ATTEMPTED SYNTHESIS OF AROMATIC BELTS

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ATTEMPTED SYNTHESIS OF AROMATIC BELTS

By

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Abstract

In this thesis, the synthesis of a molecular board, which is a potential precursor to some aromatic belts, will be described.

The first synthetic approach to the molecular board in which IEDDA (inverse electron demand Diels-Alder) chemistry is involved will be discussed in Chapter 2. This approach did not lead to the formation of the molecular board due to the failure of the formation of the C-C bond between benzylic carbons. Direct alkylation and variations of Wittig reaction were employed in this approach.

The second synthetic approach that involved Sonogashira coupling successfully constructed the main body of the molecular board. A Pd-catalyzed intramolecular arylation, which is the key step in this synthesis, gave rise to the molecular board.

Further investigation of converting this molecular board into corresponding aromatic belts has not met with the success due to the serious solubility problem. Future work should be directed into this concern.

Acknowledgements

First, I would like to thank my supervisor Dr. Graham J. Bodwell for giving me the opportunity to join the project, and for his valuable advice, patient guidance and enthusiastic encouragement during these 2 years.

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Finally, I would like to thank my parents, my wife and friends.

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g

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List of Abbreviations and Symbols Used

Abs	Absolute (with ethanol)
Ac	acetyl
Borch reagent	dimethoxycarbonium tetrafluoroborate
b.p.	boiling point
Bu	butyl
cat.	catalytic
δ	chemical shift in ppm downfield from tetramethylsilane
Δ	heat
d	deuterium (in structural formula)
d	doublet (in NMR)
dd	doublet of doublets (in NMR)
DBU	1.8-diazobicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-4,5-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DMA	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
Et	ethyl
FVP	flash vacuum pyrolysis
h	hour(s)
hv	light
Hz	hertz

J	coupling constant (Hz)
kcal	kilocalorie(s)
LDA	lithium diisopropylamide
lit.	literature
m	multiplet (in NMR)
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MHz	megahertz
Min	minute(s)
mp	melting point
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance (spectroscopy)
Ph	phenyl
pyr	pyridine
q	quartet (in NMR)
rt	room temperature
s	singlet (in NMR)
t	triplet (in NMR)
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMS	tetramethylsilane (in NMR)
TMS	trimethylsilyl (in structures)
Ts	*p*-toluenesulfonyl
UV	ultraviolet (spectroscopy)
VID	valence isomerization – dehydrogenation

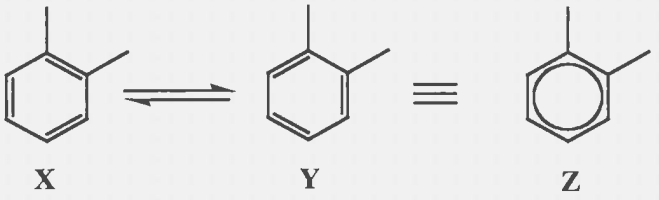
Chapter 1

Introduction

1.1 Benzene and Aromaticity

The discovery of benzene dates back to June 16, 1825 and the honour belonged to Michael Faraday, who was a laboratory assistant to Prof. Humphry Davy at the Royal Institute at the time. The paper he submitted to the Royal Society about this discovery was titled "On New Compounds of Carbon and Hydrogen, and on Certain Other Products Obtained During the Decomposition of Oil by Heat."[1, 2] In this paper, he described the isolation of a new compound, which is now known as benzene, and reported its density and melting point. Measured with the wrong atomic weight values, the empirical formula of this new compound was determined to be C_2H by Faraday. Therefore, it was named "Bicarburet of Hydrogen." By the 1860s, the correct formula of benzene, C_6H_6, was established.

However, the structure of C_6H_6 was still unclear. In 1865, inspired by a dream in which he saw a snake eating its own tail, Friederich August Kekulé proposed the now familiar cyclohexatriene structure for benzene **1**[3]. This proposal eventually gave a perfect explanation as to the question of why monosubstituted benzenes such as toluene have only one structural isomer, but disubstituted benzenes, such as xylenes, have three structural isomers (ortho, meta and para) (Scheme 1.01). Since the original Kekulé proposal implied four structural isomers (including 2 distant ortho isomers **X** and **Y**), Kekulé proposed a "mechanical motion" or oscillation of the double bonds around the ring, thereby rendering the two 1,2-disubstituted structures equivalent (i.e. **Z**). Other proposed structures for benzene are shown in Figure 1.01.



Scheme 1.01 *o*-Xylene

Figure 1.01 Proposed benzene structures

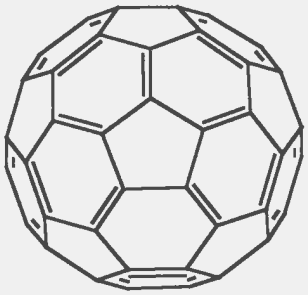
From the cyclohexatriene structure of benzene, it would be predicted that benzene would easily undergo oxidation by $KMnO_4$, addition of bromine and hydrogenation of H_2, just like other alkene systems. However, benzene shows unusual stability towards these and related reagents. P. J. Garratt described these contradictory properties, "unsaturated, yet inert", as the "Paradox of Benzene".[4]

Owing to their distinctive aromas, benzene and its derivatives came to be known as "aromatic" compounds and the phenomenon of their unusual stability as "aromaticity". These terms are firmly entrenched in modern day terminology. The ubiquity of aromatic compounds and the fundamental importance of aromaticity to the field of organic chemistry has fuelled widespread interest and discussion of these subjects, which continues unabated to this day. Much of the discussion has revolved

around the nature of aromaticity, which is a far more complex phenomenon than students of organic chemistry are led to believe at the introductory level. Hückel's rule (planar, cyclic conjugated π systems with $(4n+2)\pi$ electrons are aromatic) provides a useful starting point for discussion and, in many cases, provides an adequate level of understanding for practical purposes. However, Hückel's rule has its limitations. Many theories as to the origin, definition and quantification of aromaticity have been advanced, but no single explanation has gained universal acceptance. Various detailed accounts of aromaticity have been published and the reader is directed to consult them for a full appreciation of the depth and complexity of the subject.

1.2 Fullerenes and Fullerene Fragments

For thousands of years, graphite and diamond were the only two known allotropes of carbon. However, the discovery of the fullerenes toward the end of the 20th century introduced a whole new family of carbon allotropes. The most abundant and highly symmetric fullerene, I_h C_{60} **2** (Figure 1.02), was first isolated and characterized by Kroto and co-workers at the University of Sussex[5] in 1985. For the discovery of fullerenes, Robert F. Curl, Harold W. Kroto and Richard E. Smalley shared the Nobel Prize for Chemistry 1996.



2

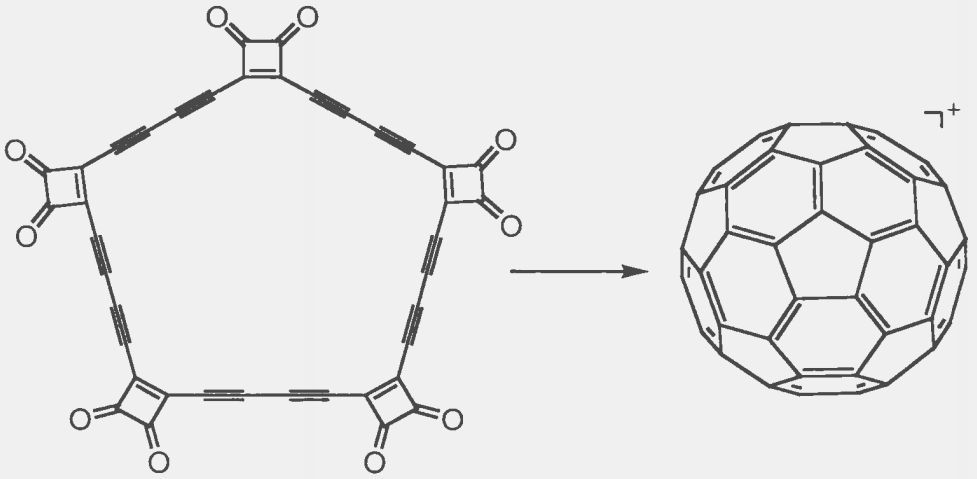
Figure 1.02 Fullerene C_{60} 2

The fullerene, C_{60} **2**, was predicted to be a stable, soccer-ball-shaped molecule[6] before its discovery, but this was not confirmed experimentally until the 1985 communication by Harold W. Kroto. The name "buckminsterfullerene" was given to the C_{60} model because of its similarity to the famous geodesic domes that were designed by the American architect, Buckminster Fuller. Kroto said that the newly discovered carbon cage molecule was named buckminsterfullerene "because the geodesic ideas associated with the constructs of Buckminster Fuller had been instrumental in arriving at a plausible structure."

The original two carbon allotropes, graphite and diamond, have various applications in our daily lives. Graphite can be used as a refractory material due to its high temperature stability and chemical inertness. It also has applications in chemical industry acting as anodes in some electrolytic processes. In electrical applications, it is mainly used as an electrical conducting material in the manufacture of carbon brushes in electric motors. Other areas of application include metallurgy, batteries, pencil

production, coatings, lubricants, and paint production. Diamonds can be divided into two categories according to usage; gem diamonds and industrial diamonds. In industrial application, they can be used for grinding or polishing optics and glass, for drill bits, surgical equipment, saws for cutting resistant materials, and for shaping very fine wires or for dressing turning, boring and milling tools. The new allotropes of carbon have received tremendous interest in a very broad cross-section of the scientific community, especially the fields of materials science, physics and chemistry.

From the perspective of the synthetic organic chemistry community, the challenge of synthesizing fullerenes is as appealing as it is formidable. Several groups have focused their research towards this goal. One promising approach involves the collapse of polyethynlylated cyclic ¶–systems such as compound **3** (Scheme 1.02).[7] A cation attributed to $\mathbf{2}^+$ has been formed in laser desorption Fourier transform mass spectrometric experiments on **3**.[8] However, the isolation of fullerenes from this approach has not been accomplished.



3 $\mathbf{2}^+$

Scheme 1.02 Synthesis of C_{60}^+

Another interesting approach is based on the synthesis of fullerene fragments with an eye to synthesizing fullerenes *via* elaboration of these fragments. Fullerenes can be viewed as curved aromatic surfaces, so the fullerene fragments must be curved compounds as well. The smallest fullerene fragment with a nonplanar lowest energy conformation is corannulene **4** (Figure 1.03). This nonplanar geometry is a consequence of a trade-off between different geometric preferences. Planar corannulene would require the distortion of bond lengths away from their ideal values and would also suffer from some angle strain. In contrast, bowl-shaped corannulene contains pyramidalized carbon atoms, but can accommodate normal bond lengths. Bond length distortion is much more costly in energy than bond angle distortion (including pyramidalization), so the bowl-shaped structure is the energy minimum.

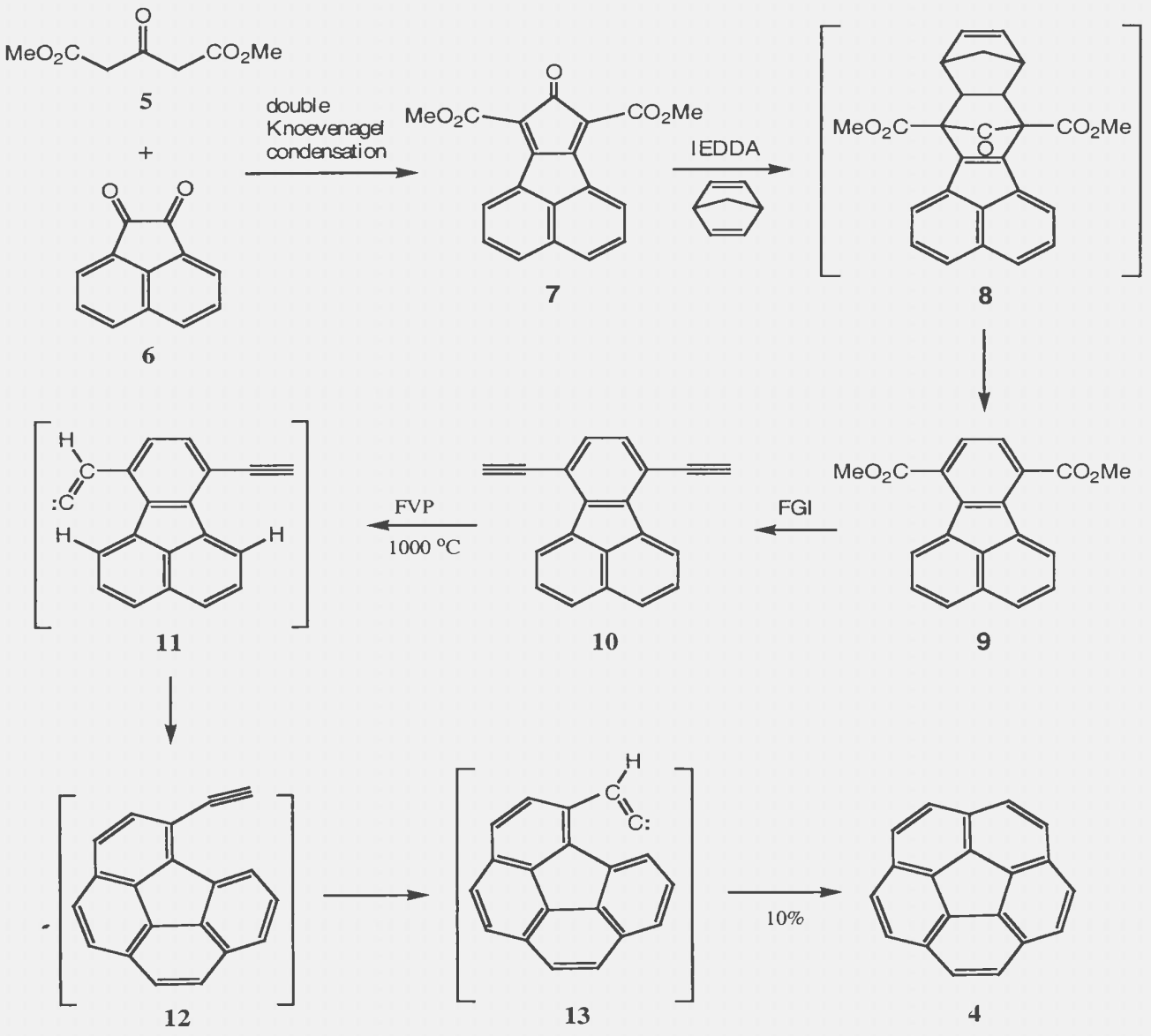
4 **2**

Figure 1.03 Corannulene 4

The first successful synthesis of corannulene **4** was published by Barth and Lawton in a formidable 16-step synthesis in 1966,[9] at which time the notion of a soccer-ball-shaped allotrope of carbon would have seemed preposterous. The discovery of the fullerenes gave new importance to corannulene and its synthesis was revisited by

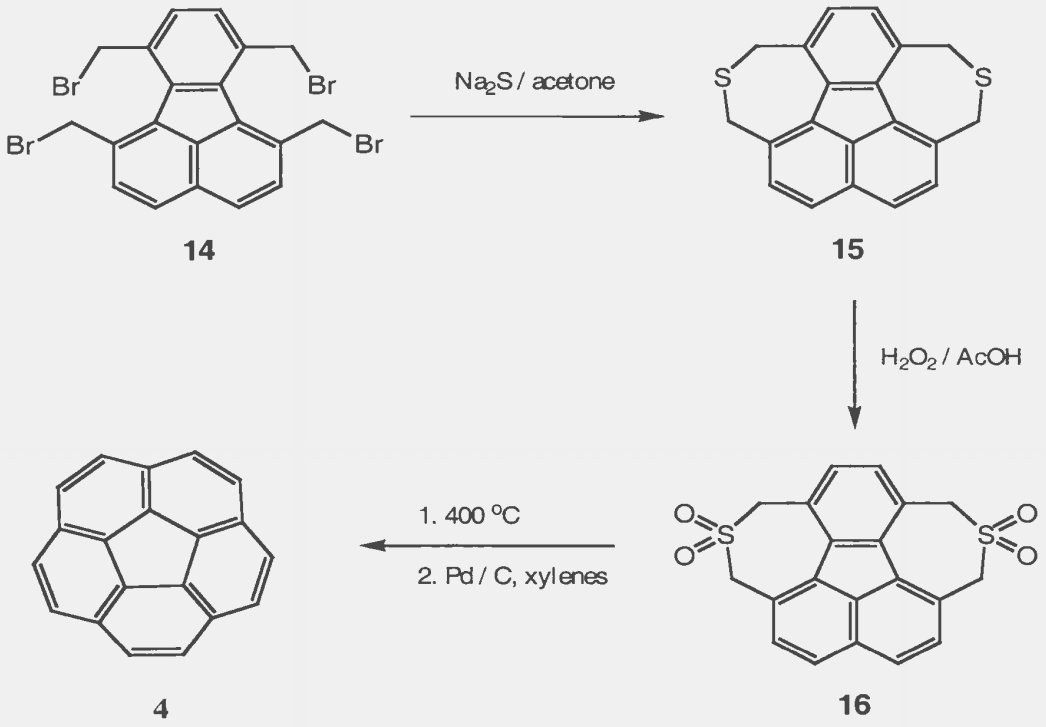
several groups. In 1992, Scott reported a concise synthesis of corannulene **4** (Scheme 1.03).[10, 11] The synthesis started with a double Knoevenagel condensation to form cyclopentadienone **7**, followed by an inverse electron demand Diels-Alder (IEDDA) cycloaddition of norbornadiene. The unstable intermediate **8** then underwent chelotropic loss of carbon monoxide and retro Diels-Alder loss of cyclopentadiene to give diester **9** in 49% yield This was converted to dialkyne **10** after a few functional group interconversions (FGI) in a yield of 27% over four steps. The vinylidene carbene **11** was formed via thermal isomerisation of **10** under flash vacuum pyrolysis conditions (1000 °C).[12] The highly reactive carbene **11** underwent insertion into the proximate C-H bond to form intermediate **12**. A subsequent isomerization/insertion process then gave corrannulene **4** in 10% yield. The pyrolysis conditions were assumed to be crucial for both steps from **10** to **4**. The first step, which involved a 1,2-H-shift to form vinylidene carbene, only happened at temperatures above 700 °C, and temperatures up to 1200 °C are normally used in this process.[12] In the second step, the curved conformation was brought to **4**. High temperature is needed in this step as well because the two reacting centers are far away from each other; at high temperatures the intermediate has sufficient energy to deviate severely from the planar geometry and the two reacting centers can come close enough and in a suitable orientation for reaction to occur.

The success of the pyrolytic ring closure provided a reliable way to the synthesis of corannulene **4**. Several similar routes were reported in the years following Scott's original approach, the most efficient of which has an overall yield of 40%.



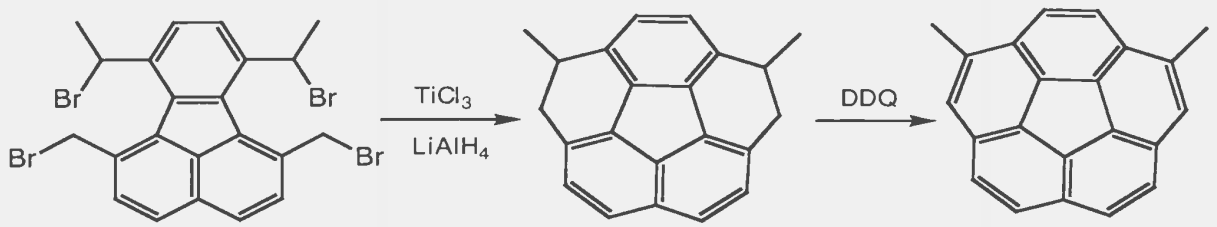
Scheme 1.03 Scott's synthesis of corannulene 4

In 1992, Siegel's group reported the first nonpyrolytic synthesis of corannulene **3** (Scheme 1.04).[13] In this synthesis, sodium sulfide was used to convert the tetrabromide **14** to the dithiacyclophane **15**, followed by oxidation to form the disulfone **16**. Sulfur dioxide extrusion at 400 °C and dehydrogenation afforded corannulene **4** in 7% yield.



Scheme 1.04 Siegel's synthesis of corannulene 4

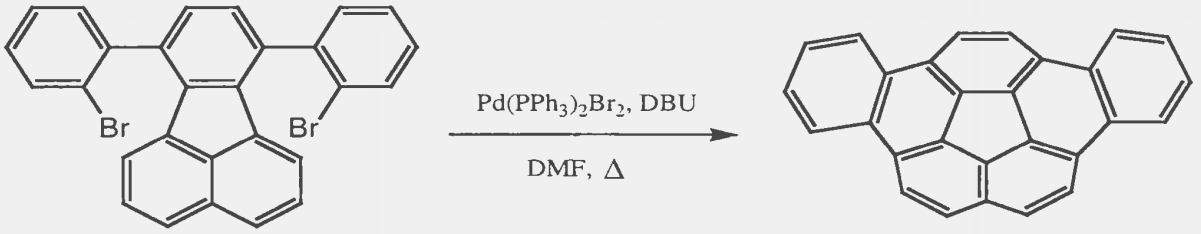
Since a thermolytic step, which put limitations on introducing functional groups into the system, was still needed (400 °C) in the sulfur dioxide extrusion process in Siegel's synthesis, it still was not considered by all to be a truly nonpyrolytic route. Not until 1996 did Siegel's group develop an undisputably nonpyrolytic synthesis of corannulene derivative **19** (Scheme 1.05).[14] Under reductive coupling conditions, intermolecular coupling of tetrabromide **17** provided compound **18**, which underwent a dehydrogenation by DDQ to give dimethylcorannulene **19** in an overall yield of 18%. This work had great importance because it provided the possibility of constructing strained systems such as fullerene fragments under mild conditions.



17 18 19

Scheme 1.05 Nonpyrolytic synthesis of dimethyl corannulene 19

A new method to form the 5-membered and 6-membered rings was developed in recent years, in which the involvement of Pd-catalyst increased the yields significantly (Scheme 1.06). Intramolecular arylation of dibromide **20** provided corannulene derivative **21** in 50 – 60% yield, compared to 38% from the same conversion under FVP conditions.[15] This approach might be a possible way to build highly strained molecules under mild conditions.

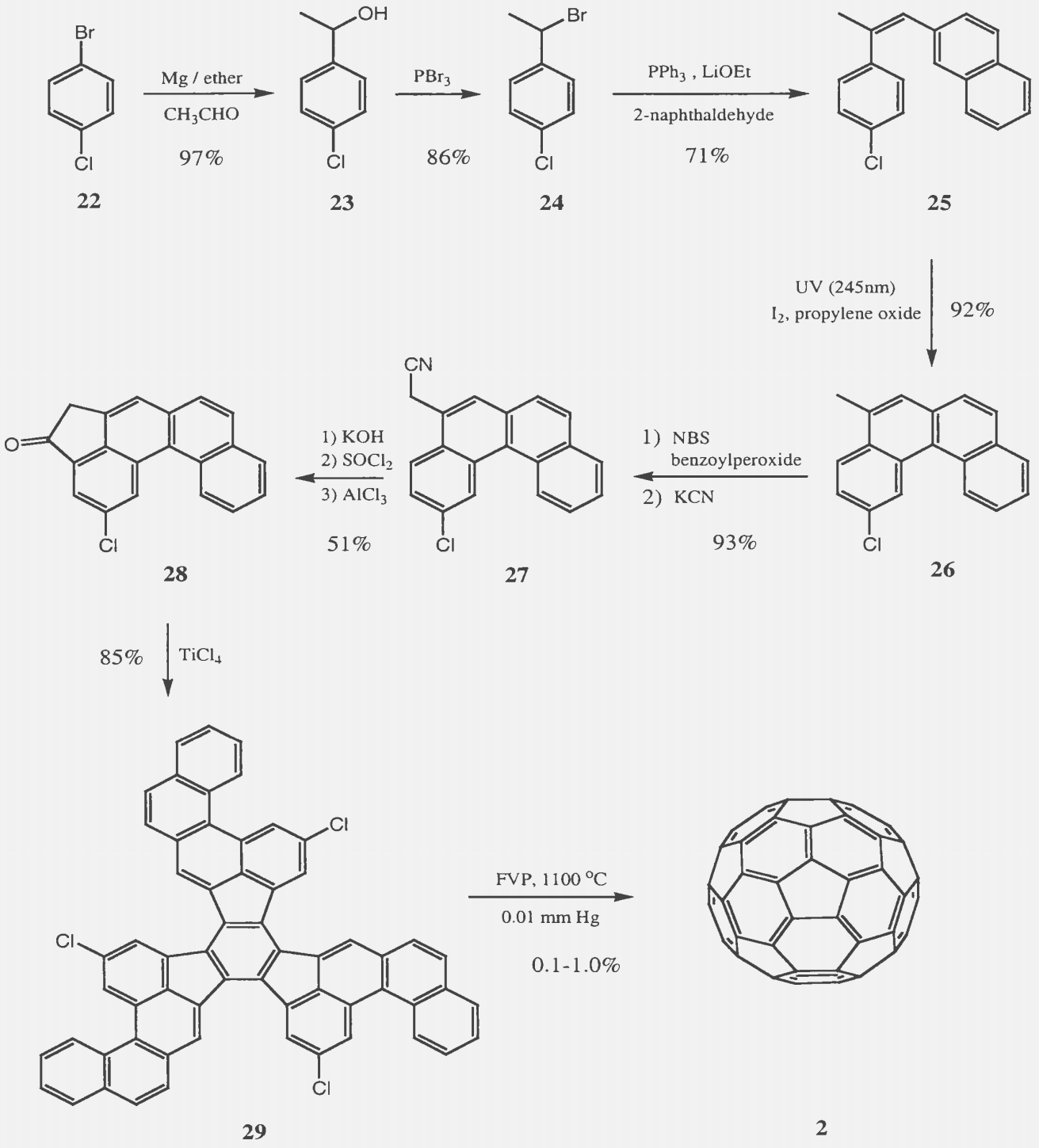


20 21

Scheme 1.06 Synthesis of dibenzyl corannulene 21

The year 2004 stood as a milestone in the history of fullerene chemistry. The first synthesis of C_{60} was published by Scott.[16, 17] The strategy is first to form a relatively strain-free, threefold symmetric, polycyclic aromatic intermediate **29** that contains all of the required 60 carbons, and then to "stitch it up" to the ball-shaped C_{60}.

This novel synthesis started with 1-bromo-4-chlorobenzene **22**. Through a Grignard reaction, followed by a bromination, bromide **24** was formed in 83% yield over two steps (Scheme 1.07). The subsequent Wittig reaction afforded alkene **25** in 71% yield, which then underwent a photochemical stilbene-phenanthrene-type cyclization to give compound **26** in 92% yield. Functional group interconversions then gave cyanide **27** in 93% yield over two steps. The cyanide was converted in two steps to the corresponding acyl chloride, which then provided ketone **28** upon intramolecular Friedel-Crafts acylation in 51% yield. The following acid-catalyzed aldol trimerization of three molecules of ketone **28** constructed the parent $C_{60}H_{27}Cl_3$ **29** in 85% yield. The final FVP step gave the desired product C_{60}, which was isolated in 0.1–1% yield. The key point here is that C_{60} was *isolated*, albeit in very low yield. In the 2002 communication, the product was merely *detected* and some members of the chemical community did not view this as sufficient to qualify the generation of C_{60} as a *bona fide* synthesis.



Scheme 1.07 Scott's synthesis of C_{60} 2

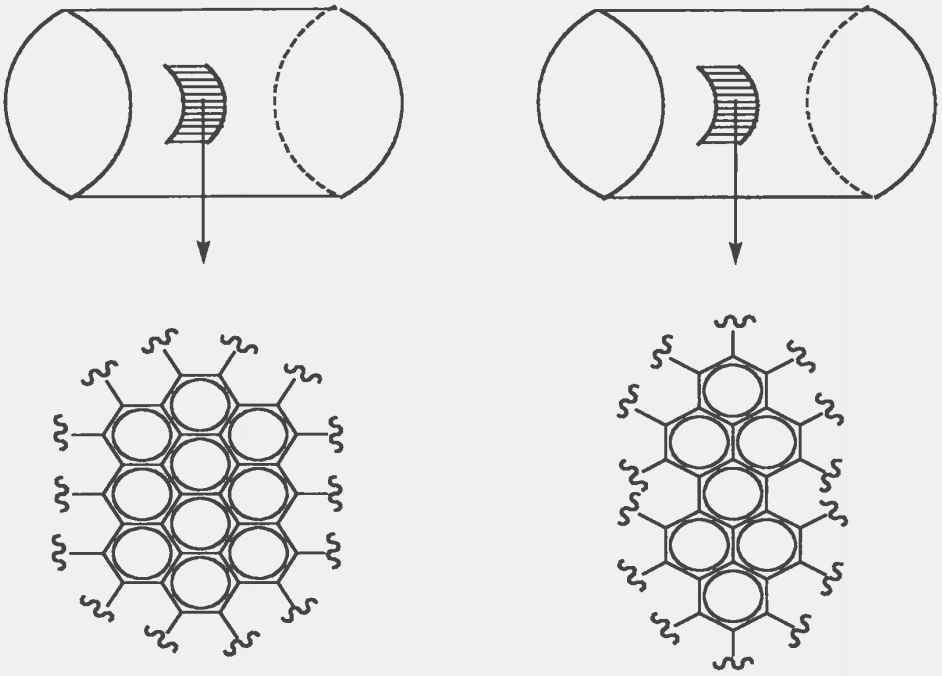
1.3 Carbon Nanotubes

Since their discovery in 1991 by Iijima and co-workers, carbon nanotubes have attracted a great deal of interest, not only from a fundamental point of view, but also for potential future applications. Carbon nanotubes are extremely thin (their diameter is about 10,000 times smaller than a human hair), hollow cylinder-shaped molecules made of carbon atoms, and they are considered to be another class of carbon allotropes.

Single-walled carbon nanotubes (SWNT) could be viewed as long wrapped graphite sheets. They consist of two separate regions with different physical and chemical properties. One is the sidewall of the tube and another one is the terminal hemispheric cap, which is structurally similar to fullerenes such as C_{60}.

There are three types of SWNTs: zigzag structure, armchair structure and chiral structure. In Figure 1.04, some simple pieces of the zigzag structure and armchair structure are shown. Further discussion of SWNT structures is outside the scope this thesis so it will not be given.

SWNTs have a variety of potential applications in areas such as energy storage, molecular electronics, nanoprobes and sensors, and materials science. They are expected to show special properties with regard to chemical reactivity, electrical conductivity, optical activity and mechanical strength.



30 zigzag structure

31 armchair structure

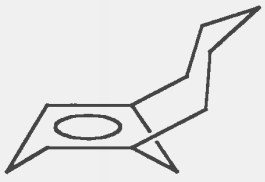
Figure 1.04 Zigzag and armchair structure SWNTs

Generally, carbon nanotubes are synthesized by three main techniques: laser ablation, arc discharge and chemical vapor deposition (CVD). In laser ablation, a high-power laser beam impinges on a volume of carbon-containing feedstock gas (methane or carbon monoxide). Laser ablation produces small amounts of clean nanotubes. By contrast, in arc discharge, a vapor is produced by an arc discharge between two carbon electrodes, from which self-assembly produces nanotubes that usually contain large quantities of impure material. Chemical vapor deposition results in the formation of multi walled nanotubes or poor quality SWNTs. The SWNTs produced with CVD have a large diameter range, which can be only poorly controlled.

From the perspective of the synthetic organic chemists, SWNTs are very challenging targets. Since SWNTs are macromolecules, lab synthesis must be directed toward the shortest conceivable nanotubes, which can also be viewed as aromatic belts. The connection between nanotubes and aromatic belts will be discussed in detail later in this chapter.

1.4 Nonplanarity in Aromatics

Nonplanar aromatic compounds have been the subjects of considerable interest in recent years. As described by Hopf,[18] nonplanarity can be induced by the presence of non-six-membered rings in certain polycyclic aromatic systems, *e.g.* fullerenes and fullerene fragments.[5, 10, 11] Furthermore, the presence of a short bridge (*e.g.* [5] metacyclophane **32**) or the presence of repulsive non-bonded (*e.g.* [6]helicene **33**) interactions can also cause nonplanar geometries to be preferred (Figure 1.05).



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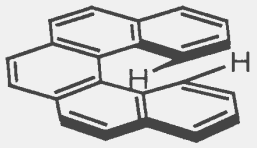


33

Figure 1.05 Curvature of aromatic rings due to tethering (32) and sterics (33)

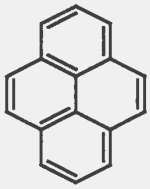
In compound **32** the aromatic ring is tethered by a pentamethylene bridge. The tether is not long enough for the aromatic ring to maintain a planar geometry. The degree of

distortion in this class of compounds varies with different tether length and the way in which the tether is attached to the aromatic ring. For example, if a particular tether is attached to *para* positions, the degree of distortion would be the greatest. For compound **33**, to be planar, the two indicated C-H units would have to occupy the same space, which is highly unfavourable. The molecule therefore adopts a helical shape to avoid this situation. If bulkier groups replaced the indiated H atoms (*e.g.* CH_3), greater deviation from planarity can be achieved.

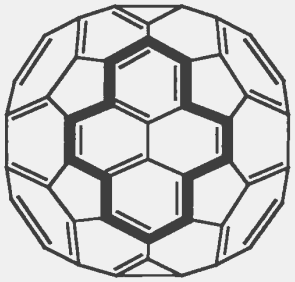
A common strategy to make highly strained cyclophanes is to form the strained aromatic system late in the synthesis. The energy released from formation of aromatic system (~ 37 kcal/mol resonance energy), is used to compensate for the strain energy that is introduced into the compound by the nonplanarity. This allows such reactions to proceed under relatively mild conditions. This strategy to form curved aromatic systems is conceptually superior to the pyrolytic approach that has been used in the synthesis of fullerene fragments, because it offers the potential to be compatible with a variety of functional groups and the product is not presented with the opportunity to decompose under severe conditions of its formation.

1.5 Pyrenophanes

Pyrenophanes are a specific class of cyclophanes with pyrene unit(s) as the aromatic nucleus. The curved pyrene unit can be mapped onto the surface of some fullerenes such as D_{5h}-C_{70} **35**, as well as some nanotubes such as **31** (Figure 1.06).[19]



34
pyrene



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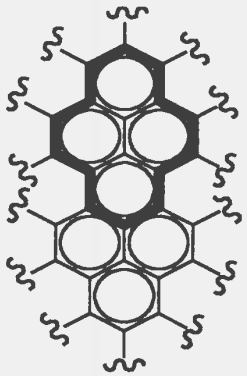
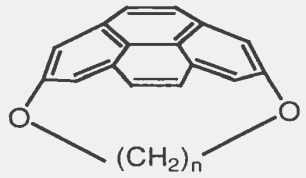


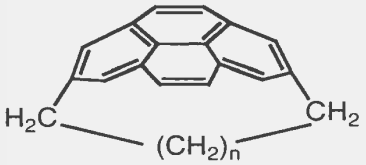
31
armchair structure

Figure 1.06 Nonplanarity in pyrene unit(s)

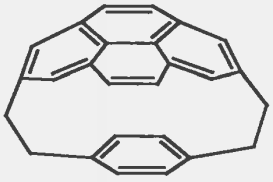
The Bodwell group is particularly interested in these types of molecules and thay have reported the synthesis of a series of (2,7)pyrenophanes (Figure 1.07).[20-26]



36 - 41
n = 5, 6, 7, 8, 9, 10



42 -44
n = 7, 8, 9



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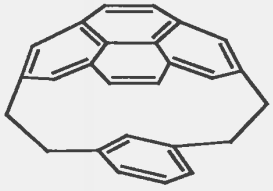

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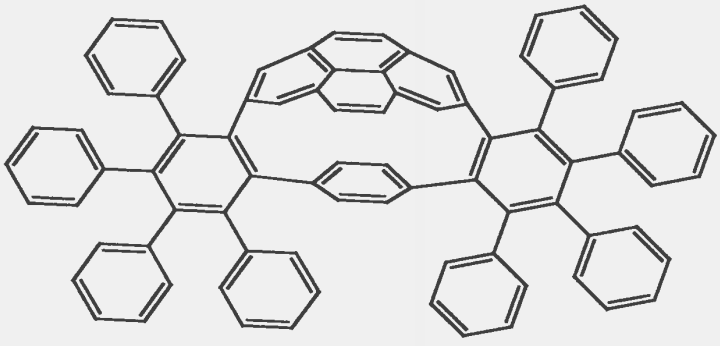

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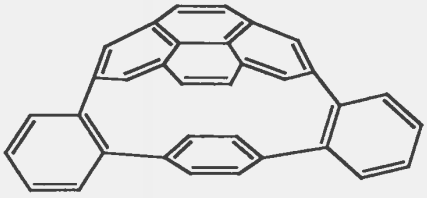

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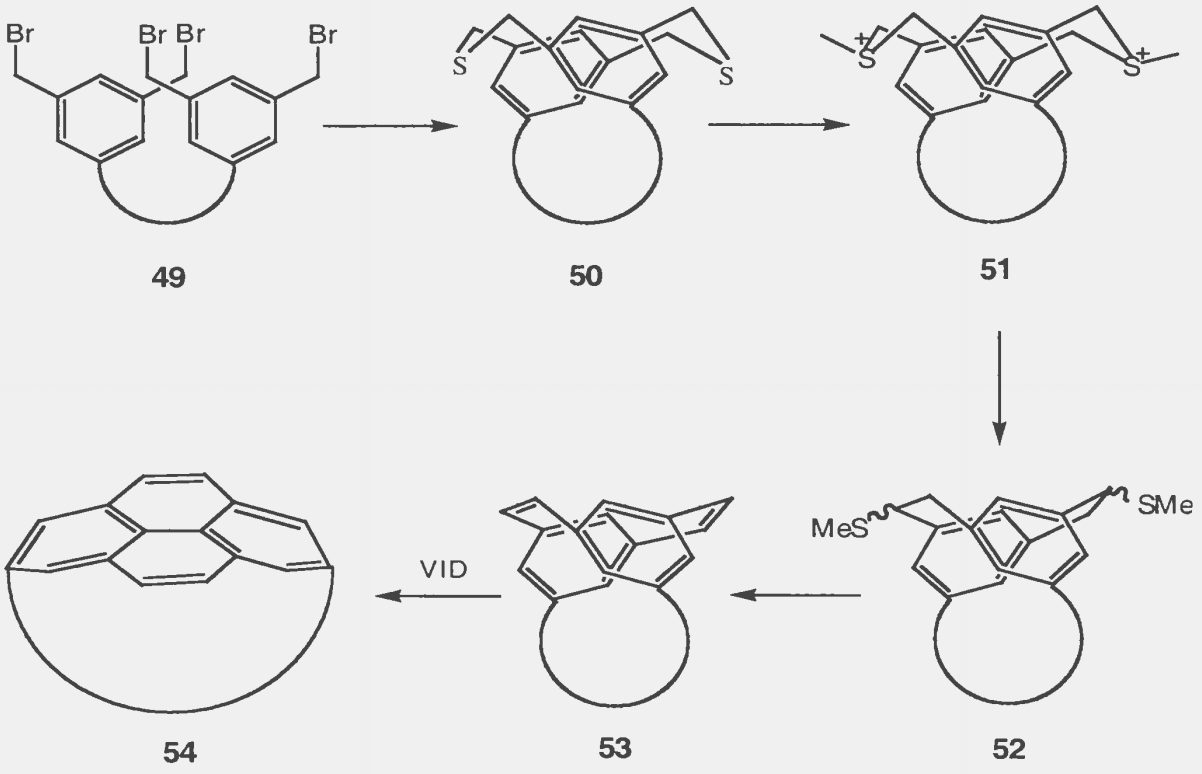
Figure 1.07 [*n*](2,7)Pyrenophanes synthesized by the Bodwell group

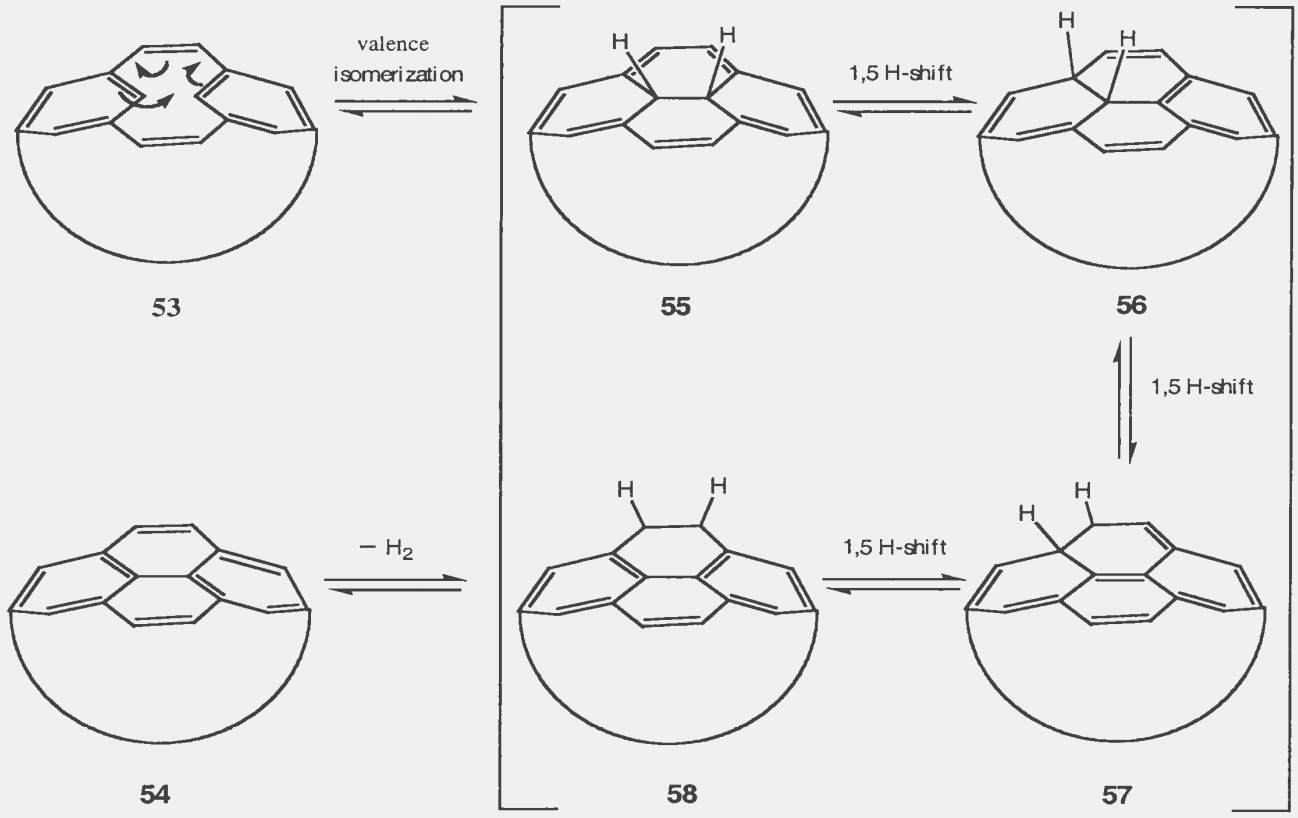
The Bodwell strategy to synthesize [*n*](2,7)pyrenophanes typically starts with the tethering of two appropriately functionalized aromatic rings followed by functional group interconversion to give a tetrabromide **49**. An intermolecular coupling using Na_2S/Al_2O_3 provides a dithiacyclophane **50**, which is then *S*-methylated to give **51**, which is subjected to a Stevens rearrangement to form methylthioether **52**. Another *S*-methylation followed by Hofmann elimination affords a cyclophanediene **53**, which is dehydrogenated by DDQ to give the pyrenophane **54** (Scheme 1.08).



Scheme 1.08 VID methodology for making pyrenophanes

The final step is the key step in this methodology. This is the step in which the nonplanar aromatic system is generated. The reaction is called the "VID" reaction

because it involves a valence isomerization (VI) process to give the dihydropyrene, followed by a series of 1,5 H-shifts and dehydrogenation (D) at any stage to form the pyrenophane (Scheme 1.09). The formation of the pyrene unit in last step is an aromatization step, which releases some resonance energy that can compensate for the introduced strained energy.

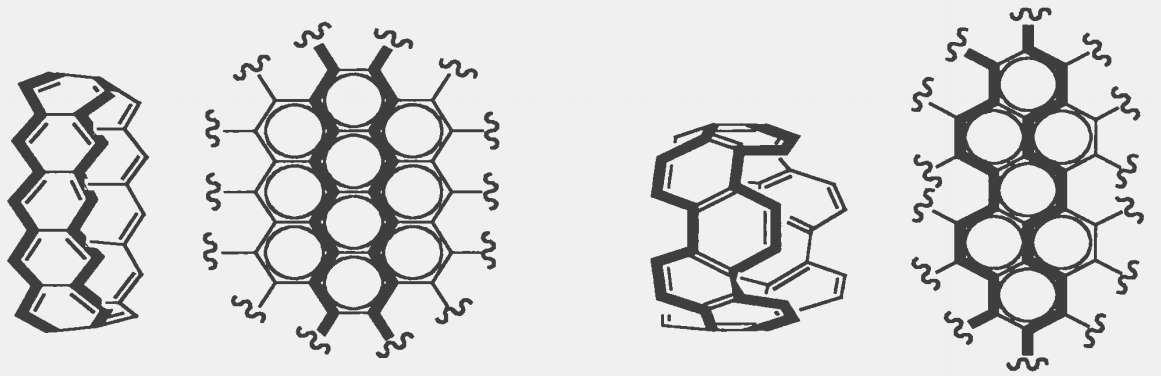


Scheme 1.09 Mechanism of the VID process

1.6 Aromatic Belts

Aromatic belts have stood as synthetic targets for a long time, even before the discovery of fullerenes and nanotubes. Research interest in aromatic belts can be divided into two main categories, cyclacenes and their derivatives, and

cyclophenacenes and their derivatives. As shown in Figure 1.08, [10]cyclacene **59** can be mapped onto zigzag nanotubes and [10]cyclophenacene **60** can map onto armchair nanotubes. Therefore, aromatic belts are the shortest version of nanotubes. There is no clear distinction line between wide belts and short nanotubes.



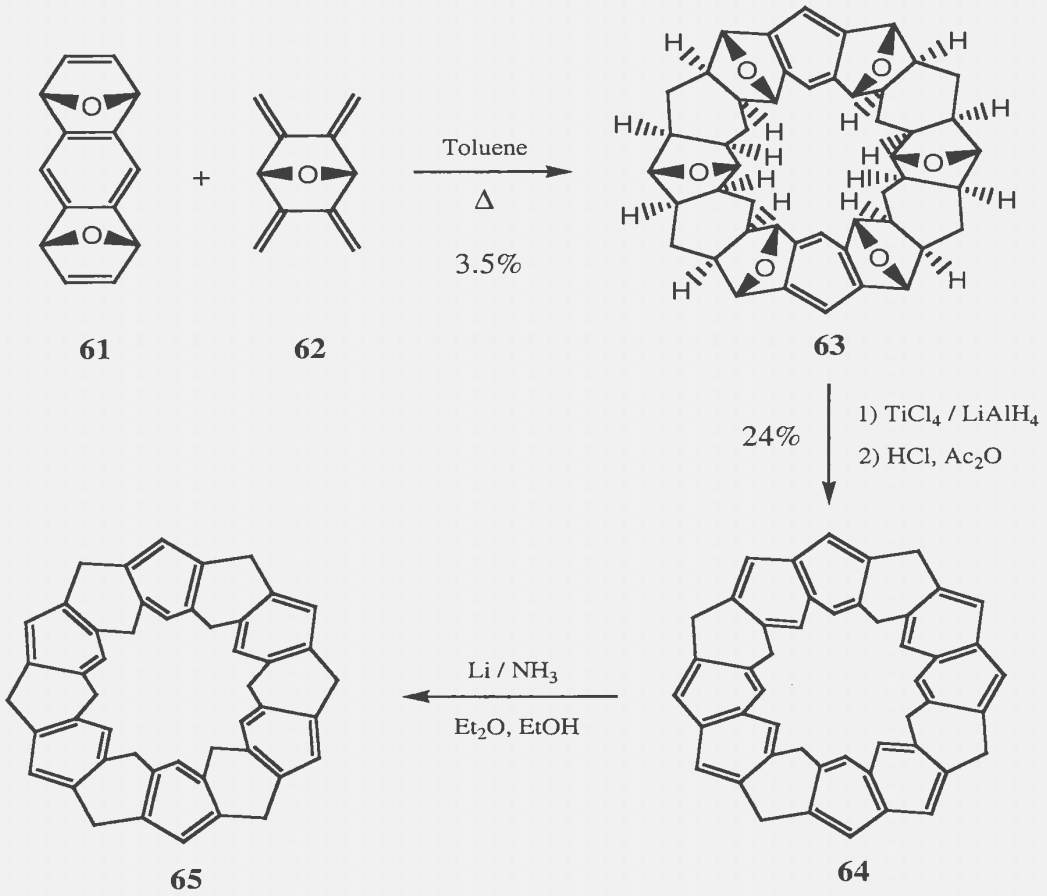
59 **30** **60** **31**

zigzag structure armchair structure

Figure 1.08 [10]Cyclacene 59 and [10]cyclophenacene 60

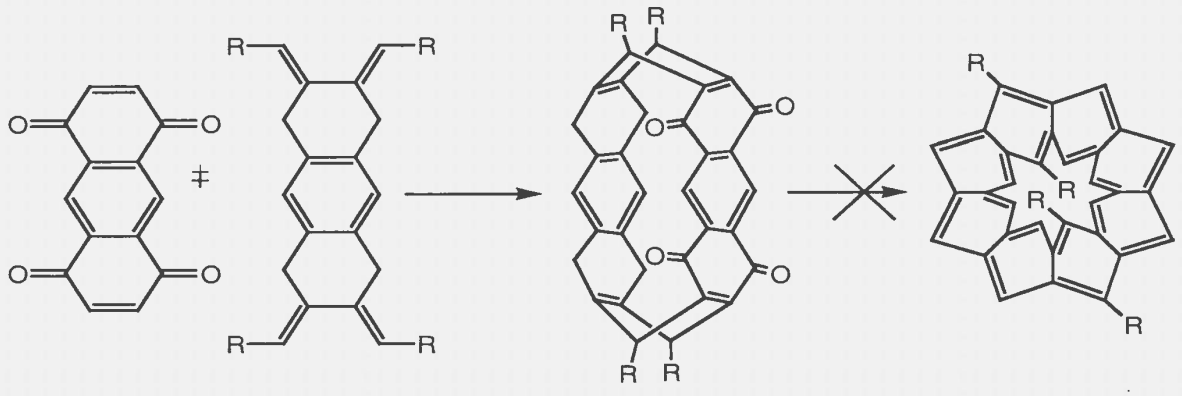
Many attempts have been made toward the synthesis of aromatic belts, some of which ended up with molecular belts, but not fully aromatic ones. As discussed below, aromatization of such systems could not be achieved.

An early approach to [12]cyclacene was reported by Stoddart's group using a Diels-Alder reaction of bis(dienophile) **61** and bis(diene) **62** (Scheme 1.10).[26] An oxygenated molecular belt **63** was generated in 3.5% yield. Reduction followed by dehydration of **63** gave the partially-hydrogenated [12]cyclacene **64** in 24% yield. Then Birch reduction of **64** afforded a compound believed to be [12]collarene **65** but no yield was reported. Attempts at further reduction did not proceed.



Scheme 1.10 Stoddart's approach to [12]cyclacene

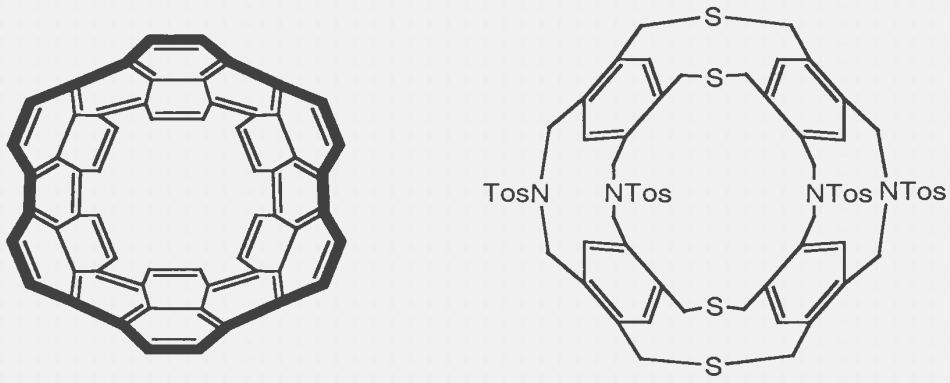
A similar approach was proposed by Cory, in which flexible bis(diene)s were employed instead of the rigid bis(diene)s in Stoddart's work (Scheme 1.11).[27] A double Diels-Alder reaction of bis(diene) **67** and bis(dienophile) **66** provided quinoid cyclophane **68**, which was hoped to undergo further reduction and dehydrogenation to achieve the fully aromatic [8]cyclacene **69**. However, **68** could not be converted into an aromatic belt despite considerable effort.



66 67 68 69

Scheme 1.11 Cory's approach to a [8]cyclacene derivative 69

Cyclophenacenes are another class of aromatic belts that have attracted significant interest from several groups. Vögtle proposed pyrenoid belts such as **70** as synthetic targets (Figure 1.09). He reported the synthesis of a tetrathiatetraazacyclophane **71** (Figure 1.09), which might be a precursor to the corresponding pyrenoid belt, but no successful attempts to extrude the sulfur and nitrogen atoms was ever reported.[28]

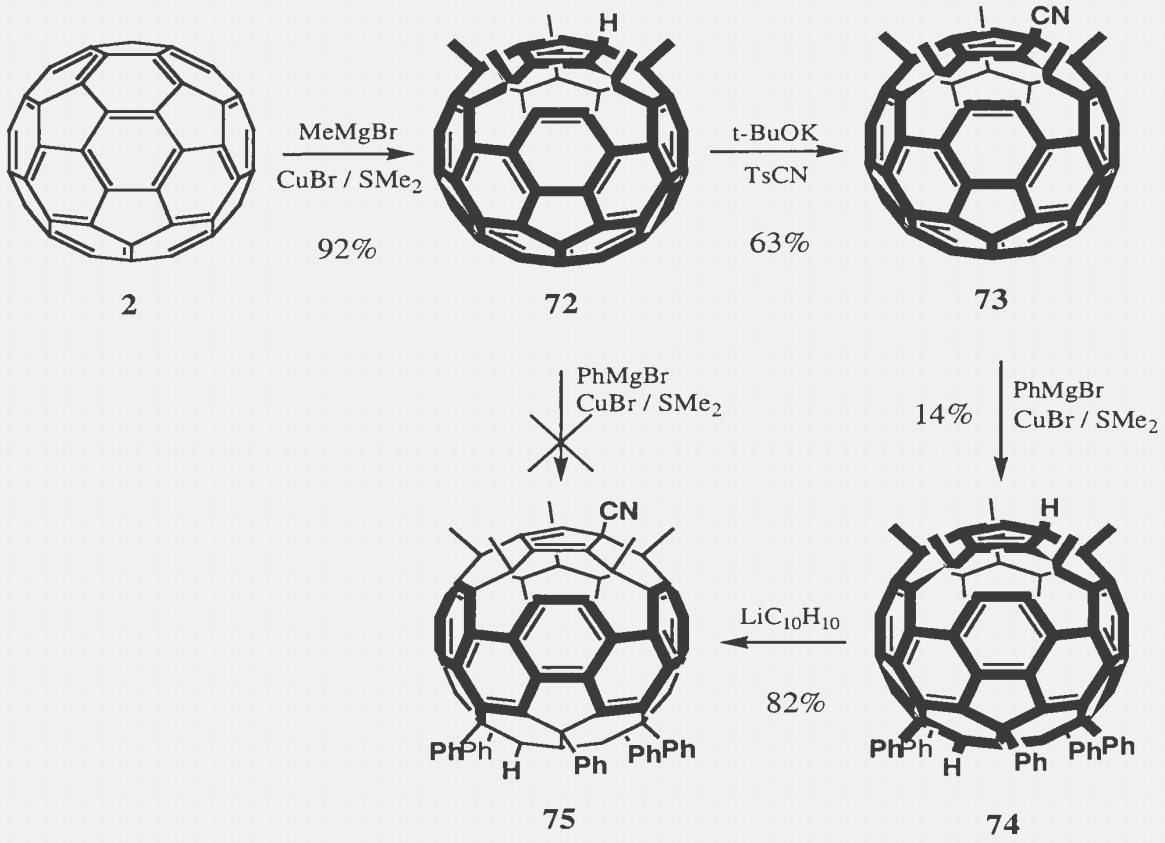


70 71

Figure 1.09 Vögtle belt 70

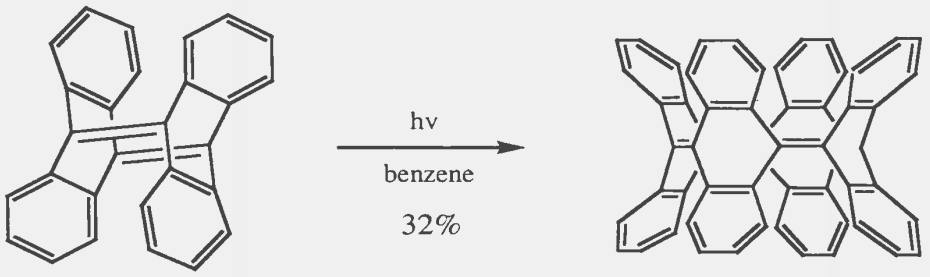
The only successful "synthesis" of aromatic belts so far was reported in 2003 by Nakamura and co-workers.[29] A [10]cyclophenacene derivative **75** was synthesized from C_{60} (Scheme 1.12). The top and bottom part of C_{60} were selectively reduced using special organometallic reagents and the equatorial part that remained is clearly a [10]phenacene belt. C_{60} was reacted with an organocopper reagent to give the methylated C_{60} **72** in 92% yield. A similar direct phenylation did not proceed to form the desired product **75**. It was suspected that the copper reagent deprotonated **72** to give the corresponding anion, which is extremely unreactive toward further addition reactions. Therefore, a protection step was carried out by introducing a cyano group in 63% yield. The protected molecule **73** underwent a pentaphenyl addition to afford compound **74** in 14% yield. Then the cyano group was removed to form the belt **75** in 82% yield.

Rather than making the belt by assembling small building blocks, they started with a material in which the belt is already there. In the view of the synthetic organic chemist, this "synthesis" could hardly be called a synthesis, because nothing has really been done to contribute to the formation of the belt. The final product is not a free-standing belt either. Furthermore, this strategy is not a universal method for making aromatic belts because it can only work on this particular belt. However, it did provide an aromatic belt, and more importantly, it provides the chance to investigate the properties of aromatic belts.



Scheme 1.12 Nakamura's synthesis of a [10]cyclophenacene derivative 75

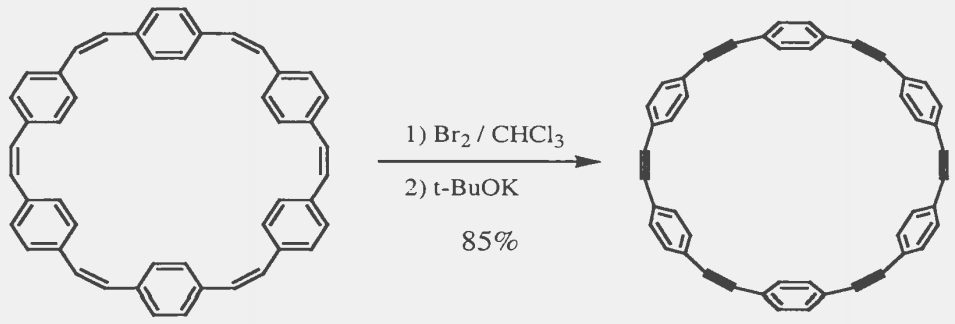
Other approaches to belt-like molecules include the synthesis of "picotube" **77** (Scheme 1.13) by Herges and co-workers in 1996.[30] This is the first isolated compound with fully conjugated radially oriented p orbitals. Tetradehydrodianthracene (TDDA) **76** was employed because it has a well-suited structure for the synthesis of a tubelike molecule. Also, its highly strained system provides the driving force for the ring –expanding metathesis. The "picotube" **77** is unreactive to *m*-CPBA and bromine at room temperature, and it is stable even at 450 °C. Cyclodehydrogenation of **76** would afford a fully aromatic belt, which can also be considered to be a small nanotube. Unfortunately, this approach has not yet met with success.



76 77

Scheme 1.13 Herges's synthesis of "picotube" 77

Within the same year that "picotube" was synthesized, Oda and co-workers reported the synthesis of the cyclic paraphenyleneacetylene **79** (6-CPPA) (Scheme 1.14).[31] Cyclic alkene **78** , which was derived from the McMurry coupling of 4,4'-diformyl-(Z)-stilbenzene, was brominated with bromine, followed by treatment with *t*-BuOK to give cyclic alkyne **79** in 85% yield. Very recently, it was discovered that ¶-–linked macrocycles are able to encircle hydrocarbon guests, and 6-CPPA could form a remarkably strong complex with C_{60}.[32] The electron-deficient convex exterior of C_{60} matches the electron-rich inner surface of 6-CPPA both electronically and geometrically.



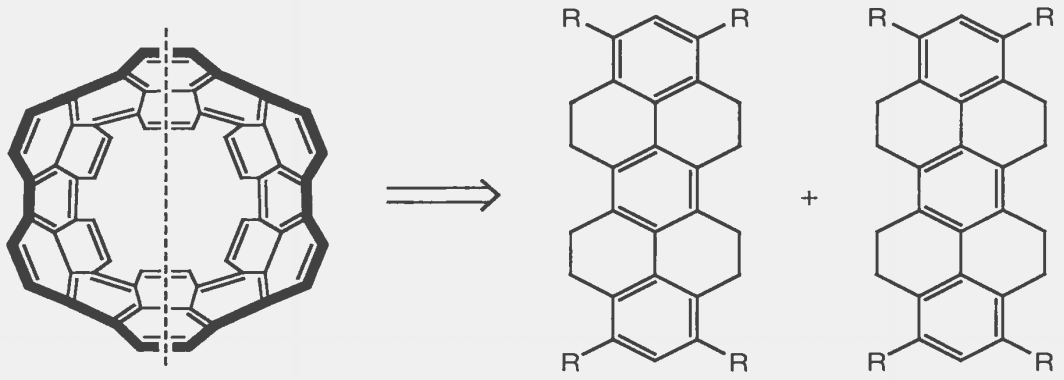
78 79

Scheme 1.14 Oda's synthesis of 6-CPPA 79

As introduced in previous sections, our group has achieved great progress in pyrenophane chemistry. The ultimate goal is to synthesize an aromatic belt such as **70**, which we have dubbed "Vögtle Belts"[33] because Vögtle was the first one to propose this class of compounds as synthetic targets. We are very interested in making this type of molecules because they show great synthetic challenge due to their highly strained structure, and as we can see from the shown examples above, the success on this topic has not yet been achieved.

Our strategy is first to make relatively planar precursors, which we call "molecular boards", then apply pyrenophane chemistry to connect two boards together to form the nonplanar aromatic system. As illustrated in previous examples, all of the approaches to aromatic belts faced the same problem: a partially hydrogenated aromatic belt was formed first, then attempts were made to aromatize it. However, the final aromatization did not proceed in every case. In our approach, the nonplanarity and aromaticity will be introduced into the system at the same time. Therefore, it is a conceptually different strategy. Moreover, here we found a very powerful method for aromatization, which might provide us the way to aromatic belts.

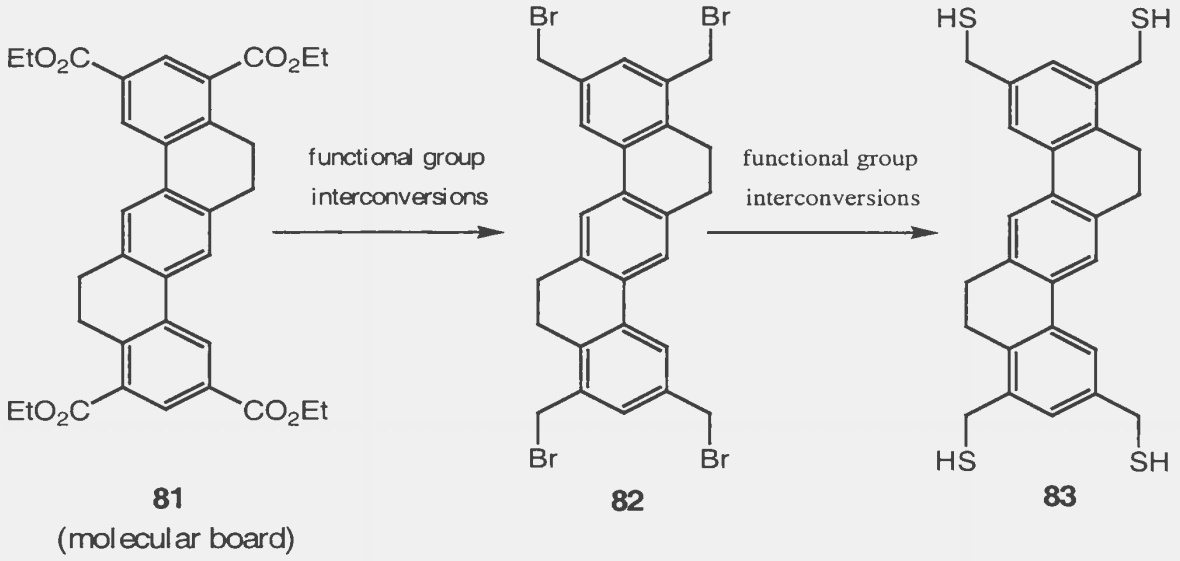
Retrosynthetically, by cutting the sixfold-symmetric target molecule **70** right through the middle, it breaks down to two identical pieces **80** (Scheme 1.15). Unfortunately, the synthesis of this particular precursor by Rolf Vermeij, a former member of our group, was not successful. This will be discussed in detail in Chapter 2.



70 80 80

Scheme 1.15 Retrosynthetic analysis of Vögtle belt 70

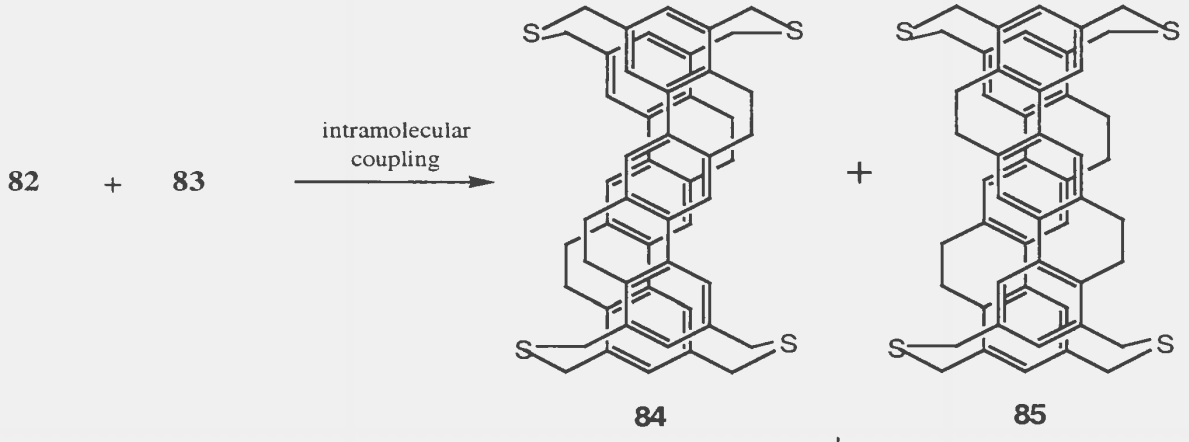
Due to the failure to synthesize precursor **80**, a simpler molecular board **81** was proposed. By employing the pyrenophane chemistry on **81**, two aromatic belts would form (Scheme 1.16). By some functional group interconvertsions, molecular board **81** should provide access to tetrathiol **83** and tetrabromide **82**. A coupling reaction of **82** and **83** under high dilution conditions would be expected to form tetrathiacyclophanes **84** and **85**, which, *via* Stevens rearrangement and Hofmann elimination, would give rise to cyclophanetetraenes **88** and **89**, respectively. The final VID step using DDQ would aromatize the molecule to provide the fully aromatic compounds **90** and **91**, which are the targets of this project.



81
(molecular board)

82

83



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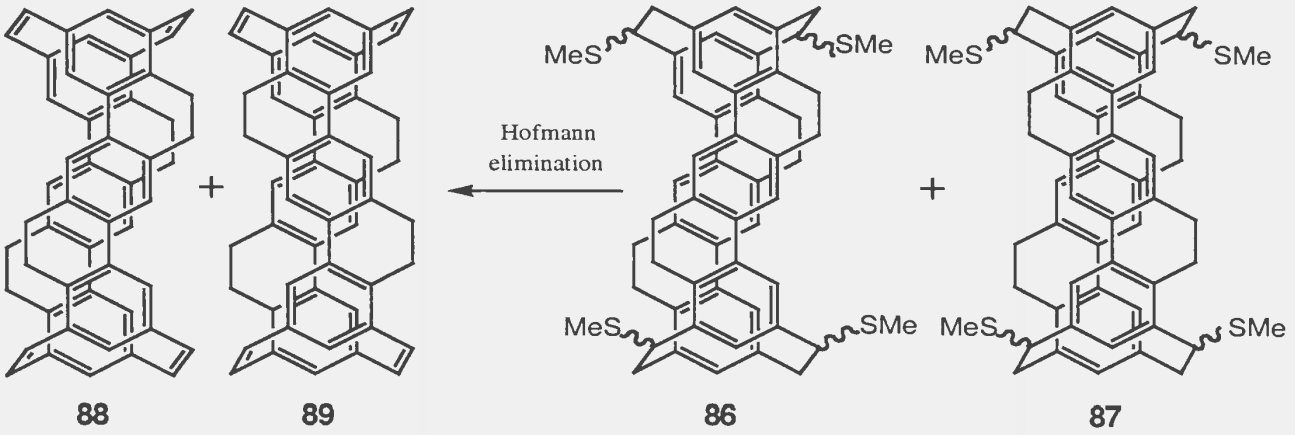
85

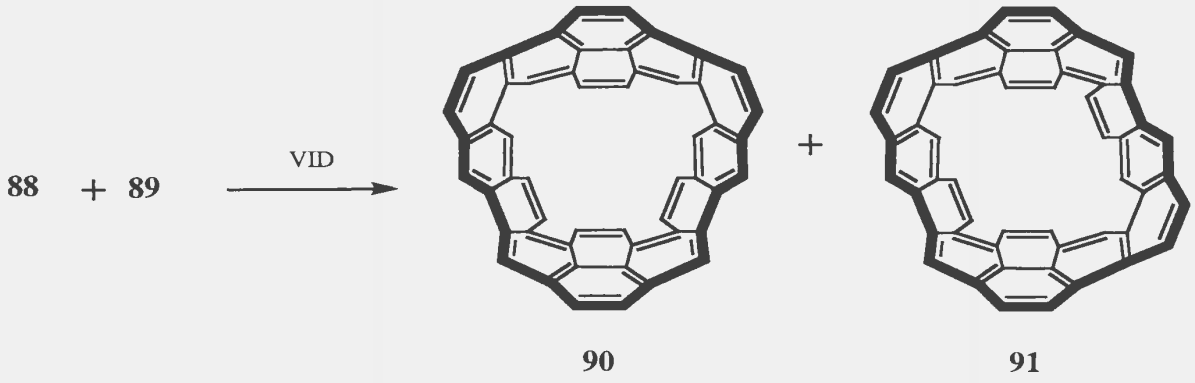


88

89

86

87



Scheme 1.16 Proposed synthetic approach to aromatic belts 90 and 91

1.7 Conclusions

The molecular board **81** is an important precursor in the synthesis toward the aromatic belts. If this point can be reached, the rest of the work would be the well-established pyrenophane chemistry. Also, once the approach has been validated, it might be applicable to the synthesis of a variety of other molecular boards. Multigram quantities of the molecular board are needed for the further application of pyrenophane chemistry. In the next two chapters, the synthesis of the molecular board will be discussed in detail.

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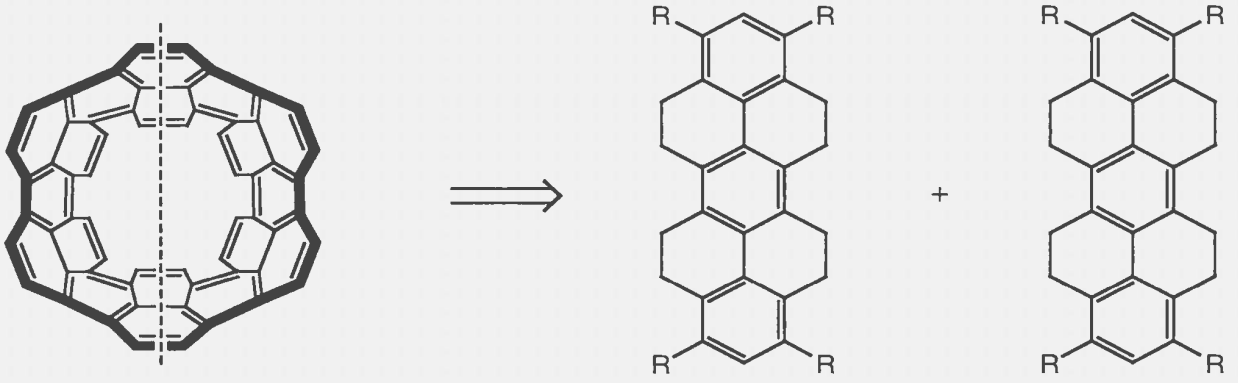
Chapter 2

First Attempted Synthesis of a Molecular Board

2.1 Introduction

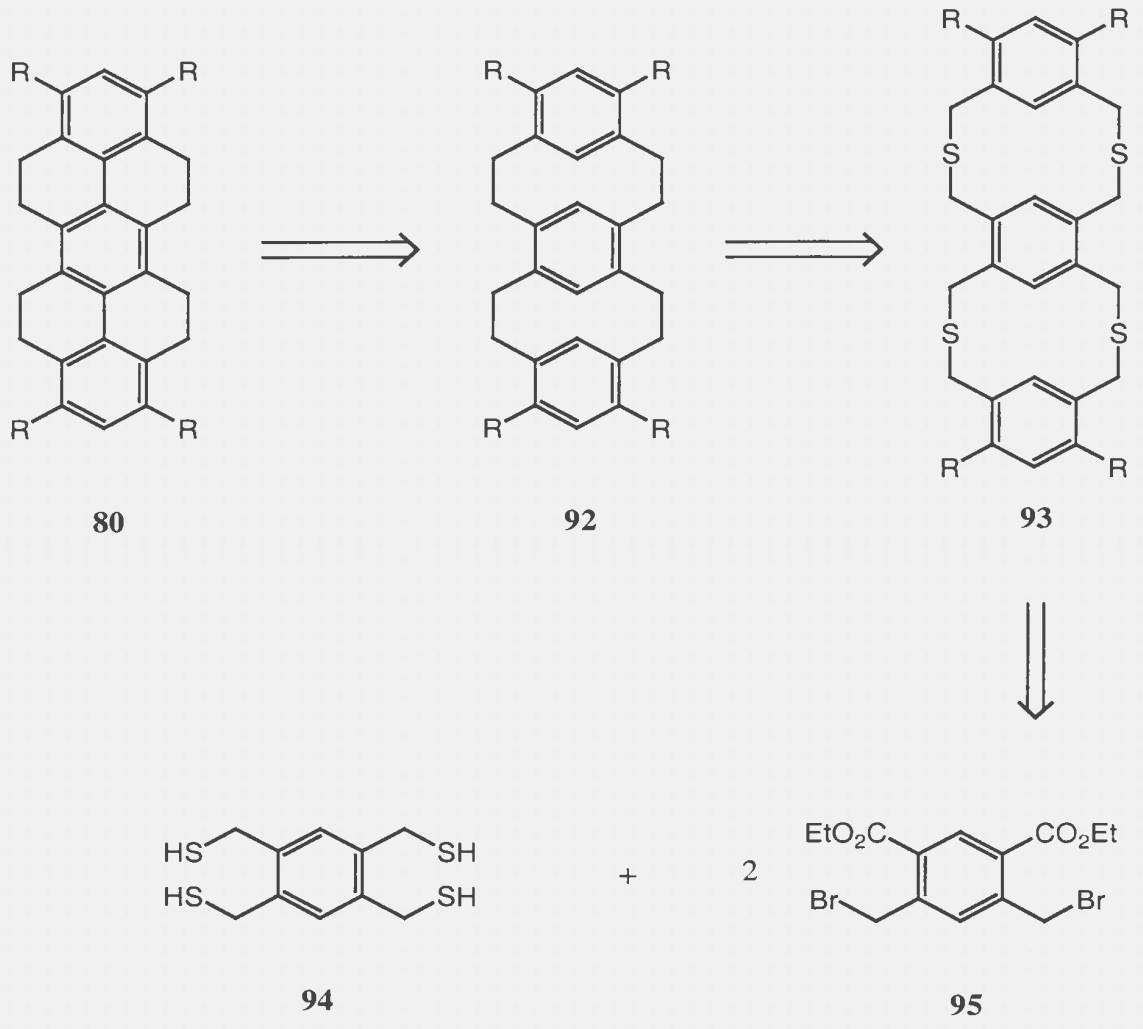
A former member the Bodwell group, Rudolf Vermeij, attampted to synthesize molecular board **80**, which was envisioned as a precursor to aromatic belt **70** (Scheme 2.01).



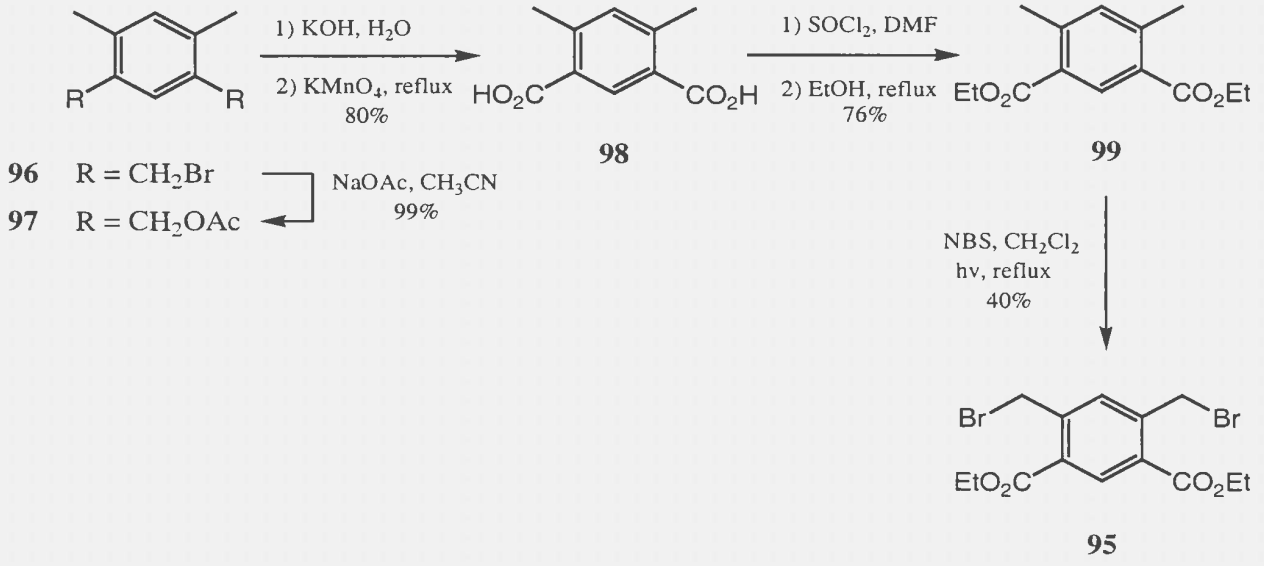
70 **80** **80**

Scheme 2.01

Two 4,5,9,10-tetrahydropyrene units can be identified in compound **80** (Scheme 2.02). As such, the synthetic approach was based upon the known conversion of [2.2]metacyclophanes to 4,5,9,10-tetrahydropyrenes upon treatment with iron filings and bromine in the dark[1] or pyridinium perbromide.[2] The yields of such transformations are usually very high. It was envisioned that cyclophane **92** would be accessible from tetrathiacyclophane **93**, which could break down to two small building blocks **95** and **94**.



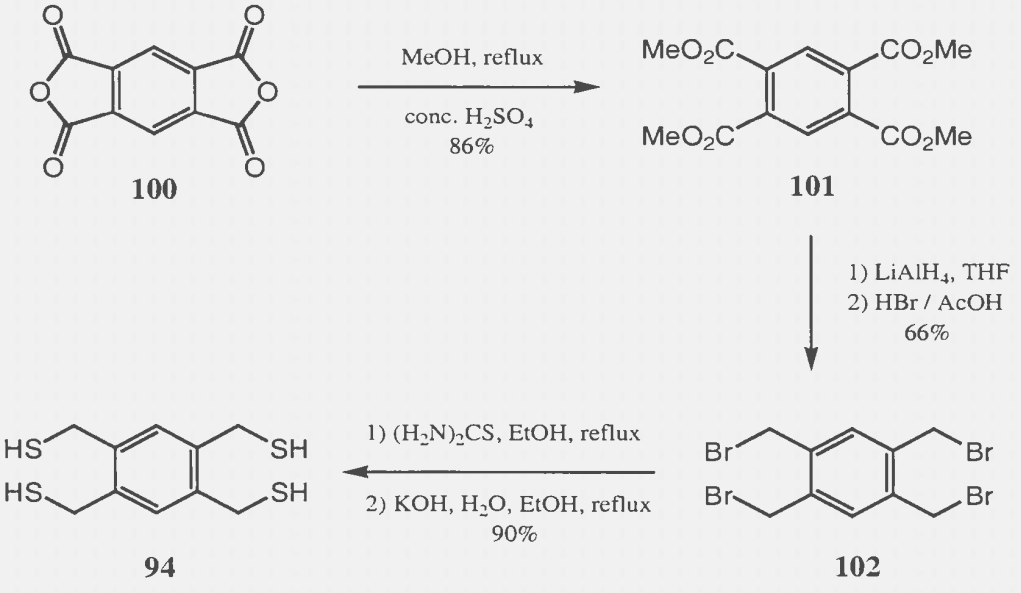
Scheme 2.02 Retrosynthetic analysis of precursor 80



Scheme 2.03 Synthesis of 95

The synthesis started with the conversion of dibromide **96**[3] into diacetate **97** (99%). Oxidation of diacetate **97** yielded the diacid **98** (80%) and esterification then gave diester **99** (76%). Double free radical benzylic bromination of diester **99** provided **95** in 40% yield (Scheme 2.03).

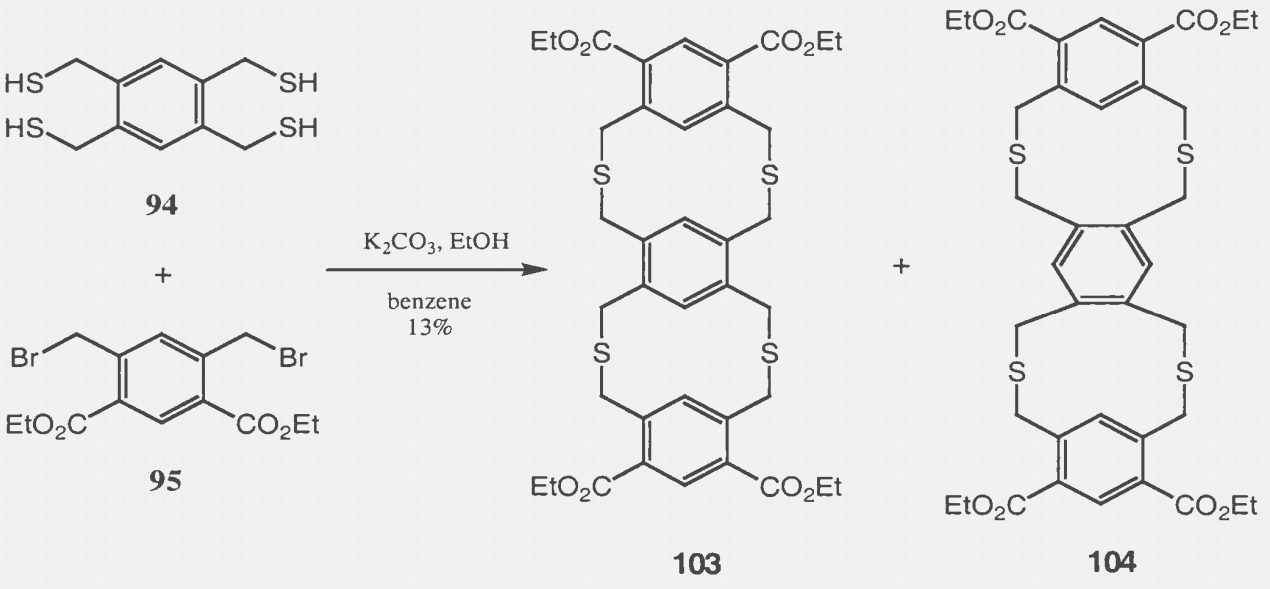
The second required building block, tetrathiol **94**, was synthesized from pyromellitic anhydride **100** (Scheme 2.04). Under Fischer esterification conditions, anhydride **100** was converted to tetramethyl ester **101** in 86% yield. $LiAlH_4$ reduction of **101**, followed by immediate treatment of the intermediate 1,2,4,5-tetrakis(hydroxymethyl)benzene with conc. HBr in acetic acid, afforded tetrabromide **102** (66%, 2 steps). Finally, tetrabromide **102** was converted into tetrathiol **94** by converting it into the corresponding tetrakis(isothiouronium) salt, hydrolysis of which gave **94** in 90% yield.



100 **101** **94** **102**

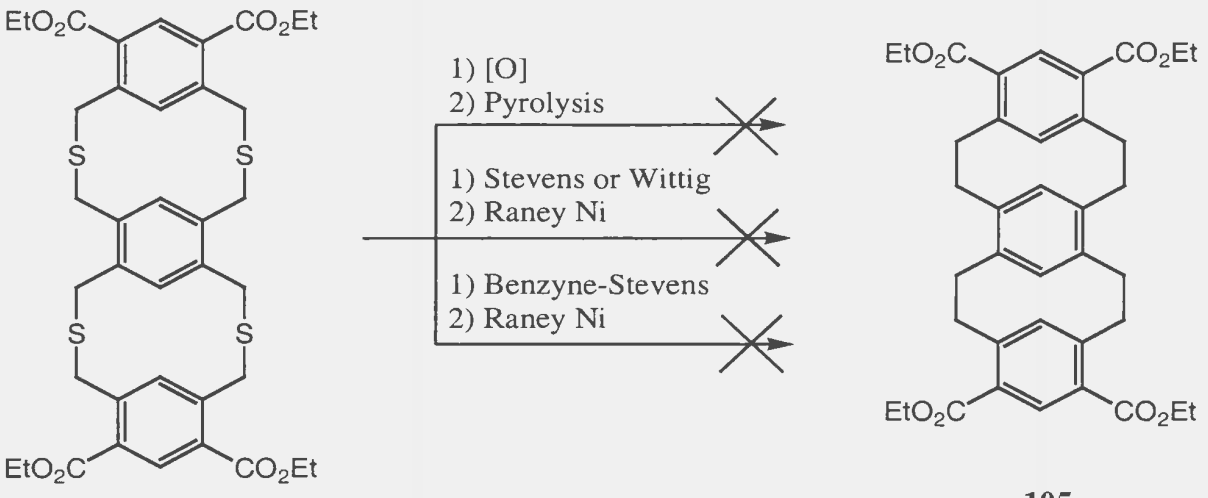
Scheme 2.04 Synthesis of 94

Reaction of tetrathiol **94** with dibromide **95** led to the formation of two tetrathiacyclophanes (Scheme 2.05), the desired product **103** (13%) and the undesired "*ortho/meta*" isomer **104** (19%). Chromatographic separation of these two cyclophanes proved to be difficult and time consuming, but useable amounts of **103** could eventually be obtained.



Scheme 2.05 Synthesis of 103 and 104

Many methods for the ring contraction of dithia[3.3]metacyclophanes to give [2.2]metacyclophanes are known.[4,5] Unfortunately, all attempts to achieve this conversion using Stevens rearrangement, Wittig rearrangement and benzyne-Stevens rearrangement[6] failed (Scheme 2.06).



103 **105**

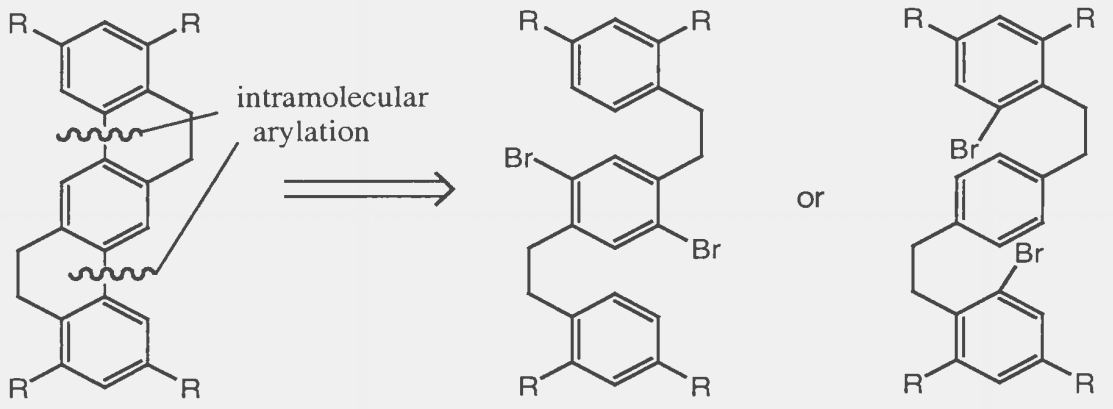
Scheme 2.06 Attempts towards 105

The most problematic step in the attempted synthesis of **80** was obviously the ring contraction. Although further work may have led to a solution, the prospects that this approach could deliver multigram quantities of **80** seemed bleak and work in this area was halted. It is worth noting that all of the cyclophane chemistry used in this approach was developed in the 1960's and 1970's. This raises the possibility that a totally new synthetic approach based on more modern chemistry could be developed.

2.2 Retrosynthetic Analysis

The problems associated with the synthesis of molecular board **80** led to the identification of the smaller target **92**, a partially hydrogenated dibenzo[*a*,*h*]anthracene derivative (Scheme 2.07). The partial hydrogenation was included as a means to diminish anticipated solubility problems with the corresponding fully unsaturated system. Dibenzo[*a.h*]anthracene itself has been reported to have poor solubility in most organic solvents.[7] Intramolecular palladium-catalyzed arylation was chosen as

the key ring closing reaction. Although this methodology does not have broad precedent, its elegant application to the synthesis of natural products[8] as well as novel PAHs[9] was very encouraging. Retrosynthetic cleavage of the biaryl bonds of **92** according to this methodology leads back to either **106** or **107**.

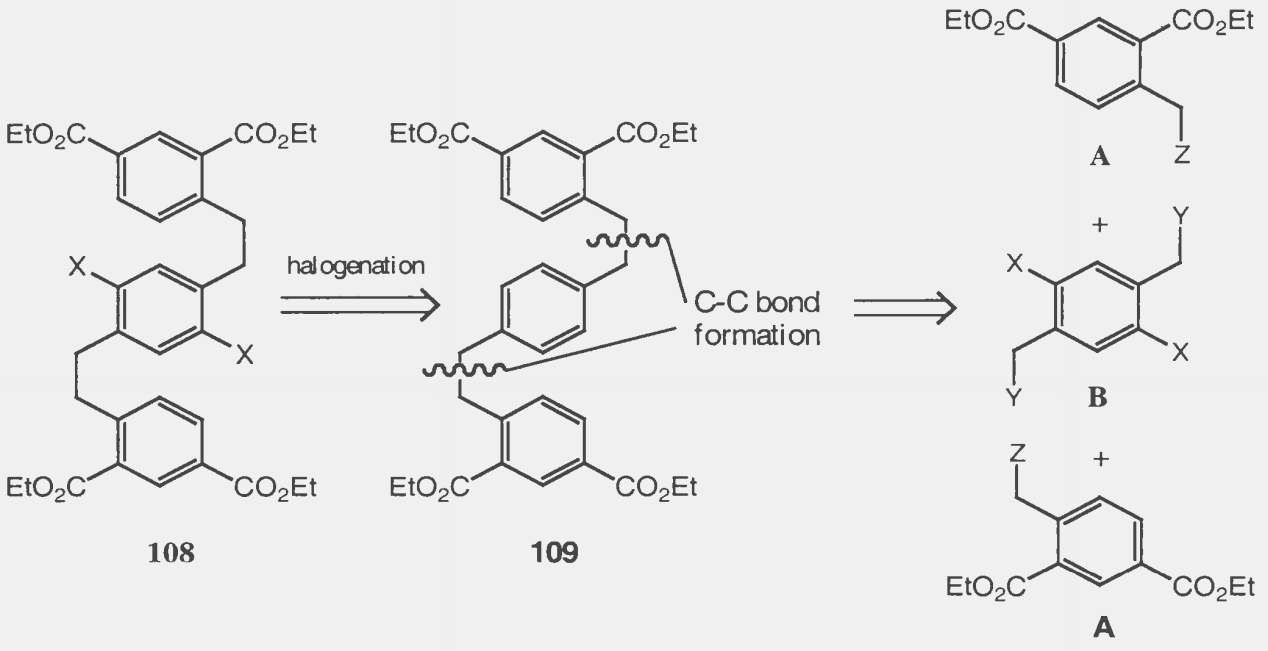


Scheme 2.07 Retrosynthetic analysis of 92

Compound **106** appeared to be a more easily accessible precursor than **107** because the central rings in these two molecules are activated toward electrophilic aromatic substitution by the two methylene groups. By comparison, the top and bottom rings are each strongly deactivated by two ester groups when R=CO_2Et. This suggested that the central ring of tetraester **106** could be halogenated very selectively. On the other hand, if compound **107** were chosen to be the precursor, the bromine atoms would need to be installed by a method other than electrophilic aromatic substitution. Indeed, no straightforward route to **107** from readily available materials could be identified.

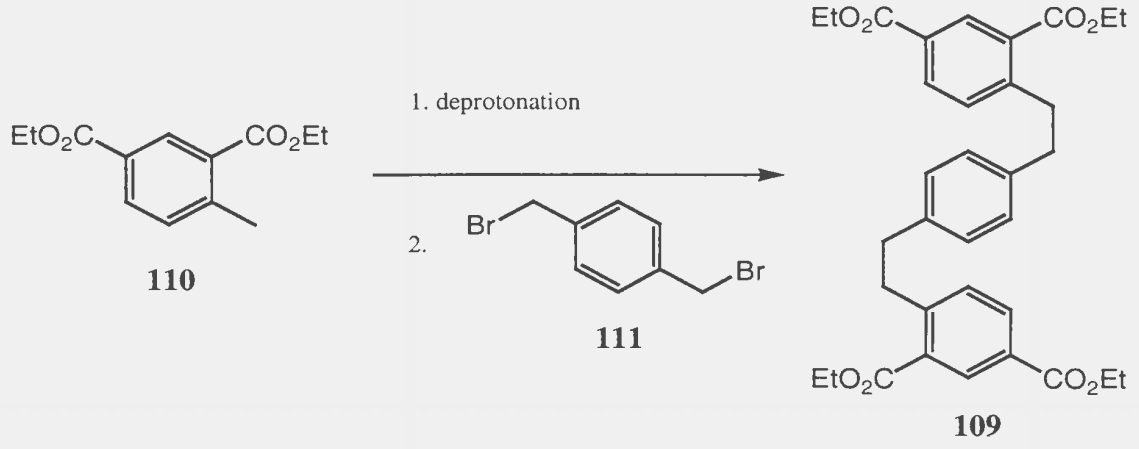
The first generation retrosynthetic plan involved scission of the central bond of each of the two ethano units as the key C-C bond forming step, either before of after the electrophilic aromatic bromination step (Scheme 2.08). This afforded systems **A** and

B as precursors. The availability of various C-C bond forming reactions (*vide infra*) provided a degree of flexibility to this strategy.



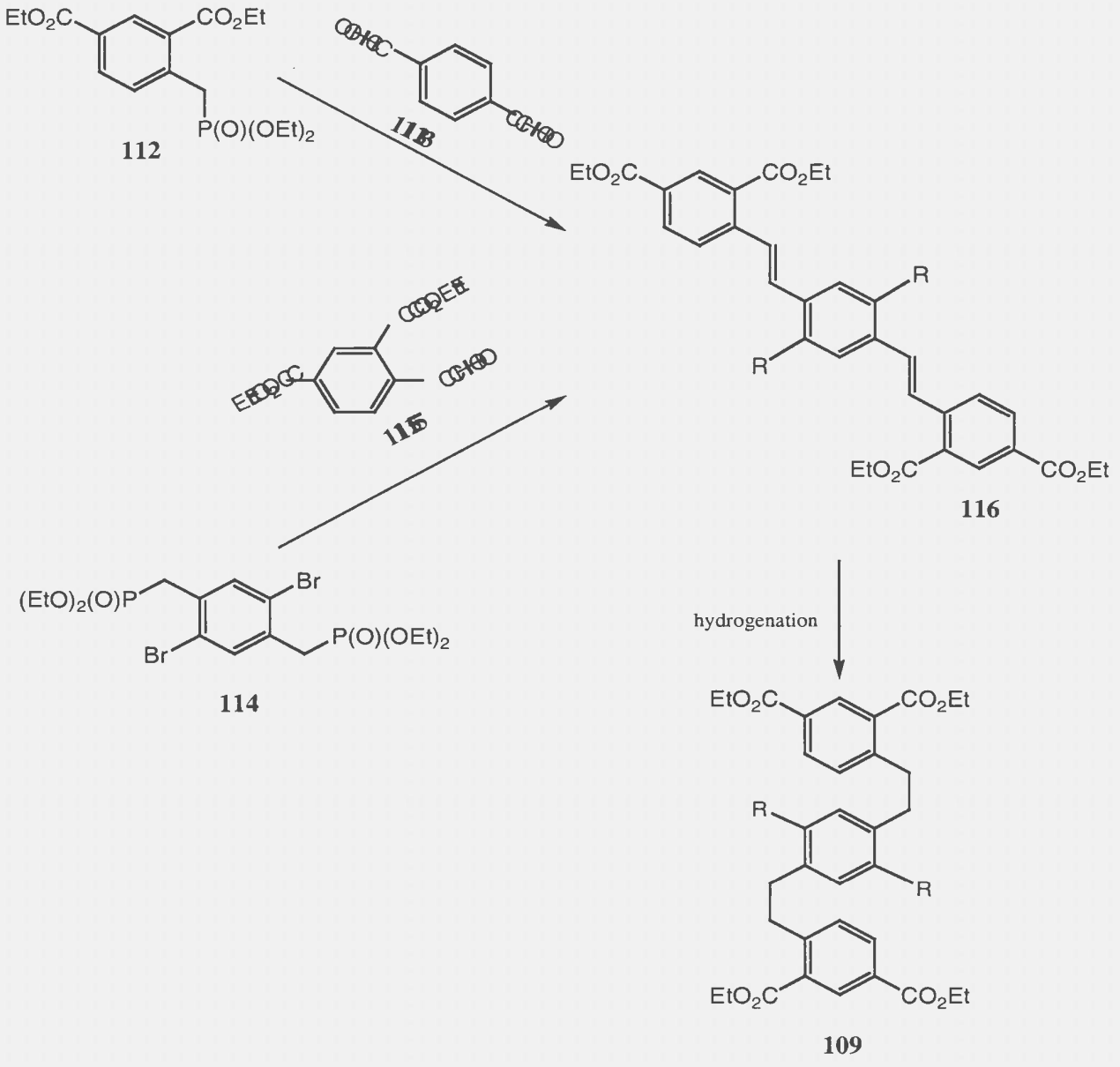
Scheme 2.08 Retrosynthetic analysis of 108

Two approaches that initially presented themselves were the alkylation of the anion (extended enolate) derived from isophthalate ester **110** with commercially available dibromide **111** (Scheme 2.09) and the use of the Wittig reaction (Scheme 2.10). The alkylation approach would require the synthesis of **110**, which was previously prepared in the Bodwell group using inverse electron demand Diels-Alder (IEDDA) chemistry.[10]



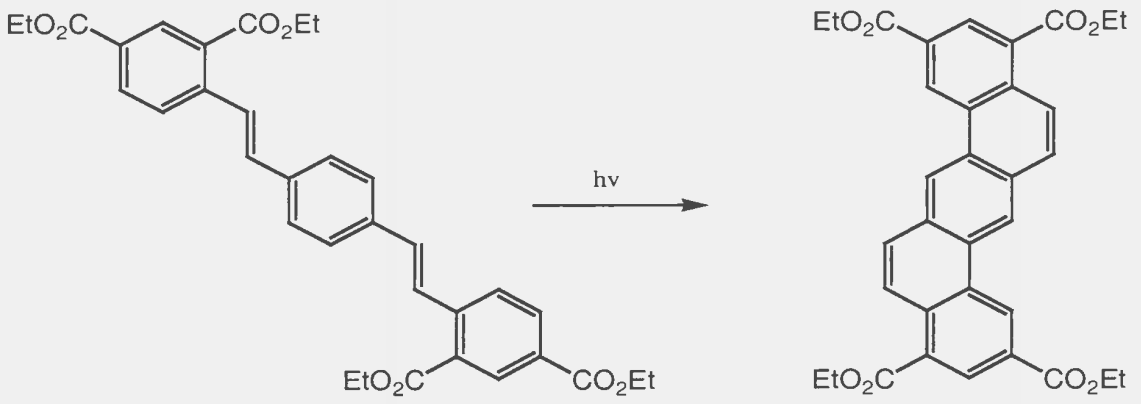
Scheme 2.09 Proposed approach to 109

The Wittig approach could conceivably be effected using either possible aldehyde/ylide pairing. Both reactions would be expected to form the *trans* diene **116**, which could be converted to the desired product **109** by catalytic hydrogenation.



Scheme 2.10 Alternative proposed approach to 109

The possibility of using a photochemical stilbene-phenanthrene conversion to afford molecular board **117** was not considered to be viable for two reasons (Scheme 2.11). First, it is known that 1,4-distyrylbenzene is a very poor substrate for this reaction.[11] Second, the planar nature of the product was expected to lead to solubility problems.



116 **117**

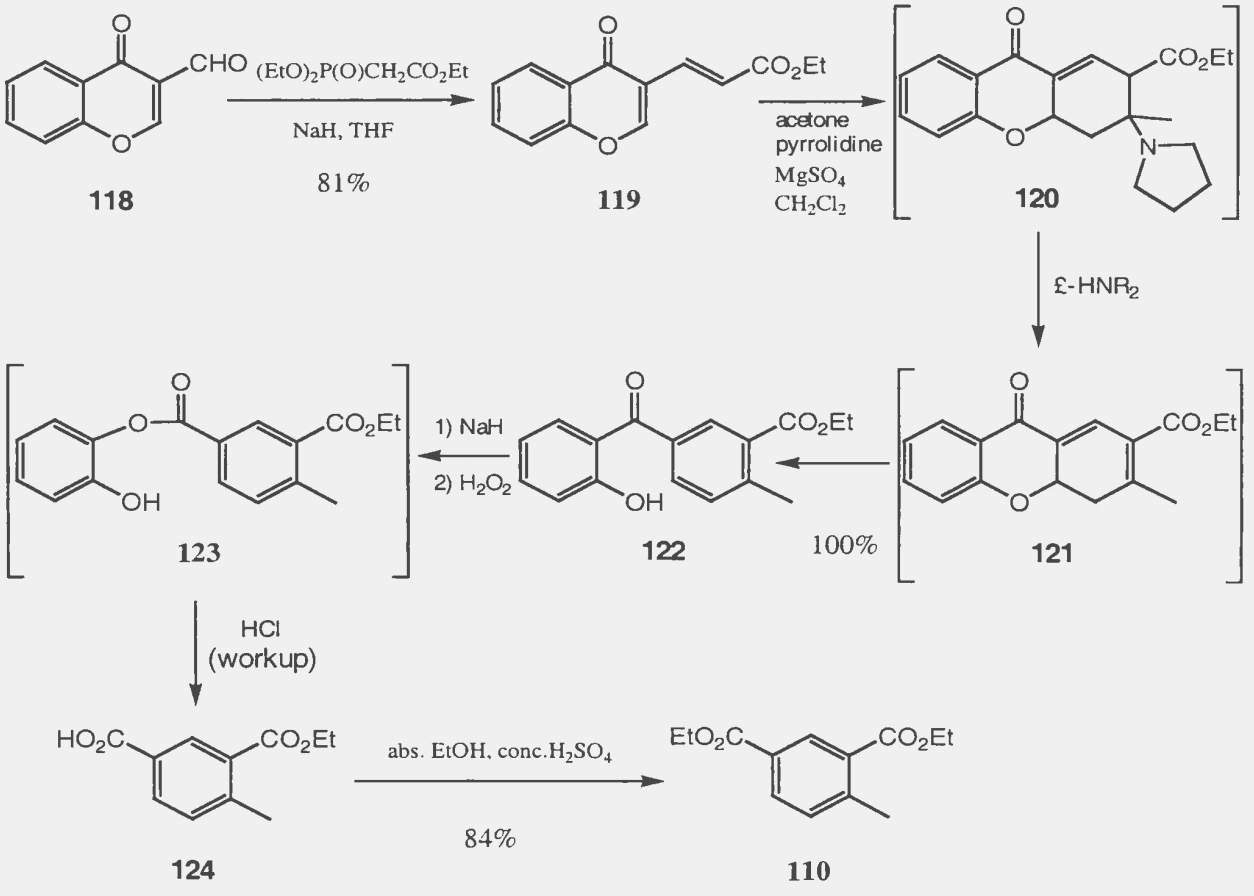
Scheme 2.11 Proposed approach to 117

2.3 Attempted Synthesis of Molecular Board

Pursuit of the alkylation strategy began with the synthesis of diester **110** using chemistry that was developed by Krista Hawco in the Bodwell group.[10]

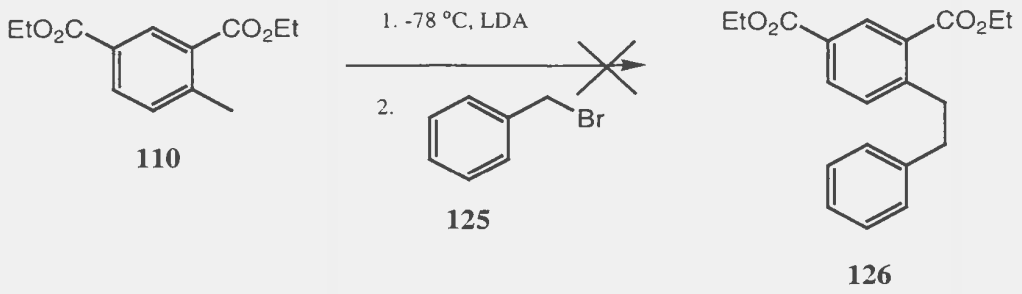
The synthesis started with commercially available 3-formylchromone **118**, which was subjected to a Horner-Wadsworth-Emmons reaction to afford electron deficient diene **119** (81%) (Scheme 2.12). An IEDDA reaction between diene **119** and the *in situ* generated enamine **120** then led to the formation of 2-hydroxybenzophenone derivative **122** in 100% yield. The formation of **122** can be explained by a domino IEDDA/elimination/intramolecular elimination sequence. The hydroxy group ortho to the carbonyl group in **122** renders this substance a suitable substrate for the Dakin reaction.[12] Upon treatment of **122** with NaH (deprotonation of the OH group), followed by the addition of H_2O_2, this compound underwent a Baeyer-Villiger type rearrangement, in which an O atom was inserted selectively to afford **123**. Under

acidic workup conditions, 4-methylisophthalic acid 3-ethyl ester **124** formed. Without purification, the crude acid was esterified under Fischer esterification conditions to provide diester **110** in 84% yield over two steps. The diester **110** is an important intermediate in this synthesis of molecular board **81** (see page 33). The two ester groups not only provide appropriately positioned functionality for the eventual cyclophane-forming chemistry, but they also enhance the acidity of the benzylic protons. It was therefore anticipated that the benzylic anion could be easily formed and alkylated upon treatment with base and then an alkylating agent.



Scheme 2.12 Synthesis of 110

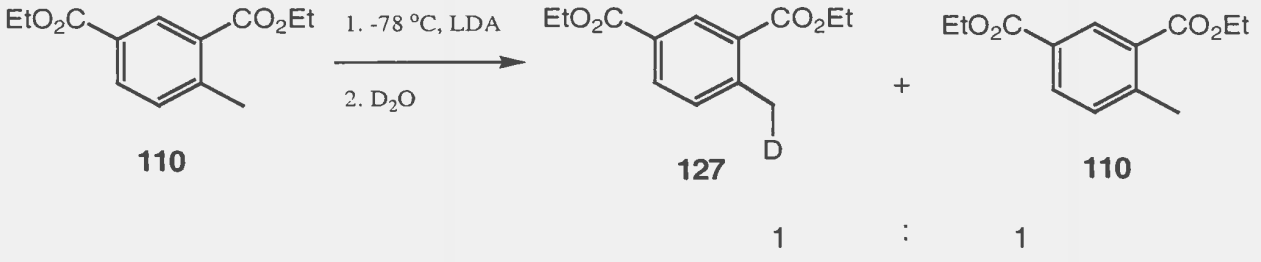
A model reaction was performed to test the feasibility of the anion alkylation strategy (Scheme 2.13). When LDA was added to the diester **110** at –78 °C, a bright red colour did appear, which is presumably due to the anion.[13] However, the addition of benzyl bromide **125** led to the recovery of the starting material.



110 **125** **126**

Scheme 2.13 Attempt towards 126

To determine whether or not deprotonation had occurred, diester **110** was treated with LDA at –78 °C and the resulting dark red solution was quenched with an excess of D_2O (Scheme 2.14).



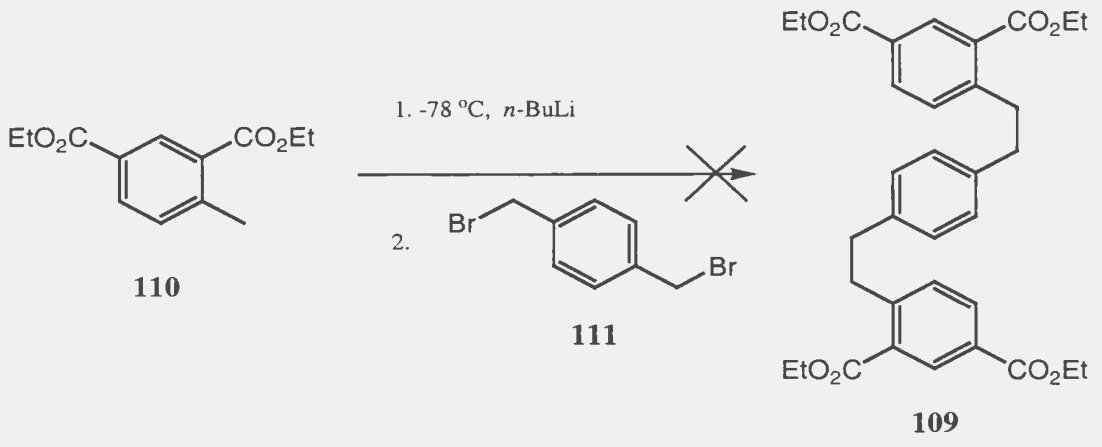
110 **127** **110**

1 : 1

Scheme 2.14 Deuterium-proton exchange of 110

^{1}H NMR analysis of the crude product indicated that a *ca.* 1:1 mixture of the starting material **110** and deuterated diester **127** had formed. This showed that the deprotonation occurred in at least half of the molecules. The actual degree of deprotonation may have been higher, but internal return of the acidic proton may have occurred to afford **110**. Further experiments would be required to determine this, but it was nevertheless shown that a significant degree of deprotonation could be achieved with LDA.

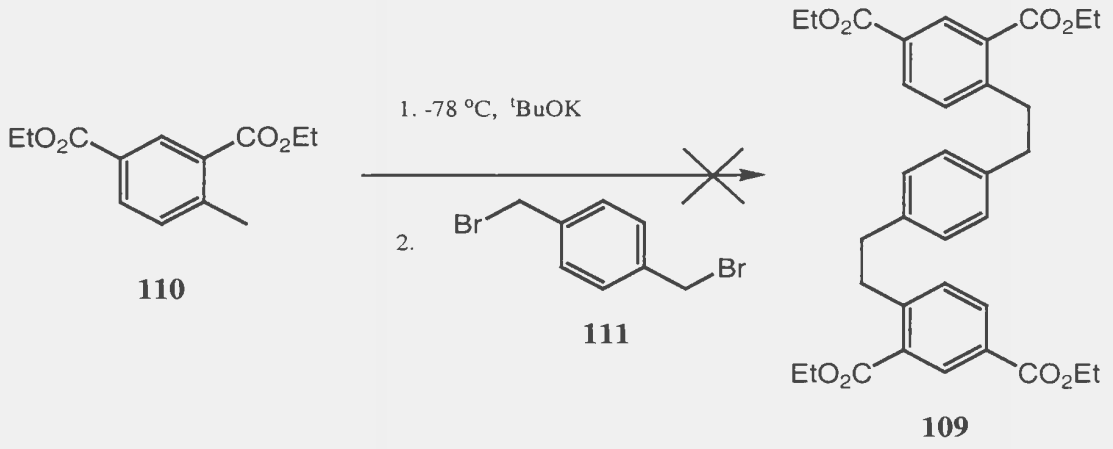
It was then decided to use *n*-BuLi as a base because the conjugate acid (butane) would not form complexes with the anion. An attempt to prepare the desired tetraester **109** was then made by deprotonating the diester **110** with *n*-BuLi and the resulting anion was treated with α,α'-dibromo-*p*-xylene (Scheme 2.15).



110 **111** **109**

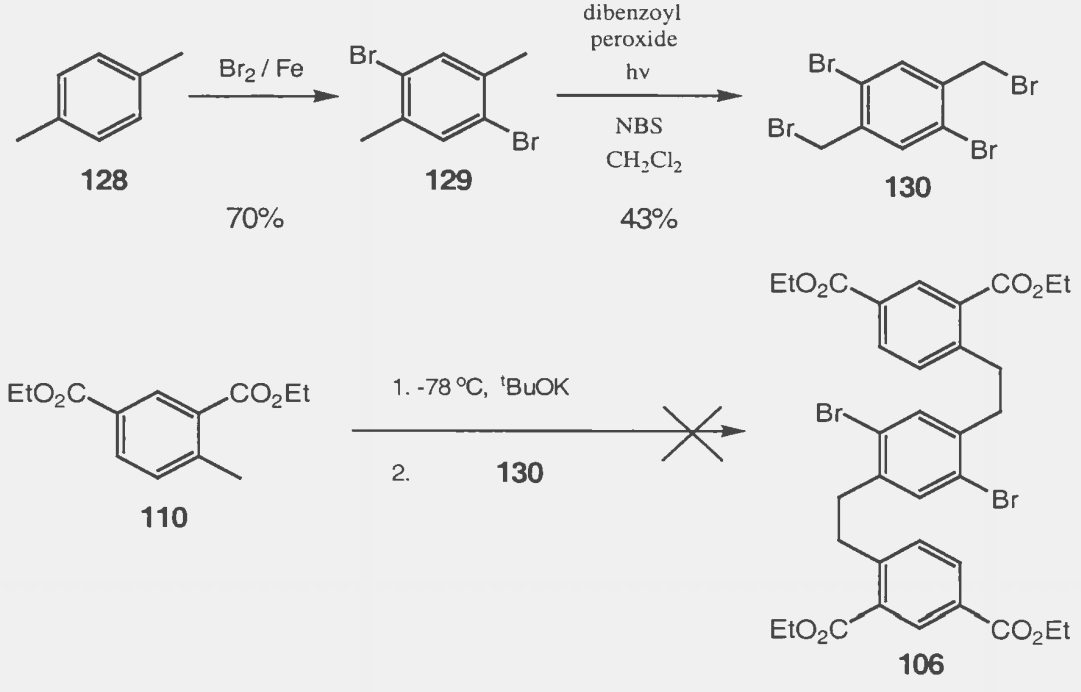
Scheme 2.15 Attempt towards 109

This time the starting materials were fully consumed. However, as seen in the ^{1}H NMR spectrum of the crude product, a complex product mixture formed. No product was isolated and no conclusions regarding nature of the mixture could be drawn from the spectroscopic data. It may be that the *n*-BuLi might have acted as a nucleophile instead of a base to some extent. Another reaction was carried out using *t*-BuOK as the base (Scheme 2.16). Still, despite the formation of a dark red solution, the result turned out to be disappointing as the reaction afforded an intractable mixture.



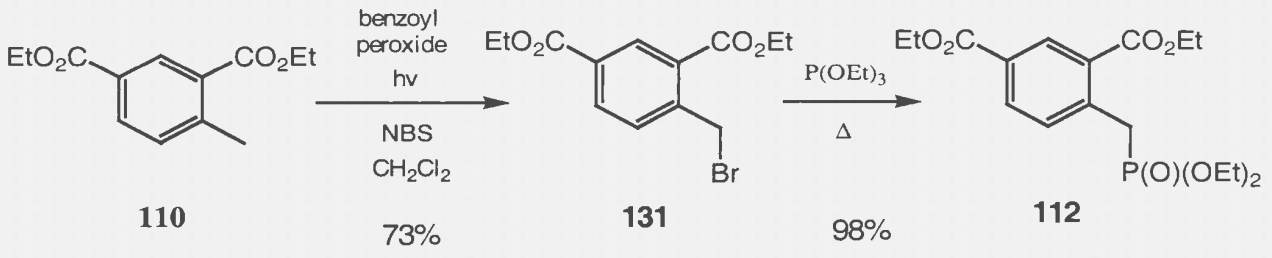
Scheme 2.16 Attempt towards 109

Not surprisingly, a similar result was obtained when the electrophile was changed from **111** to tetrabromide **130**. This electrophile was prepared according to a procedure described by a previous Bodwell group member, Tom Houghton.[14] *p*-Xylene was brominated with Br_2/Fe to afford dibromide **129** (70%).[14] Free radical bromination of the benzylic positions was then achieved using NBS/dibenzoyl peroxide/hv. Tetrabromide **130** was obtained in 43% (Scheme 2.17).



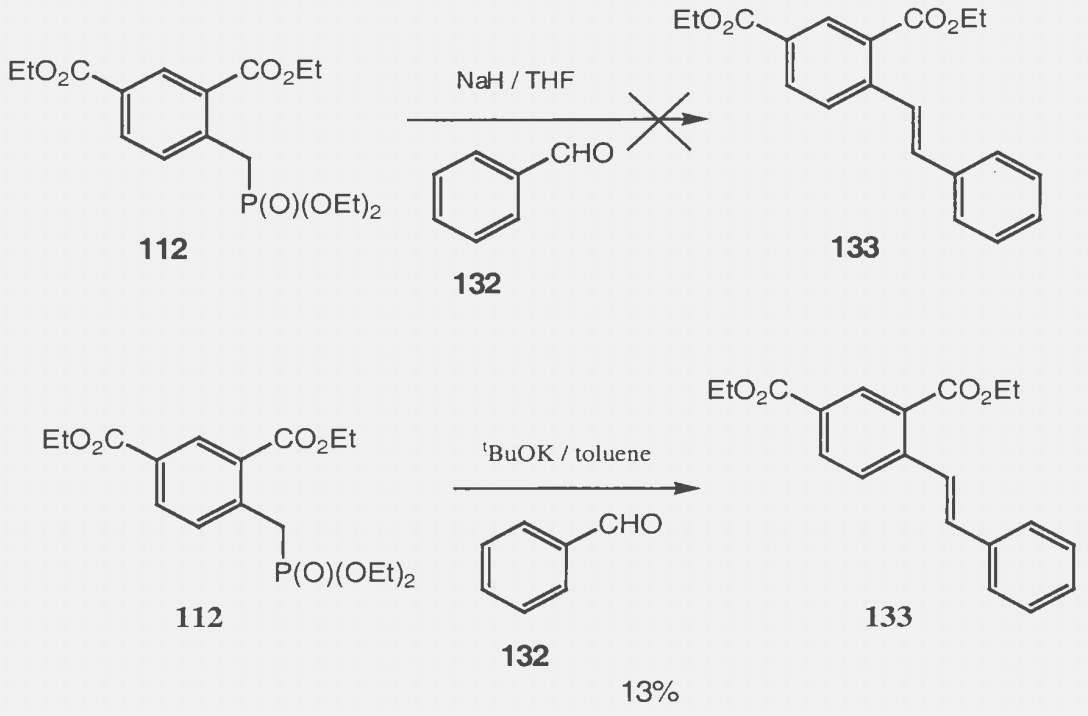
Scheme 2.17 Attempt towards 106

After the unsuccessful attempts to form the desired C-C bonds using the alkylation strategy, it was decided to pursue the Wittig approach. Owing to its reported success in the synthesis of distyrylbenzenes,[15] a variant of the Wittig reaction, the Horner-Wadsworth-Emmons reaction, was chosen. The benzylic position of diester **110** was brominated using NBS/dibenzoyl peroxide/hv to provide compound **131** (73%), which was consequently converted to corresponding phosphonate **112** by Arbuzov reaction with $P(OEt)_3$ in 98% yield (Scheme 2.18).



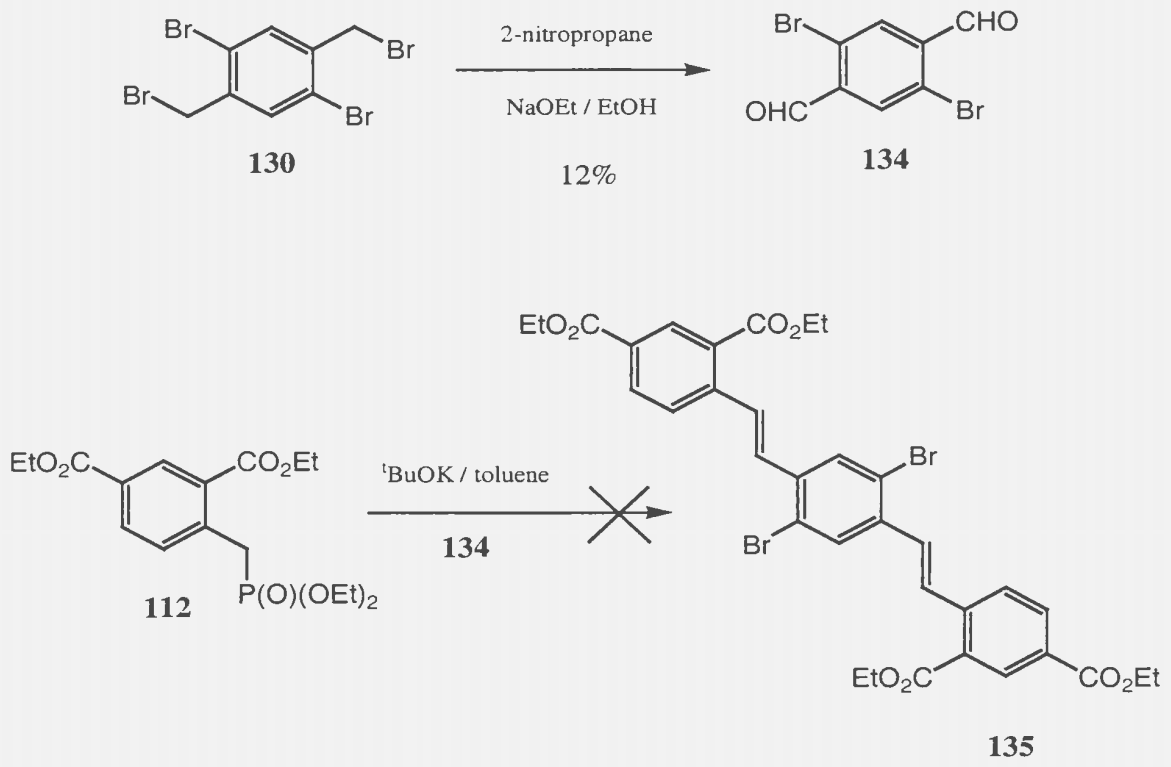
Scheme 2.18 Synthesis of 112

A model reaction was investigated first. Phosphonate **112** was treated with NaH and then benzaldehyde (Scheme 2.19), but there was no apparent reaction even under reflux. When *t*-BuOK was used as the base and the solvent was changed to toluene, a small amount (13%) of the desired product **133** was obtained.



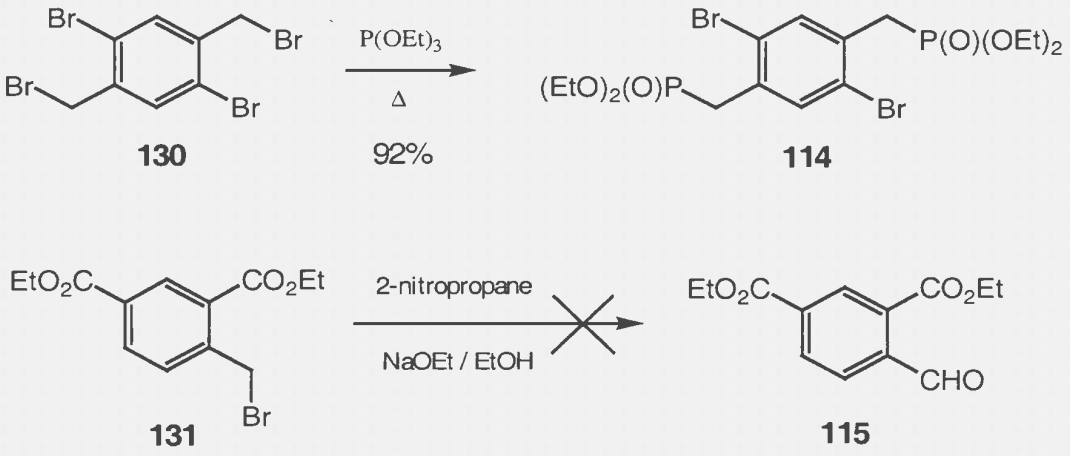
Scheme 2.19 Synthesis of 133

With the yield of **133** being just 13%, the prospects for success with a dialdehyde appeared bleak. However, **134** would be expected to be a better electrophile than benzaldehyde, so the synthesis of **134** was undertaken. Reduction of tetrabromide **130** with 2-nitropropane under basic conditions afforded dialdehyde **134** in 12% yield. A Horner-Wadsworth-Emmons reaction of phosphonate **112** and dialdehyde **134** was then performed under the conditions used for making alkene **135** (Scheme 2.20). Unfortunately, a complex mixture of products was produced.



Scheme 2.20 Attempt towards 135

The poor results obtained using phosphonate **112** may be a consequense of the stability, and thus low reactivity, of the ylid that forms upon deprotonation. If this is the case, then the complementary pairing of aldehyde and phosphonate should prove to be more amenable to Horner-Wadsworth-Emmons reaction. Dibromide **130** was converted to phosphonate **114** by Arbuzov reaction with $P(OEt)_3$ in 92% yield, but initial attempts at the conversion of bromide **131** to the corresponding aldehyde were not successful (Scheme 2.21). At this point, a decision to stop working in this area and pursue a different (and ultimately successful) strategy (see Chapter 3) was made.



Scheme 2.21 Synthesis of 114 and attempt toward 115

2.4 Conclusions and Future Work

In this chapter a general strategy to the desired molecular board was proposed. This involved the formation of a C-C bond between benzylic carbons on each building block. Unfortunately, the two methods that were investigated, alkylation and Horner-Wadsworth-Emmons reaction, led to only minimal success at best. There is clearly much room for further investigation of this strategy. The alkylation approach might still prove to be successful if the appropriate combination of base, solvent and additive can be found. The Horner-Wadsworth-Emmons reaction between **114** and **115** certainly requires further attention, but will have to await the successful preparation of aldehyde **115**. Other C-C bond forming reactions, *e.g.* the alkylation of cuprates, might be worthy of investigation.

2.5 Experimental

General. All chemicals were reagent grade and were used as received. Chromatographic separations were performed on Merck silica gel 60 (particle size 40 – 63 μm, 230 – 400 mesh). Melting points were determined on a Fisher-Johns apparatus and are uncorrected. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were obtained on a Bruker spectrometer: ^{1}H shifts are relative to internal tetramethylsilane; ^{13}C shifts are relative to the solvent resonance ($CDCl_3$: δ = 77.23). All experiments with moisture- or air-sensitive compounds were performed in anhydrous solvents under nitrogen unless otherwise stated. Solvents were dried and distilled according to standard procedures.

1,4-Dibromo-2,5-bis(bromomethyl)benzene (130)

2,5-Dibromo-*p*-xylene (33.37 g, 126.4 mmol) and NBS (47.28 g, 266.8 mmol) were combined in CH_2Cl_2 (1 L) and the suspension was heated under reflux. A spatula tip of dibenzoyl peroxide was then added and a bright light shone on the flask to promote radical formation. Heating was continued for a period of 3 h. The reaction was washed with water (500 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was recrystallized from acetone to give **130** (22.86 g, 43% yield) as colourless crystals. mp 160-161 °C (lit.[ref] 161-162 °C); ^{1}H NMR (500 MHz , $CDCl_3$) δ 7.66 (s, 2H), 4.51 (s, 4H).

***E*-3-(2-(ethoxycarbonyl)vinyl)-chromen-4-one (119)**

NaH (60% dispersion in mineral oil, 6.89 g, 172 mmol) was suspended in dry THF

(150 mL) under a nitrogen atmosphere. Triethylphosphonoacetate (41.29 g, 183.5 mmol) was added dropwise to this suspension, followed by the dropwise addition of a solution of 3-formylchromone (20.00 g, 114.9 mmol) in dry THF (450 mL). The resulting orange solution was stirred at room temperature for 23 h. The solvent was removed under reduced pressure. The orange residue was dissolved in CH_2Cl_2 (150 mL), then washed with saturated $NaHSO_3$ solution (100 mL), water (100 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (2% EtOAc / CH_2Cl_2) to give **119** (22.59 g, 81%) as a bright yellow solid. mp 107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, J = 8.0 Hz, 1H), 8.12 (s, 1H), 7.74 – 7.68 (m, 1H), 7.49 – 7.43 (m, 2H), 7.41 (s, 1H), 7.32 (s, 1H), 4.26 (q, J = 7.0 Hz, 2H), 1.33 (t, J = 7.0 Hz, 3H).

Ethyl 5-(2-hydroxybenzoyl)-2-methylbenzoate (122)

To a stirred solution of *E*-3-(2-ethoxycarbonyl)vinyl)-chromen-4-one **119** (14.00 g, 71.7 mmol), $MgSO_4$ (8.45 g, 71.7 mmol) in CH_2Cl_2 (150 mL), was added acetone (37.60 g, 573.1 mmol) and pyrrolidine (5.11 g, 71.7 mmol). The reaction mixture was stirred for 25 min. The solids were removed and the filtrate was washed with 1 M HCl solution (100 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2) to give **122** (16.50 g, 100%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.96 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 6.92 – 6.87 (m, 1H), 4.38 (q, J = 7.0 Hz, 2H), 2.70 (s, 3H), 1.40 (t, J = 7.0 Hz, 3H).

Diethyl 4-methylisophthalate (110)

To a stirred suspension of NaH (60% dispersion in mineral oil, 1.95 g, 48.81 mmol) in

dry THF (400 mL) was added dropwise a solution of ethyl ester-5-(2-hydroxybenzoyl)-2-methylbenzoate **122** (11.09 g, 39.06 mmol) in dry THF (100 mL) and the resulting yellow solution was stirred for 10 min. To the resulting solution was added H_2O_2 (30% aqueous solution, 5.29 g, 46.6 mmol) and the mixture was stirred for 20 h. The reaction mixture was concentrated under reduced pressure, and concentrated HCl solution (50 mL) was added. The resulting white precipitate was collected by suction filtration and washed with a small amount of ice water. The solid was dried *in vacuo* and then suspended in absolute EtOH (250 mL). To this suspension was added concentrated H_2SO_4 (4 mL) and the mixture was heated under reflux for 20 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was redissolved in CH_2Cl_2 (150 mL) and washed with water (150 mL), saturated aqueous $NaHCO_3$ solution (150 mL) solution, saturated aqueous NaCl (150 mL) solution and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2) to give **110** (7.62 g, 84%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 4.41 – 4.37 (m, 4H), 2.65 (s, 3H), 1.43 – 1.39 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 166.1, 145.4, 132.6, 132.0, 131.9, 130.4, 128.5, 61.3, 61.2, 22.0, 14.5.

Diethyl 4-(bromomethyl)isophthalate (131)

Diethyl 4-methylisophthalate **110** (1.45 g, 6.12 mmol) and NBS (1.20 g, 6.73 mmol) were combined in CH_2Cl_2 (50 mL). To this stirred solution was added a spatula tip of dibenzoyl peroxide and a bright light shone on the flask to promote radical formation. The reaction mixture was stirred for 28 h, then washed with water (50 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was

purified by column chromatography (35% CH_2Cl_2 / hexanes)to give **131** (1.40 g, 73%) as a pale yellow solid. mp 71 – 73 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 4.98 (s, 2H), 4.47 – 4.40 (m, 4H), 1.47 – 1.41 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 165.5, 143.7, 133.2, 132.5, 132.0, 130.1, 130.0, 61.9, 61.6, 14.5, 14.4.

Diethyl 4-(triethylphosphono)methylisophthalate (112)

Diethyl 4-(bromomethyl)isophthalate **131** (3.24 g, 10.3 mmol) and $P(OEt)_3$ (1.71 g, 10.3 mmol) were combined together and the reaction mixture was heated at 80 °C for 20 h. The residue was purified by column chromatography (35% CH_2Cl_2 / hexanes) to give **112** (3.75 g, 98%) as yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 4.44 – 3.91 (m, 4H), 4.03 – 3.98 (m, 4H), 3.87 (d, J = 24 Hz, 2H), 1.45 – 1.40 (m, 6H), 1.23 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 165.8, 138.4, 132.6, 132.5, 132.1, 130.9, 129.5, 62.5, 61.6, 32.1, 16.4, 14.3.

Stilbene-2,4-dicarboxylic acid diethyl ester (133)

To a slurry of *t*-BuOK (49 mg, 0.44 mmol) in toluene (20 mL), was added a solution of **112** (179 mg, 0.48 mmol) in toluene (5 mL), followed by benzaldehyde (43 mg, 0.40 mmol). The reaction mixture was heated at reflux for 22 h. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), washed with saturated $NaHSO_3$ solution (20 mL), water (20 mL), saturated aqueous NaCl solution (20 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2) to

give **133** (16 mg, 13%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, J = 2.0 Hz, 1H), 8.14 (dd, J = 8.0, 2.0 Hz, 1H), 8.02 (d, J = 16.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.38 (t, J = 8.0 Hz, 2H), 7.30 (t, J = 8.0 Hz, 1H), 7.12 (d, J = 16.0 Hz, 1H), 4.45 – 4.39 (m, 4H), 1.45 – 1.41 (m, 6H).

2,5-Dibromoterephthalaldehyde (134)

To a solution of NaOEt (made from Na (64 mg, 2.80 mmol) and EtOH (1.1 mL)) in EtOH (9.3 mL), was added 2-nitropropane (249 mg, 2.80 mmol), followed by a solution of 1,4-dibromo-2,5-bis(bromomethyl)benzene **130** (536 mg, 1.27 mmol) in EtOH (5 mL). The reaction mixture was stirred at room temperature for 24 h. The solvent was removed and the residue was dissolved in CH_2Cl_2 (20 mL), washed with H_2O (20 mL), 10% aqueous NaOH solution (20 mL), saturated aqueous NaCl solution (20 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (50% CH_2Cl_2 / hexanes) to afford **134** (45 mg, 12%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.35 (s, 2H), 8,16 (s, 2H).

1,4-Dibromo-2,5-bis(triethylphosphono)methylbenzene (114)

1,4-Dibromo-2,5-bis(bromomethyl)benzene **130** (1.29 g, 3.06 mmol) and $P(OEt)_3$ (1.02 g, 7.12 mmol) were combined together and the reaction mixture was heated at 80 °C for 21 h. The residue was purified by column chromatography (CH_2Cl_2) to give **114** (1.51 g, 92%) as off-white solid. mp 107 – 109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 2H), 4.11 – 4.05 (m, 8H), 3.34 (d, J = 20.5 Hz, 2H), 1.28 (t, J = 7.0 Hz, 12H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 135.4, 132.8, 123.8, 62.6, 33.0, 16.5.

2.6 References

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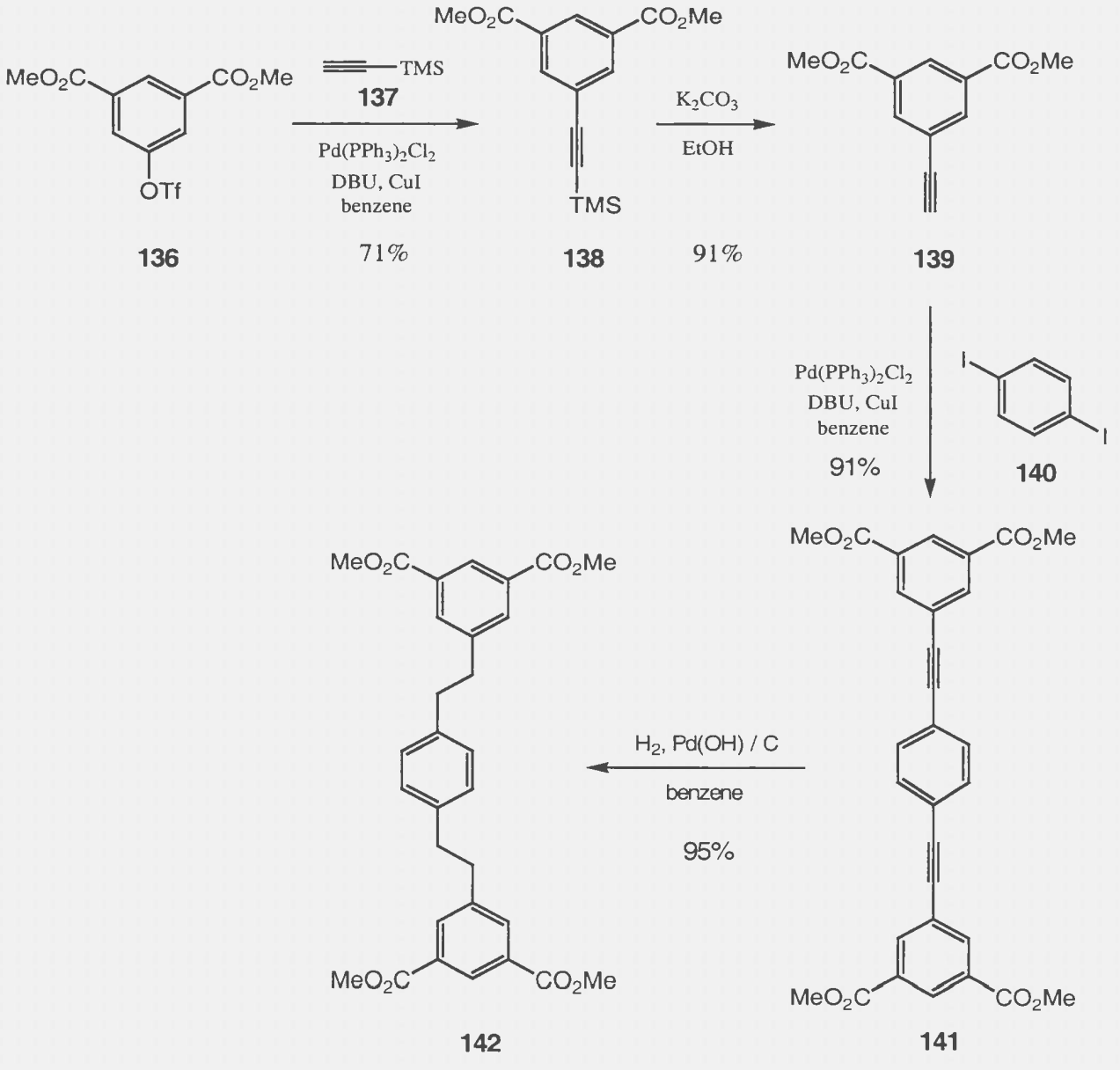
Chapter 3

Synthesis of a Molecular Board and Attempts to Prepare Aromatic Belts

3.1 Introduction

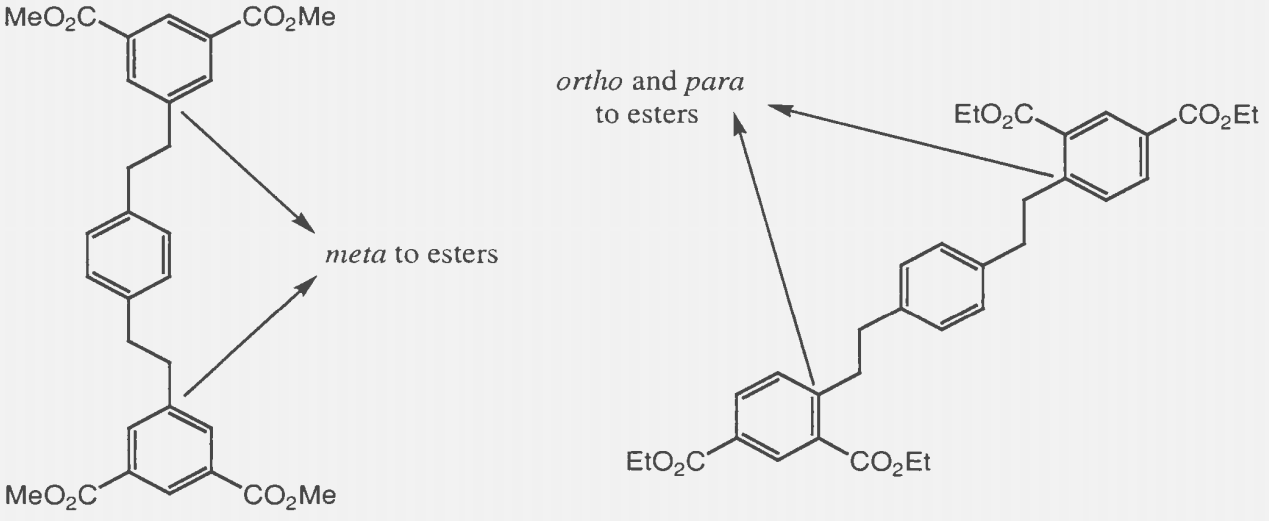
After the failed attempt to synthesize the desired molecular board using the alkylation and Wittig methods (Chapter 2), it was decided to focus attention on the employment of some Pd-catalyzed cross-coupling reactions, especially the Sonogashira reaction, which had proven to be effective in related work in the Bodwell group. Bodwell and Vermeij reported the synthesis of tetraester **142** by the sequence of reactions shown in



Scheme 3.01 Rolf Vermeij's synthesis of 142

Scheme 3.01. Sonogashira reaction of triflate **136** with TMS acetylene **137** gave, following protiodesilylation of **138**, alkyne **139**. This was then used in a further Sonogashira reaction with 1,4-diiodobenzene. Catalytic hydrogenation of the resulting diyne **141** afforded tetraester **142**.

As shown in Figure 3.01, it can be seen that the only structural difference between compound **142** and the desired product **109** is the point of attachment of the ethano units to the isophthalate rings. In **142**, the alkyl substituent is *meta* to the two ester groups, but in **109** it is *ortho* and *para* to the two ester groups. This structural similarity suggested that Sonogashira coupling might also be a reliable methodology for the construction of **109**.

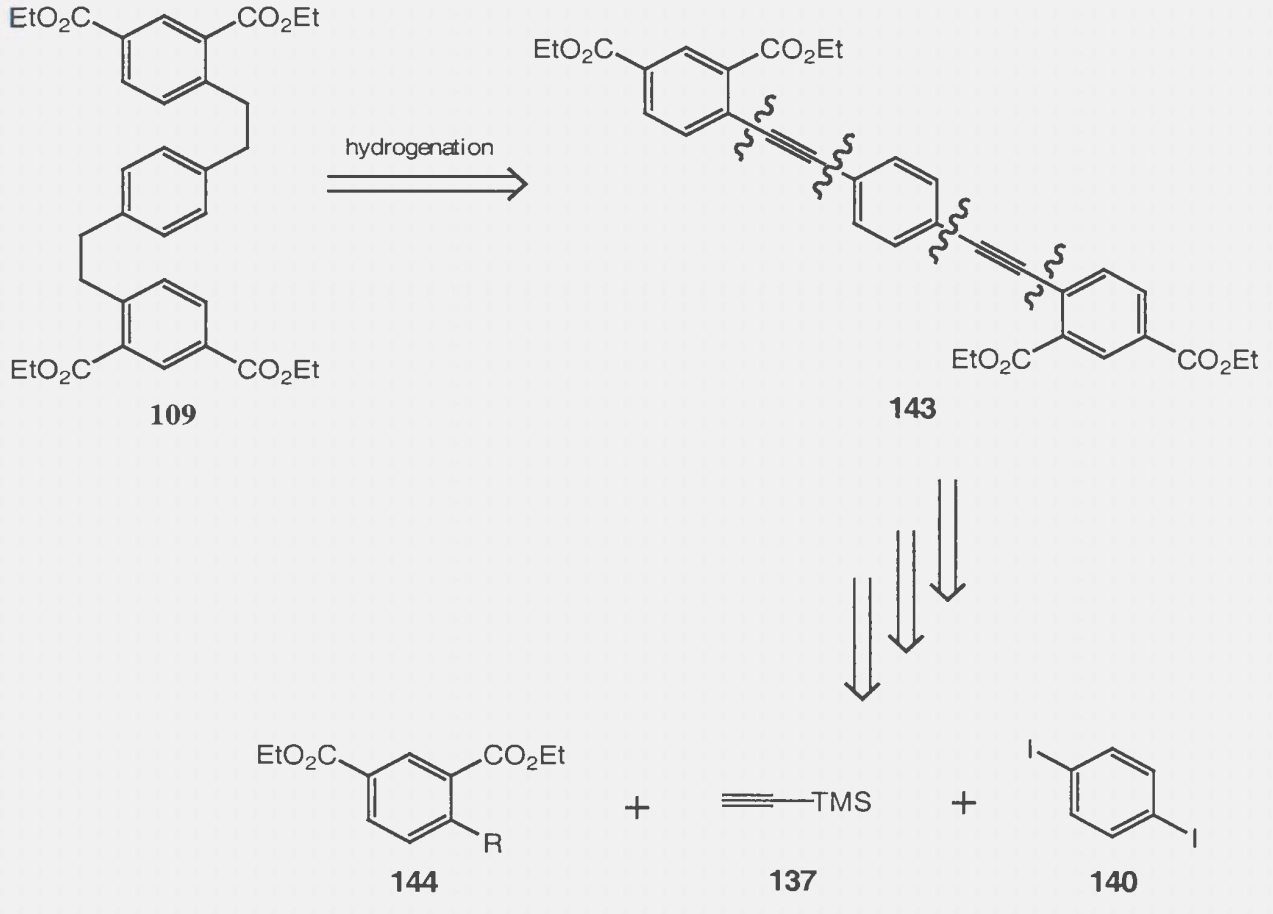


142 **109**

Figure 3.01 Comparison of 142 and 109

3.2 Retrosynthetic Analysis

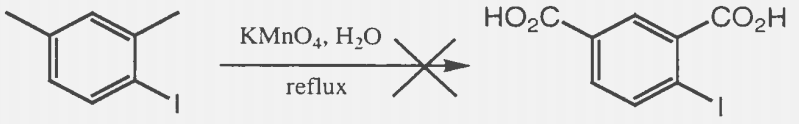
Retrosynthetically, the ethylene groups in tetraester **109** could be derived from alkyne units in compound **143** by a catalytic hydrogenation transform (Scheme 3.02). Through two double Sonogashira transforms, diyne **143** could then be broken down to three building blocks: diethyl isophthalate derivative **144**, trimethylsilylacetylene **137** and 1,4-diiodobenzene **140**, the latter two of which are commercially available. The substituent R in **144** would have to be appropriate ones for Sonogashira coupling such as OTf, Br or I. Compound **144** is not commercially available, but it was not expected to pose a significant synthetic challenge.



Scheme 3.02 Retrosynthetic analysis of 109

3.3 Synthesis of Molecular Board 150

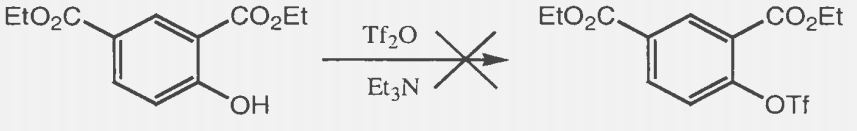
The order of reactivity of substrates for the Sonogashira reaction is typically: I > OTf °÷ Br. Therefore, the first choice for the functional group R in **144** was I. Accordingly, the oxidation of 4-iodo-*m*-xylene **145** by $KMnO_4$ was attempted. However, this reaction failed to deliver 4-iodoisophthalic acid **146** (Scheme 3.03). The iodine atom may have been oxidized under these conditions.



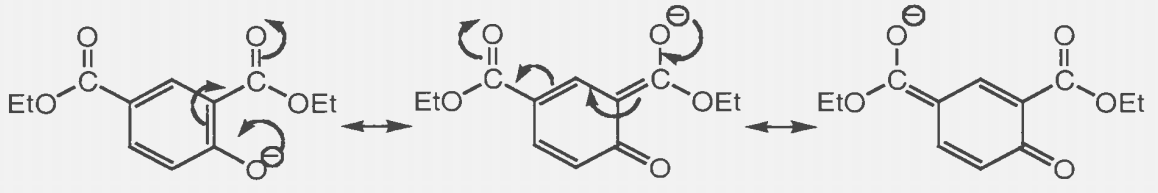
145 **146**

Scheme 3.03 Attempt towards 146

Attention was then turned to the synthesis of the corresponding triflate **148**. Unfortunately, this synthesis was unsuccessful. Reaction of diethyl 4-hydroxyisophthalate **147** with Tf_2O/Et_3N did not appear to progress at all. The problem in this reaction was presumably the resonance stabilization of the phenoxide **149**, which presumably rendered it very non-nucleophilic (Scheme 3.04).



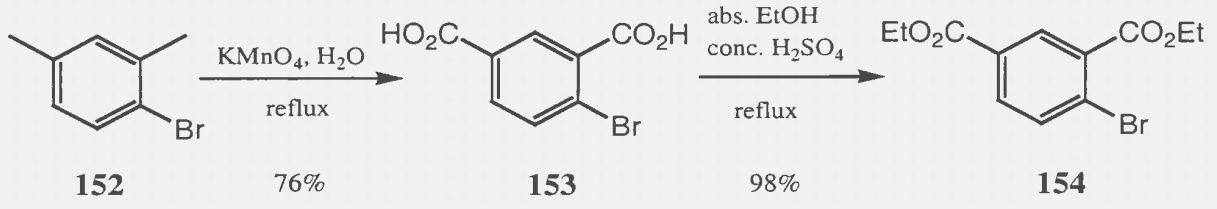
147 **148**



149 **150** **151**

Scheme 3.04 Attempt towards 148

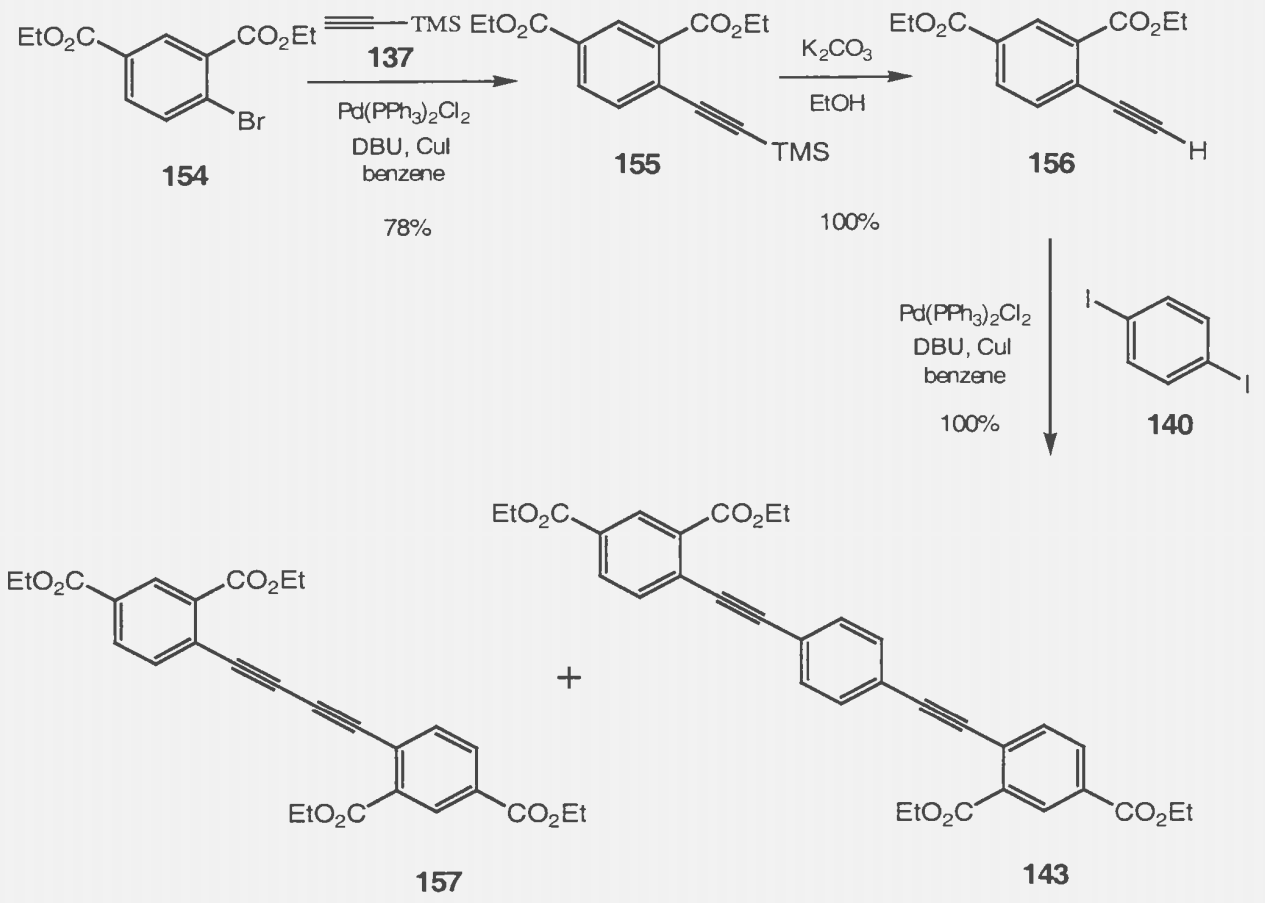
Although Br was the last choice of substituent, the synthesis of diethyl 4-bromoisophthalate **154** proved to be the easiest (Scheme 3.05). 4-Bromoisophthalic acid **153** is a commercially available compound, but it is relatively expensive. Oxidation of relatively inexpensive 4-bromo-*m*-xylene **152** by $KMnO_4$ successfully provided diacid **153** in 76% yield. Then diacid **153** was then refluxed in EtOH in the presence of conc. H_2SO_4 to give diester **154** in 98% yield.



Scheme 3.05 Synthesis of 154

The first attempt to synthesize diyne **143** started with diester **154**. By performing a Sonogashira coupling between trimethylsilylacetylene **137** and diester **154**, alkyne **155** was formed in 78% yield. Subsequent protiodesilylation of protected alkyne **155** gave terminal alkyne **156** in 100% yield. A second Sonogashira coupling, this time between 1,4-diiodobenzene **140** and terminal alkyne **156** provided the desired diyne **143**, along with the byproduct **157** in a conversion rate, of *ca.* 100% (Scheme 3.06).

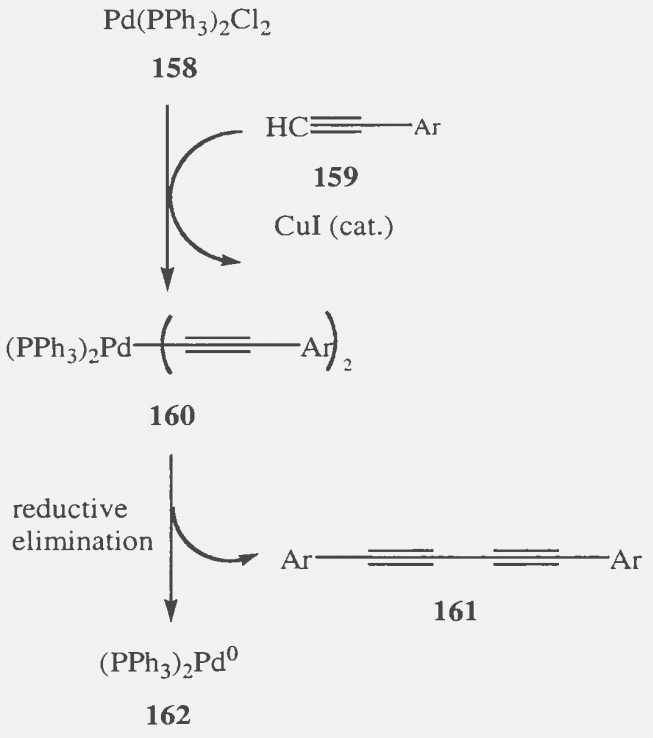
The byproduct **157** coeluted on TLC with **143** under a variety of conditions. Attempted recystallization from a variety of solvents did not work very well either.



Scheme 3.06 First Synthesis of 143

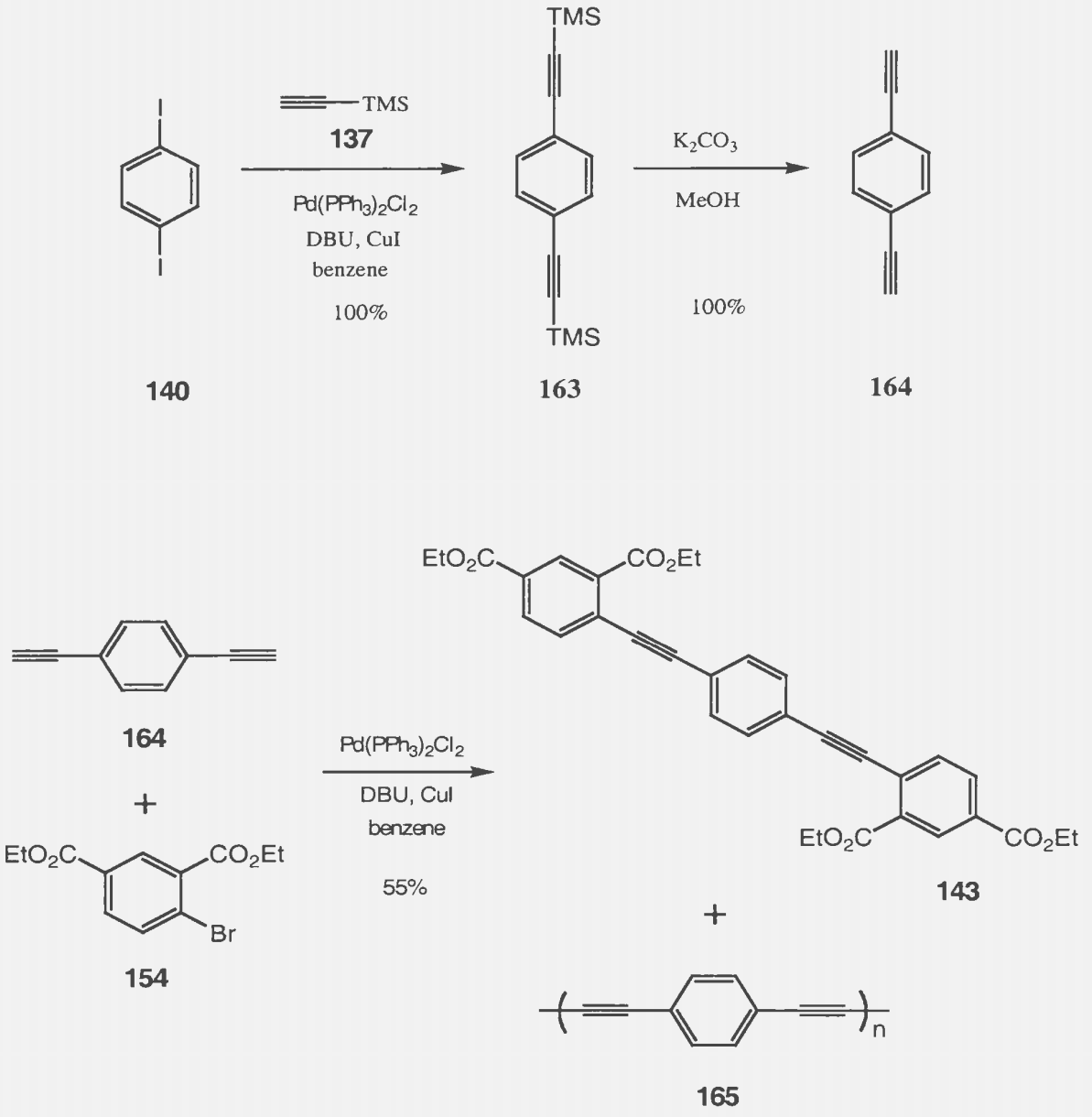
From the mechanism of Sonogashira coupling using Pd(II) as the catalyst,[1] it could be seen that the forming of this byproduct is inevitable (Scheme 3.07).

During the process of forming the catalytically active Pd (0), which is required for the Sonogashira coupling, $(PPh_3)_2PdCl_2$ **158** first reacts with two alkyne molecules **159** under CuI catalysis to provide the intermediate Pd-alkyne complex **160**. Reductive elimination of **161** affords the active catalyst **162**.



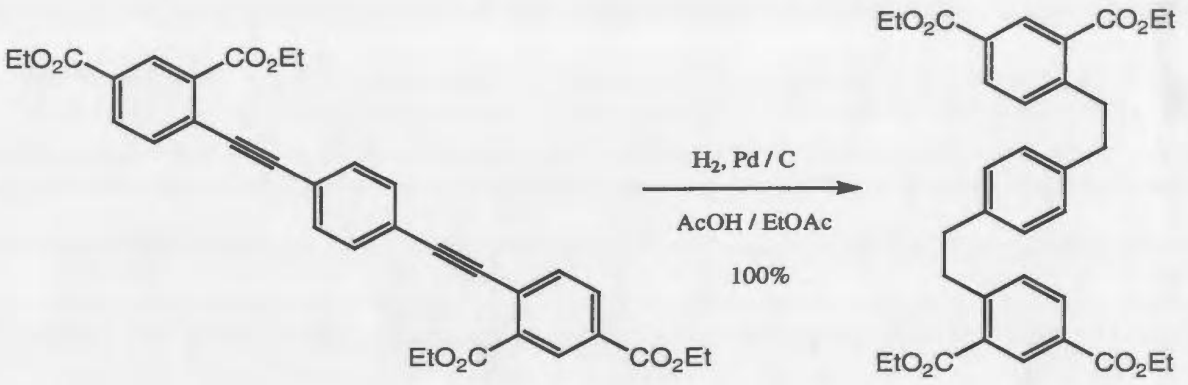
Scheme 3.07 Partial Mechanism of Sonogashira coupling

Rather than focus on finding suitable conditions for the separation of **143** and **157**, another synthetic approach that avoided forming inseparable byproduct **157** was proposed (Scheme 3.08). Starting from 1,4-diiodobenzene **140**, Sonogashira coupling with trimethylsilylacetylene **137** yielded compound **163** in 100% yield. Protodesilylaiton of compound **163** then gave diyne **164**, also in 100% yield. Another Sonogashira coupling of compound **164** and diester **154** provided diyne **143** in 55% yield. In this synthesis, the desired product **147** could easily be separated from any byproducts **165** by column chromatography.



Scheme 3.08 Second synthesis of 143

The next step was the catalytic hydrogenation of diyne **143** to give tetraester **109**, which proceeded in 100% yield (Scheme 3.09).

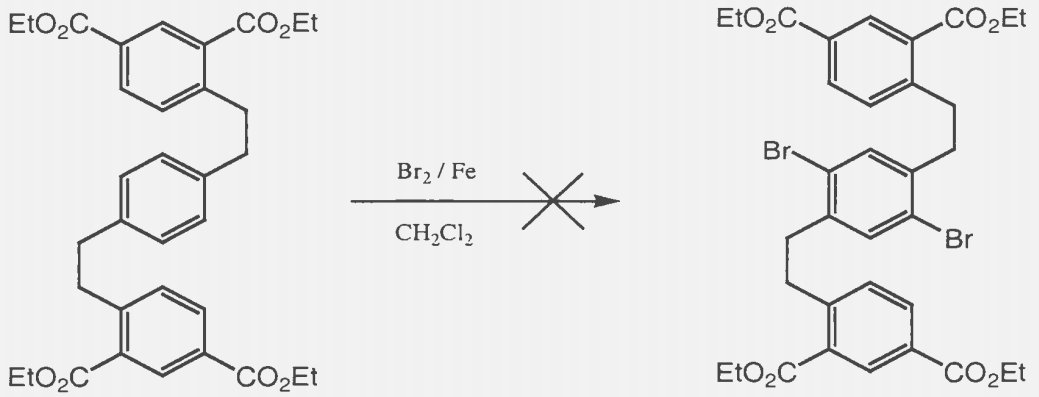


143 109

Scheme 3.09 Synthesis of 109

The next goal was to introduce two *para*-related bromine atoms to the central ring. As discussed in Chapter 2, this might be achieved either by the direct bromination of **109** or by installing these bromine atoms in advance.

The direct electrophilic aromatic bromination was tried first (Scheme 3.10). Tetraester **109** was treated with 2.0 equivalents of Br_2 in the presence of iron filings. The reaction was first performed in CH_2Cl_2 at 0 °C and room temperature, and there was no reaction at all. The reaction was then heated at reflux for two days. TLC analysis indicated that small quantities of some new products had formed, but the signals at ~ _ 4.5 in the ^1H NMR spectrum of the crude product indicated that these were in fact benzylic bromides and not aryl bromides. These presumably arise from an ambient light-initiated free radical process. Attempts were also made to reflux the reaction in a higher boiling point solvent like $CHCl_3$, but again, no desired product formed. Increasing the proportion of Br_2 to 4.0 equivalents did not help either.

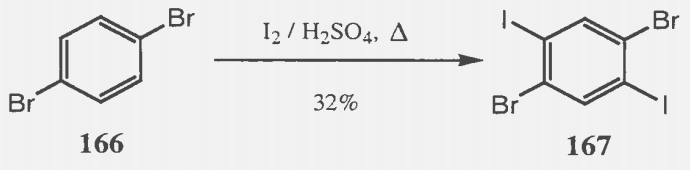


109 **106**

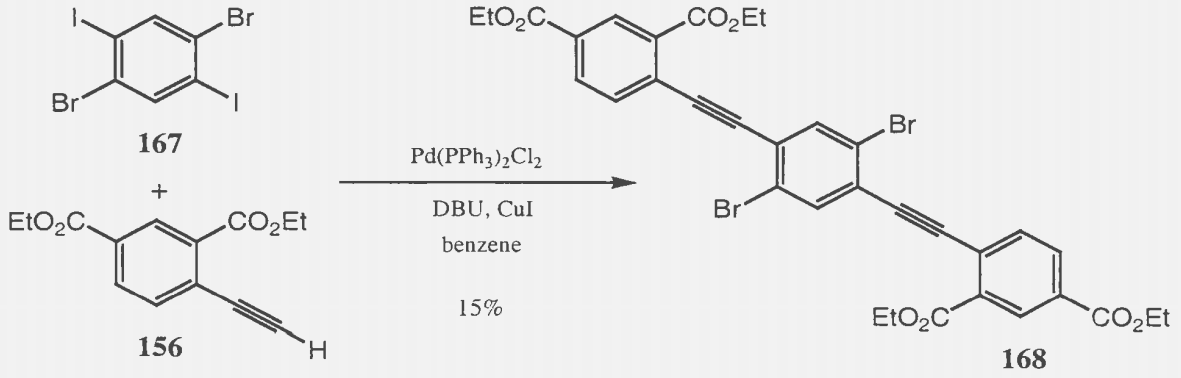
Scheme 3.10 Attempt towards 106 using Br_2/Fe

It was then decided to pursue the alternative strategy of installing the Br atoms at an earlier stage.

1,4-Dibrombenzene **166** was iodinated by I_2/conc. H_2SO_4 to give tetrasubstituted benzene **167** in 32% yield.[2] Under Sonagashira coupling conditions, compound **167** coupled with terminal alkyne **156** to afford dibromodiyne **168** in 15% yield (Scheme 3.11).

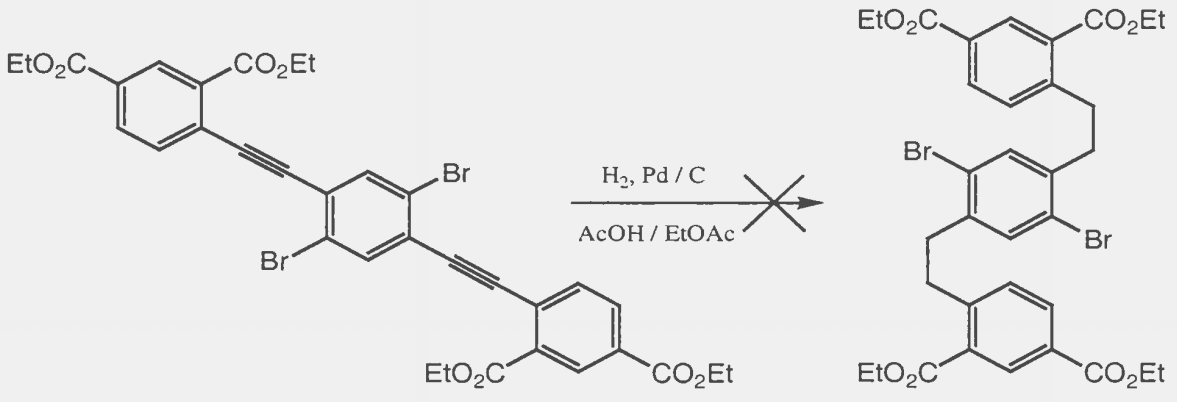


166 **167**



Scheme 3.11 Synthesis of 168

Unfortunately, the subsequent hydrogenation, which was expected to proceed smoothly, did not give any of the desired product **106** (Scheme 3.12). It may be that the Br atoms, in conjunction with the ester groups that are *ortho* to the alkyne units, provide sufficient steric hindrance to prevent the approach of the alkynes to the catalyst surface. Furthermore, the electron-withdrawing nature of the bromine atoms would be expected to lower the electron density of the triple bonds, thus rendering them less reactive towards catalytic hydrogenation. Although there is plenty of scope for further investigation in this area (variation of the catalyst, solvent and conditions), this disappointing result prompted a return to the original strategy.

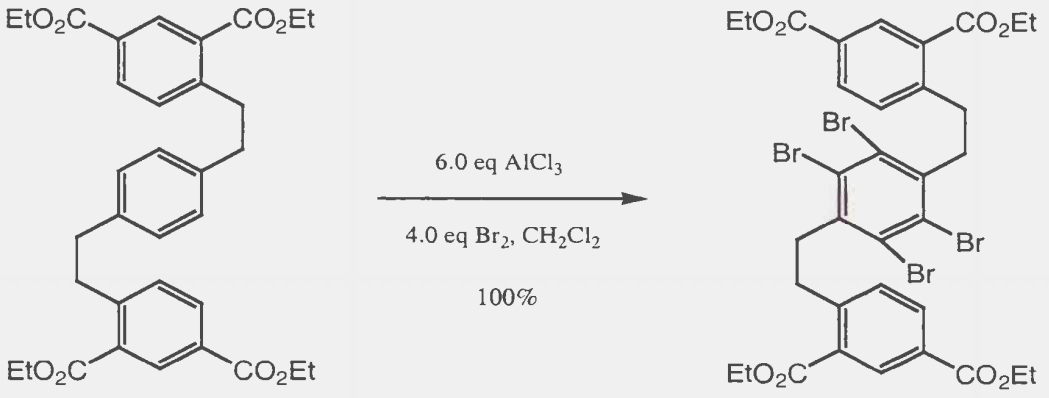


168 **106**

Scheme 3.12 Attempt towards 106 by hydrogenation of 168

Revisitation of the direct bromination approach commenced with the use of a different Lewis acid catalyst, namely $AlCl_3$. Initially 2.0 equivalents of $AlCl_3$ and 2.0 equivalents of Br_2 were used. A very faint, but promising new spot was observed by tlc analysis. The reaction was then carried out at higher temperatures (37 °C), using an increased amount of Br_2 (4.0 equivalents). Unfortunately, the reaction still did not appear to proceed significantly further. Moreover, by refluxing overnight, benzylic

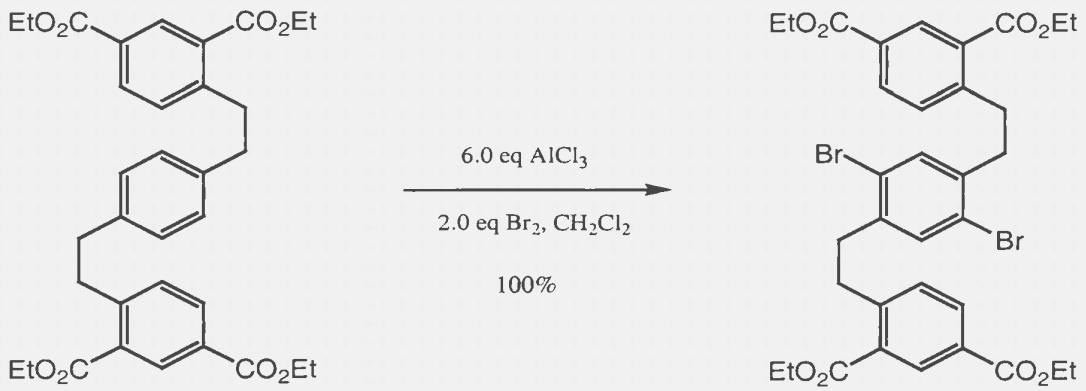
bromination was observed. It seemed at this point that this bromination was just difficult to accomplish. Although it had initially not been expected that each of the four ester groups would complex irreversibly with one equivalent of $AlCl_3$, the possibility that this was indeed the case was then considered. If this were true, then anything less than 4.0 equivalents of $AlCl_3$ of would leave no free catalyst in the system and the reaction would not be expected to proceed. Therefore, 6.0 equivalents of $AlCl_3$ were used with 4.0 equivalents of Br_2 (Scheme 3.13). Excess Br_2 was used because it was anticipated that the third and fourth brominations would not be easy. Surprisingly, the reaction finished very rapidly (in 20 minutes) and ended up giving tetrabrominated product **169** in an almost quantitative yield.



109 **169**

Scheme 3.13 Synthesis of 169

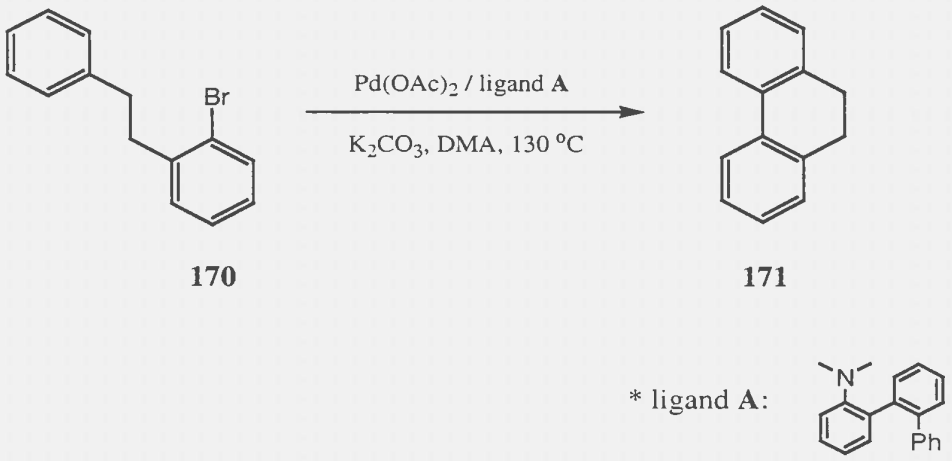
This result was quite amazing because both steric and eletronic considerations would appear to work against the third and fourth brominations. Another reaction with 6.0 equivalents of $AlCl_3$ and exactly 2.0 equivalents of Br_2 was then tried. The dibromide **106** successfully formed in 100% yield (Scheme 3.14).



109 **106**

Scheme 3.14 Synthesis of 106

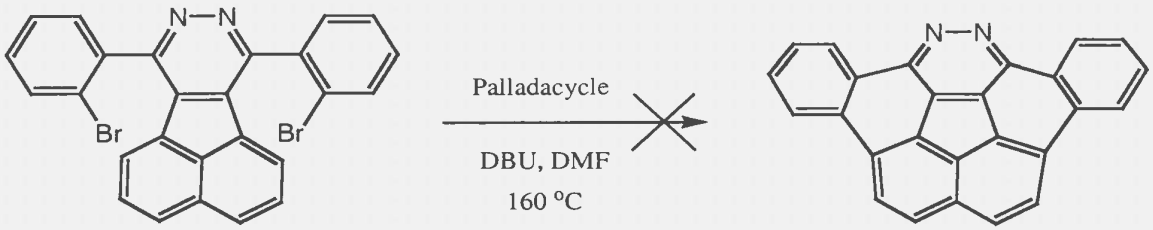
Now came the crucial Pd–catalyzed twofold intramolecular arylation to form the molecular board. A related twofold intramolecular arylation was successfully achieved by Scott (see **20** to **21** in Chapter 1) and Fagnou recently described an even more closely related series of transformations.[3] For example, bromide **170** was converted to dihydroanthracene **171** (Scheme 3.15).



170 **171**

Scheme 3.15 Reported synthesis of 171

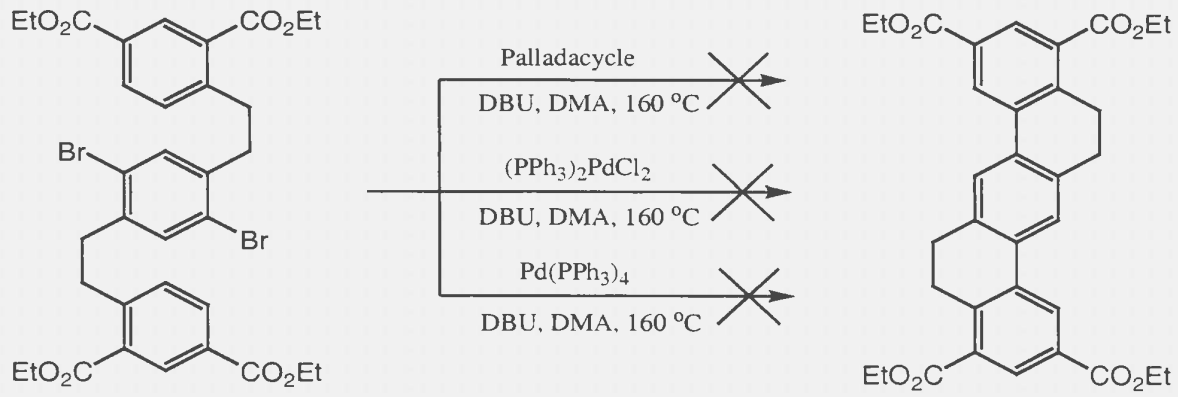
The first attempt to make the molecular board **81** employed Hermann's palladacycle as the catalyst, DBU as the base and DMA as the solvent. These conditions were taken from a failed attempt by former Bodwell group member, Stephen Arns, to prepare the strained hetero Buckybowl **173** from precursor **172** (Scheme 3.16).



172 173

Scheme 3.16 Stephen Arns's attempt towards 173

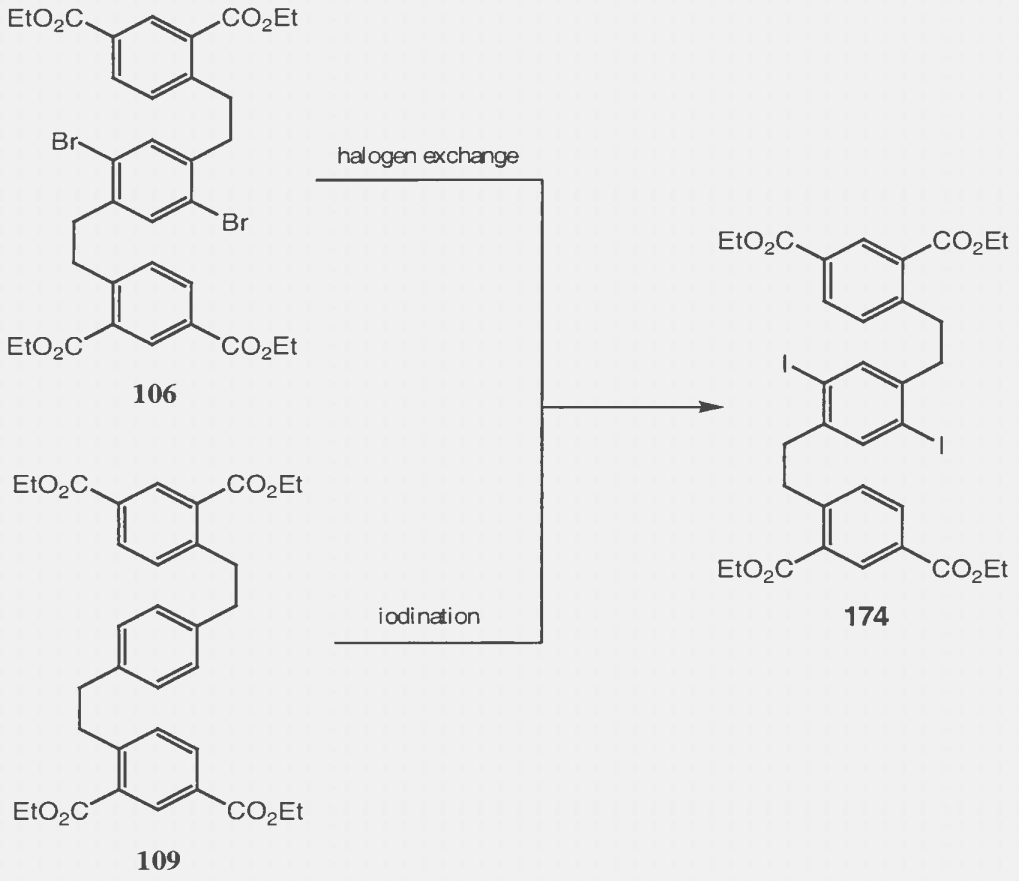
Unfortunately, the starting material **106** was recovered (86%). From the literature,[4] it could be seen that $(PPh_3)_2PdCl_2$ and $Pd(PPh_3)_4$ are the more frequently used catalysts. Therefore, another two reactions were performed using $(PPh_3)_2PdCl_2$ and $Pd(PPh_3)_4$, respectively (Scheme 3.17). After the reactions had been heated for two days, disappointing results were obtained again. In both cases, tlc and ^1H NMR analysis of the crude mixture indicated that a complex mixture of products formed and no clear evidence for the formation of desired product could be seen. At the very least, the starting material had been consumed, so a degree of optimism could be taken from these results.



106 81

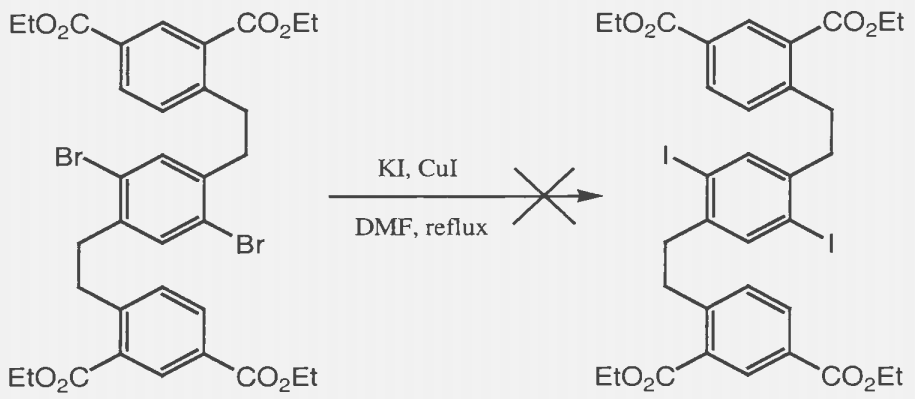
Scheme 3.17 Initial attempts towards 81

Considering that aryl iodides are typically superior to bromides as substrates for many Pd–catalyzed coupling reactions, it was decided to prepare diiodide **174**. Two routes presented themselves immediately (Scheme 3.18). Either a halogen exchange of **106**[5] or an iodination of tetraester **109** would conceivably give diiodide **174**.



Scheme 3.18 Proposed approach to 174

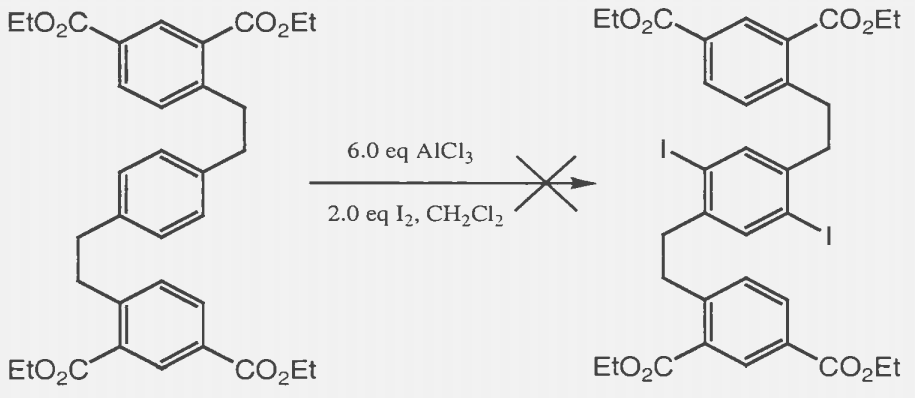
The halogen exchange method was tried first. The dibromide was mixed with KI and CuI,[5] and the mixture was refluxed in DMF for 3 d (Scheme 3.19). A complex mixture was obtained, in which none of desired product could be identified. Another method for halogen exchange involves the use of *n*-BuLi followed by a source of electrophilic iodine. However the presence of four ester groups in **109**, which might serve as electrophiles for the very nucleophilic *n*-BuLi, was a sufficient cause not to attempt this reaction. No further attempts to achieve halogen exchange were made.



106 **174**

Scheme 3.19 Attempted halogen exchange of 106

Attention then was focused on the direct iodination of tetraester **109**. Conditions analogous to those used for the bromination of **109** were employed (Scheme 3.20). Unfortunately, it did not work in this case. A mixture of products formed and some of them were isolated, but no firm conclusions about their identity could be drawn from the spectroscopic data.

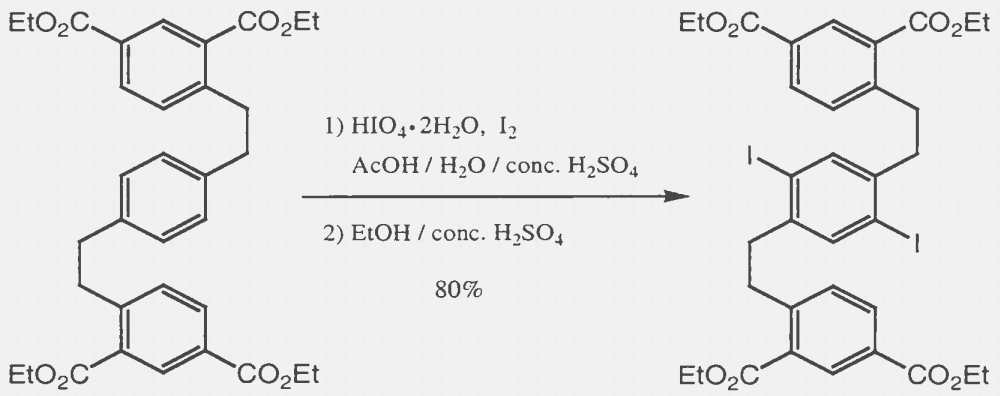


109 **174**

Scheme 3.20 Attempted iodination towards 174

Another attempt to iodinate **109** was made using I_2/periodic acid (Scheme 3.21).[6] This method led to the formation of some of the desired product **174**. By adjusting the

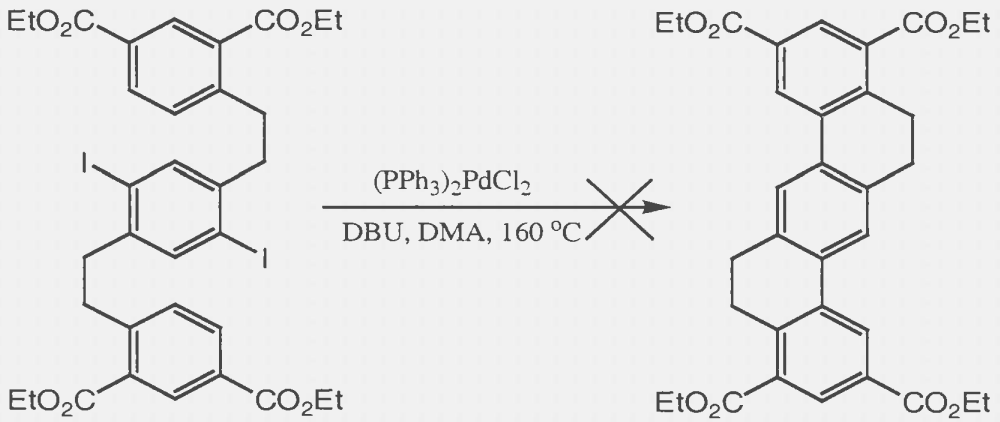
amount of $HIO_4 \cdot 2H_2O$ and I_2 that were used, the yields went up to 80%. In fact this is a two-step reaction. The ester groups hydrolyzed in the first step to form the corresponding tetracarboxylic acid, which was then esterified (EtOH, H_2SO_4) in a second operation to give diiodide **174**.



109 **174**

Scheme 3.21 Synthesis of 174

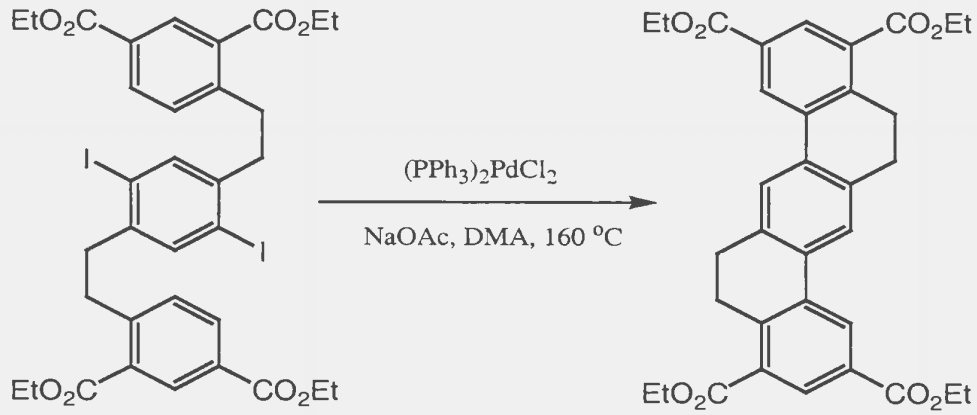
Intramolecular arylation using the diiodide substrate **174** was then tried using $(PPh_3)_2PdCl_2$ as the catalyst (Scheme 3.22). Disappointingly, the desired reaction still did not proceed. As with dibromide **106**, the starting material was consumed, but no evidence of the desired product could be seen from the resulting mixture.



174 **81**

Scheme 3.22 Attempt towards 81

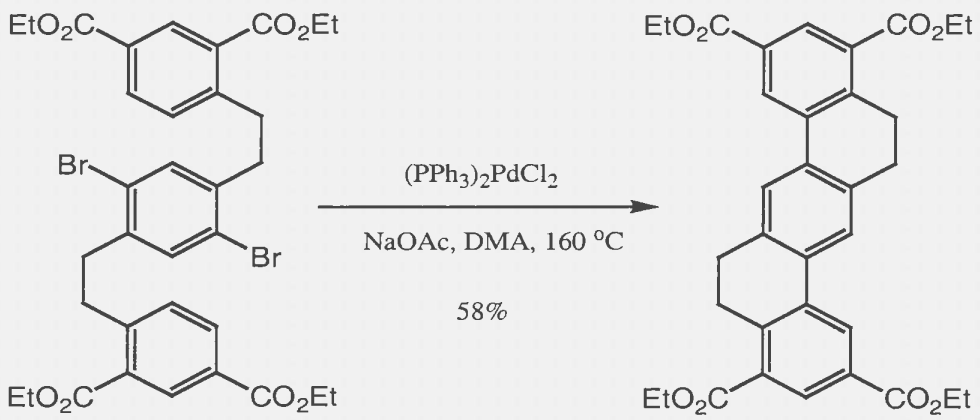
Having varied the catalyst and substrate to no avail, variation of the base was then explored. The use of a number of different bases has been reported in the literature,[3, 4] including NaOAc, $NaOCO^tBu$, Cs_2CO_3 and K_2CO_3. NaOAc was selected as the first choice. With 50 mol% (25 mol% for each arylation) $(PPh_3)_2PdCl_2$ loading, a mixture of diiodide **174** and NaOAc was heated at 160 °C in DMA (Scheme 3.23). Some promising signs were evident upon tlc analysis. The starting material was consumed and a bright fluorescent spot was obtained at a place where it might be expected to be. Isolation and characterization showed that the corresponding fraction consisted mainly of starting material, but contained trace amount of what appeared to be the desired product. This was an exciting result because it demonstrated that the desired ring closure could indeed take place.



174 **81**

Scheme 3.23 Modified attempt to 81

Having had some success with diiodide **174**, the more easily prepared dibromide **106** was then subjected to the same conditions (Scheme 3.24). Surprisingly, the dibromide worked much better than the diiodide. This time a yield of 58% was obtained.

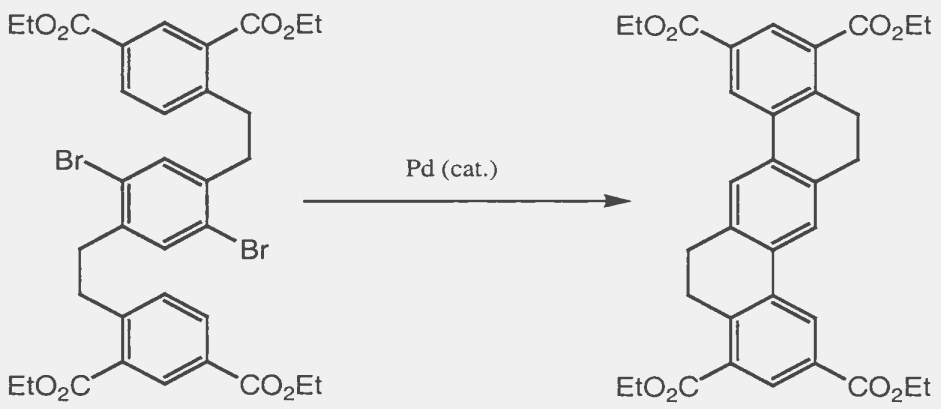


106 **81**

Scheme 3.24 Synthesis of 81

This reaction was done on a 73 mg scale. Another reaction was performed under the same conditions on a 2 g scale and the yield was only 9%. Bearing in mind that to synthesize an aromatic belt from the molecular board **81** would require multigram quantities of **81**, it was immediately apparent that it was critical to increase the reaction scale as well as the yield. Furthermore, it had been observed that the reaction stopped after partial conversion and required the repeated addition of more catalyst to proceed further. Suspecting that this might be due to autocatalytic formation of Pd-black, it was decided to lower the loading of the catalyst in subsequent experiments.

Due to its high boiling point (169 °C), DMA was difficult to remove from the system. The workup procedure involved many washings by water and many extractions by CH_2Cl_2, which presumably contributed to product loss. The use of other more easily removed solvents might be helpful. One reaction was tried with benzene as the solvent. Unfortunately, but not surprisingly, the reaction did not work at all. No other solvents were investigated, but this may warrant further investigation in the future. A series of reactions with DMA as the solvent were performed under various conditions to find superior conditions (Table 3.01).



106 **81**

entry	catalyst system	mol% Pd (mol% Ag)	base	temp (°C)	scale	yield (%)
1	$Pd(OAc)_2$ PPh_3 Ag(OAc)	50 200	NaOAc	~130	73 mg	16
2	$Pd(OAc)_2$ PPh_3 Ag(OAc)	10 200	NaOAc	~130	73 mg	18
3	$Pd(OAc)_2$ PPh_3 Ag(OAc)	10 200	K_2CO_3	~130	73 mg	NA
4	$Pd(OAc)_2$ ligand **A** Ag(OAc)	10 200	K_2CO_3	~130	73 mg	NA
5	$Pd(OAc)_2$ ligand **A** Ag(OAc)	10 200	K_2CO_3	~140	73 mg	NA
6	$Pd(OAc)_2$ ligand **A** Ag(OAc)	20 200	K_2CO_3	~130	73 mg	trace amount product
7	$(PPh_3)PdCl_2$	10	NaOAc	~140	73 mg	90
8	$(PPh_3)PdCl_2$	10	NaOAc	~140	300 mg	69
9	$(PPh_3)PdCl_2$	10	NaOAc	~140	1.2 g	91
10	$(PPh_3)PdCl_2$	5	NaOAc	~140	300 mg	15

* ligand **A**:

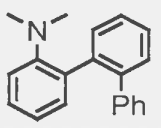


Table 3.01 Optimization towards 81

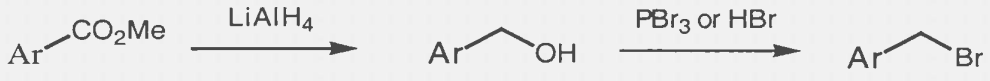
From Entry 1 to 2, the Pd loading was changed from 50 mol% to 10 mol%, and the yield was effectively unchanged, which suggested that 10 mol% Pd is good enough. The use of the additive Ag(OAc) was invesgated on the advice of Prof. K. Fagnou.[3] From Entry 2 to 3, it could be seen that when K_2CO_3 was used as the base, the reaction did not proceed. In Entries 4, 5 and 6, a different ligand **A**, which had been reported to work well for intramolecular arylation,[3] was employed. Apparently, it is not effective for our system although the choice of base may be responsible for the failure of these reactions. Only when 20 mol% Pd was employed were trace amounts of the desired product seen. $(PPh_3)_2PdCl_2$ was then reinvestigated as the catalyst. In Entry 7, the Pd loading was reduced to 10 mol% from 50 mol% that was used previously. Under these conditions, a very gratifying result was obtained. After the reaction was complete, the mixture was cooled to 0 °C and the desired product **81** precipitated. A simple suction filtration afforded the product in "pure" form and in excellent yield (90%). After a few modifications on the workup procedure, the yields were up to 91% on a 1.2 g scale. Since reducing the Pd loading led to such a success, the possibility of further reducing the catalyst loading was investigated. However, a further decrease of the Pd loading ended up with a dramatic drop in yield (15%, entry 10).

Although much more rigorous and systematic optimization could have been conducted at this point, an efficient gram-scale method for the key arylation reaction was at hand. It was therefore decided to direct future efforts toward the conversion of the synthetically useful amounts of molecular board **81** into aromatic belts **90** and **91**.

3.4 Attempted Synthesis of Aromatic Belts 90 and 91

With an appropriately functionalized molecular board **81** successfully synthesized, the next stage of the plan would be the functional group interconversion of the ester groups to bromomethyl groups. Based on substantial precedent in the Bodwell group, this transformation was expected to be straightforward.

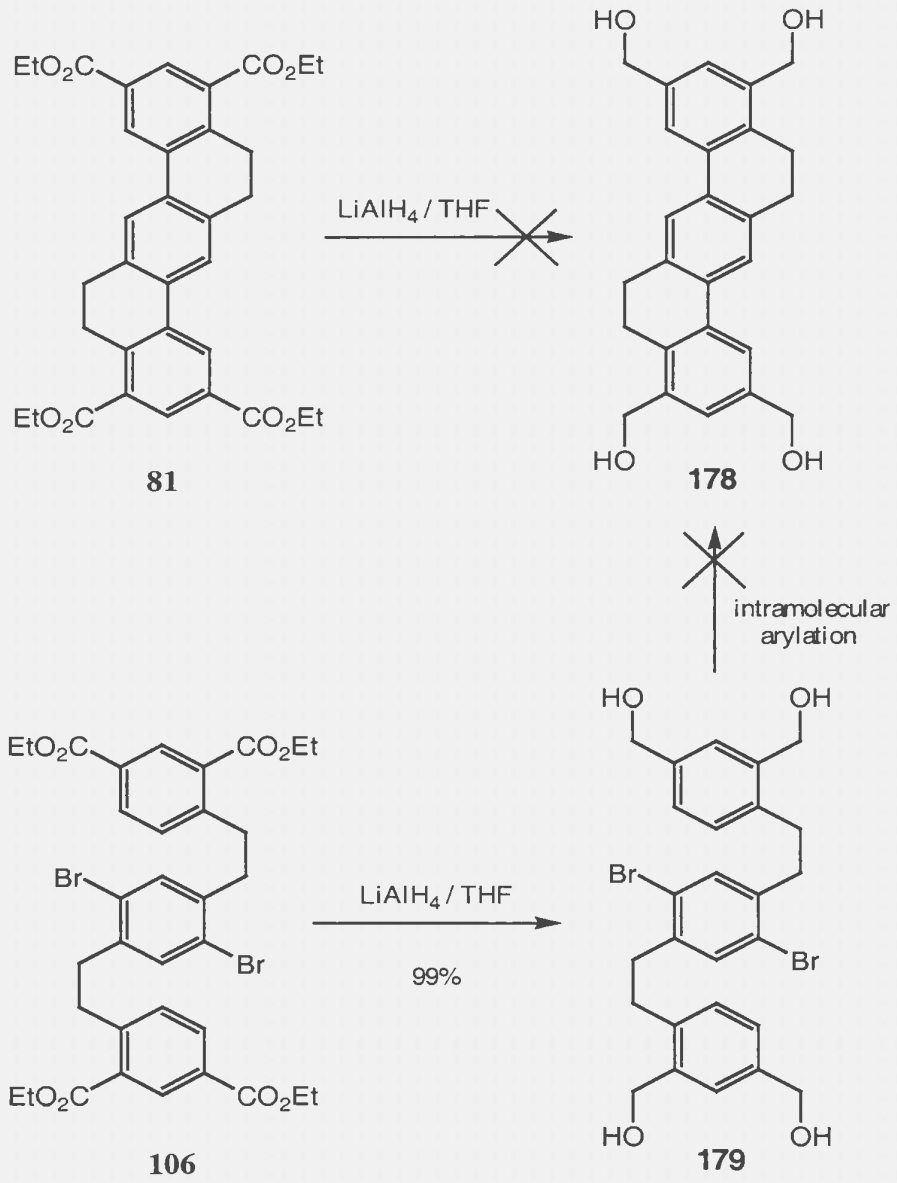
The method that is normally used in the Bodwell group is to reduce the ester **175** to the corresponding alcohol **176** using $LiAlH_4$, followed by bromination (PBr_3 or HBr) to form the bromide **177** (Scheme 3.25). Worthy of note is that this transformation has been successfully achieved in a numerous tetrafunctional systems.



175 **176** **177**

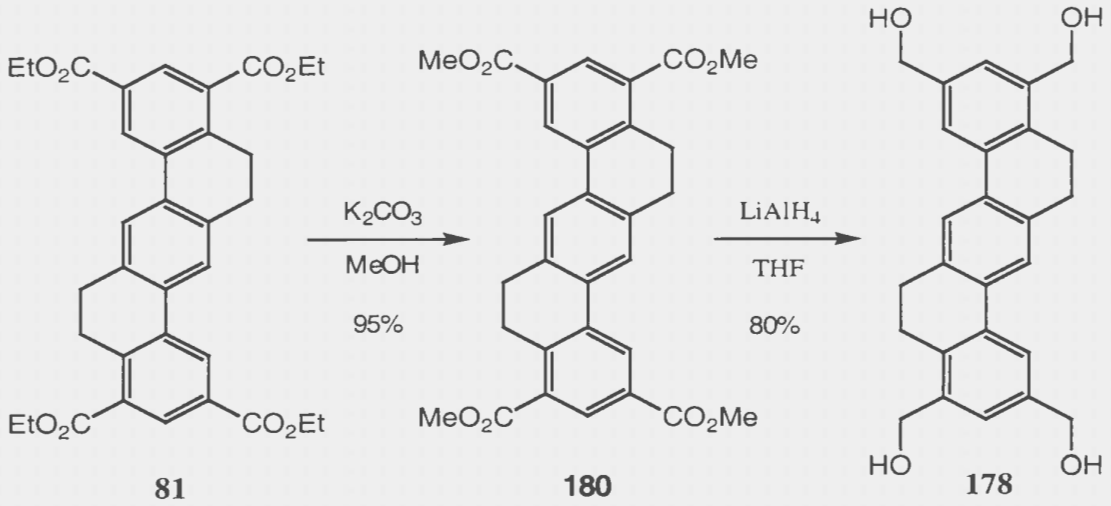
Scheme 3.25 General procedure from ester 175 to bromide 177

Unfortunately, reduction of tetraester **81** with $LiAlH_4$ in THF did not afford the desired tetraol (Scheme 3.26). A mixture of products was obtained, along with some starting material. In an attempt to circumvent this problem, it was then decided to switch the order of the arylation and the reduction. The reduction of dibromide **106** worked successfully to give tetraol **179**, but the ring closure of **179** did not give the desired product **178** when subjected to the conditions used for the conversion of **106** to **81**. Instead, a complex mixture was obtained (Scheme 3.26). No attempt to make this reaction work was made.



Scheme 3.26 Attempts towards 178

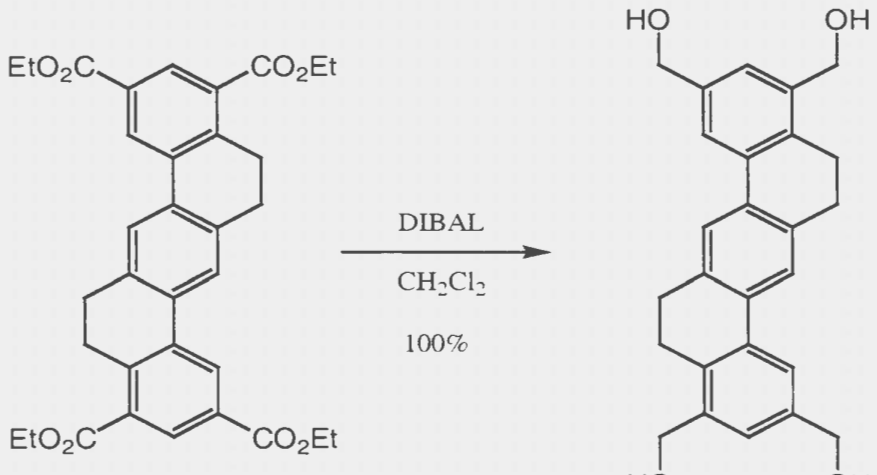
Noticing that all of the precedent in the Bodwell group for the ester-to-bromomethyl-group conversion involved the use of methyl esters, it was decided to convert the ethyl esters in **81** to methyl esters and then perform the $LiAlH_4$ reduction. This approach did work. Transesterification of **81** (MeOH, K_2CO_3) afforded **180** in 95% yield and reduction of this ester with $LiAlH_4$ afforded tetraol **178** in 80% yield (Scheme 3.27).



81 180 178

Scheme 3.27 First synthesis of 178

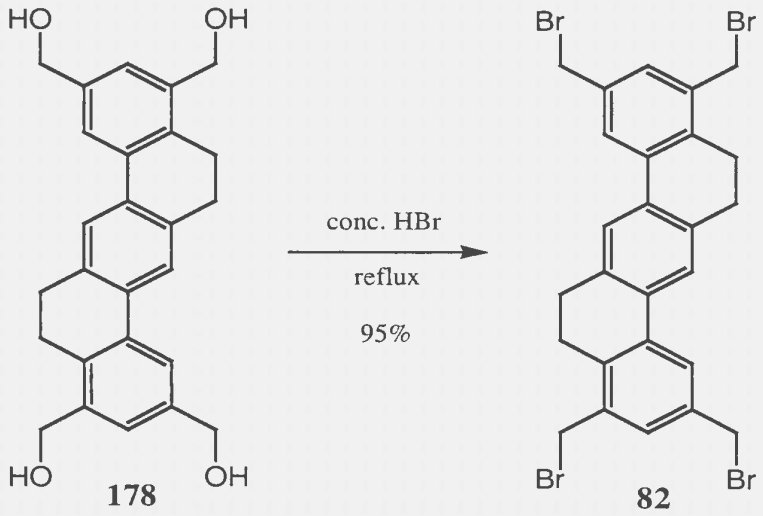
Although this tactic was successful, it added a step to the synthesis as well as a degree of inelegance. Obviously, the introduction of methyl esters at the beginning of the synthesis would solve this problem, but it was decided at this time that it would be preferable to press forward. Accordingly, other reducing reagents were considered. DIBAL was employed and it turned out to be an excellent choice. The reduction of **81** gave the desired product **178** in 100 % yield (Scheme 3.28).



81 178

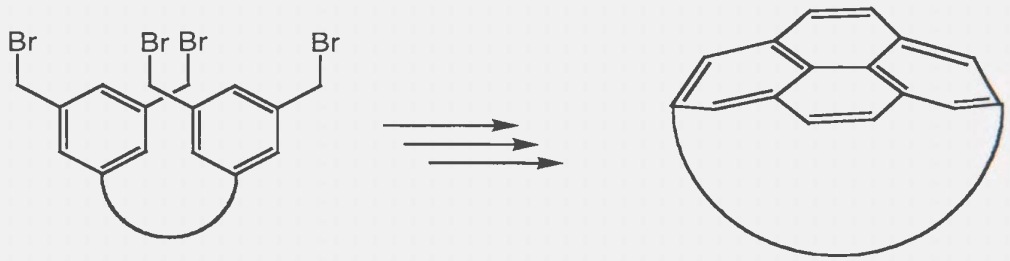
Scheme 3.28 Optimized synthesis of 178

For the subsequent bromination, one commonly used reagent is PBr_3. However, it consistently gave a mixture of products that were difficult to separate and in low yield (10 – 30%). 48% aqueous HBr solution was then found out to be a much better reagent. It gave tetrabromide **82** in 95% yield (Scheme 3.29). Additionally, the tetrabromide **82** could be isolated in an acceptably pure form by suction filtration. Both **178** and **82** exhibited rather low solubility in common organic solvents, which did not bode well for the subsequent steps in the synthesis. Nevertheless, work aimed at achieving the ultimate goal of preparing an aromatic belt was initiated.



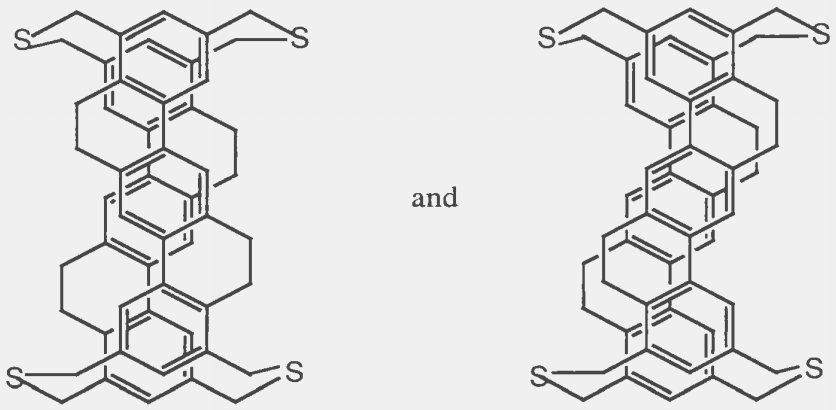
Scheme 3.29 Synthesis of 82

Compared to the tetrabromide precursors **49** (Scheme 3.30), which are precursors to the [*n*](2,7)pyrenophanes, tetrabromide **82** has a considerably more rigid skeleton.



Scheme 3.30 Formation of pyrenophane 54 from tetrabromide 49

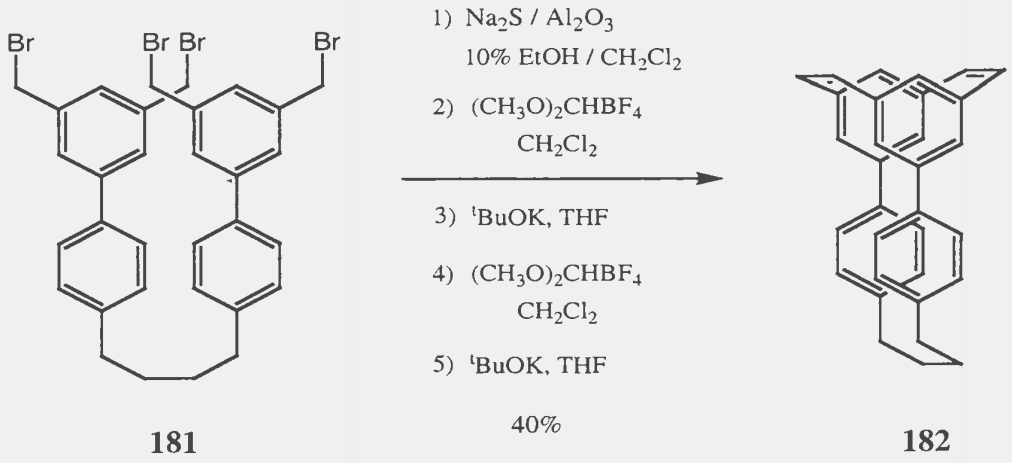
Thus in the planned Na_2S/Al_2O_3 coupling reaction, it cannot undergo an intramolecular coupling. Instead, intermolecular coupling must take place to form, hopefully, a dimer. In addition, the fact that the two faces of **82** are enantiotopic means that there are two possible dimers that can form: face-to-face **85** (D_2) or face-to-back **84** (C_{2h}) (Figure 3.02).



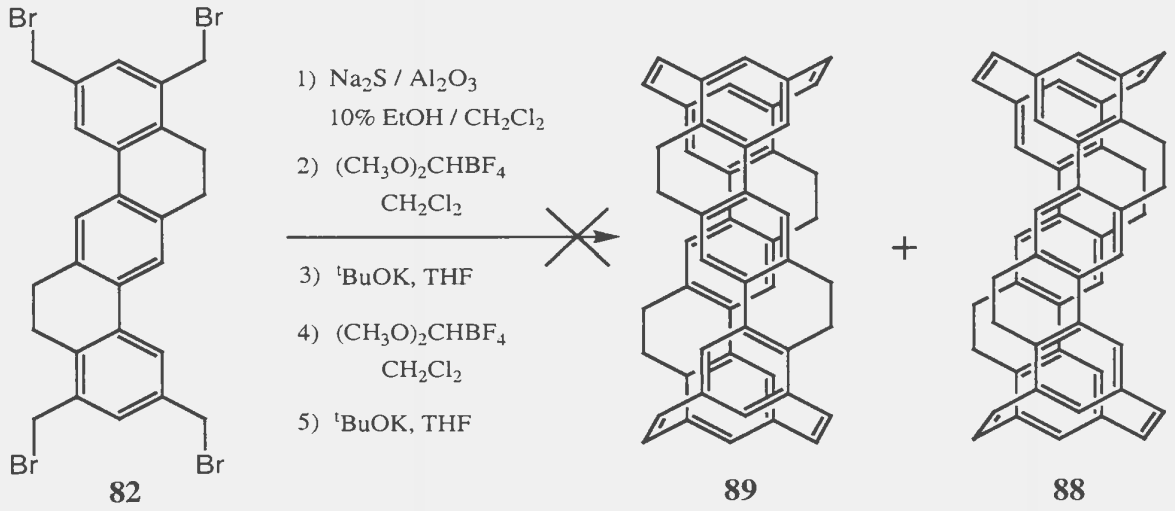
85 **84**

Figure 3.02 Two possible tetrathiacyclophanes 85 and 84

Tetrabromide **82** was subjected to a Na_2S/Al_2O_3 coupling reaction. The starting material was consumed within 30 min. After workup, an insoluble white solid was obtained. No attempts to purify or characterize this product were made. Instead, the crude material was put directly through a methylation/Stevens rearrangement/methylation/Hofmann elimination sequence without purification or characterization at any stage (Scheme 3.31). This tactic had been previously employed successfully by Rolf Vermeij in the synthesis of diene **181** from tetrabromide **182**. The cyclophanedienes are normally relatively soluble compared to their presursor thiacyclophanes and it was hoped that product isolation could be achieved at that stage. Unfortunately, none of the desired cyclophanetetraenes **89** and **88** could be identified from the spectroscopic data.



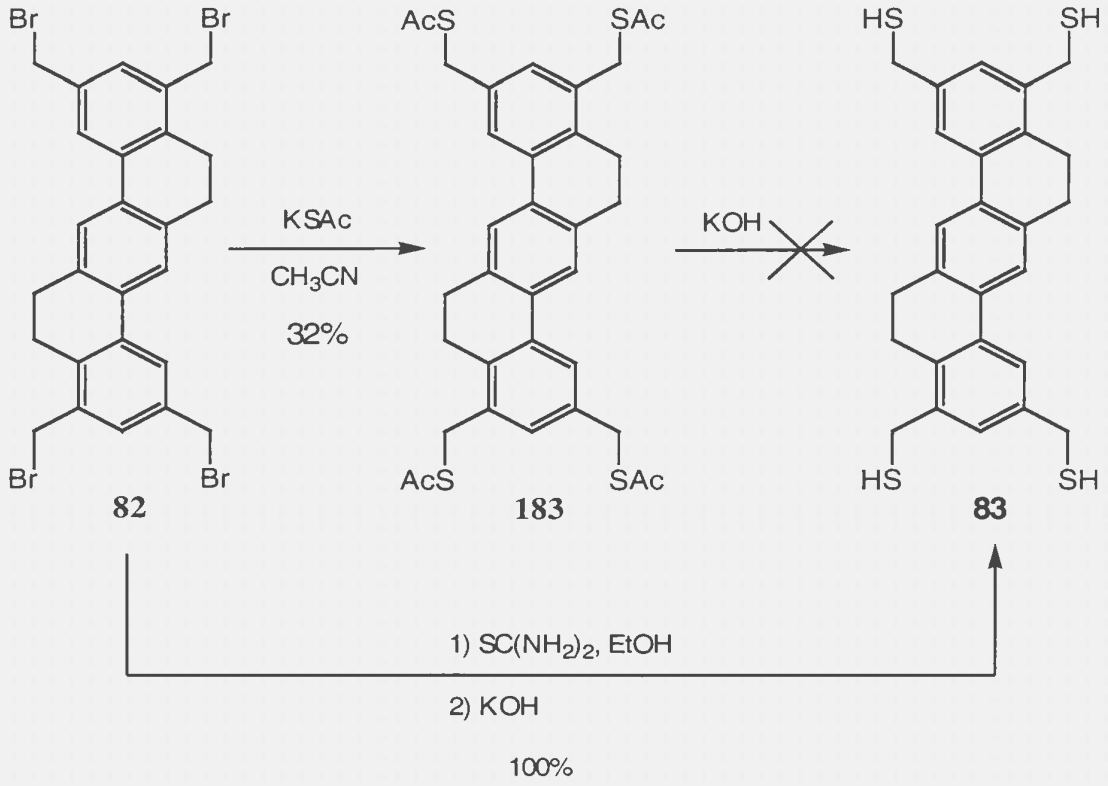
181 **182**



82 **89** **88**

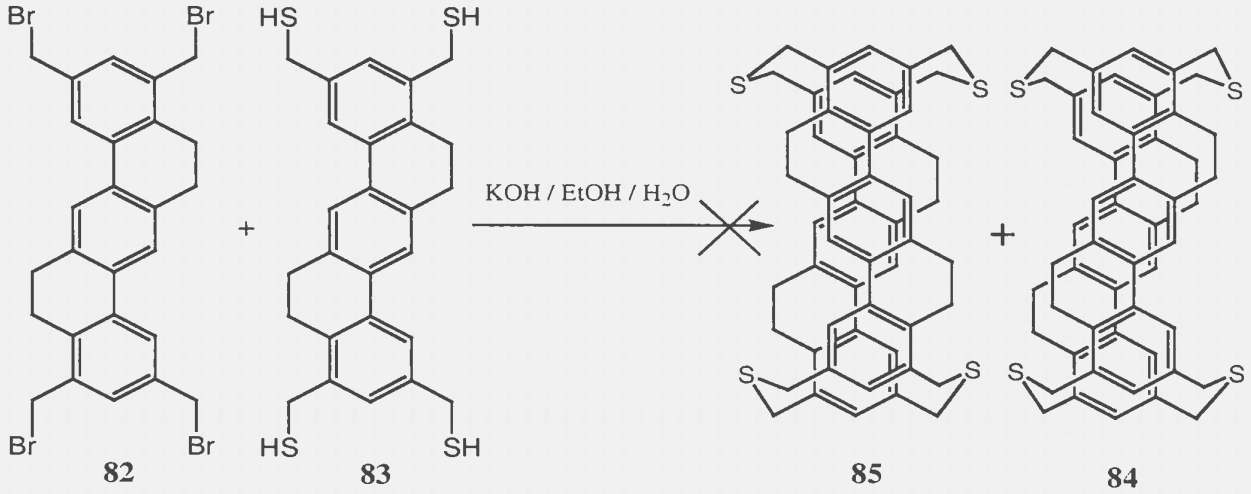
Scheme 3.31 Attempt toward 89 and 88

Since the direct coupling was not successful, it was decided to convert the tetrabromide **82** to tetrathiol **83**, and then use the traditional method of coupling these two components under basic conditions to give **85** and **84**. Compound **82** reacted with KSAc to give tetrakis(thioacetate) **183** in 32% yield. However, the ensuing hydrolysis did not afford the expected tetrathiol **83** (Scheme 3.32). A black solid formed, which could not be identified. Therefore, an alternative pathway was pursued. Tetrabromide **82** was converted into tetrathiol **83** by reacting it first with thiourea to form a tetrakis(isothiouronium) salt, followed by hydrolysis of that salt under basic conditions (Scheme). The overall yield of tetrathiol **83** was 100%.



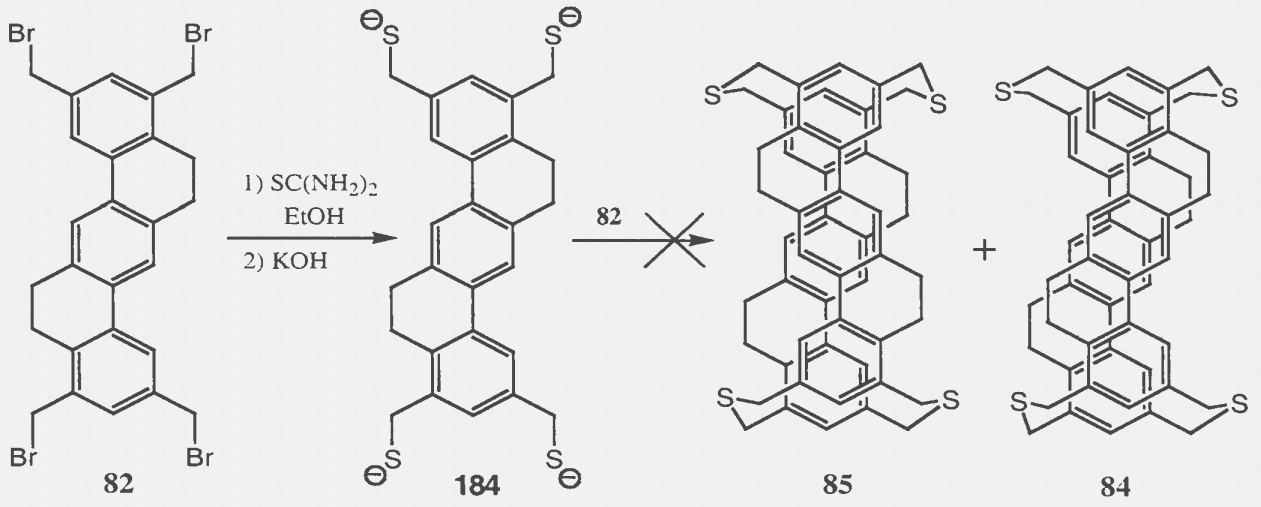
Scheme 3.32 Synthesis of 83

An equimolar slurry of tetrabromide **82** and tetrathiol **83** in CH_2Cl_2 was slowly added to an ethanolic KOH solution under vigorous stirring (Scheme 3.33). After heating at reflux for 20 h, only the two starting materials were recovered (80% for **82** and 77% for **83**). The expected deprotonation of tetrathiol by KOH may not have occurred due to the low solubility of the tetrathiol.



Scheme 3.33 Attempt toward 85 and 84

Therefore, to make sure that the sulfur anion does form, a modification was applied to this reaction. In the synthesis of tetrathiol **83** from tetrabromide **82** using the thiourea hydrolysis method, the sulfur anion **184** should be present in the solution prior to the acidification that is part of the workup. At that point, tetrabromide **82** was added into the solution (Scheme 3.34). The reaction was refluxed for four days and a mixture of products was obtained. In this case, chromatographic separation of this mixture led to the isolation of two compounds. One of them proved to be the tetrabromide **82** (32%), according to its ^{1}H NMR spectrum. The other product's ^{1}H NMR spectrum did not correspond to either starting material or either of the desired products **85** and **84**. The identity of this compound (or compounds) could not be established. No further investigation of the coupling reaction was conducted.

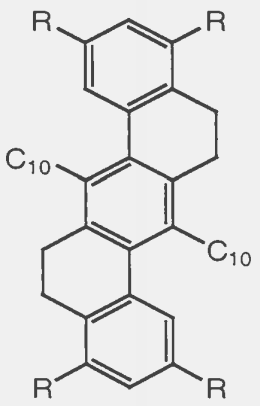


Scheme 3.34 Alternative attempt toward 85 and 84

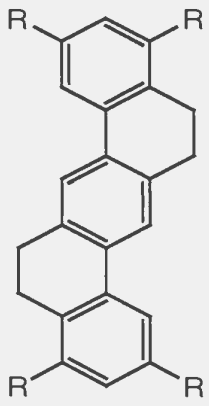
3.5 Conclusions and Future Work

In this Chapter, the synthesis of a molecular board **81**, which is a potential precursor to the aromatic belts **90** and **91**, was described. It is prepared by an 8-step synthesis and most steps are high yielding and reproducible. The overall yield from 4-bromo-*m*-xylene to **81** is 37%. Unfortunately, the intermolecular coupling reaction to form the tetrathiacyclophanes **85** and **84** had not yet been achieved.

In the attempted synthesis of tetrathiacyclophanes **85** and **84**, the low solubility of the precursor tetrabromide **82** and tetrathiol **83** is a serious problem. Even the use of a partially hydrogenated board was not enough to overcome this anticipated roadblock. Because the thiacyclophanes are typically less soluble than their precursors, the prospects for success in this particular system seem bleak. To solve this problem, attaching long alkyl chains to the central ring would presumably be helpful (Figure 3.03). Indeed, Cory's potential cyclacene precursors were found to be considerably more soluble than Stoddart's (see Chapter 1), which lacked these solubilizing groups.



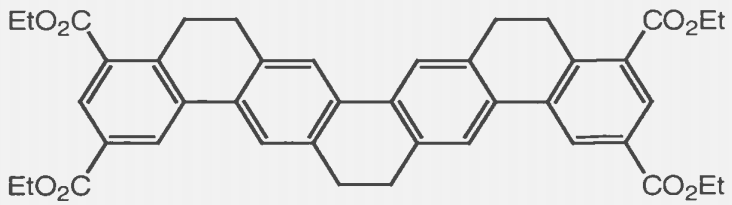
185



186

Figure 3.03 More soluble molecular board 185

If the approach to tetrabromide **82** can be successfully applied to a synthesis of **185** (R = CH_2Br) and this can be converted to the corresponding cyclophanetetraenes, the ability of the VID reaction to produce aromatic belts can finally be tested. Should this methodology prove to be ineffective, then longer molecular boards, *e.g.* **187**, would have to be constructed (Figure 3.04). These would be precursors to larger belts with less curved, and therefore less strained, surfaces.

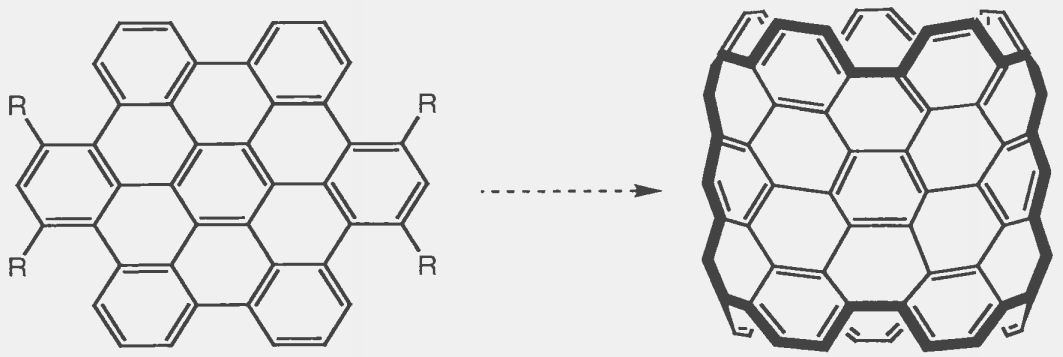


187

Figure 3.04 Larger molecular board 187

The approach to the molecular board described in this thesis could conceivably be applied to the syntheses of both **185** and **187**. The intramolecular arylation reaction would again form the key step in these syntheses and may prove to have even broader synthetic applicability.

If aromatic belts can indeed be made using the VID chemistry, it may also be possible to apply a similar approach to the syntheses of aromatic tubes like **189** from wider boards such as **188** (Scheme 3.35).



188 **189**

Scheme 3.35 Proposed approach to 189

3.5 Experimental

General. All chemicals were reagent grade and were used as received. Chromatographic separations were performed on Merck silica gel 60 (particle size 40 – 63 μm, 230 – 400 mesh). Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Mass spectroscopic (MS) data were obtained on a V. G. Micromass 7070HS instrument. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were obtained on a Bruker spectrometer: ^{1}H shifts are relative to internal tetramethylsilane; ^{13}C shifts are relative to the solvent resonance ($CDCl_3$: ¶f= 77.23). All experiments with moisture- or air-sensitive compounds were performed in anhydrous solvents under nitrogen unless otherwise stated. Solvents were dried and distilled according to standard procedures.

4-Bromoisophthalic acid (153)

4-Bromo-*m*-xylene (4.78 g, 25.79 mmol) and $KMnO_4$ (18.75 g, 118.6 mmol)were combined in water (250 mL) and the reaction mixture was heated under reflux

overnight. The reaction mixture was cooled to room temperature and suction filtered. The filtrate was acidified with aqueous 6M HCl solution (50 mL), and the precipitate **153** (4.82 g, 76%) was collected by suction filtration; mp 288 –291 °C (lit[7] 287 °C); ^{1}H NMR (500 MHz, acetone-*d*6) δ 8.48 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, acetone-*d*6) δ 167.1, 166.7, 134.6, 133.5, 131.5, 127.5.

Diethyl 4-bromoisophthalate (154)

4-Bromoisophthalic acid **153** (8.56 g, 34.93 mmol) was suspended in absolute EtOH (100 mL) and concentrated H_2SO_4 (4 mL) was added. The reaction mixture was heated under reflux overnight. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was redissolved in EtOAc (50 mL) and washed with water (50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), saturated aqueous NaCl solution (50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **154** (10.30 g, 98%) as colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 4.46 – 4.38 (m, 4H), 1.44 – 1.38 (m, 6H); ^{13}C NMR (125 MHz , $CDCl_3$) δ 165.5, 165.1, 134.6, 133.0, 132.9, 132.2, 129.8, 126.8, 62.0, 61.6, 14.4, 14.2.

1,4-Bis(trimethylsilylethynyl)benzene (163)

To a solution of $Pd(PPh_3)_2Cl_2$ and CuI in degassed benzene (150 mL) under a nitrogen atmosphere, was added 1,4-diiodobenzene. After 5 min a solution of DBU and trimethylsilylacetylene in degassed benzene (75 mL) was added dropwise through a dropping funnel. The reaction mixture was stirred in a cold water bath for 15 min.

Suction filtration removed the solids and the filtrate was concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 (200 mL) and washed with saturated aqueous NH_4Cl solution (200 mL), water (200 mL), saturated aqueous NaCl solution (200 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by column chromatography (hexanes) to give **163** as colorless crystals; mp 119-120 °C (lit.[8] 122 °C); ^{1}H NMR (500 MHz , $CDCl_3$) δ 7.38 (s, 4H), 0.24 (s, 18H).

1,4-Diethynylbenzene (164)

K_2CO_3 and 1,4-bis(trimethylsilylethynyl)benzene **163** were combined in methanol (50 mL) and the reaction mixture was stirred for 30 min. The mixture was poured into ice water (100 mL) and the resulting white solid **164** was collected by suction filtration; mp 94 – 95 °C (lit.[8] 95 – 96 °C); ^{1}H NMR (500 MHz , $CDCl_3$) δ 7.44 (s, 4H), 3.16 (s, 2H).

4-(Trimethylsilylethynyl)benzene-1,3-dicarboxylic acid diethyl ester (155)

To a solution of $Pd(PPh_3)_2Cl_2$ (1.17 g, 0.17 mmol) and CuI (634 mg, 1.66 mmol) in degassed benzene (200 mL) under a nitrogen atmosphere, was added diethyl 4-bromoisophthalate **154** (10.00 g, 33.2 mmol). After 5 min a solution of DBU (7.57 g, 49.8 mmol) and trimethylsilylacetylene **137** (4.56 g, 46.5 mmol) in degassed benzene (50 mLl) was added dropwise through a dropping funnel. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure. The residue was redissolved in CH_2Cl_2 (200 mL) and washed with saturated aqueous NH_4Cl solution (250 mL), water (250 mL), saturated aqueous NaCl solution (250 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure.

The residue was purified by column chromatography (80% CH_2Cl_2 / hexanes) to give **155** (8.28 g, 78%) as a brown oil; ^{1}H NMR (500 MHz , $CDCl_3$) δ 8.53 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 4.44- 4.38 (m, 4H), 1.44 – 1.39 (m, 6H); ^{13}C NMR (125 MHz , $CDCl_3$) δ 165.9, 165.5, 134.9, 133.2, 132.0, 131.4, 130.2, 127.5, 103.5, 102.8, 61.7, 14.5, 0.2.

4-Ethynylbenzene-1,3-dicarboxylic acid diethyl ester (156)

4-(Trimethylsilylethynyl)benzene-1,3-dicarboxylic acid diethyl ester **155** (1.94 g, 6.09 mmol) and K_2CO_3 (1.09 g, 7.92 mmol) were combined in EtOH (50 mL). The reaction mixture was stirred at room temperature for 30 min. K_2CO_3 was removed by suction filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL), washed with H_2O (50 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and **156** (1.50 g, 100%) was obtained as a dark brown oil; ^{1}H NMR (500 MHz , $CDCl_3$) δ 8.59 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 4.46 – 4.39 (m, 4H), 3.56 (s, 1H), 1.44 – 1.40 (m, 6H); ^{13}C NMR (125 MHz , $CDCl_3$) δ 165.5, 165.4, 135.2, 133.3, 132.3, 131.5, 130.6, 126.9, 85.4, 81.7, 61.9, 61.8, 14.5, 14.4.

1,4-Bis(2,4-bis(ethoxycarbonyl)phenylethynl)benzene (143)

To a solution of $Pd(PPh_3)_2Cl_2$ (119 mg, 0.17 mmol) and CuI (130 mg, 0.68 mmol) in degassed benzene (150 mL) under a nitrogen atmosphere, was added diethyl 4-bromoisophthalate **154** (10.24 g, 34.0 mmol). After 5 min a solution of DBU (5.69 g, 37.4 mmol) and 1,4-diethynylbenzene **164** (2.14 g, 17.0 mmol) in degassed benzene (75 mL) was added dropwise through a dropping funnel. The reaction mixture was

stirred at room temperature for 18 h. The solvent was removed under reduced pressure. The residue was redissolved in CH_2Cl_2 (200 mL) and washed with saturated aqueous NH_4Cl solution (200 mL), water (200 mL), saturated aqueous NaCl solution (200 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by column chromatography (1% EtOAc / CH_2Cl_2) to give **143** (5.30 g, 55%) as a bright yellow solid; mp 126 – 127 °C; ^{1}H NMR (500 MHz , $CDCl_3$) δ 8.63 (s, 2H), 8.15 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H), 7.59 (s, 4H), 4.48 – 4.40 (m, 8H), 1.45 – 1.41 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 134.5, 132.8, 132.6, 132.4, 132.0, 130.4, 128.0, 123.8, 61.9, 14.8.

1,4-Bis(2-(2,4-bis(ethoxycarbonyl)phenyl)ethyl)benzene (109)

To a solution of 1,4-bis(2,4-bis(ethoxycarbonyl)phenylethynyl)benzene **143** (0.38 g, 0.67 mmol) in EtOAc (500 mL), was added Pd/C (75 mg) and AcOH (1 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 5 min and under a hydrogen balloon for 18 h. The reaction mixture was filtered through a plug of $MgSO_4$ and the filtrate was concentrated under reduced pressure. The residue was dried *in vacuo* to give **109** (0.39 g, 100%) as white solid; mp 95 – 97 °C; ^{1}H NMR (500 MHz , $CDCl_3$) δ 8.54 (s, 2H), 8.04 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.11 (s, 4H), 4.42 – 4.38 (m, 8H), 3.31 – 3.28 (m, 4H), 2.90 – 2.87 (m, 4H), 1.43 – 1.39 (m, 12H); ^{13}C NMR (125 MHz , $CDCl_3$) δ 167.1, 166.1, 148.7, 139.3, 132.6, 132.1, 131.6, 130.4, 128.8, 61.4, 37.6, 36.9, 14.6.

1,4-Dibromo-2,5-diiodobenzene (167)

To a solution of *p*-dibromobenzene (9.97 g, 42.3 mmol) in conc. H_2SO_4 (125 mL) that

was preheated at 125 °C, was added I_2 (42.91 g, 169.1 mmol). The reaction mixture was stirred for 3.5 h. After cooling to room temperature, the reaction mixture was poured into ice water (500 mL). The resulting solid was dissolved in CH_2Cl_2 (200 mL), then washed with saturated $NaHSO_3$ solution (200 mL), water (200 mL), saturated aqueous NaCl solution (200 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was recrystallized from benzene to afford **167** (6.58 g, 32%) as white solid; ^{1}H NMR (500 MHz , $CDCl_3$) δ 8.05 (s, 2H); ^{13}C NMR (125 MHz , $CDCl_3$) δ 142.6, 129.4, 102.3.

1,4-Dibromo-2,5-bis(2-(2,4-bis(ethoxycarbonyl)phenyl)ethynyl)benzene (168)

To a solution of $Pd(PPh_3)_2Cl_2$ (64 mg, 0.09 mmol) and CuI (63 mg, 0.33 mmol) in degassed benzene (80 mL) under a nitrogen atmosphere, was added 1,4-dibromo-2,5-diiodobenzene **167** (888 mg, 1.82 mmol). After 5 min a solution of DBU (0.69 g, 4.55 mmol) and 4-ethynlbenzene-1,3-dicarboxylic diethyl ester **156** (986 mg, 4.01 mmol) in degassed benzene (40 mL) was added dropwise through a dropping funnel. The reaction mixture was stirred at room temperature for 15 min. The solvent was removed under reduced pressure. The residue was redissolved in CH_2Cl_2 (80 mL) and washed with saturated aqueous NH_4Cl solution (80 mL), water (80 mL) and saturated aqueous NaCl solution (80 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by column chromatography (1% EtOAc / CH_2Cl_2) to give **168** (201 mg, 15%) as pale yellow solid; mp 170 –173 °C; ^{1}H NMR (500 MHz , $CDCl_3$) δ 8.65 (s, 2H), 8.17 (d, J = 8.0 Hz, 2H), 7.86 (s, 2H), 7.78 (d, J = 8.0 Hz, 2H), 4.47 – 4.41 (m, 8H), 1.46 – 1.40 (m, 12H).

1,4-Dibromo-2,5-bis(2-(2,4-bis(ethoxycarbonyl)phenyl)ethyl)benzene (106)

To a solution of 1,4-bis(2-(2,4-bis(ethoxycarbonyl)phenyl)ethyl)benzene **109** (4.35 g, 7.57 mmol) and $AlCl_3$ (6.06 g, 45.4 mmol) in CH_2Cl_2 (120 mL), was added Br_2 (2.42 g, 15.2 mmol). The reaction mixture was stirred at room temperature for 20 min, washed with saturated $NaHSO_3$ solution (100 mL), water (100 mL), saturated aqueous NaCl solution (100 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **106** (5.54 g, 100%) as white solid; mp 142 – 144 °C; ^1H NMR (500 MHz , $CDCl_3$) δ 8.55 (s, 2H), 8.07 (d, J = 8.0 Hz, 2H), 7.40 (s, 2H), 7.30 (d, J = 8.0 Hz, 2H), 4.44 – 4.39 (m, 8H), 3.30 – 3.27 (m, 4H), 3.01 – 2.98 (m, 4H), 1.45 – 1.40 (m, 12H); ^{13}C NMR (125 MHz , $CDCl_3$) δ 166.9, 166.0, 147.9, 140.6, 134.4, 132.8, 132.2, 131.6, 130.4, 123.4, 61.5, 61.4, 37.3, 34.8, 14.6.

1,4-Diiodo-2,5-bis(2-(2,4-bis(ethoxycarbonyl)phenyl)ethyl)benzene (174)

A mixture of conc. H_2SO_4 (0.5 mL), H_2O (1 mL) and AcOH (5 mL) was poured into a round bottom flask (15 mL) charged with 1,4-bis(2-(2,4-bis(ethoxycarbonyl)phenyl)ethyl)benzene **109** (80 mg, 0.14 mmol), I_2 (61 mg, 0.24 mmol) and $HIO_4 \cdot 2H_2O$ (18 mg, 0.08 mmol). The reaction mixture was heated at 90 °C and stirred for 1.5 h. Then CH_2Cl_2 (50 mL) was added. The purple organic layer was washed with saturated $NaHSO_3$ solution (20 mL), water (20 mL), saturated aqueous NaCl solution (20 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The resulting white solid was refluxed in a solution of EtOH (20 mL) and conc. H_2SO_4 (0.5 mL) for 2.5 h. The solvent was removed and CH_2Cl_2 (20 mL) was added. The solution was washed with water (20 mL), saturated $NaHCO_3$ solution (20 mL), water (20 mL), saturated aqueous NaCl solution (20 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was

purified by column chromatography (CH_2Cl_2) to give **174** (92 mg, 80%) as a white solid; ^{1}H NMR (500 MHz , $CDCl_3$) δ 8.57 (s, 2H), 8.07 (d, *J* = 8.0 Hz, 2H), 7.63 (s, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.42 (m, 8H), 3.25 (m, 4H), 2.96 (m, 4H), 1.43 (m, 12H); ^{13}C NMR (125 MHz , $CDCl_3$) δ 166.9, 166.0, 147.7, 144.1, 139.9, 132.8, 132.2, 131.6, 130.4, 129.0, 61.5, 61.4, 41.5, 35.1, 14.6.

5,6,12,13-Tetrahydrodibenz[*a,h*]anthracene-2,4,9,11-tetracarboxylic acid tetraethyl ester (81)

1,4-Dibromo-2,5-bis(2-(2,4-bis(ethoxycarbonyl)phenyl)ethyl)benzene **106** (1.17 g, 1.60 mmol), $Pd(PPh_3)_2Cl_2$ (112 mg, 0.16 mmol) and NaOAc (788 mg, 9.60 mmol) were combined in DMA (40 mL). The reaction mixture was stirred at room temperature for 5 min. Then the flask was plunged into an oil bath preheated at 140 °C and the reaction mixture was stirred for 2.5 h. The reaction mixture was cooled to 0 °C and the resulting solid was collected by suction filtration. The solid was then dissolved in CH_2Cl_2 (50 mL) and washed with water (50 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure to provide **81** (833 mg, 91%) as a white solid. A small amount of **81** was recrystallized from EtOAc to afford white needles; mp: 249 – 250 °C; ^{1}H NMR (500 MHz , $CDCl_3$) δ 8.58 (s, 2H), 8.42 (s, 2H), 7.71 (s, 2H), 4.46 – 4.41 (m, 8H), 3.33 – 3.30 (m, 4H), 2.94 – 2.92 (m, 4H), 1.47 – 1.43 (m, 12H); ^{13}C NMR (125 MHz , $CDCl_3$) δ 167.5, 166.2, 143.8, 136.4, 136.2, 133.4, 131.1, 130.3, 129.0, 128.1, 124.0, 61.6, 28.3, 26.5, 14.6.

2,4,9,11-Tetrakis(hydroxymethyl)-5,6,12,13-tetrahydrodibenz[*a,h*]anthracene (178)

To a solution of 5,6,12,13-tetrahydrodibenz[*a,h*]anthracene-2,4,9,11-tetracarboxylic acid tetraethyl ester **81** (228 mg, 0.40 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C, was added dropwise a solution of 1 M DIBAL / CH_2Cl_2 (6.4 mmol). The reaction mixture was stirred for 18 h as the temperature was allowed to reach room temperature slowly. 1 M HCl solution (5 mL) was then added dropwise and the reaction mixture was stirred for 30 min. The resulting solid **178** (161 mg, 100%) was collected by suction filtration; mp decomposes > 246 °C; ^{1}H NMR (500 MHz , DMSO-d^6) δ 7.72 (s, 2H), 7.68 (s, 2H), 7.31 (s, 2H), 5.17 (t, J = 5.0 Hz, 2H), 5.09 (t, J = 5.0 Hz, 2H), 4.58 (d, J = 5.0 Hz, 4H), 4.55 (d, J = 5.0 Hz, 4H), 2.86 – 2.83 (m, 4H), 2.81 – 2.78 (m, 4H).

2,4,9,11-Tetrakis(bromomethyl)-5,6,12,13-tetrahydrodibenz[*a,h*]anthracene (82)

2,4,9,11-Tetrakis(hydroxymethyl)-5,6,12,13-tetrahydrodibenz[*a,h*]anthracene **178** (503 mg, 1.25 mmol) and 48% aqueous HBr (100 mL) were mixture together and the reaction mixture was heated at reflux for 20 h. The reaction mixture was cooled to room temperature and the white solid **82** (777 mg, 95%)was collected by suction filtration; mp decomposes > 246 °C; ^{1}H NMR (500 MHz , $CDCl_3$) δ 7.81 (s, 2H), 7.62 (s, 2H), 7.33 (s, 2H), 4.58 (s, 4H), 4.55 (s, 4H), 2.96 (s, 8H).

2,4,9,11-Tetrakis(thioacetyl)-5,6,12,13-tetrahydrodibenz[*a,h*]anthracene (183)

2,4,9,11-Tetrakis(bromomethyl)-5,6,12,13-tetrahydrodibenz[*a,h*]anthracene **82** (196 mg, 0.30 mmol) and KSAc (206 mg, 1.80 mmol) were combined in CH_3CN (25 mL) and the reaction mixture was heated at reflux for 20 h. The reaction mixture was then poured into ice water (50 mL) and **183** (60 mg, 32%) was collected as a brown solid

by suction filtration; mp decomposes > 195 °C; ^{1}H NMR (500 MHz , $CDCl_3$) δ 7.64 (s, 2H), 7.55 (s, 2H), 7.18 (s, 2H), 4.20 (s, 4H), 4.15 (s, 4H), 2.89 – 2.87 (m, 4H), 2.83 – 2.81 (m, 4H), 2.37 (s, 6H), 2.36 (s, 6H).

2,4,9,11-Tetrakis(thiomethyl)-5,6,12,13-tetrahydrodibenz[*a,h*]anthracene (83)

2,4,9,11-Tetrakis(bromomethyl)-5,6,12,13-tetrahydrodibenz[*a,h*]anthracene **82** (131 mg, 0.20 mmol) and thiourea (62 mg, 0.82 mmol) were combined in EtOH (30 mL) and the reaction mixture was heated at reflux for 1.5 h. A degassed solution of KOH (132 mg of 85%, 2.0 mmol) in H_2O (10 mL) was added and the reaction mixture was heated at reflux for 1.5 h. The reaction mixture was cooled to 0 °C, and 9 M H_2SO_4 (1 mL) was then added. Tetrathiol **83** (93 mg, 100%) was collected as a white solid by suction filtration; mp decomposes > 270 °C; ^{1}H NMR (500 MHz , DMSO-d^6) δ 7.77 (s, 2H), 7.73 (s, 2H), 7.23 (s, 2H), 3.82 (d, J = 4.0 Hz, 4H), 3.77 (d, J = 4.0 Hz, 4H), 2.92 (t, J = 4.0 Hz, 2H), 2.87 (m, 8H), 2.77 (t, J = 4.0 Hz, 2H).

3.7 References

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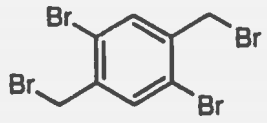
Appendix A



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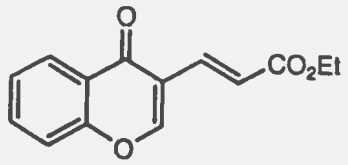

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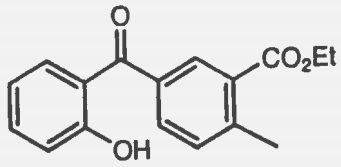

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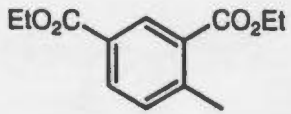

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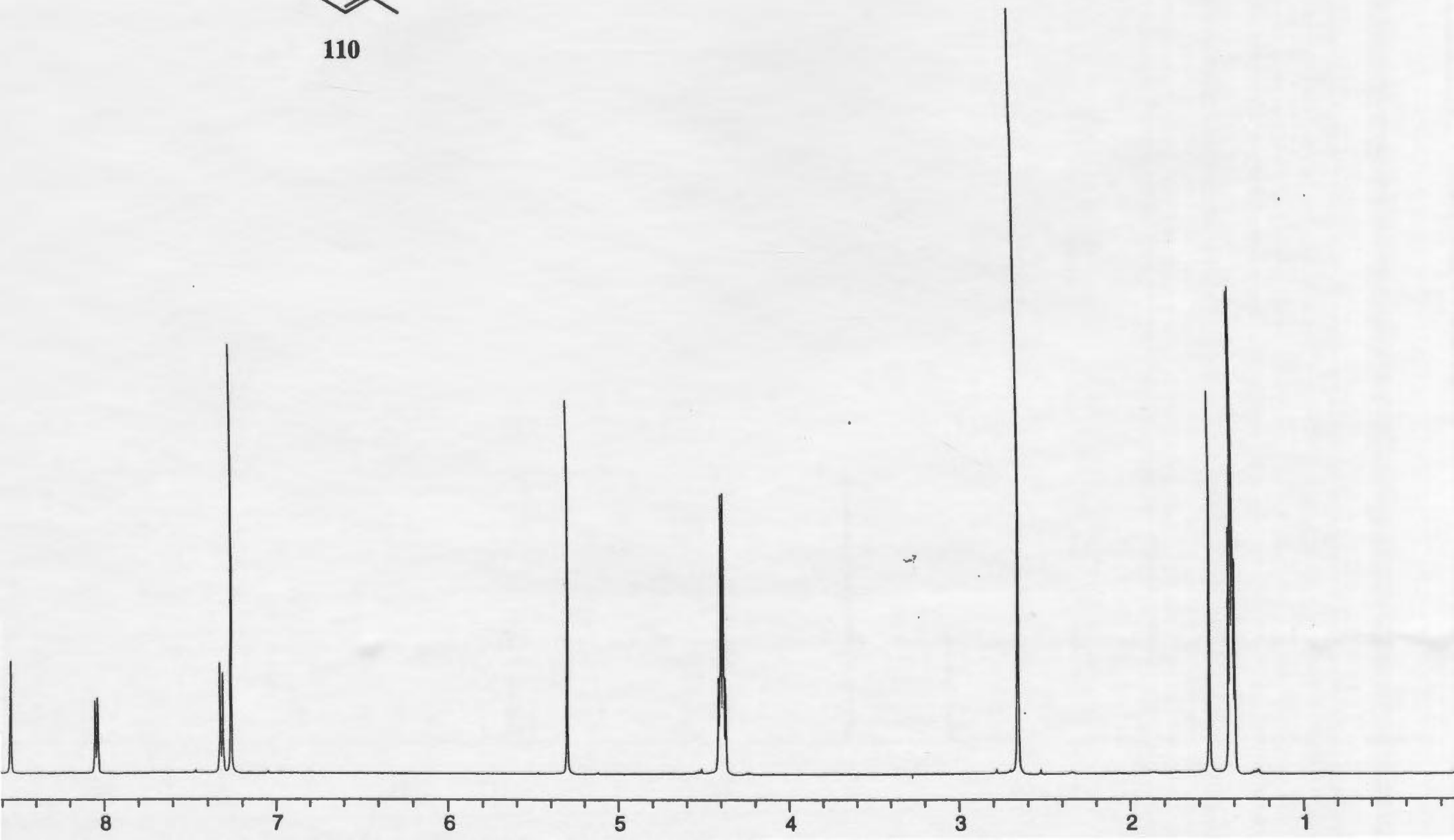

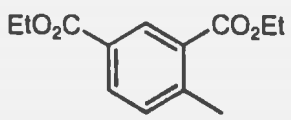

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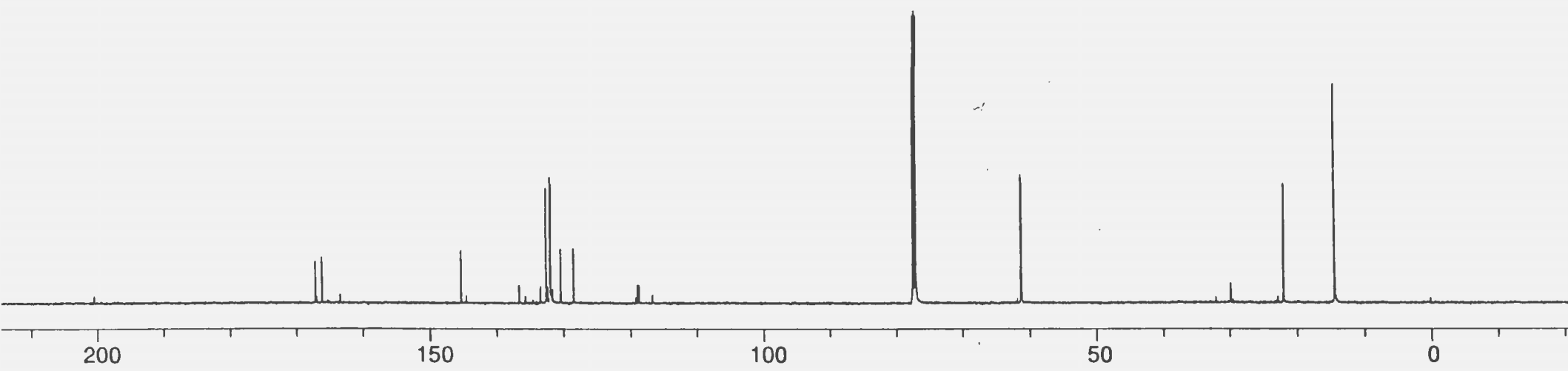

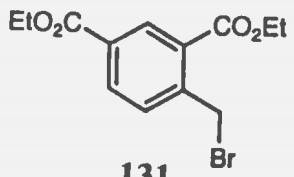

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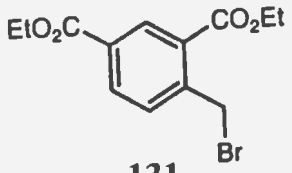

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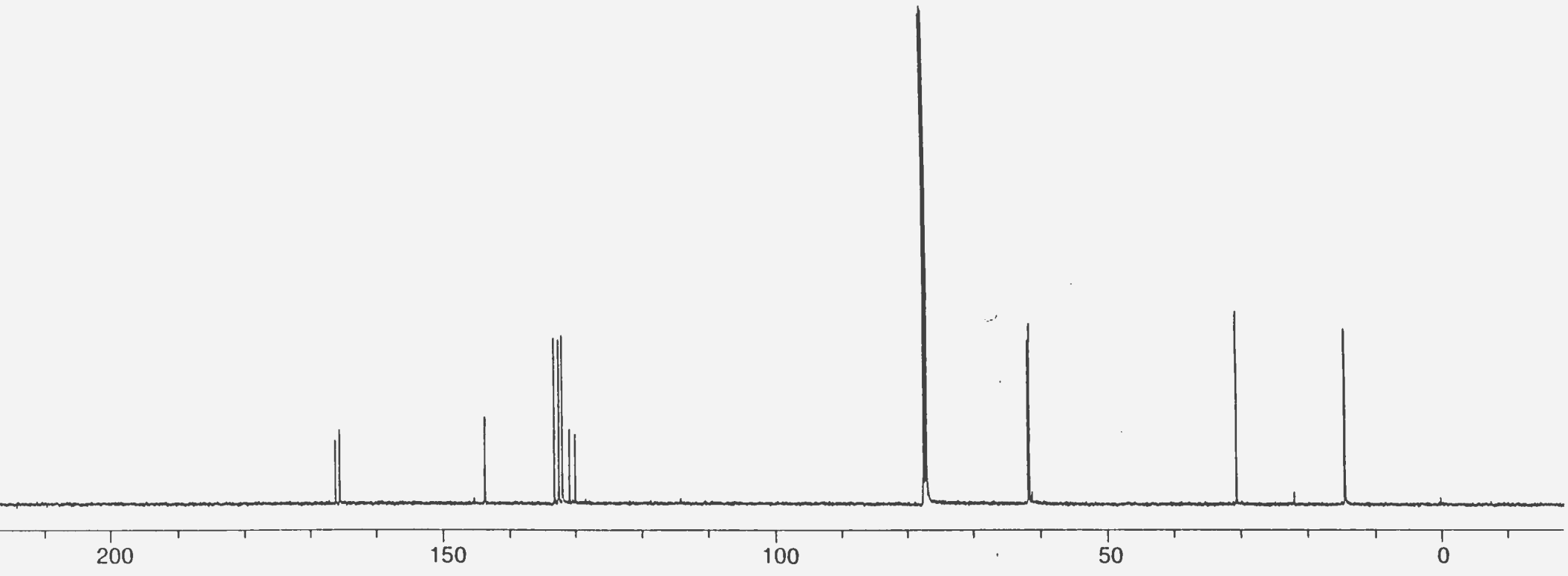

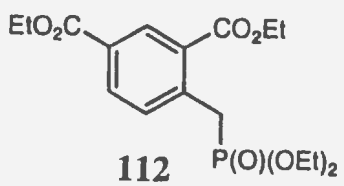

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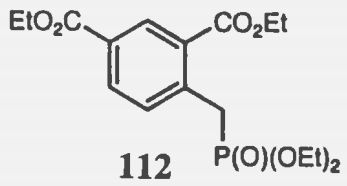

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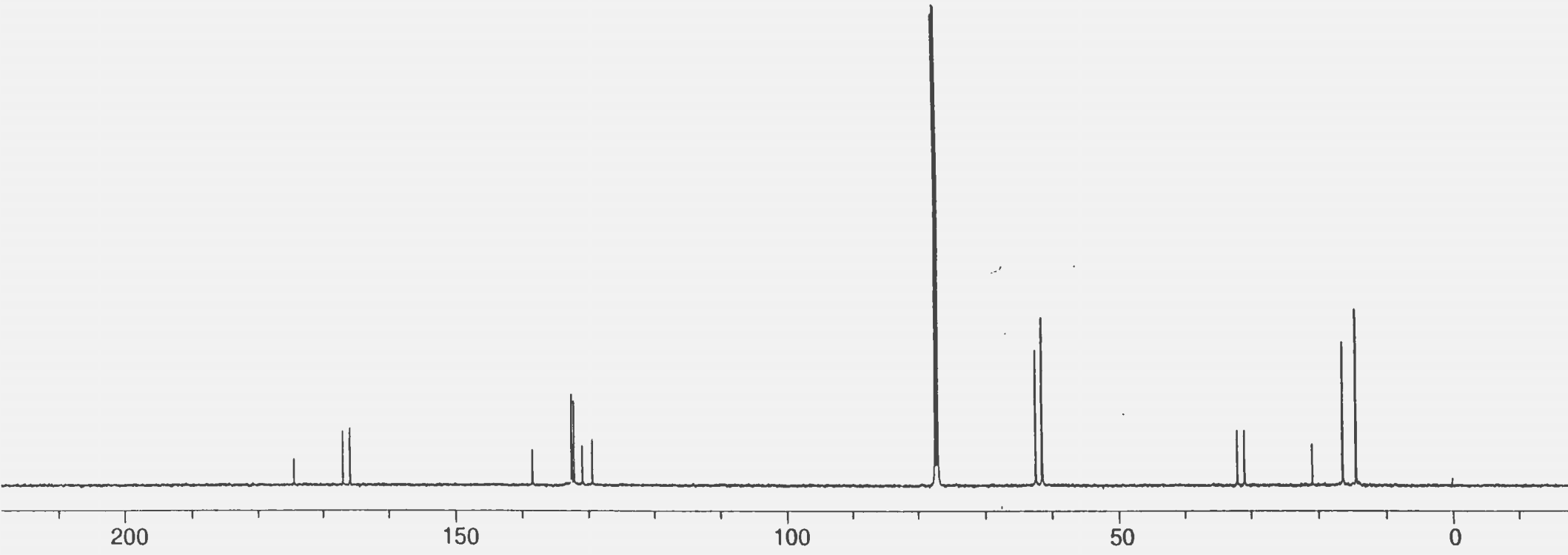

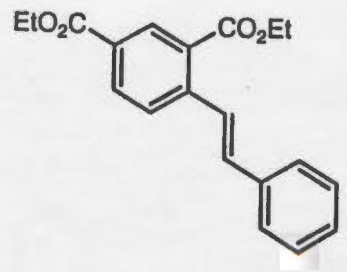

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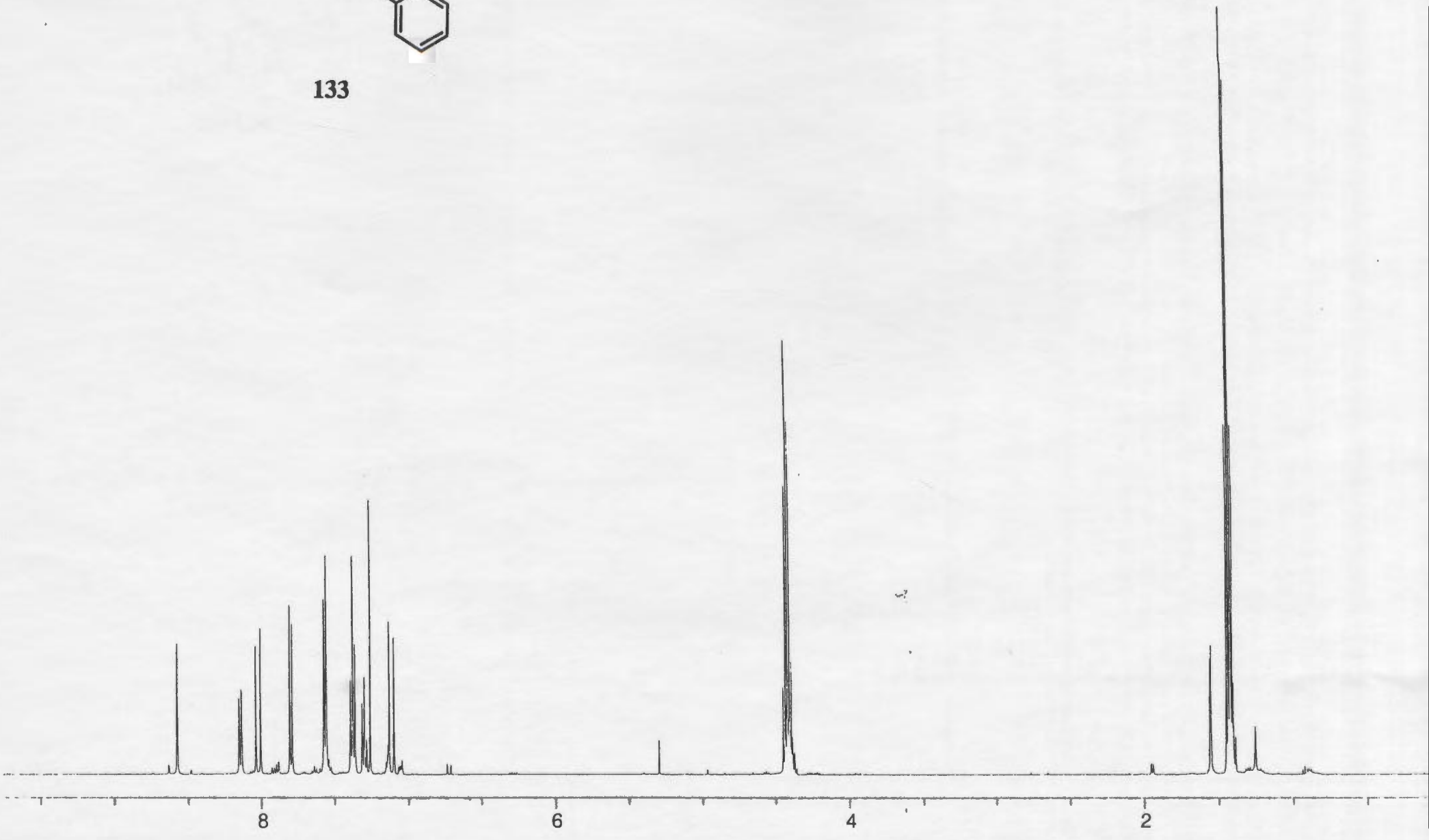

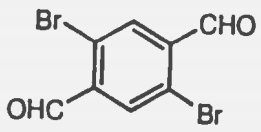

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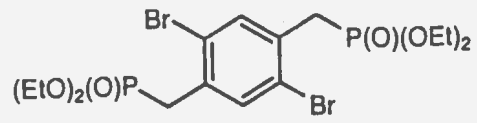

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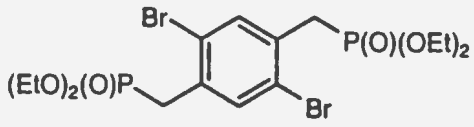

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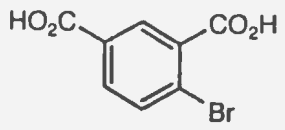

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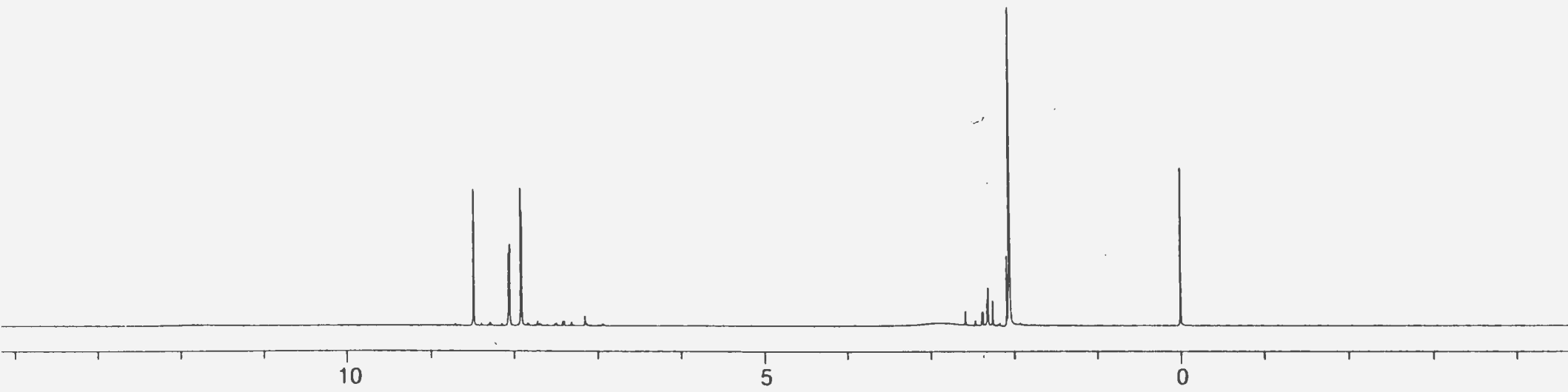

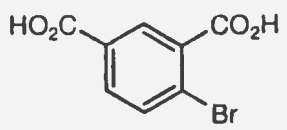

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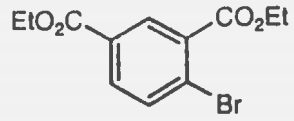

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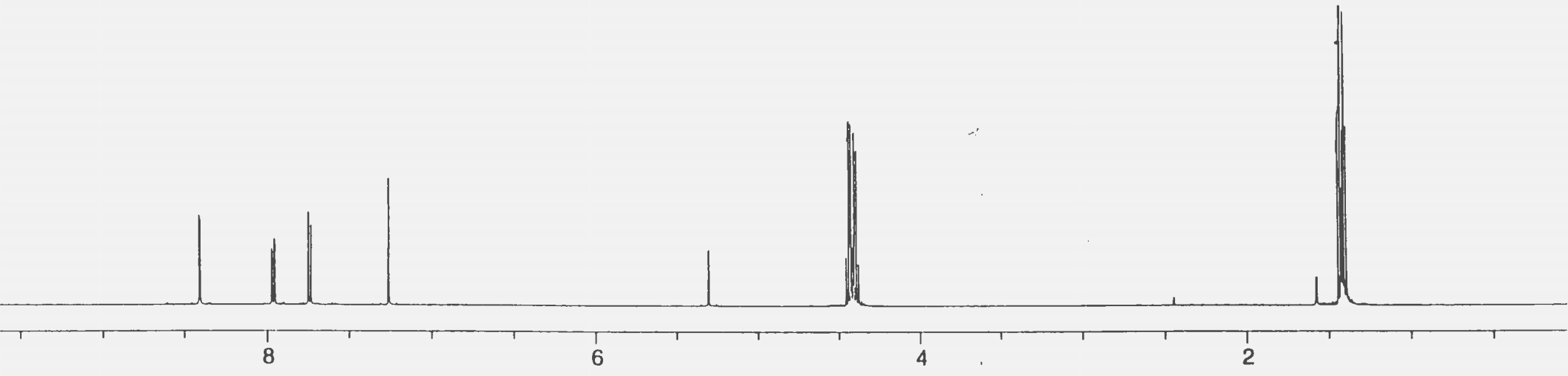

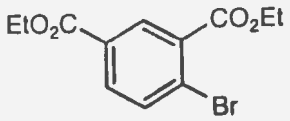

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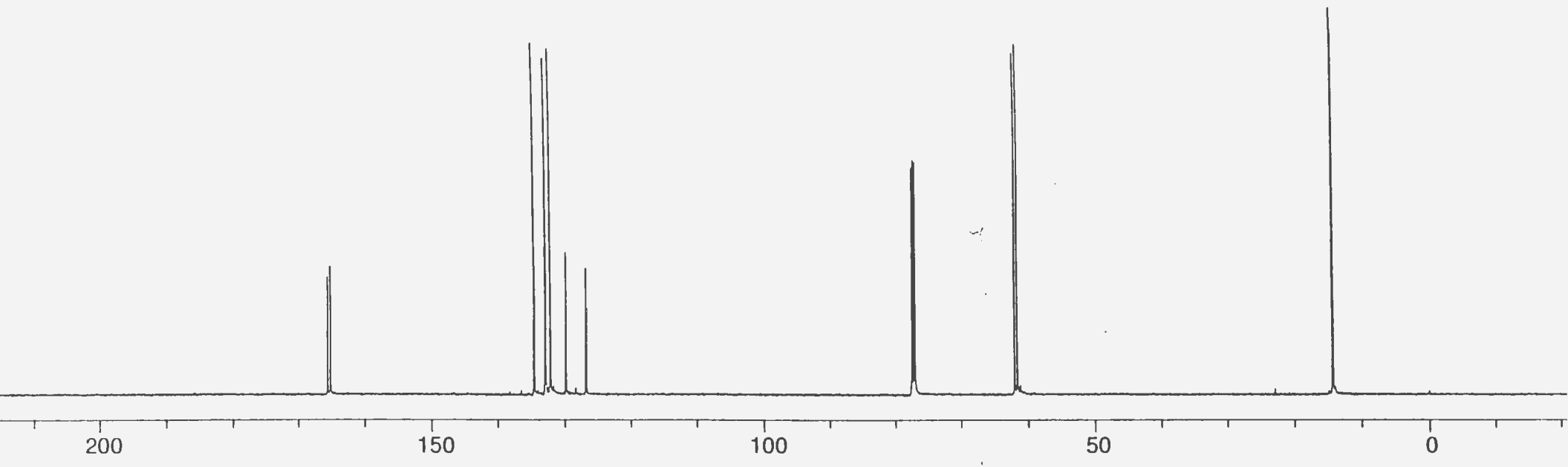

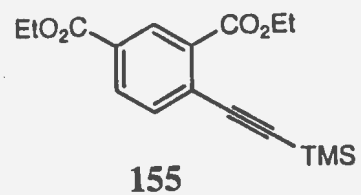

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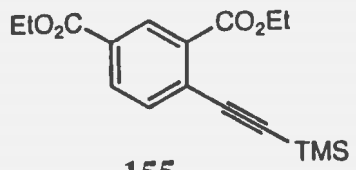

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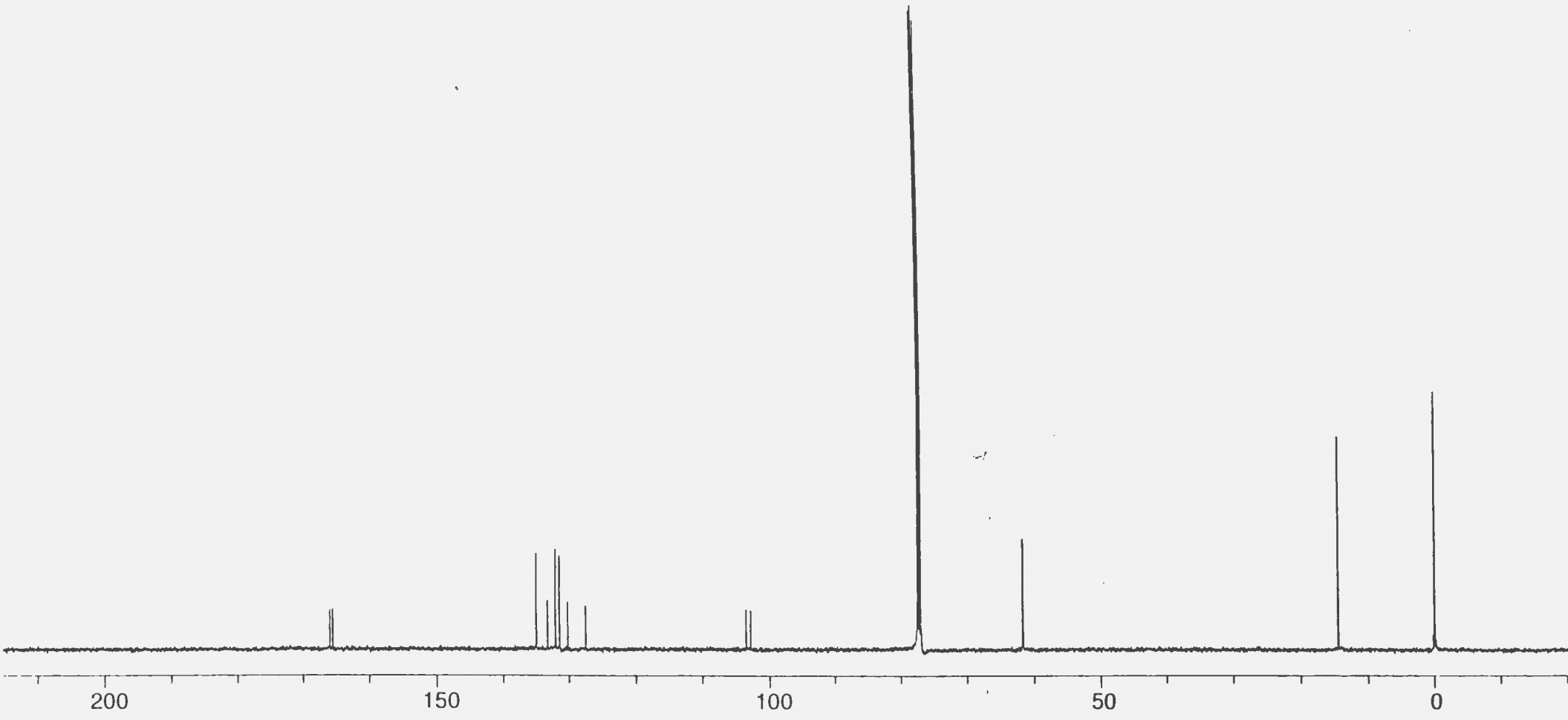

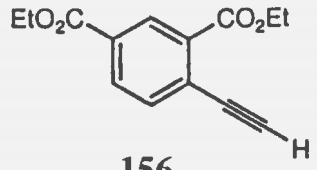

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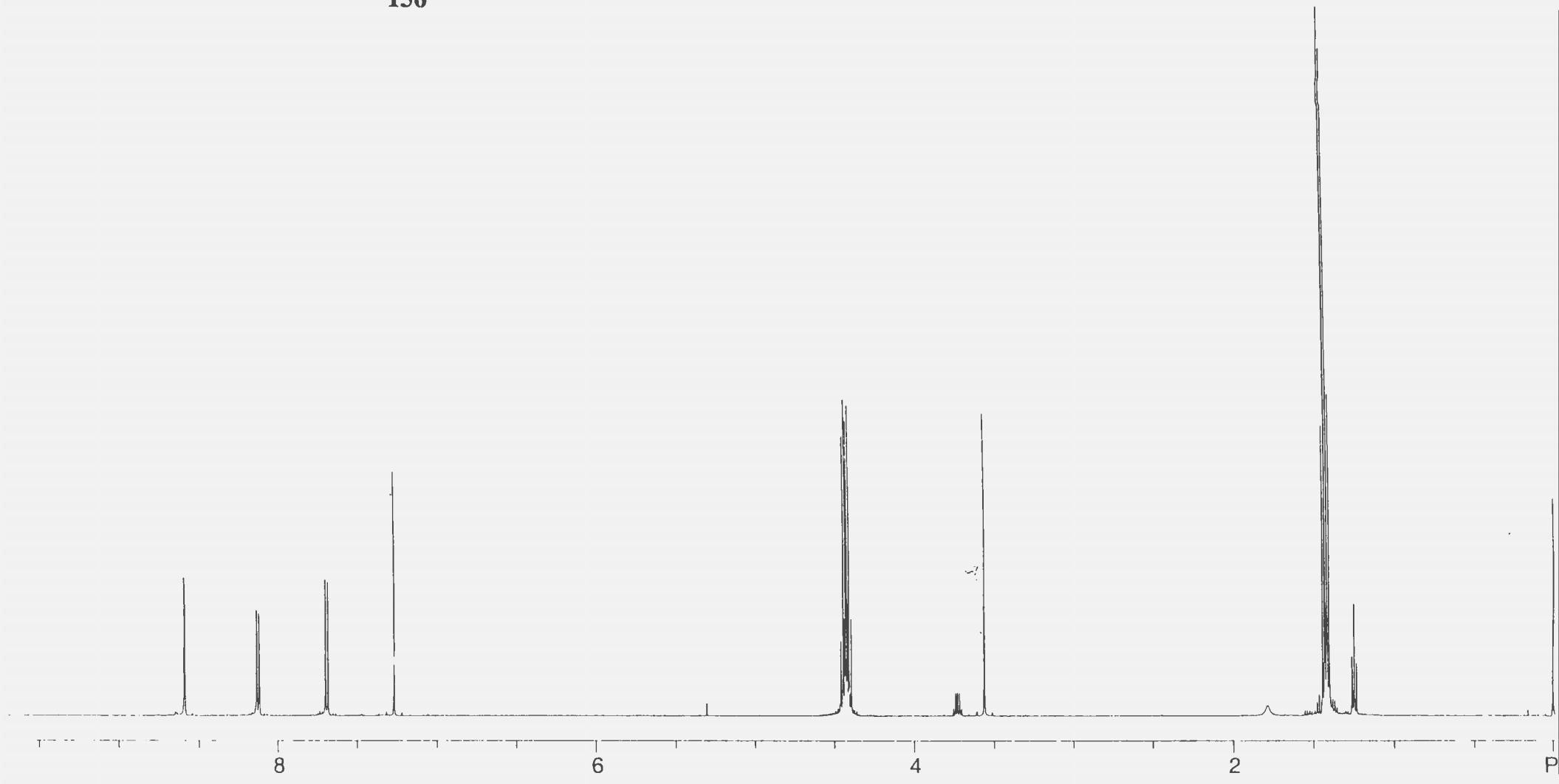

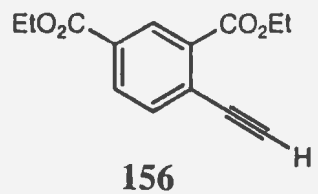

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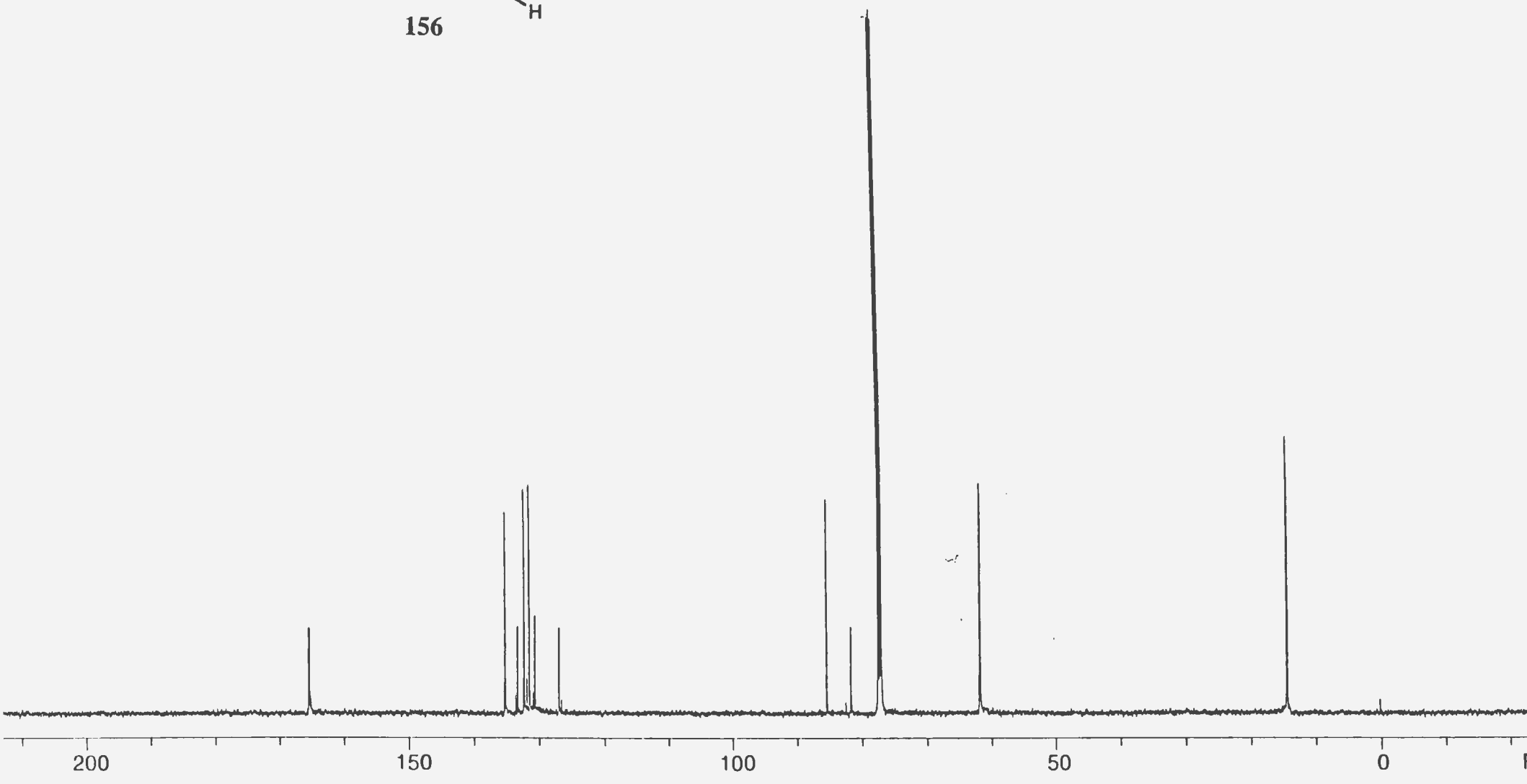

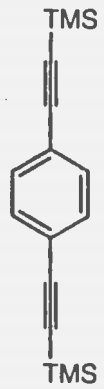

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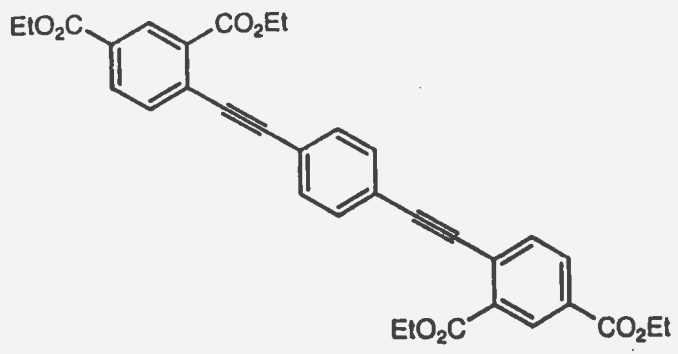

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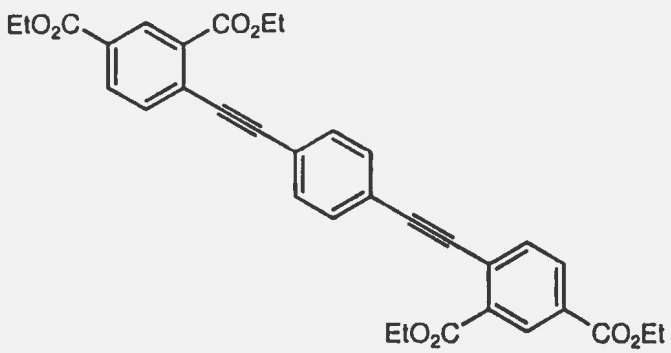

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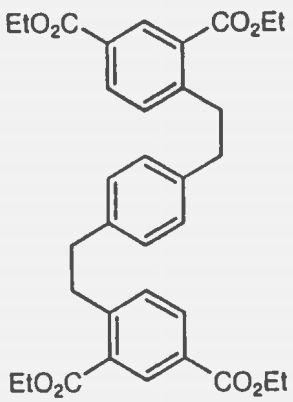

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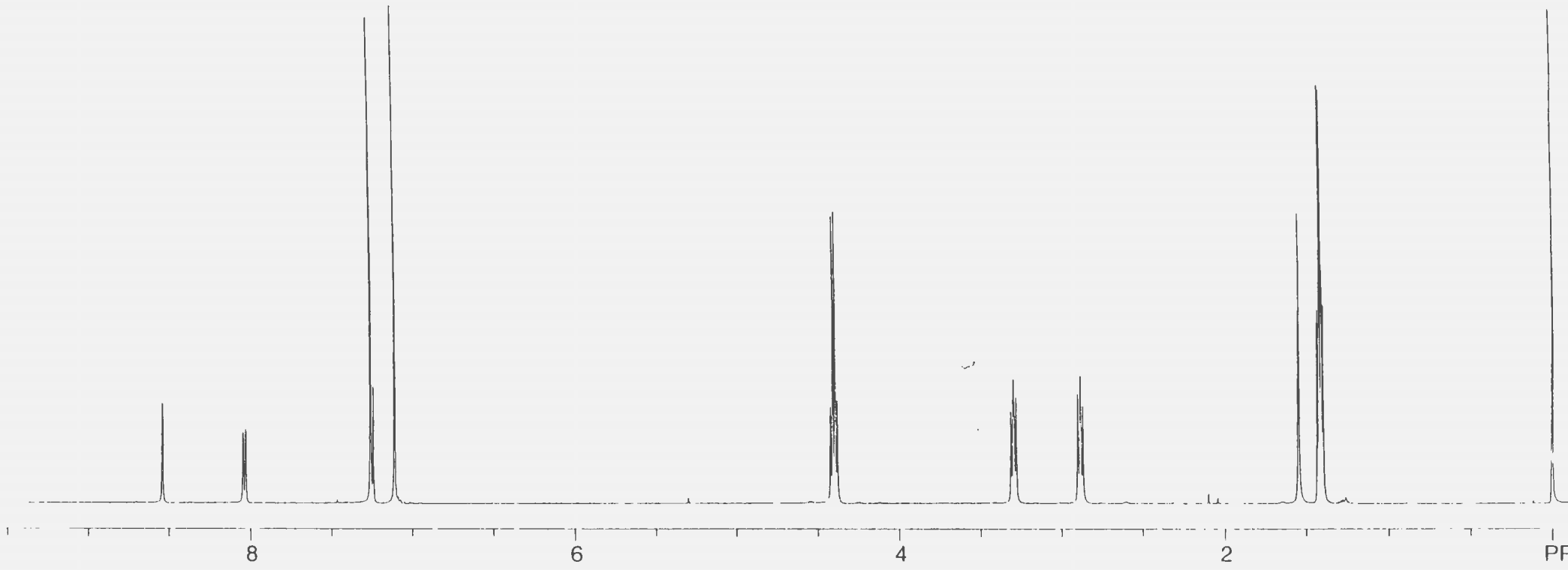

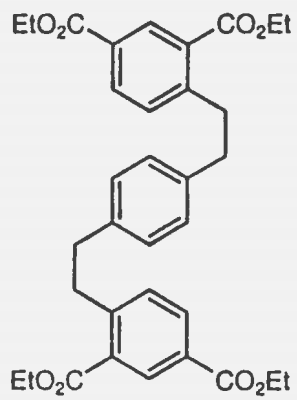

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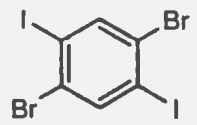

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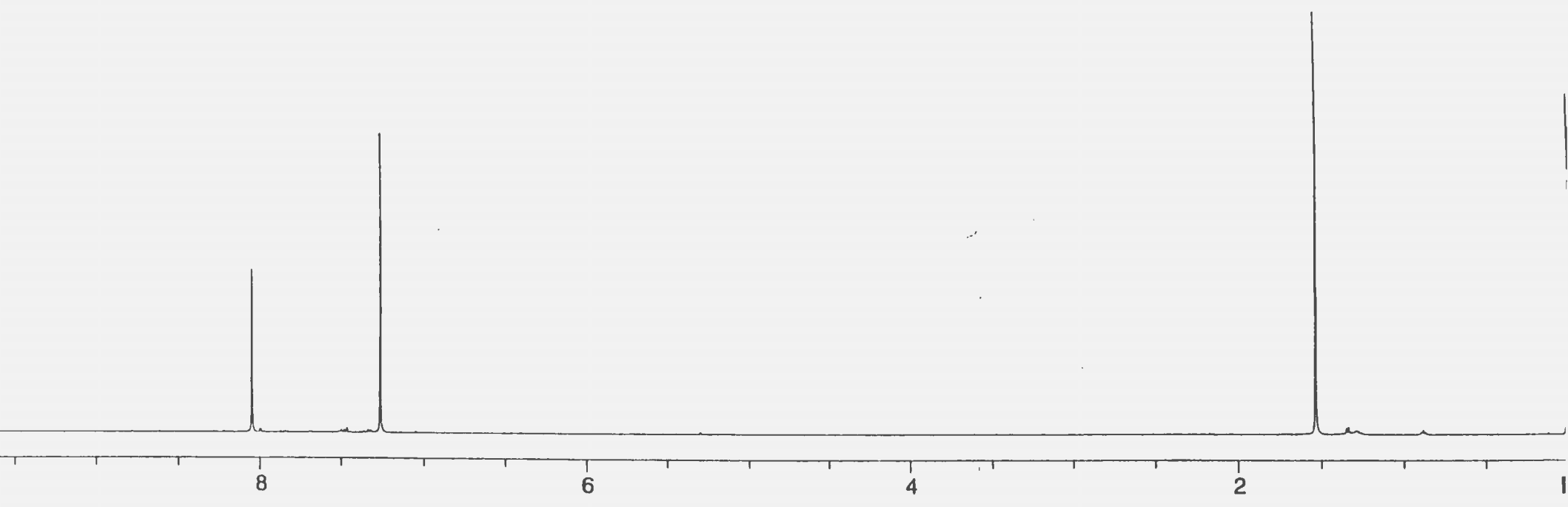

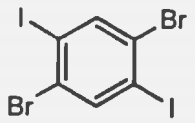

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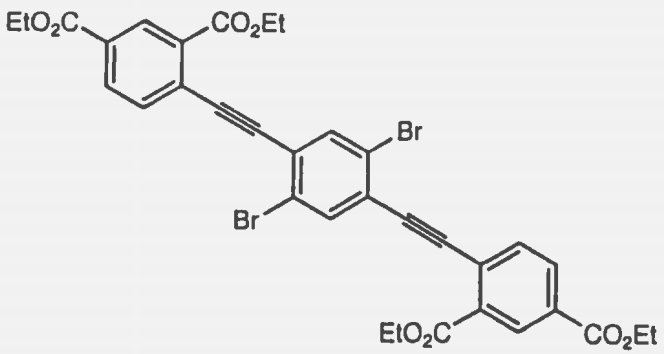

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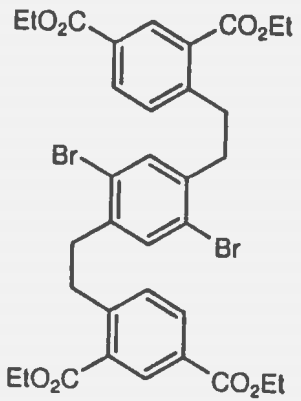

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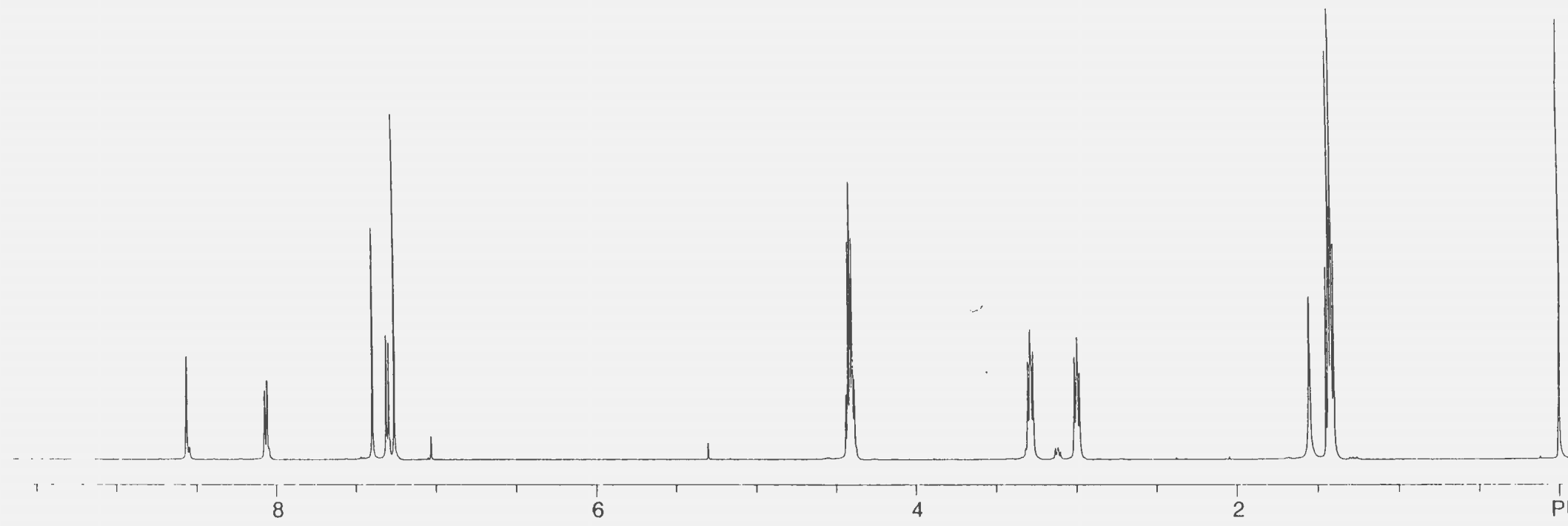

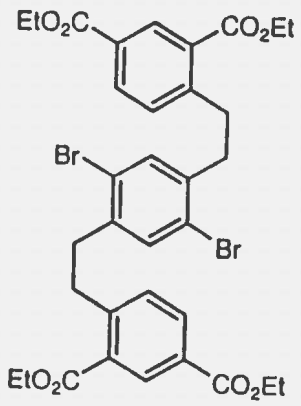

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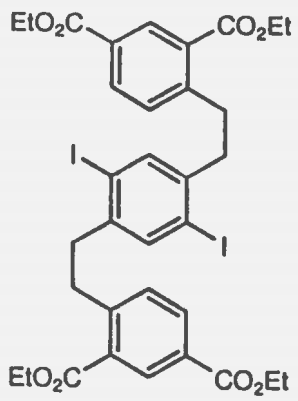

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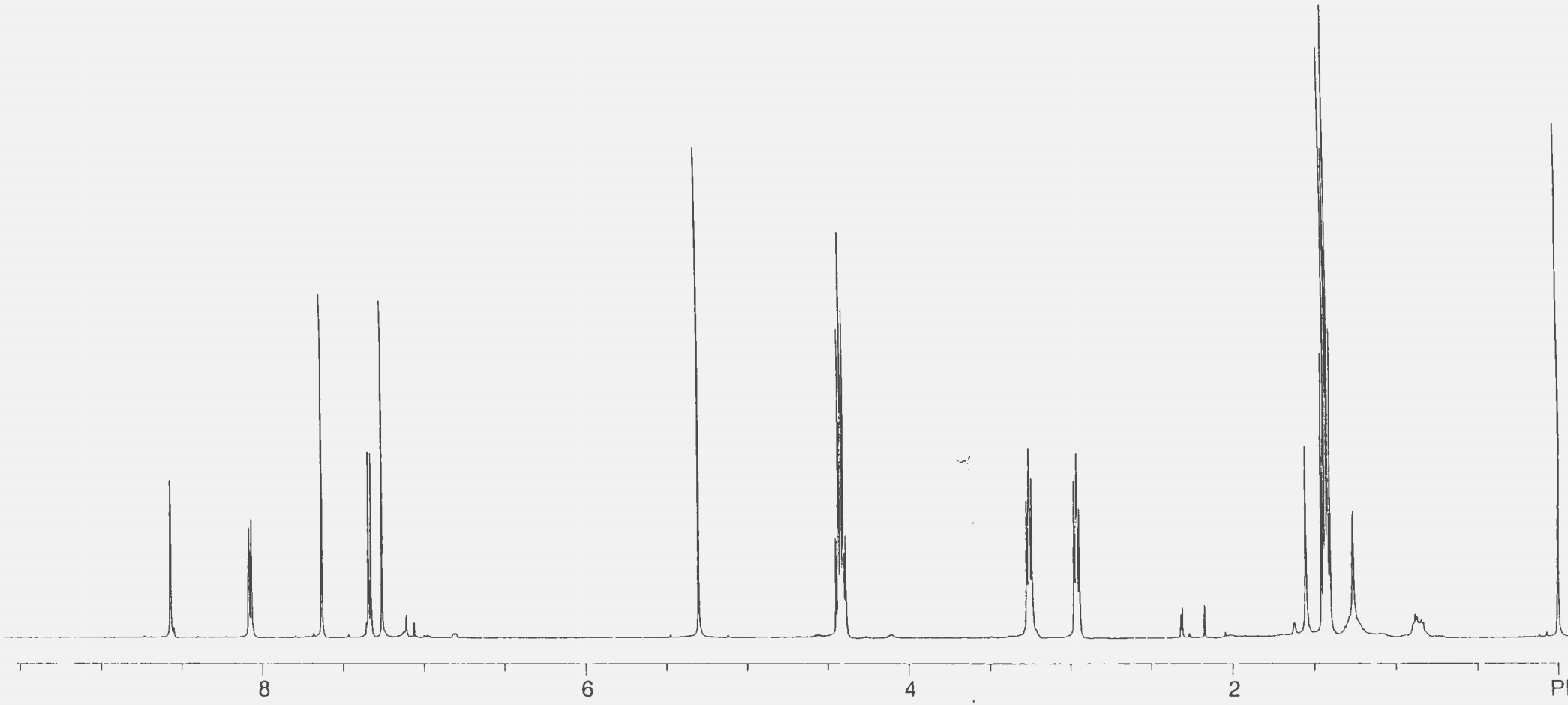

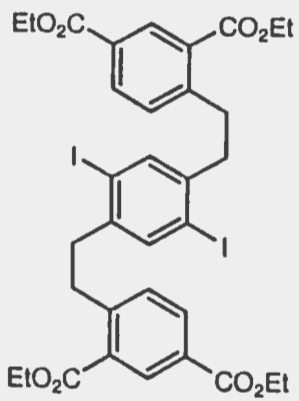

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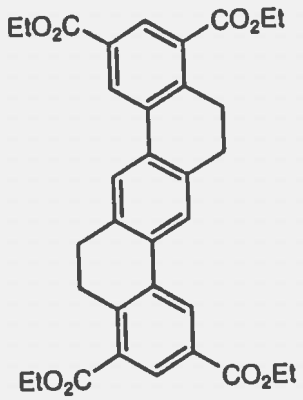

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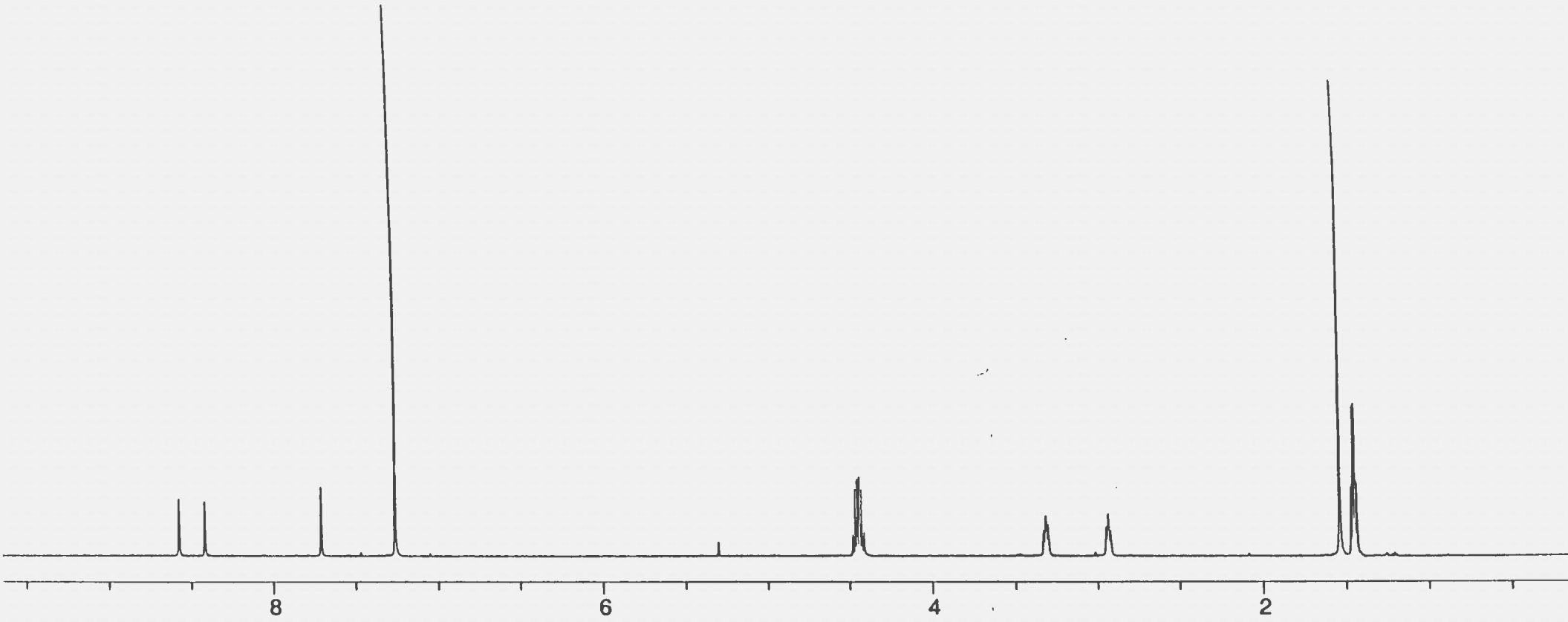

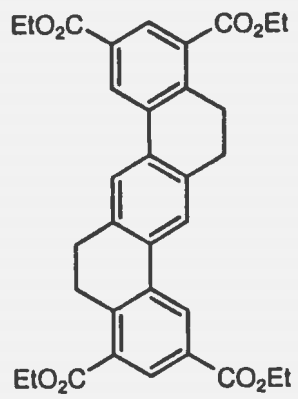

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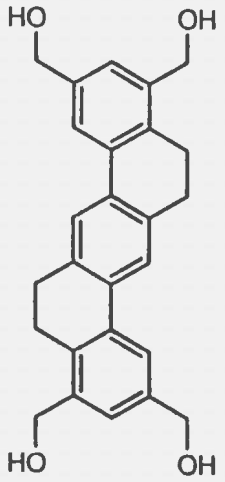

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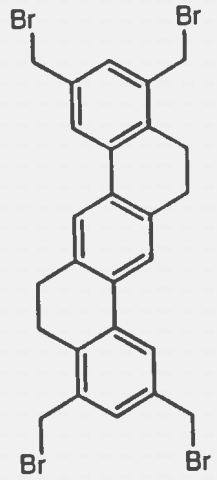

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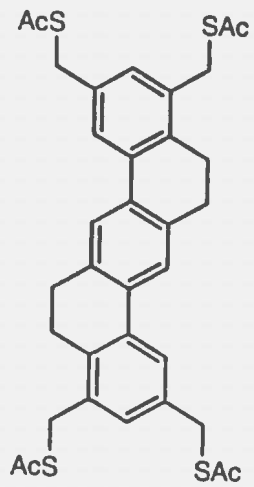

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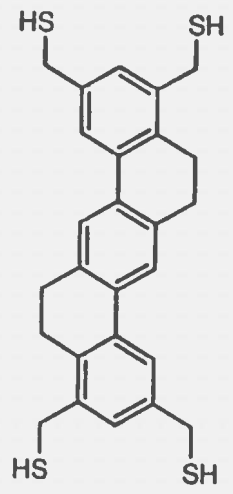

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