THE SYNTHESIS OF PRECURSORS TO CONJUGATED POLYMERS

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The Synthesis of Precursors to Conjugated Polymers

by

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Abstract

Poly(benzo[*c*]thiophene) (PBcT) was prepared by Wudl *et al.* in 1984 from the monomer benzo[*c*]thiophene (BcT) and was found to have a bandgap of 1.0 eV, the lowest bandgap polymer reported at that time. Since this finding, very few substituted BcTs have been prepared.

Two substituted BcTs, 5,6-dioxymethylenebenzo[*c*]thiophene **52** and 5,6-bis(methylcarboxylate)benzo[*c*]thiophene **57**), were prepared using adapted literature procedures in four and six steps, respectively, in good yields. In the case of **57** a novel monomer, several approaches were taken, one of which led to the discovery of NBS and silica as a rather unique benzylic brominating agent.

Other compounds of interest included terheterocycles, 1,3-dithienylbenzo[*c*]thiophenes **85**. The following compounds, 5,6-dimethoxythiophthalic anhydride **105**, 5,6-methylenedioxyphthalaldehyde **112** and 5,6-ethylenedioxyphthalic acid **171**, were prepared as potentially useful precursors for the synthesis of substituted terheterocycles. Compound **105** was prepared by the hydroxymethylation of 3,4-dimethoxybenzoic acid **117** followed by the reaction with sulfur. Upon its isolation, it was reacted with two equivalents of 2-thienyllithium and also with one equivalent of 2-thienyllithium followed by methyliodide to form 1-thienoyl-2-methylthiacarbonyl-5,6-dimethoxybenzene **108**. Compound **112** was prepared in four steps starting from piperonal and **171** was prepared by a Diels-Alder reaction of a 3,4-disubsituted thiophene, EDT **157**, and

dimethylacetylene dicarboxylate. The literature synthesis of **157** gave disappointing results, but modifications to this procedure led to a significant improvement in the yield of this important thiophene.

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Contents

Glossary of Abbreviations

Ac	acetyl
BcT	benzo[*c*]thiophene
tBHC	*t*-butyl hypochlorite
bp	boiling point
Bn	benzyl
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAD	dimethylacetylenedicarboxylate
DMB	2,3-dimethyl-1,3-butadiene
DMF	*N,N*-dimethyl formamide
DMSO	dimethyl sulfoxide
DTBcT	1,3-dithienylbenzo[*c*]thiophene
ECC	effective conjugation coordinate
EDT	3,4-ethylenedioxythiophene
EDG	electron donating group
EI	electron ionization
Et	ethyl
EWG	electron withdrawing group
FT	Fourier Transform
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
$h\nu$	visible light
LDA	lithium diisopropylamide
LR	Lawesson's Reagent
LUMO	lowest unoccupied molecular orbital

Me	methyl
MOM	methoxymethyl
mp	melting poing
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NIR	near infrared
NMR	nuclear magnetic resonance (spectroscopy)
PA	polyacetylene
PAn	polyaniline
PAT	poly(3-alkylthiophene)
PBcT	poly(benzo[*c*]thiophene)
PDHBcT	poly(1,3-dihydrobenzo[*c*]thiophene)
PCC	pyridinium chlorochromate
Ph	phenyl
PPA	polyphosphoric acid
PPP	poly(*p*-phenylene)
Ppy	polypyrrole
PT	polythiophene
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsily
TEAF	tetraethylammonium fluoride
TEAP	tetraethylammonium perchlorate
TCNQ	7,7,8,8-tetracyanoquinodimethane
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TFOP	2-(trifluoromethylsulfonyloxy)pyridine
TMS	trimethylsilyl
p-TsOH	*para*-toluenesulfonic acid
UV	ultraviolet

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Chapter 1

Introduction

1.1 Theory of Conjugated Polymers

Conjugated polymers are a class of organic polymers which contain extended π-conjugated systems and a few examples of these polymers are illustrated in Figure 1. Polyacetylene (PA), a well known conjugated polymer (Figure 1), essentially launched the study of organic-based conjugated polymers. These polymers are commonly prepared by either the chemical or electrochemical polymerization of an appropriate precursor monomer unit.

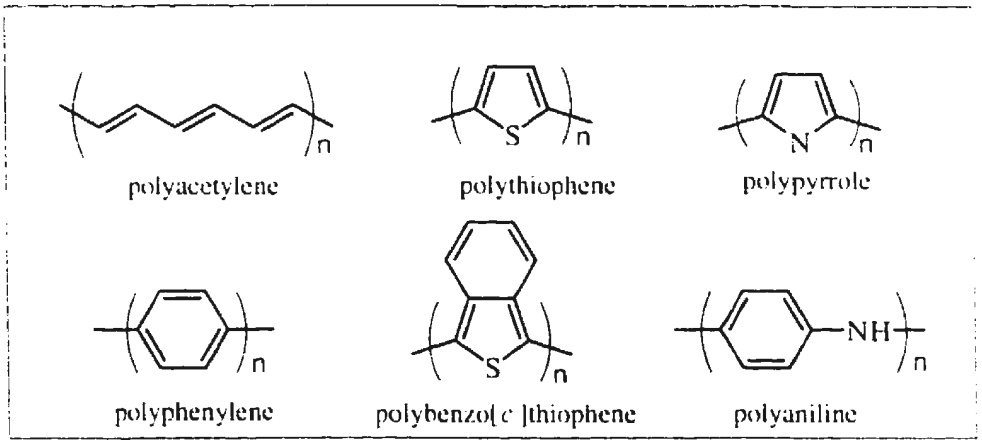


Figure 1: Some Examples of Conjugated Polymers

The field of conjugated polymers, now a large area of study, was arguably sparked in 1974 after Shirakawa's reportedly accidental preparation of PA films from acetylene using a Ziegla-Natta type catalyst[4, 5]. Although the resulting silvery film had insulating properties, Chiang *et al.* subsequently discovered in 1977 that conductive films could be obtained by means of oxidative doping[6]. Their polymer was reported to exhibit conductivities of 10^3 S·cm^{-1}. As a comparison, Teflon, an insulator, has a conductivity of 10^{-18} S·cm^{-1} and the conductivity of silver is 10^6 S·cm^{-1}[4]. The high conductivies of PA were viewed with much interest due to the intriguing possibility of some day preparing a fully organic conductor with metallic conductivity.

Interest in these compounds stems in part from the numerous commercial possibilities that exist, including electrical applications, some of which are already in use. For example, some advanced batteries already employ conjugated polymers[7]. Other electrical applications include smart windows, electrochromic displays[8], electromagnetic shielding[9], sensor technology[10], and molecular electronics [11, 12]. These applications are in various stages of development.

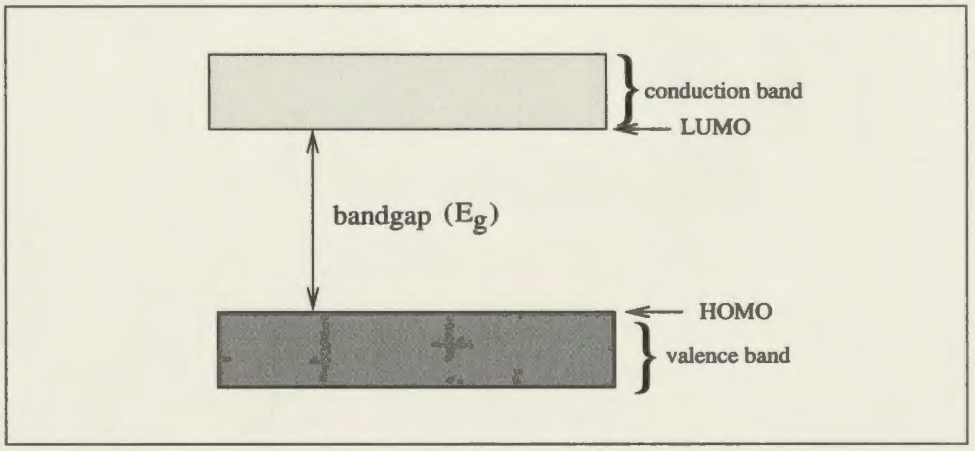


Figure 2: General View of a Polymer Bandgap

Owing to the similarity between conjugated polymers and semiconductors, much of the terminology is shared. The bandgap of a conjugated polymer (E_g) is defined as the energy difference that exists between the valence band and conduction band (Figure 2). These bands are comprised of the occupied molecular orbitals and unoccupied molecular orbitals respectively. At the top of the valence band lies the highest occupied molecular orbital (HOMO), while the lowest unoccupied molecular orbital (LUMO) is at the bottom of the conduction band. The electrons associated with an atom or molecule exist in definite fixed energy levels (Figure 3)[12]. When several atoms or molecules interact, the energy levels begin to split. The formation of energy bands in solids are a result of the interactions between the building blocks of the

solid in a three-dimensional lattice and the stronger these interactions, the broader the energy bands will be. In the case of metals, these interactions are very strong, resulting in broad energy bands which overlap. Organic materials however have weaker interactions compared to metals and give rise to narrow, discrete energy bands.

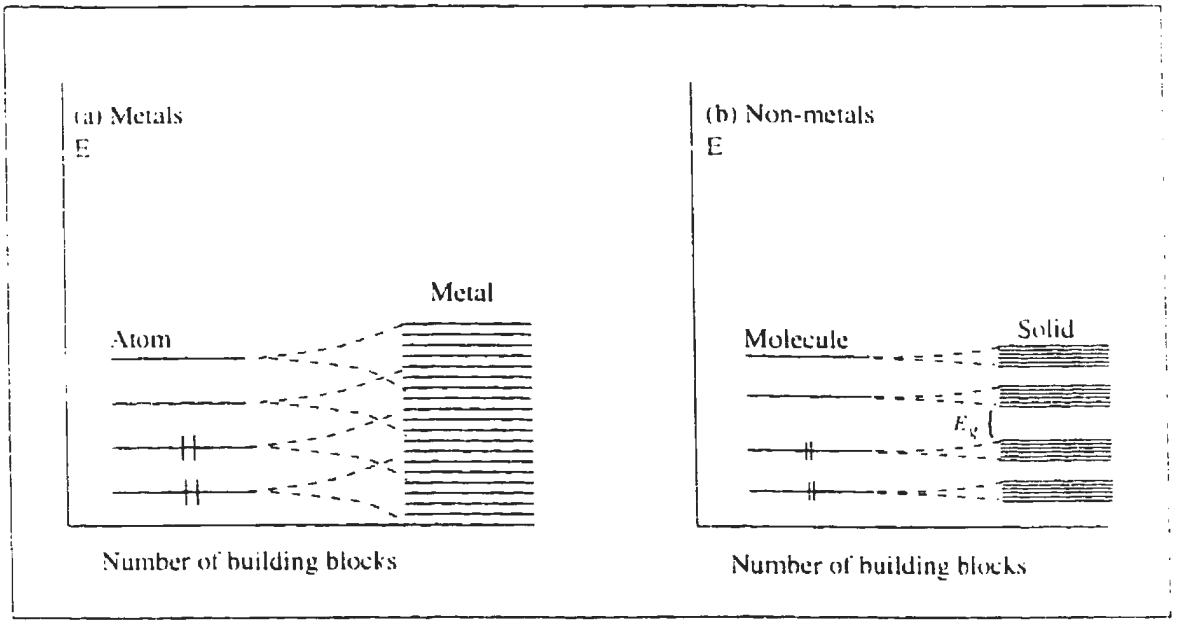


Figure 3: Band Structures for a Metal and Non-metal

The magnitude of a polymer's bandgap cannot be determined from the precursor monomer's HOMO-LUMO energy gap ($\pi \longrightarrow \pi^*$), but, it has been shown recently that band gaps can be estimated by density functional theory/hybrid (DFT/Hybrid) approach [13–15]. From the DFT/Hybrid calculations, Salzner *et al.* obtained band gaps within 0.1 eV for a series of oligomers[14]. Usual experimental methods for determining polymer band gaps include electronic spectroscopy and cyclic voltammetry. The HOMO-LUMO transition can be measured from the $\pi \longrightarrow \pi^*$ absorption in the UV/vis/NIR spectrum and E_g is usually taken as the minimal (onset) energy of this absorption. Alternatively, the HOMO-LUMO gap can be determined electrochemically. The oxidation (E_{ox}) and reduction (E_{red}) potentials can be determined from

the cyclic voltammagram and the bandgap is estimated from the difference between the two onset potentials: $E_g \sim (E_{ox} - E_{red})$.

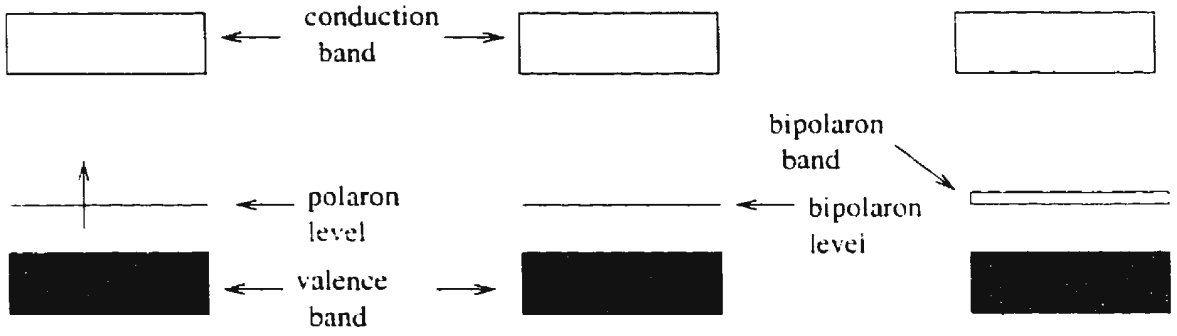


Figure 4: Doping Process

Bandgaps of conjugated polymers are generally fairly large (>2 eV) and as a result, in the neutral state, conjugated polymers behave as insulators. In spite of the bandgap, conjugated polymers may be made conducting by doping, a process which can be carried out either electrochemically or chemically. Doping the conjugated polymer serves to increase the concentration of *extrinsic* charge carriers either by the addition of electrons to the conduction band or removal of electrons from the valence band and there are two ways to accomplish this: oxidative (p-doping) or reductive (n-doping) with p-doping being more common.

In the case of p-doping an electron is removed from the valence band creating a radical cation or "hole". This hole does not completely delocalize, but only partially over several monomer units[4]. This causes a destabilizing of the bonding orbital that is associated with the radical cation and therefore it is higher in energy than the energy associated with the valence band and its energy is in the bandgap (Figure 4). In solid state physics terms, a radical cation that is only partially delocalized over

the polymer segment is known as a polaron. Removal of the second electron from the polaron level leads to the formation of a bipolaron level. As the polymer becomes increasingly doped, the energies of the bipolaron levels tend to overlap to form new bands (Figure 4).

n-Doping, a reductive process, is analogous to p-doping, but, in this case, an electron is added to the polymer creating a radical anion. Generally, only polymers containing electron deficient groups, e.g. pyridine, can be n-doped, and do so only at very negative potentials although polythiophene (PT) can also be n-doped[16, 17]. The resulting n-doped polymers tend to be very reactive, especially towards electrophiles. As a consequence of this instability, little attention has been paid to n-doping[17] and it is not nearly so prevalent in the literature as oxidative doping, although some interesting examples have been demonstrated[17–19].

When high potentials are required to produce a conductive conjugated polymer, whether using oxidative or reductive doping, the resulting doped polymer is thermodynamically unstable. In the case of a hypothetical conjugated polymer with a zero or near vanishing bandgap, room temperature thermal excitation of electrons from the valence band to the conduction band may occur and should lead to the formation of *intrinsic* charge carriers by the enhancement of the thermal population of the conduction band. This parallels semiconductors and such an achievement could ultimately lead to conjugated polymers behaving as organic metals and therefore be conductive without the need for doping.

In order to reduce the bandgap, an understanding of the factors responsible for its existence is needed. From theoretical studies, it was concluded that the following energy factors have an influence on the magnitude of the bandgap: degree of bond length alternation or ($E^{\delta r}$), mean deviation from planarity (E^{θ}), the aromatic

resonance energy of the individual aromatic rings of the polymer (E^{Res}), inductive effects of substituents (E^{Sub}), and the interaction between polymer chains (E^{Int}) (Figure 5)[20]. Collectively, these terms describe the overlapping of the π orbitals which affects the extent of conjugation of the polymer.

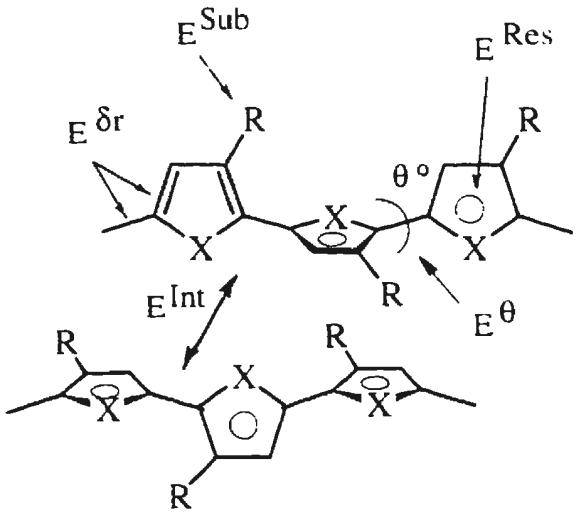


Figure 5: Factors That Influence Polymer Bandgaps

The degree of bond length alternation, is reported to be the most important factor[16, 20–22] and is defined as the average between the difference of neighbouring long and short C–C bonds[22]. Theoretical studies agree that a reduction in the degree of bond length alternation should lead to materials with a reduced bandgap[23–25].

The term E^{θ}, considers the interannular rotations that may occur within the polymer chain. This deviation from planarity results from rotations about what essentially become single bonds between aromatic rings. Orbital overlap varies approximately with the cosine of the dihedral angle θ [26, 27] and, in a perfectly planar system, p_z orbitals overlap to effect electron delocalization. This electron delocalization should run

down the length of the infinite polymer chain and a loss of planarity will discourage such overlap and therefore result in an increase of E_g [20].

The third term, E^{Res}, takes into consideration the competition that exists between the delocalization along the chain length[28] *versus* delocalization within the aromatic ring. Again this will have a negative impact on the delocalization along the polymer chain resulting in an increase to E_g. This problem however remains largely unaddressed[20].

The fourth term E^{Sub}, refers to the influence of substituents grafted onto the polymer backbone. Substituents may be expected to play a lesser role but have only been considered by a few theoretical works[29, 30]. Substituents themselves are not expected to have much of an effect, if any, on the bandgap itself but there are ways in which the substituents can be utilized to influence it indirectly, and this will be discussed later.

The fifth parameter, E^{Int} deals with the interactions between individual molecules. Interchain coupling occurs in the solid state on a bulk level between molecules and this effect has been said to contribute to the minimization of the coupling of electrons with phonons (the quantum of energy in the elastic wave or lattice vibration of a solid)[31].

The search for organic polymers with very small or near vanishing bandgaps is an immense topic and there are two routes typically followed[23]. One method explores fully fused ring hydrocarbon systems (Figure 6). These systems, polyacene-like systems or polyperinaphthalene correspond to one dimensional analogues of graphite structures[23].

The second route involves the modification of the electronic properties of known polymers in the field by the use of substituents. By using a parent polymer with well

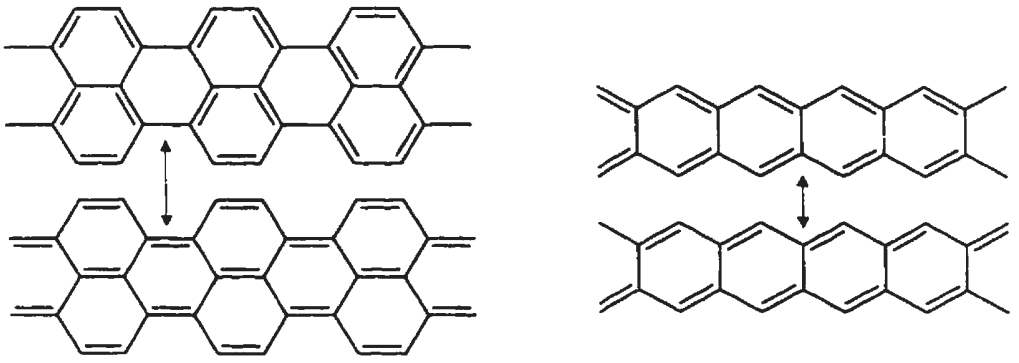


Figure 6: Examples of Fully Fused Ring Hydrocarbon Systems

defined properties, such as relatively low bandgap energies, stability and that also lends itself well to the addition of substituents, a multitude of new possibilities open up.

There are various existing parent polymers available for study that newer polymers are based upon. Examples of such parent polymers include polyaromatic poly(*p*-phenylene) (PPP), other polymers such as polyanalines (PAn), and polyheterocyclic polymers such as polypyrrole (Ppy) and polythiophene (PT). When compared to PA, the polyheterocyclic polymers are more attractive for study. PA, despite its good conductivity, lacks good mechanical properties and is atmospherically unstable (moisture sensitive) which limits its usefulness. By substituting a heteroatom in the backbone, more stable polymers are generally obtained[12]. Unlike PA with its degenerate ground state, the aromatic- and heteroatomic-based polymers have a nondegenerate ground state (Figure 7). Two limiting mesomeric forms, aromatic and quinoid, exist as resonance hybrids. These two forms are not energetically equivalent and therefore polymers with nondegenerate ground states tend to prefer one form over the other. For example, PT and Ppy tend to be aromatic in character[32].

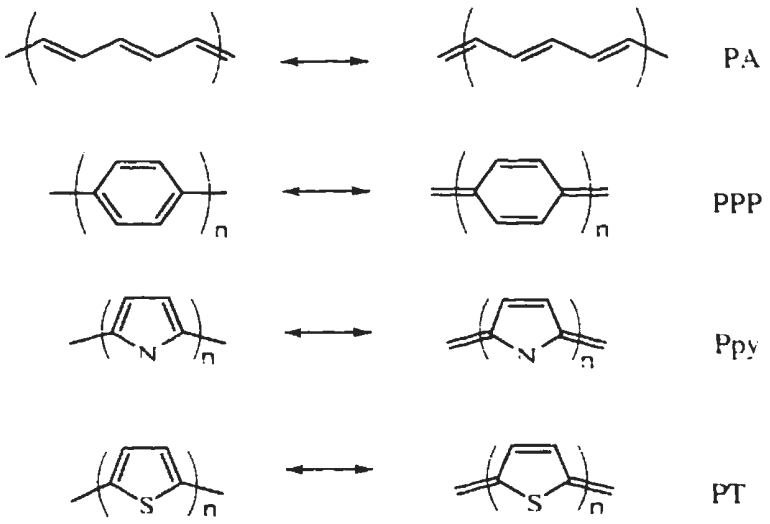


Figure 7: Limiting Mesomeric Forms

Of the two heteroaromatic polymers shown in Figure 7, PT has received a large portion of attention and has been recognized as an excellent target. The interest in PT stems from its relatively low bandgap (2.0 eV), the relative ease with which substitutents can be placed in the 3 and/or 4 positions without introducing large steric effects as well as the ability of the thiophenes to be polymerized chemically and electrochemically (through the 2 and 5 positions)[20]. Improvements to mechanical properties such as processibility have been made to PT through the use of different substituents at the 3 and 4-positions. For example it has been shown that substituting PTs in the 3-position with long chain alkyl substitnents, poly(3-alkylthiophenes) (PATs), improves the solubility of the polymer[20]. Conductivities however, were found to decrease with the increasing length of the alkyl chain but as a whole, conductivities remained as high as 70 S·cm^{-1}. Other 3-substituents investigated include branched alkyl chains, and ethers[10, 33]. Substitution with ethers

have been reported to impart useful properties. For example, substitution of thiophene with oligo(oxethylene) chains leads to improved solubilities and hydrophilic character which could be important for specialized applications such as selective electrodes, and solid state batteries[33]. Another interesting example of an ether type substituted system is a polythiophene-based pseudopolyrotaxane which is employed as a chemoresistive sensory membrane[34]. Other types of substituents have also included aryl groups which are reported to be interesting polymers as the phenyl groups provide interesting sites for further functionalizations. The grafting of the phenyl group is, however, expected to introduce a steric hindrance between the thiophene units which will affect the planarity of the PT backbone[33]. Some work has also been carried out on fluoroalkyl substituted PTs and it has been shown that the introduction of up to 50% of fluorine in the polymer leads to elastomeric materials with higher electroactivity than PATs[33]. These are only just a few examples of how substituents have been able to modify polymer processibility.

There has been some other work with substituents concerning their effects on the redox potentials. Electron-donating groups (EDG) substituted on PT tend to result in a decrease of the electrochemical oxidation potential, whereas the substitution of electron-withdrawing substituents (EWG) tend to induce an increase in the oxidation potentials required for anodic polymerization. For this reason, the study of EWG substituted polymers are seldom studied.

An interesting strategy that has emerged from the study of substitutents on parent polymers is the concept of copolymers. The preparation of heteroaryl copolymers has received little attention but the introduction of structurally different units in a single π-conjugated polymer chain may lead to modified properties[35]. Several systems that have been studied to date have shown interesting behaviour[36, 37]. Some studies

on copolymers consisting of alternating electron donor-electron acceptor type units have been published for PTs[36, 38] heteroquinoid chromophores[39], polysquaraines and polycroconaines[40]. The idea put forth by Havinga *et al.* to explain reduced bandgaps from alternating donor-acceptor substituted units is summarized in Figure 8[40]. Extension of the donor and acceptor regions is suggested to lead to a case similar to the inorganic n-i-p-i super lattice structures[40]. In this instances, both the valence and conduction bands are curved by space charge effects. The bandgap E_{go} has not changed locally *per se*, but the net bandgap is expected to decrease as indicated by E_{gx}[40].

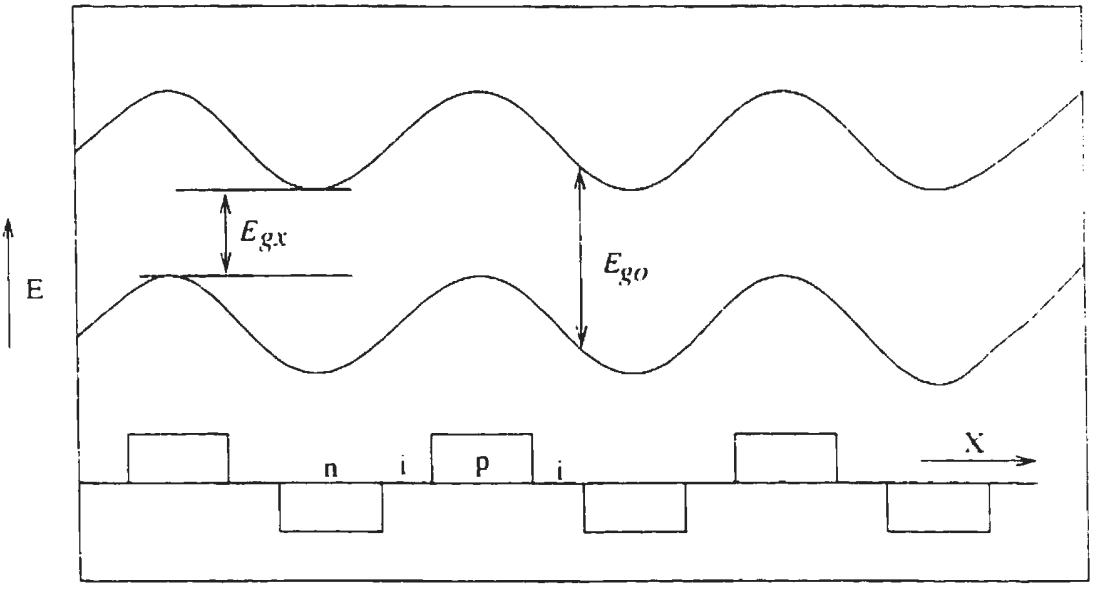


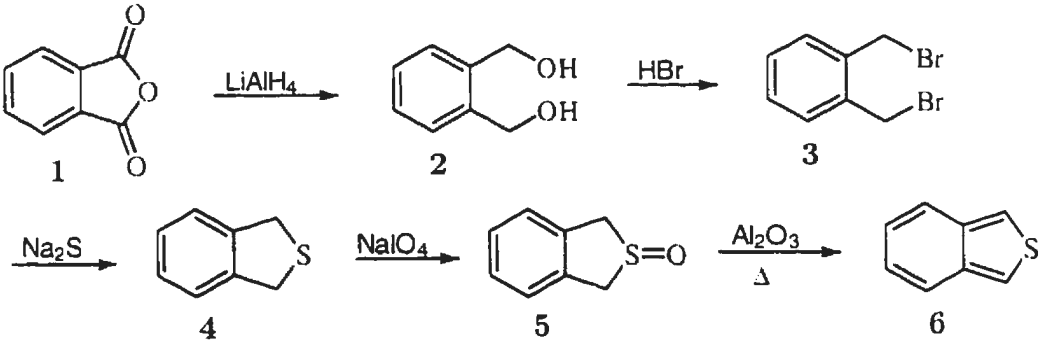
Figure 8: Expected Bandgap With the Alternation of Donor and Acceptor Units

In addition to synthetic studies, PT has also been the target of theoretical studies and it was shown that, although the preferred ground state structure was aromatic in nature[32], a PT in the quinoidal mesomeric form should have a bandgap roughly half that of aromatic PT[41]. This led to the strategy of utilizing substituents as a means of coercing the thiophene polymers to adopt more of a quinoidal structure. This was

achieved with the rediscovery of benzo[*c*]thiophene **6** by Wudl *et al.* in 1984[2].

1.2 Benzo[*c*]thiophene

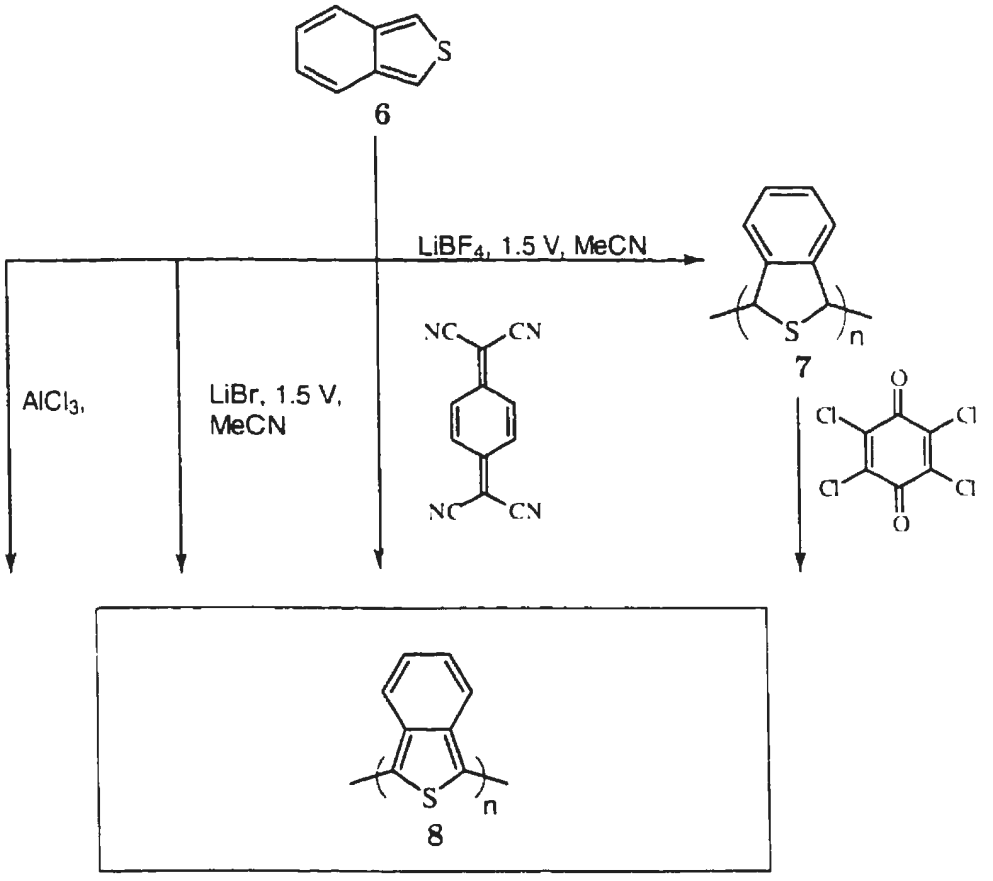
As late as 1970, benzo[*c*]thiophene (BcT) **6** had been claimed by some to exhibit biological activity[42], but was not considered to be of much commercial importance. Following on from works in the literature on 3-substituted and 3,4-disubstituted polythiophenes[10, 20, 33], the continued study into the use of substituents to modify electronic behaviour led to the rediscovery of BcT by Wudl, Kobayash and Heeger in 1984. They investigated the polymer polybenzo[*c*]thiophene (PBcT) **8** as an extension of their most recent study on PTs[43, 44] and viewed this polymer as a precursor for a new type of substituted PT[2]. Monomer, BcT **6** was prepared following the synthesis of Cava *et al.* (Scheme 1)[1].



Scheme 1: Synthesis of BcT by Cava *et al.* [1]

The resulting monomer **6** was polymerized oxidatively using several approaches (Scheme 2)[2]. It was reported that the electropolymerization was strongly electrolyte dependent. Non-nucleophilic anions ($^{-}BF_4$, $^{-}ClO_4$) produced poly(dihydrobenzo[*c*]-thiophene) (PDHBcT) **7** as a white powder whereas nucleophilic anions (Br^{-}, Cl^{-}) resulted in the formation of PBcT[2]. The monomer **6** was also polymerized chemically

using aluminum chloride, 7,7,8,8-tetracyanoquinodimethane (TCNQ) and also from heating polymer **7** in the presence of tetrachloro-*p*-benzoquinone in chlorobenzene[2]. More recently however it was shown that polymer **8** could be prepared electrochemically by repetitive anodic potential scans in solutions containing electrolytes such as tetraethylammonium perchlorate (TEAP), tetraethylammonium fluoride (TEAF) or tetrabutylammonium fluoride (TBAF) in acetonitrile[20].



Scheme 2: Polymerization Methods by Wudl *et al.* [2]

The bandgap of this new polymer **8** was found experimentally from the band edge in the near IR (from the transmission through thin films at low doping levels) to be 1100 nm or $\sim$ 1 eV. PBcT was the first example of a transparent, highly conducting

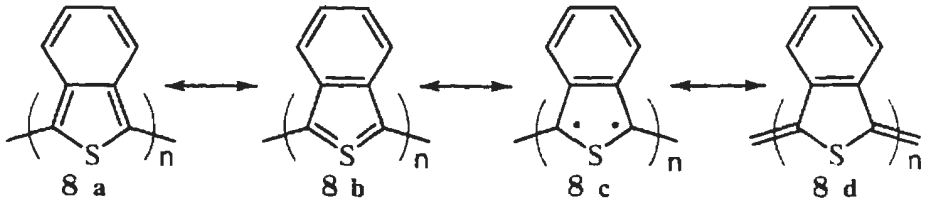


Figure 9: Resonance Forms of PBcT

($\sim$ 50 S·cm^{-1}) polymer with a bandgap less than or equal to 1 eV[45], an energy gap which is one full eV lower than that of PT itself. The fused ring system of **8**, quickly became the focus of much theoretical debate as to its preferred ground state structure. As with PT, mesomeric forms exit. By referring to the thiophene portion of the system, **8a** is described as aromatic and **8d** is described as quinoidal (Figure 9).

As a result of the resonance contributors **8b** and **8c** (Figure 9), this new polymer was expected to display higher stability than PT. These resonance contributors were expected to be important in the stabilization of open-shelled species and delocalization along the backbone, stabilizing the quinoid form. This conclusion of a stabilized quinoidal form can also be reached by the consideration of the effect of fusing benzene and thiophene; only one of the cycles can accommodate an aromatic sextet (Figure 10). By comparing aromatic resonance (E_r) energies for thiophene (1.26 eV) and benzene (1.56 eV) (Figure 10)[20], it appears more likely that the benzene ring will exhibit a greater tendency to remain aromatic at the expense of the thiophene ring.

Initially it was concluded that PBcT in its ground electronic state has the aromatic structure of **8a**[21, 45]. Band structure calculations were carried out using VEH pseudopotential techniques[23], which have provided estimates of electronic parameters such as ionization potentials, π-π^* transitions and bandgaps for a large series

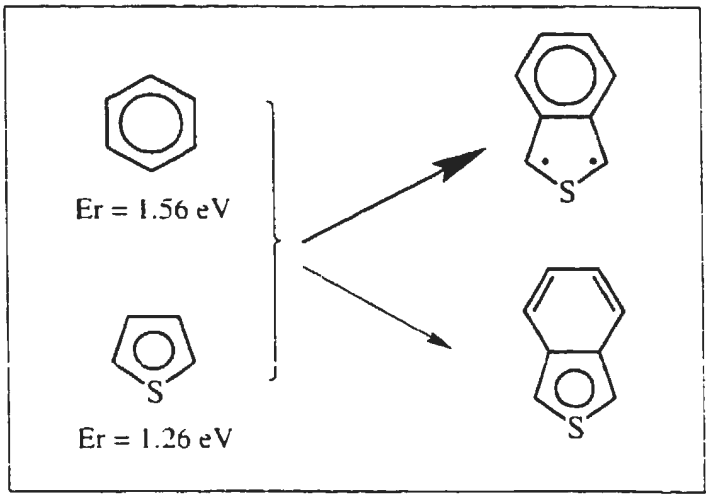


Figure 10: Comparison of Aromatic Resonance Energies for Benzene and Thiophene

of hydrocarbons and sulfur-containing conjugated systems. These calculations were used to rationalize the decrease in bandgap energy observed for PBcT compared to PT and, in so doing, developed a relationship between the magnitude of bandgaps of aromatic systems and the importance of quinoid contributions to electronic structures. The concept of increasing quinoidal contributions was also linked to bond length alternation[23]. Using these calculations, Brédas *et al.* proposed aromatic PBcT to have a bandgap of 0.54 eV[23].

Lee and Kertesz on the other hand, suggested a quinoidal structure on the basis of their optimized geometry calculations[22]. From their calculations they suggested that the preferred mesomeric form of PBcT is quinoidal (**8d**). Using the band theory of solids at the MNDO level for energy calculations, they first examined PT and then extended the optimized geometry calculations to PBcT. From their study, band theory calculations confirmed the aromatic nature of PT, and predicted quinoid PT, using Hückel calculations, to have a bandgap of 0.47 eV. This value is much lower than that calculated for aromatic PT (1.83 eV). The optimized geometry calculations,

using periodic boundary conditions[22], of **8** suggested a quinoidal structure (**8d**) for the polymer (Figure 11). The inter-ring C-C distance that they calculated, was 1.362 Å which they considered appropriate for a quinoidal structure. Based on this quinoid structure for **8**, they calculated the bandgap to be 1.16 eV. This value is close to the experimental value reported for **8** (1 eV).

A question then arises: if the polymer **8** is quinoidal, why is E_g much larger than for quinoidal PT? Interaction diagrams were used to illustrate the effects of the mixing of the frontier molecular orbitals of PT and butadiene (Figure 12 (A)). By adding orbitals of butadiene to PT(Q), the HOMO of the resulting quinoid PBcT becomes stabilized and drops in energy while the LUMO becomes destabilized. This results in an increase of the bandgap of PBcT(Q) compared to PT(Q). Looking at the case for aromatic PBcT (PBcT(A)), the order of symmetry is reversed. The addition of orbitals of butadiene to those of PT(A) results in the destabilization of the HOMO along with a stabilization of the LUMO and the resulting E_g of PBcT(A), calculated to be 0.73 eV, is smaller than PBcT(Q) (1.16 eV). Overall, PBcT(Q) was calculated to be more stable than PBcT(A). The more stable form has the larger bandgap.

Shortly after the suggestions put forth by Lee and Kertesz, Kürti and Surján proposed a mixed structure with the middle part essentially quinoidal and aromatic regions at both ends after pointing out that a quinoidal PBcT structure implies terminal doubly bonded sp^2 carbon at each end of the polymer chain[46].

Hoogmartens and coworkers later then suggested that the energy difference between the quinoidal and aromatic states were too small (2.4 kcal·mol^{-1}) to allow for a definitive assessment for the structure of **8**. This notion was based on ^{13}C NMR data for a series of suitable model compounds[47].

Zerbi *et al.* found the structure of **8** to be quinoidal using Raman spectroscopy to

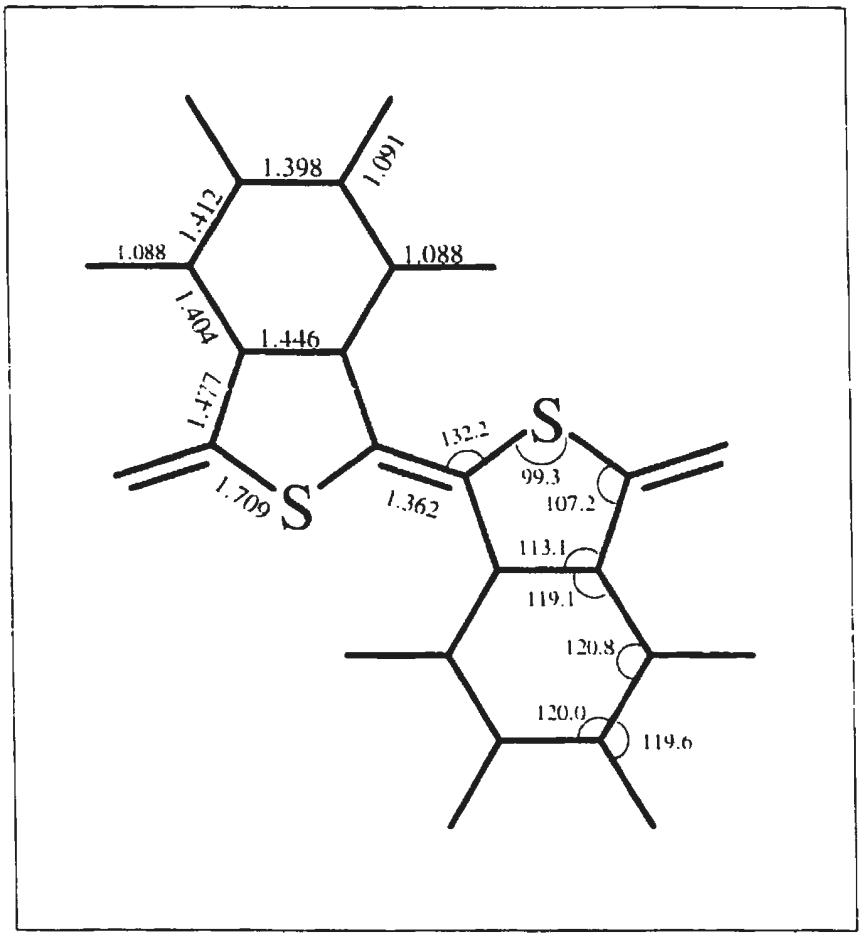


Figure 11: MNDO Optimized Geometry For PBcT

study several model compounds which mimic either the aromatic type structure or quinoidal structure on the basis of effective conjugation coordinate (ECC) theory[48]. It is interesting to note that this was the first time that experimental evidence from vibrational spectroscopy had indicated a quinoid structure for a low bandgap poly-conjugated aromatic material in its pristine state.

Further studies on BcT oligomers, from monomers up to the tetramer were carried out by Quattrocchi *et al.* by investigations of their optical absorption spectra with a combined theoretical and experimental approach[49]. Disilylated BcT oligomers

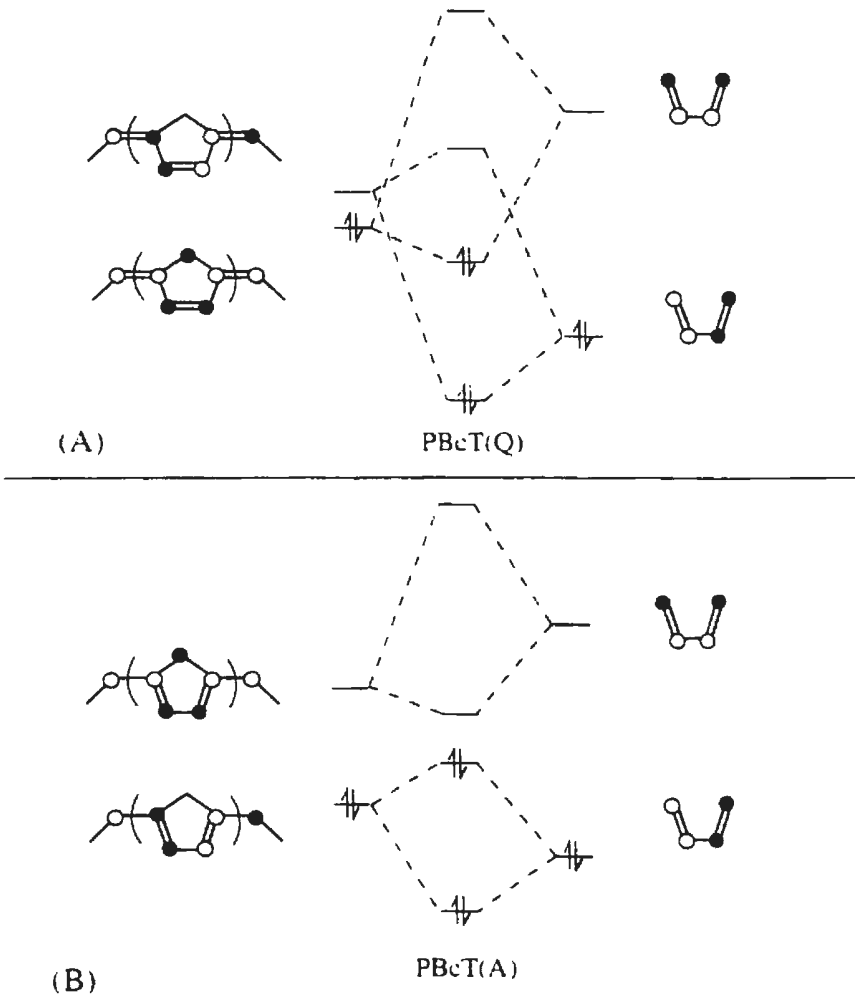
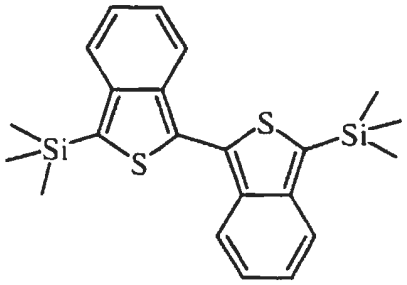


Figure 12: Frontier Molecular Orbital Diagram for Quinoidal and Aromatic Forms of BcT

were prepared and geometry optimizations were performed with the semiempirical AM1 method. The calculated parameters were compared to parameters obtained from the single-crystal x-ray structure of 3,3'-bis(tert-butyldimethylsily)-1,1'-bibenzo[*c*]thiophene **9**.

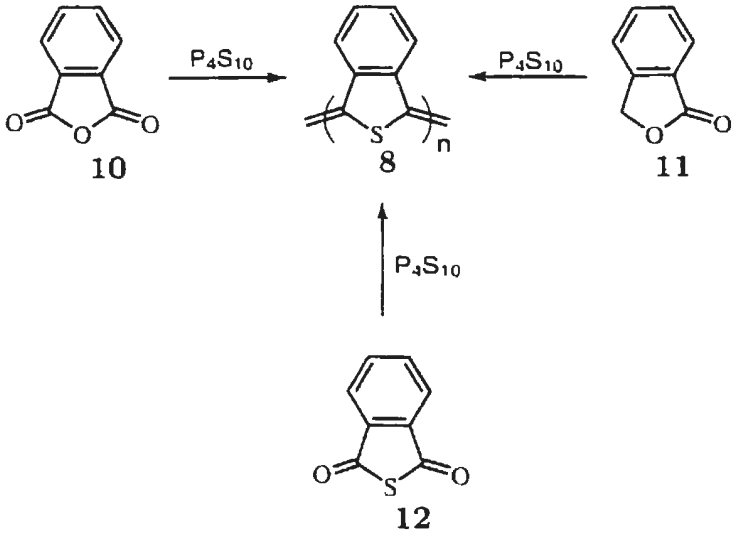
Optical absorption spectra of the oligomers were also simulated theoretically (intermediate neglect of differential overlap method, coupled to single configuration interaction) and compared to experimental spectra[49]. From the experimental optical



9

absorption spectra, the $\pi \longrightarrow \pi^*$ type transition from the HOMO level to the LUMO level is shifted to lower energies as the chain length is increased. Extrapolations made from the HOMO LUMO transitions of the BcT oligomers (monomer to the tetramer) to the bandgap energy of aromatic **8** led to an estimated bandgap of 0.63 eV for a planar system. By extrapolation of the X-ray structure of the dimer (syn conformation with a dihedral angle of 50°) a value of 1.55 eV was predicted for the bandgap for PBcT[49]. These results suggested that, in solution, the aromatic oligomers adopt a strongly nonplanar conformation which significantly increase the HOMO LUMO transition relative to the planar aromatic system[49].

In addition to methods described above to preparing polymer **8**, other synthetic routes to **8** have also been reported by Chen and Lee[50]. Dehydrogenation of the dihydro species **7** to produce **8** was carried out using sulfuryl chloride[50] or *t*-butyl hypochlorite (tBHC)[51] in the presence of pyridine as a stabilizing agent. van Asselt *et al.* have reported the preparation of **8** from the both the reaction of phthalic anhydride and phthalide with phosphorus pentasulfide [52] and also from the reaction of thiophthalic anhydride and phosphorus pentasulfide[53] (Scheme 3).



Scheme 3: Alternative Methods for Preparing PBcT

1.3 Benzo[*c*]thiophene Syntheses

Benzo[*c*]thiophene is the currently accepted name for **6** in the *Chemical Abstracts* (*CA*) although isothianaphthene (or isothionaphthene) are frequently used in the literature (and to a lesser extent isobenzothiophene and 2-thiaindene). The ring system in the *CA* is numbered as shown in Figure 13 for BcT **6a** although the alternative system of numbering as in **6b** occurs in some of the early literature[42].

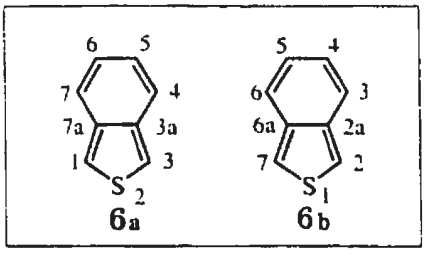
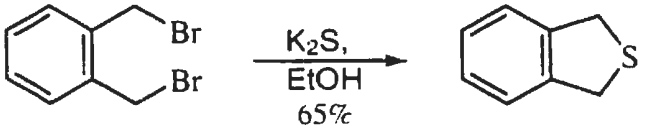


Figure 13: CA Numbering System for BcT

The first reference to a benzo[*c*]thiophene-type system in the literature was in

1884 with the synthesis of 1,3-dihydrobenzo[*c*]thiophene **4** (Scheme 4) by Leser[54]. A saturated aqueous solution of potassium sulfide was added to α,α'-dibromo-*o*-xylene and the reaction mixture was then refluxed. The reaction was judged complete when the authors could no longer smell the α,α'-dibromo-*o*-xylene!

It is noted with much interest, that **4**, although reported to be stable in the absence of air for several months, formed a deep red liquid in air from which an amorphous blue solid of unknown identity precipitated[55]. Although not recognized, this amorphous blue solid may have been one of the first appearances of PBcT in the literature.

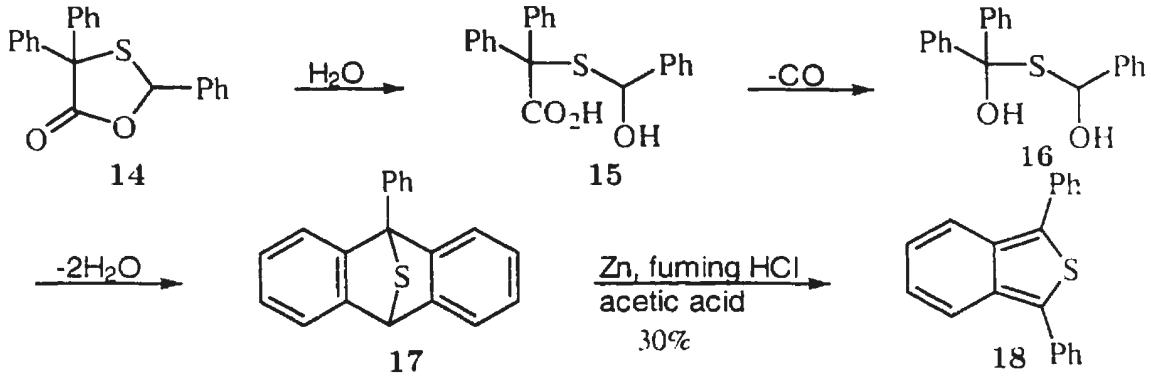


13 **4**

Scheme 4: Leser's Synthesis of 1,3-Dihydrobenzo[*c*]thiophene

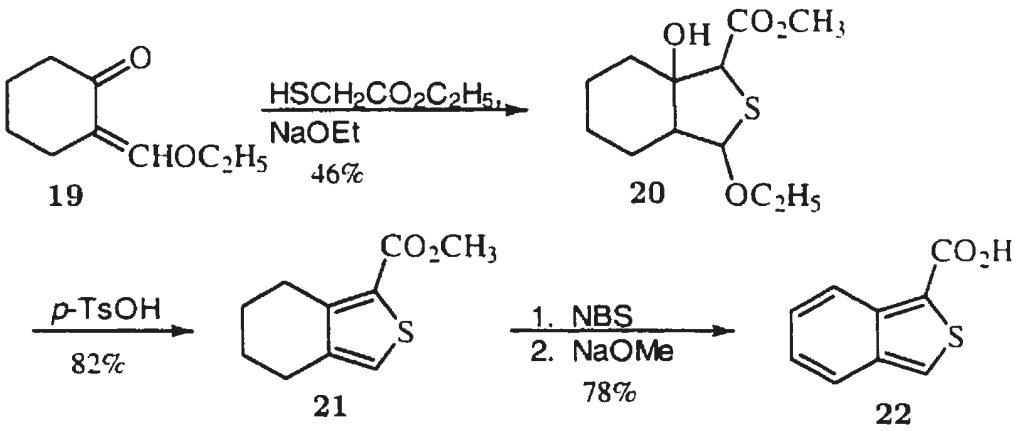
The first synthesis of a benzo[*c*]thiophene system, 1,3-diphenylbenzo[*c*]thiophene (**18**) was published in 1922 by Bistrzycki and Brenken using a rather curious procedure[56] (Scheme 5). This BcT was prepared by a four step synthesis starting from the lactone sulfide **14**. Hydrolysis followed by loss of carbon monoxide reportedly leads to the diol **16**, which, upon dehydration, leads to **17**. Cleavage of **17** using zinc and acid afforded **18** as a colourless solid in 30% yield. The parent heterocycle **6** was first prepared in 1962 by Mayer *et al.* [57] by the low-pressure (20 mm) vapour-phase catalytic dehydrogenation of **4** at 330 °C under nitrogen (Scheme 7). Their method to preparing this heterocycle was based on a route that had been suggested earlier by Hartough and Meisel[58]. Hartough and Meisel had also suggested the possibility

of preparing benzo[c]thiophene by heating *o*-xylene with sulfur[59], but it is unclear whether this was carried out later or not.



Scheme 5: Synthesis of the First BcT System

Other early routes to **6** include the decarboxylation of **22**, a substituted BcT prepared in three steps[60] (Scheme 6) using copper in quinoline[42] (Scheme 7).

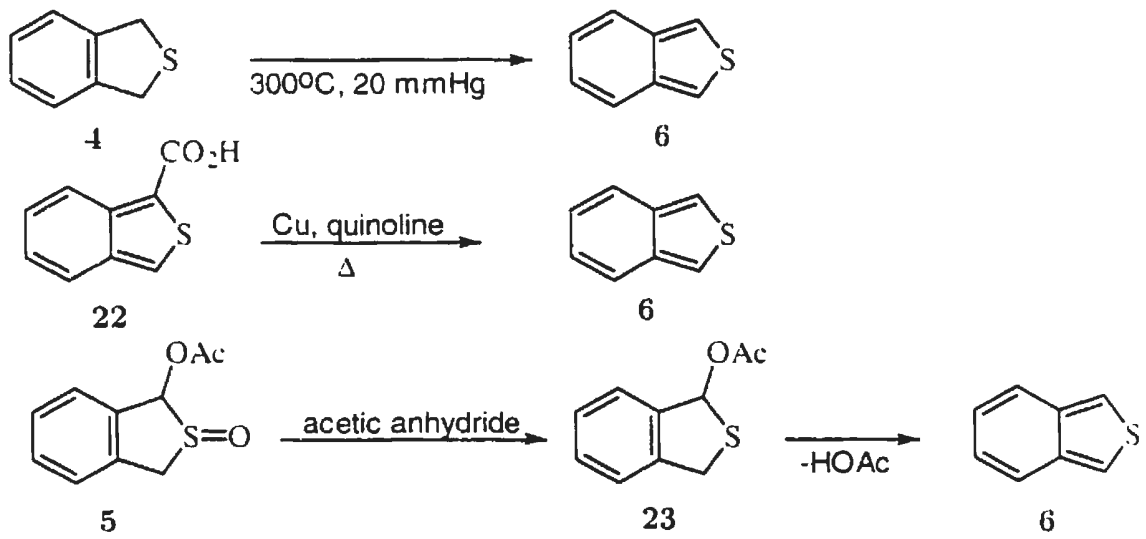


Scheme 6: Synthesis of Benzo[c]thiophene-1-carboxylic acid

Condensation of ethoxymethylenecyclohexanone **19** with ethyl mercaptoacetate in

the presence of sodium ethoxide was reported to give **20** (46%), which was then dehydrated with *p*-toluenesulfonic acid (*p*-TsOH) to give the tetrahydrobenzo[*c*]thiophene **21** (82%). The authors reported that while the use of palladized carbon, selenium and chloranil under various conditions was unsuccessful in dehydrogenating **21**, reaction of **21** with *N*-bromosuccinimide (NBS) followed by sodium methoxide-induced dehydrohalogenation was reported curiously enough, to give 2-carboxybenzo[*c*]thiophene **22** (78%).

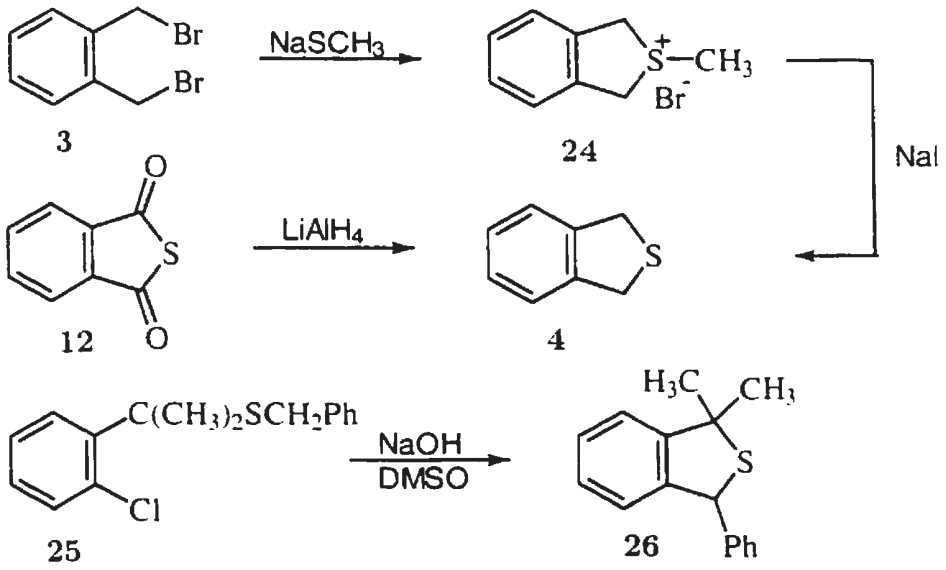
In addition to decarboxylation, alternative methods include the conversion of the sulfoxide **5** to **6** by dehydration using acetic acid and has been suggested to occur *via* a Pummerer rearrangement[42] (Scheme 7).



Scheme 7: Early Methods for the Preparation of BcT

Two other early methods that lead to the sulfide **4** are shown in (Scheme 8). With the first reaction, the dibromide **3** was reacted with sodium methanethiolate to give **24**, which can then be reacted with sodium iodide to give **4**. In the second method, **4** was prepared by the lithium aluminum hydride reduction of thiophthalic

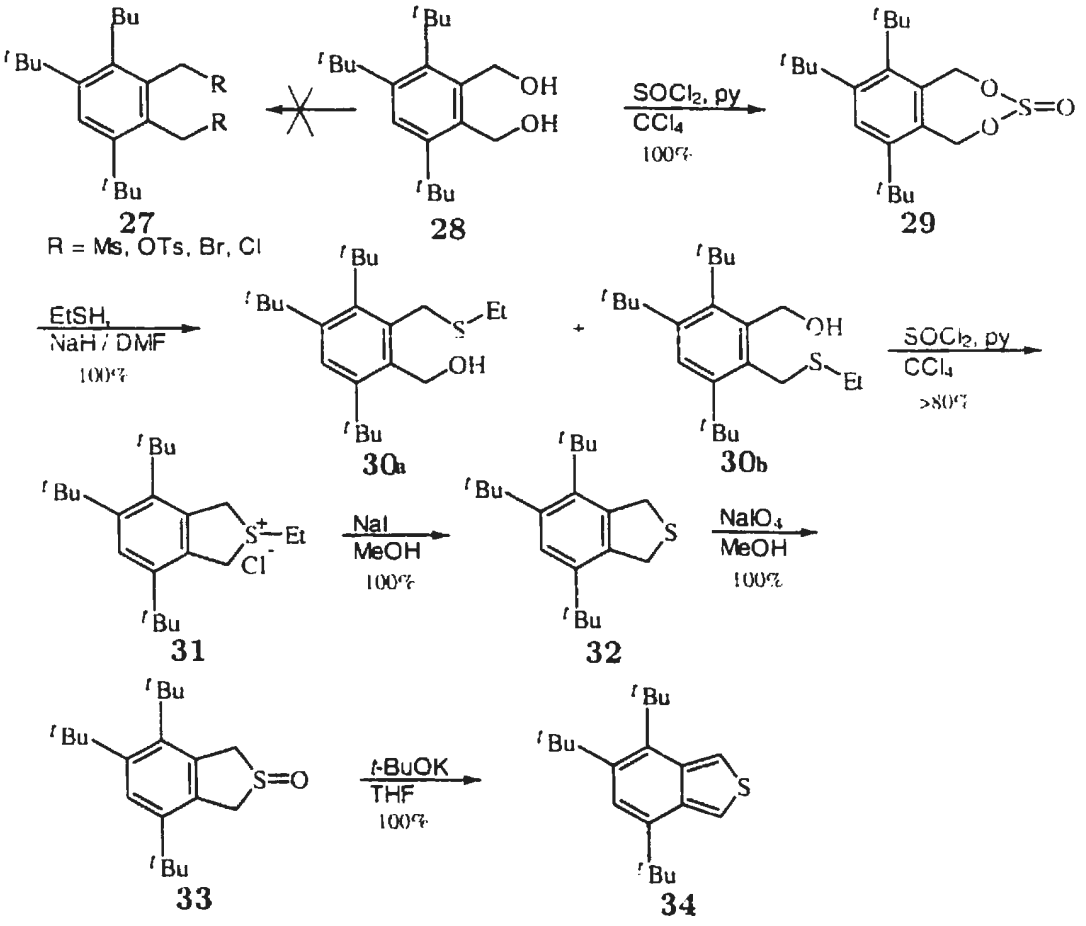
anhydride **12**. Another interesting method that leads to the BcT skeleton was reported by Petersen, Lassen and Ammitzboell[61].Cyclization of the sulfide **25** to **26** was accomplished by heating it in DMSO in the presence of sodium hydroxide. Using this technique, a variety of systems with substitution patterns of the same nature as **26** have been prepared[42].



Scheme 8: Other Methods for Preparing BcT Precursors

Some more recent syntheses have been reported which led to a 4,5,7-trisubstituted BcT[62] (Scheme 9) and also 1,3-disubstituted BcTs[63] (Scheme 10). Both these approaches use the same underlining principles as previously mentioned, but with some variations.

In the first case (Scheme 9), El-Shishtawy *et al.* published the synthesis of a unique BcT by the oxidation of the sulfide **32** to the sulfoxide **33** and subsequent dehydration to the BcT **34**[62]. In this case though, **32** was prepared *via* an interesting cyclic sulfite.

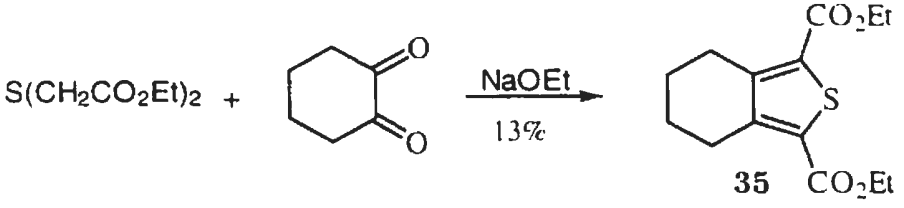


Scheme 9: Synthesis of 4,5,7-tri-*t*-butylbenzo[*c*]thiophene

Starting from the diol **28**, the sulfide **32** was prepared *via* the cyclic sulfite **29** in four steps. Interestingly, El-Shishtawy *et al.* reported that the preparation of the corresponding dimesylate, ditosylate, dibromide and/or dichloride **27** from the diol was unsuccessful and that the products were obtained as mixtures containing benzodihydrofuran. Instead, they found that by treating the diol with thionyl chloride in the presence of pyridine, the cyclic sulfite **29** was obtained in quantitative yield. Nucleophilic attack of ethanethioxide anion of **29** led to a mixture that was essentially

1:1 of the regioisomers and following the treatment with thionyl chloride and deethylating with sodium iodide was reported to lead to the sulfide **32** in high yield. After oxidation of **32** using sodium periodate, the resulting sulfoxide **33** was subsequently dehydrated employing potassium *t*-butoxide **34**. Despite the high yields, this is still a lengthy procedure to synthesize the sulfide.

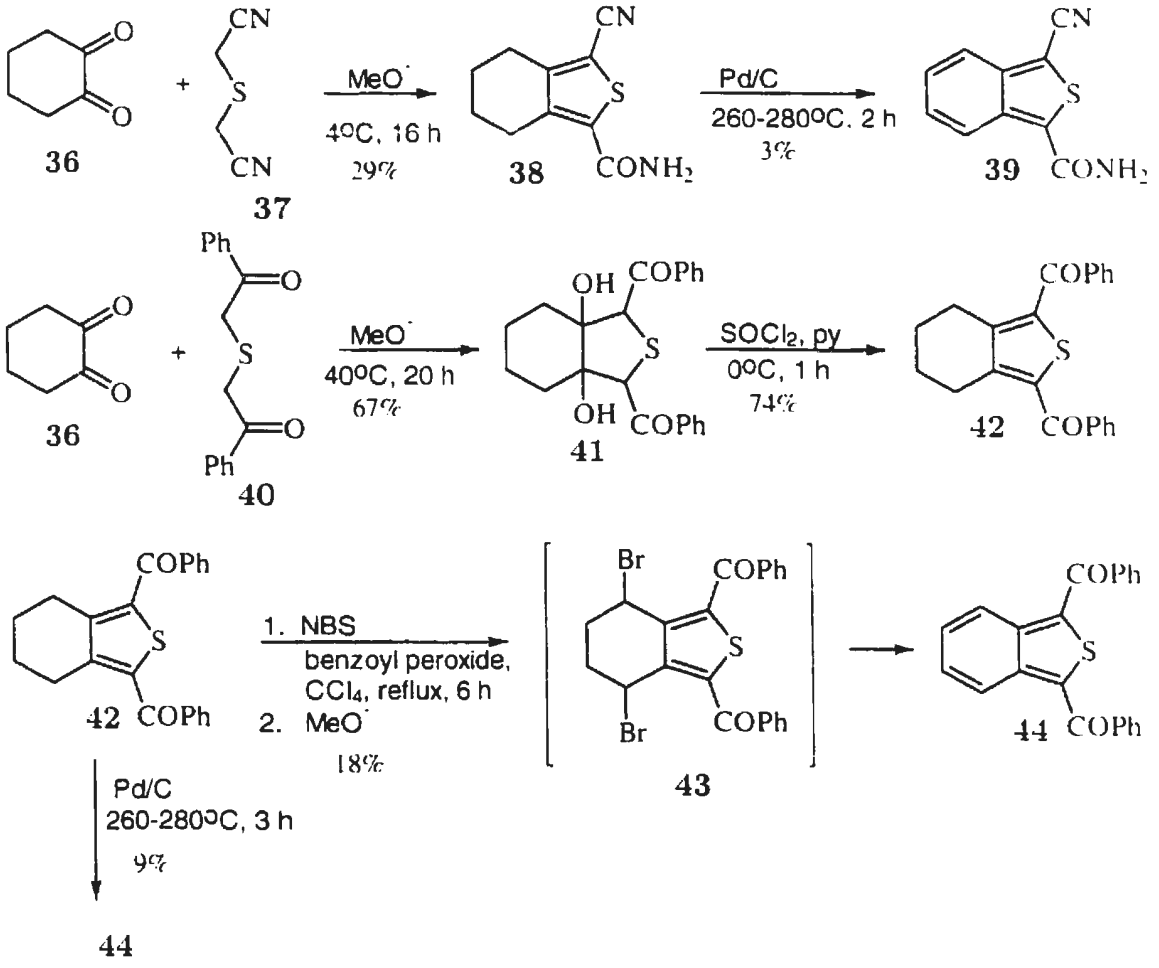
In the next case, 1,3-disubstituted BeTs were prepared *via* a tetrahydrobenzo[*c*]thiophene. This method had been carried out previously by Mayer *et al.* in 1963[64]. The condensation of ethyl thioglycolate with 1,2-cyclohexanedione resulted in the formation the tetrahydrobenzo[*c*]thiophene **35** (Scheme 10) with a yield of 13%[64]. More recently, Volz and Voss published the synthesis of tetrahydrobenzo[*c*]thiophenes using a modified Hinsberg reaction and the aromatization of the six-membered ring was accomplished equally by both allylic bromination followed by loss of hydrogen bromide and dehydrogenation using palladium on carbon[63] (Scheme 11).



Scheme 10: Synthesis of 1,3-Bis(ethylcarbonyl)-4,5,6,7-tetrahydrobenzo[*c*]thiophene

This reaction has the potential of providing a useful route to various substituted benzo[*c*]thiophenes. For example, if the 1,3 substituents were functionalized for linking (C-C) purposes (ie Br, CHO, etc) co-polymers, of alternating donor-acceptor units could possibly be prepared. The yields for the aromatization steps, however, are rather low and employing palladium on carbon reportedly gave yields of 3-9%.

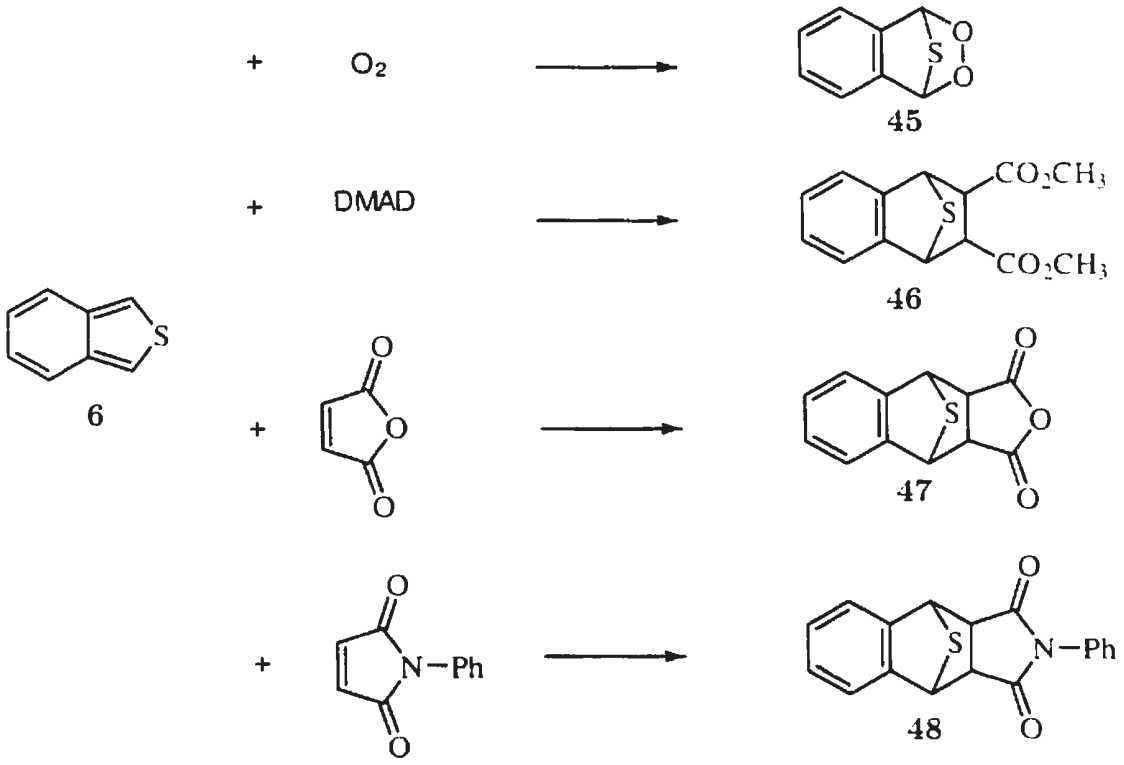
The method of brominating followed by loss of hydrogenation was not much better since yields from the bromination were low (15%), as was the sodium methoxide-induced dehydrohalogenation (18%).



Scheme 11: Synthesis of 1,3-Dibenzoylbenzo[*c*]thiophene

BcT **6** itself, a colourless, low melting solid with a naphthalene-like odour, is reported to be stable as a solid stored under nitrogen for a few days at -30 °C. The highly reactive 1- and 3-positions are responsible for instability of **6** as there is a strong driving force for the re-aromatization of the six-membered ring which occurs.

for example, with the reaction with dienophiles. As a result of this driving force, Diels-Alder adducts of **6** are readily formed with oxygen, dimethyl acetylenedicarboxylate, maleic anhydride, and *N*-phenylmaleimide (Scheme 12).



Scheme 12: Reactions of BcT

The BcT ring system can be stabilized by substitution, especially at the 1- and 3-positions. For example, BcT **18** is reported to be moderately stable[42] (although no time frame was given). Even substitution in the 5-position seems to provide some stability as methyl benzo[c]thiophene-5-carboxylate **51** is reported to be stable in air for 2 days at room temperature and at -20 °C for at least a month[65].

1.3.0.1 Substituent Effects On BcT

To date, only a few other substituted BcTs have been prepared with substituents

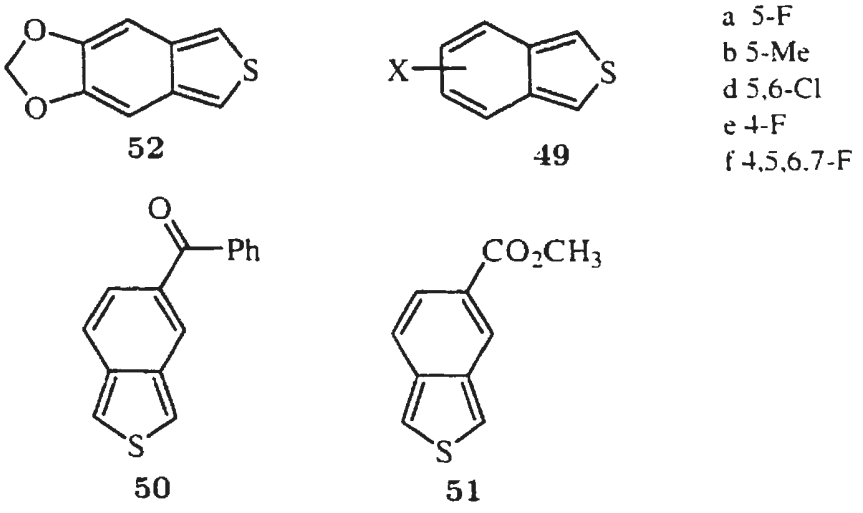
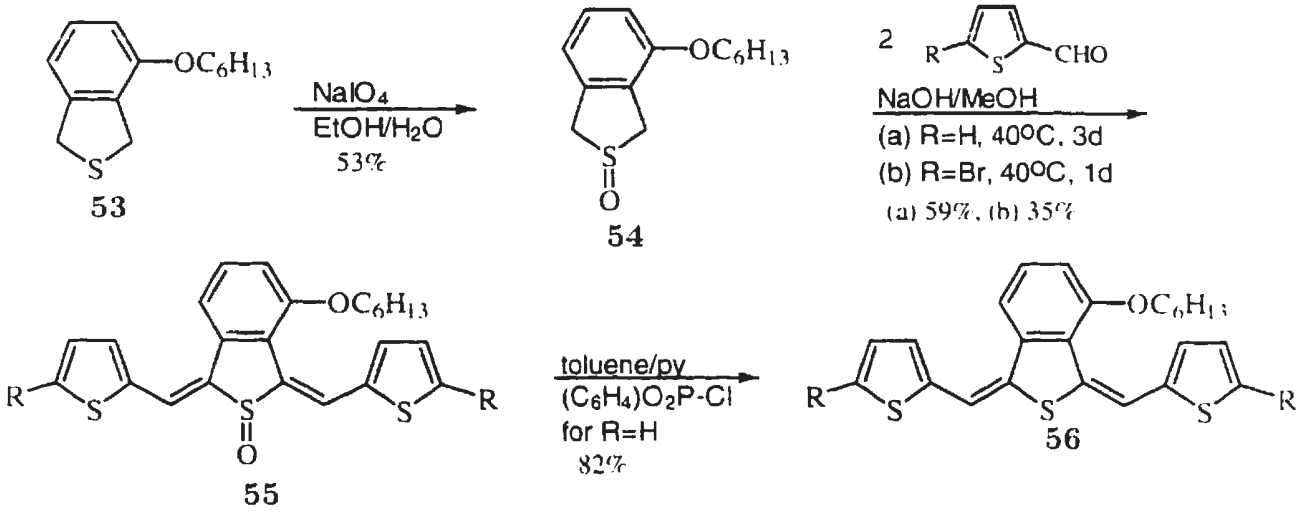


Figure 14: Recent Examples of Substituted BcTs

in the 5-and 6-positions. Examples include halogenated BcTs **49**[16, 66], methylenedioxy substituted BcT **52**[67], long chain alkyl substituents on BcT[20], and also a BcT substituted with a benzoyl fragment[16] (Figure 14). The halogenated (electron withdrawing) BcTs showed that while there was little effect on the p-doping potentials, the substitution considerably facilitated n-doping[66]. Looking at fluorine substitution, 5-fluorinated **49a** led to a positive shift of the onset potential for n-doping while 4-F **49e** produced the reverse effect, possibly due to steric reasons[20]. Full substitution by fluorine seems to increase the bandgap to 2.10 eV, an effect thought to be a result of both electronic and steric effects[47, 68]. The electron donating, methylenedioxy group had very little effect on the bandgap of the polymer but slightly increased the oxidation potential compared to PBcT and considerably decreased conductivity to nearly one-tenth that of PBcT[67].

Another substituted BcT system that recently has received attention, poly(bibenzo[c]thiophene-methine)[69–71], incorporates a methine linkage. Theoretical studies predicted a low bandgap of 0.7 eV[71] for these systems and a few have been

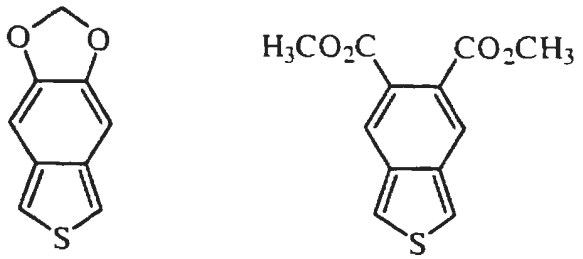
synthesized from the corresponding 2-thiophene carbaldehydes by Knoevenagel-like condensations with 2,5-dihydrothiophene-1-oxide (Scheme 13)[70]. Despite the interesting properties reported for these compounds, the extensively conjugated precursors such as **56** lead to rather stable cation radicals and, as a consequence, electropolymerization leads to the formation of dimers only[20].



Scheme 13: Synthesis of a Poly(bibenzo[*c*]thiophene-methine) From Knoevenagel condensation

Our research interests were concerned with optimizing the syntheses of substituted BcTs and in the process, add to the relatively short list of these interesting compounds. In particular, we felt it was possible to make improvements in the synthesis of the BcT precursor, the sulfide **63** taking advantage of existing solid support methodology[72, 73]. To achieve this, two targets were chosen (Figure 15). We chose to prepare 5,6-methylenedioxybenzo[c]thiophene **52** using a heavily modified version of a synthesis recently reported[67] and it was hoped that this new procedure could then be extended to the preparation of other novel BcTs such as diester **57**.

Annelated terheterocycles, 1,3-dithienylbenzo[c]thiophenes (DTBcT) also known



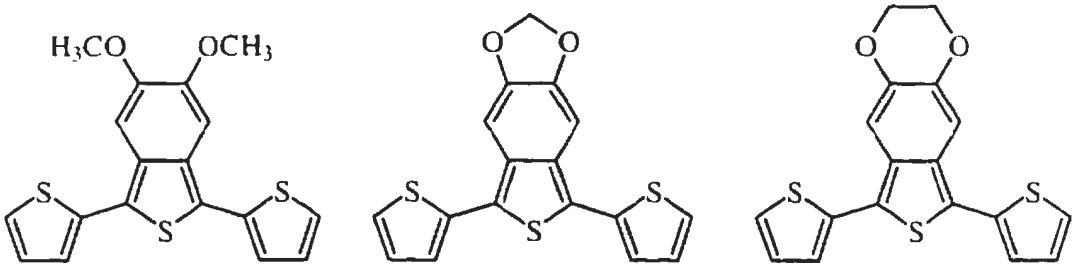
52 57

Figure 15: Substituted BcT Targets

as 1,3-dithienylisothianaphthenes, have recently attracted some attention[53, 74–76]. Polymers of this type possess segments of thiophene and BcT and are expected to combine both the steric and electronic characteristics of the parent polymers PT and PBcT[74]. Theoretical calculations carried out on polymers containing thiophene and BcT units predicted a decrease in the bandgap compared to that of PT alone. Molecular modeling calculations have been used to show that steric interactions occur between the sulfur and the hydrogens at the 4,7-positions in BcT dimers[77]. As a result of this interaction, adjacent rings are not coplanar with each other, the dihedral angles calculated to be 43°[78]. The incorporation of the thiophene units was expected to provide some relief from this interaction and a smaller dihedral angle of 36° between adjacent rings was predicted[77].

We were also interested in these systems and chose to investigate approaches towards the terheterocycles 1,3-dithienyl-5,6-dimethoxybenzo[*c*]thiophene **58**, 1,3-dithienyl-5,6-methylenedioxybenzo[*c*]thiophene **59** and 1,3-dithienyl-5,6-ethylenedioxybenzo[*c*]thiophene **60** (Figure 16). In addition to the advantages mentioned mentioned above, these trimeric species are also conveniently set up for the construction of copolymers consisting of alternating donor-acceptor subunits. This, however, is only

possible once a consistent and reliable synthetic procedure is established. From the literature, there appears to be a variety of ways to prepare DTBcTs, but there appears to be considerable disagreement as to which of the methods are reproducible.



58 **59** **60**

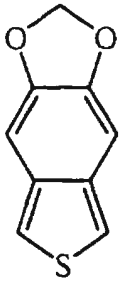
Figure 16: DTBcT Targets

The current synthetic methodologies towards DTBcTs will be presented and discussed in further detail in Chapter 4 along with our approaches towards these compounds.

Some of the theory behind conjugated polymers and why they are of interest has been reviewed in this introduction. The origin of BcT **6** was presented along with the debate concerning the structure of the corresponding polymer PBcT **8** and the different methods for obtaining this important monomer and polymer. The need exists for an optimized general synthesis of substituted BcTs and reliable syntheses for substituted DTBcTs.

Chapter 2

5,6-Dioxymethylenebenzo[*c*]thiophene



2.1 Results and Discussion

As described in the introduction, there are several existing methods to the preparation of BcTs, starting from appropriately substituted phthalic anhydrides, substituted α, α'-dihalo-o-xylene derivitives and from other sources (see Section 1.3). Preparation of a substituted BcT from the α, α'-dihalo-o-xylene derivitive can be achieved in three steps. Conversion of such a compound to the sulfide is followed by its oxidation to the corresponding sulfoxide and subsequent dehydration to the BcT.

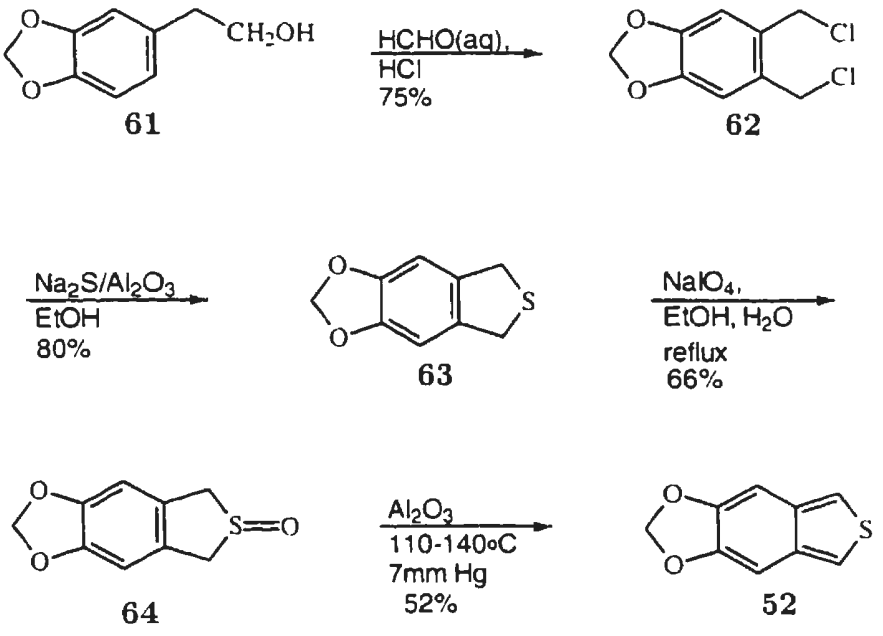
Traditional methods for the preparation of sulfides generally use dilution conditions with slow, careful addition of the reagents. These methods typically involve long reaction times and give low yields. In an effort to overcome this problem and improve overall yields to the substituted BcT, the use of supported reagent methodology[72, 73]was investigated.

Sodium sulfide adsorbed on alumina (Na_2S/Al_2O_3) has been reported to be an alternative reagent to $Na_2S{\cdot}9H_2O$ [79] and its preparation was described first by Czech *et al.* [79] for the synthesis of dialkyl sulfides from primary alkyl halides. Its use was later reported for the synthesis of cyclic sulfides from straight chain α,ω-dibromides by Tan *et al.* [80]. The reagent has also been used occasionally in synthetic and methodological studies[81-84]. The use of sodium sulfide adorbed on alumina in cyclophane chemistry has also been reported by Bodwell *et al.* who described an optimized procedure for the synthesis of symmetrically substituted syn-2,11-dithia[3·3]metacyclophanes[85]. In comparison with older $Na_2S{\cdot}9H_2O$ methodologies, the procedure and work-up were simplier, only moderate dilution and shorter reaction times were required, and the reagent could be used in the presence of base sensitive groups.

In order to determine whether Na_2S/Al_2O_3 would be effective for the synthesis

of sulfide precursors to BcTs, a known BcT **52**, which had originally been prepared using $Na_2S{\cdot}9H_2O$ methodology, was selected as the first synthetic target.

5,6-Dioxymethylenebenzo[*c*]thiophene **52** was first prepared by Ikenoue, Wudl and Heeger in 1991[67]. To effect the key cyclization step, they employed $Na_2S{\cdot}9H_2O$ and reported a yield of 51% for the sulfide **63** after a lengthy reaction time of 25 hours. Our synthesis (Scheme 14) follows the published route with modification of the cyclization step (**62** → **63**):



Scheme 14: Modified Synthesis of 5,6-Methylenedioxybenzo[*c*]thiophene

As described by Ikenoue *et al.*, chloromethylation and chlorination of piperonyl alcohol **61** (prepared from the reduction of piperonal) was carried out employing aqueous formaldehyde that had been saturated with hydrogen chloride at 0 °C. The resulting 1,2-bis(chloromethyl)-4,5-dioxymethylenebenzene **62** was obtained in a yield of 75% comparable to literature results[67].

Using the modified procedure reported by Bodwell *et al.* [85], freshly prepared Na_2S/Al_2O_3 and was added in one portion to a solution of **62** in neat absolute ethanol. Ring closure to the corresponding sulfide **63** proceeded smoothly in 2.5 hours and in a yield of 80%. By comparison, the previously reported procedure required 25 hours, much higher dilution and afforded only 51% of **63**. A noteworthy, but not particularly surprising, feature of this reaction was that Na_2S/Al_2O_3 reacted readily with the benzylic chlorides. All previously reported uses of this reagent were with bromides.

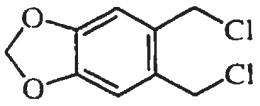
The resulting sulfide **63** was then oxidized to the sulfoxide **64** using sodium periodate in refluxing ethanol/water for 15 hours in an unoptimized yield of 66%. The literature yield for this reaction was 91%. Dehydration of the sulfoxide **64** was achieved by heating on neutral activated alumina under vacuum. Under these conditions, the substituted BcT, **52** was sublimed onto a cold finger (*ca.* 5 °C). Compound **52** is unstable in air and consequently stored under nitrogen at -28 °C. Compounds **63**, **62** and **64** are also unstable in air but can be stored for several months at - 28 °C.

2.2 General Procedures.

Unless otherwise noted, all commercial chemicals were used without further purification. Tetrahydrofuran was distilled over sodium/benzophenone. Toluene and benzene were distilled over calcium hydride and stored over 4Å molecular sieves. Thin layer chromatography was performed on E. Merck 60 F_{254} precoated silica plates. Column chromatography was carried out on 60 (E. Merck, 230-400 mesh) silica gel (unless otherwise noted) using flash technique. Melting points (mp) were obtained on a Fisher-Johns apparatus and are uncorrected. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a GE GN-300NB spectrometer at 300 MHz and 75 MHz respectively, unless otherwise specified, in $CDCl_3$ solution unless otherwise noted. Chemical shifts are in ppm relative to internal standards: Me_4Si for ^{1}H and $CDCl_3$ (δ 77.0 ppm) for ^{13}C NMR. Individual peaks in the ^{1}H NMR spectra are reported as chemical shift, multiplicity (s=singlet, d=doublet, dd=doublet doublets, t=triplet, q=quartet, m=multiplet), number of hydrogens and coupling constants. Individual peaks in the ^{13}C NMR spectra are reported as chemical shift. Low resolution mass spectra (MS) were determined on a V.G. Micromass 7070HS instrument. MS data are reported as m/z and percent relative intensity.

2.3 Experimental

2.3.0.2 1,2-Bis(chloromethyl)4,5-dioxymethylenebenzene (62)[67]

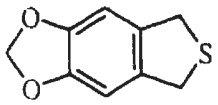


Piperonyl alcohol (2.00 g, 13.2 mmol) was added in one portion to a solution of aqueous formaldehyde (37%, 4 ml) saturated with HCl (g) and hydrochloric acid (8 ml). The resulting mixture was stirred for 15 h and poured into cold water (50 ml). The aqueous mixture was extracted with two portions of diethyl ether and the combined extracts were dried over anhydrous Na_2SO_4. Removal of solvent afforded the crude product as an off-white solid. Purification by column chromatography (50% hexane/CH_2Cl_2) gave **62** as a colourless solid (2.17 g, 9.91 mmol, 75%): mp 68.5–70 °C (lit.[67] 66–70 °C): ^{1}H NMR δ 6.87 (s, 2H), 6.01 (s, 2H), 4.67 (s, 4H); ^{13}C NMR δ 145.5, 123.5, 107.9, 99.0, 40.6; MS *m/z* (%): 218 (M^+, 18), 185 (32), 183 (100), 148 (23), 89 (28), 63 (21).

2.3.0.3 Preparation of Solid-Supported Sulfide Reagent (Na_2S/Al_2O_3)[85]

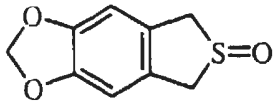
Sodium sulfide nonahydrate (14.04 g, 14.04 mmol) was dissolved in deionized water (60 ml) and filtered. Basic alumina (13.94 g Fluka 5016A) was added to the filtrate and most of the solvent was then removed on a rotary evaporator (bath temperature 50–60 °C). The resulting mixture was subsequently ground with a mortar and pestle and then dried to constant weight with gentle warming (50–60 °C) under high vacuum to give a final mass of 22.58 g (2.59 mmol Na_2S/g reagent).

2.3.0.4 1,3-Dihydro-5,6-dioxymethylenebenzo[*c*]thiophene (63)



Freshly prepared Na_2S/Al_2O_3[85] (3.11 g 8.08 mmol) was added in one portion to a solution of 1,2 bis(chloromethyl)-4,5-dioxymethylenebenzene (1.00 g, 4.56 mmol) in absolute ethanol (320 ml). The resulting solution was stirred vigourously under N_2 at rt for 2.5 h. Al_2O_3 was removed by filtration and the solvent removed by rotary evaporation. CH_2Cl_2 was added to the residue and it was then refiltered. Removal of solvent afforded an off-white solid. Purification by column chromatography (50% hexane/CH_2Cl_2) gave **63** as a colourless solid (0.66 g, 3.66 mmol 80%): mp 117.5 119 °C (lit.[67] 117 119 °C; ^{1}H NMR δ 6.63 (s, 2H), 5.93 (s, 2H), 4.17 (s, 4H); ^{13}C NMR δ 144.4, 130.3, 101.8, 98.8, 35.0; MS *m/z* (%): 180 (M^+, 93), 179 (100), 150 (13), 135 (11), 122 (10), 121 (25), 77 (12).

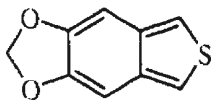
2.3.0.5 1,3-Dihydro-5,6-dioxymethylenebenzo[*c*]thiophene-2-oxide (64)[67]



A solution of $NaIO_4$ (0.52 g, 2.5 mmol) in H_2O (14 ml) was added to **63** (0.40 g, 2.2 mmol) in 98 ml of hot ethanol (95%). The resulting solution was heated under reflux for 10 h. The reaction solution was then filtered and the solvent removed using rotary evaporation. The resulting residue was redissolved in CH_2Cl_2 and dried over

Na_2SO_4. Removal of solvent gave a yellow solid. Purification by column chromatography (50% CH_2Cl_2 in EtOAc) afforded **64** as a colourless solid (0.29 g, 1.5 mmol, 66%): mp 126.5-128.0 °C (lit.[67] 127–128 °C). ^{1}H NMR δ 6.79 (s, 2H), 5.99 (s, 2H), 4.23 (2H, AB half spectrum, J = 15.0 Hz), 4.03 (2H, AB half spectrum, J = 15 Hz); ^{13}C NMR δ 145.6, 125.0, 103.7, 99.0, 56.1; MS m/z (%): 196 (M^+, 23), 148 (100), 147 (35), 89 (14).

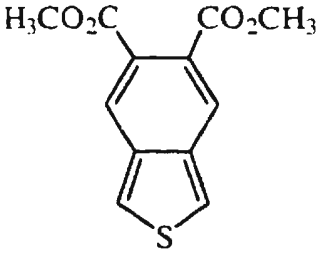
2.3.0.6 5,6-Dioxymethylenebenzo[*c*]thiophene (52)[67]



A mixture of **64** (0.25 g, 1.3 mmol) and activated neutral alumina was heated at 110-140 °C under 7 mm Hg in a sublimation apparatus for 30 min. Colourless crystals were obtained from the cold finger (cooled with cold water, *ca* 5 °C) (0.12 g, 0.67 mmol, 52%): mp 133.5–134.5 °C (lit.[67] 133.5–134.5 °C) ^{1}H NMR δ 7.33 (s, 2H), 6.82 (s, 2H), 5.93 (s, 2H); ^{13}C NMR δ 145.1, 132.5, 111.4, 98.2, 93.5; MS m/z (%): 178 (M^+, 100), 122 (18), 120 (45), 94 (11), 89 (9), 69 (16), (11), 28 (16).

Chapter 3

5,6-
Bis(methylcarboxylate)benzo[*c*]thiophene

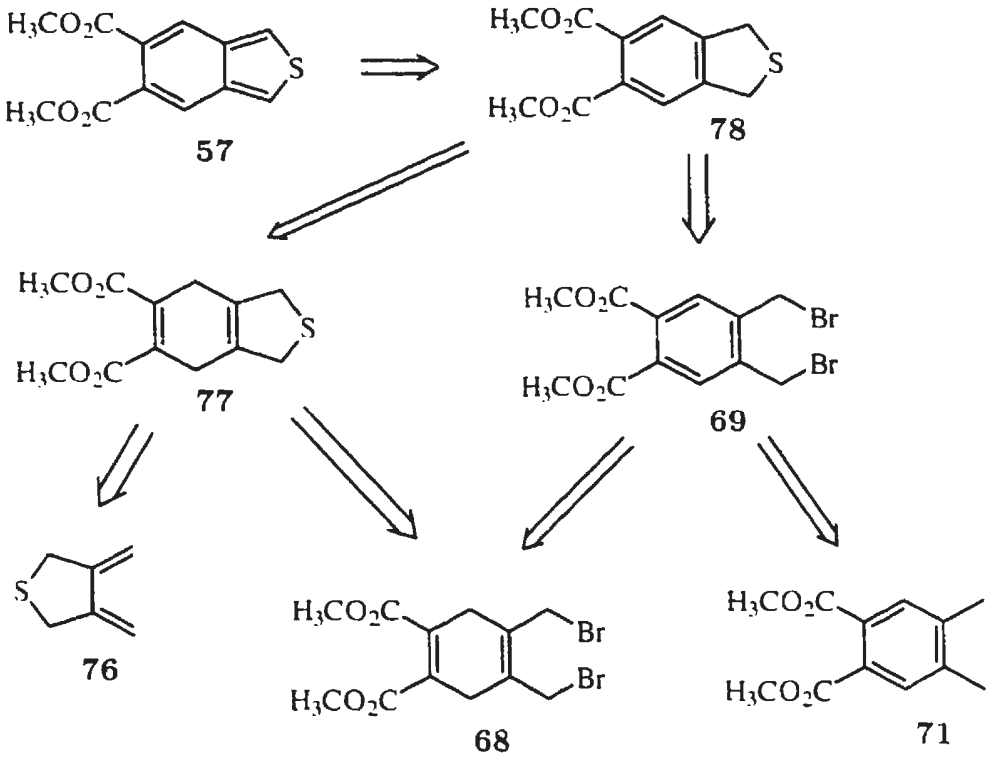


3.1 Results and Discussion

One of the long term goals of this work was the synthesis of BcT polymers with alternating electron-rich and electron-deficient monomer units. Having successfully synthesized an electron-rich monomer **52**, attention was then turned to the synthesis of an electron-deficient monomer. The diester **57** was chosen as a target because the ester groups are strongly electron-withdrawing and are easily converted into other electron-withdrawing functional groups. In addition, this compound had not yet appeared in the literature and would therefore be a test for the generality of the new solid-supported sulfide methodology (Na_2S/Al_2O_3) developed during the synthesis of **52**. The important precursor **69** possesses a relatively high degree of symmetry and, despite the fact it does not have a great deal of structural complexity, a variety of pathways to it and also the more advanced synthetic target **78** were conceived.

The four approaches to BcT **57** are outlined in Scheme 15. The first two approaches focused on the dibrominated precusor **69**, while the other two centred on the sulfide **78**. Each of the proposed synthetic sequences relies upon a Diels-Alder reaction for construction of the six-membered ring.

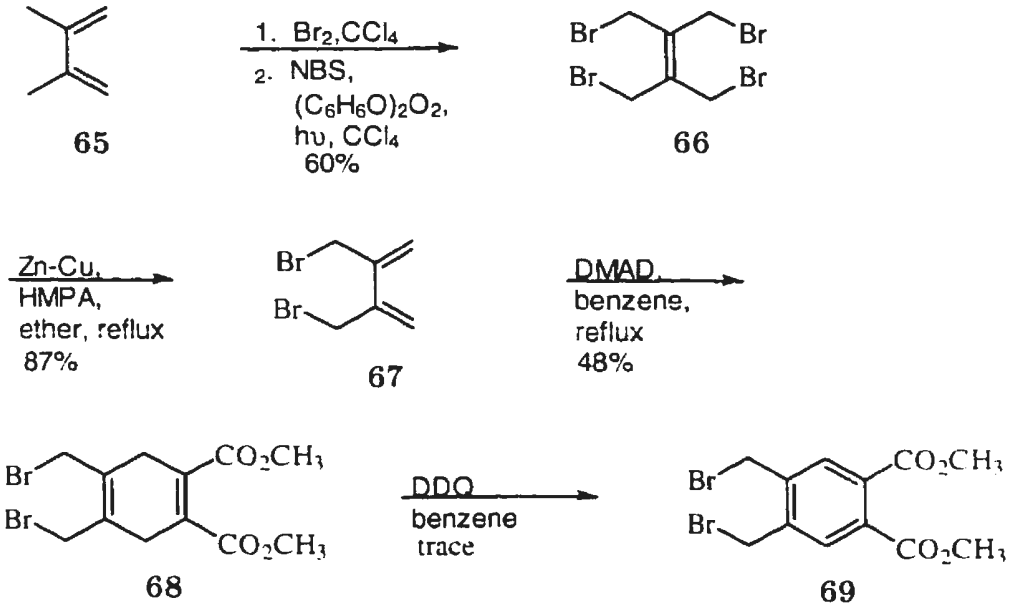
Preparation of compound **69** was first attempted according to Scheme 16. Tetrabromide **66** was prepared using a literature synthesis[86] involving the reaction of 2,3-dimethyl-1,3-butadiene with bromine followed by allylic bromination (NBS, hν, benzoyl peroxide) to give **66** in 60% yield. Compound **66** was subsequently debrominated with Zn–Cu couple[87] using a literature method[88], to afford 2,3-bisbromomethyl-1,3-butadiene **67** in a crude yield of 87%. As reported earlier[88], **67** was found to be stable only in cold dilute solutions. As such, this diene was prepared as required and used immediately in the next step, the Diels-Alder reaction with DMAD. Xylene, toluene and benzene were employed as solvents with the latter giving the best results.



Scheme 15: Retrosynthetic Scheme for the Synthesis of 5,6-Bis(methylcarboxylate)benzo[*c*]thiophene

The yield, however, never exceeded 48%.

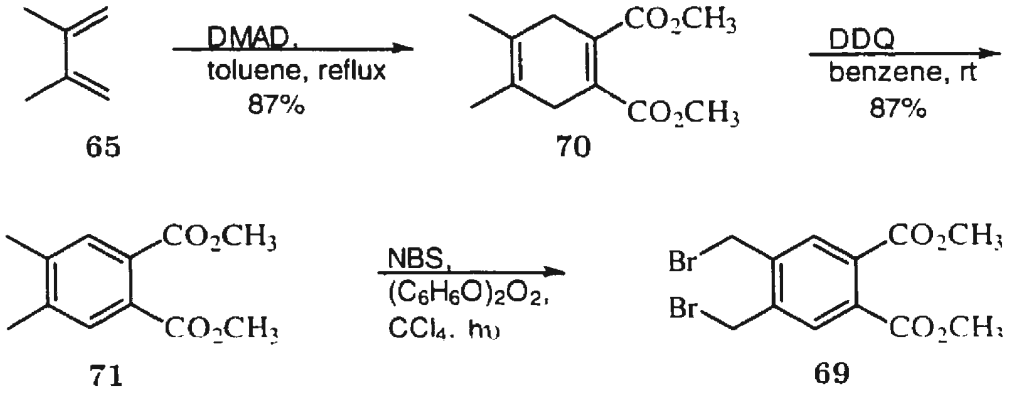
The seeming straightforward aromatization step presented difficulties. DDQ was used as the oxidant, but failed to give the aromatized product **69** in significant yields. Several aromatic solvents (toluene, xylenes and benzene) were employed at both room temperature and at reflux but to little avail. The reactions were very difficult to monitor by TLC due to extensive streaking. The lack of formation of the usual tan precipitate 2,3-dichloro-5,6-dicyano-1,4-hydroquinone indicated that the DDQ was not reacting in the required manner. Removal of the solvent after refluxing invariably yielded a black, tarry substance. From the reaction carried out in refluxing benzene, a small amount (<1%) of the aromatized product **69**, confirmed by ^{1}H NMR analysis.



Scheme 16: First Approach to Dimethyl 4,5-bis(bromomethyl)phthalate

was isolated by sublimation from the tar. Next, the solvent system was changed to THF/HBr(aqueous) since it has been reported that the dehydrogenation rates are enhanced in more polar solvents[89] but **69** was not observed by ^{1}H NMR analysis. These disappointing results led to the investigation of the second route (Scheme 17)

The first step of the sequence was the Diels-Alder reaction between 2,3-dimethyl-1,3-butadiene **65** and DMAD (refluxing toluene, 4 h) to give the adduct **70** in a yield of 87%. As a matter of convenience, this reaction was generally carried out in refluxing benzene in spite of the longer reaction times required (8 hours) with comparable yields. The success of this reaction compared to that of **67** may be attributable to steric effects. Since a bromomethyl group is larger than a methyl group, the s-cis conformation (required for a Diels-Alder reaction to occur) of **67** may be more sterically encumbered and therefore less populated than that of **65** (Figure 17).



Scheme 17: Second Approach to Dimethyl4,5-bis(bromomethyl)phthalate

In addition, the greater steric requirements of a bromomethyl group may also hinder the approach of the dienophile. Indeed Xidos *et al.* have recently shown that the facial selectivity of Diels-Alder reaction is very sensitive to steric effects[90–94]. In stark contrast to the previous route, the next step, aromatization, proceeded smoothly in an extremly exothermic and rapid manner at room temperature to give the product **71** in a yield of 91%. The reason for such a dramatic difference is not immediately obvious and may have its roots in steric effects. For example, in conformation **72** (Figure 17), where the two bulky bromine atoms are well separated, both faces of the cyclohexadiene ring would encounter steric hinderence upon the approach of DDQ. Low level calculations, using semi-empircal methods (AM1), revealed 22 possible conformers. The conformer with the lowest heat of formation is bromo0014, illustrated in Table 1. In this conformer, two bulky bromine atoms are situated on opposite faces of the cyclohexadiene ring which would be expected to hinder the approach of DDQ.

In addition to the suggestion of sterics, the brominated species **70** is a more electron-deficient system than **71**. The ease of dehydrogenation is dependent upon

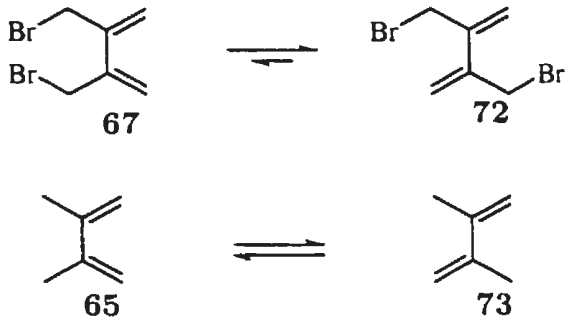


Figure 17: Two Existing Conformations for the Dienes
2,3-Bis(bromomethyl)-1,3-butadiene and 2,3-dimethyl-1,3-butadiene

the degree of stabilization of the incipient carbonium ion in the transition state[95] and therefore this must also be of consideration.

Conformer	ΔH(kJ/mol)
bromo0014	-615.296
bromo0023	-615.288
bromo0030	-615.166
bromo0020	-614.672
bromo0008	-614.459
bromo0011	-614.203
bromo0004	-614.241
bromo0011	-614.203
bromo0010	-614.095
bromo0034	-613.249
bromo0031	-610.440
bromo0024	-610.440
bromo0019	-610.440
bromo0017	-610.432
bromo0002	-610.423
bromo0035	-610.403
bromo0027	-610.319
bromo0009	-610.285
bromo0028	-609.616
bromo0013	-608.854
bromo0006	-608.318
bromo0007	-608.142
bromo0012	-606.325

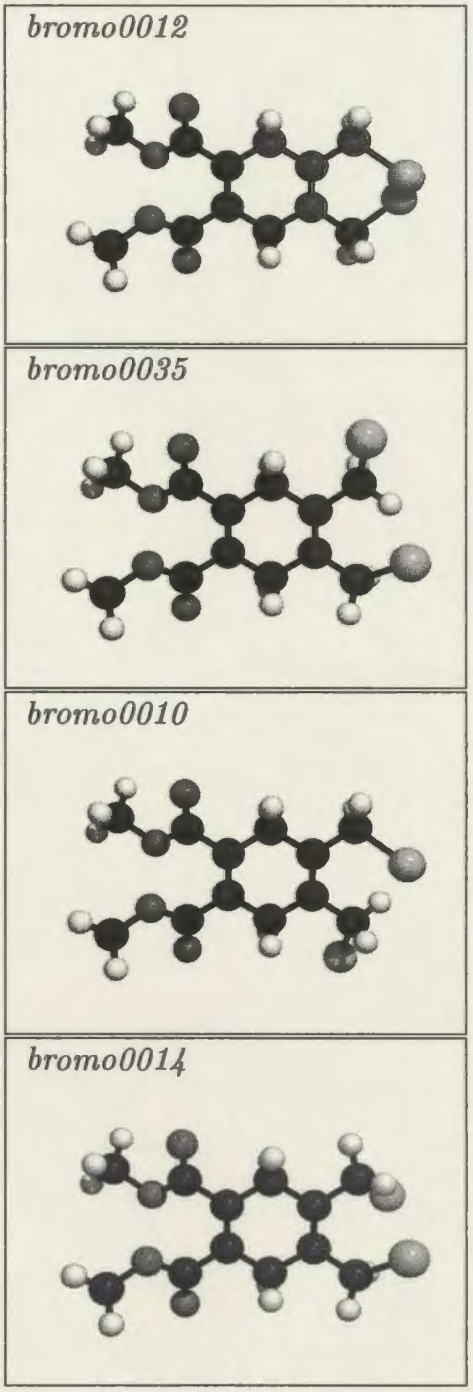


Table 1: Heats of Formation for Conformers of Dimethyl 4,5-bis(bromomethyl)cyclohexa-1,4-diene-1,2-dicarboxylate with Selected Conformers Shown

The next step was the two-fold benzylic bromination of **71** with NBS to give **69**. This reaction has been used extensively in the formation of α,α'-dibromo-*m*-xylenes[96]. As is frequently seen in *m*-xylene substrates, this reaction gave a mixture of products, monobrominated **74**, dibrominated **69** and tribrominated **75** (Figure 18). Attempted separations however, of the desired compound **69** from this mixture by column chromatography, sublimation, or recrystallization were uniformly unsuccessful and this led to the investigation of the third route.

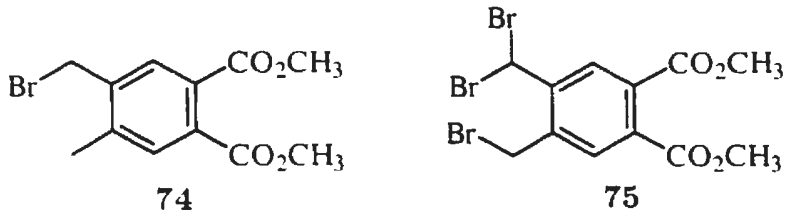


Figure 18: Side Products Obtained from the Benzylic Bromination of Dimethyl 4,5-dimethylphthalate

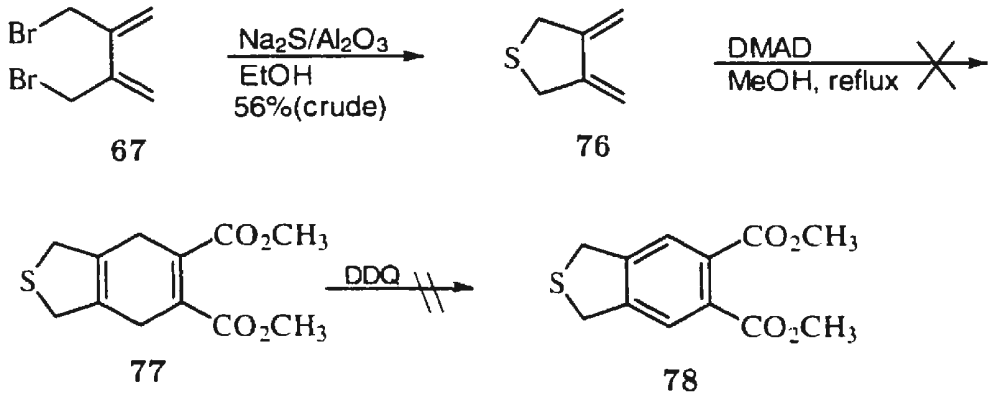
In an effort to get around the problems associated with the benzylic bromination, the third route (Scheme 18), which centred around a Diels-Alder reaction of 3,4-dimethylenethiolane **76**[88] and DMAD, was investigated. Thiolane **76** was prepared from 2,3-bis(bromomethyl)-1,3-butadiene **67** upon reaction with Na_2S/Al_2O_3.

This compound was previously reported by Gaoni and Sadeh[88] from the reaction between **67** and $Na_2S{\cdot}9H_2O$. The reported yield of **76** (80–85%) was curiously determined by UV spectroscopy on the basis of ϵ =6000 at 240 nm for the pure compound. Compound **76** was said to polymerize in the solid state, but could nevertheless be purified by evaporation of the solvent and distilled.

To confirm **76** had indeed formed in the Na_2S/Al_2O_3 reaction, a comparison was made between the ^1H NMR spectrum of the crude product and literature values.

Like the starting material **67**, it was found to be stable only in cold, dilute solution. Attempts to purify **76** by vacuum distillation (using the reported conditions) consistently resulted in decomposition. The yield of the crude product was 56% and subsequent reactions were performed using unpurified **76**.

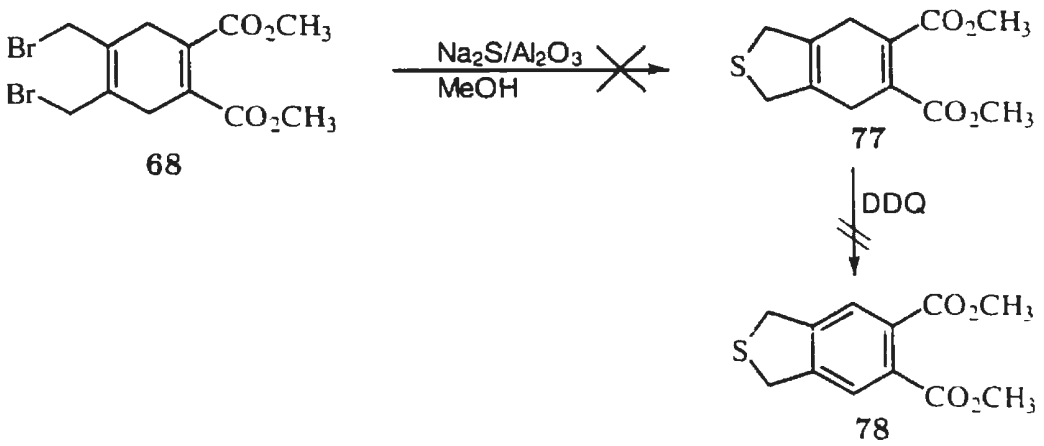
Contrary to the findings of Gaoni and Sadeh,[88] **76** proved to be unreactive towards DMAD in a Diels-Alder sense. In the hopes that the adduct **77** could be trapped *in situ*, the reaction was attempted in the presence of a small amount of DDQ. However neither **77** nor **78** were observed.



Scheme 18: Third Approach

Finally, the preparation of **76** from **67** was carried out in the presence of excess DMAD in CH_2Cl_2/MeOH at both room temperature and reflux. Again, no Diels-Alder reaction was observed.

It was previously observed that **68** was not aromatized by DDQ under the conditions used and this was ascribed to steric and/or electronic effects. It was then reasoned that flattening the system would be advantageous. It was envisaged that this could be accomplished by the reaction of **68** with Na_2S/Al_2O_3. Somewhat surprisingly, this reaction afforded a complex mixture. In the hopes that some of the

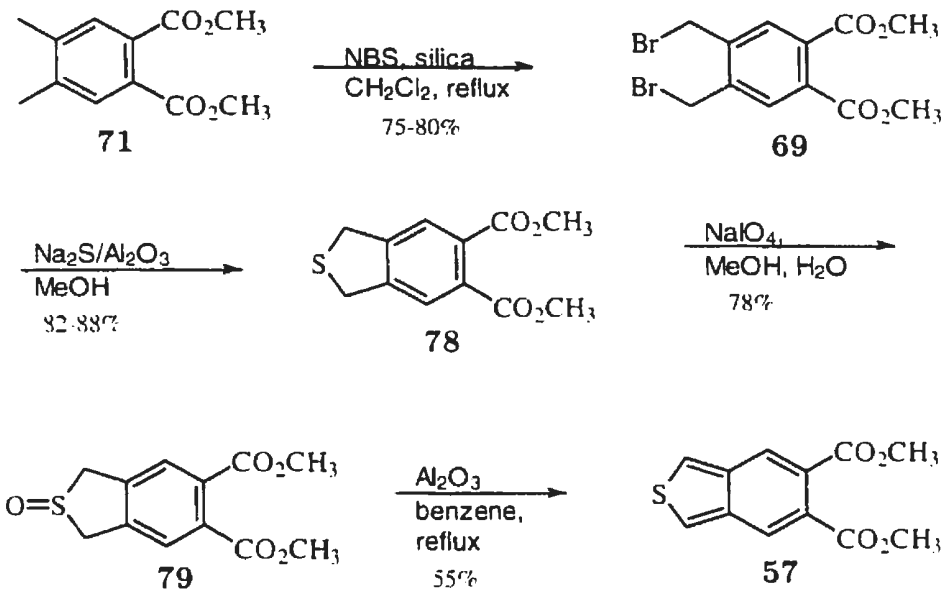


Scheme 19: Alternative Approach to
1,3-Dihydro-5,6-bis(methylcarboxylate)benzo[*c*]thiophene

adduct had been formed, DDQ was added, but none of the aromatized product **78** could be observed.

At this point, the most promising route appeared to be the one outlined earlier in Scheme 17. Its downfall was the two-fold benzylic bromination to give **69**. Attention was then turned to the possibility of using other reagents to accomplish this transformation. Of particular interest were reports that NBS/SiO_2 was an effective reagent for the ring bromination of electron rich arenes (aromatic amines and phenols[97], alkoxybenzenes[98] and indols and benzimadazoles[99]). Since no electron-deficient arenes were included in this study, it was of interest to determine whether this reagent could achieve benzylic bromination of electron-deficient arenes such as **69**, more selectively than NBS and hν.

Treatment of **71** with NBS/SiO_2 (hν excluded) in refluxing dichloromethane afforded a mixture of dibromide **69** and monobromide **74**. The combined yield was 92% and the ratio of **69**:**75** roughly 4:1, as determined by ^{1}H NMR spectroscopy.



Scheme 20: Successful Approach to 5,6-Bis(methylcarboxylate)benzo[*c*]thiophene Using an Alternative Method for Benzylic Bromination

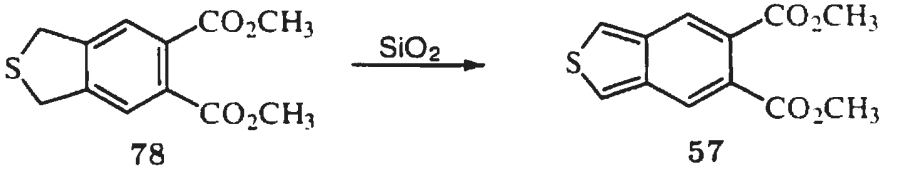
Compound **69** could be obtained pure by column chromatography and multiple recrystallization, but the yield dropped drastically. Fortunately, the original mixture of **69** and **75** could be used in the following step without further purification. Thus, the reaction of this mixture with Na_2S/Al_2O_3 afforded 82–88% (based on 75–80% purity of starting material) of sulfide **78** after purification by column chromatography on neutral alumnina (based on the estimated amount of **69** in the starting mixture). Compound **78** was then oxidized with sodium periodate in a refluxing mixture of methanol/water to give the sulfoxide **79** in 78% yield.

This left only the dehydration step to be achieved. Unfortunately, subjection of **79** to the conditions employed for the conversion of **64** to **52** was not successful. The problem lay with the reluctance of **57** to sublime. When the alumina was extracted at an intermediate time, signals in the ^{1}H NMR spectrum attributable to starting

material and product could be observed. Longer reaction times led to complete consumption of the starting material and decay of the product.

Dehydration of the sulfoxide **79** was accomplished instead by heating with activated neutral alumina in refluxing benzene under nitrogen. After refluxing overnight, the alumina was removed by filtration and the alumina extracted using dry benzene. The desired BcT **57** was obtained as a yellow oil in a yield of 55%. From the ^{1}H NMR spectrum, three singlets, as expected, were observed 8.07 (s 2H), 7.88 (s 2H), 3.92 (s 6H).

Initial attempts to purify the sulfide **78** on silica led to the formation of several side products. These side products were not observed by TLC prior to the column and it was concluded **78** was not stable on the silica, hence the purification using neutral alumina as support. Upon closer examination of the fractions by ^{1}H NMR analysis, peaks associated with the BcT **57** were observed. This initially discouraging result, instability of **78** on the silica, may instead now be considered beneficial as it may be possible to proceed directly from the sulfide **78** to **57** although the reaction mechanism is unknown.



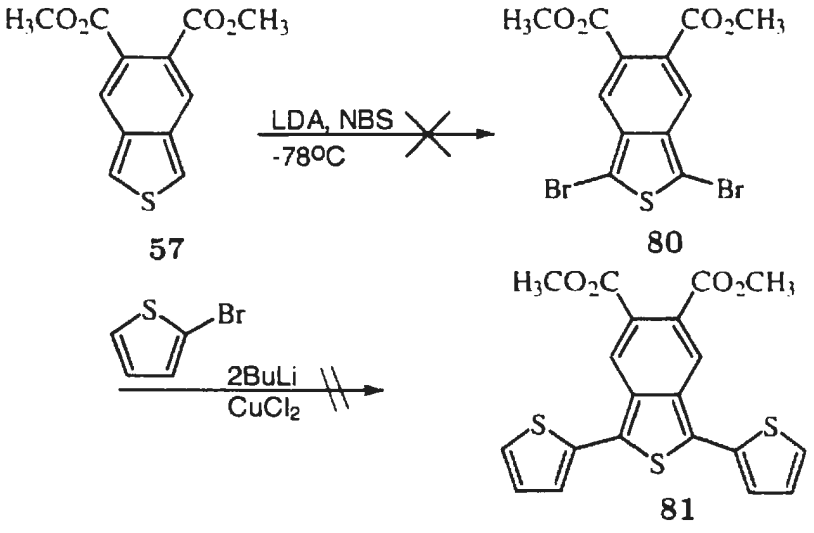
78 57

Scheme 21: Dehydrogenation of
1,3-Dihydro-5,6-bis(methylcarboxylate)benzo[*c*]thiophene to BcT By Silica

A small amount of **78** was stirred with silica in benzene at room temperature for several days. The reaction appears very slow but along with starting material **78**, compound **57** was also observed by TLC and this was confirmed by ^{1}H NMR

analysis. This reaction may be further enhanced by elevation of reaction temperature or perhaps absorbing compound **78** directly onto silica and allowing to stand for a period of time. Although the exact nature of this reaction is unknown, particularly the mechanism and why this particular sulfide **78** underwent the transformation on silica while the other sulfide **63** did not, the initial results appear very promising. The potential of eliminating a reaction step (oxidation of sulfide to sulfoxide) and hence possibly increasing the overall yield to the novel BcT **57** should not be dismissed.

3.1.1 Bromination of 5,6-Bis(methylcarboxylate)benzo[c]thiophene



Scheme 22: Synthesis of 1,3-Dithienyl-5,6-bis(methylcarboxy)benzo[c]thiophene

After the successful synthesis of **57** efforts were then turned to modification of this monomer to synthesize an alternating donor-acceptor monomer. It was thought that this could be achieved according to the route illustrated by Scheme 22: bromination of the substituted BcT followed by coupling with two equivalents of thiophene using

literature methods[100].

An initial attempt to brominate **57**, was carried out using LDA and NBS but a complex mixture was obtained (as observed by ^{1}H NMR analysis, along with multiple spots and streaking by TLC analysis). This result was rather unfortunate as this method may have provided a convenient synthetic procedure to preparing other 5,6-disubstituted DTBcTs from corresponding 5,6-disubstituted BcTs which in turn can be prepared from the well established BcT synthetic methodology. Furthermore, this approach could have been used to synthesize new monomers which could incorporate the alternating donor-acceptor theme to give monomers such as **82** and **83** (Figure 19) using appropriately substituted thiophenes. Bromination of **57** was not repeated however, but due to the synthetic potential of this reaction, other methods of brominating BcTs should be further investigated.

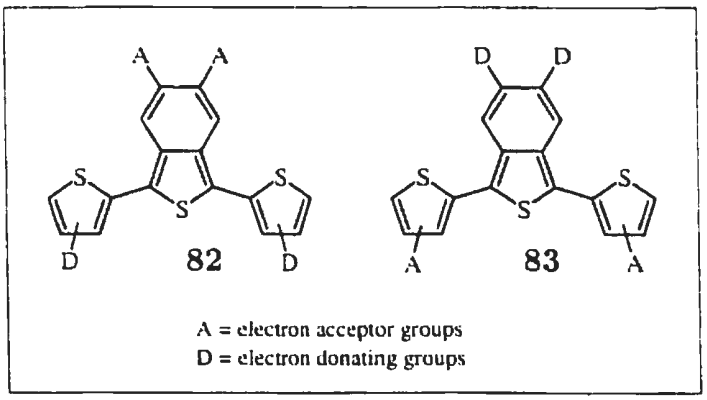
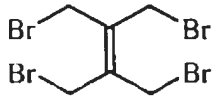


Figure 19: Monomers Displaying the Alternating Donor-Acceptor Sub-Units

3.2 Experimental

Note, for General Procedures, see Section 2.2.

3.2.0.1 1,4-Dibromo-2,3-bis(bromomethyl)-2-butene (66)[86]



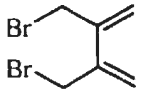
A solution of bromine (2.95 mL, 2.90 g, 57.6 mmol) in 25 mL of carbon tetrachloride was added dropwise over 1 h, to a magnetically stirred solution of 2,3-dimethyl-1,3-butadiene (6.50 mL, 4.72 g, 57.4 mmol) in 60 mL of carbon tetrachloride in a flask fitted with a drying tube (containing anhydrous calcium chloride). After complete addition of bromine, the reaction solution was cooled to 0 °C (ice/water bath) and NBS (20.45 g, 114.9 mmol) was added in one portion followed by benzoyl peroxide (0.46 g, 0.19 mmol). The reaction mixture was then slowly allowed to warm to rt and was then refluxed for 8 h. The hot reaction solution was filtered and, upon cooling, **66** crystallized as a bright yellow solid. Recrystallization from EtOAc afforded **66** as a pale yellow solid (13.74 g, 34.37 mmol, 60%): mp 156.0–157.0 °C (lit.[86] 157–159 °C): ^{1}H NMR δ 4.16 (s, 8H); ^{13}C NMR δ 134.4, 24.9; MS m/z (%): 400 (M^+, 10), 319 (83), 159 (37), 79 (97), 39 (100).

3.2.0.2 Zn–Cu Couple[88]

Zinc dust (25 g) was placed in a sintered glass funnel and slurried with and filtered from the following solutions: 4 x 20 mL portions of aqueous 3% HCl solution, 5 x 50 mL portions of water, 2 x 40 mL portions of aqueous 2% copper sulfate solution, 5 x 50 mL portions of water and 5 x 50 mL portions of anhydrous diethyl ether. After

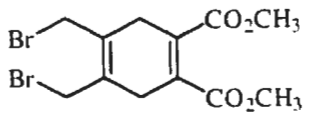
air drying in the funnel for several min, the resulting dark powder was then dried in a vacuum desiccator overnight.

3.2.0.3 2,3-Bis(bromomethyl)-1,3-butadiene (67)[88]



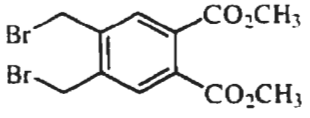
1,4-Dibromo-2,3-bis(bromomethyl)-2-butene **66** (3.00 g, 7.50 mmol) was refluxed in diethyl ether (50 mL) with good stirring in the presence of Zn-Cu couple (1.50 g). After 20 min of stirring, HMPA (4.5 mL) was added dropwise over 15 min, followed by a further addition of Zn-Cu couple (0.60 g). After each hour at reflux, further portions of Zn-Cu (0.60 g) were added; total reflux time was 4.5 h. The reaction solution was subsequently filtered through Celite and the filtrate was concentrated using rotary evaporation. The resulting oil was redissolved in pentane (*ca.* 15 mL), washed once with a saturated NH_4Cl solution, three times with water, and once with a saturated NaCl solution. The pentane solution was then dried over Na_2SO_4 (anhydrous) and filtered. Removal of the solvent by rotary evaporation afforded **67** as colourless crystals (1.57 g, 6.54 mmol, 87 %). The following signals attributed to **67** were recorded on a Bruker WP 100SY ^{1}H NMR (100 MHz) δ 5.53 (s, 2H), 5.48 (s, 2H), 4.15 (s, 4H). The crude product was used immediately in the next step without further purification.

3.2.0.4 Dimethyl 4,5-bis(bromomethyl)cyclohexa-1,4-diene-1,2-dicarboxylate (68)



A solution of 2,3-bis(bromomethyl)-1,3-butadiene (4.00 g, 16.67 mmol) and DMAD (2.43 g, 17.10 mmol) in benzene (15 mL) was stirred under reflux conditions for 48 h. Evaporation of solvent by reduced pressure gave a yellow oil (9.38 g). Purification by column chromatography (1% CH_3CO_2H/CH_2Cl_2 gave **68** as a colourless oil (3.08 g, 8.06 mmol, 48%), recrystallization (hexanes) gave **68** as a colourless oil (lit.[88] colourless solid mp 75–76 °C); literature ^{1}H NMR data[88] agree. ^{1}H NMR δ 4.03 (s, 4H), 3.80 (s, 6H), 3.19 (s, 4H); ^{13}C NMR δ 164.6, 128.7, 126.8, 49.7, 28.7, 26.5; MS *m/z* (%): (M^+ not observed) 349 (7), 301 (28), 271 (100), 243 (13), 190 (37), 162 (54), 134 (44), 103 (25), 50 (36).

3.2.0.5 Attempted Syntheses of Dimethyl 4,5-bis(bromomethyl)phthalate (69)



A solution of **68** (1.01 g, 2.64 mmol) in benzene (10 mL), was treated with DDQ (0.60 g, 2.6 mmol). The flask was fitted with a drying tube and the solution was stirred at rt. TLC and ^{1}H NMR analysis after stirring for 2 h did not indicate the formation of **69** and the reaction mixture was then refluxed for 4 days. Removal of solvent using rotary evaporation gave a dark brown viscous material. Along with other

material unidentifiable by NMR, only trace amounts of yellow aromatized product **69** were obtained through sublimation (<1%). ^{1}H NMR δ 3.92 (s, 6H), 4.63 (s, 4H), 7.73 (s, 2H).

In a second attempt to obtain synthetically useful quantities of **69**, DDQ (0.50 g, 2.6 mmol), followed by 48% HBr (*ca.* 0.2 mL) was added to a solution of **68** (0.80 g, 2.1 mmol) in THF (15 mL). The resulting solution was stirred for 1 h at rt and was then refluxed for 2.5 h. ^{1}H NMR analysis revealed only a trace amount of aromatized product **69**.

3.2.0.6 Dimethyl 4,5-bis(bromomethyl)phthalate (69)

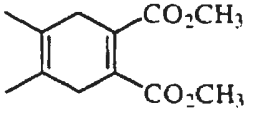
A flask containing a solution of **71** (1.00 g, 4.50 mmol), NBS (2.40 g, 13.5 mmol) and benzoyl peroxide (0.02 g, 0.01 mmol) in CCl_4 (20 mL), was fitted with a drying tube containing calcium chloride, refluxed for 8 h and illuminated with strong visible light. The reaction mixture was filtered and the solvent was removed by rotary evaporation to yield a yellow oil. Column chromatography (20% ethyl acetate/petroleum ether) yielded **69** as a pale yellow solid (0.09 g, 0.2 mmol, 5%): ^{1}H NMR δ 7.73 (s, 2H), 4.63 (s, 4H), 3.92 (s, 6H).

3.2.0.7 Dimethyl 4,5-bis(bromomethyl)phthalate (69) from NBS and Silica

To a stirred solution of prepared **71** (0.51 g, 2.29 mmol) in CH_2Cl_2 (25 mL), NBS (0.89 g, 5.0 mmol) followed by silica (2.38 g) was added. The resulting mixture was refluxed for 15 h, after which the reaction solution was filtered and filtrate washed with water and dried with anhydrous Na_2SO_4. Removal of the solvent afforded crude **69** as a pale yellow oil which solidified upon standing (0.80 g). The amount of side products (mono, and tri brominated) was estimated to be 10-15 % from ^{1}H NMR

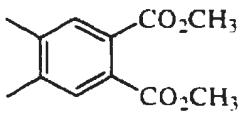
analysis (crude **69** 75–80%). Pure **69** was obtained from column chromatography (25% EtOAC/hexanes) followed by several recrystalizations (methanol/water). Fractions containing compounds **74** and **75** were isolated by column chromatography (25% EtOAC/hexanes). The following signals were recorded on a Bruker WP 100SY. ^{1}H NMR (100 MHz) **74**: δ 7.70 (s, 1H), 7.49 (s, 1H), 4.50 (s, 2H), 3.90 (s, 3H) 3.91 (s, 3H), 2.45 (s, 3H); ^{1}H NMR (100 MHz) **75**: δ 8.29 (s, 1H), 7.65 (s, 1H), 7.01 (s, 1H), 4.55 (s, 2H), 3.94 (s, 3H), 3.91 (s, 3H); **69**: mp 93.0 94.5 °C. ^{1}H NMR δ 7.74 (s, 2H), 4.64 (s, 4H), 3.93 (s, 6H); ^{13}C NMR δ 164.2, 136.8, 129.8, 128.7, 50.1, 25.2; MS *m/z* (%) 380 (M^+, 2), 348 (15), 298 (100), 270 (12), 220 (33), 189 (87), 146 (7), 102 (16), 77 (20). HRMS calcd for $C_{12}H_{12}{}^{79}Br_2O_4$ 377.91026, found 377.9111.

3.2.0.8 Dimethyl 4,5-dimethyl)cyclohexa-1,4-diene-1,2-dicarboxylate (70)



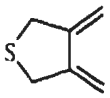
A solution of 2,3-dimethyl-1,3-butadiene (7.33 g, 89.2 mmol) and DMAD (19.9 g, 98.1 mmol) in toluene (15 mL) was refluxed under a nitrogen atmosphere for 3 h. The solvent was removed by rotary evaporation and purification by dry flash chromatography (25% EtOAc/hexanes) gave **70** as a pale yellow solid (17.4 g, 77.6 mmol, 87%); recrystallization (hexanes) gave **70** as a colourless solid: mp 72 73 °C: ^{1}H NMR δ 3.78(s, 6H), 2.93(s, 4H), 1.67(s, 6H); ^{13}C NMR δ 165.7, 130.0, 118.8, 49.4, 31.4, 15.2; MS *m/z* (%) 224 (M^+, 0.3), 177 (100), 133 (28), 105 (35), 91 (27), 77 (15), 59 (31).

3.2.0.9 Dimethyl 4,5-dimethylphthalate (71)



DDQ (5.09 g, 22.4 mmol) was added in one portion to a solution of **70** (5.00 g, 22.3 mmol) in benzene (20 mL) and the resulting mixture was left to stir overnight at rt. The precipitated hydroquinone was removed by filtration and the solvent was removed by rotary evaporation to give crude **71** as an orange solid. Purification by dry flash column chromatography (alumina, CH_2Cl_2), furnished **71** as a colourless solid (4.31 g, 19.4 mmol, 87%): mp 51.5–53.0 °C; ^{1}H NMR δ 7.49 (s, 2H), 3.88 (s, 6H), 2.31 (s, 6H); ^{13}C NMR δ 168.3, 140.3, 130.1, 129.4, 52.5, 19.7; MS *m/z* (%): 222 (M^+, 20), 192 (11), 191 (100), 163 (6), 120 (5), 105 (6), 91 (6), 77 (6).

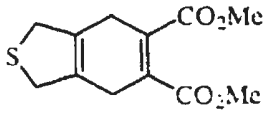
3.2.0.10 3,4-Dimethylenethiolane (76)



To stirred solution of **67** in absolute ethanol (1.50 g, 6.26 mmol), freshly prepared Na_2S/Al_2O_3 [85] (3.62 g, 9.38 mmol) was added as a finely ground powder in one portion. After stirring for 2.5 h, the solution was filtered and the solvent was removed using rotary evaporation. The residue was redissolved in CH_2Cl_2 (*ca.* 100 mL), and filtered once more. The filtrate was then washed successively with aqueous 1.0 M sodium bicarbonate and water, and dried over anhydrous Na_2SO_4. Rotary evaporation of the solvent gave a pale yellow oil (0.39 g). ^{1}H NMR analysis (Bruker WP 100SY) indicated **76** was present: ^{1}H NMR (100 MHz) δ 3.61 (s), 5.01 (s), 5.45

(s)[88]). Attempts to purify the thiolane according to the literature[88] resulted in its decomposition.

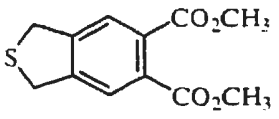
3.2.0.11 Attempted Synthesis of Dimethyl 3-thiabicyclo[4.3.0]nona-1(5),7-diene-7,8-dicarboxylate (77)



Freshly prepared Na_2S/Al_2O_3 [85] (0.80 g, 2.1 mmol)was added in one portion to a solution containing freshly prepared **68** (0.55 g, 1.4 mmol) in methanol (120 mL) and the reaction mixture was stirred at rt for 6 h. The alumina was removed by filtration and solvent was removed by rotary evaporation. The residue was redissolved in CH_2Cl_2 and the remaining alumina was removed by filtration. Removal of solvent gave material unidentifiable by ^{1}H NMR analysis.

Next, freshly prepared Na_2S/Al_2O_3 [85] (6.42 g, 16.9 mmol) was added to a solution containing **67** (2.69 g, 11.2 mmol) and DMAD (1.60 g, 12.4 mmol) in a solvent system of 9:1 dichloromethane/methanol (100 mL) and the resulting solution was stirred at rt for 19 h. The reaction solution was then filtered and removal of the solvent by rotary evaporation gave a dark red oily residue. Column chromatography eluting initially with petroleum ether followed by petroleum ether/CH_2Cl_2 (9:1) gave materials unidentifiable by ^{1}H NMR analysis.

3.2.0.12 Attempted Synthesis of 1,3-Dihydro-5,6-bis(methylcarboxylate)-benzo[*c*]thiophene (78)

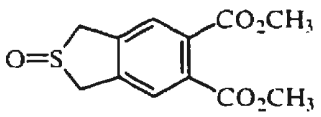


A solution of crude **76** (0.39 g) (prepared from Section 3.2.0.10), DMAD (0.91 g, 6.4 mmol) and DDQ (0.02 g, 0.09 mmol) in methanol (50 mL) was stirred at rt for 5.5 h. Compound **78** was not observed by ^{1}H NMR, and the reaction mixture was then refluxed for 8 h. Other material unidentifiable by ^{1}H NMR analysis was obtained; **78** was not observed.

3.2.0.13 1,3-Dihydro-5,6-bis(methylcarboxylate)benzo[*c*]thiophene from 69 from Section 3.2.0.7 (78)

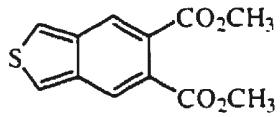
To a solution of **69** (1.26 g, 3.32 mmol 75–80% pure) in methanol (300 mL), freshly prepared Na_2S/Al_2O_3 [85] (1.89 g, 4.95 mmol) was added in one portion and the reaction mixture was vigorously stirred for 2.5 h. The reaction mixture was filtered and the solvent was removed using rotary evaporation. The yellow residue was redissolved in CH_2Cl_2, filtered to remove the remaining alumina, and the solvent was removed by rotary evaporation. Purification by dry flash column chromatography on neutral alumina (CH_2Cl_2) gave a yellow solid (0.56 g, 82–88% based on 75–80% pure starting material): mp 77.5–77 °C; ^{1}H NMR δ 7.62 (s, 2H), 4.29 (s, 4H), 3.91 (s, 6H); ^{13}C NMR δ 144.0, 130.9, 125.3, 52.7, 37.6, carbonyl signal not observed; MS *m/z* (%) 252 (M^+, 30), 221 (37), 219 (12), 193 (15), 134 (21), 94 (14). A sample of high purity for HRMS was not obtained due to the apparent instability of **78**.

3.2.0.14 1,3-Dihydro-5,6-bis(methylcarboxylate)benzo[*c*]thiophene-2-oxide (79)



A solution of **78** (0.63 g, 2.5 mmol) in methanol (110 mL) was heated to near reflux. Sodium periodate (0.59 g, 2.8 mmol) in hot water (15 mL) was added to the hot solution and the reaction mixture was heated at reflux for 15 h. The reaction solution was filtered, concentrated and the residue was dissolved in CH_2Cl_2 and refiltered. The filtrate was washed twice with water and dried over anhydrous $MgSO_4$. Removal of the solvent by rotary evaporation afforded **79** as an off-white solid (0.52 g, 1.9 mmol, 78%). Recrystallization (methanol/water) gave **79** as a colourless solid: mp 155.0 156.0 °C; ^{1}H NMR δ 7.76 (s 2H), 4.33 (2H, AB half spectrum, J = 16.5 Hz), 4.22 (2H, AB half spectrum, J = 16.5 Hz), 3.92 (s 6H); ^{13}C NMR δ 164.6, 136.3, 124.6, 117.6, 56.5, 50.1; MS m/z 268 (M^+, 48), 237 (18), 220 (82), 189 (100), 161 (6), 130 (9), 118 (9), 102 (18), 90 (15), 77 (25). HRMS calcd for $C_{12}H_{12}SO_5$ 268.04046, found 268.0394.

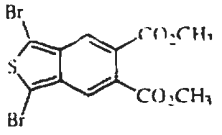
3.2.0.15 5,6-Bis(methylcarboxylate)benzo[*c*]thiophene (57)



Activated neutral alumina (0.65 g) was added to a solution of **79** (0.21 g, 0.78 mmol) in dry benzene (10 mL) and the resulting mixture was refluxed for 10 h. Filtration of the alumina under nitrogen, followed by removal of solvent under reduced pressure

gave a yellow oil (0.11 g, 0.44 mmol, 55%): ^{1}H NMR δ 8.07 (s, 2H), 7.88 (s, 2H), 3.92 (s, 6H); ^{13}C NMR δ 168.3, 136.6, 126.5, 125.0, 120.8, 52.5; MS m/z (%): 250 (M^+, 52), 219 (100), 204 (7), 160 (10), 133 (28), 132 (16), 89 (20), 82 (7), 69 (11). HRMS calcd for $C_{12}H_{12}SO_4$ 250.02991, found 250.0298.

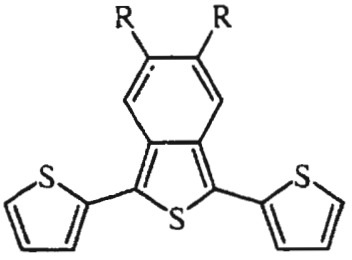
3.2.0.16 1,3-Dibromo-5,6-Bis(methylcarboxy)benzo[*c*]thiophene (80)



A solution of diisopropylamine (0.17 mL, 1.3 mmol) in anhydrous THF (5 mL) was cooled to 0 °C (ice/water) and *n*-BuLi (1.3 M in hexane, 0.90 mL, 1.2 mmol) was added. After stirring for 30 min, a solution of **57** in anhydrous THF (5 mL) was added slowly and stirring at 0 °C was continued for 1.5 h. NBS (0.48 g, 2.7 mmol) was then added in one portion and stirred at 0 °C for 2 h. The reaction mixture was allowed to warm to rt and then quenched by pouring into water and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried over anhydrous $MgSO_4$. Removal of the solvent employing rotary evaporation furnished material unidentifiable by ^{1}H NMR analysis.

Chapter 4

Substituted 1,3-Dithienylbenzo[*c*]thiophenes



4.1 Results and Discussion

As described in 3.1.1, the attempt to prepare dimethyl 1,3-dibromobenzo[*c*]thiophene-5,6-dicarboxylate **80** had been unsuccessful and efforts to synthesize this compound and proceed with Scheme 22 were discontinued. Instead, the syntheses of appropriate precursors which could eventually lead to DTBcTs **58**, **59** and **60** (Figure 20) were investigated.

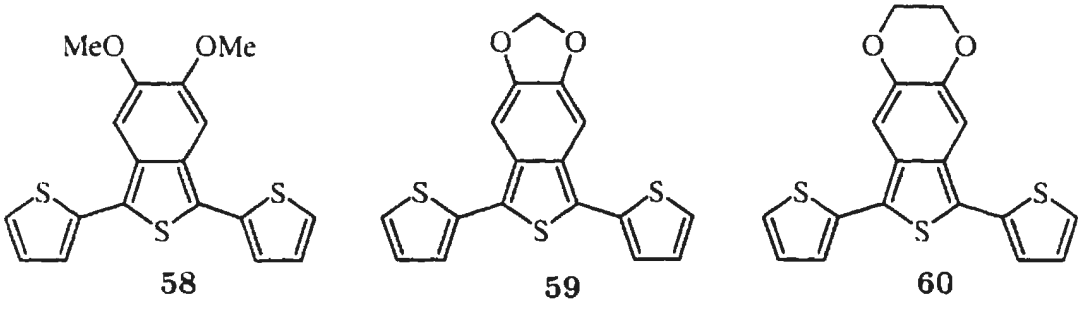
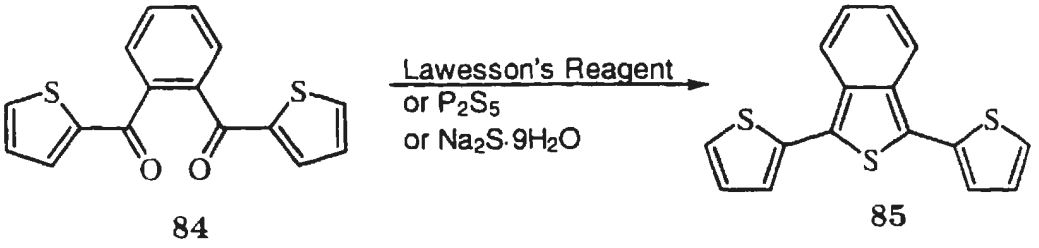


Figure 20: Targeted DTBcTs

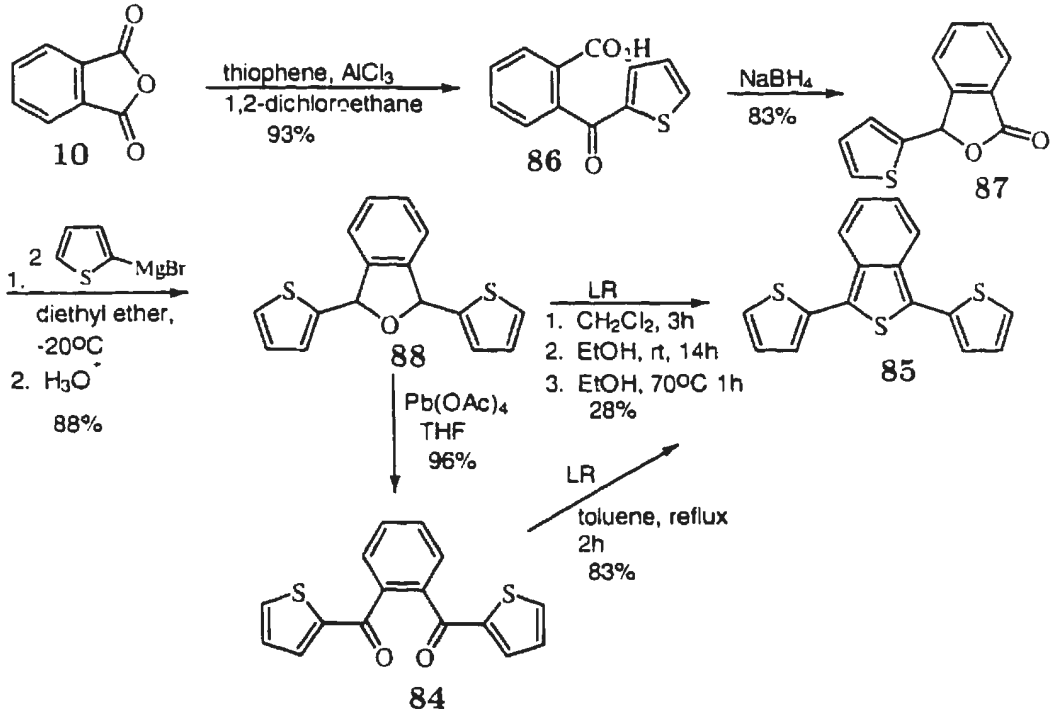


Scheme 23: Direct Route to DTBcTs

According to the literature, DTBcTs can be prepared from the thiation of an appropriate *o*-diacylarene (Scheme 23)[74]. The difficulty however lies with the synthesis of the *o*-diacylarene itself. Several strategies have been put forth which lead to the critical *o*-diacylarenes, but there does appear to be considerable disagreement as to which of these are reproducible.

4.1.1 First Synthesis of Parent DTBcT

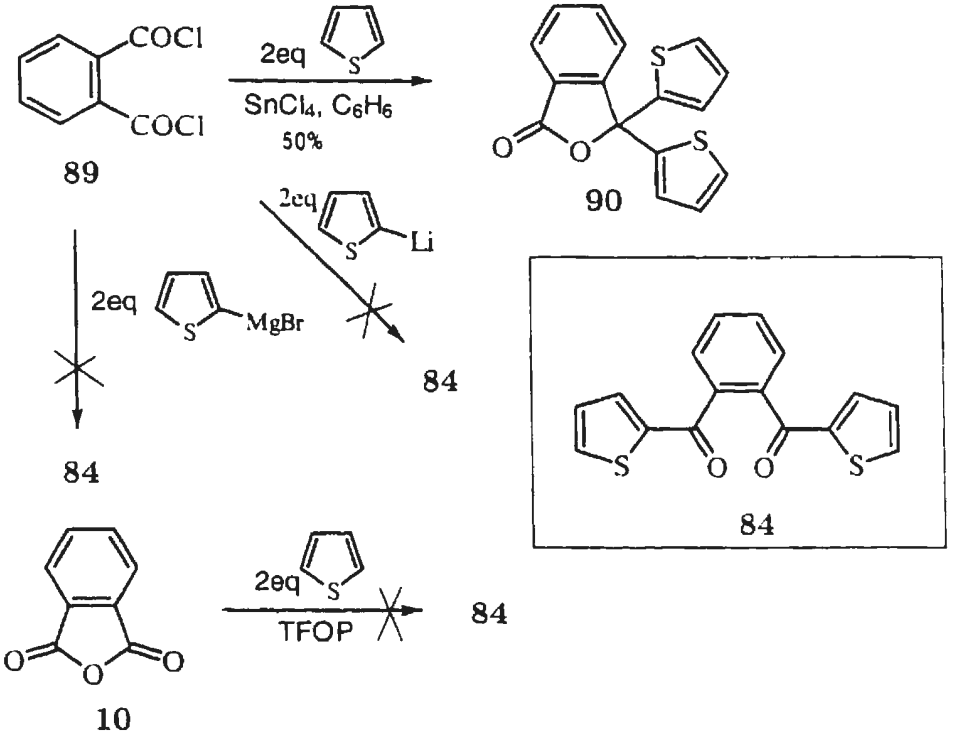
The first syntheses of the parent DTBcT **85** were reported simultaneously in 1992 by Baüerle *et al* (Scheme 24)[75] Lorcy and Cava (Scheme 26)[76], each group employing similar methods. Baüerle *et al* prepared the intermediate 1-(2-thienyl)phthalide **87** from the reaction of phthalic anhydride with thiophene in the presence of aluminum chloride (93%) followed by the reduction of the resulting *mono*-acylated *o*-(2-thienoyl)benzoic acid **86** with sodium borohydride. The initially formed alcohol readily lactonized to afford **87** (83%).



Scheme 24: Baüerle *et al.* Synthesis of DTBcT

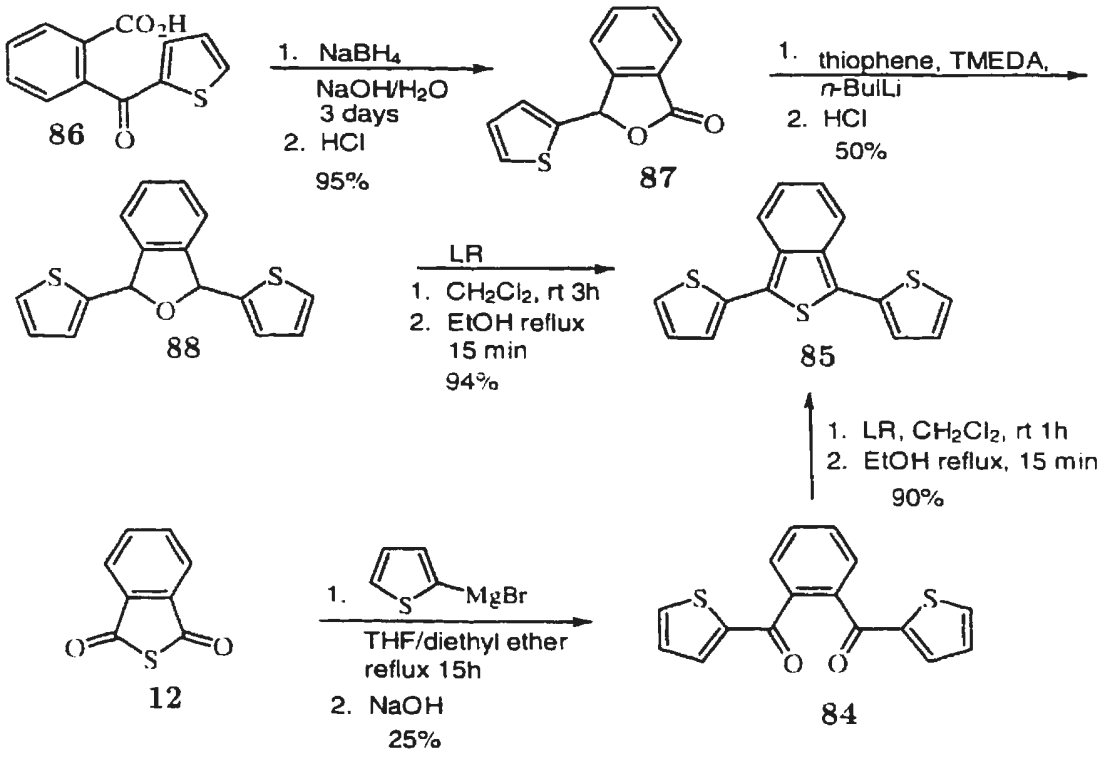
Baüerle *et al.* then reacted the phthalide **87** with 2-thienylmagnesium bromide to afford the substituted dihydrobenzo[*c*]furan **88**. The reaction of **88** with lead tetraacetate yielded the *o*-diacylarene **84** which, upon reaction with Lawesson's Reagent

(LR), reportedly gave the terheterocycle **85** (83%). They also prepared **85** from the direct thiation of the dihydrobenzo[c]furan **88** with LR, but the yield of **85** was much lower (28%).



Scheme 25: Additional Reactions Carried out By Baüerle *et al.*

It is worth noting that they also reported approaches which failed to afford **84** (Scheme 25). Acylation reaction of phthaloyl dichloride **89** with 2eq of thiophene in the presence of tin(IV) chloride in benzene resulted in the formation of **90** (50%). Reaction of **89** with the Grignard and lithium derivatives of 2-bromothiophene failed to produce **84** (nature of resulting product(s) not given), as did the reaction of phthalic acid with thiophene under 2-(trifluoromethylsulfonyloxy)pyridine (TFOP) catalysis[75]

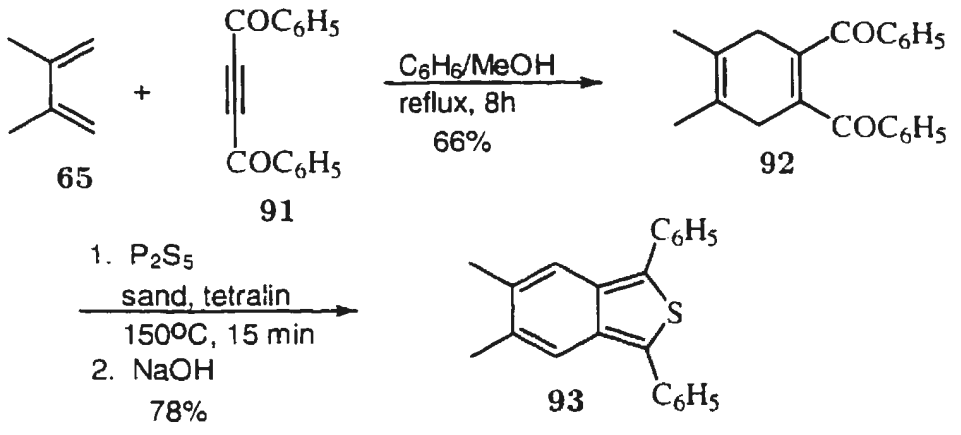


Scheme 26: Lorcy and Cava's Synthesis of DTBcT

In the synthesis presented by Lorcy and Cava (Scheme 26), the substituted dihydrobenzo[*c*]furan **88** was prepared from the reaction of the phthalide **87** and 2-thienyllithium (50%) and this was then reacted with LR to afford **85** in a yield of 94%. They also reported the synthesis of **84** (25%) by the reaction of thiophthalic anhydride **12** with 2-thienylmagnesium bromide under Grignard conditions[76]. The *o*-diacylarene was then converted to **85** in high yield (90%) using, once again, LR.

Subsequent to the procedures presented by Baüerle *et al.* and Lorcy and Cava, other methods have been employed in the preparation of *o*-diacylarenes. Successful Diels-Alder reactions have been carried out[101, 102] (Scheme 27)[102] and Grignard

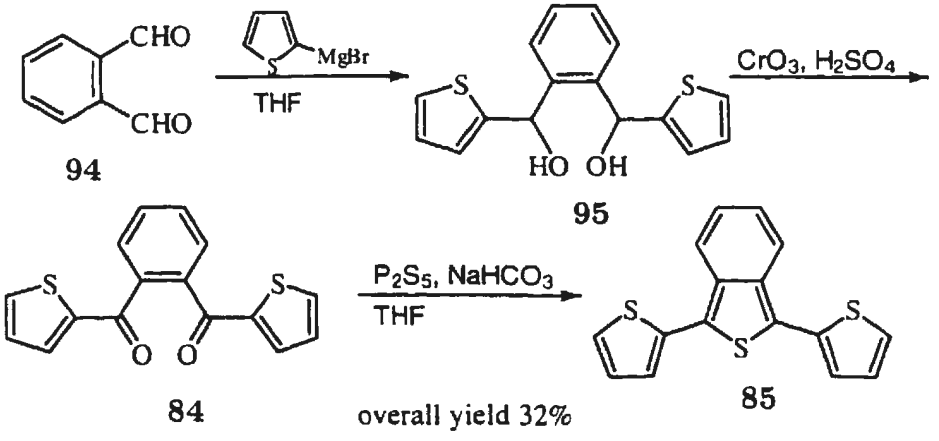
reactions on the following compounds have been reported: phthalic anhydrides, thiophthalic anhydrides, phthalaldehydes and phthaloyl dichlorides.



Scheme 27: Diels-Alder-Based Approach to a 1,3-Disubstituted BcT

4.1.2 Grignard Reaction Methods

4.1.2.1 Phthalaldehydes

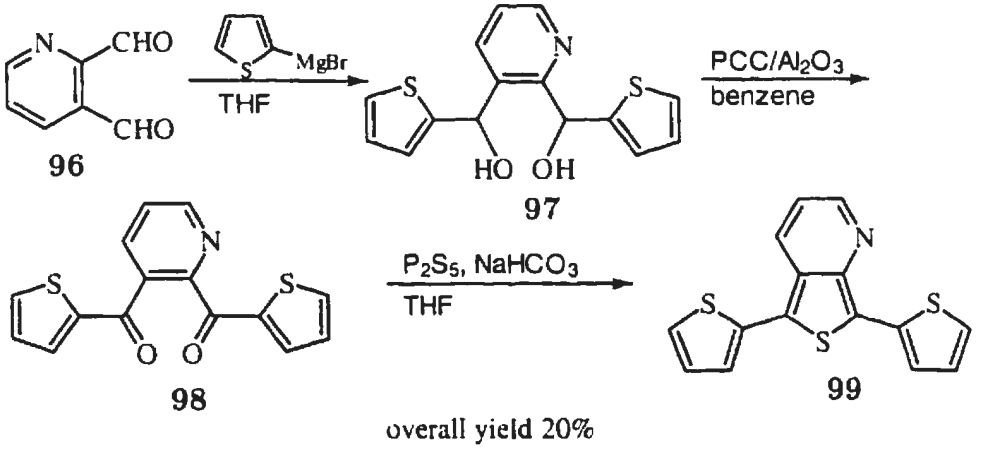


Scheme 28: Musmanniand Ferraris's Synthesis of DTBcT

Several successful Grignard reactions have been reported on phthalaldehydes. For example, Lee *et al.* reported a successful synthesis of aromatic *o*-diacylarenes in yields of 55-75%[103] using this approach.

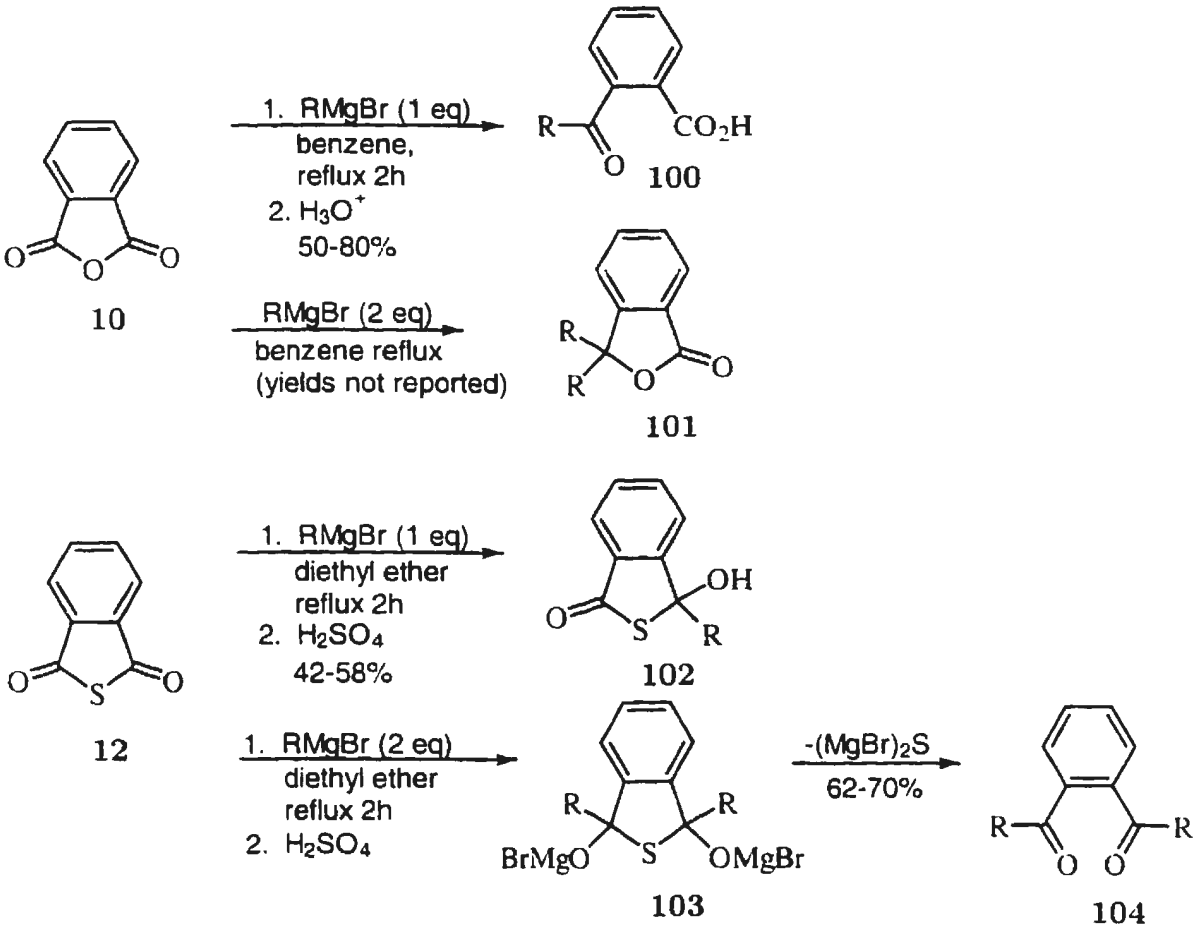
Musmanni and Ferraris also reported a successful Grignard reaction of phthalaldehyde **94**[77] using an earlier method[104] (Scheme 28). Compound **94** was added to 2-thienylmagnesium bromide to afford diol **95**, which was then oxidized to the *o*-diacylarene **84**. Subsequent reaction of **84** with phosphorus pentasulfide under buffered conditions achieved the cyclization to **85**. Unfortunately, experimental details, such as reaction conditions or yields for individual steps were not given. The overall yield from **94** to **85** was reported to be 32%.

They also reported another instance of a Grignard reaction on 2,3 pyridinedicarbaldehyde[105] (Scheme 29) using similar conditions. The overall yield for the three-step synthesis was reported to be 'about 20%'. As with the previous case, yields for the individual steps were not given.



Scheme 29: Synthesis of 2,5-Di(2-thienyl)pyridino[*c*]thiophene

4.1.2.2 Phthalic and Thiophthalic Anhydrides

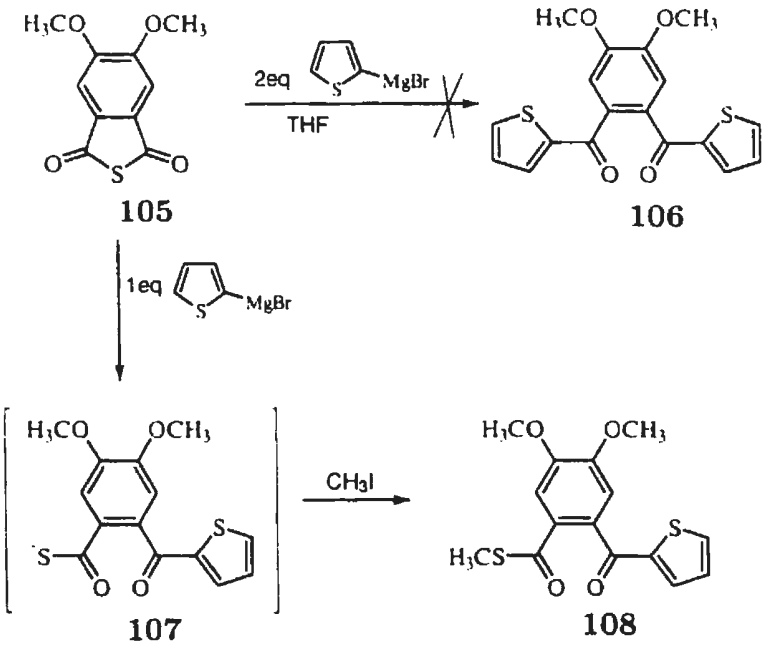


Scheme 30: Grignard Reactions of Phthalic and Thiophthalic Anhydride

Grignard reactions with phthalic and thiophthalic anhydrides have been reported, but results appear to be contradictory. Early reports indicate that Grignard reactions with phthalic anhydride **10** did not result in the formation of *o*-diacylarenes, but instead, one equivalent of Grignard reagent reacted to give *o*-aroylbenzoic acid **100** and two equivalents reacted to give primarily 3,3-dialkylphthalide **101** due to ring opening[106](Scheme 30). Later, in 1973, Omran and Harb concluded that unlike **10**, the action of Grignard reagents on thiophthalic anhydrides did not result in

ring opening[106]. These authors published a series of successful reactions of thiophthalic anhydride with a variety of Grignard reagents employing one equivalent (Scheme 30)[106].

According to Omran and Harb, thiophthalic anhydride reacted with one equivalent of the Grignard reagents by a 1,2-addition to the carbonyl group, without ring opening to give 3-alkyl-3-hydroxy-2-thiophthalides **102** (Scheme 30)[106]. It was further claimed that when two equivalents of Grignard reagents with the substituents R = $C_6H_4CH_3$-*p* and R = C_6H_5-, were employed, *o*-diaroyl benzene derivitives **104** were formed in 70% and 62% respectively.



Scheme 31: Paulussen's Synthesis of a Thioester

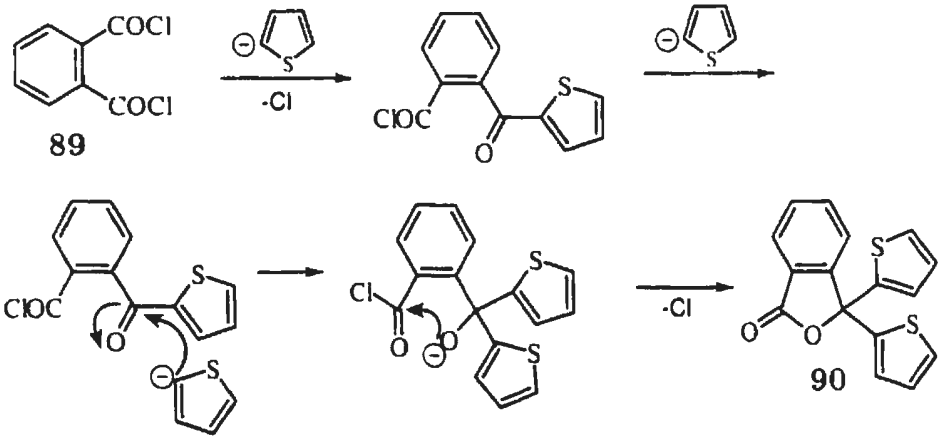
Contrary to the findings of Omran and Harb, Paulussen *et al.* reported that a Grignard reaction with a dimethoxy substituted thiophthalic anhydride **105** and 2-thienylmagnesium bromide did not lead to the *o*-diacylarene **106** (Scheme 31). They

suggested that ring opening did occur and the thiolate **107** was formed as an intermediate after the reaction of the first equivalent of Grignard reagent. Compound **107** was not isolated, but was reacted *in situ* with methyl iodide to form the methyl thioester **108**; synthetic details were not given[107]. They had intended to react compound **108** with another equivalent of 2-thienylmagnesium bromide, but it is not clear whether or not this was actually carried out.

Kiebooms *et al.* reported very low yields for Grignard reactions of 2-thienylmagnesium bromide with both phthalic anhydride (15%) and thiophthalic anhydride (40%)[74]. Elsewhere, Paulussen *et al.* published yields ranging from 0-60% depending on the solvent employed[53].

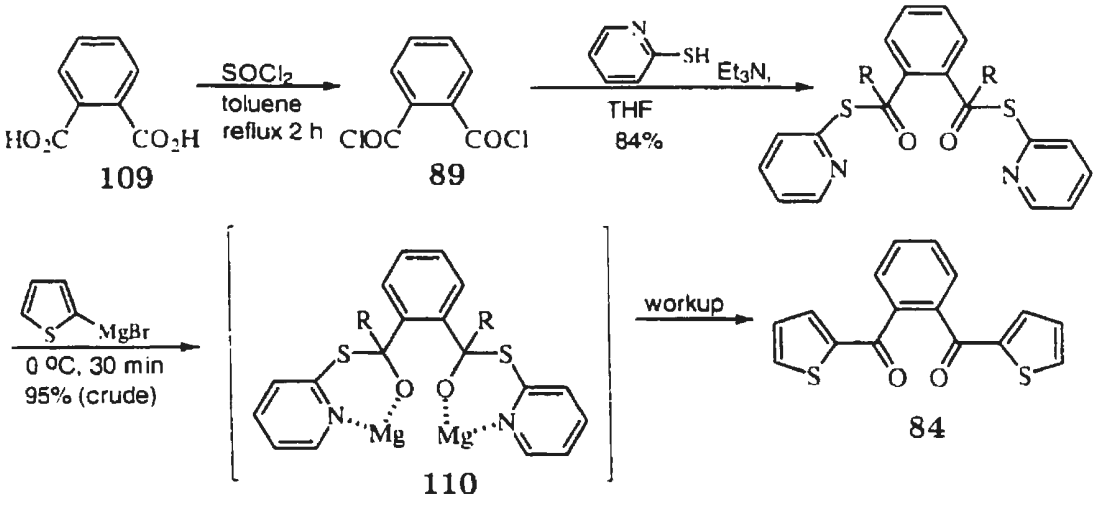
4.1.2.3 Phthaloyl Dichlorides

As mentioned earlier (Section 4.1.1), moderate-yielding Friedel-Crafts acylations of phthaloyl dichloride **89** with thiophenes have been reported[75], and the reaction of Grignard reagent with phthaloyl dichloride **89** gave low yields (0-10%)[53].



Scheme 32: Formation of 3,3-Dithienylisobenzofuran-1(3H)-one

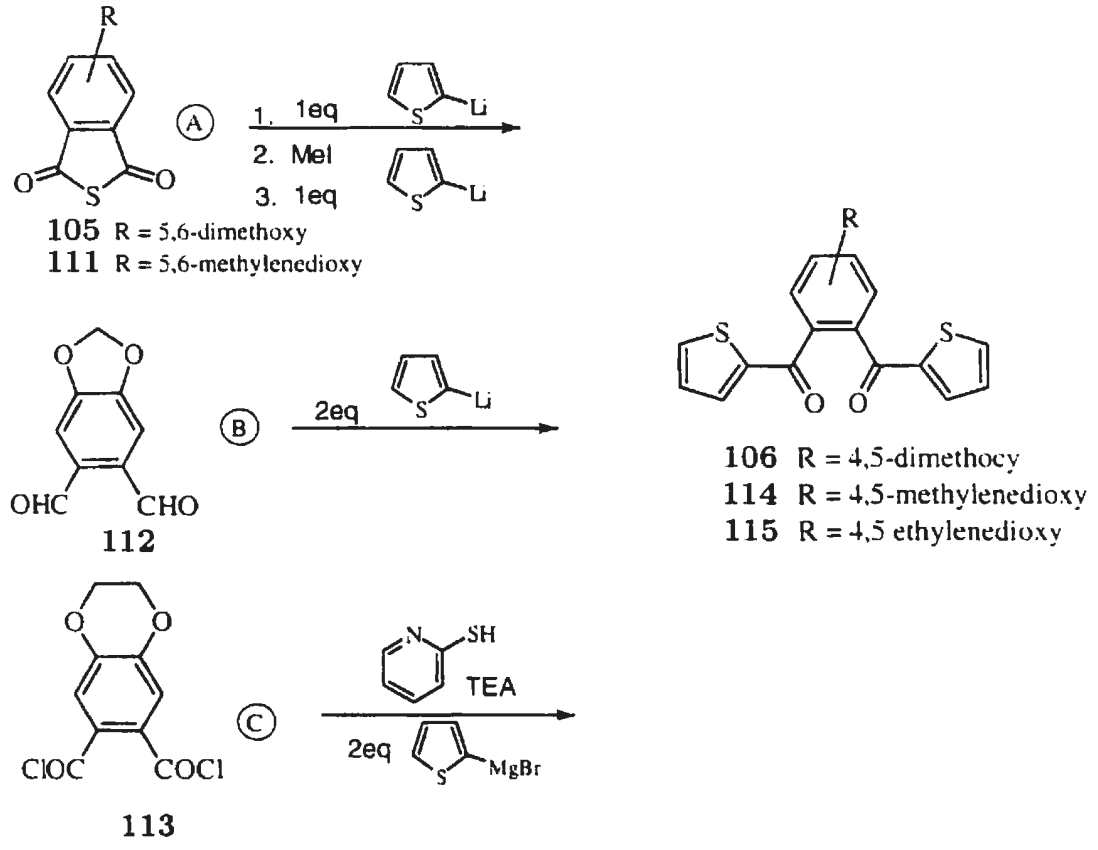
Paulussen *et al.* and Kiebooms *et al.* also reported that the reaction of 2-thienylmagnesium bromide with **89** gave very low yields of the *o*-diacylarene **84** and this was attributed to the intramolecular attack of the oxygen atom of one of the carbonyl groups which would result in disubstituted phalide **123** (Scheme 32). Aside from a poor yield of **84**, the formation of alcohols and many other side products were observed. The reason given for these results was that *ortho* situated acid chlorides are too reactive towards the nucleophilic substitution[74].



Scheme 33: Kieboom's Synthesis of *o*-Dithienoylbenzene

Kiebooms *et al.* did report successful Grignard reactions when the compound **89** was converted to a thioester and then reacted with 2-thienylmagnesium bromide[53, 74]. The notion of converting phthaloyl dichlorides to thioesters before undergoing Grignard reactions has been reported elsewhere[108, 109] and, according to more recent results[74], appears quite promising for the synthesis of a variety of DTBcTs. Thus, **89** was converted to the thioester bis(*S*-(2-pyridinyl))benzenedithioate

before performing the Grignard reaction[110] and this method resulted in the preparation of fluorinated and deuterated analogues[74]. The success of this method was attributed to the formation of a stable magnesium complex **110**, which prevents overreaction and intramolecular reaction (Scheme 33)[74].



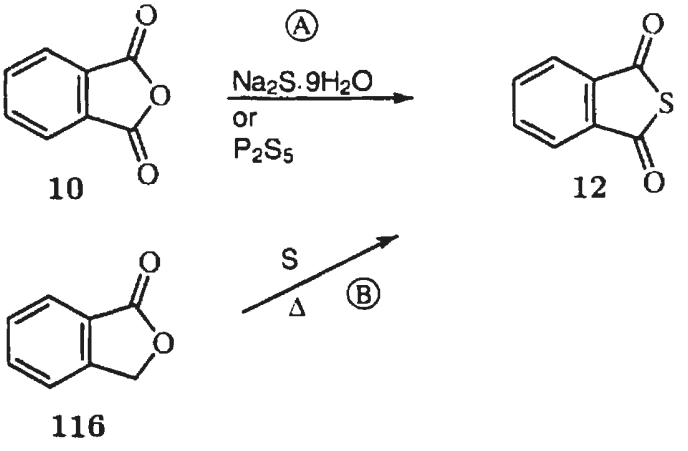
Scheme 34: Some Strategies Towards Substituted *o*-Diacylarenes

Of the known strategies described thus far, Grignard-type reactions were chosen for initial study (Scheme 34) and the following compounds were identified as starting points: 4,5-dimethoxythiophthalic anhydride **105**, 4,5-methylenedioxythiophthalic anhydride **111**, 4,5-methylenedioxyphthalaldehyde **112** and 4,5-ethylenedioxyphthaloyl dichloride **113**. With the first reaction (A), there are several advantages worth

noting. Employing this particular method, two equivalents of thiophene can be added in a stepwise manner providing more control and flexibility to the reaction which could lead to both symmetrically substituted or nonsymmetrically substituted DTBcTs. This is in contrast to the other Grignard-type reactions mentioned (B and C) which lead only to symmetric DTBcTs.

4.1.3 Approaches Towards 1,3-Dithienoyl-4,5-Dimethoxybenzene (106)

Although some work has been carried out towards **106**[107], its successful preparation from a Grignard reaction with the thiophthalic anhydride **105** has not yet been reported to our knowledge. Our approach to this compound was based upon Paulussen's method[107] with the intent of reacting the thioester **108** with a second equivalent of a thiophene (Scheme 40 *vide infra*) and eventually effect ring closure to **58**.

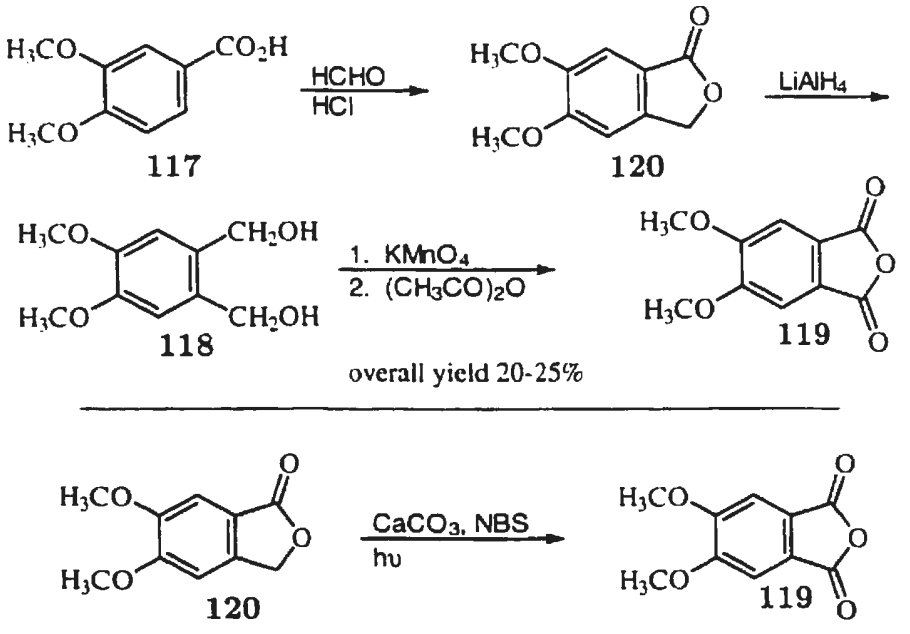


Scheme 35: Methods to Preparing Substituted Thiophthalic Anhydride

There are at least two methods for the preparation of thiophthalic anhydrides:

sulfurization of the corresponding phthalic anhydride **10** (Path A Scheme 35); or by the reaction of sulfur with a phthalide **116** (Path B Scheme 35).

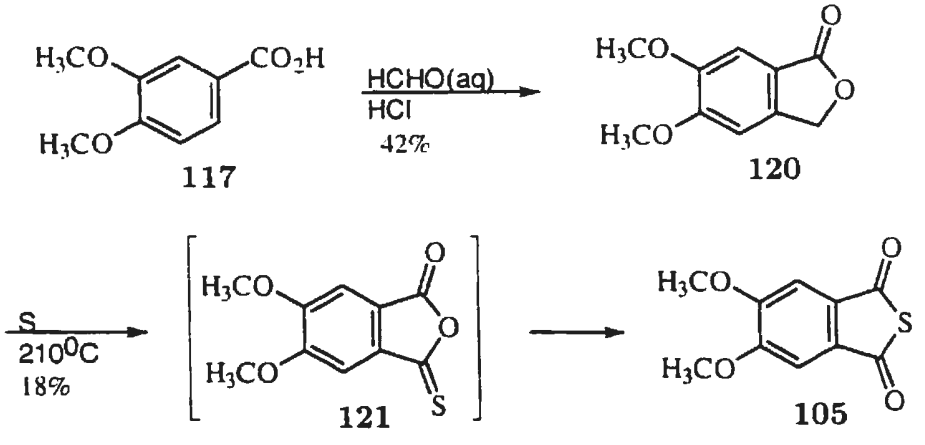
Both methods appear convenient and, in the first case, typical sulfurization reagents such as P_2S_5, $Na_2S{\cdot}9H_2O$ and LR give good yields[74]. Routes leading to substituted phthalic anhydrides, however, can be rather lengthy. For example, 5,6-dimethoxyphthalic anhydride **119** can be prepared from the corresponding acid **117** in four steps (Scheme 36)[53]. Reaction of **117** with aqueous formaldehyde saturated with hydrogen chloride yields the hydroxymethylated product **120** and reduction of this phthalide using lithium aluminum hydride gives the diol **118**. Oxidation of **118** to the diacid can accomplished with potassium permagnate and finally, dehydration leads to **119** (Scheme 36)[53]. As a result, overall yields to 5,6-dimethoxythiophthalic anhydride **105** tend to be low (20–25%).



Scheme 36: Methods to Preparing 4,5-Dimethoxyphthalic Anhydride

Another method for the preparation of **105**, based on the thiation of **119**, worth consideration is the oxidation of **120** to **119**. Despite reports of unsuccessful attempts to oxidize **120** to the diacid[53] using literature methods[111], it may have be possible to oxidize **120** using allylic brominating methods reported by Finucane and Thomson ($CaCO_3$, NBS and $h\nu$)[112] (Scheme 36) and would thus save a step in the synthesis of **119**.

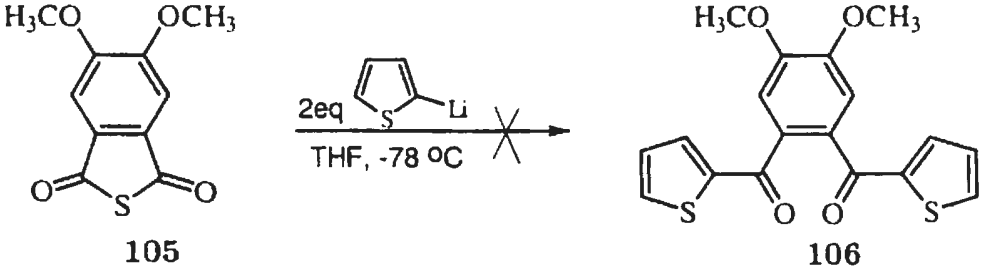
A more recent publication describes the synthesis of **105** by the sulfurization of **120**. Although this reaction might be dismissed initially due to the seemingly poor yield, (15-20%)[53], its advantage of convenience might outweigh the poor yield. Paulussen *et al.* explained this low yield as a result of incomplete conversion of **120** to **105** and reported that after two and half hours of heating, column chromatography yielded 70% of unreacted starting material which could be recycled[53]. For our purposes, the second method (Pathway B) was chosen for the preparation of **105** and the phthalide **120** was prepared using literature methods from 3,4-dimethoxybenzoic acid **117** (Scheme 37)[111].



Scheme 37: Synthesis of 4,5-Dimethoxythiophthalic Anhydride

The acid **117**, was heated for 7 hours at 60–70 °C with an aqueous formaldehyde solution that had been saturated with hydrogen chloride. The solution was then left to stir at room temperature overnight and following workup, afforded a light brown solid, which was easily purified using dry flash column chromatography methods on silica gel to give the phthalide **120** in 42% yield. In the next step, **120** was melted directly along with sulfur at 210 °C, for two and a half hours[53]. The resulting black residue was extracted several times with chloroform, and purification of the concentrated extracts using column chromatography on silica gel, gave **105** as a bright yellow, pungent solid in 19% yield.

Despite the moderate yields obtained for both steps, the initial step of hydroxymethylation can be carried out on a large scale basis to provide synthetically useful quantities of **120**. Overall, the two step process yielding **105** was found to be quite reliable.



Scheme 38: Attempted Synthesis of 1,2-Dithienoyl-4,5-Dimethoxybenzene

Compound **105** was then reacted initially with two equivalents of a thienyllithium solution to test for our satisfaction, whether or not this method leads to the *o*-diacylarene **106** (Scheme 38). 2-Thienyllithium in THF (at -78 °C), freshly prepared from the halogen-metal exchange reaction of 2-bromothiophene and *n*-butyllithium,

was added to a cooled solution (-78 °C) of **105** in THF. After stirring for approximately 15 hours at -78 °C, the reaction was quenched using dilute hydrochloric acid to give the crude product as a reddish brown oil. Purification by column chromatography, using either silica gel or Sephadex did not result in product separation. Further attempts using neutral alumina (activity V) yielded a small amount (33%) of a reddish brown powdery solid.

The mass spectrum of the fraction that was isolated showed M^+ ion with m/z of 358, which could correspond to the desired *o*-diacylarene **106** or the phthalide **123**. The ^{1}H NMR spectrum was not consistent with **106**; the symmetry expected of **106** was not reflected in the ^{1}H NMR spectrum, but most likely the isomeric **123** was formed (Figure 21). Had compound **105** behaved in a manner similar to that of **12** reported by Omran and Harb (Scheme 30)[106], the *o*-diacylarene **106** or, more likely, the tertiary alcohol **122** would have been observed (Figure 21).

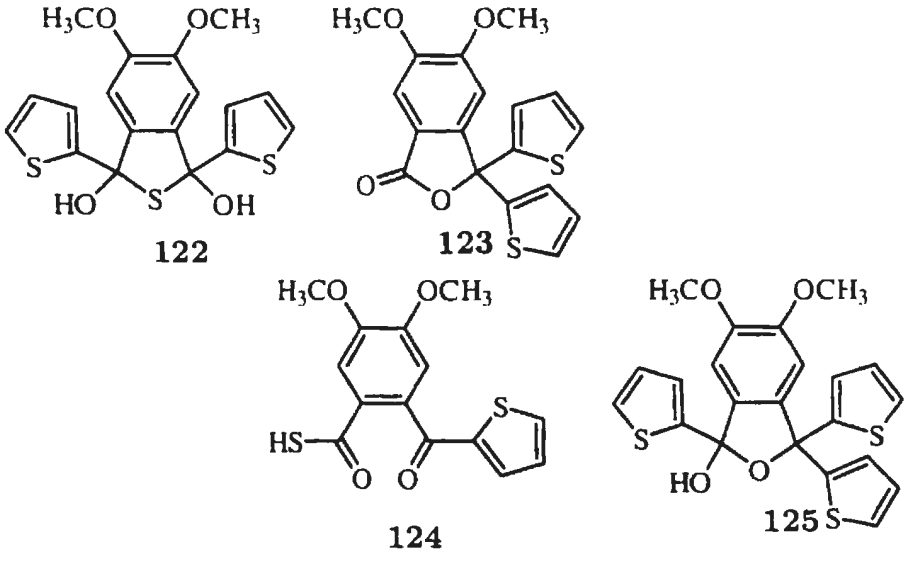
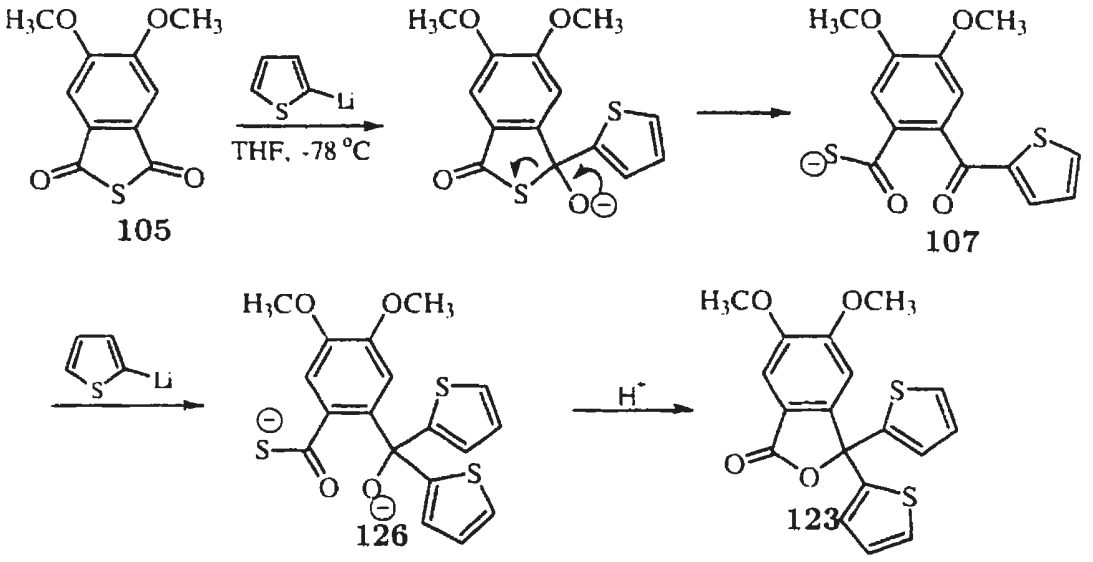


Figure 21: Potential Side Products from the Reaction of 4,5-Dimethoxythiophthalic anhydride and 2-Thienyllithium

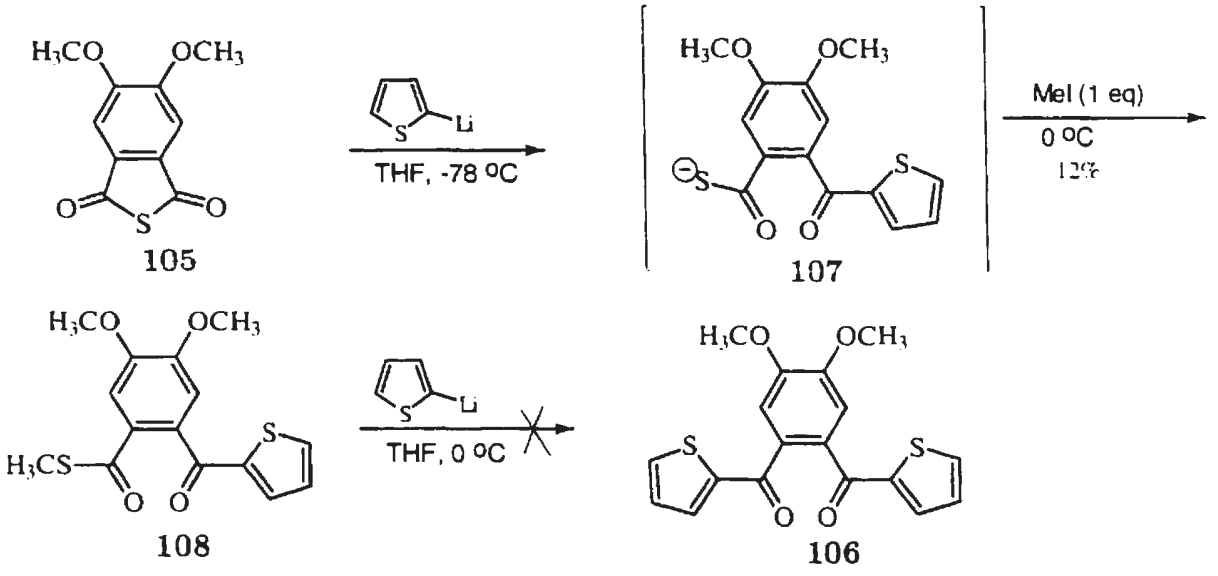


Scheme 39: Possible Mechanism for the Formation of
3,3-Dithienyl-5,6-Dimethoxyphthalide

From experimental observations, it appears as though the addition of two equivalents of 2-thienyllithium to **105** did not lead to the *o*-diacylarene **106** supporting more recent findings[74, 107] that ring opening was occurring (Scheme 39). If ring opening was occurring, then it should be possible to trap the thiolate **107** as the thioester **108** using methyl iodide, as Paulussen *et al.* reported[107](Scheme 40).

A freshly prepared solution of 2-thienyllithium (one equivalent) in THF (at -78 °C) was added to a solution of the thiophthalic anhydride **105** in THF. As in the previous case, the reaction was carried out -78 °C and left to stir overnight and slowly warm up. When the temperature had reached 0 °C, methyl iodide (one equivalent) was added and the reaction was quenched after stirring for an additional 30 minutes. Purification of the resulting crude mixture was difficult, as experienced in the previous case, but column chromatography using neutral alumina afforded a small amount (12%) of a

very light pink solid.



Scheme 40: Second Attempted Synthesis of 1,2-Diethienoyl-4,5-dimethoxybenzene

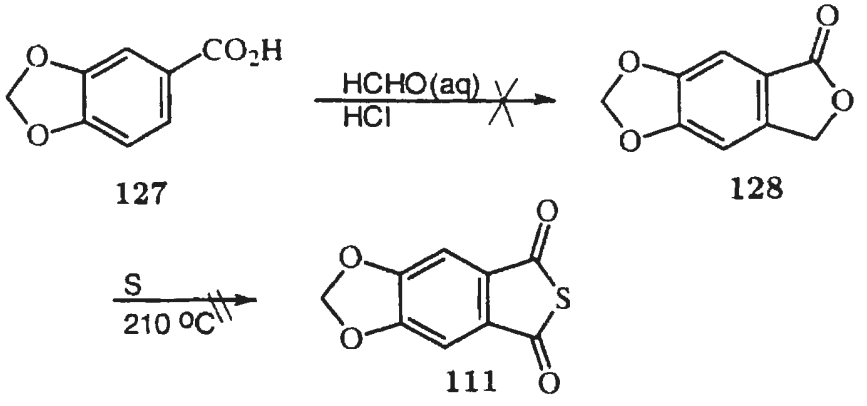
The ^{1}H NMR spectrum of this fraction is consistent with **108**. The mass spectrum did not show the molecular ion peak (m/z = 322), but M^+ -SCH_3 (m/z = 275) was observed and peak patterns consistent with the fragmentation of M^+ -SCH_3 were also observed. Mass spectrometric analysis a using lower energy ionization method also did not show the molecular ion peak. The same was true for analysis by GC-MS. In light of the lability of thioesters, it is not surprising that the SCH_3 group cleaved readily under EI conditions.

Compound **108** was then reacted with one equivalent of 2-thienyllithium using the same conditions as described for **105** (Scheme 40). Unfortunately, the results were inconclusive. Analysis of the fraction isolated by column chromatography by mass spectrometry, suggests that **106** or, at the very least, its isomer **123** may have been formed. Mass spectrometry revealed a small peak corresponding to the parent ion.

m/z 358, and a very large peak with m/z of 275 corresponding to the loss of thienoyl C_4H_3SCO (m/z 111). The ^1H NMR spectrum of this fraction showed that it was a mixture and **106** was not detected.

4.1.4 Approaches to 1,2-Dithienoyl-4,5-Methylenedioxybenzene

Following on from the successful synthesis of the thioester **108**, thiophthalic anhydride **111** was also targeted as a precursor to the *o*-diacylarene **114**. Recalling that the hydroxymethylation of the dimethoxy derivative **117** had proceeded smoothly, it was anticipated that repeating these reaction conditions with piperonylic acid would lead to 4,5-methylenedioxyphthalide **128** (Scheme 41). This was found not to be the case.



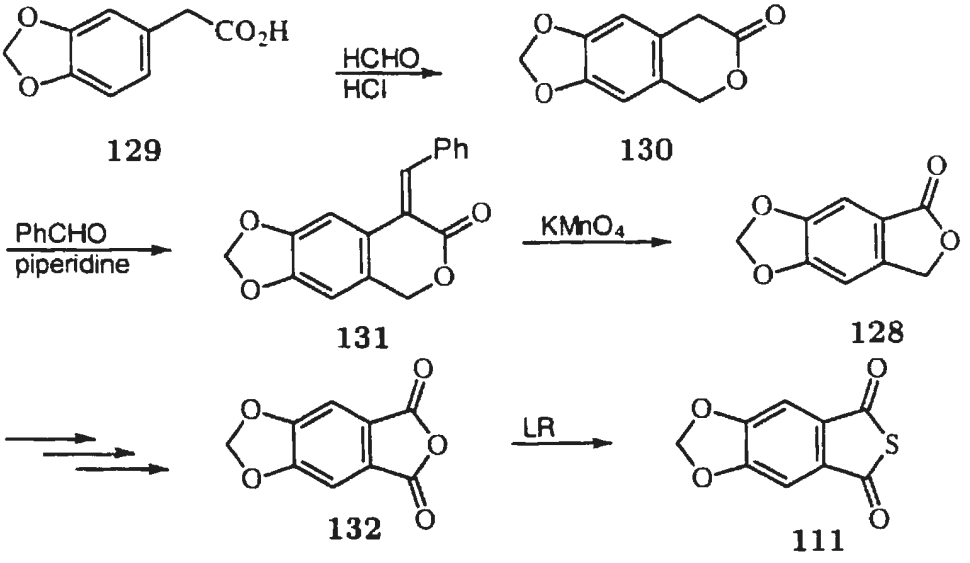
Scheme 41: Proposed Method to 4,5-Methylenedioxythiophthalic Anhydride

Piperonylic acid **127** was heated for 7 hours at 60–70 °C with an aqueous formaldehyde solution that had been saturated with gaseous hydrochloric acid. The solution was then left to stir at room temperature overnight; workup led to only trace amounts

of the phthalide **128** (< 6%). The reaction was repeated with several modifications. For example, glacial acetic acid was included to aid solubility, and concentrated hydrochloric acid was also added. These modifications did not result in the formation of **128** and gave instead complex mixtures.

The lack of reactivity of the piperonylic acid **127** towards the acidified aqueous formaldehyde was perplexing. Although the electron-withdrawing ability of the acid functional group can be expected to deactivate the aromatic ring somewhat towards electrophilic substitution, it was assumed that the other functional group methylenedioxy group at the 3 and 4 position would be sufficient to activate the system.

Acetal hydrolysis may also have taken place to some extent, thus complicating the reaction mixture. This was not actively studied and further attempts to hydroxymethylate **127** using these methods were discontinued.

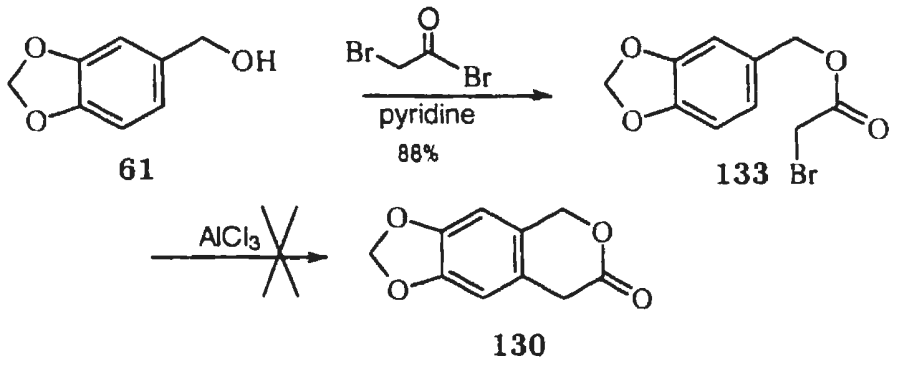


Scheme 42: Alternative Method for Synthesis of 4,5-Methylenedioxyphthalide Leading to 4,5-Methylenedioxythiophthalic Anhydride

A literature method where the phthalide **128** figured as an intermediate leading to

the synthesis of the anhydride **132** is illustrated in Scheme 42. From this approach, the phthalide **128** is reportedly available from homopiperonylic acid in three steps[113].

Rather than hydroxymethylate the homoacid **129** to the homophthalide **130**, the preparation of **130** was attempted from the ring closure of a bromoester **133** using Friedel-Crafts conditions (Scheme 43). Intramolecular Friedel-Crafts acylations have appeared frequently in synthetic works for fusing six-membered rings to aromatic rings[114, 115] and it was thought this method may lead to **130** which could then be used to prepare **128** (Scheme 42).



Scheme 43: Attempted Synthesis of 4,5-Methylenedioxy homophthalide

Alcohol **61** was treated with bromoacetyl bromide in the presence of pyridine and was allowed to stir overnight. Purification by dry flash column chromatography on silica gel afforded **133** as a pale amber oil in 88% yield. Ring closure of **133** was then attempted using aluminum chloride as the Lewis acid catalyst. Compound **130** was not observed, but rather a somewhat insoluble shiny green material was obtained. This reaction was repeated using more dilute conditions, but these conditions also failed to yield **130**. The use of milder catalysts was not investigated.

At this point, it was decided it would be more prudent to go back and synthesize

the homoacid **129** and then continue on to prepare the phthalide **128** as illustrated in Scheme 42. The intention was to prepare compound **129** by the oxidation of homopiperonal **140** using a mild oxidizing agent, sodium chlorite, under buffered conditions. This reagent has been used successfully in K. Suzuki's synthesis of Gilvocarcin M[116] during the oxidation of the aldehyde **134** to the acid **135** (Figure 22). Nicolaou's synthesis of Brevetoxin B[116] also featured sodium chlorite in the oxidation of the aldehyde **136** to the acid **137** (Figure 22). The yields for these reactions were reportedly high.

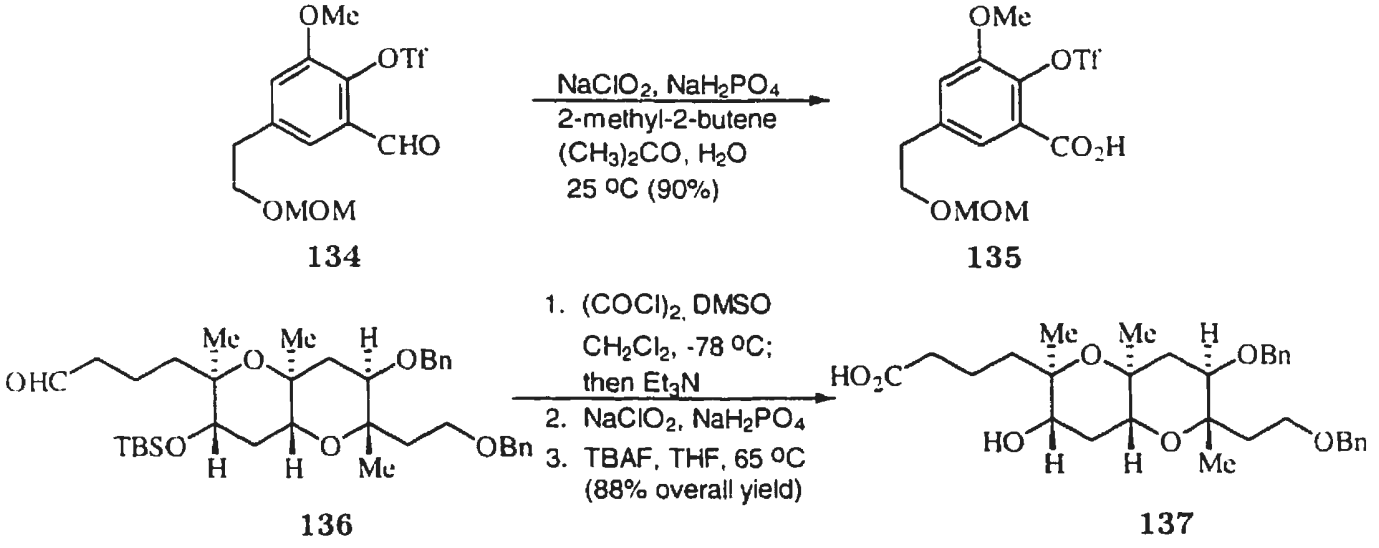
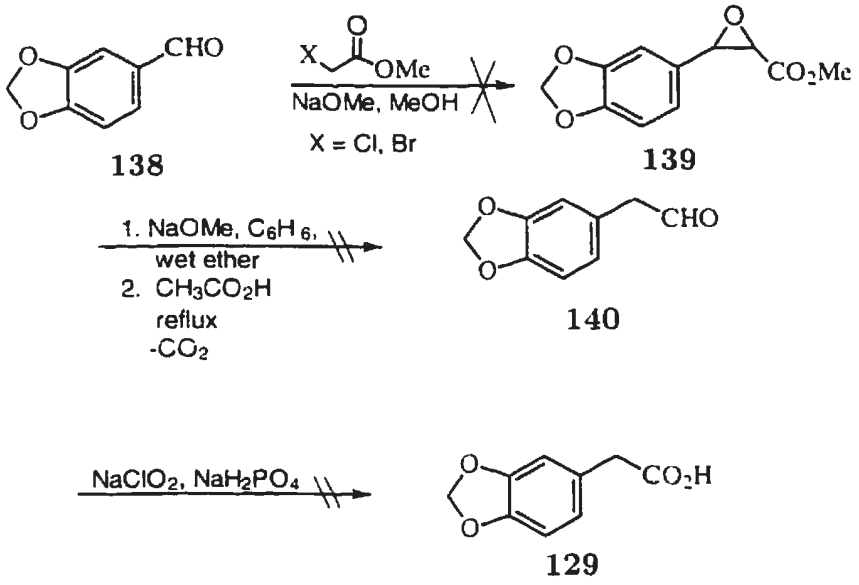


Figure 22: Examples of Oxidations Using Sodium Chlorite

To prepare homoaldehyde **140**, a method employed by Dhoubhadel and Joshi in their synthesis of ψ-baptigenin, from the acylation of piperidine enamine of **140**[117], was selected. Dhoubhadel and Joshi had prepared **140** from the Darzen's reaction of **138** with methyl chloroacetate. They hydrolyzed the resulting glycidate ester **139** and then decarboxylation was reported to lead to **140**.

Taking a similar approach (Scheme 44), piperonal **138** was combined with methyl



Scheme 44: Attempted Synthesis of Homopiperonylic Acid

bromoacetate and added to a freshly prepared solution of sodium methoxide. Upon workup, crude **139** failed to precipitate and an oily yellow layer was obtained. Examination of this crude material by ^{1}H NMR analysis indicated a complex mixture, in which the presence of compound **139** was not immediately obvious and the reaction was then repeated using methyl chloroacetate. Similar results as obtained previously with methyl bromoacetate were obtained, contrary to findings of Dhoubhadel and Joshi[117] and this avenue of investigation was discontinued.

To summarize, efforts to prepare the phthalide **128** by the hydroxymethylation of the acid **127** was unsuccessful, as were attempts to prepare the homophthalide **130** and homoaldehyde **140**, both of which may have been useful for the preparation of **128**. In a final attempt to prepare **128**, formylation of piperonyl alcohol was investigated.

To formylate aromatic systems there are several methods that exist that use

Friedel-Crafts type conditions. The Vilsmeier-Haack reaction is one such method[118, 119]. The reactive electrophile with this method is a chloroiminium ion, generated by the reaction of phosphorus oxychloride and a *N,N*-dialkylamide. This species acts as an electrophile in the absence of a Lewis acid but only reacts with aromatic systems that are sufficiently reactive. The piperonyl system, from our previous experiences, did not appear to be very reactive and it was decided that it would most likely not be a good candidate to undergo this type of reaction.

Other reactions include the Gatterman reaction[120] and Gatterman-Koch reaction[121].In the first instance (Gatterman reaction), the reagents HCN and HCl (or $Zn(CN)_2$ and HCl) are used to effect formylation and in the second, (Gatterman-Koch), formylation is achieved using CO and HCl with $AlCl_3$. Both of these reactions, with their strongly acidic nature, may present problems with the piperonyl system, specifically the methylenedioxy substituent. Recall that in the case of hydroxymethylation of piperonylic acid (Scheme 41), it was suspected that the strongly acidic conditions were responsible for the complex mixtures. Another aromatic formylation reaction is the Reimer-Tiemann reaction[122], but this method is only for phenols and certain heterocyclic compounds, such as pyrroles and indoles. Therefore, these conditions would not be suitable for the piperonyl system.

From the various formylating reactions presented, it would seem that the formylation methods at our disposal for the piperonyl system were somewhat limited. One other Friedel-Crafts type method that held some promise was the use of dichloromethyl ethers as a precursor of the formyl group[115] (Figure 23).

The formylation of piperonyl alcohol, was attempted using dichloromethyl methyl ether with titanium (IV) chloride (Scheme 45). Titanium (IV) chloride was added

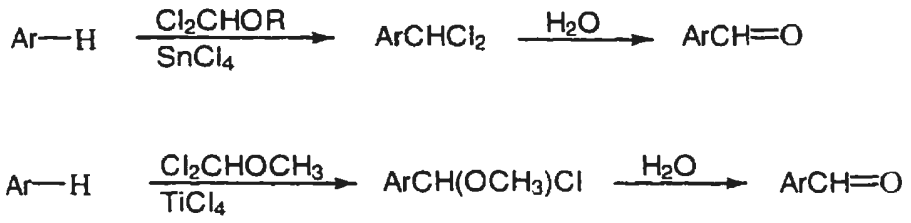
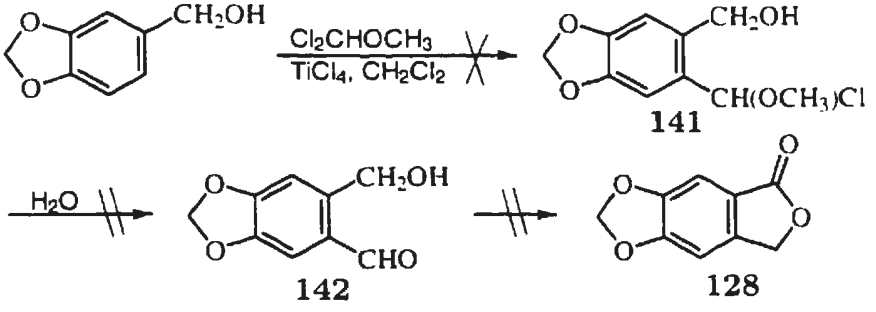


Figure 23: Chloromethylations

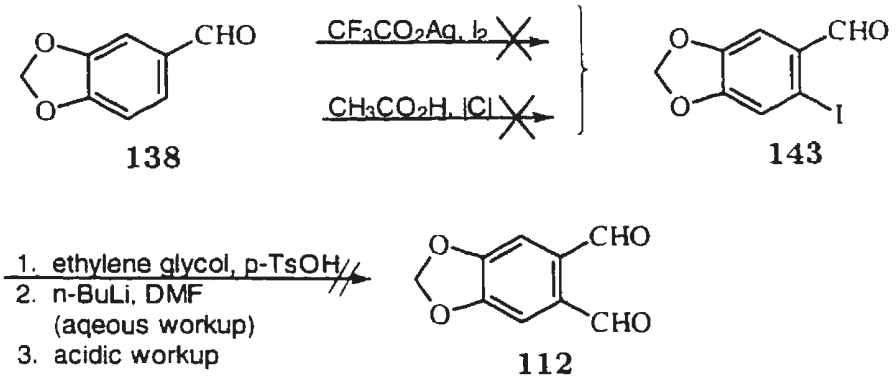
rapidly to a solution of piperonyl alcohol in dry dichloromethane, cooled using a salt-ice bath followed by dichloromethyl methyl ether. Workup yielded an intractable, complex mixture as observed by both TLC and ^{1}H NMR analysis, which prevented the definite assessment of product formation. The exact cause of the failure of this reaction was not identified, but perhaps under these reaction conditions, once again, cleavage or partial cleavage of the acetal functional group might have occurred.



Scheme 45: Attempted Synthesis of 4,5-Methylenedioxyphthalaldehyde

Efforts were then focused on preparing the 4,5-methylenedioxyphthalaldehyde **112** using formylation methods. The phthaladehyde **112**, might ultimately be used as a precusor to the *o*-diacylarene **114** by employing Grignard-type conditions as mentioned earlier (Section 4.1.2.1).

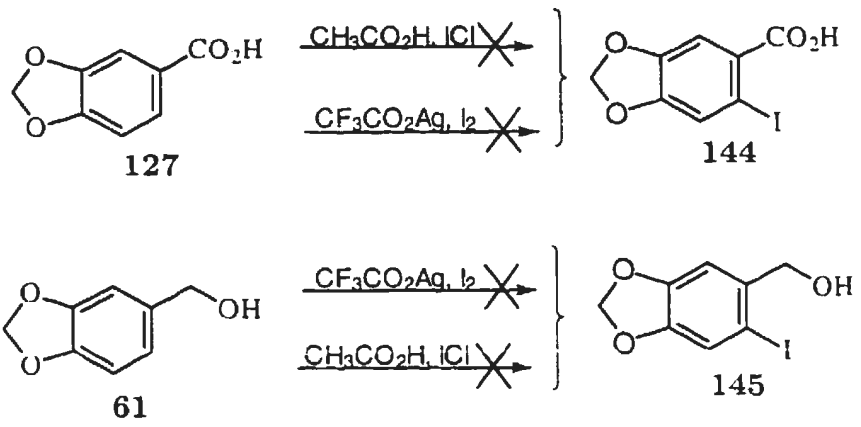
To achieve the formylation, the halogen-metal exchange reaction followed by addition of a formyl precursor, *N,N*-dimethylformamide[123], was thought to be advantageous since this method does not use acidic conditions. Intially, endeavours were carried out on the synthesis of an iodo-substituted piperonyl system (Schemes 46 and 47).



Scheme 46: First Approach Towards 4,5-Methylenedioxyphthalaldehyde

To effect iodination, several useful techniques have been developed[124–128]. Attempts using iodine monochloride and silver trifluoroacetate with iodine on piperonal, piperonylic acid and alcohol were unsuccessful.

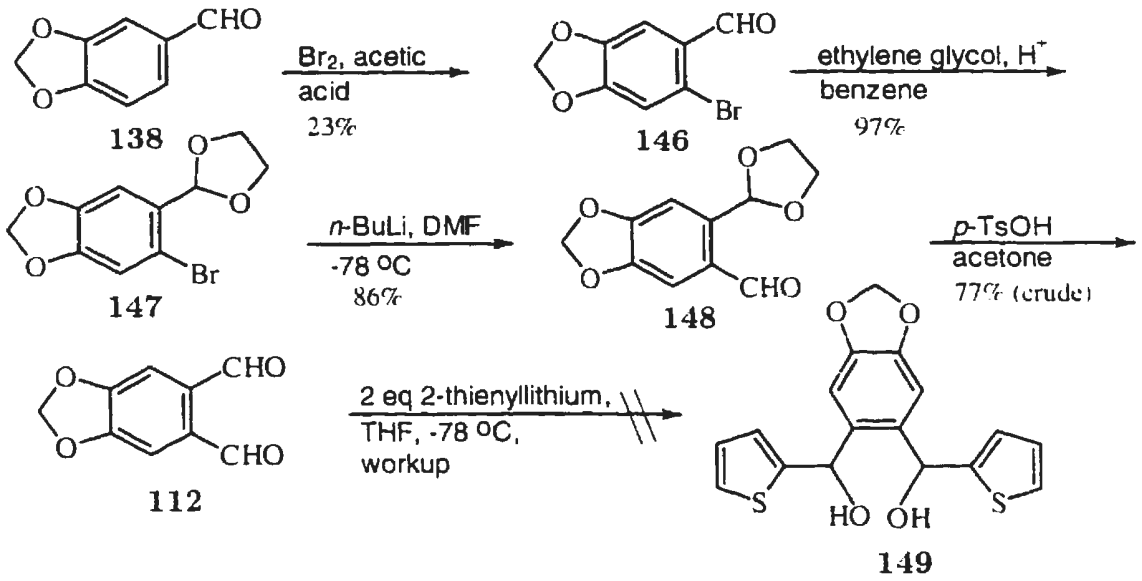
The attempt to iodinate **138** (Scheme 46) was initially carried out using iodine monochloride in glacial acetic acid[128]. No product was observed and starting material was recovered upon workup as verified by ^{1}H NMR analysis. The reaction was repeated using the same reagents but, with gentle heating (60 °C). However, workup gave unidentifiable material, as indicated by ^{1}H NMR analysis. Iodination of piperonal was also attempted using an adapted procedure[129], namely iodine with silver trifluroacetate in chloroform. This reaction was not successful and starting material was recovered.



Scheme 47: Attempted Synthesis of 6-Iodopiperonylic Acid and Alcohol

Next iodination of both the acid **127** and alcohol **61** was attempted employing adapted literature procedures[129] that employed the reagents iodine and silver trifluroacetate in chloroform and also using iodine monochloride in glacial acetic acid[128]. Both of these methods also proved to be unsuccessful. Iodine can effect substitution only on very reactive aromatic systems[115]. Since the failure to obtain iodo-substituted piperonyl compounds was observed, this suggests a low reactivity of this particular system towards electrophilic substitution. Unlike iodine, chlorine and bromine are reactive towards aromatic systems[115] and therefore, bromination of piperonal appeared more likely to succeed. 6-Bromopiperonal **146** was targeted next using a literature procedure[130] (Scheme 48).

Piperonal **138** was converted to **146** in yield of 23% after purification by column chromatography and recrystallization. Prior to the reactions leading to formylated product, **112**, the aldehyde functional group of **146** was first protected as a 1,3-dioxolane, employing literature methods[131] **147** (97%). The protected aldehyde was subsequently treated with *n*-BuLi to accomplish the halogen-metal exchange reaction, followed by the addition of dry DMF[131]. Upon aqueous workup, the

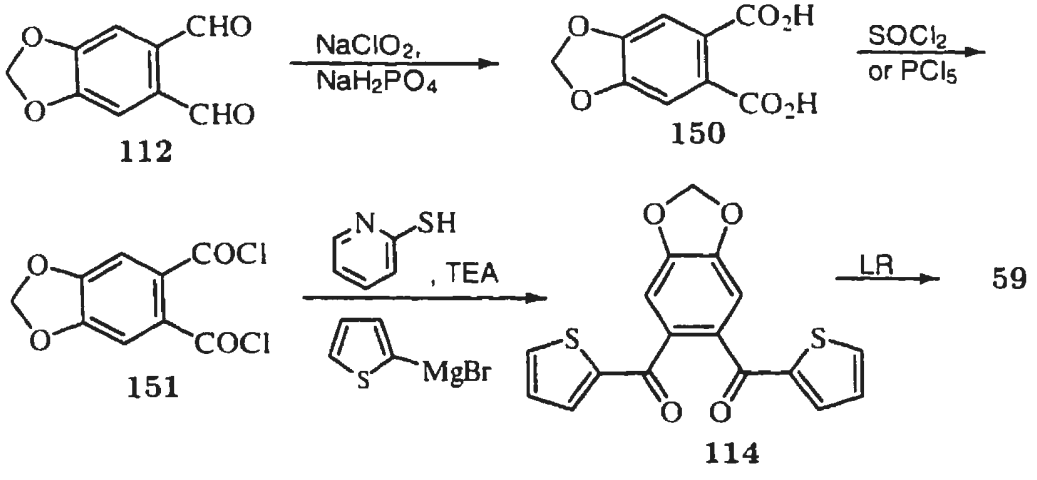


Scheme 48: Synthesis of 4,5-Methylenedioxyphthalaldehyde and Subsequent Reaction with 2-Thienyllithium

resulting formylated product was obtained in a 86% yield.

Initial attempts to deprotect the aldehyde functional group employing dilute hydrochloric acid resulted in an oily mixture. Attempts to purify this oil using column chromatography on silica gel appeared to result in further complications. Decomposition of the crude mixture by some unknown mechanism was thought to be occurring. Deprotection was more successful when a milder method of stirring the protected dialdehyde **148** using catalytic amounts of *p*-TsOH in acetone was used. However, the crude product obtained from this method decomposed very quickly on silica gel, and this was evident from TLC analysis. A rapidly-forming dark streak formed while the plate was eluting. The reaction solution containing the crude product **112** in acetone was filtered rapidly through neutral alumina and the alumina was rinsed several times with portions of acetone to give crude **112** in 77% yield. Analysis by ^{1}H NMR indicated a small amount of starting material was present.

Initial cursory reactions of **112** with two equivalents of freshly prepared 2-thienyllithium were carried out and ^{1}H NMR analysis indicated that a mixture of compounds were formed. The reaction was subsequently repeated and, after the addition of the first equivalent of 2-thienyllithium had been added, the reaction was then allowed to stir for several hours before the addition of the second equivalent. For reasons that are not clear at this time, this reaction gave undefined products and analysis by ^{1}H NMR of the crude product upon workup showed, once more, that a mixture of compounds had formed and **149** was not readibly detected. Extractions of the crude oil with hexanes yielded a small amount of crystalline material. Analysis of this residue by ^{1}H NMR indicates a mixture and it is not entirely clear whether the diol **149** was obtained. Further work is required on this reaction to determine the nature of the products obtained.



Scheme 49: Future Work for 4,5-Methylenedioxyphthalaldehyde

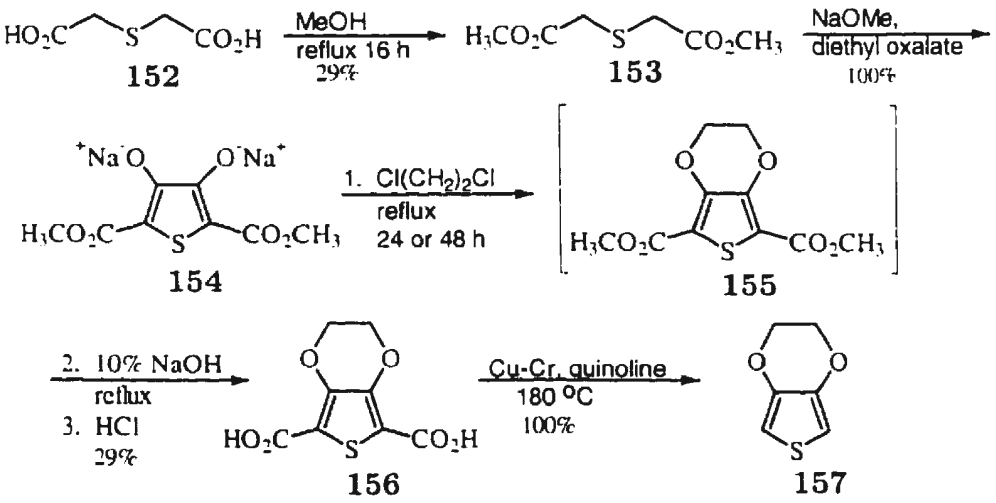
In the future, it may be more advantageous to oxidize the crude **112** to the *o*-dicarboxylic acid, compound **150** perhaps using sodium chlorite under buffered conditions as shown earlier (Figure 22). This compound could then be converted to

the corresponding phthaloydichloride **151** using typical chlorinating reagents (thionyl chloride or phosphorus pentachloride) and further reacted with 2-mercaptopyridine, followed by reaction with a suitable Grignard reagent (Scheme 49) which could lead to the critical *o*-diacylarene **114**.

4.1.5 Approaches to 1,2-Dithienoyl-4,5-Ethylenedioxybenzene (115)

It was envisaged that the approach towards *o*-diacylarene **115** would rely upon a Diels-Alder reaction between 3,4-ethylenedioxythiophene (EDT) and DMAD for the construction of the basic skeleton (Scheme 55 *vide infra*).

4.1.5.1 Synthesis of EDT



Scheme 50: Synthesis of EDT by Pei *et al.* [3]

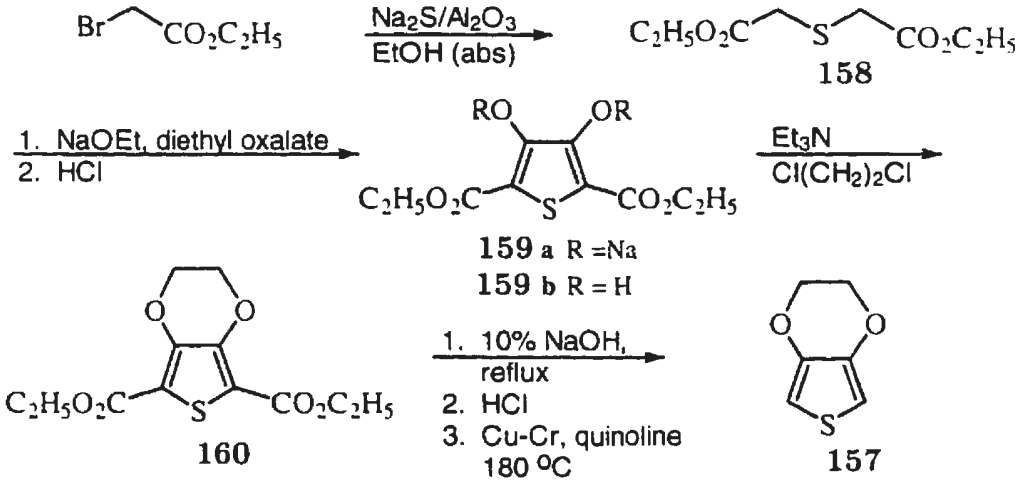
EDT is a known compound[3], but, upon attempting to repeat the literature synthesis (Scheme 50), the published yields could not be achieved reliably. In addition, there appeared to be room for improvement in the methodology. For a start, according

to the reported method[3], the yield (29%) of the diester **153**, from the esterification of thiodiglycolic acid **152** in refluxing methanol is rather poor. The thiophene ring itself was reportedly prepared from the reaction of **153** with diethyl oxalate and freshly prepared sodium ethoxide to give the disodium salt **154** in 100% yield. Subsequent to the isolation of compound **154**, they refluxed this salt in 1,2-dichloroethane for 24 or 48 hours. The suspension was filtered to remove starting material and the intermediate thiophene 2,5-bis(methoxycarbonyl)-3,4-ethylenedioxythiophene **155** was subsequently hydrolyzed. Interestingly, the yield for formation of **160** prior to hydrolysis was not given, but the overall yield for the two steps is reportedly 29%. The hydrolysis step most likely gives high yields and therefore the step prior to the hydrolysis is the one likely to have given the very poor yields.

Rather than prepare the sulfide **158** from the esterification of the corresponding acid, the use of the solid supported reagent Na_2S/Al_2O_3, (previously used to prepare 1,3-dihydro-5,6-methylenedioxybenzo[*c*]thiophene **63** and 1,3-dihydro-5,6-bis(methylcarbonyl)benzo[*c*]thiophene **78**), was investigated (Scheme 51). The reaction of ethyl bromoacetate and Na_2S/Al_2O_3 proceeded in an exothermic manner and stirring for 2.5 hours afforded **158** as a pale yellow oil in 73% yield. Carrying out subsequent reactions from the literature synthesis, the disodium salt **154** was prepared in a good yield (>95%), but it was found that the next step, refluxing in 1,2-dichloroethane, gave very low yields. Despite several attempts, refluxing initially for 24 hours then 48 hours, yields never exceeded 3%. The low solubility of **154** was suspected to be a contributing factor to the low yield.

Instead of pursuing the literature synthesis, a modified procedure which kept some aspects of the literature synthesis intact was developed (Scheme 51). The disodium salt **159a** was prepared in the usual manner, but rather than isolate this salt, it

was protonated using hydrochloric acid to give the diol **159b** in 90% yield. The reaction of **159b** with triethylamine in a large excess of 1,2-dichloroethane helped to overcome the solubility problems experienced with the reaction of **154** in the chlorinated solvent for the formation of **160**. This new method not only gave good yields of **160** (95%), but also the reaction time was shortened substantially from 24 or 48 hours to approximately 15 hours. The remaining steps to EDT **157** were carried out in a manner similar to that of the literature synthesis. Hydrolysis of the esters with 10% potassium hydroxide gave the acid **156** in 87%. Contrary to the literature, decarboxylation of the diacid to give EDT **157**, by heating in freshly distilled quinoline (180 °C for 30 minutes) in the presence of copper chromite, gave yields that did not exceed 61%.



Scheme 51: Modified Synthesis of EDT

Overall, the steps in this modified reaction sequence gave good yields and a reduction in the reaction times for two key steps, preparation of the sulfide **158** and the thiophene **160**. In addition to this, very clean products were obtained and crude

products could be carried through the synthesis with only the final product EDT requiring purification.

4.1.5.2 Diels-Alder Reaction of EDT

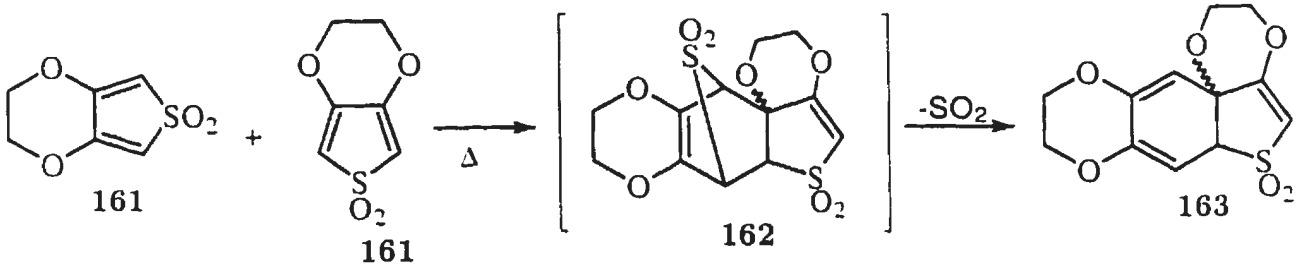
Normally, substituted thiophenes are not expected to be very reactive dienes towards Diels-Alder reactions. The statement such as "thiophenes do not undergo Diels-Alder type reactions" had found its place in several textbooks[132] after unsuccessful attempts to carry out the Diels-Alder reactions were reported[133]. This lack of reactivity is based upon the known chemistry of thiophenes, which are regarded as aromatic systems that are not expected to readily undergo a concerted Diels-Alder reaction[134]. It was thought that in order for Diels-Alder type reaction to occur, the thiophene must first be oxidized to thiophene-1,1-dioxide.

Thiophene-1,1-dioxide was first prepared by Bailey and Cummings[135] and, although this compound is very reactive and is only stable over a short period in cold solution, some substituted thiophene-1,1-dioxides have been prepared[136]. These findings prompted the hasty, if not somewhat prejudiced, thinking that in order for EDT to react with DMAD in a Diels-Alder manner, it must first be converted to the 1,1-dioxide, **161**.

Various attempts were made to oxidize EDT, but these were unsuccessful. These endeavours initially included oxidation of EDT employing a literature preparation[137] using *m*-chloroperoxybenzoic acid, but this led to a black, viscous, unresolved complex mixture.

Another method of oxidation that was of some interest, was the use of Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) and solid support methods[138, 139]. Support reagents in

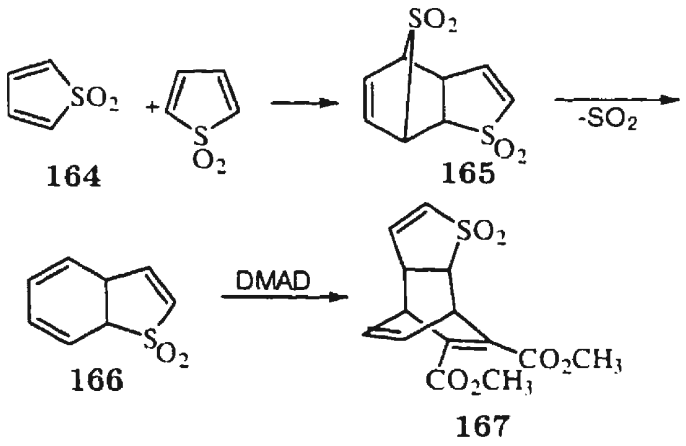
general have been reported to be useful for various oxidations[140-142], such as oxidation of alcohols[143] and cyclic ketones[139]. There have been several reports of the successful oxidation of both alkyl and cyclic sulfides to sulfoxides and sulfones using Oxone in the presence of 'wet' Montmorillonite clay[138], but no reports appear to have been given for substituted thiophenes. Following in the interests of solid-supported reagents, this method warranted some attention as it may provide an alternative and convenient general method for the oxidation of thiophenes. The Montmorillonite clay was prepared according to the literature[138] by the addition of 10% by weight of water, followed by thorough shaking. The resulting 'wet clay' was then added to a solution of **157** in dichloromethane followed by the addition of the oxidizing reagent, Oxone. After stirring for 48 hours at reflux temperature, the oxidized species **161** was not observed by ^{1}H NMR analysis. The reaction was repeated and the solvent was changed to ethyl acetate, but ^{1}H NMR analysis did not indicate the formation of **161**.



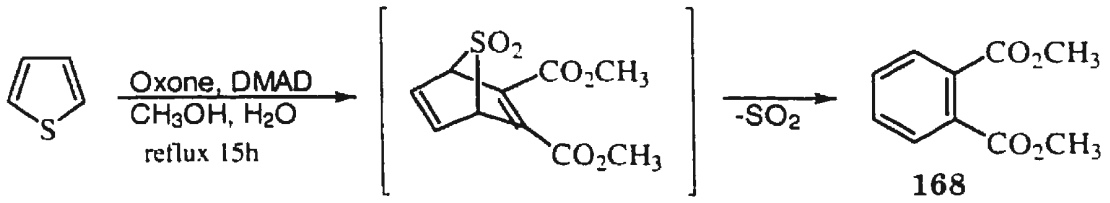
Scheme 52: Possible Dimerization of Oxidized EDT

Further attempts to oxidize EDT using Oxone in aqueous solutions also gave poor results. Although the oxidized species was not directly observed using the described methods of Oxone or *m*-CPBA, this does not necessarily mean that **161** was not formed at some point. In fact, the oxidized species, if formed, may be highly reactive

and, as a result, may quite readily undergo dimerization type reactions (Scheme 52). Thiophene 1,1-dioxides reportedly undergo dimerizations even below room temperature in a manner where one molecule acts as the diene with the other behaving as a dienophile (Scheme 53). The adduct **165** that forms could then spontaneously extrude sulfur dioxide. The resulting 1,3-diene **166** can then undergo further reactions with another dienophile such as DMAD to form **167**[136] (or even another molecule of the thiophene 1,1-dioxide[136]).



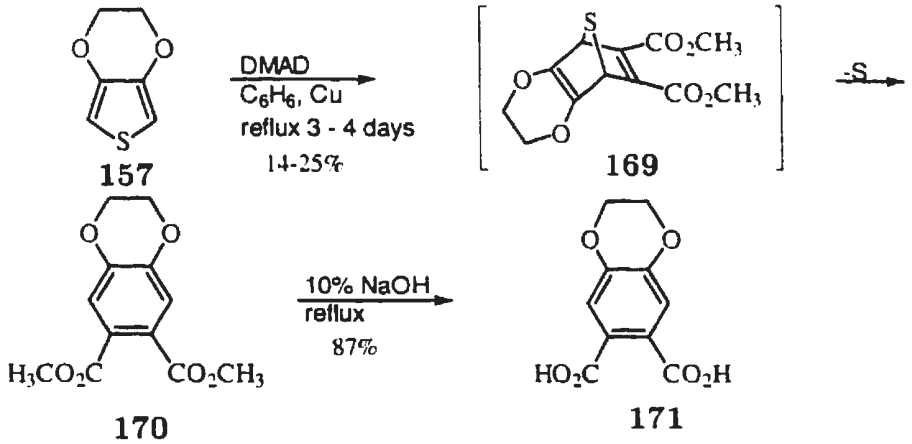
Scheme 53: Dimerization of Oxidized Thiophene and Subsequent Reaction with DMAD



Scheme 54: *In situ* Oxidation of Thiophene and Subsequent Diels-Alder reaction with DMAD

In light of this, oxidation of thiophene itself to the 1,1-dioxide was attempted using Oxone but in the presence of a large excess of DMAD (Scheme 54). It was hoped that

as oxidized thiophene was formed, it would react immediately with DMAD to yield the adduct **168**. This method failed to produce dimethyl phthalate in any detectable amounts. Further investigations into reactions of substituted thiophenes and thiophene 1,1-dioxides in the literature revealed that some substituted thiophenes have indeed been reported to undergo Diels-Alder type reactions. Successful reactions of alkyl-substituted thiophenes with dienophiles such as dicyanoacetylene to form phthalonitriles[103], and DMAD to form dimethyl phthalates[111, 115] have been reported. More recently, reactions of methoxythiophenes with DMAD to form dimethyl phthalates or thienyl fumarates (depending on reaction conditions) have been reported[144]. Based on these recent findings, we were intrigued as to whether EDT **157** would react in a Diels-Alder fashion with DMAD to give the dimethyl phthalate, **170**. The substituted thiophene is speculated to form the bicyclic intermediate **169** upon cycloaddition with DMAD. Collapse of this intermediate leads to the extrusion of sulfur[132], a small stable species, and the reaction becomes irreversible. In addition to this, the formation of a stable benzenoid system is also a most likely contributing driving force.



Scheme 55: Diels-Alder Reaction of EDT **157** and Subsequent Hydrolysis

The reaction (Scheme 55), was carried out in refluxing benzene in the presence of an excess of the dienophile, DMAD, employing adapted literature conditions[144]. The resulting odiferous crude mixture was quite dark and viscous and, although the desired adduct **170** was clearly indicated in this crude mixture by ^{1}H NMR analysis, it was very difficult to isolate.

Depending on the type of substituents on the thiophene ring, there are at least three modes by which the intermediate **169** could collapse: Path A to give back the original starting materials via a retro-Diels-Alder reaction; Path B, collapse to give a new substituted thiophene by a different retro-Diels-Alder reaction; or via Path C to the desired arene through the extrusion of sulfur (Figure 24).

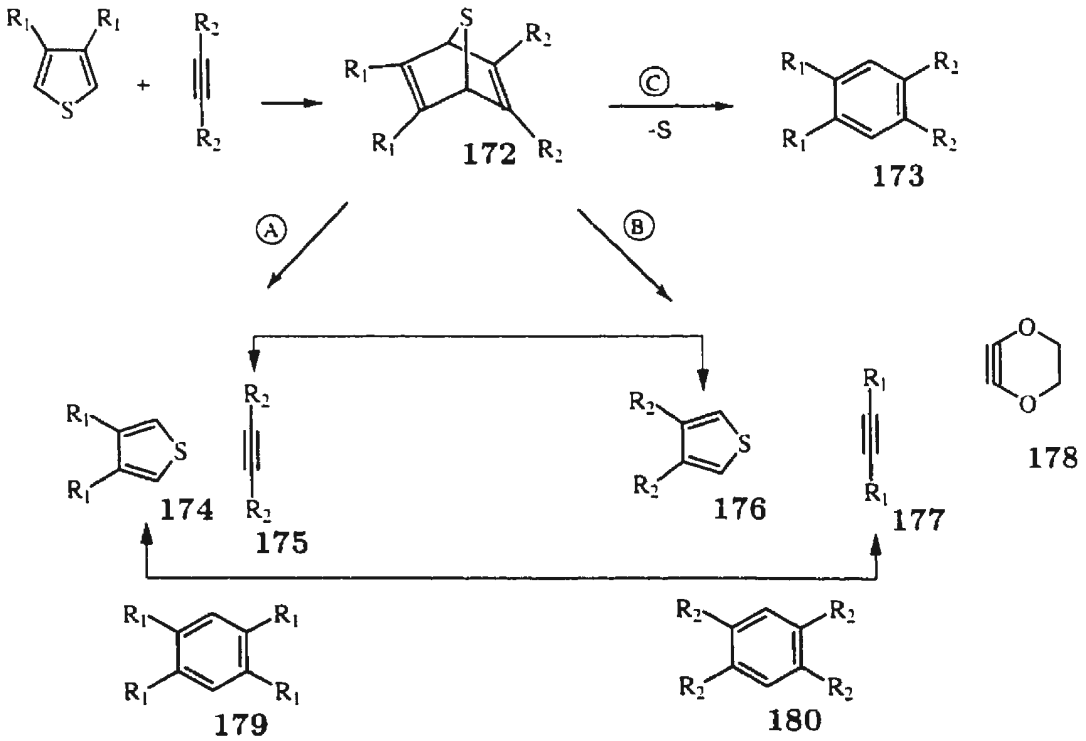
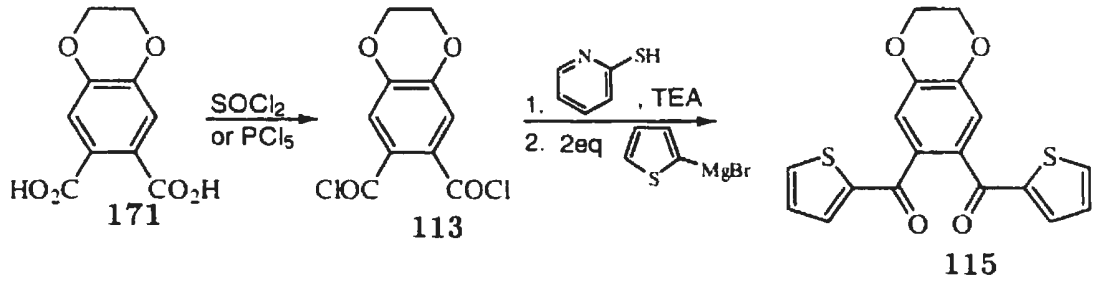


Figure 24: Three Modes of Collapse of the Bicyclic Intermediate **172** and Products Formed

The first mode of collapse (Path A), would not be so disastrous since the original starting materials are obtained, but, in the second case (Path B), this could be a problem for some substituted thiophenes (Figure 24). Combinations of the side products **174** with **177** could lead to the formation of **179** and in a similar fashion, **175** and **176** could also combine to give **180**, complicating the reaction mixture. Note that in the case of EDT as the substituted thiophene, this second mode (Path B) is not as likely to occur since the resulting dieneophile formed **178** would be highly strained.

The extruded sulfur itself is also a potential source for side products by reaction with DMAD. It has been reported that sulfur can react with acetylenic dienophiles[146] and thus the possiblity exists in our case that DMAD may also be reacting with the extruded sulfur to form a 2,3,4,5-tetra(methylcarbonyl)thiophene.



Scheme 56: Future Work for 4,5-Ethylenedioxyphthalic acid

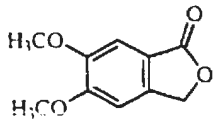
Taking this into consideration, activated copper was added to the reaction mixture as a means of 'mopping' up the sulfur as copper sulfide and aid in the purification process of isolating **170**. Yields for this reaction at this stage are variable 14–25% after purification by column chromatography on silica gel. Examination of **170** by ^{1}H NMR analysis suggested pure compound, but mass spectrometry showed a rather curious peak at m/z 285 which could not be accounted for.

Next, the adduct **170** was hydrolyzed using 10% sodium hydroxide to give the acid **171** in 87% yield. All that remains with this system is the preparation of the phthaloyl dichloride **113** which should be possible with either thionyl chloride or phosphorus pentachloride. Once the preparation of **113** is achieved, the method employed by Kiebooms *et al.*, can be investigated. This will involve conversion of **113** to a thioester from the reaction with 2-mercaptopyridine and subsequent Grignard reaction with 2-bromothiophene (Scheme 56).

4.2 Experimental

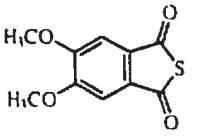
Note, for General Procedures, see Section 2.2.

4.2.0.3 3,4-Dimethoxyphthalide (120)[111]



A solution of 3,4-dimethoxybenzoic acid (26.84 g, 147.3 mmol) and aqueous formaldehyde (37%, 165 mL) that had been saturated with HCl (g) was heated for 7h at 60–70 °C. The resulting mixture was then left to stir overnight. After concentrating the the solution, water was added and the solution was neutralized with aqueous ammonia. The crude product was collected by filtration as a light brown solid. Dry flash column chromatography (neutral alumina, 9% EtOAc/CH_2Cl_2) gave **120** as a colourless solid (11.97 g, 61.64 mmol, 42%): mp 144.0–146.0 °C (lit.[111] 154–156 °C): ^{1}H NMR δ 7.32 (s, 1H), 6.91 (s, 1H), 5.23 (s, 2H), 3.99 (s, 3H), 3.95 (s, 3H); ^{13}C NMR δ 220.6, 152.1, 147.7, 138.3, 114.9, 103.3, 100.7, 66.4, 53.6, 53.5; MS *m/z* (%) 194 (M^+, 52), 165 (100), 95 (12), 77 (13).

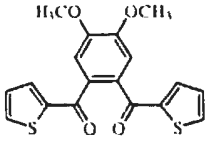
4.2.0.4 3,4-Dimethoxythiophthalic Anhydride (105)[53]



A mixture of 3,4-dimethoxyphthalide **120** (0.54 g, 2.8 mmol) and sulfur (0.45 g, 14 mmol) was melted at 210 °C under a nitrogen atmosphere for 2.5 h. After cooling, chloroform (15 mL) was added and the reaction mixture was filtered. Removal

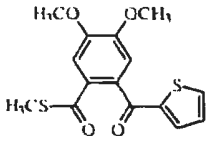
of the solvent by rotary evaporation gave a dark brown solid. Purification by column chromatography (30% hexane/CH_2Cl_2) afforded thiophthalic anhydride **105** as a bright yellow solid (0.12 g, 0.54 mmol, 19%): mp 195.0–195.5 °C (lit.[53] 181.3 °C): ^{1}H NMR δ 7.36 (s, 2H), 4.03 (s, 6H); ^{13}C NMR δ 186.3, 152.0, 130.2, 102.0, 54.0; MS *m/z* (%) 224 (M^+, 100), 164 (74), 136 (90), 93 (30), 78 (11), 62 (15), 50 (40).

4.2.0.5 Attempted Synthesis of 1,2-Dithienoyl-5,6-dimethoxybenzene (106)



A solution of 2-thienyllithium (0.75 M in hexane, 2.0 mL, 1.5 mmol) in THF (5 mL) cooled to 0 °C was added dropwise a solution of thiophthalic anhydride **105** (0.11 g, 0.49 mmol) in THF (7 mL) under a nitrogen atmosphere. The reaction mixture was then stirred at 0 °C for 12 h after which the reaction mixture was quenched with the addition of a saturated solution of NH_4Cl (15 mL). CH_2Cl_2 was added to the mixture and the organic layer was removed and the aqueous layer was extracted with another portion of CH_2Cl_2. The organic extracts were combined, washed with water and dried over anhydrous $MgSO_4$. The solvent was removed by rotary evaporation to the afford crude product as a reddish brown oil. Column chromatography (alumina, CH_2Cl_2 yielded 0.06 g of a red-brown powder. ^{1}H NMR analysis indicated this powder was a mixture of compounds and did not clearly show the presence of **106**: MS of this fraction contained the following peaks: *m/z* (%) 358 (59), 314 (39), 283 (100), 247 (13), 111 (22).

4.2.0.6 1-Thienoyl-2-methylthiacarbonyl-5,6-dimethoxybenzene (108)

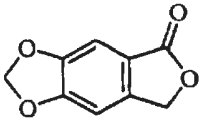


2-Thienyllithium was prepared by treating a solution of 2-bromothiophene (0.13 mL, 1.3 mmol) in THF (15 mL) cooled to -78 °C (acetone/dry ice), with *n*-butyllithium (0.90 M solution in hexane, 1.5 mL, 1.4 mmol) under a nitrogen atmosphere. The resulting solution was stirred for 45 min and added slowly to a solution of **105** (0.30 g, 1.3 mmol) in THF (20 mL) cooled to 0 °C and stirred under a nitrogen atmosphere at 0 °C for 18 h. CH_3I (0.090 mL, 1.4 mmol) was added. The solution was then allowed to warm to rt and after stirring for a further 30 min the reaction was poured in a solution of dilute HCl/ice water (2% HCl). Following the addition of CH_2Cl_2 to the resulting mixture, the organic layer was removed and the aqueous layer was extracted with another portion of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporation of the solvent gave crude **108** as a red-brown oil. Column chromatography on neutral alumina (CH_2Cl_2) afforded **108** as a light pink solid (0.050 g, 0.16 mmol, 12%): mp 121.0-122.0 °C; ^{1}H NMR δ 7.69 (dd, 1H, J=3.6, 1.2 Hz), 7.44 (s, 1H), 7.34 (dd, 1H, J=3.0, 1.2 Hz), 7.08 (dd, 1H, J=3.6, 1.2 Hz), 6.99 (s, 1H), 4.02 (s, 3H), 3.94 (s, 3H), 2.34 (s, 3H); the following signals were observed in ^{13}C spectrum: δ 131.5, 131.3, 125.2, 108.2, 108.0, 53.6, 53.5, 9.5; MS m/z (%) (M^+ not observed), 275 (100), 265 (13), 209 (28), 84 (17).

4.2.0.7 Attempted Synthesis of 1,2-Dithienoyl-5,6-dimethoxybenzene(106) from 108

A solution of 2-thienyllithium in THF (10 mL) was prepared according to the procedure described previously (Section 4.2.0.6) using 2-bromothiophene (0.18 mL, 1.8 mmol), in THF (10 mL) and *n*-butyllithium (2.1 mL, 1.8 mmol). The solution of 2-thienyllithium was added slowly to a solution of crude **108** (prepared according to Section 4.2.0.6) (0.60 g, 1.9 mmol) in THF (40 mL) cooled to 0 °C. The reaction (under nitrogen atmosphere) was left to stir at 0 °C for 12 h. The solution was poured into H_2O (50 mL), CH_2Cl_2 (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvent furnished the crude product as a red–brown oil. Column chromatography (5%EtOAc/CH_2Cl_2) gave a red brown oil (0.20 g); ^{1}H NMR analysis did not indicate clearly the presence of **106**: MS of this fraction contained the following peaks: *m/z* (%): 358 (1), 314 (3), 283 (8), 275 (100) 231 (9), 203 (4), 111 (19).

4.2.0.8 Attempted Synthesis of 3,4-Methylenedioxyphthalide (128)



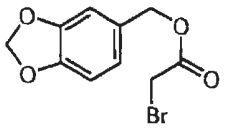
A suspension of piperonylic acid (5.00 g, 30.1 mmol) in aqueous formaldehyde (37 %, 5 mL), that had been saturated with HCl (g), was heated to 70-80 °C for 7 h and then stirred at rt overnight. The mixture was concentrated, poured into water and the resulting mixture was neutralized with aqueous ammonia. A light beige precipitate was filtered (0.05 g), but was found to contain a significant amount of

starting material by ^{1}H NMR analysis.

Reaction was repeated with the addition of concentrated HCl (10 mL). A complex mixture was obtained as observed by ^{1}H NMR analysis.

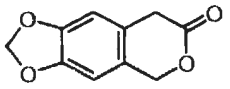
The reaction was repeated with the addition of acetic acid (5 mL); complex mixture was obtained as observed by ^{1}H NMR analysis.

4.2.0.9 Piperonyl bromoacetate (133)



A solution of piperony alcohol (8.07 g, 53.0 mmol) in anhydrous diethyl ether (75 mL) was cooled to 0 °C (ice bath). To the cooled solution, pyridine (4.60 mL, 57.4 mmol) was added dropwise over 10 min. Next, a solution of bromoacetyl bromide (4.10 mL, 46.6 mmol) in anhydrous diethyl ether was added slowly over 30 min and the resulting solution was stirred overnight at rt. The precipitate that had formed was removed by filtration and the filtrate was washed successively with aqueous 1 M HCl, aqueous saturated $NaHCO_3$ solution, then with an aqeous saturated solution of NaCl and dried over anhydrous Na_2SO_4. Removal of solvent following removal of drying agent afforded a pale yellow oil (11.75 g) and purification by dry flash column chromatography with 4% ethyl acetate/CH_2Cl_2 gave a pale amber oil (11.20 g, 41.01 mmol, 88 %): bp 233 °C (starts to decompose at >210 °C). ^{1}H NMR δ 6.84–6.76 (m, 3H), 5.95 (s, 2H), 5.07 (s, 2H), 3.83 (s, 2H); ^{13}C NMR δ 166.9, 147.7, 128.5, 122.5, 109.0, 108.2, 100.9, 67.6, 25.8; MS m/z (%) 273 (M^+, 2.5), 272 (24), 193 (25), 151 (70), 135 (100), 93 (27), 77 (38). HRMS calcd for $C_{10}H_9{}^{79}BrO_4$ 271.96841, found 271.9698.

4.2.0.10 Attempted Syntheses of 3,4-Methylenedioxyhomophthalide (130)

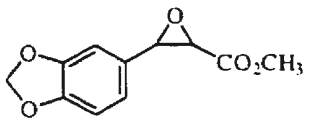


A rapidly magnetically stirred suspension of anhydrous aluminum chloride (0.98 g, 7.4 mmol) in anhydrous CH_2Cl_2 (500 mL) was cooled to 0 °C (ice/water bath) in a flask equipped with a drying tube (containing anhydrous calcium chloride). To the suspension, a solution of **133** (2.00 g, 7.32 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 1.5 h and the reaction mixture was then allowed to warm up to rt. After stirring overnight, the reaction was quenched by pouring into dilute aqueous HCl (*ca.* 1 M) and extracted with several portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were successively washed with aqueous 1 M $NaHCO_3$, then water and subsequently dried over anhydrous $MgSO_4$. Filtration followed by rotary evaporation of solvent furnished a shiny green powder (0.57 g) containing material unidentifiable by ^1H NMR analysis.

The reaction was subsequently repeated using a prepared solution of PPA. Phosphorus pentoxide (P_2O_5) (90.0 g, 634 mmol) was added to flask equipped with a mechanical stirrer and drying tube (containing calcium chloride). The reaction flask was cooled to 0 °C (ice-water bath) and *o*-phosphoric acid(30 mL, 50 g) was added. After stirring for approximately 1 h, the ice bath was replaced with a oil bath and the viscous solution was heated to 105–110 °C for 2 days. Compound **133** was added to the PPA solution, stirred for 30 min at 105 °C and was then poured in *ca.* 200 g ice. The resulting mixture was then extracted several times with CH_2Cl_2, and the combined organic extracts were then washed successively with aqueous 1 M $NaHCO_3$,

followed by water and dried over anhydrous Na_2SO_4. Removal of solvent after filtration gave a brown oil which, analysis by ^1H NMR indicated to be a complex mixture.

4.2.0.11 Attempted Synthesis of 3,4-Methylenedioxy Glycidate (139)



A solution of piperonal (5.40 g, 36.0 mmol), methylbromoacetate (8.26 g, 54.0 mmol) and anhydrous methanol (15 mL) was added over 3 h to a fresly prepared solution of sodium methoxide (prepared from freshly cut sodium (1.43 g, 62.2 mmol) and methanol (25 mL) cooled to -10 °C (ice-salt bath) and stir for 2 h. The reaction solution was then left to stir overnight and slowly warm to rt. The reaction was poured into ice water containing acetic acid (2 mL) and the resulting mixture was transferred to a separatory funnel and was extracted several times with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed once with water and then dried over anhydrous Na_2SO_4. Removal of the solvent, following filtration, yielded a yellow oil of a complex nature by ^1H NMR analysis.

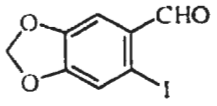
The reaction was repeated using methylchloroacetate (8.31 g, 54.0 mmol) in place of methylbromoacetate, compound **139** was not observed by ^1H NMR analysis.

4.2.0.12 Attempted Synthesis of 3,4-Methylenedioxyphthalide (128) Employing Friedel-Crafts Type Conditions

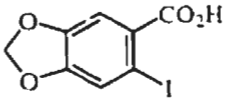
A solution of piperonyl alcohol (1.00 g, 6.57 mmol) in anhydrous CH_2Cl_2 (15 mL) was cooled to -0.5-0 °C (salt/ice bath) in a flask equipped with a dropping funnel, a reflux condenser and a drying tube (containing anhydrous calcium chloride). To the solution was added titanium (IV) chloride (1.20 mL, 10.9 mmol) followed by the

dropwise addition of chloromethyl methyl ether (0.50 mL, 5.5 mmol). The solution was stirred at 0 °C for a further 30 min. The salt-ice bath was removed, and after the solution warmed to rt, the temperature was elevated to 30–35 °C and stirring was continued for an additional 15 min. The crude mixture was transfered to a separatory funnel containing ice (*ca.* 3 g) and the CH_2Cl_2 layer was removed. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed with water and dried over anhydrous $MgSO_4$. Removal of solvent following filtration gave a brown solid (0.35 g). Analysis by ^{1}H NMR revealed a complex mixture.

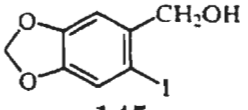
4.2.0.13 Attempted Iodination of Piperonyl Aldehyde, Alcohol and Acid Employing Iodine Monochloride



143



144



145

A solution of iodine monochloride (0.55 g, 3.4 mmol) in acetic acid (5 mL) was added dropwise over 15 min to a rapidly stirring solution of piperonal (0.50 g, 3.3 mmol) in acetic acid (10 mL). After stirring overnight at rt, the resulting dark solution was poured into water (20 mL) and extracted twice with CH_2Cl_2. The combined organic extracts were washed successively with aqueous metabisulphite followed by water and dried over anhydrous $MgSO_4$. Rotary evaporation of the solvent, following filtration, furnished starting material as determined by ^{1}H NMR analysis.

This reaction was repeated on the same scale, but the temperature was elevated to 60-65 °C. Workup as reported above gave only starting material as determined by ^{1}H NMR analysis.

This reaction was repeated on the same scale with both piperonyl alcohol (0.51 g,

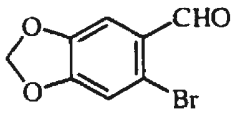
3.4 mmol) with iodine monochloride (0.55 g, 3.4 mmol), and piperonylic acid (0.53 g, 3.2 mmol) with iodine monochloride (0.55 g, 3.4 mmol). Workup as reported above did not result in iodinated products as determined by ^{1}H NMR analysis.

4.2.0.14 Attempted Iodination of Piperonyl Aldehyde, Alcohol and Acid Employing CF_3CO_2Ag and I_2

Iodine (8.18 g 32.2 mmol) was added in small portions to a vigourously stirred suspension of piperonyl alcohol (1.50 g, 9.86 mmol) and silver trifluoroacetate (3.11 g, 14.1 mmol) in chloroform (25 mL). After complete addition of iodine, the resulting dark solution was stirred for 3 h. The reaction mixture was filtered and the filtrate was washed successively with aqueous 20 % sodium thiosulfate, then water and dried over anhydrous $MgSO_4$. Evaporation of the solvent yielded a brown oil. The resulting oil was redissolved in carbon tetrachloride and after treating with activated charcoal was filtered. Evaporation of solvent furnished only starting material as determined by ^{1}H NMR analysis.

The same reaction conditions were carried out on both piperonyl aldehyde (1.49 g, 9.83 mmol) with silver trifluoroacetate (3.11 g, 14.1 mmol) and piperonylic acid (1.63 g, 9.84 mmol) with silver trifluoroacetate (3.11 g, 14.1 mmol). In both cases, the repeated reaction conditions gave only starting materials.

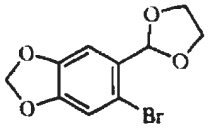
4.2.0.15 6-Bromopiperonal (146)[130]



A solution of bromine (40.0 mL, 770 mmol) in acetic acid (100 mL) was slowly added over 3 h to a solution of piperonal (100 g, 666 mmol) in acetic acid (200 mL)

and the reaction mixture was left to stir overnight. Precipitated 6-bromopiperonal was separated by filtration. The filtrate was mixed with water and the resulting solid was isolated by filtration. The collected solid was then heated in a solution of aqueous 20 % sodium hydrogen sulfite, filtered and the remaining solid was stirred in diethyl ether and filtered once more. The ethereal filtrate was extracted several times with aqueous 20 % sodium hydrogen sulfite and 6-bromopiperonal was recovered from the aqueous extracts upon the addition of Na_2CO_3. Column chromatography (33% hexanes/CH_2Cl_2) of crude product afforded **146** as a colourless solid (35.8 g 156 mmol, 23%): mp 124.5–126 °C (lit.[130] 129.0 °C); ^{1}H NMR δ 10.19 (s, 1H), 7.37 (s, 1H), 7.07 (s, 1H), 6.09 (s, 2H); ^{13}C NMR δ 187.6, 169.0, 150.6, 145.4, 118.8, 110.5, 105.4, 100.0; MS *m/z* (%) 229 (M^+, 98), 228 (100), 201 (26), 143 (20), 120 (19), 90 (16).

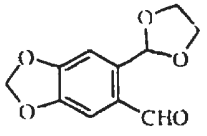
4.2.0.16 1-(2-Bromo-4,5-methylenedioxy)-1,3-dioxolane (147)[131]



6-Bromopiperonal (10.36 g 45.23 mmol) was dissolved in benzene (280 mL) and a catalytic amount of *p*-TsOH (1 mg) and ethylene glycol (5.4 mL) were added. The reaction flask was equipped with a Dean-Stark trap (for the removal of water) and the reaction was refluxed for 17 h was fitted with a Dean-Stark trap and the reaction was refluxed for 17 h. Potassium carbonate (4.0 g) was added in one portion and the resulting mixture was filtered through basic alumina. The solvent was removed using rotary evaporation to afford **147** as a pale colourless oil which solidified upon standing to yield a colourless solid (12.04 g, 44.09 mmol, 97%): mp 65.0–66.5 °C;

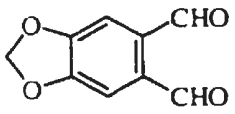
^{1}H NMR δ 7.08 (s, 1H), 7.01 (s, 1H), 6.02 (s, 1H), 5.99 (s, 2H), 4.18–4.03 (m, 4H, AA'BB' system): ^{13}C NMR δ 146.3, 144.7, 127.2, 125.6, 111.1, 110.0, 104.9, 99.8, 99.1, 62.7; MS *m/z* (%) 273 (M^+, 31), 229 (29), 200 (48), 133 (44), 73 (100), 63 (30), 45 (47), 29 (26).

4.2.0.17 6-(1,3-dioxolano)piperonal (148)[131]



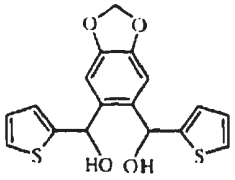
A solution of **147** (4.76 g, 17.4 mmol) in dry THF (50 mL) was cooled to -78 °C (dry ice/acetone bath) and *n*-butyllithium (1.0 M in hexane, 19.0 mL, 19.0 mmol) was added. After stirring for 1 h, dry DMF (3.80 mL) was added and the solution was stirred for an additional 5 h at -78 °C. The solution was slowly warmed to 0 °C and quenched by the addition of an aqueous saturated solution of NH_4Cl. The mixture was transferred to a separatory funnel and the THF layer was removed. The aqueous phase was extracted with several portions of CH_2Cl_2 and the combined organic extracts were dried over anhydrous $MgSO_4$. The removal of the solvent afforded crude **148** as a yellow-orange oil. Purification by column chromatography (30% EtoAc/hexanes) gave **148** as a colourless solid (3.34 g, 15.0 mmol, 86%): mp 62.0–63.5 °C, ^{1}H NMR δ 10.3 (s, 1H), 7.39 (s, 1H), 7.18 (s, 1H), 6.35 (s, 1H), 6.07 (s, 2H), 4.20–4.02 (m, 4H, AA'BB' system): ^{13}C NMR δ 186.4, 149.4, 145.9, 133.9, 126.9, 105.4, 104.1, 99.4, 97.5, 62.6; MS *m/z* (%) 222 (M^+, 10), 194 (29), 149 (100), 121 (14), 63 (33), 45 (25), 29 (21).

4.2.0.18 4,5-Methylenedioxyphthalaldehyde (112)



A solution of **148** (1.04 g, 4.68 mmol), acetone (15 mL) and a catalytic amount of p-TsOH was stirred at rt for approximately 20 h. The resulting solution was then concentrated by rotary evaporation and filtered quickly through neutral alumina (activity grade V) to give a pale yellow solid (0.64 g). This compound, for reasons not exactly known, was unstable and therefore, efforts to purify this compound were unsuccessful. Very rapid decomposition was observed on silica gel. The following signals were observed by ^{1}H NMR analysis: 10.5 (s), 7.81 (s), 6.25 (s).

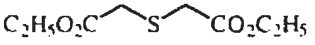
4.2.0.19 Attempted Synthesis of 1,2-Dithienylhydroxy-4,5-methylenedioxybenzene (149)



A solution of 2-thienyllithium, (prepared according to Section 4.2.0.6), from 2-bromothiophene (0.30 mL, 3.1 mmol) and *n*-butyllithium (1.1 M in hexane, 2.7 mL, 3.0 mmol) in THF (10 mL) was cooled to -78 °C (dry ice/acetone bath) and added dropwise to a solution of **112** (0.50 g, 2.8 mmol) in THF (30 mL) cooled to -78 °C. The resulting solution was stirred for 1 h, and a second portion of 2-thienyllithium, (prepared according to Section 4.2.0.6), from 2-bromothiophene (0.30 mL, 3.1 mmol) and *n*-butyllithium (1.1 M in hexane, 2.7 mL, 3.0 mmol) in THF (5 mL) cooled to

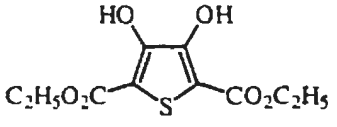
-78 °C, was added slowly and left to stir at -78 °C overnight, and slowly allowed to warm to room temperature. The reaction was quenched by the addition of an aqueous 10% HCl solution, and CH_2Cl_2 was added. The organic layer was separated and the aqueous phase was extracted once with CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$ and removal of the solvent furnished a complex mixture of materials unidentifiable by ^1H NMR analysis.

4.2.0.20 Diethyl thiodiglycate (158)



Freshly prepared Na_2S/Al_2O_3 [85] (60.9 g, 146 mmol) (prepared according to Section 2.3.0.3) was added in one portion to a solution of ethyl bromoacetate (32.4 g, 194 mmol) in absolute ethanol (130 mL) and the suspension was rapidly stirred for 2.5 h under a nitrogen atmosphere. The alumina was removed by filtration and the solvent was removed employing rotary evaporation. The residue was redissolved in CH_2Cl_2 and filtered and removal of the solvent afforded a pale yellow oil. Purification by dry flash column chromatography (alumina, CH_2Cl_2) gave **158** as a pale yellow oil (14.6 g, 71.0 mmol, 73%): ^1H NMR δ 4.13 (q, 2H, J = 7.2 Hz), 3.32 (s, 4H), 1.22 (t, 3H J = 7.2 Hz); ^{13}C NMR δ 166.9, 58.6, 30.8, 11.3; MS m/z (%) 206 (M^+, 16), 160 (74), 133 (42), 105 (51), 88 (20), 77 (51), 60 (24), 47 (29), 29 (100).

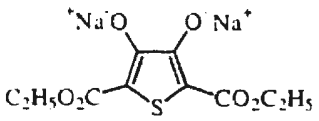
4.2.0.21 2,5-Bis(ethoxycarbonyl)-3,4-dihydroxythiophene (159))



A solution of **158** (24.5 g, 119 mmol) and diethyl oxalate (36.4 g, 249 mmol) in

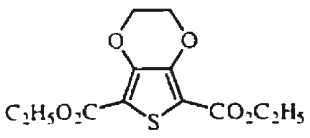
anhydrous ethanol (170 mL) was added dropwise to a freshly prepared ethanolic solution of sodium ethoxide (prepared from sodium (29.0 g, 1.26 mmol) and anhydrous ethanol (130 mL) cooled to 0 °C (ice/water bath). The resulting mixture was gently refluxed for 2 h. The precipitated disodium salt was filtered, rinsed with copious amounts of absolute ethanol, dissolved in water and acidified with aqueous concentrated HCl. The colourless precipitate that formed was filtered and rinsed with water. Drying with gentle warming (50 °C) under high vacuum afforded **159** as a colourless solid which was used without further purification (27.4 g, 106 mmol, 90%): mp 130.0-131.0 °C; ^{1}H NMR δ ^{1}H NMR (D_2O) δ 9.37 (s, 2H), 4.40 (q, 2H, J = 7.2 Hz), 1.40 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 162.9, 117.6, 104.4, 59.1, 11.4; MS m/z (%) 260 (M^+, 33), 214 (100), 186 (14), 168 (82), 100 (70), 72 (14).

4.2.0.22 2,5-Bis(ethoxycarbonyl)-3,4-bis(dioxy)-disodium thiophene (154)[3]



A solution of **158** and diethyl oxalate (36.4 g, 249 mmol) in anhydrous ethanol (170 mL) was added dropwise to a freshly prepared solution of sodium ethoxide (prepared from sodium (29.0 g, 1.26 mmol) and anydrous ethanol (130 mL) cooled to 0 °C (ice/water bath). The resultant mixture was gently refluxed for 2 h. The precipitated disodium salt was filtered off and rinsed with copious amounts of absolute ethanol and dried under high vacuum to yield **154** as a yellow solid (2.86 g, 9.40 mmol, 97%): mp of this solid was not determined, decomposed at temperatures greater than 215 °C; ^{1}H NMR (D_2O) δ 4.06 (q, 2H, J = 7.2 Hz), 1.12 (t, 3H, J = 7.2 Hz); ^{13}C NMR (D_2O/DMSO-$d6$ 233.9, 164.5, 117.6, 57.7, 11.1.

4.2.0.23 2,5-Bis(ethoxycarbonyl)-3,4-ethylenedioxythiophene (160) from 154[3]

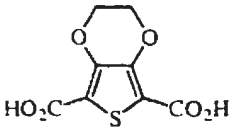


A suspension containing **154** (5.02 g, 16.5 mmol) in 1,2-dichloroethane (60 mL) was refluxed for 24 h. The resulting yellow suspension was filtered to remove unreacted starting material and the residue was washed with several portions of CH_2Cl_2. Removal of the solvent by rotary evaporation and afforded **160** as a light yellow solid (0.14 g, 0.49 mmol, 3%): ^{1}H NMR δ 4.41 (s, 4H), 4.36 (q, 2H, J = 7.2 Hz), 1.37 (t, 3H, J = 7.2 Hz).

4.2.0.24 2,5-Bis(ethoxycarbonyl)-3,4-ethylenedioxythiophene (160)

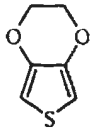
A solution of **159** (20.0 g, 76.9 mmol), triethylamine (40.0 mL) and 1,2-dichloroethane (150 mL) was refluxed overnight.(approximately 15 h.) Most of the solvent was removed by rotary evaporation and, following the addition of CH_2Cl_2 (150 mL), undissolved solid was removed by filtration. The filtrate was washed successively with aqueous 2M HCl, water and dried over anhydrous Na_2SO_4. Removal of the solvent gave **160** as a colourless solid which was used without further purification (21.0 g, 73.3 mmol, 95%): mp 116–118 °C; ^{1}H NMR δ 4.41 (s, 4H), 4.36 (q, 2H, J = 7.2 Hz), 1.37 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 158.1, 142.2, 109.1, 62.0, 58.6, 11.5; MS m/z MS (%) 286 (M^+, 5), 260 (32), 241 (8), 214 (100), 186 (13), 169 (34), 146 (13), 100 (74), 85 (13), 69 (16), 45 (29).

4.2.0.25 3,4-Ethylenedioxythiophene-2,5-dicarboxylic acid (156)[3]



A suspension of **160** (21.0 g, 73.3 mmol) in 10% sodium hydroxide solution (200 mL) was heated to reflux for 2 h. After cooling to room temperature, the reaction solution was filtered and acidified with aqueous concentrated HCl. The precipitate was collected by filtration and washed with copious amounts of water. Drying by gentle heating (50 °C) under high vacuum, gave **171** as a light brown solid (14.7 g, 63.9 mmol, 87%). Purification by recrystallization (methanol) yielded a colourless solid: mp of this solid was not determined, decomposition occurred at temperatures greater than 200 °C: ^{1}H NMR (D_2O-NaOD) δ 4.13 (s, 4H); ^{13}C NMR D_2O/NaOD/DMSO-*d*6) δ 194.5, 163.0, 137.3, 59.3; MS *m/z*(%) 230 (M^+, 38), 186 (93), 142 (40), 90 (21), 69 (30) 44 (100).

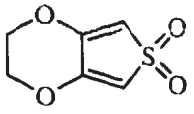
4.2.0.26 3,4-Ethylenedioxythiophene (157)[3]



To a suspension containing **171** (2.0 g, 8.7 mmol) in freshly distilled quinoline (20 mL) barium promoted Cu-Cr (0.80 g) was added. The reaction mixture was then heated at 180 °C for 0.5 h under a nitrogen atmosphere. After cooling to rt, diethyl ether (50 mL) was added and the catalyst was removed by suction filtration. The filtrate was washed successively with aqueous 1 M HCl, aqueous 1 M NaOH, water and finally dried over Na_2SO_4. Removal of solvent yielded crude **157** as a brown oil.

Purification by dry flash column chromatography (toluene) afforded **157** as a pale amber oil (0.76 g, 5.3 mmol, 61%): bp 206 °C; ^{1}H NMR δ 6.34 (s, 2H), 4.20 (s, 4H); ^{13}C NMR δ 139.0, 96.9, 61.9; MS *m/z* (%) 142 (M^+, 100), 127 (11), 116 (17), 69 (29).

4.2.0.27 Attempted Synthesis of 3,4-Ethylenedioxythiophene-1,1-dioxide (161) Employing *m*-CPBA



A solution of **157** (0.39 g, 2.7 mmol) and *m*-CPBA (1.2 g, 7.0 mmol) was dissolved in hot 1,2-dichloroethane (15 mL) and refluxed for 48 h. Precipitated *m*-chlorobenzoic acid was removed by filtration and the filtrate was washed several times with aqueous 10% Na_2CO_3 followed by water. The organic layer was dried over anhydrous Na_2SO_4 and evaporation of the solvent afforded a complex mixture as determined by ^{1}H NMR analysis.

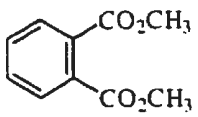
4.2.0.28 Attempted Synthesis of 3,4-Ethylenedioxythiophene (161) Employing Oxone and 'Wet' Montmorillonite Clay

To a suspension containing Oxone, (2.71 g, 4.40 mmol), CH_2Cl_2 (10 mL) and "wet clay" (prepared by the addition of 2 mL of deionized water in 8 portions with vigorous shaking) **157** (0.25 g, 1.8 mmol) was added in one portion. After stirring under a nitrogen atmosphere at rt for 1.5 h, the reaction mixture was filtered to remove the clay which was washed with several portions of CH_2Cl_2. Rotary evaporation of the solvent furnished unidentifiable material as determined by ^{1}H NMR analysis

The reaction was repeated on the same scale and the solvent was changed to EtOAc, but workup and removal of solvent furnished material unidentifiable by ^{1}H

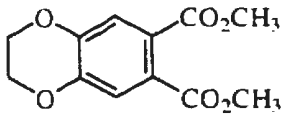
NMR analysis.

4.2.0.29 Attempted Synthesis of 1,2-Bis(methoxycarbonyl)benzene (168)



To a solution of Oxone (6.39 g, 10.4 mmol) in water (12 mL), a solution of thiophene (0.25 g, 3.0 mmol) and DMAD (6.36 g, 10.4 mmol) in methanol (20 mL) was added dropwise. The resulting suspension was refluxed for 15 h. Filtration of the remaining solid and removal of solvent by rotary evaporation yielded a complex mixture as determined by ^{1}H NMR analysis.

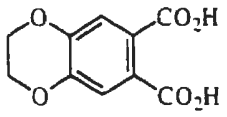
4.2.0.30 4,5-Ethylenedioxy dimethylphthalate (170)



A suspension of **157** (2.67 g, 18.8 mmol), DMAD (7.98 g, in xylenes (90 mL) and copper (activated by washing with aqueous 1 M HCl followed by rinsing with diethyl ether and drying under vacuum) (2.30 g) was refluxed for 4 days. The reaction mixture was filtered and removal of the solvent yielded a dark red-brown oil. Purification by column chromatography (100:10:1 CH_2Cl_2:EtOAc:acetic acid) afforded **170** as a pale yellow solid (1.16 g, 4.60 mmol, 25%); recrystallization from hexanes afforded **170** as a colourless solid: mp 60.0–61.5 °C; ^{1}H NMR δ 7.23 (s, 2H), 4.30 (s, 4H), 3.87 (s, 6H); ^{13}C NMR δ 164.7, 142.7, 122.8, 115.7, 61.7, 49.7; MS *m/z* (%) 285 (9), 252 (M^+, 33), 221 (100), 191 (4), 162 (5), 134 (3), 107 (3). HRMS calcd for $C_{12}H_{12}O_6$

252.06330, found 252.0638.

4.2.0.31 4,5-Ethylenedioxyphthalic acid (171)



A suspension of **170** (1.42 g, 5.63 mmol) in 10% sodium hydroxide solution (40 mL) was heated to reflux for 1 h. The reaction solution was filtered and the filtrate was acidified with concentrated HCl. Precipitated **171** was collected by suction filtration and washed with copious amounts of water and dried by gentle heating (50 °C) under high vacuum. Compound **171** was obtained as an off-white solid (1.12 g, 5.00 mmol, 89%). Recrystallization ($MeOH/H_2O$) furnished **171** as a colourless solid: mp 223-224 °C; ^1H NMR (DMSO-*d*6) δ 7.63 (s, 2H), 4.27 (s, 4H), $CO_2\underline{H}$ not observed; ^{13}C NMR (DMSO-*d*6) δ 165.6, 142.4, 124.0, 115.1, 61.9; MS *m/z* (%) 224 (M^+, 2), 162 (79), 134 (86), 50 (100). HRMS calcd for $C_{10}H_8O_6$ 224.03202, found 224.0307.

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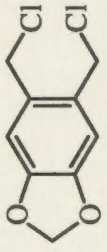
Appendix

The selected ^{1}H spectra of the synthetic examples were arranged according to the order in which they appear in the text. For the intruments, see **General Procedures** in Section 2.2.



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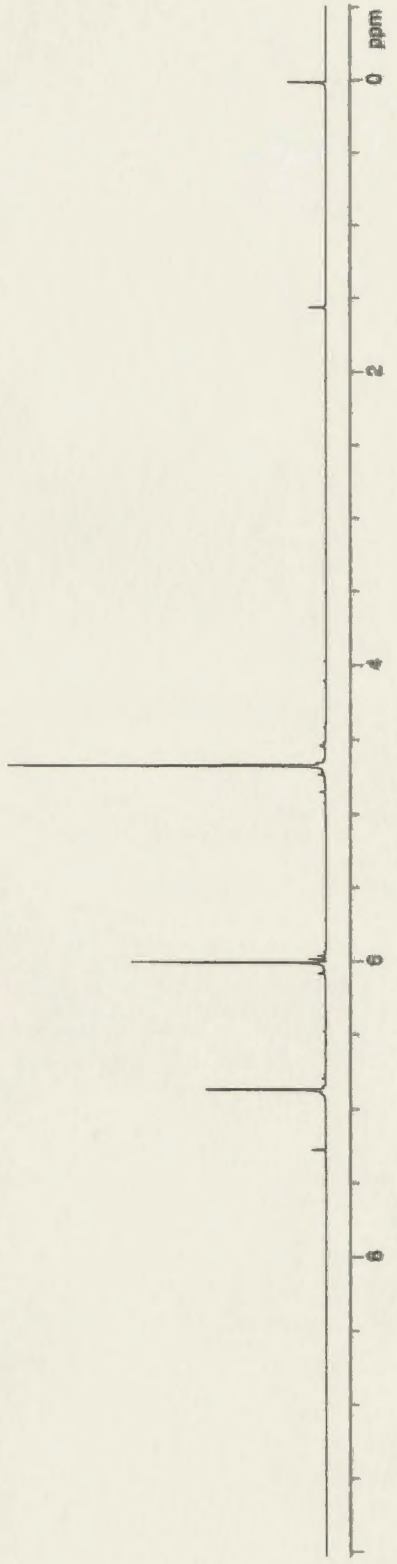

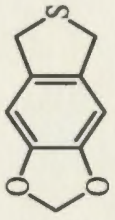

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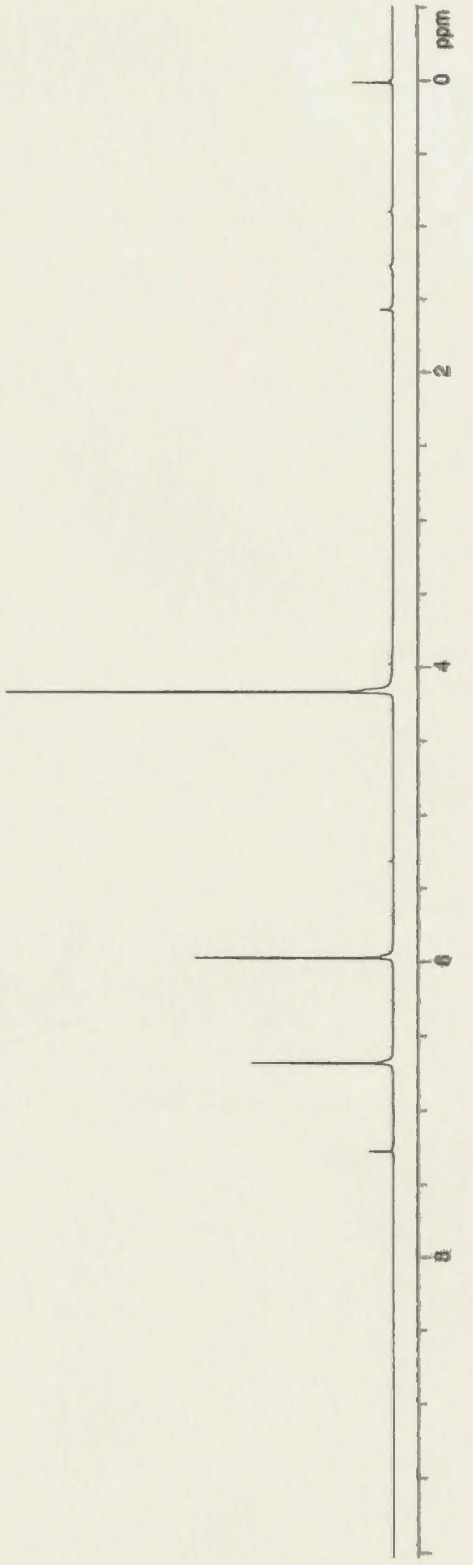

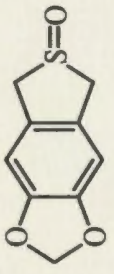

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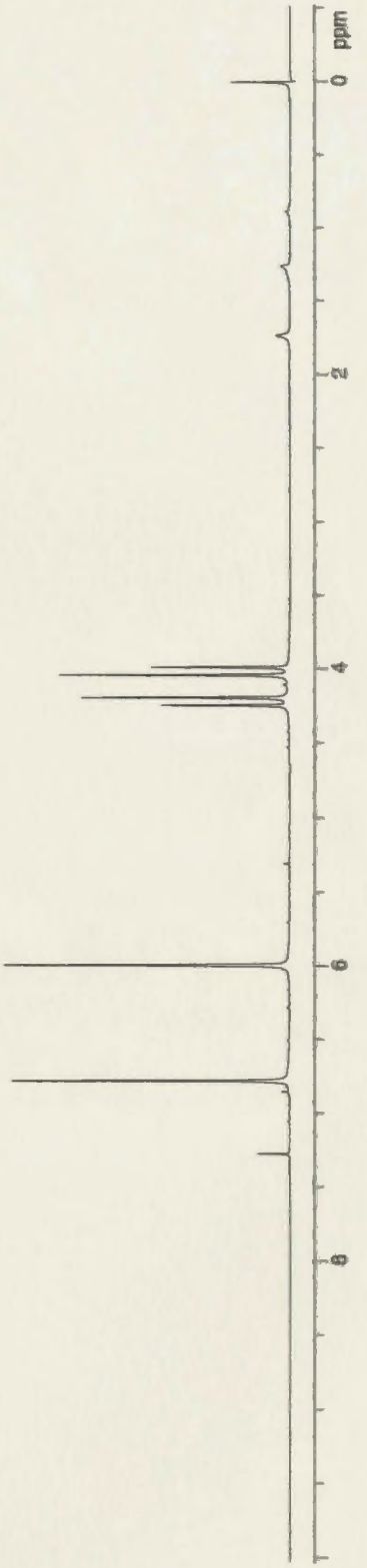

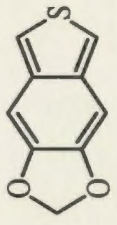

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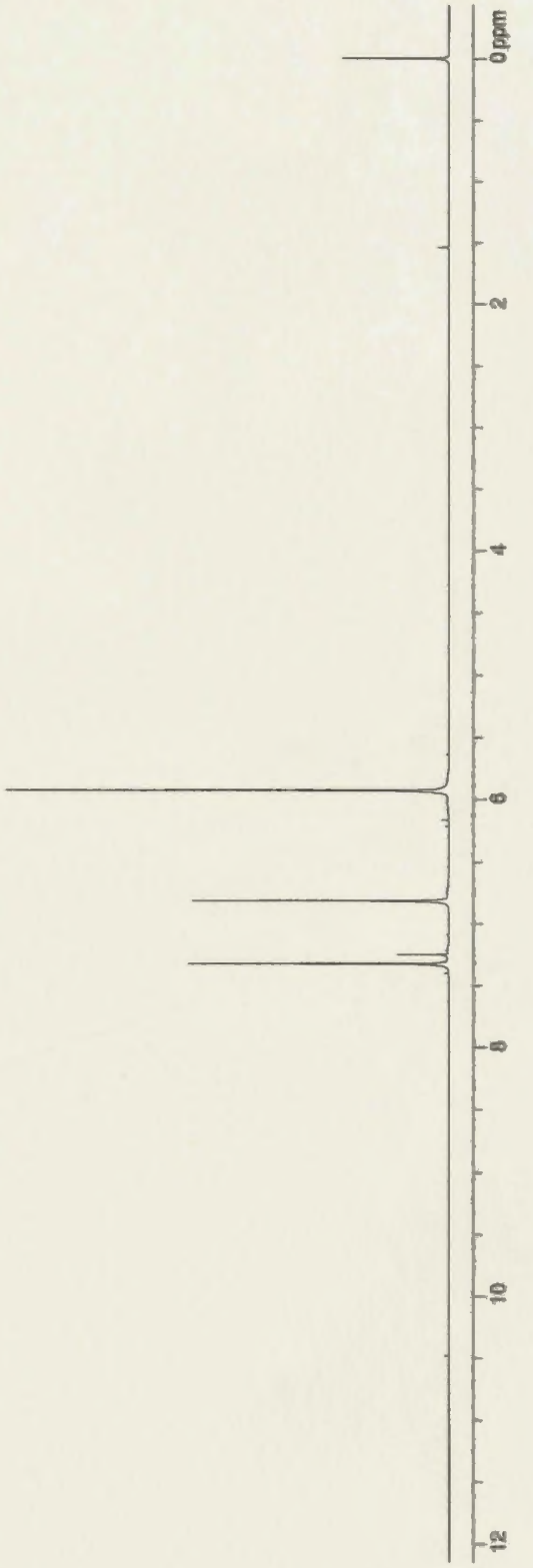

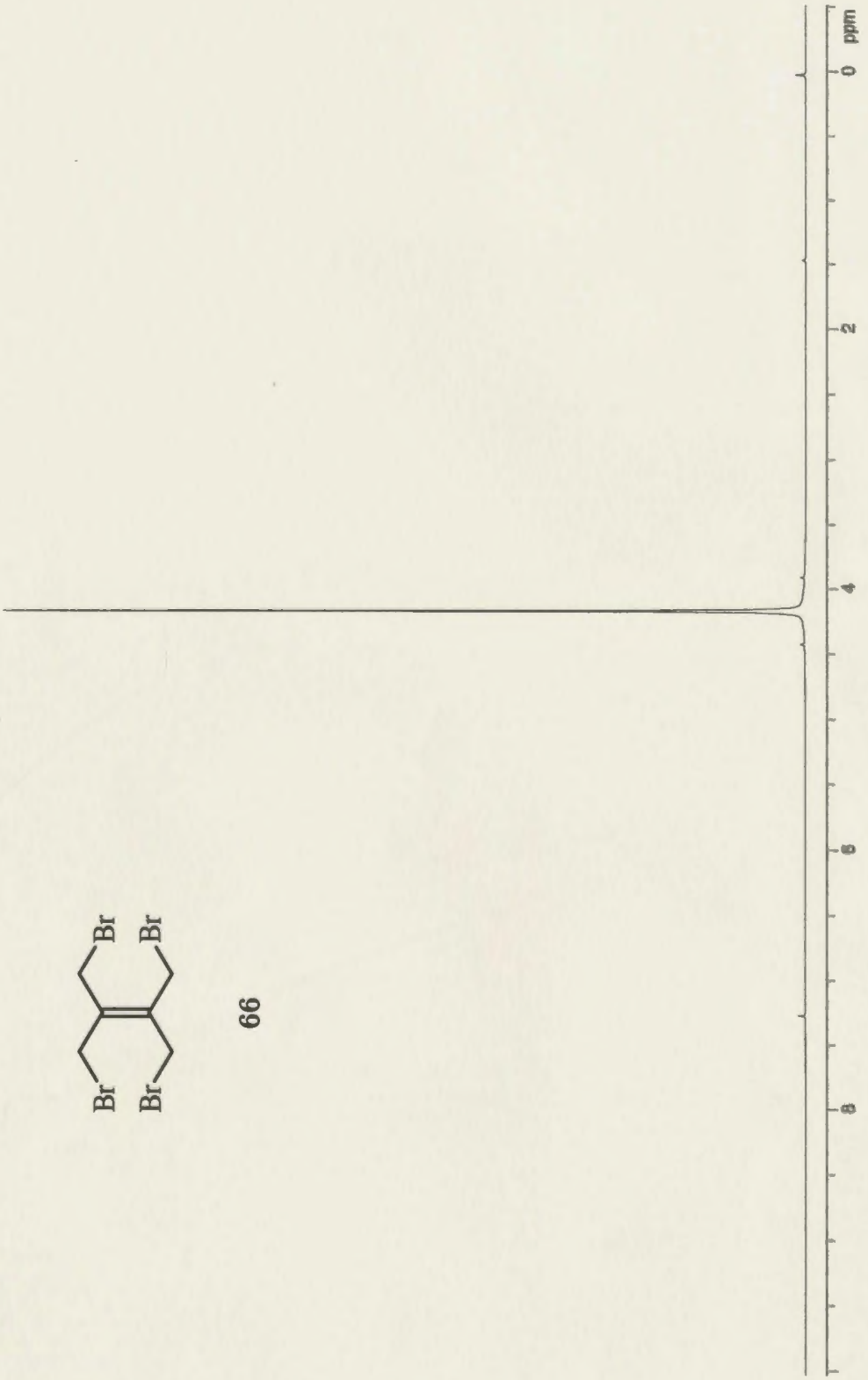

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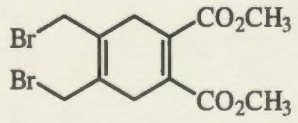

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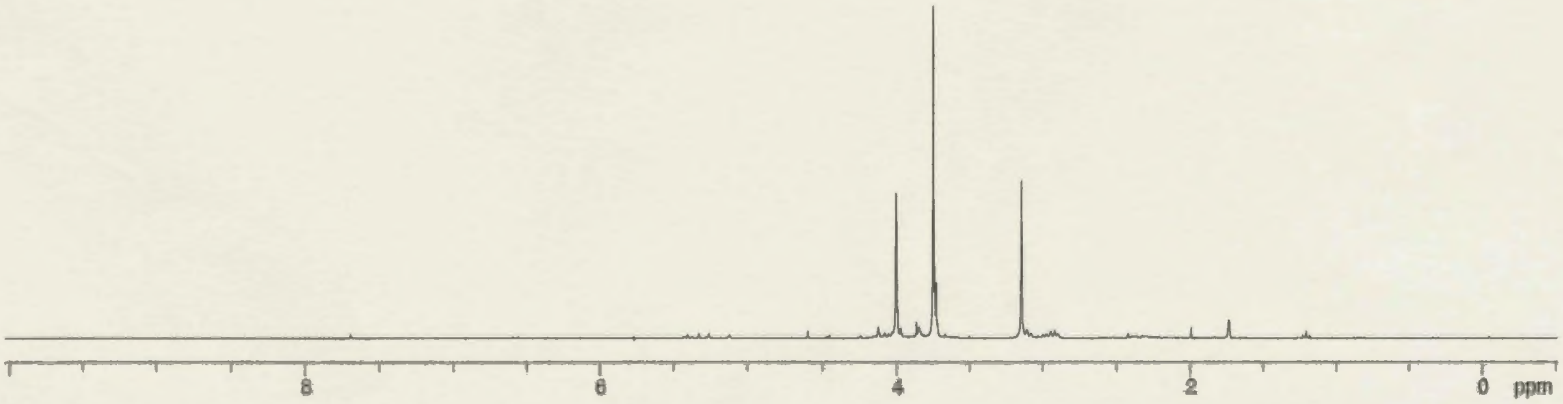

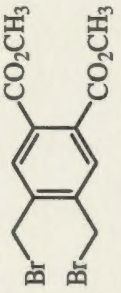

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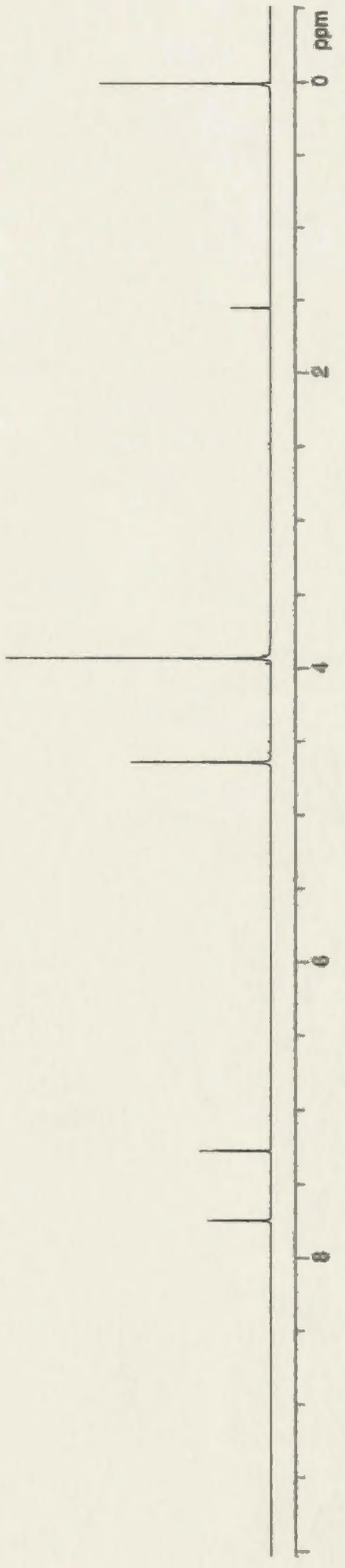

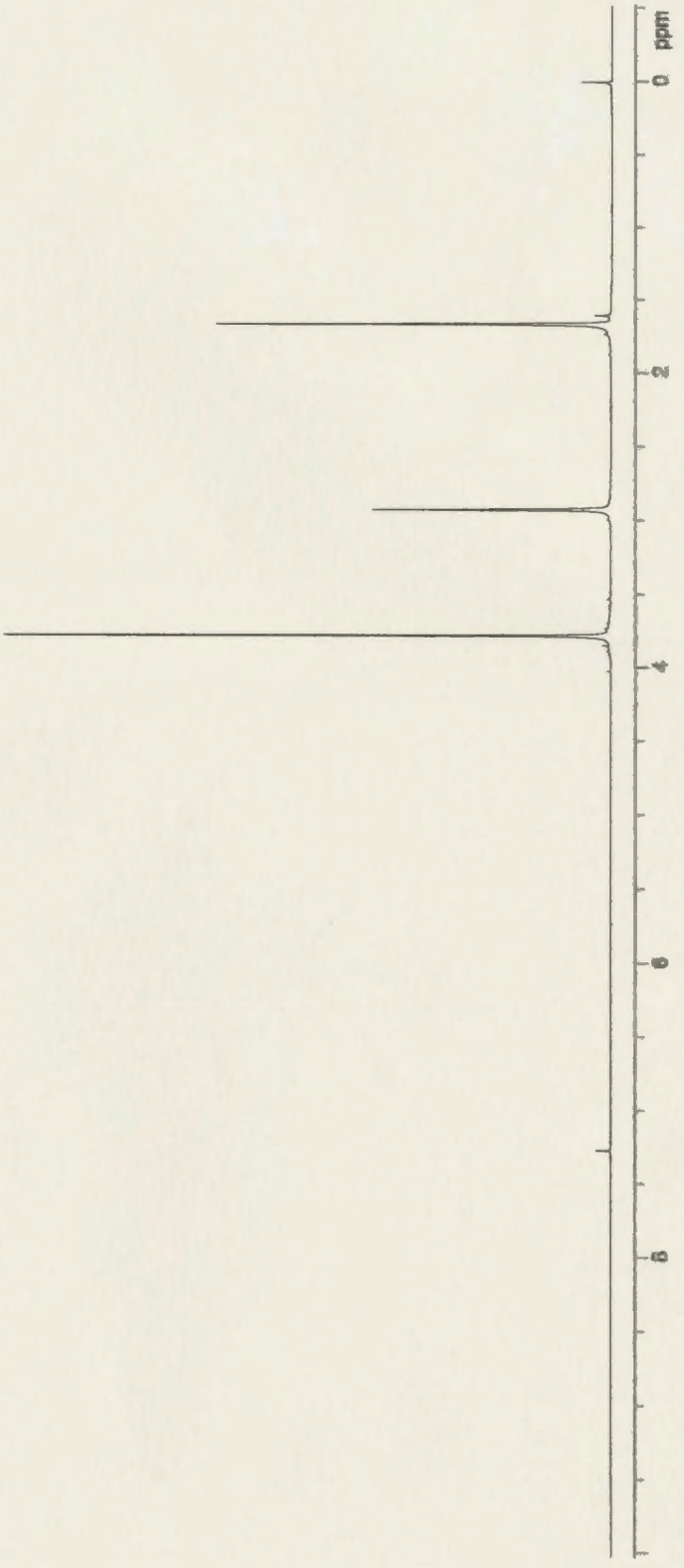

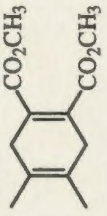

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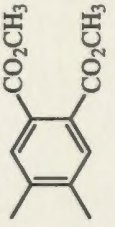

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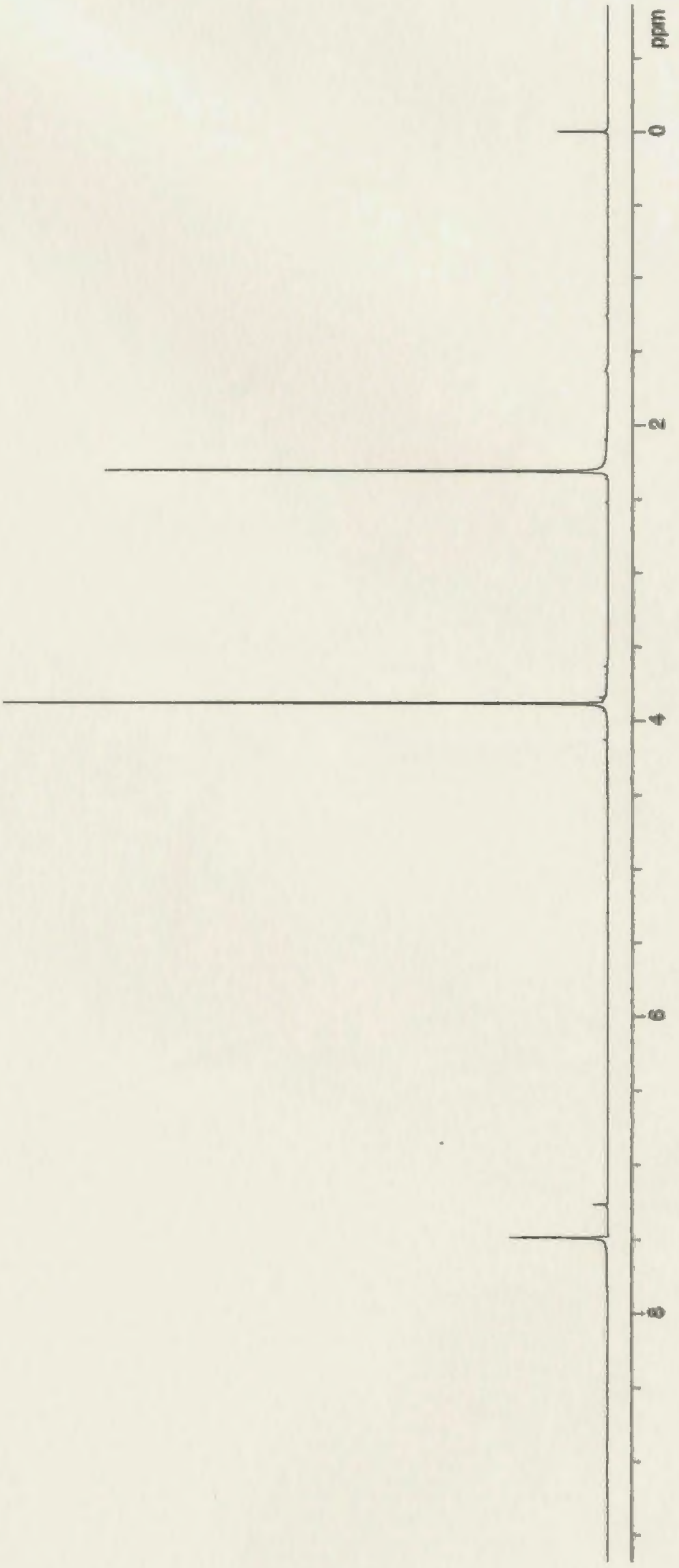

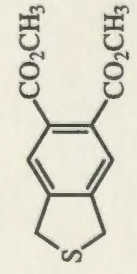

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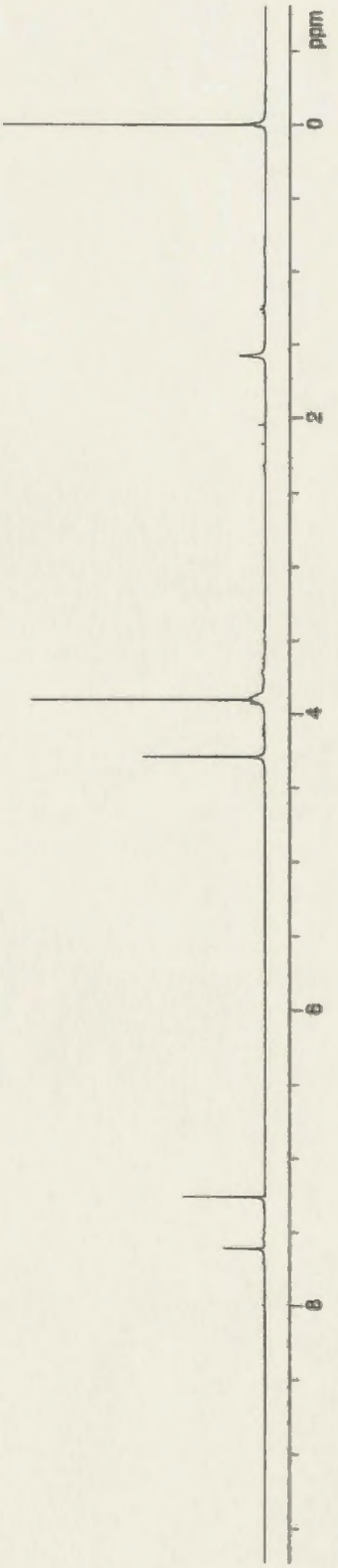

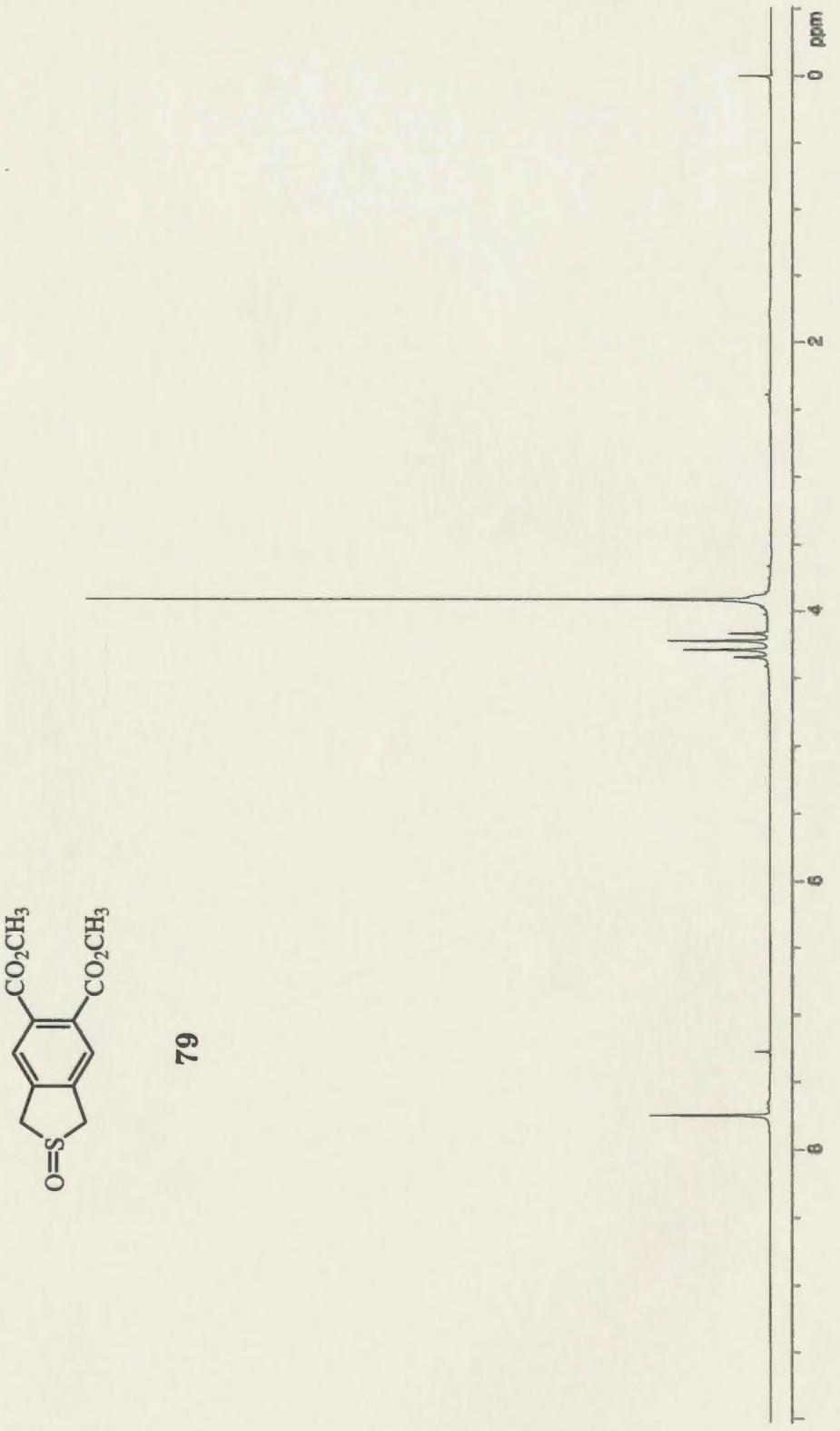

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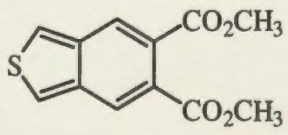

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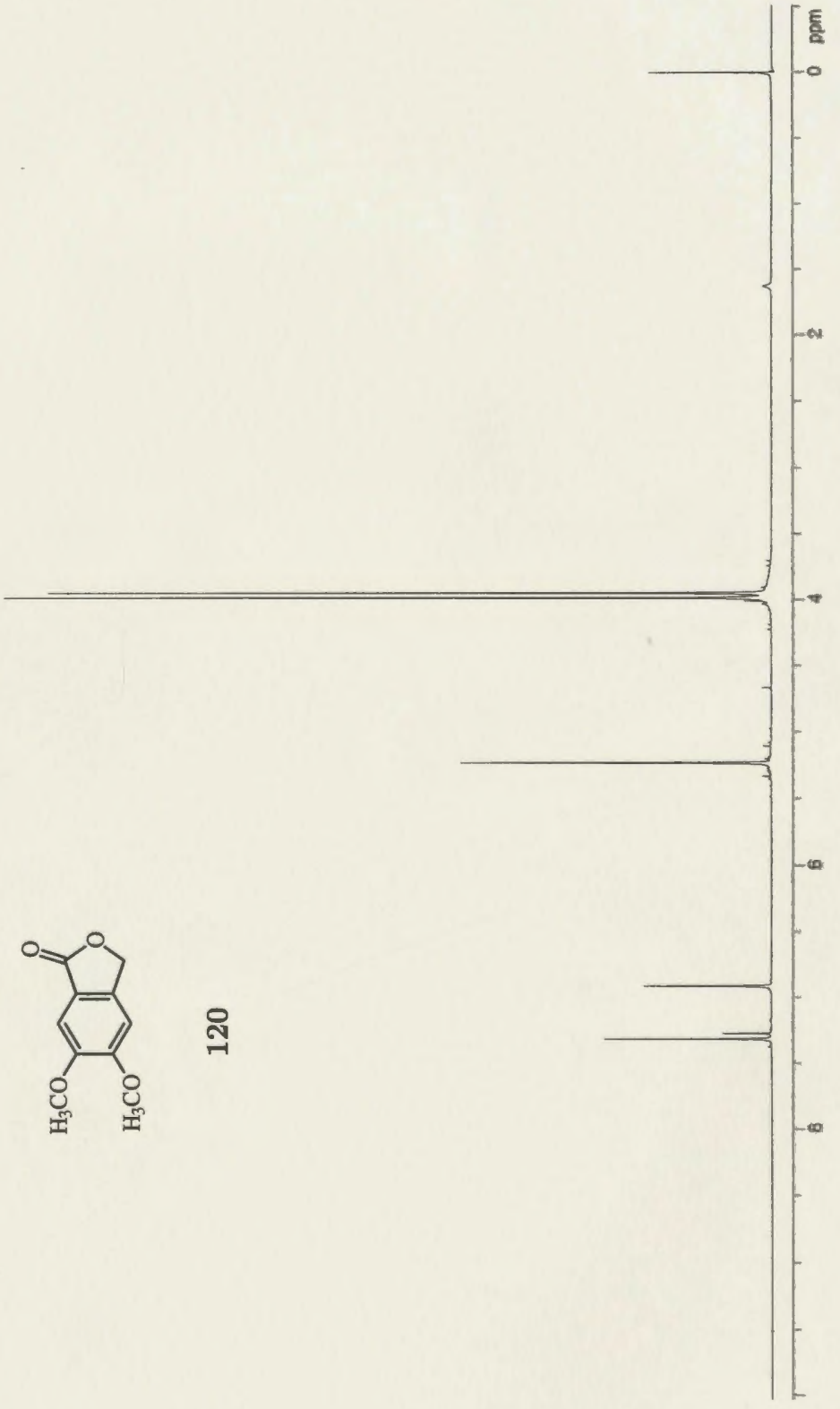

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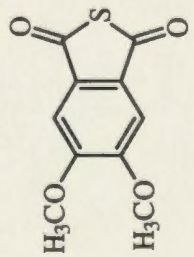

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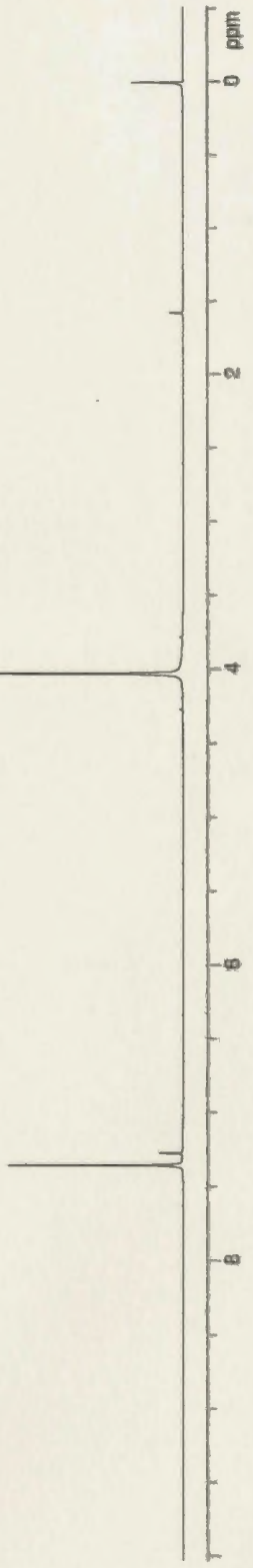

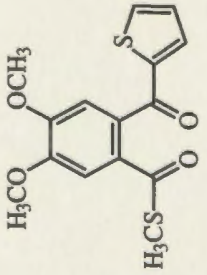

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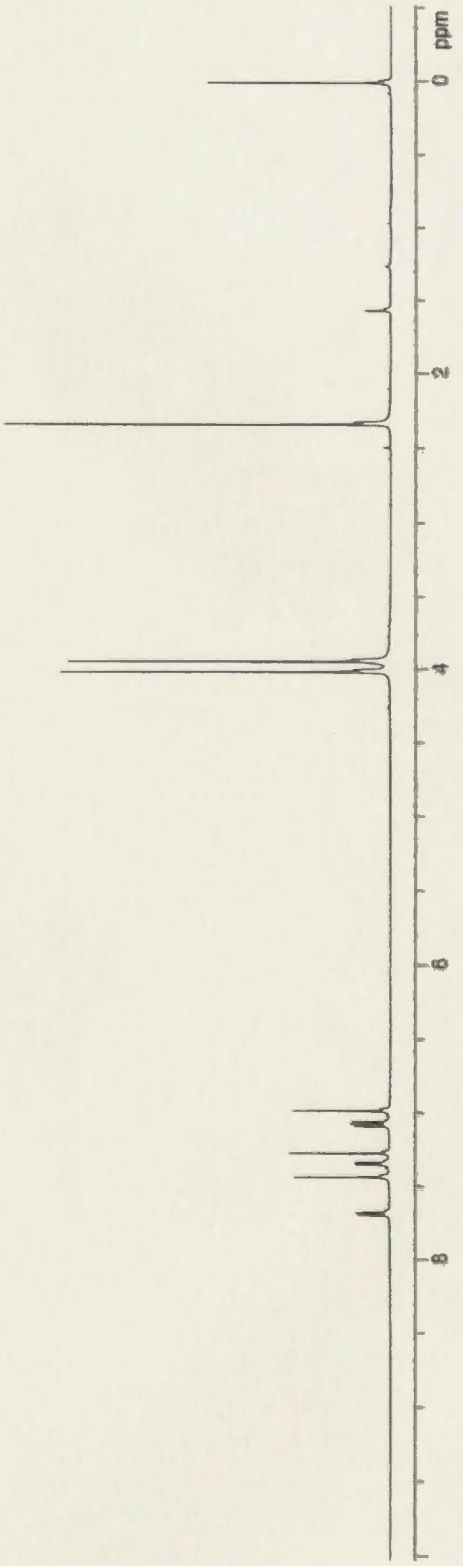

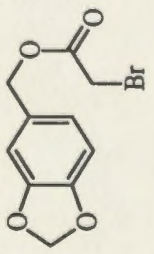

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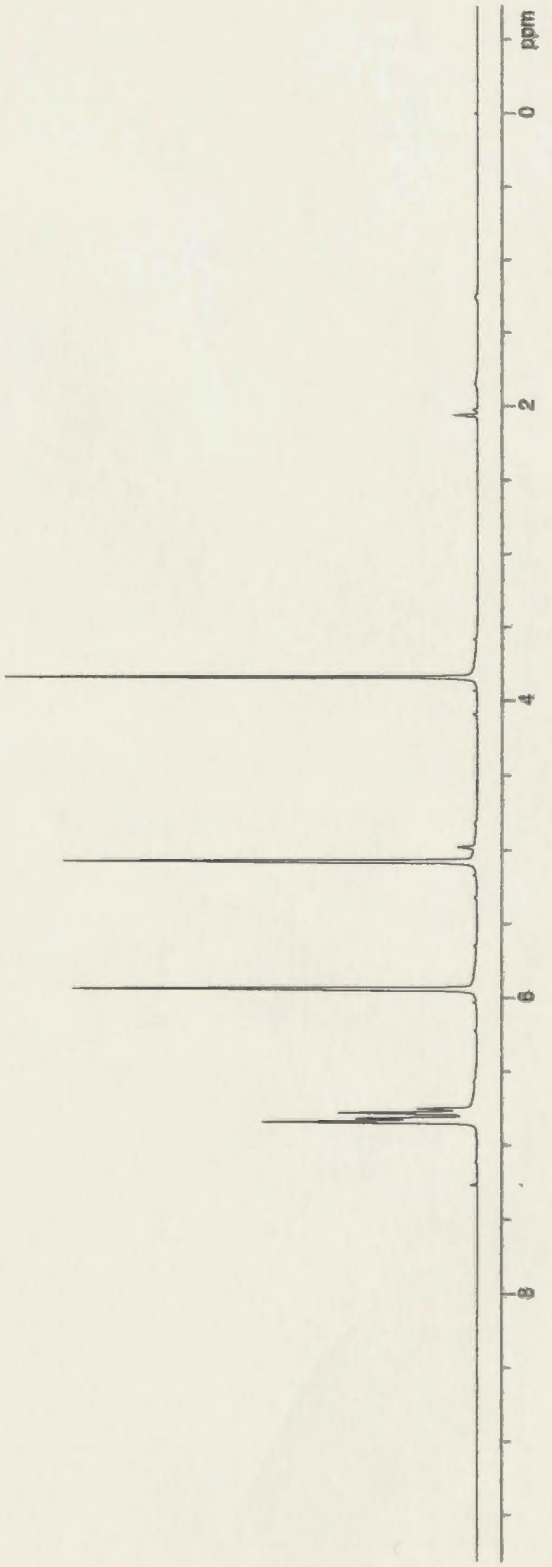

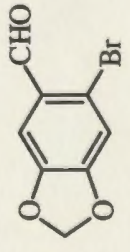

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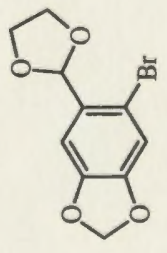

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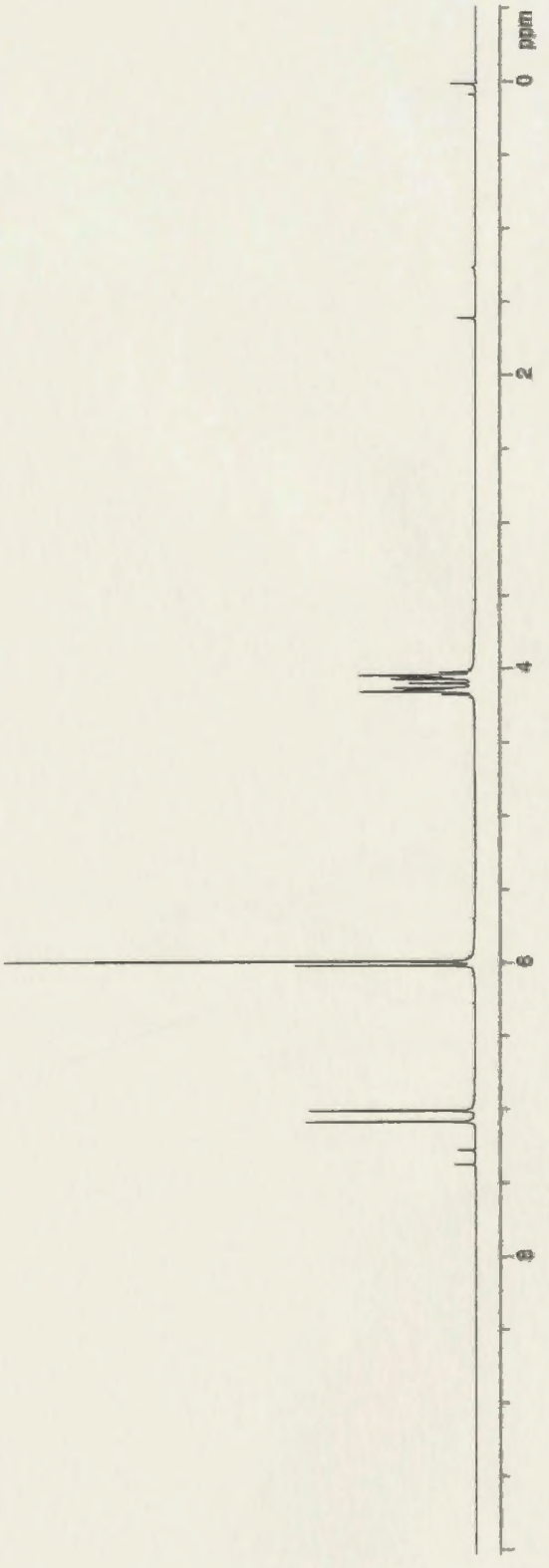

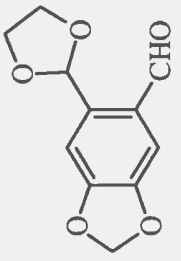

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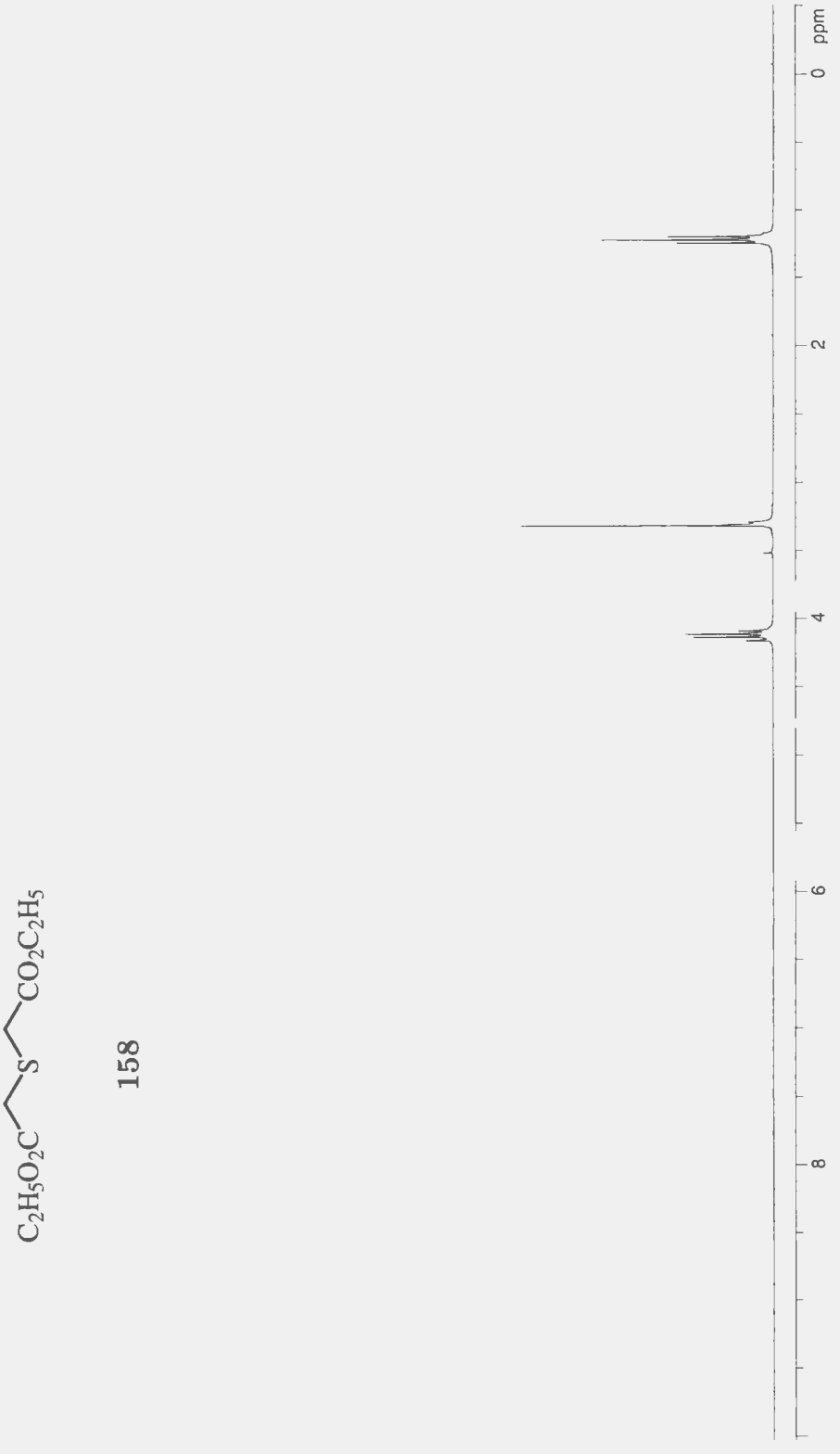
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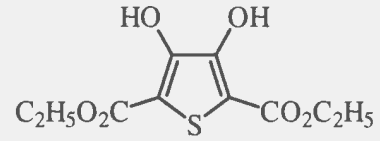

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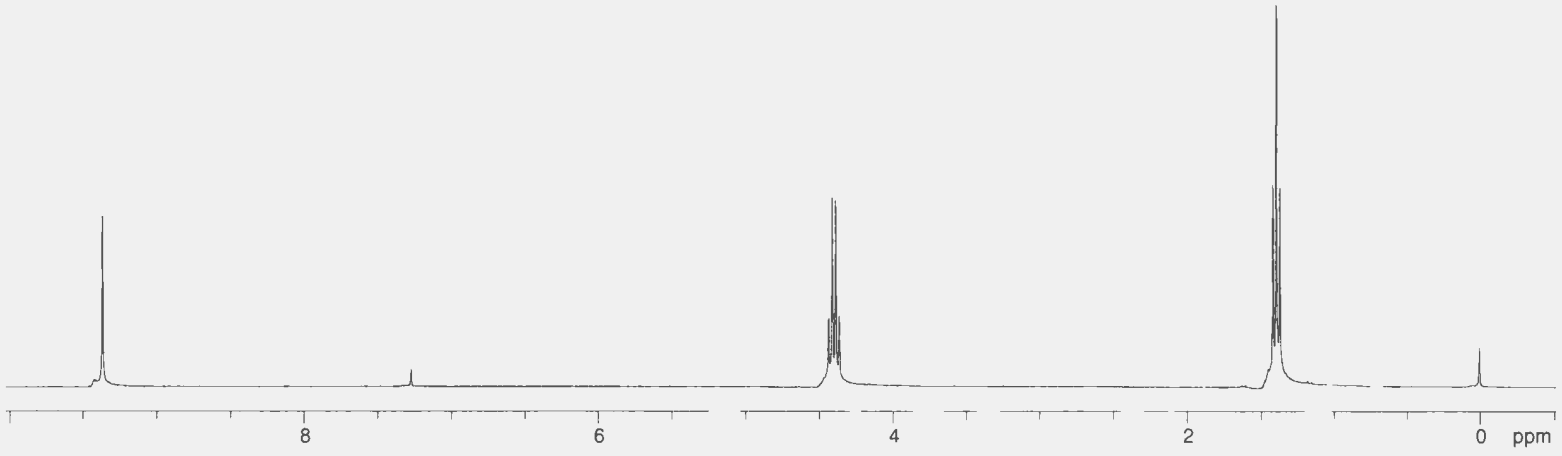

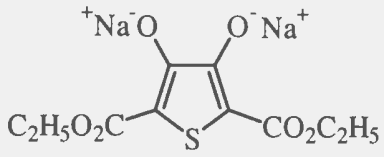

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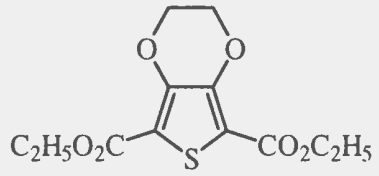

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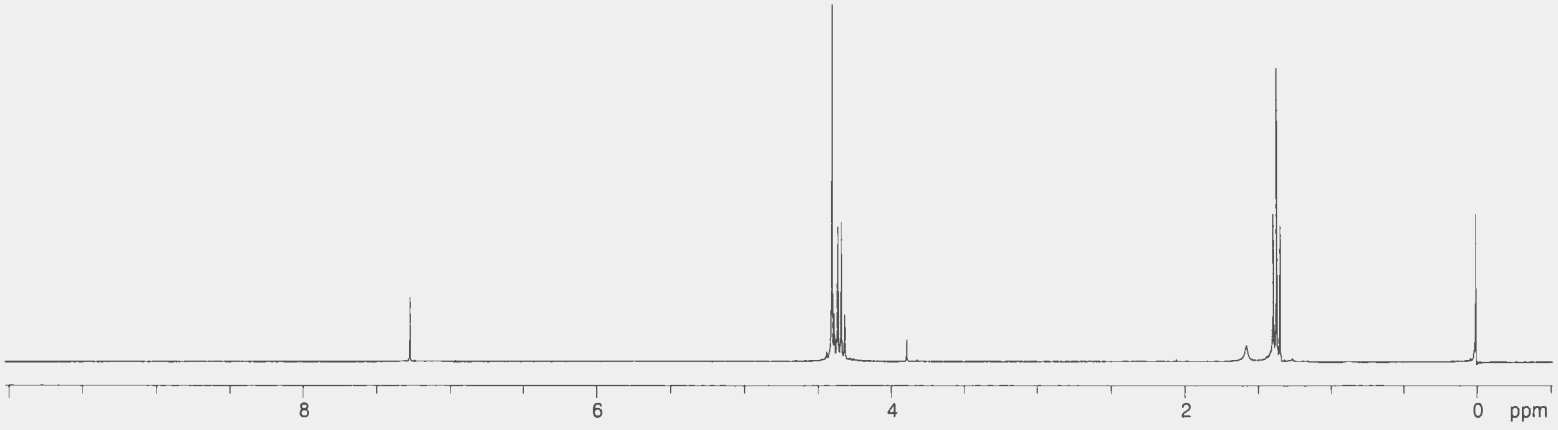

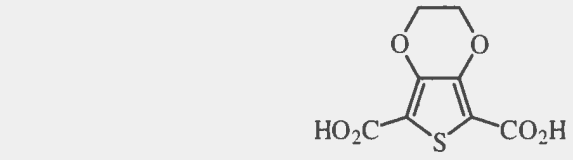

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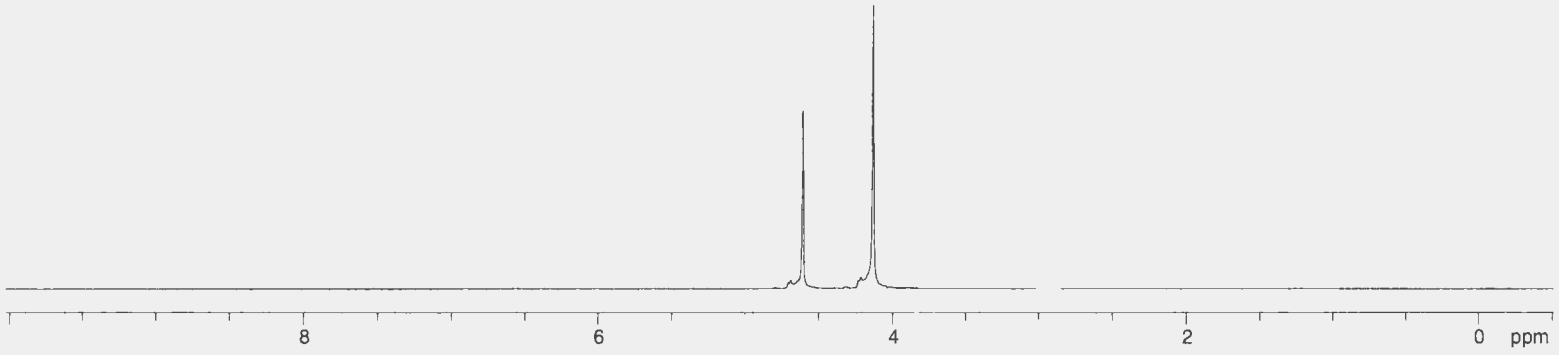

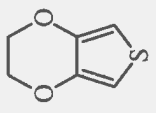

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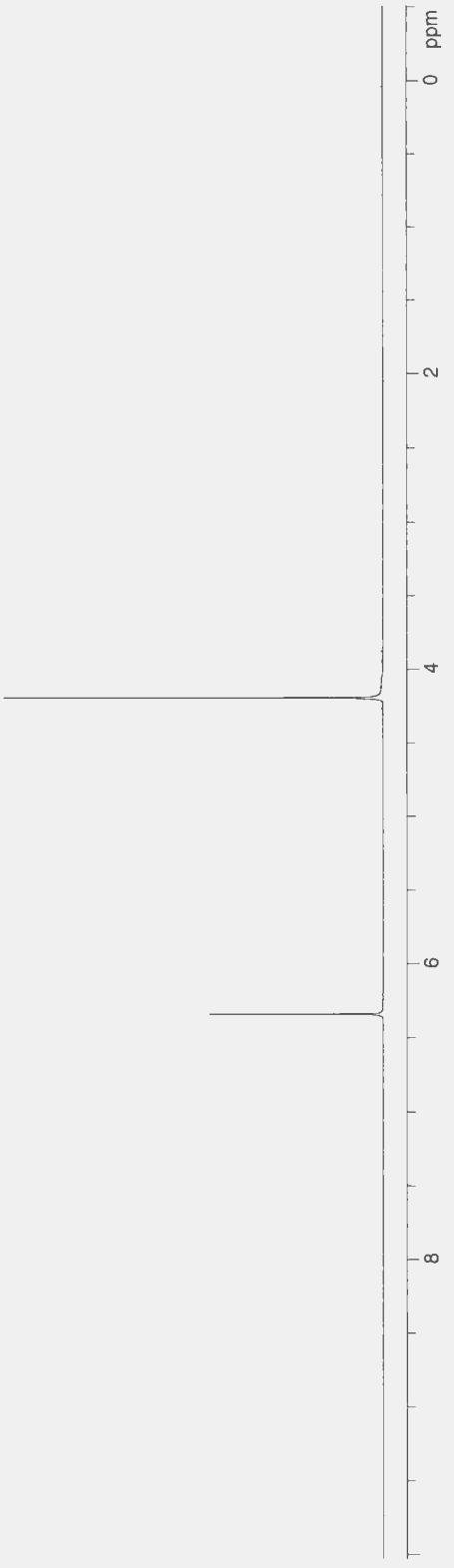

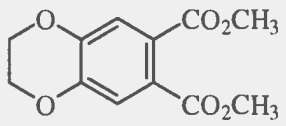

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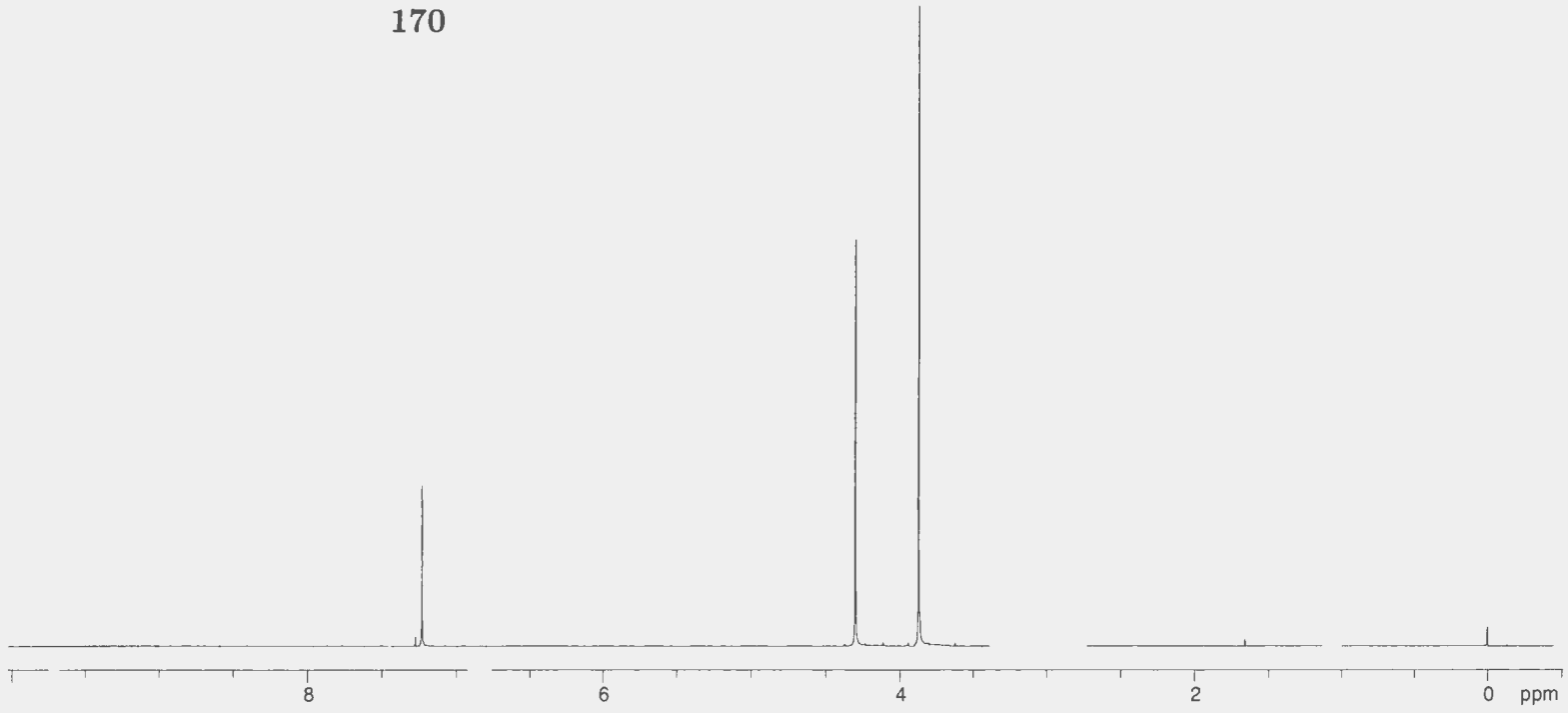

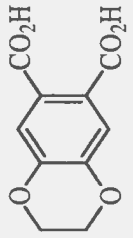

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