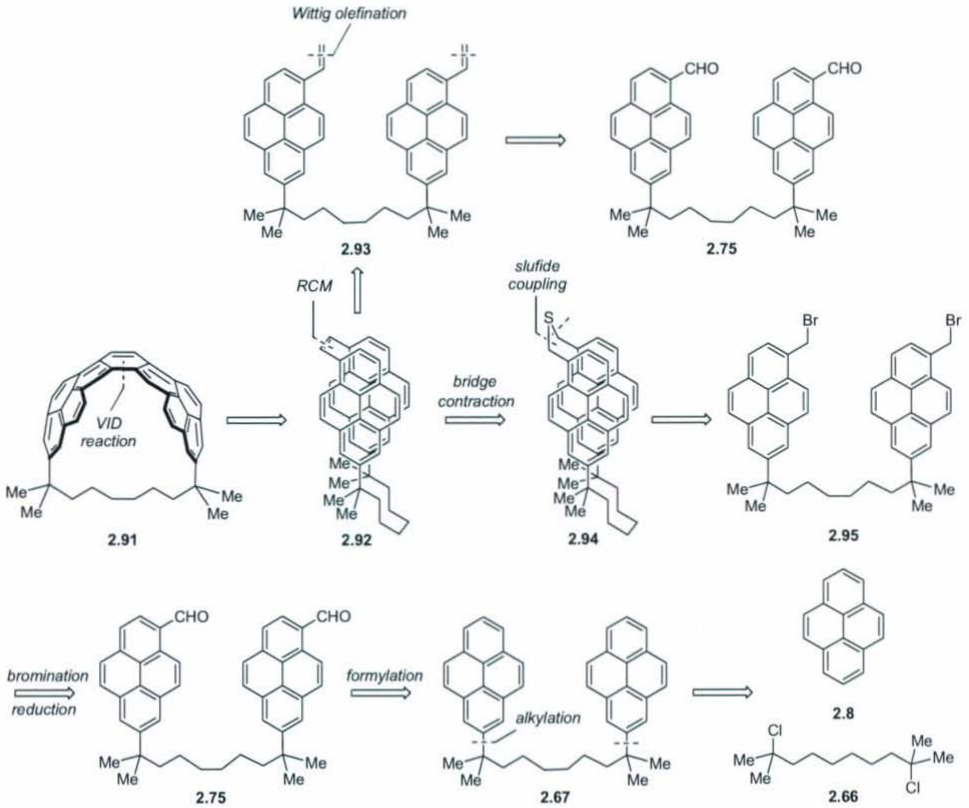
product of the first RCM reaction would be less strained in the *cis* configuation. Furthermore, if the desired RCM reaction of **2.89** failed, it could be used instead as a precursor to tetraaldehyde **2.76** via an ozonolysis reaction. Unfortunately, attempted Kumada coupling of tetrabromide **2.88** with vinylmagnesium bromide failed to furnish **2.89**. Once again, the introduction of four functional groups in one synthetic operation was unsuccessful. With direct tertafunctionalization of **2.67** proving to be difficult, attention was turned to an alternative approach, which instead relied upon difunctionalization of **2.67** to give a modified cyclophane target.



SCHEME 2.21: Attempted Kumada coupling and other routes to cyclophanediene **2.90**

2.4 A Difunctionalization Strategy

In Section 1.5.2 (Chapter 1), the importance of [3.3]dithiacyclophane intermediates in the synthesis of [*n*](2,7)pyrenophanes and other (2,7)pyrenophanes that have been synthesized in the Bodwell group was discussed. Of the over 20 reported pyrenophane syntheses, all of them proceeded through a dithiacyclophane intermediate that was prepared from a tetrakis(bromomethyl) precursor. In view of the difficulties that had been encountered in attempting to synthesize tetrakis(bromomethyl) compounds **2.50** and **2.68**, it was decided to investigate the possibility of exploiting the results of some of the failed tetrafunctionalizations. Specifically, Rieche formylation of 2,9-dimethyl-2,9-bis(2-pyrenyl)decane (**2.67**) had been found to afford dialdehyde **2.75** in high yield. Bringing this compound through the original synthetic plan would lead to a new target **2.91** (Scheme 2.22), which differs from the original target **2.15** in that it lacks an etheno group.



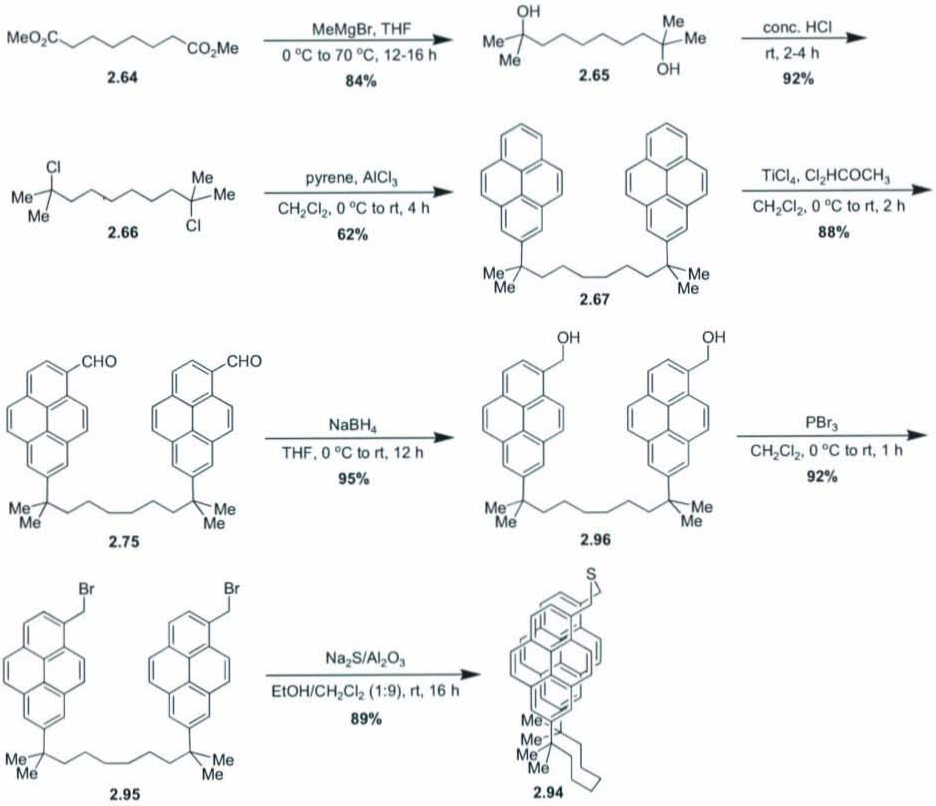
SCHEME 2.22: Retrosynthetic analysis of modified cyclophane target **2.91**

The modification to the synthetic target did not change the direction of this work, but rather, raised the question of whether or not the VID reaction would proceed with only one ethenylene bridge between the two pyrene units. The use of the VID reaction to generate a phenanthrene system had not previously been explored in the Bodwell group. In theory, the same set of Woodward-Hoffmann rules for electrocyclic ring closure would apply to this system, as the precursor [*n*.2]cyclophane would also be held in a *syn*-conformation, which renders the electrocyclic ring closure suprafacial and thus thermally

favoured. If successful, this would be a complement to the well-known photochemical stibene-phenanthrene reaction, which proceeds through an *anti* conformation. The electrocyclic ring closure in this case is conrotatory and thus photochemically favoured.

Another concern was that the planned ring contraction of thiacyclophane intermediate **2.94** may be problematic. In the vast majority of thioether ring contractions, a second bridge has been present. Nevertheless, several methods for achieving this transformation were available.[29] The possibility of using RCM of diene **2.93** was also considered. Either way, the retrosynthetic analysis came back to dialdehyde **2.75**.

Grignard reaction of methylmagnesium bromide with dimethyl suberate secured multi-gram quantities of tertiary diol **2.65** (Scheme 2.23). Conversion of **2.65** to **2.66** was accomplished using concentrated hydrochloric acid. Friedel-Crafts alkylation of **2.66** with an excess of pyrene (5 to 6 molar equivalents) furnished 2,9-dimethyl-2,9-bis(2-pyrenyl)decane (**2.67**) in 62% yield.[30] Once again, the use of an excess of pyrene was paramount in minimizing the formation of unwanted byproducts (*vide supra*) and giving a reproducible isolated yield (45–60%)[31] of **2.67**. Rieche formylation of **2.67** using the optimized conditions of Scheme 2.14 gave dial **2.75**. The reduction of dialdehyde **2.75** took place smoothly using either Dibal-H or $NaBH_4$ to afford diol **2.96** in high yield. Intially, Dibal-H was chosen as the source of hydride in this reaction due the high solubility of the starting material in dichloromethane. However, the use of sodium borohydride in THF proved to be superior. In fact, the diol isolated from this reaction did not require purification after work-up. Treatment of diol **2.96** with PBr_3 in dichloromethane gave dibromide **2.95** in 92% yield.

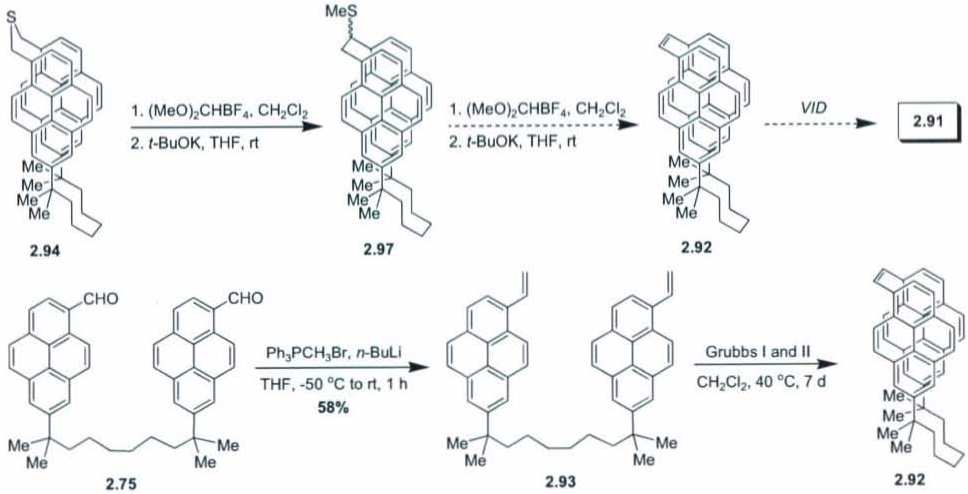


SCHEME 2.23: Synthesis of thiacyclophane **2.94**

Again, no purification was required in most cases. In instances when the material obtained after work-up was contaminated with some unknown impurities or byproducts, trituration with warm hexanes served to provide analytically pure samples of dibromide **2.95**. Subjecting dibromide **2.95** to Na_2S/Al_2O_3[32] brought about a very productive and high yielding coupling reaction, whereby thiacyclophane **2.94** was isolated in 89% yield. The yield is unusually high compared to others that have been carried out previously in the Bodwell group. However, all previous reactions involved a two-fold coupling event

and were conducted on substituted benzene-based systems instead of pyrene-based. Indeed, a π-stacking interaction between the two pyrene units of **2.95** may have contributed to the anomalously high yield.

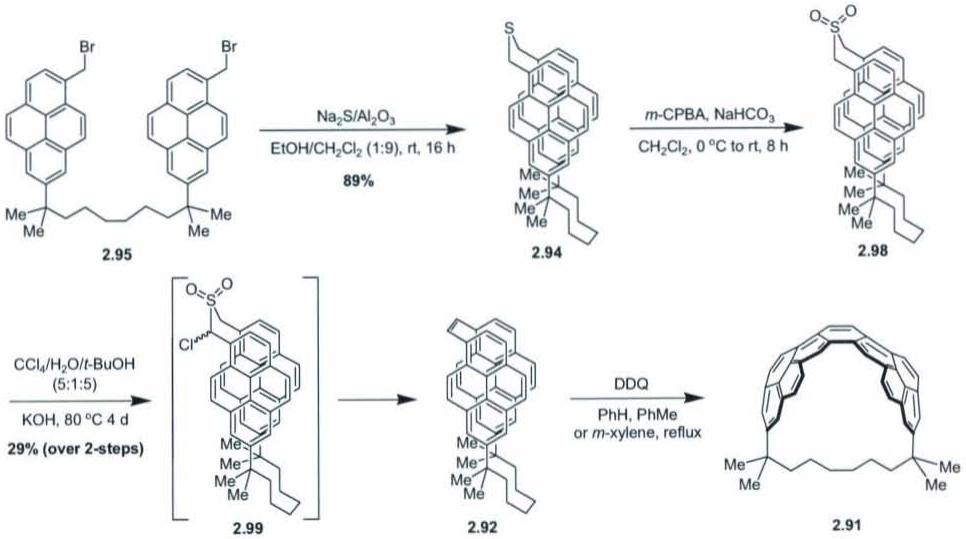
With thiacylophane intermediate **2.94** in hand, bridge contraction was attempted. An *S*-methylation (Borch reagent) / thia-Stevens rearrangement (*t*-BuOK) sequence, which had been used for all previous syntheses [*n*](2,7)pyrenophanes, was unsuccessful despite several attempts (Scheme 2.24). In all instances, no tractable products were isolated. Monitoring the reaction by TLC and MS analysis never provided any evidence to support the formation of the desired thioether **2.97**. Presumably, the methylation step proceeded as expected,[33] but the subsequent rearrangement did not.



SCHEME 2.24: Attempted ring contractions and RCM to **2.92**

The application of a ring-closing metathesis (RCM) protocol in the synthesis of [*n*](2,7)pyrenophanes has been on the Bodwell group's drawing board for quite some

time. However, due to the consistent success of the aforementioned four-step procedure for bridge contraction (*S*-methylation/thia-Stevens rearrangement, *S*-methylation/Hofmann elimination), it has never been necessary to explore its feasibility. Wittig olefination of dial **2.75** using the ylide derived from methyltriphenylphosphonium bromide furnished diolefin **2.93** in 58% yield. Unfortunately, treatment of **2.93** with Grubbs' first or second generation catalyst[34] never resulted in the formation of any of the desired [8.2]cyclophane **2.92** (Scheme 2.25).



SCHEME 2.25: Ramberg-Bäcklund approach to alternative target **2.91**

The [1,2]-Wittig rearrangement, which has been used extensively by other groups for the bridge contraction of [3.3]dithiacyclophanes,[35] also failed to afford any trace of **2.97**. Likewise, application of a modified thia-Stevens rearrangement, namely the benzyne-Stevens rearrangement, did not enable the synthesis of an *S*-Ph thioether

intermediate akin to **2.97**. Considering the large size of thiacyclophane **2.94** (an [8.3](1,7)pyrenophane), it could also be viewed as a macrocyclic thioether rather than a small cyclophane. Interestingly, in macrocylic thioether synthesis, the Ramberg-Bäcklund reaction has often been employed successfully.[36] In contrast, it typically fails in the synthesis of small cyclophanes. As such, it seemed appropriate to apply it here. Using the Meyers variant of the Ramberg-Bäcklund reaction[37] afforded the desired cyclophane **2.92** in 29% overall yield from thiacyclophane **2.94**. Despite the low yield of **2.92**, it seemed like a small price to pay for the successful installation of an unsaturated bridge. However, exposure of **2.92** to standard (DDQ, benzene, reflux) and slightly more forcing (DDQ, toluene or *m*-xylene reflux) VID conditions did not result in the conversion of **2.92** to **2.91**. Only starting material was recovered from this reaction.

2.4.1 Summary

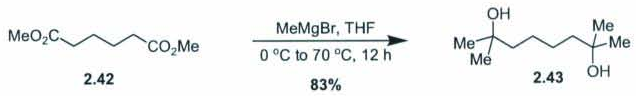
To this point, the difunctionalzation strategy towards the synthesis of large nonplanar pyrenoid frameworks seemed like the best option for future work and synthesis planning. Despite the inability to capitalize on cyclophanemonoene-**2.92** in a productive VID reaction to afford cyclophane **2.91**, an iterative bridge formation strategy based on the difunctionalization approach was beginning to emerge (see Chapter 3). However, before prematurely jumping into a new synthesis plan, it seemed wise to develop this chemistry on a model system, 2-*tert*-butylpyrene. This work is described in the following chapter.

2.5 General Experimental Procedures and Characterization Data

All reactions were performed under an atmosphere of nitrogen unless otherwise indicated. Experiments involving moisture sensitive compounds were carried out using anhydrous solvents and oven-dried (120 °C) glassware. Solvents for these reactions were dried and distilled according to standard procedures. All other solvents and chemicals were used as received. Solvents were removed under reduced pressure using a rotary evaporator. Chromatographic separations were achieved using Silicycle silica gel 60, particle size 40-63 μm. Column dimensions are recorded as height × diameter. Thin-layer chromatography (TLC) was performed using commercially precoated plastic-backed POLYGRAM® SIL G/UV254 silica gel plates, layer thickness 200 μm. Compounds on TLC plates were visualized using a UV lamp (254 and 365 nm). Melting points were obtained using a Fisher-Johns apparatus. Infrared (IR) spectra were recorded using neat samples on a Bruker TENSOR 27 instrument. ^{1}H (500.133 MHz) and ^{13}C (125.77 MHz) nuclear magnetic resonance (NMR) spectra were obtained from $CDCl_3$ solutions using a Bruker Avance 500 MHz spectrometer. Chemical shifts (δ) are relative to internal standards: TMS (δ_H = 0.00 ppm) and $CDCl_3$ (δ_H = 7.27 ppm; δ_C = 77.23 ppm), respectively. ^{1}H NMR data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, t = triplet, q = quartet, m = multiplet), coupling constants (*J*, Hz). Low-resolution and high-resolution mass spectrometric (MS) data were obtained using an Agilent 1100 Series LC/MSD instrument and a Waters Micromass® GCT PremierTM instrument. MS data are presented as

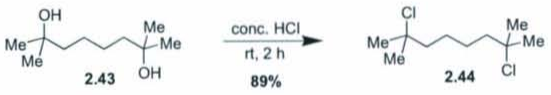
follows: ionization mode, *m/z* (relative intensity), assignment (when appropriate), calculated mass and found mass for the given formula.

2,7-Dimethyl-2,7-octanediol (2.43)



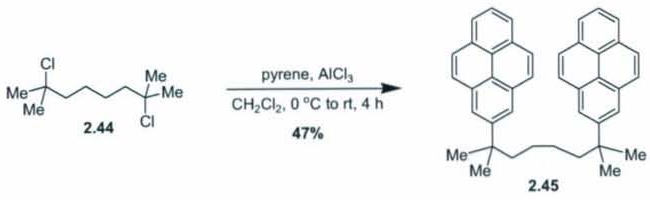
A solution of dimethyl adipate (**2.42**) (10.4 g, 59.7 mmol) in anhydrous THF (100 mL) was added dropwise over a period of 30 min to a stirred 0 °C solution of methylmagnesium bromide (3.0 M in Et_2O, 89 mL, 0.27 mol). After the addition was complete, the reaction mixture was heated at reflux for 12 h. The reaction mixture was cooled to room temperature and quenched by the addition of a saturated ammonium chloride solution (100 mL). The layers were separated and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to yield a white solid, which was recrystallized from heptane to give 2,7-dimethyl-2,7-decanediol (**2.43**) (8.63 g, 83%) as a white powder: m.p. 61–62 °C (heptane); ^{1}H NMR: δ 1.21 (s, 12H), 1.33–1.36 (m, 4H), 1.41 (br s, 2H), 1.47–1.49 (m, 4H); ^{13}C NMR: δ 25.03, 29.30, 44.10, 71.15; LCMS (APCI-negative) *m/z* (rel. int.) 173.2 (M–*H*) 100); HRMS (CI) calculated for $C_{10}H_{23}O_2$ (M*H*)$^+$ 175.1698, found 175.1692.

2,7-Dichloro-2,7-dimethyloctane (2.44)



A mixture of 2,7-dimethyl-2,7-octanediol (**2.43**) (6.34 g, 36.4 mmol) and concentrated aqueous HCl solution (100 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into ice water (300 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (2 × 50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 2,7-dichloro-2,7-dimethyloctane (**2.44**) (6.83 g, 89%) as a light yellow oil, that was used without purification. ^{1}H NMR: δ 1.48–1.52 (m, 4 H), 1.54 (s, 12 H), 1.76–1.81 (m, 4 H); ^{13}C NMR: δ 25.38, 32.65, 46.10, 71.15; LCMS (APCI positive) *m/z* 211.1 $(MH)^+$. No HRMS data could be obtained for this compound.

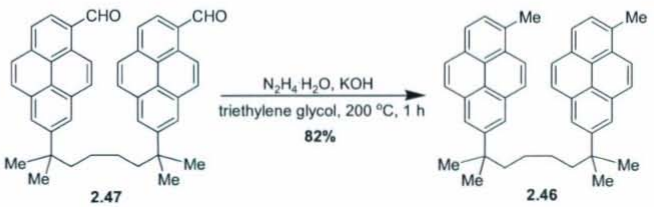
2,7-Dimethyl-2,7-bis(2-pyrenyl)octane (2.45)



Aluminum chloride (1.25 g, 9.38 mmol) was added to a stirred 0 °C solution of pyrene (**2.8**) (4.75 g, 23.5 mmol) and 2,7-dichloro-2,7-dimethyloctane (**2.44**) (0.97 g, 4.60 mmol) in dichloromethane (40 mL). The resulting slurry was allowed to warm to room temperature and stirred for 4 h. The reaction was poured into ice water (200 mL) and the

layers were separated. The aqueous layer was extracted with dichloromethane (2 × 50 mL) and the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The solid yellow residue was subjected to column chromatography (20 × 5 cm; 1:9 dichloromethane/hexanes) to yield 2,7-dimethyl-2,7-bis(2-pyrenyl)octane (**2.45**) as a white solid (1.17 g, 47%): R_f = 0.34 (1:9 dichloromethane/hexanes); m.p. 204–205 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J*=7.5 Hz, 4H), 8.12 (s, 4H), 8.07–7.98 (m, 10H), 1.73–1.70 (m, 4H), 1.47 (s, 12H), 1.03–1.00 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 148.18, 131.32, 131.27, 128.12, 127.54, 125.93, 125.10, 125.00, 123.29, 123.18, 45.54, 38.73, 30.35, 27.89; LCMS (APCI-positive) *m/z* (rel. int.) 545 (10), 544 (48), 543 ($(MH)^+$, 100), 369 (65); HRMS (EI) calculated for $C_{42}H_{38}$ $(M)^+$ 542.2974, found 542.2970.

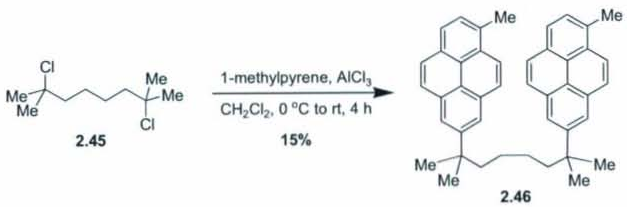
2,7-Bis(6-methylpyren-2-yl)-2,7-dimethyloctane (2.46)



A 50% solution of hydrazine hydrate (0.314 g, 3.14 mmol) and powdered potassium hydroxide (0.156 g, 2.78 mmol) were added to a suspension of 2,7-bis(6-formylpyren-2-yl)-2,7-dimethyloctane (**2.47**) (0.625 g, 1.05 mmol) in triethylene glycol (30 mL). The reaction was heated to 200 °C for 1 h and the mixture was then cooled and poured into ice water (100 mL). The resulting solution was extracted with dichloromethane (3 × 40 mL).

The combined organic extracts were washed with 1 M HCl (50 mL), a saturated solution of sodium bicarbonate (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The solid orange residue was subjected to column chromatography (30 × 3 cm, 1:5 dichloromethane/hexanes) to afford 2,7-bis(6-methylpyren-2-yl)-2,7-dimethyloctane (**2.46**) as a white solid (0.466 g, 82%). R_f = 0.32 (1:9 dichloromethane/hexanes); m.p. 210–212 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J*=9.5 Hz, 2H), 8.05–8.02 (m, 6H), 8.00 (d, *J*=9.3 Hz, 2H), 7.94 (d, *J*=9.4 Hz, 2H), 7.89 (d, *J*=8.9 Hz, 2H), 7.80 (d, *J*=7.4 Hz, 2H), 2.94 (s, 6H), 1.73–1.71 (m, 4H), 1.47 (s, 12H), 1.03–1.01 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 148.79, 132.40, 132.06, 131.24, 130.63, 128.14, 125.73, 124.76, 124.51, 122.95, 122.63, 122.40, 122.36, 122.18, 122.03, 45.22, 38.66, 29.76, 26.06; 20.08 LCMS (APCI-positive) *m/z* (rel. int.) 573 (13), 572 (52), 571 ($(MH)^+$, 100), 355 (15); HRMS (EI) calculated for $C_{44}H_{42}$ $(M)^+$ 570.3287, found 570.3281.

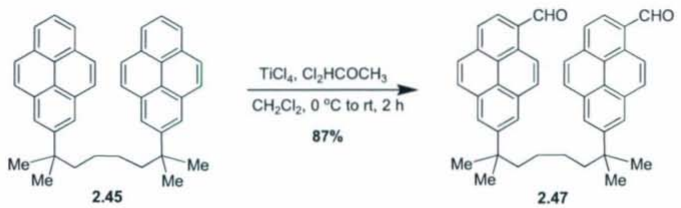
2,7-Bis(6-methylpyren-2-yl)-2,7-dimethyloctane (2.46)



Aluminum chloride (0.489 g, 3.68 mmol) was added to a stirred 0 °C solution of 1-methylpyrene (**2.37**) (0.831 g, 3.84 mmol) and 2,7-dichloro-2,7-dimethyloctane (**2.44**) (0.368 g, 1.75 mmol) in dichloromethane (20 mL). The resulting slurry was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was poured into ice

water (100 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 20 mL) and the combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The solid orange residue was subjected to column chromatography (25 × 3 cm; 1:9 dichloromethane/hexanes) to yield 2,7-bis(6-methylpyren-2-yl)-2,7-dimethyloctane (**2.46**) as a white solid (0.148 g, 15%).

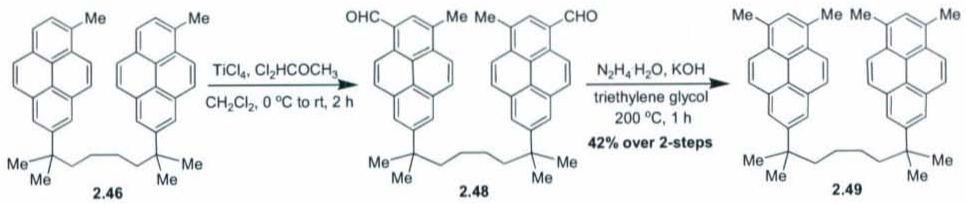
2,7-Bis(6-formylpyren-2-yl)-2,7-dimethyloctane (2.47)



Titanium(IV) chloride (1.40 g, 7.38 mmol) was added to a stirred 0 °C solution of 2,7-dimethyl-2,7-bis(2-pyrenyl)octane (**2.45**) (1.59 g, 2.94 mmol) and dichloromethyl methyl ether (0.848 g, 7.38 mmol) in dichloromethane (30 mL). The ice bath was removed and the reaction was stirred at room temperature for 2 h. The reaction mixture was poured into ice water (150 mL) and the layers were separated. The aqueous layer extracted with dichloromethane (2 × 30 mL) and the combined organic extracts were washed with a saturated solution of sodium bicarbonate (40 mL), washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a brown solid. The resulting solid was purified via chromatography (25 × 3 cm; dichloromethane) to yield 2,7-bis(6-formylpyren-2-yl)-2,7-dimethyloctane (**2.47**) (1.53 g, 87%) as a bright yellow solid: R_f = 0.23; m.p. 129–131 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ

10.71 (s, 2H), 9.28 (d, *J*=9.0 Hz, 2H), 8.29 (d, *J*=7.8 Hz, 2H), 8.17–8.13 (m, 6H), 8.10 (d, *J*=7.6 Hz, 2H) 8.05 (d, *J*=8.9 Hz, 2H), 7.93 (d, *J*=8.9 Hz, 2H), 1.75–1.73 (m, 4H), 1.50 (s, 12H), 1.05–1.02 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 193.20, 148.54, 135.44 131.18, 131.11, 131.01, 130.95, 130.89, 130.34, 127.38, 127.11, 125.03, 124.74, 124.62, 124.43, 122.98, 122.69, 45.31, 38.46, 29.56, 25.82; LCMS (APCI-positive, *m/z* (rel. int.)) 601 (11), 600 (49), 599 ($(MH)^+$, 100), 571 (18); HRMS (EI) calculated for $C_{44}H_{38}O_2$ $(M)^+$ 598.2872, found 598.2870.

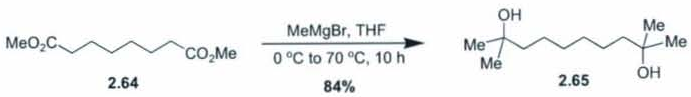
2,7-Dimethyl-2,7-bis(6,8-dimethylpyren-2-yl)octane (2.49)



Titanium(IV) chloride (0.372 g, 1.96 mmol) was added to a stirred 0 °C solution of 2,7-bis(6-methylpyren-2-yl)-2,7-dimethyloctane (**2.46**) (0.418 g, 0.733 mmol) and dichloromethyl methyl ether (0.216 g, 1.88 mmol) in dichloromethane (25 mL). The ice bath was removed and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was poured into ice water (100 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 25 mL) and the combined organic extracts were washed with a saturated solution of sodium bicarbonate (40 mL), washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 2,7-bis(6-formyl-8-methylpyren-2-yl)-2,7-dimethyloctane (**2.48**) as a light brown solid. A 50% aqueous solution of hydrazine hydrate (0.566 g, 2.21 mmol) and

powdered potassium hydroxide (0.19 g, 2.09 mmol) were added to a suspension of the isolated material (**2.48**) in triethylene glycol (20 mL). The reaction was heated at 200 °C for 1 h, cooled and poured into ice water (100 mL). The resulting solution was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with 1 M HCl solution (30 mL), washed with a saturated solution of sodium bicarbonate (30 mL), washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The solid orange residue was subjected to column chromatography (25 × 3 cm; 1:5 dichloromethane/hexanes) to afford 2,7-bis(1,3-dimethylpyren-7-yl)-2,7-dimethyloctane (**2.49**) as a white sold (0.184 g, 42%). R_f = 0.27 ((1:9) dichloromethane/hexanes); m.p. 227–230 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J*=9.1 Hz, 4H), 8.04 (s, 4H), 7.96 (d, *J*=9.1 Hz, 4H), 7.71 (s, 2H), 2.94 (s, 12H), 1.75–1.72 (m, 4H), 1.49 (s, 12H), 1.04–1.02 (m, 4H); LCMS (APCI-positive) *m/z* (rel. int.) 601 (14), 600 (54), 599 ($(MH)^+$, 100), 355(15); HRMS (EI) calculated for $C_{46}H_{46}$ $(M)^+$ 598.3600, found 598.3591.

2,9-Dimethyl-2,9-decanediol (2.65)

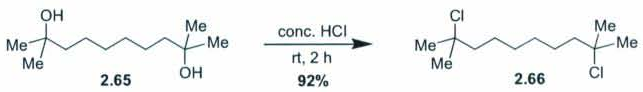


2.64 84% 2.65

A solution of dimethyl suberate (**2.64**) (9.82 g, 48.5 mmol) in anhydrous THF (100 mL) was added dropwise over a period of 30 min to a stirred 0 °C solution of methylmagnesium bromide (3.0 M in Et_2O, 73 mL, 0.22 mol). After the addition was complete, the reaction mixture was heated at reflux for 10 h. The reaction mixture was

cooled to room temperature and quenched by the addition of a saturated ammonium chloride solution (100 mL). The layers were separated and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to yield a white solid, which was recrystallized from heptane to give 2,9-dimethyl-2,9-decanediol (**2.65**) (8.21 g, 84%) as a white powder: m.p. 64–65 °C (lit.[38] 67 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22 (s, 12H), 1.31–1.36 (m, 8H), 1.44–1.48 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 24.73, 26.94, 30.57, 44.38, 71.40; LCMS (APCI-negative) *m/z* (rel. int.) 201.2 (M-*H*, 100); HRMS (CI) calculated for $C_{12}H_{27}O_2$ $(MH)^+$ 203.2011, found 203.2011.

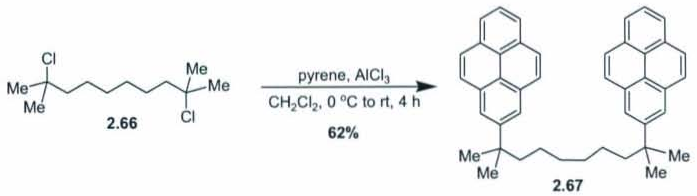
2,9-Dichloro-2,9-dimethyldecane (2.66)



A mixture of 2,9-dimethyl-2,9-decanediol (**2.65**) (4.52 g, 22.3 mmol) and concentrated aqueous HCl solution (100 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into ice water (200 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (2 × 50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 2,9-dichloro-2,9-dimethyldecane (**2.66**) (4.92 g, 92%) as a light yellow oil, which was used without purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33–1.37 (m, 4H), 1.46–1.50 (m, 4H), 1.57 (s, 12H), 1.72–1.75 (m, 4H); ^{13}C

NMR (125.77 MHz, $CDCl_3$): δ 25.46, 29.98, 32.82, 46.45, 71.63; LCMS (APCI positive) *m/z* 239 $(MH)^+$.

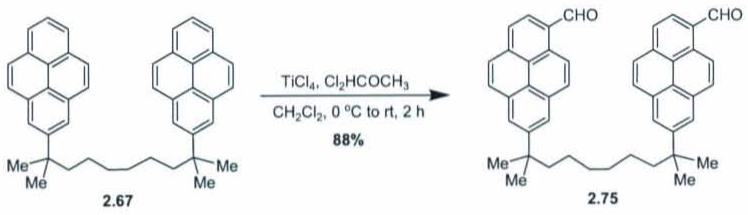
2,9-Dimethyl-2,9-bis(2-pyrenyl)decane (2.67)



Aluminum chloride (2.29 g, 17.2 mmol) was added to a stirred 0 °C solution of pyrene (**2.8**) (8.70 g, 43.1 mmol) and 2,9-dichloro-2,9-dimethyldecane (**2.66**) (2.05 g, 8.61 mmol) in dichloromethane (100 mL). The resulting slurry was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was poured into ice water (400 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 100 mL) and the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The solid yellow residue was subjected to column chromatography (25 × 6.5 cm; (1:9 dichloromethane/hexanes) to yield 2,9-dimethyl-2,9-bis(2-pyrenyl)decane (**2.67**) as a white solid (3.04 g, 62%): R_f = 0.35 ((1:9) dichloromethane/hexanes); m.p. 149–151 °C (1:9 dichloromethane/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J*=7.6 Hz, 4H), 8.08 (s, 4H), 8.03–7.98 (m, 8H), 7.96–7.93 (m, 2H), 1.75–1.72 (m, 4H), 1.46 (s, 12H), 1.09–1.07 (m, 4H) 0.98–0.95 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 148.10, 131.38, 131.30, 128.05, 127.58, 125.91, 125.13, 125.03, 123.25, 123.21, 45.52, 38.64, 30.54, 29.94, 25.21; LCMS (APCI-

positive) *m/z* (rel. int.) 573 (14), 572 (49), 571 ($(MH)^+$, 100), 369 (65) M-$C_{16}H_{10}$; HRMS (EI) calculated for $C_{44}H_{42}$ $(M)^+$ 570.3287, found 570.3285.

2,9-Bis(6-formylpyren-2-yl)-2,9-dimethyldecane (2.75)

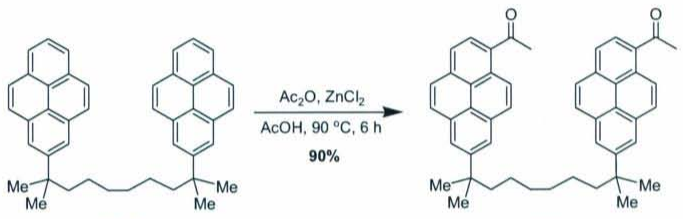


2.67 2.75

Titanium(IV) chloride (1.78 g, 9.36 mmol) was added to a stirred 0 °C solution of 2,9-bis(2-pyrenyl)-2,9-dimethyldecane (**2.67**) (2.14 g, 3.75 mmol) and dichloromethyl methyl ether (1.08 g, 9.36 mmol) in dichloromethane (40 mL). The ice bath was removed and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was poured into ice water (200 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 30 mL) and the combined organic extracts were washed with a saturated solution of sodium bicarbonate (40 mL), washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The solid brown-yellow residue was subjected to column chromatography (20 × 3.5 cm; dichloromethane) to yield 2,9-bis(6-formylpyren-2-yl)-2,9-dimethyldecane (**2.75**) as a bright yellow solid (2.07 g, 88%): R_f = 0.25 (dichloromethane); m.p. 205–207 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.74 (s, 2H), 9.34 (d, *J*=9.3 Hz, 2H), 8.36 (d, *J*=7.9 Hz, 2H), 8.22 (d, *J*=9.3 Hz, 2H), 8.20–8.16 (m, 6H) 8.12 (d, *J*=8.9 Hz, 2H), 8.01 (d, *J*=8.9 Hz, 2H), 1.77–1.74 (m, 4H), 1.48 (s, 12H), 1.12–1.10 (m, 4H), 1.00–0.98 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 193.52, 148.94, 135.75, 132.22, 131.54,

131.51, 131.33, 131.25, 131.15, 130.63, 127.67, 127.36, 125.33, 124.96, 124.70, 123.26, 122.63, 45.36, 38.69, 30.41, 29.84, 25.12; LCMS (APCI-positive) *m/z* (rel. int.) 629 (13), 628 (50), 627 ((M*H*)$^+$, 100), 613 (16); HRMS (EI) calculated for $C_{46}H_{42}O_2$ $(M)^+$ 626.3185, found 626.3184.

2,9-Bis(6-acetylpyren-2-yl)-2,9-dimethyldecane (2.77)

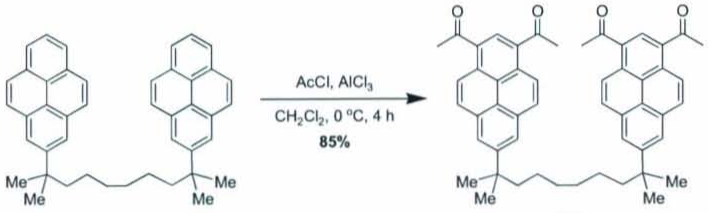


2.67 **2.77**

Acetic anhydride (0.934 g, 9.09 mmol) was added to a stirred solution of 2,9-bis(2-pyrenyl)-2,9-dimethyldecane (**2.67**) (0.863 g, 1.52 mmol) and zinc chloride (0.405 g, 2.98 mmol) in glacial acetic acid (20 mL). The reaction mixture was heated at 90 °C for 6 h, after which it was cooled and poured into ice water (100 mL). The solution was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (2 × 50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The brown residue was subjected to chromatography (30 × 3 cm; dichloromethane) to afford 2,9-bis(6-acetylpyren-2-yl)-2,9-dimethyldecane (**2.77**) as a bright yellow solid (0.894 g, 90%): R_f = 0.38 (dichloromethane); m.p. 218–221 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (d, *J*=9.3 Hz, 2H), 8.23 (d, *J*=7.4 Hz, 2H), 8.12–8.09 (m, 6H), 8.01 (d, *J*=8.7 Hz, 2H), 7.99 (d, *J*=8.1 Hz, 2H), 7.90 (d, *J*=8.9 Hz, 2H) 2.83 (s, 6H), 1.75–1.72 (m,

4H), 1.47 (s, 12H), 1.10–1.08 (m, 4H), 0.99–0.94 (m, 4H); LCMS (APCI-positive) *m/z* (rel. int.) 657 (11), 656 (55), 655 ((M*H*)$^+$, 100); HRMS (EI) calculated for $C_{48}H_{46}O_2$ (M)$^+$ 654.3498, found 654.3492.

2,9-Bis(6,8-diacetylpyren-2-yl)-2,9-dimethyldecane (2.78)

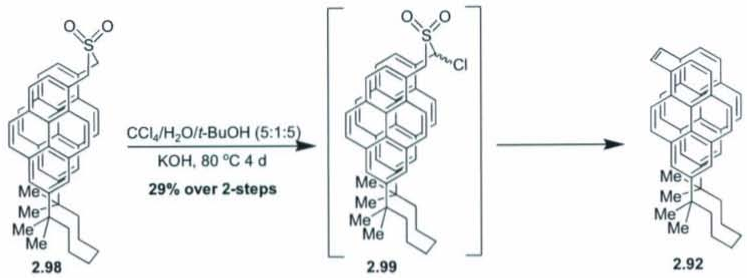


2.67 **2.78**

Aluminum chloride (3.97 g, 29.8 mmol) was added to a stirred 0 °C solution of acetyl chloride (1.11 g, 14.2 mmol) and 2,9-bis(2-pyrenyl)-2,9-dimethyldecane (**2.67**) (1.93 g, 3.38 mmol) in dichloromethane (40 mL). The resulting mixture was kept at 0 °C and stirred for 4 h. After which, it was poured into ice water (200 mL) and diluted further with dichloromethane (50 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The organic extracts were combined and washed with a saturated solution of sodium bicarbonate (50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The yellow mass isolated was subjected to recrystallization from acetone to afford 2,9-bis(6,8-diacetylpyren-2-yl)-2,9-dimethyldecane (**2.78**) as a bright yellow solid (2.11 g, 85%): R_f= 0.25 (dichloromethane); m.p. 211–212 °C (acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.96 (d, *J*=9.0 Hz, 4H), 8.68 (s, 2H), 8.22 (d, *J*=9.0 Hz, 4H), 8.19 (s, 4H), 2.94 (s, 12H), 1.78–1.75 (m, 4H), 1.48 (s, 12H), 1.12–1.10 (m, 4H), 1.02–0.98 (m, 4H); ^{13}C NMR (125.77

MHz, $CDCl_3$) δ 201.85, 149.29, 132.40, 132.06, 131.24, 130.63, 128.14, 125.73, 124.76, 122.51, 45.22, 38.66, 30.89, 30.33, 29.76, 25.06, 21.46; LCMS (APCI-positive) *m/z* (rel. int.) 741 (13), 740 (56), 739 ($(MH)^+$, 100); HRMS (EI) calculated for $C_{52}H_{50}O_4$ $(M)^+$ 738.3709, found 738.3700.

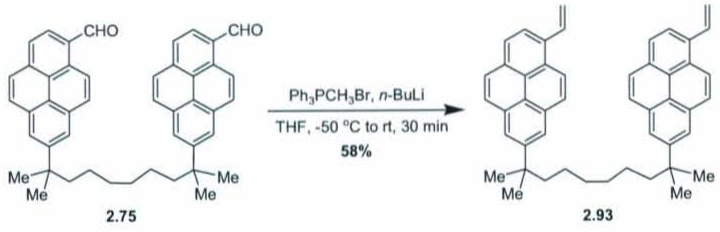
(*Z*)-1,1,8,8-tetramethyl[8.2](7,1)pyrenophane (2.92)



Potassium hydroxide (0.048 g, 1.21 mmol) was added to a stirred room temperature solution of sulfone **2.98** (0.040 g, 0.061 mmol) in carbon tetrachloride (2.5 mL), water (1 mL) and *tert*-butanol (2.5 mL). The resulting mixture was heated at 80 °C for 4 d, until all of the starting material had been consumed (TLC analysis). The reaction was cooled to room temperature, poured into water (25 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give an orange mass, which was adsorbed onto silica gel in preparation for column chromatography. Chromatography (15 × 1.5 cm; 1:5 dichloromethane/hexanes) afforded (*Z*)-1,1,8,8-tetramethyl[8.2](7,1)pyrenophane (**2.92**) as a bright yellow oil (0.021 g, 58%): R_f = 0.52 (1:5 dichloromethane/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J*=7.8 Hz, 2H),

7.89 (d, *J*=7.8 Hz, 2H), 7.86–7.84 (m, 4H), 7.81 (d, *J*=8.9 Hz, 2H), 7.73 (s, 2H), 7.65 (poorly resolved doublet, 2H), 7.52 (s, 2H), 7.10 (poorly resolved doublet, 2H), 1.61–1.58 (m, 4H), 1.40 (s, 12H), 1.02–1.00 (m, 4H), 0.49–0.46 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 146.36, 133.38, 131.01, 130.32, 130.00, 127.77, 127.43, 127.24, 127.04, 126.06, 125.28, 125.54, 124.22, 122.80, 122.61, 122.49, 46.42, 38.18, 30.75, 24.42 (only 20 of 22 carbons observed) LCMS (APCI-positive), *m/z* (rel. int.) 597 (12), 596 (53), 595 (100, $(MH)^+$); HRMS (EI) calculated for $C_{46}H_{42}$ $(M)^+$ 594.3287, found 594.3281.

2,9-Dimethyl-2,9-bis(6-vinylpyren-2-yl)decane (2.93)



2.75 2.93

A solution of 1.0 M *n*-butyllithium (0.283 mL, 0.283 mmol) in hexanes was added to methyltriphenylphosphonium bromide (0.101 g, 0.283 mmol) in THF (5 mL) at –50 °C. The reaction was maintained at –50 °C for 15 min and then a solution of 2,9-bis(6-formylpyren-2-yl)-2,9-dimethyldecane (**2.75**) (0.050 g, 0.080 mmol) in THF (10 mL) was added. The cold bath was removed and the reaction was stirred at room temperature for 30 min until all of the aldehyde starting material had been consumed (TLC analysis). The solvent was evaporated under reduced pressure and the resulting oily yellow mass was taken up into dichloromethane (20 mL), washed with a 1 M HCl solution (10 mL), washed with a saturated sodium bicarbonate solution (20 mL), washed with brine (20

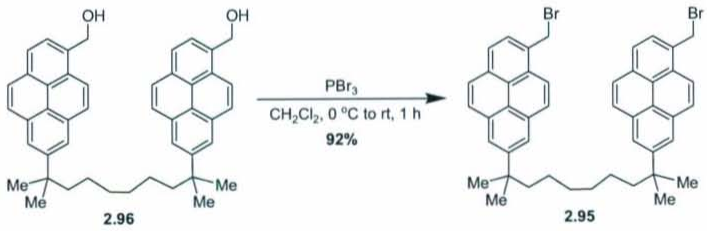
mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow foam, which was adsorbed onto silica gel in preparation for chromatography. Chromatography (15 × 2 cm; 1:9 dichloromethane/hexanes) afforded 2,9-bis(6-vinylpyren-2-yl)-2,9-dimethyldecane (**2.93**) as a light yellow oil (0.029g, 58%): R_f = 0.37 (1:9 dichloromethane/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J*=9.3 Hz, 2H), 8.15 (d, *J*=8.0 Hz, 2H), 8.09 (d, *J*=8.0 Hz, 2H), 8.07 (s, 4H), 8.03 (d, *J*=9.3 Hz, 2H), 7.97–7.95 (m, 4H), 7.79 (dd, *J*=17.3, 11.0 Hz, 2H), 5.98 (dd, *J*=17.3, 1.1 Hz, 2H), 5.61 (dd, *J*=11.0, 1.1 Hz, 2H), 1.79–1.76 (m, 4H), 1.49 (s, 12H), 1.15–1.12 (m, 4H), 1.04–1.00 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 147.97, 134.49, 132.33, 131.43, 131.01, 130.82, 128.20, 128.03, 127.72, 127.40, 125.14, 125.00, 123.47, 123.32, 123.29, 123.06, 123.01, 117.09, 45.25, 38.38, 30.29, 29.67, 24.96; LCMS (APCI-positive) *m/z* (rel. int.) 625 (12), 624 (51), 623 ($(MH)^+$, 100); HRMS (EI) calculated for $C_{48}H_{46}$ $(M)^+$ 622.3600, found 622.3603.

Thiacyclophane (2.94)

Na_2S/Al_2O_3 (0.198 g, 0.497 mmol) was added in three equal portions to a stirred room temperature solution of 2,9-bis(6-(bromomethyl)pyren-2-yl)-2,9-dimethyldecane (**2.95**) (0.250 g, 0.331 mmol) in 1:9 (v/v) EtOH/dichloromethane (75 mL) over a 20 min period.

The resulting slurry was stirred vigorously for 16 h and the reaction mixture was suction filtered. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography (25 × 3 cm; 2:5 dichloromethane/hexanes) to yield **2.94** as a light yellow oil (0.184 g, 89%): R_f = 0.62 (2:5 dichloromethane/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 2H), 8.01 (d, *J*=7.9 Hz, 2H), 7.98–7.94 (m, 24), 7.96 (d, *J*=7.7 Hz, 2H), 7.71 (s, 2H) 6.82 (s, 4H), 4.41 (s, 4H), 1.73–1.69 (m, 4H) 1.54 (s, 12H), 1.20–1.17 (m, 4H), 0.91–0.87 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 146.94, 131.33, 131.08, 130.99, 130.41, 128.80, 127.78, 127.63, 127.34, 127.28, 125.42, 123.97, 123.36, 122.95, 122.88, 122.85, 45.36, 38.36, 34.13, 30.30, 30.11, 24.05; LCMS (APCI-positive), *m/z* (rel. int.) 631 (12), 630 (51), 629 (100, $(MH)^+$); HRMS (EI) calculated for $C_{46}H_{44}S$ $(M)^+$ 628.3164, found 628.3162.

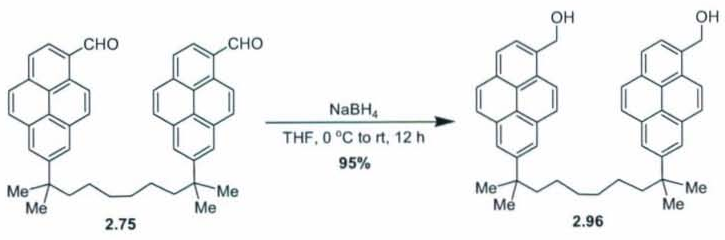
2,9-bis(6-(bromomethyl)pyren-2-yl)-2,9-dimethyldecane (2.95)



Phosphorus tribromide (0.398 g, 1.48 mmol) was added to a solution of 2,9-bis(6-(hydroxymethyl)pyren-2-yl)-2,9-dimethyldecane (**2.96**) (1.24 g, 1.97 mmol) in dichloromethane (25 mL) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 1 h. Water (25 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined

organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield 2,9-bis(6-(bromomethyl)pyren-2-yl)-2,9-dimethyldecane (**2.95**) as a light yellow solid (1.38 g, 92%). This material was used in further experiments without purification: R_f = 0.22 (15% dichloromethane/hexanes); m.p. 193–194 °C ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J*=9.2 Hz, 2H), 8.14–8.12 (m, 6H), 8.03 (d, *J*=7.8 Hz, 2H), 7.99 (d, *J*=8.9 Hz, 2H) 7.94 (d, *J*=8.9 Hz, 2H), 7.92 (d, *J*=7.8 Hz, 2H), 5.21 (s, 4H), 1.75–1.73 (m, 4H), 1.46 (s, 12H), 1.10–1.08 (m, 4H), 0.99–0.94 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 148.55, 133.21, 131.41, 130.97, 130.76, 129.31, 128.88, 128.69, 127.76, 127.52, 125.47, 125.03, 123.91, 123.88, 123.24, 123.07, 45.45, 38.64, 32.74, 30.49, 29.88, 25.17; LCMS (APCI-positive), *m/z* (rel. int.) 679 (12), 678 (41), 677 (100, $(M-^{79}Br)^+$), 676 (42), 675 (92, $(M-^{81}Br)^+$); HRMS (EI) calculated for $C_{46}H_{44}Br_2$ $(M)^+$ 754.1810, found 754.1804.

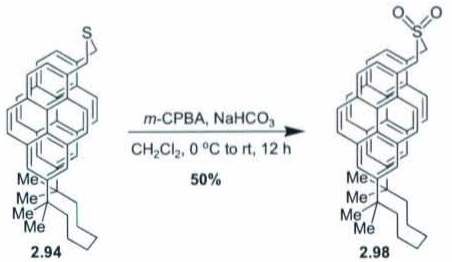
2,9-Bis(6-(hydroxymethyl)pyren-2-yl)-2,9-dimethyldecane (2.96)



Sodium borohydride (0.356 g, 9.57 mmol) was added to a stirred 0 °C solution of 2,9-bis(6-formylpyren-2-yl)-2,9-dimethyldecane (**2.75**) (1.50 g, 2.39 mmol) in THF (30 mL). The resulting slurry was allowed to warm slowly to room temperature over a 12 h period. The solvent was evaporated under reduced pressure and the solid residue was taken up in

dichloromethane (30 mL). This solution was cooled to 0 °C and a 1 M HCl solution was added until the solution was at acidic pH. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (50 mL), washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield 2,9-bis(6-(hydroxymethyl)pyren-2-yl)-2,9-dimethyldecane (**2.96**) as a clear straw-colored oil (1.43 g, 95%). This compound was used in further experiments without purification: R_f = 0.35 (1:9 EtOAc/dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J*=9.2 Hz, 2H), 8.07 (s, 4H), 8.05 (d, *J*=7.7 Hz, 2H), 8.00 (d, *J*=9.2 Hz, 2H) 7.96–7.94 (m, 4H), 7.93 (d, *J*=7.7 Hz, 2H), 5.27 (s, 4H) 1.99 (br s, 2H), 1.76–1.73 (m, 4H), 1.46 (s, 12H), 1.08–1.05 (m, 4H), 0.98–0.94 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 148.22, 133.98, 131.50, 131.42, 130.96, 128.99, 128.53, 128.10, 127.56, 126.07, 125.30, 124.87, 123.57, 123.48, 123.35, 123.18, 64.25, 45.44, 38.61, 30.47, 29.51, 25.31; LCMS (APCI-positive, *m/z* (rel. int.)) 615 (15), 614 (50), 613 (100, $(M\text{-}OH)^+$); HRMS (EI) calculated for $C_{46}H_{46}O_2$ $(M)^+$ 630.3498, found 630.3496.

Sulfone (2.98)



3-Chloroperoxybenzoic acid (0.066 g, 0.381 mmol) and sodium bicarbonate (0.107, 1.27 mmol) were added to a stirred 0 °C solution of thiacyclophane **2.94** (0.080 g, 0.127 mmol) in dichloromethane (6 mL). The reaction was allowed to warm slowly to room temperature and stirred for 12 h. The reaction was poured into water (20 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with water (20 mL), washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give an orange residue, which was directly subjected to chromatography (15 × 2 cm; dichloromethane) to afford **2.98** as a light orange oil (0.042 g, 50%): R_f = 0.28 (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16–8.13 (m, 4H), 8.09 (d, *J*=1.4 Hz, 2H), 8.06 (d, *J*=8.9 Hz, 2H), 8.01 (d, *J*=8.9 Hz, 2H), 7.63 (d, *J*=1.4 Hz, 2H), 6.80 (d, *J*=9.3 Hz, 2H), 6.62 (d, *J*=9.3 Hz, 2H), 5.07 (s, 4H), 1.70–1.67 (m, 4H), 1.46 (s, 12H), 1.16–1.14 (m, 4H), 0.81–0.78 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 147.57, 132.25, 131.22, 130.58, 130.41, 129.05, 128.95, 128.38, 127.28, 125.34, 125.03, 123.97, 123.79, 122.72, 122.42, 121.60, 56.71, 45.51, 38.63, 30.43, 30.18, 24.20; LCMS (APCI-positive), *m/z* (rel. int.) 663 (11), 662 (49), 661 (100, $(MH)^+$); HRMS (EI) calculated for $C_{46}H_{44}SO_2$ $(M)^+$ 660.3062, found 660.3058

2.6 References and Notes:

[1] For failed attempts see: (a) Cory, R. M.; McPhail, C. L. *Adv. Theor. Interesting Mol.* **1998**, *4*, 53-80; (b) Cory, R. M.; McPhail, C. L. *Tetrahedron Lett.* **1996**, *37*, 1987-1990; (c) Cory, R. M.; McPhail, C. L.; Dikmans, A. J.; Vittal, J. J. *Tetrahedron Lett.* **1996**, *37*, 1983-1986; (d) Giresser, U.; Giuffrida, D.; Kohnke, F. H.; Mathias, J. P.; Philip, D.; Stoddart, J. F. *Pure Appl. Chem.* **1993**, *65*, 119-126; (e) Ashton, P. R.; Brown, G. R.; Isaacs, N. S.; Giuffrida, D.; Kohnke, F. H.; Mathias, J. P.; Slawin, A. M. Z.; Smith, D. R.; Stoddart, J. F.; Williams, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 6330-6353; (f) F. H. Kohnke, F. H.; Stoddart, J. F. *Pure Appl. Chem.* **1989**, *61*, 1581-1586; (g) Stuparu, M.; Lentz, D.; Rüegger, H.; Schlüter, A. D. *Chem. Eur. J.* **2007**, *14*, 1628-1637.

[2] For a definition of a molecular or aromatic belt, see: Yao, T.; Yu, H.; Vermeij, R. J.; Bodwell, G. J. *Pure Appl. Chem.* **2008**, *80*, 543-558.

[3] Vogtle, F. *Top. Curr. Chem.* **1983**, *115*, 157-159.

[4] Umemoto, T.; Kawashima, T.; Sakata, Y.; Misumi, S. *Tetrahedron Lett.* **1975**, *16*, 1005-1006.

[5] (a) Sato, T.; Wakabayashi, M.; Okamura, Y. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2363-2365; (b) Allinger, N. L.; Goldon, B. J.; Hu, S. E.; Ford, R. A. *J. Org. Chem.* **1967**, *32*, 2272-2278; (c) Sato, T.; Nishiyama, K. *J. Org. Chem.* **1972**, *37*, 3254-3260; (d) Yamato, T.; Ide, S.; Tokuhisa, K.; Tashiro, M. *J. Org. Chem.* **1992**, *57*, 271-275; (e) Yamato, T.; Matsumoto, J.; Tokuhisa, K.; Shigekuni, M.; Suehiro, K.; Tashiro, M. *J. Org. Chem.* **1992**, *57*, 395-396.

[6] Formylation of 2,7-di-*tert*-butylpyrene: Hu, J. Y.; Paudel, A.; Yamato, T. *J. Chem. Res.* **2009**, 109-113.

[7] Miura, Y.; Yamano, E.; Tanaka, A.; Yamaguchi, J. *J. Org. Chem.* **1994**, *59*, 3294-3300. Isolation of pure 2-*tert*-butyl pyrene via this procedure requires careful recrystallizations. In the paper from Miura and co-workers, it would seem that the solid isolated from the first recrystallization is simply subjected to a hexanes recrystallization. In fact the methanol mother liquor has to be concentrated and then recrystallized again. The solid isolated in the first recrystallization is 2,7-di-*tert*-butylpyrene. Müllen and co-workers report that chromatography from low-boiling petroleum ether affords pure 2-*tert*-butylpyrene: see reference 8.

[8] To the best of my knowledge this is the only account of a direct 1,3-difuntionalization of 2-*tert*-butylpyrene: Figueira-Duarte, T. M.; Simon, S. C.; Wagner, M.; Druzhinin, S. I.; Zachariasse, K. A.; Müllen, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 10175-10178. See also Chapter 3 compound **3.72**.

[9] (a) Yamato, T.; Miyazawa, A.; Tashiro, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3127-3137; (b) Yamato, T.; Fujimoto, M.; Nagano, Y.; Miyazawa, Y.; Tashiro, M. *Org. Prep. Proced. Int.* **1997**, *29*, 321-330.

[10] LCMS analysis of the crude reaction indicated that there were primarily two byproducts of this reaction: dialkylated pyrene and a compound that incorporated three pyrenes and two tethers.

[11] Rieche, A.; Gross, H.; Höft, E. *Chem . Ber.* **1960**, *93*, 88-94.

[12] The procedure used by Yamato and co-workers was quite involved and unnecessary for this system.

[13] V-65 (2,2′-azobis(2,4-dimethylvaleronitrile): CAS Registry Number: 4419-11-8 is only available for purchase through four Chinese chemical companies.

[14] V-65 has been reported to decompose upon shipment. While the material received looked to be in good order, the quality of the sample can only be tested based on its reactivity. This radical initiator has shown to decompose much more rapidly than AIBN ($t_{1/2}$ V-65 = 12 min at 80 °C, $t_{1/2}$ AIBN = 90 min at 85 °C): Fukuyama, T.; Rahman, M. T.; Kamata, N.; Ryu, I. *Beilstein J. Org. Chem.* **2009**, *5*, No. 34.

[15] Zhang, B. Z.; Manning, G. P.; Dobrowlski, M. A.; Cyranski, M. K.; Bodwell, G. J. *Org. Lett.* **2008**, *10*, 273-276.

[16] After chromatography, LCMS and ^{1}H NMR analysis indicate that **2.51** is the major product of this reaction. However, there is clearly more than one compound present in the ^{1}H NMR and quantification of the purity of **2.51** was difficult. The identification and removal of this impurity was not possible.

[17] Rudimentary characterization of this intermediate include ^{1}H NMR and LCMS: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J*=9.1 Hz, 4H), 7.92 (s, 2H), 7.67 (s, 4H), 7.60 (d, *J*=9.1 Hz, 4H), 4.79 (d, *J*=15.5 Hz, 4H), 4.47 (d, *J*=15.5 Hz, 4H), 1.60 (s, 12H), (other aliphatic methylene protons cold not be definitively assigned due to impurities in the sample); LCMS (APCI-positive), *m/z* (rel. int.) 661 (17), 660 (51), 659 ($(MH)^+$, 100).

[18] Inoue, J.; Fukui, K.; Kubo, T.; Nakazawa, S.; Sato, K.; Shiomi, D.; Morita, Y.; Yamamoto, K.; Takui, T.; Nakasuji, K. *J. Am. Chem. Soc.* **2001**, *123*, 12702-12703.

[19] The implied compound, 1,3-dibromo-7-*tert*-butylpyrene, was prepared during the course of this work (Chapter 3) and also by Müllen and co-workers using temperature controlled conditions and a stiochiometric amount of bromine: See reference 8 and Chapter 3 (compound **3.72**) for experimental details.

[20] Due to the insolubility of the isolated material from this reaction and based on the isolation of the corresponding 1,3-subsituted dialdehyde, it is assumed that **2.57** is the sole product and not a hexabromide intermediate.

[21] For references on bromomethylation of substituted benzenes see: (a) Nazarov, I. N.; Semenovosky, A. V. *Russ. Chem. Bull.* **1957**, *6,* 25-228; (b) Mitchell, R. H.; Iyer, V. S. *Synlett* **1989**, 55; (c) van der Made, A. W.; van der Made, R. H. *J. Org. Chem.* **1993**, *58*, 1262-1263.

[22] For references on bromomethylation of substituted naphthalenes see: (a) Tran, H. A.; Miller, D. O.; Georghiou, P. E. *J. Org. Chem.* **2005**, *70*, 1115-1121; (b) Tran, H. A.; Georghiou, P. E. *New J. Chem.* **2007**, *31*, 921-926.

[23] For bromomethylation procedure with MOMBr see: Chiron, J.; Galy, J. P. *Synlett* **2003**, 2349-2351. For chloromethylation procedure see: Wei, C.; Mo, K. F.; Chan, T. L. *J. Org. Chem.* **2003**, *68*, 2948-2951.

[24] (a) Okamoto, H.; Arai, T.; Sakuragi, H.; Tokumaru, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2881-2890; (b) Alashikhin, S.; Finney, N. S. *J. Am. Chem. Soc.* **2008**, *130*, 12846-12847.

[25] Barfield, M.; Collins, M. J.; Gready, J. E.; Sternhell, S.; Tansey, C. W. *J. Am. Chem. Soc.* **1989**, *111*, 4285-4290.

[26] The well-known iodoform reaction (or test) has been used in the past for the identification of methyl ketones. For a review of this and other related reactions see: Fuson, R. C.; Bull, B. A. *Chem. Rev.* **1934**, *34*, 275-309.

[27] The implied electrophiles are chloroacetyl chloride and oxallyl chloride.

[28] Ichihara, J. *Chem. Commun.* **1997**, 1921-1922.

[29] Mitchell, R. H. *Heterocycles* **1978**, *11*, 563-586.

[30] It was discovered at this stage that **2.65** could also be treated with pyrene under the same reaction conditions as **2.66** to give **2.67** in comparable yield.

[31] Using stiochiometric amounts of pyrene or 2–3.5 molar equivalents always gave lower isolated yield of **2.67**. As well, using a larger excess of pyrene (*i.e.* 8–10 molar equivalents) never resulted in increasing the yield of this reaction and only served to complicate purification.

[32] Na_2S/Al_2O_3 reagent reference: Bodwell, G. J.; Houghton, T. J.; Koury, H. E., Yarlagadda, B. *Synlett* **1995**, 751-752. Generally the yields for these reactions have been moderate (50-70%). In instances where there is restricted rotation and possible π-stacking interactions the yields tend to be much higher. See reference 15

[33] In all instances, treatment of the thiacyclophane intermediate with Borch reagent resulted in the more polar (baseline) spot by TLC analysis and the isolation of a fluffy pink solid (indicative of the tetrafluoroborate salt).

[34] Grubbs First generation catalyst: Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; *J. Am. Chem. Soc.* **1992**, *114*, 3974-3975. Grubbs second generation catalyst: Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.

[35] (a) Lai, Y.-H.; Yap, A. H.-T.; *J. Chem. Soc., Perkin Trans 2* **1993**, 703-708; (b) Lai, Y.-H.; Zhou, Z.-L. *J. Org. Chem.* **1997**, *62*, 925-931. Also, see reference 29.

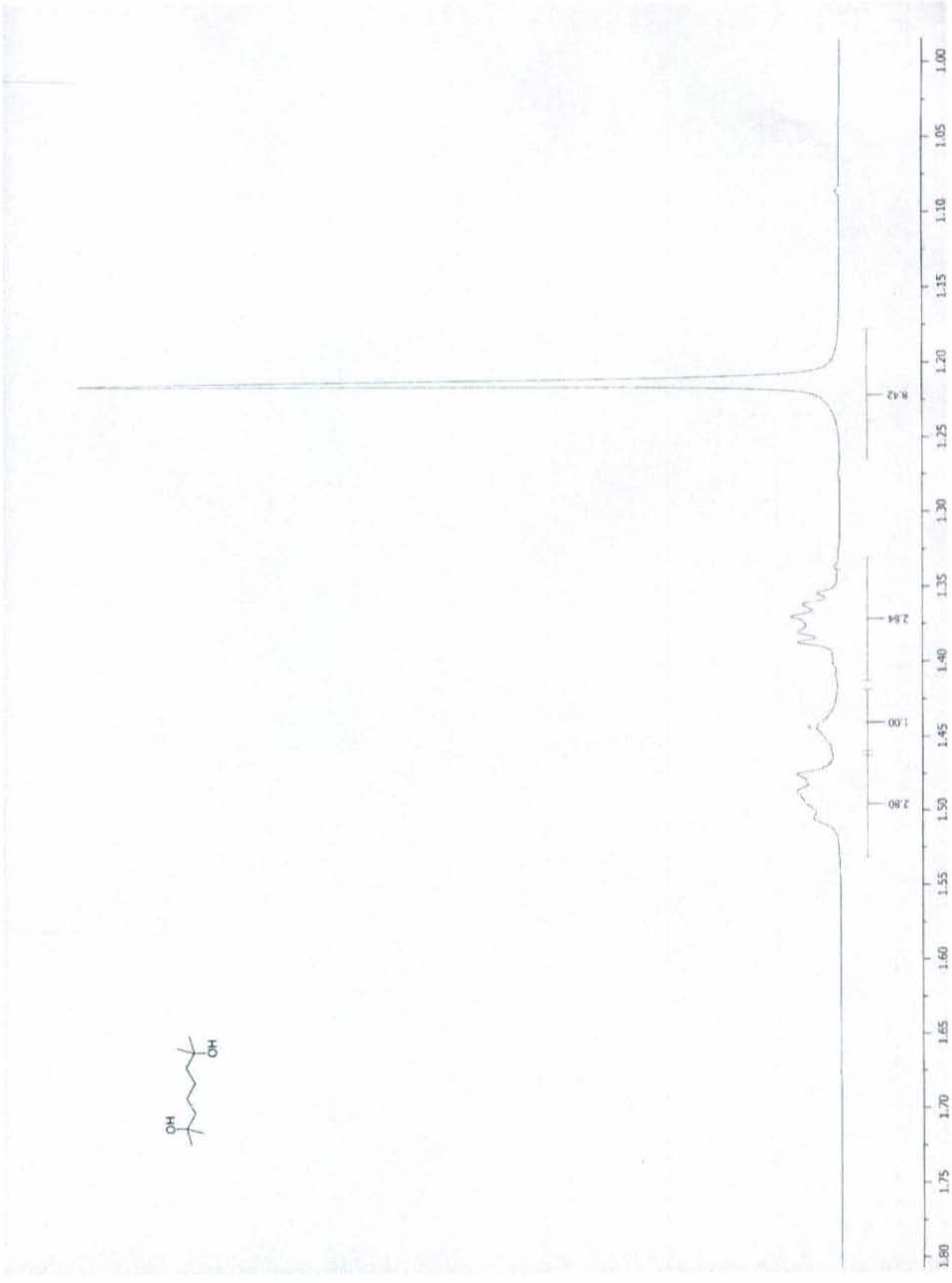
[36] For a recent example of the Ramberg-Bäcklund reaction in such a macrocyclic ring-contraction see: Nicoloau, K. C.; Saralah, D.; Wu, T. R.; Zhan, W. *Angew. Chem. Int. Ed.* **2009**, *48*, 6870-6874.

[37] Snyder, S. A.; Zografos, A. L.; Lin, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 8186-8191.

[38] Ziegler, K.; Späth, A.; Schaff, E. Schumann, W.; Winkleman, E. *Justus Liebigs Ann. Chem.* **1942**, *551*, 80-119.

Appendix 1

Selected ^{1}H and ^{13}C NMR Spectra for Chapter 2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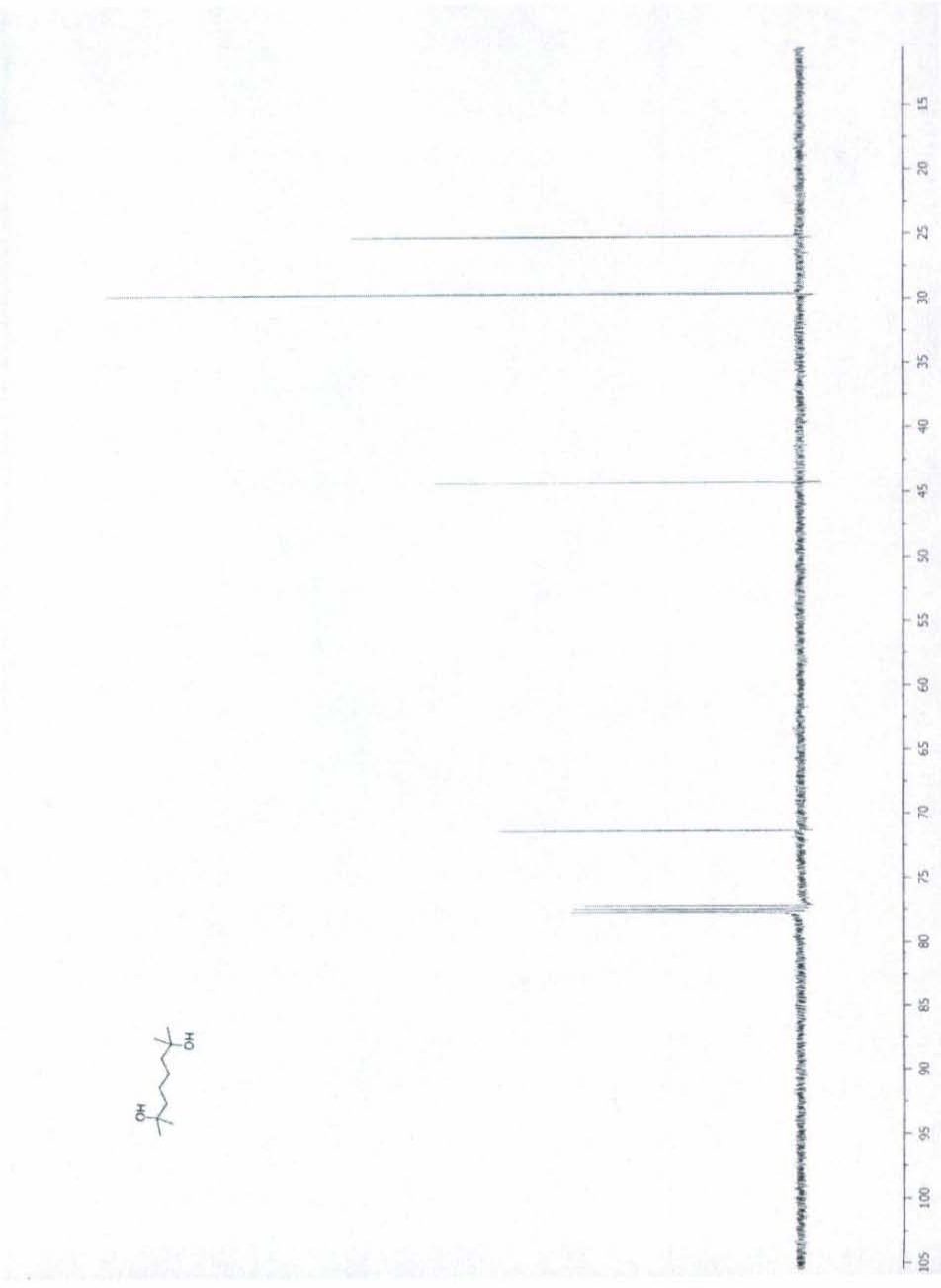
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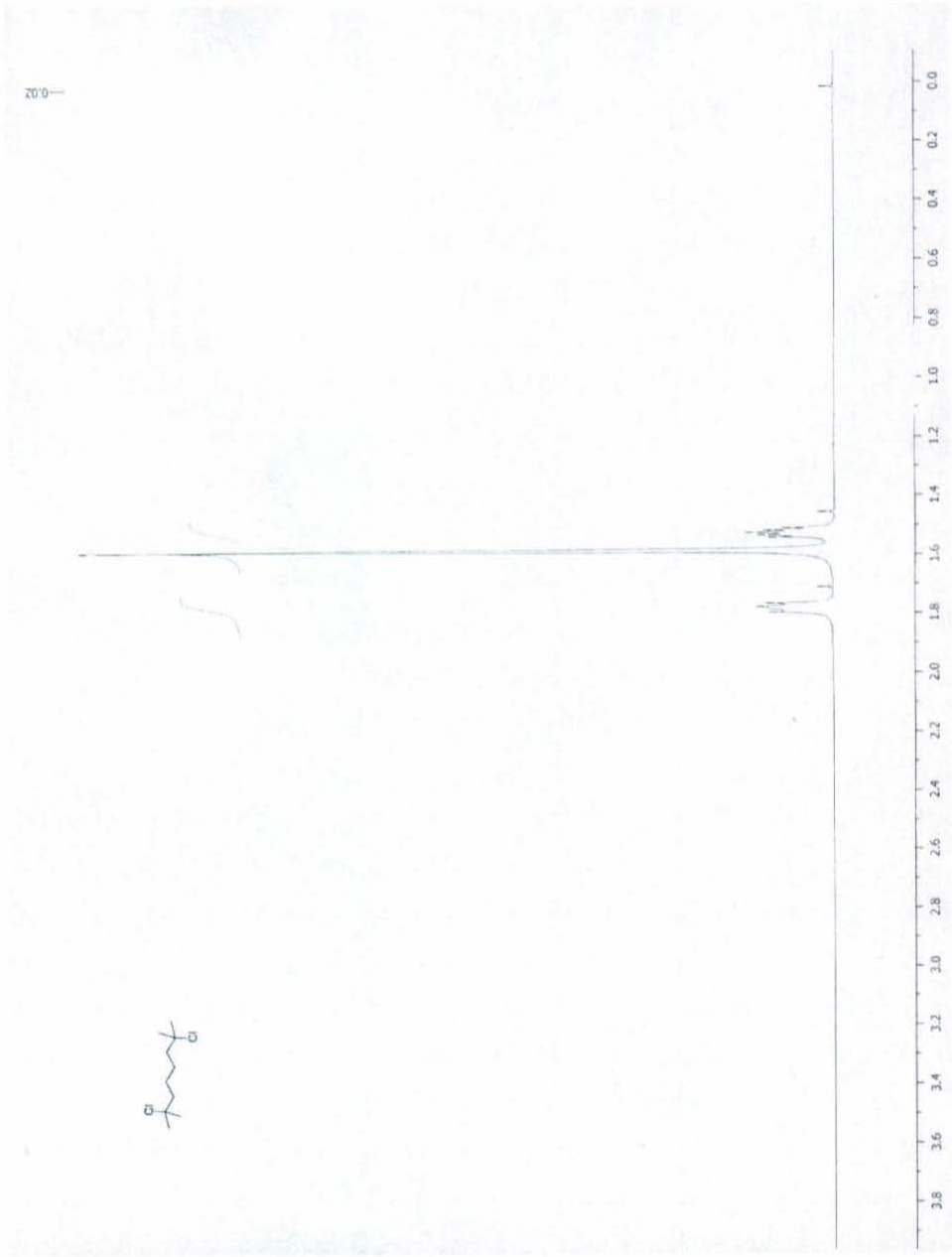
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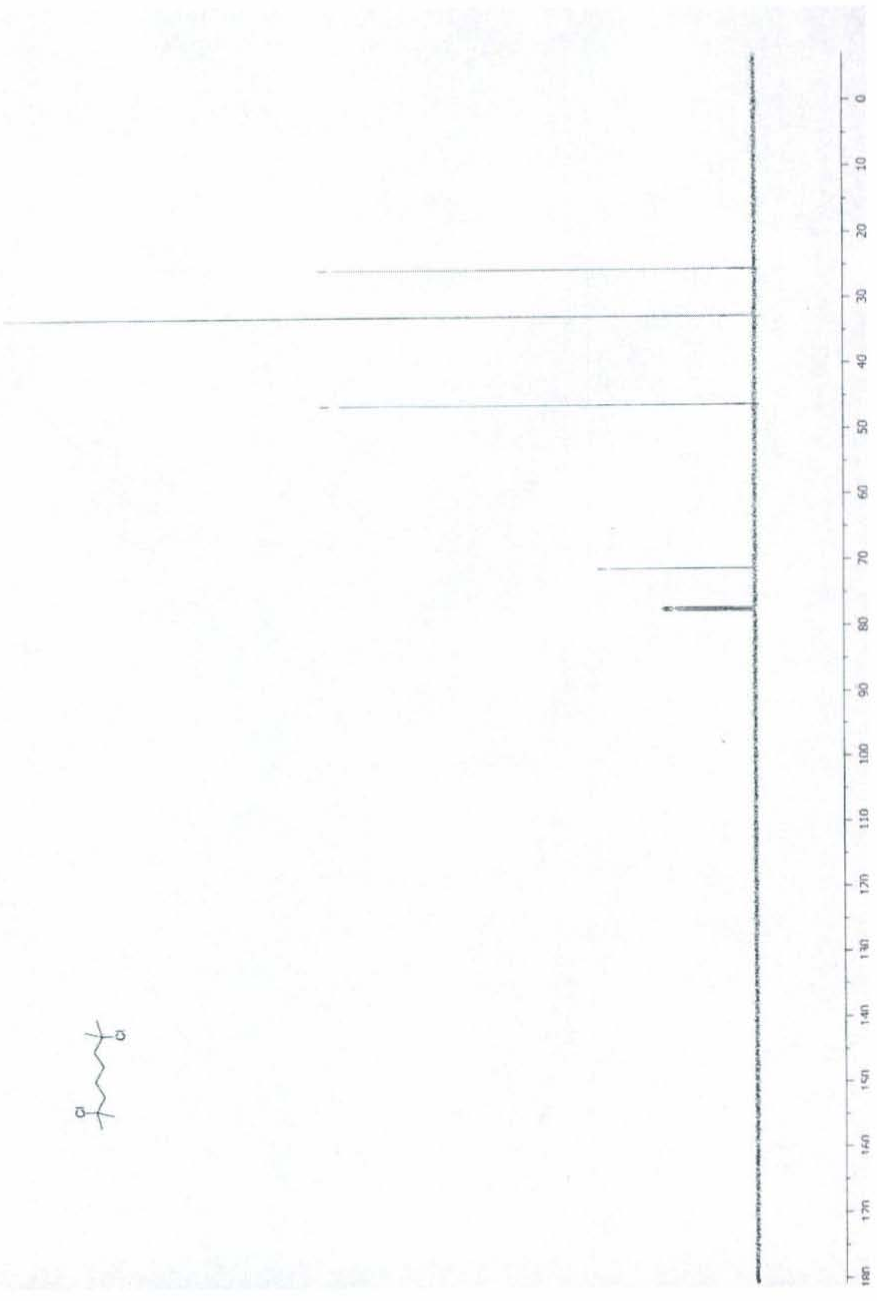
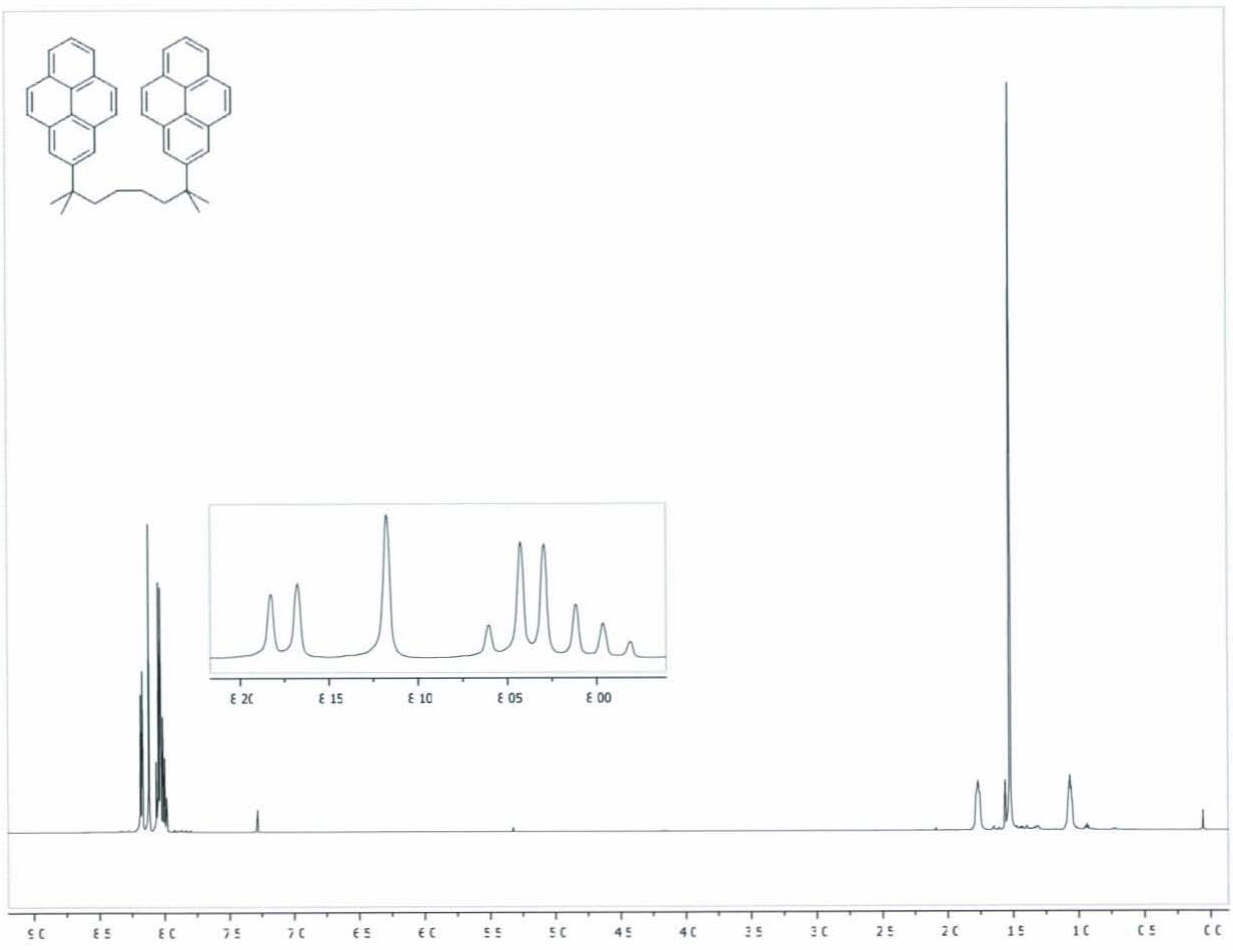
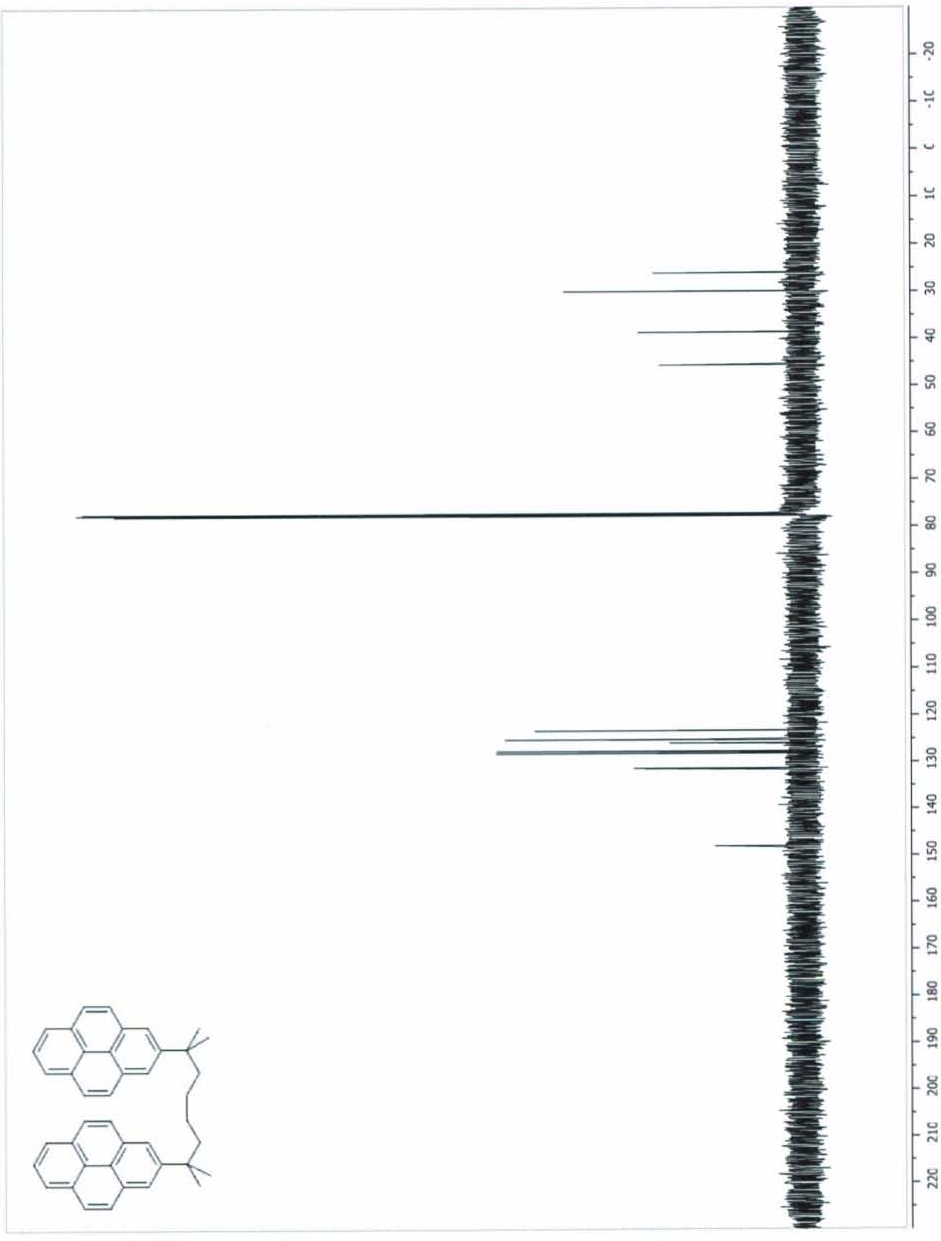
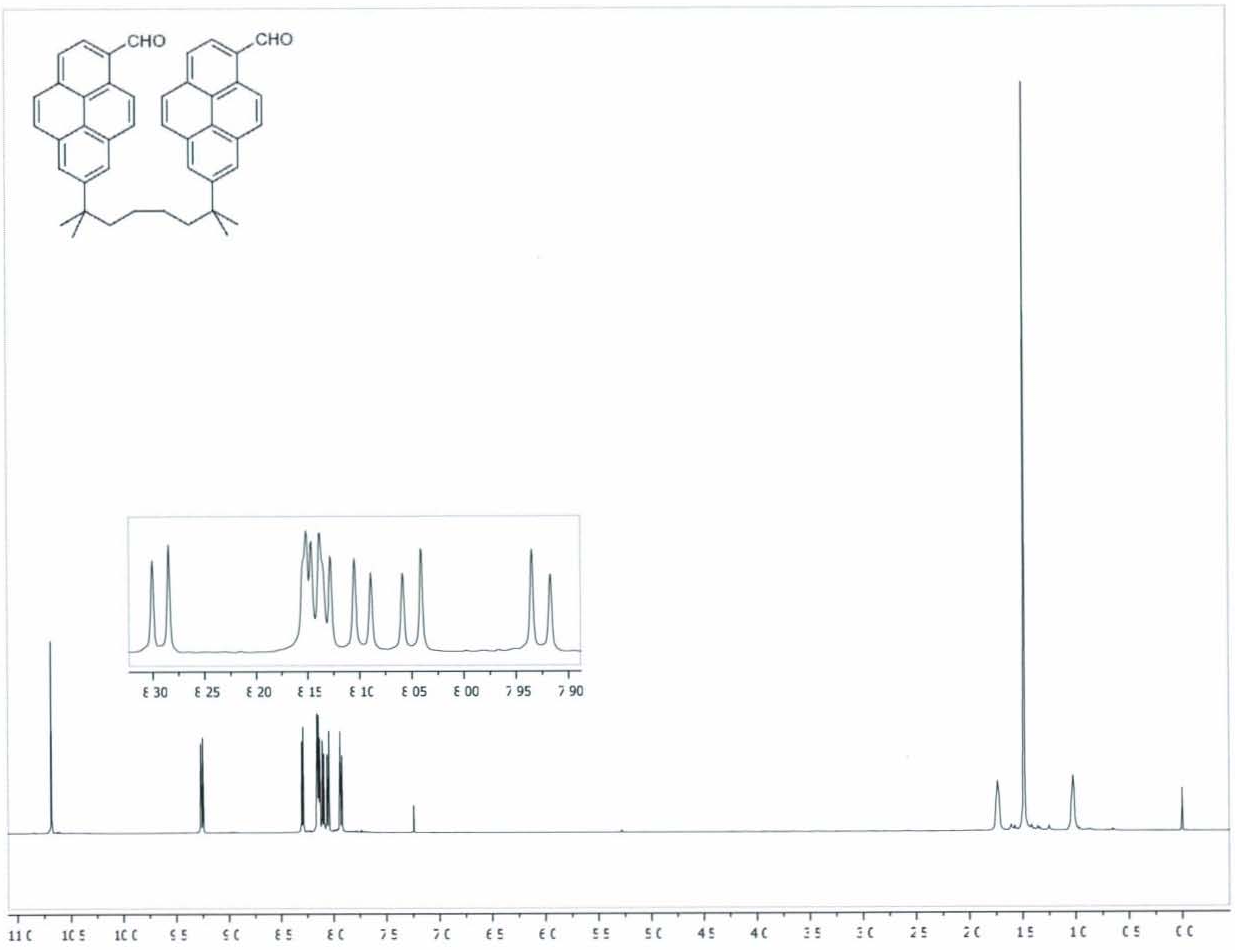
Cl





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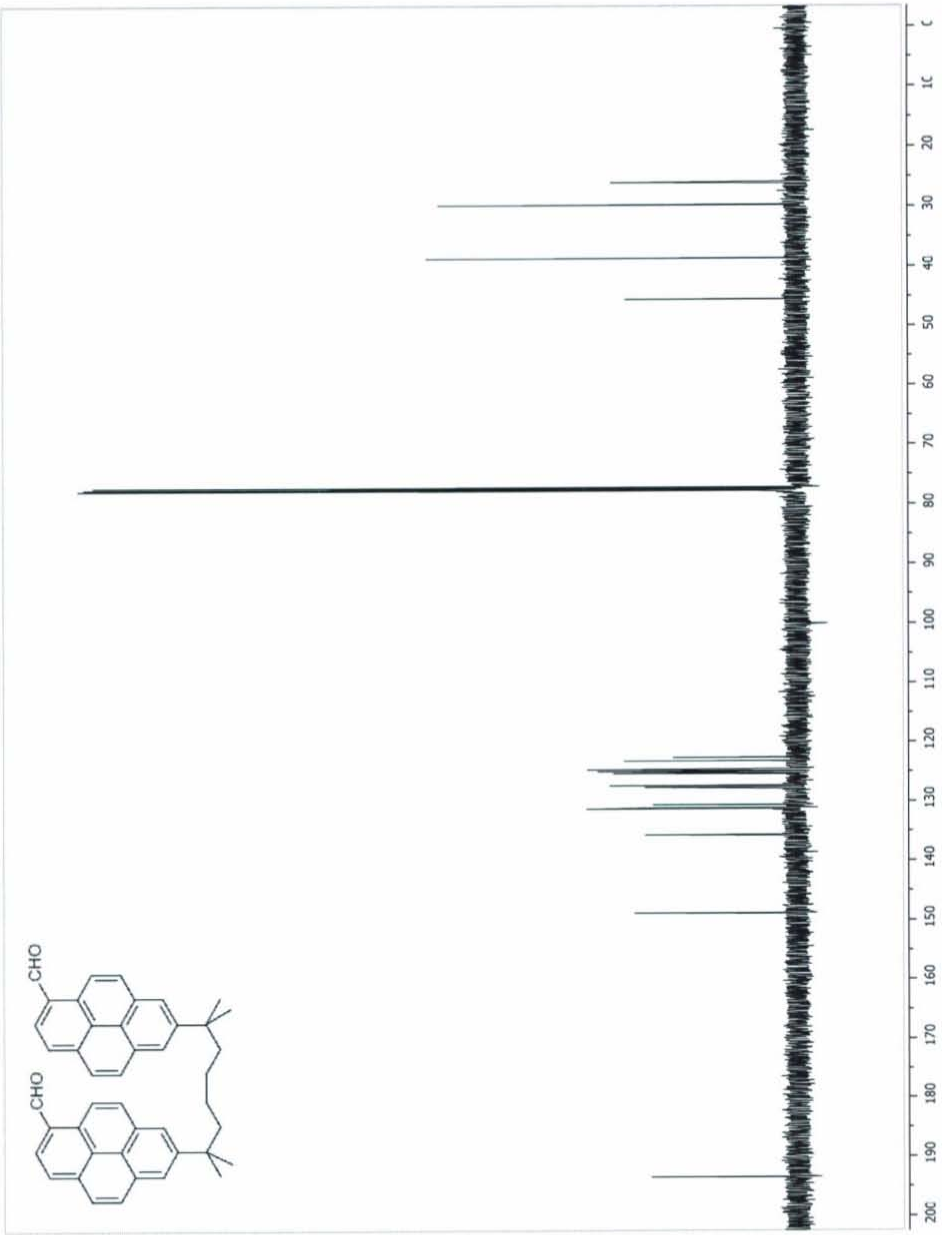
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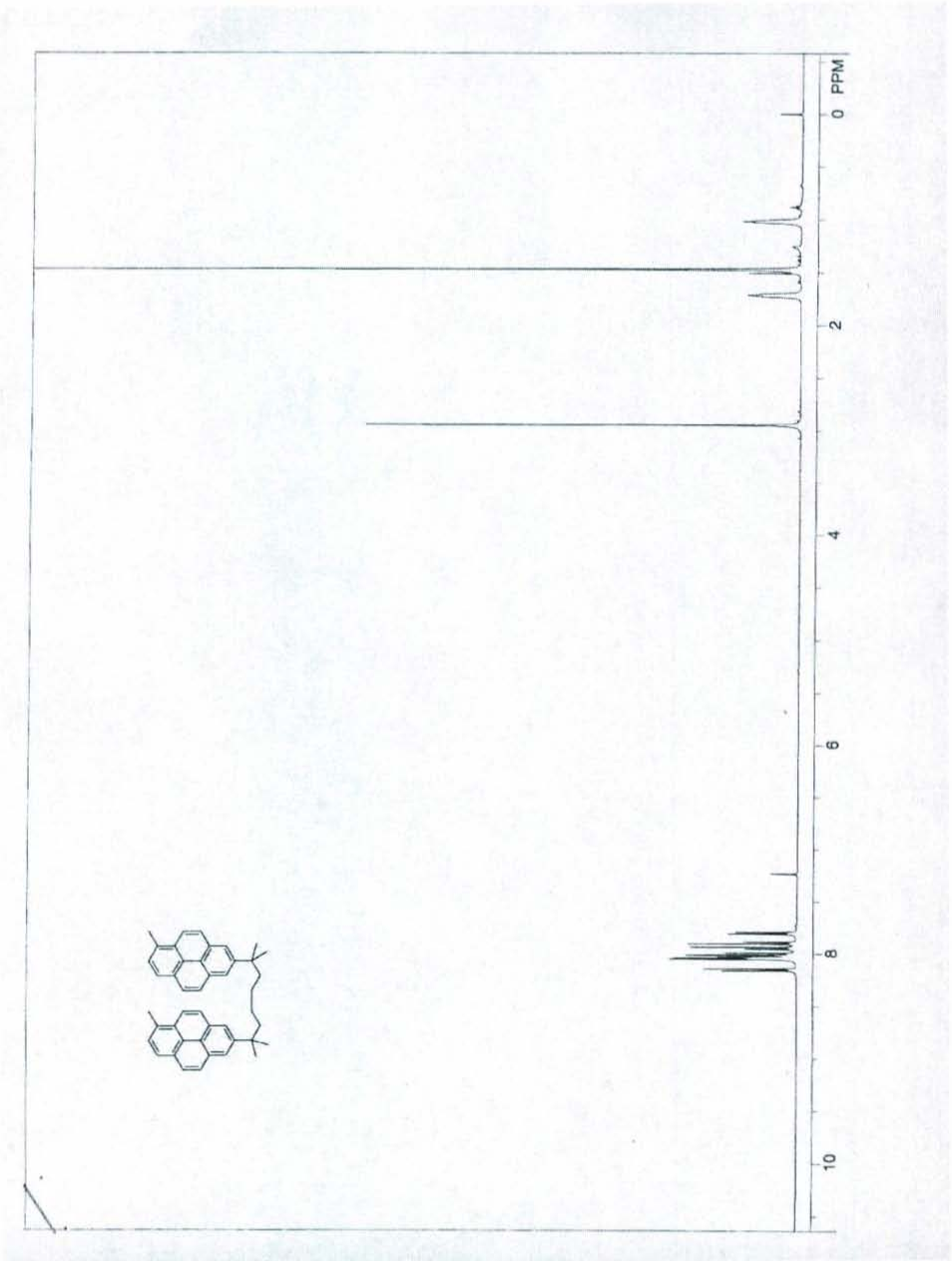
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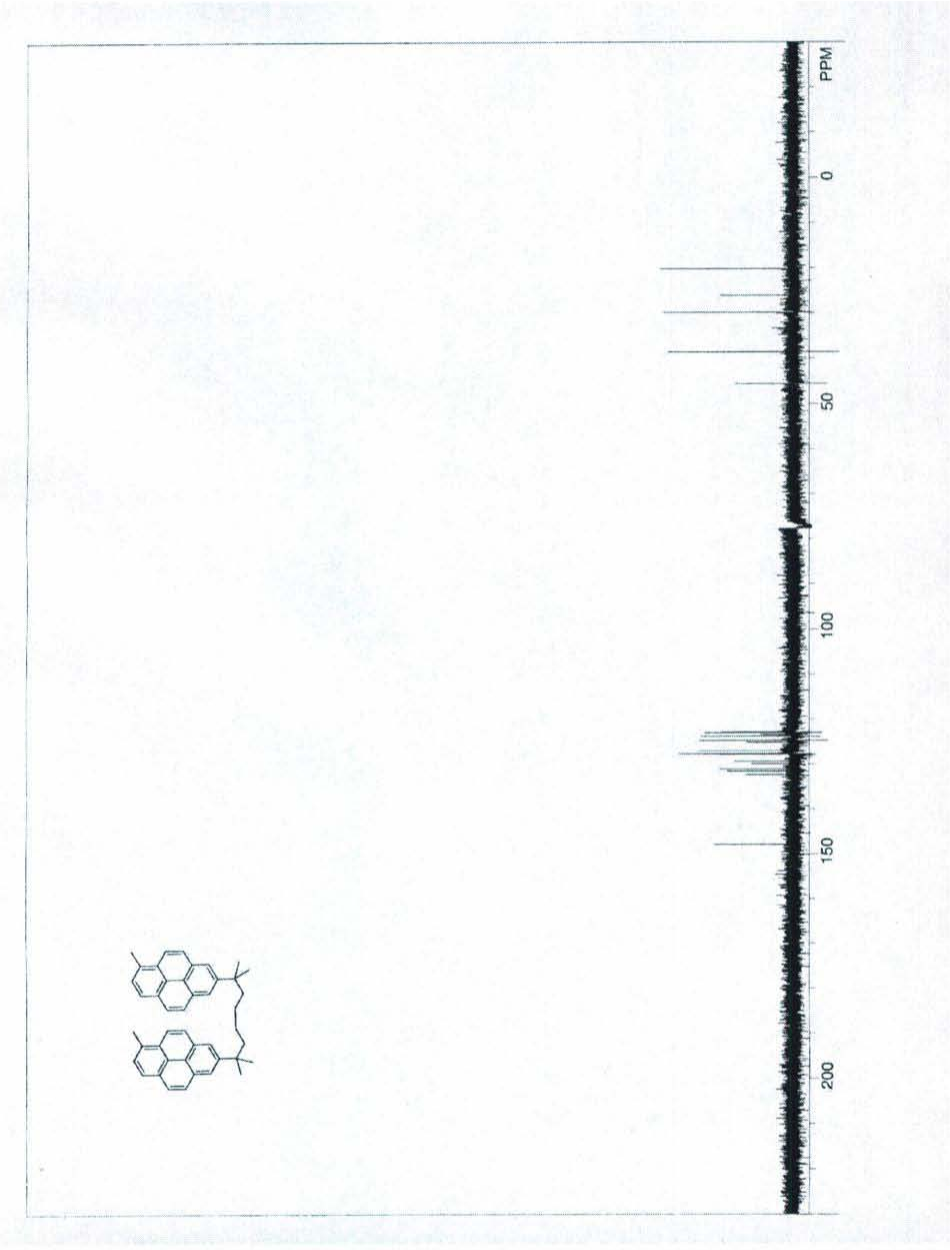
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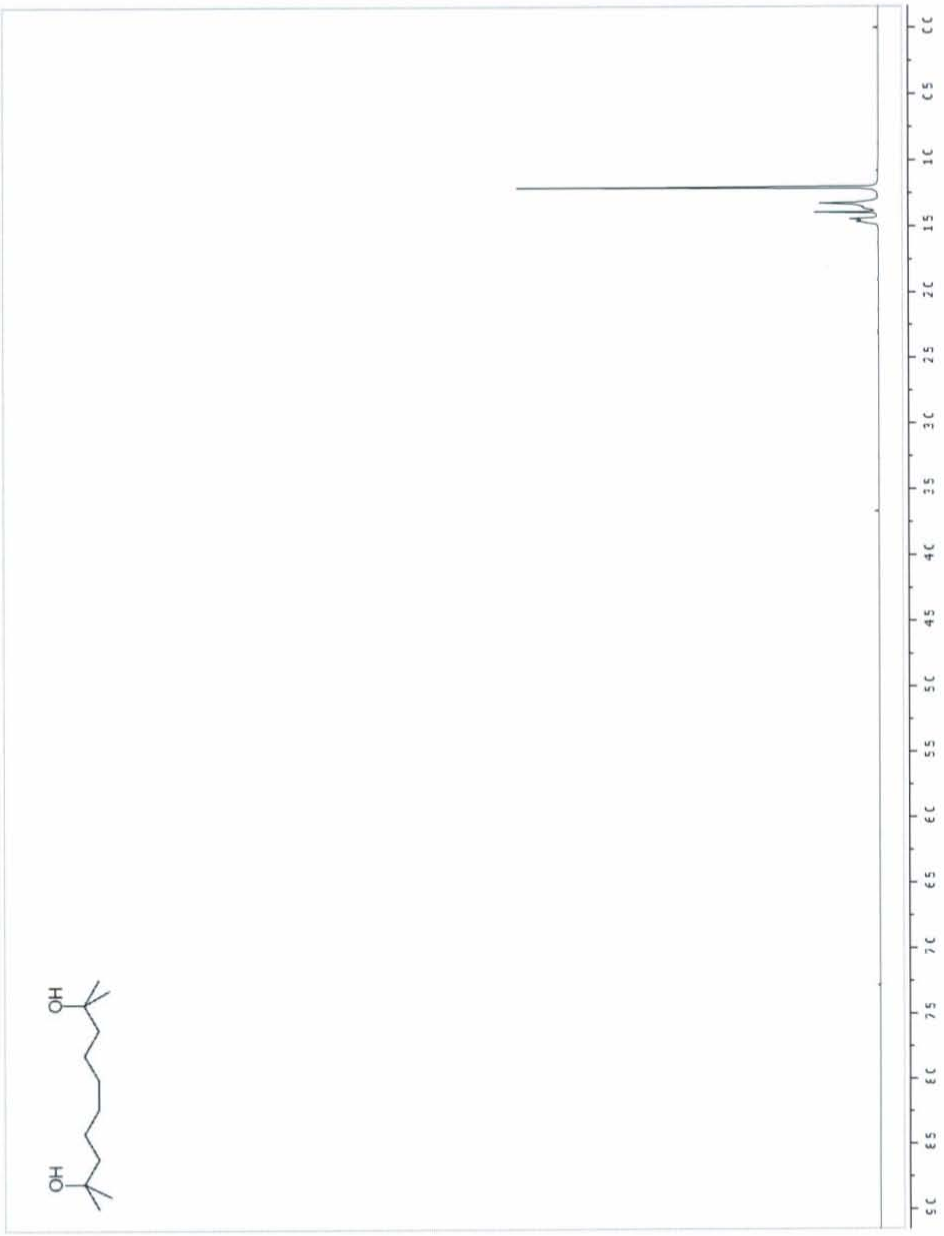
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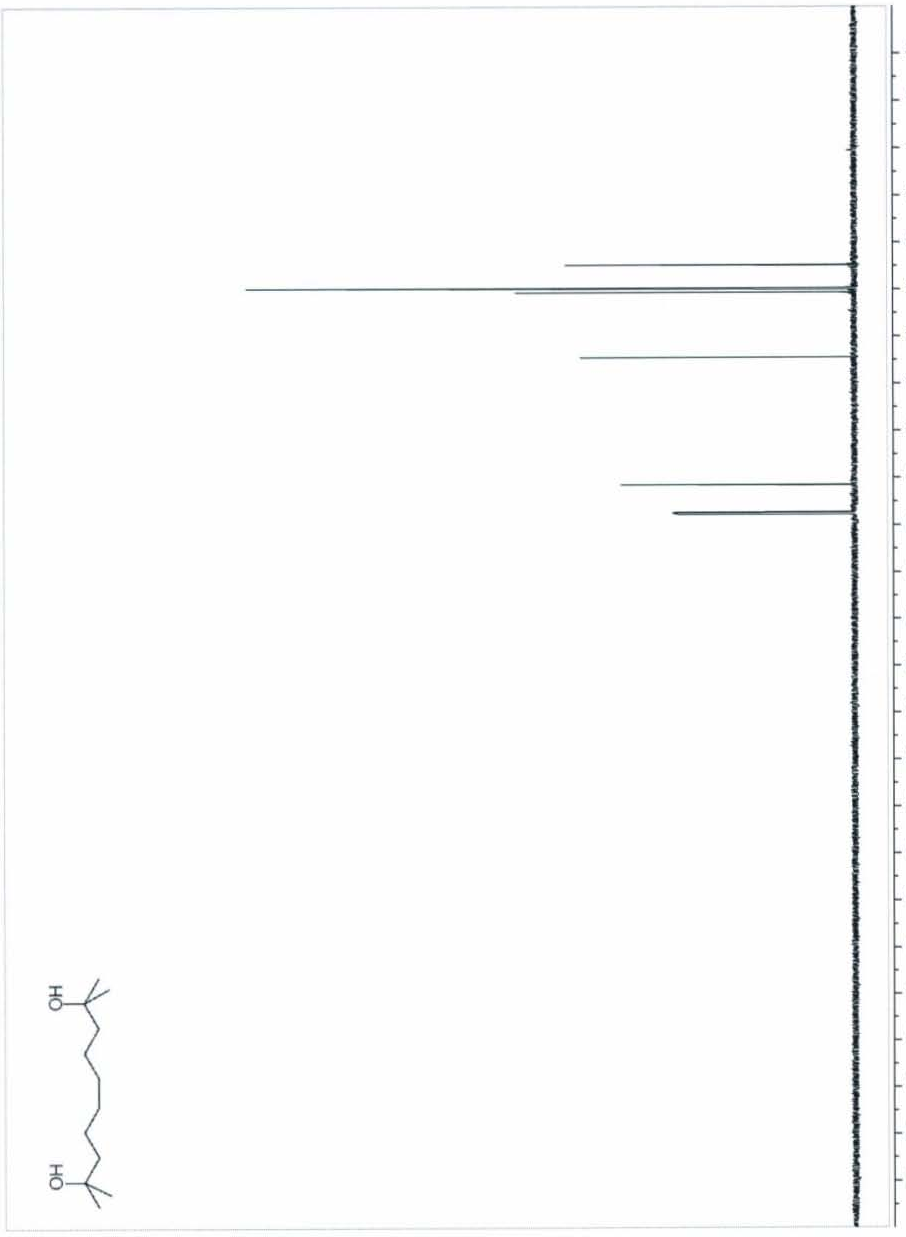
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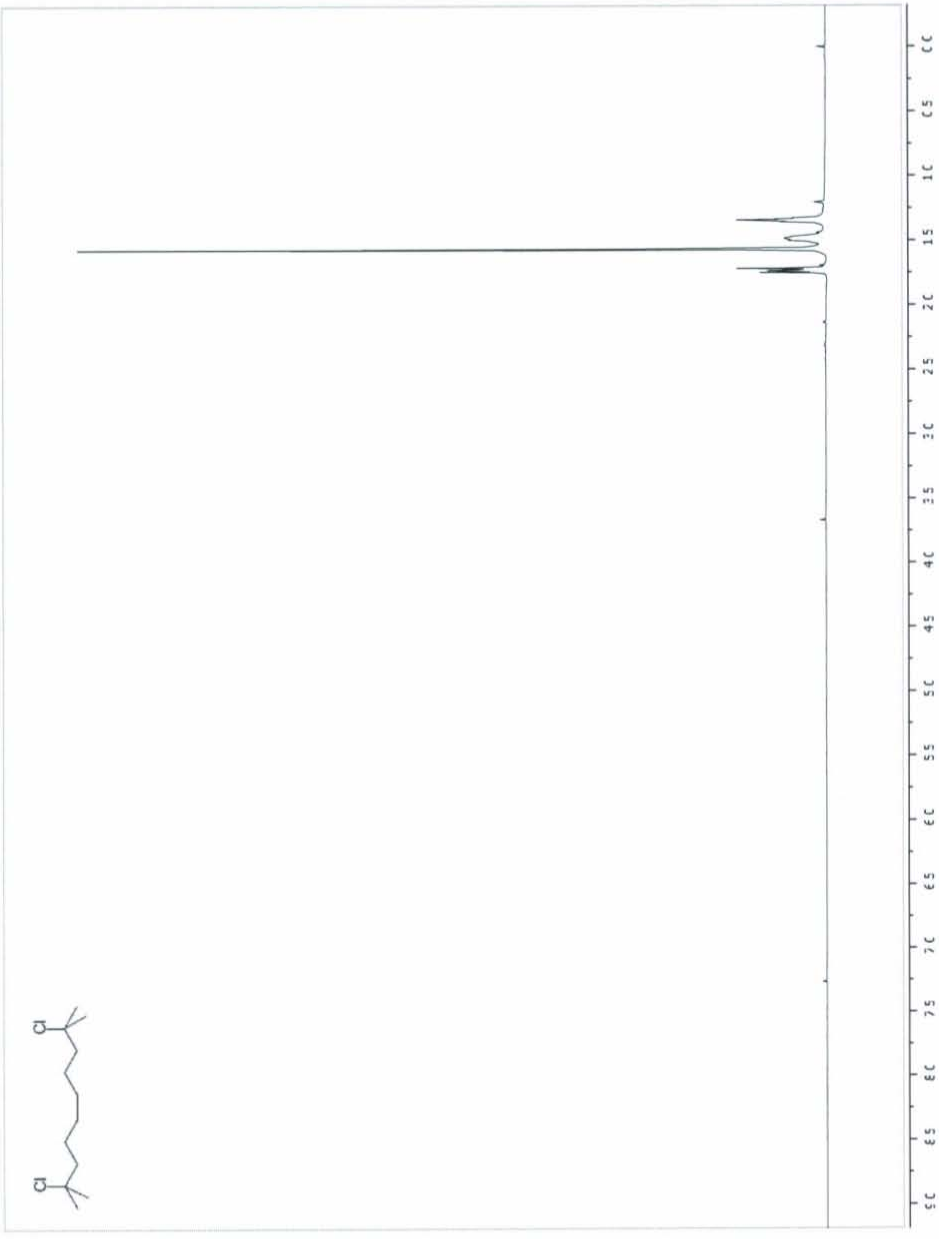
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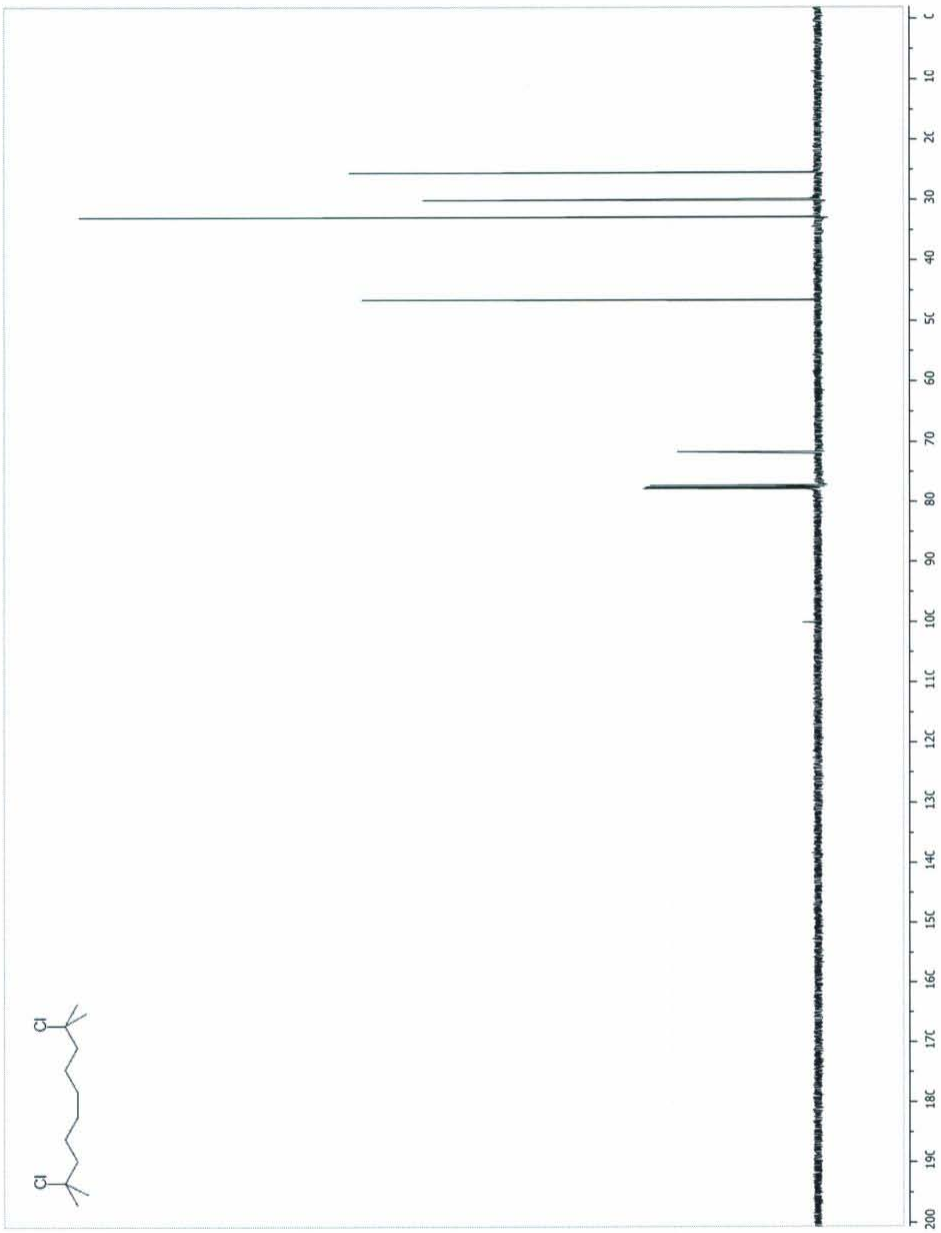
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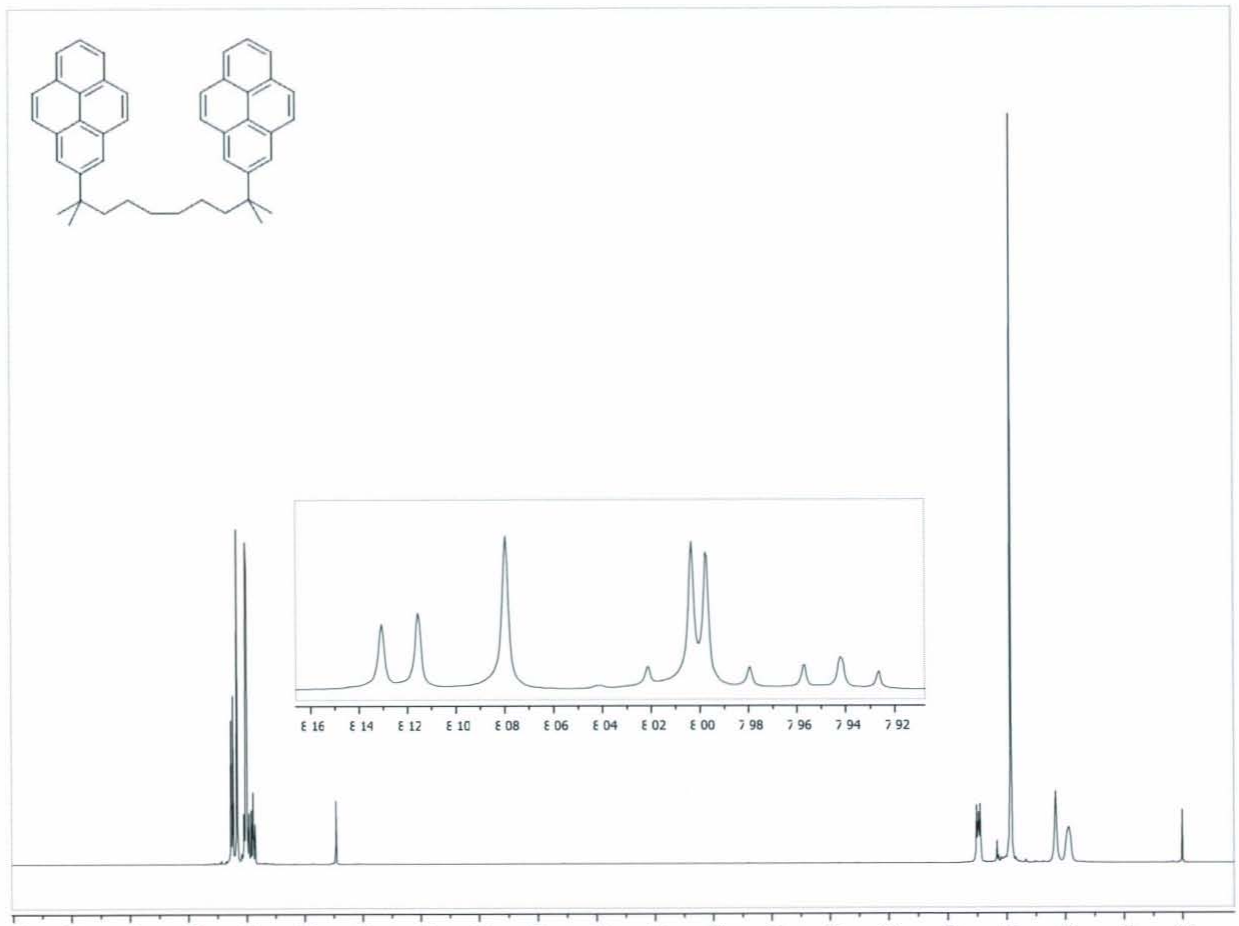
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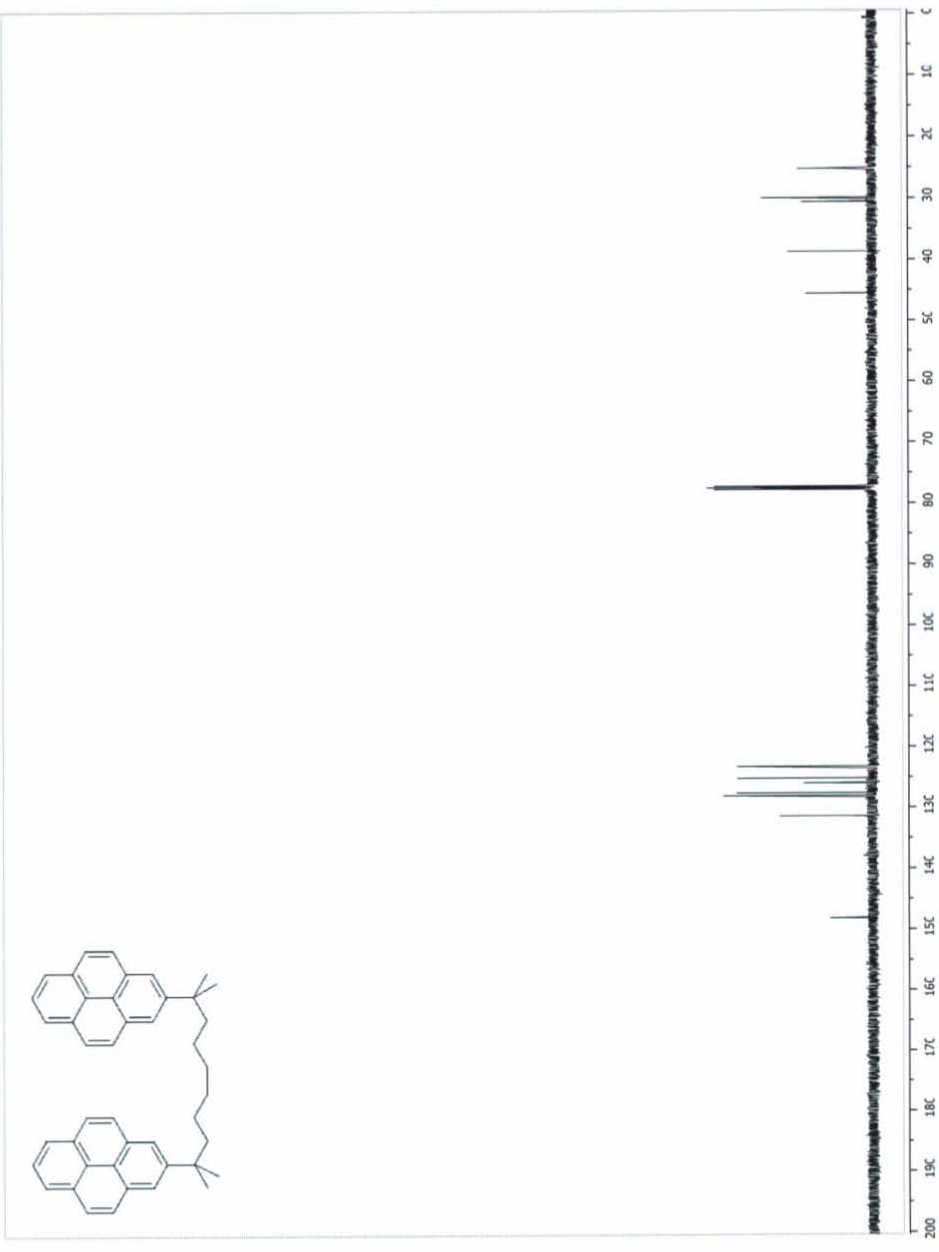

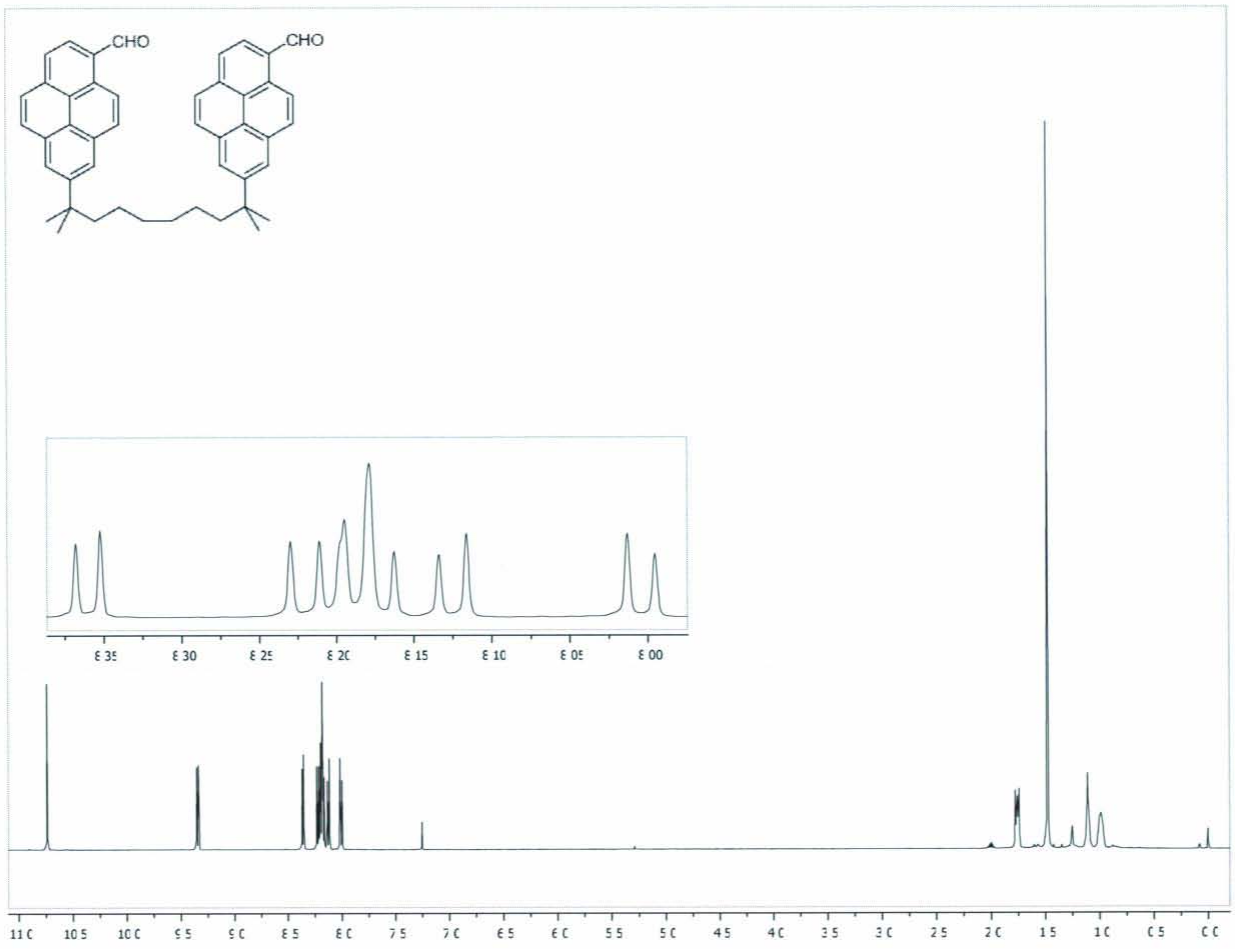
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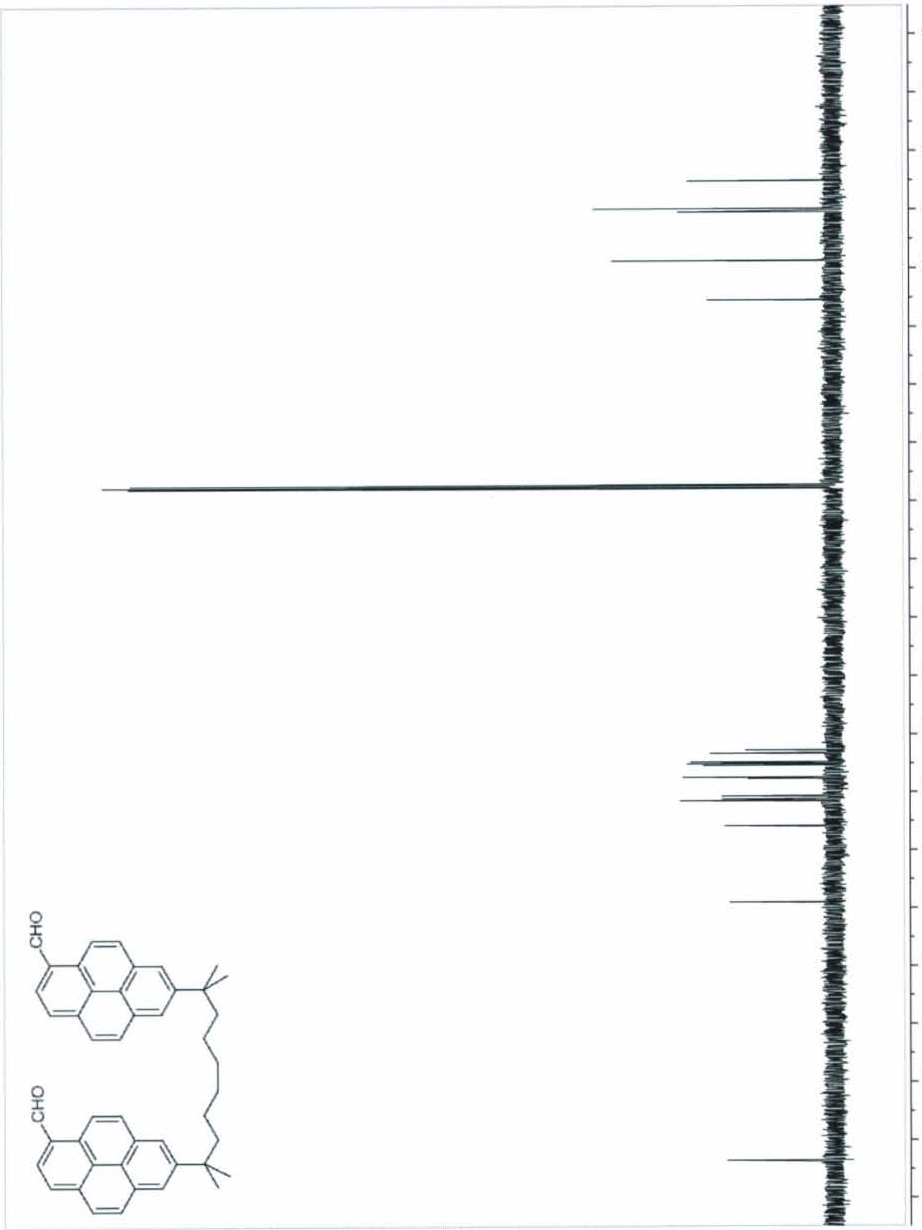
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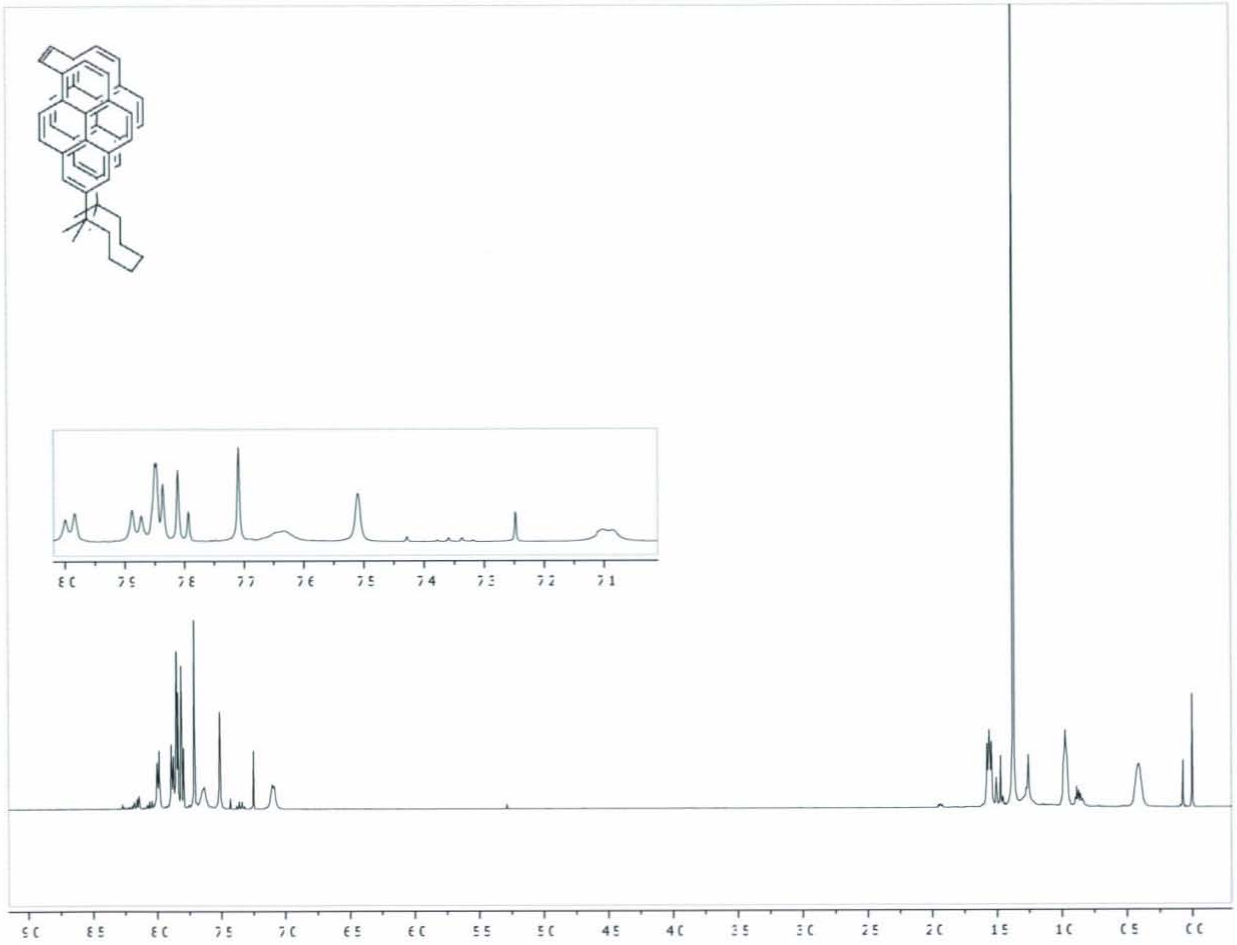

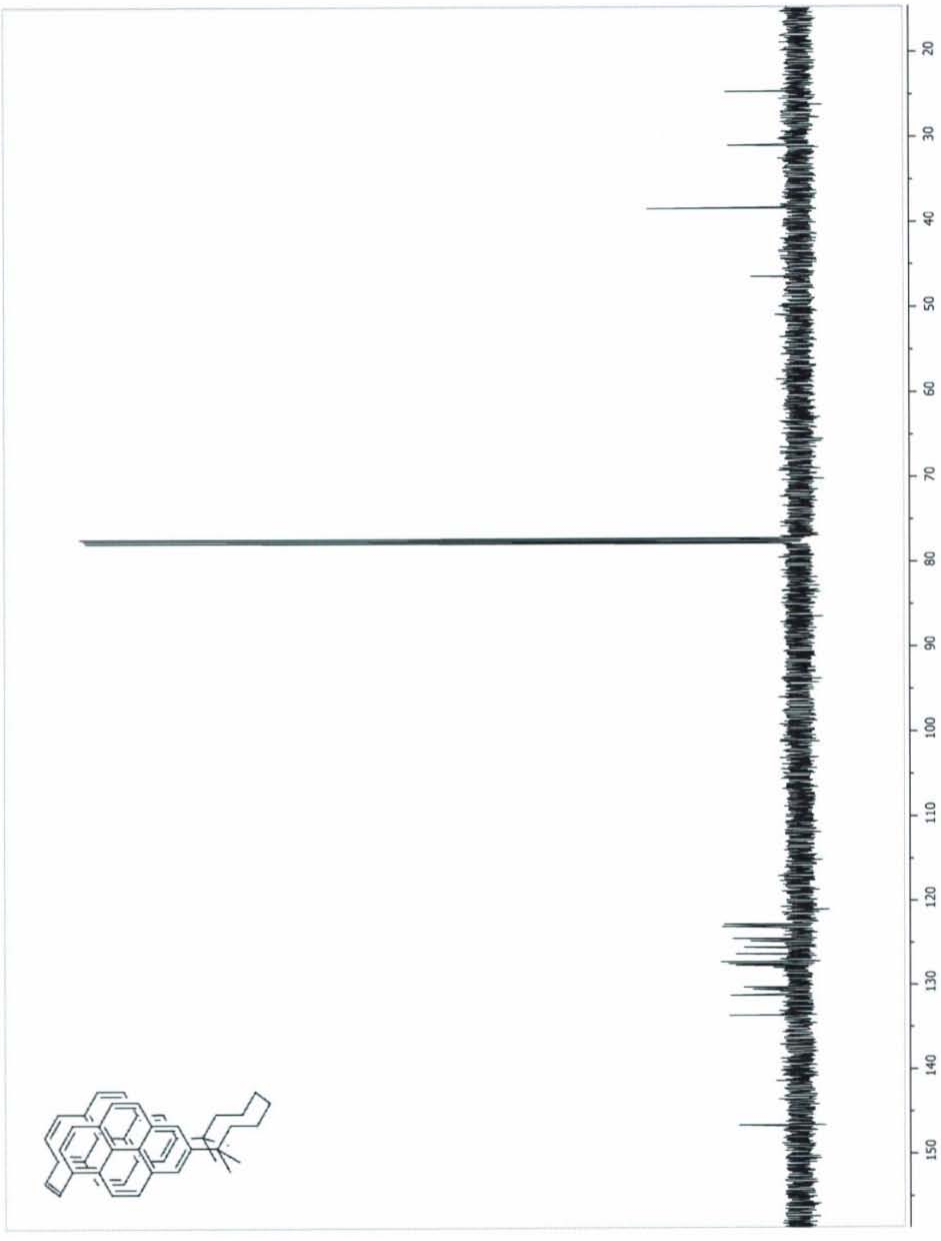
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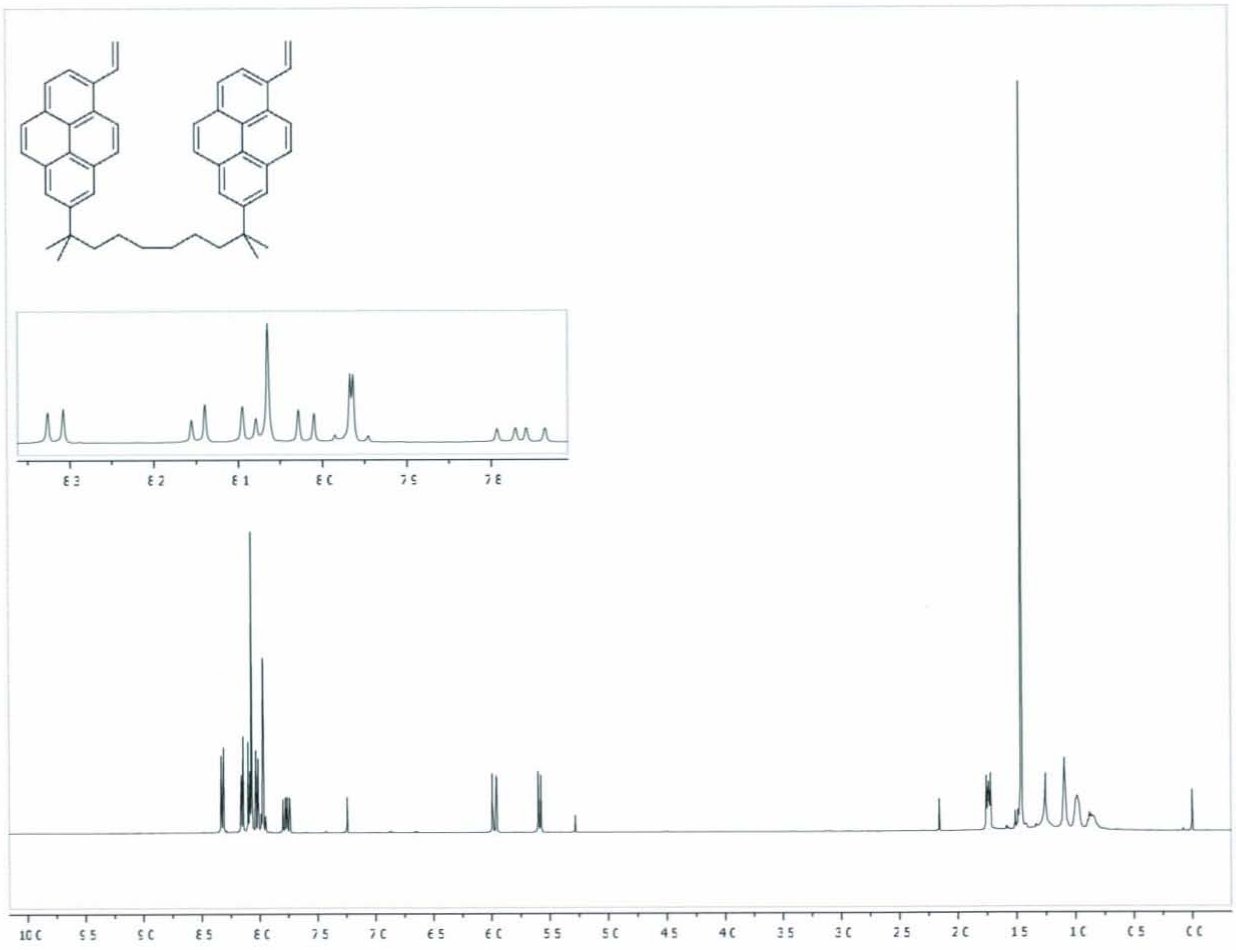

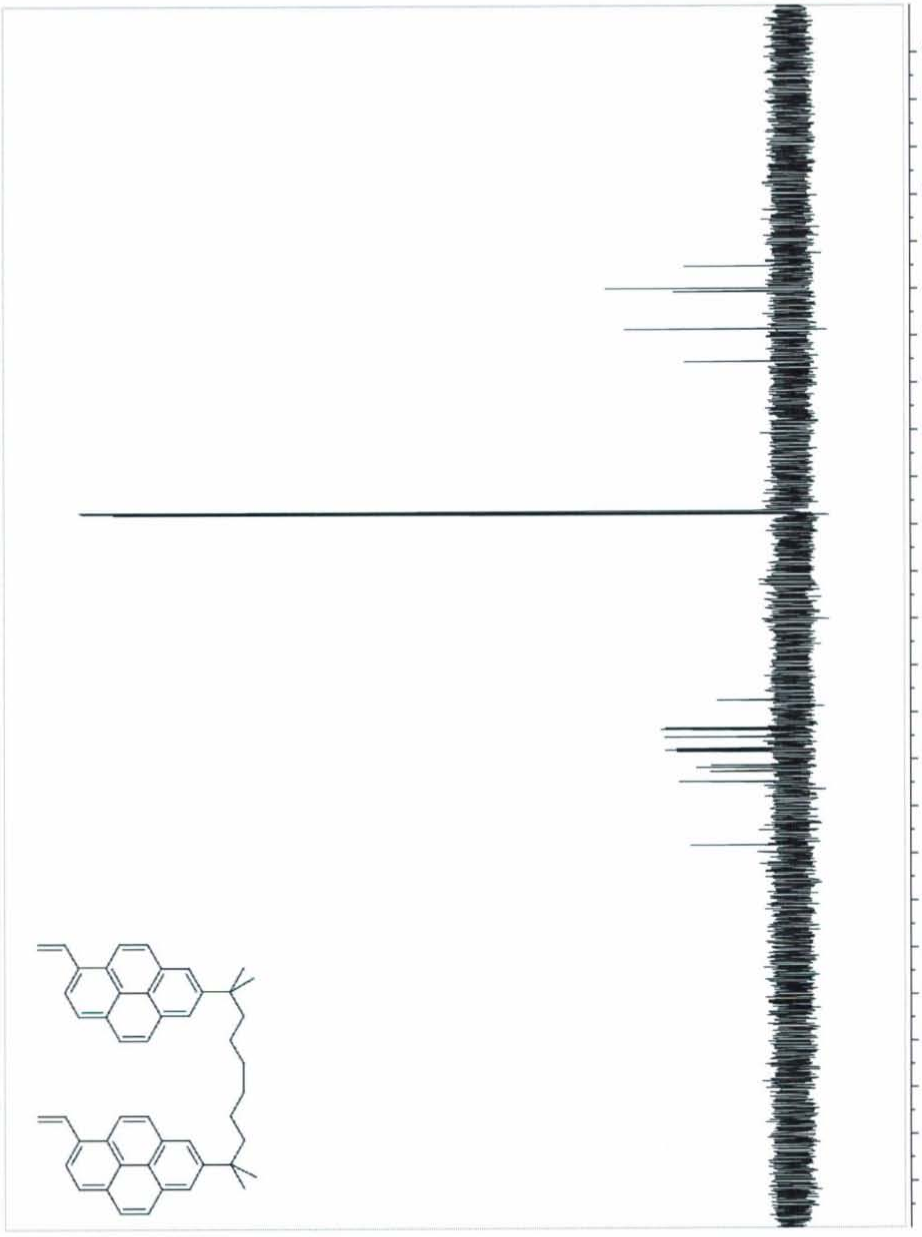

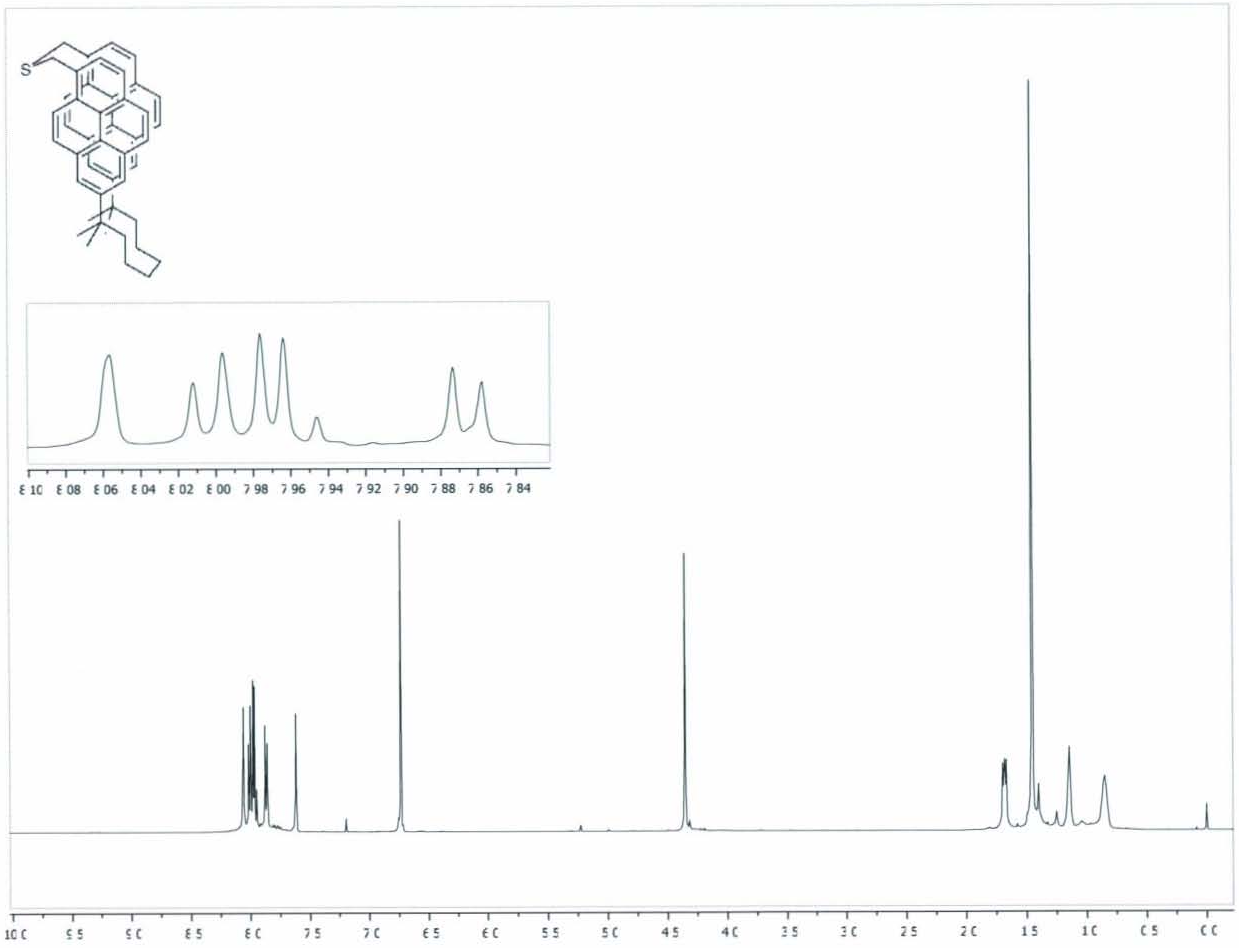
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10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


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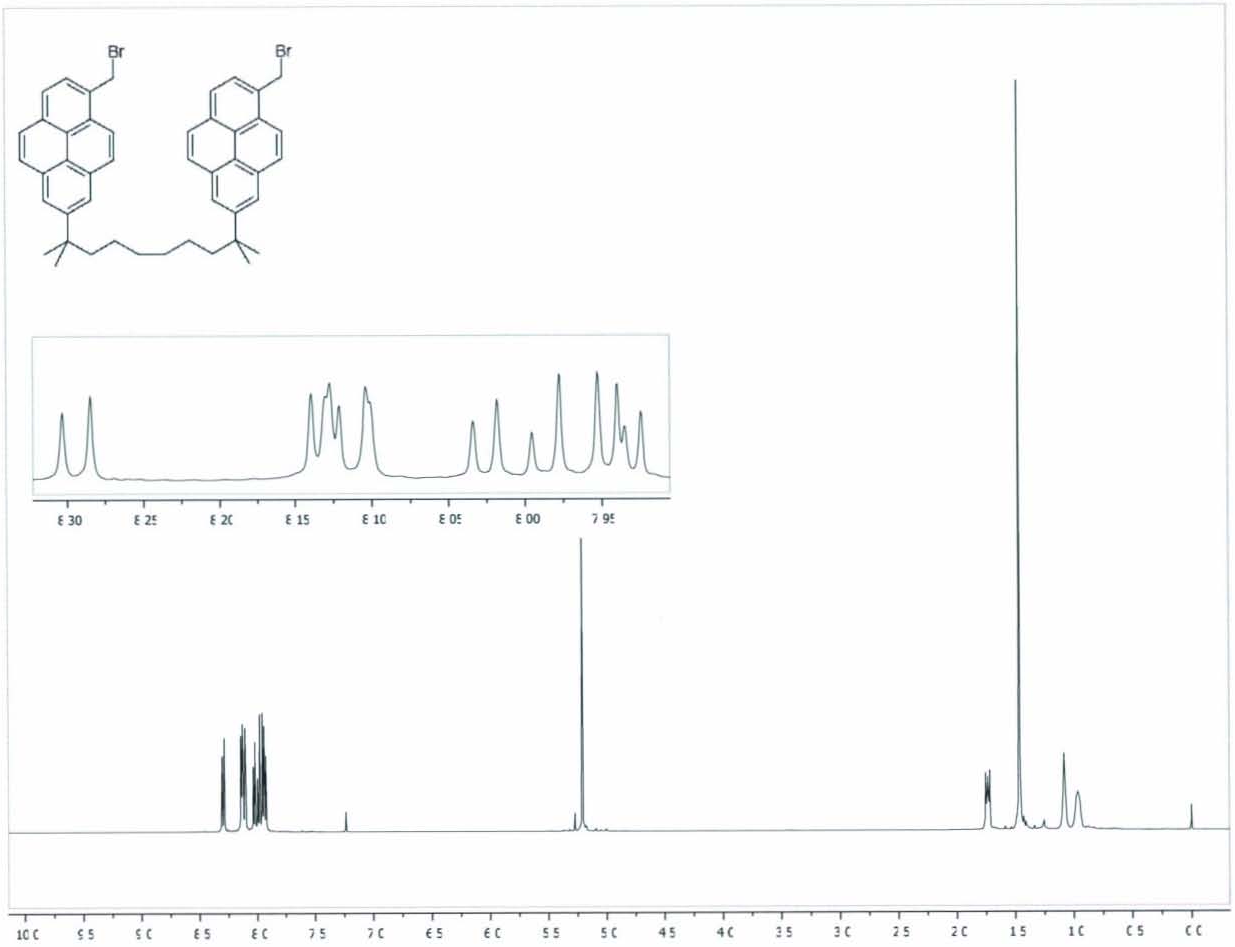
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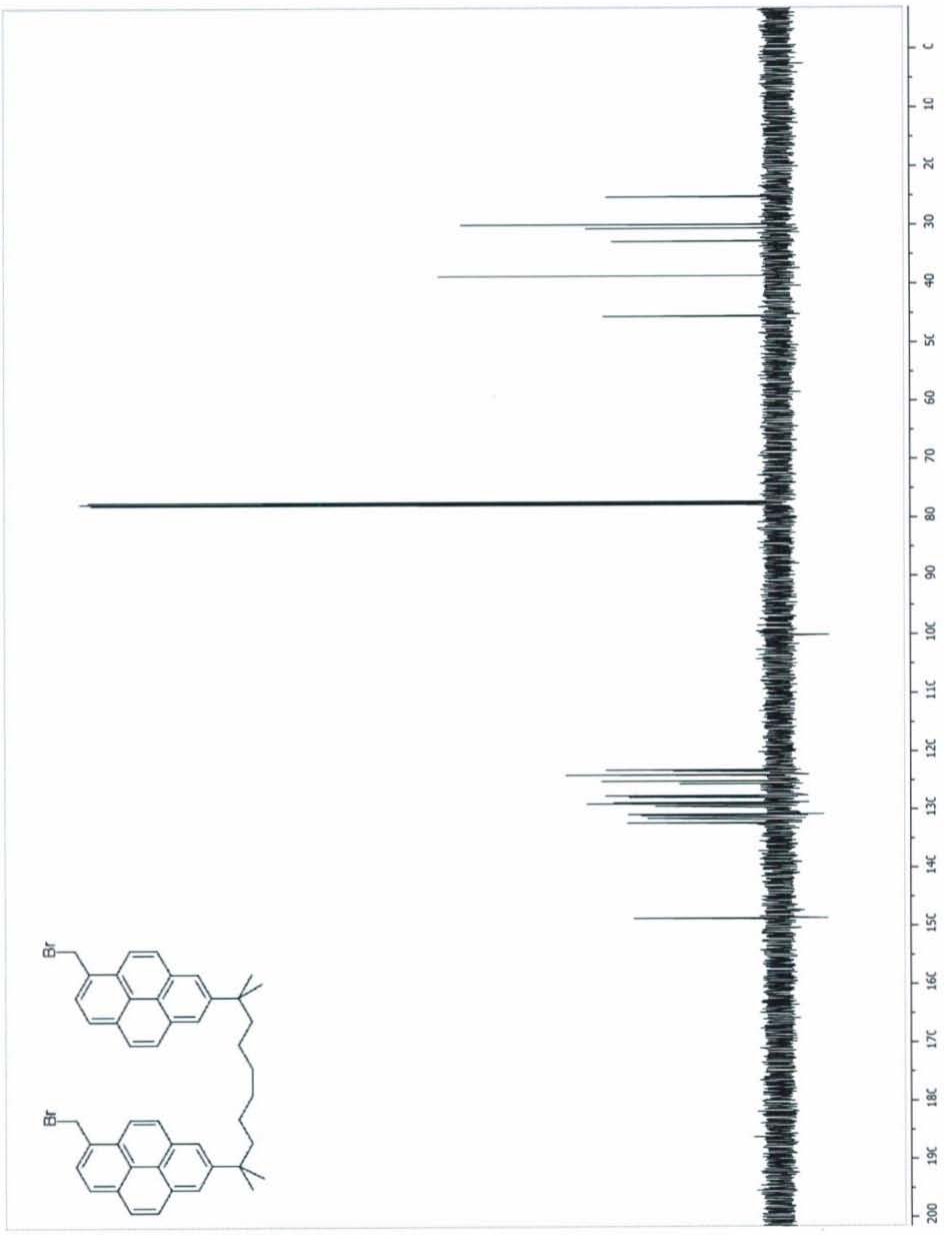
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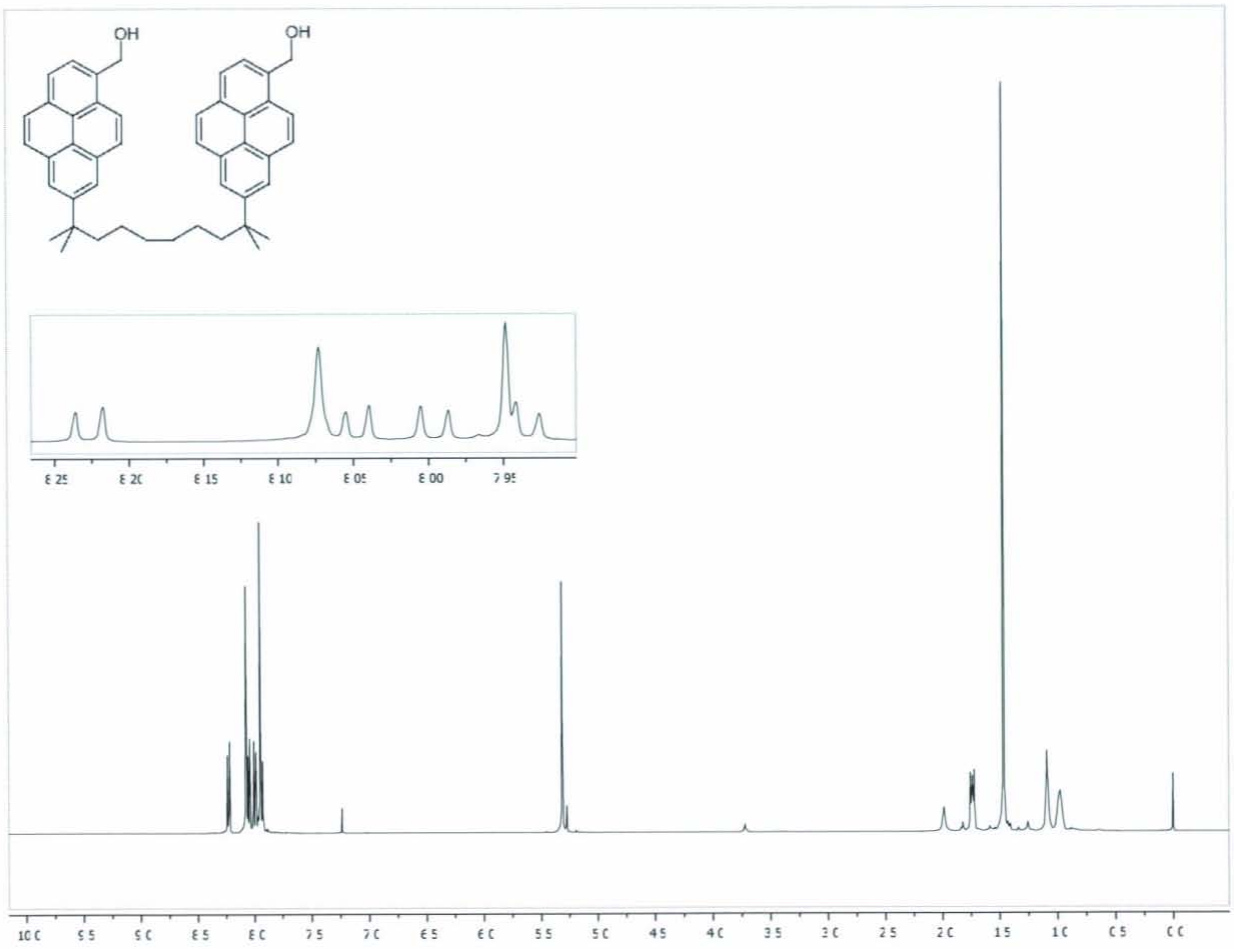
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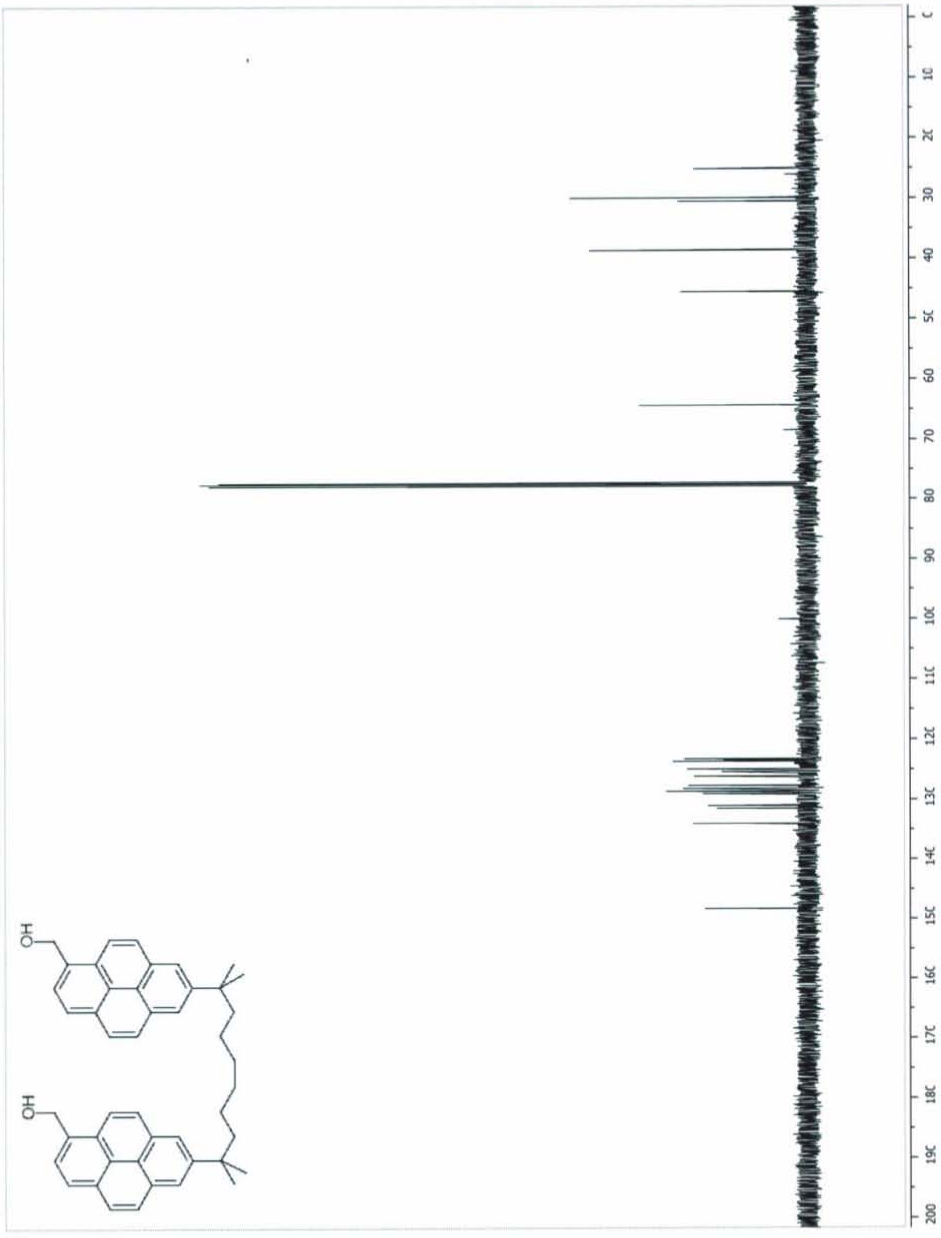
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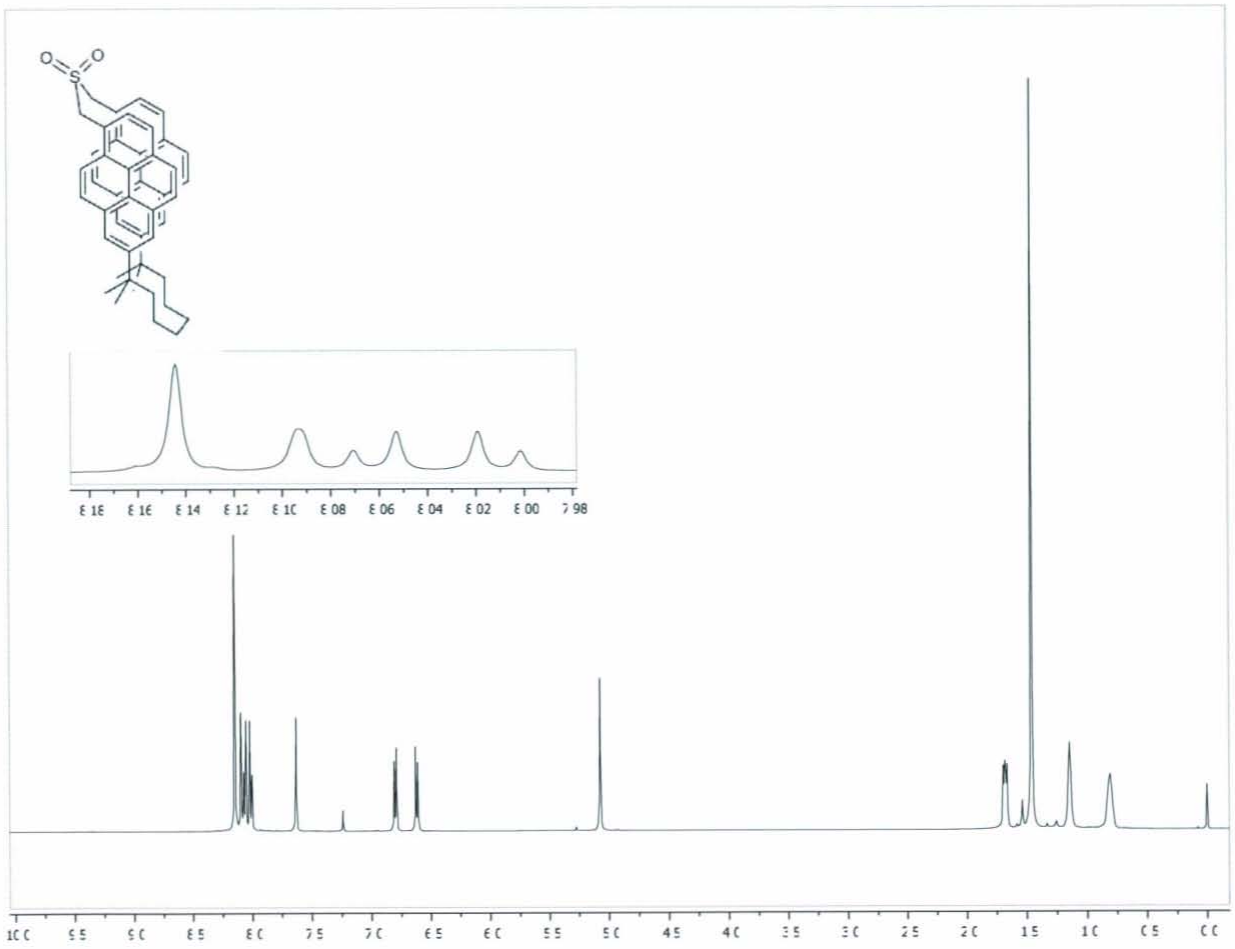
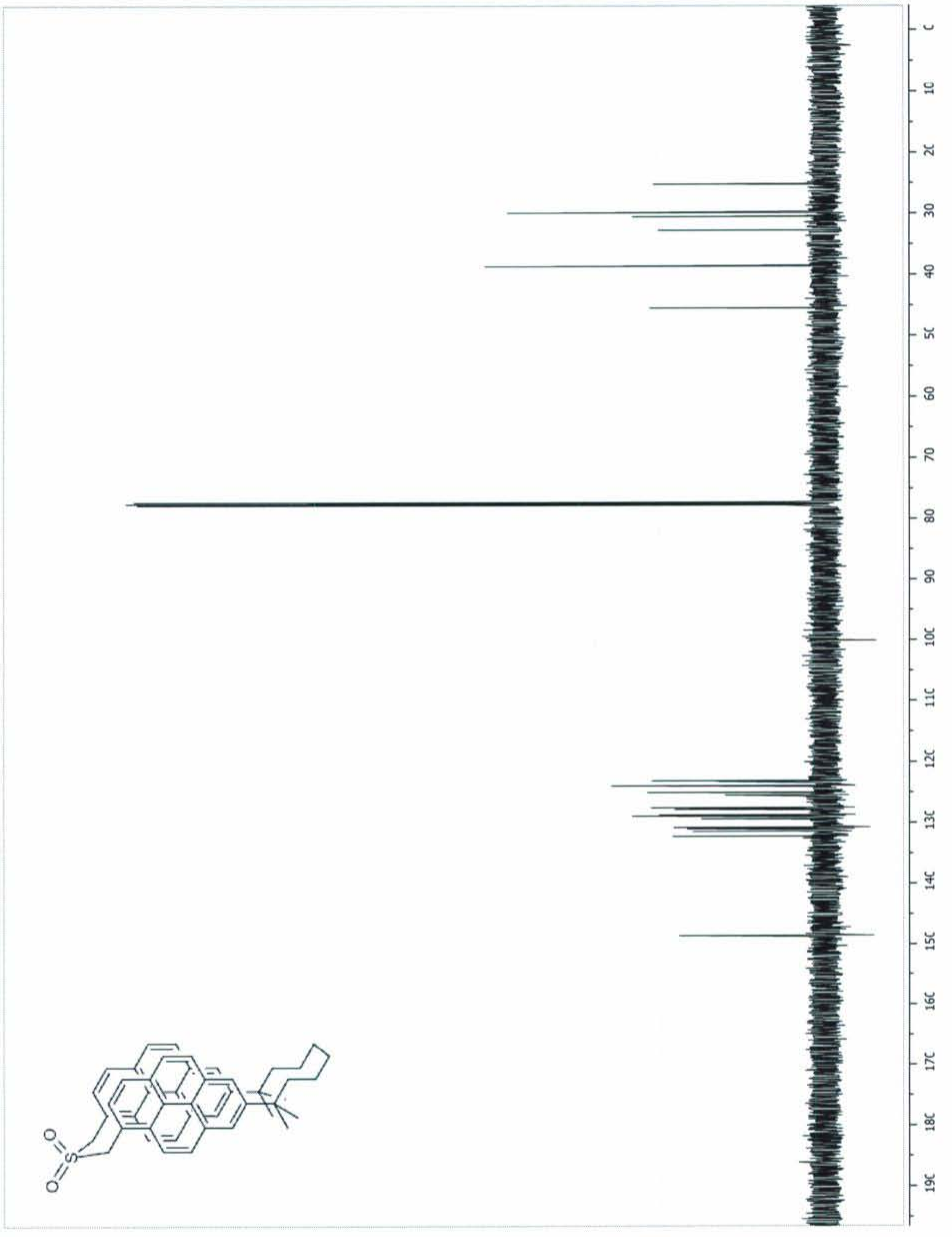




CHAPTER 3: Attempted Synthesis of 2,11-Di-*tert*-butylteropyrene as a Model Compound for 1,1,*n*,*n*-Tetramethyl[*n*](2,11)teropyrenophanes

3.1 Frustrations in Organic Synthesis

The introductory chapter of this dissertation addressed the design elements that are an essential component of target-oriented synthesis. While the selection of a target molecule (whether a natural product or a designed molecule) is the first step in a synthesis project, designing and executing a synthetic route are the most important tasks. In some cases, chemists select synthetic targets for the purpose of showcasing key bond-forming reactions or methodologies, often their own.[1]

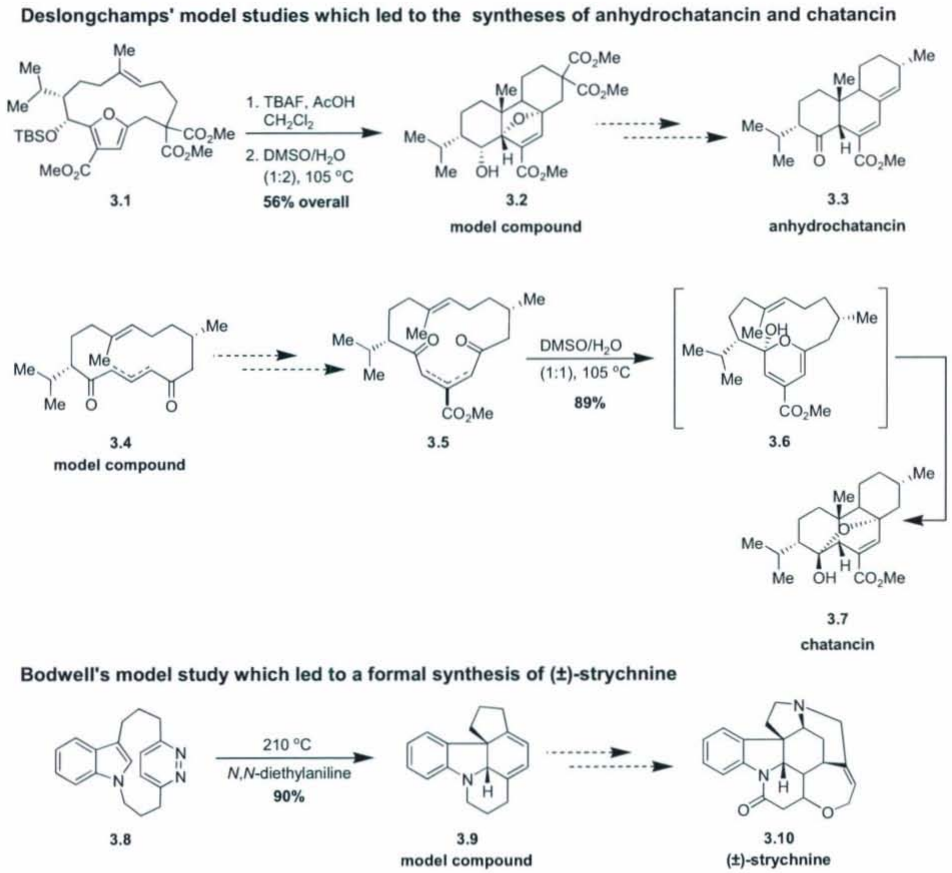
Applying a particular chemical transformation in a target-oriented synthesis is an important exercise because it provides clear evidence for its usefulness. Completing such an exercise can be problematic. In some cases, the planned key reaction is never even tested because the synthesis of the precursor substrate may prove to be overly challenging. On the other hand, it may be that an insurmountable hurdle is encountered subsequent to the successful key reaction, in which case the development of a new synthetic route that does not involve the key reaction is necessitated. As discussed in Chapter 2, the quest for a synthetic route to 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes (**2.15**), the former scenario appeared to be developing. The key step in the synthesis plan of the desired targets is a VID reaction, but the synthesis of a suitable [2.2]metacyclophanediene analog[2] proved to be very challenging using established approaches. Thus, new chemistry with respect to joining two pyrene units together had to be developed.

3.1.1 Model Studies in Organic Synthesis

There are numerous examples in total synthesis where a research team reports methodology for the construction of a structural motif that comprises a portion of a natural product. In such cases publication is warranted based on the intellectual and scientific contributions from the group, however, the "possible application" of this method in the total synthesis of a specific target makes for an attractive feature to those engaged in this area of organic synthesis.[3] Such model studies often form substantial portions of doctoral dissertations,[4] but whether or not they find application in the synthesis of the originally intended target is by no means guaranteed and often unclear. In many cases a methodology or key reaction that works well in a model system fails when applied to the system of interest. On the other hand, newly-fashioned methodologies or reagents can sometimes find application in the synthesis of other synthetic targets or reactions that were not conceived of by the original authors, which ultimately demonstrates the synthetic utility of the methodology or reagent.[5] In either case, this is the nature of target oriented synthesis and model studies play a pivotal role in the creation of new science and advancement of synthetic chemistry.

Scheme 3.1 illustrates the total synthesis of three natural products that came to fruition following model studies. All of these examples involve the use of cyclophane intermediates that participate in transannular Diels-Alder (TADA) reactions to furnish complex polycyclic systems. In the case of Deslongchamps' synthesis of anhydrochatancin (**3.7**),[6] it was discovered that furanophane **3.1** participated in a highly diastereoselective TADA reaction to give **3.2**, a tetracyclic intermediate that closely resembled the tricyclic core of this natural product and a related congener chatancin.

While the initial goal of their model study was to delineate a route to the former compound,[7] conversion of a more suitable analog of **3.2** into chatancin was not possible using this cyclophane approach. However, the synthesis of the related natural product anhydrochatancin (**3.3**) was possible.[8] Difficulties encountered during an attempted oxidative ring-expansion reaction of an analog of **3.2** to **3.7** (chatancin), serendipitously gave only the elimination and natural product anhydrochatancin.[6] The Deslongchamps group was able to complete a synthetic route to chatancin in the same year using a second



SCHEME 3.1: Model studies that involve cyclophane intermediates in total syntheses

cyclophane approach, which featured a TADA reaction of a pyranophane intermediate **3.6**. As in the case of anhydrochanticin (**3.3**), important synthetic details that were necessary to generate advanced intermediate **3.5** were gleaned through the aid of a model study.[9]

During the course of Bodwell's formal synthesis of (±)-strychnine, it was discovered via a model study that a pentacyclic analog corresponding to the core of several *strychnos* alkaloids could be assembled in short order from a transannular Diels-Alder reaction of [3](3,6)pyridazino[3](1,3)indolpahne (**3.8**).[1f] In this case, applying their strategy to the natural system[1d] proved to be more efficient than the model compound and to date, of the 14 synthesis of strychnine (**3.10**) that have been reported, Bodwell and Li's stands as the shortest and arguably most productive.[10]

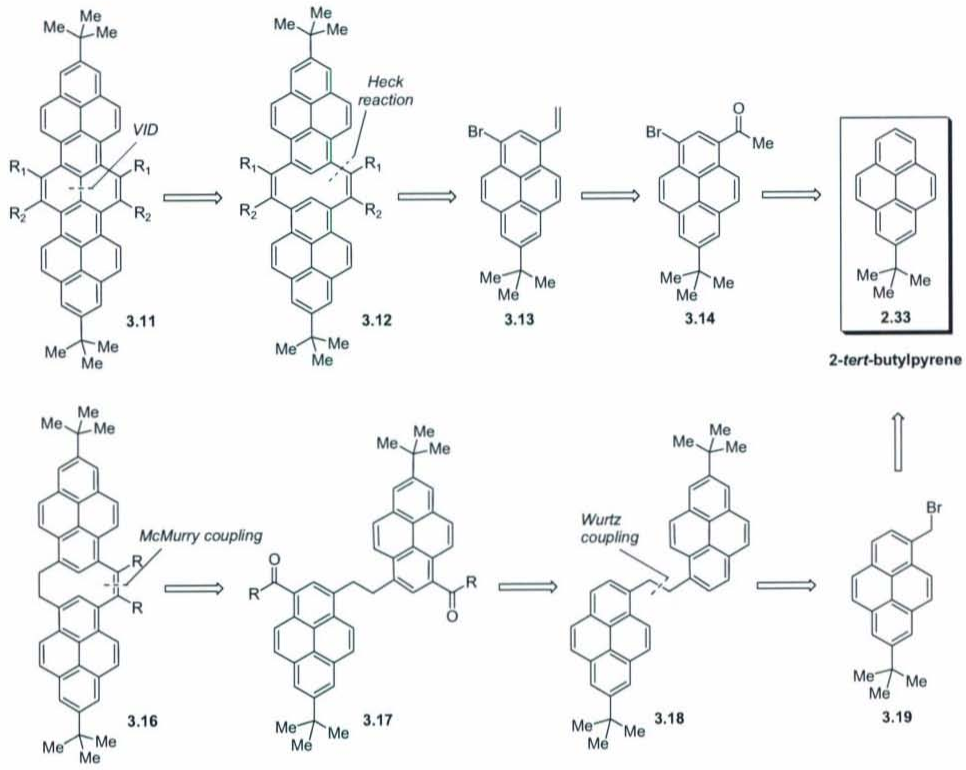
3.1.2 Designing a Model Teropyrene System

The failure to secure a reliable synthetic route towards the sub-targeted dithiacyclophanes **2.51** (see Scheme 2.9) prompted the implementation of a model study. Although the use of bis(2-pyrenyl)-dimethylalkane (**2.20**, Scheme 2.2) starting materials for exploratory work was not overly costly synthetically (just three steps were required),[11] only 1–3 g batches could be made comfortably. 2-*tert*-Butylpyrene presented itself as a very good model system for the bis(2-pyrenyl)-dimethylalkane substrates because it could be prepared on a relatively large scale[12] and the end product of the model study, 2,11-di-*tert*-butylteropyrene (**3.11**, R_1=R_2=H), would provide a benchmark against which the nonplanar teropyrene systems in the targeted teropyrenophanes **2.15** (Chapter 2, Section 2.2) could be meaningfully compared.

The primary objective of the model study was to establish a reliable route to 2,11-di-*tert*-butylteropyrene (**3.11**, R_1=R_2=H), which could then be applied to the synthesis of [*n*](2,11)teropyrenophanes. Since the VID reaction was to be the key and final step of the teropyrenophane synthesis, it was also planned for the final step of the synthesis of 2,11-di-*tert*-butylteropyrenes (**3.11**). The problem was thus reduced to the synthesis of (1,3)pyrenophanediene **3.12**. A secondary objective of the model study was to explore the possibility of improving upon classical cyclophane chemistry by discovering synthetic routes that do not proceed through the corresponding dithiacyclophane intermediates. With this in mind, the McMurry and Heck coupling reactions were considered for the necessary olefin forming reactions.

While the McMurry reaction has been shown to be applicable for the generation of strained olefin systems,[13] it has seen very limited successful applications in the synthesis of [2.2]metacyclophanes.[14] In contrast, there is no example of the Heck reaction in the synthesis of [2.2]metacyclophanes. Both of these reactions could conceivably enable the installation of the unsaturated bridges in **3.12** from a single synthetic precursor, thereby circumventing the multistep sequence that is necessary when going through dithiacyclophane intermediates. Such is the case for the synthesis of the (2,7)pyrenophanes discussed in Chapter 1. While both disconnections are very tempting, there are two key considerations to bear in mind: (1) the implications of the double bond geometry and (2) the increase in strain energy that accompanies the formation of the desired [2.2]metacyclophanediene unit. In the event that the first-formed bridge is *trans* configured, formation of the second bridge becomes impossible. With regard to strain,

[2.2]metacyclophanedienes are inherently strained systems. However, during their

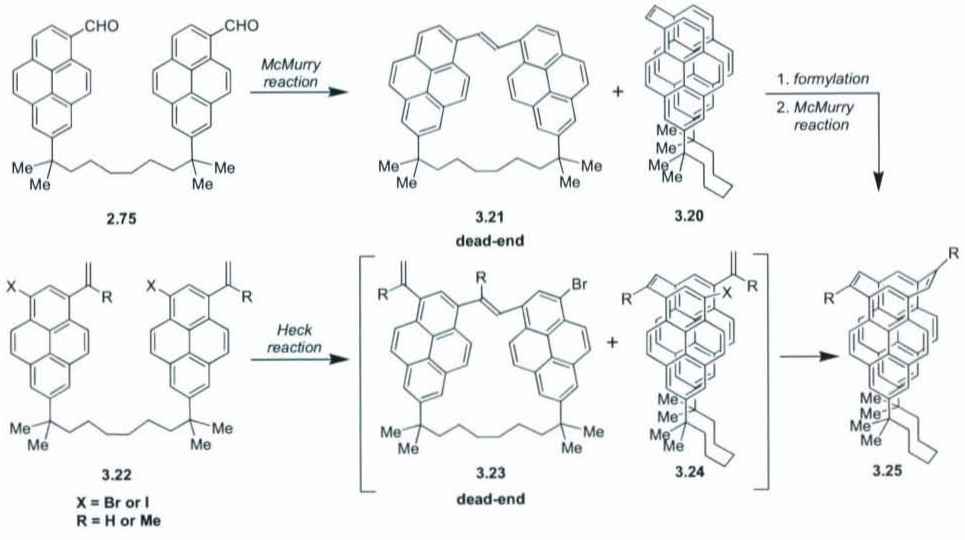


SCHEME 3.2: Disconnective analysis of teropyrene model system **3.11**

synthesis by way of a McMurry or Heck reaction, the majority of this strain would be introduced during the formation of the second unsaturated bridge. As such, the key reaction that installs the second bridge must be sufficiently favourable to be able to withstand the effects of developing strain. The issue of *syn*/*anti* isomerism in **3.12** was also considered, but this was not expected to be a problem. Cyclophanediene **3.12** would be expected to adopt an *anti* conformation, whereas **3.25** (*vide infra*) would be constrained to a *syn* conformation. The same notion can be anticipated for

[2.2](1,3)pyrenophane **3.16** and the analogous tethered system **3.41** (Scheme 3.6). Although the valence isomerization of **3.12** is thermally disfavoured, there is ample precedent for the valence isomerization of *anti*-[2.2]metacyclophanedienes.[15]

With all of these issues in mind, a sequential bridge-forming strategy was formulated, a key feature of which was the introduction of the first bridge in a saturated form. The basis for devising this approach was that both the Heck and McMurry reactions are highly selective for *trans*-configured double bonds. Although this tactic was necessary for the synthesis of the model system **3.12**, the need for its use in the case of the ultimately targeted cyclophane systems (1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes) was an open question. The tether that would link the 2-postions of the two pyrene units



SCHEME 3.3: Potential outcome of McMurry and Heck reactions in **2.75** and **3.22**

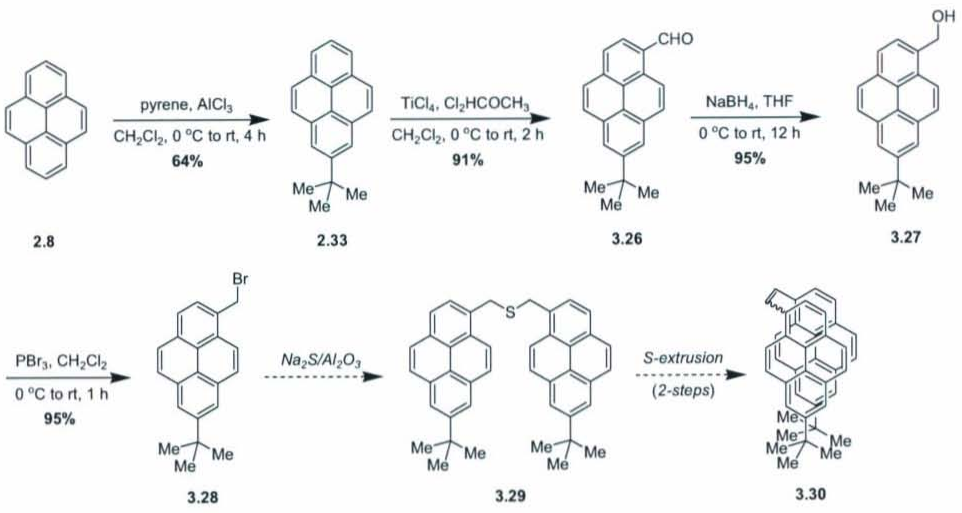
of 2,9-bis(6-formylpyren-2-yl)-2,9-dimethyldecane (**2.75**) or bis(2-pyrenyl)dimethylalkane **3.22** might render the *trans* isomer, the product of an intramolecular McMurry or Heck reaction, more strained than the corresponding *cis* isomer (Scheme 3.3). As such, both of these strategies may find successful application in the synthesis of [2.2]metacyclophanediene analog **3.25** and thus warrant the synthesis of model intermediates.

Returning to the model system, the Heck-based retrosynthetic pathway leading back from 2,11-di-*tert*-butylteropyrene (**3.11**) to **3.12**, **3.13** and **3.14** (Scheme 3.2) appeared to hold less promise than the McMurry-based pathway leading back to the mono-unsaturated [2.2](1,3)pyrenophane **3.16**, dicarbonyl compound **3.17** and 1,2-bis(2-pyrenyl)ethane (**3.18**). Thus, a model study that focused on the union of two pyrene units (at their 1-positions) via a carbon-carbon (sp^3–sp^3) bond-forming reaction such as a Wurtz coupling to furnish a saturated (ethano) bridge was pursued. Additionally, the synthesis of other "model" intermediates that would unlikely be used in the preparation of a teropyrene model compound, but potentially amenable to the tethered systems (*i.e.* **2.75** and **3.22**)[16] were considered at this stage. If these direct coupling strategies prove to be unsuccessful when applied to the designed model systems, then the preparation of these compounds would delineate a route that could (potentially) be applicable (to bis(2-pyrenyl)-dimethylalkanes) in the synthesis of the desired teropyrenophane targets.

3.2 Reactions of 2-*tert*-butylpyrene

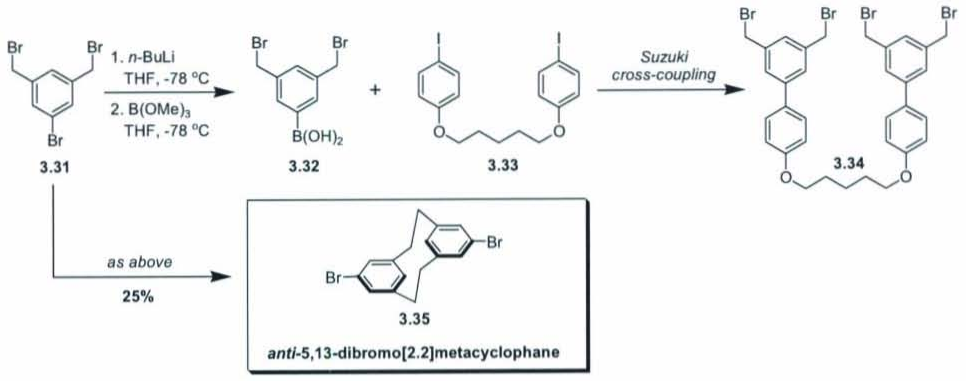
As was described in Chapter 2, the strategy for preparing 2,11-di-substituted teropyrenes hinges upon the ability to exploit the predictable substitution chemistry of

pyrene, or more specifically, 2-*tert*-butylpyrene (**2.33**). The monoformylation of 2,9-dimethyl-2,9-bis(2-pyrenyl)decane (**2.67**) proved to be a very reliable reaction at the outset of this work and, fortunately, it was also found to be a reliable transformation with 2-*tert*-butylpyrene. Aldehyde **3.26** was prepared in high yield and subsequently reduced to alcohol **3.27** via reaction with sodium borohydride. Bromination of the newly furnished alcohol was accomplished with phosphorous tribromide in dichloromethane to afford 1-(bromomethyl)-7-*tert*-butylpyrene (**3.28**). All of the chemical yields to this stage were very high (82% overall yield for three steps) and only a single chromatographic separation was required, at the aldehyde stage. The synthesis of a thiacyclophane intermediate from a bromide akin to **3.28** was accomplished in Chapter 2 (see Scheme 2.25). While the viability of its conversion to an olefin bridge was demonstrated via a Ramberg-Bäcklund reaction, other standard conversions failed in this instance. Due to these difficulties and the low yields that were encountered, treatment of bromide **3.28** with Na_2S/Al_2O_3 was not opted for at this juncture. Instead, the possibility of directly connecting two 1-(bromomethyl)-7-*tert*-butylpyrene units through carbon-carbon bond forming reactions was explored.



SCHEME 3.4: Synthesis of 1-(bromomethyl)-7-*tert*-butylpyrene (**3.28**)

In 2004 Bodwell and co-workers discovered that *anti*-5,13-dibromo[2.2]metacyclophane (**3.35**) could be generated from the direct treatment of tribromide **3.31** with *n*-BuLi.[17] Thus, it was decided to subject 1-(bromomethyl)-7-*tert*-butylpyrene (**3.28**) to these conditions (Scheme 3.6) to form the crucial carbon-carbon bond. The synthesis of cyclophane **3.35** had been achieved unintentionally during an attempt to generate the boronic acid of **3.32**, which was to be used in a planned Suzuki cross-coupling reaction with diiodide **3.33** as part of a synthetic approach to a new (2,7)pyrenophane. Subjecting 1-(bromomethyl)-7-*tert*-butylpyrene (**3.28**) to *n*-butyllithium at –15 °C furnished 1,2-bis(7-*tert*-butylpyren-1-yl)ethane (**3.18**) in 59% yield. The moderate yield of this reaction was of small consequence as the direct union of the two pyrene units in this manner served to eliminate several synthetic steps that were necessary in the original thiacyclophane plan (Chapter 2, Scheme 2.24).

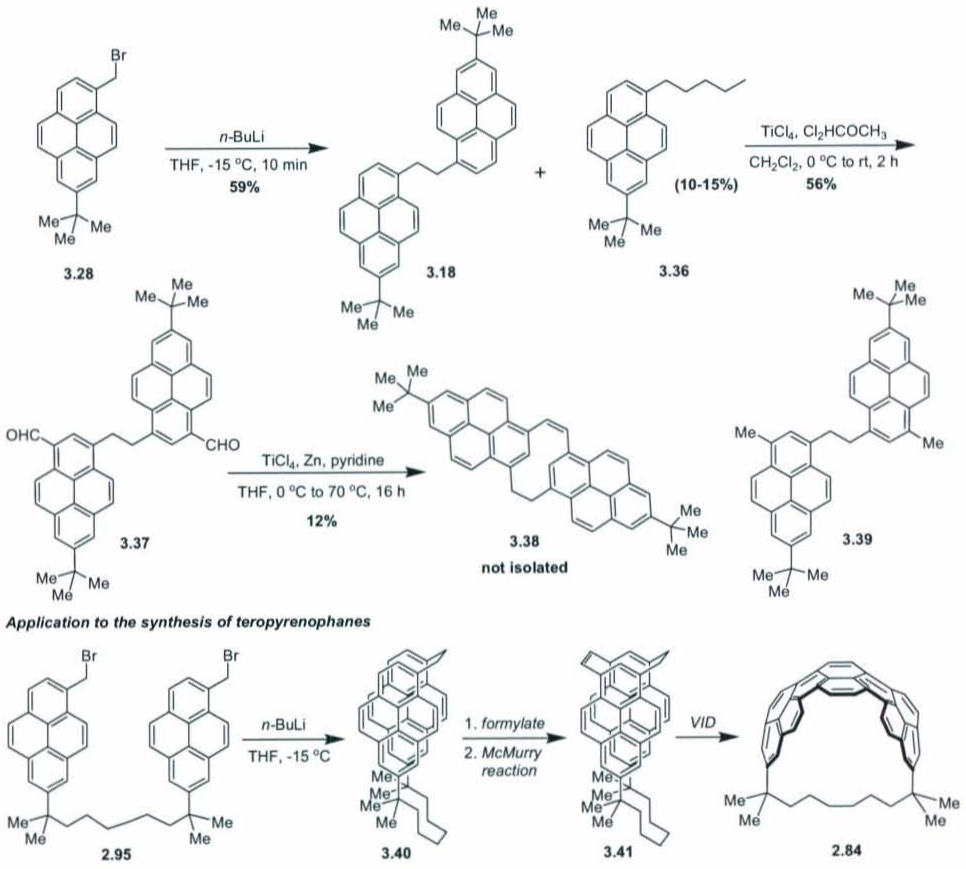


SCHEME 3.5: Unexpected synthesis of *anti*-[2.2](5,13)dibromometacyclophane (**3.35**)

Varying the temperature, concentration and reaction time gave very little change in the product distribution or isolated yields. In fact, at temperatures below –15 °C the reaction proved to be very sluggish. Routinely, a 50–60% yield of the desired product could be obtained, along with approximately 10–15% of the substitution byproduct **3.36**. The opportunity to improve the efficiency of this reaction would present itself in the intramolecular variant of the analogous dibromide **2.95** (Scheme 3.6). Conversion of **3.18** to the corresponding dialdehyde **3.37** was achieved in 56% yield. The uncharacteristically low yield of this reaction can probably be attributed to the low solubility of the dialdehyde system (in dichloromethane and other common organic solvents), which made for difficult isolation, purification and characterization.[18] A more serious concern was how this solubility issue would affect the outcome of the ensuing intramolecular McMurry reaction.[19]

To address this issue directly, it was envisioned that the synthesis of the analogous diketone **3.42** (Scheme 3.7) would aid the solubility of this system. While diketone **3.42**

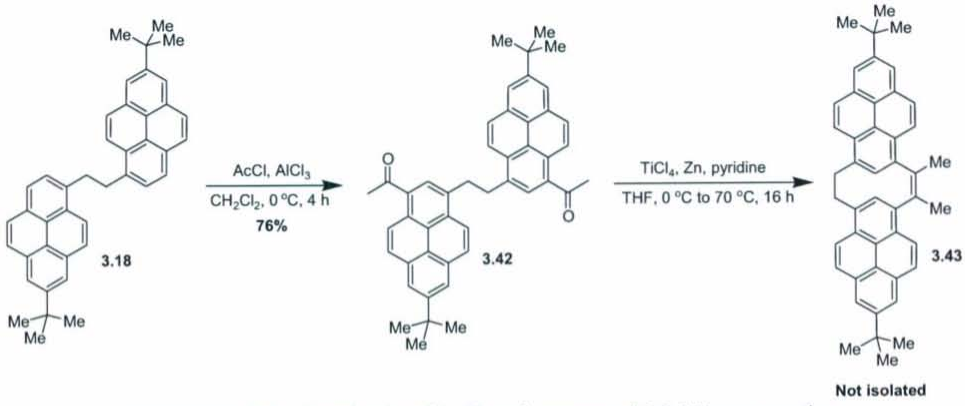
was considerably more soluble in dichloromethane than dialdehyde **3.18**, it too showed low solubility in both THF and 1,4-dioxane (solvents typically used in the McMurry reaction)



SCHEME 3.6: Attempted synthesis of 2,11-di-*tert*-butylteropyrene

and neither it nor the analogous aldehyde participated in a productive McMurry reaction.[20] In the case of the latter, LCMS analysis indicated that a species with the correct molar mass (m/z = 567 $(MH)^+$) had formed during the reaction, but the intensity of

this signal was low and many others were present. Isolation of [2.2]cyclophane **3.38** proved to be elusive and only the over-reduced product **3.39** was isolated in just 12% yield. In the case of diketone **3.42**, the McMurry reaction appeared to proceed nicely as evidenced by TLC analysis, and it seemed as if the more soluble of the two substrates was in fact undergoing a productive McMurry reaction. However, the LCMS and ^{1}H NMR data obtained for the isolated material did not point to the desired compound.[21]



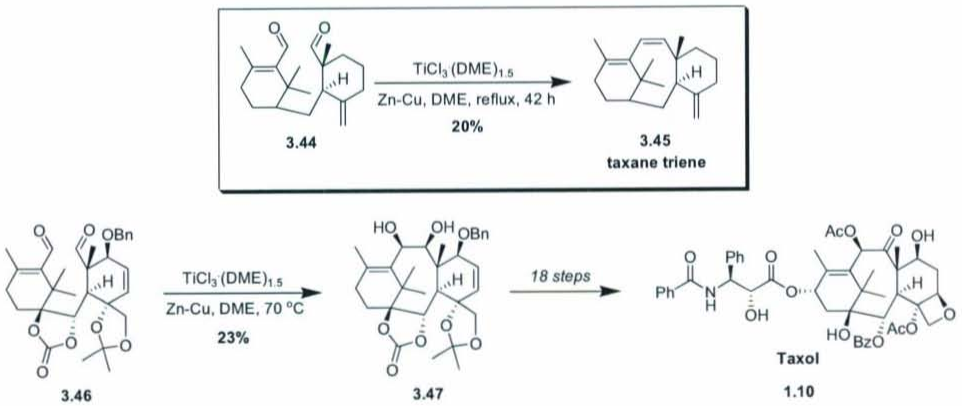
SCHEME 3.7: Synthesis of **3.42** and attempted McMurry reaction

3.2.1 Difficulties Associated with the McMurry Reaction

Since its discovery in 1973 (by three independent research groups)[22a-c] the McMurry reaction has emerged as a powerful synthetic method for the preparation of strained olefin systems. While this reaction has been successful in the synthesis of sterically hindered ethenes that could not be prepared through other olefination techniques, its application in the synthesis of [2.2]metacyclophanes has not been met with the same success. Fortunately, several variations of the McMurry reaction have been reported in the literature.[22] Some of these conditions were screened at this juncture in the

study to discover which would be the most suitable for the pyrene aldehydes (or ketones) in hand. While there have been several authoritative reviews published on addressing exactly which conditions are optimal in both inter- and intramolecular McMurry reactions,[23] the generation of the low-valent titanium intermediates for effective reductive couplings can be highly substrate- and even "co-worker-dependent".[24] Often, conditions that are found to be optimal for one system can fail when applied to an analogous substrate or simply in the hands of another scientist.[25]

Other than its virtual absence in the direct synthesis of [2.2]metacyclphanes (which constitute strained systems), Nicolaou's synthesis of Taxol is illustrative of the onerous task associated with securing optimal conditions for this reaction.[26] Generation of the 8-membered ring of Taxol (**1.10**) proved to be the most difficult challenge in their



SCHEME 3.8: McMurry reaction in Nicolaou's total synthesis of Taxol

synthesis, and this was reflected in the 23% yield obtained for this step. In fact, only the variant of the McMurry reaction shown in Scheme 3.8 proved to be effective in furnishing pinacol derivative **3.47**. At the outset of their synthesis plan, the assembly of

the strained eight-membered ring of Taxol was seen as one of the biggest challenges that the molecule posed. Guided by pioneering work of Kende and co-workers,[27] who had employed a McMurry reaction in the synthesis of unsaturated analog **3.45**, which represents the taxane skeleton, the Nicolaou group decided that a McMurry/pinacol strategy was their best option. For the model study at hand, of all the possible conditions that were screened[22] it was the Lenoir[24f] variant of the McMurry reaction that was found to be most well-suited for pyrene aldehydes and ketones.

3.2.2 Application of the McMurry Reaction in the Synthesis of Model Teropyrenes

While the McMurry reaction was unsuccessful in delivering a [2.2](1,3)pyrenophane (**3.38**), the possibility that this reductive coupling strategy could find application in the synthesis of the target teropyrenophanes or even the synthesis of a different model compound was not abandoned. Dione **3.54** was targeted (Scheme 3.9) with the intention of performing an intramolecular McMurry reaction, which would solve the *cis*/*trans* isomer issue of the first olefin-forming reaction. Generation of a 5- or 6-membered ring via an intramolecular McMurry reaction is typically a facile process[28] and the synthesis of disubstituted cyclopentene **3.56** was no exception.

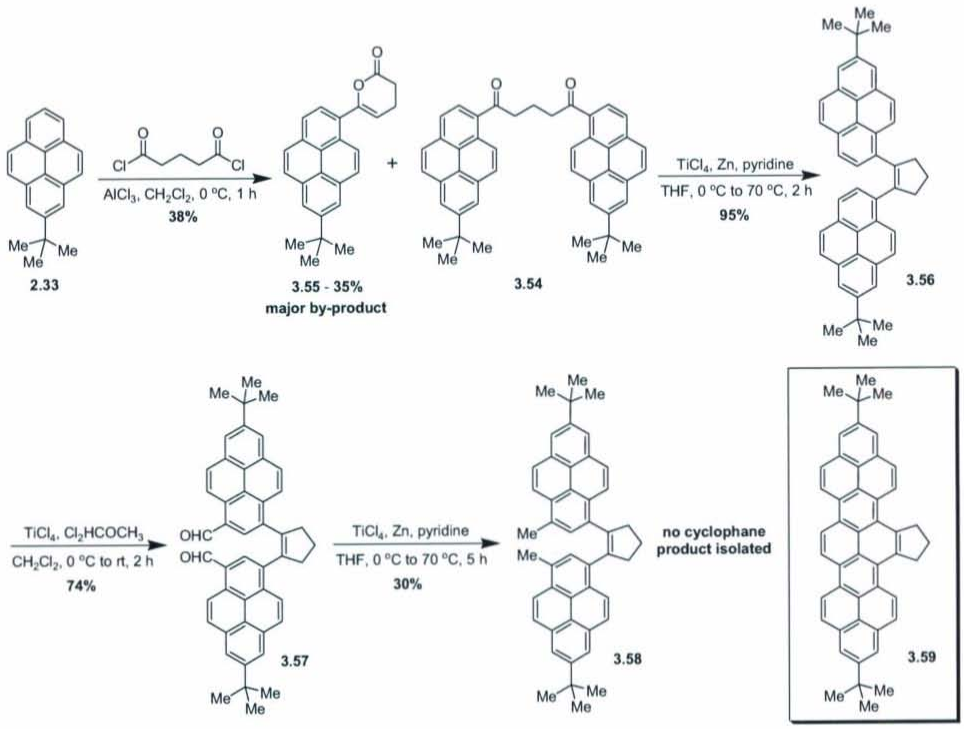
Treatment of **2.33** with glutaryl dichloride under Friedel-Crafts acylation conditions furnished diketone **3.54** in 38% yield. While this reaction was quite fast and capable of affording gram quantities of the desired diketone, it was plagued by the formation of undesired lactone **3.55** as a major byproduct (35%). Fortunately, separation of these two compounds was straightforward and acquiring pure diketone **3.54** was never a problem (despite a small difference in R_f values: R_f(**3.54**) = 0.35 and R_f(**3.55**) = 0.32).

The use of glutaryl dichloride in Friedel-Crafts acylation reactions is not without precedent, but the number of examples is limited.[29] Examples in which purely hydrocarbon aromatic systems have been employed suffer from low chemical yields. In fact, even when benzene was used as solvent for the reaction (as well as the substrate), a modest yield of 58% was obtained.[30] For the other few examples reported, the yields are in the range of 15–25%. Thus, 38% for the formation of dione **3.54** was a very respectable result.

Applying the Lenoir variant of the McMurry reaction to dione **3.54** furnished cyclpentene **3.56** in near quantitative yield (Scheme 3.10). The success of this reaction demonstrated that the McMurry reaction should be a viable strategy in the synthesis of cyclopenta-annulated 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophane analogs. If the McMurry reaction of the bis(6-formylpyren-2-yl)-dimethylalkanes (dialdehydes of **2.20**) or bis(6-acetylpyren-2-yl)-dimethylalkanes (bis(methylketones) of **2.20**) systems proved to be unsuccessful, then resorting to the use of glutaryl dichloride should rectify the situation. However, it was known from the screening process described below[22] that pyrene-1-carbaldehyde (**2.28**) and 7-*tert*-butylpyrene-1-carbaldehyde (**3.26**) undergo successful McMurry reaction using the Lenoir conditions. What remained to be seen was whether a *cis* or *trans* olefin (or in what ratio) would arise when a tether was introduced at the 7-position (pyrene numbering).

With cyclopentene **3.56** in hand, completion of the synthesis of two possible model compounds was pursued. Conversion of **3.56** to dialdehyde **3.57** was accomplished using the Rieche formylation. Compared to the ethano-bridged system **3.37**, dialdehyde **3.57** proved to be much more soluble in THF and dichloromethane and

was thus easier to work with. However, the fate of the McMurry reaction was identical to

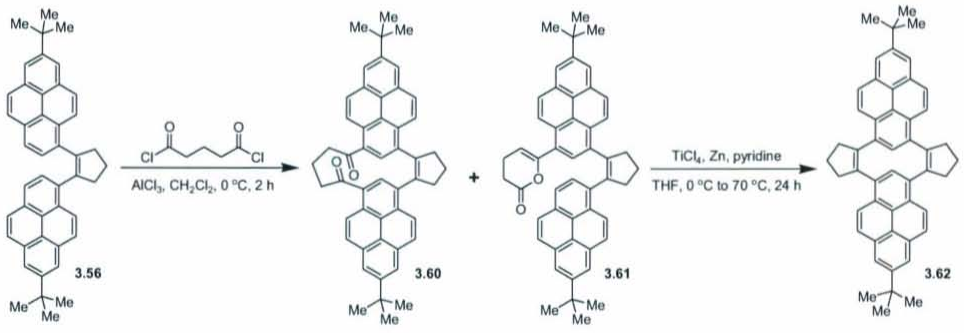


SCHEME 3.9: Attempted synthesis of teropyrene model compound **3.59**

that of dialdehyde **3.37** (which formed **3.39**, see Scheme 3.6), and only the over reduced dimethyl byproduct **3.58** was isolated from the reaction mixture. The fact that the annulated olefinic bridge of **3.57** holds the molecule in a conformation that seems to be amenable to a second McMurry reaction, but does not proceed at elevated temperatures, speaks to the strained nature of the desired [2.2](1,3)pyrenophane (*cf.* [2.2]metacyclophane) system. Despite this discouraging result, the anticipated difference in conformation between the [2.2]metacyclophane **3.38** derived from the model

dialdehyde **3.37** (*anti*) and the one derived from the tethered dialdehyde **3.40** (*syn*) was sufficient cause to not yet abandon the McMurry reaction approach. Furthermore, the presence of this tether in addition to the 2-atom bridge would be expected to provide an entropic advantage over the model system.

Staying with the model system, a possible solution to the problematic second McMurry reaction would be to acylate both pyrene units a second time with glutaryl dichloride and attempt a second cyclopentene-forming McMurry reaction. The anticipated advantage of this approach was that the McMurry reaction of [5.2]cyclophane **3.60** would be transannular *versus* intramolecular (*cf.* dialdehyde **3.57**). Subjecting cyclopentene **3.56** to glutaryl dichloride under Friedel-Crafts acylation conditions resulted in complete consumption of the starting material after two hours. Analysis of the material obtained from this reaction using ^{1}H NMR and LCMS indicated that the crude mixture consisted of both [5.2]cyclophane **3.60** and lactone **3.61** in approximately a 1:1 ratio. This mixture was not separable, but it was anticipated that only **3.60** should participate in a McMurry reaction. Moreover, the resulting cyclized product **3.62** would be considerably less polar than **3.61**, so separation at this stage was envisioned. Unfortunately, no cyclized or even tractable products were produced. While it was beginning to seem that preparation of a model teropyrene was going to be elusive, some useful lessons about the chemistry of 2-*tert*-butylpyrene had been learned, which would prove to be valuable later.



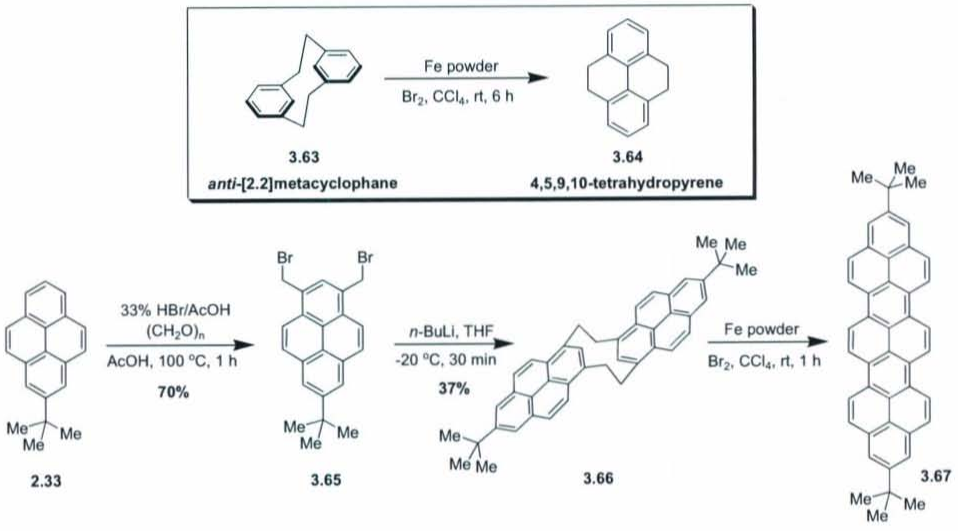
SCHEME 3.10: Attempted synthesis of teropyrene precursor **3.62**

3.2.3 A Different [2.2](1,3)Pyrenophane Approach to 2,11-Di-*tert*-butylteropyrene

In a final attempt to afford a model 2,11-di-*tert*-butylteropyrene, it was reasoned that the application of chemistry akin to what had been used by Misumi and co-workers in their synthesis of teropyrene (Chapter 2, Scheme 2.1) might be useful. Although Misumi's approach should be feasible in generating a model compound, its downfall was that it would not be applicable in the synthesis of the target teropyrenophanes.

While preparing a 2,11-di-substituted teropyrene would require a multi-step synthesis if the same layered metacyclophane approach is to be adopted here, it was envisioned that if 1,3-bis(bromomethyl)-7-*tert*-butylpyrene could be prepared directly from 2-*tert*-butylpyrene, then application of a Wurtz-type coupling should give [2.2](1,3)pyrenophane **3.66**. While direct bromomethylation of the bis(2-pyrenyl)-dimethylalkane substrates (discussed in Chapter 2) proved to be problematic, the same was not true for 2-*tert*-butylpyrene (**2.33**). Using the conditions that had proved to be ineffective for the synthesis of **2.69**, treatment of **2.33** with 33% HBr/AcOH and paraformaldedhye in glacial acetic acid furnished 1,3-bis(bromomethyl)-7-*tert*-

butylpyrene (**3.65**) in 70% yield. However, this result was obtained only on a single occasion and multiple attempts to reproduce the synthesis of **3.65** in high purity were unsuccessful.[31] Nonetheless, with a usable quantity of pure **3.65** in hand, exposure of this material to *n*-BuLi in THF gave the desired [2.2]cyclophane **3.66** in 37% yield.



SCHEME 3.11: Attempted synthesis of 2,11-di-*tert*-butylteropyrene via **3.65**

There are numerous examples where [2.2]metacyclophane systems have been converted directly to 4,5,9,10-tetrahydropyrenes.[32] Indeed, a pyridinium perbromide-driven cyclodehydrogenation reaction was used by Misumi and co-workers in their synthesis of peropyrene (**2.11**) and teropyrene (**2.14**). The same transannular ring-closing strategy was envisioned here, with the exception that larger aromatic building blocks (pyrene) would be used in the place of benzene rings. With only a small quantity (*ca.* 10 mg) of **3.66** available and the difficulty in reproducing the synthesis of its precursor **3.65**, careful consideration of which conditions to apply for this reaction was taken. The most

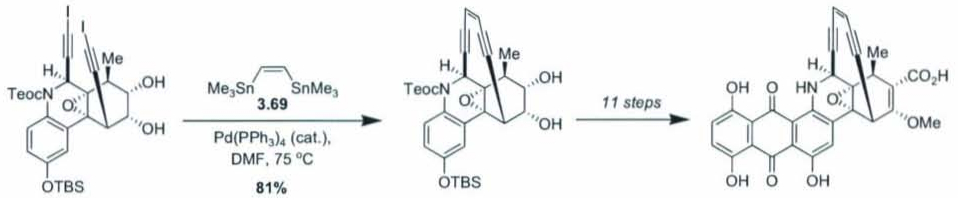
reliable method(s) available in the literature seemed to be those reported by Sato and co-workers, which utilize iron powder and bromine (Scheme 3.12).[33] Treatment of **3.66** under these conditions resulted in complete consumption of starting material in less than 1 hour. However, only a complex mixture that contained none of the desired compound (by ^{1}H NMR and LCMS analysis) was obtained.

When this model study was initiated, there were two main objectives: (1) the discovery of novel chemistry for the 2-*tert*-butylpyrene system that would be applicable to the bis(2-pyrenyl)-dimethylalkanes (and the targeted teropyrenophane) systems and (2) the preparation of a model (planar) teropyrene compound to which the physical data of a nonplanar teropyrene system in a teropyrenophane could be directly compared. While the groundwork and a strategy for the union of two pyrene units at their 1-postions had been established as well as demonstrating that further functionalization of these systems is possible, preparation of a model system using this chemistry was, unfortunately, not.

3.2.4 Preparation of Other Potentially Useful Model Compounds

The completion of this study on the functionalization of the 2-*tert*-butylpyrene system involved the synthesis of two compounds that would not be suitable precursors to a model teropyrene system, but rather serve as "models" for chemistry that might ultimately be used in the synthesis of the 1,1,*n*,*n*,-tetramethyl[*n*](2,11)teropyrenophanes and related analogs. The concept of using palladium catalyzed cross-coupling reactions in the synthesis of cyclophanes, specifically with respect to installing two-atom

unsaturated bridges, is one that has seen virtually no applications (*vide supra*).

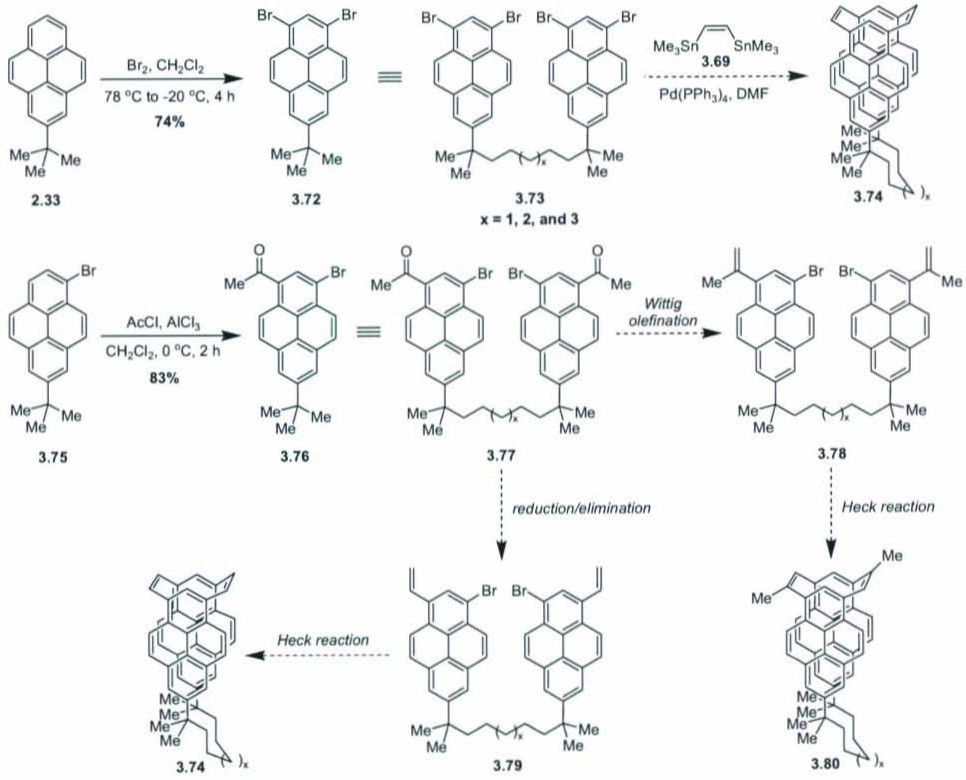


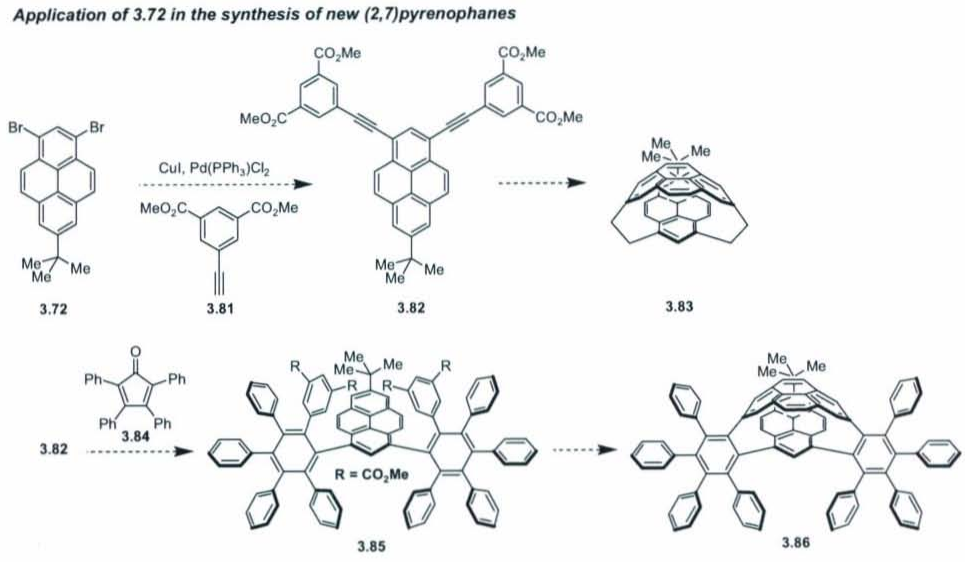
SCHEME 3.12: Application of *cis*-1,2-bis(trimethylstannyl)ethene (**3.69**) in Danishefsky's dynemicin A synthesis

Directly incorporating the olefin bridges may be possible through a Stille cross-coupling reaction of bromide **3.73** and *cis*-1,2-bis(trimethylstannyl)ethene (**3.69**) to form **3.74** (Scheme 3.13). This reagent was used quite effectively in Danshefsky's synthesis of dynemicin A to install the enediyne portion of the anti-cancer natural product (Scheme 3.12).[34] Successful application of this reaction could potentially shorten the synthesis of all pyrenoid cyclophanes that have been prepared to date in our group and enable a very brief synthesis of the targeted teropyrenphanes.

Selective dibromination of 2-*tert*-butylpyrene was possible using temperature-controlled conditions to afford 1,3-dibromo-7-*tert*-butylpyrene (**3.72**) in 74% yield. In fact, no overbrominated product (1,3,6-tribromide **2.52**, Chapter 2) was observed in this reaction and only a minor amount of the monobromide **3.75** was isolated from the mother liquor. Dibromide **3.72** was also seen as being (potentially) a very useful compound in the synthesis of new (2,7)pyrenophanes that contain multiply linked pi-systems (*vide infra*). Additionally, this bromination protocol might be applicable to the synthesis of tetrabromide **3.73**. Acetylation of the monobrominated byproduct **3.75** using standard

Friedel-Crafts alkylation conditions furnished bromoketone **3.76** in 83% yield. The bis(2-pyrenyl)-dimethylalkane analog of this material (**3.77**) could also be a useful intermediate for a possible Heck coupling strategy for **3.74** or **3.80**. Both of these cyclophanediene intermediates would be valuable compounds to test in the VID reaction for the generation of a highly distorted teropyrene nucleus.





SCHEME 3.13: Potential routes to cyclophanediene **3.74** and **3.80** using 2-*tert*-butylpyrene as a model and potential use of **3.72** in the synthesis of pyrenophanes **3.83** and **3.86**

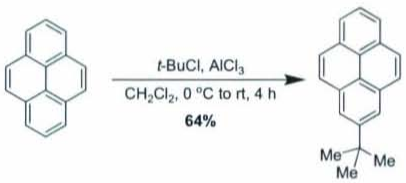
3.3 Conclusions

During the course of this model study, key observations with respect to joining two pyrenyl units at their 1-positions were made. These findings ultimately served as a guide in the completion of the synthesis of the desired teropyrenophane targets. While access to a model teropyrene system was not possible using the chemistry that was developed here, the carbon-carbon bond forming reactions that were realized seem much better suited for the bis(2-pyrenyl)-dimethylalkane (**2.20**) systems. The ultimate objective of this study was to develop a suitable strategy for connecting two pyrene units of **2.75** via an etheno or an analogous saturated two-atom bridge and further functionalize these systems such that a second carbon-carbon bond forming reaction could be tested. Both of

these goals were met in the form of the Wurtz-type and McMurry coupling reactions. The remaining chapter will deal with the application of these strategies in the synthesis of a series of 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes.

3.4 Experimental Procedures and Characterization Data

2-*tert*-Butylpyrene (2.33)[13]

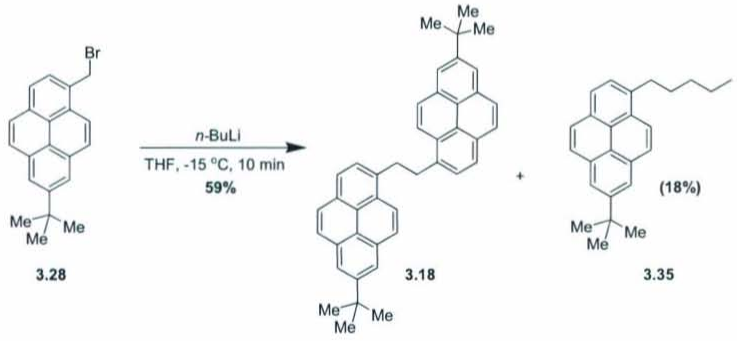


2.8 **2.33**

Aluminum chloride (16.2 g, 121 mmol) was added in roughly four equal portions over a two minute period to a stirred 0 °C solution of pyrene (22.3 g, 110 mmol) and 2-chloro-2-methylpropane (13.0 g, 143 mmol) in dichloromethane (150 mL). The resulting slurry was allowed to warm to room temperature and stirred for 4 h. The reaction was poured into ice water (500 mL), the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (100 mL), washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The solid yellow residue was recrystallized from methanol to afford 2,7-di-*tert*-butylpyrene (**2.34**) as an off-white solid (4.5 g, 13%): R_f= 0.38 (hexanes); m.p. 208–209 °C (MeOH) (lit.[35] 210–212 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 4H), 8.00 (s, 4H), 1.57 (s, 18); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 148.78, 131.00, 127.64, 123.08, 122.21, 35.41, 32.19.; LCMS (APCI-

positive) *m/z* (rel. int.) 259 (45), 260 (13), 261(4) 315 (100, $(MH)^+$), 316 (27), 317 (8); HRMS (EI) calculated for $C_{20}H_{18}$ $(M)^+$ 314.2034, found 314.2038. The mother liquor was then concentrated under reduced pressure and the resulting light yellow solid was recrystallized from hexanes to afforded 2-*tert*-butylpyrene (**2.33**) as a light beige solid (18.2 g, 64%): R_f = 0.38 (hexanes); m.p. 104–106 °C (hexanes) (lit.[36] 109–110 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 2H), 8.17 (d, *J*=8.0 Hz, 2H), 8.07–8.02 (m, 4H), 7.97–7.94 (m, 1H) 1.61 (s, 9H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 149.21, 131.20, 131.18, 127.78, 127.45, 125.69, 124.93, 124.83. 123.13, 122.41, 35.45, 32.18.; LCMS (APCI-positive) *m/z* (rel. int.) 259 (100, $(MH)^+$), 260 (24), 261 (6); HRMS (EI) calculated for $C_{20}H_{18}$ $(M)^+$ 258.1409, found 258.1406.

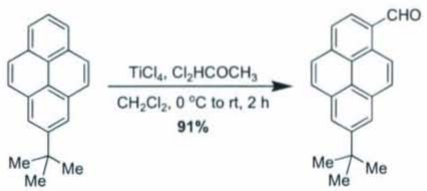
1,2-Bis(7-*tert*-butylpyren-1-yl)ethane (3.18) and 7-*tert*-butyl-1-*n*-pentylpyrene (3.35)



n-Butyllithium (0.75 mL, 0.75 mmol) as a 1.0 M solution in hexanes was added to a stirred solution of –15 °C 1-(bromomethyl)-7-*tert*-butylpyrene (**3.28**) (0.398 g, 1.13 mmol) in THF (15 mL). After 1 h, water (15 mL) was added to the reaction mixture. THF was evaporated under reduced pressure and the resulting aqueous mixture was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were

washed with a 1.0 M HCl solution (20 mL), washed with a saturated solution of sodium bicarbonate (40 mL), washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was preadsorbed onto silica gel and purified by column chromatography (25 × 2 cm; 1:9 dichloromethane/hexanes). Eluted first was 7-*tert*-butyl-1-*n*-pentylpyrene (**3.35**), which was isolated as a clear colorless oil (0.066 g, 18%); R_f = 0.65 (1:9 dichloromethane/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J*=9.3 Hz, 1H), 8.27–8.25 (m, 2H), 8.15–8.11 (m, 2H), 8.07–8.03 (m, 2H) 7.88 (d, *J*=7.8 Hz, 2H), 3.31 (t, *J*=6.7 Hz, 2H) 1.97–1.94 (m, 2H), 1.57 (s, 9H), 1.49–1.44 (m, 4H), 0.95 (t, *J*=6.7 Hz, 3H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 149.03, 137.36, 131.54, 131.02, 129.74, 128.66, 127.61, 127.46, 127.06, 126.86, 125.24, 124.77, 123.64, 122.56, 122.25, 122.09, 122.04, 35.49, 33.74, 32.24, 32.16, 31.82, 22.90; LCMS (APCI-positive) *m/z* (rel. int.) 330 (26), 329 (100, $(MH)^+$), 274 (8), 273 (36); HRMS (EI) calculated for $C_{25}H_{28}$ $(M)^+$ 328.2191, found 328.2192. Eluted second was 1,2-bis(7-*tert*-butylpyren-1-yl)ethane (**3.18**), which was isolated as a white solid (0.360 g, 59%): R_f = 0.28 (1:9 dichloromethane/hexanes); m.p. 280–281 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J*=9.4 Hz, 2H), 8.24–8.22 (m, 4H), 8.14 (d, *J*=9.4 Hz, 2H), 8.04–7.99 (m, 6H), 7.79 (d, *J*=7.9 Hz, 2H), 3.82 (s, 4H) 1.59 (s, 18H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 149.17, 136.03, 131.52, 131.01, 130.02, 128.73, 127.86, 127.64, 127.16, 127.06, 125.21, 124.85, 123.55, 122.45, 122.35, 122.22, 35.77, 35.43, 32.18; LCMS (APCI-positive) *m/z* (rel. int.) 545(12), 544(48), 543(100, $(MH)^+$); HRMS (EI) calculated for $C_{42}H_{38}$ $(M)^+$ 542.2974, found 542.2972.

7-*tert*-Butylpyrene-1-carbaldehyde (3.26)

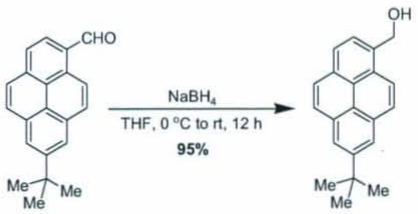


2.33 **3.26**

Titanium(IV) chloride (1.24 g, 6.51 mmol) was added to a stirred 0 °C solution of 2-*tert*-butylpyrene (**2.33**) (1.39 g, 5.42 mmol) and dichloromethyl methyl ether (0.748 g, 6.51 mmol) in dichloromethane (30 mL). The cooling bath was removed and the resulting mixture was stirred for 1 h while warming to room temperature. The reaction was poured into ice water (100 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 30 mL) and the combined organic extracts were washed with a saturated solution of sodium bicarbonate (40 mL), washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a brown residue that was subjected to column chromatography (25 × 4 cm; 2:1 dichloromethane/hexanes) to yield 7-*tert*-butyl-pyrene-1-carbaldehyde (**3.26**) as a bright yellow solid (1.41 g, 91%): R_f = 0.48 (2:1 dichloromethane/hexanes); m.p. 135–136 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.73 (s, 1H), 9.33 (d, *J*=9.3 Hz, 1H), 8.37–8.34 (m, 3H) 8.26 (d, *J*=7.9 Hz, 1H), 8.17 (d, *J*=8.9 Hz, 1H), 8.14 (d, *J*=7.9 Hz, 1H), 8.01 (d, *J*=8.9 Hz, 1H), 1.62 (s, 9H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 193.20, 150.01, 135.47, 131.15, 131.13 131.03, 130.99, 130.98, 127.42, 127.07, 124.67, 124.57, 124.44, 124.22, 123.02, 122.43, 35.50, 32.08 (18 of 19 signals observed); IR (neat) 3116, 2928, 2857, 1670, 1520, 1463

(cm^{-1}); LCMS (APCI-positive, *m/z* (rel. int.)) 288 (23), 287 (100, $(MH)^+$); HRMS (EI) calculated for $C_{21}H_{18}O$ $(M)^+$ 286.1358, found 286.1358.

(7-*tert*-Butyl-pyren-1-yl)-methanol (3.27)

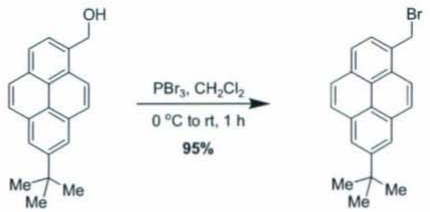


3.26 **3.27**

Sodium borohydride (0.93 g, 25 mmol) was added to a stirred 0 °C solution of 7-*tert*-butyl-pyrene-1-carbaldehyde (**3.26**) (1.77 g, 6.19 mmol) in THF (30 mL). The resulting slurry was allowed to slowly warm to room temperature over a 12 h period. The solvent was evaporated under reduced pressure and the solid residue was taken up into dichloromethane (30 mL). This solution was cooled to 0 °C, diluted with H_2O (30 mL) and acidified using 1 M HCl solution. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (40 mL), washed with brine (40 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield (7-*tert*-butyl-pyren-1-yl)-methanol (**3.27**) as an off-white solid (1.69 g, 95%). Purification of this compound was not necessary and the material was used in further experiments: R_f = 0.12 (dichloromethane); m.p. 157–159 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J*=9.2 Hz, 1H), 8.25 (s, 2H), 8.09–8.06 (m, 2H), 8.05 (d, *J*=8.9 Hz, 1H) 8.01 (d, *J*=8.9 Hz, 1H), 7.95 (d, *J*=7.7 Hz, 1H), 5.33 (s, 2H), 2.09 (br s, 1H), 1.59 (s, 9H); ^{13}C NMR (125.77 MHz,

$CDCl_3$) δ 149.33, 133.76, 131.34, 131.27, 130.87, 128.76, 128.24, 127.80, 127.42, 125.80, 125.04, 124.66, 123.19, 123.01, 122.79, 122.67, 63.98, 35.44, 32.15; LCMS (APCI-positive, *m/z* (rel. int.)) 272 (23), 271 (100, ([*M*-H_2O]*H*)$^+$); HRMS (EI) calculated for $C_{21}H_{20}O$ $(M)^+$ 288.1514, found 288.1518.

1-(Bromomethyl)-7-*tert*-butylpyrene (3.28)

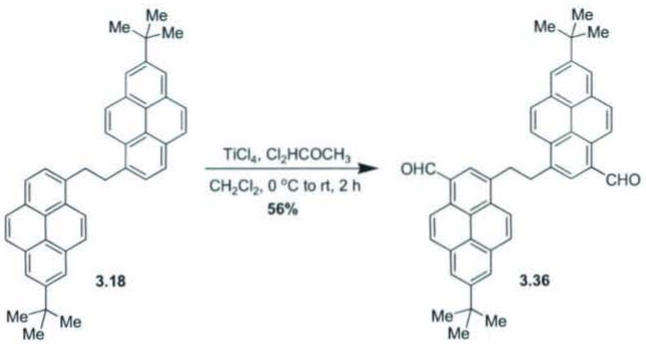


3.27 **3.28**

Phosphorus tribromide (0.649 g, 2.40 mmol) was added to a stirred 0 °C solution of (7-*tert*-butyl-pyren-1-yl)-methanol (**3.27**) (0.92 g, 3.20 mmol) in dichloromethane (20 mL). The cooling bath was removed and the resulting mixture was stirred for 1 h at room temperature. Water (20 mL) was added to the reaction and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 30 mL) and the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield 1-(bromomethyl)-7-*tert*-butylpyrene (**3.28**) as a light yellow solid (1.06 g, 95%). Purification of **3.28** was not necessary and the material was used in further experiments: R_f = 0.56 (1:1 dichloromethane/hexanes); m.p. 198–200 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J*=9.2 Hz, 1H), 8.31 (d, *J*=1.8 Hz, 1H) 8.27 (d, *J*=1.8 Hz, 1H), 8.24 (d, *J*=9.2 Hz 1H), 8.11–8.07 (m, 2H), 8.03 (d, *J*=8.9 Hz, 1H) 7.97 (d, *J*=7.8 Hz, 1H), 5.27 (s, 2H), 1.60 (s, 9H); ^{13}C NMR

(125.77 MHz, $CDCl_3$) δ 149.69, 132.01, 131.29, 130.85, 130.56, 129.11, 128.65, 128.46, 127.56, 127.39, 125.27, 124.85, 123.14, 123.09, 122.93, 35.47, 32.48, 32.21 (18 of 19 carbons observed); LCMS (APCI-positive) *m/z* (rel. int.) 274 (25), 273 (98, [(M–^{81}Br)*H*]$^+$), 272 (26), 271 (100, [(M–^{79}Br)*H*]$^+$); HRMS (EI) calculated for $C_{21}H_{19}{}^{79}Br$ $(M)^+$ 350.0670, found 350.0674.

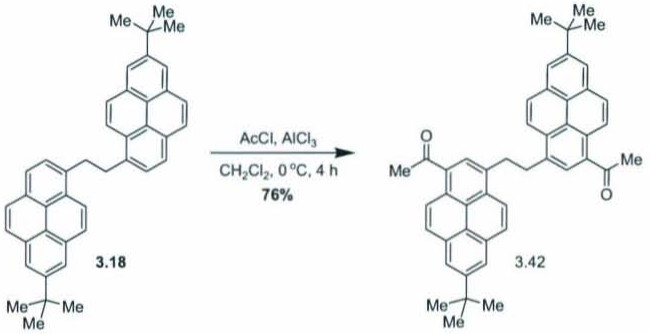
1,2-Bis(3-formyl-7-*tert*-butylpyren-1-yl)ethane (3.36)



1.0 M Titanium(IV) chloride (0.65 mL, 0.65 mmol) was added to a stirred 0 °C solution of 1,2-bis(7-*tert*-butylpyren-1-yl)ethane (**3.18**) (0.141 g, 0.258 mmol) and dichloromethyl methyl ether (0.074 g, 0.646 mmol) in dichloromethane (20 mL). The cooling bath was removed and the resulting mixture was stirred for 2 h while warming to room temperature. The reaction was poured into ice water (100 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL) and the combined organic extracts were washed with a saturated solution of sodium bicarbonate (40 mL), washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a solid brown residue, which was subjected to column chromatography (20 × 2 cm; dichloromethane) to yield 1,2-bis(3-formyl-7-*tert*-

butylpyren-1-yl)ethane (**3.36**) as a bright yellow solid (0.086 g, 56%): R_f = 0.27 (dichloromethane); m.p. 225–228 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.76 (s, 2H), 9.35 (d, *J*=8.5 Hz, 2H), 8.31–8.23 (m, 10H), 3.96 (s, 4H), 1.58 (s, 18H); ^{13}C NMR (adequate data could not be obtained due to low solubility of this compound); LCMS (APCI-positive) *m/z* (rel. int.) 615 (12), 614 (46), 613 (100) 600 (6), 599 (18, $(MH)^+$); HRMS (EI) calculated for $C_{44}H_{38}O_2$ $(M)^+$ 598.2872, found 598.2867.

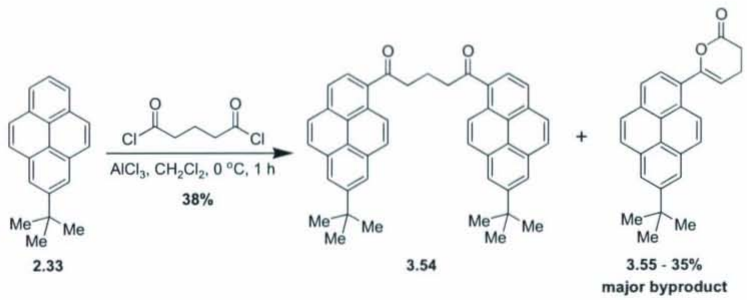
1,2-Bis(3-acetyl-7-*tert*-butylpyren-1-yl)ethane (3.42)



Aluminum chloride (0.051 g, 0.38 mmol) was added to a stirred 0 °C solution of acetyl chloride (0.013 g, 0.17 mmol) and 1,2-bis(7-*tert*-butylpyren-1-yl)ethane (**3.18**) (0.040 g, 0.073 mmol) in dichloromethane (10 mL). The resulting mixture was stirred at 0 °C for 4 h, at which point the reaction was poured into ice water (50 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (30 mL), washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The brown residue was subjected to column chromatography (20 × 2 cm; dichloromethane) to yield 1,2-bis(3-acetyl-7-*tert*-butylpyren-1-yl)ethane (**3.42**) as a

pale yellow solid (0.034 g, 76%): R_f = 0.28 (dichloromethane); m.p. 208–210 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (d, *J*=7.6 Hz, 2H), 8.32–8.28 (m, 6H), 8.19–8.15 (m, 4H), 7.85 (s, 2H) 3.92 (s, 4H), 2.53 (s, 6H) 1.61 (s, 18H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 203.35, 150.04, 134.93, 134.91, 132.49, 132.38, 132.36 130.94, 130.45, 129.87, 129.85, 128.43, 126.21, 125.01, 123.98, 123.22, 122.91, 35.33, 31.97, 30.62 (20 of 21 signals observed); LCMS (APCI-positive) *m/z* (rel. int.) 629 (13), 628 (51), 627 (100, $(MH)^+$); HRMS (EI) calculated for $C_{46}H_{42}O_2$ $(M)^+$ 626.3185, found 626.3188.

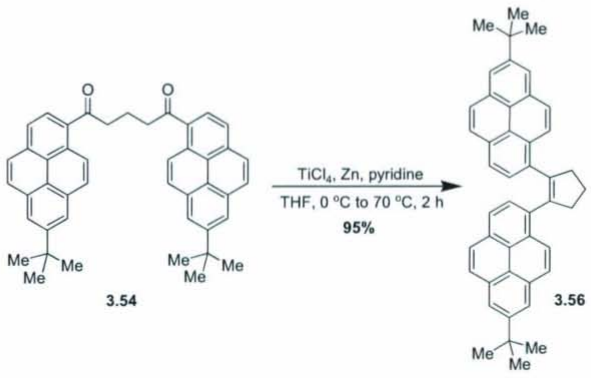
1,5-Bis(7-*tert*-butylpyren-1-yl)-1,5-pentanedione (3.54)



Aluminum chloride (3.20 g, 24.0 mmol) was added to a stirred 0 °C solution of glutaryl dichloride (0.99 g, 5.9 mmol) and 2-*tert*-butylpyrene (**2.33**) (3.02 g, 11.7 mmol) in dichloromethane (20 mL). After 1 h, the reaction mixture was poured into ice water (100 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL) and the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The brown residue was subjected to column chromatography (45 × 4 cm; dichloromethane) to

yield 1,5-bis(7-*tert*-butylpyren-1-yl)-1,5-pentanedione (**3.54**) as a pale yellow solid (1.36 g, 38 %): R_f = 0.35; m.p. 231–233 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (d, *J*=9.4 Hz, 2H), 8.33 (d, *J*=8.0 Hz, 2H), 8.29 (br s, 4H), 8.18 (d, *J*=9.4 Hz, 2H), 8.13 (d, *J*=8.9 Hz, 2H), 8.09 (d, *J*=8.0 Hz, 2H), 7.99 (d, *J*=8.9 Hz, 2H) 3.46 (t, *J*=7.0 Hz, 4H), 2.49 (p, *J*=7.0 Hz, 2H), 1.60 (s, 18H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 204.65, 149.79, 133.83, 132.18, 131.14, 130.60, 129.89, 129.78, 129.39, 127.09, 126.24, 125.12, 124.86, 124.03, 123.79, 123.44, 122.75, 41.25, 35.45, 32.10, 20.51; LCMS (APCI-positive) *m/z* (rel. int.) 615 (13), 614 (51), 613 (100, $(MH)^+$), 355 (12); HRMS (EI) calculated for $C_{45}H_{40}O_2$ $(M)^+$ 612.3028, found 612.3018. Eluted second was 6-(7-*tert*-butylpyren-1-yl)-3,4-dihydropyran-2-one (**3.55**) as light brown oil (35%): R_f = 0.32 (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, *J*=9.3 Hz, 1H), 8.27 (s, 2H), 8.13–8.08 (m, 3H), 8.04–8.01 (m, 2H), 5.71 (t, *J*=4.7 Hz, 1H), 2.91–2.88 (m, 2H), 2.70–2.66 (m, 2H), 1.59 (s, 9H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 169.14, 151.96, 149.59, 131.94, 131.35, 130.82, 128.80, 128.65, 128.56, 128.35, 127.32, 126.51, 124.96, 124.57, 124.49, 123.16, 123.09, 122.93, 101.44, 36.48, 32.16, 28.81, 20.04; IR (neat) 3102, 2953, 2889, 1752, 1594, 1546, 1460 (cm^{-1}); LCMS (APCI-positive) *m/z* (rel. int.) 355 (62, $(MH)^+$), 356 (17), 387 (100, $(MNa)^+$), 388 (27); HRMS (EI) calculated for $C_{25}H_{22}O_2$ $(M)^+$ 354.1620, found 354.1622.

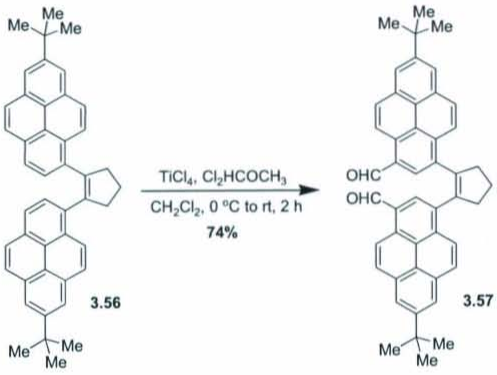
1,2-Bis(7-*tert*-butylpyren-1-yl)cyclopentene (3.56)



Titanium(IV) chloride (1.34 g, 7.22 mmol) was added to a stirred 0 °C slurry of zinc dust (0.461 g, 7.05 mmol) in THF (45 mL). After the addition was complete, the reaction was heated to reflux for 1 h, at which point a dark black color persisted. Pyridine (0.2 mL) was added to the mixture, which was stirred at reflux for 10 min. A solution of 1,5-bis(7-*tert*-butylpyren-1-yl)-1,5-pentanedione (**3.54**) (0.540 g, 0.882 mmol) in THF (20 mL) was then added and the reaction was heated at 70 °C for 2 h. The reaction mixture was then poured without significant cooling into chloroform (50 mL). The resulting solution was concentrated under reduced pressure and adsorbed onto silica gel in preparation for column chromatography. Aqueous work-up for this reaction is not recommended as layer separation can be quite problematic and the yields are typically lower. The preadsorbed sample was subjected to column chromatography (20 × 3.5 cm; 1:9 dichloromethane/heaxanes) to yield 1,2-bis(7-*tert*-butylpyren-1-yl)cyclopentene (**3.56**) as a light green oil (0.487 g, 95%): R_f = 0.34 (1:9 dichloromethane/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, *J*=9.2 Hz, 2H), 8.22 (d, *J*=1.8 Hz, 2H), 8.18 (d, *J*=1.8 Hz, 2H), 8.04 (d, *J*=9.2 Hz, 2H), 7.94 (d, *J*=8.9 Hz, 2H), 7.87–7.85 (m, 4H), 7.80 (d, *J*=7.9 Hz,

2H), 3.43 (t, *J*=7.4 Hz, 4H?) 2.57 (p, *J*=7.4 Hz, 2H), 1.60 (s, 18H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 148.93, 141.49, 134.64, 131.28, 130.92, 130.01, 128.48, 127.19, 127.15, 126.53, 125.55, 125.53, 124.54, 123.26, 122.18, 122.11, 122.09 41.24, 35.32, 32.10, 24.33; LCMS (APCI-positive) *m/z* (rel. int.) 583 (11), 582 (49), 581 (100, $(MH)^+$); HRMS (EI) calculated for $C_{45}H_{40}$ $(M)^+$ 580.3130, found 580.3129.

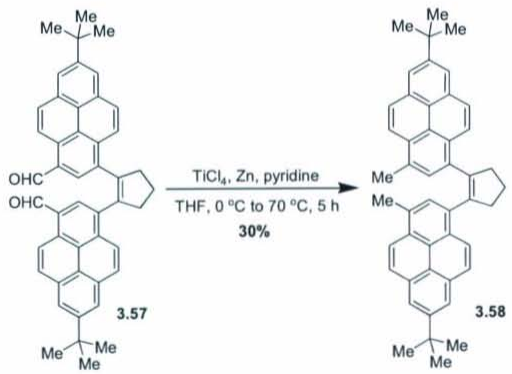
1,2-Bis(7-*tert*-butyl-3-formylpyren-1-yl)cyclopentene (3.57)



Titanium(IV) chloride (0.51 mL, 0.51 mmol, 1.0 M solution in dichloromethane) was added to a stirred 0 °C solution of 1,2-bis(7-*tert*-butylpyren-1-yl)cyclopentene (**3.56**) (0.116 g, 0.201 mmol) and dichloromethyl methyl ether (0.057 g, 0.502 mmol) in dichloromethane (12 mL). The cooling bath was removed and the reaction was allowed to warm to room temperature. The reaction mixture was stirred for 2 h and then poured into ice water (50 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 20 mL) and the combined organic extracts were washed with a saturated solution of sodium bicarbonate (20 mL), washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The brown residue was

subjected to column chromatography (20 × 2.0 cm; 2:1 dichloromethane/hexanes) to yield 1,2-bis(7-*tert*-butyl-3-formylpyren-1-yl)cyclopentene (**3.57**) as a light brown oil (0.095 g, 74%): R_f = 0.17 (2:1 dichloromethane/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.74 (s, 2H), 9.16 (d, *J*=9.3 Hz, 2H), 8.37 (d, *J*=9.1 Hz, 2H), 8.28 (s, 2H), 8.17 (s, 4H), 8.10 (d, *J*=9.3 Hz, 2H), 8.07 (d, *J*=9.1 Hz, 2H), 3.39 (t, *J*=7.4 Hz, 4H), 2.58 (q, *J*=7.4 Hz, 2H), 1.53 (s, 18H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 193.38, 150.24, 141.96, 134.97, 133.91, 132.89, 131.84, 131.46, 130.75, 128.72, 126.04, 125.11, 125.08 124.77, 124.63, 123.13, 123.10, 42.34, 35.18, 32.37, 27.46 (only 21 of 22 signals observed); LCMS (APCI-positive) *m/z* (rel. int) 639 (12), 638 (52) 637 (100, $(MH)^+$), 581 (14, $[(M–t\text{-Bu})H]^+$); HRMS (EI) calculated for $C_{47}H_{40}O_2$ $(M)^+$ 636.3028, found 636.3036.

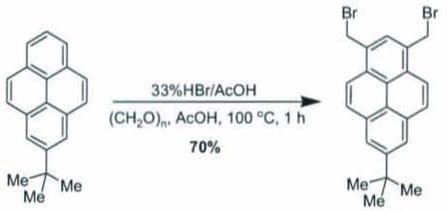
1,2-Bis(3-methyl-7-*tert*-butylpyren-1-yl)cyclopentene (3.58)



Titanium(IV) chloride (0.119 g, 0.627 mmol) was added to a stirred 0 °C slurry of zinc dust (0.041 g, 0.784 mmol) in THF (8 mL). After the addition was complete, the reaction was heated to reflux for 1 h, at which point a dark black color persisted. Pyridine (0.1 mL) was added and the mixture was stirred at reflux for 10 min. A solution of 1,2-bis(3-

formyl-7-*tert*-butylpyren-1-yl)cyclopentene (**3.57**) (0.041 g, 0.066 mmol) in THF (4 mL) was added and the mixture was heated at 70 °C for 5 h. The reaction mixture was then poured without significant cooling into chloroform (20 mL). The resulting solution was concentrated under reduced pressure and adsorbed onto silica gel in preparation for column chromatography. Aqueous work-up for this reaction is not recommended as layer separation can be quite problematic and the yields are typically lower. The preadsorbed sample was subjected to column chromatography (20 × 2 cm; 1:9 dichloromethane/heaxanes) to yield 1,2-bis(7-*tert*-butyl-3-methylpyren-1-yl)cyclopentene (**3.58**) as a light green oil (0.012 g, 30%): R_f = 0.43 (1:9 dichloromethane/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J*=9.1 Hz 2H), 8.05 (s, 4H) 7.97 (d, *J*=9.2 Hz, 2H), 7.88 (d, *J*=9.2 Hz, 2H), 7.84 (d, *J*=9.1 Hz, 2H), 7.60 (s, 2H), 3.27 (t, *J*=7.4 Hz, 4H) 2.68 (s, 6H), 2.47 (q, *J*=7.4 Hz, 2H) 1.48 (s, 18H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 149.03, 141.48, 137.68, 134.76, 131.88, 131.63, 131.47, 128.83, 128.56, 127.44, 127.19, 126.52, 126.07, 126.03, 124.02, 123.81, 122.37, 122.26, 41.85, 35.65, 32.45, 20.21; LCMS (APCI-positive) *m/z* (rel. int.) 611 (11), 610 (52), 609 (100, $(MH)^+$), HRMS (EI) calculated for $C_{47}H_{44}$ $(M)^+$ 608.3443, found 608.3444.

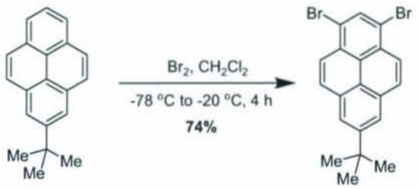
1,3-Bis(bromomethyl)-7-*tert*-butylpyrene (3.65)



2.33 **3.65**

33% HBr in acetic acid (1.73 mL, 9.90 mmol) was added to a stirred solution 2-*tert*-butylpyrene (**2.33**) (0.318 g, 1.23 mmol) and paraformaldehyde (0.295 g, 9.86 mmol) in glacial acetic acid (10 mL) at room temperature. The reaction was heated to 100 °C for 1 h and subsequently poured into water (100 mL). The resulting solution was extracted with dichloromethane (3 × 20 mL) and the combined organic extracts were washed with a saturated solution of sodium bicarbonate (2 × 50 mL), washed with water (50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was preadsorbed onto silica gel and subjected to column chromatography (20 × 3 cm; 1:1 dichloromethane/hexanes) to yield 1,3-bis(bromomethyl)-7-*tert*-butylpyrene (**3.65**) as a yellow solid (0.382 g, 70%): R_f = 0.45 (1:1 dichloromethane/hexanes); m.p. 227–229 °C (dichloromethane/hexanes, Lit[37] 229–231 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 2H), 8.27 (d, *J*=9.1 Hz, 2H), 8.20 (d, *J*=9.1 Hz, 2H), 7.95 (s, 1H), 5.12 (s, 4H), 1.58 (s, 9H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 150.14, 131.04, 130.44, 129.88, 129.25, 126.72, 125.89, 123.89, 123.11, 122.84, 35.47, 32.14, 31.89; LCMS (APCI-positive, *m/z* (rel. int.)) 447 (49), 445 (100), 443 (51); HRMS (EI) calculated for $C_{22}H_{20}{}^{79}Br_2$ $(M)^+$ 441.9932, found 441.9938.

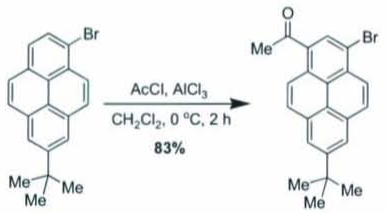
1,3-Dibromo-7-*tert*-butylpyrene (3.72)



2.33 **3.72**

Bromine (1.84 g, 11.6 mmol) as a solution in dichloromethane (20 mL) was added by syringe to a stirred –78 °C solution of 2-*tert*-butylpyrene (**2.33**) (1.51 g, 5.81 mmol) in dichloromethane (20 mL) over a 5 min period. The reaction was warmed slowly to –20 °C over a 4 h period, at which point a saturated solution of $NaHSO_4$ (50 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with water (30 mL), washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting yellow solid was recrystallized from dichloromethane/hexanes to afford 1,3-dibromo-7-*tert*-butylpyrene (**3.72**) as a white solid (1.78 g, 74%): R_f = 0.51 (hexanes); m.p. 296–297 °C (dichloromethane/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.34 (d, *J*=9.2 Hz, 2H), 8.29 (s, 2H), 8.16 (d, *J*=9.1 Hz, 2H), 1.59 (s, 9H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 150.67, 133.13, 131.19, 129.62, 129.20, 127.13, 125.85, 123.80, 121.91, 119.41, 35.52, 32.07; LCMS (APCI-positive) *m/z* (rel. int.) 416 (52), 415 (100, $(MH)^+$), 414 (51), 402 (24), 401 (52), 400 (23); HRMS (EI) calculated for $C_{20}H_{16}{}^{79}Br_2$ $(M)^+$ 413.9619, found 413.9618.

1-(3-Bromo-7-*tert*-butylpyren-1-yl)-ethanone (3.76)



3.75 3.76

Aluminum chloride (0.378 g, 2.84 mmol) was added to a stirred 0 °C solution of acetyl chloride (0.101 g, 1.29 mmol) and 1-bromo-7-*tert*-butylpyrene (**3.75**) (0.192 g, 0.572 mmol) in dichloromethane (20 mL). The reaction was poured into a large excess of ice water (100 mL) after 2 h and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 30 mL) and the combined organic extracts were washed with a saturated solution of sodium bicarbonate (50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a bright yellow solid. The resulting solid was purified via column chromatography (25 × 2 cm; dichloromethane) to yield 1-(3-bromo-7-*tert*-butylpyren-1-yl)-ethanone (**3.76**) as a bright yellow solid (0.180 g, 83%): R_f = 0.42 (dichloromethane); m.p. 180–182 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (d, *J*=9.5 Hz, 1H), 8.54 (s, 1H), 8.37 (d, *J*=8.9 Hz, 1H), 8.31–8.28 (m, 2H), 8.21 (d, *J*=9.2 Hz, 1H) 8.18 (d, *J*=9.3 Hz, 1H), 2.89 (s, 3H), 1.62 (s, 9H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 200.90, 150.50, 132.40, 131.53, 130.98, 130.91, 130.72, 130.51, 129.57, 128.84, 126.32, 125.74, 124.82, 124.44, 124.34, 122.12, 118.81, 32.06, 31.81, 30.61; LCMS (APCI-positive) *m/z* (rel. int.) 382 (22), 381 (98), 380 (25), 379 (100, $(MH)^+$); HRMS (EI) calculated for $C_{22}H_{19}{}^{79}BrO$ $(M)^+$ 378.0619, found 378.0614.

1-(3-Acetyl-7-*tert*-butyl-pyren-1-yl)-ethanone (3.89)

2.33 **3.89**

Aluminium chloride (2.82 g, 21.1 mmol) was added to a stirred 0 °C solution of 2-*tert*-butylpyrene (**2.33**) (1.24 g, 4.80 mmol) and acetyl chloride (0.357 g, 4.56 mmol) in dichloromethane (30 mL). The resulting slurry was stirred at 0 °C for 2 h. The reaction was poured into ice water (150 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 40 mL) and the combined organic extracts were washed with a saturated solution of sodium bicarbonate (50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a bright yellow solid. The resulting solid was subjected to chromatography (20 × 3.5 cm; dichloromethane) to yield 1-(3-acetyl-7-*tert*-butyl-pyren-1-yl)-ethanone (**3.89**) as a bright yellow solid (1.40 g, 85%): R_f = 0.22 (dichloromethane); m.p. 161–162 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (d, *J*=9.5 Hz, 2H), 8.59 (s, 1H), 8.29 (s, 2H), 8.14 (d, *J*=9.5 Hz, 2H), 2.87 (s, 6H), 1.58 (s, 9H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 201.41, 150.21, 131.93, 131.69, 130.65, 130.33, 128.01, 125.24, 124.85, 124.43, 122.12, 35.29, 31.97, 30.52; LCMS (APCI-positive) *m/z* (rel. int.) 344 (26), 343 (100, $(MH)^+$), 302 (9), 301 (34); HRMS (EI) calculated for $C_{24}H_{22}O_2$ $(M)^+$ 342.1620, found 342.1616.

3.5 References and Notes

[1] For examples of methodologies/key reactions and their application to total syntheses, see: Overman's aza-Cope/Mannich strategy in the synthesis of strychnine: (a) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc*, **1993**, *115*, 9293-9294; Vollhardt's cobalt-mediated [2+2+2] cycloaddition in the syntheses of estrone: (b) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1979**, *101*, 215-217 and strychnine: (c) Eichberg, M. J.; Dorta, R. L.; Lamottke, K.; Vollhardt, K. P. C. *Org. Lett.* **2000**, *2*, 2479-2481. Bodwell's transannular inverse electron demand Deils-Alder strategy in the formal synthesis of (±)-strychnine: (d) Bodwell, G. J.; Li, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 3261-3262.

For examples that demonstrate the use of these methodologies see: (e) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352-359.; (f) Bodwell, G. J.; Li, J. *Org. Lett.* **2002**, *4*, 127-130.

[2] The term "analog" is chosen here in preference to the term precursor, as the system in question is in fact a [2.2](1,3)pyrenophane *i.e.* directly "analogous" to a [2.2]metacyclophane. Both terms could serve the same purpose in this instance.

[3] For examples of methodology based studies and their applications to total synthesis see: ref. 1(f) (model) then, ref 1(d) (formal synthesis of (±)-strychnine; (a) Yamaguchi, J.; Seiple, I. B.; Young, I. S.; O'Malley, D. P.; Maue, M.; Baran, P.S. *Angew. Chem. Int. Ed.* **2008**, 47, 3578-3580 (model); then, (b) Su, S.; Seiple, I. B.; Young, I. S.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 16490-16491 (synthesis of massadine and massadine chloride).

[4] For examples of Ph.D. dissertations that involve model studies toward the synthesis of natural products see: (b) Dinsmore, Jason Matthew. Ph.D. Thesis, North Carolina State University, 2007; (b) Matunas, Robert. Ph.D. Thesis, Princeton University, 2007; (c) Cacatian, Salvacion Tabara. Ph.D. Thesis, Purdue University, 2003; (d) Cuniere, Nicolas Lucien. Ph.D. Thesis, Ohio State University, 2001; (e) Calvo, Rebecca Lynn. Ph.D. Thesis, State University of New York, Buffalo, 1999; (f) Merriam, Gregory Harold. Ph.D. Thesis, Ohio State University, 1990.

[5] For Examples see: (a) Nicolaou and co-workers use of IBX for the oxidation of alcohols, aldehydes and ketones to the corresponding α,β-unsaturated carbonyl systems: Nicolaou, K. C.; Zheng, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596-7597; (b) Jacobsen and Balskas' application of Corey and co-workers oxazaborrolidine cataylst in Intramolecular and TADA reactions: Balaskas, E. P.; Jacobsen, E. N. *Science* **2007**, *317*, 1736-1740; (c) Baran and co-workers use of Ag(II) picolinate as an oxidatant in the synthesis if (±)-Axinellamines A and B: O'Malley, D. P.; Yamaguchi, J.; Young, I. S.; Seiple, I. B.; Baran, P. S. *Angew. Chem. Int. Ed.* **2008**, *47*, 3581-3583.

[6] Total synthesis of anhydrochatancin: Toró, A.; Deslongchamps, P. *J. Org. Chem.* **2003**, *68*, 6847-6852.

[7] Model study toward the synthesis chatancin: Toró, A.; Wang, Y.; Drouin, M.; Deslongchamps, P. *Tetrahedron Lett.* **1999**, *40*, 2769-2772.

[8] Total synthesis of chatancin: Soucy, P.; L'Heureux, A.; Toró, A.; Deslongchamps, P. *J. Org. Chem.* **2003**, *68*, 9983-9987.

[9] Toró, A.; L'Heureux, A.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 2737-2740.

[10] for a detailed account of this synthesis and for concurrent commentary on the quality of this work see : Hudlicky, T.; Reid, J. W. *The Way of Synthesis*: *Evolution of Design and Methods for Natural Products,* **2007**, Wiley-VCH, Weinheim, 810-812.

[11] The Friedel-Crafts alkylation step of this sequence requires 5 equiv. of pyrene, which has to be eluted slowly during chromatography. Byproducts formed during the reaction have R_f values that are very close to the desired bis(2-pyrenyl)-dimethylalkane and makes for difficult separation on a large scale. For example, on a 5 g (pyrene) scale approximately 8 L of solvent was required for adequate chromatographic sepration. Solvent cannot be recycled, since the initial fractions contain the excess pyrene starting material.

[12] Miura, Y.; Yamano, E.; Tanaka, A.; Yamaguchi, J. *J. Org. Chem.* **1994**, *59*, 3294-3300.

[13] Due to the enthalpic driving force that is associated with the generation of TiO_2 in the McMurry reaction, some of the most strained ethylene systems known have been prepared using this reductive coupling method. For supporting reference see: (a) ref. 23; (b) Lenoir, D. *Synthesis* **1989**, 883-897; and (c) Fürstner, A.; Bogdanović, B. *Angew. Chem. Int. Ed.* **1996**, *35*, 2442-2469.

[14] The following chapter will give examples of the varying degrees of success that have been met with this reaction and its application in synthesis of [2.2]metacyclophane systems (see Chapter 4, Section 4.2).

[15] Mitchell, R. H. *Advances in Theoretically Interesting Molecules*, **1989**, *1*, 35-199; JA1 Press, Greenwich.

[16] 7-*tert*-Butyl analogs of the desired tethered systems were targeted as a means to generate new chemistry of the 2-*tert*-butylpyrene (and analogous) system(s).

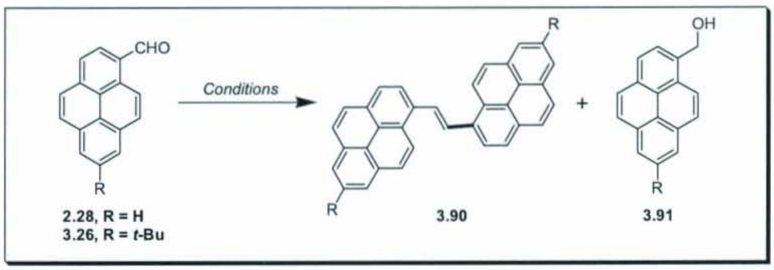
[17] Merner, B. L.; Bodwell, G. J. *unpublished results*

[18] The low solubility of compound **3.37** in common NMR solvents made obtaining suitable ^{13}C NMR data for this compound impossible.

[19] Dialdehyde **3.37** was virtually insoluble in THF and even upon heating only a suspension could be obtained.

[20] The McMurry reaction conditions applied here were chosen as a result of a screening experiment with two pyrene aldehydes:

Screening McMurry reaction condtions for pyrene aldehydes



Conditions	Results
1. $TiCl_3/LiAlH_4$, THF, 0 °C to 70 °C, 6 to 24 h	1. **3.91** <10% and starting material (<10%)
2. $TiCl_4/LiAlH_4$, THF, 0 °C to 70 °C, 6 to 24 h	2. trace amount of **3.91**
3. $TiCl_3(DME)_{1.5}$, DME, 0 °C to 70 °C, 6 to 24 h	3. only starting material recovered (<50%)
4. $TiCl_4$, Zn, pyridine, THF, 0 °C to 70 °C, 6 h	4. **3.90** (~30%) and starting material (~50%)

[21] By TLC analysis only a single new spot forms. Isolation of this compound was possible, however characterization was not. Clearly from ^1H NMR and LCMS analysis, the isolated compound was not the desired [2.2]cyclophane or the over reduced ethyl substituted system.

[22] (a) $TiCl_4$/Zn: Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, *2*, 1041-1044; (b) $TiCl_3$/Mg: Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chim. Fr.* **1973**, 2147-2148; (c) $TiCl_3/LiAlH_4$: McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708-4709 (d) $TiCl_3$/K: McMurry, J. E.; Fleming, M. P. *J. Org. Chem.* **1976**, *41*, 896-897; (e) $TiCl_3$/Zn-Cu: McMurry, J. E. Krepski, L. R. *J. Org. Chem.* **1976**, *41*, 3929-3930; (f) $TiCl_4$/Zn, pyridine: Lenoir, D. *Synthesis* **1977**, 553; (g) $TiCl_3(DME)_{1.5}$/Zn-Cu: McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.* **1989**, *54*, 3748-3749.

[23] See: Takeda, T. Ed. *Modern Carbonyl Olefination* **2004**, pp. 223-285; WILEY-VCH, Weinheim.

[24] McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513-1524.

[25] See: Ephritikhine, M. *Chem. Commun.* **1998**, 2549-2554 and ref. 13(c).

[26] Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367,* 630-634.

[27] Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513-3515.

[28] Zeng, D. X.; Chen, Y. *Synlett* **2006**, 490-492.

[29] For examples see: Nakamura, Y.; Fujii, T.; Nishimura, J. *Chem. Lett.* **2001**, 970-971; (b) Zavarzin, I. B.; Smirnova, N. G.; Yarovenko, V. N.; Krayushkin, M. M. *Russ. J. Org. Chem.* **2007**, *43*, 753-757; (c) Akazawa, M.; Uchida, K.; de Jong, J. J. D.; Areephong, J.; Stuart, M.; Caroli, G.; Browne, W. R.; Feringa, B. L. *Org. Biomol. Chem.* **2008**, *6*, 1544-1547.

[30] Nakamura, Y.; Yamazaki, T.; Nishimura, J. *Org. Lett.* **2005**, *7*, 3259-3262.

[31] When 1,3-bis(bromomethyl)-7-*tert*-butylpyrene was prepared in pure form, the compound had accidentally crystallized in a column fraction.

[32] For examples see: (a) Sato, T.; Nishiyama, K.; Morita, A.; Iitaka, Y. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2366-2369; (b) Tashiro, M.; Yamato, T.; Kobayashi, K.; Arimura, T. *J. Org. Chem.* **1987**, *52*, 3196-3199; (c) Yamato, T.; Ide, S.; Tokuhisa, K.; Tashiro, M. *J. Org. Chem.* **1992**, *57*, 271-275; (d) Bodwell, G. J.; Frim, R.; Hopf, H.; Rabinovitz, M. *Chem. Ber.* **1993**, *126*, 167-175; (e) Yamato, T.; Matsumoto, J.; Tashiro, M. *J. Chem. Res. Synop.* **1994**, 246-2477.

[33] Sato, T.; Wakabayashi, M.; Okamura, Y.; Amada, T.; Hata, K. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2362-2365.

[34] Shair, M. D.; Yoon, T.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1995**, *34*, 1721-1723.

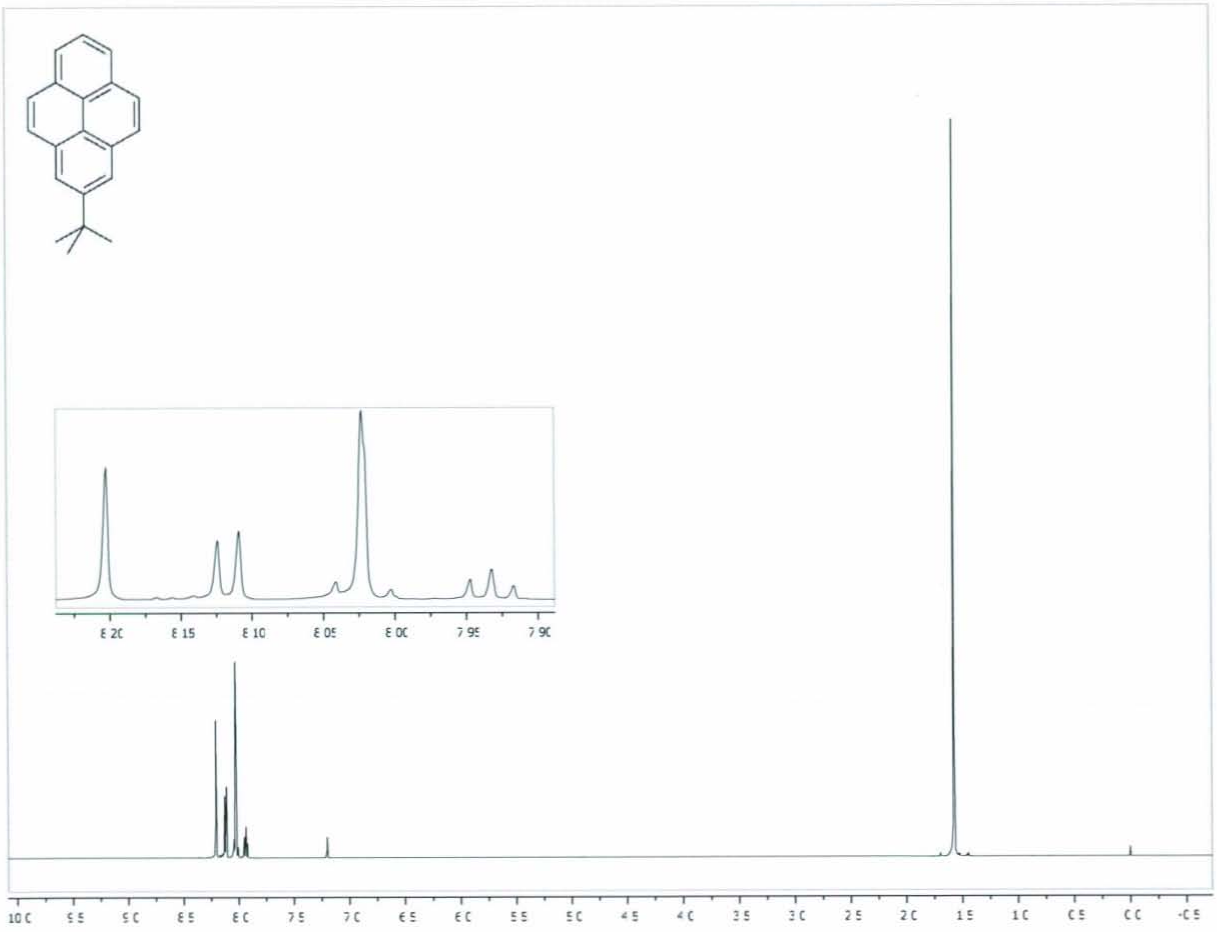
[35] Tashiro, M.; Yamato, T. *J. Am. Chem. Soc.* **1982**, *104*, 3701-3707.

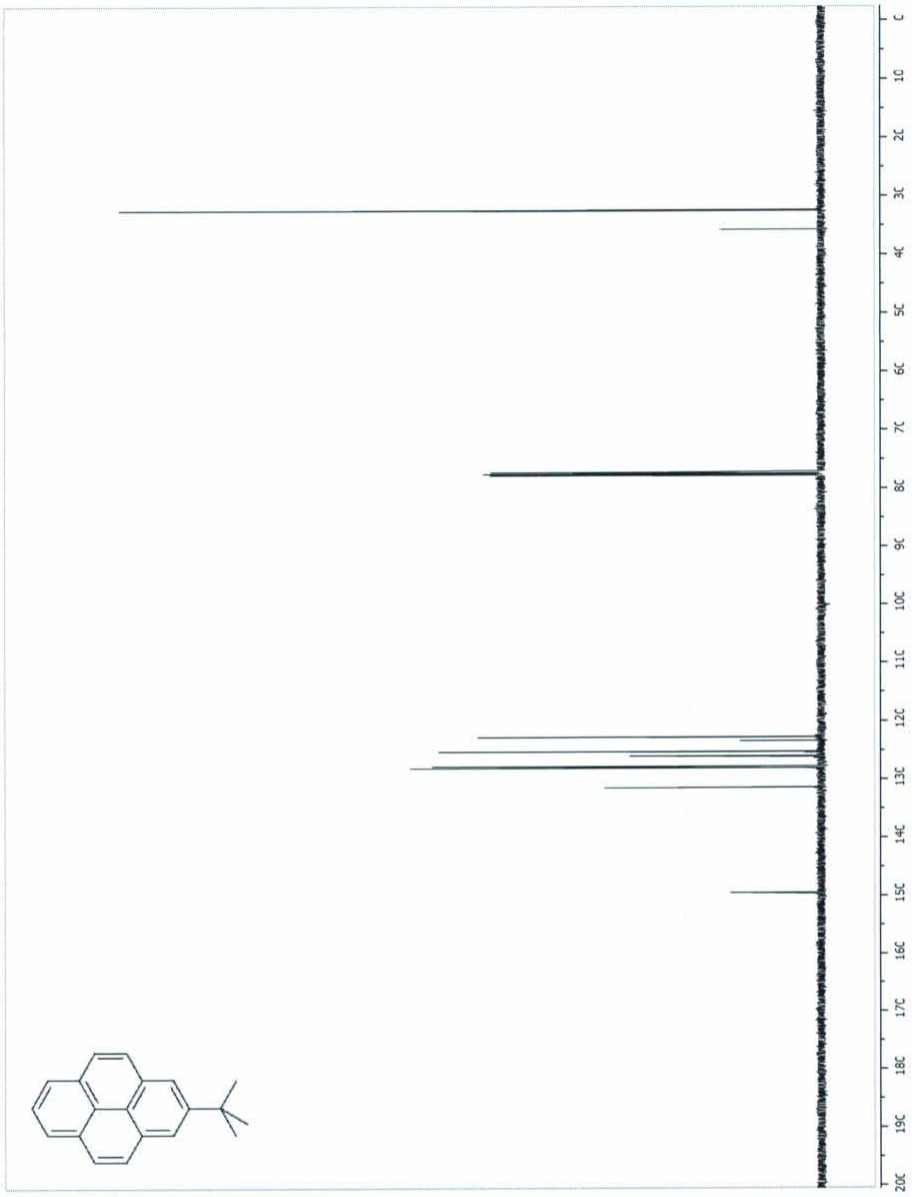
[36] Tashiro, M.; Yamato, T.; Kobayashi, K.; Arimura, T. *J. Org. Chem.* **1987**, *52*, 3196-3199.

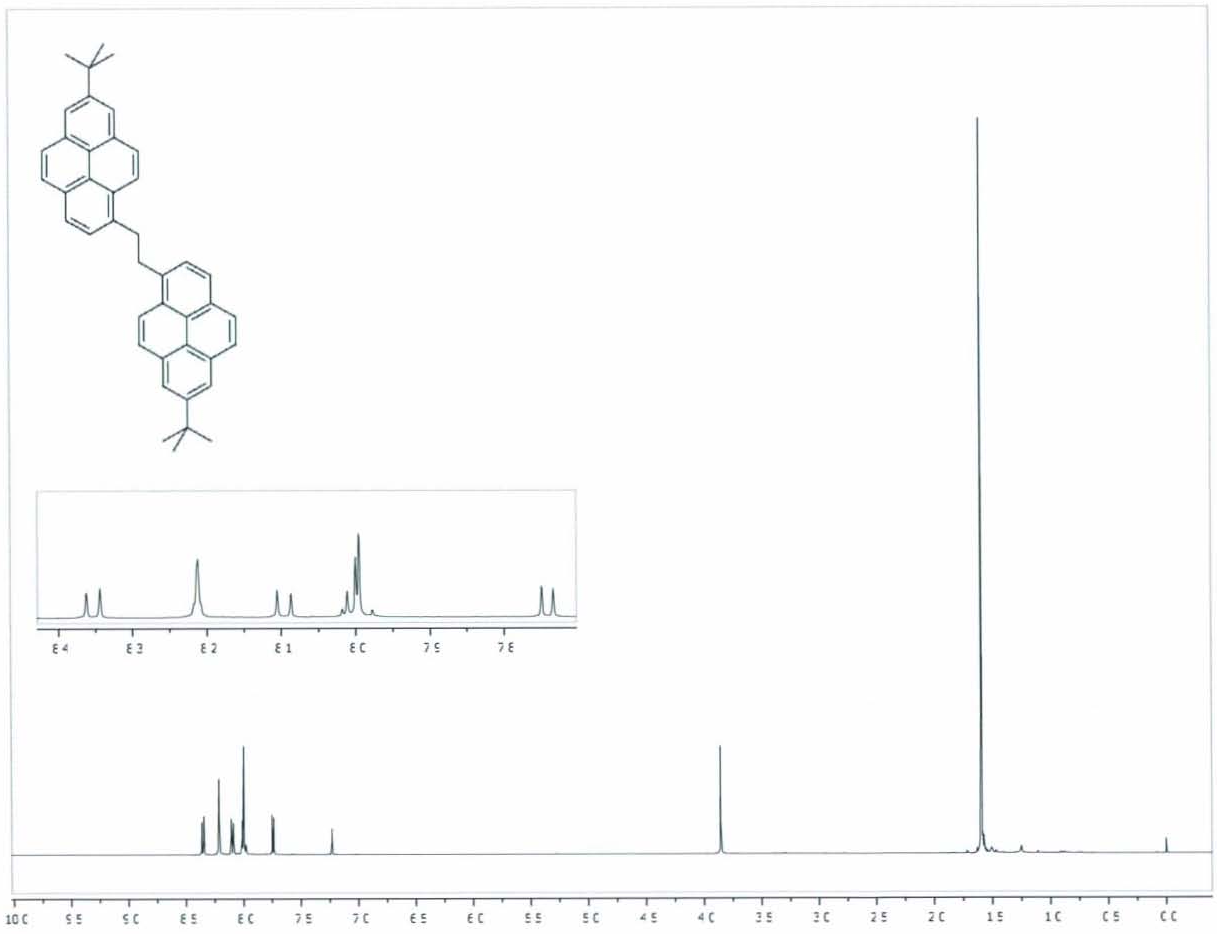
[37] Yamato, T.; Miyazawa, A.; Tashiro, M. *J. Chem. Soc.* **1993**, 3127-3137.

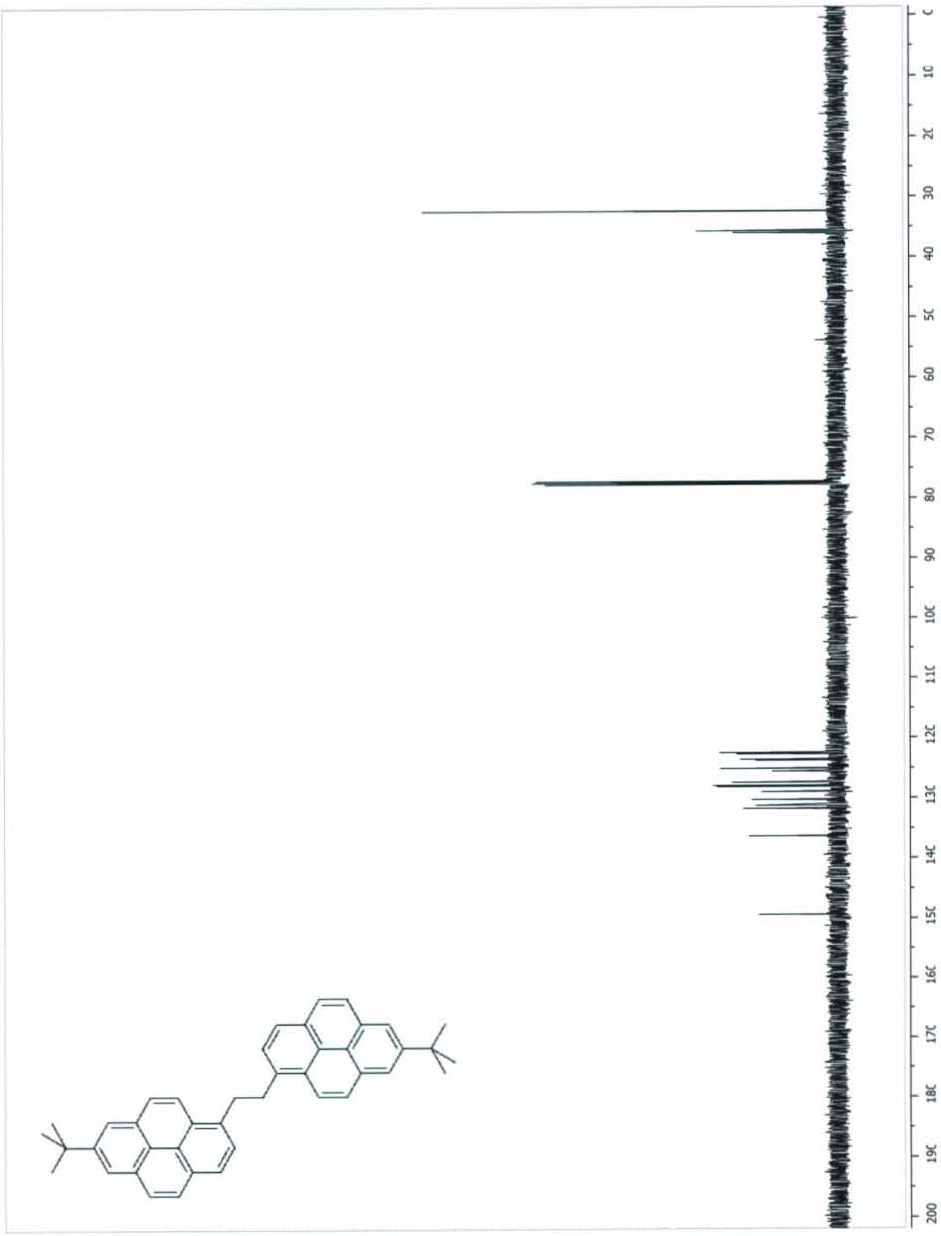
Appendix 2

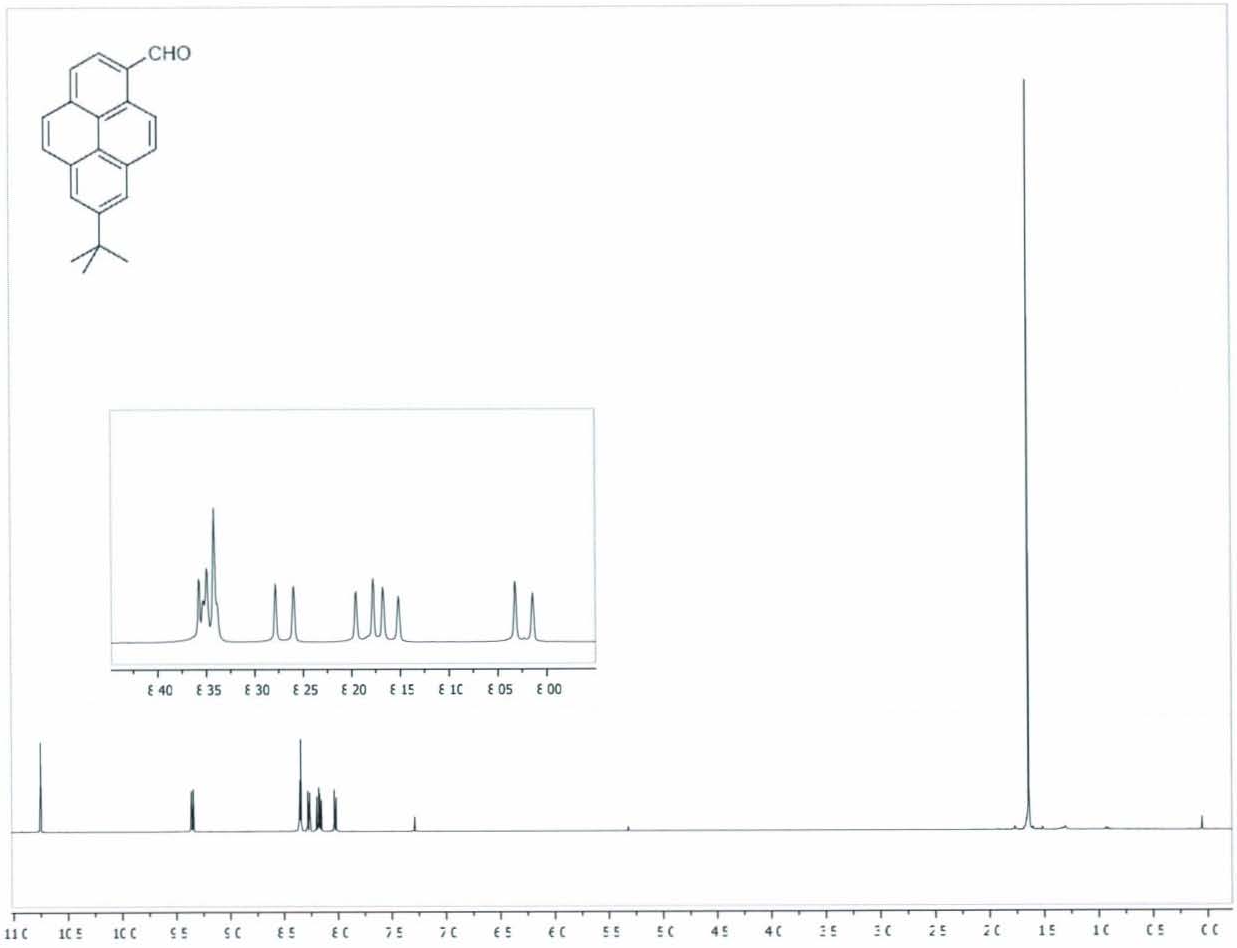
Selected ^{1}H and ^{13}C NMR Spectra for Chapter 3







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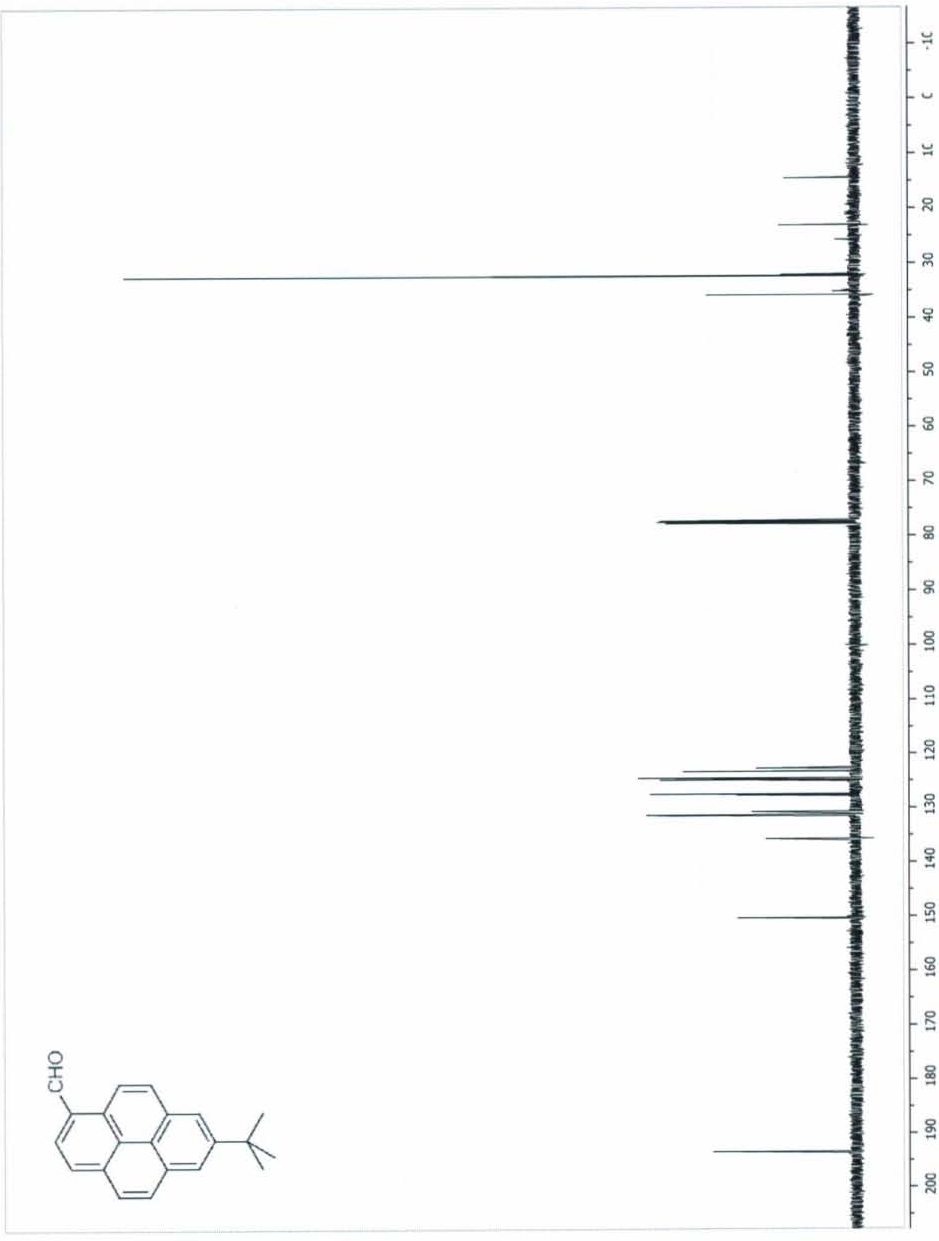
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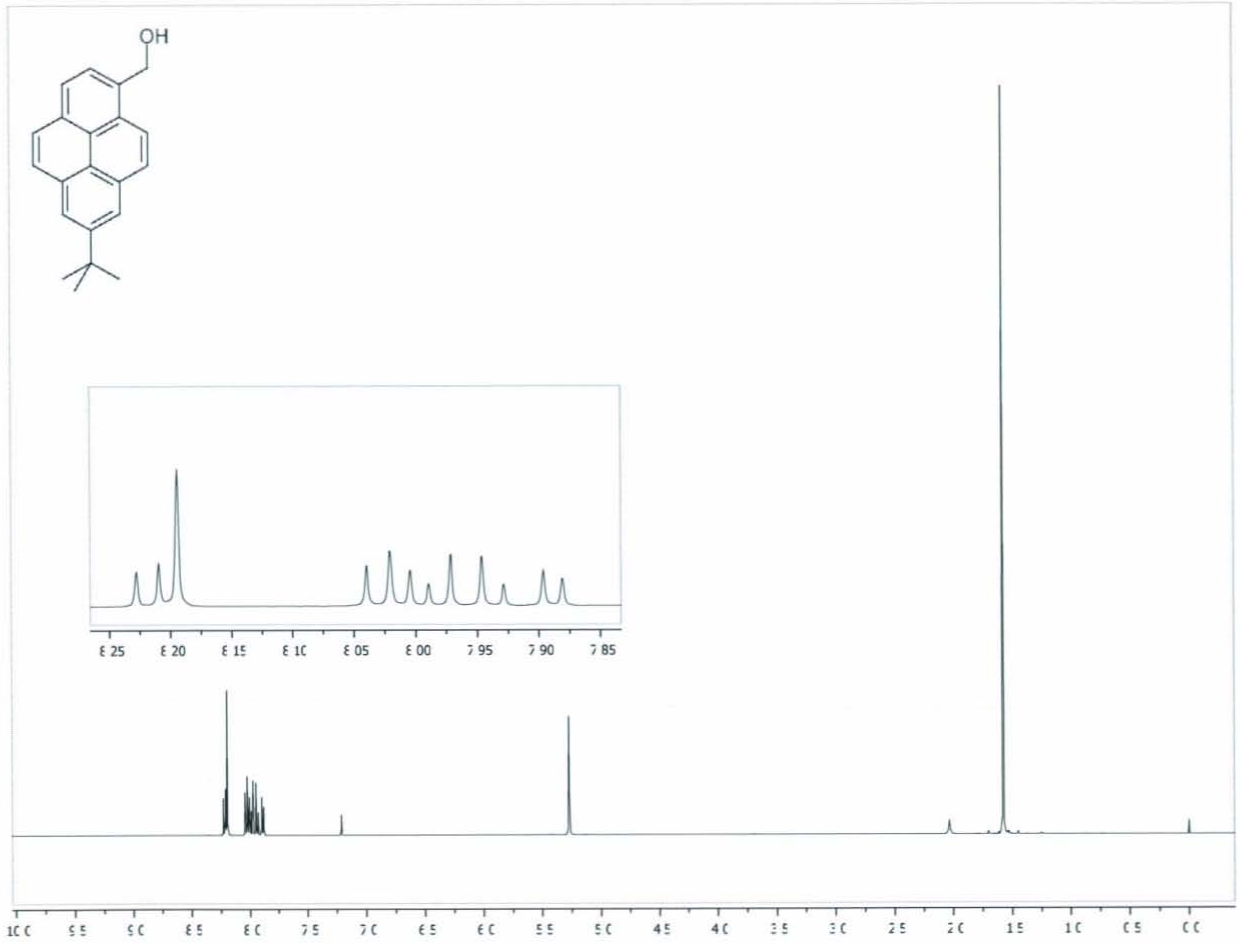
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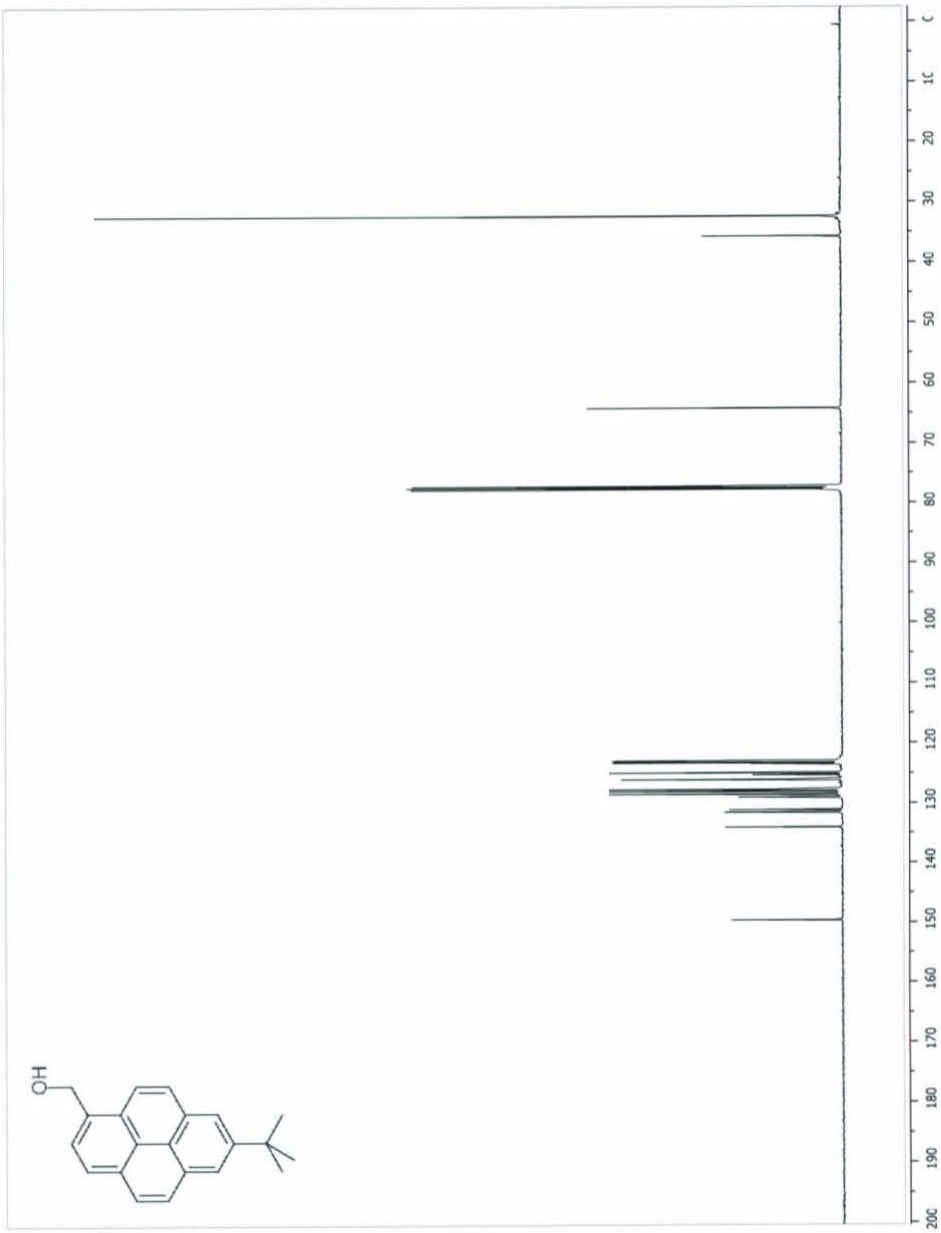
7.85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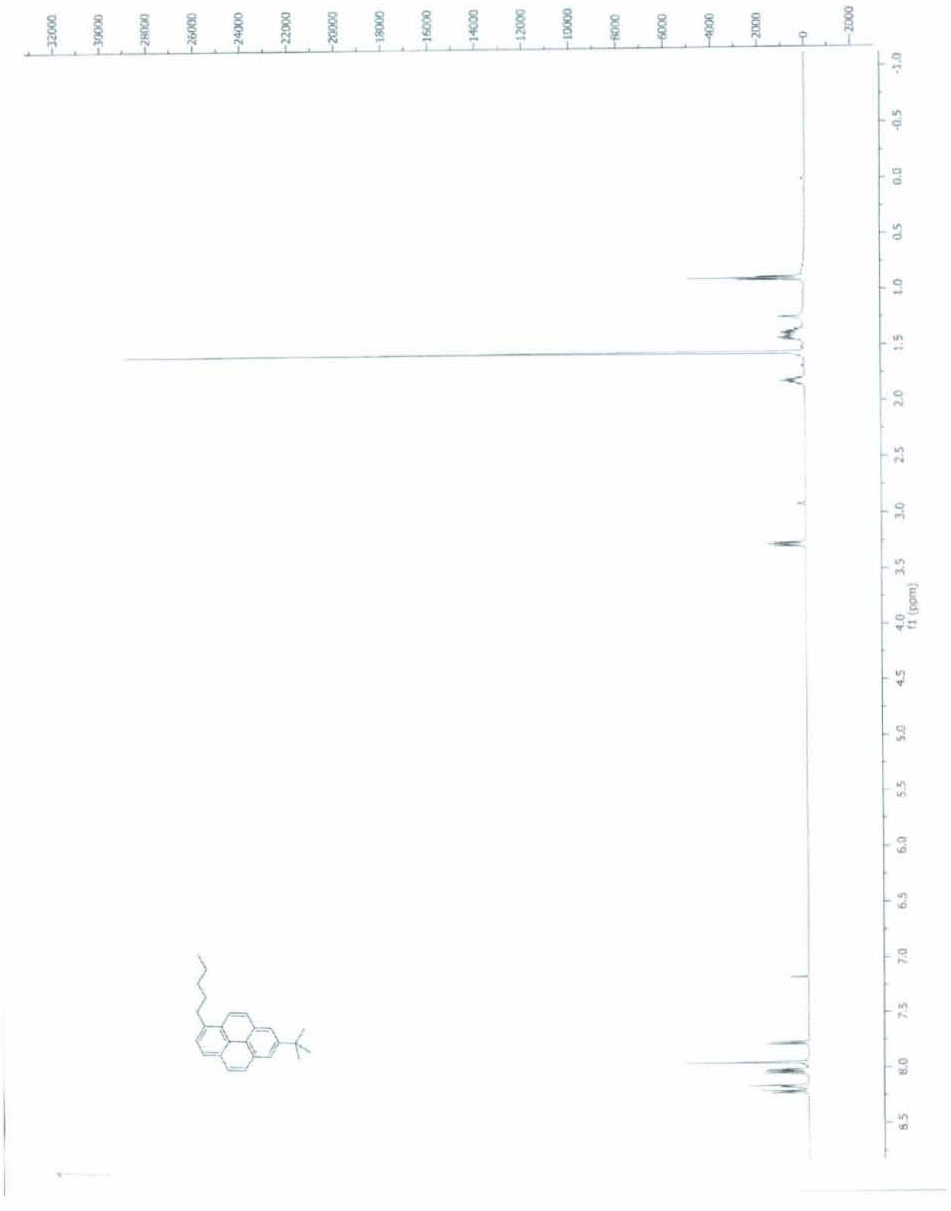
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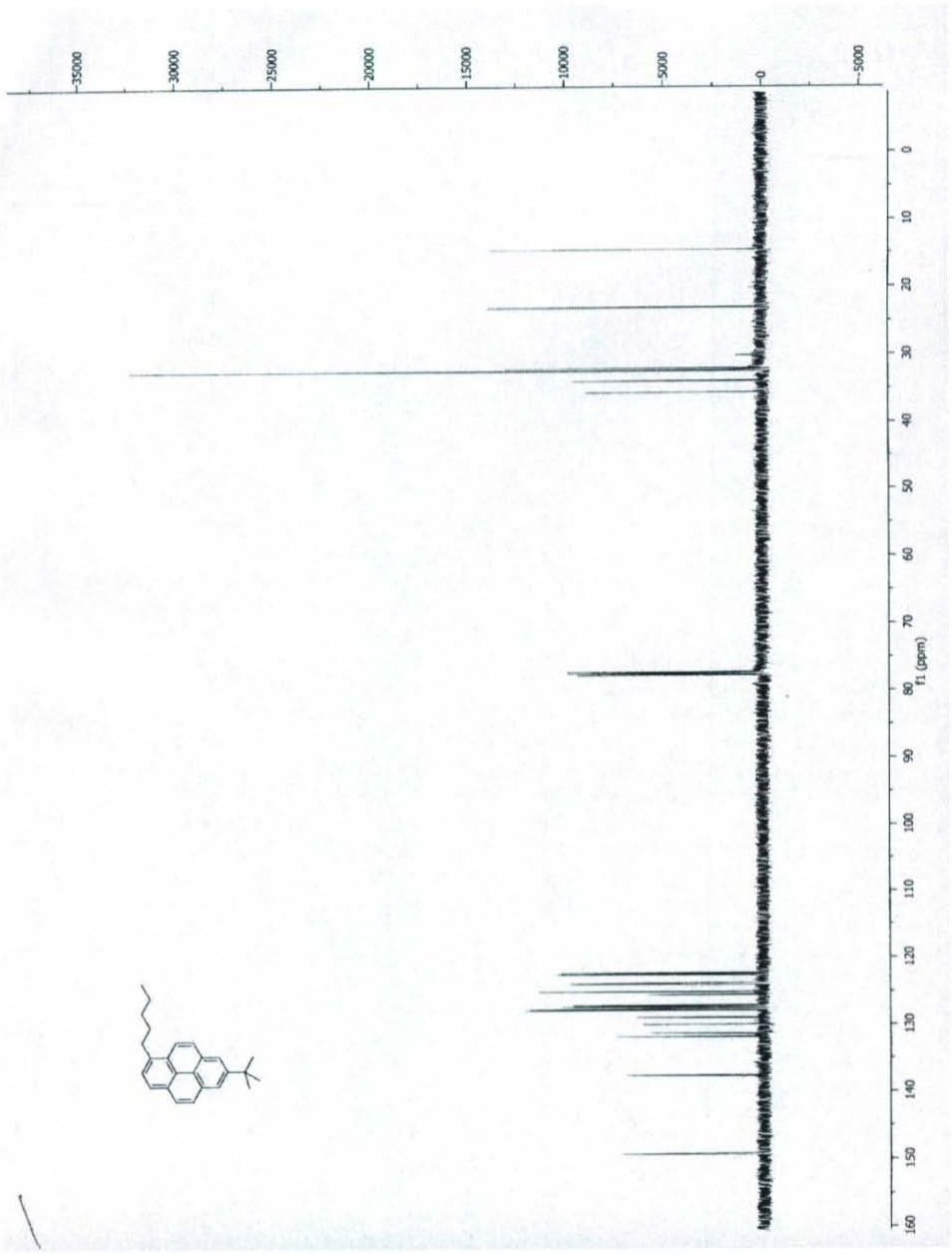
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110
120
130
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150
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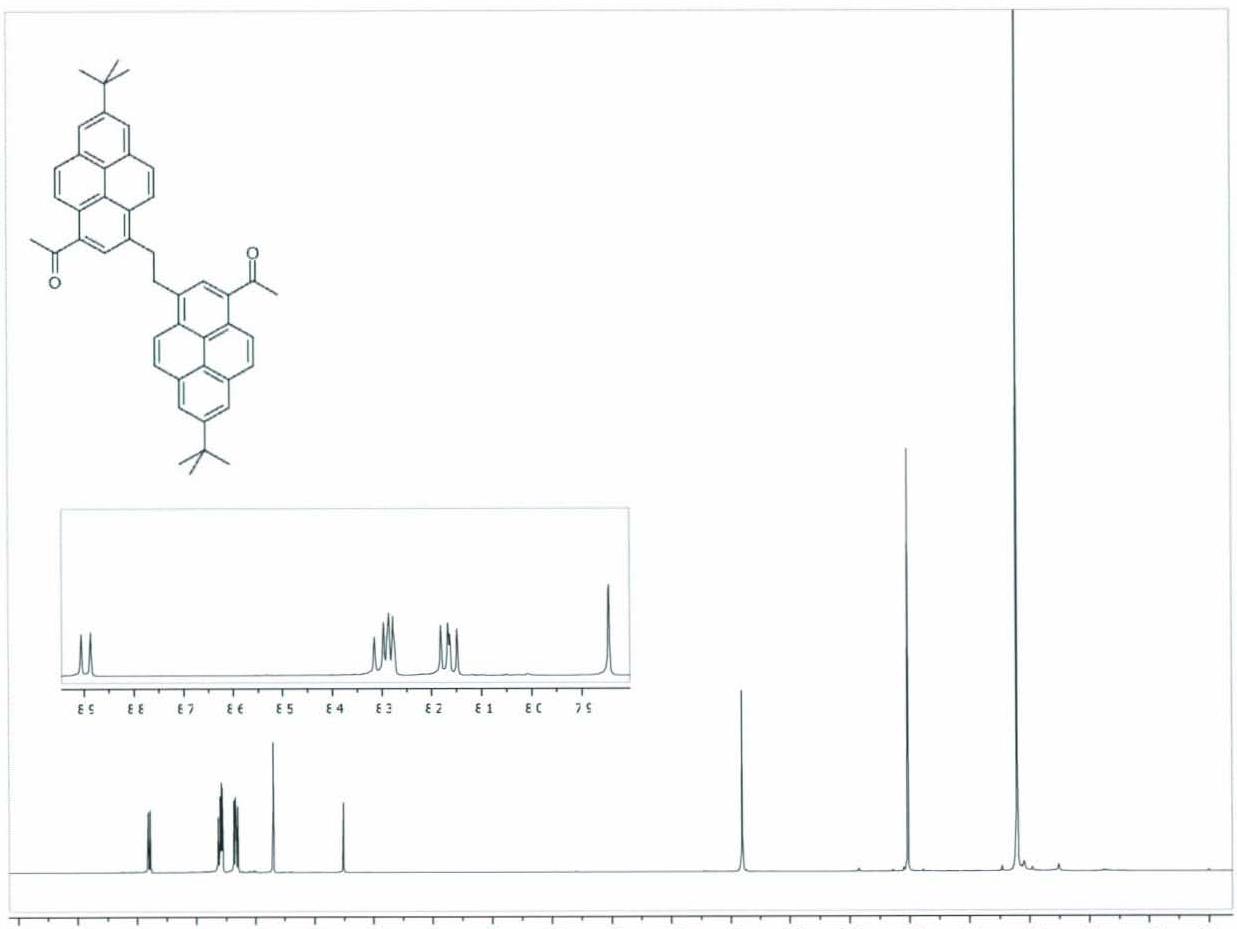
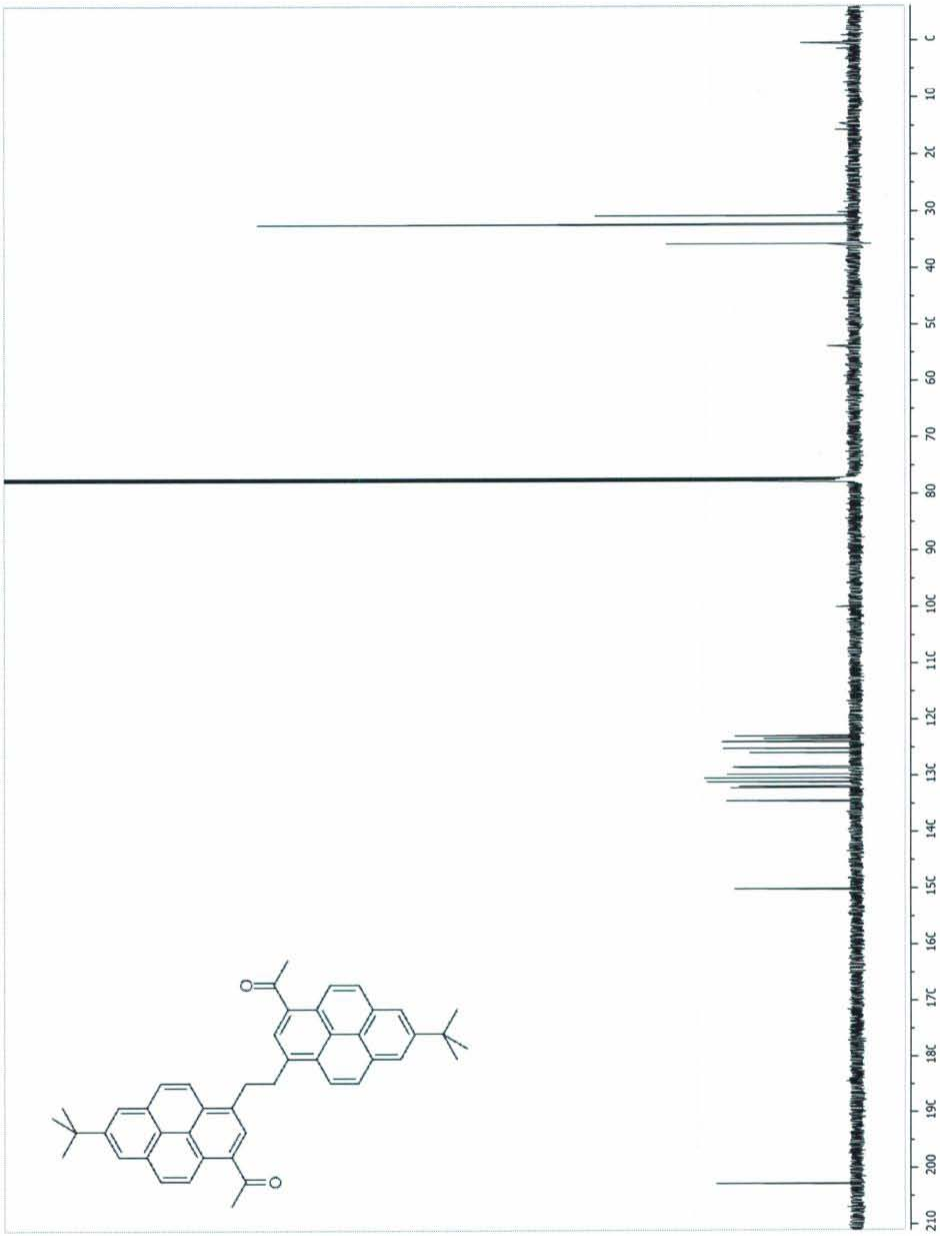
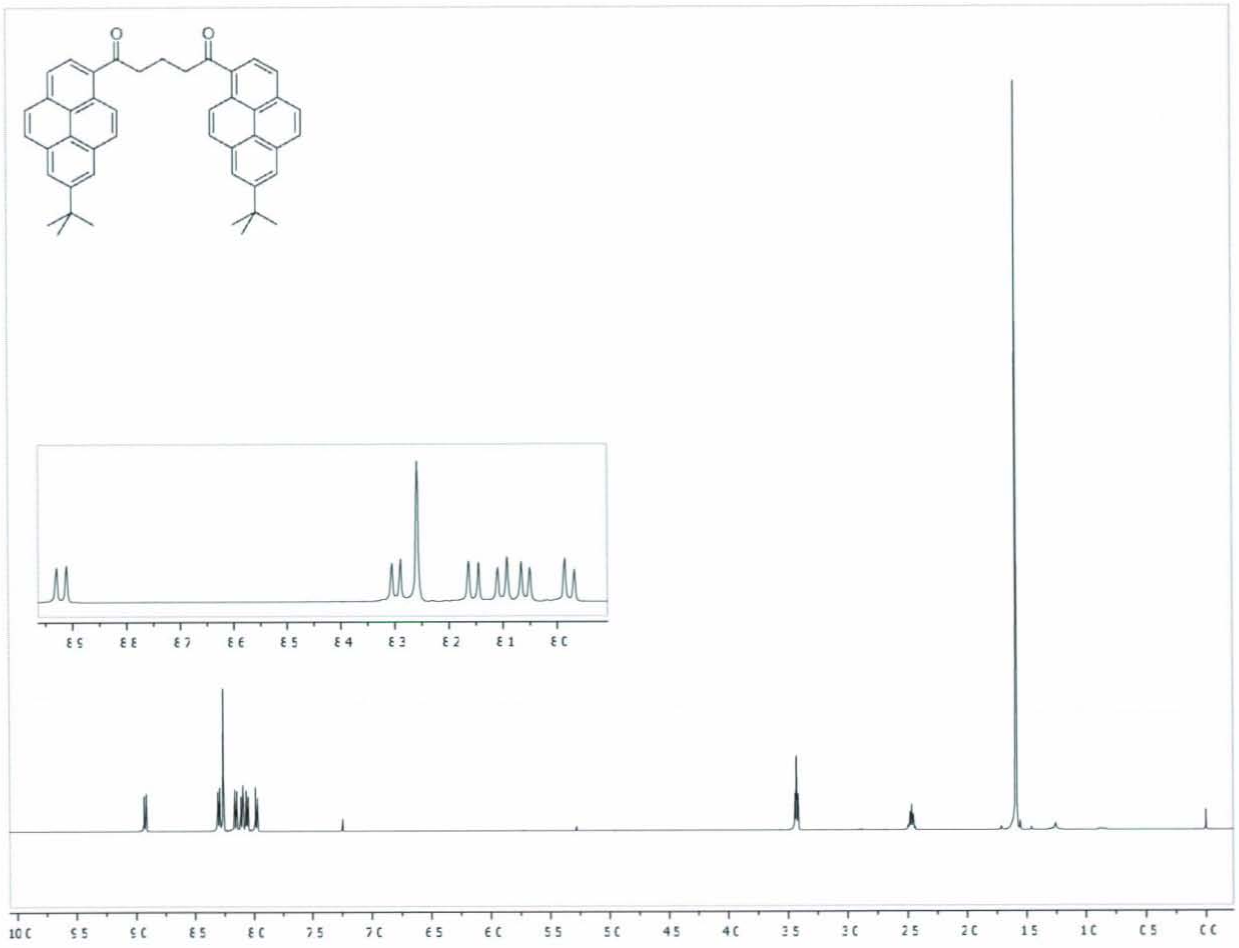
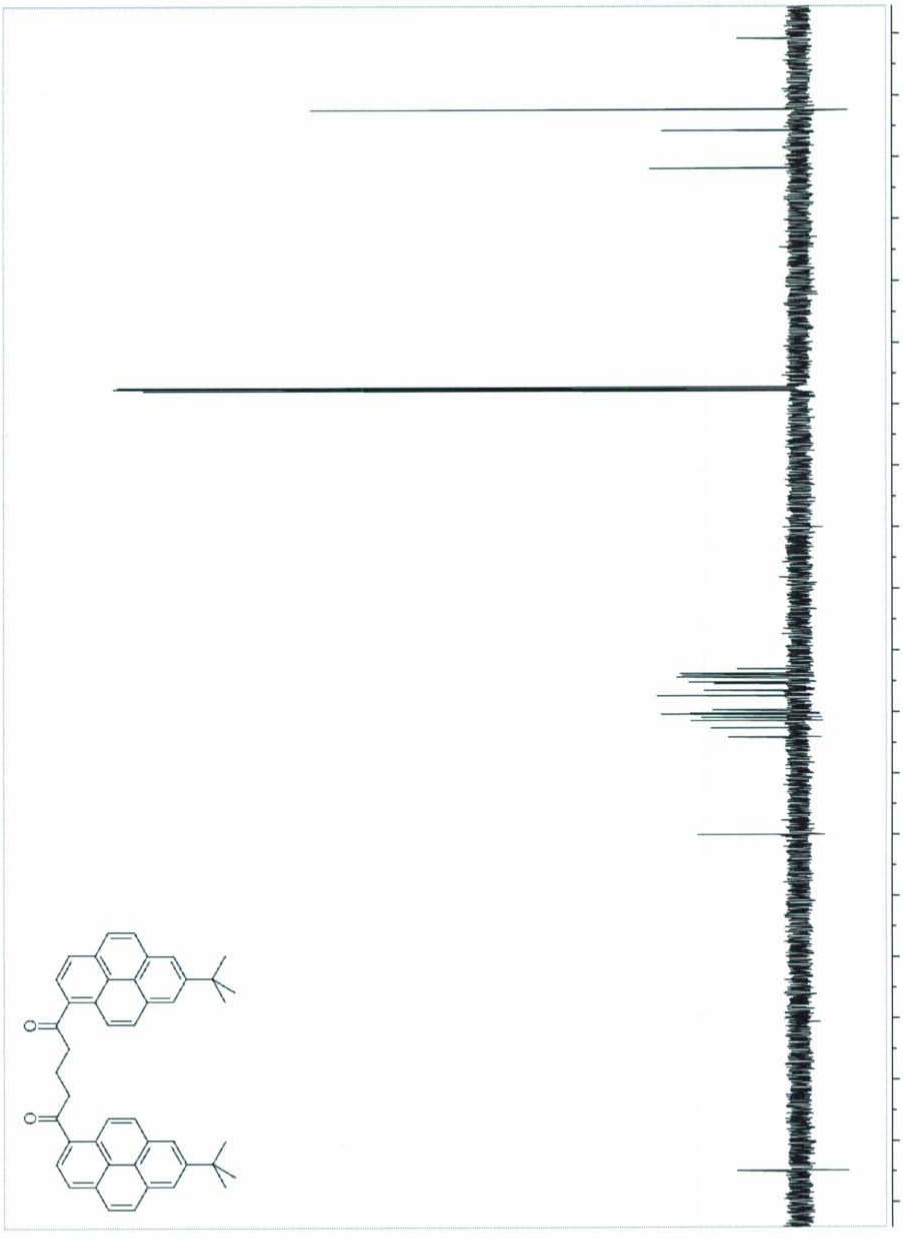
f1 (ppm)





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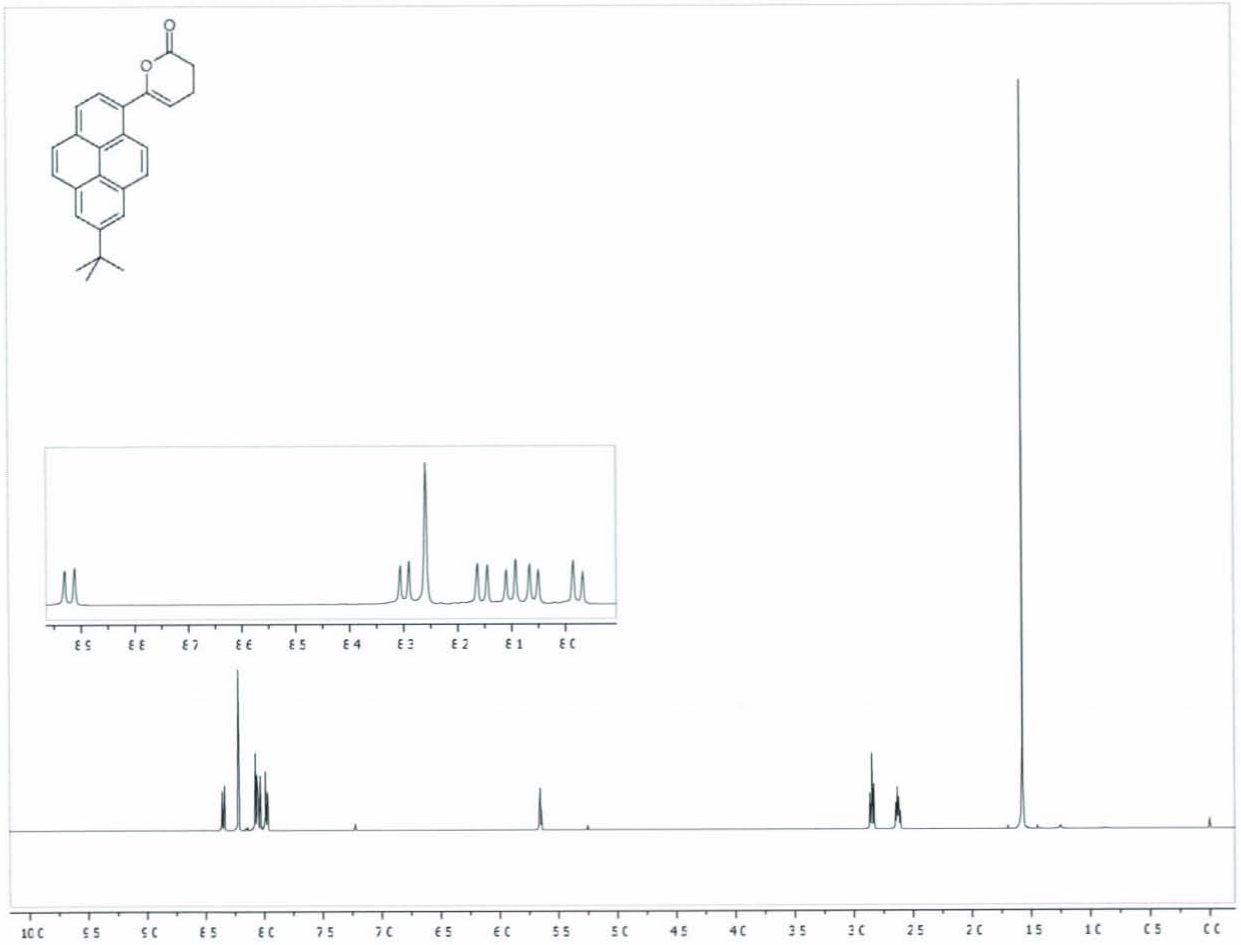

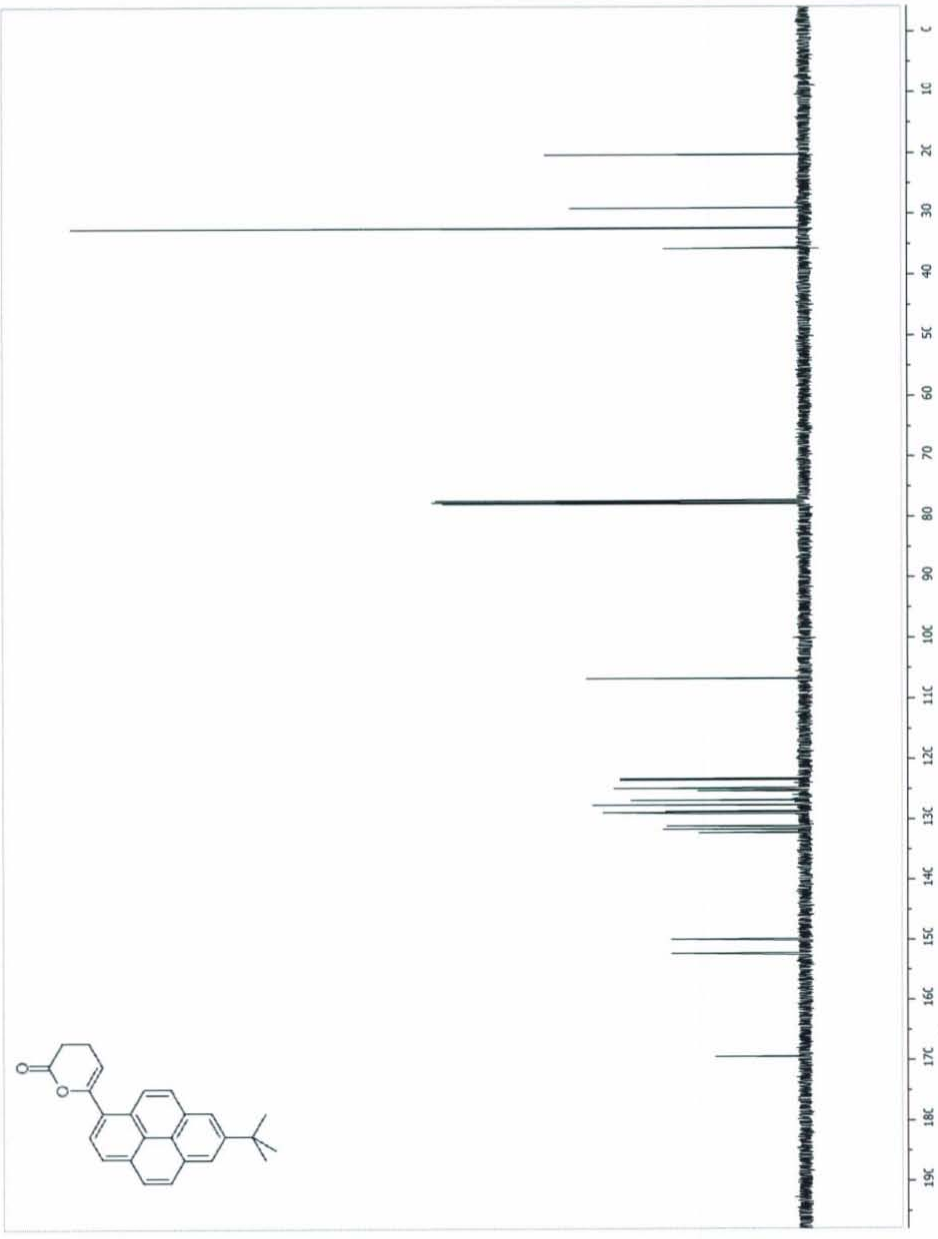

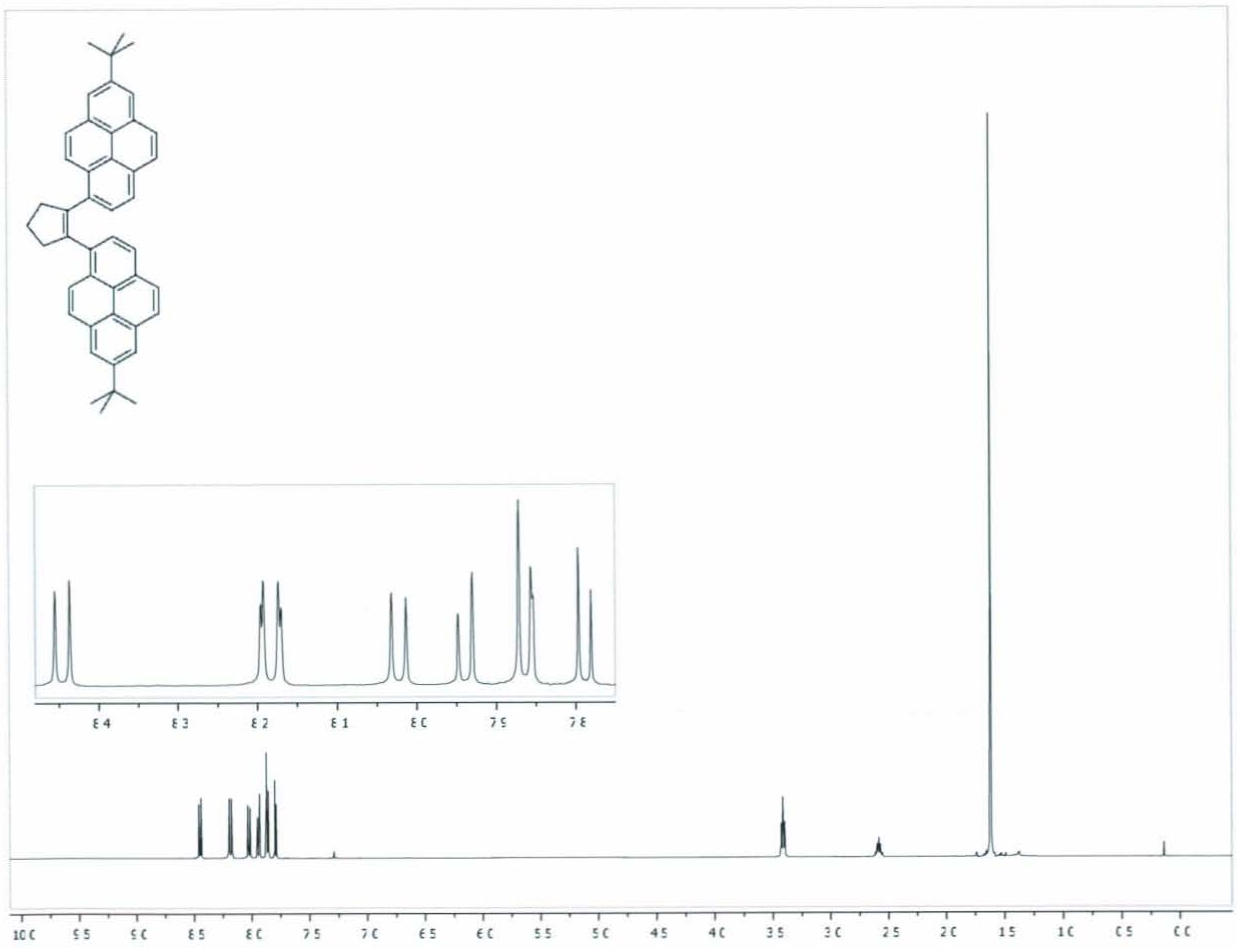
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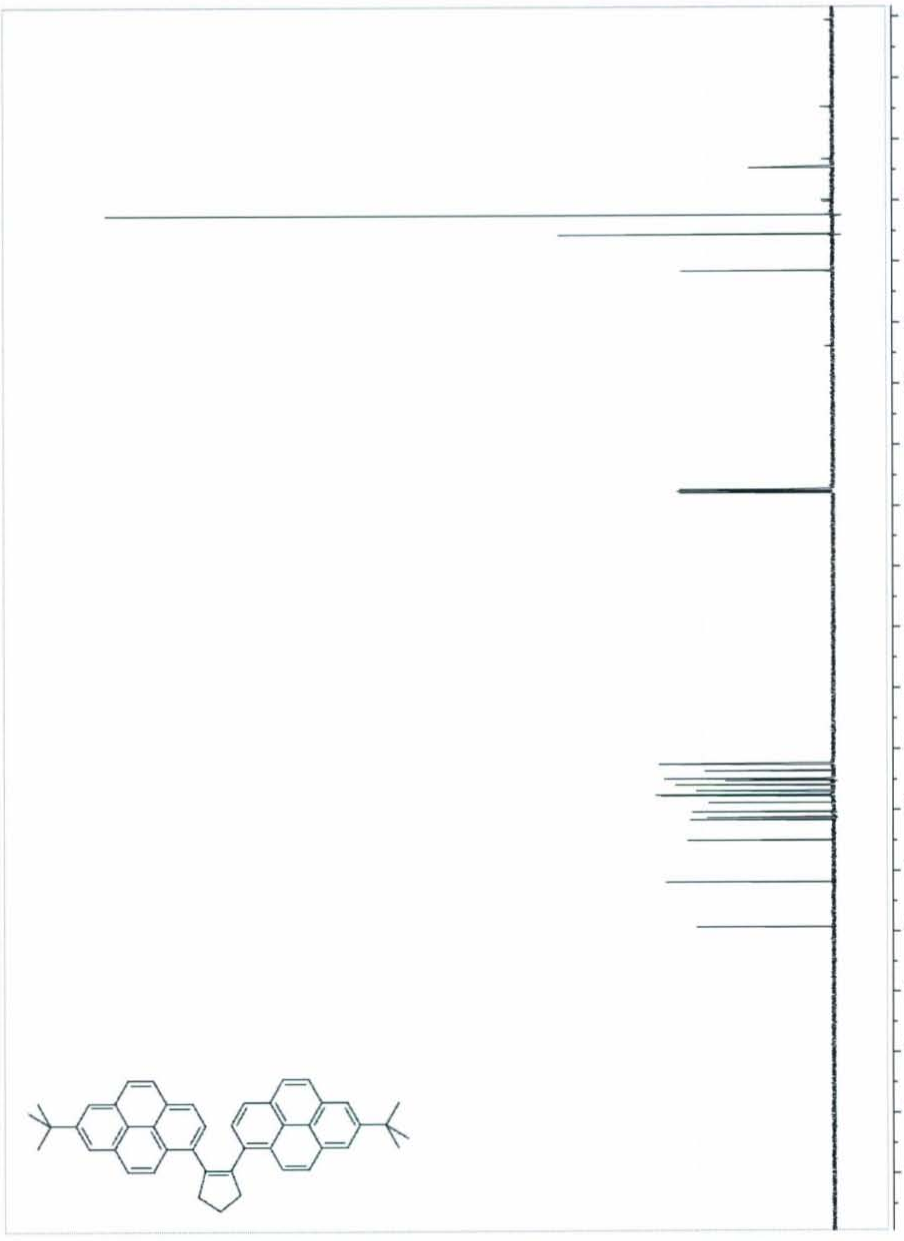
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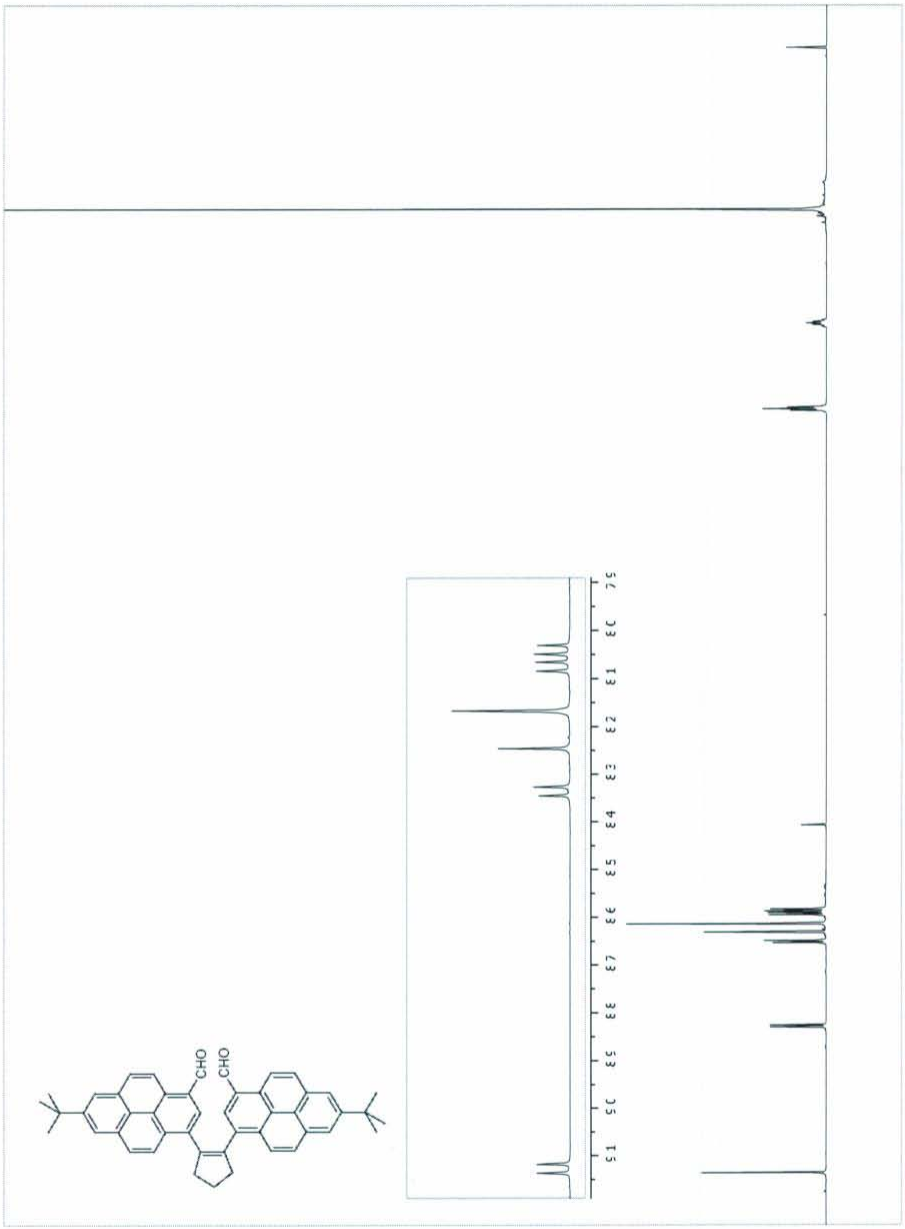
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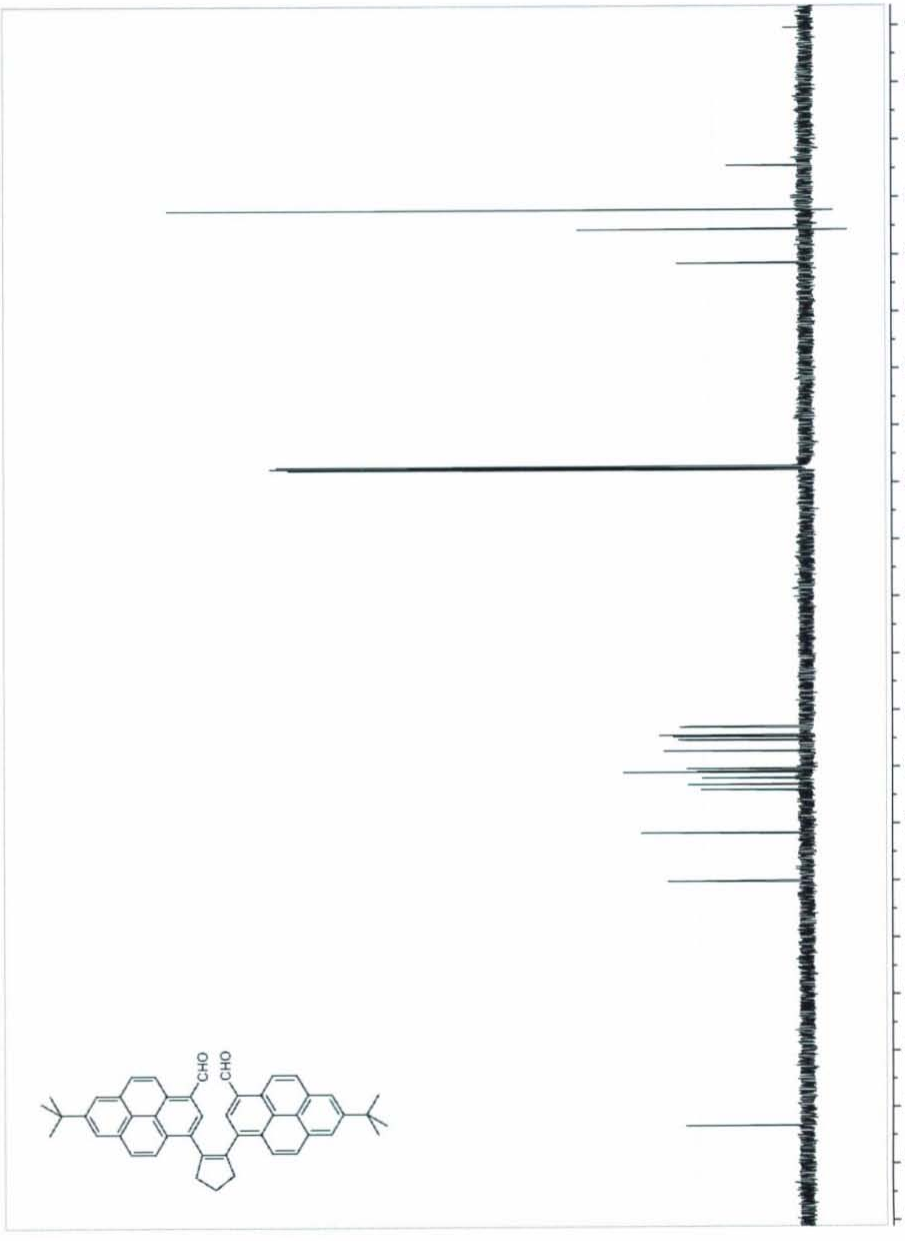
CHO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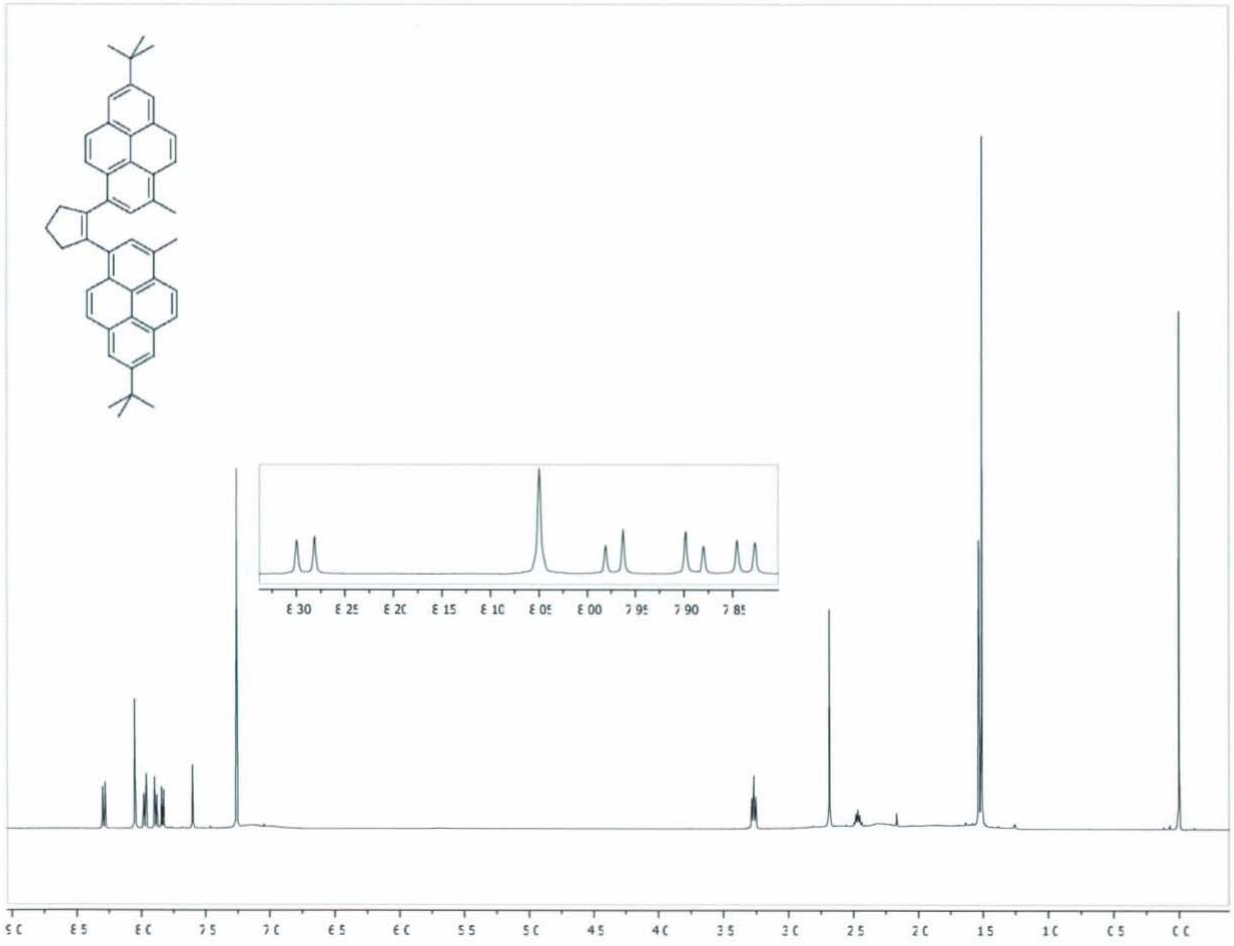

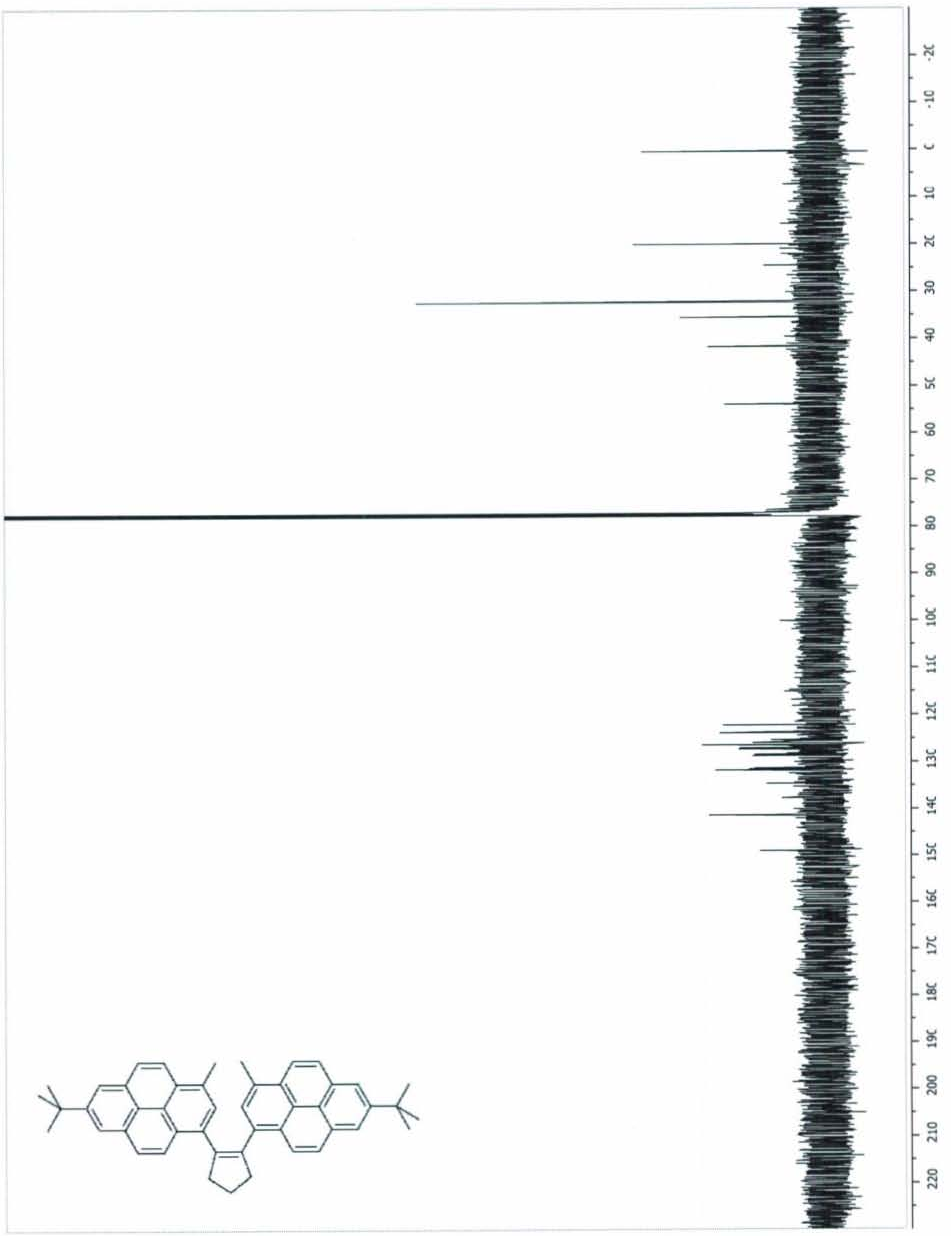

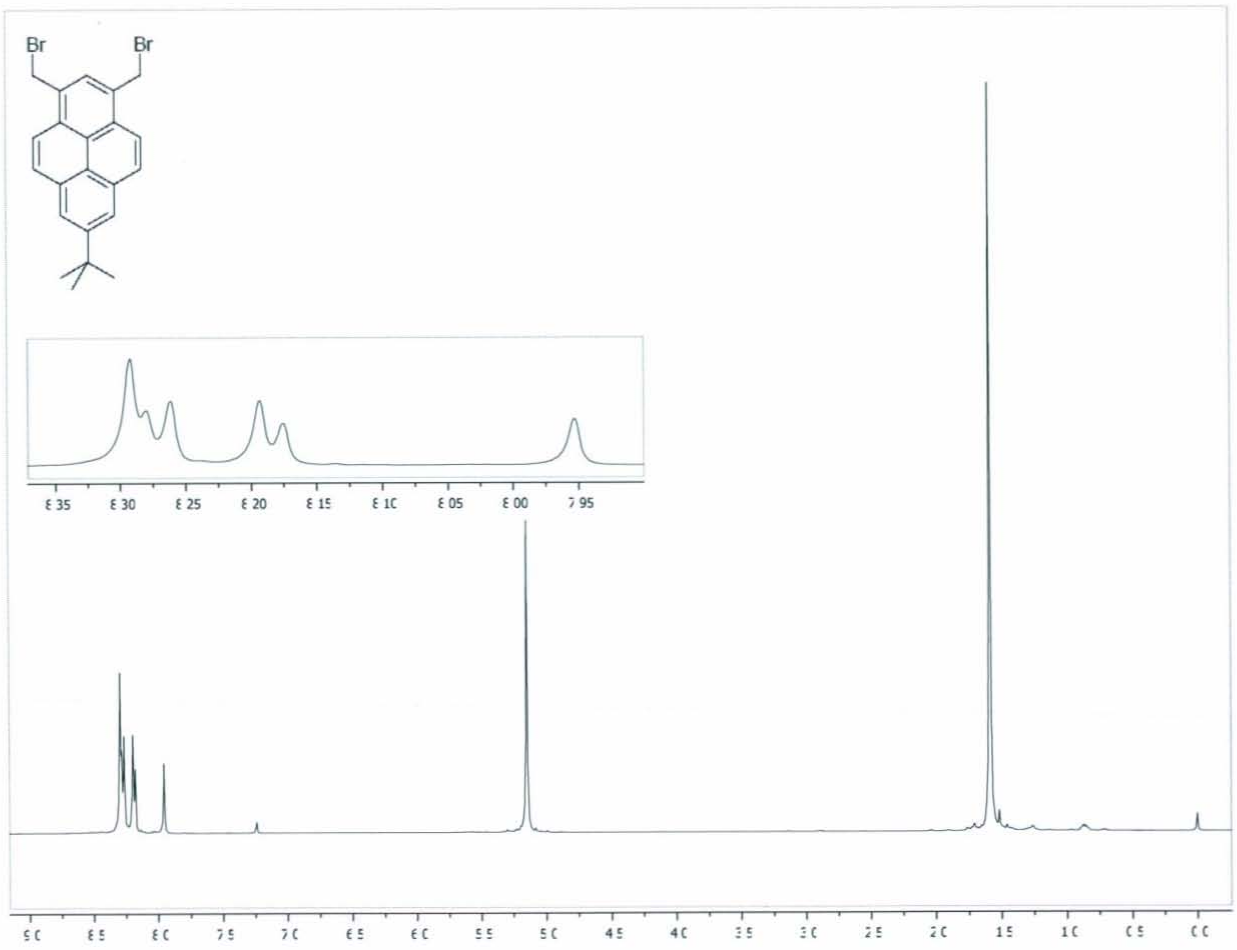
Br
Br
8 35
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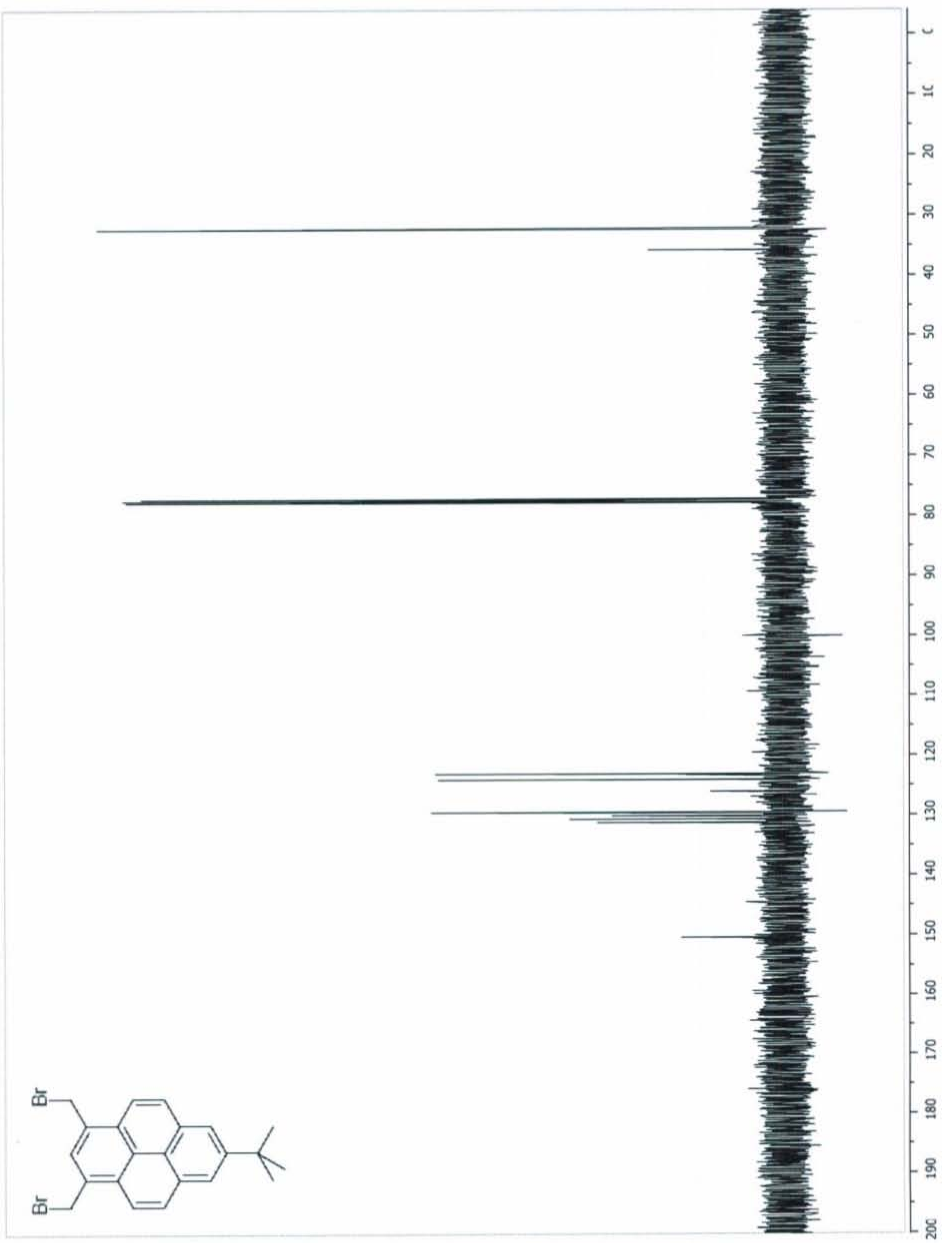
8 25
8 20
8 15
8 10
8 05
8 00
7 95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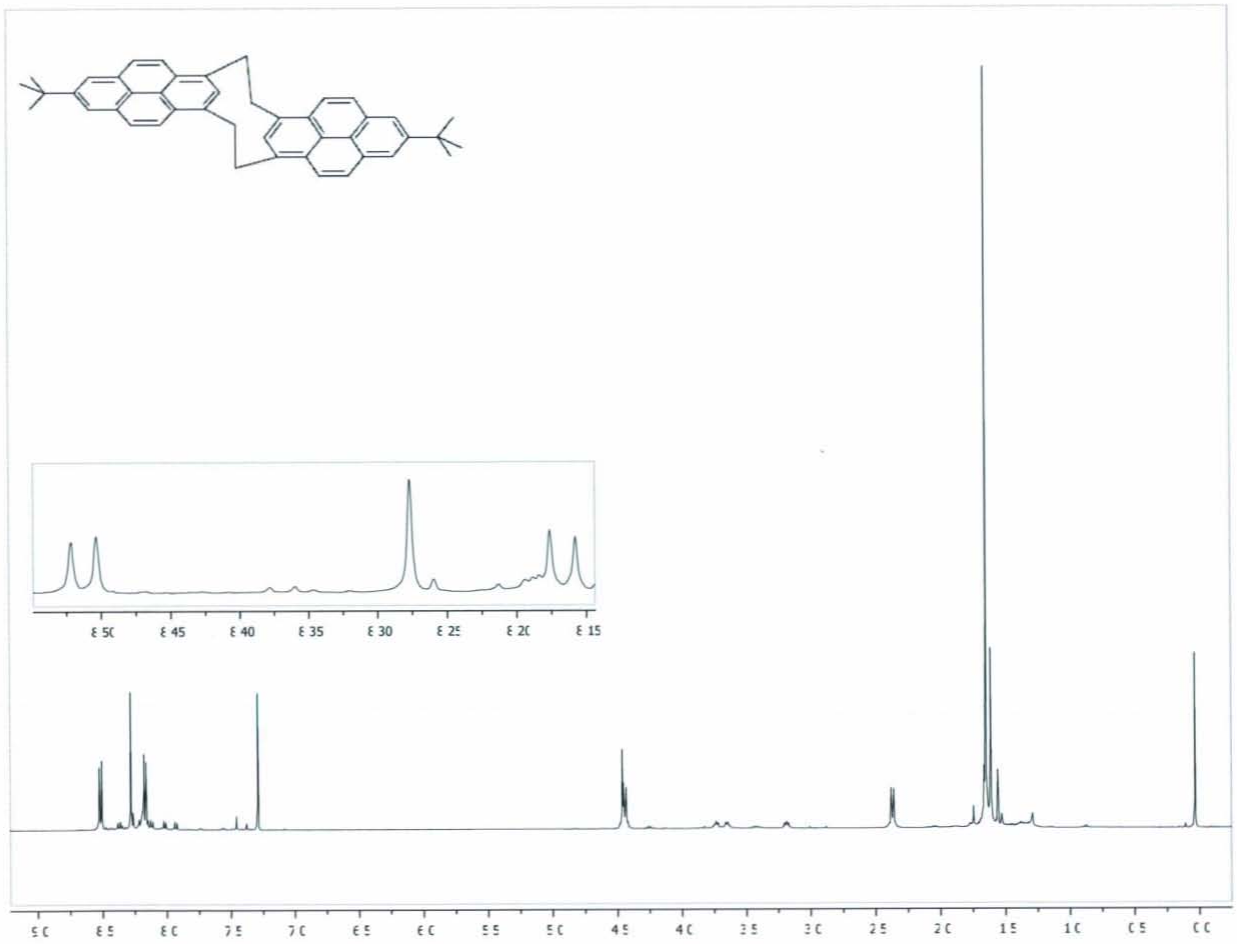

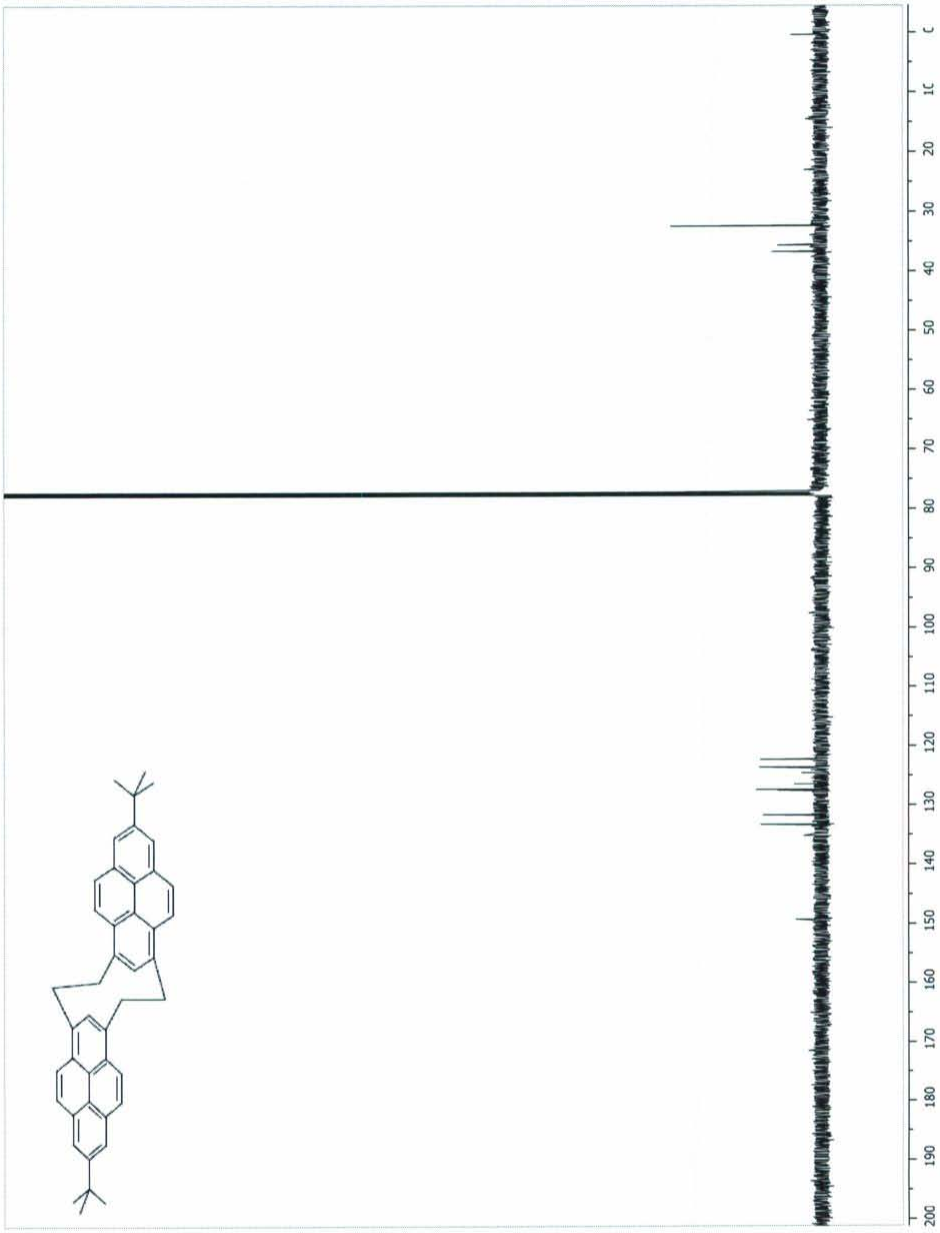

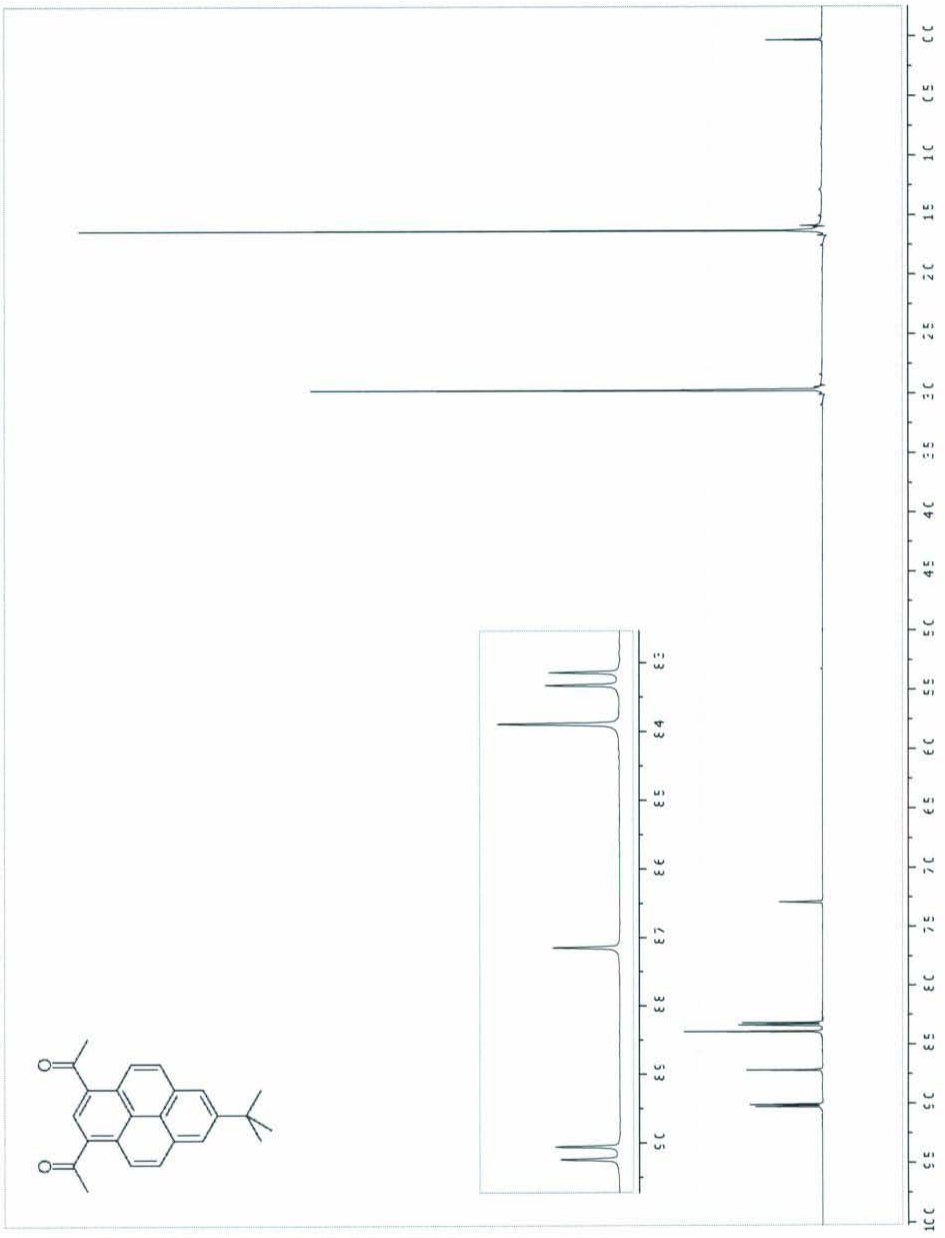

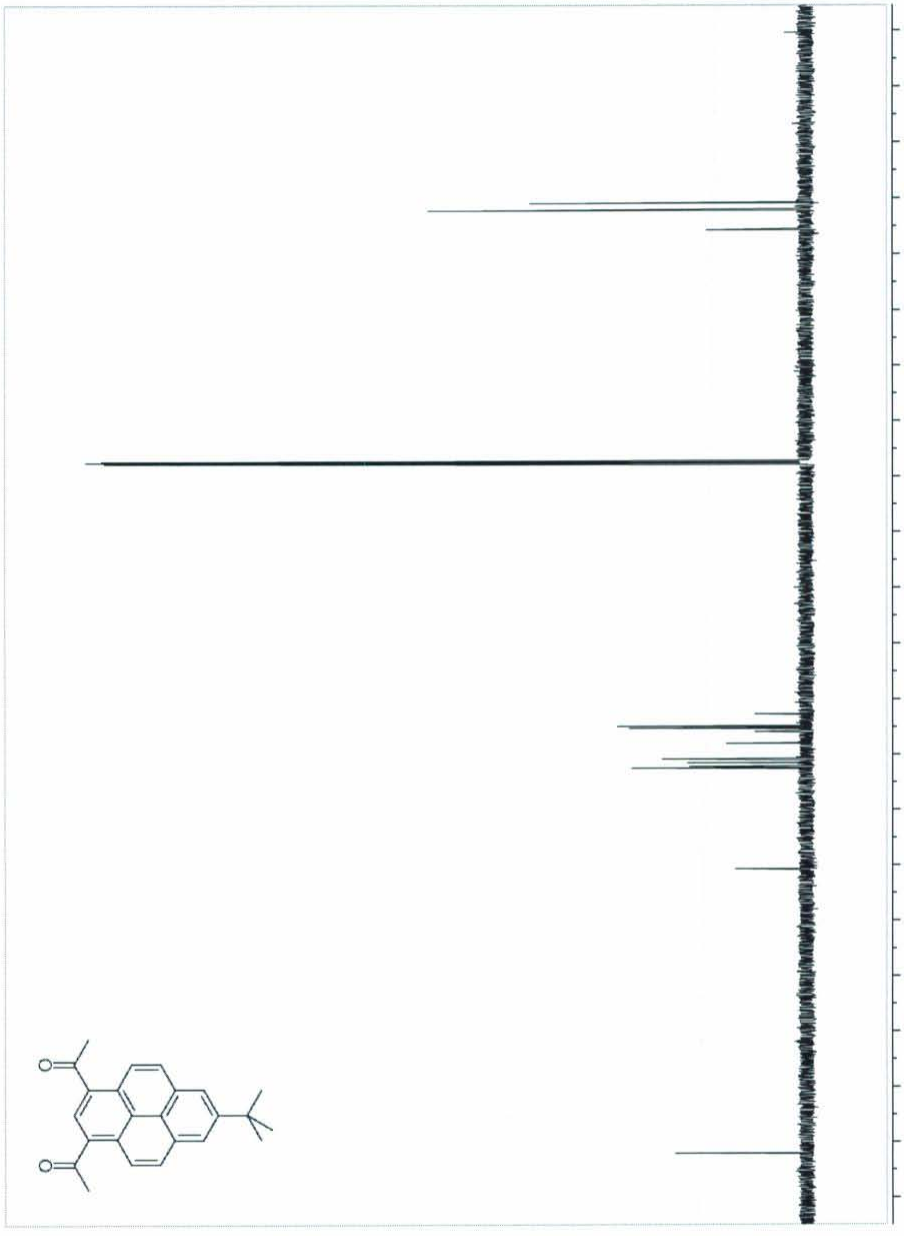
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f1 (ppm)

CHAPTER 4: Synthesis of 1,1,*n*,*n*-Tetramethyl[*n*](2,11)teropyrenophanes

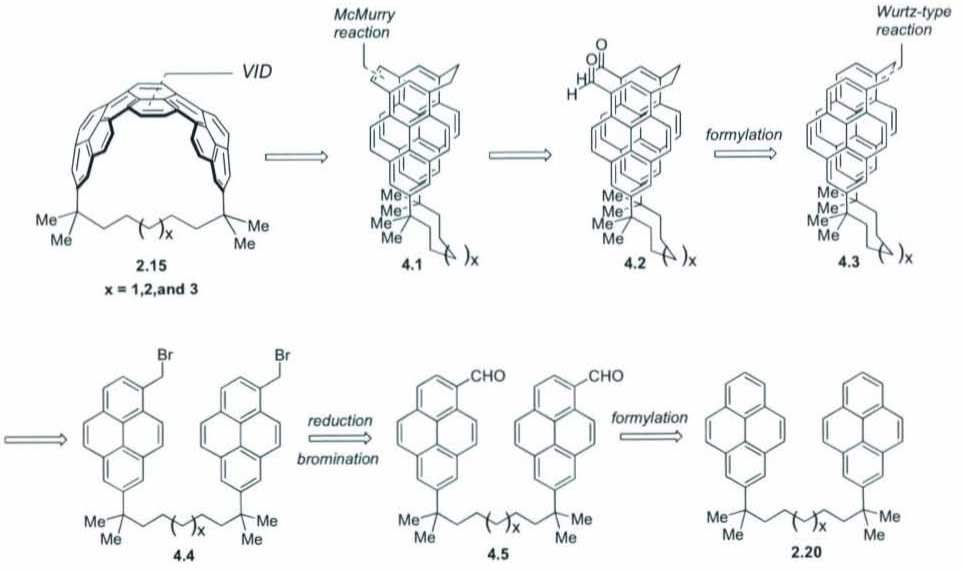
4.1 Application of the Model Study?

The risk-reward situation associated with any model study and its application towards the synthesis of a target molecule has already been discussed. While the application of the model study that was the subject of Chapter 3 was not guaranteed to succeed, it seemed unlikely that application of the chemistry discovered during its course would be met with disappointment. This is because all of the key carbon-carbon bond forming reactions that will further connect the two pyrene moieties of the bis(2-pyrenyl)-dimethylalkane(s) (**2.20**) are intramolecular processes, which have a distinct entropic advantage over the intermolecular reactions of the model systems based on 2-*tert*-butylpyene. Thus, the crucial carbon-carbon bond forming reactions (*i.e.* Wurtz-type coupling and McMurry reaction) should work with equal or superior efficiency. The McMurry reactions of the (1,7)pyrenophanes (*i.e.* **4.2**) have the additional advantages that only the *Z* configuration of the resulting double bonds will be formed and only the *syn*-conformation will be available to the resulting cyclophanes.[1] With these points in mind, the synthetic plan towards the synthesis of 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes was modified and the following disconnective analysis was devised.

4.1.1 Second Generation Retrosynthetic Analysis of Target Teropyrenophanes 2.15

Similar to the first synthesis plan that was outlined in Chapter 2 (Scheme 2.2), the revised retrosynthetic analysis of the teropyrenophane targets (**2.15**) commences with a

VID transform. Lowering the symmetry of the teropyrenophane precursor to a tethered *syn*-[2.2](1,3)pyrenophane (**4.1**) that contains two different two atom bridges (one saturated, one unsaturated), allows for the application of the Wurtz-type coupling that proved its worth in Chapter 3. While it was tempting to directly apply the Friedel-Crafts acylation reaction of glutaryl chloride and construct the desired alkene bridge(s) (annulated as a cyclopentene) at this stage of the synthesis plan, solving the early problems of the synthesis and preparation of the desired pyrenoid hydrocarbons (**2.15**) was the initial focus. However, the synthesis of analogs that are of segments of (8,8) SWCNTs would not change the direction of this work and would be a welcome addition to this study. Further discussion on this strategy and concepts regarding its application are the subjects of a later section of this chapter.



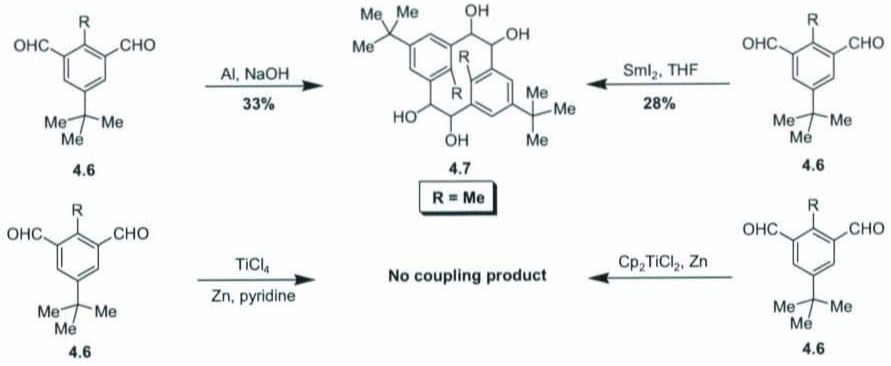
SCHEME 4.1: Retrosynthetic analysis of **2.15** – application of model study

Scission of the unsaturated bridge of 1,1,*n*,*n*-tetramethyl[*n*.2.2](7,1,3)pyrenophane (**4.1**) simplifies the synthetic objective to dialdehyde **4.2**. While application of the McMurry reaction at a similar stage in the attempted synthesis of a teropyrene model compound was unsuccessful, dialdehyde **4.2** represents a more suitable candidate for this reaction as entropic preorganization and possible π-stacking interactions between the connected pyrene units should promote the reductive coupling reaction. Simplification of dialdehyde **4.2** to [*n*.2](7,1)pyrenophane **4.3** presents the opportunity to showcase the utility of the Wurtz-type reaction in the synthesis of a novel pyrenophane bridging motif. In the forward sense, treatment of dibromide **4.4** (the synthesis of which, from dialdehyde **4.5**, was discussed in Chapter 2) with *n*-BuLi should bring about the desired coupling of the benzylic halides.

4.2 McMurry and Pinacol Coupling Reactions in [2.2]Metacyclophane Synthesis

The importance of [2.2]metacyclophanediene precursors in the construction of both planar and nonplanar pyrene units was discussed at length in Chapter 1. Bodwell's, along with others', approach towards these intermediates has typically involved the use of [3.3]dithiacyclophane intermediates and subsequent bridge contractions to furnish the desired two-atom bridges.[2] The use of more direct synthetic methods such as the McMurry reaction[3] to install unsaturated two-atom bridges obviates the need to go through one or more thiacyclophane intermediates. As such, the application of this reaction is desirable in planning a synthesis where these structural units / motifs are required. However, the McMurry reaction has not seen anything more than sporadic (and

often unsuccessful) application in the synthesis of such cyclophanes. This may be due to the large energy barrier associated with the carbon-carbon bond forming step that would generate a strained system. While the initial pinacol reaction may be feasible via this strategy, the subsequent deoxygenation step(s) to furnish unsaturated bridges can pose an insurmountable barrier.[4] Despite ample precedent for this reaction to form highly strained ethylene systems,[5] no report of its application in the direct synthesis of a [2.2]metacyclophanediene has appeared in the literature. Furthermore, the highly reductive nature of the low-valent titanium reagent that is necessary for this reaction can lead to over-reduced byproducts and often other pinacol reaction conditions are required.



SCHEME 4.2: Pinacol coupling reactions in the synthesis of [2.2]metacyclophanes

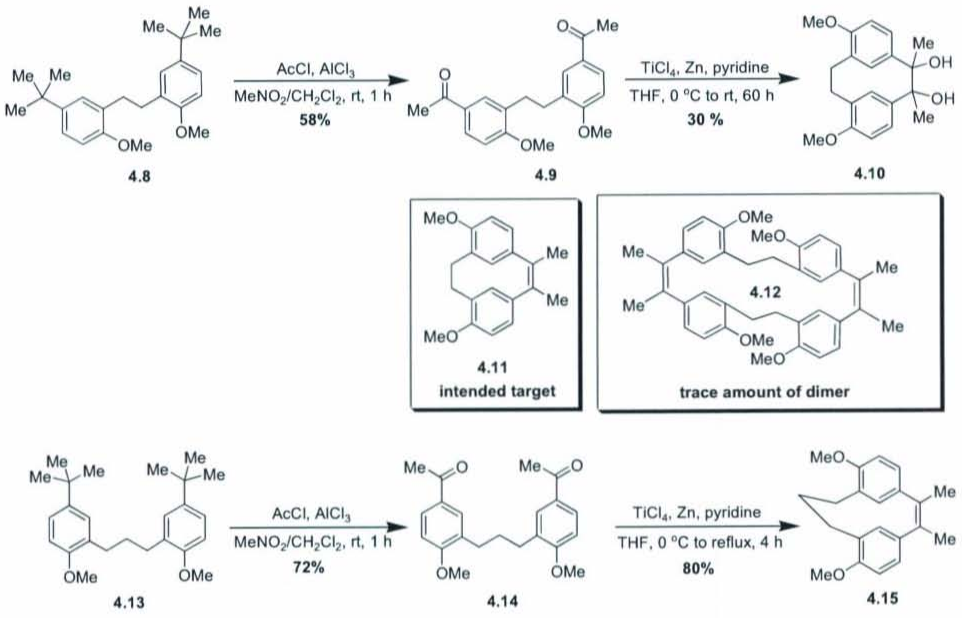
Mataka and co-workers investigated the possibility of directly coupling substituted isophthalaldehydes under various pinacol coupling conditions (Scheme 4.2). In their study, it was discovered that subjecting dialdehyde **4.6** to various McMurry reaction conditions afforded complex mixtures, from which none of the desired pinacol or olefin products were obtained.[4] In fact, they only observed a modest coupling event when

aluminium or samarium(II) iodide were used. Also, whether the *syn* or *anti*-diol adducts were obtained proved to be variable and non-reproducible. Mitchell and co-workers have also made use of the pinacol coupling reaction to install glycol bridges in the synthesis of [2.2]metacyclophanes.[6]

The role of entropy and the associated pre-organization of the substrate in facilitating the McMurry reaction, as it is applies to the synthesis plan, was alluded to above and in Chapter 3. To this end, it is instructive to highlight the work of both Yamato[7] and Hopf[8] with respect to the synthesis of unsaturated bridges in cyclophanes using both intramolecular and transannular McMurry reactions. Yamato's group conducted a systematic study, by which they investigated the effects of sequentially lengthening the number of methylene units between two functionalized benzene rings that contained a ketone functional group. This variable tether would ultimately represent one of the bridges of a metacyclophane system, whereby the main objective of the work was to establish the conditions under which unsaturated 2-atom bridges could be formed.

Treatment of 1,2-diarylethane **4.8**[9] with $AlCl_3$-$MeNO_2$ in the presence of acetyl chloride brought about an *ipso*-acylation reaction to furnish diketone **4.9** (Scheme 4.3). Subjecting the resulting ketone **4.9** to McMurry reaction conditions that utilize $TiCl_4$ and zinc dust in the presence pyridine and THF resulted in formation of only 30% of the pinacol adduct **4.10** and a trace amount of the dimeric McMurry product **4.12**. Several experiments, in which the temperature and the amount of pyridine added to the reaction were varied, were performed. It was found that conducting the reaction at room temperature was optimal for the preparation of diol **4.10**. None of the desired [2.2]metacyclophane **4.11** was observed in this study, and Yamato and co-workers cite

reasons that have already been discussed as to the fate of this particular reaction.[10] Despite the failure of the McMurry reaction in the preparation of an unsaturated bridge in the [2.2]metacyclophane series, Yamato's group did find successful application of this

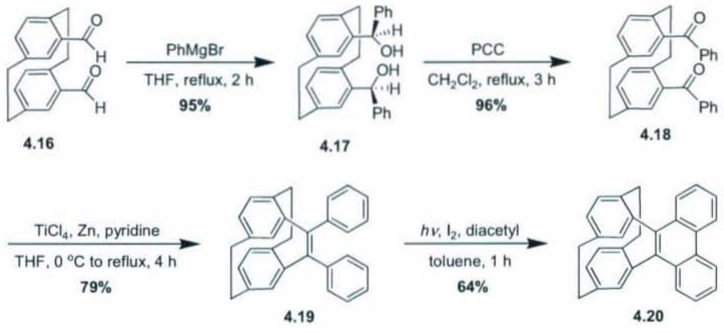


SCHEME 4.3: McMurry reaction in Yamato's synthesis of [2.*n*]cyclophanes (**4.15**)

reaction in synthesis of olefin bridges when the second bridge (*n*) of the [*n*.2]metacyclophane contained more than two carbons. In fact, simply extending the tether of the diarylalkane precursor by one methylene group (**4.14**) brought about a very efficient McMurry reaction, where 80% of the desired [3.2]metacyclophane **4.15** was afforded (Scheme 4.3).

Work conducted by the Hopf group on the synthesis of cyclophanes that contain orthogonally linked π-systems represents one of the few examples known to successfully employ the McMurry reaction in the synthesis of an ethenylene bridge in a

metacyclophane system. Their synthesis of [2.2.2](1,2,4)cyclophane **4.20** commenced with a completely diastereoselective Grignard reaction of 4,13-diformyl[2.2]paracyclophane (**4.17**)[11] with phenylmagnesium bromide in 95% yield. The fact that the Grignard reaction proved to be completely diastereoselective for **4.17** is a point of interest, but of no consequence in this particular synthesis as the resulting diol was oxidized to the corresponding diketone **4.18** via a PCC oxidation. The McMurry reaction of diketone **4.18** under the modified conditions of Lenoir,[12] furnished the desired stilbene derivative **4.19** in 79% yield. Photoisomerization followed by dehydrogenation gave the desired [2.2.2](1,2,4)cyclophane **4.20** in good yield.



SCHEME 4.4: McMurry reaction in Hopf and co-workers' synthesis of cyclophane **4.20**

4.2.1 Application of the Chapter 3 Model Study Toward the Synthesis of 1,1,8,8-Tetramethyl[8](2,11)teropyrenophane (2.84)

Key reactions, such as the Wurtz-type and McMurry couplings, that were discovered to be viable for pyrene systems in Chapter 3 were initially applied towards the synthesis of 1,1,8,8-tetramethyl[8](2,11)teropyrenophane (**2.84**). This particular target was selected as a starting point in the synthesis of a homologous series of cyclophanes

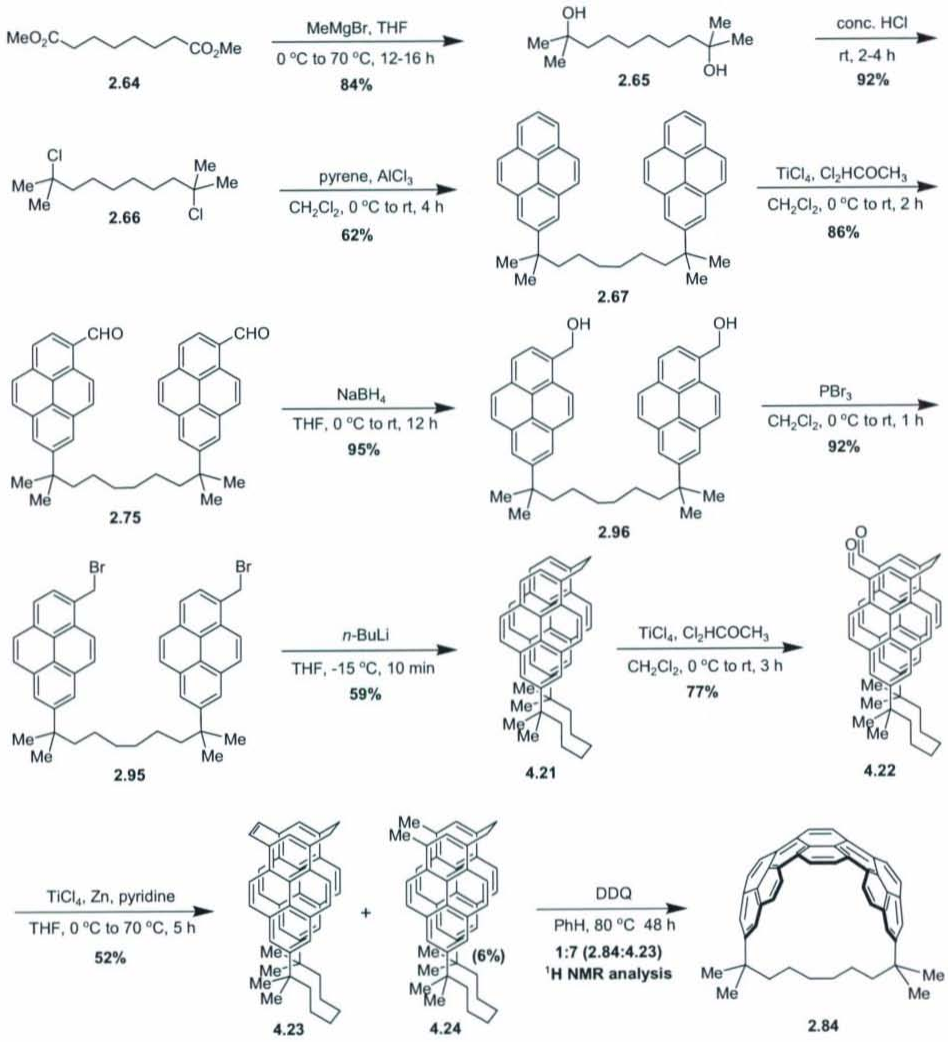
due to the comparatively higher yield that was obtained in the initial Friedel-Crafts alkylation reaction to afford bis(2-pyrenyl)-dimethylalkane (**2.20**) systems (Chapter 2), which provided access to larger quantities of important early synthetic intermediates. As well, this particular teropyrenophane was intermediate in size of the three 1,1,*n*,*n*-tetramethyl[*n*]teropyrenophanes (*n*=7, 8, and 9) proposed in the retrosynthetic analysis and success or failure of the VID reaction in this instance (*n*=8) would lend valuable insight as to the viability of the syntheses of other homolgs. Semi-empirical calculations at the AM1 level of theory have proved to be a very useful guide in the past as to the capabilities of the VID reaction (Section 4.5), and early calculations of the bend imposed upon the central pyrene unit embedded in the teropyrene system suggested that the *n*=8 series should be obtainable.[13] However, it was not known at that time whether direct application of what has proven to be a useful tool in the [*n*](2,7)pyrenophanes would be transferable to the 1,1,*n*,*n*-tetramethyl[*n*]teropyrenophane targets since the π-system is quite different. Considered as a whole, there are three separate pyrene substructures that can be traced onto the teropyrene surface, each of which is distorted from planarity by imposing an alkyl bridge at the 2 and 11 positions of the teropyrene system. Furthermore, the bend associated with this π-system will be distributed over the entire aromatic surface and therefore, may not be dependent on the degree of distortion of a single pyrene moiety – a factor that may play a pivotal role in the success of the VID reaction.

With regard to the degree of bend that is imposed on the teropyrene nucleus, calculations suggest that the central pyrene unit is considerably more bent than the two flanking pyrene substructures, when the same criterion for θ angles is applied.[14] The

AM1-calculated θ value for the central pyrene unit of **2.84** (n = 8) is 92.6°, while the side ring systems are predicted to have θ angles of 71.5° and 71.6° (see Figure 4.4, Section 4.5). The overall bend angle in the isolated teropyrene system (the smallest angle formed by the planes defined by C1-C2-C3 and C10-C11-C12, teropyrene numbering) is 172.6°. When the β angles[15] of the cyclophane are included (the reasons for including these angles are discussed in Section 4.3.2), a total bend angle of 182.0° is predicted. Such a bend angle implies that the $C_{bridgehead}$–$C_{benzylic}$ bonds of **2.84** are positioned slightly past a parallel alignment. Moreover, the successful synthesis of 1,1,8,8-tetramethyl[8](2,11)teropyrenophane (**2.84**) using the plan outlined in Scheme 4.1 or otherwise, would support the notion that the VID reaction should capable of delivering more ambitious targets such as the aromatic belts discussed in Chapters 1 and 2.

The synthesis of 2,9-bis(6-(bromomethyl)pyren-2-yl)-2,9-dimethyldecane (**2.95**) was described in Chapter 2 (Scheme 2.23). Treatment of dibromide **2.95** with *n*-butyllithium at –15 °C for 10 minutes furnished [8.2](7,1)pyrenophane **4.21** in 59% yield. While the isolated yield of this reaction is somewhat low and comparable to the intermolecular variant (Chapter 3), it is very reliable and independent of scale up to 500 mg.[16] Linking together the two pyrene units of **2.95** in short order, using one of the key reactions discussed in Chapter 3, was a gratifying result at this stage in the project.

Having secured a much more expedient route to an [8.2](7,1)pyrenophane (*cf.* the synthesis of **2.92** – Chapter 2), **4.21** was subjected to the Rieche formylation conditions that had previously proved to be successful. Treatment of **4.21** with dichloromethyl methyl ether and titanium(IV) chloride furnished dialdehyde **4.22** in 77% yield and set the



SCHEME 4.5: Synthesis of teropyrenophane **2.84** – Route A

stage for the pivotal McMurry reaction. Screening McMurry reaction conditions in Chapter 3 indicated that the Lenoir variant of the McMurry reaction was best suited for pyrene aldehydes such as dialdehyde **4.22**.[17] Treatment of **4.22** with low-valent titanium generated from $TiCl_4$, zinc dust and pyridine in THF furnished cyclophane **4.23** in 52%

yield. At this juncture, a detailed explanation of the experimental procedure of this particular reaction would be instructive, as it requires very precise conditions to be reproducible.

4.2.2 Important Experimental Considerations in the McMurry Coupling Reaction

For the successful application of the McMurry reaction to dial **4.25**, it was necessary that the following procedure be followed diligently. All glassware must be oven-baked at 120 °C overnight or flame dried and cooled down under an atmosphere of nitrogen. While adding zinc dust (<10 μm, >98% as received from Sigma-Aldrich) to a three-neck flask, two of the three joints should be sealed with rubber septa (the other with a glass stopper) and kept under an atmosphere of nitrogen. After the reaction flask has been charged with zinc dust and a water condenser has been secured, the reaction flask should remain under nitrogen for the duration of the experiment. In preliminary trials of this experiment, it was discovered that opening the reaction system for TLC analysis only served to lower yields and caused a slight discoloration (black to brown) of the reaction mixture over time. This was especially true if the experiment was exposed to air within the first 30 minutes (after aldehyde addition) of the reaction.

In generating the low-valent titanium reagent, it is essential to add $TiCl_4$ to a cooled (at or below 0 °C) slurry of zinc dust and THF.[18] The reaction mixture is then heated to reflux for at least one hour, upon which a dark black solution forms. Addition of dialdehyde **4.22** as a solution in THF in one portion is feasible as long as a molarity of approximately 0.04 mM is maintained. Slow addition or use of a syringe pump does not

augment the isolated yield of **4.23** and often results in an increase of the amount of over-reduced product (**4.24**) formed.[19] Generally, the reaction is complete in 4 to 6 hours after which, no starting material can be seen by TLC and LCMS analysis. Aqueous work-up of this reaction is an onerous task and results in lower isolated yields (20–30%) of **4.23**. As a result, simply diluting the reaction mixture with chloroform and directly pre-adsorbing the contents of this solution onto silica gel in preparation for column chromatography is optimal.

With 1,1,8,8-tetramethyl[8.2.2](7,1,3)pyrenophane (**4.23**) in hand, standard VID reaction conditions[20] were applied to the material obtained (*ca.* 5 mg) from the McMurry reaction. Heating a benzene solution of **4.23** at reflux in the presence of two equivalents of DDQ for 48 hours gave a mixture of 1,1,8,8-tetramethyl[8](2,11)teropyrenophane (**2.84**) and starting material (1:7 **2.84**:**4.23** by ^{1}H NMR analysis). Surprisingly, despite the sluggish nature of this reaction, no intermediate tetrahydro- or dihydroteropyrenophane was observed in the mass spectrum of the reaction mixture or subsequent ^{1}H NMR. However, separation of the starting material from the teropyrenophane product was quite difficult as only a subtle R_f difference of 0.46 (**4.23**) and 0.48 (**2.84**) in 1:4 dichloromethane/hexanes was observed. TLC analysis in less polar solvent mixtures gave even smaller R_f differences and both the starting material and the product move as one apparent spot on the TLC plate. Nonetheless, the presence of the desired teropyrenophane system is unmistakable by TLC analysis as it shows bright yellow fluorescence at 365 nm and a yellow-orange color to the naked eye. Prolonged heating of the benzene solution of **4.23** in the presence of DDQ did not furnish an appreciable increase in the amount of the desired target and served to, presumably,

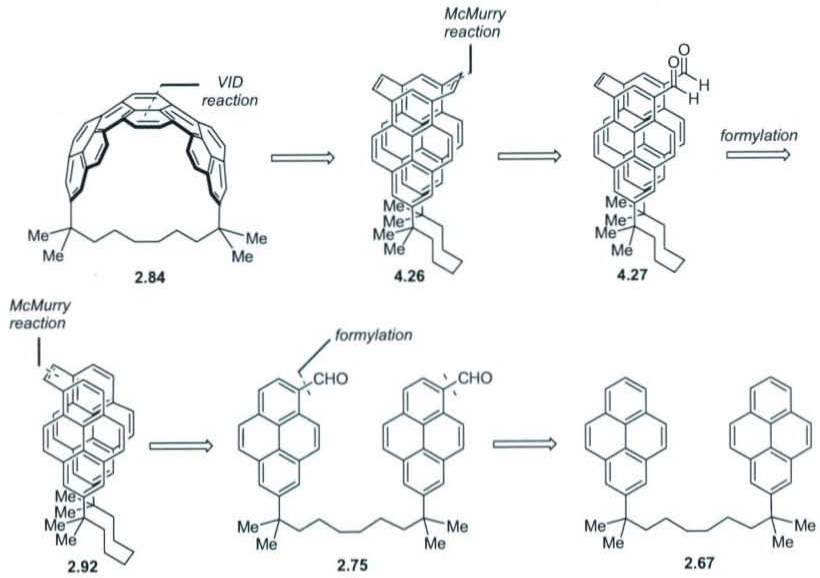
decompose any new product that had formed. After two weeks of reaction, only a small amount (*ca.* 1 mg out of 5 mg) of starting material was recovered and none of the teropyrenophane was isolated.

Despite the failure of the VID reaction (under standard conditions) to give complete conversion of starting material into product in the case of **4.23**, the rudimentary MS and ^{1}H NMR characterization that was obtained was encouraging. Due to the success of the McMurry reaction to furnish the unsaturated bridge of [8.2.2](7,1,3)pyrenophane **4.23** under carefully formulated conditions (*vide supra* and Chapter 3), the notion of introducing an unsaturated bridge at an earlier stage in the synthesis began to emerge. Moreover, the synthesis of a cyclophanediene system akin to **4.23** (*i.e.* **2.16** – Chapter 2) would be much more desirable in providing a true test of the VID methodology, since all other pyrenophane precursors prepared before have had this structural requirement. To this end, the synthesis 1,1,8,8-tetramethyl[8](2,11)teropyrenophane using a cyclophanediene intermediate was initiated.

4.3 Third Generation Retrosynthetic Analysis of Teropyrenophane 2.84

Utilizing a cyclophanediene in the VID reaction as a possible precursor to 1,1,8,8-tetramethyl[8](2,11)teropyrenophane (**2.84**) can also serve to increase the brevity of the synthesis, if the retrosynthetic analysis outlined in Scheme 4.6 were to be successful. Further, the success of the McMurry reaction with regard to the preparation of cyclophane **4.23**, prompted us to revisit the possibility of coupling tetraaldehydes or tetraketones (discussed in Chapter 2) directly to furnish the requisite cyclophanedienes. Unfortunately, these substrates did not react productively in the McMurry reaction (using

the conditions described in Section 4.2.3). However, application of the iterative bridge formation/formylation/bridge formation sequence that had proven to be successful thus far was the main focus in the third-generation retrosynthetic analysis of **2.84** (Scheme 4.6).

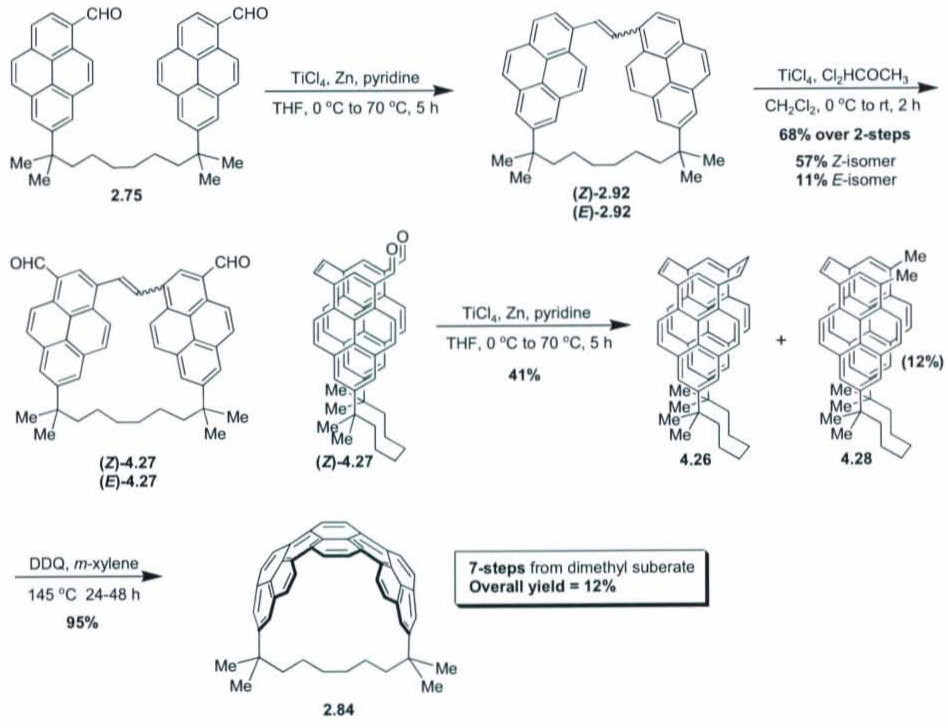


SCHEME 4.6: Third generation retrosynthetic analysis of teropyrenophane **2.84**

4.3.1 Synthesis of 2.84 via a Double Formylation/McMurry Coupling Strategy

Treatment of aldehyde **2.75** using the McMurry reaction conditions described in Section 4.2.3 gave an inseparable mixture of *E* and *Z* alkenes, for which no ratio of products could be determined by ^{1}H NMR analysis.[21] Direct formylation of the isomer mixture furnished a separable mixture of (*E*)- (11%) and (*Z*)-ene-dialdehydes (57%) in a combined overall yield of 68%. The yield of the initial McMurry reaction for this particular dialdehyde system (**2.75**) is acceptable (40–80%) on a 100 mg scale, but

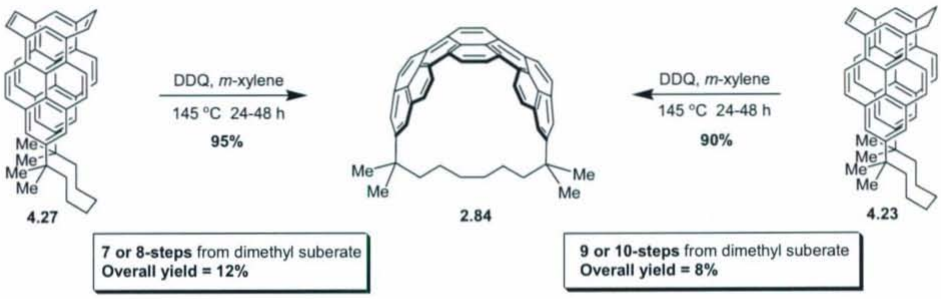
scaling up the reaction resulted in much lower yields. For instance, carrying out this reaction on *ca.* 1 g of dialdehyde **2.75** gave a lower yield of 17% over two steps. Even on a 500 mg scale, the yields were still consistently low (*ca.* 20%). Nonetheless, synthetically usable quantities of (*Z*)-**4.27** and reproducible yields were obtained when the reaction was conducted on a 100 mg scale.



SCHEME 4.7: Synthesis of teropyrenophane **2.84** – Route B

McMurry reaction of (*Z*)-**4.27** gave 1,1,8,8-tetramethyl[8.2.2](7,1,3)pyrenophane-19,31-diene (**4.26**) as the major product in 41% yield. The slightly lower yield of this reaction, compared to the analogous saturated precursor **4.23** (52%), can be attributed to

the increase in strain energy that accompanies the formation of the corresponding [2.2]cyclophanediene – due to the restricted rotation of the carbon-carbon bond in the first olefin bridge. As such, less of the diene product was formed and approximately 12% (*cf.* 6% in saturated system **4.24**) of the over-reduced dimethyl compound **4.28** was obtained from this reaction. However, the brevity of this route to **4.27** more than made up for the slightly lower yield of the second McMurry reaction and, with the desired cyclophanediene in hand, the VID reaction was once again attempted using the conditions described in Scheme 4.5.



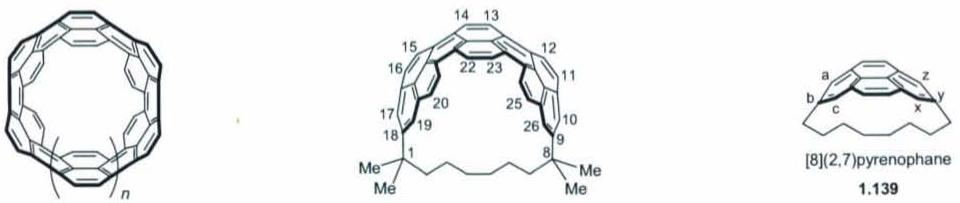
SCHEME 4.8: Synthesis of **2.84** from [8.2.2](7,1,3)pyrenophanes **4.23** and **4.27**[22]

Similar to what had been observed for the monoene system (**4.23**), the reaction of diene **4.27** with DDQ in refluxing benzene was sluggish. Moving to a higher boiling solvent (*m*-xylene) and heating the reaction at 145 °C brought about an immediate change in the TLC and MS analysis. The previously observed, and believed to be 1,1,8,8-tetramethyl[8](2,11)teropyrenophane, spot by TLC analysis became much more intense and the increase in product formation was evident in the mass spectrum. After 48 h in refluxing *m*-xylene, 1,1,8,8-tetramethyl[8](2,11)teropyrenophane (**2.84**) was obtained in

near quantitative yield. Furthermore, using *m*-xylene as the solvent for the VID reaction with cyclophanemonoene **4.26** (Scheme 4.5) also furnished teropyrenophane **4.27** in comparable (90%) yield.

4.3.2 Implications of Bending the Teropyrene System: Discussion of its Physical Data and Homology to an Armchair (8,8) SWCNT

Fortunately, crystals suitable for X-ray crystallography (recrystallization from ethanol) of 1,1,8,8-tetramethyl[8](2,11)teropyrenophane (**2.84**) were obtained and this permitted quantification of the bent π-system. In addition to the remarkable structural characteristics discussed below, teropyrenophane **2.84** is noteworthy because it is just the second teropyrene system to have been synthesized,[23] and also because teropyrene is now largest aromatic system to have been incorporated into an [*n*]cyclophane (*i.e.* one aromatic system and one bridge).[24] The teropyrene system (36 carbons) in **2.84** contains



Vögtle belts

2.3 (*n*=1)
2.4 (*n*=2)
2.5 (*n*=3)

1,1,8,8-tetramethyl[8](2,11)teropyrenopane

2.84

[8](2,7)pyrenophane

1.139

FIGURE 4.1: Vögtle belts and teropyrenophane **2.84** – half an aromatic belt

more than half of the carbon atoms in the D_{6h}-symmetric Vögtle belts **2.3** (60 carbons) and **2.4** (70 carbons). However, as outlined below, its structure (including the benzylic

carbon atoms) more closely resembles a substructure of the D_{8h}-symmetric Vögtle belt **2.5** (80 carbons), which is, in turn, a segment of an (8,8) SWCNT.

A single crystal X-ray structure determination of **2.84** revealed two independent molecules in the asymmetric unit, one of which is shown in Figure 4.2 (see Appendix 4 for other views). As dictated by the 8-atom bridge, each independent molecule has a highly nonplanar teropyrene unit. In the [*n*](2,7)pyrenophanes, the nonplanarity of the pyrene system is most commonly characterized by the angles formed by adjacent planes of atoms and, more generally, by the angle (θ)[14] formed between the two terminal planes of atoms (C(a)-C(b)-C(c) and C(x)-C(y)-C(z) in **1.139**).[25] An analogous treatment can be applied to **2.84**, in which three pyrene substructures can be identified. Thus, three θ angles (θ_1 and θ_3 for the terminal pyrene units and θ_2 for the central pyrene unit) and a total bend angle (θ_{tot} = the angle formed by the two terminal planes of atoms in the teropyrene system (*i.e.* C(9)-C(10)-C(26) and C(17)-C(18)-C(19)) can be measured (Figure 4.2). The angles (β)[15] formed by the $C_{bridgehead}$–$C_{benzylic}$ bonds and the terminal planes (Figure 4.4) of the teropyrene system have also been included in the analysis for the calculation of the overall bend in the system (see Appendix 4 for a full list of angles between planes). Key distances (Figure 4.2) are d_1 (distance between the bridgehead carbon atoms), d_2 (distance between the benzylic carbon atoms), d_3 (distance between the centroids of the $C_{bridgehead}$–$C_{benzylic}$ bonds) and d_4 (distance between the centroid of d_3 and the centroid of the central bond of the central pyrene unit of the teropyrene system) (Figure 4.3).

Metric	Molecule A	Molecule B
β_1 [°]	5.2	6.1
θ_1 [°]	68.0	67.5
θ_2 [°]	95.9	92.8
θ_3 [°]	69.8	70.4
β_2 [°]	4.7	6.5
θ_{tot} [°]	167.6	166.4
overall bend [°]	178.5	179.0
d_1 [Å]	9.033(4)	9.084(4)
d_2 [Å]	9.101(5)	9.082(4)
d_3 [Å]	9.067(6)	9.082(5)
d_4 [Å]	6.19(2)	6.12(2)

FIGURE 4.2: POV-Ray ball-and-stick representation of **2.84** in the crystal

The two independent molecules of **2.84** (Molecules A and B) have some small local differences in their structures, but the general features are essentially the same. The teropyrene system is not far from being bent through 180° (θ_{tot} = 166.4–167.6°), which invites comparison to a Vögtle belt or an armchair SWCNT (Figure 4.1). It is useful to include the benzylic carbon atoms in the analysis, even though they are not part of the aromatic system. In the D_{8h}-symmetric Vögtle belt **2.5** (or an (8,8) SWCNT), the bonds corresponding to the two $C_{bridgehead}$–$C_{benzylic}$ bonds in **2.84** are parallel. In **2.84**, the observed overall bend ($\theta_{tot} + \beta_1 + \beta_2$ = 178.5° and 179.0° for Molecules A and B, respectively) is indeed very close to 180°. This near-parallel orientation is also reflected in the values of d_1, d_2 and d_3 (range = 9.03–9.08 Å), which should be identical in a parallel orientation.

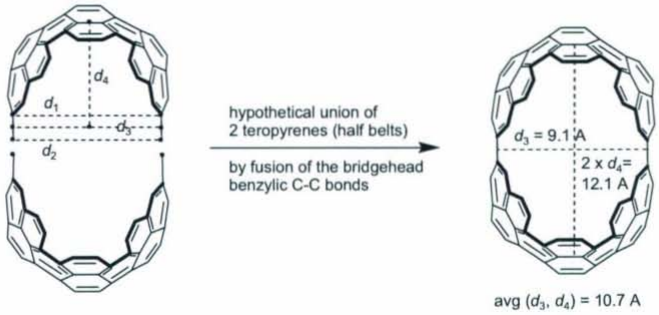


FIGURE 4.3: Hypothetical union of two teropyrene units (half-belts) of **2.84** to form an armchair (8,8) SWCNT

The two terminal pyrene units of the teropyrene system are less severely bent (θ_1 and θ_3 = 67.5–70.4°) than the central pyrene unit (θ_2 = 92.8–95.9°), which means that the cross-section of the teropyrene system more closely resembles a portion of an ellipse rather than that of a circle. In fact, the hypothetical union of two half-belt systems (teropyrene + $2C_{benzylic}$) by fusion of the $C_{bridgehead}$–$C_{benzylic}$ bonds (Figure 4.3) affords an ellipsoidal segment of **2.5** or an (8,8) SWCNT. The short axis of the ellipse measures 9.08 Å (the average value of d_3) and the long axis measures 12.3 Å (double the average value of d_4). The average of these distances is 10.7 Å, which is very close to the calculated value for an (8,8) SWCNT (10.86 Å).[26] Thus, the cross-section of the half-belt system corresponds to the more curved half of an ellipse. This is also reflected in the angles between planes of atoms in **2.84** that correspond to angles between planes related by the 8-fold symmetry in **2.5** or an (8,8) SWCNT. In **2.84**, these angles range from 34.7° to 65.4° and average 52.1° and 52.0° for Molecules A and B, respectively (see Appendix 4), which exceed the 45° angle dictated by the 8-fold symmetry.

The ^{1}H NMR spectrum of teropyrenophane **2.84** contains a set of low field signals at δ 8.62 (H-13, H-14, H-22, H-23), 8.39 (H-12, H-15, H-21, H-24), 7.71 (H-11, H-16, H-20, H-25) and 7.42 (H-10, H-17, H-19, H-26) for the aromatic protons and a set of high field signals at δ 1.32 (CH_3), 0.72 (H-2, H-7), –0.26 (H-4, H-5) and –0.67 (H-3, H-6) for the aliphatic protons. As with the [*n*](2,7)pyrenophanes, the anisotropic effect of the aromatic π-system in **2.84** causes the aliphatic protons to resonate at unusually high field.

The absorption spectrum of **2.84** in acetonitrile (Appendix 4, Figure A8) exhibits three major bands, each one with some fine structure. The longest wavelength maximum is observed at 489 nm. By comparison, the longest wavelength absorption maximum of teropyrene (in 1,2,4-trichlorobenzene) is reported to be at 537 nm,[22] which may suggest that, in contrast to what is observed in the [*n*]paracyclophanes[27] and [*n*](2,7)pyrenophanes,[28] bending the teropyrene system causes a significant blue shift. The fluorescence spectrum (Figure A8, excitation at 370 nm) shows what appears to be two overlapping bands with λ_{max} = 509 and 530 nm. The fluorescence quantum yield (ϕ_{em}) is 0.11.[29]

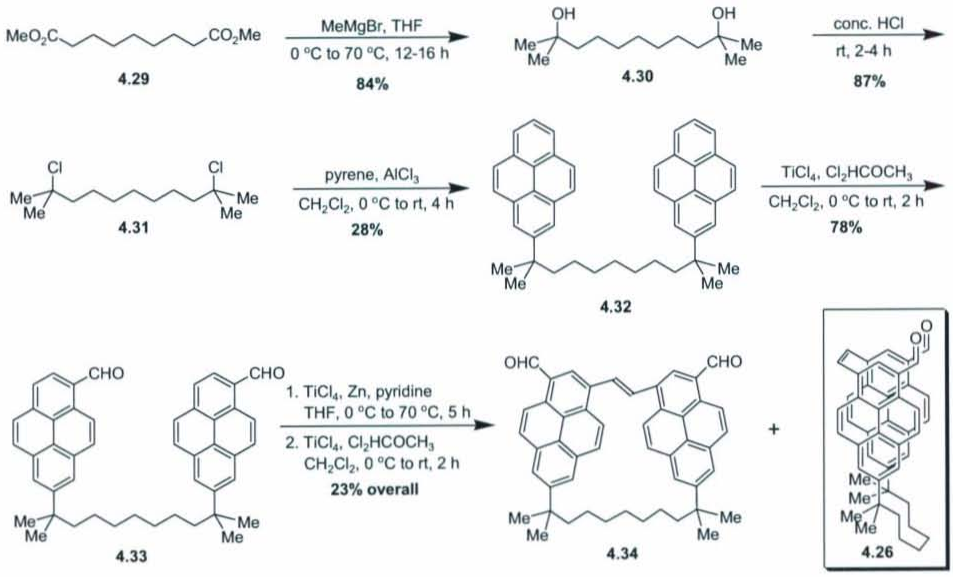
4.4 The Synthesis of a Homologous Series of (2,11)Teropyrenophanes

With two routes in place for the synthesis of 1,1,8,8-tetramethyl[8](2,11)teropyrenophane (**2.84**), it seemed likely that the synthesis of the next higher (*n*=9) and lower homologs (*n*=7) would be feasible through application of one or both of these routes. The obvious starting point was to apply the shorter of the two routes (Route B, the diene route) to the synthesis of 1,1,9,9-tetramethyl[9](2,11)teropyrenophane

(**4.41**). However, it was expected that the first McMurry reaction would give a higher ratio of the undesired *trans* olefin isomer. Nevertheless, it was hoped that a significant proportion of the desired *cis* isomer would be formed and that the isomers would be separable following subsequent formylation, as they were in the synthesis of 1,1,8,8-tetramethyl[8](2,11)teropyrenophane (**2.84**). If a major problem were to be encountered at this juncture, recourse could be made to Route A (the monoene route).[30]

4.4.1 Application of Route B to the Synthesis of Teropyrenophane 4.41

At the outset of this project, 2,10-dimethyl-2,10-bis(2-pyrenyl)undecane (**4.32**) was not used in exploratory chemistry since the starting diester (dimethyl azelate) was available in only 80% purity (technical grade) from commercial sources. Despite the low purity of this diester, it was hoped that pure synthetic intermediates could be isolated at an early stage in the synthesis. The synthesis of teropyrenophane **4.41** commenced with the Grignard reaction of dimethyl azelate (commercial material) with methylmagnesium bromide to furnish tertiary diol **4.30**. Treatment of **4.30** with concentrated aqueous hydrochloric acid gave dichloride **4.31** in 83%. Subsequent reaction with pyrene under Friedel-Crafts alkylation conditions afforded 2,10-dimethyl-2,10-bis(2-pyrenyl)undecane (**4.32**) in 28% yield.[31] Rieche formylation of **4.32** furnished dialdehyde **4.33**. At this stage, the material obtained from the formylation reaction was of low purity (~80–85% by ^{1}H NMR analysis) and attempts to purify dialdehyde **4.33** via chromatography, trituration and recrystallization gave only minimal improvements (~85–90%) in the sample purity.



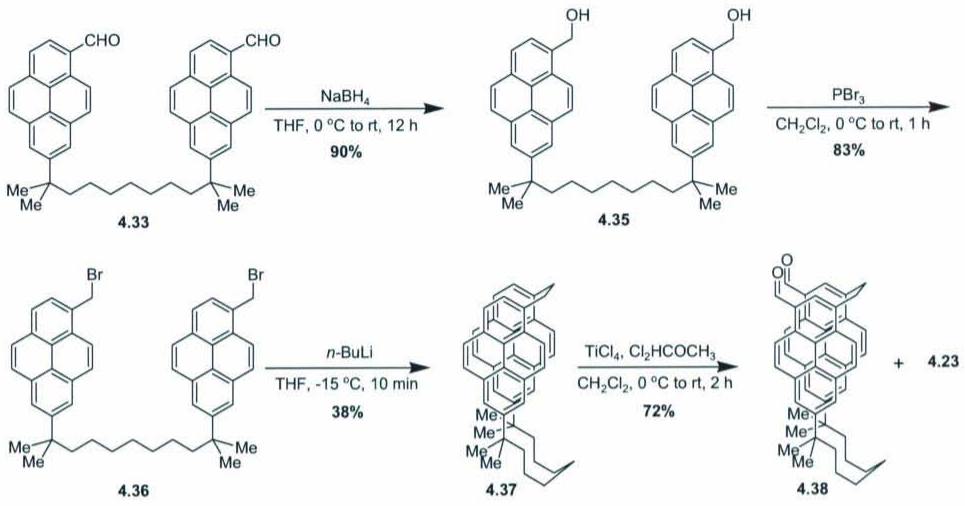
SCHEME 4.9: Attempted synthesis of teropyrenophane **4.41** via Route B

The low purity of dialdehyde **4.33** was cause for concern. However, it was decided that continuing with this material would be worthwhile because it would provide valuable information about the stereochemical outcome of the first McMurry reaction and thus establish whether or not Route B was viable. McMurry reaction of 2,10-bis(6-formylpyren-2-yl)-2,10-dimethylundecane (**4.33**) gave an inseparable mixture of alkenes. As before, formylation of the mixture furnished chromatographically separable ene-dialdehydes and it was at this stage in the synthesis that pure material was finally obtained and the nature of impurity that had been carried through the synthesis could be identified. (*Z*)-Ene-dialdehyde **4.26** (*eight* atom tether) was isolated as a minor byproduct, which means that the starting diester, dimethyl azealate, was contaminated with dimethyl suberate.[32] Unfortunately, only the *trans* isomer of the desired

intermediate **4.34** was obtained from the McMurry/formylation sequence. In light of this result, work on Route B was discontinued and the application of Route A to the synthesis of 1,1,9,9-tetramthyl[9](2,11)teropyrenophane (**4.41**) was pursued.

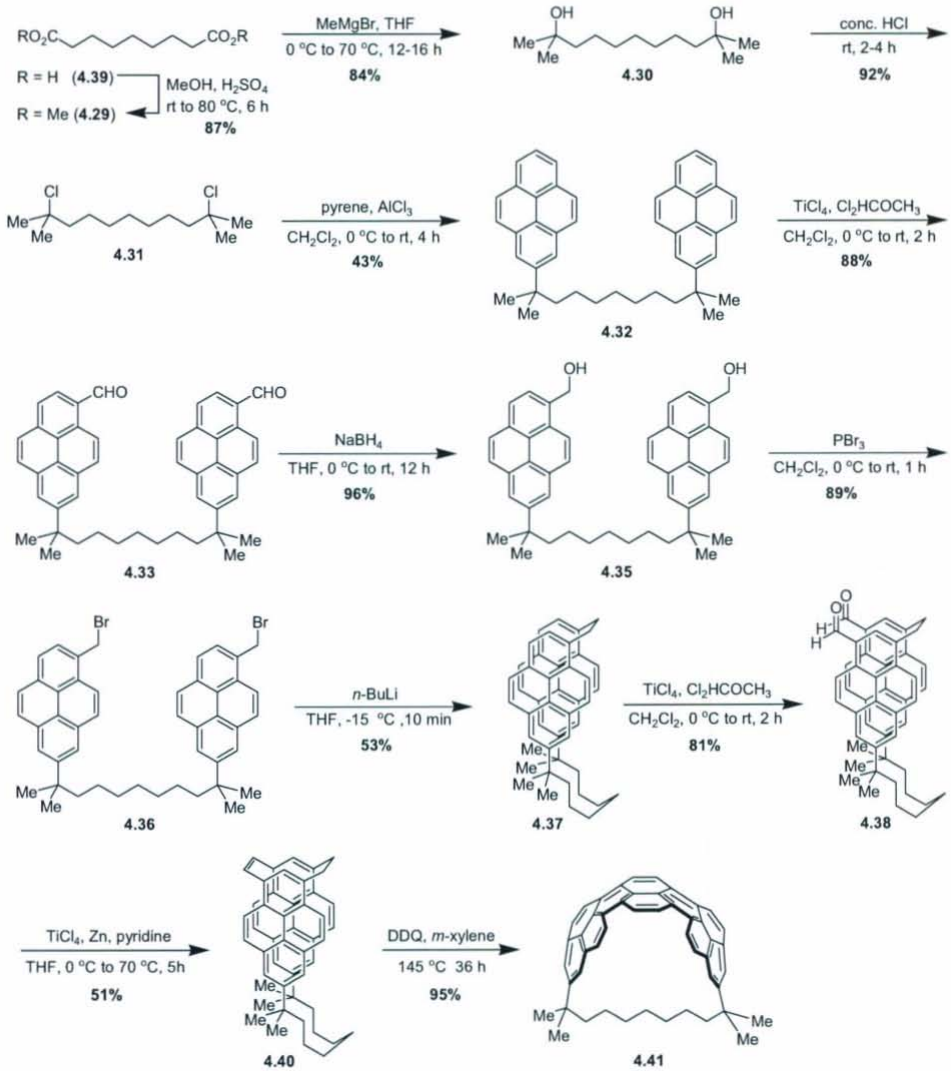
4.4.2 Application of Route A Towards the Synthesis Teropyrenophane 4.41

As a starting point for the application of Route A to the synthesis of 1,1,9,9-tetramethyl[9](2,11)teropyrenophane (**4.41**), impure dial **4.33** (Scheme 4.9) was used to synthesize advanced intermediate **4.38** (Scheme 4.10). As before (Route B), it was only after the formation of a functionalized [9.2](7,1)pyrenophane that pure material was obtained and a similar impurity (**4.23**, derived from dimethyl suberate) was isolated. Since isolation of pure synthetic intermediates would only be possible at a very late stage in the synthesis using commercial dimethyl azelate, it was necessary to synthesize this starting material in pure form. To this end, dimethyl azelate was prepared via a Fischer esterification of commercial azelaic acid, which was available in high purity (98%). The esterification was high yielding and could be carried out on a large scale (*ca.* 30 g). Applying the synthetic sequences described in Schemes 4.9 and 4.10 to pure diester **4.29** provided entry to all of the former synthetic intermediates in pure form and also served to increase the yields (Scheme 4.11).



SCHEME 4.10: Synthesis of advanced intermediate **4.38** via Route A

McMurry reaction of dial **4.38** proceeded smoothly and was comparable in efficiency (51% yield) to the one used in the synthesis of 1,1,8,8-tetramethyl[8](2,11)teropyrenophane (**2.84**) using route A (*cf.* 52% for **4.23**, Scheme 4.5). The synthesis of 1,1,9,9-tetramethyl[9](2,11)teropyrenophane (**4.41**) was completed with successful application of the VID reaction to [9.2.2](7,1,3)pyrenophane **4.40** to furnish **4.41**. Although teropyrenophane **4.41** is less strained than teropyrenophane **2.84**, reflux in *m*-xylene was required to bring about the VID reaction of **4.40**. However, monitoring the reaction closely by TLC and LCMS analysis revealed that this VID reaction is faster (initially) than that of **4.27**. Even still, complete conversion of the starting material to product required 24–48 h of heating. For both teropyrenophanes that have been synthesized to this point, it is essential that the VID reactions be monitored closely by TLC, as prolonged reaction time can lead to a significant decrease in product yield,



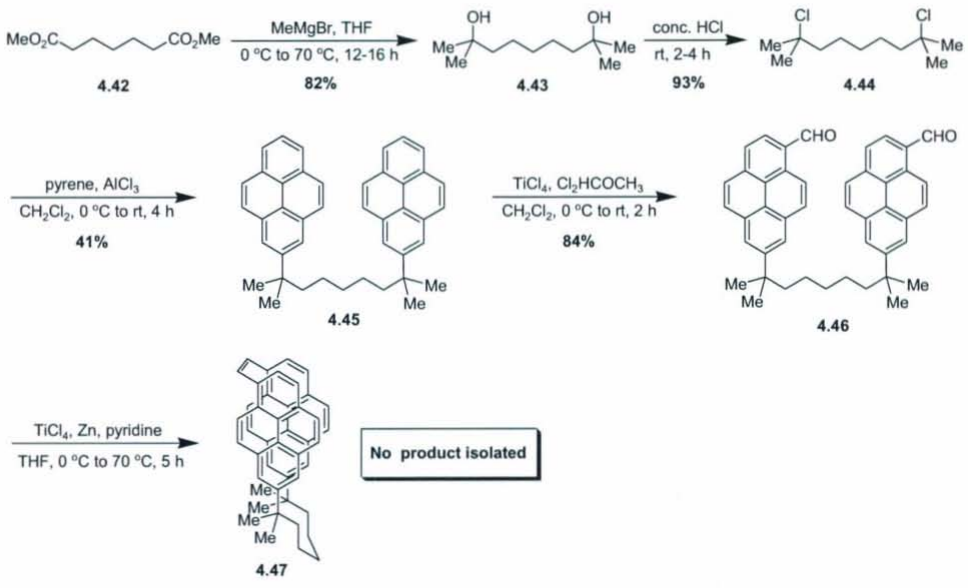
SCHEME 4.11: Synthesis of 1,1,9,9-tetramethyl[9](2,11)teropyrenophane **4.41**

presumably by decomposition through strain-relief-driven processes. It was observed that concentration plays a very important role in this reaction and paying close attention to the volume of solvent present is essential for high yields. In cases when significant amounts

of the solvent had evaporated during the course of the reaction, product losses increased. More discussion on the attention that these VID reactions require appears in the following section.

4.4.3 The Synthesis of Teropyrenophane 4.54

Shortening of the bridge that connects the 2 and 11 positions of the teropyrene system obviously results in an increase in the strain energy. Thus, moving to the final homolog (n=7) in the series of targets was no doubt going to push the limits of the VID methodology. Of the two routes that had been established and effective in the synthesizing teropyrenophanes **2.84** (n=8) and **4.41** (n=9), it was initially envisioned that Route B would be best suited for the synthesis of teropyrenophane **4.54**. Given that the first McMurry reaction of dialdehyde **2.75** (n=8 series) gave approximately a 5:1 ratio in favour of the desired stereoisomer, it was expected that shortening of the tether would exclusively afford *cis*-isomer **4.47**. The synthetic route to dialdehyde **4.46** is identical to those previously described (for **2.75** (n=8) and **4.33** (n=9)) and comparable in efficiency (Scheme 4.12). However, application of the McMurry reaction conditions to this system always failed[33] and, after multiple attempts to achieve the reductive coupling of dial **4.46**, it was necessary to pursue the synthesis of 1,1,7,7-tetramethyl[7](2,11)teropyrenophane (**4.54**) via Route A.

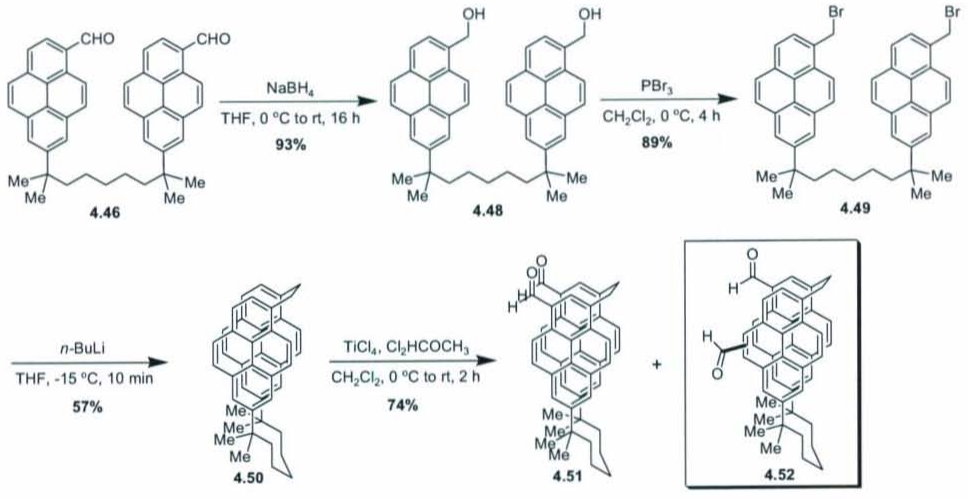


SCHEME 4.12: Attempted synthesis of advanced intermediate **4.47** via Route B

Reduction of dial **4.46** using sodium borohydride furnished diol **4.48** in 93% yield for which no purification was necessary (Scheme 4.13). Direct bromination of **4.48** using phosphorus tribromide required a slightly longer reaction time and closer monitoring of the temperature than had been previously necessary. For no obvious reason, the yield of this reaction was somewhat lower (65–70%) when the previously described conditions (Schemes 4.5 and 4.11) were applied. Nonetheless, dibromide **4.49** was obtained in high yield when the reaction was kept at 0 °C. Treatment of dibromide **4.49** with *n*-BuLi in THF at –15 °C gave the desired coupling product **4.50** in 57% yield. The ^{1}H NMR spectrum of cyclophane **4.50** was more complex than expected and several signals were broad. This indicated that the molecule is conformationally mobile and near coalescence

at 25 °C. Such dynamic behaviour in cyclophane systems is well documented.[34] A VTNMR experiment on a related compound (**4.22** (n=8)) is presented in Appendix 4.

Formylation of [7.2](7,1)pyrenophane **4.50** gave dialdehyde **4.51** in 74% yield. As in the other two Route A syntheses, a small (*ca.* 5%) amount of a separable dial byproduct **4.52** was obtained. The ^{1}H NMR spectrum of this system contains 14 different proton signals in the aromatic region and two different aldehyde signals of equal intensity. Formylation evidently occurred at a position other than the 1 position on one of the pyrene systems of **4.50**. Consideration of the multiplicities of the aromatic protons



SCHEME 4.13: Synthesis of dialdehyde **4.51** via route A

and agreement of the chemical shift value of one of the aldehyde protons (δ 10.49 ppm) with that of 2,7-di-*tert*-butyl-4-formylpyrene (δ 10.51 ppm)[35] points to the anomalous substitution having occurred at either the 4 or the 5 position of one of the pyrene systems of **4.50**. A suite of 2D NMR experiments may have led to a conclusive structural

assignment, but insufficient quantities of this byproduct were isolated. By the same token, the isolated material was an oil, so X-ray analysis was ruled out.

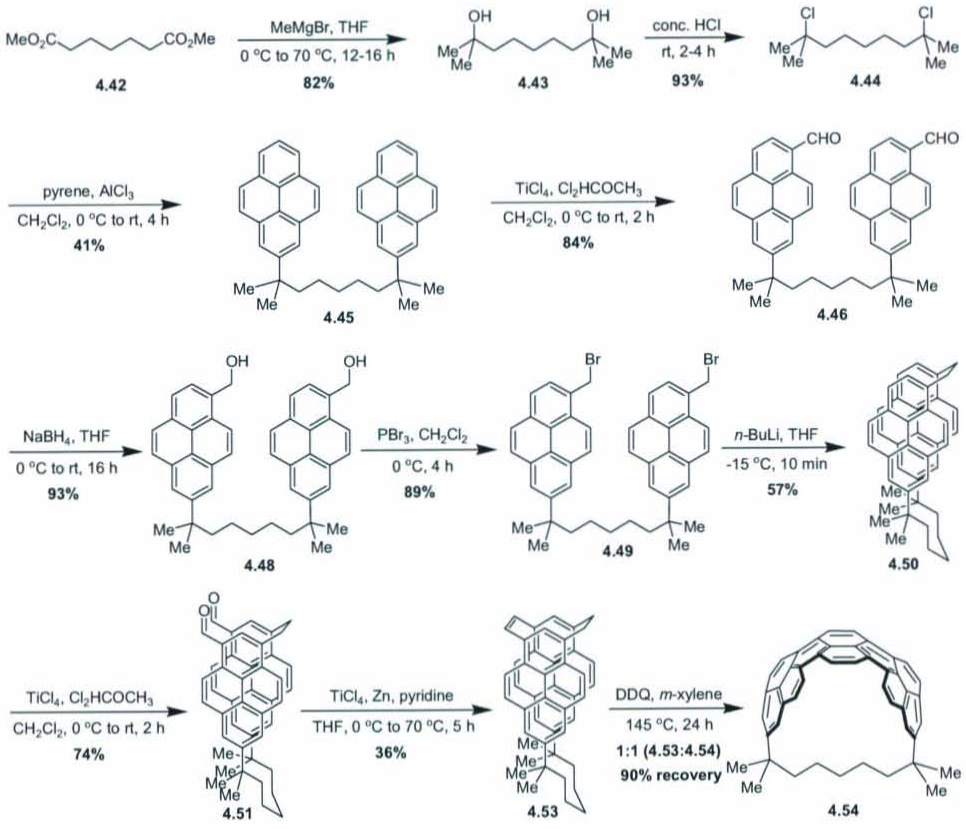
Despite the reluctance of dial **4.46** to participate in a productive McMurry reaction, cyclophanedialdehyde **4.51** reacted under reductive coupling conditions to give 1,1,7,7-tetramethyl[7.2.2](7,1,3)pyrenophane (**4.53**) in 37% yield. Application of the VID reaction conditions that had proven successful in two other instances were chosen initially. Well aware of the fact that the teropyrenophane system that is to be generated in this step is more strained than the others prepared to this point, close attention was paid to this critical reaction.

Temperature control proved to be very important in the successful preparation of homologs **2.84** (n=8) and **4.41** (n=9). Moving to a higher boiling solvent obviously had its benefits, however, at the same time the molecules being formed were found to decompose slowly under the conditions of their formation (*vide supra*). Treatment of **4.53** with DDQ in the same manner as before, gave a positive TLC and LCMS result that supported the formation of the desired teropyrenophane **4.54**. The initial rate of formation of this highly strained π-system appeared to be comparable to that of 1,1,8,8-teramethyl[8](2,11)teropyrenophane (**2.84**), but somewhat slower as the reaction progressed. In the early stages of monitoring this reaction, it seemed that complete conversion of starting material to product was not likely and after two days of reflux and several additions of small portions (*ca.* 0.2–0.5 equiv) of fresh DDQ, the reaction would progress to a small extent and then stall. As mentioned before, prolonged heating of 1,1,9,9-tetramethyl[9](2,11)teropyrenophane provided low isolated yields, presumably

due to product decomposition. Due to the normal[36] appearance of the TLC analysis of this reaction, prolonged heating of this system became a concern. As such, after two days of heating and what appeared to be approximately a *ca.* 2:1 ratio of product to starting material (by TLC analysis), the reaction was worked-up. It was at this stage that the reactive and unstable nature of the newly formed product became obvious.

Previously, a "crumb" (or a few crystals) of hydroquinone was added to the reaction mixtures of all other VID reactions after cooling to quench any remaining DDQ. Gently passing a stream of nitrogen gas over the cooling solution of *m*-xylene (to evaporate the high boiling solvent) followed by direct adsorption of the residue onto silica gel and subsequent chromatography proved to be sufficient work-up for this reaction. Application of these conditions, initially, resulted in decomposition of the 1,1,7,7-tetramethyl[7](2,11)teropyrenophane (**4.54**) that had formed. It was unclear if this was due to an increase in concentration during the work-up procedure or due to silica gel chromatography.

At this juncture it seemed that isolation of the desired product in pure form would be an especially challenging endeavour. Thus, it was decided that a short (15 × 2.0 cm) silica gel column to remove the baseline impurities would be performed, where no attempt to separate the remaining starting material from product would be pursued (see Section 4.8 for chromatography details). This notion proved to be very rewarding as 1,1,7,7-tetramethyl[7](2,11)teropyrenophane was eventually isolated as a mixture of approximately 1:1 **4.53** and **4.54** (*ca.* 90% mass balance) and characterized by ^{1}H NMR and HRMS.



SCHEME 4.14: Synthesis of teropyrenophane **4.54** via Route A

Unfortunately, attempts to grow crystals suitable for X-ray analysis of 1,1,9,9-tetramethyl[9](2,11)teropyrenophane or 1,1,7,7-tetramethyl[7](2,11)teropyrenophane have been unsuccessful and a conclusive discussion of the teropyrene systems of both of these cyclophanes will have to wait.

4.5 Bending Teropyrene: ^{1}H NMR Data and Calculated Distances and Angles

One of the defining features of a research program that sets its sights on bending an aromatic or polynuclear aromatic hydrocarbon out of its preferred planar conformation, using the *cyclophane approach* (Chapter 1), is the systematic preparation of a series of homologous cyclophanes. The synthetic project comes to an end when the most strained or unstable target has been prepared or fails to form when the key reaction is applied. Such is the case for this study on the teropyrene system. While the upper limit in bending the teropyrene system of the 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes prepared in this study ends with n=7, for future considerations it would be useful to attempt the synthesis of the n=6 homolog using one or both of the routes described above. The following discussion of key distances and angles in the nonplanar teropyrene nucleus of these cyclophane systems will include both lower and higher homologs of the teropyrenophanes that have been prepared in this work for comparison.

Semi-empirical AM1 calculations have served as a useful guide for predicting the outcome of various VID reactions in the synthesis of several [*n*](2,7)pyrenophanes. Generally, if the calculated θ angle is below 113°, then the designed pyrenophane system has been expected to be a viable target. In fact, of all the pyrenophane targets that have been synthesized by the Bodwell group, the AM1-based guideline has never failed. The AM1-calculated bend angle θ in the [*n*](2,7)pyrenophanes is generally 4–8° greater than the measured value (X-ray crystal structure) for a given target.

Consideration of the bending that takes place in the teropyrene system when a tether is imposed at the 2 and 11 positions was discussed in Section 4.3.2. Figure 4.4

summarizes the various θ angles (described in Section 4.3.2) that have been calculated for the 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes (*n*=6–10) using the same semi-empirical treatment that has been used for the [*n*](2,7)pyrenophanes. A discussion of the nonplanar teropyrene system of teropyrenophane **2.84** was presented in Section 4.3.2 and the important angles and distances calculated as an average for Molecules A and B in the asymmetric unit of **2.84** are presented in Figure 4.4 for comparative purposes.

Both calculated and experimentally determined values of θ for 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes indicate that central pyrene system (θ_2) of the teropyrene nucleus is distorted considerably more than the two flanking pyrene systems (θ_1 and θ_3). Moreover, AM1-calculations systematically predict approximately an 8° increase in θ_2 for shortening the bridge that connects the 2 and 11 positions of the teropyrene system by a single methylene group, while θ_1 and θ_3 are predicted to increase by approximately 4°. Like the [*n*](2,7)pyrenophanes, the AM1 caluclations overestimate the values of θ_1 and θ_3 (1.2–4° for molecules A and B in the asymmetric unit of **2.84**). However, the calculated value of θ_2 is *lower* (0.2–3°) than those determined from X-ray data. The value of θ_{tot} is once again overestimated by approximately 5° for both teropyrene systems in the asymmetric unit of **2.84**. A more meaningful comparison of these numbers will be possible when X-ray structures for the other teropyrenophanes (*n*=7 and 9) synthesized in this work become available. The calculated value θ_{tot} for the teropyrene of **4.54** at 184.7°, bodes well for the application the VID reaction in the synthesis of aromatic belts, such as **2.5** (80 carbons).

Metric	$n = 6$	$n = 7$	$n = 8$	$n = 8$ (X-Ray)*	$n = 9$	$n = 10$
β_1 [°]	4.0	3.8	4.7	5.6	5.0	5.3
β_2 [°]	4.0	3.8	4.8	5.6	5.0	5.3
θ_1 [°]	79.6	75.6	71.5	67.8	67.2	62.8
θ_2 [°]	108.0	100.6	92.6	94.4	85.2	78.2
θ_3 [°]	79.6	75.5	71.6	70.1	67.2	62.7
θ_{tot} [°]	196.1	184.7	172.5	167.0	160.5	148.1
$\theta_{tot} + \beta_1 + \beta_2$[°]	208.1	192.3	182.0	178.8	170.5	158.6
d_1 [Å]	7.1	8.0	8.9	9.1	9.8	10.7
d_2 [Å]	6.5	7.7	8.9	9.1	10.1	11.2
d_3 [Å]	6.8	7.8	8.9	9.1	10.0	11.0
d_4 [Å]	6.5	6.3	6.1	6.2	5.9	5.6

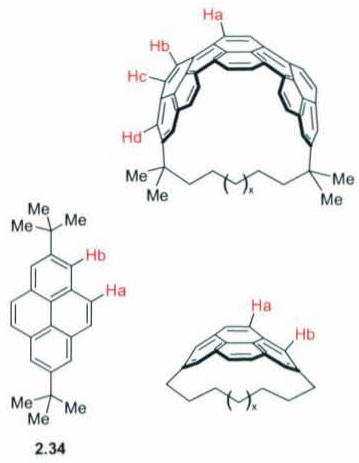
**angles and distances used for n = 8 (X-Ray) are average values of Molecules A and B of the asymmetric unit.*

FIGURE 4.4: Angles and distances in 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes

As described in Chapter 3, preparation of a suitable model compound was not possible using the chemistry that ultimately led to the synthesis of the three teropyrenophanes described above. While the main objective of the model study was fulfilled, construction of a 2,11-di-*tert*-butylteropyrene system would have been useful for the comparison of physical properties of the planar hydrocarbon with that of the nonplanar teropyrene systems of teropyrenophanes **2.84**, **4.41** and **4.54**. Nonetheless, some meaningful comparisons of these three nonplanar teropyrene systems can be made

based on their individual ^{1}H NMR data. To do this, the aromatic signals of **2.84**, **4.41** and **4.54** needed to be assigned unambiguously.[37]

A general trend in the ^{1}H NMR spectra obtained for the homologous [*n*](2,7)pyrenophanes (*n*=7–9) is that as θ increases the chemical shift values of the protons H(a) and H(b) decrease (*i.e.* they move to higher field). Comparison of the chemical shift values of protons H(a) and H(b) to those of 2,7-di-*tert*-butylpyrene (**2.34**) illustrates this phenomenon. While the same comparison to 2,11-di-*tert*-butylteropyrene cannot be made here, it is evident that the same general chemical shift trend is associated with bending the teropyrene system. The larger change in the chemical shift of H(a) in the 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes is consistent with the larger increase in the value of θ_2 (Figure 4.5) for the central pyrene systems of **4.54**, **2.84** and **4.41**. Moreover, the change in chemical shift value for the indicated protons in Figure 4.5 is larger per degree change in the angle θ in the 1,1,*n*,*n*-tetramethyl[*n*](2,11)tero-pyrenophanes (0.024 ppm/°) than it is in the [*n*](2,7)pyrenophanes(*cf.* 0.009 ppm/°). This last facet may be a consequence of the PAH (teropyrene), however, since no ^{1}H NMR data of teropyrene was reported by Yamato and co-workers,[22] it is hard to make any definitive statements at this stage.



x	δ Ha	δ Hb	δ Hc	δ Hd
1 (**4.54**)	8.46	8.26	7.62	7.29
2 (**2.84**)	8.62	8.39	7.71	7.42
3 (**4.41**)	8.77	8.52	7.80	7.50

x	δ Ha	δ Hb	θ_{calc}
1 (**1.140**)	7.67	7.34	104.6
2 (**1.139**)	7.84	7.59	87.0
3	7.91	7.75	70.3
(**2.34**)	8.00	8.17	

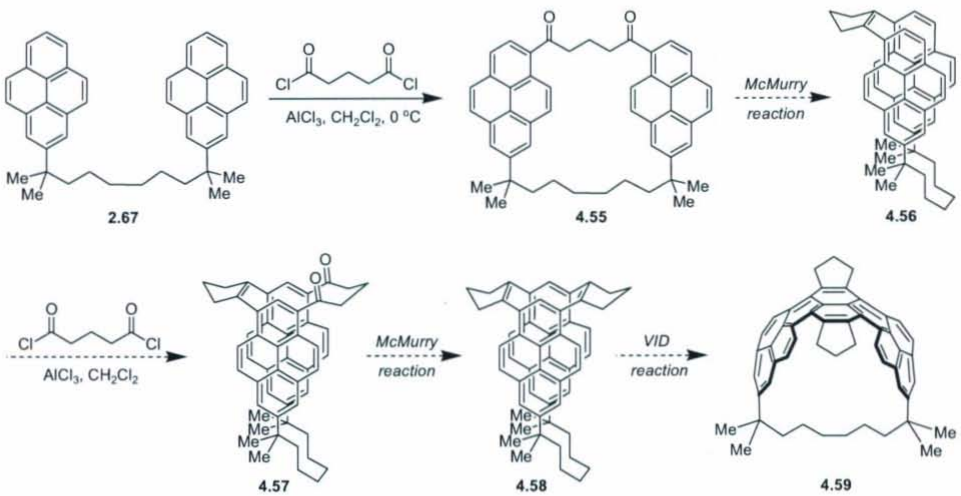
FIGURE 4.5: ^{1}H NMR data for teropyrenophanes and [*n*](2,7)pyrenophanes (*n*=7–9)[14]

4.6 Future Directions and Further Applications of the Chapter 3 Model Study

Having demonstrated the power and synthetic utility of the VID reaction in the synthesis of the largest nonplanar aromatic systems to be contained within a cyclophane scaffold, a logical extension of this work would be to continue to push the limits of this reaction through the synthesis of a series of derivatives or teropyrenophane analogs. This may be useful in further understanding the reactivity and aromaticity of the teropyrene system. Moreover, the lessons learned about the VID reaction in the synthesis of teropyrenophanes may be valuable in related projects aimed at the synthesis of other large nonplanar hydrocarbons, including defined segments of monodisperse single-walled carbon nanotubes (*vide supra*).

In the model study conducted on 2-*tert*-butylpyrene (**2.33**, Chapter 3), it was discovered that two of these molecules could be linked together at their 6 positions upon Friedel-Crafts acylation with glutaryl chloride. While the yield of this reaction was low

in the model system (38%) and plagued by the formation of an undesired lactone byproduct (see Scheme 3.10, Chapter 3), the application of this chemistry towards the synthesis of cyclopentaannulated teropyrenophanes was initially pursued. If the acylation reaction is successful when applied to any of the three bis(2-pyrenyl)-dimethylalkane systems discussed above, the subsequent McMurry reaction would furnish a cyclopentene ring as one of the bridges in the cyclophane. Thus, only a *Z*-configured alkene would be possible (Scheme 4.15). This would address a major problem that is associated with the first McMurry reaction of dialdehyde systems such as **2.75** and **4.33**. Moreover, this McMurry reaction has the potential to be much more efficient than all other reductive couplings attempted in the synthesis of the 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes, since the reaction will be transannular and involve the formation of a 5-membered ring – recall the near quantitative yield that was obtained in the Chapter 3 model study (Scheme 3.10, **3.54** → **3.56**).

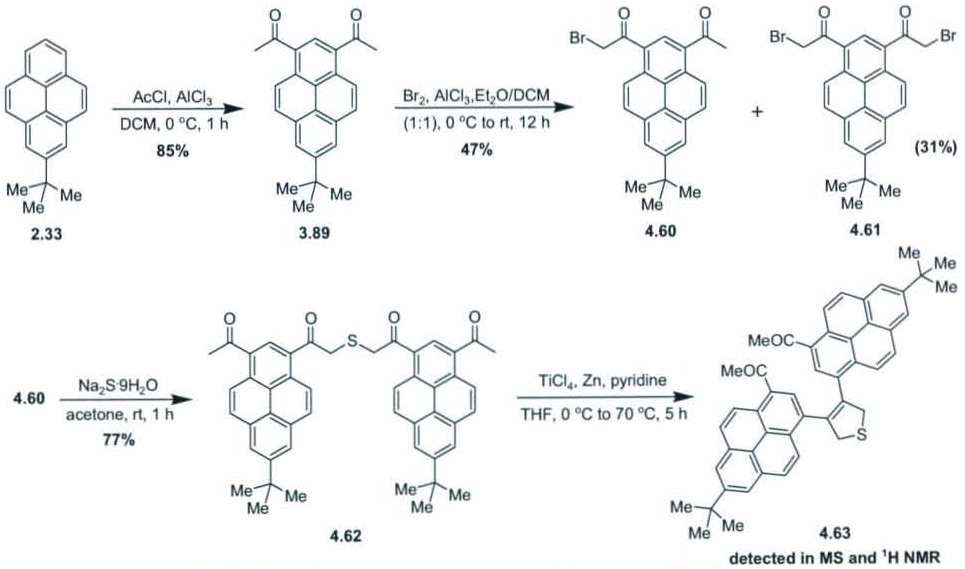


SCHEME 4.15: Application of glutaryl chloride strategy towards the synthesis of **4.59**

Unfortunately, despite what seemed to be an obvious solution to the McMurry coupling strategy, the Friedel-Crafts acylation reaction of **2.67** and glutaryl chloride never gave any desired product (**4.55**). This particular acylation reaction seemed to be much more sluggish than with the model system. Exploration to find the optimal reaction conditions for this reaction proved to be fruitless. In all cases, complete consumption of starting material within in a reasonable time frame did not occur and no tractable products were isolated (only recovered **2.67**). TLC and LCMS analysis of the reaction and the isolated crude products did not support the formation of **4.55**.

Overcoming the somewhat problematic initial McMurry reaction in the synthesis of 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes, where it was never possible to isolate exclusively the desired *cis*-olefin, would be a worthwhile effort in future work on this or a related project. While the direct Friedel-Crafts acylation reaction of **2.67** with glutaryl chloride was unsuccessful, it was discovered that sulfide coupling of α-bromoketone **4.60** could furnish the analogous 3-thia-dione systems **4.62** in good yield (Scheme 4.16). In principle, this bromination reaction should be applicable to tetraketone **2.78** (Scheme 4.18), which is readily prepared from the Friedel-Crafts acylation of **2.67** with acetyl chloride (Chapter 2). Furthermore, it was discovered that controlling the bromination of diketone **3.89** was possible by modification of the solvent and the reaction temperature. The main objective of this study was to delineate the necessary conditions for mono- and dibromination, and to test the viability of Bodwell's sodium sulfide conditions in the desired coupling reaction. To this end, no attempts to optimize the reaction conditions

were made in the remaining discussion and the results described below are preliminary at this stage.

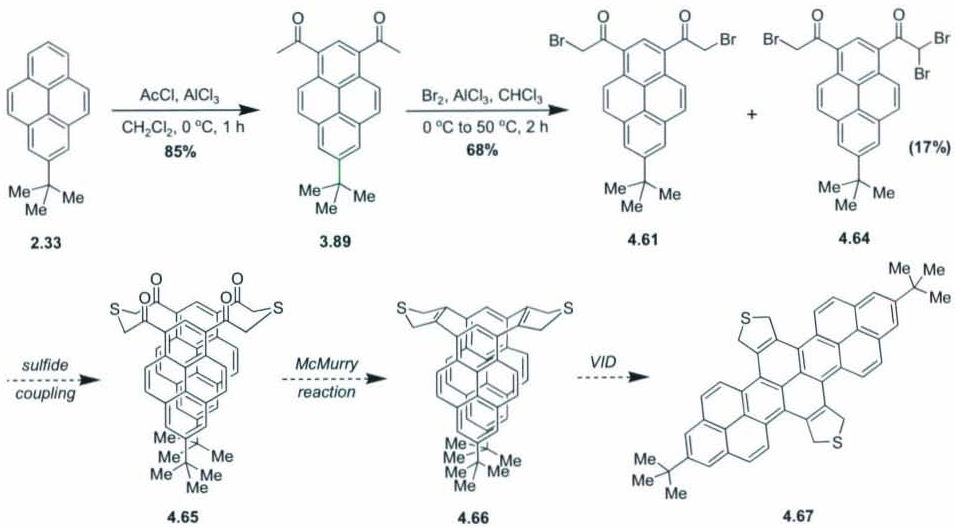


SCHEME 4.16: Sulfide coupling approach to annulated teropyrenes

Diketone **3.89** was treated to with bromine and a catalytic amount of aluminium chloride in a 1:1 mixture of diethyl ether/dichloromethane to furnish bromoketone **4.60** in 47% yield. The application of an *Organic Syntheses* procedure that deals with the preparation of α-bromoacetophenone[38] was not viable in this instance due to the low solubility of the starting material in diethyl ether. However, using dichloromethane as a co-solvent (1:1) in the reaction facilitated the bromination of **3.89**, but at the price of forming 31% of dibromoketone **4.61** in the process. The separation of these two compounds was trivial using flash chromatography and with pure samples of both bromoketones in hand, testing the sulfide coupling reaction was the next objective. Treatment of monobromoketone **4.60** with sodium sulfide in acetone gave tetraketone

4.62 (no purification necessary) in 77% yield and made probing the subsequent McMurry reaction possible. Using the optimal McMurry reaction conditions described in Section 4.2.3, on a small scale (*ca.* 20 mg), gave the desired product **4.63** (MS and ^{1}H NMR analysis). At the initial stage of investigation, the material isolated from the McMurry reaction was contaminated with what appears to be pinacol and McMurry coupling products of the proximal methyl ketones.

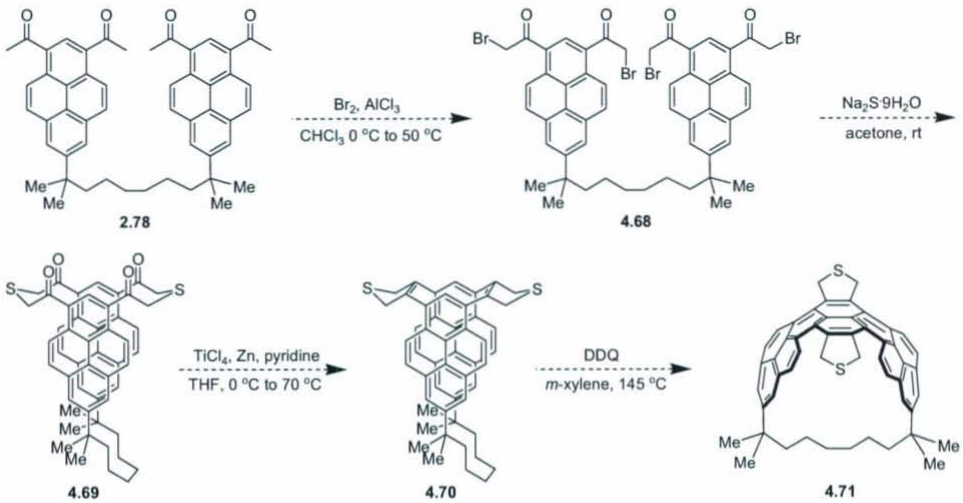
A second investigation of securing a synthetic route to dibromoketone **4.61** was put forth in hope that it may find application into the synthesis of disulfides **4.65** and



SCHEME 4.17: Proposed sulfide coupling approach to teropyrene **4.67**

4.69. Treating diketone **3.89** with the same reagents described in Scheme 4.16, but changing the solvent to chloroform and heating to 50 °C, gave dibromide **4.61** in 68% yield (Scheme 4.17). As in the previous bromination reaction, over-bromination of **3.89** resulted in the formation of tribromide **4.64** (17%). Separation of these products was

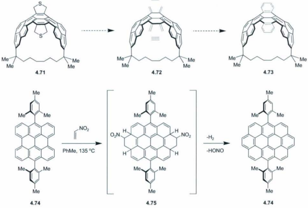
once again trivial using flash chromatography. While sulfide coupling of **4.61** was not tested, it should be as productive as it was in the synthesis of **4.62**, especially in the case of dibromide **4.68**. Both subsequent McMurry reactions of **4.65** and **4.69** should be highly favoured due to their transannular nature. Moreover, this particular model study may have significantly more promise in providing a planar teropyrene model compound.



SCHEME 4.18: Proposed sulfide coupling approach to teropyrenophane **4.71**

If the proposed synthesis in Schemes 4.17 and 4.18 are successful and dihydrothiophene annulated teropyrenophane **4.71** can in fact be generated, then the next step would be to oxidize the sulfur atoms and thermally extrude SO_2 to generate a diene system (**4.72**), which could potentially undergo Diels-Alder reactions with various dienophiles to give benzannulated analogs such as **4.73** (Scheme 4.19). The four bay regions of the teropyrene system could potentially serve as dienes in a different Diels-Alder reaction to expand the polycyclic system. Recent work by Scott and co-workers[39] has demonstrated the viability of nitroethylene as an acetylene equivalent[40] in the Diels-

Alder reaction with the bay regions of perylene and related polycyclic aromatic hydrocarbons (Scheme 4.19). The implications of their studies are that it is conceivable that armchair SWCNTs can be prepared via chemical synthesis using a suitable PAH template. This fascinating and simple solution to growing carbon nanotubes will no doubt serve to inspire many groups in the years to come.



SCHEME 4.19: Diels-Alder approach to annulated teropyrenophanes

4.7 Conclusions and Outlook

The difficulty of designed molecule synthesis was exemplified by the 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes. Having designed several synthetic routes at the outset of this project (Chapter 2) that hoped to capitalize on known reactions of pyrene, it

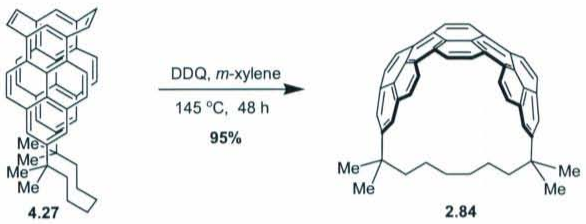
was not nearly enough to conquer these highly distorted π-systems. The invention of novel chemistry, as it applies to pyrene and pyrenophanes, was necessary to overcome what sometimes seemed like impossible targets.

Some of the most gratifying accomplishments of this work include the discovery that the McMurry reaction can be used exclusively to generate a [2.2]metacyclophanediene system and that a Wurtz-type coupling can provide an alternative route for the synthesis of (2,11)teropyrenophanes. Moreover, the discovery that the VID reaction can be applied to a tethered[2.2]metacyclophane system that contains only one unsaturated bridge and, in the process, deliver unprecedented cyclophanes that contain the largest bend angles known, will be very useful in future synthetic efforts of the Bodwell group.

The knowledge that has been gleaned from this work and showcasing the Bodwell group's key reaction has demonstrated that the valence isomerization / dehydrogenation reaction is one of the most powerful tools available to the synthetic community in generating nonplanar pyrenoid π-systems. To date, the teropyrene systems of the teropyrenophanes **2.84**, **4.41** and **4.54** (at 36 carbon atoms) represent the largest PAH systems that have been considerably distorted from planarity using a cyclophane approach. What once seemed inconceivable through wet chemical methods of relatively small aromatic building blocks is now a reality - thanks to the VID reaction. Further, its application towards the synthesis of aromatic belts would seem inevitable and synthesis that conquers these elusive targets will hopefully be reported in the near future.

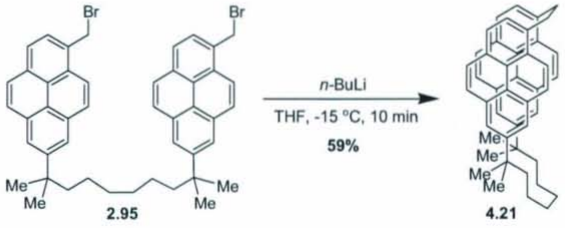
4.8 General Experimental Procedures and Characterization Data

1,1,8,8-Tetramethyl[8](2,11)teropyrenophane (2.84)



A solution of 1,1,8,8-tetramethyl[8.2.2](7,1,3)pyrenophane-19,31-diene (**4.27**) (0.022 g, 0.036 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.032 g, 0.14 mmol) in *m*-xylene (5 mL) was heated at 145 °C for 48 h. The hot solvent was evaporated under a stream of nitrogen gas. The residue was taken up into dichloromethane and preadsorbed onto silica gel in preparation for column chromatography. The preadsorped sample was subjected to column chromatography (30 × 2.0 cm; 1:4 dichloromethane/hexanes) to yield 1,1,8,8-tetramethyl[8](2,11)teropyrenophane (**2.84**) as an orange solid (0.021 g, 95 %), which exhibits yellow fluorescence at 365 nm: R_f = 0.46 (1:4 dichloromethane/hexanes); m.p. >300 °C (dec.) (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 4H), 8.39 (d, *J*=9.5 Hz, 4H), 7.71 (d, *J*=9.5 Hz, 4H), 7.42 (s, 4H), 1.32 (s, 12H), 0.74–0.70 (m, 4H), -0.24 to -0.27 (m, 4H), -0.65 to -0.70 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 145.69, 137.84, 137.51, 130.25, 129.12, 128.54, 126.57, 123.80, 123.01, 122.62, 122.52, 46.93, 38.15, 30.98, 29.80, 24.78; LCMS (APCI-positive, *m/z* (rel. int.)) 619 (13), 618 (52), 617 ((M*H*)$^+$, 100); HRMS (CI) calculated for $C_{48}H_{41}$ (M*H*)$^+$ 617.3208, found 617.3211.

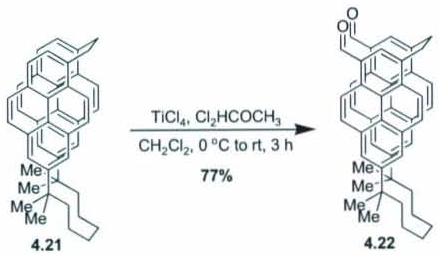
1,1,8,8-Tetramethyl[8.2](7,1)pyrenophane (4.21)



A solution of *n*-butyllithium (1.0 M, 0.40 mL, 0.40 mmol) in hexanes was added to a stirred –15 °C solution of 2,9-bis(6-(bromomethyl)pyren-2-yl)-2,9-dimethyldecane (**2.95**) (0.401 g, 0.529 mmol) in THF (45 mL). After 10 min, water (15 mL) was added to the reaction mixture. THF was evaporated under reduced pressure and the resulting aqueous solution was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with 1 M HCl (30 mL), washed with a saturated solution of sodium bicarbonate (30 mL), washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was preadsorbed onto silica gel and purified by column chromatography (25 × 3 cm; 15% dichloromethane/hexanes) to yield 1,1,8,8-tetramethyl[8.2](7,1)pyrenophane (**4.21**) as a clear, colorless oil (0.186 g, 59%): R_f = 0.32 (15% dichloromethane/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (br d, 2H), 8.15 (br d, 2H), 8.02 (d, *J*=9.4 Hz, 2H), 7.89–7.84 (m, 4H), 7.35 (s, 2H) 6.68–6.50 (m, 4H), 3.89 (s, 4H) 1.66–1.58 (m, 4H), 1.43–1.28 (m, 12H), 1.12–1.06 (m, 4H), 0.57–0.43 (m, 2H), 0.30–0.18 (m, 2H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 146.10, 131.05, 129.98, 129.91, 129.80, 127.62, 127.16, 127.00, 125.54, 125.04, 125.02, 124.67, 122.85, 122.53, 122.36, 122.05, 46.44, 38.11, 36.47, 31.45, 30.48, 24.22; LCMS (APCI-positive,

m/z (rel. int.)) 599 (12), 598 (53), 597 (100 $(MH)^+$); HRMS (EI) calculated for $C_{46}H_{44}$ $(M)^+$ 596.3443, found 596.3436.

13,23-Diformyl-1,1,8,8-tetramethyl[8.2](7,1)pyrenophane (4.22)



A solution of titanium(IV) chloride (1.0 M, 0.50 mL, 0.50 mmol) in dichloromethane was added to a stirred 0 °C solution of 1,1,8,8-tetramethyl[8.2](7,1)pyrenophane (**4.21**) (0.120 g, 0.201 mmol) and dichloromethyl methyl ether (0.058 g, 0.50 mmol) in dichloromethane (10 mL). The reaction was allowed to slowly warm to room temperature and poured into ice water (50 mL) after 3 h. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 15 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (20 mL), washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The solid brown residue was subjected to column chromatography (30 × 2.5 cm; dichloromethane) to yield 13,23-diformyl-1,1,8,8-tetramethyl[8.2](7,1)pyrenophane (**4.22**) as a bright yellow solid (0.102 g, 77 %): R_f = 0.28 (dichloromethane); m.p. 296–297 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$, T = –25 °C) δ 10.95 (s, 2H), 9.36 (d, *J*=9.2 Hz, 2H), 8.62 (s, 2H), 8.16 (d, *J*=9.2 Hz, 2H), 8.00 (s, 2H) 7.44 (s, 2H), 6.78 (d, *J*=9.1 Hz, 2H), 6.59 (d, *J*=9.1 Hz, 2H), 3.95 (s, 4H), 1.77 (s, 2H), 1.70–1.65 (m, 2H),

1.49–1.45 (m, 2H), 1.37 (s, 6H), 1.31 (s, 6H) 1.01–0.96 (m, 2H) 0.58–0.51 (m, 2H) 0.15–0.10 (m, 2H); ^{13}C NMR (125.77 MHz, $CDCl_3$ T = –25 °C) δ 193.60, 147.41, 135.98, 134.70, 132.87, 130.74, 130.46, 130.18, 129.70, 129.26, 127.59, 124.86, 124.70, 124.42, 122.48, 122.38, 121.98, 46.09, 38.40, 36.43, 32.16, 30.13, 28.09, 24.02; LCMS (APCI-positive, *m/z* (rel. int.)) 655 (12), 654 (53), 653 ((M*H*)$^+$, 100) HRMS (EI) calculated for $C_{48}H_{44}O_2$ (M)$^+$ 652.3341, found 652.3328.

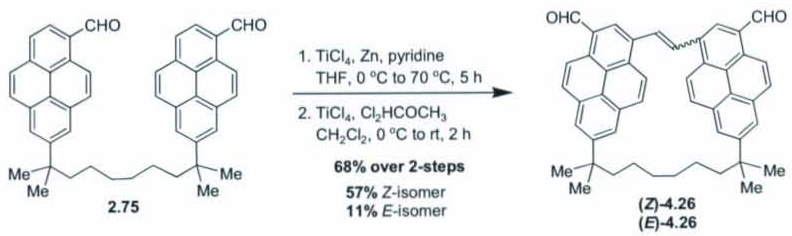
,1,8,8-Tetramethyl[8.2.2](7,1,3)pyrenophane-19-monoene (4.23)

4.22 **4.23**

Titanium(IV) chloride (0.047 g, 0.248 mmol) was added to a 0 °C slurry of zinc dust (0.016 g, 0.248 mmol) and THF (5 mL). After the addition was complete, the reaction was heated to reflux for 1 h, at which point a dark black color persisted, indicative of the low–valent titanium species desired. Pyridine (0.05 mL) was added to the mixture and stirring at reflux was continued for 10 min. A solution of 13,23-diformyl-1,1,8,8-tetramethyl[8.2](7,1)pyrenophane (**4.22**) (0.020 g, 0.031 mmol) in THF (5 mL) was then added. The mixture was heated at 70 °C for 4 h, after which it was poured, without significant cooling, into chloroform (15 mL). The resulting solution was concentrated under reduced pressure and adsorbed onto silica gel in preparation for column chromatography. Aqueous work-up for this reaction is not recommended as layer

separation can be quite difficult and the yields are lower. The preadsorbed sample was subjected to column chromatography (25 × 2 cm; 1:5 dichloromethane/heaxanes) to afford 1,1,8,8-tetramethyl[8.2.2](7,1,3)pyrenophane-19-monoene (**4.23**) as a pale-green oil (0.010 g, 52%): R_f = 0.48 (1:4 dichlormethane/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 2H), 7.82 (d, *J*=9.2 Hz, 2H) 7.66–7.64 (m, 4H), 7.56 (d, *J*=1.4 Hz, 2H), 7.54 (d, *J*=1.4 Hz, 2H), 7.48 (d, *J*=9.1 Hz, 2H), 7.44 (d, *J*=9.2 Hz, 2H), 4.31–4.26 (m, 2H), 3.76–3.71 (m, 2H), 1.54–1.50 (m, 4H), 1.33 (s, 6H) 1.32 (s, 6H), 1.05–1.02 (m, 4H), 0.34–0.30 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 145.37, 138.21, 135.82, 130.01, 128.58, 128.56, 126.12, 125.33, 124.02, 123.99, 123.01, 122.98, 122.96, 122.36, 122.16, 46.72, 38.33, 30.78, 29.65, 24.74; LCMS (APCI-positive, *m/z* (rel. int.)) 623 (11), 622 (54), 621 ($(MH)^+$, 100), HRMS (EI) calculated for $C_{48}H_{44}$ $(M)^+$ 620.3443, found 620.3438.

(*Z*)-13,23-Diformyl-1,1,8,8-tetramethyl[8.2](7,1)pyrenophane ((*Z*)-4.26) and (*E*)-13,23-Diformyl-1,1,8,8-tetramethyl[8.2](7,1)pyrenophane ((*E*)-4.26)



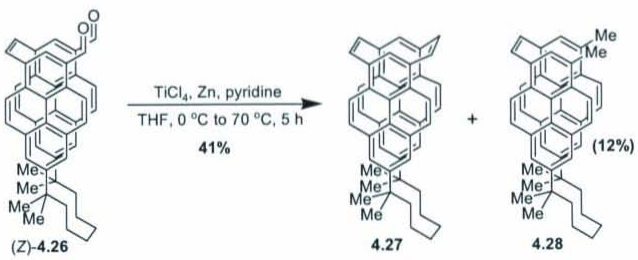
Titanium(IV) chloride (0.363 g, 1.92 mmol) was added to a stirred 0 °C slurry of zinc dust (0.125 g, 1.92 mmol) and THF (25 mL). After the addition was complete, the reaction was heated at reflux for 1 h, at which point a dark black color persisted. Pyridine (0.2 mL) was added and the mixture was stirred at reflux for a further 10 min. A solution

of 2,9-bis(6-formylpyren-2-yl)-2,9-dimethyldecane (**2.75**) (0.150 g, 0.240 mmol) in THF (20 mL) was then added and the mixture was heated at 70 °C for a further 4 h. The reaction mixture was then poured without significant cooling into chloroform (50 mL). The resulting mixture was concentrated under reduced pressure and adsorbed onto silica gel in preparation for column chromatography. Aqueous work-up for this reaction is not recommended as layer separation can be quite problematic and the yields are typically lower. The preadsorbed sample was subjected to column chromatography (20 × 3.5 cm, 15% dichloromethane/hexanes) to yield a mixture of (*E*)- and (*Z*)-1,1,8,8-tetramethyl[8.2](7,1)pyrenophane (**2.92**) as a bright yellow solid (0.113 g, 0.192 mmol): R_f = 0.32 (15% dichloromethane/hexanes); LCMS (APCI-positive, *m/z* (rel. int.)) 597 (13), 596 (51), 595 ($(MH)^+$, 100). To a stirred 0 °C mixture of (*E*)- and (*Z*)-**2.92** (0.113 g, 0.192 mmol) and dichloromethyl methyl ether (0.055 g, 0.48 mmol) in dichloromethane (15 mL) was added titanium(IV) chloride (1.0 M solution in dichloromethane, 0.48 mL, 0.48 mmol). The cooling bath was removed and the reaction was stirred at room temperature for 2 h. The reaction mixture was poured into ice water (50 mL), the layers were separated and the aqueous layer was extracted with dichloromethane (2 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting solid brown residue was subjected to column chromatography (40 × 3 cm; dichloromethane) to yield (*Z*)-13,23-diformyl-1,1,8,8-tetramethyl[8.2](7,1)pyrenophane ((*Z*)-**4.26**) (0.088 g, 57%) as a bright yellow solid: R_f = 0.25 (dichloromethane); m.p. 241–242 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.73 (s, 2H), 9.22 (d, *J*=9.2 Hz, 2H), 8.36 (s, 2H), 8.06 (d, *J*=9.2

Hz, 2H), 7.98 (s, 2H), 7.82 (s, 2H), 7.70 (br s, 2H), 7.63 (s, 2H) 7.29 (br s, 2H), 1.62–1.57 (m, 4H), 1.38 (s, 12H), 1.02–0.98 (m, 4H), 0.45–0.39 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 193.37, 147.70, 132.79, 132.72, 132.30, 131.39, 130.51, 130.38, 129.92, 129.74, 127.21, 125.14, 124.99, 124.89, 124.85, 122.75, 122.15, 45.97, 38.47, 30.56, 30.12, 24.34 (only 22 of 23 signals observed); LCMS (APCI-positive), *m/z* (rel. int.) 653 (13), 652 (53), 651 (MH^+, 100), 637 (23); HRMS (EI) calculated for $C_{48}H_{42}O_2$ (M^+) 650.3185, found 650.3182.

(*E*)-13,23-Diformyl-1,1,8,8-tetramethyl[8.2](7,1)pyrenophane ((*E*)-**2.92**) was isolated as a bright yellow solid (0.017 g, 11%): R_f = 0.23 (dichloromethane); m.p. 256 °C (dec.) ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.61 (s, 2H), 9.12 (d, *J*=9.1 Hz, 2H), 8.20 (br s, 2H), 8.01 (d, *J*=9.1 Hz, 2H), 7.93–7.85 (m, 6H), 7.71 (br d, 2H), 7.52 (br d, 2H), 1.99–1.94 (m, 1H), 1.69–1.63 (m, 1H), 1.57–1.53 (m, 2H), 1.44–1.41 (m, 12H), 1.04–0.99 (m, 1H), 0.74–0.70 (m, 4H), 0.45–0.18 (m, 2H), -0.10 to -0.16 (m, 1H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 192.96, 147.56, 132.74, 132.84, 132.43, 131.36, 130.82, 130.42, 129.90, 129.59, 127.26, 124.98, 124.95, 124.88, 124.80, 123.04, 122.27, 45.73, 38.63, 30.51, 30.18, 24.58 (only 22 of 23 signals observed); LCMS (APCI-positive), *m/z* (rel. int.) 653 (12), 652 (52), 651 ($(MH)^+$, 100), 637 (22); HRMS (EI) calculated for $C_{48}H_{42}O_2$ (M^+) 650.3185, found 650.3180.

1,1,8,8-Tetramethyl[8.2.2](7,1,3)pyrenophane-19,31-diene (4.27) and (*Z*)-1,1,8,8,13,23-Hexamethyl[8.2](7,1)pyrenophane (4.28)

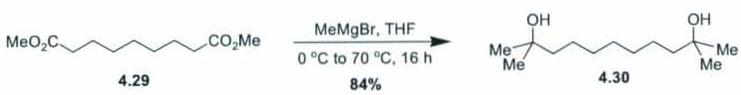


Titanium(IV) chloride (0.148 g, 0.784 mmol) was added to a stirred 0 °C slurry of zinc dust (0.051 g, 0.78 mmol) and THF (20 mL). After the addition was complete, the reaction was heated at reflux for 1 h, at which point a dark black color persisted. Pyridine (0.1 mL) was added and the mixture was stirred at reflux for a further 10 min. A solution of (*Z*)-13,23-diformyl-1,1,8,8-tetramethyl[8.2](7,1)pyrenophane ((*Z*)-**4.26**) (0.064 g, 0.098 mmol) in THF (15 mL) was then added and the reaction was heated at 70 °C for a further 4 h. The reaction mixture was then poured without significant cooling into chloroform (35 mL). The resulting mixture was concentrated under reduced pressure and adsorbed onto silica gel in preparation for column chromatography. Aqueous work-up for this reaction is not recommended as layer separation can be quite problematic and the yields are typically lower. The preadsorbed sample was subjected column chromatography (25 × 2 cm, 1:5 dichloromethane/hexanes) to yield 1,1,8,8-tetramethyl[8.2.2](7,1,3)pyrenophane-19,31-diene (**4.27**) as a light green solid (0.025 g, 41%): R_f = 0.48 (1:4 dichloromethane/hexanes); m.p. >300 °C (dec.) ($CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 4H), 8.06 (s, 2H) 7.64 (d, *J*=9.0 Hz, 4H), 7.57 (s, 4H), 7.48 (d, *J*=9.0 Hz, 4H), 1.51–1.48 (m, 4H) 1.34 (s, 12H), 1.01–0.97 (m, 4H), 0.27–0.21 (m,

4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 145.69, 137.86, 137.53, 130.36, 129.13, 128.56, 126.59, 123.83, 123.01, 122.65, 122.53, 46.96, 38.16, 30.99, 29.83, 24.80; LCMS (APCI-positive,, *m/z* (rel. int.)) 621 (13), 620 (53), 619 ($(MH)^+$, 100), HRMS (EI) calculated for $C_{48}H_{42}$ $(M)^+$ 618.3287, found 618.3290.

(*Z*)-1,1,8,8,13,23-Hexamethyl[8.2](7,1)pyrenophane (**4.28**) was isolated as a colorless oil (7 mg, 12%): R_f = 0.50 (1:4 dichloromethane/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J*=9.1 Hz, 2H), 7.88 (d, *J*=9.1 Hz, 2H), 7.86 (s, 2H), 7.80 (s, 2H), 7.64 (s, 2H), 7.54 (br d, 2H), 7.47 (s, 2H), 6.97 (br d, 2H), 2.94 (s, 6H), 1.56–1.53 (m, 4H) 1.35 (s, 12H), 0.98–0.95 (m, 4H), 0.39–0.36 (m, 4H); LCMS (APCI-positive, *m/z* (rel. int.)) 625 (11), 624 (52), 623 ($(MH)^+$, 100); HRMS (EI) calculated for $C_{48}H_{46}$ $(M)^+$ 622.3600, found 622.3598.

2,10-Dimethyl-2,10-undecanediol (4.30)

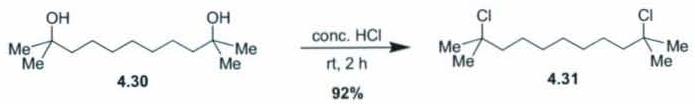


4.29 84% 4.30

A solution of dimethyl azelate (**4.29**) (10.8 g, 49.9 mmol) in anhydrous THF (100 mL) was added dropwise over a period of 30 min to a stirred 0 °C solution of methylmagnesium bromide (3.0 M, 75 mL, 230 mmol). After the addition was complete, the reaction mixture was heated at reflux for 16 h. The reaction mixture was cooled to room temperature and quenched by the addition of a saturated solution of ammonium chloride (100 mL). The layers were separated and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and

concentrated under reduced pressure to yield a white solid, which was recrystallized from heptane to give 2,10-dimethyl-2,10-undecanediol (**4.30**) (9.05 g, 84%) as a white powder. m.p. 64–66 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.52 (br s, 2H), 1.48–1.45 (m, 4H), 1.38–1.32 (m, 10H), 1.21 (s, 12H); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 71.21, 44.17, 30.32, 29.80, 29.41, 24.52; IR (cm^{-1}, neat): 3366, 2964, 2930, 2860, 1472, 1362; LCMS (APCI negative) *m/z* 216 (25) 215 $(M\text{-}H)^+$; HRMS (CI) calculated for $(MH)^+$ $C_{13}H_{29}O_2$ 217.2168, found 217.2160.

2,10-Dichloro-2,10-dimethylundecane (4.31)

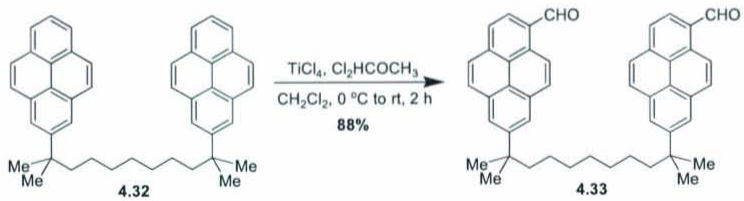


A mixture of 2,10-dimethyl-2,10-undecanediol (**4.30**) (1.75 g, 8.10 mmol) and concentrated aqueous HCl solution (40 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into a large excess of ice water (100 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (2 × 50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 2,10-dichloro-2,10-dimethylundecane (**4.31**) (1.88 g, 92%) as a light yellow oil, which was used subsequently without purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.79–1.75 (m, 4H), 1.58 (s, 12H), 1.48–1.44 (m, 4H), 1.31–1.25 (m, 6H); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 71.42, 46.32, 32.45, 29.90, 29.74, 25.01; LCMS (APCI-positive, *m/z* (rel. int.)) 253 $(MH)^+$; no HRMS data could be obtained for this compound.

2,10-Bis(2-pyrenyl)-2,10-dimethylundecnane (4.32)

Aluminum chloride (1.78 g, 13.4 mmol) was added to a stirred 0 °C solution of pyrene (**2.8**) (6.73 g, 33.3 mmol) and 2,10-dichloro-2,10-dimethylundecane (**4.31**) (1.68 g, 6.67 mmol) in dichloromethane (100 mL). The resulting slurry was allowed to warm to room temperature and stirred for 4 h. The reaction was poured into ice water (300 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 100 mL) and the combined organic extracts were washed with a saturated solution of sodium bicarbonate (50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The orange oily residue was subjected to column chromatography (25 × 6.5 cm; 1:9 dichloromethane/hexanes) to yield 2,10-bis(2-pyrenyl)-2,10-dimethylundecane (**4.32**) as an orange oil (1.67 g, 43%): R_f = 0.28 (1:9 dichloromethane/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09–8.05 (m, 8H), 7.98–7.95 (m, 8H), 7.91–7.87 (m 2H) 1.74–1.71 (m, 4H), 1.47 (s, 12H), 1.08–1.02 (m, 6H) 1.01–0.93 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 147.88, 131.14, 131.08, 127.80, 127.34, 125.64, 124.88, 124.81, 123.05, 122.97, 45.31, 38.40, 30.45, 29.72, 29.51, 24.91; LCMS (APCI-positive, *m/z* (rel. int.)) 587 (13), 586 (49), 585 ($(MH)^+$, 100), 385 (7), 384 (18), 383 (M-$C_{16}H_{10}$, 42); HRMS (EI) calculated for $C_{45}H_{44}$ $(M)^+$ 584.3443, found 584.3441.

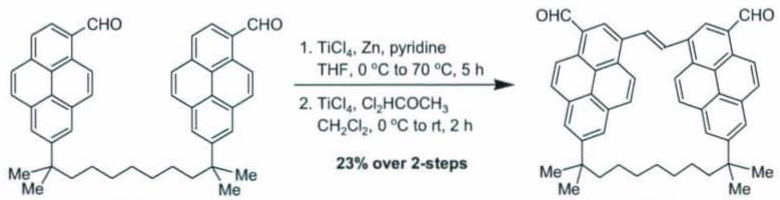
2,10-Bis(6-formylpyren-2-yl)-2,10-dimethylundecane (4.33)



Titanium(IV) chloride (0.67 g, 3.53 mmol) was added to a stirred 0 °C solution of 2,10-bis(2-pyrenyl)-2,10-dimethylundecnane (**4.32**) (0.82 g, 1.40 mmol) and dichloromethyl methyl ether (0.40 g, 3.48 mmol) in dichloromethane (30 mL). The cooling bath was removed and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was poured into ice water (100 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 30 mL) and the combined organic extracts were washed with washed with a saturated solution of sodium bicarbonate (40 mL), washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The solid brown residue was subjected to column chromatography (20 × 3.5 cm; dichloromethane) to yield 2,10-bis(6-formylpyren-2-yl)-2,10-dimethylundecane (**4.33**) as a light brown oil (0.77 g, 88%): R_f = 0.26 (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.73 (s, 2H), 9.32 (d, *J*=9.2 Hz, 2H), 8.38 (d, *J*=7.9 Hz, 2H), 8.22 (d, *J*=9.2 Hz, 2H), 8.20–8.14 (m, 6H) 8.10 (d, *J*=8.9 Hz, 2H), 8.00 (d, *J*=8.9 Hz, 2H), 1.75–1.72 (m, 4H), 1.49 (s, 12H), 1.08–1.04 (m, 6H) 0.98–0.93 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 193.52, 148.94, 135.75, 132.22, 131.54, 131.51, 131.33, 131.25, 131.15, 130.63, 127.67, 127.36, 125.33, 124.96, 124.70, 123.26, 122.63, 45.36, 38.69, 30.41,

29.84, 29.61 25.12; LCMS (APCI-positive) *m/z* (rel. int.) 643 (14), 642 (54), 641 ((M*H*)$^+$, 100), 613 (16); HRMS (EI) calculated for $C_{47}H_{44}O_2$ (M)$^+$ 640.3341, found 640.3335.

(*E*)-14,24-Diformyl-1,1,9,9-tetramethyl[9.2](7,1)pyrenophane (4.34)

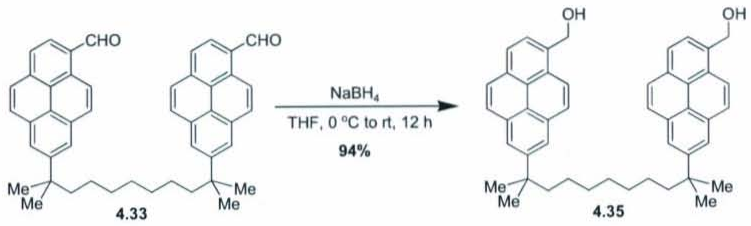


4.33 **4.34**

Titanium(IV) chloride (0.149 g, 0.794 mmol) was added to a stirred 0 °C slurry of zinc dust (0.125 g, 1.92 mmol) and THF (12 mL). After the addition was complete, the reaction was heated at reflux for 1 h, at which point a dark black color persisted. Pyridine (0.15 mL) was added and the mixture was stirred at reflux for a further 10 min. A solution of 2,10-bis(6-formylpyren-2-yl)-2,10-dimethylundecane (**4.33**) (0.062 g, 0.097 mmol) in THF (12 mL) was then added and the mixture was heated at 70 °C for a further 4 h. The reaction mixture was then poured without significant cooling into chloroform (25 mL). The resulting mixture was concentrated under reduced pressure and adsorbed onto silica gel in preparation for column chromatography. Aqueous work-up for this reaction is not recommended as layer separation can be quite problematic and the yields are typically lower. The preadsorbed sample was subjected to column chromatography (20 × 3.5 cm; 15% dichloromethane/hexanes) to yield a mixture of (*E*)- and (*Z*)-1,1,9,9-tetramethyl[9.2](7,1)pyrenophane as a bright yellow solid (0.023 g, 0.038 mmol): R_f = 0.34 (15% dichloromethane/hexanes); LCMS (APCI-positive, *m/z* (rel. int.)) 611 (14), 610 (53), 609 ((M*H*)$^+$, 100). To a stirred 0 °C mixture of (*E*)- and (*Z*)- 1,1,9,9-

tetramethyl[9.2](7,1)pyrenophane (0.023 g, 0.038 mmol) and dichloromethyl methyl ether (7.1 mg, 0.062 mmol) in dichloromethane (4 mL) was added titanium(IV) chloride (1.0 M solution in dichloromethane, 0.07 mL, 0.07 mmol). The cooling bath was removed and the reaction was stirred at room temperature for 2 h. The reaction mixture was poured into ice water (10 mL), the layers were separated and the aqueous layer was extracted with dichloromethane (2 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting solid brown residue was subjected to column chromatography (35 × 2 cm, dichloromethane) to yield (*E*)-14,24-Diformyl-1,1,9,9-tetramethyl[9.2](7,1)pyrenophane (**4.34**) as a bright yellow solid (0.014 g, 23%): R_f = 0.23 (dichloromethane); m.p. 289 °C (dec.) (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.56 (s, 2H), 9.14 (d, *J*=9.2 Hz, 2H), 8.31 (d, *J*=9.1 Hz, 2H), 8.22 (s, 2H), 8.06 (d, *J*=9.3 Hz, 2H), 8.04 (d, *J*=1.6 Hz, 2H), 7.98 (d, *J*=1.6 Hz, 2H), 7.90 (br s, 2H), 7.52 (s, 2H), 7.87 (d, *J*=9.2 Hz, 2H), 1.62–1.58 (m, 4H), 1.48 (s, 12H), 0.86–0.80 (m, 4H), 0.67–0.62 (m, 2H), 0.57–0.52 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 192.99, 147.97, 133.85, 132.92, 132.63, 132.12, 130.87, 130.36, 130.32, 130.07, 126.55, 125.13, 124.84, 122.76, 122.39, 45.39, 38.66, 30.34, 29.90, 29.53, 25.42 (only 21 of 24 signals observed); LCMS (APCI-positive), *m/z* (rel. int.) 667 (13), 666 (53) 665, $(MH)^+$, 100); HRMS (EI) calculated for $C_{49}H_{44}O_2$ $(M)^+$ 664.3341, found 664.3344.

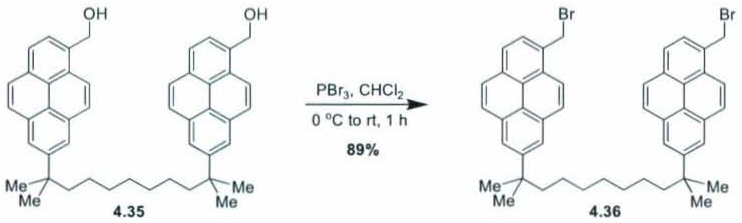
2,10-Bis(6-(hydroxymethyl)pyren-2-yl)-2,10-dimethylundecane (4.35)



Sodium borohydride (0.124 g, 3.28 mmol) was added to a stirred 0 °C solution of 2,10-bis(6-formylpyren-2-yl)-2,10-dimethylundecane (**4.33**) (0.610 g, 0.952 mmol) in THF (30 mL). The resulting slurry was allowed to slowly warm to room temperature over a 12 h period. THF was evaporated under reduced pressure and the solid residue was taken up into dichloromethane (30 mL). This solution was cooled to 0 °C and 1 M HCl was added until the solution was at acidic pH. The layers were separated and the aqueous layer extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (30 mL), washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield 2,10-bis(6-(hydroxymethyl)pyren-2-yl)-2,10-dimethylundecane (**4.35**) as a clear straw-colored oil (0.581 g, 94%). Purification of this compound was not necessary and the crude material was used in subsequent experiments: R_f = 0.13 (1:9 EtOAc/dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J*=9.2 Hz, 2H), 8.21–8.17 (m, 6H), 8.08 (d, *J*=7.8 Hz, 2H), 8.04 (d, *J*=8.9 Hz, 2H) 8.01–7.98 (m, 4H), 5.24 (s, 4H) 1.93 (br s, 2H), 1.79–1.75 (m, 4H), 1.52 (s, 12H), 1.13–1.07 (m, 6H), 1.02–0.97 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 148.06, 133.77, 131.31, 131.22, 130.75, 128.80, 128.34, 127.91, 127.35, 125.87, 125.10, 124.67, 123.39, 123.28, 123.15, 122.98, 64.05, 45.26, 38.61, 30.35,

29.68, 29.42, 25.41; LCMS (APCI-positive, *m/z* (rel. int.)) 629 (12), 628 (51), 627 (100, (M-*OH*)$^+$); HRMS (EI) calculated for $C_{47}H_{48}O_2$ $(M)^+$ 644.3654, found 644.3643.

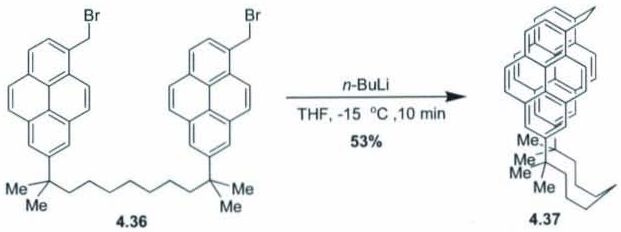
2,10-Bis(6-(bromomethyl)pyren-2-yl)-2,10-dimethylundecane (4.36)



Phosphorus tribromide (0.160 g, 0.591 mmol) was added to a stirred 0 °C solution of 2,10-bis(6-(hydroxymethyl)pyren-2-yl)-2,10-dimethylundecane (**4.35**) (0.510 g, 0.791 mmol) in dichloromethane (20 mL). The reaction was allowed to warm to room temperature and after 1 h, water (20 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with water (50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield 2,10-bis(6-(bromomethyl)pyren-2-yl)-2,10-dimethylundecane (**4.36**) as a light yellow solid (0.542 g, 89%). Purification of **4.36** was not necessary and the crude material was used in subsequent experiments: R_f = 0.22 (15% dichloromethane/hexanes); m.p. 182–183 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J*=9.3 Hz, 2H), 8.22–8.16 (m, 6H), 8.10–8.04 (m, 4H), 8.02–7.98 (m, 4H), 5.31 (s, 4H), 1.77–1.74 (m, 4H), 1.51 (s, 12H), 1.14–1.11 (m, 6H), 1.03–0.99 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 148.37, 132.00, 131.19, 130.75, 130.54, 129.79, 128.67, 128.48, 127.53, 127.30, 125.26, 124.80, 123.70, 123.67, 123.02,

122.84, 45.91, 38.88, 32.45, 30.40, 29.88, 25.01 (only 22 of 23 signals observed); LCMS (APCI-positive, *m/z* (rel. int.)) 693 (12), 692 (44), 691 (100, (^{81}*Br*M–*Br*), 690 (46), 689 (92, (^{79}*Br*M–*Br*)$^+$); HRMS (EI) calculated for $C_{47}H_{46}Br_2$ $(M)^+$ 768.1966, found 768.1961.

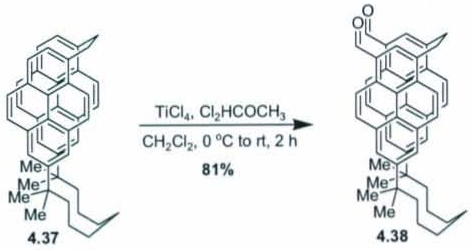
1,1,9,9-Tetramethyl[9.2](7,1)pyrenophane (4.37)



A solution of *n*-butyllithium (0.50 M, 0.61 mL, 0.31 mmol) in hexanes was added to a stirred –15 °C solution of 2,10-bis(6-(bromomethyl)pyren-2-yl)-2,10-dimethylundecane (**4.36**) (0.420 g, 0.548 mmol) in THF (30 mL). After 10 min, water (25 mL) was added to the reaction mixture. THF was evaporated under reduced pressure and the resulting aqueous solution was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were washed with a solution of 1 M HCl (30 mL), washed with a saturated solution of sodium bicarbonate (30 mL), washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was preadsorped onto silica gel and purified by column chromatography (25 × 2.5 cm; 15% dichloromethane/hexanes) to yield 1,1,9,9-tetramethyl[9.2](7,1)pyrenophane (**4.37**) as a clear, colorless oil (0.177 g, 53%): R_f = 0.31 (15% dichloromethane/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J*=9.0 Hz, 2H), 8.08 (d, *J*=9.1 Hz, 2H), 8.00 (d, *J*=9.2 Hz, 2H), 7.97–7.92 (m, 4H), 7.69 (br s, 2H), 7.24 (br d, 2H) 7.12 (d, *J*=9.0 Hz, 2H), 4.02 (s,

4H) 1.71–1.67 (m, 4H), 1.50 (s, 12H), 1.01–0.96 (m, 6H), 0.78–0.73 (m, 4H); LCMS (APCI-positive, *m/z* (rel. int.)) 613 (13), 612 (54), 611 ($(MH)^+$ 100), 598 (11), 597 (22); HRMS (EI) calculated for $(M)^+$ $C_{47}H_{46}$ 610.3600, found 610.3600.

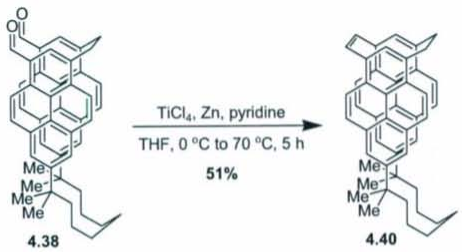
14,24-Diformyl-1,1,9,9-tetramethyl[9.2](7,1)pyrenophane (4.38)



A solution of titanium(IV) chloride (1.0 M, 0.35 mL, 0.35 mmol) in dichloromethane was added to a stirred 0 °C solution of 1,1,9,9-tetramethyl[9.2](1,7)pyrenophane (**4.37**) (0.085 g, 0.14 mmol) and dichloromethyl methyl ether (0.040 g, 0.35 mmol) in dichloromethane (15 mL). The resulting solution was stirred for 2 h while warming to room temperature. The reaction was poured into ice water (50 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 30 mL) and the combined organic extracts were washed with a saturated solution of sodium bicarbonate (30 mL), washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The yellow residue was subjected to column chromatography (25 × 2.5 cm; dichloromethane) to yield 14,24-diformyl-1,1,9,9-tetramethyl[9.2](7,1)pyrenophane (**4.38**) as a bright yellow oil (0.075 g, 81 %): R_f = 0.24 (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.83 (s, 2H), 9.24 (d, *J*=9.2 Hz, 2H), 8.43 (s, 2H), 8.11 (d, *J*=9.2 Hz, 2H), 8.00 (s, 2H) 7.69 (s, 2H), 7.14 (br s, 4H), 3.99 (s, 4H), 1.58–1.55 (m, 4H), 1.40 (s,

12H), 0.87–0.84 (m, 6H), 0.66–0.63 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 193.16, 147.69, 135.33, 134.16, 132.76, 130.42, 130.24, 129.95, 129.79, 129.72, 127.17, 124.84, 124.73, 124.51, 122.61, 122.45, 122.20, 45.43, 38.38, 35.29, 29.91, 29.83, 29.57, 24.90; LCMS (APCI-positive, *m/z* (rel. int.)) 669 (14), 668 (55), 667 ((M*H*)$^+$, 100); HRMS (EI) calculated for $C_{49}H_{46}O_2$ $(M)^+$ 666.3498, found 666.3494.

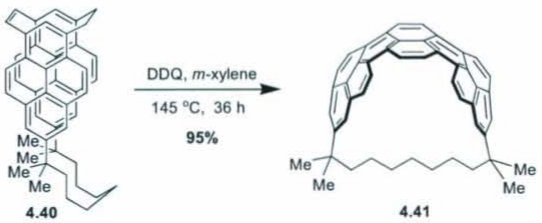
1,1,9,9-Tetramethyl[9.2.2](7,1,3)pyrenophane-20-monoene (4.40)



Titanium(IV) chloride (0.103 g, 0.544 mmol) was added to a 0 °C slurry of zinc dust (0.142 g, 1.09 mmol) in THF (15 mL). After the addition was complete, the reaction was heated to reflux for 1 h, at which point a dark black color persisted, indicative of the low–valent titanium species desired. Pyridine (0.15 mL) was added to the mixture and stirring at reflux was continued for 10 min. A solution of 14,24-diformyl-1,1,9,9-tetramethyl[9.2](7,1)pyrenophane (**4.38**) (0.069 g, 0.10 mmol) in THF (10 mL) was then added. The mixture was heated at 70 °C for 4 h, after which it was poured, without significant cooling, into chloroform (40 mL). The resulting solution was concentrated under reduced pressure and adsorbed onto silica gel in preparation for column chromatography. Aqueous work-up for this reaction is not recommended as layer separation can be quite difficult and the yields are lower. The preadsorbed sample was

subjected to column chromatography (30 × 2 cm; 1:5 dichloromethane/hexanes) to give 1,1,9,9-tetramethyl[9.2.2](7,1,3)pyrenophane-20-monoene (**4.40**) as a light green oil (0.033 g, 51%): R_f = 0.45 (1:4 dichloromethane/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 2H), 7.84 (d, *J*=9.2 Hz, 2H), 7.81 (s, 2H), 7.68 (d, *J*=9.0 Hz, 2H), 7.62 (br s, 2H), 7.61 (br s, 2H), 7.55 (d, *J*=9.2 Hz, 2H), 7.50 (d, *J*=9.0 Hz, 2H), 4.31–4.24 (m, 2H), 3.80–3.73 (m, 2H), 1.53–1.50 (m, 4H) 1.32 (s, 6H), 1.31 (s, 6H), 0.88–0.83 (m, 6H), 0.63–0.58 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 146.05, 137.38, 135.73, 130.18, 130.16, 129.38, 129.32, 128.24, 127.81, 126.47, 126.00, 123.74, 123.59, 122.65, 122.30, 122.16, 122.13, 45.92, 38.14, 30.64, 30.15, 29.36, 29.25, 28.67, 24.95; LCMS (APCI-positive, *m/z* (rel. int.)) 637 (15), 636 (54), 635 ((M*H*)$^+$, 100); HRMS (EI) calculated for $C_{49}H_{46}$ $(M)^+$ 634.3600, found 634.3602.

1,1,9,9-Tetramethyl[9](2,11)teropyrenophane (4.41)

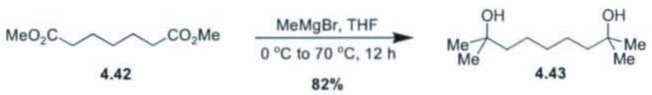


4.40 **4.41**

A solution of 1,1,9,9-tetramethyl[9.2.2](7,1,3)pyrenophane-20-monoene (**4.40**) (0.025 g, 0.039 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.039 g, 0.17 mmol) in *m*-xylene (6 mL) was heated at 145 °C for 36 h. The hot solvent was evaporated under a stream of nitrogen gas. The residue was taken up into dichloromethane and preadsorbed onto silica gel in preparation for column chromatography. The preadsorped sample was

subjected to column chromatography (30 × 2.0 cm; 1:4 dichloromethane/hexanes) to yield 1,1,9,9-tetramethyl[9](2,11)teropyrenophane (**4.41**) as an orange solid (0.023 g, 95 %), which exhibits yellow fluorescence at 365 nm. R_f = 0.43 (1:4 dichloromethane/hexanes); m.p. >300 °C (dec.) ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 4H), 8.52 (d, *J*=9.5 Hz, 4H), 7.80 (d, *J*=9.5 Hz, 4H) 7.50 (s, 4H), 1.37 (s, 12H), 0.81–0.78 (m, 4H), -0.51 to -0.55 (m, 4H), -0.99 to -1.03 (m, 6H); (APCI-positive, *m/z* (rel. int.)) 633 (16), 632 (54) 631 ((M*H*)$^+$, 100); HRMS (EI) calculated for $C_{49}H_{42}$ $(M)^+$ 630.3287, found 630.3282.

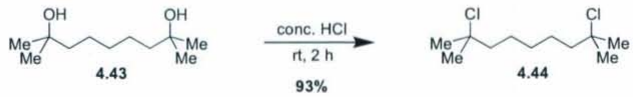
2,8-Dimethyl-2,8-nonanediol (4.43)



A solution of dimethyl pimelate (**4.42**) (10.7 g, 56.7 mmol) in anhydrous THF (100 mL) was added dropwise over a period of 30 min to a stirred 0 °C solution of methylmagnesium bromide (3.0 M, 85 mL, 0.26 mol). After the addition was complete, the reaction mixture was heated at reflux for 12 h. The reaction mixture was cooled to room temperature and quenched by the addition of a saturated solution of ammonium chloride (100 mL). The layers were separated and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to yield a white solid, which was recrystallized from heptane to give 2,8-dimethyl-2,8-nonanediol (**4.43**) (8.76 g, 82%) as a white powder: m.p. 71–72 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.72 (br s, 2H), 1.48–1.45 (m, 4H), 1.39–1.31 (m, 6H), 1.21 (s, 12H); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 71.12, 44.01, 30.79,

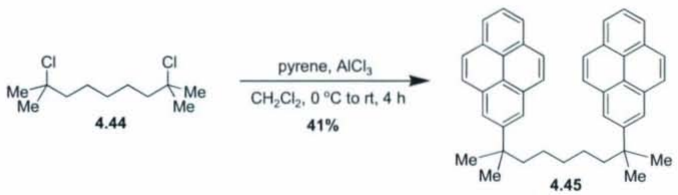
29.30, 24.41; LCMS (APCI negative) *m/z* 187 $(M\text{-}H)^+$; HRMS (CI) calculated for $(MH)^+$ $C_{11}H_{25}O_2$ 189.1855, found 189.1849.

2,8-Dichloro-2,8-dimethylnonane (4.44)



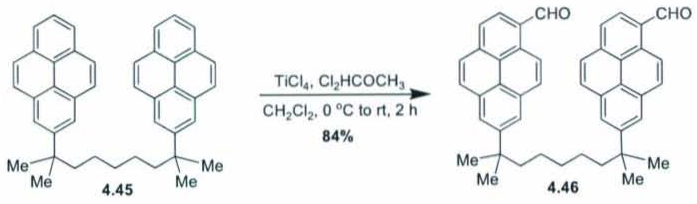
A mixture of 2,8-dimethyl-2,8-nonanediol (**4.43**) (3.42 g, 18.2 mmol) and concentrated aqueous HCl solution (50 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into a large excess of ice water (200 mL) and extracted with dichloromethane (3 × 40 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (2 × 50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 2,8-dichloro-2,8-dimethylnonane (**4.44**) (3.80 g, 93%) as a light yellow oil, which was used subsequently without purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.78–1.75 (m, 4H), 1.59 (s, 12H), 1.53–1.49 (m, 4H), 1.36–1.33 (m, 2H); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 71.30, 46.20, 32.61, 29.96, 25.21; LCMS (APCI-positive, *m/z* (rel. int.)) 225 $(MH)^+$; no HRMS data could be obtained for this compound.

2,8-Bis(2-pyrenyl)-2,8-dimethylnonane (4.45)



Aluminum chloride (1.64 g, 12.3 mmol) was added to a stirred 0 °C solution of pyrene (**2.8**) (6.21 g, 30.7 mmol) and 2,8-dichloro-2,8-dimethylnonane (**4.44**) (1.38 g, 6.14 mmol) in dichloromethane (100 mL). The resulting slurry was allowed to warm to room temperature and stirred for 4 h. The reaction was poured into ice water (200 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 100 mL) and the combined organic extracts were washed with a saturated solution of sodium bicarbonate (50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The yellow residue was subjected to column chromatography (25 × 6.5 cm; 1:9 dichloromethane/hexanes) to yield 2,8-bis(2-pyrenyl)-2,8-dimethylnonane (**4.45**) as a white solid (1.40 g, 41%): R_f = 0.26 (1:9 dichloromethane/hexanes); m.p. 207–209 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J*=7.5 Hz, 4H), 8.16 (s, 4H), 8.08–8.00 (m, 10H), 1.79–1.76 (m, 4H), 1.51 (s, 12H), 1.19–1.15 (m, 2H) 1.07–1.02 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 148.09, 131.41, 131.32, 128.04, 127.56, 125.82, 125.08, 124.99, 123.25, 123.18, 45.54, 38.54, 31.35, 29.89, 25.21; LCMS (APCI-positive, *m/z* (rel. int.)) 559 (12), 558 (47), 557 ($(MH)^+$, 100); HRMS (EI) calculated for $(M)^+$ $C_{43}H_{40}$ 556.3130, found 556.3128.

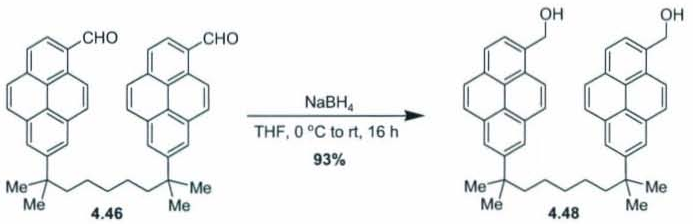
2,8-Bis(6-formylpyren-2-yl)-2,8-dimethylnonane (4.46)



Titanium(IV) chloride (0.453 g, 2.39 mmol) was added to a stirred 0 °C solution of 2,8-bis(2-pyrenyl)-2,8-dimethylnonane (**4.45**) (0.531 g, 0.953 mmol) and dichloromethyl methyl ether (0.274 g, 2.39 mmol) in dichloromethane (25 mL). The cooling bath was removed and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was poured into ice water (100 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 30 mL) and the combined organic extracts were washed with a saturated solution of sodium bicarbonate (40 mL), washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The solid brown residue was subjected to column chromatography (30 × 3 cm; dichloromethane) to yield 2,8-bis(6-formylpyren-2-yl)-2,8-dimethylnonane (**4.46**) as a bright yellow solid (0.488 g, 84%): R_f = 0.26 (dichloromethane); m.p. 165–168 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.62 (s, 2H), 9.27 (d, *J*=9.2 Hz, 2H), 8.16 (d, *J*=7.9 Hz, 2H), 8.13–8.10 (m, 4H), 8.08 (d, *J*=9.2 Hz, 2H), 8.01 (d, *J*=8.9 Hz, 2H), 7.97 (d, *J*=8.9 Hz, 2H), 7.85 (d, *J*=7.8 Hz, 2H) 1.77–1.74 (m, 4H), 1.49 (s, 12H), 1.14–1.11 (m, 2H) 0.99–0.97 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 193.34, 148.82, 135.77, 132.28, 131.49, 131.45, 131.30, 131.19, 131.11, 130.66, 127.60, 127.32, 125.29, 124.85, 124.62, 123.14, 122.62, 45.41, 38.72, 30.37, 29.80, 25.10; LCMS (APCI-positive) *m/z* (rel. int.) 615 (11),

614 (49), 613((M*H*)$^+$, 100); HRMS (EI) calculated for $C_{45}H_{40}O_2$ (M)$^+$ 612.3028, found 612.3020.

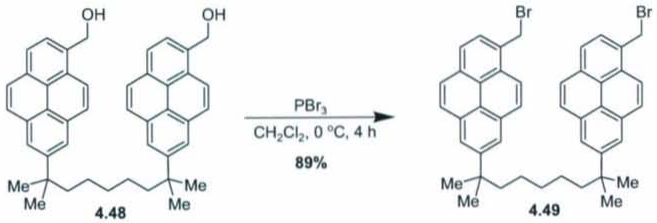
2,8-Bis(6-(hydroxymethyl)pyren-2-yl)-2,8-dimethylnonane (4.48)



Sodium borohydride (0.082 g, 2.20 mmol) was added to a stirred 0 °C solution of 2,8-bis(6-formylpyren-2-yl)-2,8-dimethylnonane (**4.46**) (0.385 g, 0.627 mmol) in THF (20 mL). The resulting slurry was allowed to slowly warm to room temperature over a 16 h period. THF was evaporated under reduced pressure and the solid residue was taken up into dichloromethane (30 mL). This solution was cooled to 0 °C and 1 M HCl was added until the solution was at acidic pH. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (30 mL), washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield 2,8-bis(6-(hydroxymethyl)pyren-2-yl)-2,8-dimethylnonane (**4.48**) as a light yellow oil (0.359 g, 93%). Purification of this compound was not necessary and the crude material was used in subsequent experiments: R_f = 0.18 (1:9 EtOAc/dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J*=9.2 Hz, 2H), 8.07 (s, 4H), 8.04 (d, *J*=7.7 Hz, 2H), 8.00 (d, *J*=9.2 Hz, 2H) 7.97–7.95 (m, 4H), 7.93 (d, *J*=7.7 Hz, 2H) 5.27 (s, 4H) 1.99 (br s, 2H), 1.76–1.73 (m,

4H), 1.46 (s, 12H), 1.00–0.97 (m, 2H), 0.91–0.87 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 148.22, 133.98, 131.50, 131.42, 130.96, 128.99, 128.53, 128.10, 127.56, 126.07, 125.30, 124.87, 123.57, 123.48, 123.35, 123.18, 64.25, 45.44, 38.61, 30.47, 29.51, 25.31; LCMS (APCI-positive, *m/z* (rel. int.)) 597 (12), 596 (51), 595 (100, (M-*OH*)$^+$); HRMS (EI) calculated for $C_{45}H_{44}O_2$ $(M)^+$ 616.3341, found 616.3334.

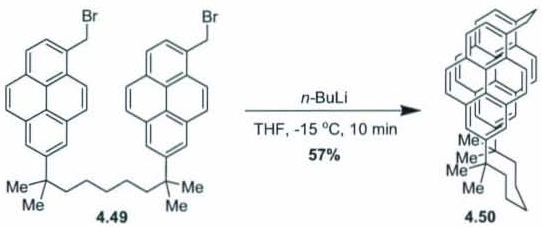
2,8-Bis(6-(bromomethyl)pyren-2-yl)-2,8-dimethylnonane (4.49)



Phosphorus tribromide (0.090 g, 0.332 mmol) was added to a stirred 0 °C solution of 2,8-bis(6-(hydroxymethyl)pyren-2-yl)-2,8-dimethylnonane (**4.48**) (0.273 g, 0.443 mmol) in dichloromethane (15 mL). After 4 h, water (15 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield 2,8-bis(6-(bromomethyl)pyren-2-yl)-2,8-dimethylnonane (**4.49**) as a light yellow solid (0.292 g, 89%). Purification of **4.49** was not necessary and the crude material was used in subsequent experiments: R_f = 0.24 (15% dichloromethane/hexanes); m.p. 103–106 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J*=9.9 Hz, 2H), 8.16–8.11 (m, 6H), 8.03 (d, *J*=7.8 Hz, 2H), 8.00–7.94 (m, 6H), 5.26 (s, 4H), 1.78–1.74 (m, 4H), 1.49 (s, 12H), 1.12–1.08 (m, 2H), 1.00–

0.96 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 148.55, 133.22, 131.40, 130.96, 130.77, 129.32, 128.88, 128.69, 127.76, 127.52, 125.49, 125.03, 123.91, 123.88, 123.24, 123.07, 45.45, 38.63, 32.73, 30.46, 29.87, 25.15; LCMS (APCI-positive, *m/z* (rel. int.)) 667(12), 666 (53), 665 (98, (M-^{79}Br)$^+$), 664 (52) 663 (100, (M-^{81}Br)$^+$); No HRMS data could be obtained for this compound.

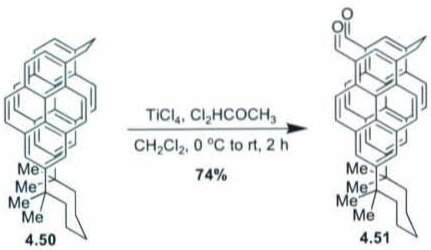
1,1,7,7-Tetramethyl[7.2](7,1)pyrenophane (4.50)



A solution of *n*-butyllithium (0.50 M, 0.31 mL, 0.16 mmol) in hexanes was added to a stirred –15 °C solution of 2,8-bis(6-(bromomethyl)pyren-2-yl)-2,8-dimethylnonane (**4.49**) (0.179 g, 0.241 mmol) in THF (20 mL). After 10 min, water (20 mL) was added to the reaction mixture. THF was evaporated under reduced pressure and the resulting aqueous solution was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (30 mL), washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was preadsorped onto silica gel and purified by column chromatography (30 × 2 cm; 15% dichloromethane/hexanes) to yield 1,1,7,7-tetramethyl[7.2](7,1)pyrenophane (**4.50**) as a clear, colorless oil (0.080 g, 57%): R_f = 0.38 (15% dichloromethane/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31–8.26 (m, 2H), 8.16–8.03 (m, 6H), 8.00–7.95 (m, 2H),

7.90–7.88 (m, 2H), 7.34 (s, 2H) 6.59–6.48 (m, 2H), 3.88 (s, 4H) 1.60–1.28 (m, 16H), 1.05–1.00 (m, 2H), 0.65–0.55 (m, 2H), 0.39–0.28 (m, 2H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 146.13, 130.93, 130.06, 130.00, 129.83, 127.67, 127.13, 127.09, 125.27, 125.10, 124.70, 123.02, 122.52, 122.28, 122.21, 46.01, 38.38, 36.82, 30.39, 29.51 25.71 (only 21 of 23 signals observed); LCMS (APCI-positive, *m/z* (rel. int.)) 585 (14), 584 (51), 583 (100, $(MH)^+$); HRMS (EI) calculated for $C_{45}H_{42}$ $(M)^+$ 582.3287, found 582.3280.

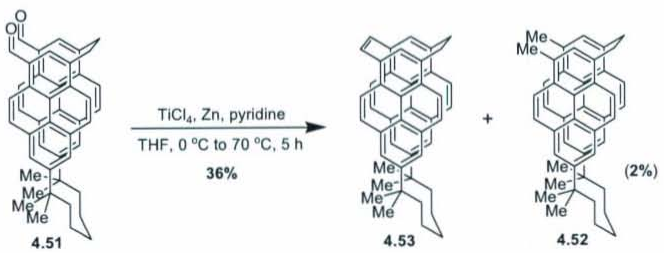
12,22-Diformyl-1,1,7,7-tetramethyl[7.2](7,1)pyrenophane (4.51)



A solution of titanium(IV) chloride (1.0 M, 0.28 mL, 0.28 mmol) in dichloromethane was added to a stirred 0 °C solution of 1,1,7,7-tetramethyl[7.2](7,1)pyrenophane (**4.50**) (0.064 g, 0.11 mmol) and dichloromethyl methyl ether (0.032 g, 0.28 mmol) in dichloromethane (12 mL). The reaction was stirred for 2 h while warming to room temperature. The reaction was poured into ice water (30 mL), the layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The solid brown residue was subjected to column chromatography (25 × 2 cm; dichloromethane) to yield 12,22-diformyl-1,1,7,7-

tetramethyl[7.2](7,1)pyrenophane (**4.51**) as a bright yellow solid (0.052 g, 74 %): R_f = 0.42 (dichloromethane); m.p. 292 °C (dec) (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$, δ 10.93 (s, 2H), 9.35 (d, *J*=9.2 Hz, 2H), 8.53 (s, 2H), 8.15 (d, *J*=9.2 Hz, 2H), 7.96 (s, 2H) 7.37 (s, 2H), 6.60 (br s, 2H), 6.47 (br s, 2H), 3.92 (br s, 4H), 1.42–1.40 (m, 12H), 1.29–1.21 (m, 4H), 0.82–0.77 (m, 2H), 0.55–0.48 (m, 2H), 0.28–0.19 (m, 2H); ^{13}C NMR (125.77 MHz, $CDCl_3$ δ 193.27, 147.20, 135.99, 134.82, 134.43, 132.74, 130.59, 130.08, 129.85, 129.64, 128.75, 127.44, 124.72, 124.42, 124.37, 122.46, 122.33, 121.80, 45.57, 38.46, 38.30, 30.18, 25.59; LCMS (APCI-positive, *m/z* (rel. int.)) 641 (10), 640 (49), 639 (100, $(MH)^+$); HRMS (EI) calculated for $C_{47}H_{42}O_2$ $(M)^+$ 638.3185, found 638.3181.

1,1,7,7-Tetramethyl[7.2.2](7,1,3)pyrenophane-18-monoene (4.53) and 1,1,7,7,12,22-hexamethyl[7.2](7,1)pyrenophane (4.52)

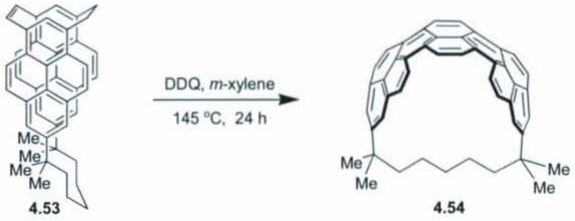


Titanium(IV) chloride (0.174 g, 0.917 mmol) was added to a 0 °C slurry of zinc dust (0.060 g, 0.92 mmol) and THF (10 mL). After the addition was complete, the reaction was heated to reflux for 1 h, at which point a dark black color persisted, indicative of the low–valent titanium species desired. Pyridine (0.1 mL) was added to the mixture and stirring at reflux was continued for 10 min. A solution of aldehyde **4.51** (0.076 g, 0.12 mmol) in THF (10 mL) was then added. The resulting mixture was heated at 70 °C for 4

h, after which it was poured, without significant cooling, into chloroform (20 mL). The resulting solution was concentrated under reduced pressure and adsorbed onto silica gel in preparation for column chromatography. Aqueous work-up for this reaction is not recommended as layer separation can be quite difficult and the yields are lower. The preadsorbed sample was subjected to column chromatography (25 × 2.5 cm; 15% dichloromethane/hexanes) to yield 1,1,7,7-tetramethyl[7.2.2](7,1,3)pyrenophane-18-monoene (**4.53**) (0.026 g, 36%): R_f = 0.46 (1:4 dichloromethane/hexanes); mp >300 °C (dec.) ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 2H), 7.80 (d, *J*=9.2 Hz, 2H), 7.63 (d, *J*=9.0 Hz, 2H), 7.62 (s, 2H), 7.53 (br s, 2H), 7.52 (br s, 2H), 7.48 (d, *J*=9.2 Hz, 2H), 7.42 (d, *J*=9.0 Hz, 2H) 4.29–4.25 (m, 2H), 3.74–3.70 (m, 2H) 1.42–1.37 (m, 4H) 1.34 (s, 6H), 1.33 (s, 6H) 0.76–0.70 (m, 2H), 0.28–0.24 (m, 4H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 145.64, 137.69, 136.14, 130.14, 130.04, 130.01, 128.28, 128.04, 126.29, 125.76, 123.99, 123.64, 122.42, 122.27, 122.21, 122.02, 46.13, 38.45, 31.02, 30.47, 28.77, 28.69, 26.54 (only 23 of 24 signals observed); LCMS (APCI-positive, *m/z* (rel. int.)) 609 (16), 608 (56), 607 ($(MH)^+$, 100); HRMS (EI) calculated for $C_{47}H_{42}$ $(M)^+$ 606.3287, found 606.3277.

1,1,7,7,12,22-Hexamethyl[7.2](7,1)pyrenophane (**4.52**) was obtained as a colorless oil (2 mg, 2%) R_f = 0.49 (1:4 dichloromethane/hexanes); LCMS (APCI-positive, *m/z* (rel. int.)) 613 (12), 612 (53), 611 (MH^+, 100), HRMS (EI) calculated for $C_{47}H_{46}$ $(M)^+$ 610.3600, found 610.3589.

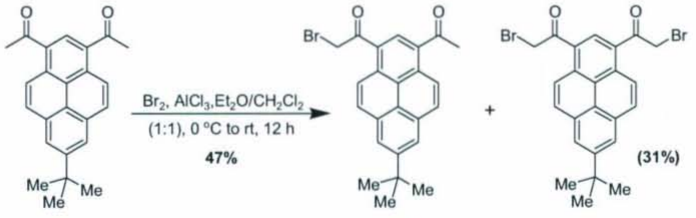
1,1,7,7-Tetramethyl[7](2,11)teropyrenophane (4.54)



4.53 **4.54**

A solution of 1,1,7,7-tetramethyl[7.2.2](7,1,3)pyrenophane-18-monoene (**4.53**) (6.0 mg, 0.010 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (9.1 mg, 0.040 mmol) in *m*-xylene (3 mL) was heated at 145 °C for 24 h. The hot solvent was evaporated under a stream of nitrogen gas. The residue was taken up into dichloromethane and preadsorbed onto silica gel in preparation for column chromatography. The preadsorped sample was subjected to column chromatography (15 × 2.0 cm; 1:4 dichloromethane/hexanes) to yield 1,1,7,7-tetramethyl[7](2,11)teropyrenophane (**4.54**) as a 1:1 mixture with **4.53** (3.0 mg, 50% recovery). An elution flow rate of greater than 4 in/min was used during chromatography. This compound was prone to decomposition and had to be chromatographed very quickly in order to be isolated. R_f = 0.47 (1:4 dichloromethane/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (s, 4H), 8.26 (d, *J*=9.6 Hz, 4H), 7.62 (d, *J*=9.6 Hz, 4H) 7.29 (s, 4H), 1.35 (s, 12H), 0.71–0.68 (m, 4H), -1.12 to -1.15 (m, 4H) (2H cannot be clearly indicated due to overlap with the starting material); LCMS (APCI-positive, *m/z* (rel. int.)) 609 (16), 608 (51), 607 ($(MH)^+$ for **4.53**, 100), 605 (14), 604 (43), 603 (82, $(MH)^+$, for **4.54**); HRMS (EI) calculated for $C_{47}H_{38}$ $(M)^+$ 602.2974, found 602.2974.

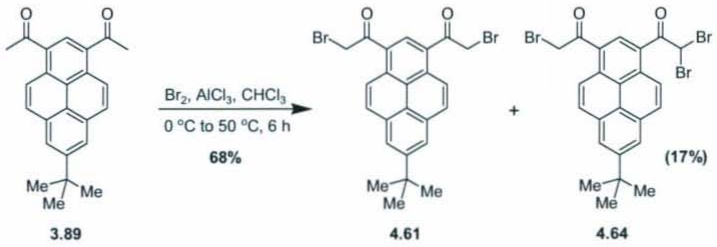
1-(3-Acetyl-7-*tert*-butylpyren-1-yl)-2-bromoethanone (4.60)



Aluminium chloride (0.033 g, 0.25 mmol) was added to a stirred 0 °C solution of 1-(3-acetyl-7-*tert*-butylpyren-1-yl)ethanone (**3.89**) (0.427 g, 1.24 mmol) and bromine (0.368 g, 2.30 mmol) in 1:1 dichloromethane/diethyl ether (30 mL). The cooling bath was removed and the reaction was stirred at room temperature for 12 h. The reaction was poured into water (100 mL), the layers were separated and the aqueous layer was extracted with dichloromethane (2 × 25 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The light brown residue was subjected to column chromatography (35 × 3.5 cm; dichloromethane) to yield 1-(3-acetyl-7-*tert*-butylpyren-1-yl)-2-bromoethanone (**4.60**) as a bright yellow solid (0.258 g, 47%): R_f = 0.39 (dichloromethane); m.p. 108 °C (dec.) (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.96 (d, *J*=9.3 Hz, 1H), 8.87 (d, *J*=9.3 Hz, 1H), 8.68 (s, 1H), 8.36 (s, 2H), 8.28–8.25 (m, 2H), 4.73 (s, 2H), 2.93 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 201.34, 194.42, 150.65, 132.86, 132.70, 132.50, 132.47, 130.81, 130.45, 130.42, 127.95, 127.32, 125.55, 125.42, 125.40, 124.55, 124.21, 122.14, 35.51, 33.99, 32.01, 30.63; LCMS (APCI-positive, *m/z* (rel. int.)) 424 (25), 423 ($(^{81}BrMH)^+$

100), 422 (27), 421 (($^{79}BrMH)^+$, 98); HRMS (EI) calculated for $C_{24}H_{21}{}^{79}BrO_2$ $(M)^+$ 420.0725, found 420.0721.

2-Bromo-1-[3-(2-bromoacetyl)-7-*tert*-butylpyren-1-yl]ethanone (4.61) and 2,2-Dibromo-1-[3-(2-bromoacetyl)-7-*tert*-butylpyren-1-yl]ethanone (4.64)



Aluminium chloride (0.045 g, 0.34 mmol) was added to a stirred 0 °C solution of 1-(3-acetyl-7-*tert*-butylpyren-1-yl)ethanone (**3.89**) (0.580 g, 1.69 mmol) and bromine (0.596 g, 3.73 mmol) in chloroform (25 mL). The cooling bath was removed and the reaction was heated to 50 °C for 6 h. The reaction was poured into water (100 mL), the layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The light brown residue was subjected to column chromatography (45 × 3.5 cm; dichloromethane) to yield 2-bromo-1-[3-(2-bromoacetyl)-7-*tert*-butylpyren-1-yl]ethanone (**4.61**) as a bright yellow solid (0.574 g, 68%): R_f = 0.56 (dichloromethane); m.p. 182–183 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (d, J=9.3 Hz, 2H), 8.68 (s, 1H), 8.33 (s, 2H), 8.20 (d, J=9.3 Hz, 2H), 4.73 (s, 4H), 1.59 (s, 9H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 194.10, 150.83, 133.39, 133.19, 130.28, 128.12, 126.93,

125.81, 125.42, 124.11, 121.80, 35.34, 33.88, 32.02; LCMS (APCI-positive, *m/z* (rel. int.)) 503 (12), 502 (51), 501 (21), 500 (100), 499 (15), 498 (($^{79}Br_2MH)^+$, 51); HRMS (EI) calculated for $C_{24}H_{20}{}^{79}Br_2O_2$ $(M)^+$ 497.9830, found 497.9823.

2,2-Dibromo-1-[3-(2-bromoacetyl)-7-*tert*-butylpyren-1-yl]-ethanone (**4.64**) was isolated as a bright yellow solid (0.166 g, 17%); R_f = 0.79 (dichloromethane); m.p. 144–146 °C (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (d, *J*=9.3 Hz, 1H), 8.82 (s, 1H), 8.60 (d, *J*=9.3 Hz, 1H), 8.36 (s, 2H), 8.26–8.24 (m, 2H), 6.93 (s, 1H), 4.74 (s, 2H), 1.59 (s, 9H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 193.96, 188.59, 151.00, 133.82, 133.61, 133.42, 133.37, 130.28, 127.40, 126.72, 126.03, 125.98, 125.40, 124.61, 124.20, 123.83, 121.71, 42.39, 35.57, 33.88, 32.02 (only 21 of 22 signals observed); LCMS (APCI-positive, *m/z* (rel. int.)) 582 (36), 580 (100), 578 (98), 576 (($^{79}Br_3MH)^+$, 34); HRMS (EI) calculated for $C_{24}H_{19}{}^{79}Br_3O_2$ $(M)^+$ 575.8935, found 575.8932.

1-(3-Acetyl-7-*tert*-butylpyren-1-yl)-2-[2-(3-acetyl-7-*tert*-butylpyren-1-yl)-2-oxoethyl-sulfanyl]ethanone (4.62)

A solution of sodium sulfide nonahydrate (0.068 g, 0.27 mmol) in distilled water (2 mL) was added to a stirred room temperature solution of 1-(3-acetyl-7-*tert*-butylpyren-1-yl)-2-bromoethanone (**4.60**) (0.191 g, 0.454 mmol) in acetone (15 mL). After 1 h, the reaction

mixture was poured into water (30 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 1-(3-acetyl-7-*tert*-butylpyren-1-yl)-2-[2-(3-acetyl-7-*tert*-butylpyren-1-yl)-2-oxoethylsulfanyl]ethanone (**4.62**) as a bright orange oil (0.126 g, 77%): R_f= 0.17 (1:19 EtOAc/dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79–8.75 (m, 4H), 8.71 (s, 2H), 8.26 (s, 2H), 8.24 (s, 2H), 8.12 (d, *J*=9.3 Hz, 2H), 8.04 (d, *J*=9.3 Hz, 2H), 4.28 (s, 4H), 2.88 (s, 6H), 1.61 (s, 18H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 201.29, 197.76, 150.36, 132.42, 132.34, 132.15, 132.07, 130.36, 130.24, 128.90, 128.08, 125.19, 125.14, 125.13, 124.40, 124.10, 121.99, 40.78, 35.47, 32.04, 30.53 (only 21 of 22 signals observed); LCMS (APCI-positive, *m/z* (rel. int.)) 717 (19), 716 (55), 715 ($(MH)^+$, 100), 674(8), 673 (18); HRMS (CI) calculated for $C_{48}H_{43}O_4S$ $(MH)^+$ 715.2882, found 715.2879.

References and Notes

[1] The formation of the *anti*-[2.2]metacyclophane is favoured in the absence of a third bridge: recall the synthesis of [*n*](2,7)pyrenophanes discussed in Chapter 1.

[2] This method was not feasible for the desired targets: recall Chapter 2.

[3] McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513-1524.

[4] Sahade, D. A.; Tsukamoto, K-i.; Thiemann, T.; Sawada, T.; Makata, S. *Tetrahedron* **1999**, *55*, 2573-2580.

[5] Recall the discussion of the McMurry reaction and its ability to generate some of the most strained ethylene systems known in Chapter 3.

[6] Mitchell, R. H.; Weerawarna, S. A. *Tetrahedron Lett.* **1986**, *27*, 453-456.

[7] Yamato, T.; Fujita, K.; Tsuzuki, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2089-2097.

[8] Hopf, H.; Mlynek, C. *J. Org. Chem.* **1990**, *55*, 1361-1363.

[9] Tashiro, M.; Yamato, T.; Fukata, G. *J. Org. Chem.* **1978**, *43*, 1413-1420.

[10] The corresponding products are just too strained to be formed under these conditions.

[11] Hopf, H.; Kleinschroth, J.; Bohm, I. *Org. Syn.* **1981**, *60*, 41.

[12] Lenoir, D. *Synthesis* **1977**, 553-554.

[13] The calculated bend angle for the central pyrene substructure of the teropyrene nucleus of **2.84** was estimated to be 92.6 °. This value is well within the limits of VID reaction. A viable target usually has a bend angle of less than 113 ° (calculated at the AM1 level of theory).

[14] Bodwell, G. J.; Fleming, J. J.; Miller, D. O. *Tetrahedron* **2001**, *57*, 3577-3585.

[15] The β angles used in this analysis of the teropyrenophane structure are directly analogous to those used for [*n*]paracyclophanes. See: Keehn, P. M.; Rosenfeld, S. M. Eds., *Cyclophanes* **1983**, pp. 69-238, Academic Press, New York.

[16] On a 10–500 mg scale, the chemical yield of this reaction was between 50–60%. See Section 4.8 for details.

[17] Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041-1044.

[18] The addition of $TiCl_4$ to zinc dust in THF is quite exothermic even at 0 °C. The reagent has to be added drop-wise over a short period.

[19] In all instances when this reaction was carried out over-reduced [*n*.2](7,1)-3,3′-dimethylpyrenophanes were obtained as a minor byproduct. The identity of these compounds was confirmed by LCMS and ^{1}H NMR.

[20] Standard VID conditions in the Bodwell laboratory are: 1 to 5 molar equivalents of DDQ, at reflux in benzene.

[21] The ^{1}H NMR spectrum of this mixture of olefins was very complicated and due to many overlapping signals, it was impossible to determine, with any certainty, the *E*:*Z* ratio.

[22] 7-steps to **2.84** via Route B if **2.65** is used in the Friedel-Crafts alkylation reaction and 8-steps if **2.66** is used. The same holds true for Route A – 9 and 10-steps respectively.

[23] The parent teropyrene is the only other teropyrene system to have been reported. See: Umemoto, T.; Kawashima, T.; Sakata, Y.; Misumi, S. *Tetrahedron Lett.* **1975**, *16*, 1005-1006. Due to its low solubility it was characterized only by its absorption spectrum.

[24] Previously the largest aromatic system to have been incorporated into an [*n*]cyclophane was corannulene (20 carbons). See: Seiders, T. J.; Baldridge, K. K.; Siegel, J. S. *Tetrahedron* **2001**, *57*, 3737-3742.

[25] Two other parameters have been used to quantify deviations form planarity in nonplanar pyrene systems: an angle α, see: Dobrowolski, M. A.; Cyrański, M. K.; Merner, B. L.; Bodwell, G. J.; Wu, J. I.; Schleyer, P. vR. *J. Org. Chem.* **2008**, *73*, 8001-8009 and a distance *h*, see: Bodwell, G. J.; Bridson, J. N.; Cyrański, M.; Kennedy, J. W. J.; Krygowski, T. M.; Mannion, M. R.; Miller, D. O. *J. Org. Chem.* **2003**, *68*, 2089-2098.

[26] The diameter of an (8,8) SWCNT was calculated (using a bond length of 1.4210 Å) according to the equation given in: Strano, M. S.; Zheng, M.; Jagota, A.; Onoa, G. B.; Heller, D. A.; Barone, P. W.; Ursey, M. L. *Nano. Lett.* **2004**, *4*, 543-550.

[27] See: Rosenfeld, S. M.; Choe, K. A. in *Cyclophanes*, *Vol. 1* (Eds: Keehn, P. M.; Rosenfeld, S. M.) Academic Press, New York, **1983**, 311-357.

[28] Bodwell, G. J.; Bridson, J. N.; Houghton, T. J.; Kennedy, J. W. J.; Mannion, M. R. *Chem. Eur. J.* **1999**, *5*, 1823-1825.

[29] ϕ_{em} was measured by Brent Myron, a member of the photophysics group at Memorial University.

[30] Hydrogenation of the olefin(s) would give the same intermediate as Route A, however, this strategy is not desirable in terms of using a McMurry coupling reaction to form one of the eventually bridges.

[31] This yield was uncharacteristically low for this type of Friedel-Crafts alkylation and all attempts to increase the chemical yield via modification of concentration and temperature proved to be fruitless.

[32] Presumably the *E*-isomer is also formed during the reaction, however, none of this compound was isolated.

[33] In all cases none of the desired McMurry product was obtained. Moreover, a complex mixture was afforded and in some instances, trace amounts of starting material could be recovered.

[34] For VTNMR studies of conformationally dynamic cyclophanes see: (a) Haley, J. F. Jr.; Rosenfeld, S. M.; Keehn, P. M. *J. Org. Chem.* **1977**, *42*, 1379-1386; (b) Tobe, Y. *Top.*

Curr. Chem. **1994**, *172*, 1-40. (c) Ernst, L. *Annu. Rep. NMR Spectroscopy* **2006**, *60*, 77-143.

[35] Reference for 2,7-di-*tert*-butyl-4-formylpyrene: (a) Miyazawa, A.; Yamato, T.; Tashiro, M. *Chem. Express* **1990**, *5*, 381-384; (b) Paudel, A.; Hu, J. Y; Yamato, T. *J. Chem. Res.* **2008**, 457-460.

[36] "normal" in the sense that compared to other analogous reactions that had been carried out on this or related systems, the intensity in color of the newly formed product by TLC is unmistakable.

[37] The ^{1}H NMR spectrum of the aromatic region of teropyrenophanes **2.84**, **4.41** and **4.54** is quite simple – 2 singlets and a pair of doublets. The two lower field aromatic signals are indicative of bay region protons (*i.e.* H(a) and H(b)). Due to the multiplicities of these signals, H(a), a singlet and H(b), a doublet, the assignment of these and the remaining two protons (H(c) and H(d)) was trivial. 2D NMR experiments (HMBC and HMQC) of **2.84** support this assignment.

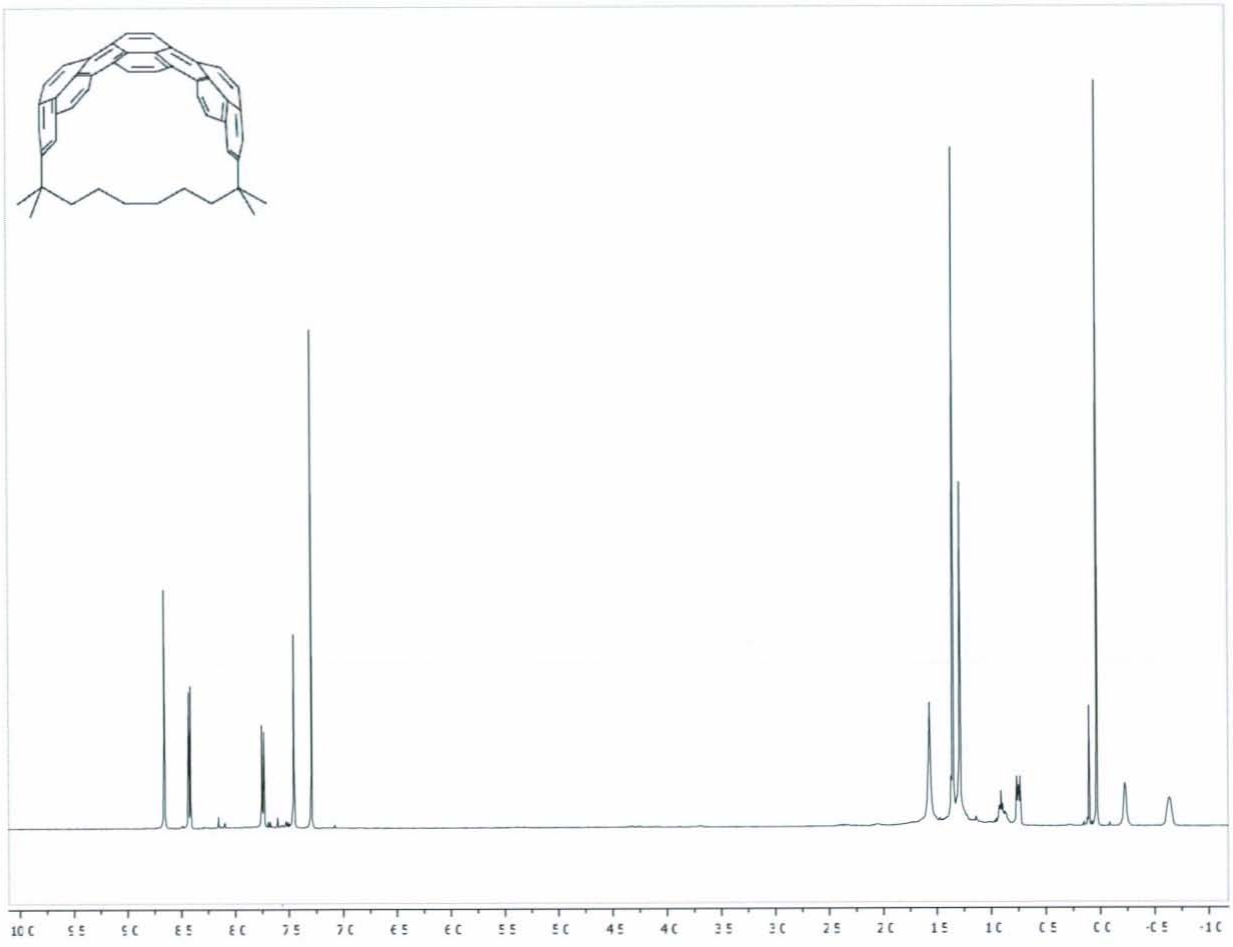
[38] Cowper, R. M.; Davidson, L. H. *Org. Syn.* **1949**, *Coll. Vol. 2*, 480-482.

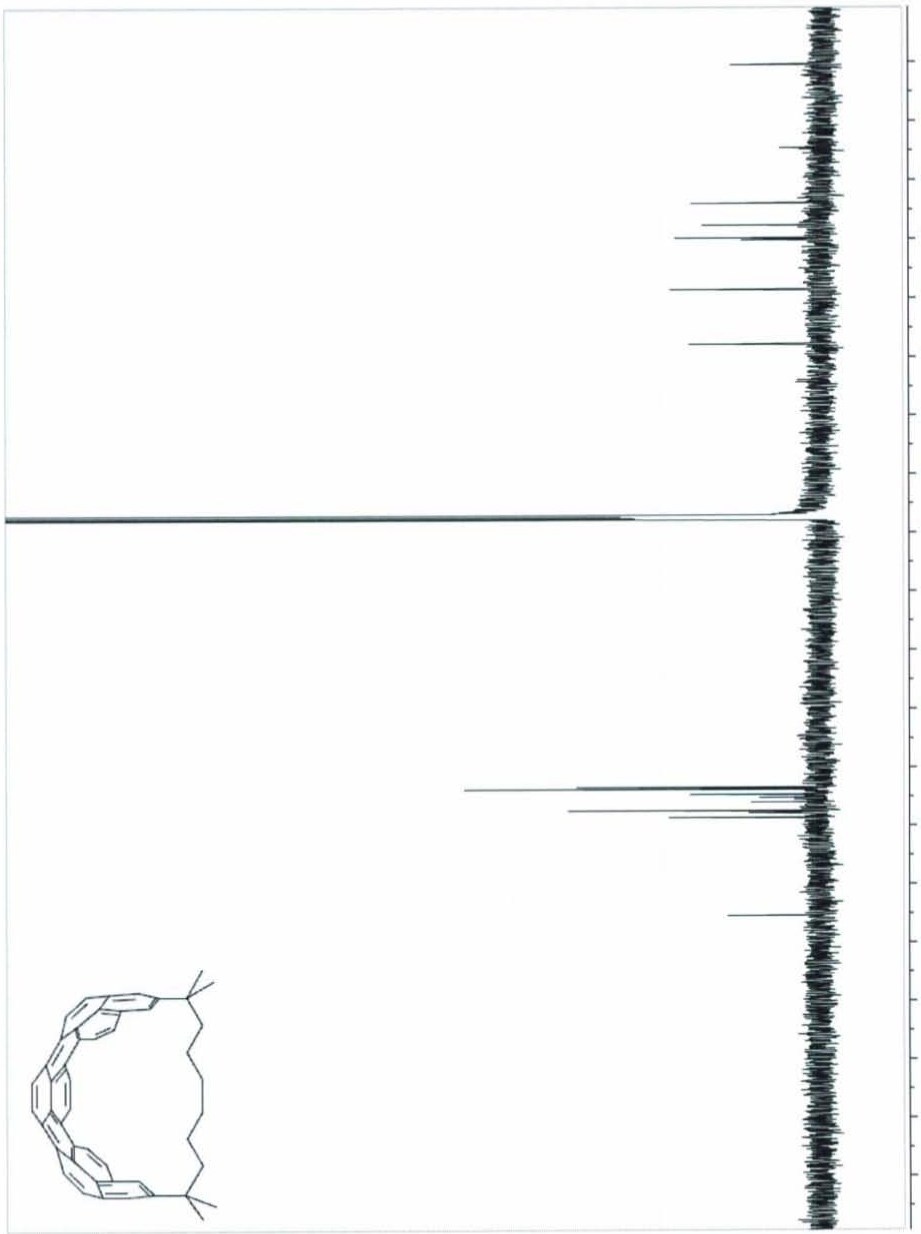
[39] Fort, E. H.; Scott, L. T. *Angew. Chem. Int. Ed.* **2010**, *49*, 6626-6628.

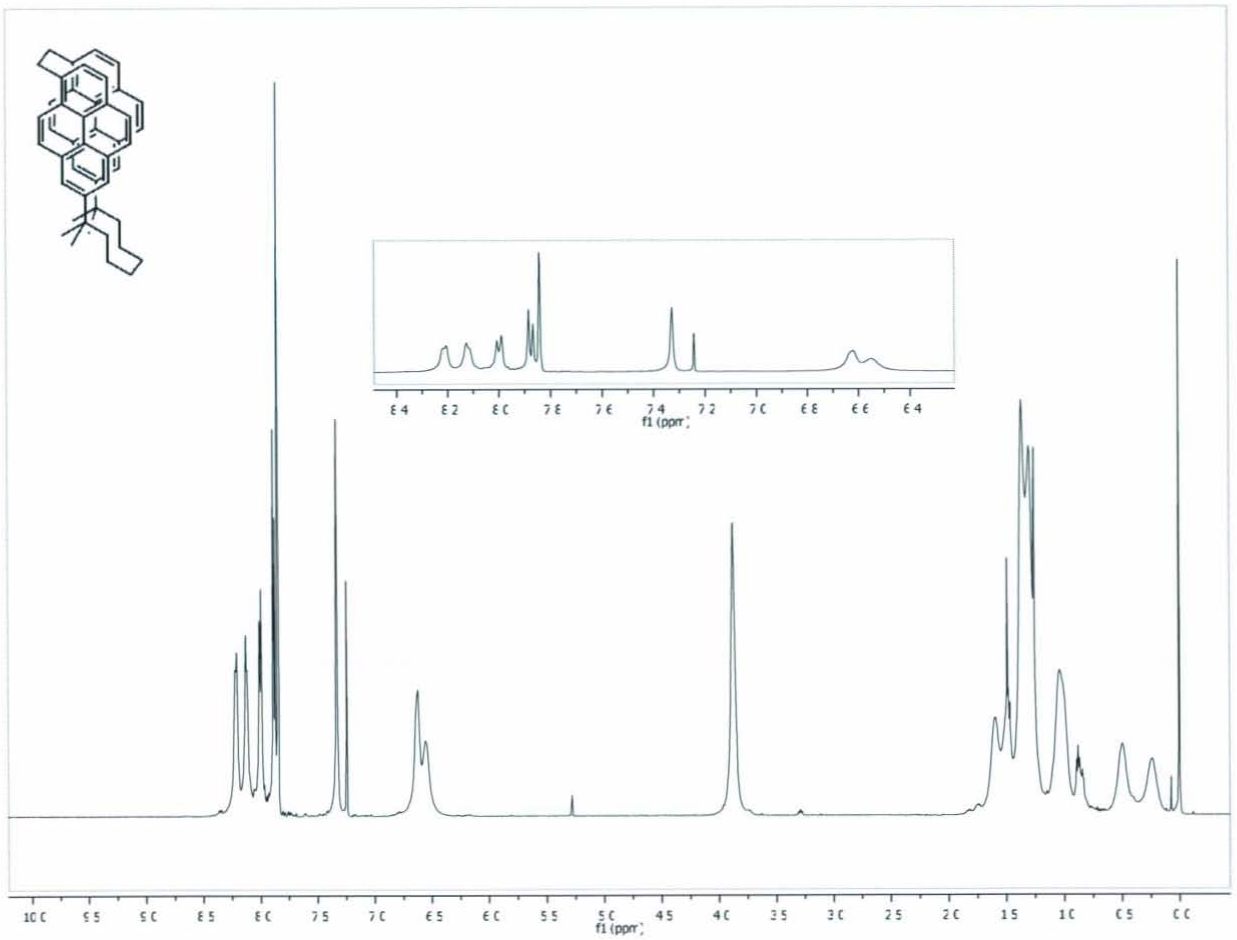
[40] Nitroethylene does in fact behave as an acetylene equivalent in the bay region Diels-Alder reaction of perylene and related (wider) systems. However, it is not a generic acetylene equivalent for all Diels-Alder reactions. In fact it appears to be limited to the aforementioned systems. However, it does perform much better than generic acetylene equivalents (such as phenyl vinyl sulfoxide) in these particular bay region Diels-Alder reactions.

Appendix 3

Selected ^{1}H and ^{13}C NMR Spectra for Chapter 4



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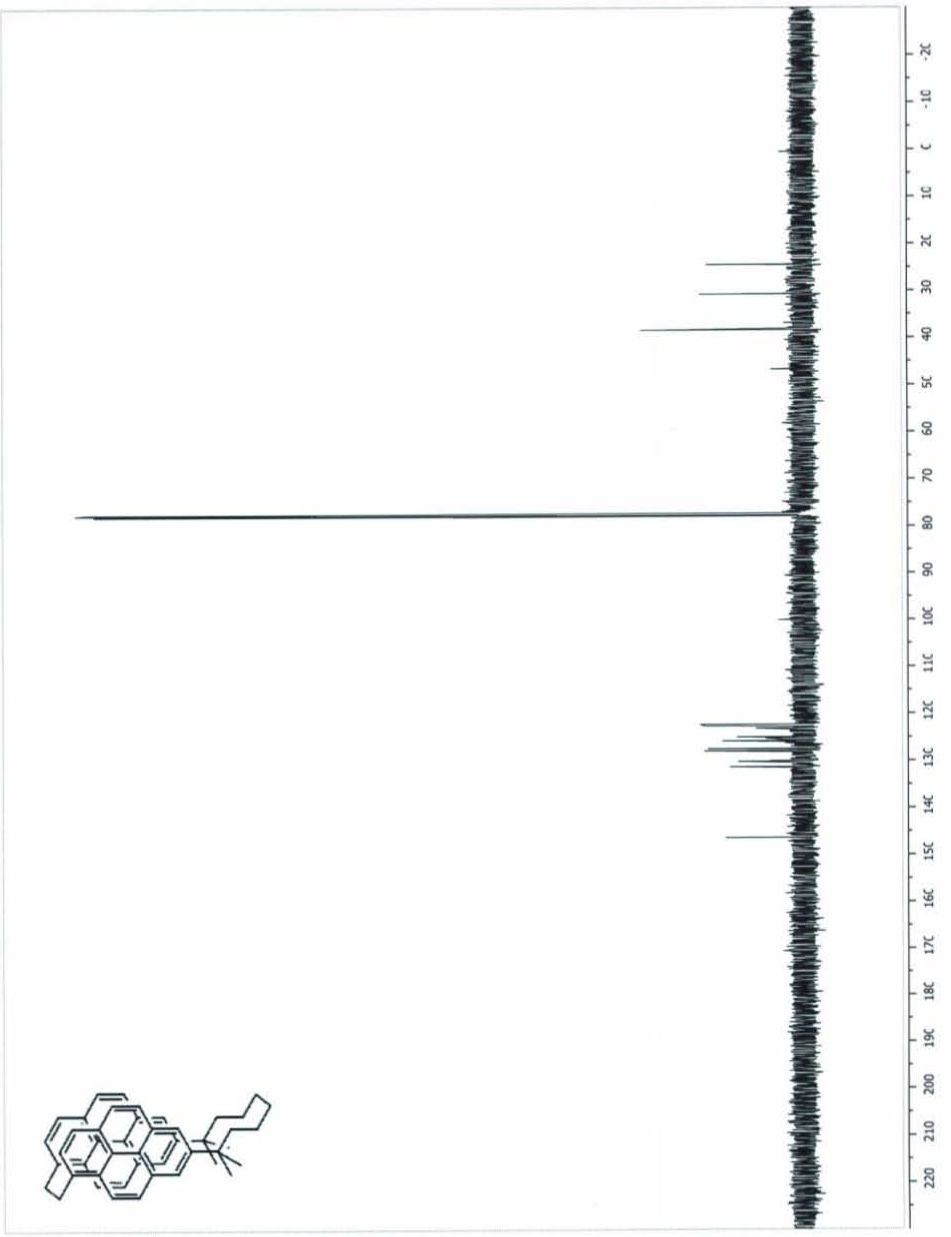
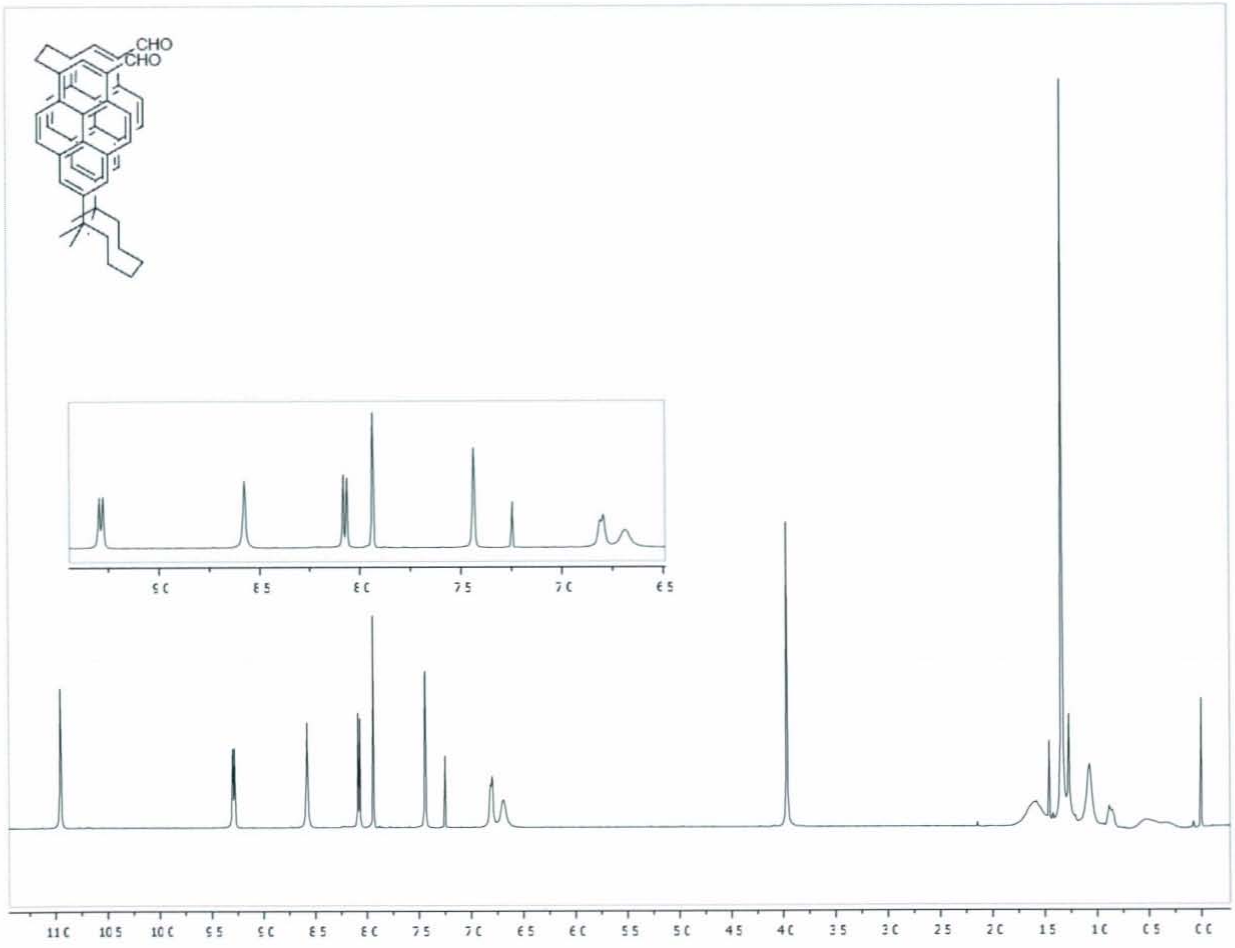
f1 (ppm)

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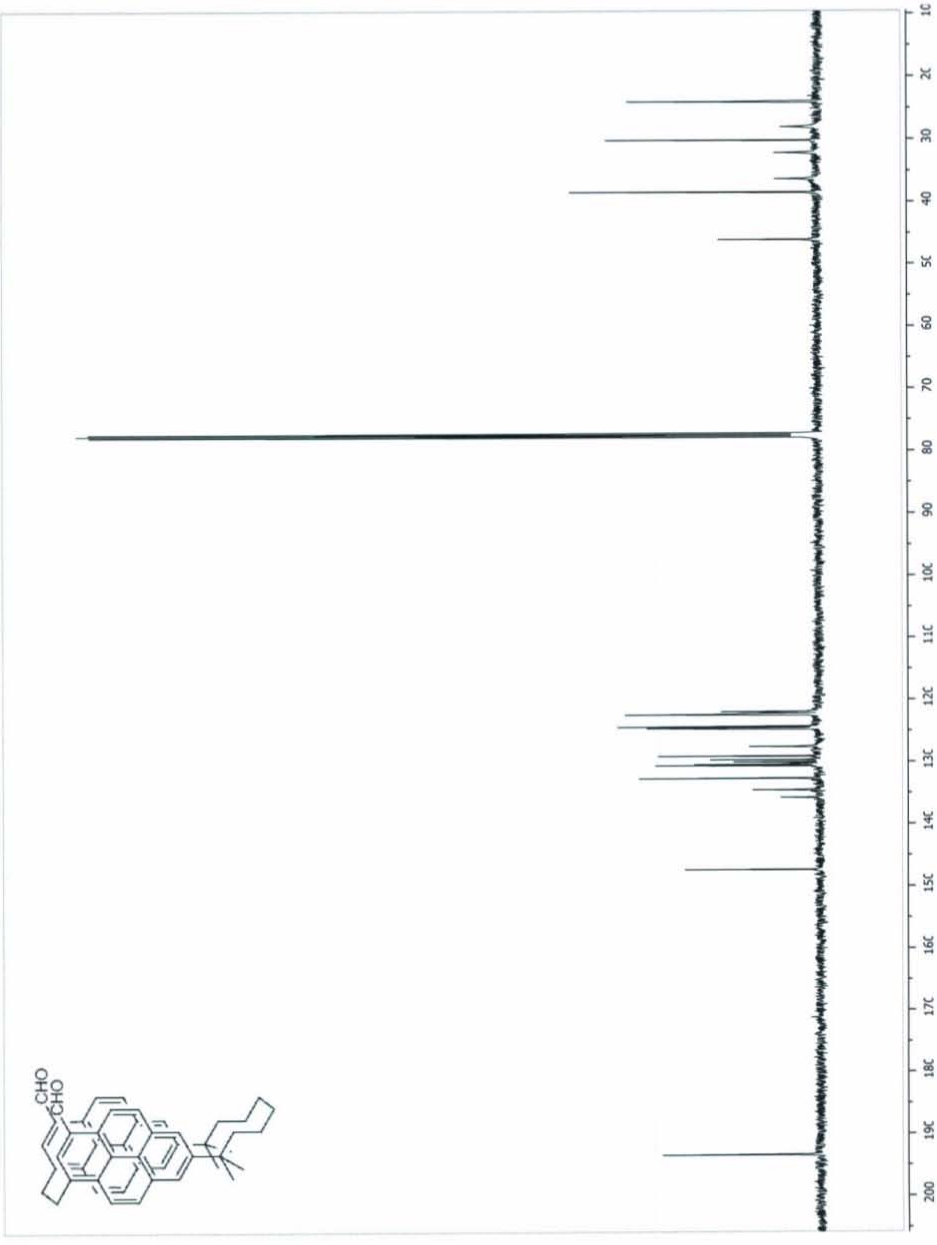
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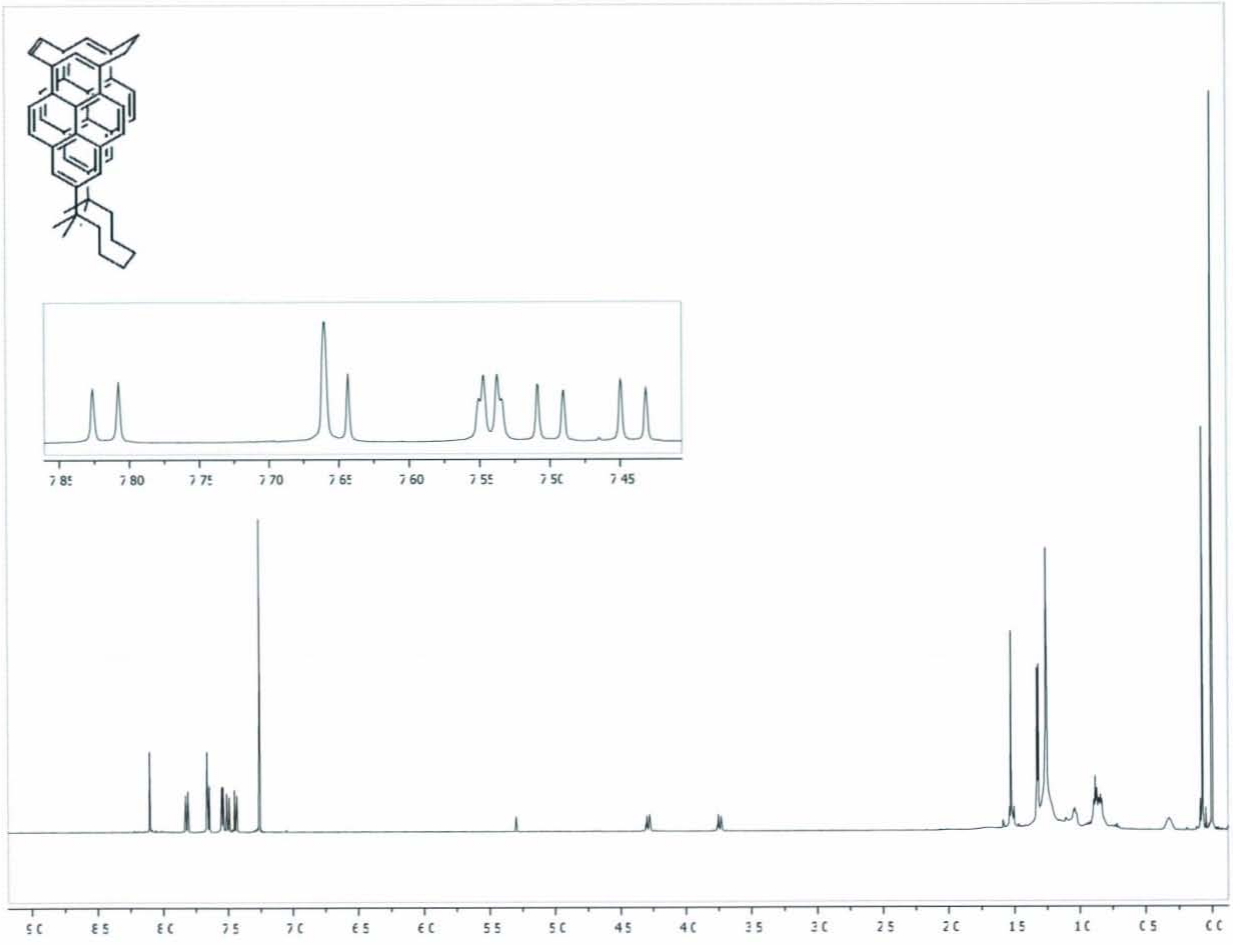

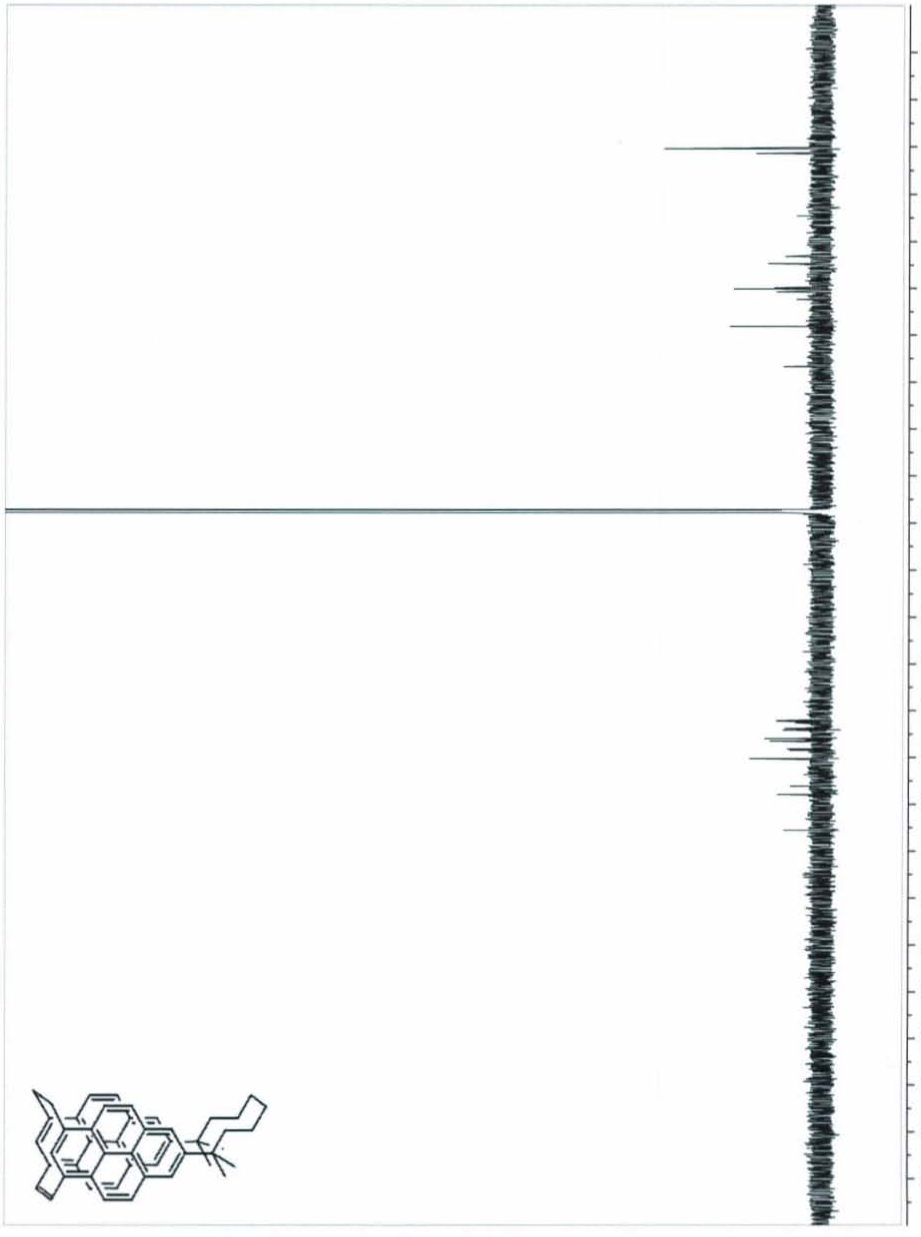

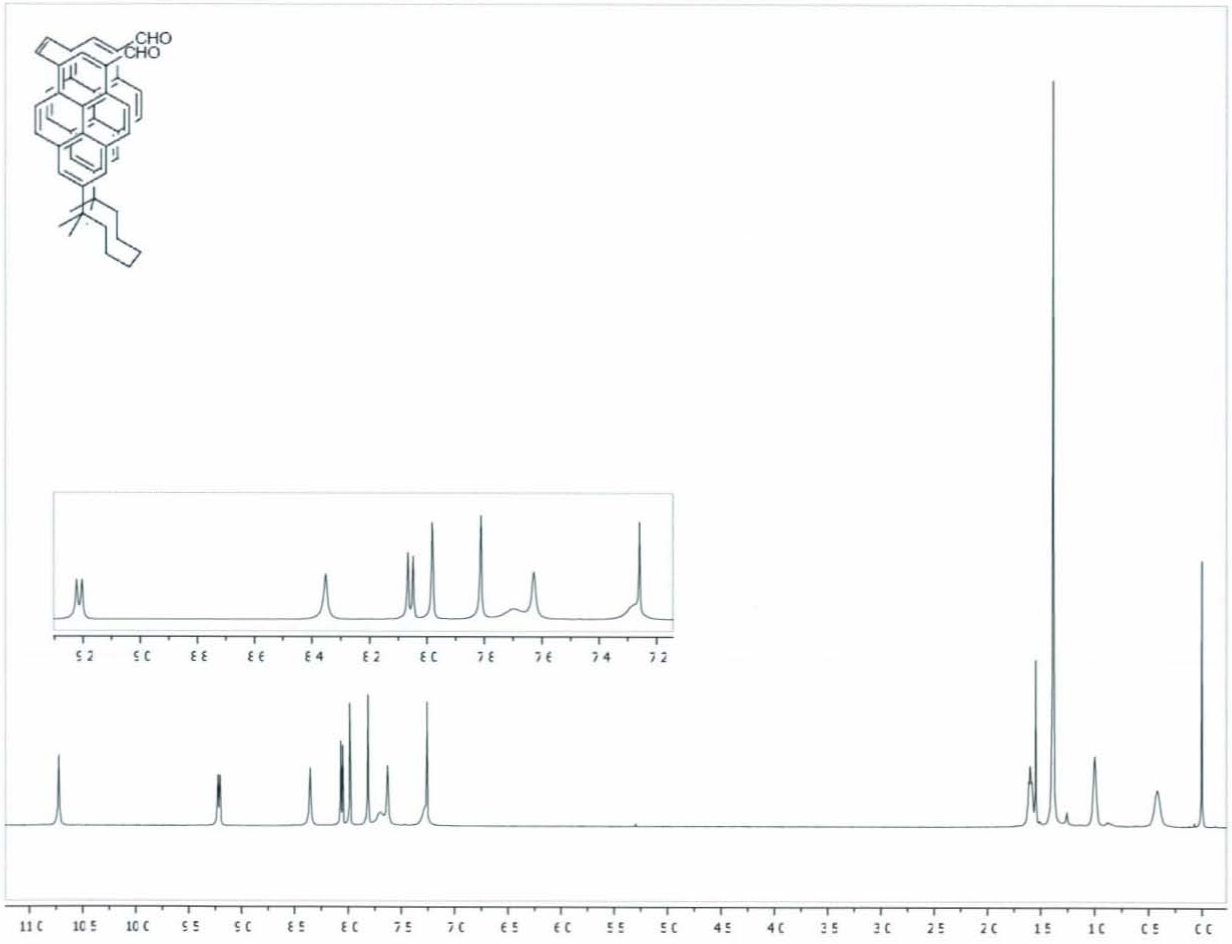
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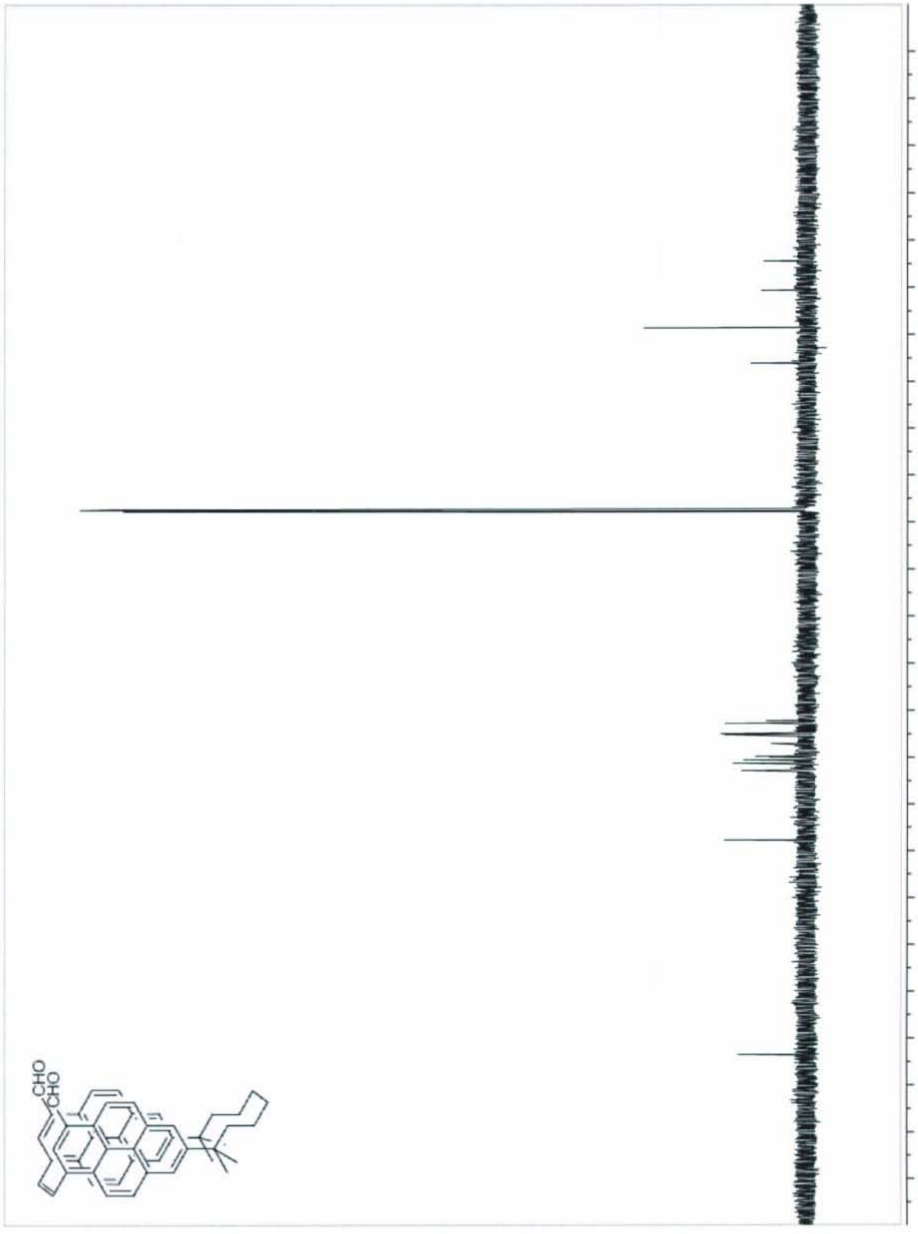
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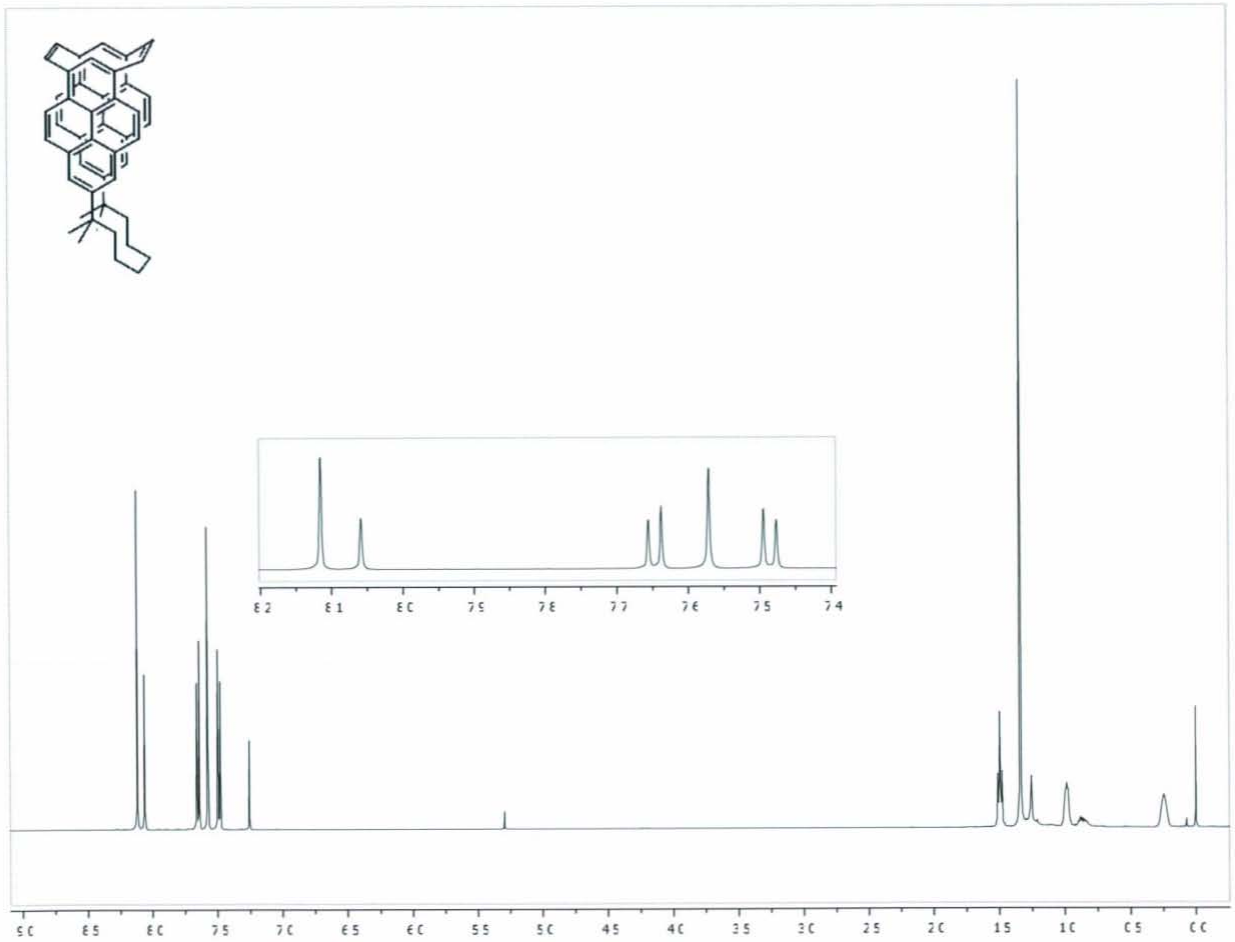

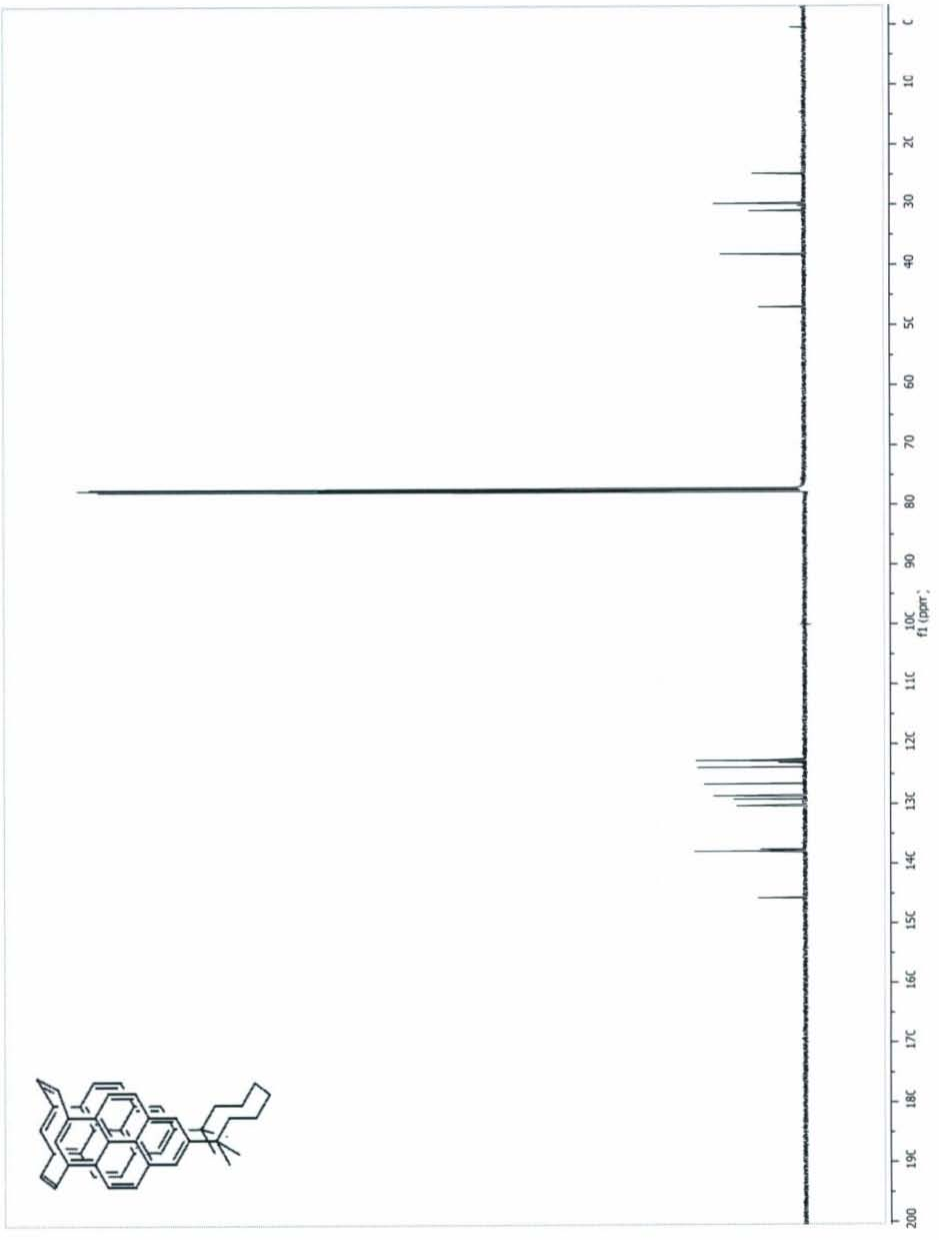
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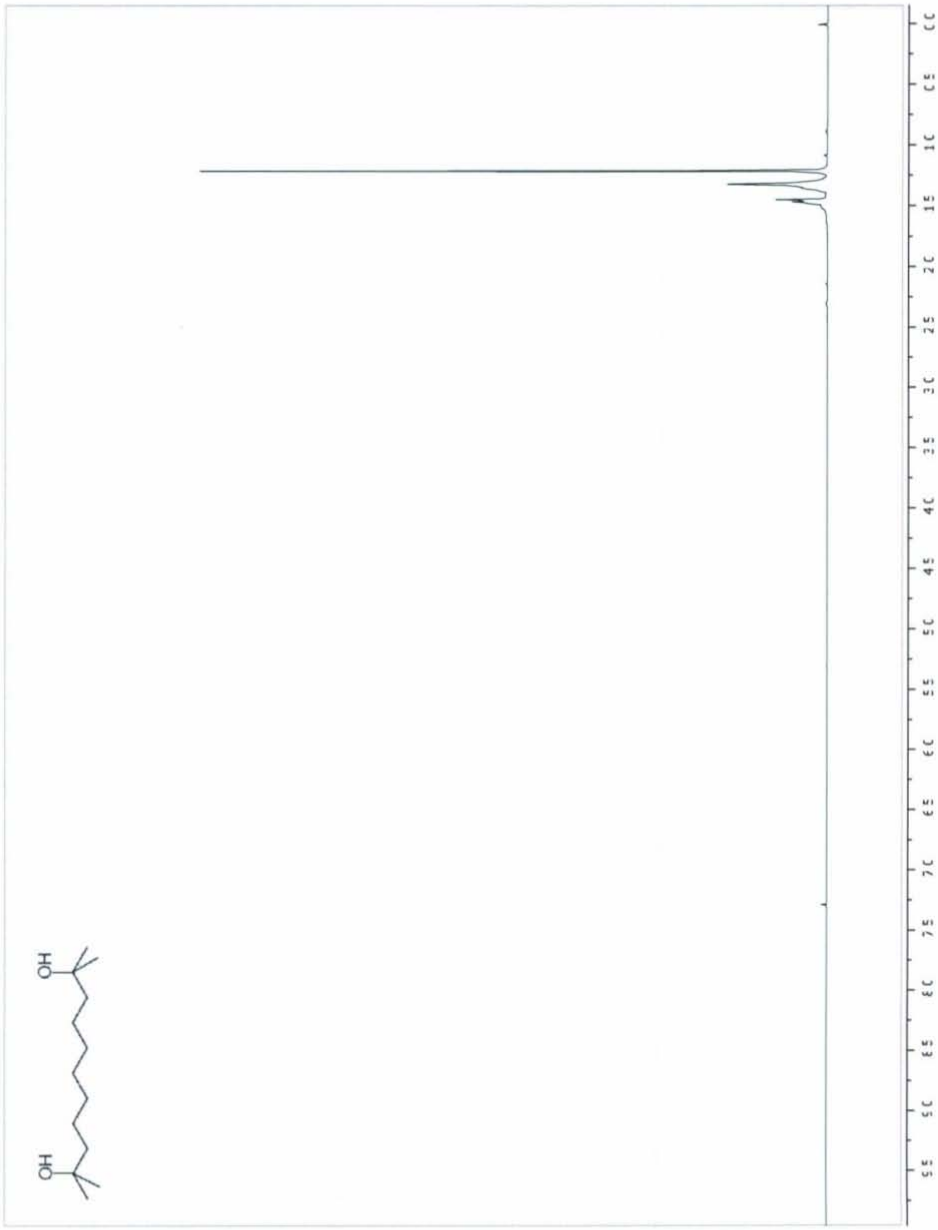
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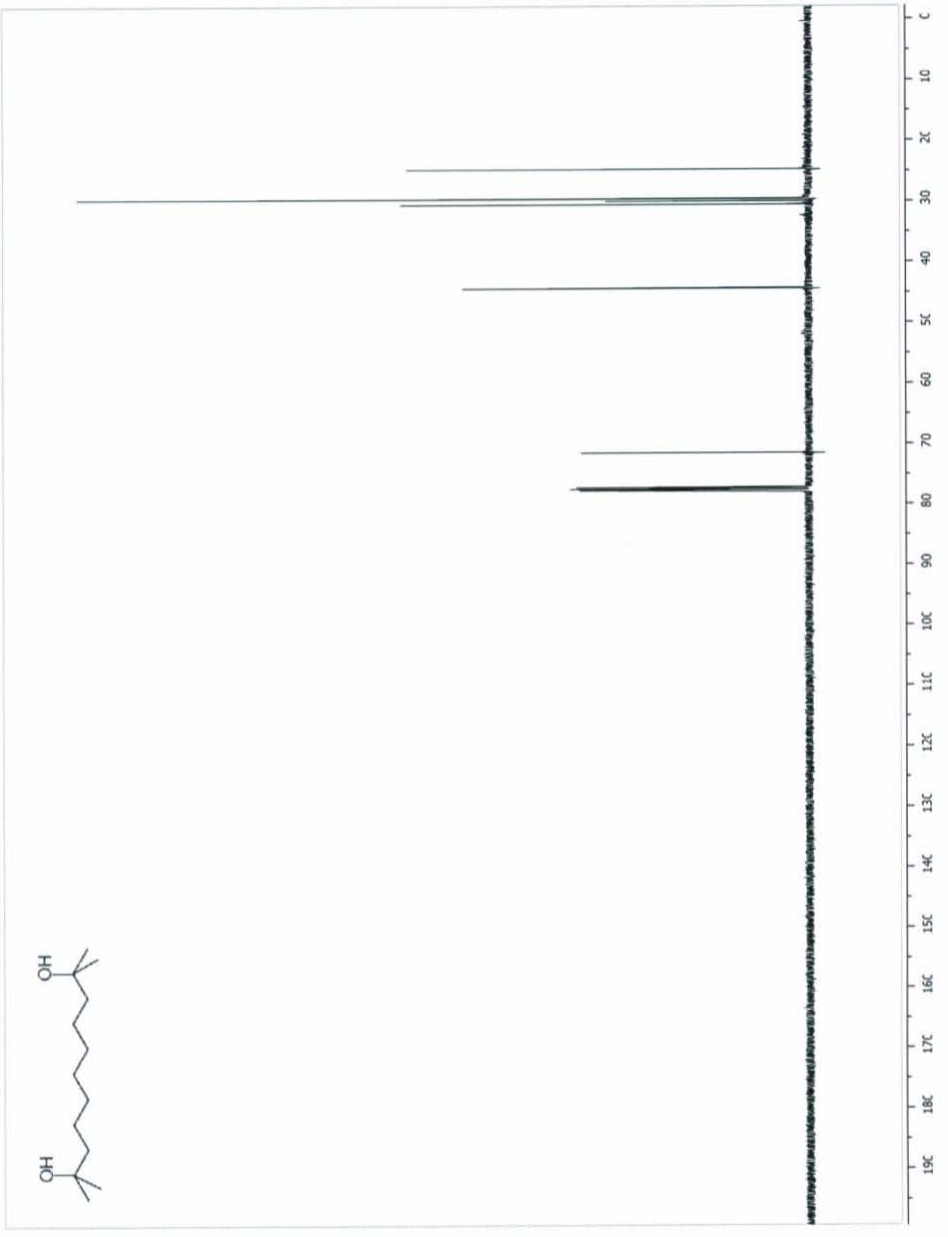
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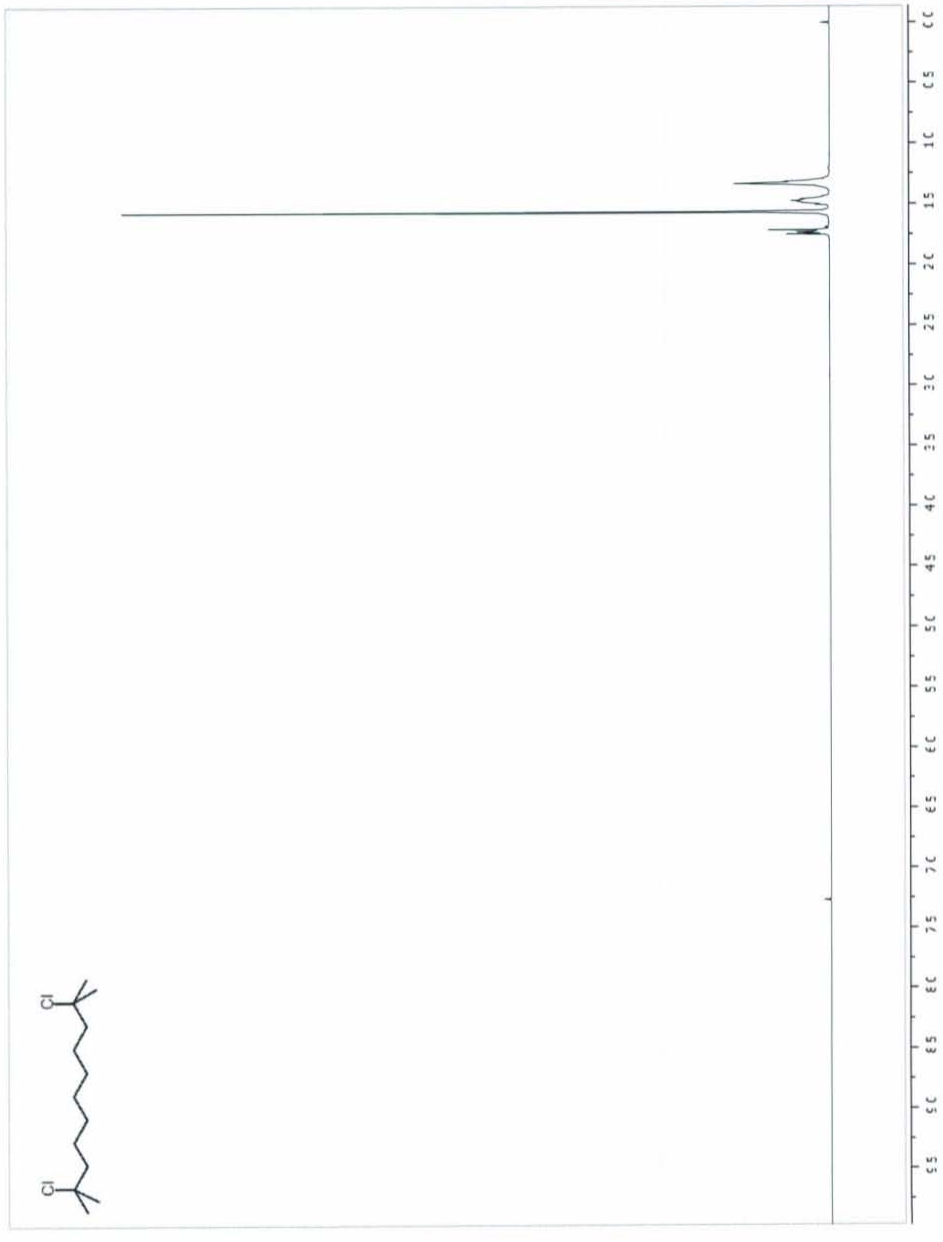
OH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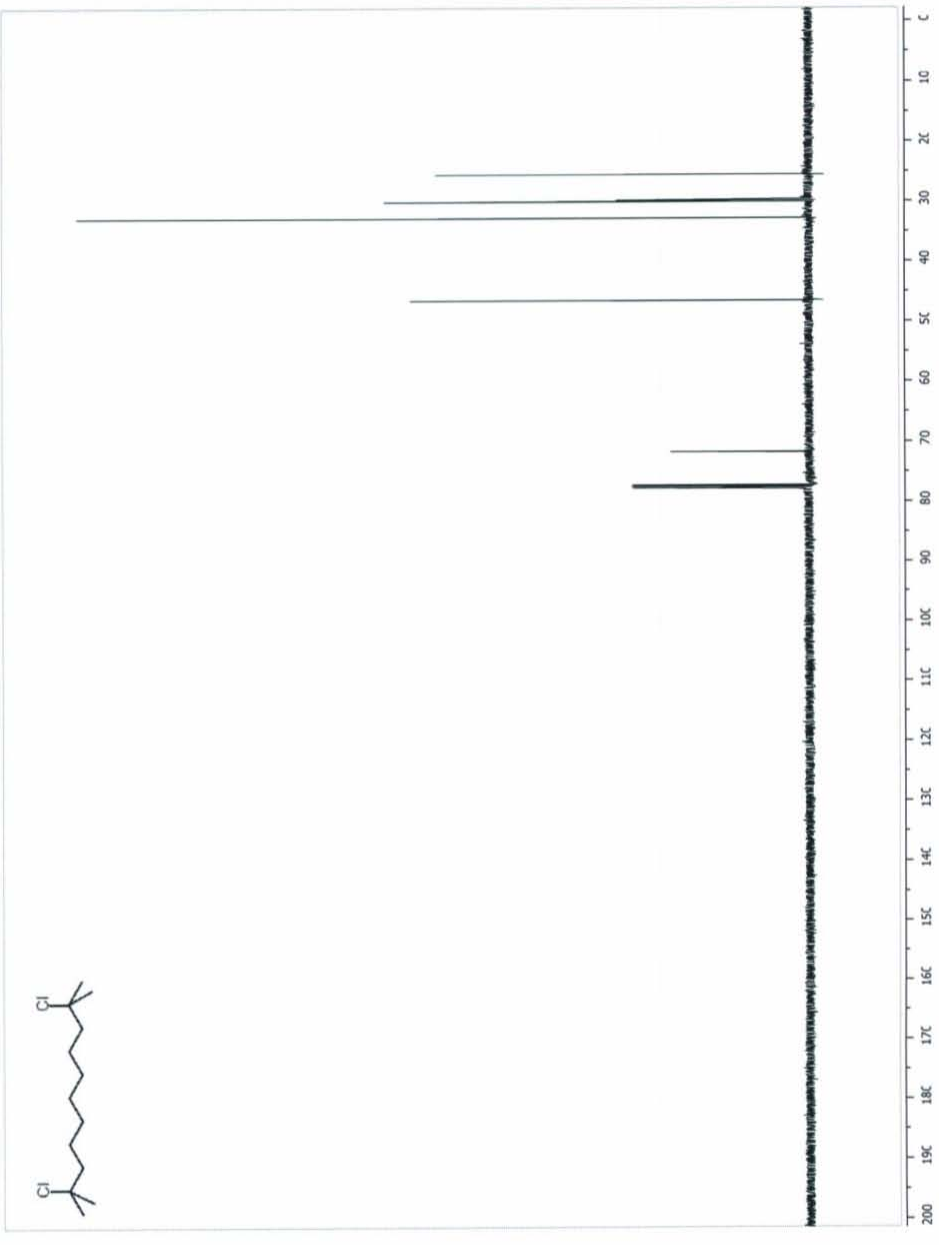
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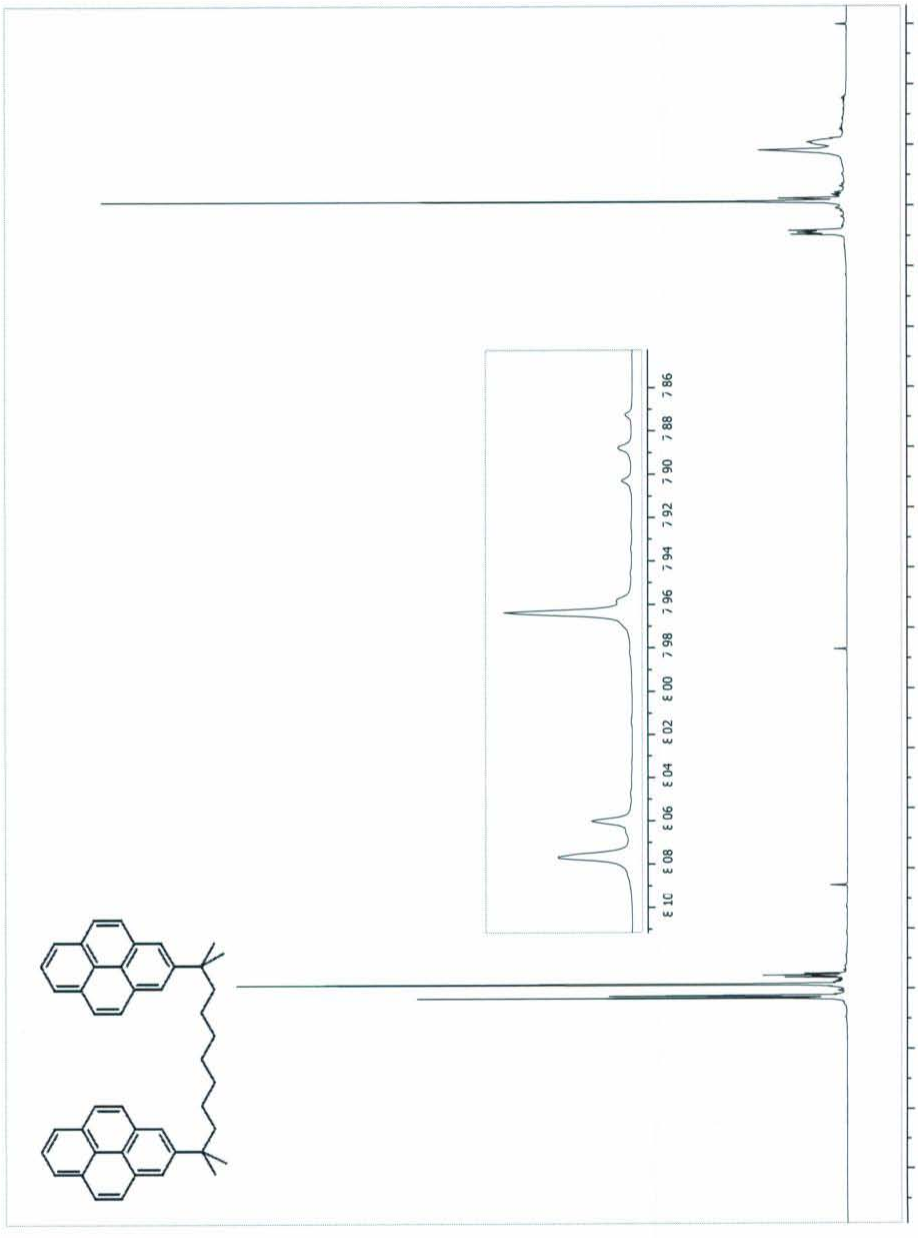

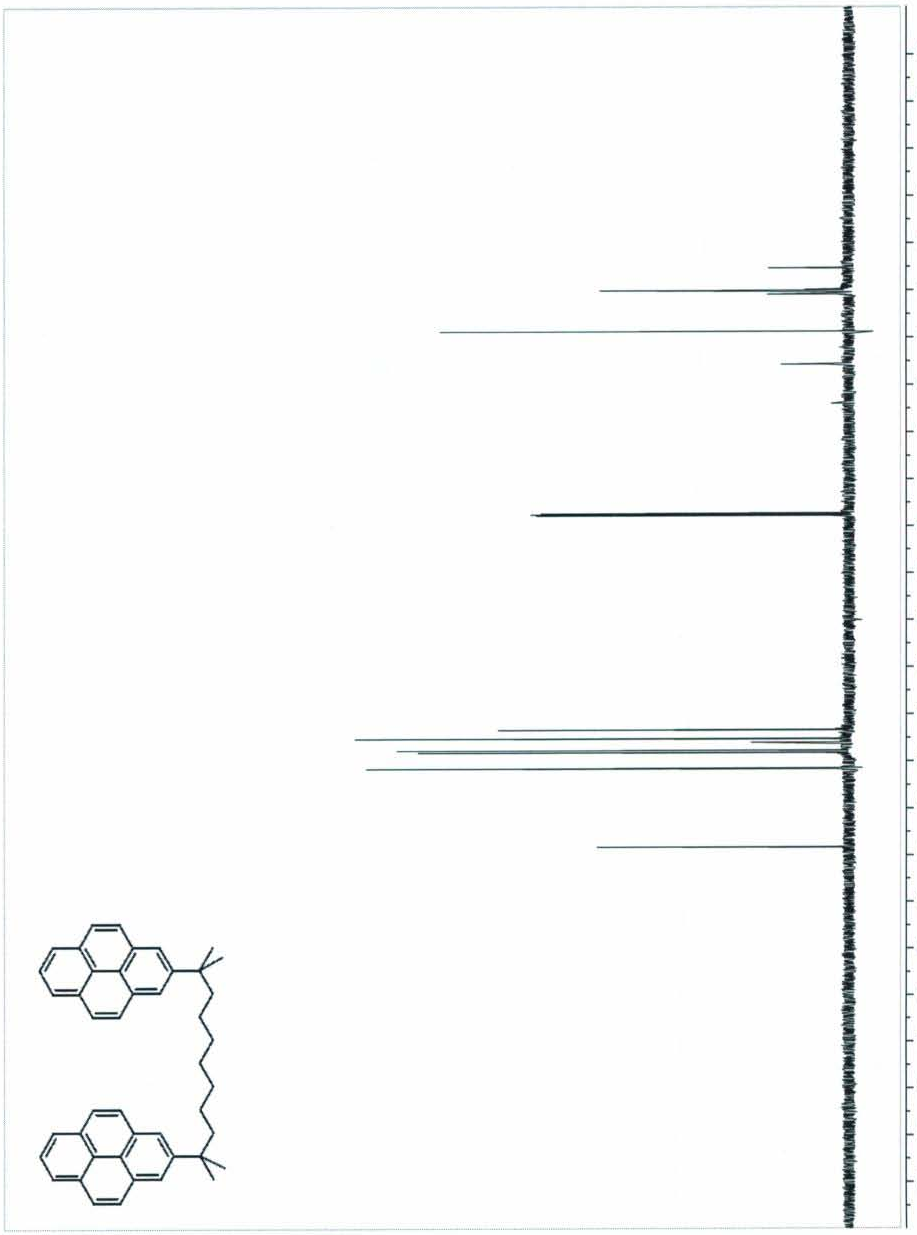

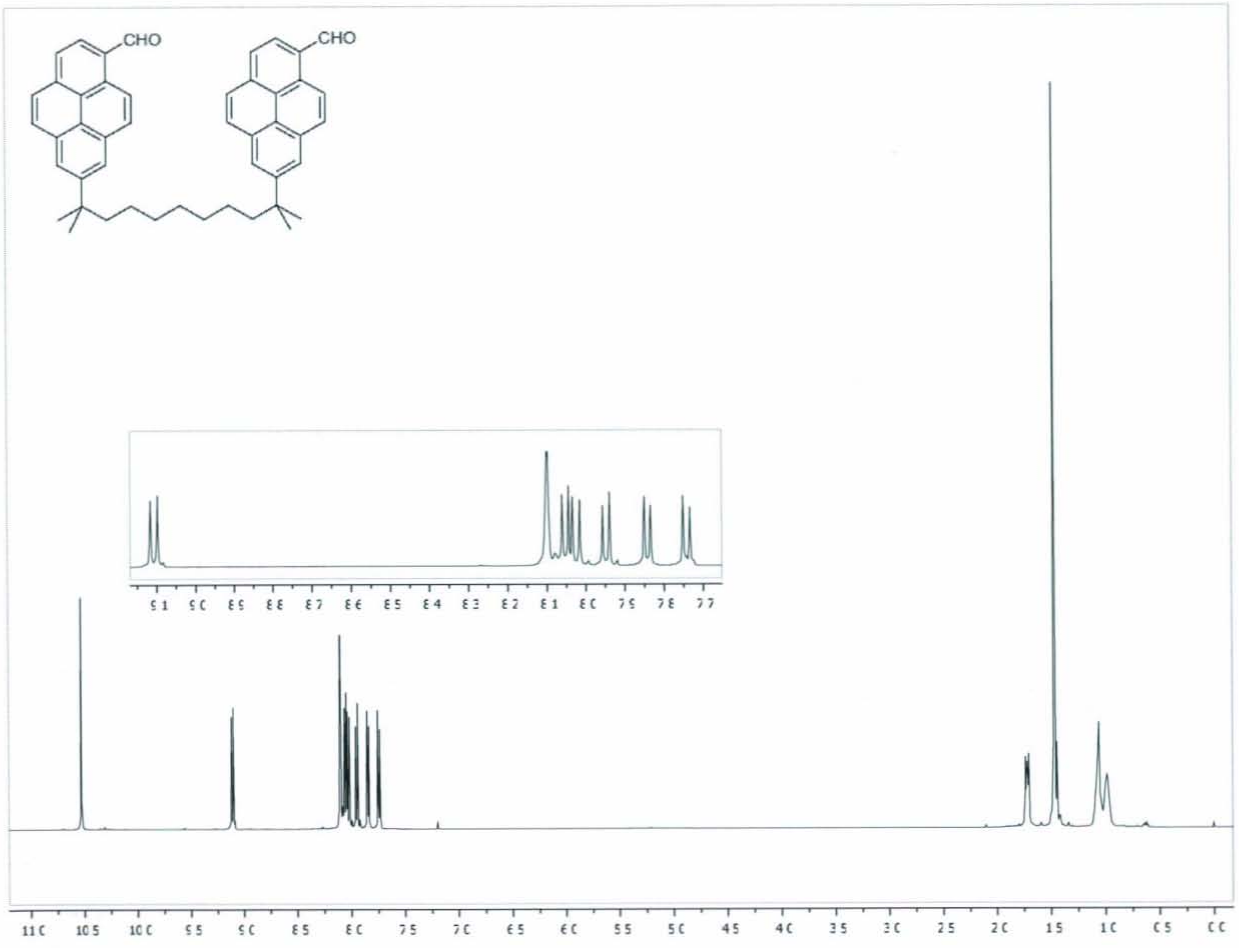
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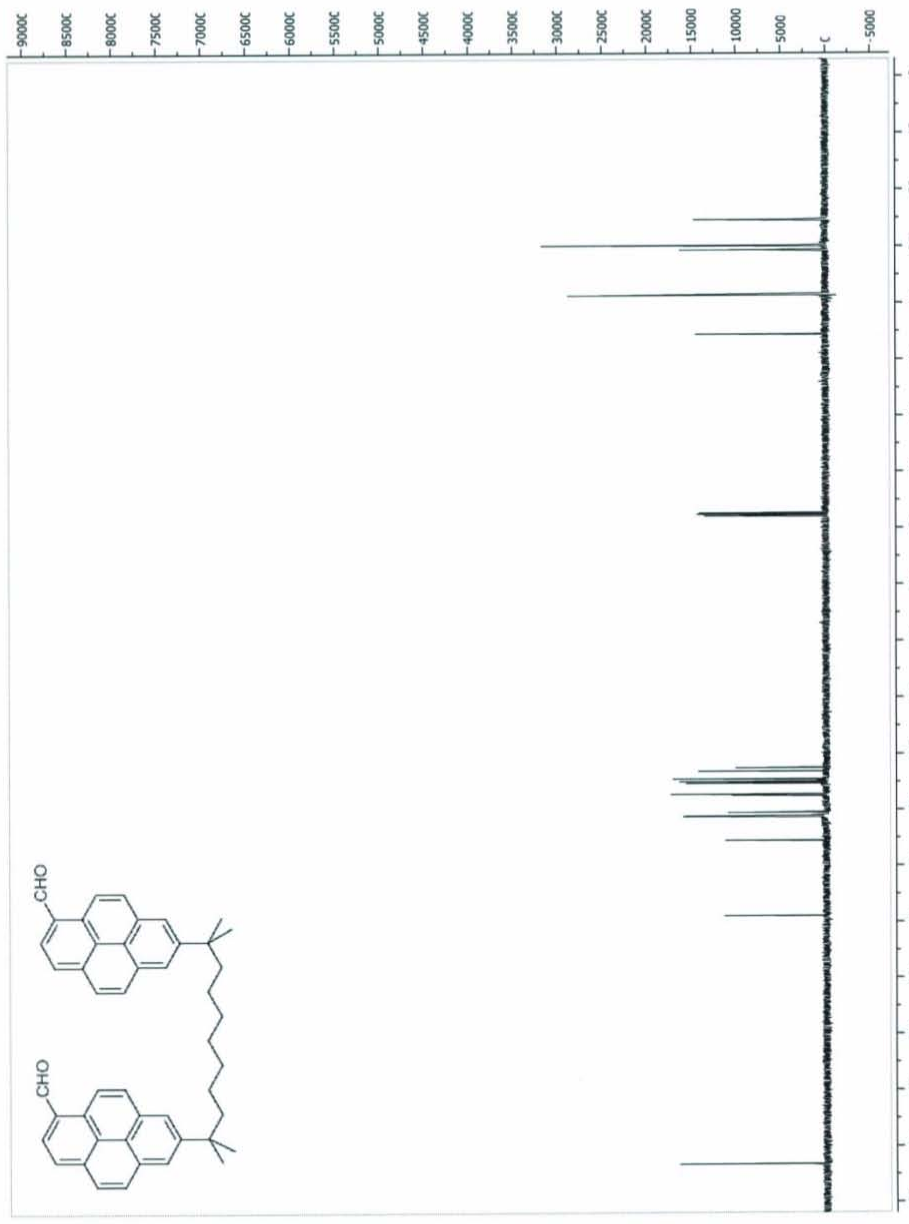
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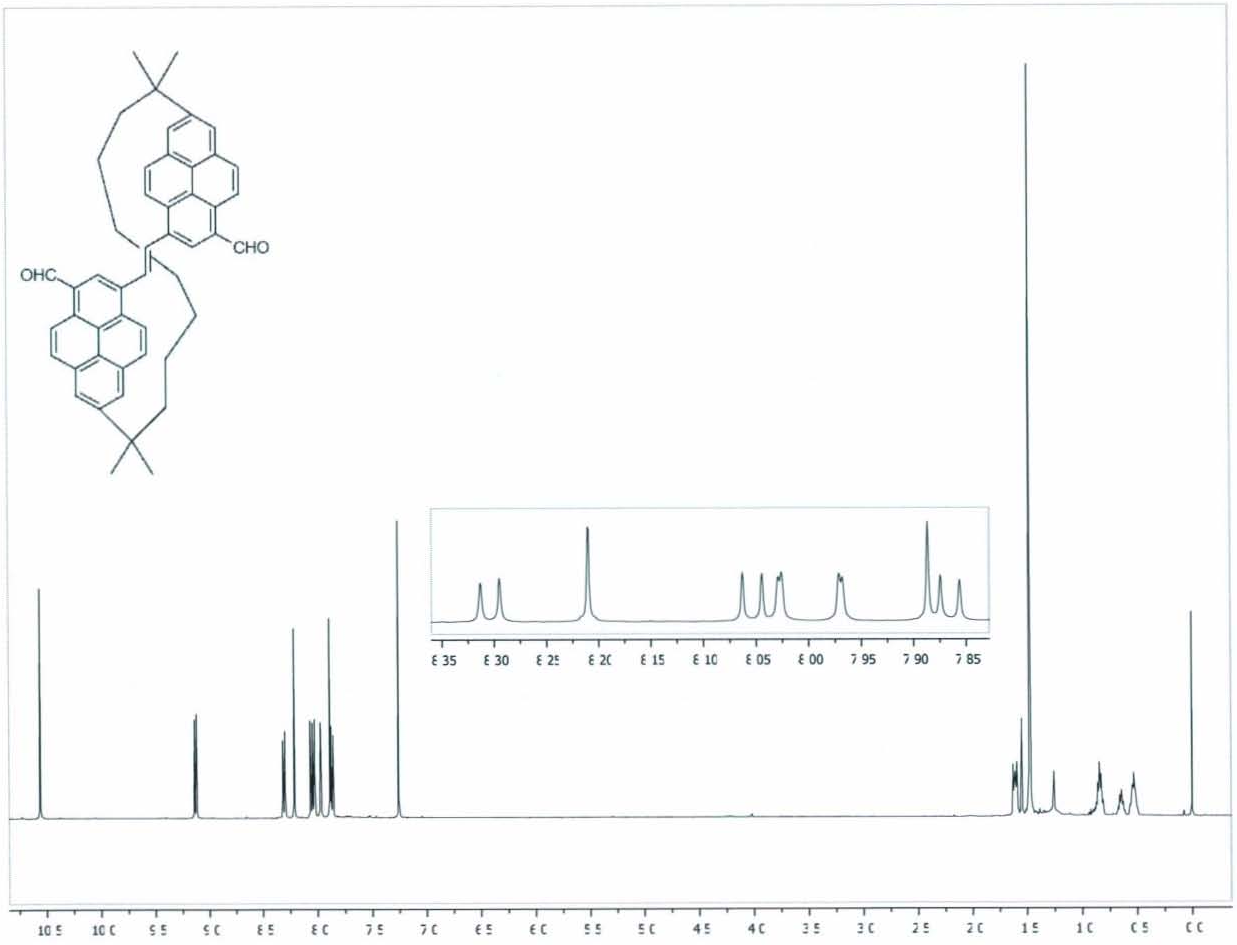
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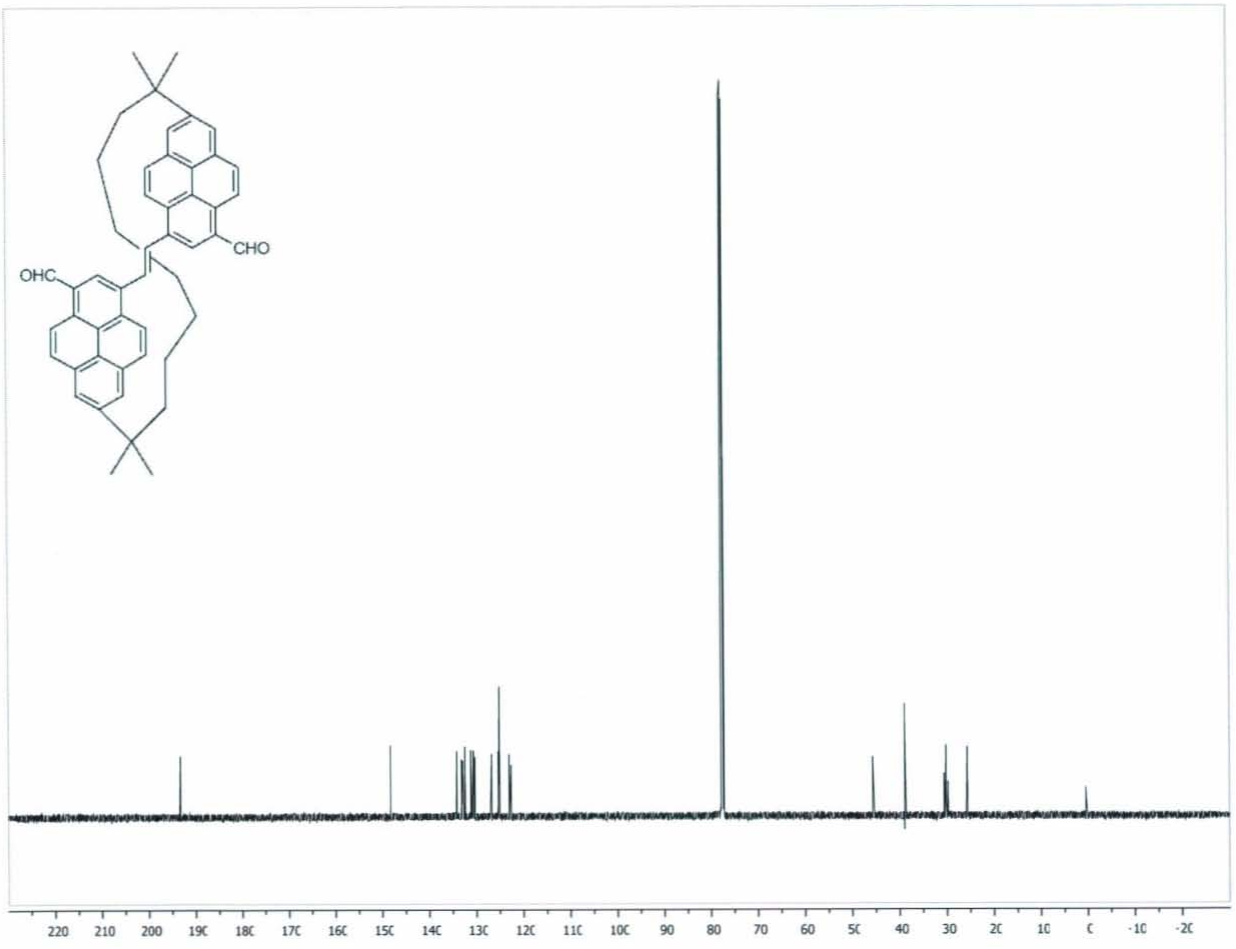
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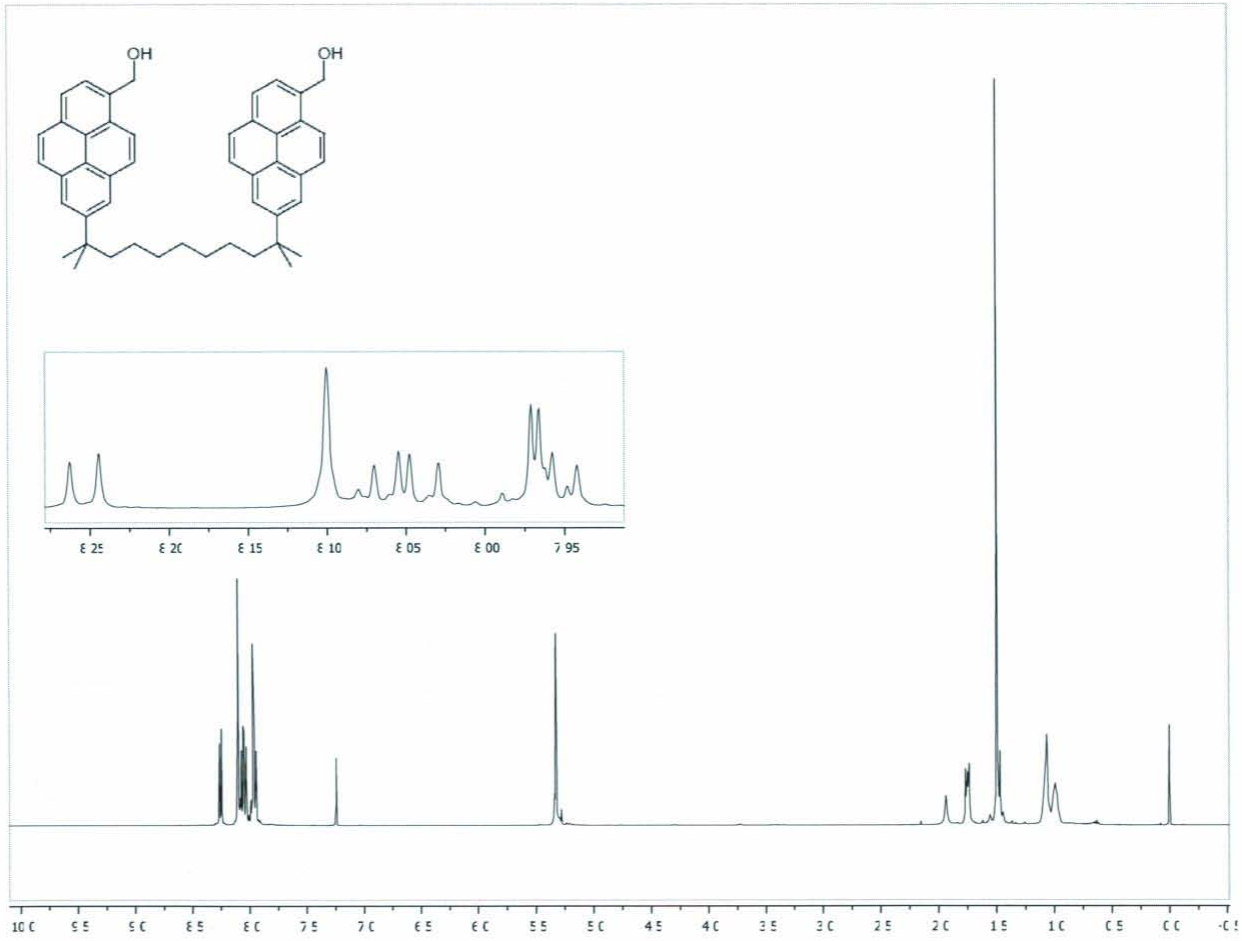
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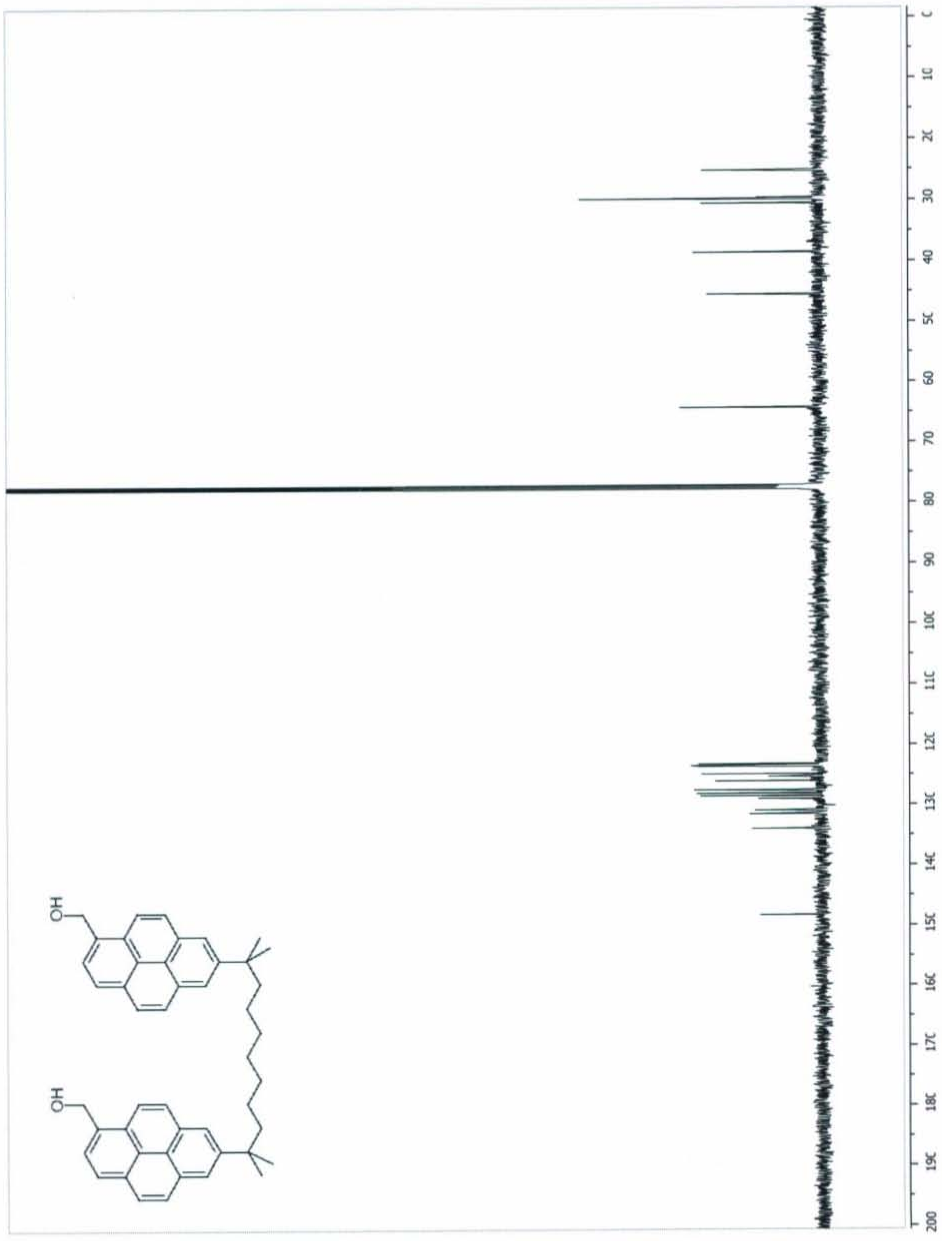
OH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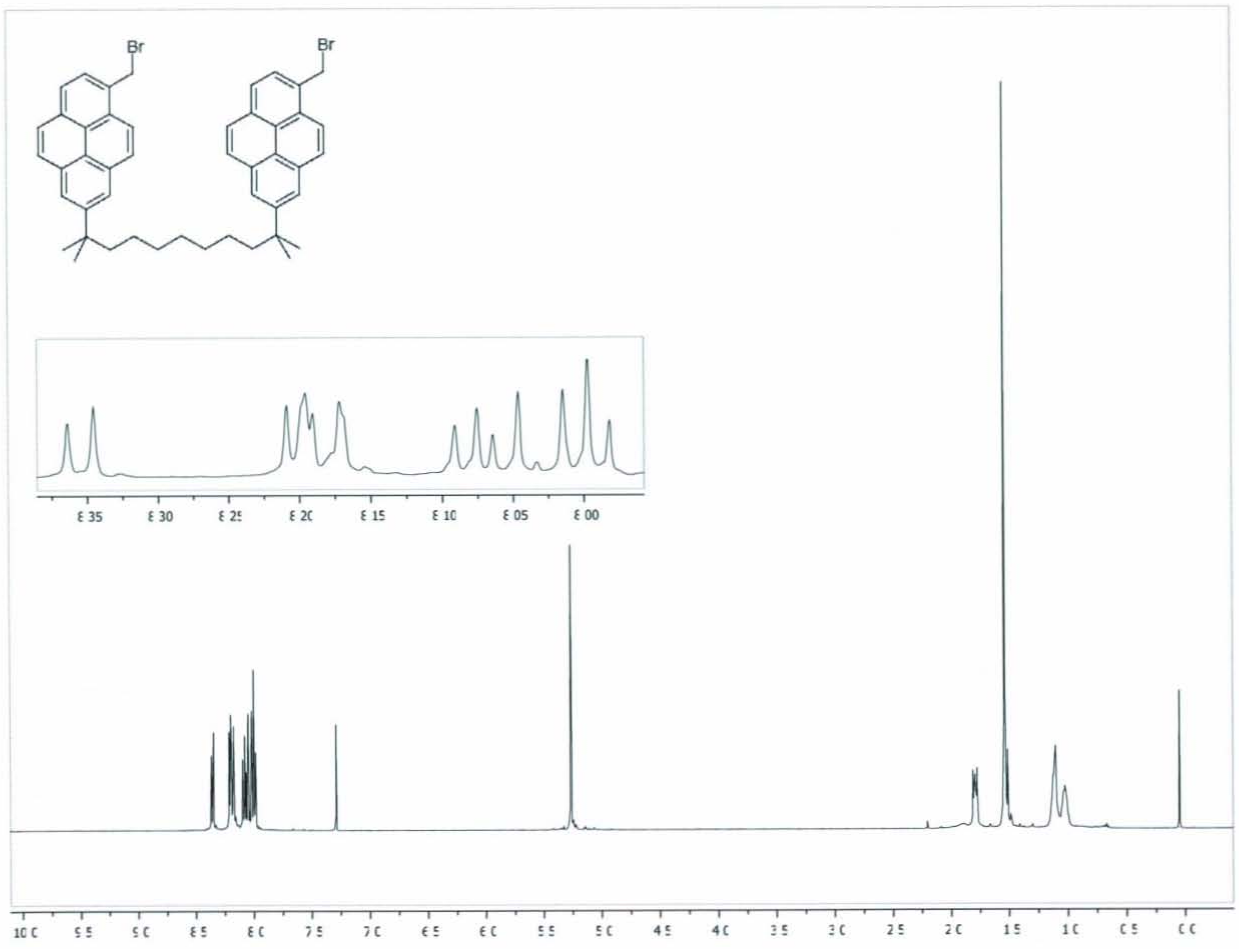
OH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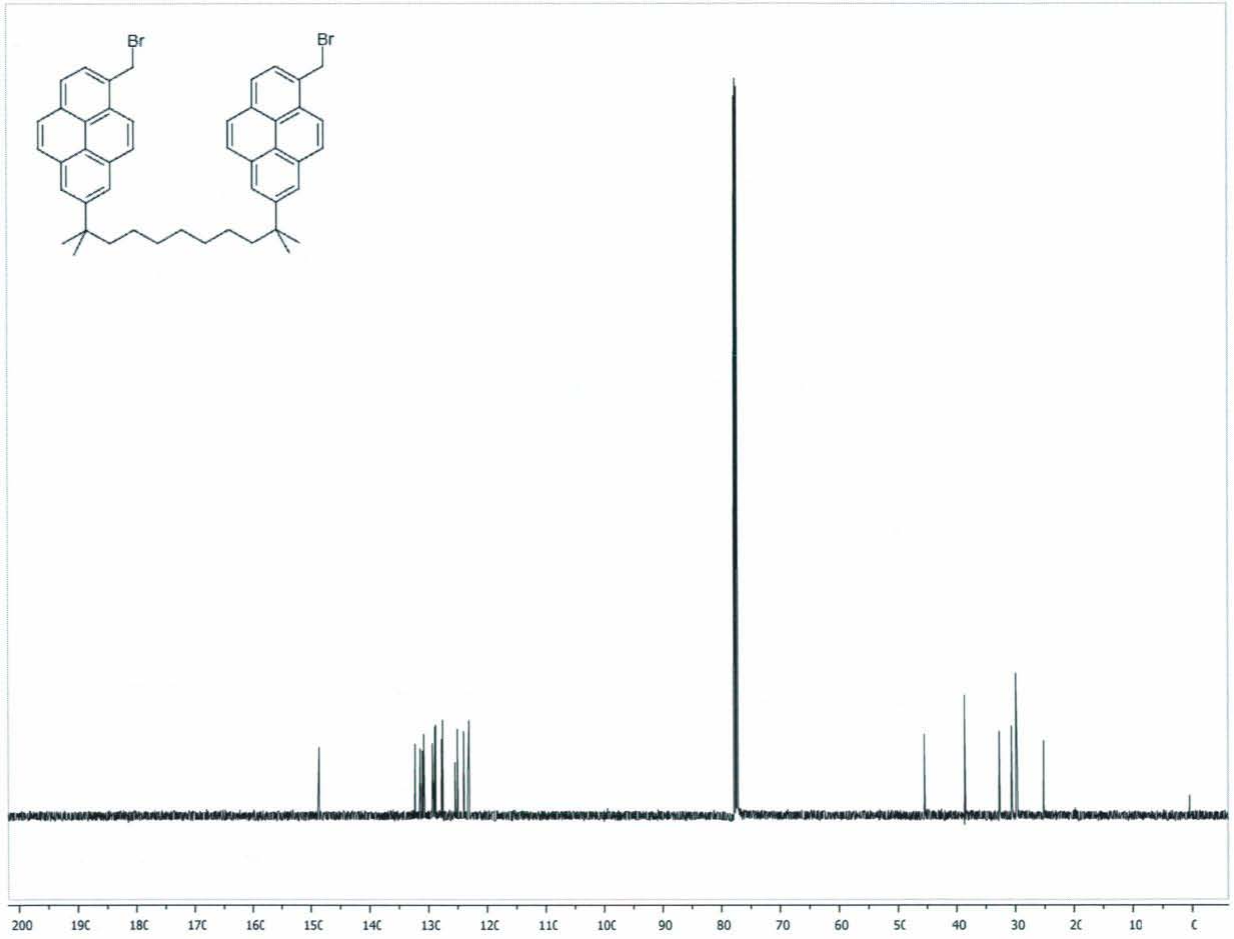
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Br
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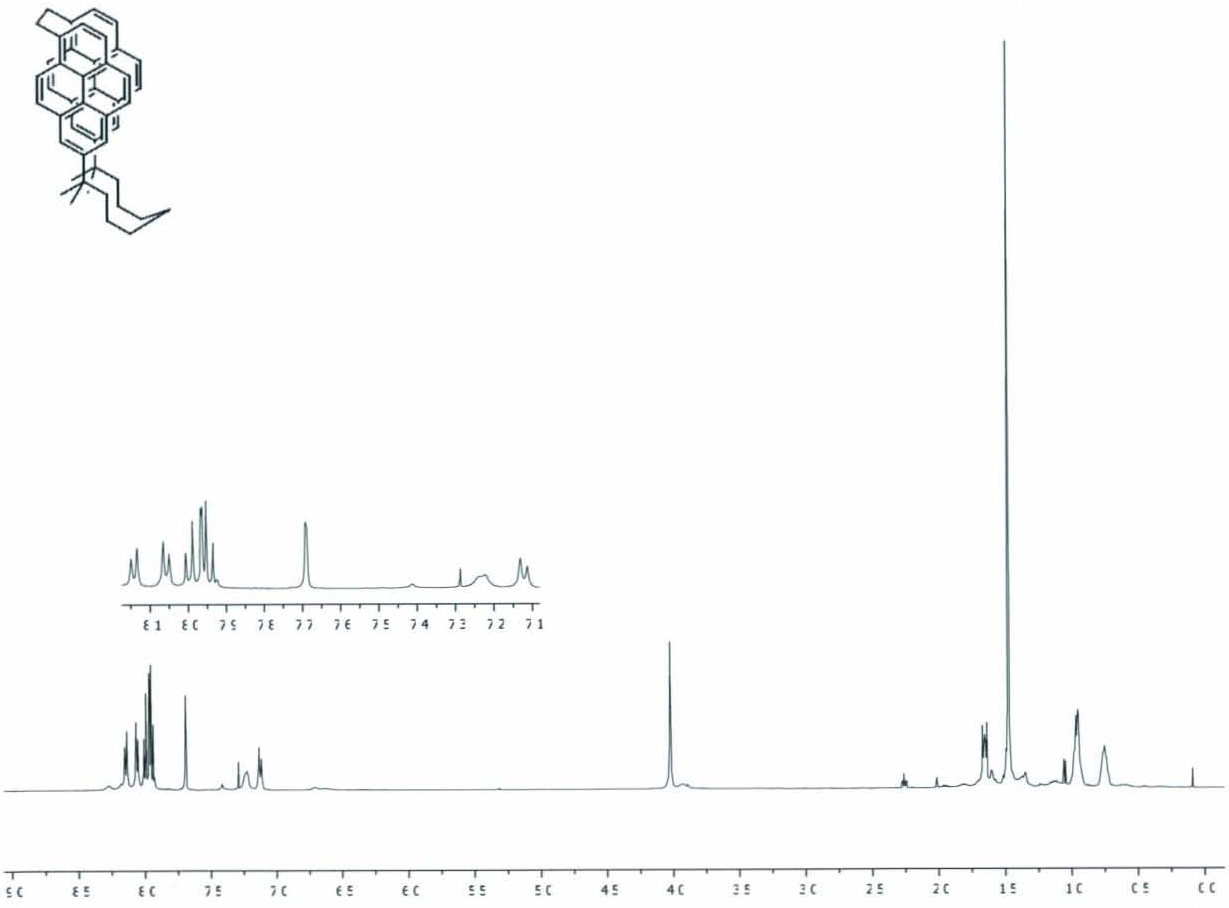

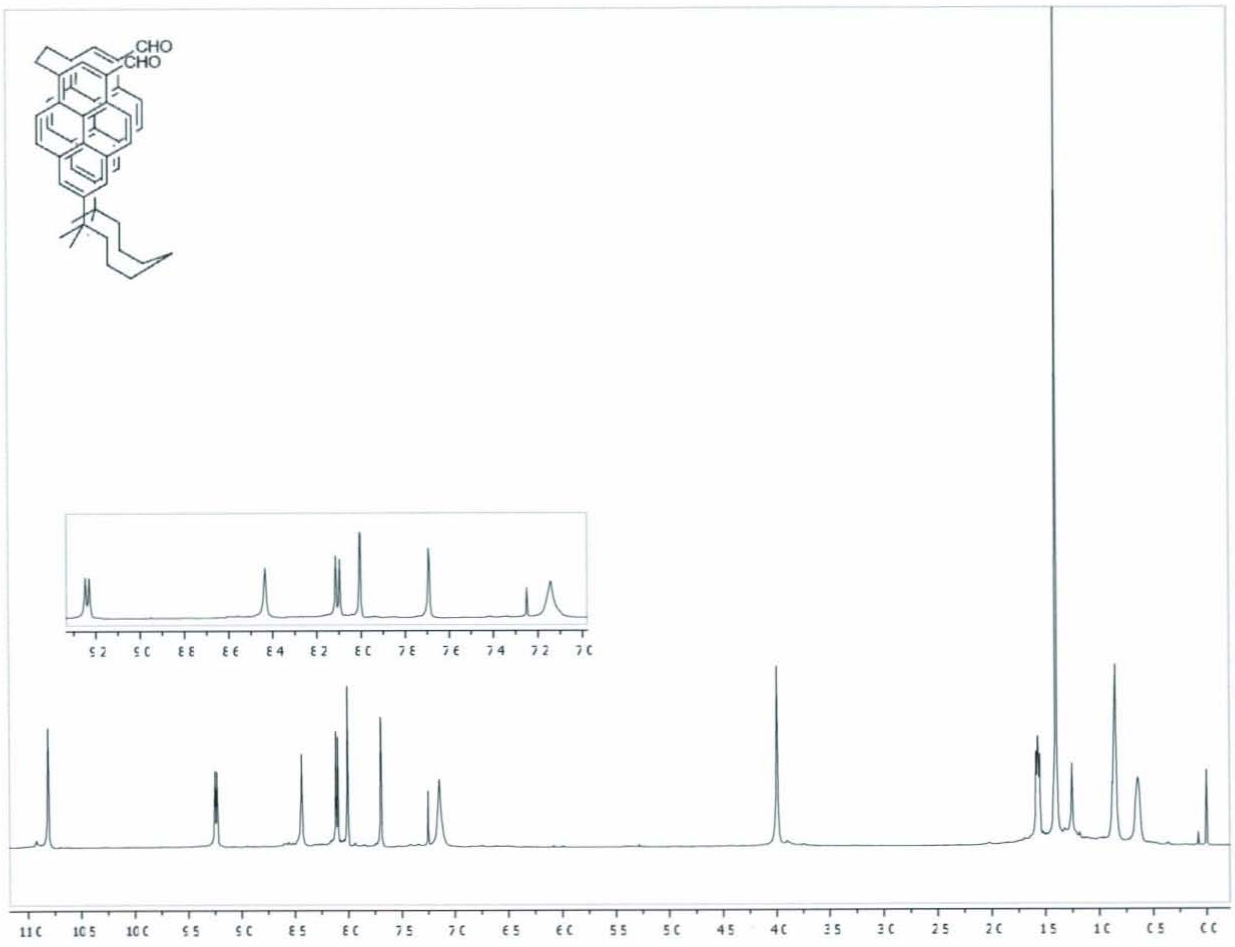
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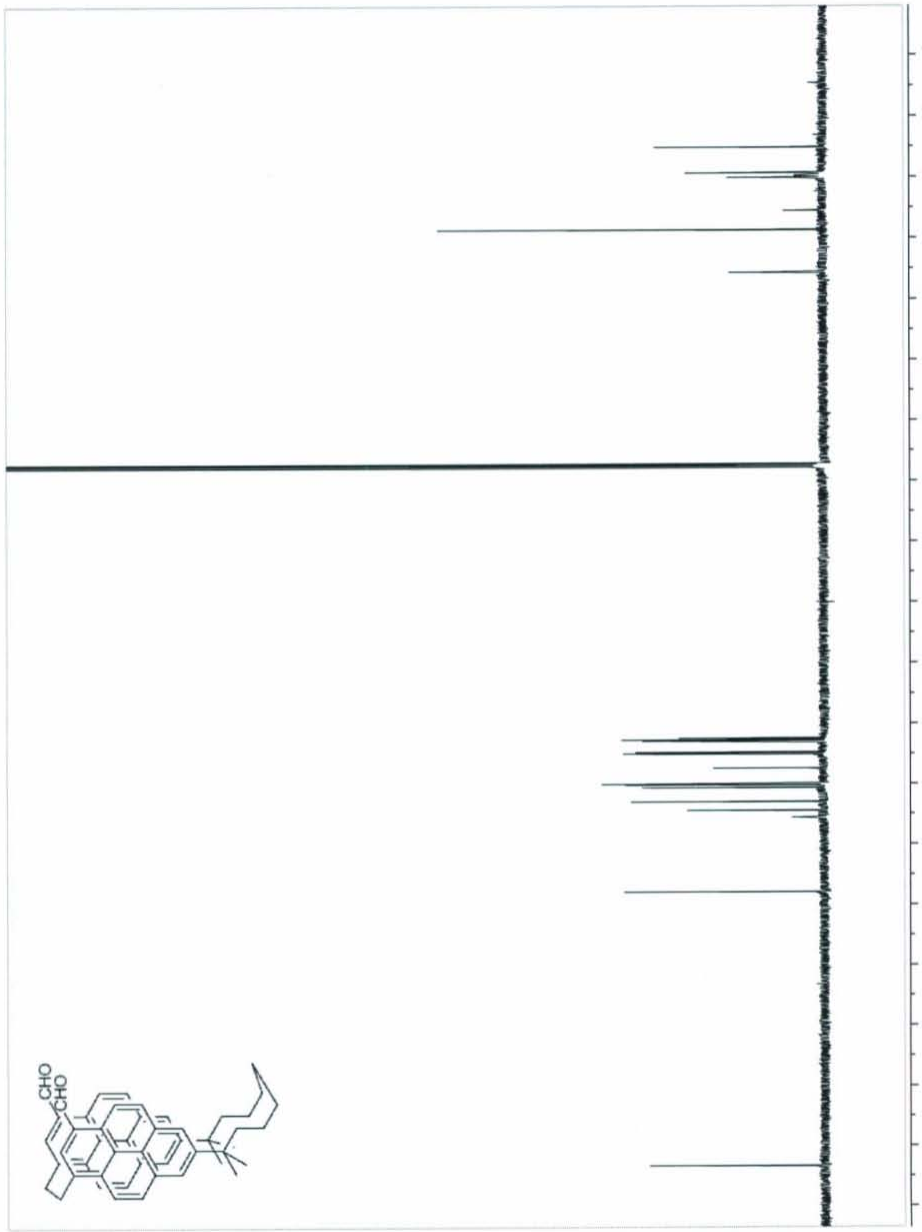
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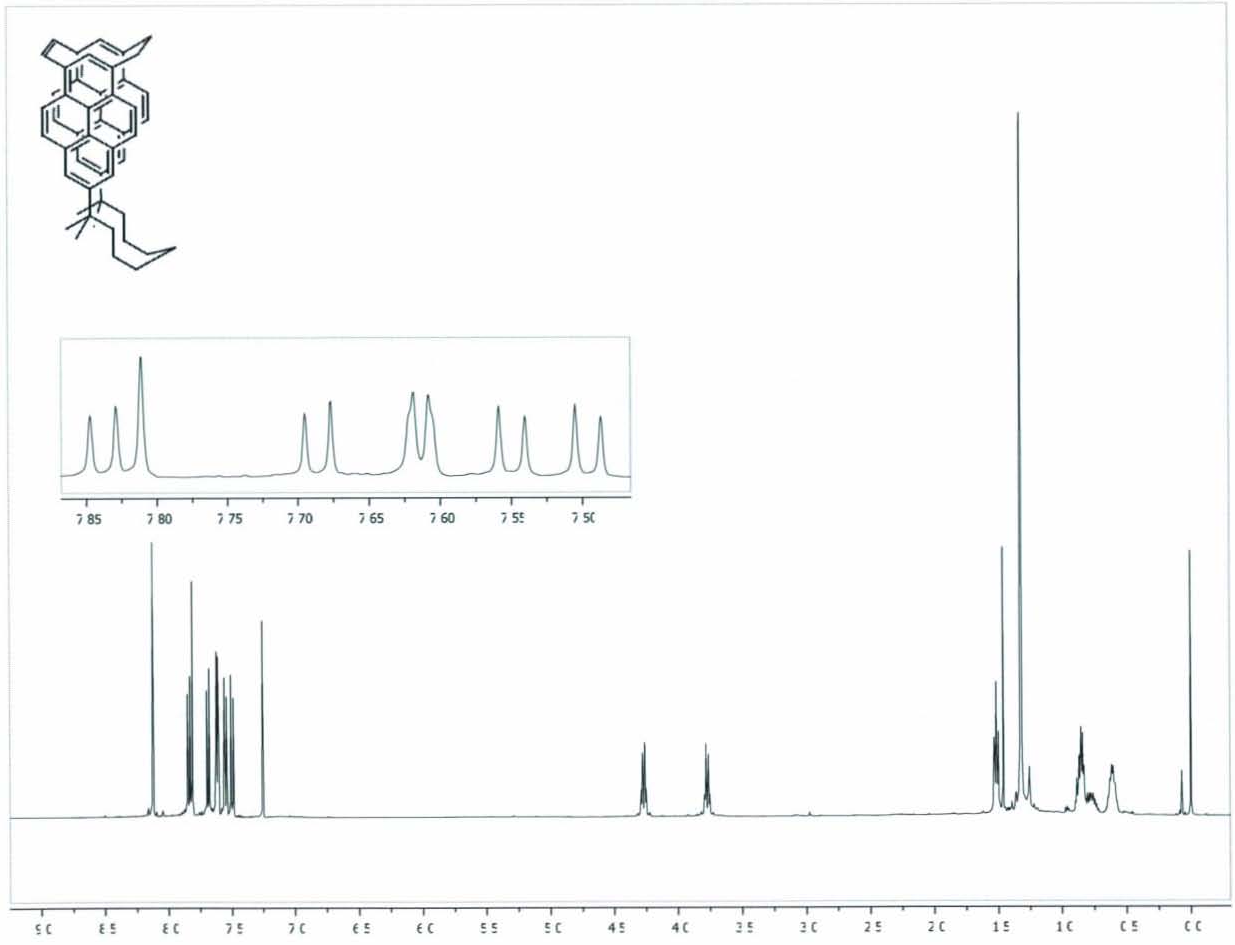
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7.75
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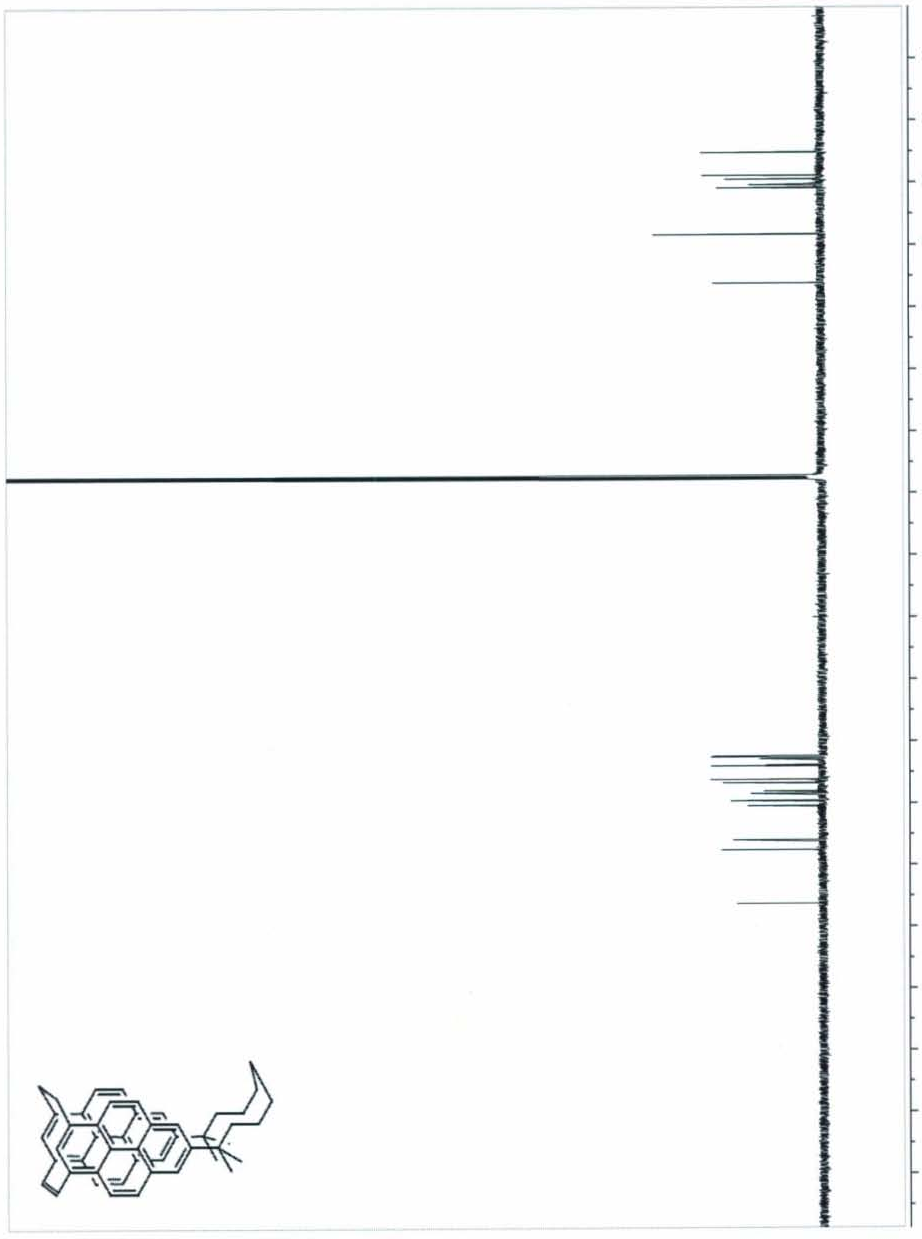
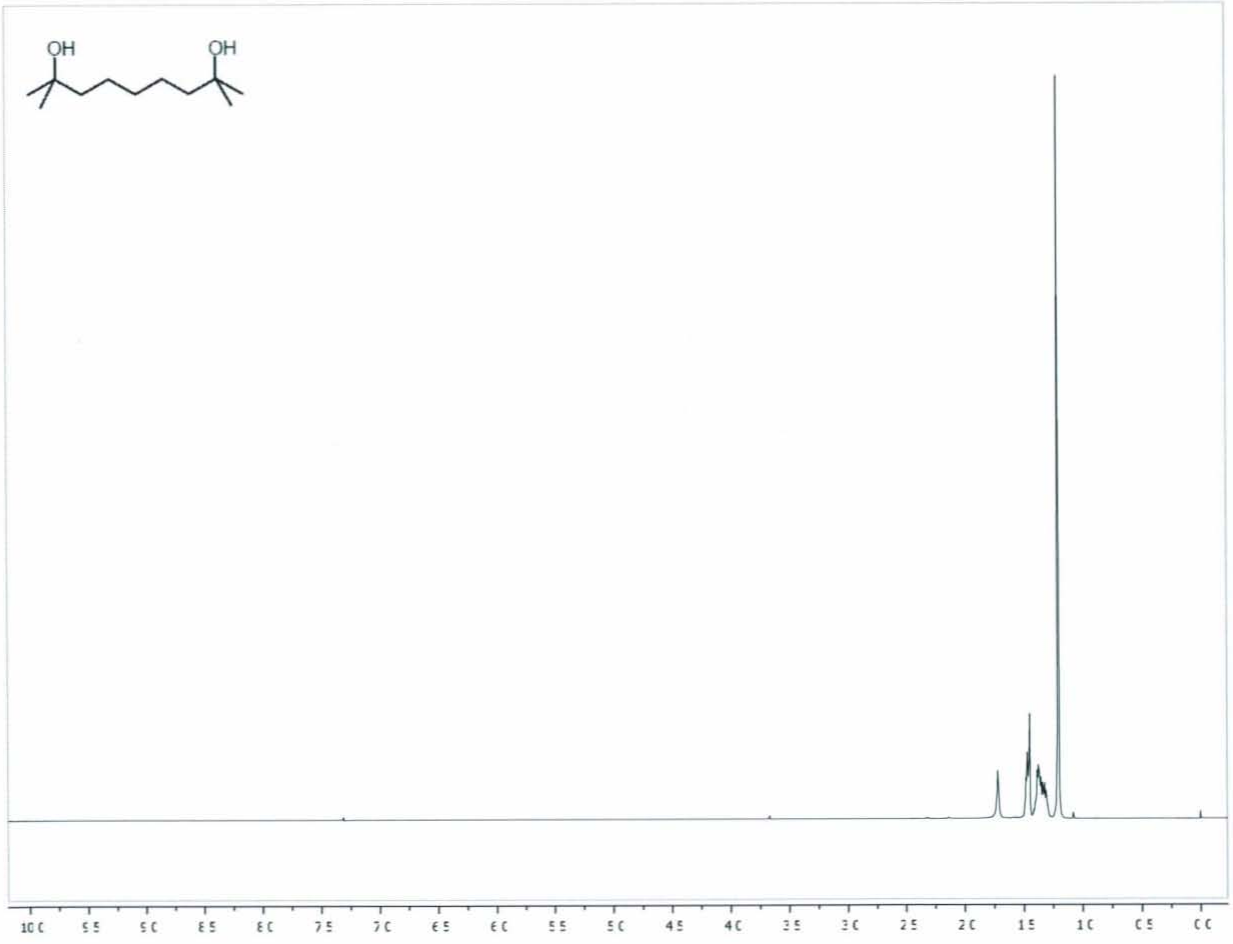
7.60
7.55
7.50

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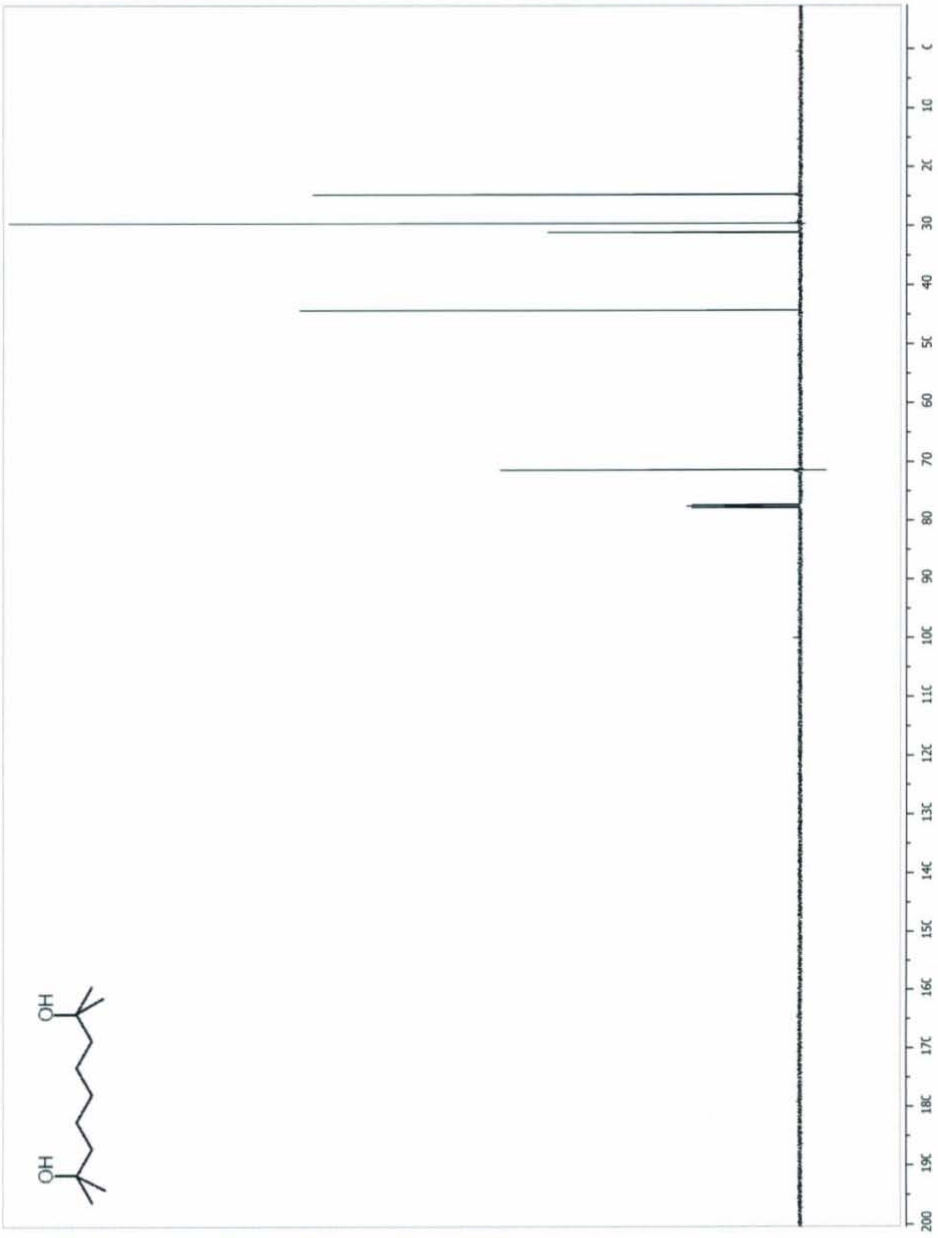
OH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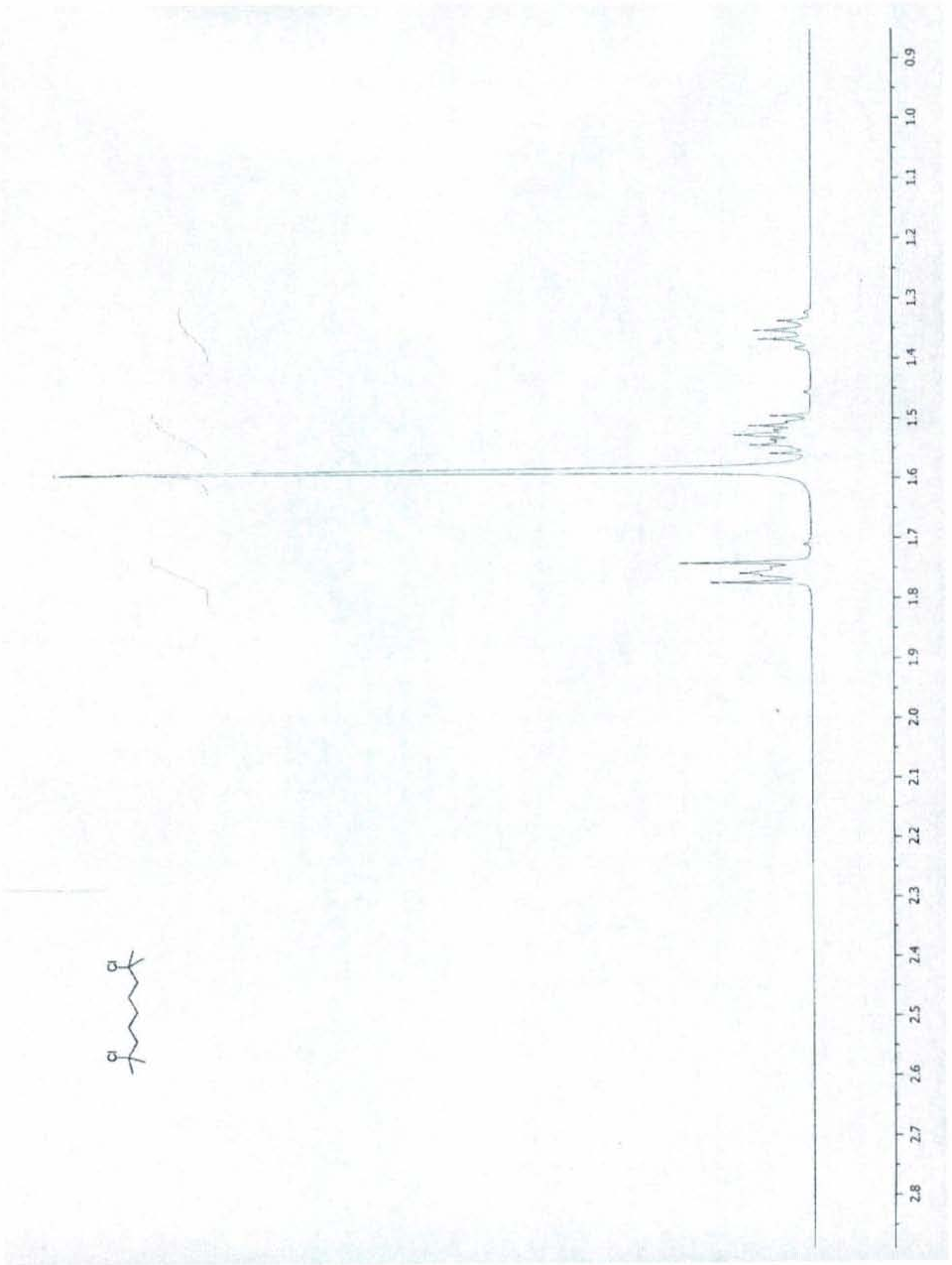
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Cl
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2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
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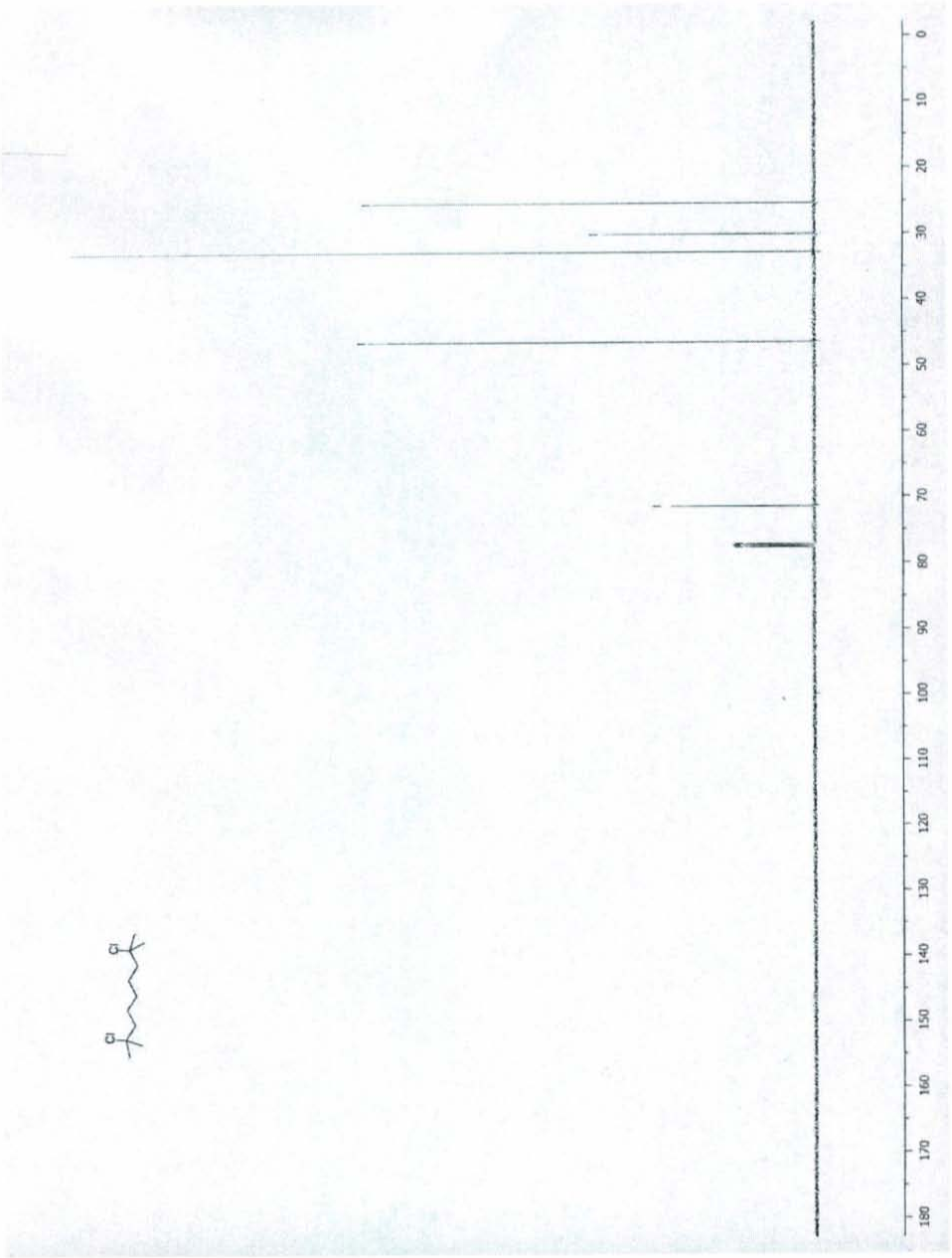
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9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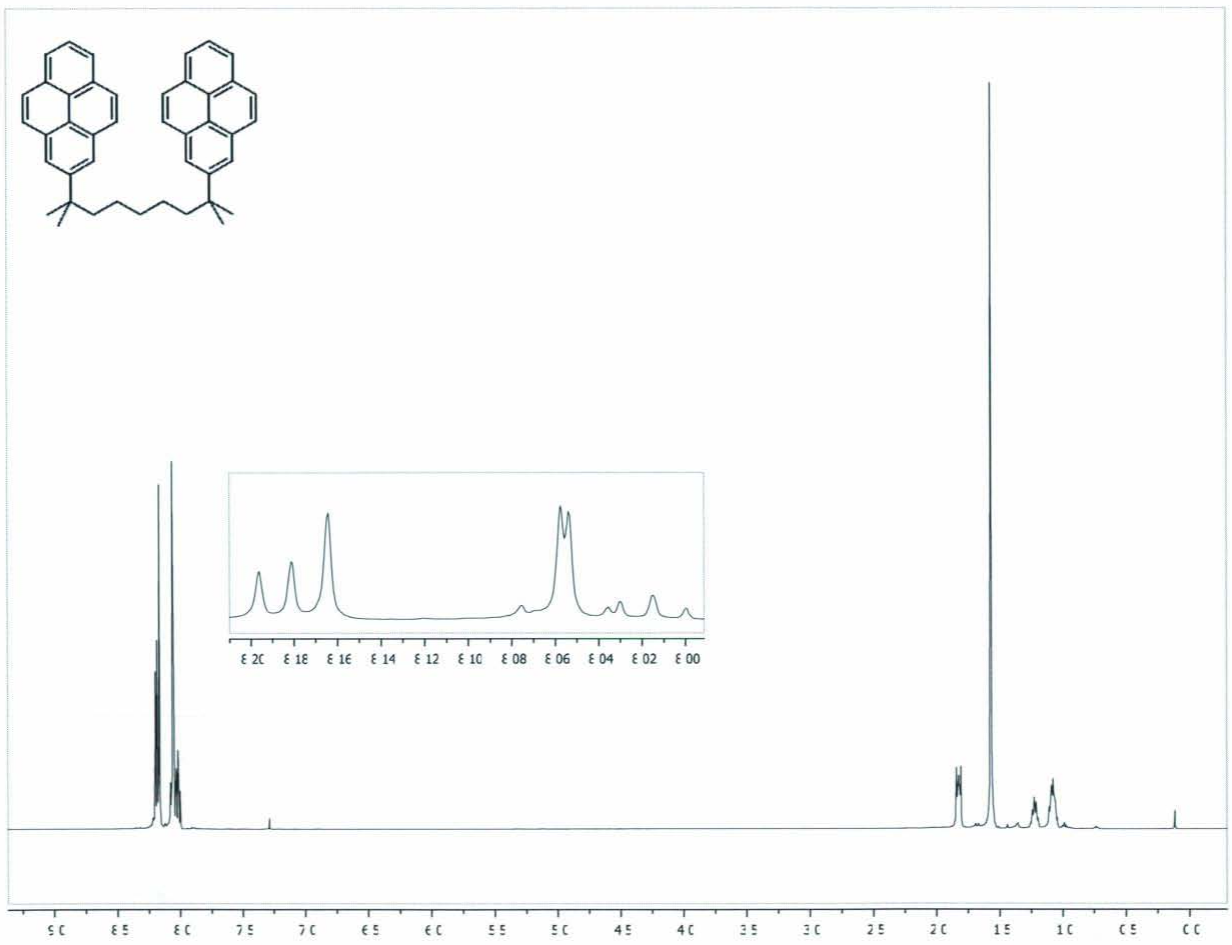

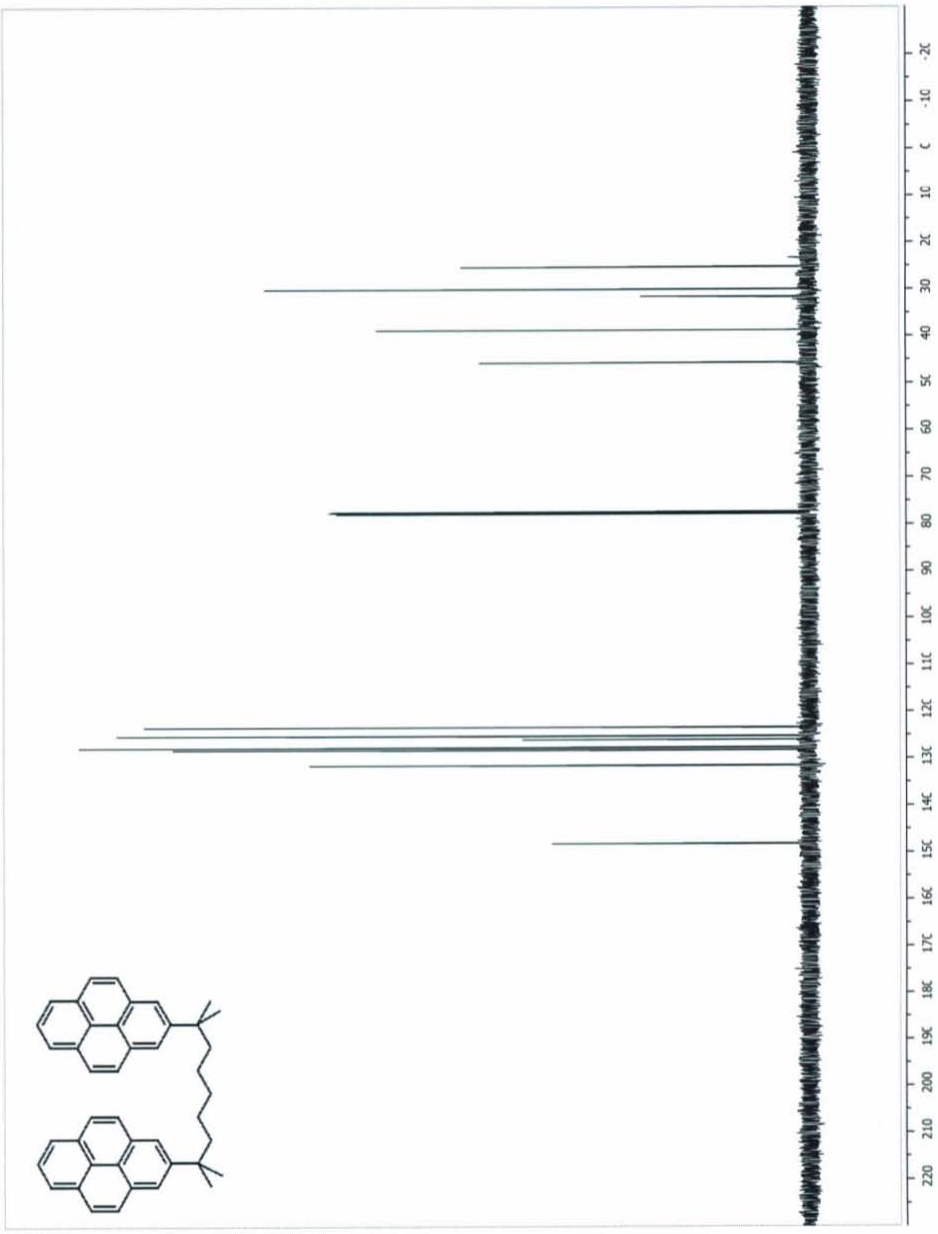

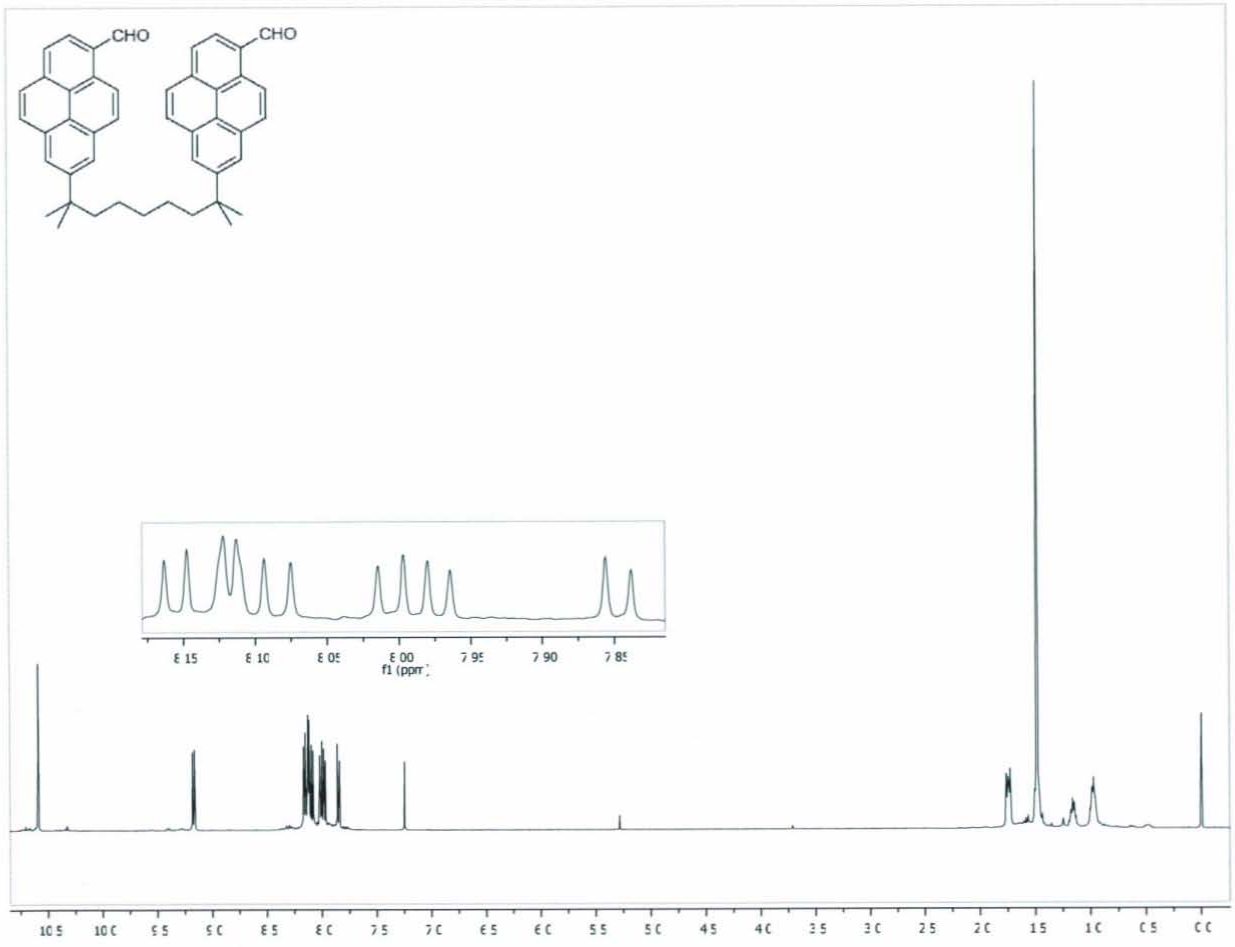
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8.10
8.05
8.00
7.95
7.90
7.85
f1 (ppm)
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10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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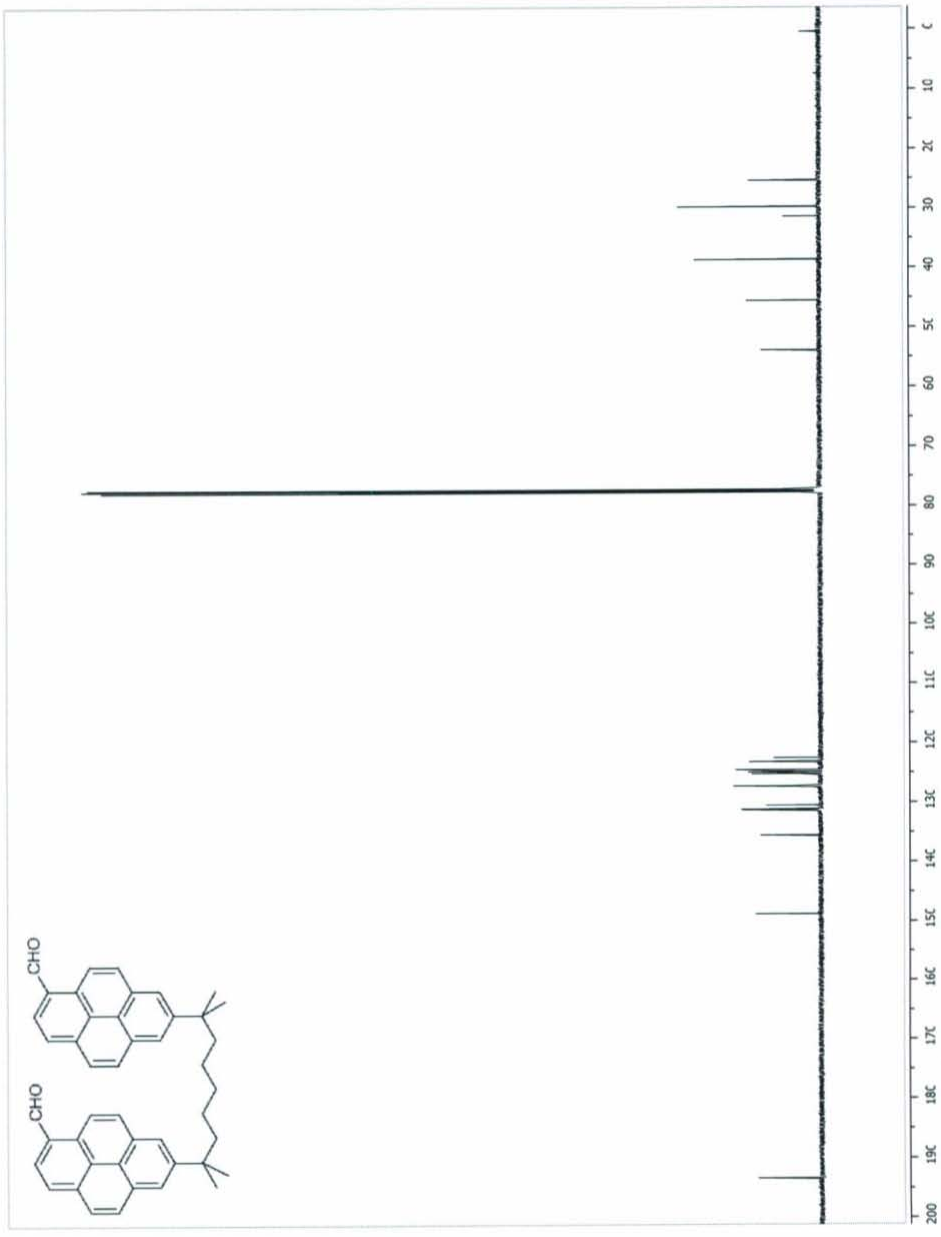
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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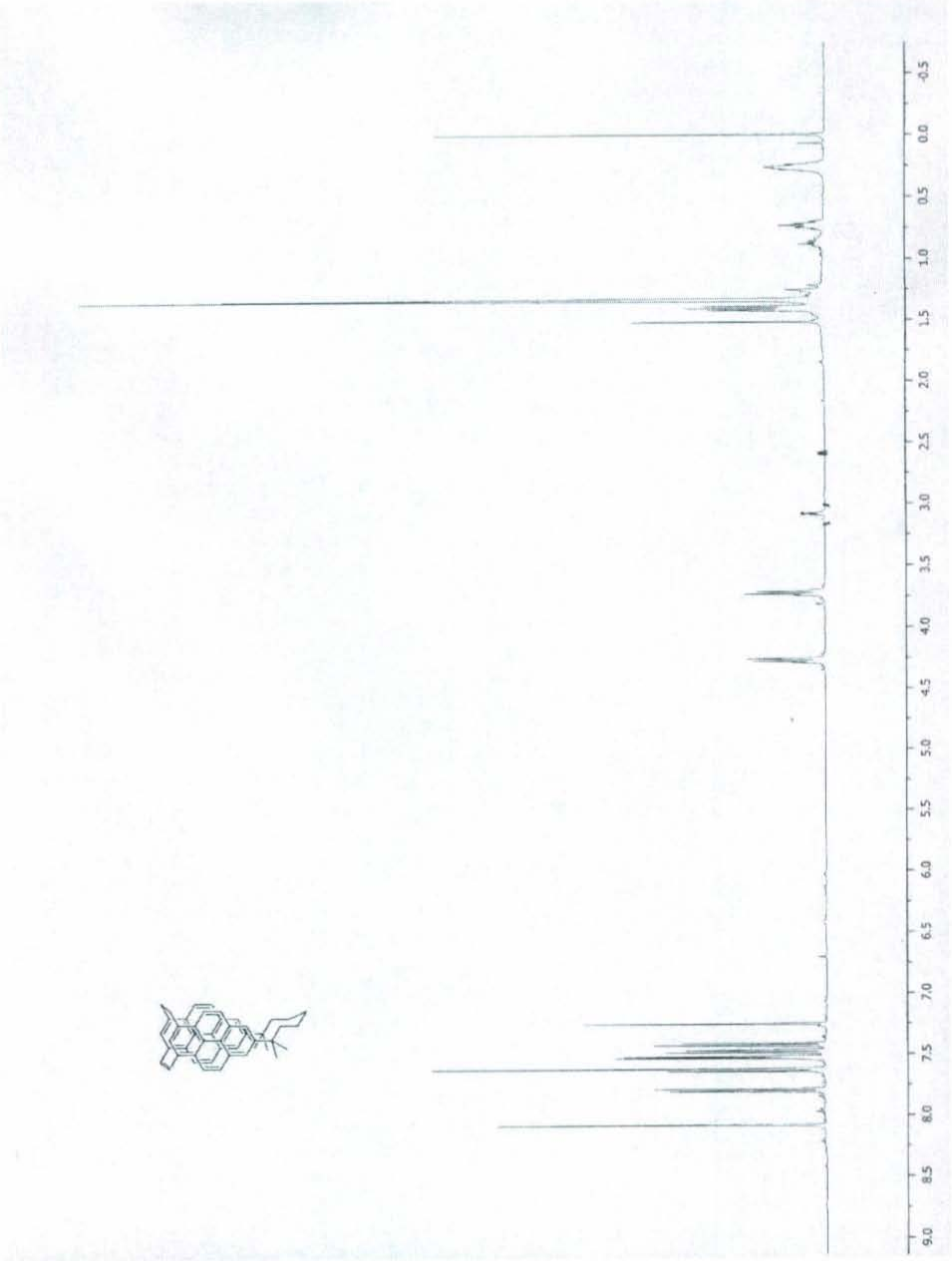
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8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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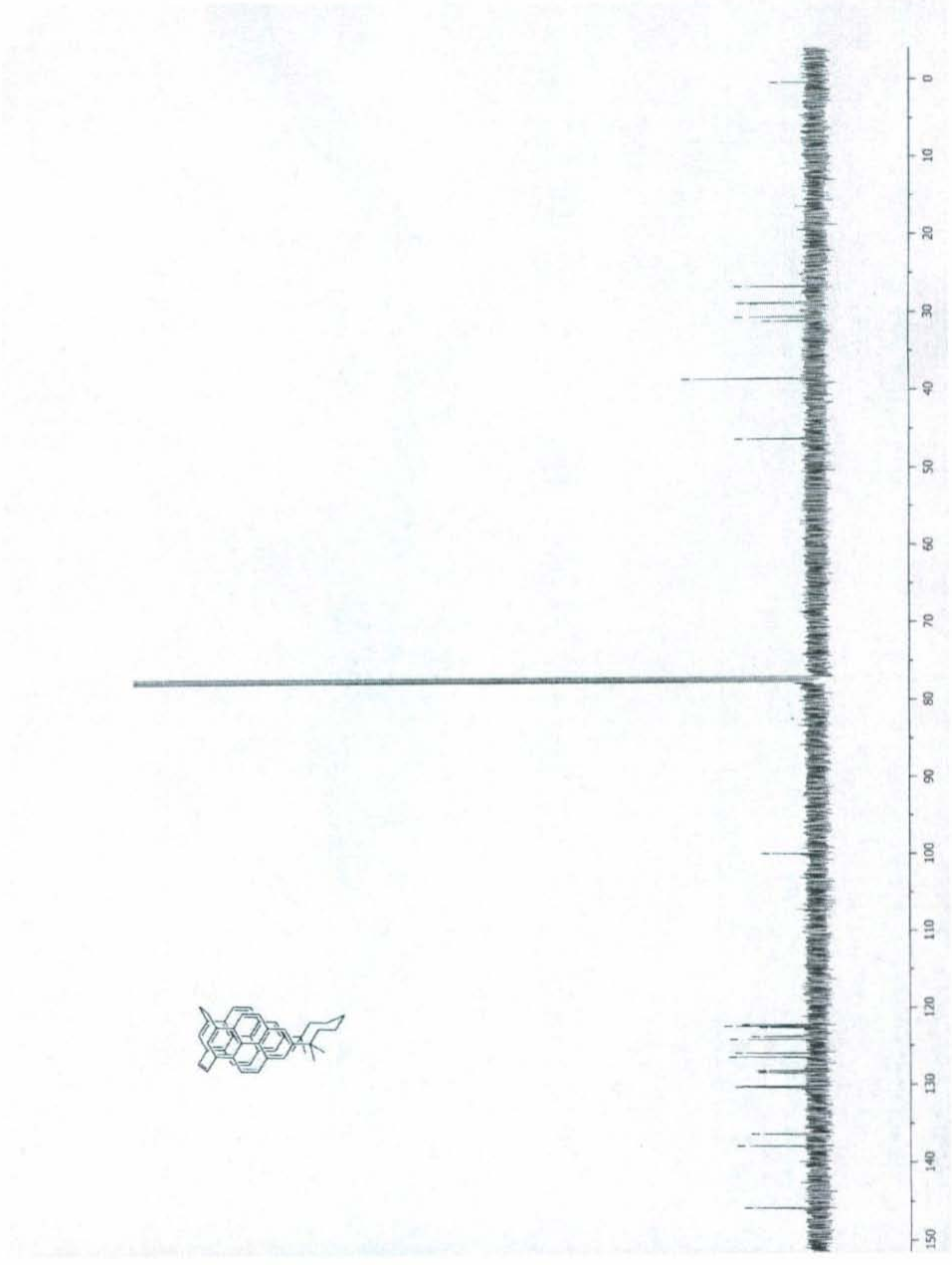
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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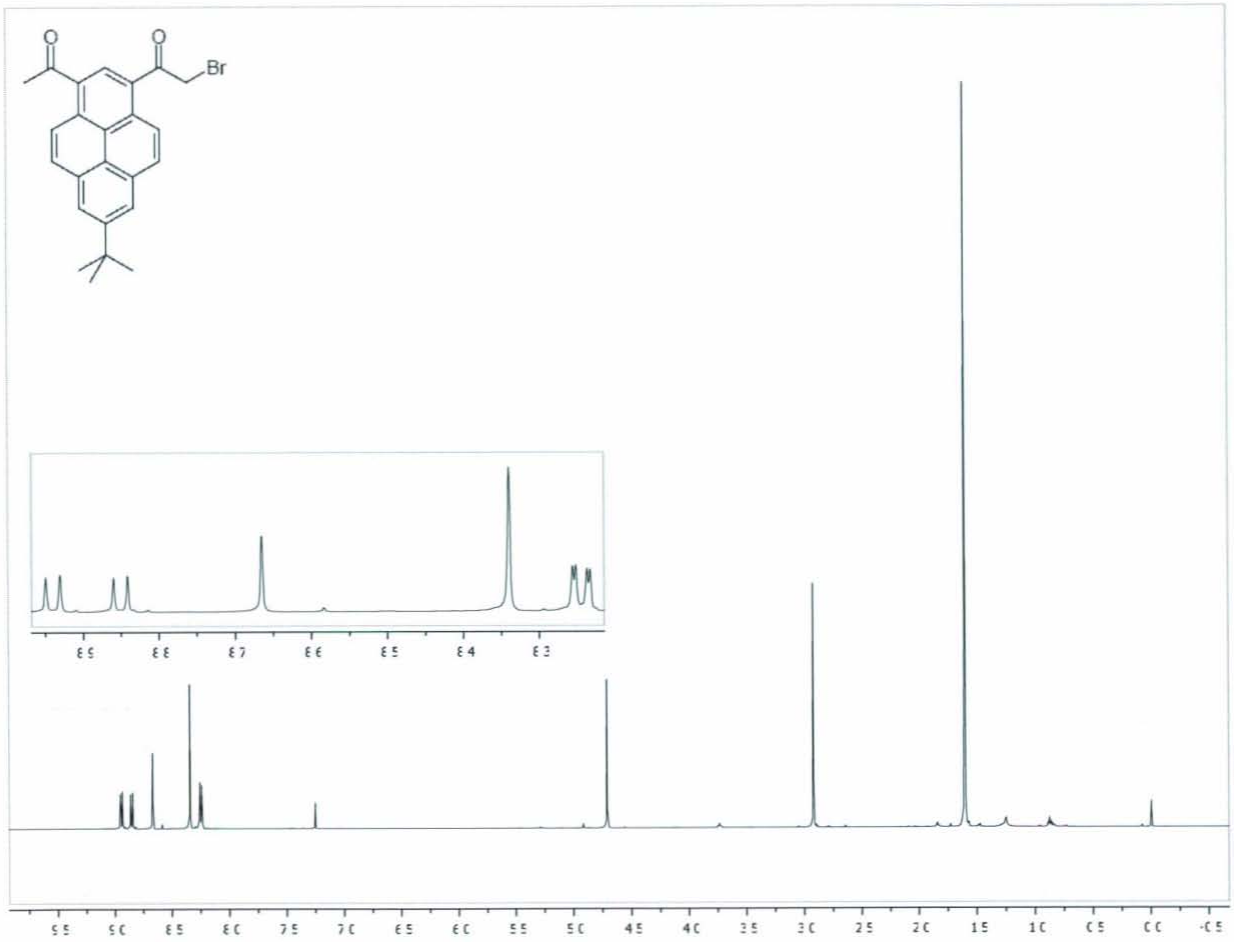
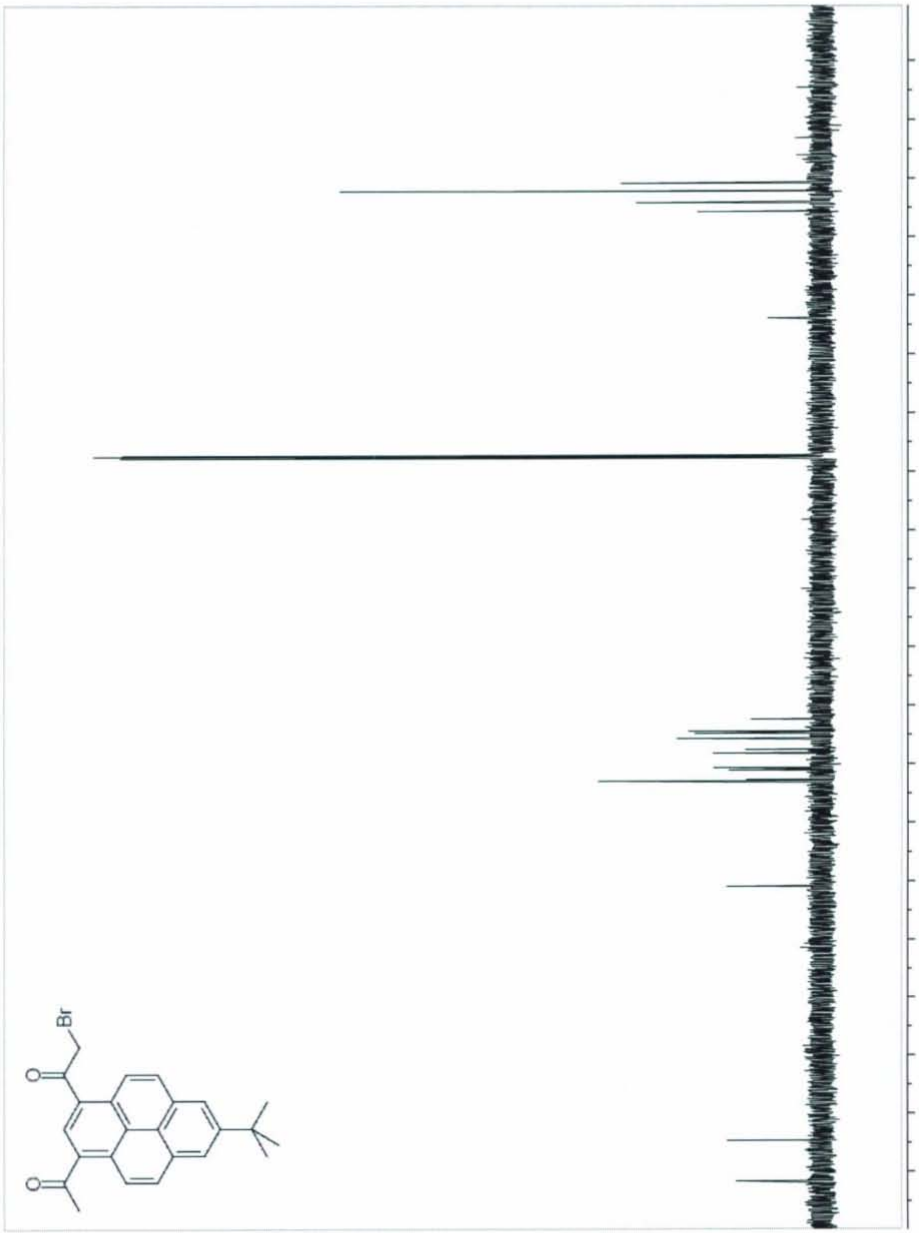

O
O
Br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O
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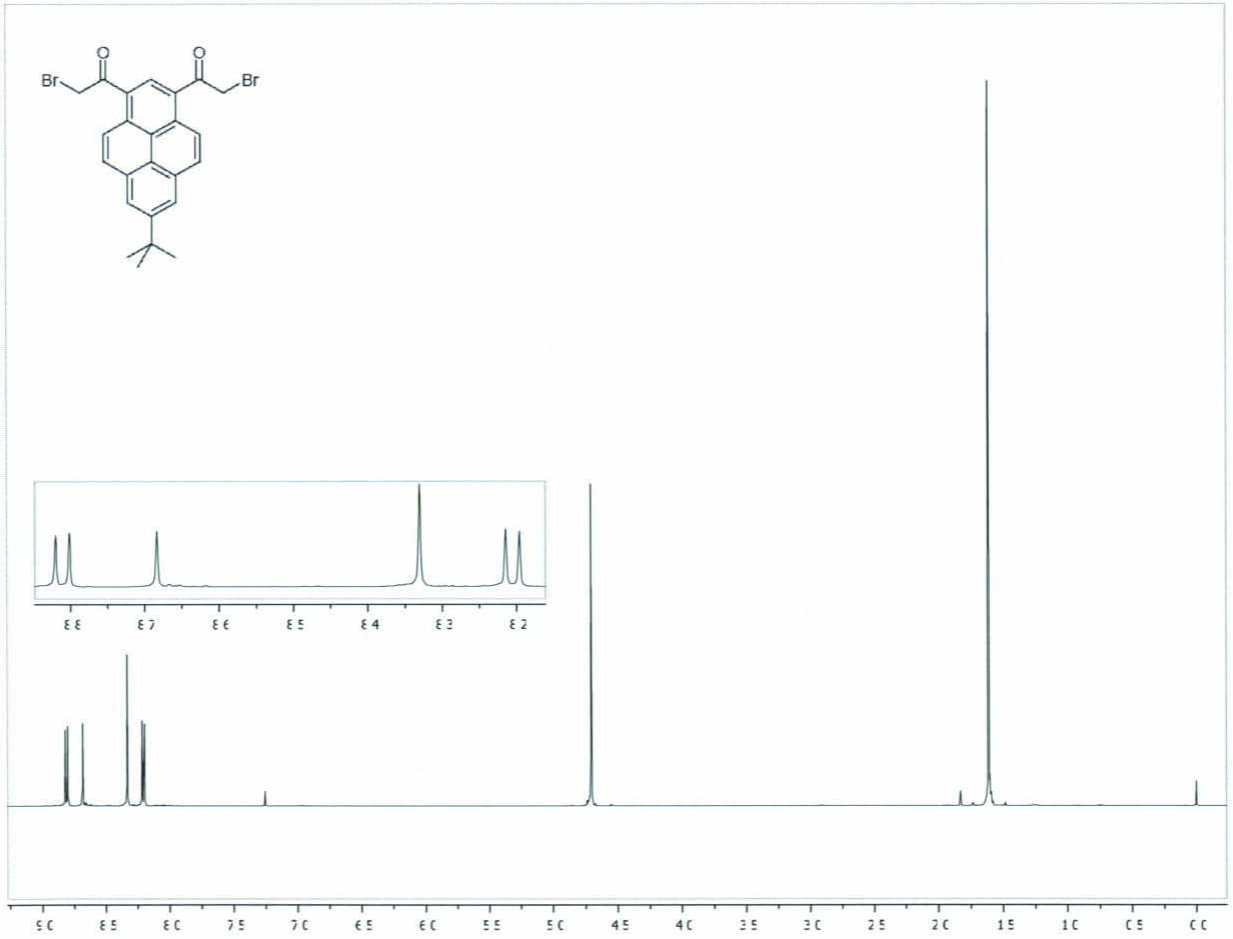
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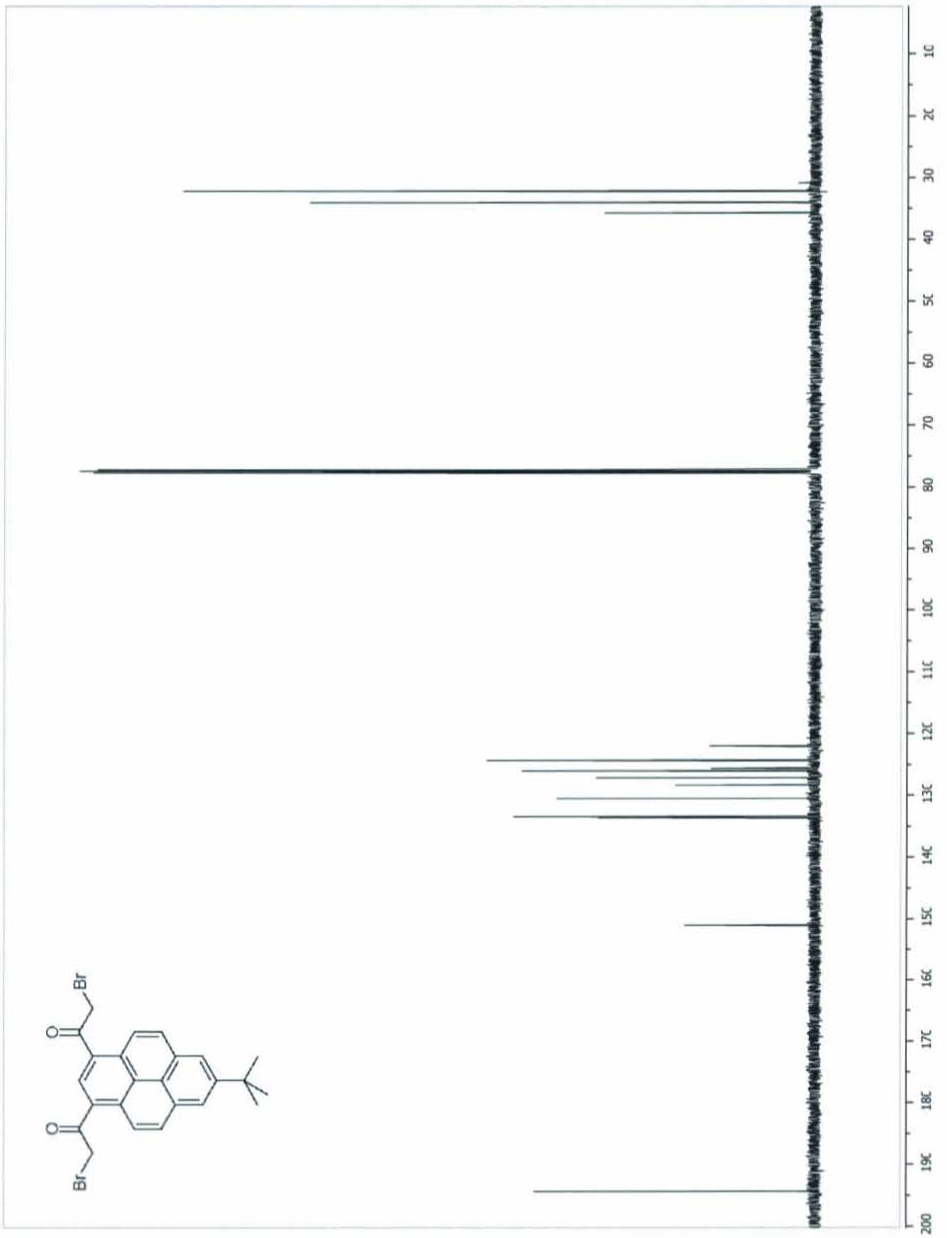
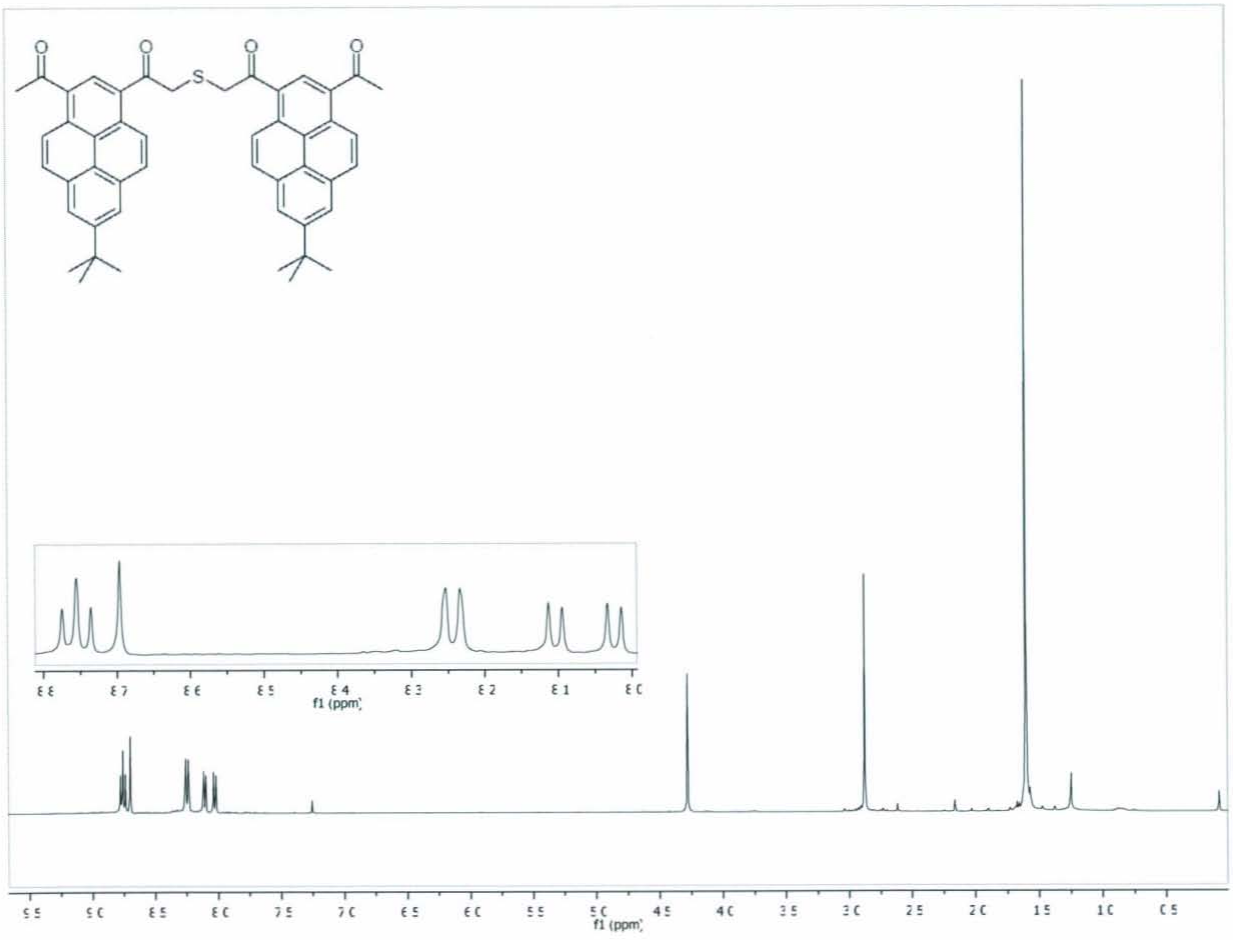
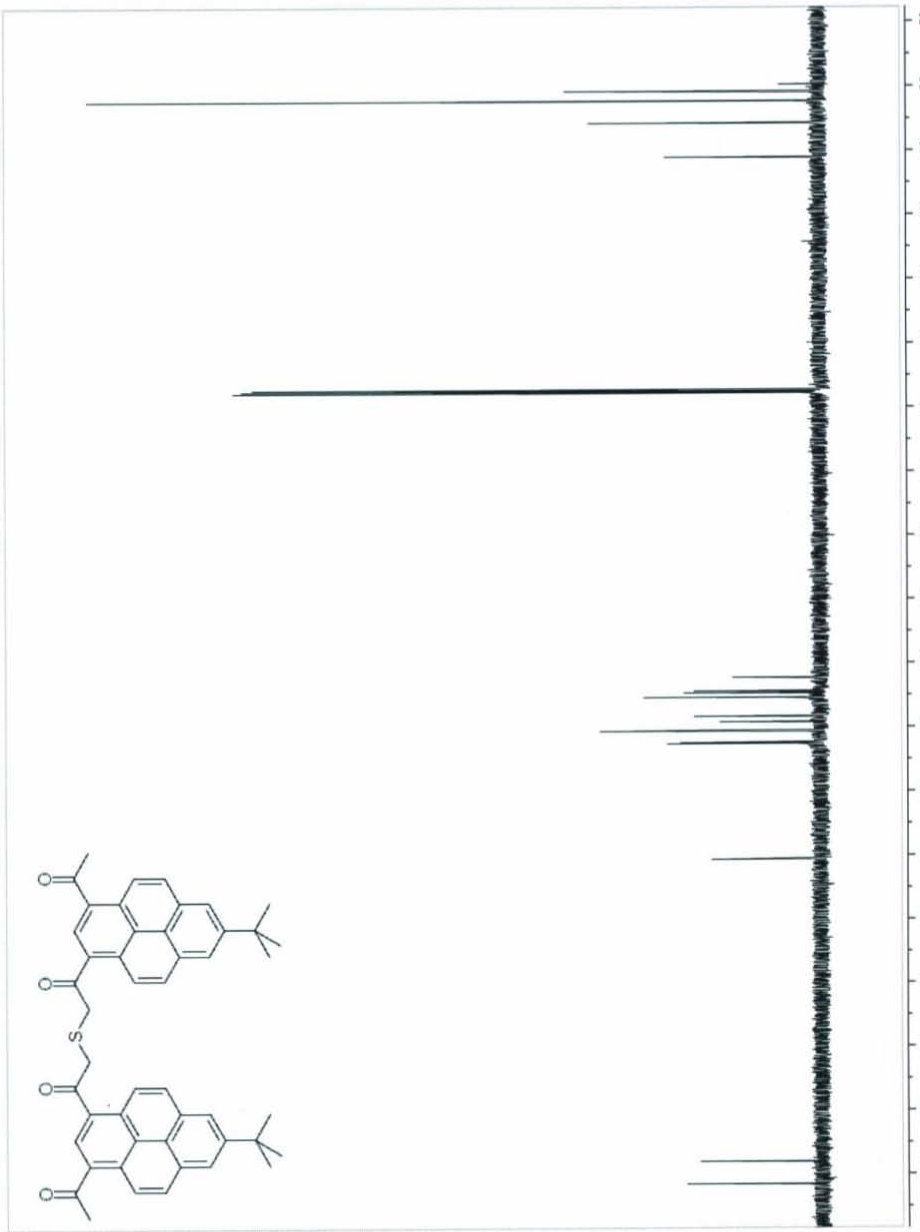
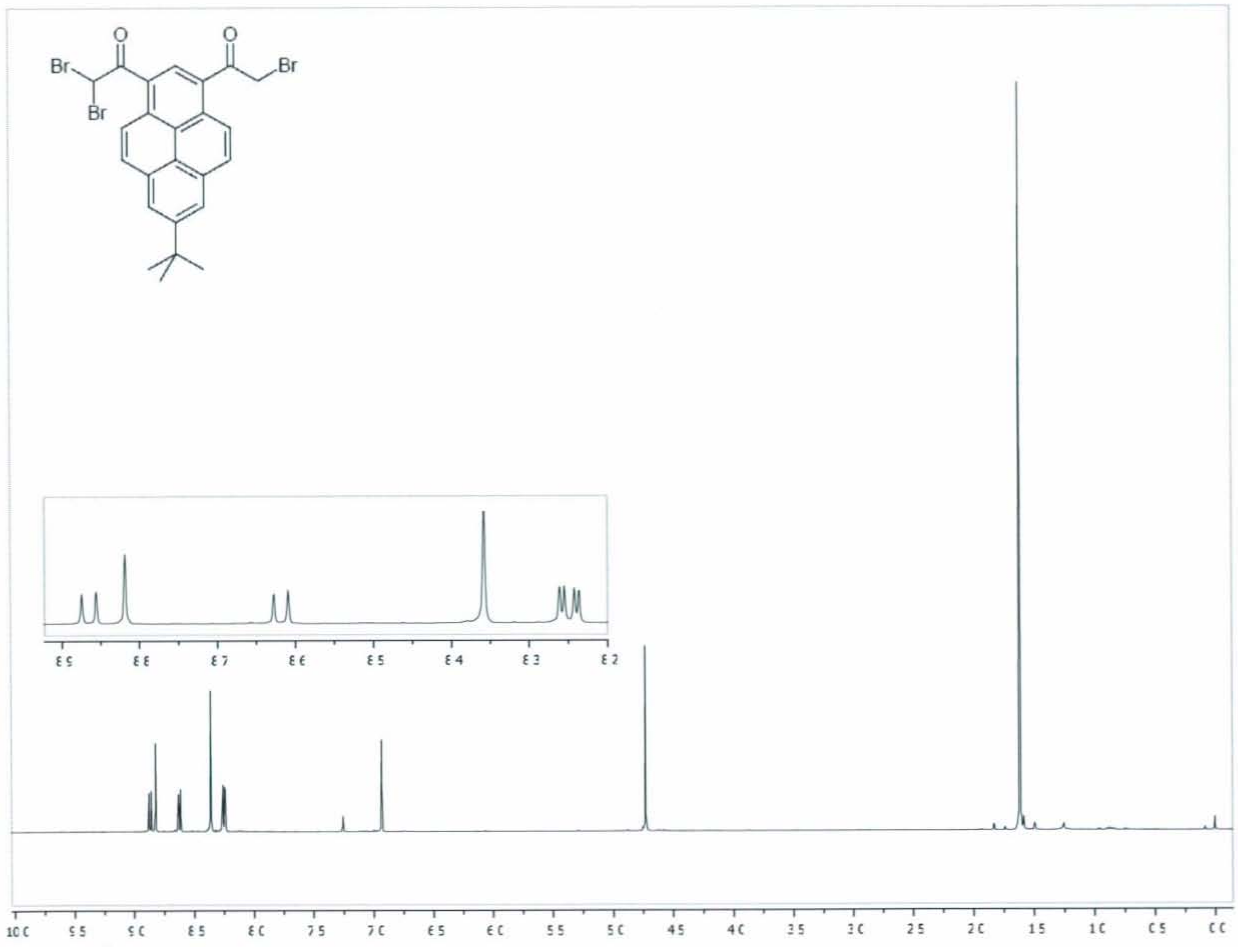
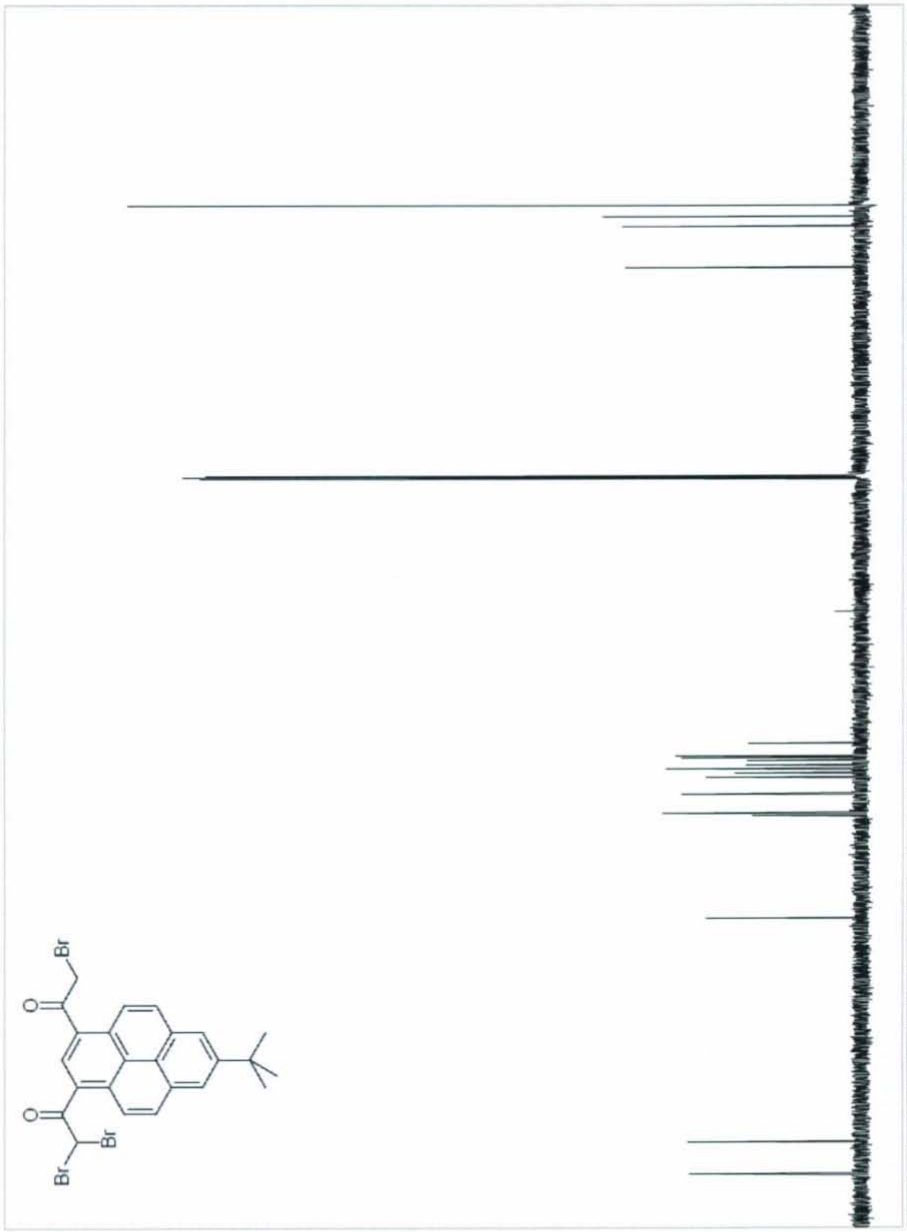
O
O
Br


Br
O
O
Br


O
O
S
O
O
f1 (ppm)
f1 (ppm)



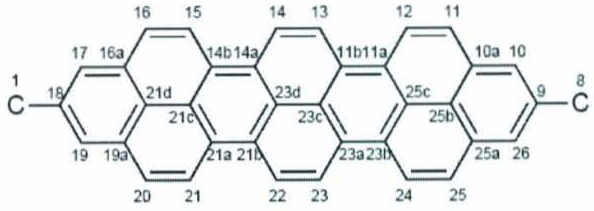

O
O
Br
Br
Br


Br
O
O
Br
Br

Appendix 4

Alternate Views of the Crystal Structure and Absorption and Emission Spectra of Teropyrenophane 2.84, and Miscellaneous Physical Data

1 Interplane Angles in the Teropyrene System of 1,1,8,8-Tetramethyl[8](2,11)teropyrenophane (2.84)



Plane	Atoms
1	C(17) C(18) C(19)
2	C(16a) C(17) C(19) C(19a)
3	C(16a) C(19a) C(21d)
4	C(15) C(16) C(20) C(21)
5	C(14b) C(21a) C(21c)
6	C(14a) C(14b) C(21a) C(21b)
7	C(14a) C(21b) C(23d)
8	C(13) C(14) C(22) C(23)
9	C(11b) C(23a) C(23c)
10	C(11a) C(11b) C(23a) C(23b)
11	C(11a) C(23b) C(25c)
12	C(11) C(12) C(24) C(25)
13	C(10a) C(25a) C(25b)
14	C(10) C(10a) C(25a) C(26)
15	C(9) C(10) C(26)

Interplane Angle	Molecule A	Molecule B
C(1)-1 (β_1)	5.24	6.14
1-2	7.28	4.65
2-3	7.87	8.95
3-4	8.91	9.43
4-5	11.15	11.64
5-6	15.27	15.95
6-7	17.55	16.91
7-8	15.67	14.60
8-9	15.12	13.90
9-10	17.03	16.82
10-11	15.27	14.64
11-12	10.32	11.79

12-13	9.08	10.19
13-14	8.61	8.48
14-15	9.44	8.43
C(8)-15 (β_2)	4.69	6.45
1–7 (θ_1)	68.03	67.53
5–11 (θ_2)	95.91	92.82
9–15 (θ_3)	69.75	70.35
1–15 (θ_{tot})	167.57	166.38
$\theta_{tot} + \beta_1 + \beta_2$	178.50	178.97

Angles between planes corresponding to those that are related by the 8-fold symmetry (*i.e.* at 45°) in 2.5 or an (8,8) SWCNT.

1-5	35.21	34.67
2-6	43.20	45.97
3-7	52.88	53.93
4-8	59.64	59.10
5-9	63.61	61.36
6-10	65.36	62.23
7-11	63.09	59.96
8-12	57.74	57.15
9-13	51.70	53.44
10-14	43.28	45.10
11-15	37.45	38.89
Average	52.10	51.97

2. Views of 1,1,8,8-Teramethyl[8](2,11)Teropyrenophane (2.84) in the Crystal

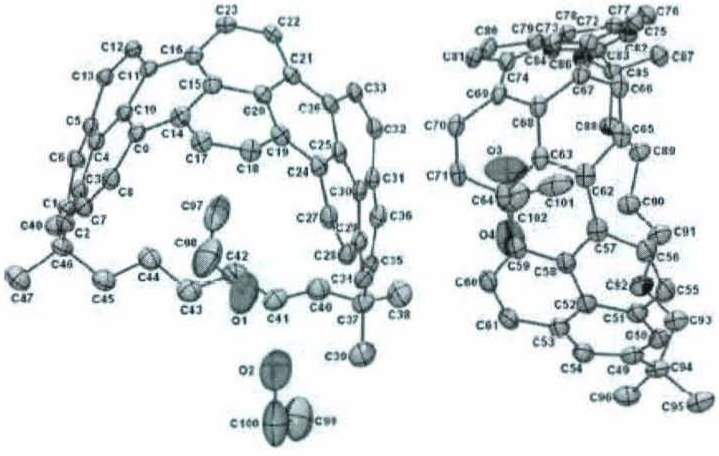


FIGURE A1: Asymmetric unit of (**2.84**) with crystallographic numbering; hydrogen atoms have been omitted for clarity

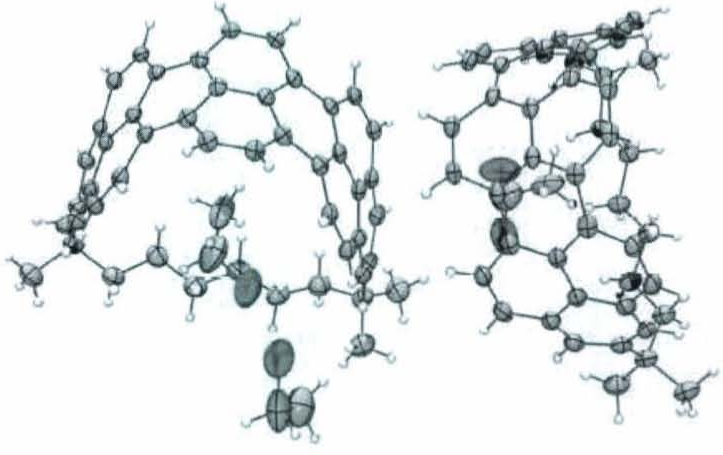


FIGURE A2: Asymmetric unit of (**2.84**) with hydrogen atoms; 50% probability thermal ellipsoids

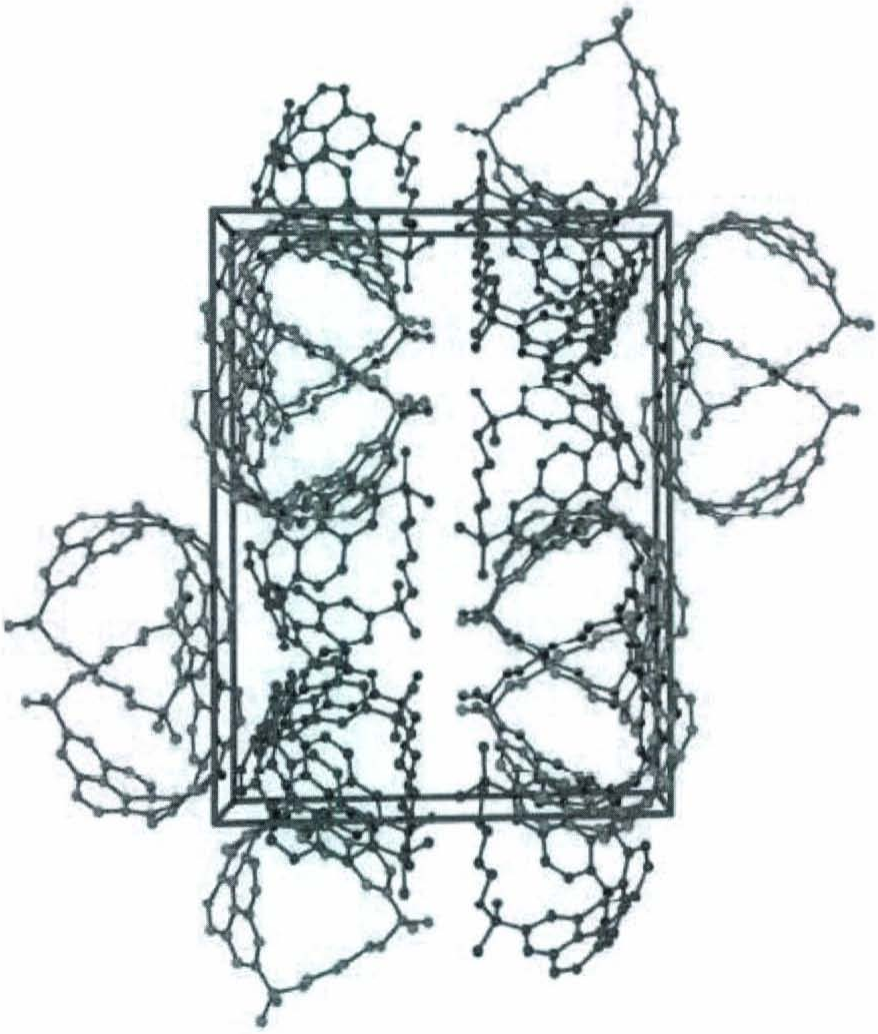


FIGURE A3: Ball-and-stick packing diagram of Molecule A (blue) and Molecule B (red); solvent molecules and hydrogen atoms have been omitted for clarity

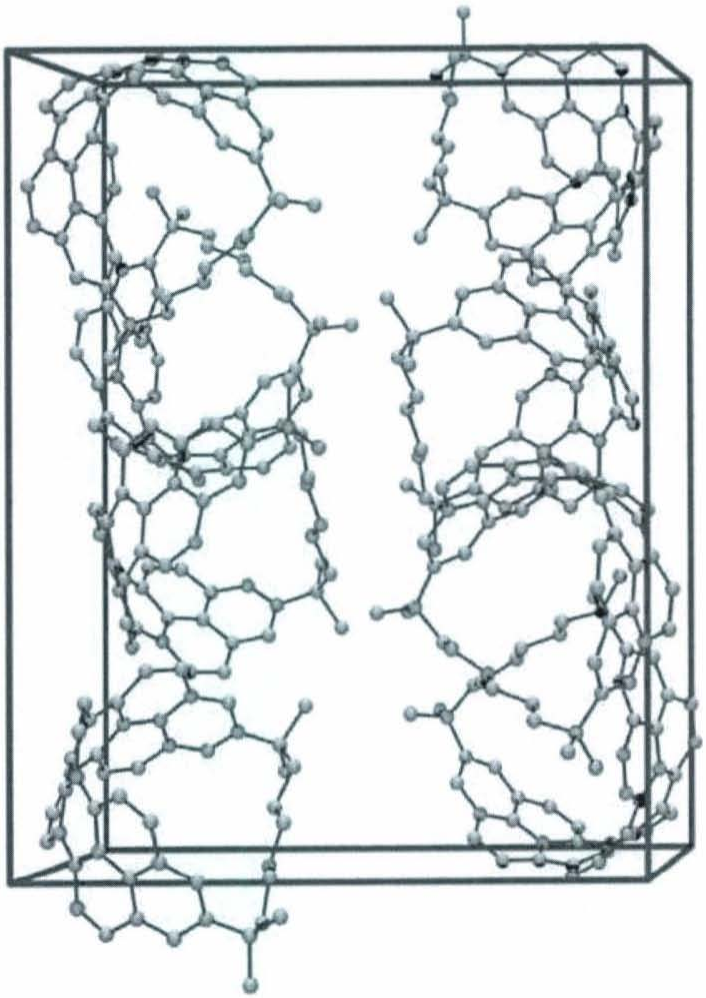


FIGURE A4: Ball-and-stick depiction of the unit cell, viewed normal to the *c*-axis; solvent molecules and hydrogen atoms have been omitted for clarity

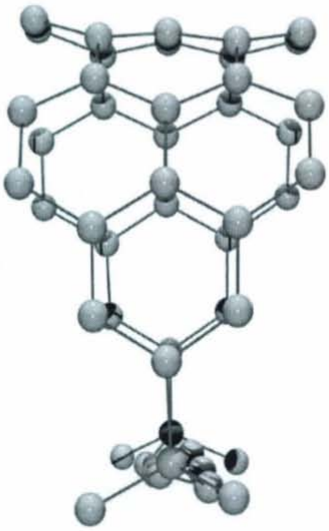


FIGURE A5: Side-view of Molecule B (ball-and-stick depiction)

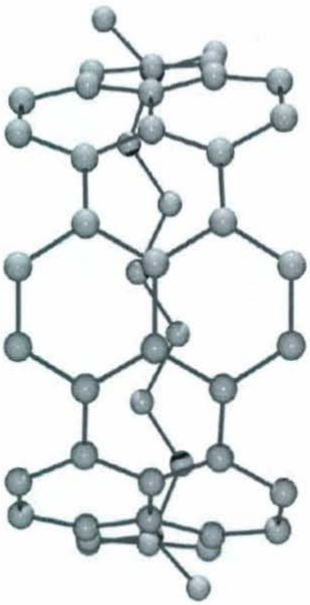


FIGURE A6: Top-view of Molecule B (ball-and-stick depiction)

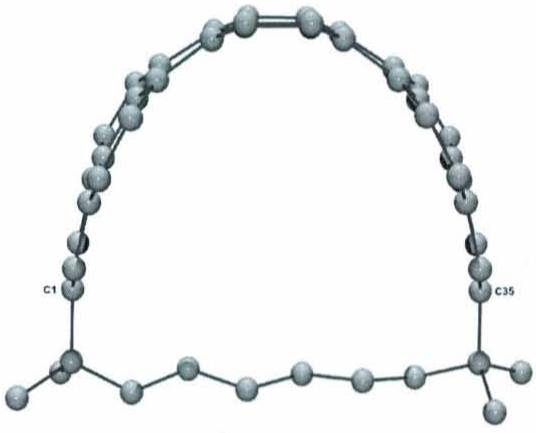


FIGURE A7: Front-view of Molecule B (ball-and-stick depiction)

3. Photophysical Data of 1,1,8,8-Tetramethyl[8](2,11)teropyrenophane (2.84)

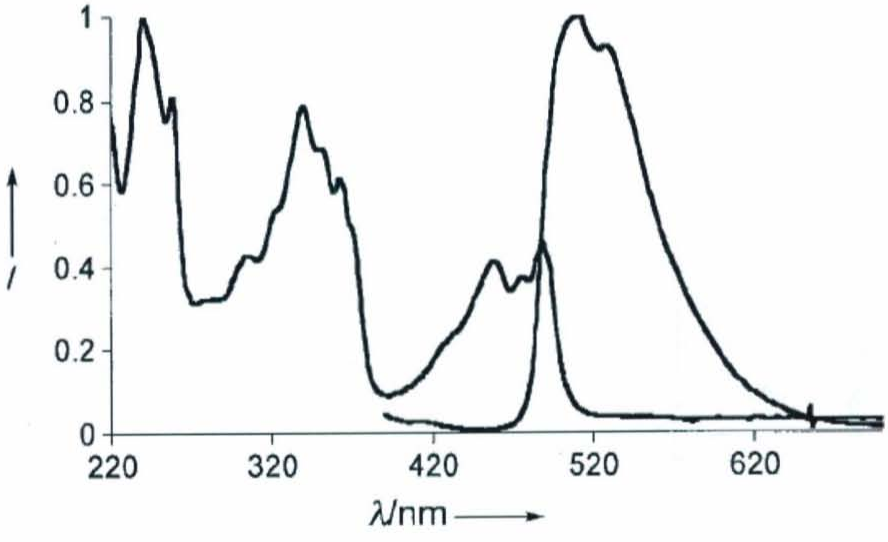


FIGURE A8: Normalized absorption and emission spectra of **2.84** (9.8×10^{-6} M in acetonitrile)

4. VTNMR Spectra of 13,23-Diformyl-1,1,8,8-tetramethyl[8.2](7,1)pyrenophane (4.22)

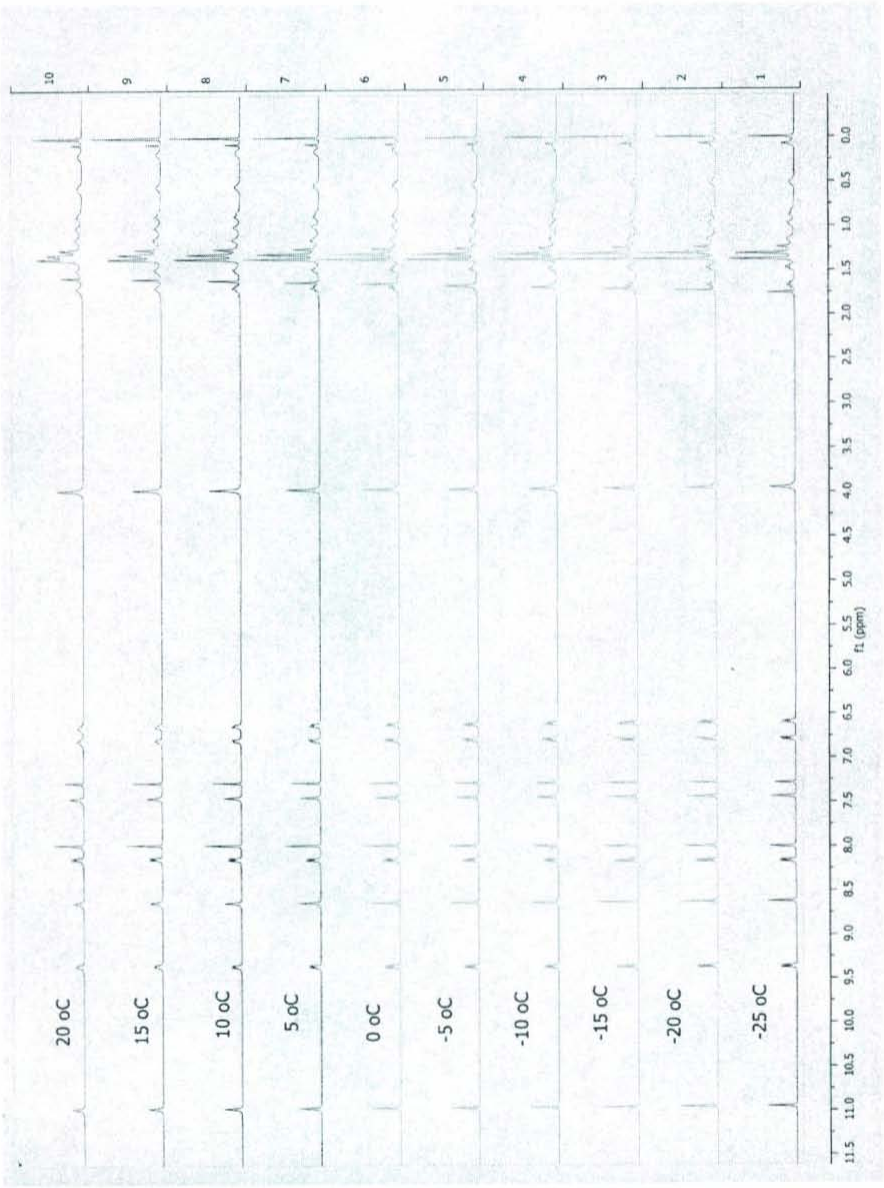


FIGURE A9: VTNMR spectra of **4.22** in $CDCl_3$ (T = -25 °C to 20 °C)

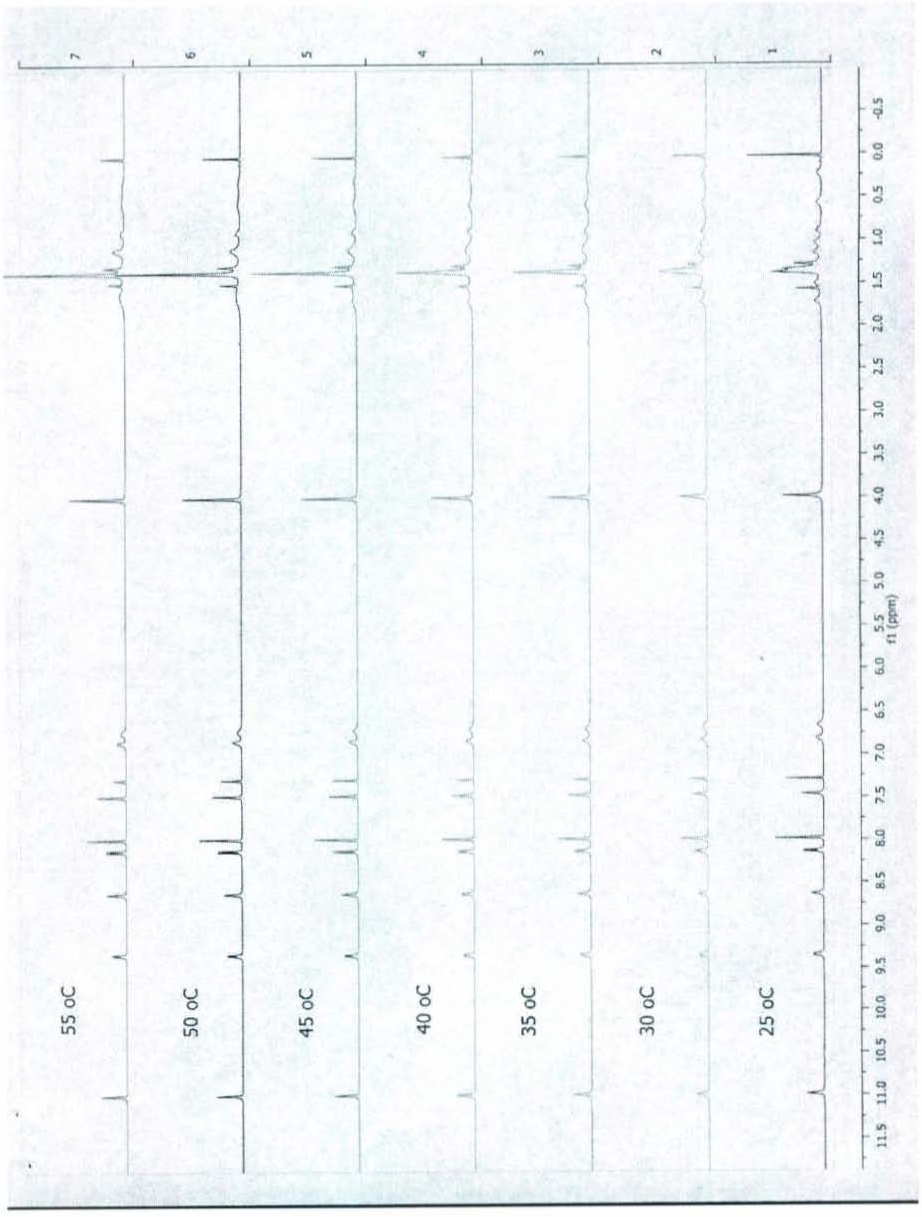


FIGURE A10: VTNMR spectra of **4.22** in $CDCl_3$ (T = 25 °C to 55 °C)

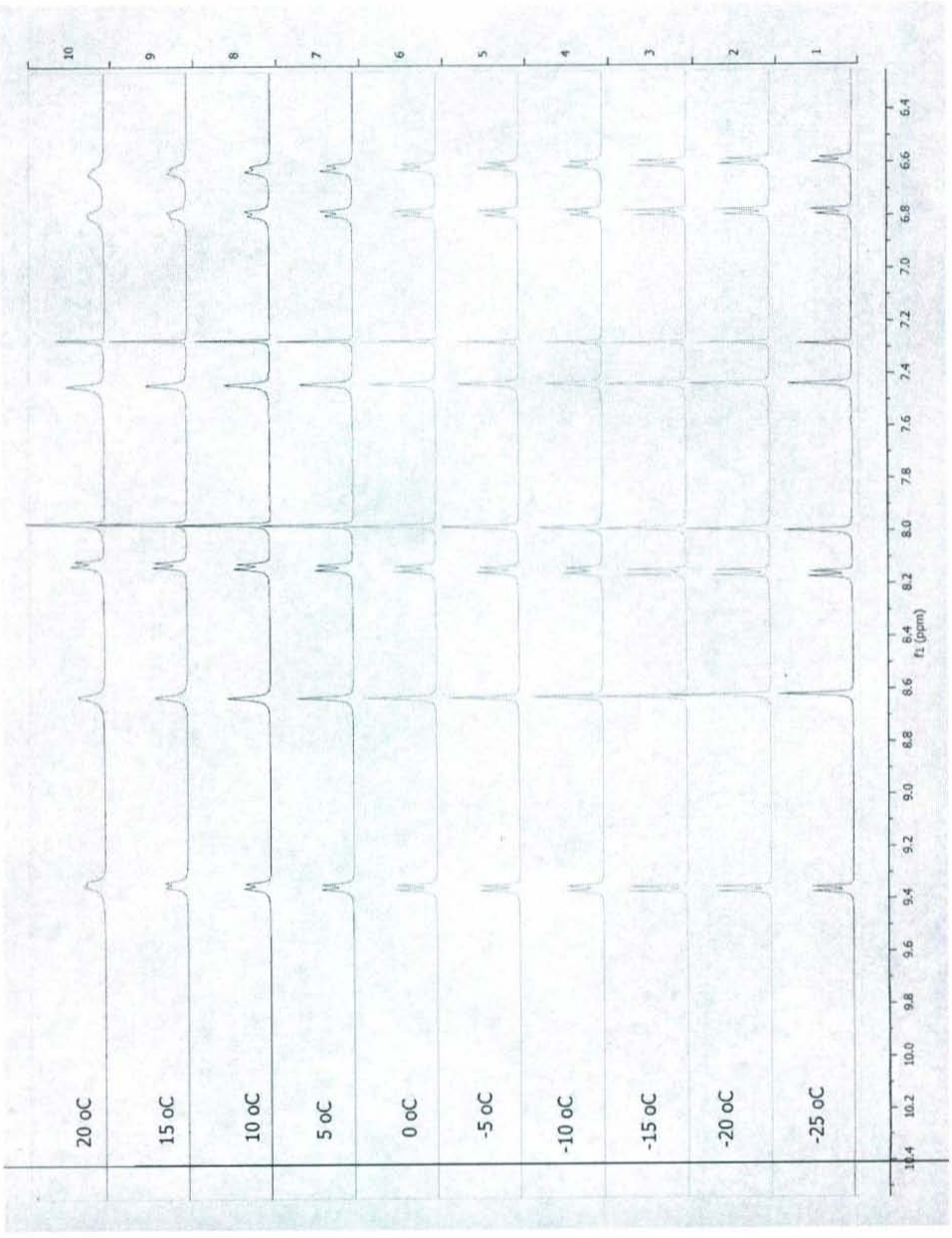


FIGURE A11: VTNMR spectra of **4.22** in $CDCl_3$ (T = -25 °C to 20 °C; 6.4 to 10.4 ppm)

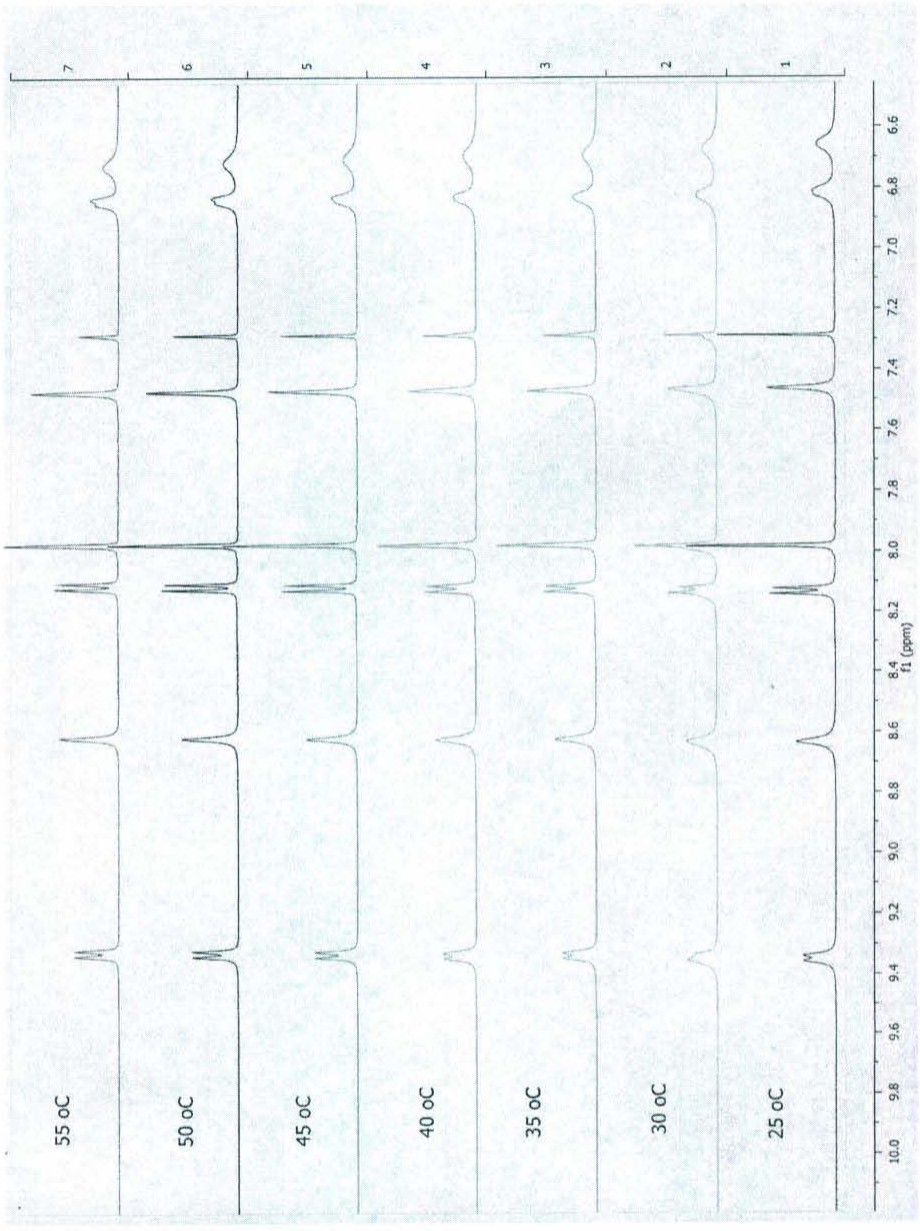


FIGURE A12: VTNMR spectra of **4.22** in $CDCl_3$ (T = 25 °C to 55 °C; 6.4 to 10.4 ppm)

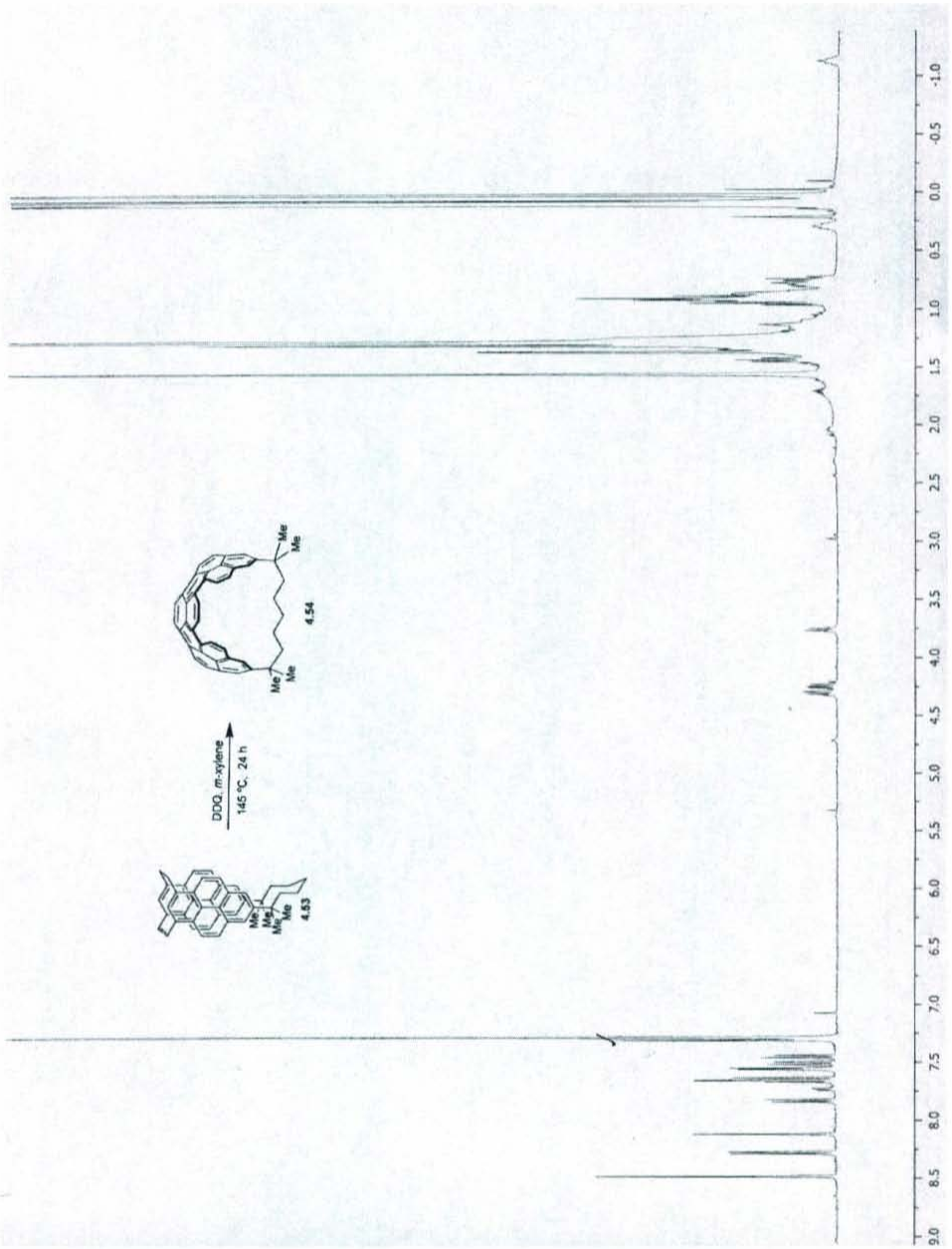


FIGURE A13: ^{1}H NMR of teropyrenophane **4.54** and **4.53** as 1:1 mixtur