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School of Chemistry

STUDIES IN THIOPHENE CHEMISTRY FOR ORGANIC ELECTRONIC MATERIALS

by

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Abstract

Thiophene-based organic semiconductor materials have seen important growth in the last two decades owing to their potential applications in many different areas. Overall, this thesis details attempts to develop rapid, efficient, cheap and scalable syntheses of small molecules and monomers of thiophene-based molecules.

After an introductory Chapter, the second Chapter in this thesis focuses on the synthesis of 7-R-anthra[2,3-*b*]thiophenes derivatives **11a-d** (R = H, Me, *i*Pr, OMe) and naphtho[2,3-*b*:6,7-*b'*]dithiophene **12**. Existing synthetic methods for the known anthra[2,3-*b*]thiophene **11a** and naphtho[2,3-*b*:6,7-*b'*]dithiophene **12** require multi-steps, toxic reagents, expensive starting materials and give low yields. However, we prepared these 7-R-anthra[2,3-*b*]thiophene derivatives **11a-d** (R = H, Me, *i*Pr, MeO) in only three steps (with average overall yields of >50%) starting from (*E*)-4-RC₆H₄CH₂(HOCH₂)C=Cl(CH₂OH). The latter are commercial or readily prepared from 2-butyne-1,4-diol **1** and ArCH₂Cl **4** (both typically costing <4 pence /g) at 10 g scales. These procedures allow selective formation of (otherwise unattainable) higher solubility 7-substituted. Similar methods allowed the preparation of naphtho[2,3-*b*:6,7-*b'*]dithiophene **12** using equally low-cost starting materials in only three steps.

A third Chapter of this report focuses on efficient synthesis and characterization of new derivatives of 3,4-ethylenedithiophene (EDTT) **149a-d** starting from tetrabromothiophene **146**. Selective 2,5-dilithiation followed by reaction with a range of aldehydes gives diols **147a-e** as mixtures of diastereomers. Only the 2 and 5 positions in tetrabromothiophene **146** react leaving the 3,4-bromides for further elaboration. The diols **147a-e** are oxidised to their corresponding diketones **148a-e** using activated MnO₂. Reaction with 1,2-ethanedithiol, by addition-elimination, provides access to novel monomers **149a-d** for the preparation of conjugated

copolymers of 3,4-ethylenedithiophene (EDTT). A range of these monomers can be attained by applying the synthesis of a series of ketones and this is applicable to further synthesis of π -extended thiophene-based organic semiconductors.

Chapter four of this thesis composed of two parts. The first part focus on the synthesis of 3,4-ethylenedioxythiophene (EDOT) dialdehyde derivatives **177** by efficient alternatives to literature chemistry, while a second part reports the optimisation of a synthesis of novel vinyl thiophenes materials.

A final Chapter gives full experimental details of all the compounds prepared in the thesis and their spectroscopic data.

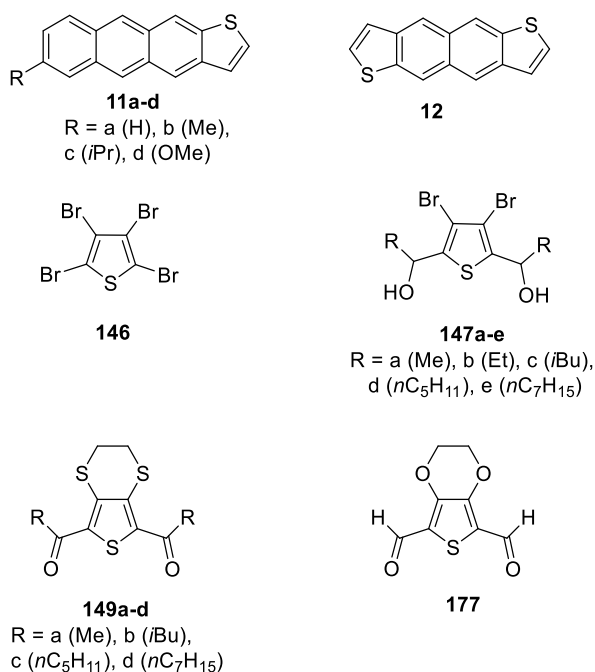


Figure i The structures of compounds **11**, **12**, **146**, **147**, **149** and **177**

List of Publications

Mustafa A. Al-jumaili, Simon Woodward, “Syntheses of 7-Substituted Anthra[2,3-*b*]thiophene Derivatives and Naphtho[2,3-*b*:6,7-*b'*]dithiophene” *J. Org. Chem.* **2018**, 83, 11437-11445.

Mustafa A-JABBAR Al-jumaili, Simon Woodward, “Efficient synthesis of 2,5-dicarbonyl derivatives of 3,4-ethylenedithiophene (EDTT) via addition- elimination reaction” *Tetrahedron* **2017**, 73, 5847-5852.

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Abbreviations

pKa	Acid dissociation constant
AcDT	Acenedithiophene
NBS	<i>N</i> -Bromosuccinimide
Bipy	2,2'-Bipyridyl
NCS	<i>N</i> -Chlorosuccinimide
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
DME	1,2-Dimethoxyethane
DIBAL-H	Diisobutylaluminum hydride
S-Phos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
eV	Electrons Volts
EDTT	3,4-Ethylenedithiothiophene
EDOT	3,4-Ethylenedioxythiophene
equiv	Equivalent
GC	Gas Chromatography
GPC	Gel Permeation Chromatography
HOMO	Highest Occupied Molecular Orbital
HRMS	High-resolution mass spectrometry
IR	Infra-Red
LUMO	Lowest Unoccupied Molecular Orbital
Mp	Melting point
mmol	Millimole
Min	Minute
NMI	<i>N</i> -Methylimidazole
NMP	<i>N</i> -Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
OFETs	Organic Field-effect Transistors
OSC	Organic Solar Cells
OLED	Organic Light Emitting Diodes
OPVs	Organic photovoltaics
PPA	Polyphosphoric acid
py	Pyridine

PCC	Pyridinium Chlorochromate
Pd-PEPPSI	[1,3-Bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
R_f	Response factor
rt	Room Temperature
THF	Tetrahydrofuran
TBAF	Tetrabutylammonium fluoride
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
PCy ₃	Tricyclohexylphosphine
p-TSA	p-Toluenesulfonic acid
TLC	Thin Layer Chromatography
UV-Vis	Ultraviolet–visible

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1 Chapter One: General Introduction

1.1 General introduction to semiconductor materials

One general definition of semiconductor materials is that they are materials which have an electrical conductivity value lying between metals and insulators. Alternatively, generally they can be defined as materials that have bandgaps between about 1 and 3 electrons volts (eV) (Figure 1).¹ Naturally, the inorganic semiconductors can be pure elements, such as silicon or germanium, or can be compounds such as gallium arsenide. In a procedure named ‘doping’ minor amounts of chemical impurities are added to pure semiconductors producing large changes in the conductivity of the material and they started to show electrical conductivity.

It is well-established that the materials with zero value bandgaps are classified as metals, and that those with bandgaps more than 3 eV are recognised as insulators.² The word bandgap refers to the energy required to promote an electron from the valence band to the conductance band.³

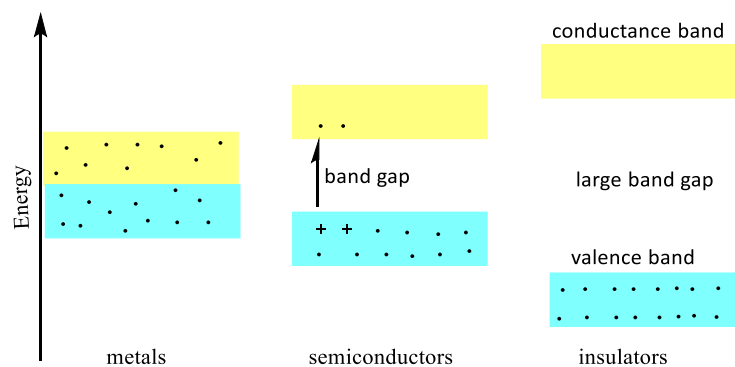


Figure 1 Bandgaps for metals, semiconductor and insulators

Although there are many semiconductors available, the most well studied are those that were first discovered: silicon (Si) and germanium (Ge). The first transistor was invented in 1947 by John Bardeen *et al.*⁴, and these early devices were typically based

on such inorganic semiconductors, especially silicon. In recent years alternative devices based on organic semiconducting materials have come to the fore and these are discussed in the next section.

1.2 Organic semiconducting materials

Modern applications of semiconductor materials cover a wide range of electronic devices such as: bank cards, televisions, computer screens, etc. These applications have become completely integrated into our daily lives with the advent of the ‘smart phone’ and similar technologies.

Due to technological limitations associated with using inorganic semiconducting materials such as high cost and low flexibility (including difficulties in processing), in the last few decades organic electronic materials have undergone a revolution in both academic and industrial fields,⁵ and substantial efforts are presently being devoted to developing new organic electronics devices.⁶ Organic semiconductor materials can possess properties not present in inorganic semiconductors including: low cost, structural flexibility, large area coverage, easy processing and sustainability characteristics. These important properties make them potentially useful in many electronic applications.⁷

These unique properties of organic electronic materials have led to their use in different applications such as organic field-effect transistors (OFETs),⁸ organic solar cells (OSC),⁹ organic light emitting diodes (OLED),¹⁰ and organic thermoelectrics devices¹¹ (Figure 2).

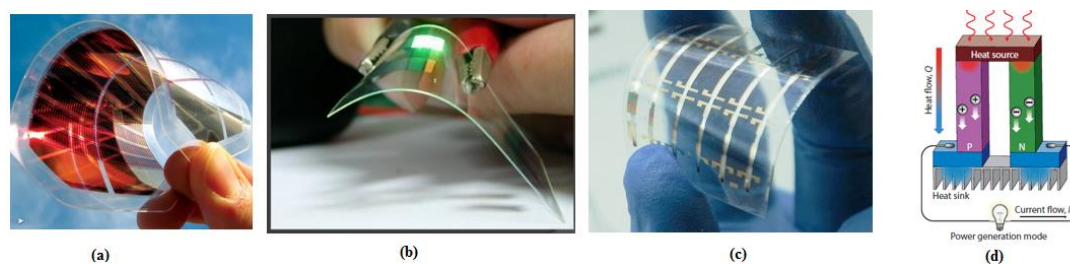


Figure 2 Examples of applications (a) organic solar cells; (b) organic light emitting diodes; (c) OFET; (d) organic thermoelectric devices

Although organic semiconductor materials were first studied fundamentally in the late 1940s,¹² they were not used as the active semiconductor layer of a device until the study of Koezuka *et al.*¹³ who in 1986 established a polythiophene-based field effect transistor (FET). In the last twenty years, thousands of studies have been published studying organic semiconducting materials for electronic applications. These studies include both small discrete molecules and polymers.

Organic semiconductor materials are most often categorised based on the size of the molecule entity used, and are divided into two main types: small molecules species and polymers. The small molecular class can be sub-divided into many types based on the morphology of the structures (Figure 3).

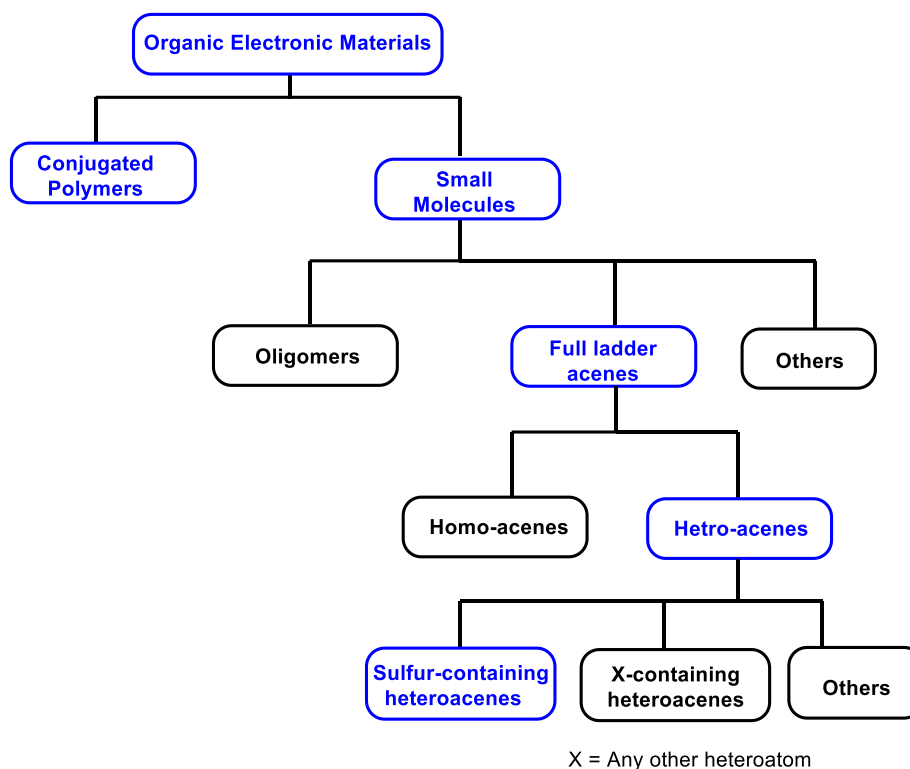


Figure 3 One arbitrary classification of organic semiconducting materials in terms of their structural features. The boxes in blue colour show the main target molecules in this thesis

1.3 Doping in organic semiconductors

The basic strategy in doping of organic semiconductor materials is the same as that in inorganic materials: by adding either electron acceptors or donors to the material, the formation of additional mobile charge carriers can be facilitated.¹⁴

Doping is critical for organic materials as the neutral π -conjugated organic materials are normally insulators.¹⁵ To make them electrically conductive we need to dope the system by introducing suitable chemical additives: electron-acceptors (oxidizing agents) to form electron deficient systems where charge transport is by p-type (hole) carriers, or doping with electron-donors (reducing agents) which create excess electrons in the system by n-type (donor) doping.¹⁶

Another way to describe this processing is the addition of electrons to the conduction band states (n-type doping), or the removal of electrons from the valence band states to generate a free hole (p-type doping) (Figure 4).

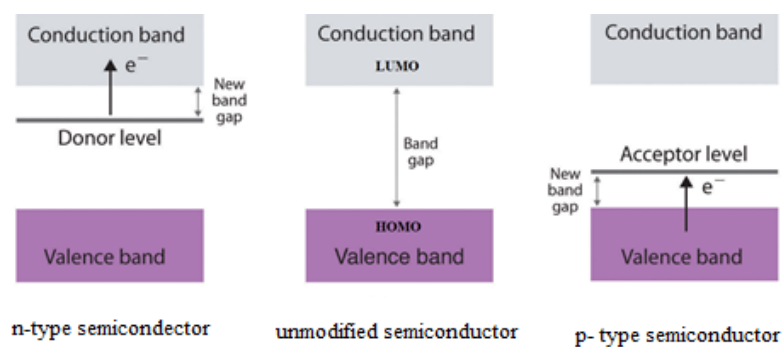


Figure 4 Doping in organic semiconductor materials

The process of doping in organic electronic materials is totally different from that used in inorganic semiconductors. Typically doping in inorganic materials (e.g. Si) requires replacement of some of the inorganic atoms with atoms having either more or less electrons than silicon in the valence band such as: P, B etc.

Doping in the case of the π -conjugated organic materials is attained by a different procedure. The doping agents never replace any atoms in the molecule, but they work simply as reagents which accept or donate electrons to create charge in the system.¹⁷

Although this thesis focuses on the synthesis of the thiophene organic materials, it is important to clarify key examples of p and n-types of these and related molecules. Presently there are thousands of organic materials recognised as p-type (hole-transporting) semiconductors and fewer, but still many, n-type semiconductors.

Listing all of known organic semiconductor compounds individually is beyond the scope of this thesis because new ones are reported every month. However, general classes can be identified herein. For example, the main representative structures of

hole-carrying heteroacenes (p-types) include the thiophene-fused-heteroacenes shown in Figure 5. The side chain groups (R) introduced into some of these structures enhance their characterisation and processing, and improve their solubility.^{8,18,19,20,21,22} Such side groups also offer opportunities to modify crystal phase packing and morphology. Some of examples of p-types heteroacenes thiophene compounds are cited in recent literature^{23,24,25,26,27} and examples of these are shown in Figure 5.

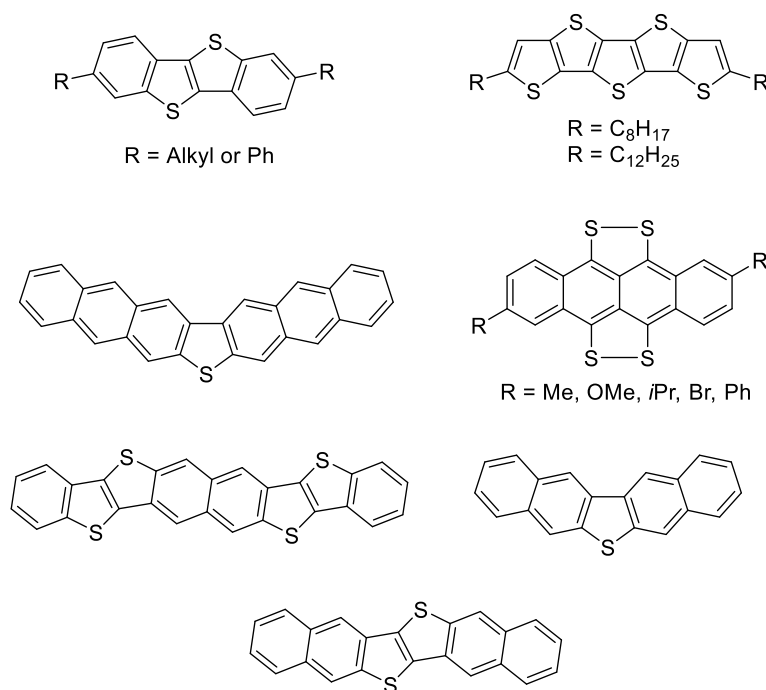


Figure 5 Representative p-type heteroacenes thiophene materials

Typically, n-type (electron-carrying) materials are less reported in the literature than p-type organic materials, this is due to the intrinsic problems in attaining air-stable radical anions.²⁸

However, a recent review in this area in 2017 “*Recent progress in the development of n-type organic semiconductors for organic field effect transistors*”, by Yuning Li *et al.* shows the recent dramatic progress being made in this area.²⁸

Further discovery of new n-type compounds will be important for making novel organic electronic devices and optimization of processing conditions and device

architectures. Figure 6 shows some recent examples of current n-type organic materials.

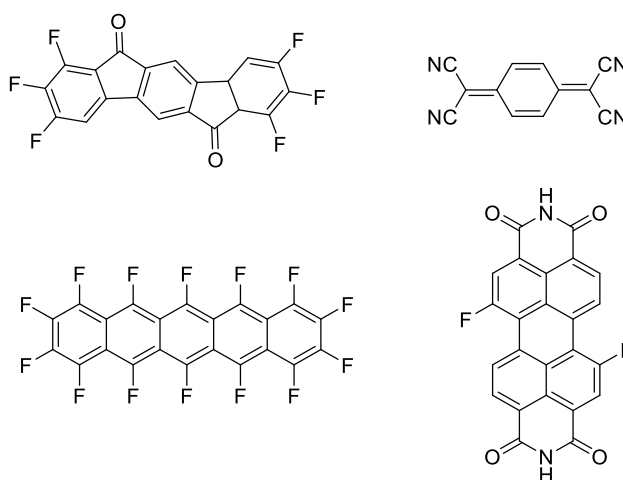


Figure 6 Representative examples of n-type materials

1.4 Methodology review

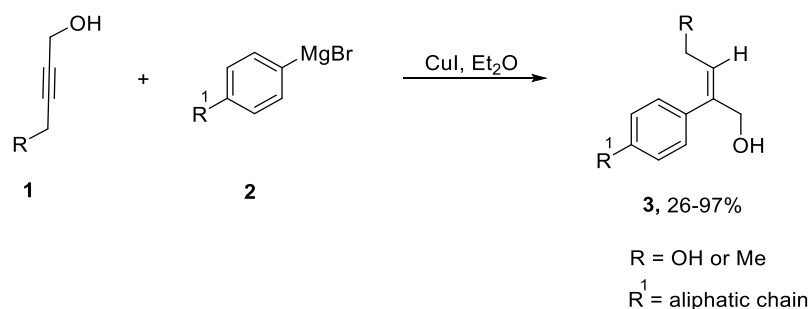
As a wide range of methodologies have been used in this thesis, so it is appropriate to give a short summary of the technologies used.

1.4.1 Carbocupration

Generally ‘carbocupration’ can be described as a reaction that involves the addition of an organometallic copper species (Cu-C bond) to an alkyne species to form a new (carbon-carbon) bond.²⁹ Normally, a strict *syn*-addition prevails but the regioselectivity is typically based on the groups present in the parent alkyne compound.³⁰ Empirically it has been found that presence of an acceptor or donor groups in close proximity to the acetylene moiety can affect the regioselectivity of the addition, and different isomers can be formed.^{31, 32,33}

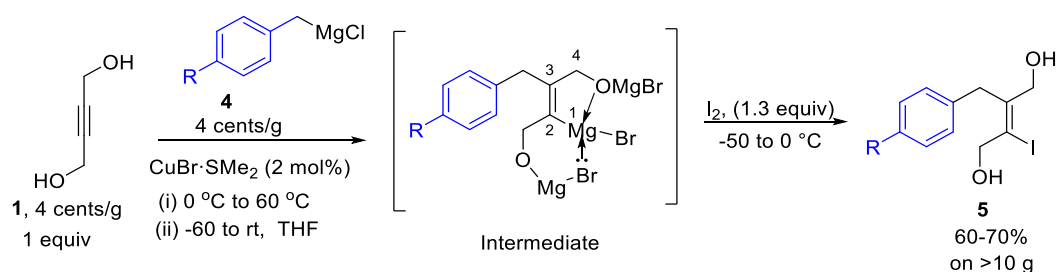
Within the Scifinder database there are many reported studies of the use of carbocupration reactions, but the specific reaction of 2-yne-1,4-diol **1** with aromatic Grignard reagents is limited to only a few studies in the literature. The first one was

reported in 1984 by Ishino *et al.* by the reaction of diol **1** with a series of phenylmagnesium bromide compounds **2** to obtain anti-diols **3** (Scheme 1).^{34,35}



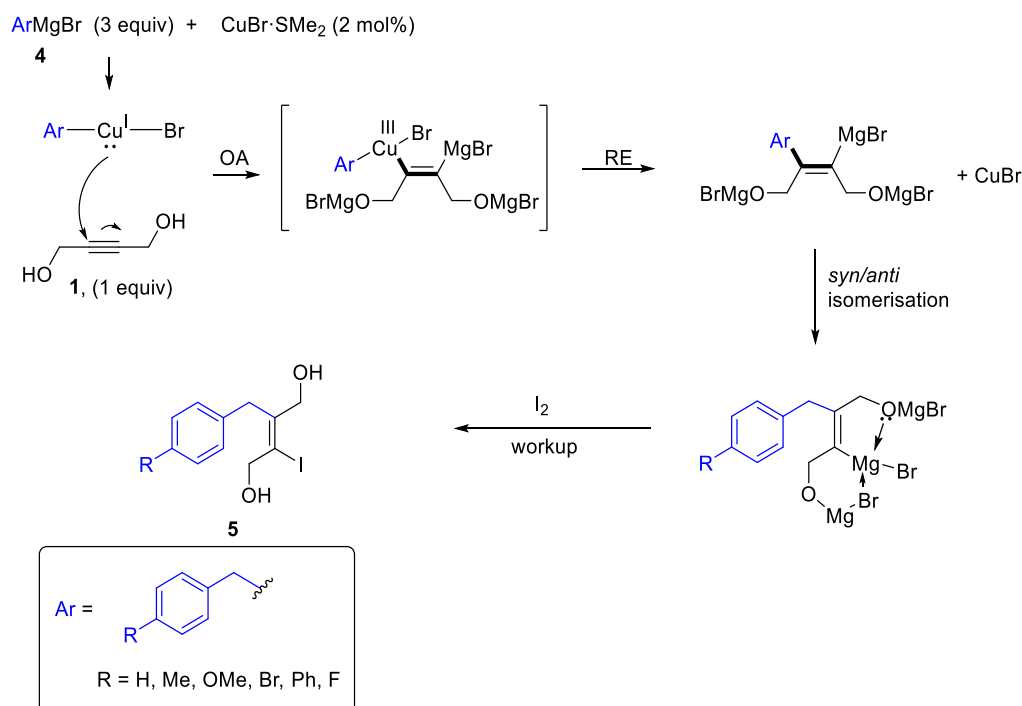
Scheme 1 The method of Ishino *et al.* to synthesise diols **3**

A recent study was reported in 2017 by the Woodward Group.³⁶ Our research group discovered it could simply, cheaply and easily synthesise the very important intermediate **5** by the reaction of diol **1** with benzyl Grignard reagent **4** in the presence of (2 mol%) of copper(I) bromide dimethyl sulfide complex (CuBr·SMe₂) as a catalyst (Scheme 2).



Scheme 2 Our research group method to synthesise diols **5**

Scheme 3 shows the general suggested mechanism of a carbocupration reaction for the formation of diols **5**.



Scheme 3 Suggested mechanism for carbocupration leading to **5**; OA = oxidation addition, RE = reductive elimination

1.4.2 Pd-catalysed cross-coupling reactions in synthesis of organic electronic materials

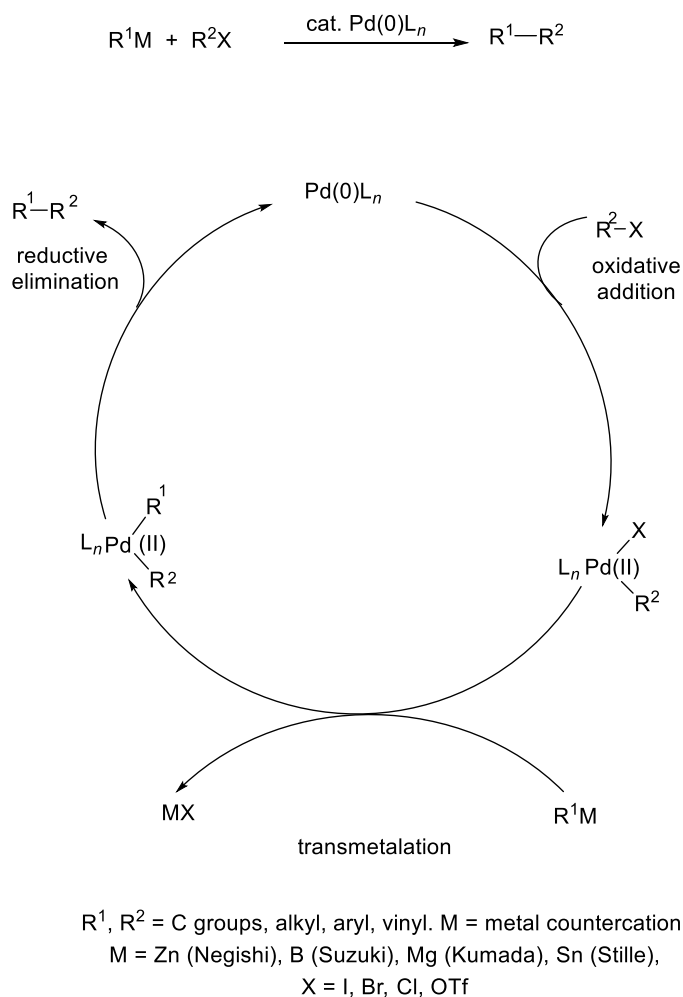
In the last 30 years, organopalladium catalysis has been used in the synthesis of a huge number of organic compounds, and has been well described in a number of comprehensive and informative books.^{37,38,39,40,41} However, among all of the types of palladium catalysed reactions, the cross-coupling of organozinc reagents (called Negishi coupling) is one of the most significant in modern organic synthetic approaches. One general definition of Negishi coupling is the palladium cross-coupling reactions of organometals which contain Zn-C bonds with organic electrophiles such as organic halides or sulfonates.⁴²

The Negishi cross-coupling reaction was demonstrated for the first time in the 1970s^{43,44,45,46,47} by Ei-ichi Negishi and co-workers, and since that time this reaction has

become widely used for the formation of (carbon-carbon) bond in modern organic synthesis.^{48,49,50,51,52,53,54,55, 56,57} Because of his inventive work in the field of palladium-catalysed cross-coupling reactions and its high impact in organic synthesis Negishi together with Heck, and Suzuki received the 2010 Nobel Prize in chemistry.^{58, 57}

In addition to the importance of the Negishi cross-coupling in the synthesis of different types of organic molecules, this reaction has recently been widely applied in the synthesis of organic electronic materials.⁵⁹ Significant numbers of reviews have reported on the application of palladium-catalysed cross-coupling reactions represented by Negishi coupling⁵⁹ together with Kumada coupling,⁶⁰ Stille coupling,⁶¹ and Suzuki coupling⁵⁸ in synthesis of polymers, oligomers and small molecule semiconducting materials.^{62,63,64,59,65,66,67}

Scheme 4 shows the general mechanism for Pd-catalysed (carbon–carbon) cross-coupling reactions. The general catalysed cycle for the Pd-cross-coupling reactions includes three main steps; first one is the oxidative insertion of the organic electrophile (RX), X is typically a halide or a sulfonate ester to the palladium catalyst (0), the second step is the transmetalation of L_nPdRX with the organometallic reagent, and the last step is the reductive elimination to release the cross-coupling product and to rejuvenate the Pd-catalyst (Scheme 4).



Scheme 4 General mechanism of Pd-catalysed cross-coupling reactions

1.4.2.1 Advantages and chemoselectivity of the Negishi coupling

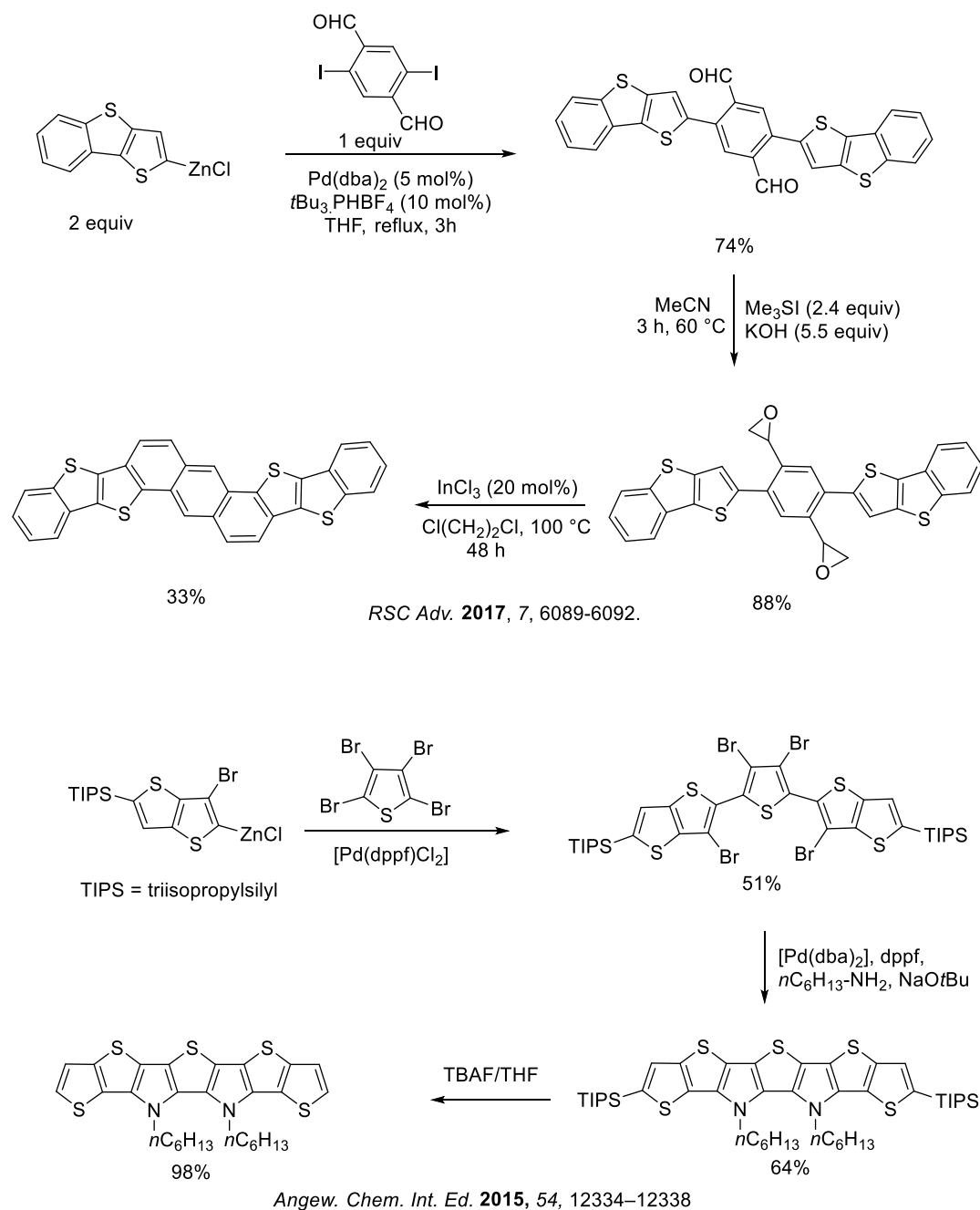
The Negishi coupling reaction has some advantageous factors for organic synthesis that we cannot find in other organometal cross couplings including: Suzuki coupling (B), Kumada coupling (Mg) and Stille coupling (Sn).⁵⁹ First of all, the Negishi coupling reaction normally delivers high yield with high chemoselectivity. The selectivity is in the formation of the cross-coupled product and in the formation of geometrically defined alkenes. Secondly, the Negishi coupling reaction has an "optimal balance" between chemoselectivity and reactivity. It has been clear that organozinc reagents normally have more reactivity than their organotin Sn and

organoboron B counterparts. However, organozinc reagents have more functional groups tolerance than their corresponding Grignard reagents.⁶⁸ Thirdly, such organozinc couplings proceed under mild conditions without promoters; while the case of Suzuki and Stille couplings these cross-coupling require other additives, such as bases or LiCl. Finally, an important factor is that organozinc reagents are not toxic, as are the organotin reagents, and the coupling with organozinc reagents is generally environmentally benign.

1.4.2.2 Synthesis of organic electronic materials via Negishi coupling

Most of the organic semiconductor materials contain π -conjugated backbones. Most of these materials include of polyaromatic or heteroaromatic units, and common building blocks have thiophenes, oligoacenes, fluorenes or fused heterocyclic rings.⁶² One key important factor to achieving significant progress with organic electronics is linked with the availability of efficient synthetic methods for coupling aromatic monomers into extended π -conjugated systems. Specifically, transition metal (TM)-catalysed cross-coupling reactions have yielded a diverse and advanced class of π -conjugated oligomers, polymers, and small molecules which has been used in organic electronics research.

Negishi coupling is one of the best available methods for this process which has achieved important progress in the last few years. As there are large numbers of publications reporting literature associated with Negishi couplings, it is hard to summarise all of these papers in this section. Hence, Scheme 5 shows representative examples from the most recent literature in the field.



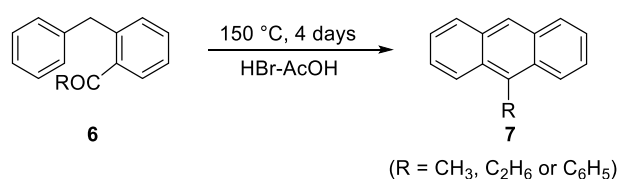
Scheme 5 Selected examples from recent publications literature using the Negishi coupling reaction.^{69,70}

1.4.3 Bradsher reaction in synthesis of organic electronic materials

The Bradsher reaction is an intramolecular variant of the Friedel-Crafts reaction, which is considered one of the most important routes to the synthesis of different types of compounds such as polyacene and heteroacene materials.⁷¹ This reaction was

developed for the first time by Bradsher in 1940 using HBr to catalyse the cyclation of orthoformyl or ortho-acyl substituted to obtain polyacenes or hetroacenes.^{72,73}

The first reported Bradsher reaction conditions need long reflux times (four days) and harsh conditions (34% HBr-MeCO₂H, 150 °C) to obtain 69–80% yields of the final products, this can be exemplified by a typical synthesis of R-anthracene **7** from the ketone **6** (Scheme 6).⁷²



Scheme 6 First synthesis of polycyclic via the Bradsher reaction⁷²

Although many satisfactory results of these classical Bradsher reaction conditions were realised, sometimes serious synthetic problems, such as competitive processes and modest yields were noted.^{71,74}

Typically one of the requirements of the Bradsher reaction is high temperatures, above 100 °C and some reactions require even higher temperatures (200–230 °C) and need to be carried out in sealed tubes for several hours.^{75,76}

Regarding the synthesis of organic electronic materials, the Bradsher reaction has been used to synthesise many different compounds using different Lewis acids. A number of acidic catalysts has been applied, Tables 1 and 2 show representative examples of the heteroacenes and acenes materials that have synthesised via the Bradsher reaction.

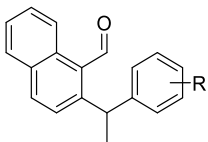
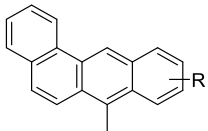
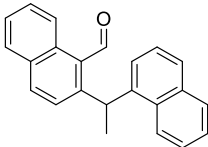
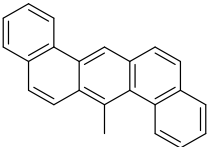
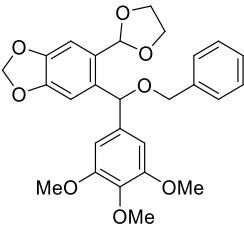
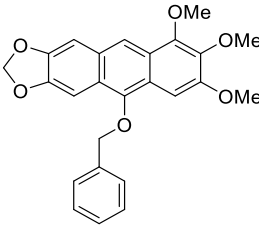
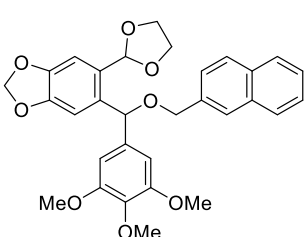
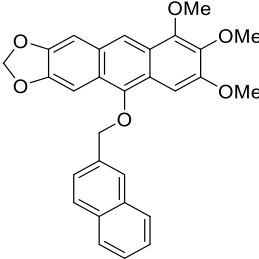
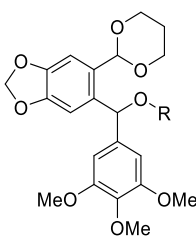
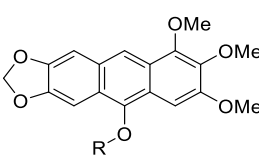
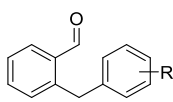
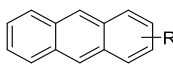
Table 1 Representative examples of thioacenes materials prepared via Bradsher reaction.

Entry	Substrate	Products	Lewis Acid	%	Ref.
1			HCl	72	71
2			In(OTf) ₃	95	75
3			Amberlyst 15	60	77
	R = C ₁₀ H ₂₁	R = C ₁₀ H ₂₁			
4			BF ₃ .Et ₂ O	91	78
5			PPA	75	79
6			Amberlyst 15	38-71	80,81,82
		R = H (46%), R = C ₆ H ₁₃ (71%) R = C ₁₂ H ₂₅ (38%)			
7			PPA	72	83
8			PPA	60	84
9			PPA or HBr	80	85
10			BF ₃ ·OEt ₂	88	78

11			HCl	95	71
12			PPA	80	83

Table 2 Representative examples of acenes materials prepared via the Bradsher reaction

No.	Substrate	Products	Lewis Acid	%	Ref.
1			TiCl ₄	8-86	36
		15 derivatives R, R = F, Cl, Br, H, Me, Ph, OMe, <i>i</i> Pr or vinyl			
2			FeCl ₃	95	71
3			In(OTf) ₃	96	75
	R = Me R = Ph	R = Me R = Ph			
4			TfOH	92-99	86
	R = Me, F, Br, CF ₃ , OMe, Ph	R = Me, F, Br, CF ₃ , OMe or Ph			
5			FeCl ₃	48-99	87
	R = Me or H	35 derivatives R ₁ , R ₂ = H, Me, OMe, Ph, F, Cl, CF ₃ , OBn, OTs, OH, OAc, NO ₂ or CN			
6			In(OTf) ₃	74	88

7			In(OTf) ₃	56-99	88
	R = H, SiMe ₃ , Cl or OMe	R = H, SiMe ₃ , Cl or OMe			
8			In(OTf) ₃	99	88
9			HCl	68	89
10			HCl	30	89
11			HCl	38-56	89
	R = Me, nC ₄ H ₉ or nC ₁₅ H ₃₁	R = Me, nC ₄ H ₉ or nC ₁₅ H ₃₁			
12			TfOH	45-95	90
		R = Me, F, Br, OMe, Ph			

1.5 Thesis aims

The main focus of this work was the synthesis of various thiophene building blocks into thiophene monomers and small thiophene molecular π -conjugated systems, with the intention to generate new methods for synthesising semiconducting materials. This work has been broken down into several sub-projects:

The aim of Chapter two was the synthesis of some thiophene-based hetroacene materials using efficient, alternatives methods to the literature. Thus, Chapter two describes the efficient synthesis of 7-R-substituted anthra[2,3-*b*]thiophenes (R = H, Me, *i*Pr, or OMe) and the unsubstituted naphtho[2,3-*b*:6,7-*b'*]-dithiophene. Also, this Chapter presents all the known methods to access these compounds.

In Chapter three the efficient synthesis of a novel 3,4-ethylenedithiophene (EDTT) derivatives via addition-elimination reaction is reported.

Chapter four has two main parts. The first part demonstrates a new route towards the synthesise of 3,4-ethylenedioxythiophene (EDOT) dialdehyde derivatives. The second part focuses on optimisation in the synthesis of novel vinyl thiophenes materials.

The final Chapter, Chapter five gives the experimental data including experimental methods for all of the compounds prepared in this thesis.

2 Chapter Two: Alternative Sustainable Syntheses of 7-Substituted Anthra[2,3-*b*]thiophene Derivatives and Naphtho[2,3-*b*:6,7-*b'*]dithiophene

Publication from this Chapter:

Mustafa A. Al-jumaili, Simon Woodward, “Syntheses of 7-Substituted Anthra[2,3-*b*]thiophene Derivatives and Naphtho[2,3-*b*:6,7-*b'*]dithiophene” *J. Org. Chem.* **2018**, 83, 11437-11445.

2.1 Introduction

Over the last 30 years, organic electronic materials have been studied extensively, and their importance and performance have increased significantly.⁹¹ Great improvements in stability, electrical conductivity, and usability have been achieved, with promising materials and applications in industry for commercial products being attained.⁹² Recently, oligothiophenes⁹³, acenes⁹⁴, and heteroacenes⁹⁵ have all received increasing attention and are the subjects of studies in this area.

Aromatic hydrocarbon acenes are some of the most well studied organic semiconductors and shows promising applications. Tetracene **8**⁹⁶ pentacene **9**⁹⁷ and rubrene **10**⁹⁸ (Figure 7) are the most commonly used examples of these acenes semiconductors. These materials show recorded maximum carrier mobilities of 0.15 cm² V⁻¹ s⁻¹, 7 cm² V⁻¹ s⁻¹ and 20 cm² V⁻¹ s⁻¹ respectively, comparative to that of amorphous silicon (~ 1 cm² V⁻¹ s⁻¹).

The reason for the high hole mobility in both pentacene **9** and rubrene **10** is the large intermolecular orbital overlap in the solid state, which is the result of the planar and rigid molecular structures associated with these largely π -extended electronic structures.⁹⁹

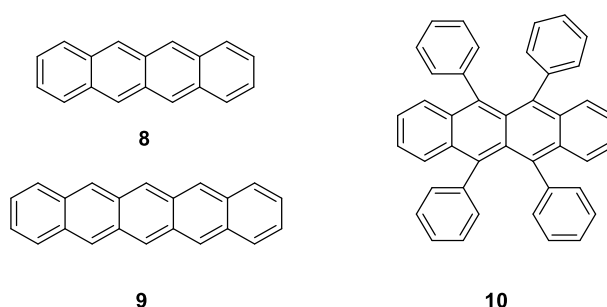


Figure 7 Structures of some common acene materials

Even though linear acenes are good to excellent p-type organic semiconductors, and are useful for multiple applications,^{100,101} most of these materials also have weaknesses

in practical applications in organic devices.¹⁰² For instance, their high-lying HOMO energy levels and narrow bandgaps make these materials sensitive to photooxidation and subsequent chemical reactivity in presence of oxygen under ambient conditions.^{100,103,104} Under such conditions, the semiconductor performance of acene based devices can fall dramatically, due to this aerial oxidation.¹⁰⁵

Consequently, for these reasons, new organic semiconducting materials are required, which should achieve both good electronic properties and high stability under ambient conditions.¹⁰²

The introduction of one or more ring structures containing a heteroatom into the overall acene structure is one successful approach to modifying the electronic chemical and physical properties of acene based molecules. Among the many classes of heteroatom units that might be considered, thiophene-based are promising building blocks for such semiconducting materials. These species can not only show excellent organic field effect transistor (OFET) performance, but they can also exhibit good stability under ambient conditions.^{106,107}

The intrinsic chemical reactivity present in thiophene-based species can be used advantageously due to their ability to allow selective functionalization at the α and β positions relative to the sulfur atom. These properties allow opportunities for the design of new semiconducting systems with improved π -conjugation.¹⁰⁸

The good stability and high performance of linear heteroacenes increase their potential in many different applications, such as thin-film transistors (TFTs), including their field effect variants (OFETs).¹⁰² Inserting sulfur heteroatoms into acene structures brings about positive outcomes on both structural and electronic properties and as well as making these compounds are more soluble.¹⁰⁹

Among all of the heteroacene materials both anthra[2,3-*b*]thiophenes **11a-d** and naphtho[2,3-*b*:6,7-*b'*]dithiophene **12** (Figure 8) are reported in this Chapter. In the literature the known anthra [2,3-*b*]thiophene **11a** has been used to derive organic field effect transistors (OFETs) showing carrier mobilities of $0.13\text{--}0.15\text{ cm}^2\text{ V}^{-1}\text{ s}^{-1}$.^{110,111} Similarly, derivatives of naphtho[2,3-*b*:6,7-*b'*]dithiophene **12** have also been used in OFET devices with even higher carrier mobilities of $0.5\text{--}1.5\text{ cm}^2\text{ V}^{-1}\text{ s}^{-1}$.¹¹² This Chapter aim was to synthesise the known species **11a** and new derivatives **11b-d**, and to prepare known species **12** using cheap more sustainable reagents and with less steps than literature methods.

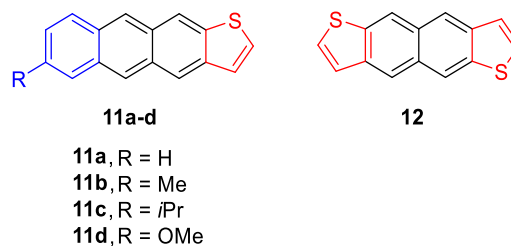


Figure 8 Target compounds for this Chapter; only **11a** and **12** are known^{112,113}

2.2 Literature methods to synthesis of anthra[2,3-*b*]thiophene **11**

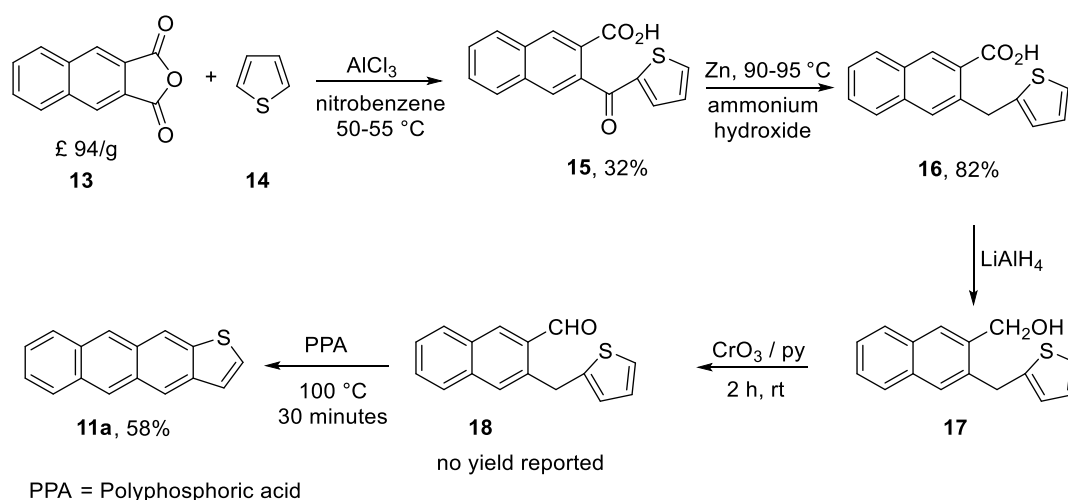
Acene-cores terminating at one or both ends with thiophene units are attractive and popular motifs for the formation of organic electronic semiconductor devices.^{114,115,116,117}

Heteroacenes core which have thiophene ring(s) have been reported since the 1960s. These materials became attractive in the field of organic semiconductors as they had the advantages of both acenes and thiophene-based compounds.⁹²

There are only a few reported methods for synthesis of such thiophene acene derivatives thus far. The main reasons for this is the difficulty in their synthesis and purification issues often caused by their poor solubility.¹⁰²

Various methodologies have been employed over the last 40 years for the preparation of the parent anthra[2,3-*b*]thiophene **11a**. Multi-step syntheses using expensive (in either cost or time), or higher toxicity or environmentally less than desirable reagents, are the norm.¹¹⁸ This Chapter will highlight all of the literature approaches to the synthesis of **11a** before starting to describe our own method.

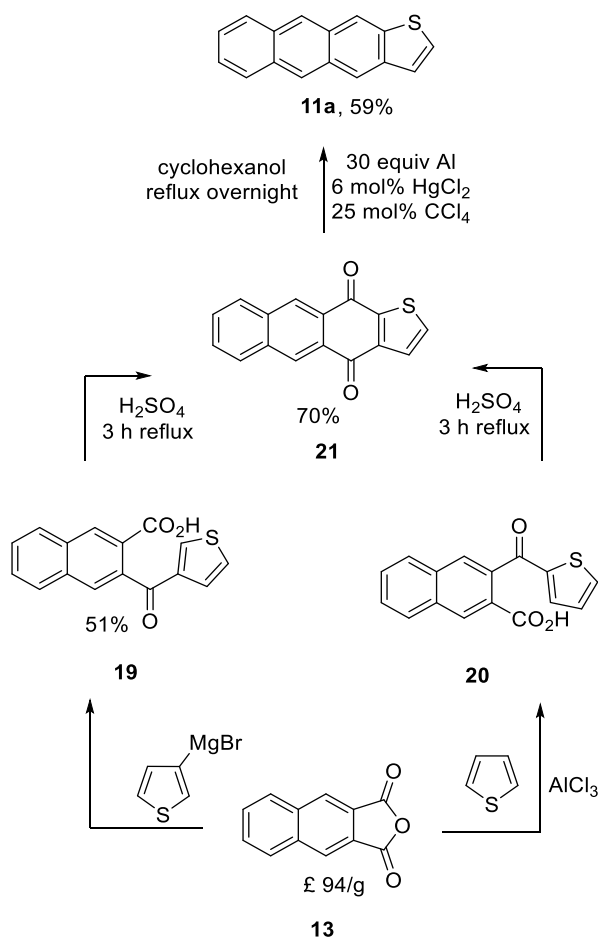
A 1981 study by Castle and coworkers¹¹³ reported anthra[2,3-*b*]thiophene **11a** starting from the commercially available 2,3-naphthalic anhydride **13** (500 mg cost £47 from Sigma Aldrich, in August 2018) providing compound **11a** in five steps and in poor overall yield (Scheme 7). This method required moderately expensive materials, some with significant toxicity.



Scheme 7 Castle *et al.* method for synthesis of anthra[2,3-*b*]thiophene **11a**

Due to the toxic reagents and the high steps count of Scheme 7, other studies have been undertaken to find an alternative method to synthesise **11a**.

In 1983 MacDowell *et al.*¹¹⁸ employed a similar approach to Castle which still required a relatively expensive starting material, but MacDowell's approach needed fewer steps (Scheme 8).

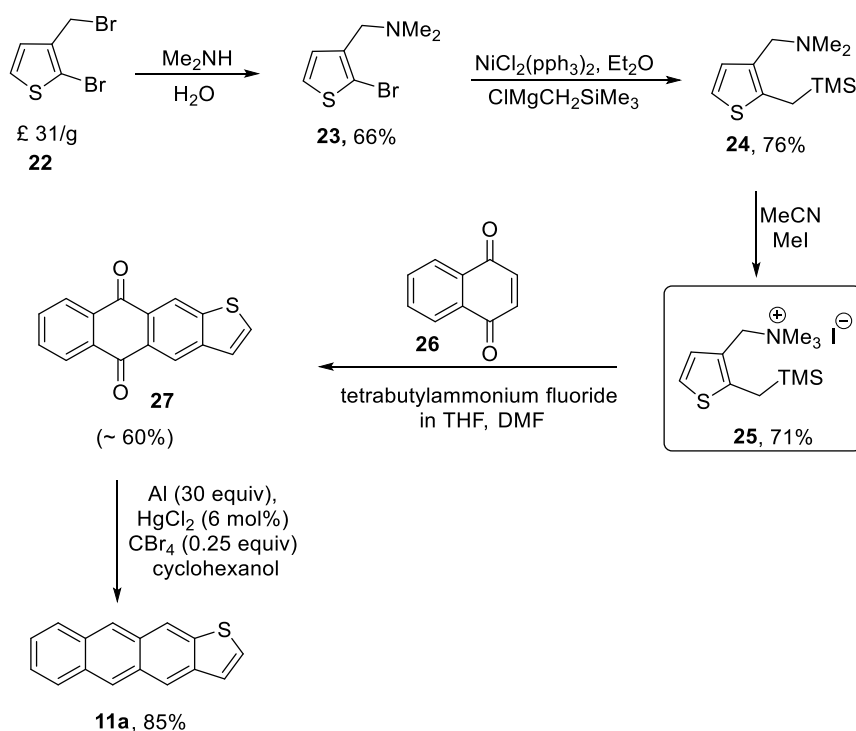


Scheme 8 MacDowell *et al.* synthesis of anthra[2,3-*b*]thiophene **11a**¹¹⁸

Although this method required fewer steps than Castle's approach, it still has the same issues regarding both the high cost of its starting materials, and that it requires a high number of equivalents of toxic reagents in the last step.

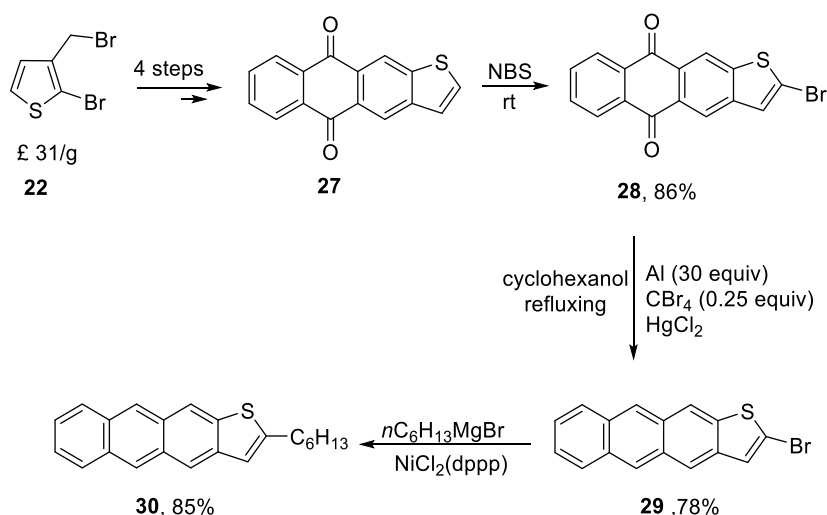
Another route to **11a** was presented in 2006 by Zhenan Bao¹¹⁰ *et al.* They started from the known compound 2-(trimethylsilylmethyl)-3-(trimethylammoniummethyl) thiophene iodide **25**. This thiophene iodide derivative **25** is not commercially available, meaning that its synthesis from expensive and toxic commercially available

2-bromo-3-(bromomethyl)thiophene **22** has to be undertaken by the known procedures.^{119,120} The clear disadvantages for this approach are the costly starting materials and the overall step count (Scheme 9). This published procedure does not give any details for the preparation of **27**. It is said to be attained in ca. 60% yield.



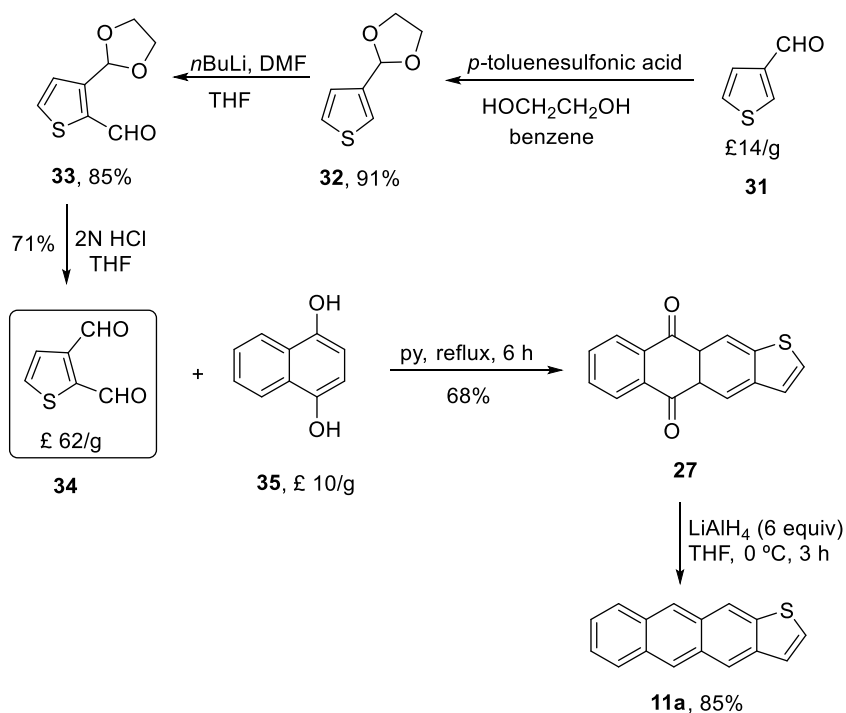
Scheme 9 Zhenan Bao *et al.* approach for synthesis of anthra[2,3-*b*]thiophene **11a**¹¹⁰

In 2008 the same research group synthesised a new anthra[2,3-*b*]thiophene derivative functionalised at the α thiophene position.¹²¹ Compound **28** (Scheme 10) was synthesised from its corresponding quinone by bromination using *N*-bromosuccinimide (NBS). Subsequently, the α -bromo quinone was reduced to give 1- (α -bromoanthra[2,3-*b*]thiophene) **29**. Finally, the last step employed a Kumada–Tamao coupling with the *n*-hexylmagnesium bromide to obtain the new hexyl derivative anthra [2,3-*b*]thiophene **30** (Scheme 10).



Scheme 10 Synthesis of (α -*n*-hexylanthra[2,3-*b*]thiophene) **30**

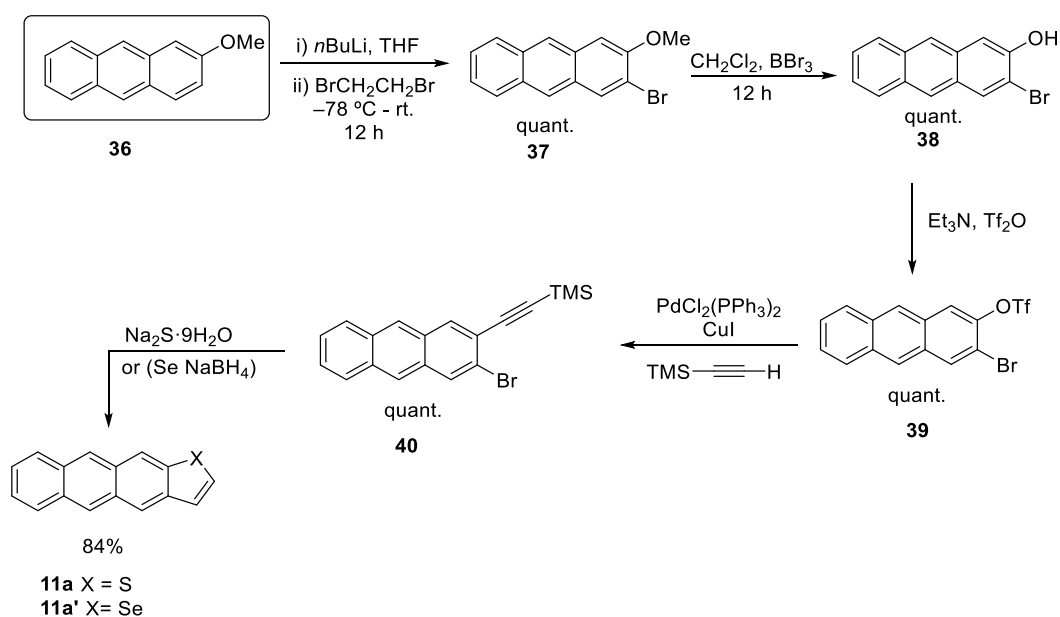
An approach by Yu-Tai Tao¹¹¹ *et al.* in 2007 has been offered as new strategy to solving the key drawbacks in previous literature approaches. This method has been used to synthesise compound **11a** starting from commercially available (£62 per gram, from Sigma Aldrich) thiophene-2,3-dicarbaldehyde **34** (Scheme 11). The key starting material **34** could be synthesised using a known procedure but this method required 3 steps to making the key starting material **34**.^{122,123}



Scheme 11 Yu-Tai Tao approach for anthra[2,3-*b*]thiophene **11a**

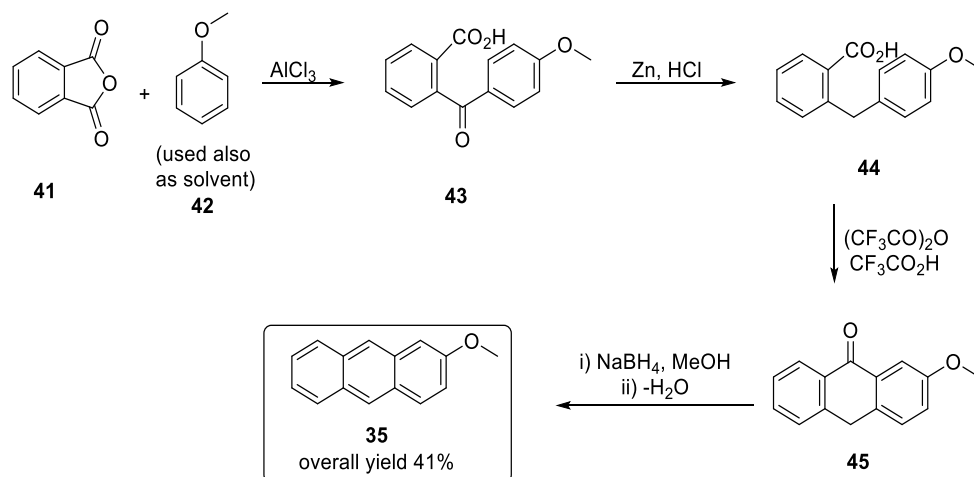
Unfortunately, in addition to the high cost of starting materials used in this approach, the method has similar problems to those found in all other approaches. Namely, a large number of steps, and high toxicity of reagents.

Improved syntheses of anthra[2,3-*b*]thiophene **11a** via Kazuo Takimiya¹²⁴ *et al.* have been reported using the non-commercial available 2-methoxyanthracene **36** as a starting point. As shown in Scheme 12 a total of 5 steps required for the synthesis of **11a**. This approach requires bromination of the key starting material **36** then its demethylation using boron tribromide (BBr₃) to give 3-bromoanthracen-2-ol **38** as the key intermediate for the sequence. Also, this method required a Sonogashira coupling to complete the synthesis.



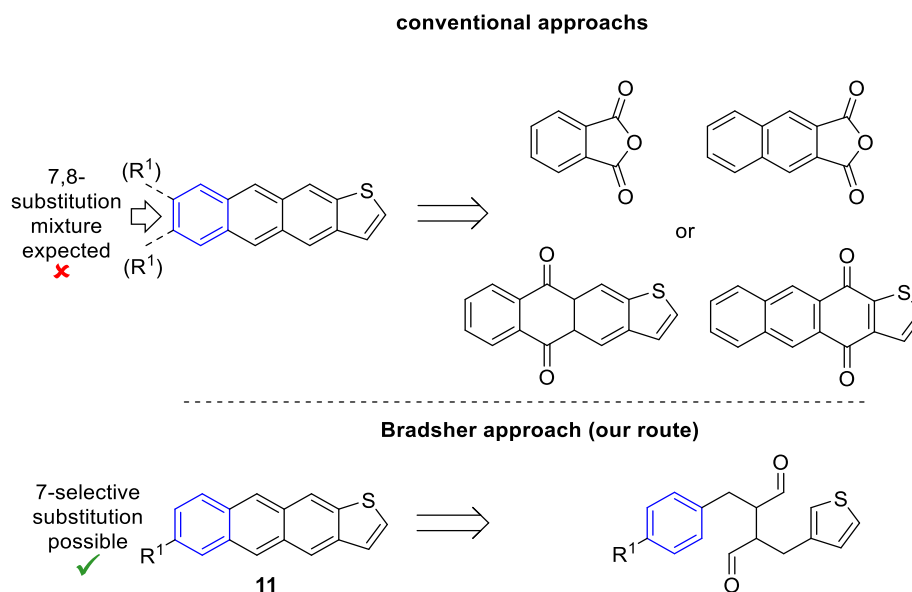
Scheme 12 Kazuo Takimiya *et al.* approach for synthesis of **11a**¹²⁴

Although this latter methodology obtains a good overall yield for these steps and allows access to selenophene **11a'**. However, this method still requires a total of nine steps, including synthesis of the non-commercially available (2-methoxyanthracene) **36**. This starting material **36** needs 4 steps¹²⁵ (Scheme 13).



Scheme 13 Synthesis of 2-methoxyanthracene¹²⁵

In conclusion, all of the reported routes to anthra[2,3-*b*]thiophene **11a** require multi-step approaches, often using expensive precursors which can also have significant lachrymatory or carcinogenicity issues. Additionally, while existing routes to anthra[2,3-*b*]thiophenes **11** can allow subsequent preparation of 2-substituted derivatives, they cannot be easily be used for mono-substitution of the terminal phenylene (Scheme 14). Their use of initial symmetric reagents would result in regio-isomeric products if substituted. However, employment of a two-directional³⁶ Bradsher¹²⁶ disconnection should be an effective alternative (Scheme 14). It is anticipated that 7-alkyl substitution would also increase the solubility of the resultant anthra[2,3-*b*]thiophenes **11**.



Scheme 14 Two directional Bradsher strategies to 7-substituted anthra[2,3-*b*]thiophene **11** vs. conventional approaches

2.3 Literature methods to a synthesis of acenedithiophenes (AcDTs) and the related materials

Acenedithiophenes (AcDTs) are compounds that have two thiophene rings at the ends of the acenes cores which have become a promising class of π -conjugated organic semiconductors. They have been used as active layers in semiconductor devices in their own right, but also deployed as important building blocks in the organic semiconductors applicable to organic electronic devices such as organic field effect transistors (OFETs)^{127,128,129} and organic photovoltaics (OPVs).^{130,131,132} Figure 9 shows the most common acenedithiophene (AcDT) cores.

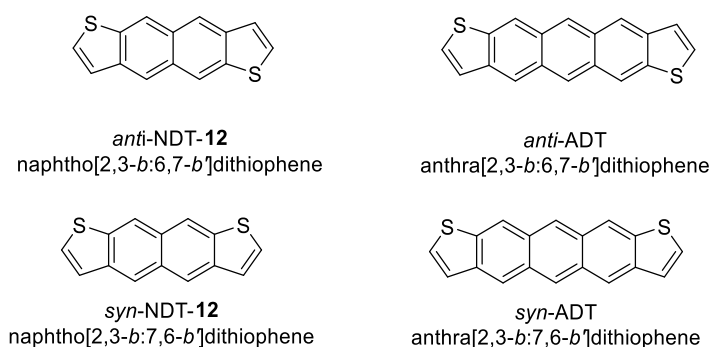


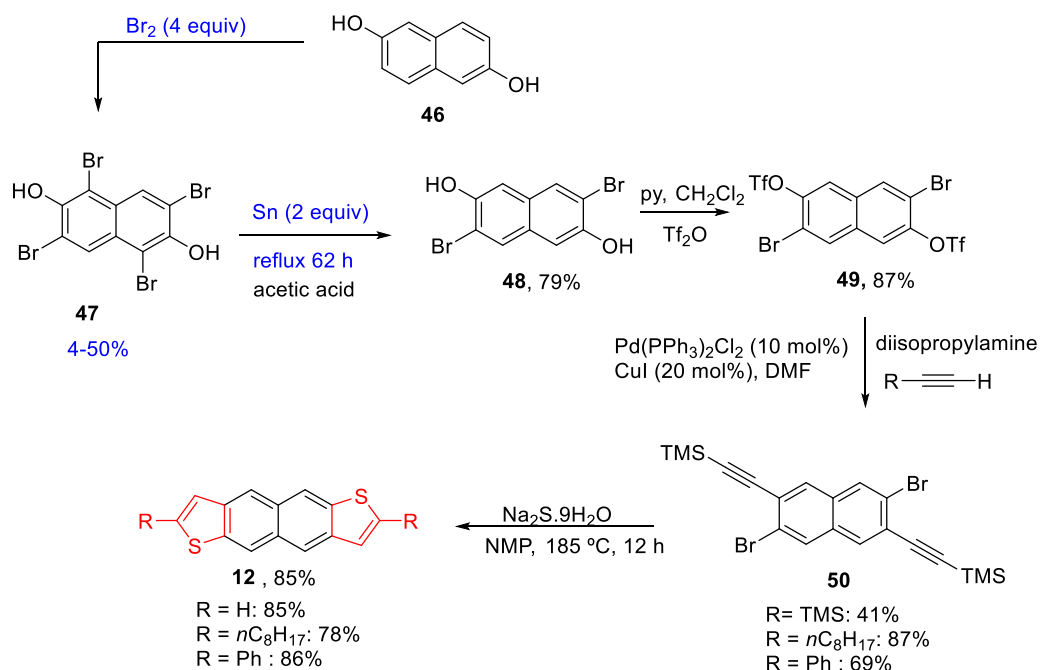
Figure 9 Molecular structures of typical acenedithiophenes cores

In addition to using the naphtho[2,3-*b*:6,7-*b'*]dithiophene **12** (NDT) framework as a core for molecular semiconductors, these fragments can be used as a structural unit for polymer semiconductors.¹³³

However, from a synthetic standpoint the chemistry of these materials presents various challenges. One of these is the selective synthesis of isometrically pure *syn*- and *anti*-ADTs.¹²⁷ In addition, there is a lack of practical approaches for the scalable synthesis of NDTs for further investigation.¹²⁸

Finally, although *anti*-NDT and *syn*-NDT have similar molecular shapes and electronic structures, the charge carrier transport properties are normally quite different.¹³⁴ These interesting results prompt us to examine the potential of new routes to NDT isomers.

In contrast to anthra[2,3-*b*]thiophenes **11**, previous literature synthesis of naphtho[2,3-*b*:6,7-*b'*]dithiophene **12**, is limited to a single approach.^{108,112,135} Commercial 2,6-dihydroxynaphthalene **46** (£52 for 5 g, from Sigma Aldrich, in August 2018), is brominated to afford 1,3,5,7-tetrabromonaphthalene-2,6-diol **47** by known procedures (Scheme 15).^{136,137} Unfortunately, the literature yields for this process are reported to be highly variable (4-51%). Additionally, a further four steps are required to convert **47** to **12**.

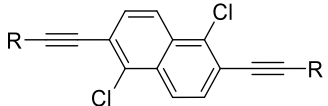
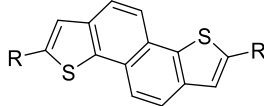
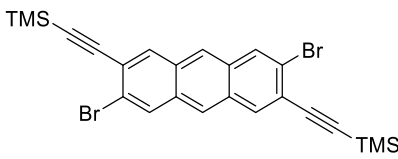
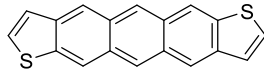
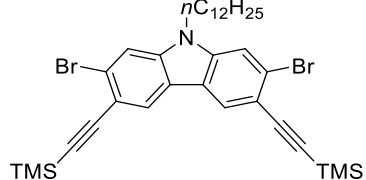
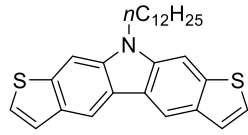
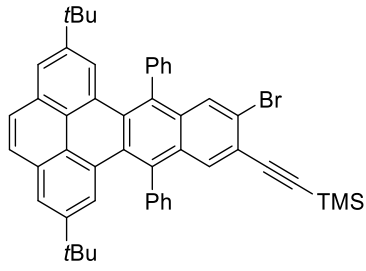
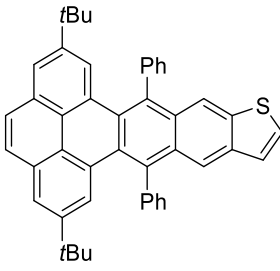
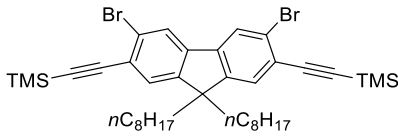
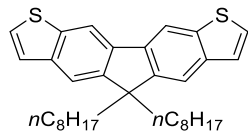


Scheme 15 Literature method to a synthesis of naphtho[2,3-b,6,7-b']dithiophene **12**¹¹²

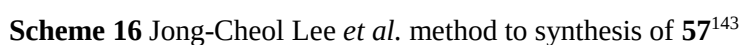
Using the same method that shown in Scheme 15, Table 3 shows all the related materials which have been prepared using sodium sulfide hydrate (Na₂S·9H₂O).

Table 3 Synthesis of Acene-thiophenes and related compounds via sodium sulfide hydrate (Na₂S·9H₂O)

Entry	Substrate	Product	Yield/ %	Ref.
1			R = TMS (H): 88 R = nC ₈ H ₁₇ : 68 R = Ph: 57	138
2			R = TMS (H): 62 R = nC ₈ H ₁₇ : 62 R = Ph: 75	138
3			R = TMS (H): 68 R = nC ₈ H ₁₇ : 95 R = Ph: 71	112

4			R = TMS (H): 90 R = $n\text{C}_8\text{H}_{17}$: 89 R = Ph: 60	112
5			Trace	139
6			68	140
7			40	141
8			50	142

However, regarding the derivatives of compound **12** in 2012 Jong-Cheol Lee¹⁴³ *et al.* synthesised a new derivatives for naphthodithiophene (Scheme 16). The key starting material 1,5-dimethoxynaphthalene-2,6-dicarbaldehyde **52** required 3 steps using known procedures.^{144,145} This method has made the target compound **57** over 8 complex steps. The final product **57** was used as monomer block for further chemistry.



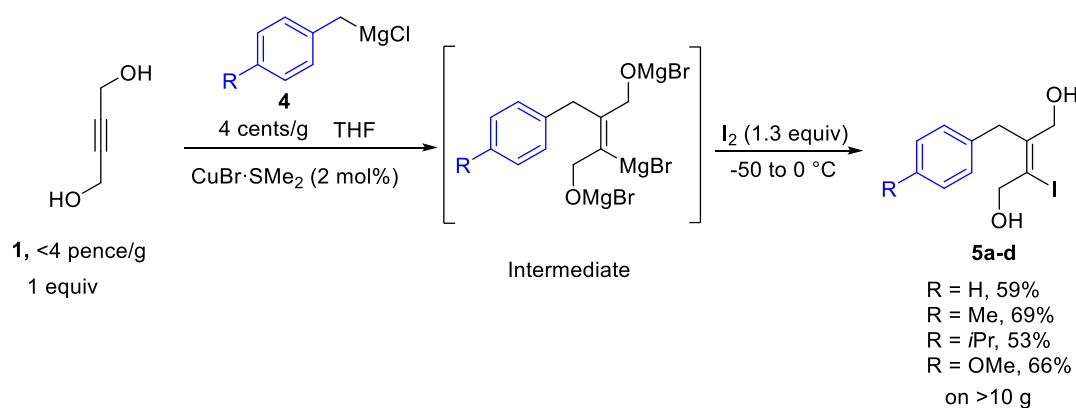
Although many methods in the literature are reported for the synthesis of anthra[2,3-*b*]thiophene **11a**, no method offered a synthesis for a 7-substituted variant of this compound. Therefore, the aim for our method is to both synthesise **11a** from an efficient alternative pathway, and also to synthesise of new 7-substituted derivatives for **11b-d**. Also, this Chapter aimed to synthesis the compound naphtho[2,3-*b*:6,7-*b'*]dithiophene **12** using a similar method for **11a-d**.

2.4 Results and discussions

2.4.1 Synthesis of 7-substituted anthra[2,3-*b*]thiophene derivatives

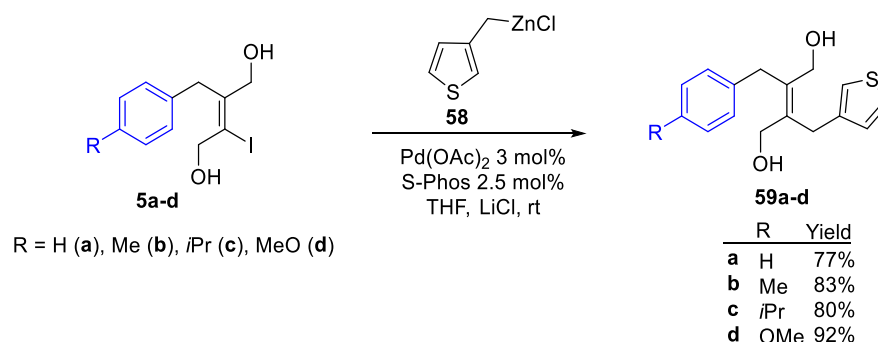
Our approach to the synthesis of 7-substituted anthra[2,3-*b*]thiophenes **11a-d** involves four steps from the commercially available¹⁴⁶ crystalline iodides **5a-d**. Alternatively, the iodides **5a-d** are easily prepared from 2-butyne-1,4-diol **1** and benzylic chlorides **4**, both of which are typically available at low cost (<4 pence/g).

Our approach to **5a-d** involves the copper catalysed carbocupration reaction of the Grignard reagents 4-RC₆H₄MgCl with 2-butyne-1,4-diol **1** carried out at 60 °C. The (*E*)-carbomagnesiation intermediates are then quenched with iodine (1.3 equiv based on diol) at -60 °C followed by slow warming to (0 °C) over one hour to yield the target iodide-diol core **5a-d**. Moderate to good yields (53-69%) are obtained on large-scale reactions (>10 g) of **5a-d**, by storing the crude material in cool Et₂O (5 °C) to crystallise overnight (Scheme 17). One clear advantage of this reaction is that it does not require any chromatography (see experimental section).



Scheme 17 Synthesis of the key diols **5a-d**

Subsequently, **5a-d** are subjected to Negishi cross coupling, using Pd(OAc)₂ (3 mol%) using S-Phos (2.5 mol%) as an associated ligand which allows direct Negishi-coupling with (thiophen-3-ylmethyl)zinc(II) chloride **58** affording **59a-d** without the need to protect the free alcohols (Scheme 18).



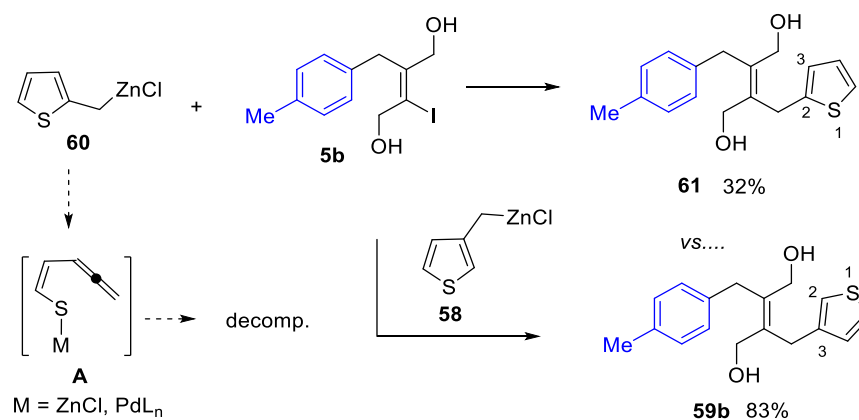
Scheme 18 The Negishi coupling of synthesis of the diols **59a-d**

Conveniently, initial crops of the soluble diols **59a-d** can be achieved via cooling the crude material at (5 °C) in ether and filtering to give sharp needle shaped colourless crystals. The rest of material can be obtained by column chromatography (3:2) (EtOAc:pentane) of the mother liquid to yield (77-92%) of **59a-d** in total. Analytically pure colourless needles can be obtained via recrystallization from hot acetonitrile then cooling to 4 °C.

Generally, organozinc reagents are sensitive to acidic hydrogens, so unprotected alcohol functional groups could inhibit the Negishi coupling due to competitive deprotonation of the organozinc reagents. However, in our case, there was no competitive protonation effect on the reaction. In fact, fast cross-coupling rather than deprotonation resulted in the presence of only 1.2 equivalent of organozinc and one equivalent of dry lithium chloride. Similar studies have been carried out by Knochel *et al.*¹⁴⁷ Strong ligand inhibition was found to occur in their studies when they added one equivalent of *i*PrOH at -10 °C; 80% of PhZnI·LiCl was protonated.

Optimization of the Negishi coupling step has been achieved by changing the position of functional group in thiophene zinc reagent from α **60** to β **58** (which is normally the less reactive position). Attempts to use the regio-isomeric Negishi reagent **60** with iodide **5b** provided only low yields of **61** (32%) (Scheme 19). Extensive catalyst

deactivation was observed in these reactions [as demonstrated by re-dosing experiments, see experimental section and (Scheme 19)].

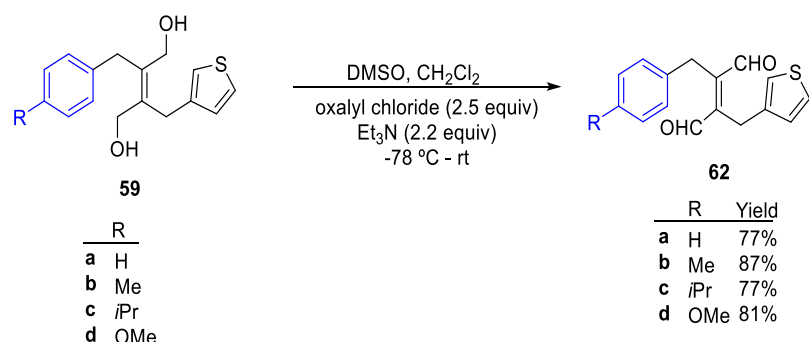


Scheme 19 Comparative coupling of diols **61** and **59b**

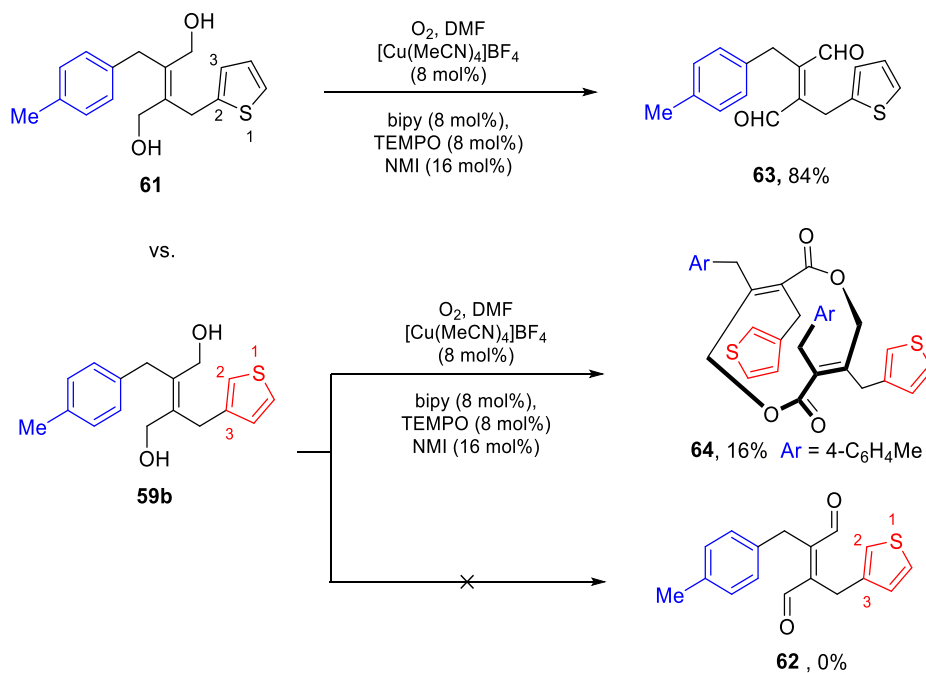
Relatively few examples of 2-thienylmethyl organometallics are present in the primary literature.^{148,149} The appearance of multiple 1:1 signal in the range δ_{H} 5.0 - 6.4 in the crude ^1H NMR spectra of **61** (assigned to $=\text{CH}_2$ units) is in accord with *anti*-elimination of **60** and subsequent decomposition of the potentially derived reactive putative allene intermediate **A**. Compound **58**, however, behaves cleanly.

Interestingly regio-isomeric alcohols **59** and **61** also show different behaviour upon their oxidation. The free alcohol functional groups on **59a-d** need first to be oxidized to the corresponding aldehydes **62a-d**, before they can undergo Bradsher cyclisation to the final product anthrathiophenes. This proved to be most challenging step in our procedure and many different methods and conditions were screened unsuccessfully. Finally, a Swern oxidation procedure was developed, which operated very well and gave us the desired aldehydes **62a-d**.

Standard Swern oxidation of **59a-d** to the yellow dialdehydes **62a-d** proceeded in good yield, provided a small additional amount of DMSO was used in the reaction to facilitate complete dissolution of **59** at low temperature (Scheme 20).

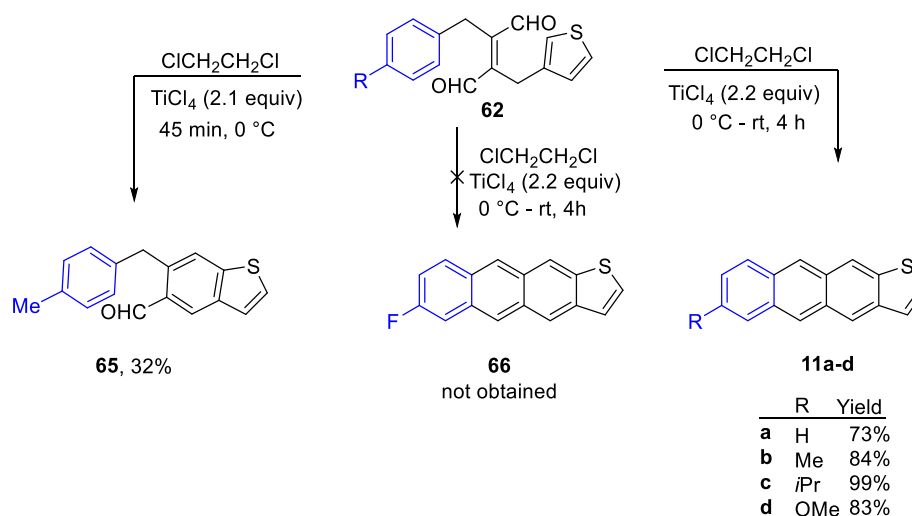
Scheme 20 Swern oxidation of diols **59a-d**

While **61** cleanly provides **63** under our preferred aerobic oxidation conditions¹⁵⁰ (Scheme 21) initial tests of **59b** led to complex mixtures under the Stahl-catalysis procedure.¹⁵⁰ Similar issues were seen on attempted use of MnO₂ and pyridinium chlorochromate (PCC) oxidants. From these complicated mixtures the only isolable product is **64** based on spectroscopic data (Scheme 21), indicating that chemoselectivity oxidation is not attained. Fortunately, this issue could be overcome by simply increasing the DMSO content of Swern-based oxidations used in general conversions of **59** to **62**.

Scheme 21 Comparative oxidation of diols **61** and **59b**

Finally, double³⁶ Bradsher closure of **62a-d** is effected cleanly in the presence of TiCl_4 . Isolation of **11a-d** is simplified by use of a 1:1 quench mixture of acetone/methanol. The titanium by-products generated in the closure are soluble in this mixture and **11a-d** may be isolated by simple filtration (use of Whatman glass microfiber GF/A filter paper makes this very straightforward, see experimental section).

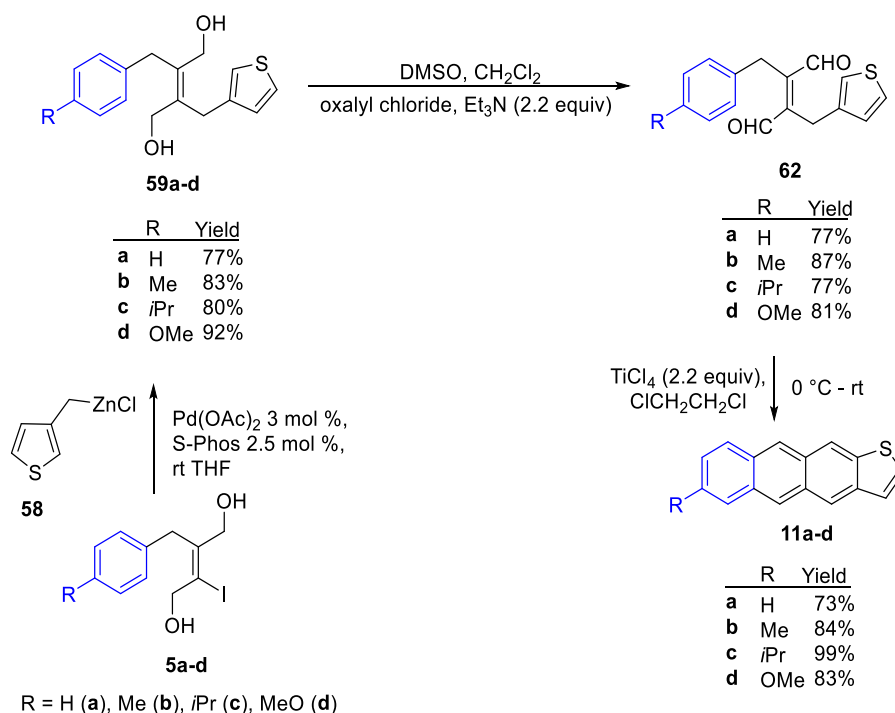
The final Bradsher closure^{36,126} easily affords **11a-d** in good yields (73-99%) as bright yellow powders. These reactions show typical Friedel-Crafts behaviour: at shorter reaction times mono closure onto just the electron-rich thiophene unit is observed. Thus, the scope of the final step in Scheme 22 is limited to the preparation of electron-rich anthra[2,3-*b*]thiophenes **11a-d**. In support of this idea closure of **62a-d** to **11a-d** where $\text{R} = \text{F}$ was not achieved. The other steps of Scheme 22 are tolerant of alkyl, aryl, and OMe substituents.³⁶



Scheme 22 Optimization of the final Bradsher closure

The chemistry of Scheme 23 shows a concise methodology for the synthesis of anthra[2,3-*b*]thiophenes **11a-d**. Nonetheless, one of the advantages of Scheme 23 is the greater solubility of the 7-alkyl derivatives **11b-d**, which allows routine acquisition of fully assigned ^{13}C NMR spectra. Additionally, **11b-d** are also easier to process in

subsequent further functionalization or device preparations. The average overall yield for the derivatives **11a-d** over the three steps of (Scheme 23) ranged from 43-61% (average 57%).

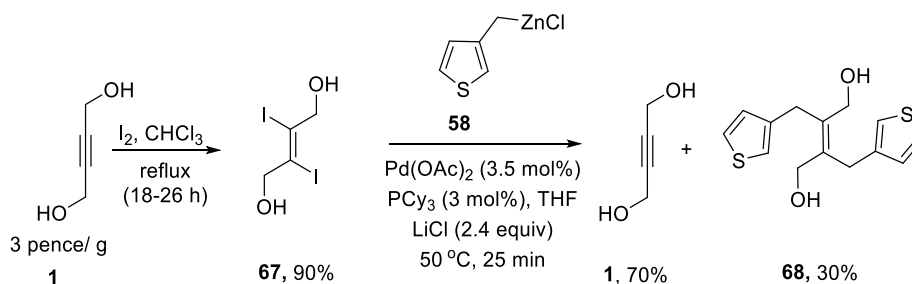


Scheme 23 Concise methodology for synthesis of anthra[2,3-*b*]thiophenes **11a-d**

2.4.2 Synthesis of naphtho[2,3-*b*:6,7-*b'*]dithiophene **12**

In support of our alternative approach to the known literature procedures to **12**,¹¹² we have introduced a new method for its synthesis. Our approach considered its preparation based on straightforward Negishi coupling of the diiodide **67**³⁶ (itself derived from low cost 2-butyne-1,4-diol **1**, Scheme 24). A solution of (thien-2-ylmethyl)zinc(II) chloride **58** was added to a mixture of (*E*)-2,3-diiodobut-2-ene-1,4-diol **67**, Pd(OAc)₂ (3.5 mol%) with simple tricyclohexylphosphine (PCy₃) (3 mol%) as an associated ligand and in the presence of dry LiCl (2.2 equiv) in dry THF. Under optimal conditions the reaction mixture is stirred over 25 min at 50 °C. In these studies,

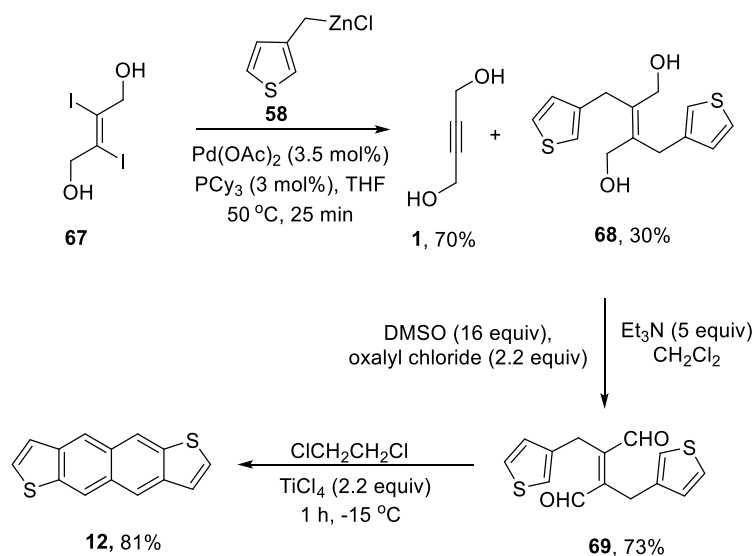
we found that the product diol **68** is acid sensitive. It is very important to wash the separated organic layer directly with saturated NaHCO_3 otherwise if there is any acidic NH_4Cl is left in the crude mixture it promotes the decomposition of the symmetric diol **68**.



Scheme 24 straightforward Negishi coupling of the diiodide **67**

Although the yield of **68** was modest (30%), due to competing transmetalation-elimination of **67**, the butyne diol by-product produced **1** was insoluble and very simply and easily separated (see the experimental section).

The remaining steps of the sequence all give good yields and involve chromatography-free work-up procedures (Scheme 25).



Scheme 25 Straightforward synthesis of naphtho[2,3-*b*:6,7-*b'*]dithiophene **12**

Preparation of **12** was confirmed by HRMS together with ^1H , ^{13}C NMR spectroscopy (Figures 10 and 11), and IR and UV-vis spectroscopy (Figure 16). Using the latter, the optical bandgaps (E_g) of **11a-d** and **12** were measured using standard Tauc plots (Table 4).

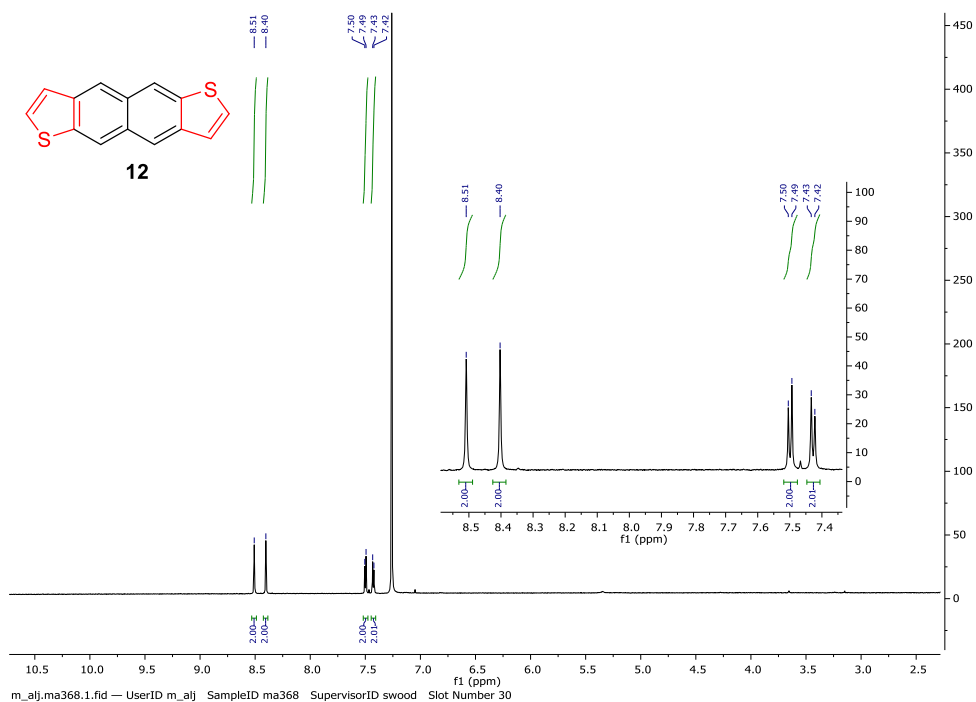


Figure 10 ^1H NMR spectrum of **12** (500.1 MHz respectively, CDCl_3)

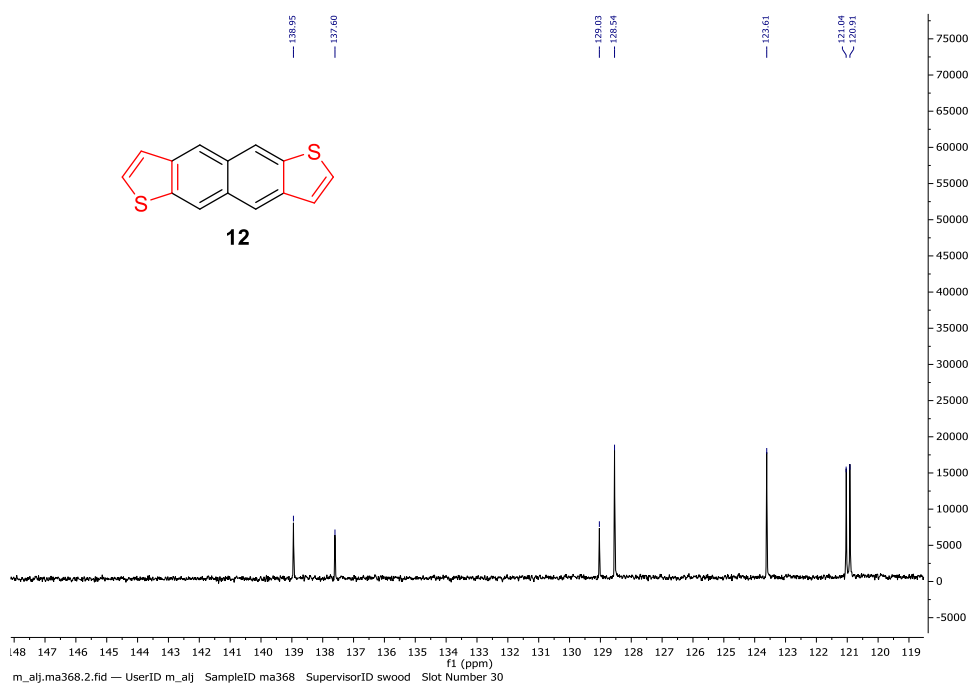


Figure 11 ^{13}C -NMR spectrum of **12** (125.8 MHz respectively, CDCl_3).

2.4.3 Calculating bandgaps using Tauc plot of UV-Vis data

UV-Vis spectroscopy is considered as an easy and straightforward technique allowing accurate calculation of optical band gap energy for organic π -conjugated materials.¹ In this work, we have measured the optical band gaps for **11a-c** and **12** attained by using Tauc plots of UV-Vis data (Figures 12-16, Table 4).

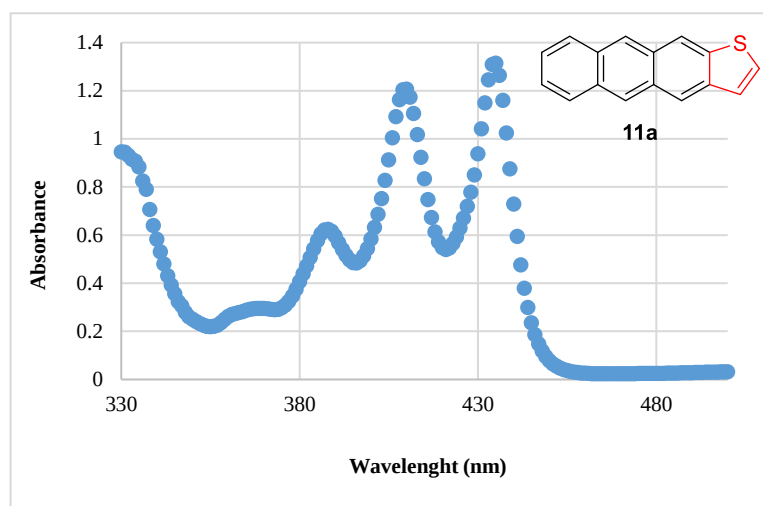


Figure 12 UV-vis spectroscopy for **11a** in CH_2Cl_2 at 10^{-4} M

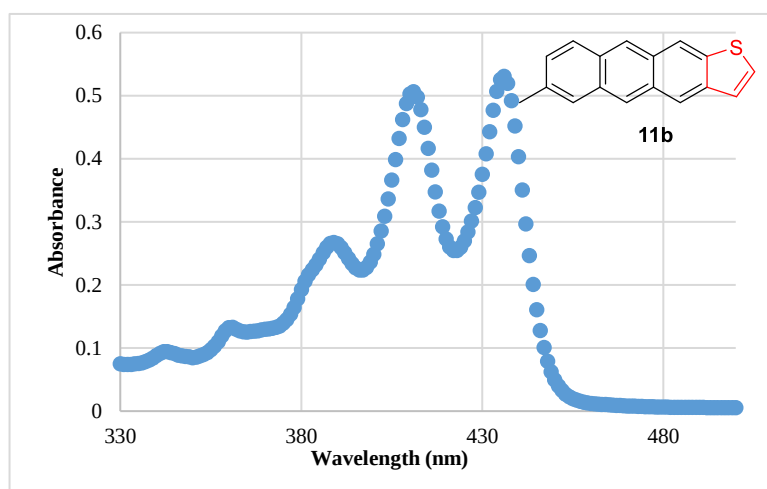


Figure 13 UV-vis spectroscopy for **11b** in CH_2Cl_2 at 10^{-4} M

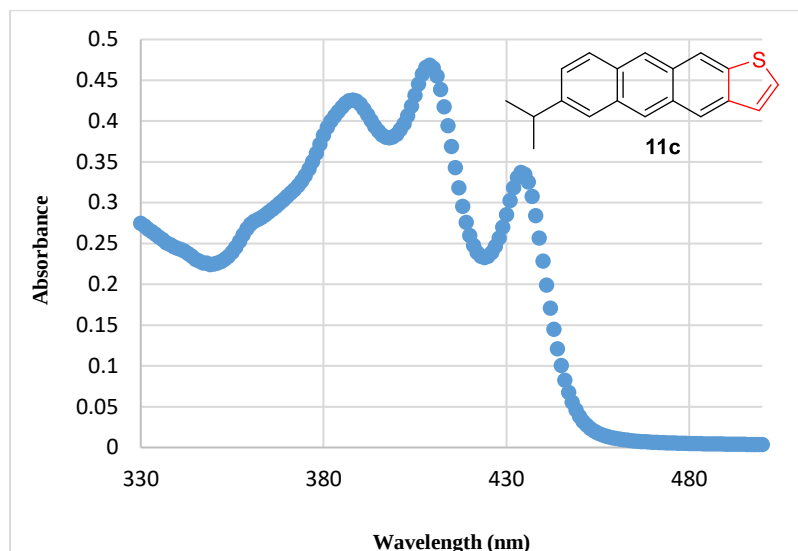


Figure 14 UV-vis spectroscopy for **11c** in CH_2Cl_2 at 10^{-4} M

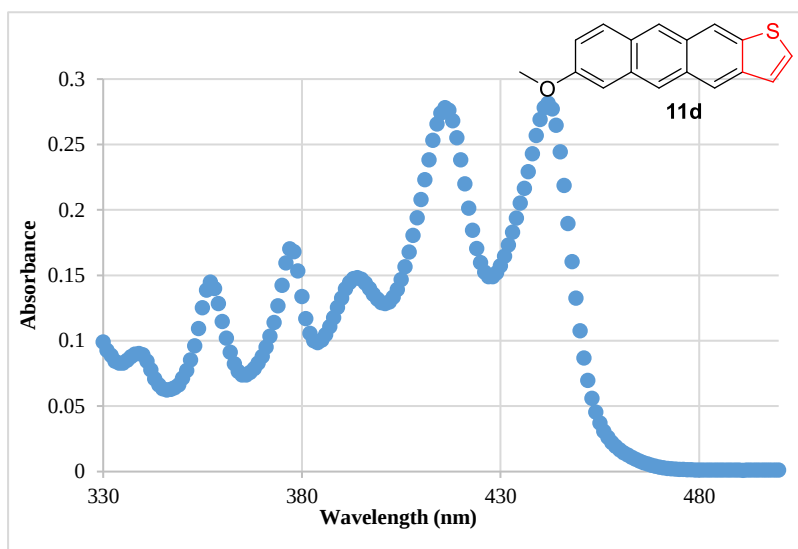


Figure 15 UV-vis spectroscopy for **11d** in CH_2Cl_2 at 10^{-4} M

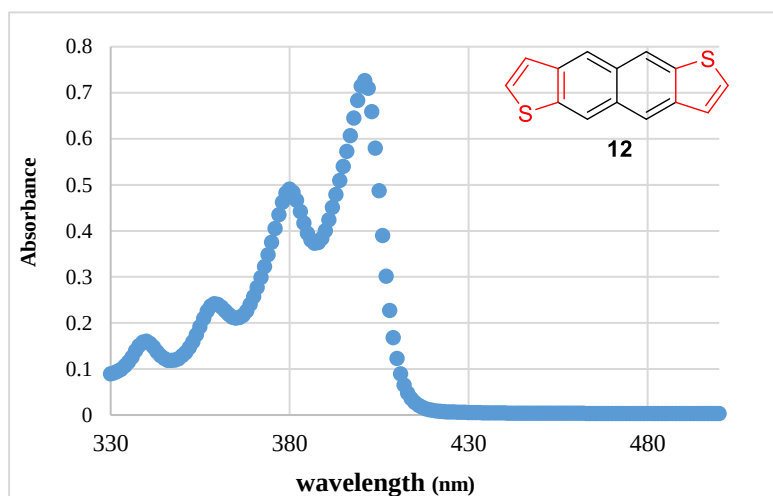


Figure 16 UV-vis spectroscopy for **12** in CH_2Cl_2 at 10^{-4} M

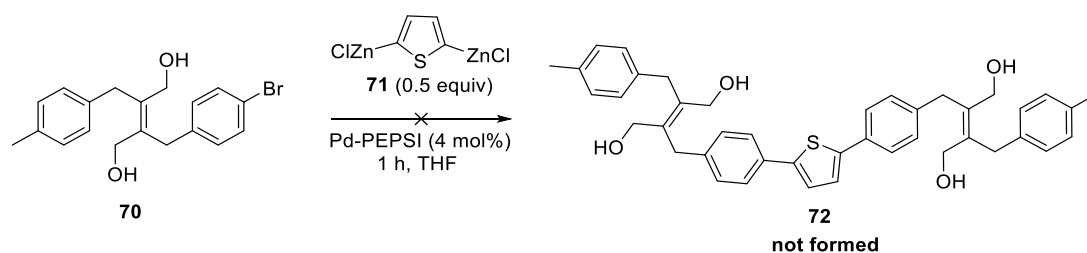
Table 4 The optical bandgaps for compounds **11a-d** and compound **12**

compound	λ_{max} (nm) ^a	E_g (eV) ^b
11a	435	2.75
11b	437	2.73
11c	436	2.72
11d	443	2.69
12	402	2.98

^a In argon saturated CH₂Cl₂; longest wavelength absorption band. ^b Determined by Tauc plot of UV-Vis data.

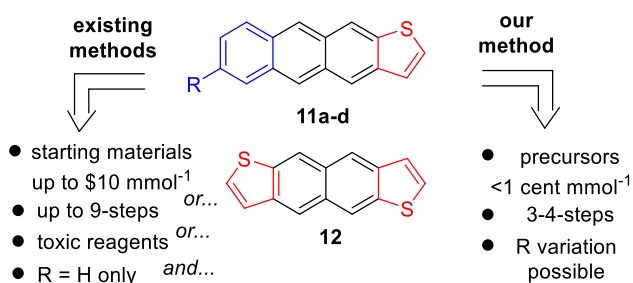
2.4.4 Attempted modification of the properties of a tetracene

As our research group is also interested in tetracene chemistry, one of the aims of my project was to try modifications of these using thiophene chemistry. Hence, our strategies to achieve these modifications was by linking one or two thiophene units to the tetracene structure. The reason for this strategy was to make the tetracene structure more stable under ambient conditions (Scheme 26). Unfortunately, the cross-coupling reaction between the diol **70** and the zinc reagent **71** in the presence of Pd-PEPSI (4 mol%) was not achieved. Although we varied the conditions for this reaction including time and temperature, we did not find any viable method to form **72**.

**Scheme 26** Attempted cross coupling of bromo-diol **70** with the zinc reagent **71**

2.5 Conclusion

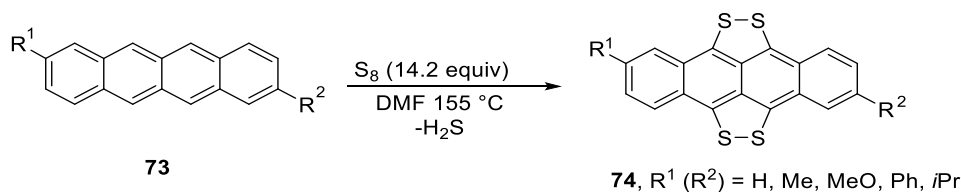
To summarise, in this Chapter, we have established new approaches for the efficient synthesis of 7-substituted anthra[2,3-*b*]thiophenes **11a-d** and the unsubstituted naphtho[2,3-*b*:6,7-*b'*]dithiophene **12**. The methods employed are simple, use low cost starting materials, the procedures are scalable, and avoid chromatography in many cases. These methods also offer simple flexible approaches to the inclusion of 7-substituted thiophene-acenes that cannot be prepared by existing approaches. Finally, in our approach compounds **11a-d** are prepared in three steps in average overall yields of >50%. Existing reported methods require multi steps to attain **11a** and **12** both in low overall yield. In some methods the final product **11a** was obtained in acceptable yield but this method requires some toxic reagents and expensive starting materials. In comparison, the approaches herein constitute useful, cleaner and more sustainable alternatives to these important classes of organic electronic fragments (Scheme 27).



Scheme 27 Summary and comparative between our approach and the literature

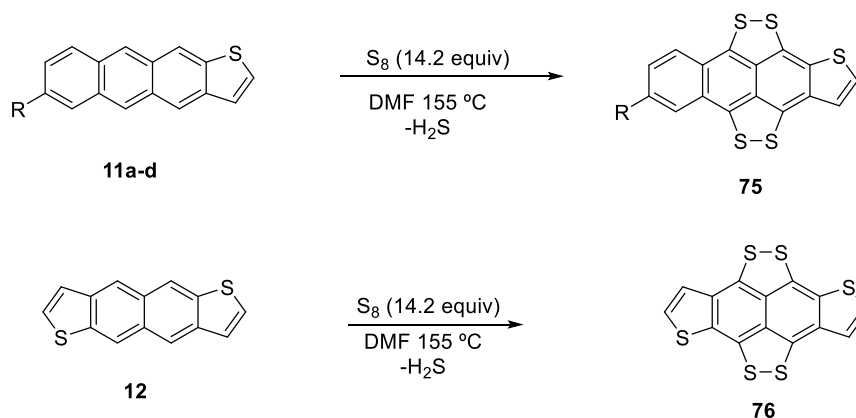
2.6 Future work and ongoing research

Because of the limited time available on this project, there are still some related area that should be investigated. According to the recent paper published by the Woodward group.²⁵ Scheme 28 shows the synthesis of substituted tetrathiotetracenes.



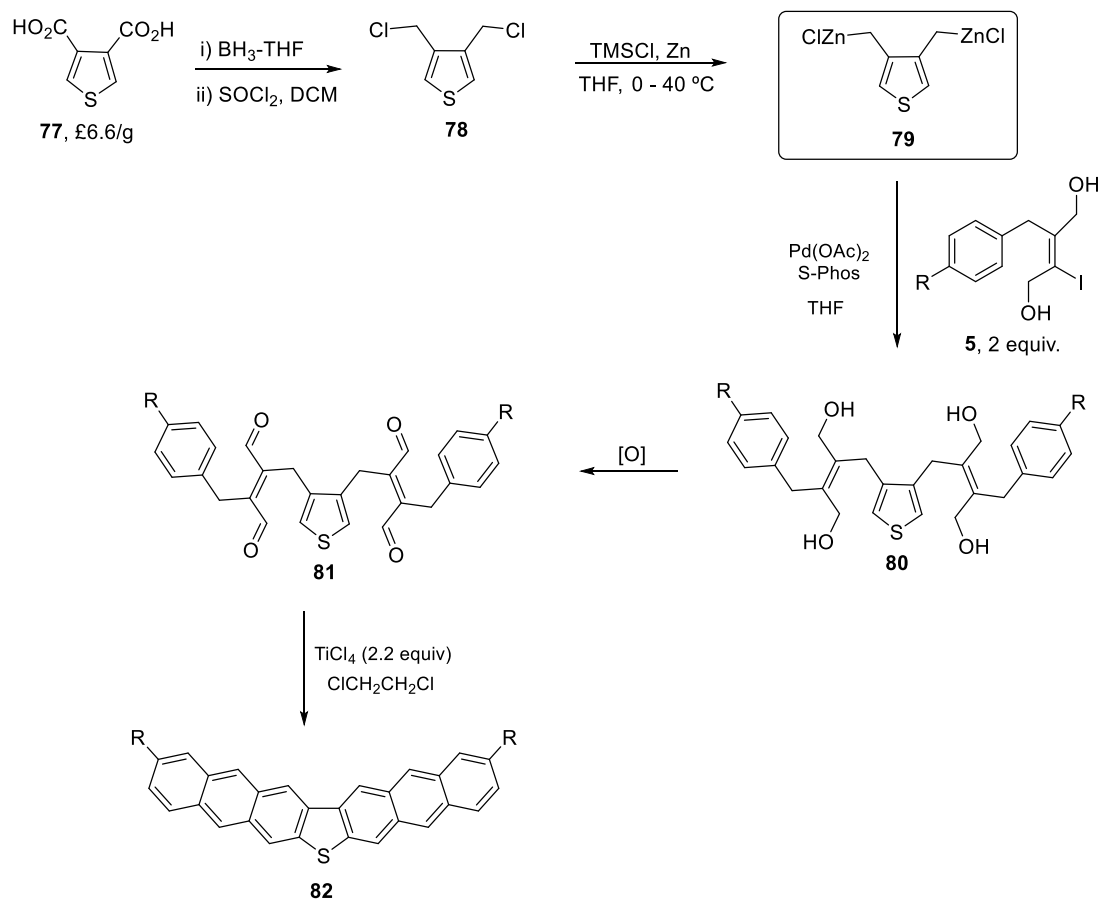
Scheme 28 Woodward *et al.* method to synthesis of tetrathiotetracenes **74**

These new compounds **74** have a reduced the optical band gap compared to tetracene, typically from 2.54³⁶ to 1.53²⁵ eV. Hence, our near future plan is to synthesise the compounds **75** and **76** using similar method of Woodward *et al.*²⁵ to attain new 2,8-substituted anthra[2,3-*b*]thiophene **75** and naphtho[2,3-*b*:6,7-*b'*]dithiophene **76** (Scheme 29).



Scheme 29 Our ongoing research

In addition, based on the results and the new methodologies that have been described in this Chapter, we propose that we can use a similar method to prepare analogues of known^{151,152} organic electronic materials to those, such as the alkyl substituted material shown in Scheme 30.



Scheme 30 Potential future work

The zinc reagent **79** can be easily made over 3 steps using the commercially available **77** as starting material (available from Key Organics), then the rest of the steps will be comparable to the method discussed in this Chapter.

3 Chapter Three: Efficient Synthesis of 2,5-Dicarbonyl Derivatives of 3,4-Ethylenedithiophene (EDTT) via Addition-Elimination Reactions

Publication from this Chapter:

Mustafa A-JABBAR Al-jumaili, Simon Woodward, “Efficient synthesis of 2,5-dicarbonyl derivatives of 3,4-ethylenedithiophene (EDTT) via addition-elimination reaction” *Tetrahedron* **2017**, 73, 5847-5852.

3.1 Introduction

Since their initial discovery in 1980 oligothiophenes have risen to become one of the most privileged structures in the organic semi-conducting materials area.^{153, 154} By appropriate choice of thiophene substituents the resultant materials' (opto) electrical properties can be modulated with a high degree of precision. Generally, specific properties for the thiophene materials such as good conjugation, are required and this requires the organic materials to achieve band gaps in the semiconductor region with high mobility, high conductivity, and electrooptical response.¹⁵⁵ Hence, this ability to tune thiophene based materials for a specific application has led to their widespread use in organic photovoltaics (OPV),¹⁵⁶ organic field effect transistors (OFET),¹⁵⁷ sensors,¹⁵⁸ and particularly in (electrochromic) organic light emitting diodes (OLED)^{159, 160} applications.

However, most of the neutral semiconducting polymers such as polythiophenes **83**, polyanilines **84**, polypyrroles **85**, show low solubility and this made them very difficult to process. Therefore, many researchers have focused on the modification of the chemical structures for these polymers, and of course their monomers, in order to modify their electronic structures and develop their electrical properties and processability through improved solubility¹⁶¹ (Figure 17).

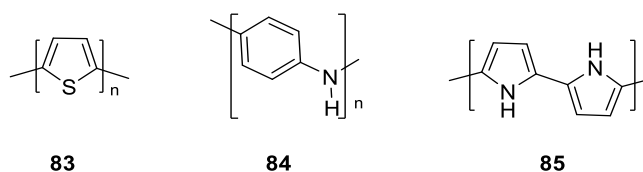


Figure 17 The structure of polythiophenes **83**, polyanilines **84** and polypyrroles **85**

In order to overcome such processing these disadvantages, many substituted derivatives of these polymers have been established,¹⁶² perhaps the greatest

development was achieved during the second half of the 1980s by scientists at the Bayer AG research laboratories in Germany, who first prepared poly(3,4-ethylenedioxythiophene) (PEDOT).¹⁶³ Likewise, similar progress came from the development of polythiophenes structure **83**.¹⁶¹ Although very important bulk PEDOT still had some disadvantages in terms of its poor solubility. In addition, another important progress was attained when PEDOT poly(3,4-ethylenedioxythiophene)/ poly(styrene sulfonate) **86** co-polymer formulations were achieved in 1990 and its subsequent marketing marked by Bayer AG (Figure 18)^{164,}

165

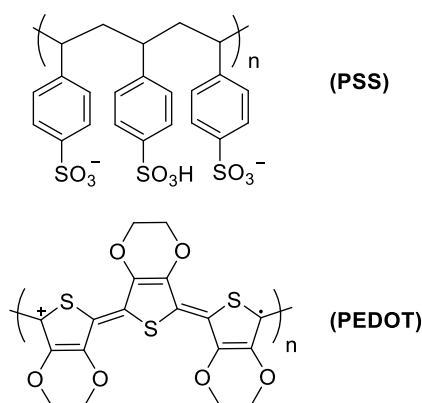


Figure 18 A representative structure for PEDOT:PSS **86**

Furthermore, PEDOT can be prepared at the reasonable cost (e.g. conducting PEDOT:PSS is about £1 per gram for a 1-2% suspension in water, from Sigma Aldrich).

On the another hand, poly(3,4-ethylenedithiathiophene) **88** (Figure 19), as one of the most important analogues of **87**, has individual electrical and optical properties and potential applications in the manufacture of rechargeable batteries, sensors, photovoltaic devices, electrochromic devices, polymer-fullerene devices, and so on but this species is much less widely available.^{166,165,167,168,169,170,171,172,}

173,174,175,176,177,178,179

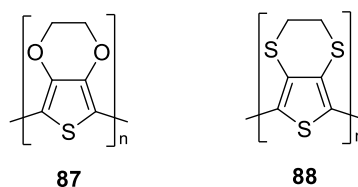
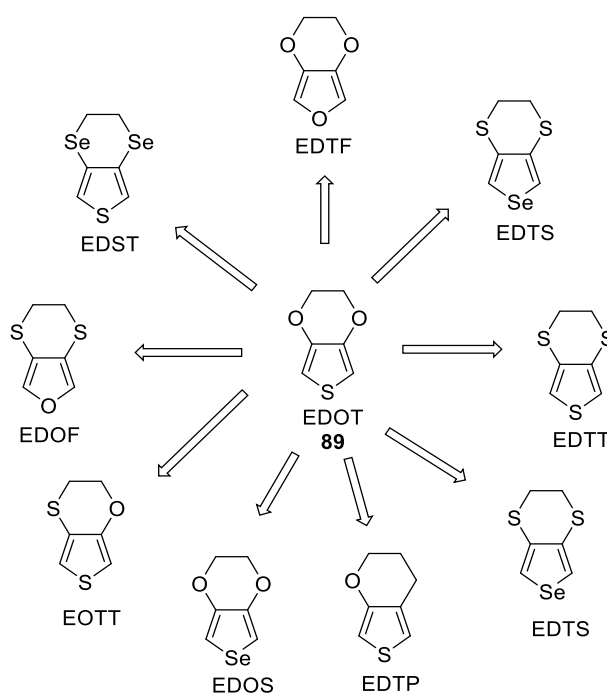


Figure 19 The structure of PEDOT **87** and its analogue PEDTT **88**

3.2 Literature approaches for 3,4-ethylenedithiophene (EDTT) **89** and its derivatives

Poly(ethylene-3,4-dioxythiophene) (PEDOT) **87** is considered one of the most common polythiophene derivatives used for device applications, this is due to its excellent hole injection properties, high conductivity and stability.¹⁶⁴ Nonetheless, although the excellent advantages for PEDOT, it is itself rather insoluble and has a high melting point, which limits its further characterization and melt processing.¹⁶⁶ Hence, considerable research in EDOT has entailed the establishment of the EDOT analogs (Scheme 31) into co-polymers, or by changing the bridging alkyl groups to give improved alternative structures.¹⁸⁰⁻¹⁸³

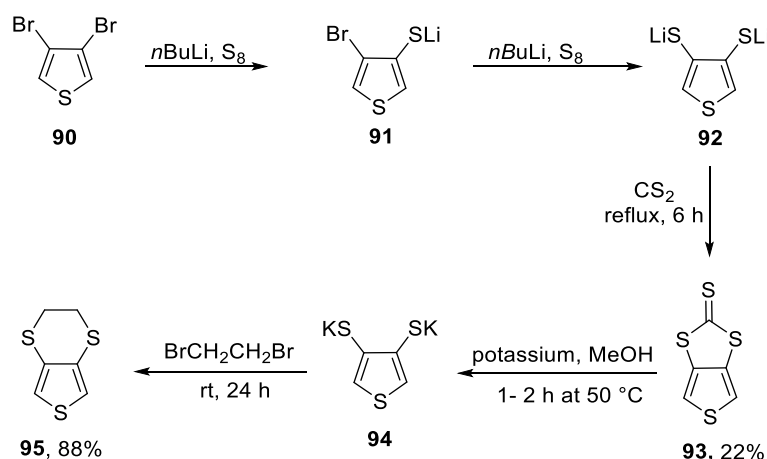


Scheme 31 Analogs derived from the structure of EDOT **89**¹⁸⁴

It is interesting to consider **88** derivatives as alternative structures for the formulation of PEDOT **87** materials, as it is completely soluble in NMP and partly soluble in THF, CHCl_3 , and other common organic solvents.¹⁶⁶ This advantage gave PEDTT more detailed spectroscopic, physicochemical, and characterization than PEDOT.¹⁶⁶

In contrast to the huge amount of studies on EDOT and its polymer PEDOT that have followed the original findings of the Bayer laboratories,¹⁶⁵ there is an obvious lack of research devoted to the sulfur analogue 3,4-ethylenedithiathiophene (EDTT) **95**. Hence, this Chapter focuses on the synthesis of new 2,5-dicarbonyl derivatives of 3,4-ethylenedithiathiophene (EDTT) and comparing these to the reported literature methods to EDTT and its derivatives.

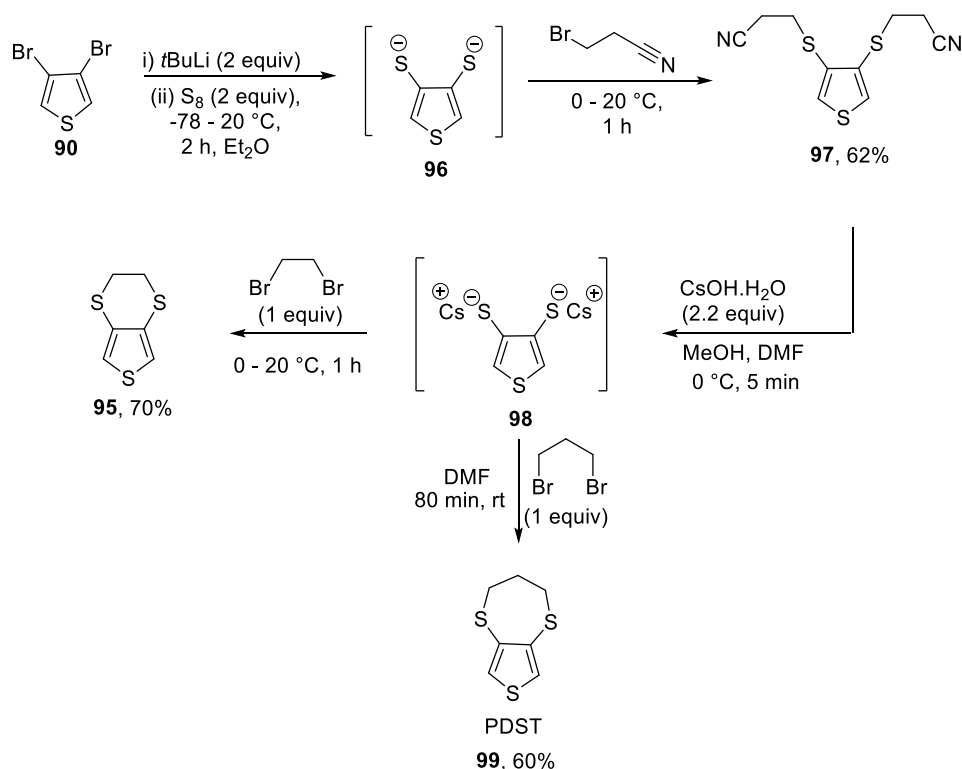
3,4-Ethylenedithiathiophene (EDTT) **95** was reported for the first time in 1995 by the method of Kanitzidis and colleagues.¹⁶⁶ They synthesised EDTT starting from known 3,4-dibromothiophene **90** via thieno[3,4-*d*]-1,3-dithiole-2-thione **93** (Scheme 32).



Scheme 32 First reported study for EDTT **95**

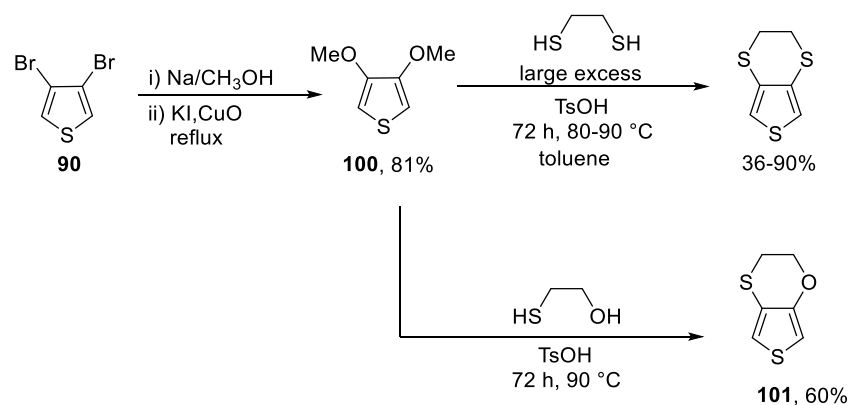
Following the method of Kanitzidis *et al.*, in 2002 the research group of Roncali¹⁸⁵ offered a new approach to synthesis of EDTT **95**, this approach started also from 3,4-dibromothiophene **90** (Scheme 33). The first step in this approach was synthesis of

the intermediate 3,4-thiophenedithiolate **96** followed by use of cyanoethyl protecting groups to obtain 3,3'-(thiophene-3,4-diylbis(sulfanediyl)) dipropanenitrile **97**. Finally, two extra steps were required to get the EDTT **95** (Scheme 33). Likewise, in 2005 the same research group¹⁸⁶ synthesised 3,4-propylenedisulfanylthiophene (PDST) **99** from 3,4-bis(2-cyanoethylsulfanyl)thiophene **98** (Scheme 33).



Scheme 33 Roncali's approach to synthesise of EDTT **95**¹⁸⁵ and PDST **99**¹⁸⁶

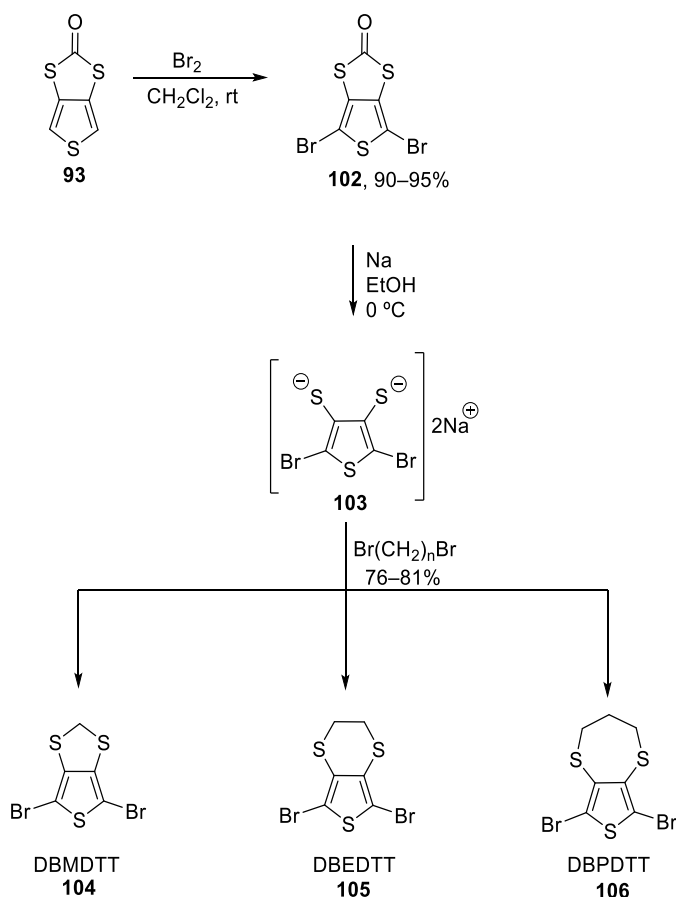
To overcome the issues regarding the larger number of steps required in these prior approaches, several studies investigating this issue have been carried out. The best literature procedure for the synthesis of EDTT **95** we could identify is shown in Scheme 34. This method was reported first by Meijer *et al.*¹⁸⁷ and this has been adopted by a number of research groups.^{188, 169, 189}



Scheme 34 Best reported method for EDTT^{188, 169, 189} and its analogue EOTT¹⁸⁹ **101**

This approach requires only two steps from 3,4-dibromothiophene **90** to add the *bis*-thioether and to prepare compound **101**.

Studies by Skabara *et al.* in 2003¹⁹⁰ have been used to access the known thieno[3,4-*d*][1,3]dithiol-2-one **93**¹⁹¹ as starting material. Over three steps they could synthesise 2,5-dibromo derivatives for MDTT **104**, EDTT **105**, PDTT **106** bearing methylenedithio, ethylenedithio and propylenedithio fractions to yields of 76–81% (Scheme 35).

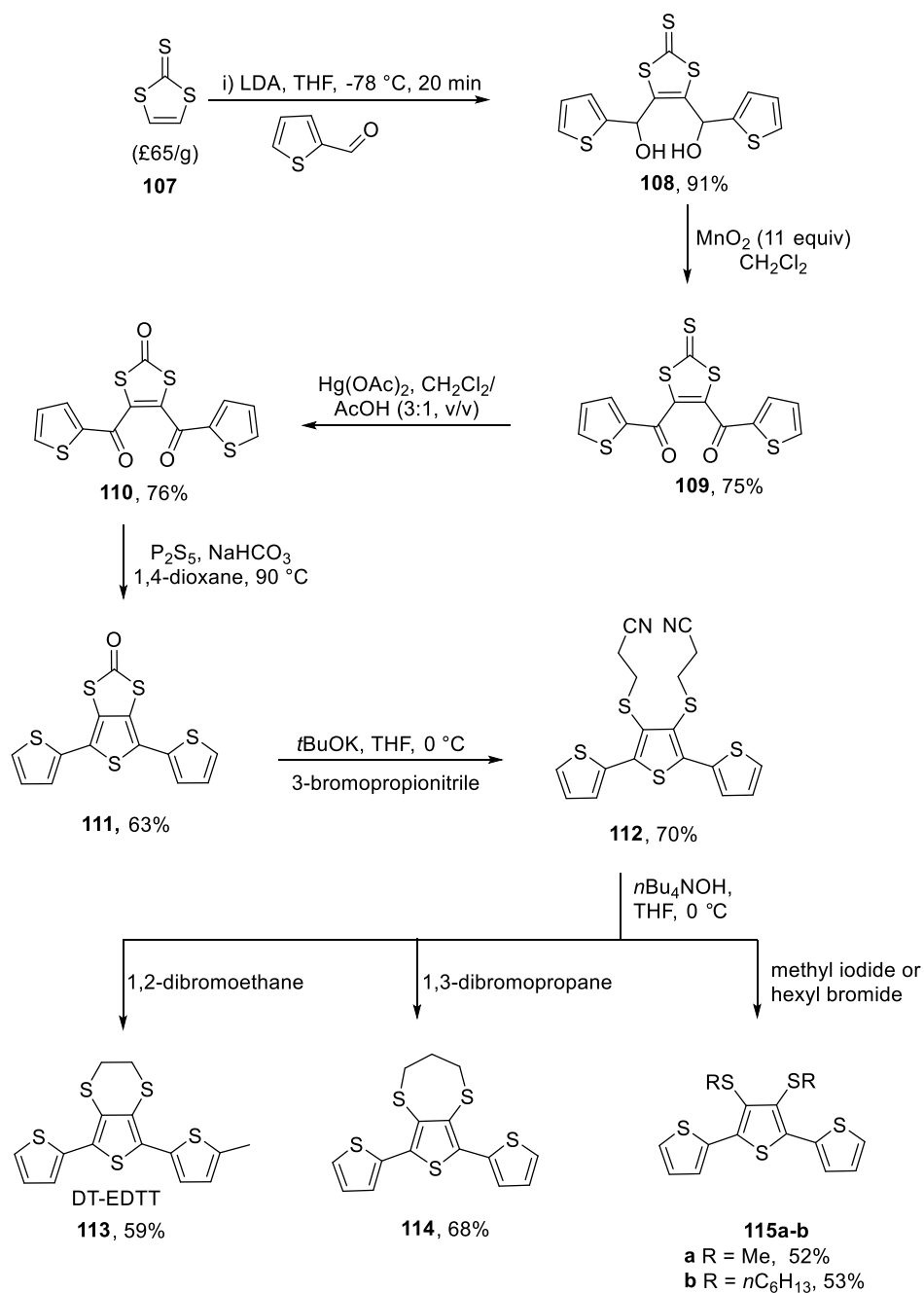


Scheme 35 Synthesis of 2,5-dibromothiophene derivatives¹⁹⁰

Moving away from synthesis of the EDTT monomer itself there are numerous other ways to attain 2,5-derivatives of 3,4-ethylenedithiophene (EDTT). Some of these methods use an EDTT unit as starting material and these are then reacted at appropriately activated α and β positions in the thiophene ring.

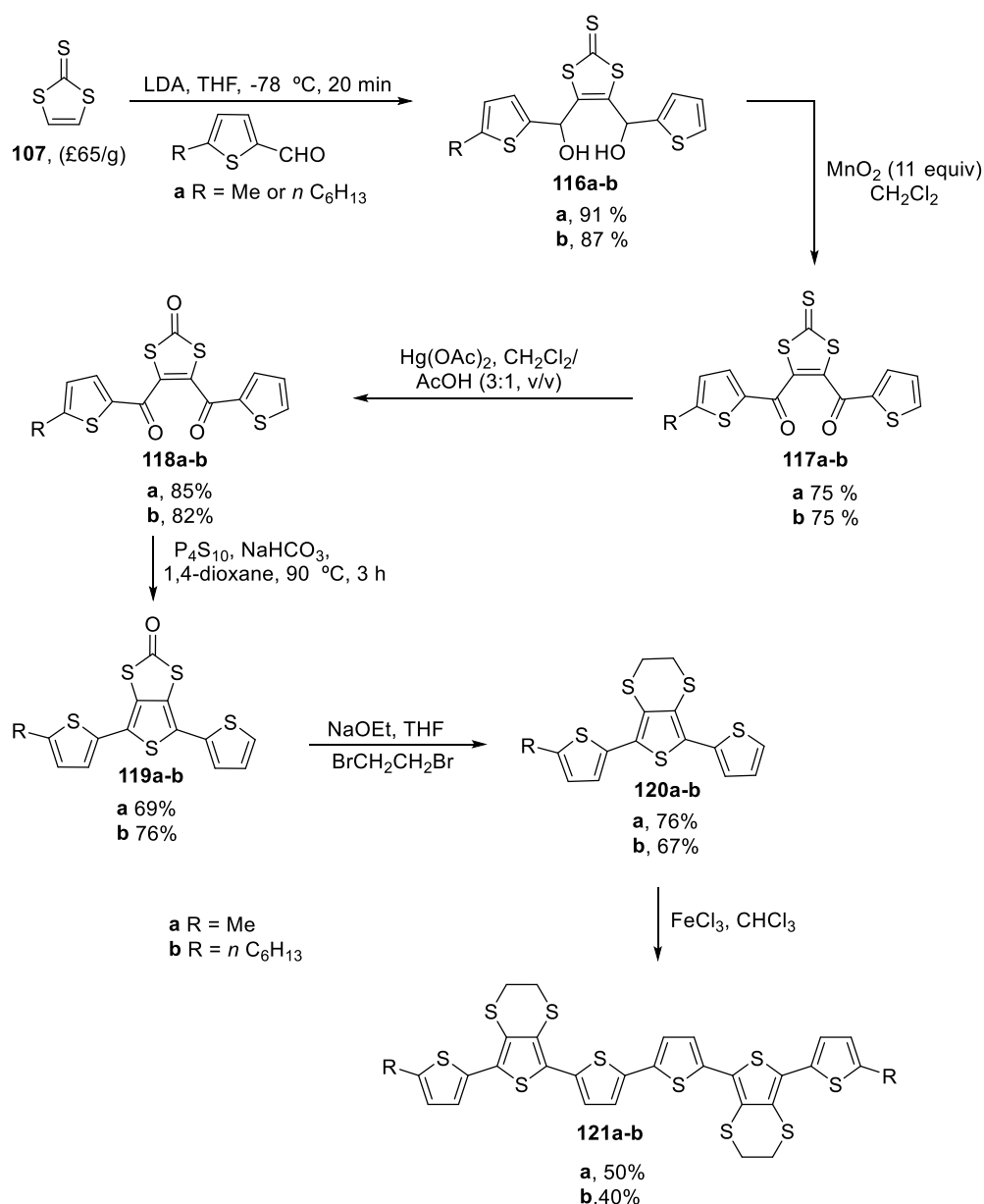
In 2002, Skabara and co-workers^{167,192} obtained a new series of monomers including 2,5-dithienyl-3,4-ethylenedithiophene (DT-EDTT) **113** (Scheme 36). This method started from the commercially available 1,3-dithiol-2-one **107** (£65/g, from Sigma Aldrich, in August 2018). Over two steps they could synthesise the known diketone **109**.¹⁹² Then diketone **109** was treated with mercury(II) acetate to afford the carbonyl analogue **110** in 76% yield. Conversion of **110** to the terthiophene derivative **111** (63%) was attained by heating of **110** in dioxane solution at 90 °C in

the presence of phosphorus pentasulfide and sodium bicarbonate. Finally, another two extra steps were required to attain **113-115**, with six overall steps (Scheme 36).



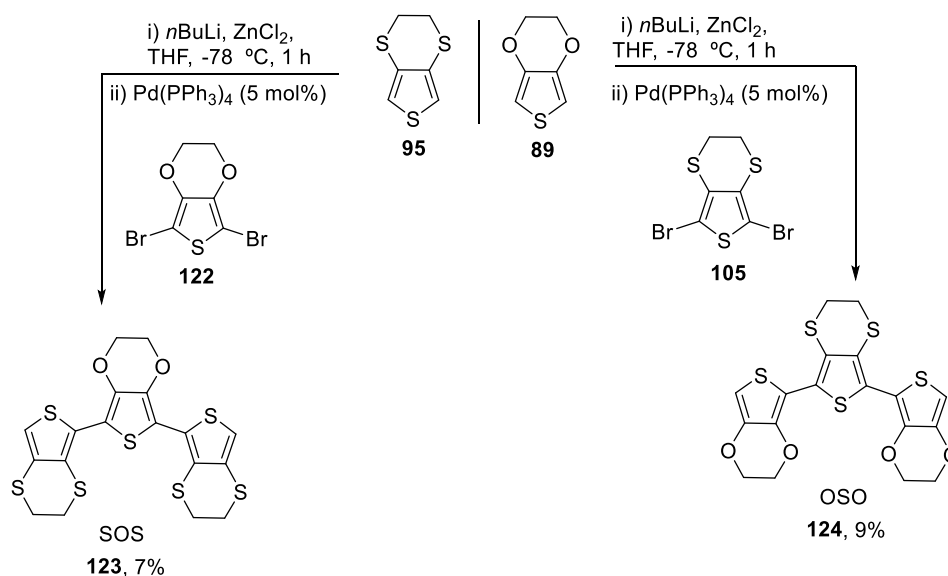
Scheme 36 Skabara approach for synthesis of thiophene-EDTT derivatives¹⁶⁷

Similarly, in 2005 the same research group of Skabara¹⁹³ could synthesise sexithiophene derivatives included two EDTT units **121**. They used **107** as main starting material over the 6 required steps (Scheme 37).



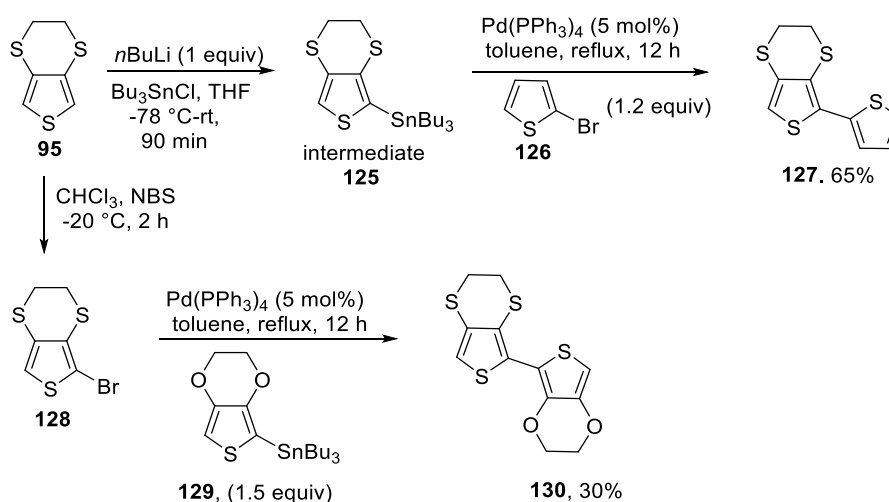
Scheme 37 Synthesis of thiophene-EDTT derivatives **121**¹⁹³

In 2005, the research group of Skabara¹⁸² offered a new method to link the EDTT **95** and EDOT **89** units together, they could synthesised of 5,7-bis(2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-yl)-2,3-dihydrothieno[3,4-*b*][1,4]dithiine (OSO) **124**, albeit in only 9% and 2,5-bis(3,4-ethylenedithiathiophene)-3,4-ethylenedioxythiophene (SOS) **123** 7% yield using EDOT and EDTT as starting materials (Scheme 38).



Scheme 38 Synthesis of 2,5-derivatives for EDTT¹⁸² **123** and **124**

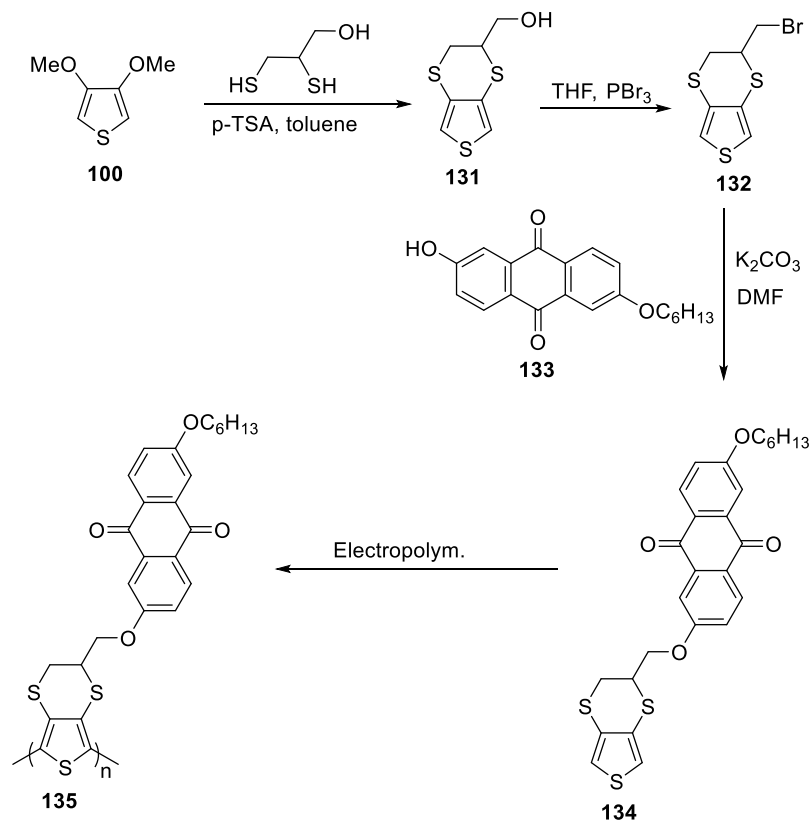
In the same year in 2005 the study by Roncali *et al.*¹⁸⁶ had a similar aim for the study of Skabara, where this studies attained a new two derivatives for EDTT. This method has used EDTT **95** as starting material and used Stille reaction conditions to obtain thiophene-EDTT **127** and EDTT-EDOT **130** monomers (Scheme 39).



Scheme 39 EDOT and thiophene derivatives for EDTT

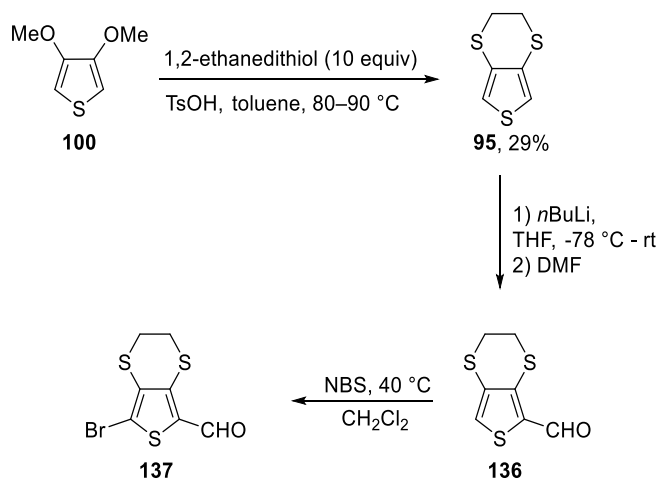
In 2008 a study, reported by Blanco *et al.*,¹⁷¹ showed the development of functionalized of a new 3,4-ethylenedithiathienophene (EDTT) derivatives. They

synthesised a novel EDTT derivative monomer linked to 9,10-anthraquinone moieties **133**. This monomer **134** was subjected to electrochemical polymerization to yield a donor–acceptor PEDTT derivative **135** (Scheme 40).



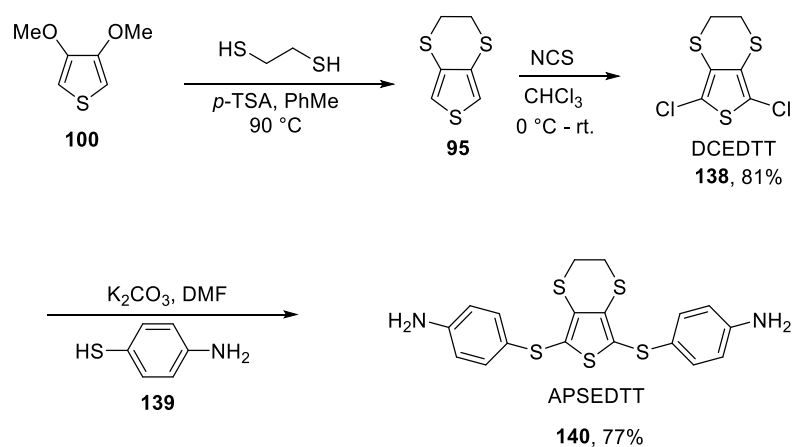
Scheme 40 Blanco *et al.*¹⁷¹ approach for synthesis of new EDTT derivatives

In 2012, Sakong *et al.*¹⁹⁴ used 3,4-dimethoxythiophene **100** as starting material (Scheme 41) for ethylenedithiathienenes. Bromination and formylation reactions of EDTT **95** were achieved using *n*BuLi in THF and DMF at -78 °C followed by *N*-bromosuccinimide (NBS) at ambient temperature, respectively. However, this study did not provide any experimental details about the synthesis of **136** and **137** and not give the percentage yield for **136** and **137** (Scheme 41).



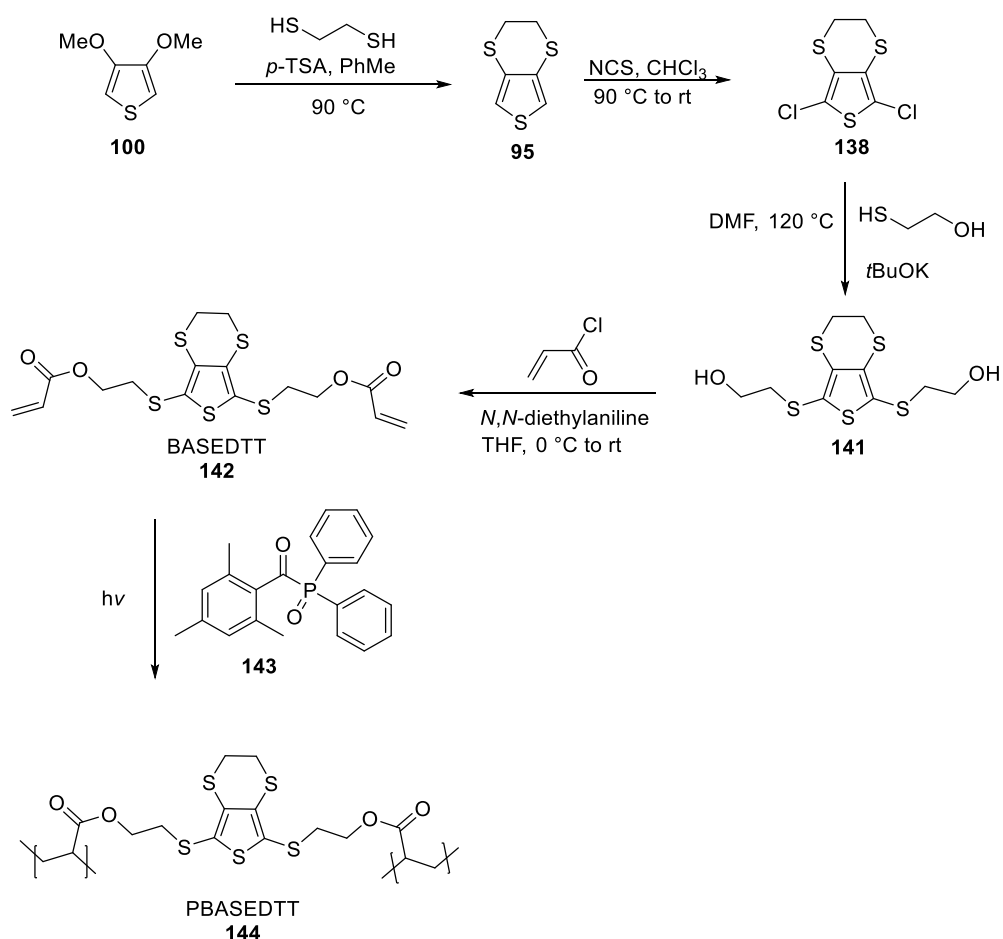
Scheme 41 Sakong *et al.*¹⁹⁴ synthetic routes of **136** and **137**

Work in 2015 by Hyeonuk Yeo and co-workers¹⁹⁵ presented a new diamine monomer, 2,5-bis(4-aminophenylenesulfanyl)-3,4-ethylenedithiothiophene **140**. This monomer **140** was synthesised by a three-step procedure using the known 3,4-dimethoxythiophene **100** as the starting material, EDTT was halogenated with *N*-chlorosuccinimide (NCS) to give 2,5-dichloro-3,4-ethylenedithiothiophene (DCEDTT) **138** in 81% yield. Finally, DCEDTT **138** was reacted with 4-aminobenzenethiol **139** to obtain the target APSEDTT **140** in 77% yield (Scheme 42). This monomer was used for further polymerization chemistry.



Scheme 42 Synthetic route for the preparation of APSEDTT **140**¹⁹⁵

In 2016 Nam-Ho You and co-workers¹⁹⁶ used a similar approach featuring the most popular methods to prepare the derivatives of EDTT. Their approach used the known 3,4-dimethoxythiophene **100** as the main starting material. Over four steps they could prepare ((2,3-dihydrothieno[3,4-*b*][1,4]dithiine-5,7-diyl)bis(sulfanediyl))bis(ethane-2,1-diyl) diacrylate (BASEDTT) **142**. The BASEDTT **142** monomer was then polymerized by UV-irradiation using diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide **143** as a photo initiator to obtain poly 1,5-bis(2-acryloylenethyl)-3,4-ethylenedithiothiophene (PBASEDTT) **144** (Scheme 43).

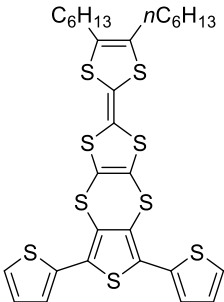
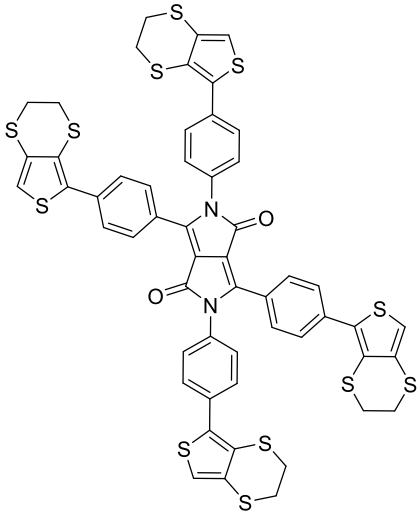
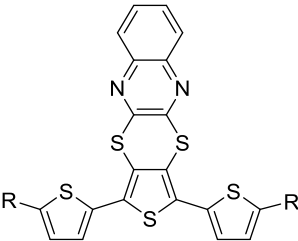
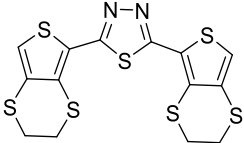
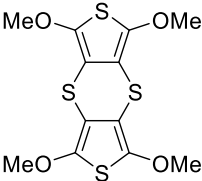
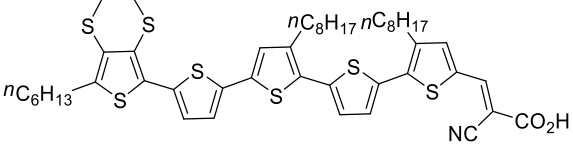


Scheme 43 Preparation of PBASEDTT **144** via UV-curing.¹⁹⁶

Some other studies have reported molecules having EDTT as a unit in their structures.

We show all these compounds in Table 5.

Table 5 Compounds containing EDTT moieties

Compound	Ref.	Compound	Ref.
	197		173
 a R = H b R = Me	198		170
	199		200

3.3 Results and discussion

3.3.1 Synthesis of 2,5-dicarbonyl derivatives of 3,4-ethylenedithiophene (EDTT)

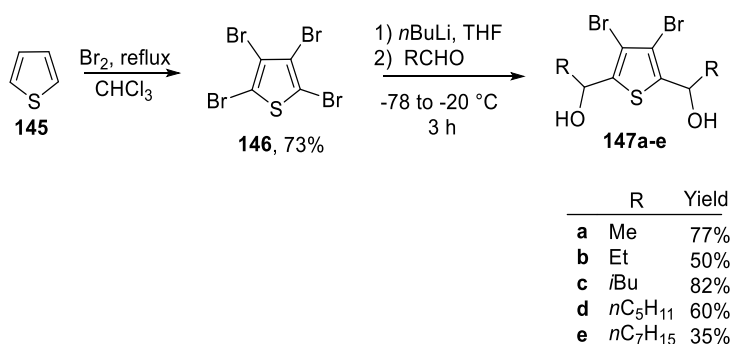
This Chapter reports work that focused on finding efficient methods to reliably attain 2,5-derivatives of 3,4-ethylenedithiophene (EDTT). In addition, the study was aimed to prepare the analogous compounds, where one of the sulfur atoms in the alkyl –SCH₂X– bridge is modified (X = S, O, NR) using addition-elimination reactions to prepare the corresponding compounds starting from the readily available crystalline tetrabromothiophene **146**.

Our strategy for the preparation of 2,5-derivatives of 3,4-ethylenedithiophene (EDTT) is quite different from traditional approaches, where normally the most common methods use EDTT as a starting material. This EDTT is commercially available but relatively expensive (£193 per gram, from Sigma Aldrich)²⁰¹ or can be made by few steps.¹⁸⁹

In our approach we used the thiophene **145** as the starting point. Tetrabromothiophene **146** is easily prepared on large scales by bromination of thiophene using chloroform as solvent and this gave 73% yield of tetrabromothiophene **146**. The HBr by-product is conveniently quenched by collecting the off-gas into a suitable water trap. The activated 2,5 positions of **146** are cleanly exchanged with *n*BuLi at -78 °C. While rearrangements (the so called “halogen dance”²⁰²) could take place at higher temperatures, reactive electrophiles are expected to intercept the dilithiated intermediate cleanly.

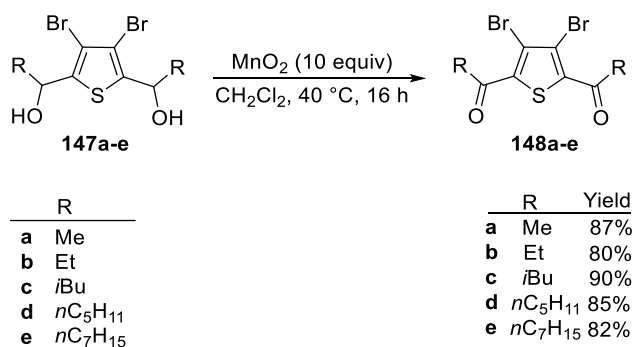
Relatively few investigations have employed this strategy only examples with: chlorotrimethylsilane²⁰³, a limited number of aldehydes²⁰⁴ and acyl chlorides²⁰⁵ are known. However, the reported yields are poor to moderate in such procedures.

From a practical perspective, addition of the aldehyde at -78 °C followed by warming to -20 °C affords the maximum yield of **147a-e** (45-82%). Compounds **147a-e** are attained as mixtures of *syn* and *anti*-diastereomers, but **147c-d** be separated by careful column chromatography (Scheme 44).



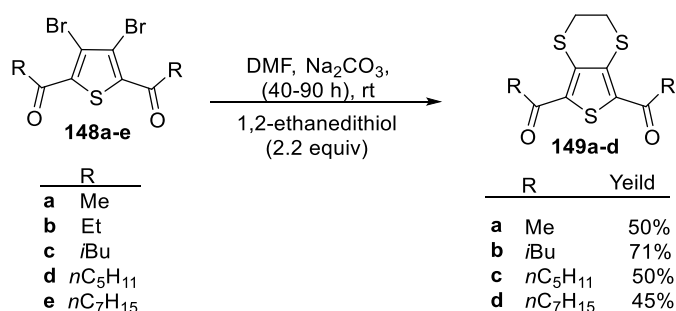
Scheme 44 synthesis of the key diols **147a-e**

The required addition-elimination step procedure requires oxidation of **147a-e** to the carbonyl oxidation level. Optimization of the oxidation step was attempted with many different reagents, but only activated MnO₂ gave good yields. Each of the diastereomeric mixtures **147a-e** converged into the corresponding ketones **148a-e** using activated MnO₂, in refluxing dichloromethane. Only simple overnight reactions are required to attain complete conversion (Scheme 45). The diketones **148a-e** were usually obtained after filtration of the crude mixture through Celite. Subsequently, the reaction mixtures were concentrated *in vacuo* to afford the corresponding ketone products as pale solids in about (82-90%) yield. These products were >98% pure by ¹H NMR spectroscopy and used directly in the next step without further purification.



Scheme 45 Synthetic route to ketothiophenes **148a-e**

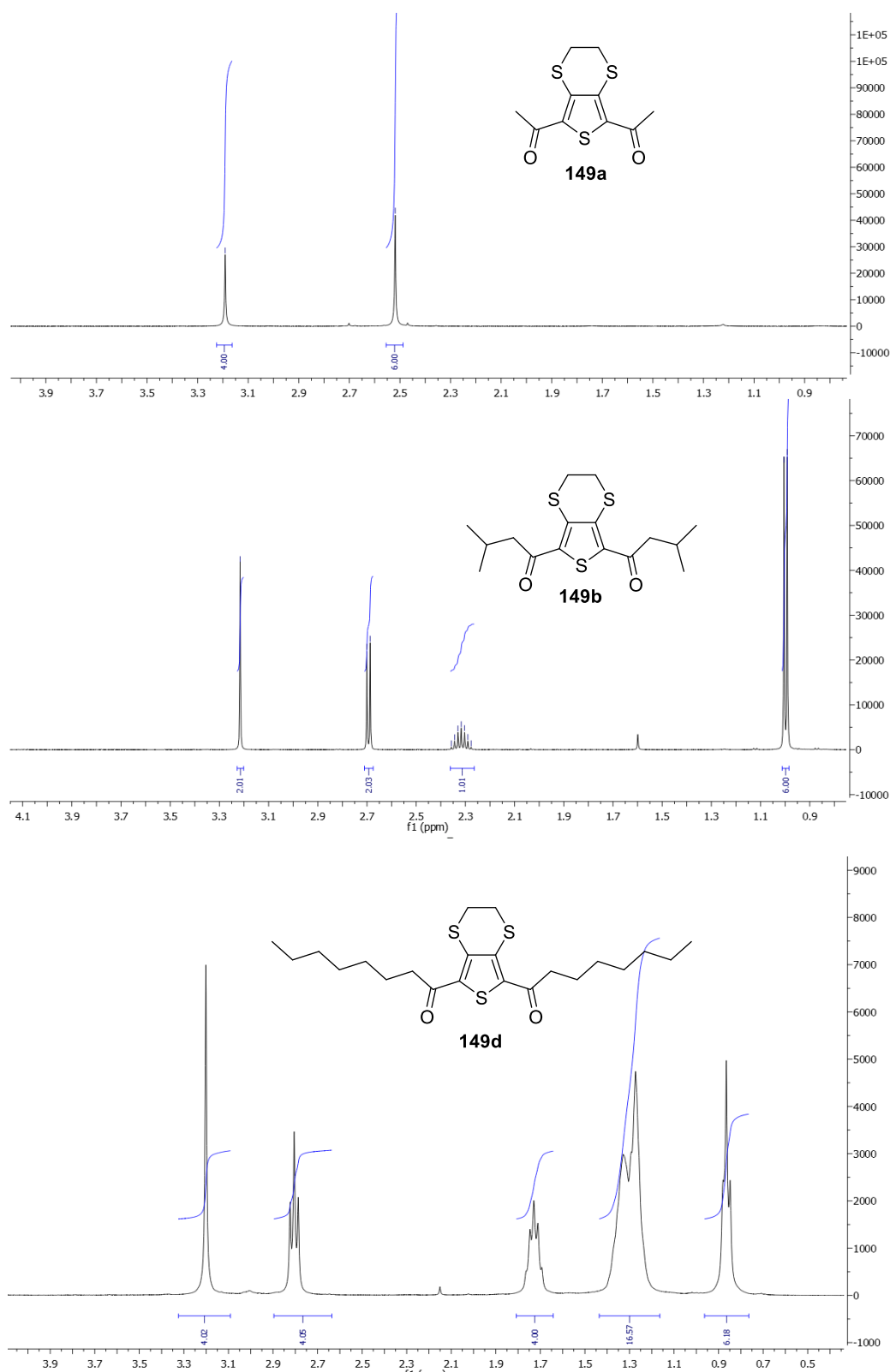
The final step required is the addition-elimination reaction (Scheme 46). This has been achieved by adding neat 1,2-ethanedithiol (2.2 equiv) to a solution of diketones **148a-e** in dry DMF in presence of Na₂CO₃. These mixtures were stirred over 40-90 h at room temperature under an atmosphere of argon (Scheme 46).



Scheme 46 addition-elimination reaction to synthesise of **149a-d**

Ketones **149a-d** are easily isolated by column chromatography as they appear as bright yellow bands (Figure 21). The resulting micro-crystalline yellow solids show spectra in accord with the proposed formulation.

The final shiny yellow compounds **149a-d** were air stable and fully characterized by ¹H NMR spectroscopy (Figure 20), ¹³C NMR spectroscopy, elemental analysis, mass spectrometry and UV-Vis spectroscopy (Figures 22-24).



Figures 20 Expansion of ^1H NMR spectra of compounds **149a**, **149b** and **149d** (400 MHz, CDCl_3).

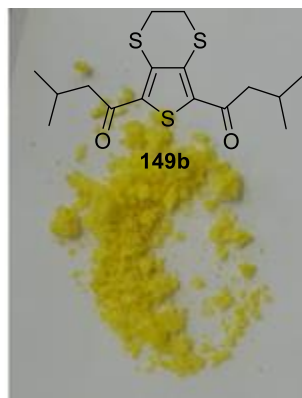
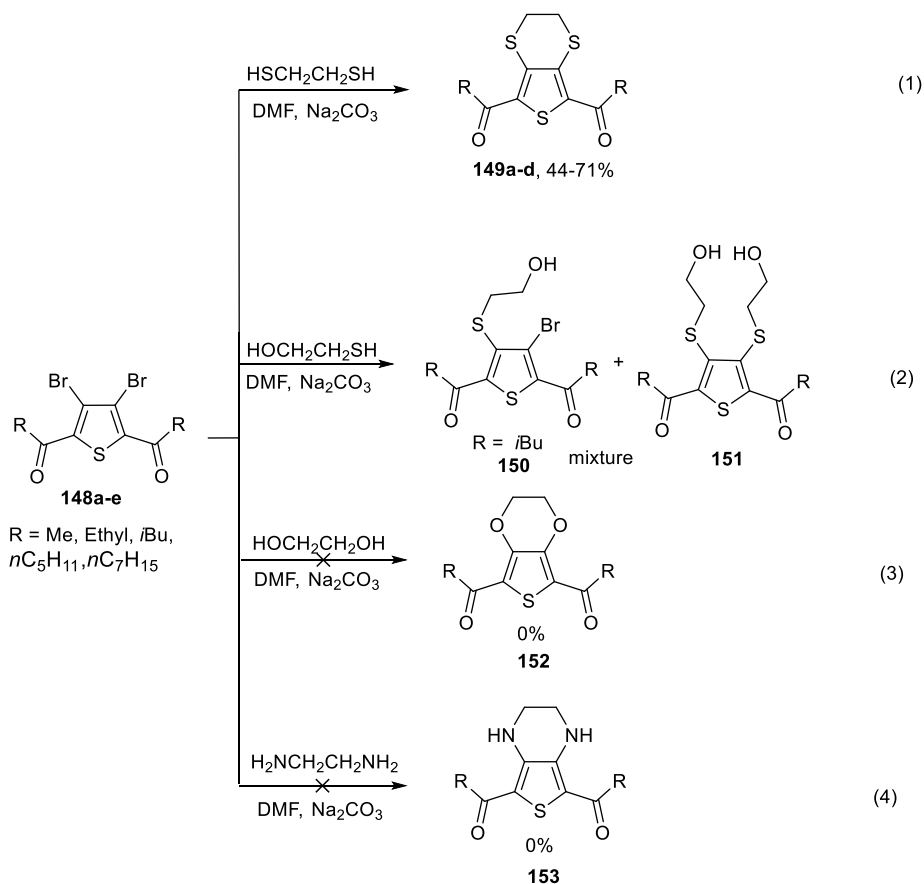


Figure 21 The shiny yellow powder of **149b** after purification

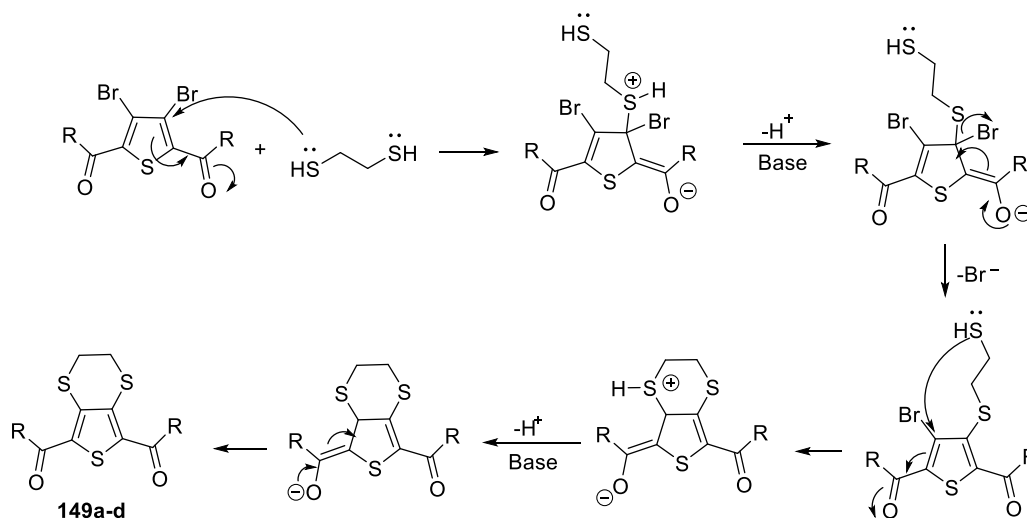
Next alternative addition-elimination reactions to prepare of keto-derivatives for 3,4-ethylenedithiothiophene EDTT **149a-d**, thieno[3,4-*b*]-1,4-oxathiane (EOTT) **150-151**, 3,4-ethylenedioxythiophene (EDOT) **152** and 1,2,3,4-tetrahydrothieno[3,4-*b*]pyrazine **153** was studied by changing one or two of the donor atoms in 1,2-ethanedithiol by N or O (Scheme 47).



Scheme 47 Attempted generalisation of the addition-elimination reaction

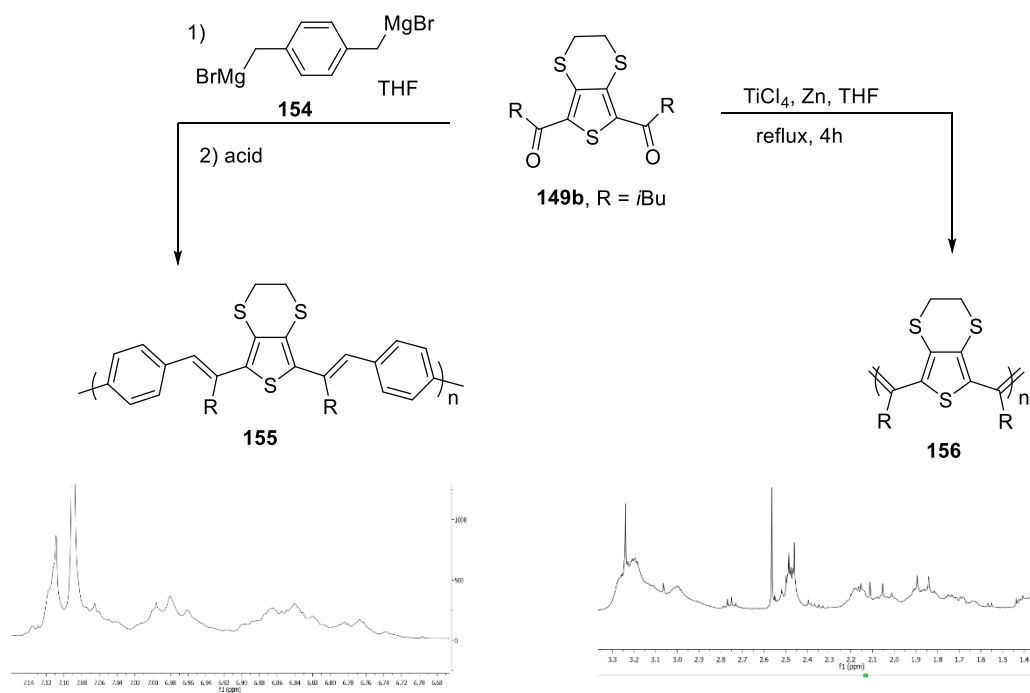
As can be seen from Scheme 47 the first reaction of these ‘diketo’ approaches works very well using 1,2-ethanedithiol. In the second reactions, changing one of the donor atoms to oxygen using 2-mercaptoethan-1-ol results in a change in the product formed. Only the sulfur nucleophilic reacts to exchange and eliminate the bromide resulting a mixture of **150** and **151**. Unfortunately, the third and fourth reactions gave us no tractable products. This is because the oxygen and the nitrogen are not nucleophilic enough to exchange and eliminate the bromide.

The suggested substitution mechanism for addition-elimination reaction in presence of Na_2CO_3 as base can be seen in Scheme 48.



Scheme 48 Substitution mechanisms for addition-elimination reaction

In conclusion, we have attained an efficient route to the synthesis of novel EDTT derivatives **149a-d** in only three steps. These monomers offer future opportunities for new conjugated polymers. In very preliminary experiment, the polymerization of these new monomers **149a-d** was tested using two different methods (Scheme 49).



Scheme 49 Preliminary polymerization test for **149b** monomers

While polymerisation of **149b** was performed using McMurry reaction, addition of **154** to the keto functional group of **149b**, was also tried. Initial GPC analyses of polymerization show that these oligomers of has about 5-7 monomer units were formed. Although further work needs to go in to optimising these polymerisations proof of principal was attained.

3.3.2 Determining of the optical bandgaps for the monomers 149b-d

The optical bandgaps for the monomers **149b-d** were determined using a Tauc plot of UV-Vis data. See Figures 22-24 and Table 6.

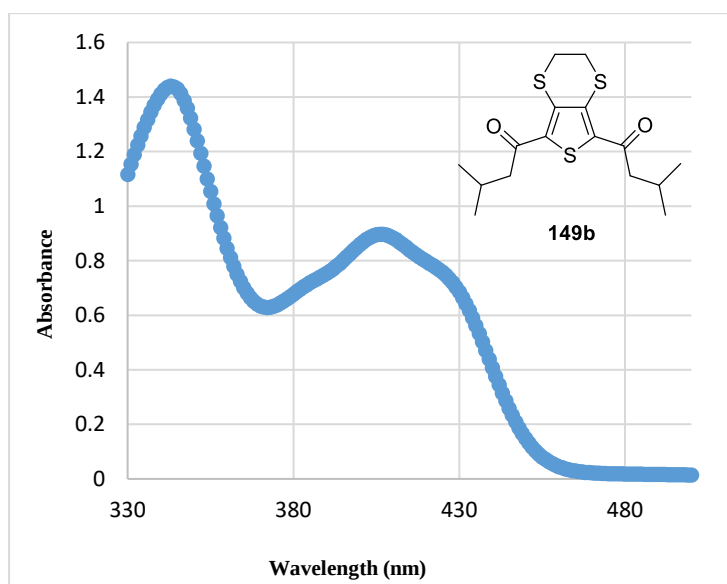


Figure 22 the UV-Vis spectroscopy for **149b**

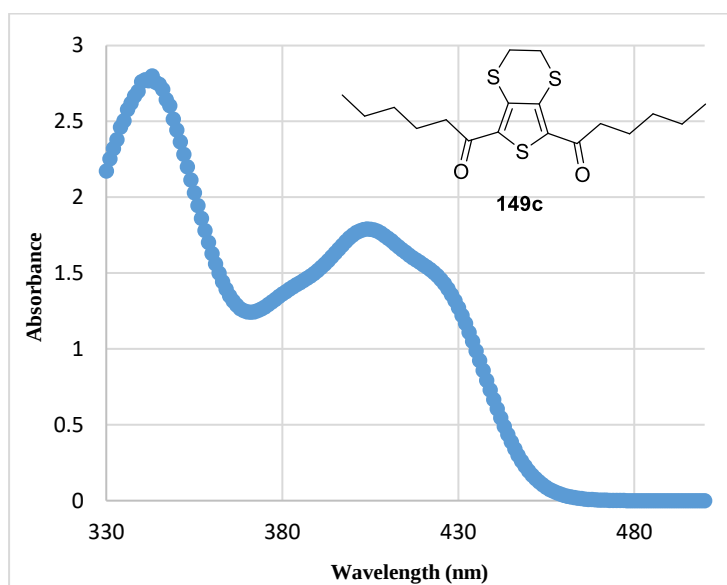


Figure 23 the UV-Vis spectroscopy for **149c**

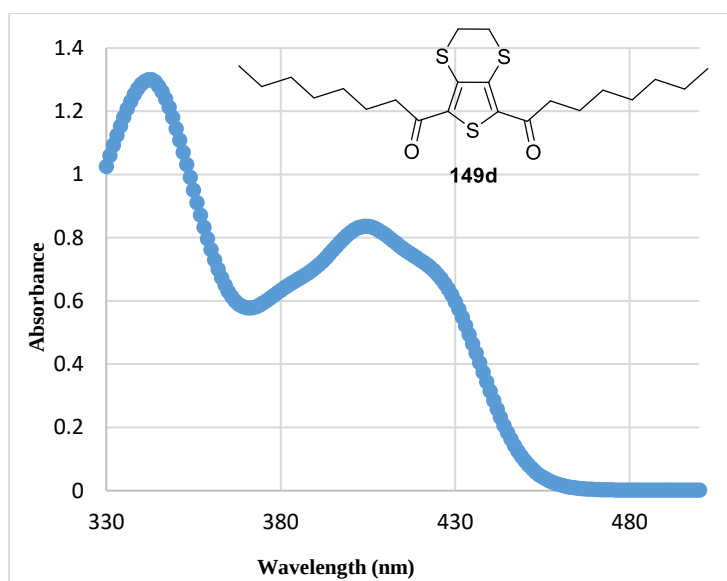


Figure 24 the UV-Vis spectroscopy for **149d**

Table 6 The optical bandgaps for **149b-d**

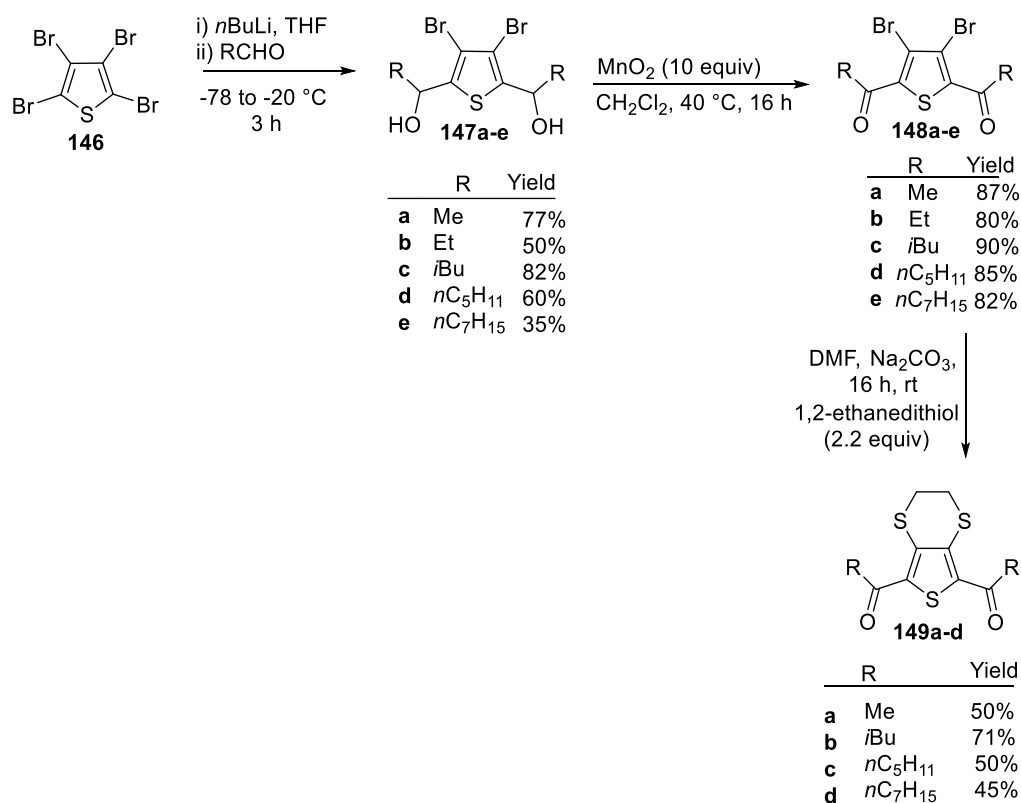
Entry	R	λ_{max} (nm) ^a	E_g (eV) ^b
1	<i>i</i> Bu	432	2.662
2	<i>n</i> C ₅ H ₁₁	426	2.681
3	<i>n</i> C ₇ H ₁₅	430	2.680

^a) In CH₂Cl₂ 10⁻⁴ M longest wavelength absorption band. ^b) Determined by Tauc plot of UV-Vis data.

The bandgaps for **149b-d** are quite similar for some common semiconductor materials such as tetracene³⁶ which has a 2.54 eV optical bandgap.

3.4 Conclusions

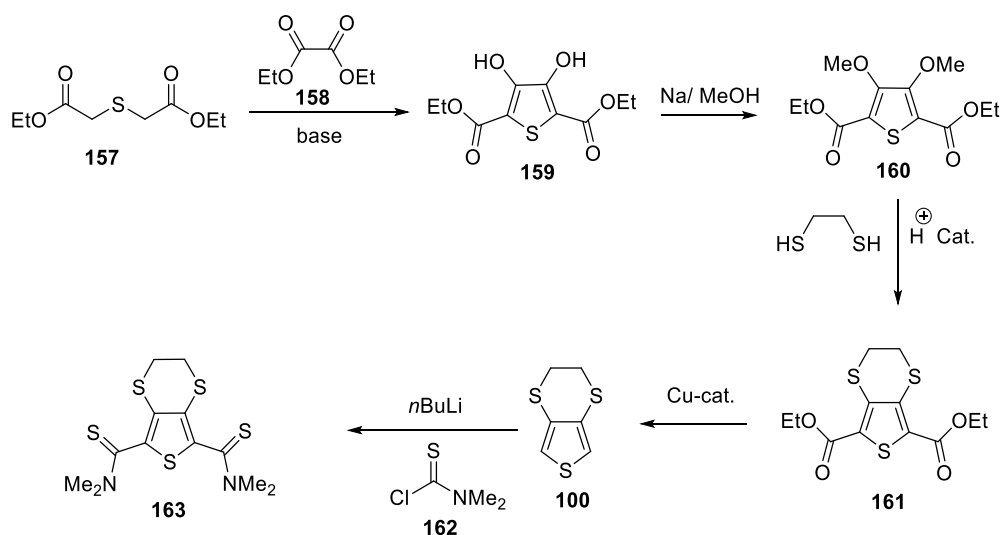
We have successfully found a new route to homologs of 3,4-ethylenedithiophene (EDTT) **100** having ketone functionalities at the 2,5-positions. From tetrabromothiophene **146**, monomers **149a-d** were obtained in three steps (Scheme 50). In addition, the monomers **149a-d** are attractive species for the future synthesis of many thiophene-based semiconductor polymers.



Scheme 50 Our strategy to synthesis of EDTT-Ketoes **149a-d**

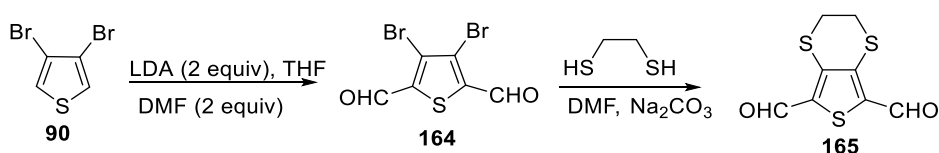
3.5 Future work

Due to the nature of a diversity-oriented synthesis project and the limited time available for this work, it was impossible to fully explore every avenue of diversification. For this reason, there were a considered a number of different compounds that could be made using different combinations of reagents or reactions that have already been noted. Some of these additional compounds that could be synthesised used the approach shown in Scheme 51.



Scheme 51 Possible synthesis of **163** starting from diethyl thiodiglycolate **157**

In addition, there are also some important methods that have not been optimised during this project. There could be potential to exploit these ideas in future research. Although this approach (Scheme 52) is in some ways similar to the investigated chemistry presented in this Chapter, time limits did not allow it to be tried.



Scheme 52 Possible synthesis of **165** from the known **90**

This monomer **165** could be polymerised with itself using McMurry reaction conditions or can be used in other further chemistry.

4 Chapter Four: Studies in Thiophene Chemistry for the Synthesis of 2,5-EDOT Derivatives and Related Thiophenes

Publication from this Chapter:

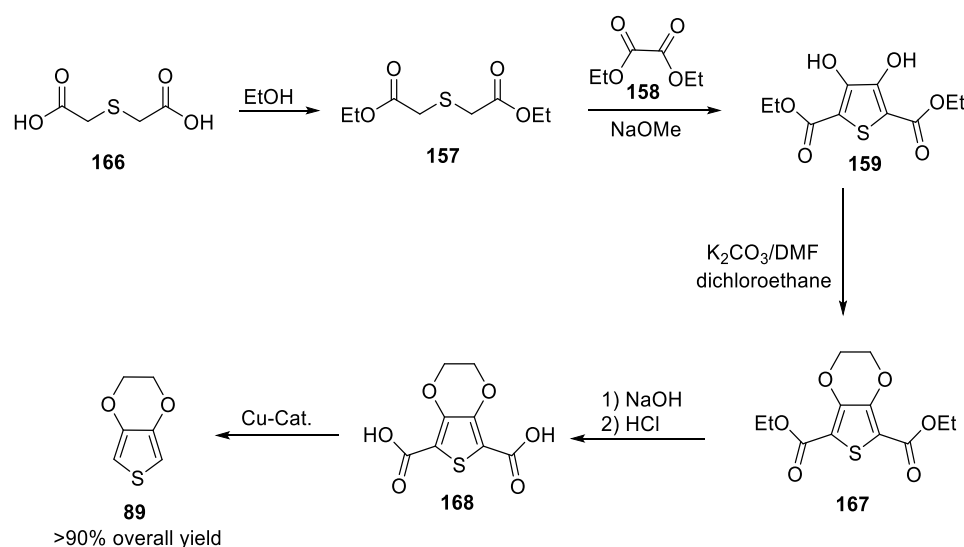
The first part in this Chapter (**Scheme 56**) has been published and included with the below paper:

Mustafa A-JABBAR Al-jumaili, Simon Woodward, “Efficient synthesis of 2,5-dicarbonyl derivatives of 3,4-ethylenedithiophene (EDTT) via addition-elimination reaction” *Tetrahedron* **2017**, 73, 5847-5852.

4.1 Introduction

3,4-Ethylenedioxythiophene (EDOT) (Scheme 53) was first synthesised in the 1980s by Bayer AG Research Laboratories. Their approach was the development method of Gogte *et al.*, starting from thiodiglycolic acid **166**, via the intermediary of EDOT-2,5-dicarboxylic acid **168**.²⁰⁶ Finally, decarboxylation using a copper salt was used to attain the **89** in a total of five steps.^{207,208,209,210,165} This monomer **89** often slowly turns dark upon exposure to air and light because of partial oxidation and polymerisation onset.

Although several alternative routes towards EDOT are known, it is prepared industrially in by Bayer method on a multi-ton scale by the chemistry of Scheme 53 due to its relative overall efficiency. Bulk EDOT is now commercially available under the name BAYTRON M (where the M refers to its monomeric nature).¹⁶⁵



Scheme 53 The industrial route to EDOT **89**

There are now thousands of publications dealing with the use EDOT **89**, and in particular its polymers PEDOT, as demonstrated in recent reviews including: in 2018 by Qiquan *et al.*,²¹¹ in 2018 by Wang *et al.*,²¹² in 2017 by Wen *et al.*,²¹³ in 2017 by

Jiayue *et al.*,²¹⁴ in 2016 by Ahmed *et al.*,²¹⁵ in 2015 by Sun *et al.*,²¹⁶ in 2015 by Ishida *et al.*,²¹⁷ and in 2015 by Franky *et al.*²¹⁸ The number of publications involving PEDOT and its many applications increased significantly from 2003 to 2015 as Figure 25 a shows. In 2015 alone there are more than 1000 publications on the development of PEDOT materials science (Figure 25).²¹³

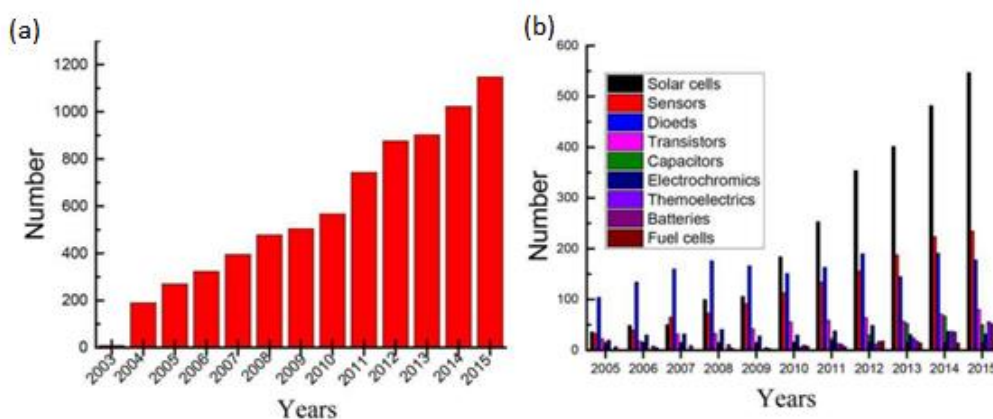
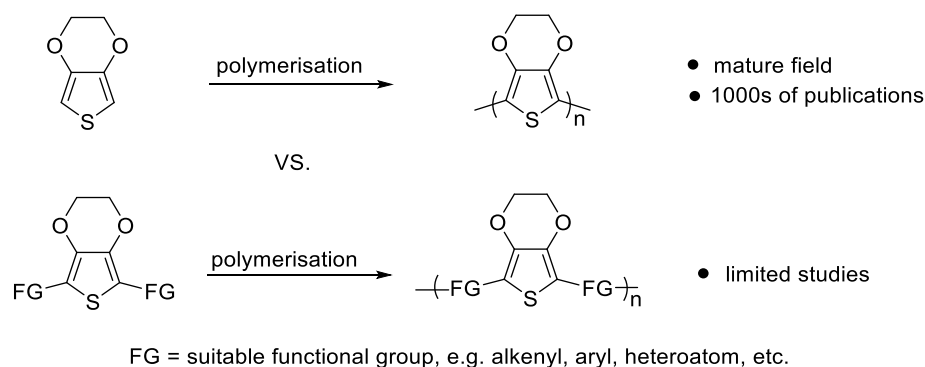


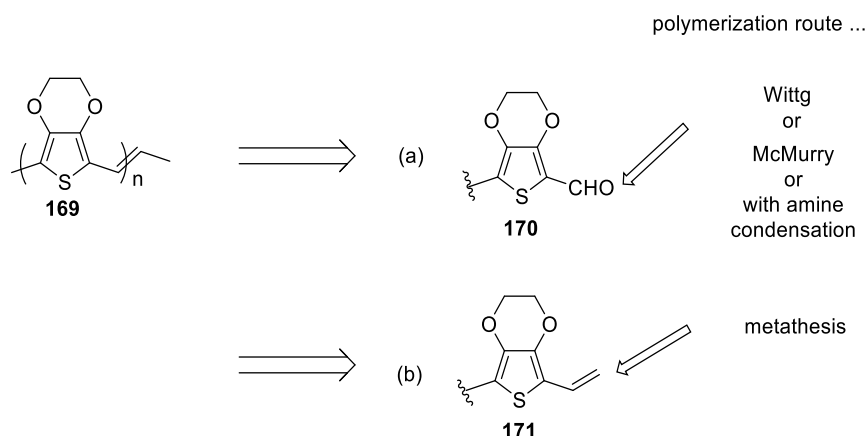
Figure 25 (a) Recent numbers of journal publications featuring the keyword ‘PEDOT’ and (b) applications of PEDOT 2005-2015.²¹³

Although there is extensive literature concerning EDOT and PEDOT over the past few years, there are only limited studies reporting 2,5-functionalised 2,5-EDOT derivatives that are suitable for related polymerisations (Scheme 54). We define these here as 3,4-ethylenedioxythiophene (EDOT) units carrying reactive functional groups (FGs) at their 2 and 5 positions capable of being polymerised (either directly or indirectly) to macromolecules.



Scheme 54 Literature approach to EDOT polymers vs. their functionalised analogues

Consequently, this Chapter will focus on synthesis of 2(5)-derivatives of EDOT (Scheme 55). Specifically, two main monomer types **170** and **171** are the target structures for this Chapter.



Scheme 55 The monomers target for this Chapter

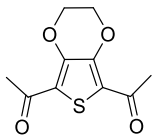
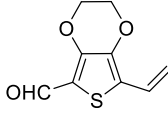
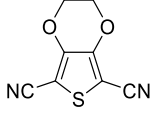
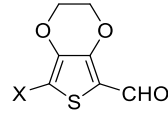
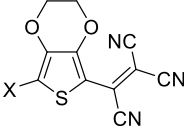
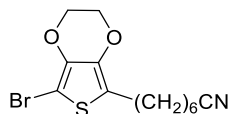
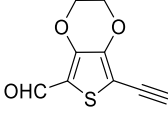
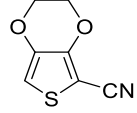
These two monomer types can potentially be used as main starting materials for new polymers, providing both of the 2,5-groups have appropriate functional groups.

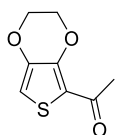
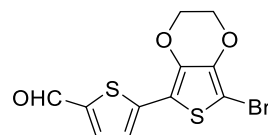
Currently, for many reasons the synthesis of PEDOT-type polymers has become a critical area in the development of new advanced organic electronic materials. One important area of development is to understand how to gain control over polymerisation structures and properties of PEDOTs through the design of new monomers.^{219,220,221,222,223,224,225,226}

Generally, there are various reported EDOT derivatives which have lower reactivity (not suitable for polymerisation) including: alkyl, alkoxy, aryl, arylalkyl, aryloxy, alkenyl, aralkyl, cycloalkyl, silyl, heterocyclic and aromatic moieties introduced into the EDOT, which formed a huge library of EDOT derivatives.^{213,220}

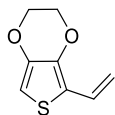
On the other hand, there are limited reported examples of EDOT monomers that have active functional groups (such as CHO, CN, COR, vinyl) at the 2 and 5 positions. These functional groups are easier to derivatise with further chemistry to provide conjugated oligomers or polymers. However, most of the present functionalised EDOT-derivatives use EDOT as a starting material and need 2-5 steps to provide the final targets. Representative literature examples from publications are shown in Table 7.

Table 7 Reported literature for 2 and 5 EDOT derivatives

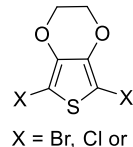
Compounds	Ref.	Compounds	Ref.
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	230		231,232
 a, X = H b, X = Br	233		234
	235		236

227,237,
238

239,240



228

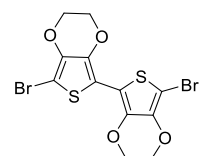
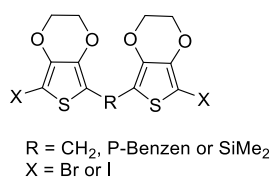
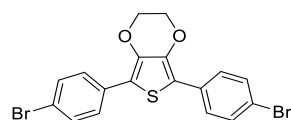
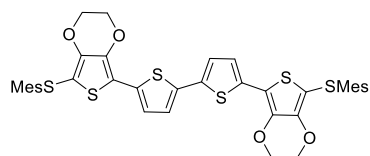
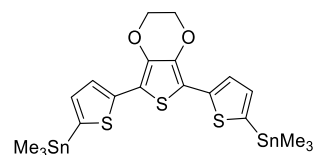
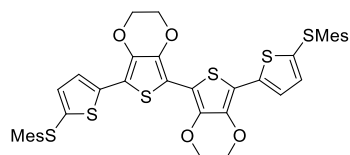
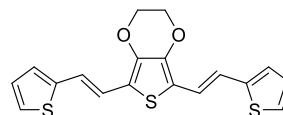
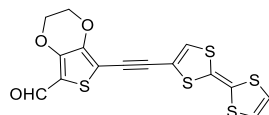
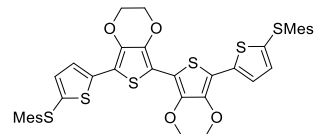
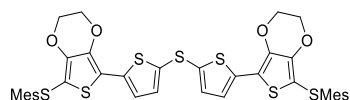
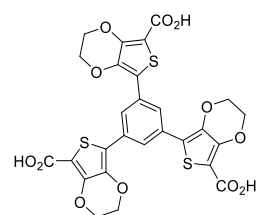
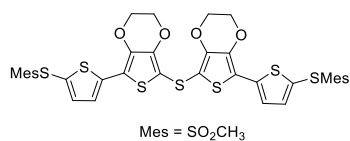
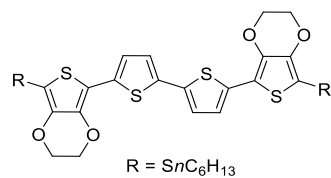
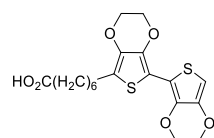
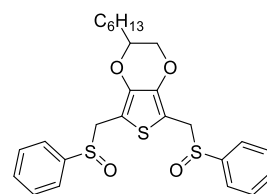
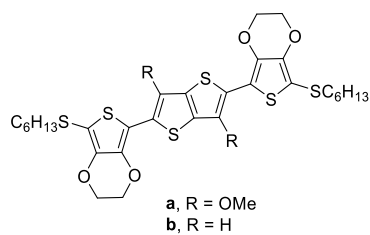
241,242,
243,244,
233

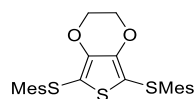
X = Br, Cl or I

In generalising the scope of Table 7, there are many EDOT derivatives which have been designed and synthesized as potential monomers. Table 8 show the representative example for these more elaborated derivatives. Their syntheses are normally very step intensive.

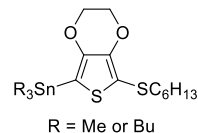
Table 8 Useful reported EDOT derivatives

Compounds	Ref.	Compounds	Ref.
Mes = SO₂CH₃	245	n = 2 or 3	246
	247	nC₁₆H₃₃	232
	248		248
	249	R = Me, Bu	250,251 ,252,246





245,246



260,253

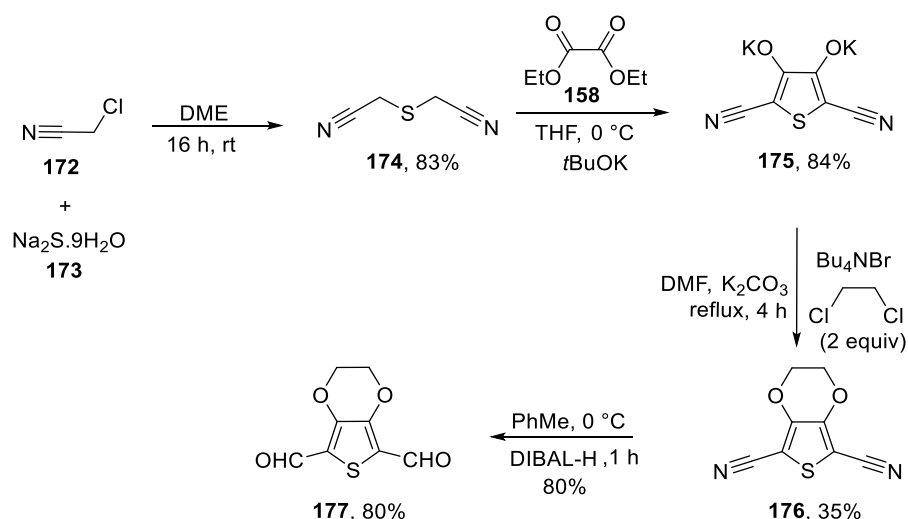
4.2 Chapter aims

After considering the published literature we thought that there was a deficiency of simple, low step, routes to 2,5 functionalised 3,4-ethylenedioxythiophene and related compounds and we decided to find ways to synthesising of 2,5 functionalised 3,4-ethylenedioxythiophene using simple, low step methods.

4.3 Results and discussion

4.3.1 An alternative route to synthesis of 2,3-dihydrothieno[3,4-*b*][1,4]dioxine-5,7-dicarbaldehyde (EDOT-Aldo) 177

The traditional method to the synthesis of EDOT has already shown in Scheme 53, this method used 2,2'-thiodiacetic acid **166** as a starting material. We wondered if a nitrile group was used instead of the carboxylates traditionally employed in EDOT synthesis, if this be possible access to 2,5-disubstituted aldehydes closely related to our diketo-EDTT species **149a-d** (see Chapter 3). This new route to such derivatives of EDOT has been investigated in this research as shown in Scheme 56.



Scheme 56 Our route for the derivatives of EDOT

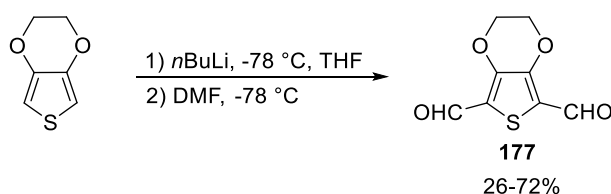
In this method compound **174** was synthesised from ultra-cheap sodium sulfide nonahydrate Na₂S·9H₂O **173** (4 pence/g, from Fisher Scientific UK Ltd, in August 2018) by alkylation with 2-chloroacetonitrile **172** (18 pence/g, from Fisher Scientific UK Ltd, in August 2018) using 1,2-dimethoxyethane (DME) as solvent and stirring over 16 h to yield 83% of **174** in excellent purity. This allows its use without purification in subsequent steps. Although the intermediate **174** has been reported in a few literature publications, these normally^{261,262} use anhydrous Na₂S as a starting material which costs about £15 per gram.

Subsequent reaction of **174** and diethyl oxalate (**158**) in the presence of *t*BuOK prepares the potassium salt **175** after only 30 minutes (judging by see precipitation) at (0 °C). This potassium salt can also be isolated by simple filtration under argon and used directly without further purification. The potassium salt **175** was directly reacted with 1,2-dichloroethane in the presence of potassium carbonate as an additional base, to access the dinitrile **176** in modest yield 35%. Such low yields are typical of EDOT-type ether formations. Common by-products are formed by E2 elimination of the 1,2-dichloroethane and the formation of cross-linked oligomers of

175. The presence of K_2CO_3 has been empirically observed to moderate these behaviours. Its probable role is to remove HBr generated by the E2 elimination of 1,2-dichloroethane.

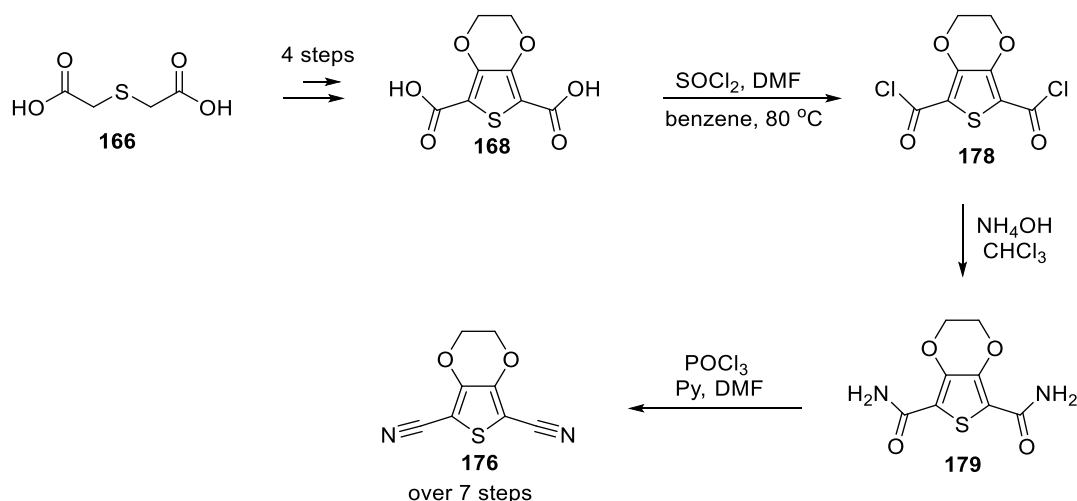
Despite its modest yield, **176** is easily isolated analytically pure after a simple filtration through a silica plug which removes oligomeric material. Finally, **176** was converted to the corresponding aldehyde **177** by its treatment with DIBAL-H at 0 °C in anhydrous toluene. Compound **177** is already recognised as an important intermediate in the synthesis of thiophene-based semiconductor polymers and oligomers.^{227,263,264,265}

In comparison, compound **177** has only been reported in the literature by a method using EDOT precursors. Deprotonation of the two reactive 2,5-positions was attained with *n*BuLi and subsequent treatment with anhydrous DMF at (-78 °C) (Scheme 57) gave **177** in 26-72% yield on aqueous quench.^{263,266,267}



Scheme 57 Synthesis of compound **177** by literature method^{263,266,267}

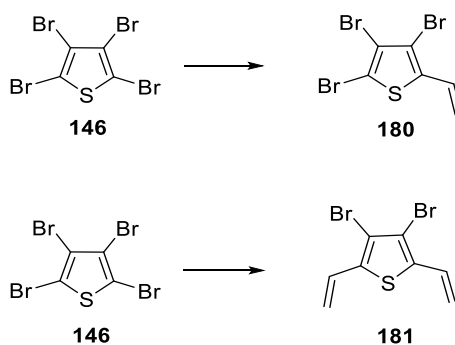
In addition, compound **176** was also reported in the literature in the study of Miroslav *et al.*,²⁶⁸ but this approach required 7 steps using the EDOT precursor 2,2'-thiodiacetic acid **166** as the starting material (Scheme 58).



Scheme 58 Literature approach to synthesis of **176**²⁶⁸

4.3.2 Optimisation synthesis of the vinyl thiophenes

As one of the aims of the work described in this Chapter was to devise ways to synthesise 2,5-disubstituted thiophenes. One approach was to introduce vinyl groups in these positions using the strategy shown in Scheme 59.



Scheme 59 Our strategy to the synthesis of **180** and **181**

This chemistry starts with known 2,3,4,5-tetrabromothiophene **146** and aims to obtain the new 2,3,4-tribromo-5-vinylthiophene **180** and 3,4-dibromo-2,5-divinylthiophene **181**. These were attempted by two different ways using cross-coupling reactions. Attempts were made to optimise the conditions used to prepare the compounds **180**

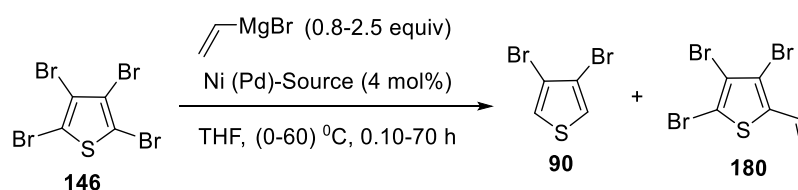
and **181**. These investigations included systematic change of the catalyst, solvent, temperature, and the equivalents of starting materials and the addition time in order to study the chemoselectivity of the reaction.

4.3.2.1 Kumada coupling for synthesis of vinyl thiophenes **180** and **181**

The Kumada coupling reaction was the first group 10 metal catalysed cross coupling reaction to be discovered. It was reported independently in 1972 by Robert Corriu²⁶⁹ and Makoto Kumada.²⁷⁰ It is considered as useful in the formation of carbon–carbon bonds *via* treatment of a Grignard reagent with a sp^2 organic halide.

Compound **146** was used as a starting material and treated with vinylmagnesium bromide in the presence of Pd or Ni catalysts. The reaction was carried out in THF at various temperatures and for different times to find the optimum conditions for the coupling. Unfortunately, all of the reactions were rather messy, and the major product was the undesired **90** (Table 9).

Table 9 Attempted optimisation of Kumada coupling to prepare **180**



Entry	equiv of Grignard	Catalyst	Temp. (°C)	Time (h)	ratio 90:180 ^[a, b]	Grignard addition time
1	1.5	NiCl ₂ (dppp)	0	0.1	3:1	(30 min)
2	1.5	NiCl ₂ (dppp)	rt	0.45	3:1	(10 min)
3	2.5	NiCl ₂ (dppp)	rt	70	^[c]	
4	1.5	NiCl ₂ (dppp)	rt	3	4:1	

5	1.12	NiCl ₂ (dppp)	rt	3	2:1	(3.4 h)
6	0.8	NiCl ₂ (dppp)	rt	0.5	3:1	(15 h)
7	0.8	NiCl ₂ (dppp)	rt	4	4:1	(4.4 h)
8	1.5	NiCl ₂ (dppp)	50	0.3	5:1	(22 min)
9	2	NiCl ₂ (dppp)	60	16	2:1	
10	1.1	Pd(PPh ₃) ₂ Cl ₂	rt	0.25	9:1	(2 h)

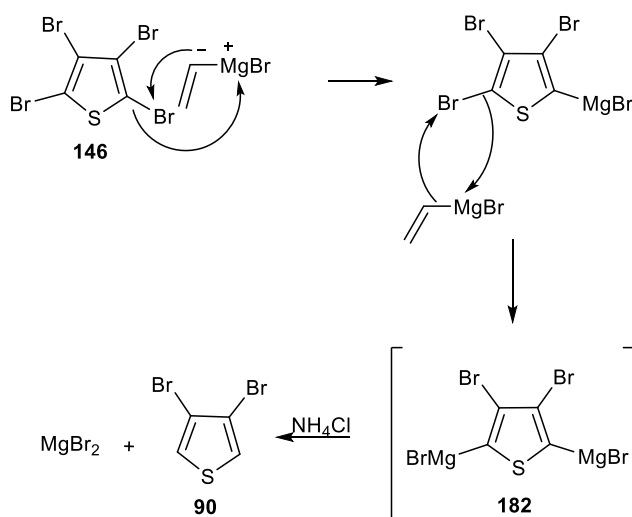
^[a] The ratio was determined by ¹H NMR spectroscopy.

^[b] Compounds **90** and **180** were identical to by GC (Gas Chromatography) and ¹H NMR spectroscopy.

^[c] Not determined as a complex mixture was attained.

It is clearly shown in Table 9 that compound **180** has been obtained but with low yield and the major product was the dibromothiophene **90**. Regardless of the changed variables: e.g. adding NiCl₂(dppp), temperature variation from 0 to 60 °C or the equivalents of vinyl magnesium bromide used, the ratio of compound **180** remained stubbornly low and became worse when the Pd(PPh₃)₂Cl₂ has been used.

It is clear that vinylmagnesium bromide reacts efficiently as a transmetalation nucleophile in this reaction. The nucleophile attacks the bromine at the 2 and 5 positions in tetrabromothiophene **146**, which are more active than 3 and 4 positions in compound, and this leads to conversion of tetrabromothiophene **146** to compound **90** via the intermediate **182**. Working up the reaction mixture with saturated ammonium chloride (NH₄Cl) gives the dibromothiophene **90** (Scheme 60).



Scheme 60 Suggested mechanism for formation of dibromothiophene **90**

In conclusion, although the coupling of some organohalide compounds with Grignard reagents can take place under mild conditions and the transmetalation completes strongly. Grignard reagents are known to suffer from a limited tolerance of different functional groups.²⁷¹ In the present case, due to the higher reactivity and basicity of vinylmagnesium bromide, the reaction is not suitable for the synthesis of the desired compound **180** and **181**. Accordingly, it was decided to try Negishi coupling conditions as an alternative route to prepare compounds **180** and **181**.

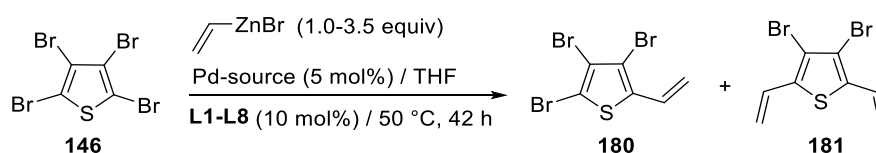
4.3.2.2 Optimisation attempts of the Negishi coupling reaction

These organozinc halide coupling reactions were investigated originally in 1976 by Ei-ichi Negishi and co-workers. The Negishi coupling reaction is a usually associated with Pd-catalysed cross-coupling. The Negishi coupling reaction can be utilized with several different types of organic zinc halides (aryl, vinyl, benzyl, or allyl) for making carbon-carbon bonds (C-C).²⁷²

4.3.2.2.1 Investigating the use of different palladium pre-catalysts and ligands for preparation of **180** and **181** by Negishi coupling

We initially attempted both Ni and Pd-based couplings, but it soon became clear that Pd-catalysts are much better than Ni-species in the cross-coupling of tetrabromothiophene **146** with vinylzinc bromide. Hence, optimisations were set to find the best palladium catalysts for the reaction. Several different types of Pd pre-catalysts and ligands were screened (Table 10).

Table 10 Optimisation of ligand structure and palladium pre-catalyst for mono-Negishi product **180** ^[a]



Entry	$\text{CH}_2=\text{CHZnBr}$ equiv	Pd-source	Ligand ^[b]	Conversion 146 (%)	Yield 180 (%)	Yield 181 (%)
1	1.2	$\text{PdCl}_2(\text{PPh}_3)_2$	-	20	15	0
2	2.4	$\text{PdCl}_2(\text{PPh}_3)_2$	-	49	33	0
3	1.2	$\text{Pd}(\text{OAc})_2$	L1	29	1	2
4	2.4	$\text{Pd}(\text{OAc})_2$	L1	75	1	11
5	1.2	$\text{Pd}(\text{dba})_3$	L2	41	1	9
6	2.4	$\text{Pd}(\text{dba})_3$	L2	85	1	16
7	1.2	$\text{Pd}(\text{dba})_3$	L3	43	11	2
8	2.4	$\text{Pd}(\text{dba})_3$	L3	80 ^[d]	13	4
9	1.2	$\text{Pd}(\text{dba})_3$	L4	98 ^[e]	1	0
10	2.4	$\text{Pd}(\text{dba})_3$	L4	56	22	3
11	1.2	$\text{Pd}(\text{dba})_3$	L5	61	36	5
12	2.4	$\text{Pd}(\text{dba})_3$	L5	95	24	11
13	1.2	$\text{Pd}(\text{OAc})_2$	L5	50	38	5
14	1.2	$\text{Pd}(\text{OAc})_2$	L6	32	16	1
15	1.2	$\text{Pd}(\text{OAc})_2$	L7	46	23	1
16	1.2	$\text{Pd}(\text{OAc})_2$	L8	62	16	1
17	1.2	$\text{Pd}(\text{dba})_3$	L5	46	32	3
18	1.2	$\text{Pd}(\text{dba})_3$	L6	33	15	0
19	1.2	$\text{Pd}(\text{dba})_3$	L7	40	24	1
20	1.2	$\text{Pd}(\text{dba})_3$	L8	48	12	1

21	1.2	$\text{PdCl}_2(\text{MeCN})_2$	L5	25	11	0
22	1.2	$\text{PdCl}_2(\text{MeCN})_2$	L6	22	3	0
23	1.2	$\text{PdCl}_2(\text{MeCN})_2$	L7	18	2	0
24	1.2	$\text{PdCl}_2(\text{MeCN})_2$	L8	32	5	0

^[a] Reactions were carried out on (**146**) 0.3 mmol in a Radley's Carousel reactor.

^[b] The structure of ligands **L1-L8** are shown in Figure 26.

^[c] Yield determined by GC vs. Internal standard (1-MeC₁₀H₇), error $\pm$ 2%.

^[d] Reaction gave many side products.

^[e] Most the conversion was to uncharacterised side products.

It was found that using the air stable pre-catalyst, $\text{Pd}(\text{OAc})_2$ (e.g. entry 13) showed the best selectivity for compound **180**. Having established that $\text{Pd}(\text{OAc})_2$ was optimal for this type of transformation, we attempted to use different ligands with $\text{Pd}(\text{OAc})_2$ to further improve the selectivity. It was shown that *tris*(4-fluorophenyl)phosphane **L5** is the best ligand of those tried. Under optimal conditions $\text{Pd}(\text{OAc})_2$ with *tris*(4-fluorophenyl)phosphine **L5** gave a yield 38% of compound **180**.

The species *tris*(4-fluorophenyl)phosphane **L5** is electron deficient, potentially making the active complex with palladium also electron deficient, leading to faster reductive elimination and higher selectivity. Although compound **181** was not synthesised in good yield, ligand **L2** showed the best selectivity towards this compound compared with the other ligands as shown in Table 10 entry 6.

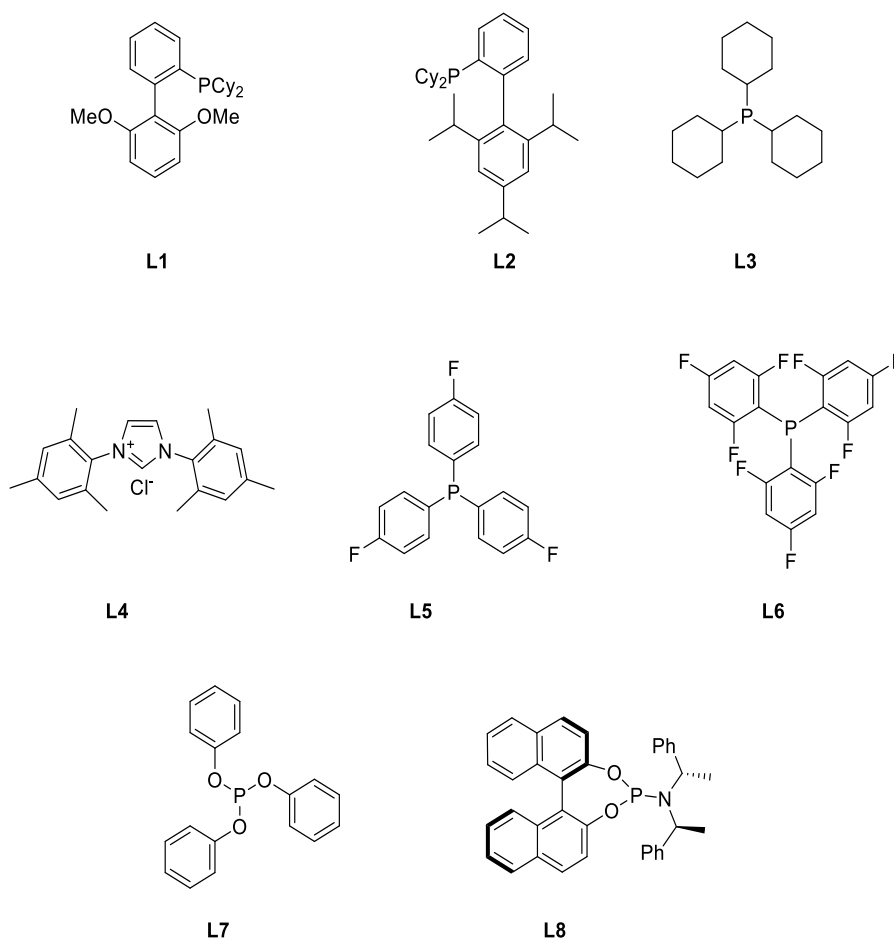


Figure 26 The structure of ligands **L1-L8** which were used in reactions in Table 10: **L1** 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos); **L2** 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos); **L3** tricyclohexylphosphine (PCy₃); **L4** 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (IMes); **L5** tris(4-fluorophenyl)phosphine **L6** tris(2,4,6-trifluorophenyl)phosphine; **L7** triphenyl phosphite; **L8** (R,S,S)-Feringa's ligand.

4.3.2.2.2 Investigation the use of different solvents for mono-Negishi product **180**

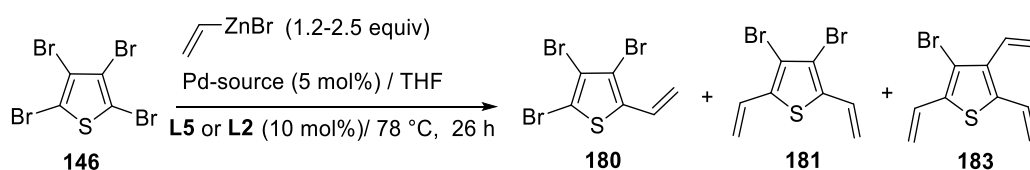
After attaining optimal catalysts and ligands for the generation of **180**, the next step was to screen for a better solvent for this reaction in hope this would further improve rate and selectivity. Consequently, solvents displaying a range of solvation properties (DMF, toluene and THF) were screened without changing the other factors. It was found that all of the solvents that were employed in this investigation (except the original THF) unfortunately gave very low yields of compound **180** and compound

181. The greatest conversions in these reactions were toward by-product mixtures. This was evident from the GC traces where many peaks and different by-products were present.

4.3.2.2.3 Effect of increased temperature and equivalents of zinc reagent in the Negishi coupling

Having established that THF is the best solvent for this reaction and that Pd(OAc)₂ shows the best chemoselectivity for the preparation of compound **180** in the presence of **L5**, reaction temperature was one of the few variables left to investigate. It was hoped that changing the temperature might also help improve the activity and selectivity to **181** shown by Pd(dba)₂ and **L2**. Hence, these best catalysts and ligands were re-deployed with increasing reaction temperature from ca. 20 to 78 °C (Table 11). In some runs, different amounts of vinylzinc bromide were also used (Table 11).

Table 11 Effect of increased temperature on the percentage of desired **180** and **181** in THF.



Entry	Zinc reagent equiv	Pd-source	Ligand	Conversion (%)	Yield (180) (%)	Yield (181) %
1	1.5	Pd(OAc) ₂	L5	91	9	4
2	2.5	Pd(dba) ₂	L2	70	30	27
3	3.5	Pd(dba) ₂	L2	90	10	11

From the results in Table 11, it is clear that by increasing the temperature to 78 °C, and with additional equivalents of zinc reagent, near total conversion (91%) of

starting material **146** can be achieved. Unfortunately, however, the increase in conversion was not toward the desired compounds **180** or **181** but was toward undesired side-products.

It was found that 50 °C is the optimal compromise temperature for this reaction as higher temperatures lead to increased opportunity for side-product formation such as compound **183**.

On the other hand, in Table 11, entries 2 and 3 when 2.5 and 3.5 equivalent of zinc reagent were used, it was discovered that most conversion was to undesired compounds such as **183** and others. It is assumed that this is due to the extra equivalents of zinc reagent leading to additional coupling with the bromines in the 3 and 4 positions of compound **146**.

In summary, from the total screening, it was determined that the optimal conditions to synthesise compound **180** were: THF as the solvent, 50 °C, with *tris*(4-fluorophenyl)phosphine **L5** and Pd(OAc)₂ as the catalyst. After 42 hours reaction time which provided **180** in 38% yield when 1.2 equivalent of BrZn(CH=CH₂) were used.

The low yield of **180** led to a challenge in its isolation reaction from the reaction mixture as the starting material **146** and product **180** have the same R_f value. Crystallization was tried as an alternative technique to chromatography for purification of compound **180**, found that this is not efficient enough to isolate the starting material from the product.

It was believed at this point that all reasonable variables had been adjusted, and that the above reaction conditions are as efficient as possible for this reaction.

4.4 Conclusion

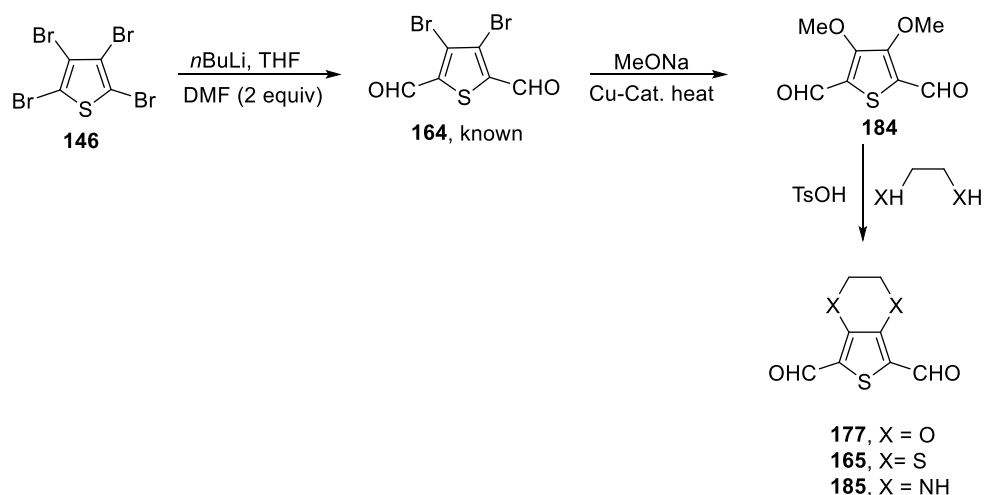
Firstly, we have reported a new route for the synthesis of the 2,5-diformyl derivative of 3,4-ethylenedioxythiophene (EDOT). The key intermediate dinitrile compound **176** is obtained using ultra-cheap $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ (4 pence/g) and 2-chloroacetonitrile (18 pence/g) in just three steps. Notably, the dinitrile compound **176** was converted cleanly to the corresponding aldehyde **177** in near quantitative yield with DIBAL-H. This novel route was compared to the alternative literature methods.

Secondly, Kumada and Negishi methodologies have been investigated in order to synthesise vinyl thiophenes **180** and **181**. The Negishi coupling were selected for optimisations; the Kumada coupling only provided non-desired dibromothiophene **90**.

On another hand, the Negishi coupling reaction was partially optimised for the preparation of **180** by screening many different catalysts, ligands, solvents, time, temperatures and amount of added $\text{ZnBr}(\text{CH}=\text{CH}_2)$. The best yield of compound **180** resulting from these studies was only 38% using $\text{Pd}(\text{OAc})_2$ and the electron deficient ligand *tris*(4-fluorophenyl)phosphine **L5** in THF as a solvent, at a temperature of 50 °C and a stirring time of 42 h. Attempting to improve this yield through heating to higher temperature led only to by-product formulation through 3,4-bromo coupling. Compound **180** could not be isolated from starting material **146** as both had very similar properties.

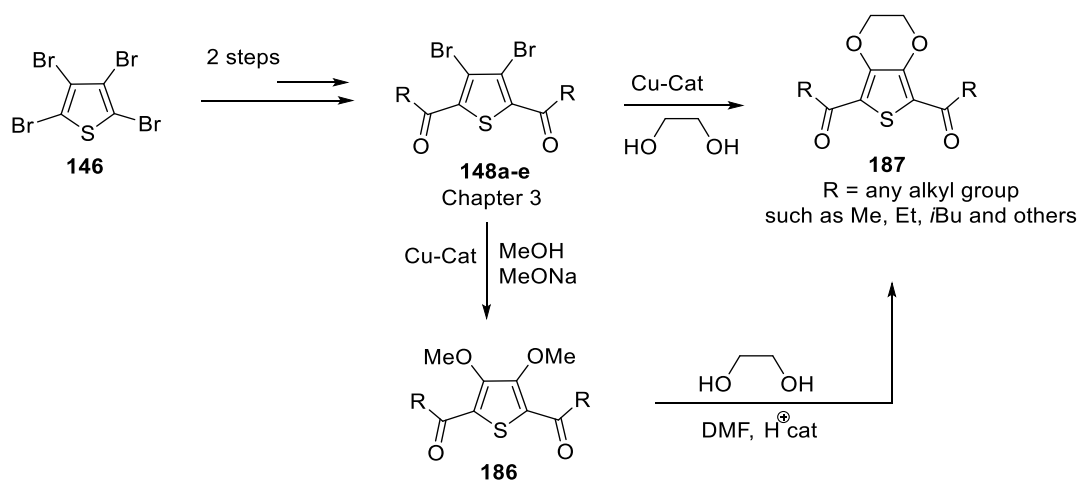
4.5 Future work

Due to the limited time available for this present project, there are still some areas that need to be investigated. As the main aim for this Chapter was to identifying novel routes to 2,5-functionalised derivatives of EDOT, good routes to reactive functional groups such aldehydes or ketones still need to be identified. Considering our successful work reported in Chapter 3, Scheme 61 shows the possible method for the synthesis of 2,5-formyl derivatives of EDOT and using the same method and only changing heteratom the (X = O, S, N) in the final step should provide access to other analogues of EDOT.



Scheme 61 Possible synthesis of 2,5-derivatives of EDOT **177** and other analogues **165** and **185**

Finally, it should be possible to extend the chemistry of our compounds **148a-e** described in Chapter 3. These known compounds should be able to react with ethylene glycol either (directly or indirectly) to obtain the novel 2,5-dicarbonyl derivatives of EDOT (Scheme 62).



Scheme 62 Possible synthesis of 2,5-dicarbonyl derivatives of EDOT via addition-elimination reaction.

5 Chapter five: Experimental

5.1 General Information

Reactions involving air-sensitive reagents were carried out under argon atmospheres in flame-dried glassware. All solvents were commercial (Sigma Aldrich and Fisher Scientific UK Ltd) and were used as supplied unless otherwise stated. Dichloromethane, dimethyl sulfoxide (DMSO), triethylamine, diisopropylethylamine and 1,2-dichloroethane were dried overnight with molecular sieves (4 Å). Tetrahydrofuran (<10 ppm water) was taken from an anhydrous solvent unit (Inert Technologies PureSolv) under argon. The compounds 2-butyne-1,4-diol **1**, iodine, PCy₃ (Cy = *cyclo*-C₆H₁₁) S-Phos (2-dicyclohexylphosphino-2,6-dimethoxybiphenyl), Pd(OAc)₂, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), [Cu (MeCN)₄] BF₄, CuBr·SMe₂ were commercial from Alfa-Aesar, Fisher, Merck or Sigma-Aldrich and used without further purification. Lithium chloride (Aldrich, anhydrous, >99%) and TiCl₄ (Fluka, >98%) were stored under argon. Benzyl chlorides were commercial (Sigma-Aldrich): BnCl, 4-RC₆H₄CH₂Cl (R = Me, MeO, F), or prepared by literature routes (R = *i*Pr).²⁷³ Starting diols **5a-d** and **67** were prepared according to a literature procedure.³⁶

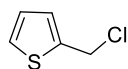
Aldehydes were distilled before use. The starting materials tetrabromothiophene **146**, 2,2'-thiodiacetonitrile **174** and activated MnO₂²⁷⁴ were prepared by modifications of literature procedures but are described here for clarity.

Zinc dust (<10 µm, Sigma Aldrich: 209988-1KG) was activated by trimethylsilyl chloride. All temperatures refer to those of the cooling and heating baths used. Thin layer chromatography was performed on foil-backed plates plated with Merck silica gel 60 F₂₅₄. Nuclear magnetic resonance spectra were recorded on Bruker DPX-400 (400.1 MHz), AV400 (400.1 MHz), AV(III)400 (400.1 MHz) or Bruker Ascend 500

(500.1 MHz) spectrometers at ambient temperature. All proton spectra were referenced to CDCl_3 ($\delta = 7.27$ ppm) or acetone- d_6 ($\delta = 2.05$ ppm) as an internal standard. All ^{13}C NMR samples were proton-decoupled and referenced to CDCl_3 ($\delta = 77.0$ ppm), acetone- d_6 ($\delta = 29.9$ ppm) or $\text{DMSO}-d_6$ ($\delta = 39.5$ ppm). Coupling constants (J) are quoted in hertz. Melting points were determined with a Gallenkamp MFB-600-010F apparatus. Infrared spectra (IR) were recorded with a Varian FTS-7000 FT-IR spectrometer using (ATR) at room temperature. UV-Vis spectra were recorded by Cary UV VIS NIR spectrometer using ca. 10^{-4} M dichloromethane solutions. Semi-quantitative $\log(\epsilon)$ values are given as a guide to relative peak height. Mass spectrometry was performed using a Bruker MicroTOF or VG Micromass AutoSpec spectrometers using electrospray (ESI), electron impact (EI) ionization modes. Elemental CH analyses were conducted on a CE-440 Elemental Analyser.

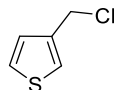
5.2 Experimental Data for Chapter 2

2-(Chloromethyl)thiophene



To a solution of thien-2-yl methanol (10.0 g, 87.6 mmol) in dry dichloromethane (350 mL) at 0 °C, thionyl chloride (12.8 mL, 175.2 mmol, 2.0 equiv) was slowly added over ca. 6 min at 0 °C. The mixture was stirred for 10 minutes at 0 °C and then stirring was continued over 20 hours at room temperature. The mixture was poured on to ice, the dichloromethane layer was separated, and the remaining aqueous layer re-extracted with dichloromethane (3 × 70 mL). The combined organics were dried (MgSO₄) and the solvent was removed under reduced pressure to give the crude 2-(chloromethyl)thiophene as a brown oil (10.4 g, 90% yield). For subsequent zinc reagent formation, the compound was distilled at 45 °C and 4 mbar to give a colourless oil. **¹H NMR** (400.1 MHz, CDCl₃) δ 7.32 (dd, *J* = 5.1, 1.2 Hz, 1H, Ar*H*-thiophene), 7.13-7.07 (m, 1H, Ar*H*-thiophene), 6.96 (dd, *J* = 5.1, 3.5 Hz, 1H, Ar*H*-thiophene), 4.82 (s, 2H, CH₂). **¹³C NMR** (100.6 MHz, CDCl₃) δ 140.2 (C), 127.8 (CH), 127.0 (CH), 127.0 (CH), 40.5 (CH₂). These data are consistent with the literature.²⁷⁵

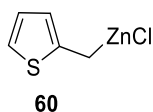
3-(Chloromethyl)thiophene



To a solution of 3-thiophenemethanol (4.57 g, 40.0 mmol) in dry dichloromethane (160 mL) at 0 °C, thionyl chloride (5.85 mL, 80.1 mmol, 2.0 equiv) was added slowly. The mixture was stirred for 10 minutes at 0 °C and then allowed to warm to room temperature over 16 hours. The mixture was poured on to ice and the

dichloromethane layer separated and the remaining aqueous layer re-extracted with dichloromethane (3×70 mL) and dried (MgSO_4). The solvent was removed under reduced pressure to give crude 3-(chloromethyl)thiophene as a brown oil. The crude compound was distilled at 70-75 °C and 16-18 mbar to give a colourless liquid (3.95 g, 67%); **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3103, 2957, 2866, 1760, 1441, 1415, 1263, 1239, 1162, 1080, 908, 857, 829, 784, 691, 671, 612, 551; **^1H NMR** (400.1 MHz, CDCl_3) δ 7.33 (dd, $J = 5.0, 3.0$ Hz, 1H, ArH-thiophene), 7.30 (m, 1H, ArH-thiophene), 7.14 (dd, $J = 5.0, 1.4$ Hz, 1H, ArH-thiophene), 4.64 (s, 2H, CH_2); **^{13}C NMR** (100.6 MHz, CDCl_3) δ 138.2 (C), 127.7 (CH), 126.8 (CH), 124.1 (CH), 40.8 (CH_2). These data are consistent with the literature.²⁷⁶

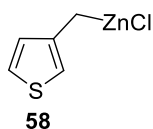
(Thien-2-ylmethyl)zinc(II) chloride 60



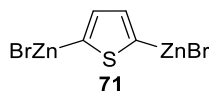
Zinc dust (<10 μm , 0.23 g, 3.57 mmol) was dried under vacuum at (0.5 mbar) at >200 °C (3-5 min), then cooled to room temperature under an atmosphere of argon. Tetrahydrofuran (3.0 mL) was then added, forming a grey suspension. The reaction mixture was cooled to 0 °C and trimethylsilyl chloride (12 μL , 95 μmol , 0.04 equiv) was added in one portion and the mixture stirred (30 min). Freshly distilled 2-(chloromethyl)thiophene (316 mg, 2.38 mmol) was added over 10 min. After addition of the 2-(chloromethyl)thiophene was complete the mixture was stirred at 0 °C over (5 h). A turbid white suspension (which normally titrated at >0.54 M, $>74\%$ yield)²⁷⁷ resulted over the remaining residual zinc powder. The supernatant solution could be

stored for up to one week at 4 °C (resulting in clear or pale-yellow supernatants), but typically the organometallic was used within (24 h).

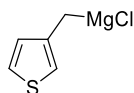
(Thiophen-3-ylmethyl)zinc(II) chloride 58



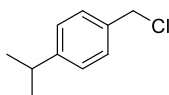
A dry, argon-flushed Schlenk flask equipped with a magnetic stirrer and a septum was charged with zinc dust <10 μm , (2.50 g, 38.7 mmol, 2.0 equiv). The flask was heated for 5 min under high vacuum (<0.5 mbar) using a heat gun. After cooling to 25 °C, the flask was flushed again with argon and dry THF (21.5 mL) was added and forming a grey suspension. The mixture was cooled to 0 °C and trimethylsilyl chloride (99 μL , 0.77 mmol, 0.04 equiv) added in one portion. The mixture allowed to stir for (35 min) at 25 °C. Freshly distilled 3-(chloromethyl)thiophene (2.57 g, 19.4 mmol) was then added slowly (over 5 min) at 25 °C. (Note: equivalent results were attained using crude 3-(chloromethyl)thiophene dried overnight at rt with calcium hydride instead of distillation). After addition of the 3-(chloromethyl)thiophene was complete the mixture was warmed to 40 °C and stirred (4 h). When titrated with iodine²⁷⁷ the reaction assayed at 80%, 0.64 M. This solution could be stored at 4 °C for at least five days but was usually used as attained.

2,2'-(Thiophene-2,5-diyl)-bis-zinc bromide 71

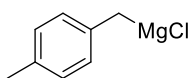
In a dry Shlenk tube, zinc dust (<10 μm , 0.94 g, 14.5 mmol) was dried under vacuum using heat gun at >200 $^{\circ}\text{C}$ (ca. 5 mins), then cooled to room temperature under an atmosphere of argon. Tetrahydrofuran (4.1 mL) was added forming a grey suspension. The reaction mixture was cooled to 0 $^{\circ}\text{C}$ before adding of trimethylsilyl chloride (41 μL , 0.33 mmol) and stirring the mixture (0.5 h) at rt. Neat 2,5-dibromothiophene (1.00 g, 0.46 mL, 4.13 mmol) was added subsequently over a period of 5 minutes to the mixture at 0 $^{\circ}\text{C}$. After addition of the 2,5-dibromothiophene was complete the reaction mixture was stirred (4 h) at 50 $^{\circ}\text{C}$. The reaction mixture was cooled to room temperature and provided a turbid white suspension over the remaining residual zinc powder. (Iodine titrations²⁷⁷ indicated >0.7 M solutions were provided, >88% yield).

(Thiophen-3-ylmethyl)magnesium chloride

Magnesium metal (3.66 g, 150 mmol) was activated by abrasion stirring at rt overnight under argon. Anhydrous THF (50 mL) was added followed by 3-(chloromethyl)thiophene (9.24 g, 69.7 mmol), added dropwise over (16 h) using a micro metering pump.²⁷⁸ The black solution when titrated with iodine indicated the desired Grignard reagent (1.077 M, 89%). The solution was used immediately to the next step. This reagent has only been described in passing in the literature.²⁷⁹

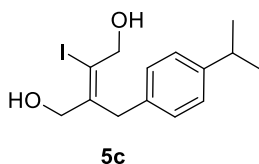
Isopropylbenzyl chloride

Neat 4-isopropylbenzyl alcohol (20.4 mL, 20.0 g, 133 mmol) was added dropwise to SOCl_2 (29.1 mL, 47.5 g, 399 mmol) under argon at 25 °C. The reaction mixture was warm to refluxed (1 h), and afterward distilled under reduced pressure (118 °C at 22 mbar) to yield (17.35 g, 77%) as a colourless oil. **^1H NMR** (500.1 MHz, CDCl_3) δ 7.32 (d, J = 8.2 Hz, 2H, ArH), 7.23 (d, J = 8.2 Hz, 2H, ArH), 4.58 (s, 2H, CH_2), 2.92 (hept, J = 6.9 Hz, 1H, CH), 1.25 (d, J = 6.9 Hz, 6H, $2 \times \text{CH}_3$); **^{13}C NMR** (125.8 MHz, CDCl_3) δ 149.4 (C), 135.0 (C), 128.8 ($2 \times \text{CH}$), 127.0 ($2 \times \text{CH}$), 46.4 (CH_2), 34.0 (CH), 24.1 ($2 \times \text{CH}_3$). The experimental data match the published values.²⁷³

Grignard reagent preparation, representative example: (4-methylbenzyl)magnesium chloride

Magnesium metal (10.0 g, 156 mmol) was activated by mechanical stirring (7 h) under argon in the presence of iodine crystals (ca. 3.0 mg) at 22 °C until its colour became black. Anhydrous tetrahydrofuran (156 mL) was then added at 20 °C giving a suspension of black activated magnesium. Distilled neat 4-methylbenzyl chloride (20.7 mL, 156 mmol) was then added dropwise to the reaction mixture over (15 h) using a syringe pump. After completion of the addition the reaction mixture was which typically titrated against the iodine to give 0.85 M equivalent to a 96% yield. The reagent was used as attained.³⁶

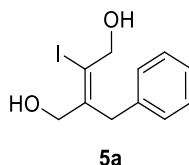
Preparation of starting diols (10a-e) representative example: (Z)-2-iodo-3-(4-isopropylbenzyl)but-2-ene-1,4-diol **5c**



A solution of (4-isopropylbenzyl)magnesium chloride (39 mL, 1.1 M tetrahydrofuran solution, 42.9 mmol) was added to a stirred solution of 2-butyne-1,4-diol **1** (1.10 g, 12.9 mmol) in dry tetrahydrofuran (23 mL) at 0 °C to form a colourless precipitate within a grey solution. The reaction mixture was allowed to warm to room temperature and stirred for 5 mins. Then, solid cuprous bromide dimethyl sulfide (52.9 mg, 0.26 mmol, 2 mol% based on diol) was added against an argon flow, and the reaction mixture promptly transferred to pre-equilibrated oil bath at 60-65 °C. After (1 h) at 60-65 °C the solid dissolved forming a dark solution which was cooled first to 25 °C and then to -60 °C in a lightly lagged bath (that would allow warming from -60 to 0 °C over ca. 1 h). Solid I₂ (4.35 g, 17.2 mmol) was added, against an argon flow, and the brown mixture stirred as it came to 0 °C over (1 h). The reaction mixture was extracted with EtOAc (3 × 70 mL) and washed with sodium metabisulfite (2 × 70 mL of 5% w/w aqueous solution) and water (1 × 50 mL). The resulting pale-yellow solution was dried over MgSO₄, filtered and the solvent evaporated. To the crude oily mixture, that contained traces of EtOAc, was added a mixture of Et₂O and pentane (1:1, ca. 75 mL) and the mixture cooled to 5 °C overnight to afforded colourless microneedles. A combined yield was attained over three crops of (2.35 g, 6.79 mmol, 53%) was attained. TLC: **R_f** (ethyl acetate) 0.53; **Mp** 74-75 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3213, 2954, 2927, 2864, 1625, 1510, 1454, 1434, 1419, 1383, 1361, 1238, 1169, 1067, 1013, 997, 918, 830, 799, 742, 705,

609, 565, 543; **¹H NMR** (500.1 MHz, CDCl₃) δ 7.17 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.10 (d, *J* = 8.2 Hz, 2H, Ar*H*), 4.50 (d, *J* = 6.6 Hz, 2H, CH₂), 4.24 (d, *J* = 6.6 Hz, 2H, CH₂), 3.77 (s, 2H, CH₂), 2.88 (hept, *J* = 6.9 Hz, 1H, CH), 2.02 (t, *J* = 6.6 Hz, 1H, OH), 1.67 (t, *J* = 6.6 Hz, 1H, OH), 1.23 (d, *J* = 6.9 Hz, 6H, 2 × CH₃); **¹³C NMR** (125.8 MHz, CDCl₃) δ 147.5 (C), 144.8 (C), 135.18 (C), 128.4 (2 × CH), 127.0 (2 × CH), 106.5 (C), 71.3 (CH₂), 67.8 (CH₂), 35.7 (CH₂), 33.8 (CH), 24.1 (2 × CH₃); **HRMS** (ESI⁺) (*m/z*): [M + Na]⁺ calcd for C₁₄H₁₉IO₂Na, 369.0322; found, 369.0311; **CHN** Anal. calcd for C₁₄H₁₉IO₂ C, 48.57; H, 5.53; found C, 48.56; H, 5.41%.

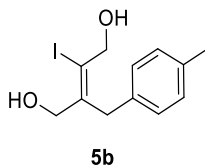
(Z)-2-Benzyl-3-iodobut-2-ene-1,4-diol 5a



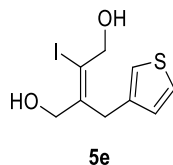
Prepared by a similar procedure to compound **5c** using freshly prepared benzyl magnesium chloride (175 mL, 0.8 M THF solution, 140 mmol), 2-butyne-1,4-diol **1** (3.61 g, 42.0 mmol) in anhydrous THF (23 mL), CuBr·SMe₂ (0.17 mg, 0.84 mmol, 2 mol%), I₂ (14.2 g, 56 mmol), yielding **5a** as a colourless microneedles (7.40 g, 24.33 mmol, 59%) after crystallisation with Et₂O/pentane (three crops). TLC: **R_f** (ethyl acetate) 0.68; **Mp** 94-95 °C; **IR** (diamond-ATR): ν_{max}/cm⁻¹ 3192, 3058, 2918, 2866, 1618, 1601, 1492, 1449, 1429, 1361, 1237, 1063, 1022, 996, 933, 888, 838, 724, 693, 656, 601, 492, 457, 423; **¹H NMR** (500.1 MHz, CDCl₃) δ 7.32-7.29 (m, 2H, Ar*H*), 7.25-7.18 (m, 3H, Ar*H*), 4.50 (d, *J* = 6.6 Hz, 2H, CH₂), 4.24 (d, *J* = 6.6 Hz, 2H, CH₂), 3.81 (s, 2H, CH₂), 1.97 (t, *J* = 6.6 Hz, 1H, OH), 1.61 (t, *J* = 6.6 Hz, 1H, OH); **¹³C NMR** (125.8 MHz, CDCl₃) δ 144.6 (C), 138.0 (C), 129.0 (2 × CH), 128.5 (2 × CH), 127.0 (CH), 107 (C), 71.2 (CH₂), 68.0 (CH₂), 36.1 (CH₂); **HRMS**

(ESI+) (m/z): $[M]^+$ calcd for $C_{11}H_{13}IO_2$, 303.9960; found, 303.9941. The experimental data were consistent with published values.³⁶

(Z)-2-Iodo-3-(4-methylbenzyl)but-2-ene-1,4-diol 5b

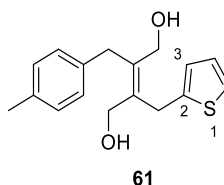


Prepared by similar procedure to compound **5c** using 4-methylbenzylmagnesium chloride (176 mL, 0.85 M THF solution, 150 mmol), 2-butyne-1,4-diol **1** (3.88 g, 45.05 mmol) in THF (25 mL), CuBr·SMe₂ (185 mg, 0.9 mmol, 2 mol%) and I₂ (15.3 g, 60.0 mmol) to yield **10b** as a colourless powder 9.91 g, 31.2 mmol (69%) on trituration with Et₂O:pentane. TLC: **R_f** (1:1 EtOAc:pentane) 0.56; **Mp** 115-116 °C; **IR** (diamond-ATR): $\nu_{\max}/\text{cm}^{-1}$ 3242, 3045, 3019, 2920, 2874, 1510, 1476, 1493, 1440, 1414, 1316, 1237, 1169, 1072, 1036, 1017, 990, 961, 921, 831, 800, 751, 658, 553, 480, 436; **¹H NMR** (500.1 MHz, CDCl₃) δ 7.11 (d, J = 8.0 Hz, 2H, ArH), 7.07 (d, J = 8.0 Hz, 2H, ArH), 4.49 (d, J = 6.5 Hz, 2H, CH₂), 4.23 (d, J = 6.5 Hz, 2H, CH₂), 3.76 (s, 2H, CH₂), 2.32 (s, 3H, CH₃) 2.01 (t, J = 6.5 Hz, 1H, OH), 1.66 (t, J = 6.5 Hz, 1H, OH); **¹³C NMR** (125.8 MHz, CDCl₃) δ 144.8 (C), 136.5 (C), 134.8 (C), 129.7 (2 × CH), 128.4 (2 × CH), 106.5 (C), 71.09 (CH₂), 67.67 (CH₂), 35.6 (CH₂), 21.0 (CH₃); **HRMS** (ESI+) (m/z): $[M + Na]^+$ calcd for C₁₂H₁₅IO₂Na, 341.0009 $[M+Na]^+$; found, 340.9998 $[M+Na]^+$. The data of the compound match published values.³⁶

(Z)-2-iodo-3-(thiophen-3-ylmethyl)but-2-ene-1,4-diol 5e

Prepared by a similar procedure to compound **5c** using (thiophen-3-ylmethyl)magnesium chloride (55 mL, 1.07 M THF solution, 59.2 mmol), 2-butyne-1,4-diol **1** (1.53 g, 17.8 mmol) in THF (14 mL) and I₂ (6.01 g, 23.7 mmol) to yield **5e** (2.00 g, 6.45 mmol, 36%) after column chromatography (2:1 dichloromethane:EtOAc). TLC: **R_f** (2:1 dichloromethane:EtOAc) 0.43; **Mp** 93-94 °C ; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3196, 3095, 2922, 2866, 1626, 1488, 1456, 1434, 1407, 1381, 1356, 1294, 1238, 1167, 1143, 1070, 1017, 997, 935, 921, 868, 833, 773, 737, 712, 699, 685, 589, 570, 501, 413; **¹H NMR** (500.1 MHz, CDCl₃) δ 7.29 (dd, *J* = 4.9, 3.0 Hz, 1H, Ar*H*-thiophene), 7.00 (m, 1H, Ar*H*-thiophene), 6.94 (d, *J* = 4.9 Hz, 1H, Ar*H*-thiophene), 4.48 (d, *J* = 6.6 Hz, 2H, CH₂), 4.28 (d, *J* = 6.6 Hz, 2H, CH₂), 3.78 (s, 2H, CH₂), 1.95 (t, *J* = 6.6 Hz, 1H, OH), 1.63 (t, *J* = 6.6 Hz, 1H, OH); **¹³C NMR** (125.8 MHz, CDCl₃) δ 144.5 (C), 138.4 (C), 128.0 (CH), 126.5 (CH), 121.7 (CH), 106.4 (C), 71.4 (CH₂), 67.8 (CH₂), 31.1 (CH₂); **HRMS** (ESI⁺): (*m/z*); calcd for C₉H₁₁IO₂S, 309.9518 (M⁺); found 309.9534 (M⁺).

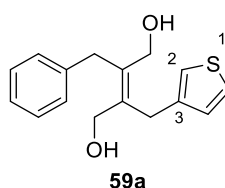
Preparation of (E)-2-(4-methylbenzyl)-3-(thien-2-ylmethyl)but-2-ene-1,4-diol 61 by heterocoupling of (Z)-2-iodo-3-(4-methylbenzyl)but-2-ene-1,4-diol 5b with (thien-2-ylmethyl)zinc(II) chloride 61



Lithium chloride (16 mg, 0.337 mmol, 1.0 equiv) was dried under vacuum (ca. 1 mbar) at >200 °C until free flowing (ca. 6 min), then cooled under an atmosphere of argon. Solid (Z)-2-Iodo-3-(4-methylbenzyl)but-2-ene-1,4-diol (100 mg, 0.314 mmol) was added. Tetrahydrofuran (0.9 mL) was added. Solid S-Phos (4.8 mg, 11 µmol, 3.8 mol%) was added followed by addition of solid Pd(OAc)₂ (2.8 mg, 12 µmol, 4 mol%) forming a dark brown coloured reaction mixture. Promptly, (thien-2-ylmethyl)zinc(II) chloride (0.7 mL of 0.7 M THF solution, 0.5 mmol, 1.5 equiv) was added slowly at rt over (ca. 5 min). After all the zinc reagent added the colour of the reaction mixture became bright orange. This reaction was monitored by TLC, and this indicated the conversion and chemoselectivity (even after addition of additional Pd(OAc)₂/S-Phos ca. 2 mol%) was not good, rationalising the low yields observed for this coupling in numerous repeats. After (3 h) the reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 mL) and the mixture extracted with ethyl acetate (4 × 5 mL). After drying with Na₂SO₄ or MgSO₄, the solution was filtered, concentrated and evaporated under reduced pressure giving a yellow solid. Purification was achieved by column chromatography (3:2 EtOAc:pentane) giving a colourless solid **61** (28.0 mg, 0.10 mmol, 32%). TLC: **R_f** (3:2 EtOAc:pentane) 0.48; **Mp** 126-128 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3383, 3317, 2950, 2920, 2853, 1510. 1482, 1433, 1332, 1292, 1252, 1213, 1119, 1076, 1064, 1033, 1014, 995, 927, 879, 848, 837, 805, 762, 748, 687, 607, 527, 497, 478, 450.); **¹H NMR** (400.1 MHz, CDCl₃) δ 7.15 (dd, *J* = 5.1, 1.2 Hz, 1H, Ar*H*-thiophene), 7.11 (app. s, 4H, Ar*H*), 6.93 (dd, *J* = 5.1, 3.4 Hz, 1H, Ar*H*-thiophene), 6.86-6.82 (m, 1H, Ar*H*-thiophene), 4.29 (s, 2H, CH₂), 4.22 (s, 2H, CH₂), 3.87 (s, 2H, CH₂), 3.66 (s, 2H, CH₂), 2.32 (s, 3H, CH₃) 1.26 (broad, 2H, 2 × OH); **¹³C NMR** (100.6 MHz, CDCl₃) δ 143.4 (C), 137.4 (C), 136.5 (C), 136.4 (C), 136.0 (C), 129.5

(2 × CH), 128.6 (2 × CH), 127.2 (CH), 125.2 (CH), 124.0 (CH), 61.9 (2 × CH₂), 35.3 (CH₂), 30.2 (CH₂), 21.1 (CH₃); **HRMS** (ESI+) (*m/z*): [M + Na]⁺ calcd for C₁₇H₁₉O₂SNa, 311.1081, found, 311.1076.

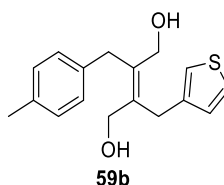
Heterocoupling of 5a-d with (Thiophen-3-ylmethyl)zinc(II) chloride 58 for disymmetric diols 59a-d, representative example: (*E*)-2-benzyl-3-(thiophen-3-ylmethyl)but-2-ene-1,4-diol 59a



Lithium chloride LiCl (57.2 mg, 1.35 mmol, 1.2 equiv) was dried under vacuum using heat gun at >200 °C for (5 min) then allow to cool to rt under an atmosphere of argon. The crystalline needles of (*Z*)-2-benzyl-3-iodobut-2-ene-1,4-diol **5a** (0.34 g, 1.13 mmol) and solid S-Phos (12.5 mg, 0.03 mmol, 2.7 mol% equiv) were added and the solid mixture left under high vacuum for few min. Thereafter under an atmosphere of argon, tetrahydrofuran (3.3 mL) was added followed promptly by solid Pd(OAc)₂ (7.6 mg, 33 μmol, 3 mol%) forming a dark brown coloured solution. (If this colour was not formed, active catalyst formation could be ensued by re-charging with the same amount of ligand and palladium). Immediately after formation of the brown active catalyst, a solution of (thiophen-3-ylmethyl)zinc(II) chloride **58** (4.0 mL of 0.45 M THF solution, 1.8 mmol, 1.6 equiv) was added in one portion. After addition of the zinc reagent the colour of the reaction mixture changed to clear yellow. The reaction was monitored via TLC. After less than one hour this showed 90% of the starting material was converted to a new entity. The reaction mixture was quenched

with saturated aqueous ammonium chloride solution (3 mL) and then extracted with ethyl acetate (4×10 mL). The organic layer was separated, and then washed with saturated aqueous sodium hydrogen carbonate (4×5 mL). The organic extracts were dried with Na_2SO_4 or MgSO_4 . The organic layer concentrated via high vacuum to yield tan solid. Purification was achieved by column chromatography (3:2 EtOAc:pentane) to give colourless solid (0.24 g, 0.87 mmol, 77%). TLC: **R_f** (3:2 EtOAc: pentane) 0.45; **Mp** 128-129 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3386, 3328, 3099, 2949, 2916, 2853, 1731, 1601, 1493, 1481, 1452, 1431, 1327, 1127, 1057, 1028, 1011, 992, 942, 855, 828, 786, 757, 729, 700, 632, 583, 493, 434; **¹H NMR** (500.1 MHz, CDCl_3) δ 7.32-7.27 (m, 3H, ArH), 7.24-7.19 (m, 3H, ArH), 6.98-6.95 (m, 2H, ArH), 4.28 (d, $J = 5.3$ Hz, 2H, CH_2), 4.22 (d, $J = 5.3$ Hz, 2H, CH_2), 3.71 (s, 2H, CH_2), 3.70 (s, 2H, CH_2), 1.25 (t, $J = 5.3$ Hz, 1H, OH), 1.20 (t, $J = 5.3$ Hz, 1H, OH); **¹³C NMR** (125.8 MHz, CDCl_3) δ 140.5 (C), 139.9 (C), 136.7 ($2 \times$ C), 128.9 ($2 \times$ CH), 128.7 ($2 \times$ CH), 128.3 (CH), 126.5 (CH), 126.2 (CH), 121.2 (CH), 62.2 (CH_2), 61.9 (CH_2), 35.8 (CH_2), 30.8 (CH_2); **HRMS** (ESI+) (m/z): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{18}\text{O}_2\text{SNa}$, 297.0920; found, 297.0918.

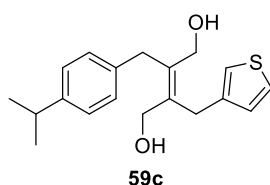
(E)-2-(4-methylbenzyl)-3-(thiophen-3-ylmethyl)but-2-ene-1,4-diol 59b



Prepared by a method analogous to **59a** using (Z)-2-iodo-3-(4-methylbenzyl)but-2-ene-1,4-diol **5b** (1.00 g, 3.71 mmol) and (thiophen-3-ylmethyl)zinc(II) chloride **58** (7.71 mL, 0.64 M THF solution, 4.71 mmol). To yield **59b** as a colourless powder (0.75 g, 2.60 mmol, 83%) after column chromatography (3:2 EtOAc:pentane). TLC: **R_f**

(ethyl acetate) 0.66. Colourless thin needles from hot acetonitrile on cooling to ambient, then 4 °C with **Mp** 127-129 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3381, 3310, 3101, 2950, 2917, 1509, 1482, 1433, 1383, 1331, 1298, 1205, 1128, 1065, 1011, 992, 942, 926, 880, 855, 829, 806, 783, 760, 722, 699, 627, 523, 491; **¹H NMR** (500.1 MHz, CDCl₃) δ 7.28-7.26 (m, 1H, ArH-thiophene), δ 7.12-7.08 (m, 4H, ArH), 7.97-6.94 (m, 2H, ArH-thiophene), 4.27 (s, 2H, CH₂), 4.21 (s, 2H, CH₂), 3.68 (s, 2H, CH₂), 3.66 (s, 2H, CH₂), 2.32 (s, 3H, CH₃), 1.43 (broad, 2H, 2 $\times$ OH); **¹³C NMR** (125.8 MHz CDCl₃) δ 140.5 (C), 136.9 (C), 136.6 (C), 136.4 (C), 129.5 (2 $\times$ CH), 128.5 (2 $\times$ CH), 128.3 (CH), 126.2 (CH), 121.2 (CH), 62.2 (CH₂), 61.9 (CH₂), 35.4 (CH₂), 30.8 (CH₂), 21.1 (CH₃). **HRMS** (ESI+) (m/z): [M + Na]⁺ calcd for C₁₇H₁₉O₂SNa, 311.1076; found, 311.1075. **CHN Anal.** calcd For C₁₇H₂₀O₂S C, 70.80; H, 6.99; found C, 70.61; H, 6.94%.

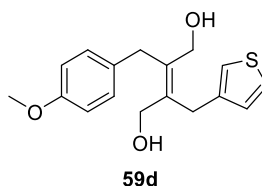
(E)-2-(4-isopropylbenzyl)-3-(thiophen-3-ylmethyl)but-2-ene-1,4-diol 59c



Prepared by a method analogous to **59a** using (Z)-2-iodo-3-(4-isopropylbenzyl)but-2-ene-1,4-diol **5c** (1.50 g, 4.33 mmol) and (thiophen-3-ylmethyl)zinc(II) chloride **58** (10.0 mL 6.70 mmol, 0.67 M THF solution). To yield **59c** as a colourless powder (1.1 g, 4.48 mmol, 80%) after column chromatography (3:2 EtOAc:pentane). TLC: **R_f** (3:2 EtOAc:pentane) 0.41; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3389, 3334, 3103, 2956, 2889, 2869, 1511, 1481, 1467, 1432, 1415, 1382, 1333, 1296, 1128, 1064, 1009, 990, 942, 928, 880, 856, 837, 784, 719, 700, 623, 550; **¹H NMR** (500.1 MHz, CDCl₃) δ 7.28 (dd, J = 4.8, 3.0 Hz, 1H, ArH-thiophene), 7.17 (d, J = 8.0 Hz, 2H, ArH), 7.13

(d, $J = 8.0$ Hz, 2H, ArH), 6.97 (m, 2H, ArH-thiophene), 4.27 (d, $J = 5.4$ Hz, 2H, CH₂), 4.22 (d, $J = 5.4$ Hz, 2H, CH₂), 3.69 (s, 2H, CH₂), 3.67 (s, 2H, CH₂), 2.88 (hept, $J = 7.0$ Hz, 1H, CH), 1.32 (t, $J = 5.4$ Hz, 1H, OH), 1.29 (t, $J = 5.4$ Hz, 1H, OH), 1.24 (d, $J = 7.0$ Hz, 6H, 2 × CH₃); ¹³C NMR (125.8 MHz CDCl₃) δ 147.1 (C), 140.5 (C), 137.0 (C), 136.8 (C), 136.5 (C), 128.5 (2 × CH), 128.4 (CH), 126.9 (2 × CH), 126.1 (CH), 121.2 (CH), 62.2 (CH₂), 62.0 (CH₂), 35.4 (CH), 33.8 (CH₂), 30.8 (CH₂), 24.2 (2 × CH₃); HRMS (ESI+) (m/z): [M+Na]⁺ calcd for C₁₉H₂₄O₂SNa, 339.1389; found, 339.1384.

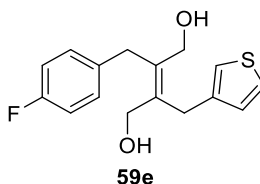
(E)-2-(4-methoxybenzyl)-3-(thien-3-ylmethyl)but-2-ene-1,4-diol 59d



Prepared by a method analogous to **59a** using (Z)-2-iodo-3-(4-methoxybenzyl)but-2-ene-1,4-diol **5d** (0.34 g, 1.00 mmol) and (thien-3-ylmethyl)zinc(II) chloride **58** (2.30 mL, 0.64 M tetrahydrofuran solution 1.50 mmol) to yield **59d** as colourless plates (0.28 g, 0.92 mmol, 92%) after column chromatography (3:2 EtOAc:pentane). TLC: **R_f** (3:2 EtOAc: pentane) 0.46; **Mp** 109-111 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3387, 3324, 3100, 2928, 2834, 1609, 1580, 1508, 1481, 1461, 1432, 1327, 1301, 1247, 1174, 1127, 1062, 1033, 1010, 990, 942, 879, 829, 783, 763, 722, 691, 625, 513; ¹H NMR (500.1 MHz, CDCl₃) δ 7.30-7.24 (m, 1H, ArH-thiophene), 7.11 (d, $J = 8.6$ Hz, 2H, ArH), 6.94 (m, 2H, ArH-thiophene), 6.84 (d, $J = 8.6$ Hz, 2H, ArH), 4.27 (s, 2H, CH₂), 4.19 (s, 2H, CH₂), 3.78 (s, 3H, OCH₃), 3.68 (s, 2H, CH₂), 3.63 (s, 2H, CH₂), overlapped by 1.76 (m, 2H, 2 × OH); ¹³C NMR (125.8 MHz CDCl₃) δ 158.3 (C), 140.4 (C), 137.1 (C), 136.3 (C), 131.6 (C), 129.6 (2 × CH), 128.3 (CH), 126.2 (CH),

121.2 (CH), 114.3 (2 × CH), 62.1 (CH₂), 61.8 (CH₂), 55.4 (OCH₃), 35.0 (CH₂), 30.9 (CH₂); **HRMS** (ESI+) (*m/z*): [M+Na]⁺ calcd for C₁₇H₂₀O₃SNa, 327.1025; found, 327.1024.

(E)-2-(4-fluorobenzyl)-3-(thiophen-3-ylmethyl)but-2-ene-1,4-diol 59e

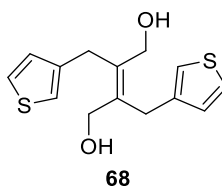


Prepared by a method analogous to **59a** using: (Z)-2-(4-fluorobenzyl)-3-iodobut-2-ene-1,4-diol **5e** (1.20 g, 3.73 mmol) and (thiophen-3-ylmethyl)zinc(II) chloride **58** (8.7 mL, 0.64 M THF solution, 5.6 mmol). The crude brown product obtained after evaporation of the organic layer was triturated with Et₂O and cooled to 5 °C, to provide an initial crop. The rest of product come from column chromatography (EtOAc:pentane 3:2) to provide a combined yield of **59e** as a tan powder (0.94 g, 3.42 mmol, 87%). Colourless needles crystallised from hot acetonitrile on cooling to ambient, then 4 °C. TLC: **R_f** (3:2 EtOAc:pentane) 0.51; **Mp** 115-117 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3367, 3306, 2949, 2916, 2893, 1603, 1506, 1481, 1433, 1383, 1334, 1297, 1221, 1156, 1128, 1095, 1063, 1013, 992, 942, 879, 851, 832, 782, 771, 724, 689, 624, 525, 498, 461; **¹H NMR** (400.1 MHz, CDCl₃) δ 7.28 (dd, *J* = 4.9, 3.0 Hz, 1H, Ar*H*-thiophene), 7.19-7.15 (m, 2H, Ar*H*-thiophene), 7.02-6.92 (m, 4H, Ar*H*), 4.26 (s, 2H, CH₂), 4.19 (s, 2H, CH₂), 3.68 (s, 2H, CH₂), 3.67 (s, 2H, CH₂), 1.36 (broad, 2H, 2 × OH); **¹³C NMR** (101 MHz, CDCl₃) δ 161.6 (d, *J*_{CF} = 244.4 Hz, C), 140.4 (C), 136.6 (d, *J*_{CF} = 6.6 Hz, C), 135.4 (d, *J*_{CF} = 3.1 Hz, C), 130.1 (d, *J*_{CF} = 7.9 Hz, CH), 128.3 (CH), 126.30 (CH), 121.2 (CH), 115.7 (CH), 115.5 (CH), 62.1 (CH₂),

61.6 (CH₂), 34.9 (CH₂), 30.9 (CH₂). ¹⁹F NMR (376.4 MHz, CDCl₃) δ -116.88.

HRMS (ESI+) (*m/z*): [M+Na]⁺ calcd for C₁₆H₁₇FO₂SNa, 315.0815; found, 315.0825.

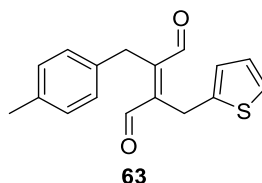
Homocoupling of (*E*)-2,3-diiodobut-2-ene-1,4-diol **67 to the symmetrical diol (*E*)-2,3-bis(thien-3-ylmethyl)but-2-ene-1,4-diol **68****



In dry Schlenk tube LiCl (0.12 g, 2.94 mmol, 2.4 equiv) was heated using heat gun for (5 min) under high vacuum at >200 °C until free flowing, and then cooled under an argon atmosphere to 25 °C. The diol **67** (0.50 g, 1.47 mmol) was added followed by tricyclohexylphosphine (12.3 mg, 44 μmol, 3 mol%) and the solid mixture held under high vacuum for 30 min. Under an atmosphere of argon THF (5.6 mL) was added and the colourless solution was heated to 50 °C. Solid Pd(OAc)₂ (11.6 mg, 55 μmol, 3.5 mol%) was added to the heated mixture to form a dark chocolate coloured mixture. Promptly (thien-2-ylmethyl)zinc(II) chloride **58** (0.42 M in THF, 8.8 mL, 3.7 mmol, 2.5 equiv) was added in one portion forming a clear yellow mixture. After 25 min the reaction became dark and TLC analysis (3:2 EtOAc:pentane) showed the starting material was >90% consumed and new spots appeared due to **68** and HOCH₂C≡CCH₂OH. The mixture cooled to room temperature, quenched with saturated ammonium chloride solution (4 mL) and extracted with EtOAc (3 × 10 ml). The organic layer was washed immediately with saturated NaHCO₃ (3 × 4 mL), dried (Na₂SO₄), filtered and concentrated giving a crude yellow solid. Purification by column chromatography (3:2 EtOAc: pentane) gave **68** as a colourless solid (0.13 g, 0.46 mmol, 31%). [Important note: in our experience **68** is rather acid sensitive.

Concentration of EtOAc its solutions containing even traces of residual NH_4OAc (pK_a 4.8) led to decomposition; washing with hydrogen carbonate avoids this]. TLC: **R_f** (3:2 EtOAc: pentane) 0.35; **Mp** 117-118 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3373, 3312, 3099, 2943, 2901, 2850, 1533, 1481, 1433, 1411, 1383, 1337, 1246, 1202, 1127, 1069, 992, 945, 878, 856, 829, 777, 709, 686, 636, 572; **¹H NMR** (500.1 MHz, CDCl_3) δ 7.28 (dd, J = 4.8, 3.0 Hz, 2H, ArH-thiophene), 7.01-6.92 (m, 4H, ArH-thiophene), 4.26 (d, J = 5.5 Hz, 4H, $2 \times \text{CH}_2$), 3.68 (s, 4H, $2 \times \text{CH}_2$), 1.24 (t, J = 5.5 Hz, 2H, $2 \times \text{OH}$); **¹³CNMR** (125.6 MHz CDCl_3) δ 140.4 ($2 \times \text{C}$), 136.5 ($2 \times \text{C}$), 128.3 ($2 \times \text{CH}$), 126.3 ($2 \times \text{CH}$), 121.2 ($2 \times \text{CH}$), 62.1 ($2 \times \text{CH}_2$), 30.8 ($2 \times \text{CH}_2$). **HRMS** (ESI+) (m/z): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{16}\text{O}_2\text{S}_2$ 303.0484; found 303.0476.

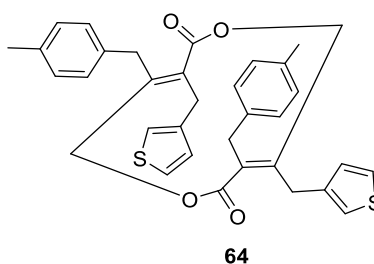
2-(4-Methylbenzyl)-3-(thien-2-ylmethyl)fumaraldehyde **63**



Diol **61** was oxidized by aerobic oxidation using a modified procedure of Stahl.¹⁵⁰ Diol **61** (40.0 mg, 0.138 mmol) was dissolved in DMF (0.8 mL) without any O_2 flowing. The following reagents were promptly added to the reaction mixture sequentially: $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (3.46 mg, 0.01 mmol, 8 mol%), 2,2-bipyridyl (1.72 mg, 0.011 mmol, 8 mol%), TEMPO (1.71 mg, 0.01 mmol, 8 mol%), and finally *N*-methylimidazole (NMI, 1.76 μL , 1.81 mg, 0.02 mmol, 16 mol%). The colour of the reaction mixture was dark orange/brown. The oxygen flow (~5 bubbles per sec) immediately was started. After a few minutes the colour of the mixture changed to green, after about 30 min the reaction mixture became a deep green and TLC analysis (1:2 EtOAc:pentane) showed consumption of diol **61** (**R_f** 0.13) and complete

formation of **63** (**Rf** 0.85, yellow, visible to the eye). The O₂ flow was stopped and the mixture extracted with EtOAc (3 × 5 mL). The organic layer was washed with 2 M HCl (3 × 5 mL) and water (2 × 5 mL). The organic extracts were dried (MgSO₄) and evaporated by rotary evaporator to yield yellow solid (33.0 mg, 0.116 mmol, 84%); **Mp** 94-96 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3094, 2910, 2872, 2856, 1665 (C=O), 1512 1446, 1398, 1249, 1130, 1075, 1045, 967, 899, 874, 849, 810, 753, 686, 577, 513, 491, 473; **¹H NMR** (400.1 MHz, CDCl₃) δ 10.47-10.46 (m, overlapped, 2H, 2 × CHO), 7.15 (d, *J* = 4.4 Hz, 1H, Ar*H*-thiophene), 7.09 (d, *J* = 7.9 Hz, 2H, Ar*H*), 7.03 (d, *J* = 7.9 Hz, 2H, Ar*H*), 6.93-6.86 (m, 1H, Ar*H*-thiophene), 6.78 (m, 1H, Ar*H*-thiophene), 4.29 (s, 2H, CH₂), 4.09 (s, 2H, CH₂), 2.30 (s, 3H, CH₃); **¹³C NMR** (100.6 MHz, CDCl₃) δ 193.2 (CHO), 193.0 (CHO), 147.7 (C), 146.2 (C), 140.8 (C), 136.6 (C), 134.9 (C), 129.7 (2 × CH), 128.3 (2 × CH), 127.3 (CH), 125.7 (CH), 124.7 (CH), 28.9 (CH₂), 23.9 (CH₂), 21.1 (CH₃); **HRMS** (ESI+) (*m/z*): [M⁺] calcd for C₁₇H₁₆O₂S, 284.0866; found 284.0871.

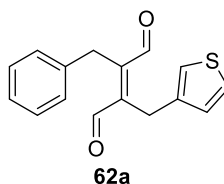
(3*E*,8*E*)-4,9-bis(4-methylbenzyl)-3,8-bis(thiophen-3-ylmethyl)-1,6-dioxecine-2,7(5*H*,10*H*)-dione **64**



Prepared serendipitously (but reproducibly) using a modified procedure of Stahl¹⁵⁰ in initial attempts to prepare **62b**. Diol **59b** (0.57 g, 1.97 mmol) was dissolved in DMF (11.5 mL) without any O₂ flowing. The following reagents were promptly added to the reaction mixture sequentially: Cu(MeCN)₄BF₄ (49.72 mg, 0.16 mmol, 8 mol%),

TEMPO (24.6 mg, 0.16 mmol, 8 mol%), and finally *N*-methylimidazole (NMI, 25.2 μ L, 25.9 mg, 0.31 mmol, 16 mol%). The colour of the reaction mixture was dark orange/brown solution. The oxygen flow (~5 bubbles per sec) immediately was started. After (ca. 10 min) the mixture colour changed to green, after (30 min) the reaction mixture became a deep green and TLC analysis (1:1 EtOAc/pentane) showed consumption of diol **59b** (**R_f** 0.35) and formation of several new species. The O₂ flow was stopped and the mixture extracted with EtOAc (3 $\times$ 30 mL). The organic layer was washed with 2 M HCl (3 $\times$ 10 mL) and water (3 $\times$ 10 mL). The organic extracts were dried (MgSO₄) and evaporated by rotary evaporator to yield oily crude materials. The crude materials were separated using column chromatography (12:1 pentane:EtOAc) to yield **64** (180 mg, 0.32 mmol, 16%) among other uncharacterised products. TLC: **R_f** (12:1 pentane:EtOAc) 0.63; **¹H NMR** (500.1 MHz, CDCl₃) δ 7.29-7.23 (m, 2H, ArH-thiophene), 7.16 (d, *J* = 8.0 Hz, 2H, ArH), 7.11 (d, *J* = 8.0 Hz, 4H, ArH), 7.04 (m, 1H, ArH-thiophene), 7.01 (dd, *J* = 4.9, 1.3 Hz, 1H, ArH-thiophene), 6.95 (d, *J* = 8.0 Hz, 2H, ArH), 6.93 (m, 1H, ArH-thiophene), 6.76 (dd, *J* = 4.9, 1.3 Hz, 1H, ArH-thiophene), 4.56-4.54 (2 $\times$ CH₂), 3.82-3.59 (m, 8H, 4 $\times$ CH₂), 2.33 (broad, 6H, 2 $\times$ CH₃). **¹³C NMR** (125.8 MHz, CDCl₃) δ 174.7 (CO₂), 174.6 (CO₂), 160.2 (C), 159.3 (C), 137.9 (C), 137.0 (C), 136.2 (C), 135.6 (C), 134.9 (C), 132.8 (C), 129.7 (CH), 129.4 (2 $\times$ CH), 128.5 (2 $\times$ CH), 128.4 (CH), 128.2 (CH), 127.7 (CH), 126.9 (CH), 126.8 (CH), 126.1 (CH), 126.0 (CH), 122.4 (CH), 121.6 (CH), 71.3 (2 $\times$ CH₂), 33.1 (CH₂), 29.2 (CH₂), 28.1 (CH₂), 24.3 (CH₂), 21.0 (2 $\times$ CH₃). **HRMS** (ESI+) (*m/z*): [M+Na]⁺ calcd for C₃₄H₃₂O₄S₂Na, 591.1639; found 591.1657.

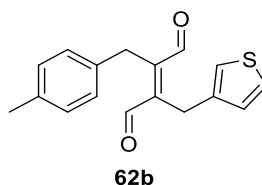
Preparation of dialdehydes 62a-d by modified Swern oxidation method, representative example: 2-benzyl-3-(thien-3-ylmethyl)fumaraldehyde 62a



A solution of dry DMSO (0.25 mL) in dry CH_2Cl_2 (1.0 mL) was added slowly to a solution of oxalyl chloride (0.15 g, 1.20 mmol, 2.5 equiv) in dry CH_2Cl_2 (2.0 mL) at -78°C , and the mixture stirred for 30 min at the same temperature. Diol **59a** (132 mg, 0.48 mmol) in dry CH_2Cl_2 (1.2 mL) and DMSO (0.26 mL) was added dropwise. The milky mixture was stirred for another 1.5 h. Dry Et_3N (0.37 mL, 2.41 mmol, 5 equiv) was added at -78°C and the mixture allow to warm to rt over (30 min) and the colour changed from milky to yellow. The reaction mixture was concentrated under reduced pressure to provide the crude compound. The solid was dissolved in the EtOAc and filtrated to remove inorganic compounds. The resultant organic layer was washed with water (10×5 mL) and dried over sodium sulphate. Concentration at reduced pressure yielded a yellow solid (100 mg, 0.37 mmol, 77%). **Mp** $100\text{-}102^\circ\text{C}$; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3329, 3090, 3025, 2940, 2909, 2873, 1755, 1666, 1598, 1495, 1452, 1396, 1231, 1202, 1127, 1075, 1031, 976, 939, 904, 870, 830, 774, 739, 697, 685, 623, 603, 574, 525, 484; **^1H NMR** (500.1 MHz, CDCl_3) δ 10.49 (s, 1H, CHO), 10.46 (s, 1H, CHO), 7.29-7.26 (m, 3H, ArH), 7.19-7.22 (m, 1H, ArH-thiophene), 7.13 (d, $J = 7.4$ Hz, 2H, ArH), 6.89 (m, 2H, ArH-thiophene), 4.13 (s, 2H, CH_2), 4.12 (s, 2H, CH_2); **^{13}C NMR** (125.8 MHz, CDCl_3) δ 193.4 (CHO), 193.3 (CHO), 147.3 (C), 147.0 (C), 138.4 (C), 138.2 (C), 129.1 ($2 \times \text{CH}$), 128.4 ($2 \times \text{CH}$),

127.8 (CH), 126.9 (CH), 126.6 (CH), 121.9 (CH), 29.3 (CH₂), 24.4 (CH₂); **HRMS** (ESI⁺) (*m/z*): [M+Na]⁺ calcd for C₁₆H₁₄O₂SNa, 293.0607; found 293.0597.

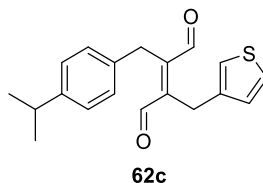
2-(4-Methylbenzyl)-3-(thien-3-ylmethyl)fumaraldehyde **62b**



A solution of dry DMSO (0.38 mL) in dry CH₂Cl₂ (1.3 mL) was added slowly to a solution of oxalyl chloride (147 μ L, 219 mg, 1.73 mmol, 2.5 equiv) in CH₂Cl₂ (2.5 mL) at -78 °C, and the mixture stirred for 30 min at the same temperature. The diol **59b** (200 mg, 0.69 mmol) in CH₂Cl₂ (1.7 mL) and DMSO (0.4 mL) was added dropwise, and the mixture was stirred for another (1.5 h) before dropwise addition of Et₃N (0.50 mL, 3.46 mmol). The reaction was left to warm to 20 °C during (30 min). The reaction mixture was concentrated under reduced pressure and the product purified by flash column chromatography (100% CH₂Cl₂) to yield **62b** (170 mg, 0.60 mmol, 87%) as yellow solid. TLC: **R_f** (CH₂Cl₂ 100%) 0.75 yellow spot; **Mp** 104-105 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3330, 3093, 2939, 2911, 2875, 2855, 2361, 2091, 1804, 1665, 1511, 1447, 1397, 1202, 1126, 1022, 938, 874, 832, 773, 750, 680, 625, 584, 490, 454, 417; **¹H NMR** (400.1 MHz, CDCl₃) δ 10.49 (s, 1H, CHO), 10.45 (s, 1H, CHO), 7.29-7.24 (m, 1H, ArH-thiophene), 7.09 (d, *J* = 8.1 Hz, 2H, ArH), 7.02 (d, *J* = 8.1 Hz, 2H, ArH), 6.91-6.86 (m, 2H, ArH-thiophene), 4.10 (s, 2H, CH₂), 4.08 (s, 2H, CH₂), 2.30 (s, 3H, CH₃); **¹³C NMR** (101.6 MHz, CDCl₃) δ 193.5 (CHO), 193.4 (CHO), 147.5 (C), 146.8 (C), 138.5 (C), 136.6 (C), 135.1 (C), 129.7 (2 $\times$ CH), 128.3 (2 $\times$ CH), 127.8 (CH), 126.6 (CH), 121.8 (CH), 28.9 (CH₂), 24.4 (CH₂), 21.1

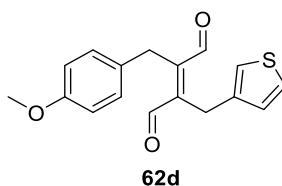
(CH₃); **HRMS** (ESI+) (*m/z*): [M+Na]⁺ calcd for C₁₇H₁₆O₂SNa, 307.0763; found, 307.0780.

2-(4-Isopropylbenzyl)-3-(thien-3-ylmethyl)succinaldehyde **62c**



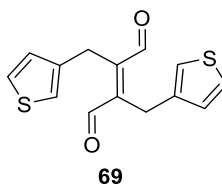
Prepared by a method analogous to **62a** from (*E*)-2-(4-isopropylbenzyl)-3-(thiophen-3-ylmethyl)but-2-ene-1,4-diol **59c** (0.25 g, 0.79 mmol), to yield **62c** as a bright yellow solid (0.19 g, 0.61 mmol, 77%), TLC: **R_f** (100% CH₂Cl₂) 0.73 yellow spot (easily visible to the eye); **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3331, 3091, 2957, 2907, 2767, 1667, 1513, 1465, 1447, 1397, 1192, 1128, 1020, 980, 938, 877, 830, 773, 681, 626, 582, 549, 506; **¹H NMR** (500.1 MHz, CDCl₃) δ 10.49 (s, 1H, CHO), 10.45 (s, 1H, CHO), 7.28-7.26 (m, 1H, ArH-thiophene), 7.14 (d, *J* = 7.9 Hz, 2H, ArH), 7.05 (d, *J* = 7.9 Hz, 2H, ArH), 6.90-6.88 (m, 2H, ArH-thiophene), 4.11 (s, 2H, CH₂), 4.09 (s, 2H, CH₂), 2.86 (hept, *J* = 6.9 Hz, 1H, CH), 1.22 (d, *J* = 6.9 Hz, 6H, 2 × CH₃); **¹³C NMR** (125.8 MHz, CDCl₃) δ 193.5 (CHO), 193.4 (CHO), 147.6 (C), 147.5 (C), 146.8 (C), 138.5 (C), 135.4 (C), 128.3 (2 × CH), 127.8 (CH), 127.1 (2 × CH), 126.6 (CH), 121.9 (CH), 33.8 (CH), 28.9 (CH₂), 24.4 (CH₂), 24.1 (2 × CH₃); **HRMS** (ESI+) (*m/z*): [M⁺] calcd for C₁₉H₂₀O₂S, 312.1178; found 312.11918.

2-(4-Methoxybenzyl)-3-(thien-3-ylmethyl)fumaraldehyde **62d**



Prepared by a method analogous to **62a** from diol **59d** (50 mg, 0.16 mmol) to providing compound **62d** as a yellow solid (needles after recrystallization from hot isopropanol) (39 mg, 0.13 mmol, 81%). TLC: **R_f** (EtOAc:pentane, 3:2) 0.84; **Mp** 120-121 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3332, 3091, 2938, 2911, 1751, 1667, 1608, 1582, 1512, 1445, 1397, 1306, 1244, 1179, 1129, 1025, 938, 877, 830, 774, 752, 704, 679, 625, 582, 528, 512, 480, 459; **¹H NMR** (500.1 MHz, CDCl₃) δ 10.49 (s, 1H, CHO), 10.44 (s, 1H, CHO), 7.29-7.24 (m, 1H, ArH-thiophene), 7.05 (d, J = 8.7 Hz, 2H, ArH), 6.90-6.87 (m, 2H, ArH-thiophene), 6.81 (d, J = 8.7 Hz, 2H, ArH), 4.10 (s, 2H, CH₂), 4.06 (s, 2H, CH₂), 3.77 (s, 3H, OCH₃); **¹³C NMR** (125.8 MHz, CDCl₃) δ 193.6 (CHO), 193.4 (CHO), 158.6 (C), 147.6 (C), 146.6 (C), 138.5 (C), 130.1 (C), 129.5 (2 $\times$ CH), 127.7 (CH), 126.6 (CH), 121.8 (CH), 114.5 (2 $\times$ CH), 55.4 (OCH₃), 28.5 (CH₂), 24.4 (CH₂); **HRMS** (ESI+) (m/z): [M+Na]⁺ calcd for C₁₇H₁₆O₃SN_a, 323.0712; found 323.0721.

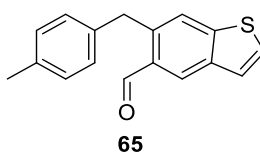
2,3-bis(Thien-3-ylmethyl)fumaraldehyde **69**



Prepared by a method similar to **62a** from (*E*)-2,3-bis(thien-3-ylmethyl)but-2-ene-1,4-diol **68** (50 mg, 0.17 mmol), to yield **69** as a yellow solid (35 mg, 0.13 mmol, 73%) after washing crude material in EtOAc with water (10 $\times$ 3 mL) to remove residual DMSO. Dried with Na₂SO₄. TLC: **R_f** (2:1 CH₂Cl₂:pentane) 0.51, crystallized from hot *i*PrOH on cooling to ambient. **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3090, 2976, 2941, 2910, 2873, 1665, 1529, 1446, 1395, 1240, 1194, 1159, 1125, 977, 941, 862, 829, 774, 675, 620, 569, 464, 425; **¹H NMR** (500.1 MHz, CDCl₃) δ 10.46 (s, 2H, 2

× CHO), 7.28 -7.26 (m, 2H, 2 × CH), 6.89-6.88 (m, broad, 4H, 4 × CH), 4.11 (s, 4H, 2 CH₂); ¹³C NMR (125.8 MHz, CDCl₃) δ 193.2 (CHO), 146.8 (CHO), 138.4 (2 × C), 127.7 (2 × C), 126.7 (2 × CH), 121.9 (2 × CH), 24.4 (2 × CH); HRMS (ESI+) (*m/z*): [M+H]⁺ calcd for C₁₄H₁₃O₂S₂, 277.0351; found, 277.0354.

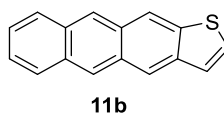
Cyclisation using TiCl₄; representative example of by-product formation, 6-(4-methylbenzyl)benzo[*b*]thiophene-5-carbaldehyde **65**



To a solution of 2-(4-methylbenzyl)-3-(thien-3-ylmethyl)fumaraldehyde **63b** (100 mg, 0.35 mmol) in dry dichloroethane (2.3 mL) under argon, titanium tetrachloride (**CAUTION!** Corrosive, toxic) (81 μL, 0.74 mmol, 2.1 equiv) was added slowly at 0 °C. The mixture was stirred at 0 °C for 45 mins, during which time it became dark brown and viscous. TLC (10:1:1 pentane:EtOAc:CH₂Cl₂) indicated complete consumption of the starting material **63b** (*R_f* 0.41). The reaction was stopped, and at 0 °C 1:1 acetone:MeOH (5 mL) was slowly added causing immediate yellow precipitation. The mixture was filtered off onto Whatman glass microfiber GF/A on a 47-mm 3-piece (Hartley) filter and washed with 1:1 acetone:MeOH, the half closure product is eluted with the (1:1 acetone:MeOH) wash. The filtered yellow powder precipitate was 7-methylanthra[2,3-*b*]thiophene **11b** which accounted for 57% of the mass balance. The organic wash solution was concentrated by high vacuum and purified by preparative TLC (8:1:1 pentane:EtOAc:CH₂Cl₂) to yield **65** (30 mg, 0.11 mmol, 32%) as yellow oil; TLC: *R_f* (9:1:1 pentane:CH₂Cl₂:EtOAc) 0.80; IR (diamond-ATR): ν_{max}/cm⁻¹ 3099, 3018, 2917, 2854, 2724, 2093, 1760, 1683, 1594,

1539, 1512, 1492, 1450, 1404, 1386, 1314, 1227, 1183, 1155, 1125, 1077, 1006, 902, 878, 833, 794, 761, 748, 725, 699, 645, 620, 577, 535, 490, 469, 429; $^1\text{H NMR}$ (500.1 MHz, CDCl_3) δ 10.29 (s, 1H, CHO), 8.31 (s, 1H, ArH), 7.70 (s, 1H, ArH), 7.48 (d, J = 5.5 Hz, 1H, ArH-thiophene), 7.43 (d, J = 5.5 Hz, 1H, ArH-thiophene), δ 7.10 (d, J = 8.0 Hz, 2H, ArH), 7.07 (d, J = 8.0 Hz, 2H, ArH), 4.52 (s, 2H, CH_2), 2.32 (s, 3H, CH_3); $^{13}\text{C NMR}$ (125.8 MHz, CDCl_3) δ 192.4 (CHO), 145.4 (C), 138.3 (C), 138.2 (C), 137.4 (C), 135.9 (C), 131.3 (C), 129.4 (2 $\times$ CH), 128.9 (2 $\times$ CH), 128.8 (CH), 127.6 (CH), 125.0 (CH), 124.5 (CH), 38.2 (CH_2), 21.1 (CH_3); **HRMS** (ESI+) (m/z): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{14}\text{OSNa}$, 289.0658; found, 289.0662.

Anthra[2,3-*b*]thiophene 11a



Dialdehyde **63a** (219 mg, 0.18 mmol) is dissolved in dry dichloroethane (5.4 mL) to form a yellow solution. The solution was cooled to 0 °C and TiCl_4 (**CAUTION!** Corrosive, toxic) (0.20 mL, 1.78 mmol, 2.1 equiv) added over 1 min at 0 °C forming a brown suspension of the TiCl_4 -aldehyde adduct. The reaction mixture was stirred for 30 min at 0 °C and at rt for (4 h). During this time the reaction mixture became dark brown and viscous. TLC (9:1:1 pentane:EtOAc: CH_2Cl_2) shown consummation of the starting material **63a** while forming a shiny yellow precipitate which is insoluble in the mixture of (acetone:MeOH 1:1). The reaction was cooled to 0 °C and 1:1 acetone:MeOH (5 mL) was slowly added forming immediate yellow precipitation of **63a**. The crude mixture was filtered off onto Whatman glass microfiber GF/A on a 47-mm 3-piece (Hartley) filter and washed with 1:1 acetone:MeOH (3 $\times$ 5 mL) and

sucked dry under a cushion of argon to provide yellow powder (138 mg, 0.59 mmol, 73%). The crude material could be further purified by vacuum sublimation (230-240 °C, 0.02 mbar) (Figure 27) to give shining bright yellow powders. **Mp** >250 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3440, 2918, 2849, 1400, 1284, 1018, 955, 899, 825, 739, 727, 661, 470, 457; **¹H NMR** (500.1 MHz, CDCl₃) δ 8.61 (s, 1H, ArH), 8.55 (s, 1H, ArH), 8.53 (s, 1H, ArH), 8.51 (s, 1H, ArH), 8.04-8.00 (m, 2H, ArH), 7.49 (d, J = 5.7 Hz, 1H, ArH-thiophene), 7.44-7.41 (overlapped, m, 3H, 2H is ArH, 1H is ArH-thiophene); **¹³C NMR** (125.8 MHz, CDCl₃) δ 139.3 (C), 138.1 (C), 131.5 (C), 131.3 (C), 129.8 (C), 129.7 (C), 128.9 (CH), 128.3 (CH), 128.2 (CH), 126.7 (CH), 125.3 (2 $\times$ CH), 125.1 (CH), 123.6 (CH), 121.9 (CH), 120.7 (CH); **HRMS** (ESI+) (m/z): [M^+] calcd for C₁₆H₁₀S 234.050; found, 234.0500; **UV/Vis** (CH₂Cl₂, 10⁻⁴ M): $\lambda_{\text{max}}/\text{nm}$ 435 (log ϵ 4.1), 410 (log ϵ 4.1), 389 (log ϵ 3.8), 368 (log ϵ 3.5). The data of this compound matches publish literatures values.^{124,110,78,280,118}

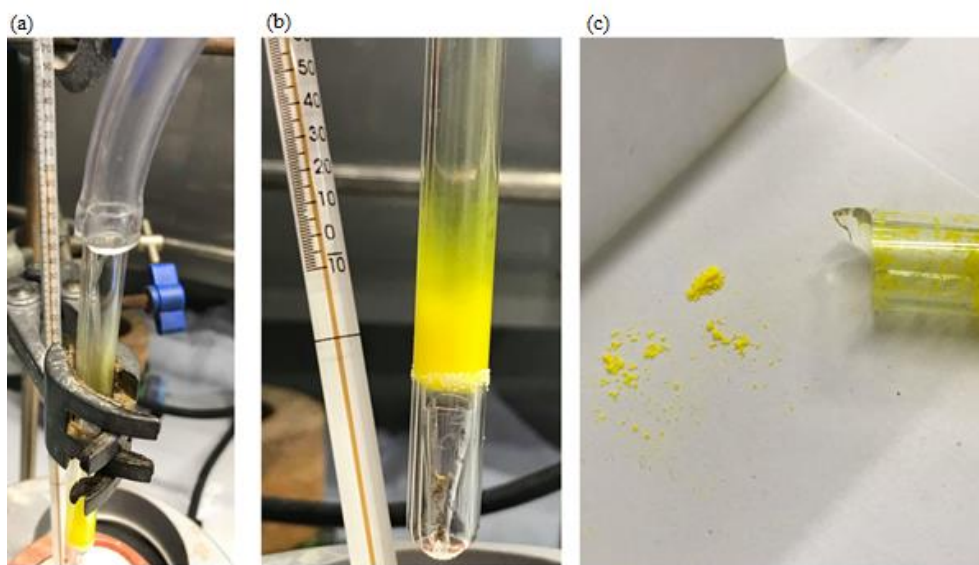
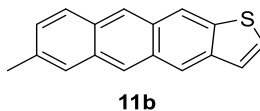
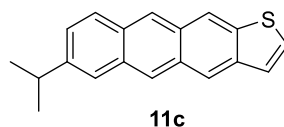


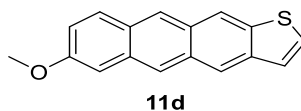
Figure 27 (a) The sublimation tube (ca. 12 cm long by 1 cm wide) inserted inside the hot sand under high vacuum. (b) After completion of the sublimation; the heated sand bath top was ca. 2-3 mm below the bottom end of the sublimed band. (c) Extraction of the anthra[2,3-*b*]thiophene, post tube-cut (**CARE!** – tube covered in electrical tape to reduce ‘sharp’ injury possible through cutting). The dark, non-sublimed, residue for 2-6% w/w of the total mass.

7-Methylantra[2,3-*b*]thiophene 11b

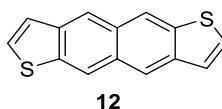
Prepared by a method equivalent to **11a** using: 2-(4-methylbenzyl)-3-(thien-3-ylmethyl)fumaraldehyde **63b** (200 mg, 0.7 mmol), TiCl₄ (**CAUTION!** Corrosive, toxic) (0.16 mL, 1.46 mmol, 2.1 equiv) in 1,2-dichloroethane (4.5 mL) at 0 °C (1 h) then warmed to rt and stirred over (4 h) to yield **11b** as a brilliant yellow powder (145 mg, 0.58 mmol, 84%). Sublimation (200-210 °C, 0.05 mbar) afforded a brilliant yellow powder. **Mp** >250 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3065, 3010, 2910, 2851, 1704, 1632, 1469, 1402, 1375, 1287, 1270, 1128, 1080, 1005, 961, 901, 827, 809, 792, 745, 723, 674, 658, 568, 469, 457; **¹H NMR** (500.1 MHz, CDCl₃) δ 8.59-8.46 (m, 4H, ArH), 7.93 (d, J = 8.7 Hz, 1H, ArH), 7.76 (s, 1H, ArH), 7.47 (d, J = 5.6 Hz, 1H, ArH-thiophene), 7.40 (d, J = 5.6 Hz, 1H, ArH-thiophene), 7.30-7.27 (m, 1H, ArH), 2.55 (s, 3H, CH₃); **¹³C NMR** (125.8 MHz, CDCl₃) δ 139.2 (C), 137.7 (C), 134.7 (C), 131.6 (C), 130.3 (C), 129.9 (C), 129.4 (C), 128.8 (CH), 128.3 (CH), 128.1 (CH), 126.3 (CH), 125.5 (CH), 125.0 (CH), 123.6 (CH), 121.8 (CH), 120.7 (CH), 22.2 (CH₃); **UV/Vis** (CH₂Cl₂, 10⁻⁴ M): $\lambda_{\text{max}}/\text{nm}$ 437 (log ϵ 3.6), 412 (log ϵ 3.7), 390 (log ϵ 3.4), 360 (log ϵ 3.1), 343 (log ϵ 3.0); **HRMS** (ESI+) (m/z): [M^+] calcd for C₁₇H₁₂S, 248.0654; found, 248.0650; **CHN** Anal. calcd for C₁₇H₁₂S C, 82.22; H, 4.87; found C, 82.30; H, 4.90%.

7-Isopropylanthra[2,3-*b*]thiophene 11c

Prepared by a method analogous to **11a** using: 2-(4-isopropylbenzyl)-3-(thien-3-ylmethyl)succinaldehyde **63c** (150 mg, 0.48 mmol), TiCl_4 (**CAUTION!** Corrosive, toxic) (0.10 mL, 1.00 mmol, 2.1 equiv) in 1,2-dichloroethane (3.1 mL) at 0 °C for (1.5 h) and then warmed to 22 °C for 10 min to yield **11c** as shiny yellow powder (130 mg, 0.47 mmol, >99%). Sublimation (210-220 °C, 0.01 mbar) afforded a brilliant yellow powder. **Mp** >250 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3070, 3015, 2955, 2926, 2900, 2863, 2100, 1631, 1510, 1470, 1380, 1309, 1284, 1182, 1128, 1081, 1039, 1016, 948, 904, 826, 803, 747, 726, 661, 620, 548, 470, 459; **^1H NMR** (500.1 MHz, CDCl_3) δ 8.53 (s, 1H, ArH), 8.52 (1H, ArH), 8.49-8.47 (m, 2H, ArH), 7.96 (d, $J = 8.9$ Hz, 1H, ArH), 7.78 (s, 1H, ArH), 7.47 (d, $J = 5.7$ Hz, 1H, ArH-thiophene), 7.40 (d, $J = 5.7$ Hz, 1H, ArH-thiophene), 7.37 (dd, $J = 8.8, 1.7$ Hz, 1H, ArH), 3.10 (hept, $J = 7.0$ Hz, 1H, CH), 1.39 (d, $J = 7.0$ Hz, 6H, $2 \times \text{CH}_3$); **^{13}C NMR** (125.8 MHz, CDCl_3) δ 145.3 (C), 139.2 (C), 137.7 (C), 131.6 (C), 130.7 (C), 129.9 (C), 129.5 (C), 128.7 (CH), 128.3 (CH), 126.1 (CH), 126.0 (CH), 125.0 (CH), 123.6 (CH), 123.4 (CH), 121.8 (CH), 120.7 (CH), 34.5 (CH), 23.7 ($2 \times \text{CH}_3$); **UV/Vis** (CH_2Cl_2 , 10^{-4} M): $\lambda_{\text{max}}/\text{nm}$ 436 (log ϵ 3.5), 410 (log ϵ 3.7), 390 (log ϵ 3.6), 362 (log ϵ 3.4), 343 (log ϵ 3.4); **HRMS** (ESI+) (m/z): $[\text{M}^+]$ calcd for $\text{C}_{19}\text{H}_{16}\text{S}$, 276.0967; found, 276.0976; **CHN** Anal. calcd for $\text{C}_{19}\text{H}_{16}\text{S}$ C, 82.57; H, 5.84; found C, 82.26; H, 5.96%.

7-Methoxyanthra[2,3-*b*]thiophene 11d

Prepared by a method analogous to **11a** using: 2-(4-methoxybenzyl)-3-(thien-3-ylmethyl)succinaldehyde **63d** (143 mg, 0.476 mmol), TiCl_4 (**CAUTION!** Corrosive, toxic) (0.11 mL, 1.05 mmol, 2.2 equiv) in 1,2-dichloroethane (4.2 mL) at 0 °C for (2 h) and then warmed to 22 °C for (1 h) to yield **11d** as a shiny yellow powder (104.4 mg, 0.39 mmol, 83%). Sublimation (210-220 °C, 0.02 mbar) afforded a brilliant yellow powder. **Mp** >250 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3094, 3062, 3005, 2965, 2937, 2836, 1800, 1630, 1585, 1473, 1417, 1346, 1285, 1230, 1218, 1172, 1026, 951, 897, 816, 803, 744, 723, 675, 663, 539, 470, 456; **^1H NMR** (500.1 MHz, CDCl_3) δ 8.50 (s, 1H, ArH), 8.46-8.42 (m, 3H, ArH), 7.91 (d, J = 9.2 Hz, 1H, ArH), 7.48 (d, J = 5.6 Hz, 1H, ArH-thiophene), 7.40 (d, J = 5.6 Hz, 1H, ArH-thiophene), 7.21-7.18 (m, 1H, ArH), 7.14 (dd, J = 9.2, 2.5 Hz, 1H, ArH), 3.98 (s, 3H, OCH_3); **^{13}C NMR** (125.8 MHz, CDCl_3) δ 157.0 (C), 139.4 (C), 137.1(C), 132.1 (C), 130.2 (C), 130.0 (CH), 128.9 (CH), 128.6 (C), 128.4 (C), 125.4 (CH), 124.3 (CH), 123.6 (CH), 121.2 (CH), 120.9 (CH), 120.8 (CH), 103.2 (CH), 55.4 (OCH_3); **UV/Vis** (CH_2Cl_2 , 10^{-4} M): $\lambda_{\text{max}}/\text{nm}$ 443 (log ϵ 3.4), 418 (log ϵ 3.4), 395 (log ϵ 3.2), 378 (log ϵ 3.2), 358 (log ϵ 3.1), 340 (log ϵ 2.9); **HRMS** (ESI+) (m/z): $[\text{M}^+]$ calcd for $\text{C}_{17}\text{H}_{12}\text{OS}$, 264.0603; found, 264.0611; **CHN** Anal. calcd for $\text{C}_{17}\text{H}_{12}\text{OS}$ C, 77.24; H, 4.58; found C, 77.27; H, 4.49%.

Naphtho[2,3-*b*:6,7-*b'*]dithiophene 12

The yellow solution of dialdehyde **69** (200 mg, 0.723 mmol) in anhydrous dichloroethane (4.5 mL) was cooled to -15 °C and treated under argon with neat TiCl₄ (0.17 mL, 1.60 mmol, 2.2 equiv) over ca. 1 min at -15 °C (**CARE!** TiCl₄ is a corrosive reactive Lewis acid; quicker additions may cause uncontrolled reaction). The dark brown thick suspension was allowed to stir at -15 °C over (1 h). After one hour the TLC (10:1:1 pentane:EtOAc:CH₂Cl₂) showed that all the starting material was consumed and that it converted to new product. The reaction was stopped and 1:1 acetone:MeOH (2 mL) was slowly added at -15 °C (**CARE!** vigorous reaction) leading to a pale yellow precipitate of the target product **12** which was filtered off onto Whatman glass microfiber GF/A on a 47-mm 3-piece (Hartley) filter, washed with 1:1 acetone:MeOH (1 × 3 mL) and sucked dry under a cushion of argon to provide crude **12** as a pale yellow powder (140 mg, 0.85 mmol, 81%). This crude material was pure enough to use directly in further chemistry, but could be further purified by vacuum sublimation (245-250 °C, 0.01 mbar, Figure 28) to afford a pale-yellow powder. **Mp** >250 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3094, 3065, 1705, 1505, 1439, 1382, 1311, 1258, 1139, 1078, 1014, 897, 826, 743, 675, 550, 501, 470, 457; **¹H NMR** (500.1 MHz, CDCl₃) δ 8.51 (s, 2H, ArH), 8.40 (s, 2H, ArH), 7.50 (d, *J* = 5.6 Hz, 2H, ArH-thiophene), 7.43 (d, *J* = 5.6 Hz, 2H, ArH-thiophene); **¹³C NMR** (125.8 MHz, CDCl₃) δ 138.9 (2 × C), 137.6 (2 × C), 129.0 (2 × C), 128.5 (2 × CH), 123.6 (2 × CH), 121.0 (2 × CH), 120.9 (2 × CH); **UV/Vis** (CH₂Cl₂, 10⁻⁴ M): $\lambda_{\text{max}}/\text{nm}$ 402 (log ϵ 3.8), 380 (log ϵ 3.7), 360 (log ϵ 3.3), 431 (log ϵ 3.2); **HRMS** (ESI⁺): [M⁺]

calcd for $C_{14}H_8S_2$, 240.0061; found, 240.0054. The data of this compound matches published literatures values.¹¹²

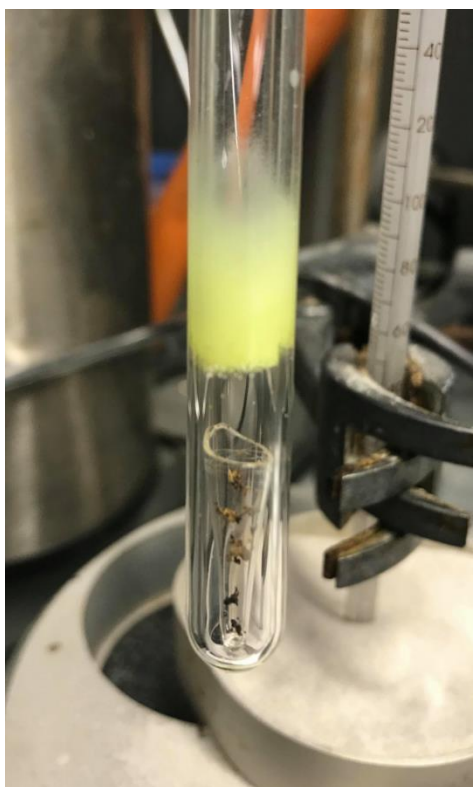
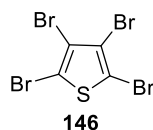


Figure 28 The picture shows the sublimation tube upon completion. The residue (non-sublimed materials) amounted to about 6% w/w of the original mass.

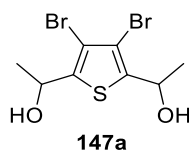
5.3 Experimental Data for Chapter 3

Tetrabromothiophene **146**



Compound **146** was prepared by modification of a literature methods.²⁸¹ Thiophene **145** (10.6 g, 0.127 mol) dissolved in chloroform (8 mL) was treated with a solution of bromine (24 mL, 0.46 mol) in chloroform (8 mL) that was added dropwise over 50 min at 0 °C. The resulting dark mixture was stirred overnight at room temperature, then additional bromine (9.0 mL, 0.17 mol) was then added and the mixture refluxed (70 °C, 57 h). After the reaction had cooled to room temperature, saturated potassium hydroxide solution (100 mL) was added over a 10 min period and the mixture refluxed again (105 °C, 18 h). The reaction was stopped and allowed to cool to room temperature. The tetrabromothiophene **146** was extracted with dichloromethane, and dried over MgSO₄, and solvent removed. The crude compound was attained as analytically pure colourless crystalline needles (39.6 g, 99.0 mmol, 78%); **Mp** 114-115 °C (lit.²⁸² 116-118 °C); ¹³C NMR (100.6 MHz, CDCl₃) δ 117.1 (2 × C), 110.4 (2 × C); **HRMS** (ESI+) (*m/z*): [*M*⁺] calcd for C₄SBr₄, 395.6448 (⁷⁹Br); found 395.6467. These properties were in accord with the literature.^{281, 283}

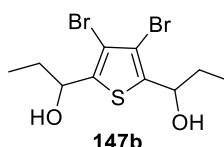
General preparation of the diols **147a-e**, representative procedure, 1,1'-(3,4-dibromothiophene-2,5-diyl)bis(1-ethanol) **147a**



To a solution of tetrabromothiophene **146** (1.10 g, 2.75 mmol) in dry THF (9 mL) under argon, *n*BuLi (3.77 mL, 1.5 M in hexane, 5.66 mmol) was added dropwise

at -78 °C. Excess acetaldehyde (0.5 mL) was added at -78 °C. The temperature of the mixture was allowed to warm slowly during (2 h) from -78 to -25 °C. The reaction was quenched with water (8 mL), extracted with EtOAc, dried (MgSO₄) and evaporated to a brown oil. Flash column chromatography (7:3 pentane:EtOAc) yielded a colourless solid (0.696 g, 77%) as a mixture of diastereomers (1:1); TLC: **R_f** (7:3 pentane:EtOAc) 0.37, 0.44; the **M_p** for the mixture of diastereomers is 96-110 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3285 (OH), 2974, 2925, 1436, 1397, 1368, 1329, 1273, 1177, 1088, 1061, 983, 885, 861, 764; **¹H NMR** (400.1 MHz, acetone-*d*₆) δ 5.16-5.10 (m, 2H, 2 × CH), 4.89-4.88 (m, 2H, OH), 1.46-1.44 (m, 6H, 2 × CH₃); **¹³C NMR** (100.6 MHz, acetone-*d*₆) δ 146.0 (2 × C), 107.9 (2 × C), 66.9 (2 × CH), 24.8 (2 × CH₃); **HRMS** (ESI+) (*m/z*): [M⁺] calcd for C₈H₁₀Br₂O₂S, 329.8748; found, 329.8747 (⁷⁹Br).

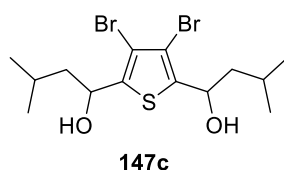
1,1'-(3,4-Dibromothiophene-2,5-diyl)bis(1-propanol) **147b**



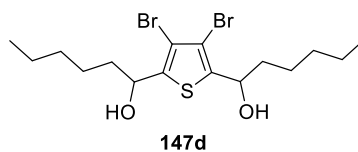
Using tetrabromothiophene **146** (0.50 g, 1.25 mmol) in dry THF (3.2 mL) under argon, *n*BuLi (1.8 mL, 1.5 M in hexane, 2.75 mmol) was added dropwise at -78 °C. Then excess propanal (0.27 mL, 3.75 mmol) was added at -78 °C. The temperature of the mixture was warmed slowly during 3 h from -78 to -65 °C. The reaction was quenched with water (5 mL) extracted with EtOAc, dried (MgSO₄), and evaporated to a brown crude product purified by flash column chromatography (8.5:1.5 light petroleum:EtOAc) yielding a yellow oil (0.215 g, 50%) as mixture of diastereomers (2:1); TLC: **R_f** (17:3 light petroleum:EtOAc) 0.10, 0.07; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3313 (OH), 2964, 2930, 2874, 1458, 1378, 1319, 1319, 1171, 1089, 1041,

971, 868; **¹H NMR** (400.1 MHz, CDCl₃) δ 4.89 (m, 2H, 2 × CH), 1.73-1.65 (m, 4H, 2 × CH₂), 1.00 (t, *J* = 7.3 Hz, 6H, 2 × CH₃), the OH signals were not observed due to exchange; **¹³C NMR** (100.6 MHz, CDCl₃) δ 143.9 (2 × C), 108.7 (2 × C), 71.6 (2 × CH), 32.0 (2 × CH₂), 10.4 (2 × CH₃); **HRMS** (ESI+) (*m/z*): [M⁺] calcd for C₁₀H₁₄Br₂O₂S, 355.9075; found 355.9092 (⁷⁹Br).

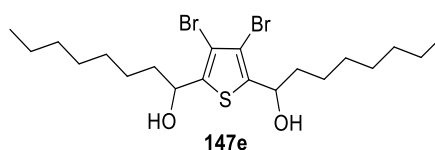
1,1'-(3,4-Dibromothiophene-2,5-diyl)bis(3-methylbutanol) **147c**



Preparation from tetrabromothiophene **146** (2.00 g, 5.00 mmol, *n*BuLi (6.9 mL, 1.6 M in hexane, 11.0 mmol) and methylbutyraldehyde (1.29 g, 15.0 mmol). The brown crude product was purified by flash column chromatography (85:15 light petroleum:EtOAc) to yield a pale yellow solid as a (2:1) mixture of diastereomers (1.70 g, 82%); TLC: **R_f** (85:15 light petroleum:EtOAc) 0.31, 0.15; **Mp** 112-113 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3220 (OH), 2955, 2923, 2868, 1743, 1467, 1384, 1367, 1236, 1180, 1108, 1067, 846, 767, 679, 595; **¹H NMR** (400.1 MHz, CDCl₃) δ 5.14-5.13 (m, 2H, 2 × CHOH), 2.22 (broad, 2H, 2 × OH), 1.82-1.57 (m, 6H, 2 × CH₂, 2 × CH); 1.04-0.96 (m, 12H, 4 × CH₃); **¹³C NMR** (100.6 MHz, CDCl₃) δ 143.1 (2 × C), 110.0 (2 × C), 68.8 (2 × CH), 47.2 (2 × CH₂), 24.9 (2 × CH), 23.3 (2 × CH₃), 22.1 (2 × CH₃); **HRMS** (ESI+) (*m/z*): [M⁺], calcd for C₁₄H₂₂Br₂O₂S 413.9687; found 413.9688 (⁷⁹Br).

1,1'-(3,4-Dibromothiophene-2,5-diyl)bis(1-hexanol) 147d

Preparation from tetrabromothiophene **146** (1.00 g, 2.50 mmol), *n*BuLi (3.7 mL, 1.5 M in hexane, 5.50 mmol) and *n*hexanal (0.9 mL, ca. 0.75 g, 7.5 mmol). The brown crude product was purified by flash column chromatography (85:15 light petroleum:EtOAc) to yield of pale yellow solid as (1:1) mixture of diastereomers (0.80 g, 72%) as colourless solid; TLC: **R_f** (6:1 pentane:EtOAc) 0.66, 0.37; **Mp** 82-84 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3296 (OH), 2954, 2921, 2851, 1642, 1464, 1367, 1316, 1248, 1182, 1164, 1058, 971, 927, 769; **¹H NMR** (400.1 MHz, CDCl₃) δ 5.24 (s, 2H, 2 $\times$ OH), 4.93 (m, 2H, 2 $\times$ CH), 1.64-1.36 (m, 16H, 2 $\times$ CH₂CH₂CH₂CH₂), 0.92 (t, *J* = 7.3 Hz, 6H, 2 $\times$ CH₃); **¹³C NMR** (100.6 MHz, CDCl₃) δ 144.2 (2 $\times$ C), 108.0 (2 $\times$ C), 70.1 (2 $\times$ CH), 38.7 (2 $\times$ CH₂), 31.5 (2 $\times$ CH₂), 25.8 (2 $\times$ CH₂), 22.8 (2 $\times$ CH₂), 14.2 (2 $\times$ CH₃); **HRMS** (ESI+) (*m/z*): [M⁺] calcd for C₁₆H₂₆Br₂O₂S, 442.0000; found 442.0007 (⁷⁹Br).

1,1'-(3,4-Dibromothiophene-2,5-diyl)bis(octan-1-ol) 147e

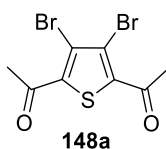
Preparation from tetrabromothiophene **146** (3.00 g, 7.50 mmol), *n*BuLi (11.0 mL, 1.5 M in hexane, 16.51 mmol) and *n*octanal (2.40 g, 18.76 mmol). The yellow crude product was purified by flash column chromatography (9:1 light petroleum:EtOAc) to yield a yellow oil as a (2:1) mixture of diastereomers (1.46 g, 40%); TLC: **R_f** (9:1 light petroleum:EtOAc) 0.30, 0.20; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 3331(OH), 2954,

2922, 2853, 1463, 1315, 1168, 1050, 1019, 907, 765; ^1H NMR (400.1 MHz, CDCl_3) δ 5.06-5.02 (m, 2H, $2 \times \text{CH}$), 1.83-1.77 (m, 4H, $2 \times \text{CH}_2$), 1.31 (m, 20H, $2 \times \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 0.88 (t, $J = 6.9$ Hz, 6H, $2 \times \text{CH}_3$), the OH signals $\sim \delta$ 2.4 were often not clearly observed due to exchange; ^{13}C NMR (100.6 MHz, CDCl_3) δ 142.8 ($2 \times \text{C}$), 110.1 ($2 \times \text{C}$), 70.6 ($2 \times \text{CH}$), 38.1 ($2 \times \text{CH}_2$), 31.9 ($2 \times \text{CH}_2$), 29.4 ($2 \times \text{CH}_2$), 29.3 ($2 \times \text{CH}_2$), 25.7 ($2 \times \text{CH}_2$), 22.8 ($2 \times \text{CH}_2$), 14.2 ($2 \times \text{CH}_3$); HRMS (ESI+) (m/z): $[\text{M}^+]$ calcd for $\text{C}_{20}\text{H}_{34}\text{Br}_2\text{O}_2\text{S}$, 496.0640; found 496.0619.

General procedure for oxidation of compounds 147a-e to corresponding ketone 148a-e

Diols **147** (1.41 mmol) were dissolved in dichloromethane (20 mL), and activated MnO_2 (10 molar equivalents) added. The dark black suspension was stirred (16 h) at 40-45 °C. Completion of the reaction was determined by TLC. After filtration through Celite, the reaction mixture was concentrated *in vacuo* to afford the corresponding ketone products as pale solids in about 90% yield. These products were >98% pure by ^1H NMR spectroscopy and used without further purification.

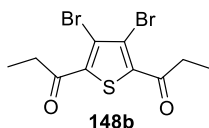
1,1'-(3,4-Dibromothiophene-2,5-diyl)bis(ethan-1-one) 148a



Prepared from diol **147a** (55 mg, 0.16 mmol) to obtain compound **148a** as a colourless solid (47 mg, 87%). TLC: **R_f** (7:3 pentane:EtOAc) 0.84; **Mp** 168-170 °C [lit.²⁸⁴ 173-174 °C]; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 2919, 2852, 1649 (C=O), 1474, 1414, 1353, 1240, 1044, 1029, 949, 870, 802, 666; ^1H NMR (400.1 MHz,

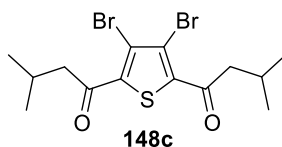
CDCl_3) δ 2.74 (s, 6H, $2 \times \text{CH}_3$); ^{13}C NMR (100.6 MHz, CDCl_3) δ 189.7 ($2 \times \text{C=O}$), 142.7 ($2 \times \text{C}$), 119.4 ($2 \times \text{C}$), 29.9 ($2 \times \text{CH}_3$); HRMS (ESI+) (m/z): $[\text{M}^+]$ calcd for $\text{C}_8\text{H}_6\text{Br}_2\text{O}_2\text{S}$ (^{79}Br) 325.8435; found 325.8431.

1,1'-(3,4-Dibromothiophene-2,5-diyl)bis(propan-1-one) **148b**



Prepared from diol **147b** (45 mg, 0.12 mmol) to obtain compound **148b** as a colourless solid (35 mg, 0.10 mmol, 82%) TLC: **R_f** (17:3 light petroleum:EtOAc) 0.70; **Mp** 118–120 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 2983, 2932, 2878, 1651(C=O), 1451, 1401, 1379, 1348, 1275, 1184, 1083, 923, 890, 869; ^1H NMR (400.1 MHz, CDCl_3) δ 3.10 (q, $J = 7.1$, 4H, $2 \times \text{CH}_2$), 1.24 (t, $J = 7.1$, 6H, $2 \times \text{CH}_3$); ^{13}C NMR (100.6 MHz, CDCl_3) δ 192.8 ($2 \times \text{C=O}$), 141.9 ($2 \times \text{C}$), 118.9 ($2 \times \text{C}$), 35.5 ($2 \times \text{CH}_2$), 8.0 ($2 \times \text{CH}_3$); HRMS (ESI+) (m/z): $[\text{M}^+]$ calcd for $\text{C}_{10}\text{H}_{10}\text{Br}_2\text{O}_2\text{S}$ (^{79}Br) 351.8762; found 351.8751.

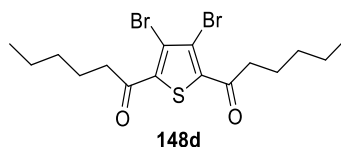
1,1'-(3,4-Dibromothiophene-2,5-diyl)bis(3-methylbutan-1-one) **148c**



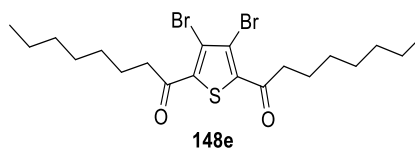
Prepared from diol **147c** (0.50 g, 1.20 mmol) to obtain compound **148c** as a colourless solid (0.44 g, 90%); TLC: **R_f** (8.5:1.5 light petroleum:EtOAc) 0.90; **Mp** 97–99 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 2956, 2930, 2871, 1649 (C=O), 1470, 1423,

1393, 1362, 1183, 1098, 1120, 1098, 984, 805, 767; **¹H NMR** (400.1 MHz, CDCl₃) δ 2.92 (d, *J* = 6.7 Hz, 4H, 2 × CH₂), 2.30 (m, 2H, 2 × CH), 1.01 (d, *J* = 6.7 Hz, 12H, 4 × CH₃); **¹³C NMR** (100.6 MHz, CDCl₃) δ 192.0 (2 × C=O), 141.9 (2 × C), 119.0 (2 × C), 50.5 (2 × CH₂), 25.2 (2 × CH), 22.7 (2 × CH₃); **HRMS** (ESI+) (*m/z*): [M⁺] calcd for C₁₄H₁₈Br₂O₂S (⁷⁹Br) 407.9388; found 407.9384. The experimental data were consistent with published values.²⁸⁵

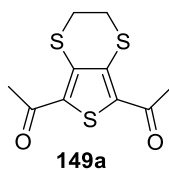
1,1'-(3,4-Dibromothiophene-2,5-diyl)bis(hexan-1-one) **148d**



Prepared from diol **147d** (0.52 g, 1.18 mmol) to obtain compound **148d** as a colourless solid (0.45 g, 87%); **Mp** 71-72 °C; TLC: **R_f** (8:1 light petroleum:EtOAc) 0.87; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 2950, 2918, 2867, 1666 (C=O), 1461, 1426, 1396, 1370, 1246, 1173, 952, 870, 848, 72; **¹H NMR** (400.1 MHz, CDCl₃) δ 3.05 (t, *J* = 7.3 Hz, 4H, 2 × CH₂), 1.75 (m, 4H, 2 × CH₂), 1.37 (m, 8H, 2 × CH₂CH₂), 0.91 (t, *J* = 7.3 Hz, 6H, 2 × CH₃); **¹³C NMR** (100.6 MHz, CDCl₃) δ 192.5 (2 × C=O), 141.9 (2 × C), 118.9 (2 × C), 41.9 (2 × CH₂), 31.4 (2 × CH₂), 23.8 (2 × CH₂), 22.6 (2 × CH₂), 14.0 (2 × CH₃); **HRMS** (ESI+) (*m/z*): [M⁺] calcd for C₁₆H₂₂Br₂O₂S (⁷⁹Br) 435.9700; found 435.9707.

1,1'-(3,4-Dibromothiophene-2,5-diyl)bis(octan-1-one) 148e

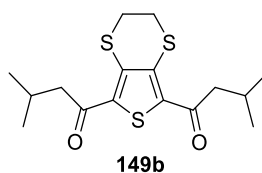
Prepared from diol **147e** (0.29 g, 0.58 mmol) to obtain compound **148e** as a pale-yellow solid (0.23 g, 0.465 mmol, 80%). TLC: **R_f** (9:1 light petroleum:EtOAc) 0.74; **Mp** 48–50 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 2954, 2916, 2847, 1666 (C=O), 1559, 1470, 1269, 1222, 1171, 770, 727; **¹H NMR** (500.1 MHz, CDCl₃) δ 3.05 (t, J = 6.7 Hz, 4H, 2 $\times$ CH₂), 1.76–1.71 (m, 4H, 2 $\times$ CH₂), 1.38–1.25 (m, 16H, 2 $\times$ CH₂CH₂CH₂CH₂CH₂), 0.88 (t, J = 6.7 Hz, 6H, 2 $\times$ CH₃); **¹³C NMR** (125.8 MHz, CDCl₃) δ 192.6 (2 $\times$ C=O), 141.9 (2 $\times$ C), 119.0 (2 $\times$ C), 41.9 (2 $\times$ CH₂), 31.8 (2 $\times$ CH₂), 29.2 (2 $\times$ CH₂), 29.2 (2 $\times$ CH₂), 24.2 (2 $\times$ CH₂), 22.7 (2 $\times$ CH₂), 14.2 (2 $\times$ CH₃); **HRMS** (ESI+) (m/z): [M^+] calcd for C₂₀H₃₀Br₂O₂S (⁷⁹Br) 492.0300; found 492.0300.

1,1'-(2,3-Dihydrothieno[3,4-*b*][1,4]dithiine-5,7-diyl)bis(ethan-1-one) 149a

Neat 1,2-ethanedithiol (83 mg, 0.9 mmol) was added to a solution of **148a** (195 mg, 0.59 mmol) and Na₂CO₃ (158 mg, 1.49 mmol) in hot DMF (10 mL) at 50 °C (NOTE: this compound dissolved in hot DMF because it is not very soluble at room temperature. The mixture was then stirred for (90 h) at 25 °C until a precipitate formed. The mixture was quenched with ice water and the extracted with ethyl acetate (3 $\times$ 15) mL. The organic layer was then washed with 15 mL (2 M HCl). The extracts

were dried (MgSO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (9:1 light petroleum:EtOAc) giving a butter cream yellow solid (67 mg, 44%); TLC: **R_f** (7:3 Pentane:EtOAc) 0.46; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 2959, 2922, 2851, 1659 (C=O), 1435, 1399, 1345, 1298, 1278, 1237, 1222, 1178, 1121, 1071, 1045, 1023, 983, 922, 909, 880, 795, 713, 685, 621, 574, 537, 478, 462; **¹H NMR** (400.1 MHz, CDCl_3) δ 3.19 (s, 4H, $2 \times \text{CH}_2$), 2.52 (s, 6H, $2 \times \text{CH}_3$). **¹³C NMR** (101 MHz, CDCl_3) δ 190.2 ($2 \times \text{C=O}$), 136.37 ($2 \times \text{C}$), 133.5 ($2 \times \text{C}$), 28.7 ($2 \times \text{CH}_3$), 26.3 ($2 \times \text{CH}_2$); **HRMS** (EI+) (m/z): [M^+] calcd for $\text{C}_{10}\text{H}_{10}\text{O}_2\text{S}_3$ 257.9837; found 257.9839.

1,1'-(2,3-Dihydrothieno[3,4-*b*][1,4]dithiine-5,7-diyl)bis(3-methylbutan-1-one)
149b



Neat 1,2-ethanedithiol (0.84 g, 9.01 mmol) was added slowly to a solution of **148c** (1.68 g, 4.10 mmol) and Na_2CO_3 (1.00 g, 9.44 mmol) in dry DMF (20.5 mL) and the mixture was stirred at room temperature under an atmosphere of argon. After (64 h) the mixture was extracted with ethyl acetate (3×100 mL). The organic layer was washed with 2 M HCl (3×30 mL) and then dried with MgSO_4 , filtered and concentrated under reduced pressure. Purification was achieved by flash column chromatography (18:1 light petroleum:EtOAc) to afford **149b** (0.991 g, 2.89 mmol, 70%) as yellow microcrystals; TLC: **R_f** (18:1 light petroleum:EtOAc) 0.26; **Mp** 99-100 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 2951, 2871, 1728, 1654 (C=O), 1442, 1411, 1398, 1362, 1278, 1183, 1035, 956, 917, 880, 688; **¹H NMR** (400.1 MHz, CDCl_3) δ 3.21 (s, 4H, $2 \times \text{CH}_2$), 2.69 (d, $J = 6.7$ Hz, 4H, $2 \times \text{CH}_2\text{CO}$), 2.36-2.28 (m,

2H, 2 × CH), 1.00 (d, $J = 6.7$ Hz, 12H, 4 × CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 192.9 (2 × C=O), 136.4 (2 × C), 133.5 (2 × C), 50.1 (2 × CH₂), 26.5 (2 × CH₂), 25.7 (2 × CH), 22.8 (2 × CH₃); UV/Vis (CH₂Cl₂, 10⁻⁴ M): λ_{max}/nm 432 (sh) (log ε 3.8), 409 (log ε 3.9), 345 (log ε 4.1), HRMS (ESI+) (m/z): [M⁺] calcd for C₁₆H₂₂O₂S₃, 342.0782; found 342.0785. CHN Anal. calcd for C₁₆H₂₂O₂S₃ C: 56.10; H, 6.47% found C: 55.97, H: 6.78%.

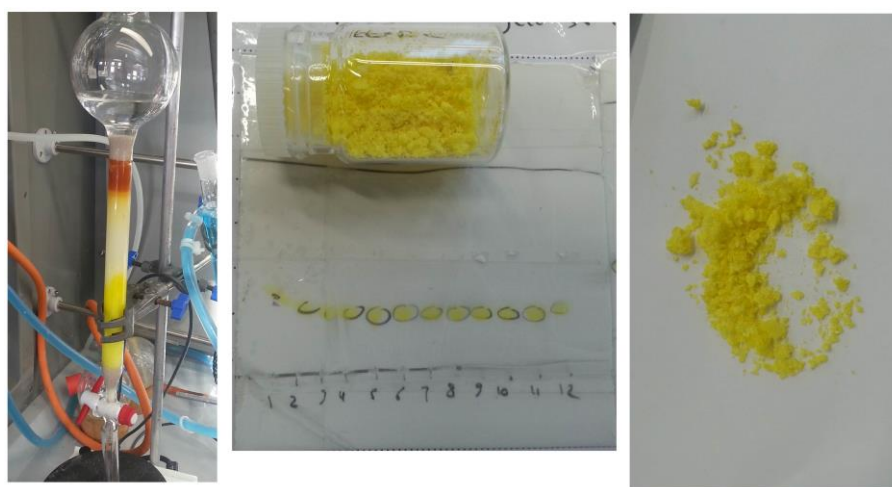
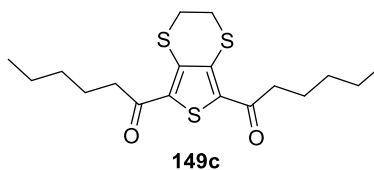


Figure 29 Purification of compound **149b**

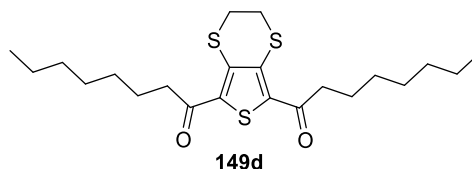
1,1'-(2,3-Dihydrothieno[3,4-*b*][1,4]dithiine-5,7-diyl)bis(hexan-1-one) 149c



Neat 1,2-ethanedithiol (83.0 mg, 0.89 mmol) was added to a solution of **148d** (156 mg, 0.36 mmol) and Na₂CO₃ (94 mg, 0.89 mmol) in dry DMF (1.8 mL) and the mixture was stirred at room temperature under an atmosphere of argon (40 h). The mixture was extracted with ethyl acetate (3 × 4 mL) and the organic layer was then washed with (2 M HCl) until DMF free. The organic extracts were dried with

MgSO₄ and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (9:1 light petroleum:EtOAc) giving a pale-yellow solid (75.0 mg, 57%); TLC: **R_f** (9:1 light petroleum:EtOAc) 0.47; **Mp** 59-60 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 2954, 2933, 2859, 1641 (C=O), 1463, 1447, 1417, 1366, 1315, 1275, 1247, 1184, 1164, 973, 848, 730; **¹H NMR** (400.1 MHz, CDCl₃) δ 3.22 (s, 4H, 2 × CH₂), 2.28 (t, *J* = 7.2 Hz, 4H, 2 × CH₂), 1.74-1.70 (m, 4H, 2 × CH₂), 1.34-1.31 (m, 8H, 2 × CH₂CH₂), 0.91 (t, *J* = 7.2, 6H, 2 × CH₃); **¹³C NMR** (100.6 MHz, CDCl₃) δ 193.3 (2 × C=O), 136.4 (2 × C), 133.2 (2 × C), 41.2 (2 × CH₂), 31.5 (2 × CH₂), 26.5 (2 × CH₂), 24.3 (2 × CH₂), 22.6 (2 × CH₂), 14.1 (2 × CH₃); **UV/Vis** (CH₂Cl₂, 10⁻⁴ M): $\lambda_{\text{max}}/\text{nm}$ 426 (sh) (log ϵ 4.1), 405 (log ϵ 4.2), 344 (log ϵ 4.4); **HRMS** (ESI+) (*m/z*): [*M*⁺] calcd for C₁₈H₂₆O₂S₃ 370.1086; found 370.1095.

1,1'-(2,3-Dihydrothieno[3,4-*b*][1,4]dithiine-5,7-diyl)bis(octan-1-one) **149d**

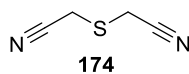


Neat 1,2-ethanedithiol (83 mg, 0.9 mmol) was added to a solution of **148e** (194 mg, 0.39 mmol) and Na₂CO₃ (104 mg, 0.98 mmol) in dry DMF (4 mL) at room temperature. The mixture was then stirred for (40 h) until a precipitate formed. The mixture was extracted with ethyl acetate (4 × 10 mL) and the organic layer was then washed with (2 M HCl) until DMF free. The extracts were dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (9:1 light petroleum:EtOAc) giving a butter cream yellow solid (75 mg, 45%); TLC: **R_f** (9:1 light petroleum:EtOAc) 0.26; **Mp** 65-67 °C; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 2953, 2928, 2850, 1646 (C=O), 1465, 1444, 1418, 1404, 1368, 1354, 1316, 1298, 1250, 1181, 1166, 1099, 1057, 1021, 970; **¹H NMR**

(400.1 MHz, CDCl₃) δ 3.20 (s, 4H, 2 $\times$ CH₂), 2.20 (t, J = 7.4 Hz, 4H, 2 $\times$ CH₂), 1.76-1.69 (m, 4H, 2 $\times$ CH₂), 1.34-1.29 (m, 16H, 2 $\times$ CH₂CH₂CH₂CH₂CH₂), 0.86 (t, J = 7.4, 6H, 2 $\times$ CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 193.2 (2 $\times$ C=O), 136.3 (2 $\times$ C), 133.1 (2 $\times$ C), 41.2 (2 $\times$ CH₂), 31.8 (2 $\times$ CH₂), 29.3 (2 $\times$ CH₂), 29.1 (2 $\times$ CH₂), 26.5 (2 $\times$ CH₂), 24.5 (2 $\times$ CH₂), 22.7 (2 $\times$ CH₂), 14.2 (2 $\times$ CH₃); UV/Vis (CH₂Cl₂, 10⁻⁴ M): λ_{max} /nm 430 (sh) (log ϵ 3.8), 405 (log ϵ 3.9), 344 (log ϵ 4.1); HRMS (ESI+) (m/z): [M⁺], calcd for C₂₂H₃₄O₂S₃ 426.1721; found 426.1721.

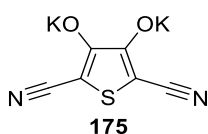
5.4 Experimental Data for Chapter 4

2,2'-Thiodiacetonitrile **174**



Solid $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ **173** (10.8 g, 45.01 mmol) was dissolved in DME (35 mL), and chloroacetonitrile **172** (4.77 g, 63.2 mmol) was then added. The mixture was allowed to stir at rt (16 h). Water was added, and the compound was extracted with chloroform (3×40 mL). The organic layer was dried (MgSO_4) and the solvent removed. Elution through a silica plug (1:1 EtOAc:pentane) yielded compound **174** as a colourless oil (3.24 g, 28.9 mmol, 91%); **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 2970, 2929, 2246 (CN), 1399, 1174, 922; **^1H NMR** (400.1 MHz, CDCl_3) δ 3.57 (s, 4H, $2 \times \text{CH}_2$); **^{13}C NMR** (100.6 MHz, CDCl_3) δ 114.9 ($2 \times \text{C}$), 17.5 ($2 \times \text{CH}_2$); **HRMS** (ESI+) (m/z): $[\text{M}^+]$, calcd for $\text{C}_4\text{H}_4\text{N}_2\text{S}$, 112.0089; found 112.0089. The above values are concordant with literature data.²⁸⁶

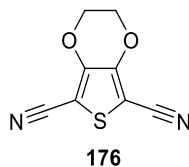
Potassium 2,5-dicyanothiophene-3,4-bis(olate) **175**



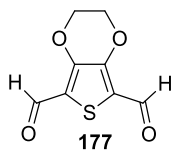
To dry $t\text{BuOK}$ (8.0 g, 71.3 mmol) in dry THF (95 mL) under argon, a solution of **174** (4.00 g, 35.6 mmol) in THF (43 mL) was added dropwise at 0 °C. The mixture was stirred for 5 min and then added a solution of diethyl oxalate **158** (5.21 g, 35.66 mmol) in dry THF (40 mL) at 0 °C. After 30 min stirring at 0 °C the precipitate was collected by vacuum filtration under argon and washed with diethyl ether and THF to obtain **175** as a brown powder (7.26 g, 84%); **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 2168 (CN), 1712, 1518, 1315, 1229, 1019, 764, 592; **^{13}C NMR** (100.6 MHz, DMSO-

d_6) δ 174.9 (2 $\times$ C), 122.8 (2 $\times$ C), 65.7 (2 $\times$ C). The compound was used as obtained directly.

3,4-Ethylenedioxythiophene-2,5-dicarbonitrile **176**



Under an argon atmosphere potassium salt **175** (0.50 g, 2.06 mmol) was dissolved in anhydrous DMF (1.5 mL) at room temperature, and dry potassium carbonate (0.11 g, 0.83 mmol) added followed by tetrabutylammonium bromide (35 mg, 0.10 mmol). The mixture was heated to 135 °C and 1,2-dichloroethane (0.41 g, 4.13 mmol) added dropwise. After stirring at 135 °C (5 h) the reaction was stopped and allowed to cool down. The mixture was extracted with ethyl acetate (3 $\times$ 10 mL), washed with 5% w/w LiCl (equiv) solution (3 $\times$ 10 mL) and the combined organic extracts dried (MgSO_4) and concentrated *in vacuo* to afford the crude product. Filtering through a silica plug with a CH_2Cl_2 wash yielded, on removal of the solvent, **176** (0.13 g, 35%) obtained as a colourless solid, TLC: **R_f** (1:1 EtOAc:hexane) 0.68; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 2946, 2215 (CN), 1632, 1504, 1449, 1078, 914, 843, 806; **¹H NMR** (400.1 MHz, CDCl_3) δ 4.42 (s, 4H, 2 $\times$ CH_2); **¹³C NMR** (100.6 MHz, CDCl_3) δ 147.8 (2 $\times$ C), 110.6 (2 $\times$ C), 91.3 (2 $\times$ C), 65.2 (2 $\times$ CH_2); **HRMS** (ESI+) (m/z): [M^+] calcd for $\text{C}_8\text{H}_4\text{N}_2\text{O}_2\text{S}$ 191.9993; found 191.9988.

3,4-Ethylenedioxythiophene-2,5- dicarbaldehyde (177)

A solution of DIBAL-H (1.08 mL, 1.2 M, 20% wt. in toluene) was added dropwise at 0 °C to a solution of **176** (100 mg, 0.52 mmol) in dry toluene (5.2 mL). The reaction was stirred (30 min) at 0 °C until the starting material was consumed as judged by TLC analysis. The reaction mixture was quenched with (1 M, HCl) and extracted with ethyl acetate (3 × 10 mL) and dried (MgSO₄), the solvent was evaporated to yield the desired dialdehyde **177** (83 mg, 80%) as a tan brown solid. TLC: **R_f** (EtOAc) 0.64; **IR** (diamond-ATR): $\nu_{\text{max}}/\text{cm}^{-1}$ 2953, 2922, 2851, 1662 (C=O), 1260, 1230; **¹H NMR** (400.1 MHz, CDCl₃) δ 10.04 (s, 2H, 2 × CHO), 4.45 (s, 4H, 2 × CH₂); **¹³C NMR** (100.6 MHz, CDCl₃) δ 181.0 (2 × CHO), 147.4 (2 × C), 124.2 (2 × C), 65.0 (2 × CH₂); **HRMS** (ESI+) (m/z): [M⁺], calcd for C₈H₆O₄S, 197.9987; found 197.9987. These values are consistent with published literature.²⁸⁷

Synthesis of vinylzinc bromide

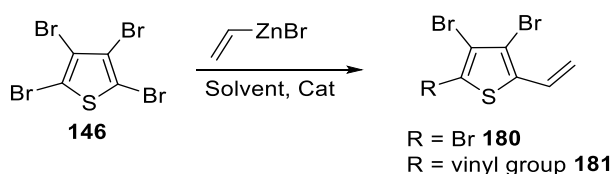
Anhydrous zinc chloride (1 M solution in ether, 12 mL, 12 mmol, 1.0 equiv) was added slowly to solution of vinylmagnesium bromide (1 M solution in THF, 12 mL, 12 mmol, 1.0 equiv) over (10 minute) while the temperature was maintained to 0 °C with an ice bath. After the addition of vinylmagnesium bromide was completed, the ice bath was removed, and the mixture allowed to come to room temperature. The

mixture was stirred (3 h) providing solutions of (vinylzinc bromide, 0.5 M in Et₂O) which were used immediately to prepare the vinyl thiophenes.

General procedure for Preparation of vinylthiophenes **180** using Kumada couplings

To a solution of tetrabromothiophene **146** (1.00 g, 2.50 mmol) in anhydrous THF (10 ml), was added of [Pd(PPh₃)₄ or NiCl₂(dppp)] catalysts (4 mol%) and the mixture stirred at room temperature (5 min). Subsequently, vinylmagnesium bromide (0.8-2.5 equiv) was added the mixture was stirred for the desired period (0.5-70 h) at 0-60 °C. After which the mixture of reaction was allowed to cool at room temperature. The reaction was monitored by TLC. The reaction mixture was quenched with saturated ammonium chloride and extracted with diethyl ether, the organic washings were combined, dried (MgSO₄), filtered, and evaporated to the crude product. Chemoselectivity **90** vs. **180** was examined by ¹H NMR spectroscopy. Full details in (Table 9).

Screening conditions for optimisation of the Negishi coupling of tetrabromothiophene **146** with vinylzinc bromide



The screening reactions were carried out in a Radley's carousel reactor. Typically, tetrabromothiophene **146** (119.9 mg, 0.30 mmol) was dissolved in an anhydrous solvent (1.2 mL) to create (0.25 M) solutions. Catalyst precursors (5 mol%) with

ligands (10 mol%) were added and the mixture was stirred at room temperature (10 min). After addition of the vinylzinc bromide solution (1.0-3.5 equiv). The mixture was stirred for (24-158 h) at 50-130 °C. After reactions the mixtures were allowed to cool to room temperature. The reactions were then quenched with (1.2 mL) of saturated ammonium chloride (NH₄Cl). Subsequently 2-methylnaphthalene [42.7 mg in Et₂O (1.0 ml), part of a stock solution] was added as an internal standard. The organic layer filtered through small silica plug and analysed by GC to determine conversions and yields. For more details of this reaction see Tables (10 and 11) in the discussion section. Compound **180**: TLC: **R_f** (100% hexane): 0.77. **¹H NMR** (500.1 MHz, CDCl₃) δ 6.82 (dd, *J* = 17.4, 11.0 Hz, 1H, Ar*H*-thiophene), δ 5.59 (d, *J* = 17.4 Hz, 1H, Ar*H*-thiophene), δ 5.33 (d, *J* = 11.0 Hz, 1H, Ar*H*-thiophene). **¹³C NMR** (125.8 MHz, CDCl₃) δ 128.5 (CH), 117.9 (C), 116.8 (CH₂), 112.8 (C), 110.0 (C), 109.5 (C). **GC Mass:** (ESI+) (*m/z*): [M⁺], calcd for C₆H₃SBr₃ (⁷⁹Br) 347.75; found 347.75.

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7 Academic activities

Publications

Mustafa A. Al-jumaili, Simon Woodward, “Syntheses of 7-Substituted Anthra[2,3-*b*]thiophene Derivatives and Naphtho[2,3-*b*:6,7-*b'*]dithiophene” *J. Org. Chem.* **2018**, 83, 11437-11445.

Mustafa A-JABBAR Al-jumaili, Simon Woodward, “Efficient synthesis of 2,5-dicarbonyl derivatives of 3,4-ethylenedithiophene (EDTT) via addition-elimination reaction” *Tetrahedron* **2017**, 73, 5847-5852.

Conference presentations

Mustafa A. Al-jumaili, ‘Studies in Thiophene Chemistry for Organic Electronics’, Postgraduate Research Symposium; Organic section, July **2018**, School of chemistry, University of Nottingham.

Poster presentations

2019 #RSCPoster Conference. Twitter Poster Conference, organised by Royal Society of Chemistry.

Mustafa A. Al-jumaili and Simon Woodward ‘EDTT Thiophenes for Organic Electronics’ EMDoc Conference, 19 September **2018**, Bishop Grosseteste University, Lincoln.

Mustafa A. Al-jumaili and Simon Woodward ‘Organic Material Based Thermoelectrics’ Organic and Biological Chemistry Postgraduate Research Symposium July **2017**, School of chemistry, University of Nottingham.

Mustafa A. Al-jumaili and Simon Woodward ‘Towards New Thiophene-Based Semiconductors’ Organic and Biological Chemistry Postgraduate Research Symposium July **2016**, School of chemistry, University of Nottingham.

Awards

Achieved 1st prize for best poster presentation, 10 January **2017**. Energy Technologies Research Institute Conference: A Sustainable Future Through New Materials For Energy, Jubilee Conference Centre, University of Nottingham.

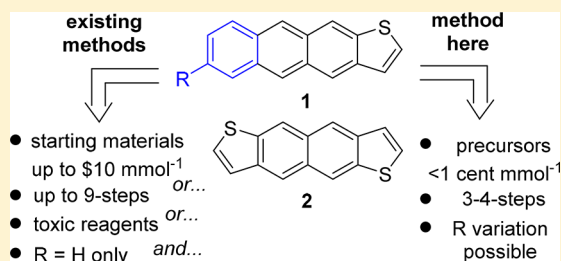
Syntheses of 7-Substituted Anthra[2,3-*b*]thiophene Derivatives and Naphtho[2,3-*b*:6,7-*b'*]dithiophene

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Supporting Information

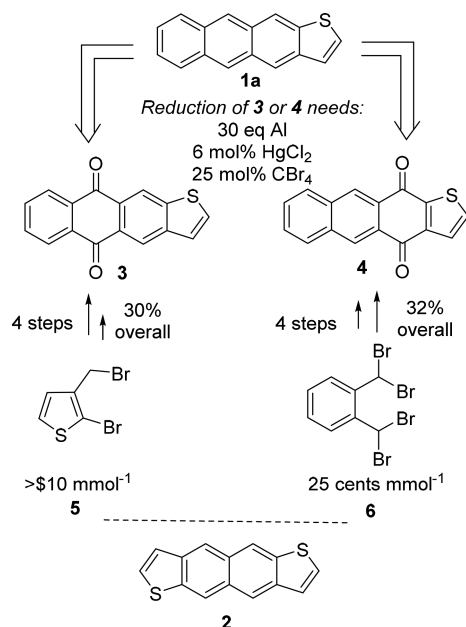
ABSTRACT: 7-*R*-Anthra[2,3-*b*]thiophene derivatives (**1**, *R* = H, Me, *i*-Pr, or MeO) are prepared in three steps (in average overall yield >50%) starting from (*E*)-4-*RC*₆H₄CH₂(HOCH₂)C=CI(CH₂OH). The latter are commercial or readily prepared from 2-butyne-1,4-diol and ArCH₂Cl (both costing <1 cent/mmol) at 10 g scales. These allow for the selective formation of (otherwise unattainable) higher solubility 7-derivatives. Similar methods allow for the preparation of naphtho[2,3-*b*:6,7-*b'*]dithiophene **2** using equally low-cost starting materials.



Acene-cores terminating at one or both ends with thiophene units are attractive motifs for the formation of organic electronic semiconductor devices.^{1–6} For example, anthra[2,3-*b*]thiophene **1a** (Scheme 1) has been used to derive organic field effect transistors (OFETs) showing carrier mobilities of 0.13–0.15 cm² V⁻¹ s⁻¹.^{7,8} Similarly, derivatives of **2** have also been used in OFET devices with even higher carrier mobilities of 0.5–1.5 cm² V⁻¹ s⁻¹.⁹

The parent anthra[2,3-*b*]thiophene **1a** has been known since 1981.^{10–15} Various methodologies have been employed for its

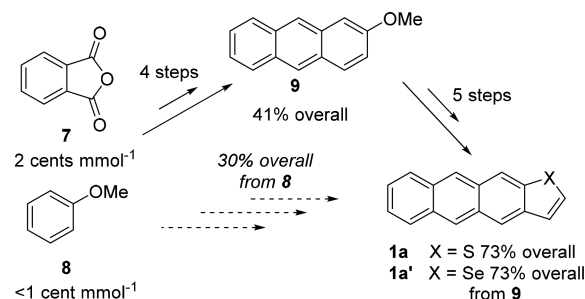
Scheme 1. Conventional Syntheses of Compound 1a Using Dihydroanthra[2,3-*b*]thiophenediones and Related 2



preparation. Multistep syntheses using expensive (in either cost or time) or higher toxicity or environmentally less than desirable reagents are the norm.^{10,11} The current best synthetic methods for **1a** use compounds **3** or **4** as key intermediates (Scheme 1), but these are not without issues. Several steps are needed to prepare **3** in 30% overall yield from lachrymatory and expensive 2-bromo-3-(bromomethyl)thiophene **5** (\$210 for 5 g¹⁶). Similarly, **4** has to be synthesized from **6**, which although it is more modest in cost (\$64 per 100 g¹⁶), it still requires four steps from this significantly carcinogenic material. Finally, the environmental metrics of the reduction of **3** or **4** to **1a** could be improved, but 30 equiv of aluminum, 6 mol % of toxic HgCl₂, and 25 mol % of CBr₄ are required.⁷

Another recent synthesis of anthra[2,3-*b*]thiophene **1a** uses noncommercial 2-methoxyanthracene **9** as the key intermediate.¹⁷ The latter requires 4 steps resulting in an overall yield of 41% to **9**.^{17,18} Thus, the total step count to **1a** by this route is rather high (Scheme 2).

Scheme 2. Synthesis of Compound 1a from 2-Methylantracene 9



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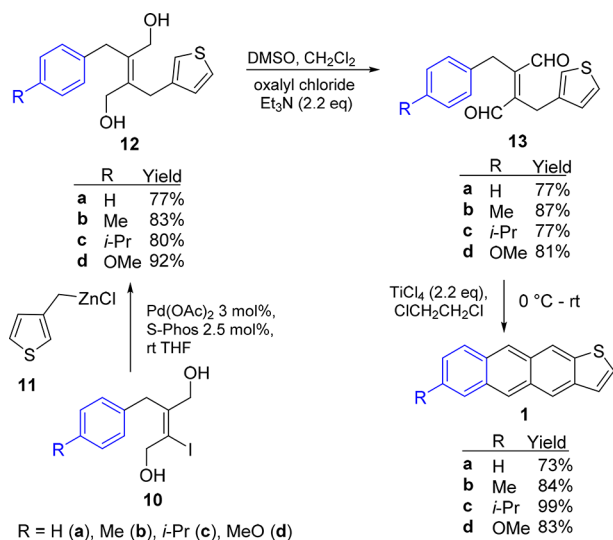
Published: August 8, 2018

Although, this latter approach uses cheap starting materials, 7 and 8, and allows access to selenophene **1a'**, it still requires a total of nine steps, including a boron tribromide promoted MeO-deprotection and a Sonogashira coupling, to complete the synthesis.¹⁷

In conclusion, the starting materials for all reported routes to anthra[2,3-*b*]thiophene **1a** require multistep synthesis, using commercially expensive precursors which often have significant toxicity issues. Finally, while existing routes to anthra[2,3-*b*]thiophenes **1** can allow subsequent preparation of 2-substituted derivatives, they cannot easily be used for regiospecific monosubstitution of the terminal phenylene. Dissymmetric reagents would result in regio-isomeric products. However, employment of a two-directional¹⁹ Bradsher²⁰ disconnection should be an effective alternative. It was anticipated that 7-alkyl substitution would also increase the solubility of the resultant anthra[2,3-*b*]thiophenes **1**.

Our approach to **1a–1d** (Scheme 3) begins with the crystalline iodides **10a–10d**, a number of which are

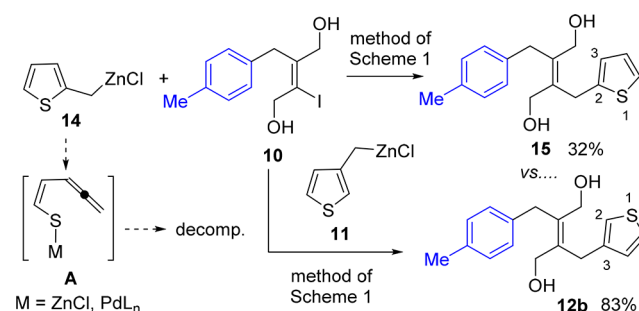
Scheme 3. Concise Methodology for the Synthesis of Anthra[2,3-*b*]thiophenes (1a–1d**)**



commercially available.²¹ Alternatively, **10a–10d** are easily prepared from 2-butyne-1,4-diol and benzylic chlorides, both of which are typically available at low cost (<1 cent mmol⁻¹). Copper-catalyzed Grignard carbocoupling allows **10a–10d** to be prepared at 10 g scales without recourse to chromatography (see the Experimental section). Use of Pd(OAc)₂ (3 mol %) and a deficiency of S-Phos (2.5 mol %) allows direct Negishi-coupling of (thien-3-ylmethyl)zinc(II) chloride (**11**), affording **12** without the protection of the free alcohols. Swern oxidation of **12** to the yellow dialdehydes **13** proceeds in a good yield, provided a small additional amount of DMSO was used in the reaction to facilitate complete dissolution of **12** at low temperature. Purification of intermediates **12–13** is facilitated by their highly crystalline nature. Finally, double¹⁹ Bradsher closure²² of **13** is effected cleanly in the presence of TiCl₄.²³ Isolation of **1a–1d** is simplified by the use of a 1:1 quench mixture of acetone/methanol. The titanium byproducts generated in the closure are soluble in this mixture, and **1** may be isolated by simple filtration (use of Whatman glass microfiber GF/A filter paper makes this very straightforward, see the Experimental section). The average overall yield for the

derivatives **1** over the three steps of Scheme 4 ranges from 43 to 61% (average 57%).

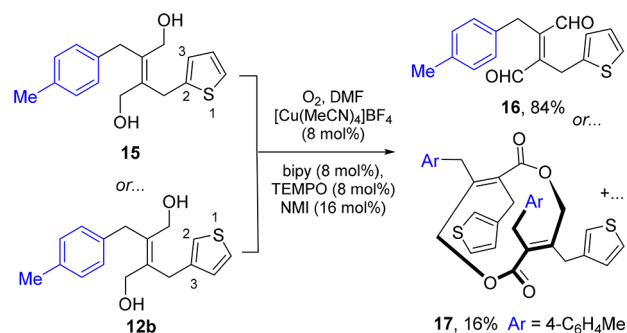
Scheme 4. Lower Stability of (Thien-2-ylmethyl)zinc(II) Chloride (14**)**



One of the advantages of Scheme 4 is the greater solubility of the 7-alkyl derivatives **1b–1d**, allowing routine acquisition of fully assigned ¹³C NMR spectra, while **1b–1d** are also easier to process in subsequent further functionalization or device preparations. Soluble diols **12a–12d** can be purified either using column chromatography to yield 70–90% or can be attained as analytically pure colorless needles by recrystallization with hot acetonitrile and cooling to 4 °C.

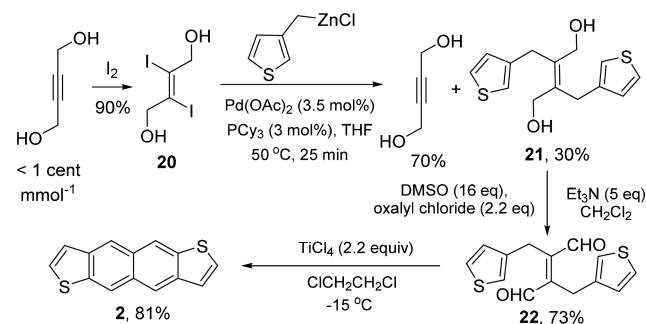
Optimization of Scheme 4 revealed interesting observations relevant to the scope and limitations of each of its steps (Schemes 4, 5, and 6). Attempts to use the regio-isomeric

Scheme 5. Comparative Oxidation of Diols **15 and **1b****



Negishi reagent **14** with iodide **10b** provided only low yields of **15** (32%) (Scheme 4). Extensive catalyst deactivation is observed in these reactions (see the Experimental section and Scheme 4).

Scheme 6. Straightforward Synthesis of Naphtho[2,3-*b*:6,7-*b'*]dithiophene (2**)**



Relatively few examples of 2-thienylmethyl organometallics are present in the primary literature;^{24,25} with these sometimes being implicated as thermo-labile species. The appearance of multiple 1:1 signals in the range of δ_{H} 5.0–6.4 in the crude spectra of **15** (assigned to $=\text{CH}_2$ units) is in accord with *anti*-elimination of **14** and subsequent decomposition of the potentially derived reactive putative allene intermediate **A**. Compound **11**, however, behaves cleanly. Interestingly, regio-isomeric alcohols **12b** and **15** also show different behaviors upon their oxidation.

While **15** cleanly provides **16** under our preferred aerobic oxidation conditions¹⁹ (Scheme 5), initial tests of **12b** led to complex mixtures under Stahl-catalysis.²⁶ Similar issues were seen on the attempted use of MnO_2 and PCC oxidants. From these complicated mixtures, the only isolable product is **17** based on spectroscopic data (Scheme 5), indicating that chemoselective oxidation is not attained. Fortunately, this issue could be overcome by simply increasing the DMSO content of Swern-based oxidations used in general conversions of **12** to **13**.

The final Bradsher closure^{19,20} step of Scheme 4 easily affords **1a–1d** in good yields (73–99%) as bright yellow powders. These reactions show typical Friedel–Crafts behavior; at shorter reactions times, mono closure onto just the electron-rich thiophene unit is observed. Thus, the scope of the final step in Scheme 4 is limited to the preparation of electron-rich anthra[2,3-*b*]thiophenes **1**. In support of this idea, closure of **13** to **1**, where $\text{R} = \text{F}$, was not achieved. The other steps of Scheme 4 are tolerant of alkyl, aryl, OR, F, and Br substituents.¹⁹

In contrast to anthra[2,3-*b*]thiophenes **1**, previous literature syntheses of naphtho[2,3-*b*:6,7-*b'*]dithiophene **2** are limited to a single route.^{9,27} Commercial 2,6-dihydroxynaphthalene (\$80 for 5 g¹⁶) **18** is brominated to afford 1,3,5,7-tetrabromonaphthalene-2,6-diol **19** by known procedures.^{28,29} Unfortunately, the literature yields for this process are reported to be highly variable (4–51%); additionally, a further four steps are required to convert **19** to **2**.

We considered alternative preparation of **2** based on Negishi coupling of the diiodide **20**¹⁹ (derived from low cost 2-butyne-1,4-diol, Scheme 6). Although the yield of **21** was modest (30%), due to competing transmetalation–elimination, the butyne diol byproduct produced is insoluble and very simply and easily separated. The remaining steps of the sequence all give good yields and involve chromatography-free workup procedures. Alternative procedures via the 3-thienyl analogue of **10** were investigated but were not as successful due to lower yields (see Experimental section).

Preparation of **2** was confirmed by HRMS together with ^1H , ^{13}C , IR, and UV–vis spectroscopy. Using the latter, the optical bandgaps (E_{g}) of **1a–1d** and **2** were measured using standard Tauc plots (Table 1). Hall effect studies suggested the carrier mobilities of our samples of **1–2** were less than $0.1 \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$.

In conclusion, we have established new approaches for the efficient synthesis of 7-substituted anthra[2,3-*b*]thiophenes **1a–1d** and the unsubstituted naphtho[2,3-*b*:6,7-*b'*]dithiophene **2**. The methods employed are simple, use low-cost starting materials, and are scalable, avoiding chromatography in many cases. These methods also offer simple flexible approaches to the inclusion of 7-substituted thiophene-acenes **1** that cannot be prepared by existing approaches. Finally, in our approach, compounds **1a–1d** are prepared in three steps

Table 1. Optical Bandgaps for Compounds 1a–1d and Compound 2

compound	λ_{max} (nm) ^a	E_{g} (eV) ^b
1a	435	2.75
1b	437	2.73
1c	436	2.72
1d	443	2.69
2	402	2.98

^aIn argon-saturated CH_2Cl_2 ; longest wavelength absorption band.

^bDetermined by Tauc plot of UV–vis data.

in average overall yields of >50%. Existing reported methods require four steps to attain key intermediates **3** and **4**, both in ca. 30% overall yield. Final reduction of **3** is high yielding but requires toxic HgCl_2 . Conversely, $\text{Al}(\text{O}-i\text{-C}_6\text{H}_{11})_3$ reduction of **4**, although environmentally benign, proceeds in a modest 59% yield. The approaches herein constitute useful cleaner and sustainable alternatives to these important classes of organic electronic fragments. The formation of bulk thermoelectric devices based on derivatives of **1–2** is the subject of our own future work.

EXPERIMENTAL

General Information. Reactions involving air-sensitive reagents were carried out under argon atmospheres in flame-dried glassware. All solvents were commercial (Sigma-Aldrich and Fisher Scientific UK, Ltd.) and were used as supplied unless otherwise stated. Dichloromethane (DCM), dimethyl sulfoxide (DMSO), triethylamine, diisopropylethylamine, and 1,2-dichloroethane were dried with a molecular sieve (4 Å). Tetrahydrofuran (anaerobic, < 10 ppm water) was from an anhydrous solvent unit (Inert Technologies PureSolv). The compounds 2-butyne-1,4-diol, iodine, PCy_3 ($\text{Cy} = \text{cyclo-C}_6\text{H}_{11}$) S-Phos (2-dicyclohexylphosphino-2,6-dimethoxybiphenyl), $\text{Pd}(\text{OAc})_2$, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), CuCN, and $\text{CuBr}\cdot\text{SMe}_2$ were commercial from Alfa-Aesar, Fisher, Merck, or Sigma-Aldrich and used as received. Lithium chloride (Aldrich, anhydrous, > 99%) and TiCl_4 (Fluka, > 98%) were stored under argon. Benzyl chlorides were commercial (Sigma-Aldrich), BnCl , $4\text{-RC}_6\text{H}_4\text{CH}_2\text{Cl}$ ($\text{R} = \text{Me}$, MeO , F), or prepared by literature routes ($\text{R} = i\text{-Pr}$).³⁰ Diols (**10a–10e**) were commercial (**10d**, Key Organics) or prepared according to a literature procedure.¹⁹ Zinc dust (<10 μm , Sigma-Aldrich: 209988-1KG) was activated by trimethylsilyl chloride. All temperatures refer to those of the cooling and heating baths used. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} . Nuclear magnetic resonance (NMR) spectra were recorded on Bruker DPX-400 (400.1 MHz), AV400 (400.1 MHz), AV(III)400 (400.1 MHz), or a Bruker Ascend 500 (500.1 MHz) spectrometers at ambient temperature. Proton spectra were referenced to CDCl_3 ($\delta = 7.27 \text{ ppm}$). All ^{13}C NMR samples were proton-decoupled and referenced to CDCl_3 ($\delta = 77.0 \text{ ppm}$). Coupling constants (J) are quoted in Hertz. Melting points were determined with a Gallenkamp MFB-600-010F apparatus. Infrared spectra (IR) were recorded with a Varian FTS-7000 FT-IR spectrometer used (ATR) at room temperature. UV–vis spectra were recorded by a Cary UV VIS NIR spectrometer using ca. 10^{-4} M dichloromethane solutions. Semiquantitative $\log(\epsilon)$ values are given as a guide to the relative peak height. Mass spectrometry was performed using a Bruker MicroTOF or VG Micromass AutoSpec spectrometers using electrospray (ESI) and electron impact (EI) ionization modes. Elemental CH analyses were conducted on a CE-440 instrument.

Preparation of Starting Materials, 2-(Chloromethyl)thiophene. To a solution of thien-2-ylmethanol (10.0 g, 87.6 mmol) in dry dichloromethane (350 mL) at 0°C , thionyl chloride (SOCl_2 , 12.8 mL, 45.2 mmol) was slowly added over ca. 6 min at 0°C . The mixture was stirred for 10 min at 0°C , and then stirring was

continued over 20 h at room temperature. The mixture was poured on to ice, the dichloromethane was separated, and the remaining aqueous layer was re-extracted with dichloromethane (3 × 70 mL). The combined organics were dried (MgSO₄), and the solvent was removed under reduced pressure to give the crude 2-(chloromethyl)-thiophene as a brown oil (10.4 g, 90% yield). For zinc subsequent reagent formation, the compound was distilled at 45 °C and 4 mbar to give a colorless oil. ¹H NMR (400.1 MHz, CDCl₃, δ): 7.32 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.13–7.07 (m, 1H), 6.96 (dd, *J* = 5.1, 3.5 Hz, 1H). ¹³C{¹H} NMR (100.6 MHz, CDCl₃, δ): 140.2, 127.8, 127.0, 127.0, 40.5. These data were consistent with literature values.³¹

(Thien-2-ylmethyl)zinc(II) Chloride (14). Zinc dust (<10 μm, 0.23 g, 3.57 mmol) was dried under vacuum at (0.5 mbar) at >200 °C (3–5 min) and then cooled to room temperature under an atmosphere of argon. Dry tetrahydrofuran (3.0 mL) was then added, forming a gray suspension. The reaction mixture was cooled to 0 °C, trimethylsilyl chloride (12 μL, 95 μmol, 0.04 equiv) was added in one portion, and the mixture was stirred (30 min). Freshly distilled 2-(chloromethyl)-thiophene (316 mg, 2.38 mmol) was added over 10 min. After the addition, the mixture was stirred at 0 °C (5 h). A turbid white suspension (which normally titrated at >0.54 M, > 74% yield) resulted over the remaining residual zinc powder. The supernatant solution could be stored for up to 1 week at 4 °C (resulting in clear or pale yellow supernatants), but typically the organometallic was used within 24 h as attained.

3-(Chloromethyl)thiophene. To a solution of 3-thienylmethanol (4.57 g, 40.0 mmol) in dry dichloromethane (160 mL) at 0 °C, thionyl chloride (SOCl₂, 5.85 mL, 80.1 mmol) was added slowly. The mixture was stirred for 10 min at 0 °C, and the mixture was allowed to warm to room temperature over 16 h. The mixture was poured onto ice, the dichloromethane was separated, and the remaining aqueous layer was re-extracted with dichloromethane (3 × 70 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to give crude 3-(chloromethyl)thiophene as a brown oil. The crude compound was distilled at 70–75 °C and 16–18 mbar to give a colorless liquid (3.95 g, 67%). IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3103, 2957, 2866, 1760, 1441, 1415, 1263, 1239, 1162, 1080, 908, 857, 829, 784, 691, 671, 612, 551. ¹H NMR (400.1 MHz, CDCl₃, δ): 7.33 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.30 (m, 1H), 7.14 (dd, *J* = 5.0, 1.4 Hz, 1H), 4.64 (s, 3H). ¹³C{¹H} NMR (100.6 MHz, CDCl₃, δ): 138.2, 127.7, 126.8, 124.1, 40.8. These data were consistent with literature values.³²

(Thienyl-3-ylmethyl)zinc(II) Chloride (11). A dry, argon-flushed Schlenk flask equipped with a magnetic stirrer and a septum was charged with zinc dust <10 μm (2.50 g, 38.7 mmol, 2.0 equiv). The flask was heated for 5 min under high vacuum (<0.5 mbar) using a heat gun. After being cooled to 25 °C, the flask was flushed again with argon, and dry THF (21.5 mL) was added, forming a gray suspension. The mixture was cooled to 0 °C, and trimethylsilyl chloride (98.6 μL, 0.77 mmol, 0.04 equiv) was added in one portion. The mixture was allowed to stir for 35 min at 25 °C. Freshly distilled 3-(chloromethyl)thiophene (2.57 g, 19.4 mmol) was added slowly (over 5 min) at 25 °C. (Note: equivalent results were attained using crude 3-(chloromethyl)thiophene dried overnight at rt with calcium hydride instead of distillation.) After the addition of the 3-(chloromethyl)thiophene was complete, the mixture was warmed to 40 °C and stirred (4 h). When titrated with iodine, the reaction assayed at 80%, 0.64 M. This solution could be stored at 4 °C for at least 5 days but was usually used as attained.

(Thienyl-3-ylmethyl)magnesium Chloride. Magnesium metal (3.66 g, 150 mmol) was activated by stirring at rt overnight under argon. Anhydrous THF (50 mL) was added, followed by 3-(chloromethyl)thiophene (9.24 g, 69.7 mmol) added dropwise over 16 h using a syringe pump. The black solution, when titrated with iodine, indicated the desired Grignard reagent (1.77 M, 88%). The solution was used immediately for the next step. This reagent has only been described in passing in the literature.³³

Isopropylbenzyl Chloride. Neat 4-isopropylbenzyl alcohol (20.4 mL, 20.0 g, 133 mmol) was added dropwise to SOCl₂ (29.1 mL, 47.5 g, 399 mmol) under argon at 25 °C. The reaction mixture was warmed to reflux (1 h), and afterward distilled under reduced pressure

(118 °C at 22 mbar) to yield isopropylbenzyl chloride (17.35 g, 77%) as a colorless oil. ¹H NMR (500.1 MHz, CDCl₃, δ): 7.32 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 4.58 (s, 2H), 2.92 (hept, *J* = 6.9 Hz, 1H), 1.25 (d, *J* = 6.9 Hz, 6H). ¹³C{¹H} NMR (125.8 MHz, CDCl₃, δ): 149.4, 135.0, 128.8, 127.0, 46.4, 34.0, 24.1. These experimental data match the published values.³⁰

Grignard Reagent Preparation: Representative Example, (4-Methylbenzyl)magnesium Chloride. Magnesium metal (10.0 g, 156 mmol) was activated by mechanistic stirring (7 h) under argon in the presence of iodine crystals (ca. 3.0 mg) at 22 °C until its color became black. Anhydrous tetrahydrofuran (156 mL) was then added at 20 °C, giving a suspension of black-activated magnesium. Distilled neat 4-methylbenzyl chloride (20.7 mL, 156 mmol) was then added dropwise to the reaction mixture over 15 h using a syringe pump. After completion of the addition, the reaction mixture was typically titrated against the iodine to give a 0.85 M equivalent to a 96% yield. The reagent was used as attained.

Preparation of Starting Diols (10a–10e): Representative Example, (Z)-2-Iodo-3-(4-isopropylbenzyl)but-2-ene-1,4-diol (10c). A solution of (4-isopropylbenzyl)magnesium chloride (39 mL, 1.1 M tetrahydrofuran solution, 42.9 mmol) was added to a stirred solution of 2-butyne-1,4-diol (1.10 g, 12.9 mmol) in dry tetrahydrofuran (23 mL) at 0 °C to form a colorless precipitate within a gray solution. The reaction mixture was allowed to warm to room temperature and was stirred for 5 min. Solid cuprous bromide dimethyl sulfide (52.9 mg, 0.26 mmol, 2 mol % based on diol) was added subsequently, against an argon flow, and the reaction mixture quickly transferred to pre-equilibrated oil bath at 60–65 °C. After 1 h at 60–65 °C, the solid had dissolved forming a dark solution which was cooled first to 25 °C and then to –60 °C in a lightly lagged bath (that would allow warming from –60 to 0 °C over ca. 2 h). Solid I₂ (4.35 g, 17.2 mmol) was added, against an argon flow, and the brown mixture was stirred as it came to 0 °C over 2 h. The reaction mixture was extracted with EtOAc (3 × 70 mL) and washed with sodium metabisulfite (2 × 70 mL of 5% w/w aqueous solution) and water (1 × 50 mL). The resulting pale yellow solution was dried over MgSO₄ and filtered, and the solvent was evaporated. To the crude oily mixture, which contained traces of EtOAc, was added a mixture of Et₂O and pentane (1:1, ca. 75 mL), and the mixture was cooled to (5 °C) overnight to afford colorless microneedles. A combined yield was attained over three crops (2.35 g, 6.79 mmol, 53%). TLC: *R*_f (ethyl acetate) 0.53. mp 74–75 °C. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3213, 2954, 2927, 2864, 1625, 1510, 1454, 1434, 1419, 1383, 1361, 1238, 1169, 1067, 1013, 997, 918, 830, 799, 742, 705, 609, 565, 543. ¹H NMR (500.1 MHz, CDCl₃, δ): 7.17 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 4.50 (d, *J* = 6.6 Hz, 2H), 4.24 (d, *J* = 6.6 Hz, 2H), 3.77 (s, 2H), 2.88 (hept, *J* = 6.9 Hz, 1H), 2.02 (t, *J* = 6.6 Hz, 1H), 1.67 (t, *J* = 6.6 Hz, 1H), 1.23 (d, *J* = 6.9 Hz, 6H). ¹³C{¹H} NMR (125.8 MHz, CDCl₃, δ): 147.5, 144.8, 135.18, 128.4, 127.0, 106, 5, 71.3, 67.8, 35.7, 33.8, 24.1. HRMS (ESI-TOF) (*m/z*): [M + Na]⁺ Calcd for C₁₄H₁₉IO₂Na, 369.0322; found, 369.0311. Anal: Calcd for C₁₄H₁₉IO₂ C, 48.57; H, 5.53; found, C, 48.56; H, 5.41%.

(Z)-2-Benzyl-3-iodobut-2-ene-1,4-diol (10a). Compound 10a was attained in a similar manner to compound 10c, using freshly prepared benzyl magnesium chloride (175 mL, 0.8 M THF solution, 140 mmol), 2-butyne-1,4-diol (3.61 g, 42.0 mmol) in THF (23 mL), CuBr·SMe₂ (0.17 mg, 0.84 mmol, 2 mol %), and I₂ (14.2 g, 56 mmol), yielding 10a as colorless microneedles (7.40 g, 24.3 mmol, 59%) after crystallization with Et₂O/pentane (three crops). TLC: *R*_f (ethyl acetate) 0.68. mp 94–95 °C. ¹H NMR (500.1 MHz, CDCl₃, δ): 7.32–7.29 (m, 2H), 7.25–7.18 (m, 3H), 4.50 (d, *J* = 6.6 Hz, 2H), 4.24 (d, *J* = 6.6 Hz, 2H), 3.81 (s, 2H); 1.97 (t, *J* = 6.6 Hz, 1H), 1.61 (t, *J* = 6.6 Hz, 1H). ¹³C{¹H} NMR (125.8 MHz, CDCl₃, δ): 144.6, 138.0, 129.0, 129.0, 128.5, 127.0, 71.2, 68.0, 36.1. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3192, 3058, 2918, 2866, 1618, 1601, 1492, 1449, 1429, 1361, 1237, 1063, 1022, 996, 933, 888, 838, 724, 693, 656, 601, 492, 457, 423. HRMS (ESI-TOF) (*m/z*): M⁺ Calcd for C₁₁H₁₃IO₂, 303.9960; found, 303.9941. The experimental data were consistent with published values.¹⁹

(*Z*)-2-iodo-3-(4-methylbenzyl)but-2-ene-1,4-diol (**10b**). Compound **10b** was prepared by a similar procedure to that of compound **10c**, using 4-methylbenzylmagnesium chloride (176 mL, 0.85 M THF solution, 150 mmol), 2-butyne-1,4-diol (3.88 g, 45.05 mmol) in THF (25 mL), CuBr·SMe₂ (185 mg, 0.9 mmol, 2 mol %), and I₂ (15.3 g, 60.0 mmol) to yield **10b** as a colorless powder (9.91 g, 31.2 mmol, 69%) on trituration with Et₂O:pentane. TLC: *R_f* (1:1 EtOAc:pentane) 0.56. mp 115–116 °C. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3242, 3045, 3019, 2920, 2874, 1510, 1476, 1493, 1440, 1414, 1316, 1237, 1169, 1072, 1036, 1017, 990, 961, 921, 831, 800, 751, 658, 553, 480, 436; ¹H NMR (500.1 MHz, CDCl₃, δ): 7.11 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 4.49 (d, *J* = 6.5 Hz, 2H), 4.23 (d, *J* = 6.5 Hz, 2H), 3.76 (s, 2H), 2.32 (s, 3H), 2.01 (t, *J* = 6.5 Hz, 1H), 1.66 (t, *J* = 6.5 Hz, 1H). ¹³C{¹H} NMR (125.8 MHz, CDCl₃, δ): 144.8, 136.5, 134.8, 129.7 (2 C), 128.4 (2 C), 106.5, 71.09, 67.67, 35.6, 21.0. HRMS (ESI-TOF) (*m/z*): [M + Na]⁺ Calcd for C₁₂H₁₅IO₂Na, 341.0009; found, 340.9998. The data of the compound match published values.¹⁹

(*Z*)-2-iodo-3-(thien-3-ylmethyl)but-2-ene-1,4-diol (**10e**). Compound **10e** was prepared by a similar procedure to that of compound **10c**, using (thien-3-ylmethyl)magnesium chloride (55 mL, 1.07 M THF solution, 59.2 mmol), 2-butyne-1,4-diol (1.53 g, 17.8 mmol) in THF (14 mL), and I₂ (6.01 g, 23.7 mmol) to yield **10e** (2.00 g, 6.45 mmol, 36%) after column chromatography (2:1 dichloromethane/EtOAc). TLC: *R_f* (2:1 dichloromethane/EtOAc) 0.43. mp 93–94 °C. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3196, 3095, 2922, 2866, 1626, 1488, 1456, 1434, 1407, 1381, 1356, 1294, 1238, 1167, 1143, 1070, 1017, 997, 935, 921, 868, 833, 773, 737, 712, 699, 685, 589, 570, 501, 413; ¹H NMR (500.1 MHz, CDCl₃, δ): 7.29 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.00 (m, 1H), 6.94 (d, *J* = 4.9 Hz, 1H), 4.48 (d, *J* = 6.6 Hz, 2H), 4.28 (d, *J* = 6.6 Hz, 2H), 3.78 (s, 2H), 1.95 (t, *J* = 6.6 Hz, 1H), 1.63 (t, *J* = 6.6 Hz, 1H). ¹³C{¹H} NMR (125.8 MHz, CDCl₃, δ): 144.5, 138.4, 128.0, 126.5, 121.7, 106.4, 71.4, 67.8, 31.1. HRMS (ESI-TOF) (*m/z*): [M + Na]⁺ Calcd for C₉H₁₁IO₂S, 309.9518; found, 309.9534.

Preparation of (E)-2-(4-Methylbenzyl)-3-(thien-2-ylmethyl)but-2-ene-1,4-diol (15) by Heterocoupling of (Z)-2-iodo-3-(4-methylbenzyl)but-2-ene-1,4-diol (10b) with (Thien-2-ylmethyl)zinc(II) Chloride. Lithium chloride (16.1 mg, 0.38 mmol, 1.0 equiv) was dried under vacuum (ca. 1 mbar) at >200 °C until free-flowing (ca. 6 min), and then it was cooled under an atmosphere of argon. Solid **10b** (0.12 g, 0.38 mmol) and THF (0.9 mL) were added. To the stirred solution solid, S-Phos (4.8 mg, 11 μ mol, 3.8 mol %) and Pd(OAc)₂ (2.8 mg, 12 μ mol, 4 mol %) were added forming a dark brown reaction mixture. Promptly, (thien-2-ylmethyl)zinc(II) chloride (0.7 mL of 0.7 M THF solution, 0.5 mmol, 1.5 equiv) was added slowly at rt over ca. 5 min. Once the zinc reagent was added, the reaction color became bright orange. The reaction was monitored by TLC, which indicated that the conversion and chemoselectivity were poorer than those for **12a–12d** (even after the addition of additional Pd(OAc)₂/S-Phos, 2 mol %). After 3 h, the reaction was stopped and quenched with saturated aqueous ammonium chloride solution (10 mL). The mixture was extracted with ethyl acetate (4 $\times$ 5 mL), dried (MgSO₄), filtered, and evaporated giving a yellow solid. Column chromatography (3:2 EtOAc:pentane) gave a colorless solid (**15**) (28.0 mg, 0.10 mmol, 32%). *R_f* (3:2 EtOAc:pentane) 0.48. mp 126–128 °C. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3383, 3317, 2950, 2920, 2853, 1510, 1482, 1433, 1332, 1292, 1252, 1213, 1119, 1076, 1064, 1033, 1014, 995, 927, 879, 848, 837, 805, 762, 748, 687, 607, 527, 497, 478, 450. ¹H NMR (400.1 MHz, CDCl₃, δ): 7.15 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.11 (s, 4H), 6.93 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.86–6.82 (m, 1H), 4.29 (s, 2H), 4.22 (s, 2H), 3.87 (s, 2H), 3.66 (s, 2H), 2.32 (s, 3H), 1.26 (broad, 2H). ¹³C{¹H} NMR (100.6 MHz, CDCl₃, δ): 143.4, 137.4, 136.5, 136.4, 136.0, 129.5 (2C), 128.6 (2C), 127.2, 125.2, 124.0, 61.9 (2C), 35.3, 30.2, 21.1. HRMS (ESI-TOF) (*m/z*): [M + Na]⁺ Calcd for C₁₇H₂₀O₂SNa, 311.1081; found, 311.1076.

(3*E*,8*E*)-4,9-Bis(4-methylbenzyl)-3,8-bis(thien-3-ylmethyl)-1,6-dioxecine-2,7(5*H*,10*H*)-dione (**17**). Compound **17** was prepared serendipitously (but reproducibly) using a modified² procedure of Stahl,²⁶ as in the initial attempts to prepare **13b**. Diol (**12b**) (0.57 g, 1.97 mmol) was dissolved in DMF (11.5 mL) without any O₂ flowing. The following were promptly added to the reaction mixture

sequentially, Cu(MeCN)₄BF₄ (49.7 mg, 0.16 mmol, 8 mol %), TEMPO (24.6 mg, 0.16 mmol, 8 mol %), and finally *N*-methylimidazole (NMI, 25.2 μ L, 25.9 mg, 0.31 mmol, 16 mol %), giving a dark orange/brown solution. The oxygen flow (~5 bubbles per sec) was immediately started. After 30 min, the reaction mixture was a deep green, and TLC analysis (1:1 EtOAc:pentane) showed the consumption of diol (**12b**, *R_f* 0.35) and the formation of a new species. The O₂ flow was stopped, and the reaction was extracted with EtOAc (3 $\times$ 30 mL). The organic layer was washed with 2 M HCl (3 $\times$ 10 mL) and water (3 $\times$ 10 mL). The organic extracts were dried (MgSO₄) and evaporated to yield oily crude materials. These were separated using column chromatography (12:1 pentane:EtOAc) to yield (**17**) (180 mg, 0.32 mmol, 16%) with uncharacterized products. TLC: *R_f* (12:1 pentane:EtOAc) 0.63. ¹H NMR (500 MHz, CDCl₃, δ): 7.29–7.23 (m, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 7.6 Hz, 4H), 7.04 (m, 1H), 7.01 (dd, *J* = 4.9, 1.3 Hz, 2H), 6.93–6.89 (m, 2H), 6.76 (dd, *J* = 4.9, 1.3 Hz, 1H), 4.55 (d, *J* = 7.7 Hz, 4H), 3.82–3.59 (m, 8H), 2.33 (broad, 6H). ¹³C{¹H} NMR (125.8 MHz, CDCl₃, δ): 174.7, 174.6, 160.2, 159.3, 137.9, 137.0, 136.2, 135.6, 134.9, 132.8, 129.7, 129.4, 128.5, 128.4, 128.2, 127.7, 126.9, 126.8, 126.1, 126.0, 122.4, 121.6, 71.3, 33.1, 29.2, 28.1, 24.3, 21.0. HRMS (ESI-TOF) (*m/z*): [M + Na]⁺ Calcd for C₃₄H₃₂NaO₄S₂, 591.1639; found, 591.1657.

Heterocoupling of (10a–10d) with (Thien-3-ylmethyl)zinc(II) Chloride (11) for Nonsymmetric Diols (12a–12d): Representative Example, (E)-2-Benzyl-3-(thien-3-ylmethyl)but-2-ene-1,4-diol (12a). Lithium chloride LiCl (57.2 mg, 1.35 mmol, 1.2 equiv) was dried under vacuum using a heat gun at >200 °C for 5 min, and then it was allowed to cool to rt. under an atmosphere of argon. Diol (**10a**) (0.34 g, 1.13 mmol) and solid S-Phos (12.5 mg, 0.03 mmol, 2.7 mol % equiv) were added, and the solid mixture was left under high vacuum for a few minutes. Thereafter, under an atmosphere of argon, tetrahydrofuran (3.3 mL) was added followed promptly by solid Pd(OAc)₂ (7.6 mg, 33 μ mol, 3 mol %), forming a dark brown-colored solution. (If this color was not formed, active catalyst formation was ensued by recharging with the same amount of ligand and palladium.) Immediately after the formation of the active catalyst, a solution of (thien-3-ylmethyl)zinc(II) chloride (**11**) (4.0 mL of 0.45 M THF solution, 1.8 mmol, 1.6 equiv) was added in one portion. After the addition of the zinc reagent, the color of the reaction mixture changed to clear yellow. The reaction was monitored via TLC. Within 1 h, this showed the conversion to **12a**. The reaction was quenched with saturated aqueous ammonium chloride solution (3 mL) and extracted with ethyl acetate (4 $\times$ 10 mL). The organic layer was washed with saturated aqueous sodium hydrogen carbonate (4 $\times$ 5 mL), and the organic extracts were dried with Na₂SO₄ or MgSO₄. The organic layer was concentrated to yield a tan solid. Column chromatography (3:2 EtOAc:pentane) gave a colorless solid (0.24 g, 0.87 mmol, 77%). TLC: *R_f* 0.45 (3:2 EtOAc:pentane). mp 128–129 °C. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3386, 3328, 3099, 2949, 2916, 2853, 1731, 1601, 1493, 1481, 1452, 1431, 1327, 1127, 1057, 1028, 1011, 992, 942, 855, 828, 786, 757, 729, 700, 632, 583, 493, 434. ¹H NMR (500.1 MHz, CDCl₃, δ): 7.32–7.27 (m, 3H), 7.24–7.19 (m, 3H), 6.98–6.95 (m, 2H), 4.28 (d, *J* = 5.3 Hz, 2H), 4.22 (d, *J* = 5.3 Hz, 2H), 3.71 (s, 2H), 3.70 (s, 2H), 1.25 (t, *J* = 5.3 Hz, 1H), 1.20 (t, *J* = 5.3 Hz, 1H). ¹³C{¹H} NMR (125.6 MHz, CDCl₃, δ): 140.5, 139.9, 136.7, 128.9 (2C), 128.7 (2C), 128.3, 126.5, 126.2, 121.2, 62.2, 61.9, 35.8, 30.8. HRMS (ESI-TOF) (*m/z*): [M + Na]⁺ Calcd for C₁₆H₁₈NaO₂S, 297.0920; found, 297.0918.

(*E*)-2-(4-Methylbenzyl)-3-(thien-3-ylmethyl)but-2-ene-1,4-diol (**12b**). Compound **12b** was prepared by a method analogous to that for **12a**, using (*Z*)-2-iodo-3-(4-methylbenzyl)but-2-ene-1,4-diol (**10a**) (1.00 g, 3.71 mmol) and (thien-3-ylmethyl)zinc(II) chloride (**11**) (7.71 mL, 0.64 M THF solution, 4.71 mmol) to yield **12b** as a colorless powder (0.75 g, 2.60 mmol, 83%) after column chromatography (3:2 EtOAc:pentane). TLC: *R_f* (ethyl acetate) 0.66. Colorless thin needles from hot acetonitrile were cooled to ambient and then 4 °C with a mp 127–129 °C. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3381, 3310, 3101, 2950, 2917, 1509, 1482, 1433, 1383, 1331, 1298, 1205, 1128, 1065, 1011, 992, 942, 926, 880, 855, 829, 806, 783, 760, 722, 699, 627, 523, 491. ¹H NMR (500.1 MHz,

CDCl_3 , δ): 7.28–7.26 (m, 1H), δ 7.12–7.08 (m, 4H), 7.97–6.94 (m, 2H), 4.27 (s, 2H), 4.21 (s, 2H), 3.68 (s, 2H), 3.66 (s, 2H), 2.32 (s, 3H), 1.43 (broad, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.8 MHz CDCl_3 , δ): 140.5, 136.9, 136.6, 136.4, 136.0, 129.5, 128.5, 128.3, 126.2, 121.2, 62.2, 61.9, 35.4, 30.8, 21.1. HRMS (ESI-TOF) (m/z): $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{19}\text{NaO}_2\text{S}$, 311.1076; found, 311.1075. Anal: calcd for $\text{C}_{17}\text{H}_{20}\text{O}_2\text{S}$, C, 70.80; H, 6.99; found, C, 70.61; H, 6.94%.

(E)-2-(4-Isopropylbenzyl)-3-(thien-3-ylmethyl)but-2-ene-1,4-diol (12c). Compound **12c** was prepared by a method analogous to that for **12a**, using (Z)-2-iodo-3-(4-isopropylbenzyl)but-2-ene-1,4-diol (**10c**) (1.50 g, 4.33 mmol) and (thien-3-ylmethyl)zinc(II) chloride (10.0 mL 6.70 mmol, 0.67 M THF solution) to yield **12c** as a colorless powder (1.10 g, 4.48 mmol, 80%) after column chromatography (3:2 EtOAc:pentane). TLC: R_f (3:2 EtOAc:pentane) 0.41. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3389, 3334, 3103, 2956, 2889, 2869, 1511, 1481, 1467, 1432, 1415, 1382, 1333, 1296, 1128, 1064, 1009, 990, 942, 928, 880, 856, 837, 784, 719, 700, 623, 550. ^1H NMR (500.1 MHz, CDCl_3 , δ): 7.28 (dd, $J = 4.8, 3.0$ Hz, 1H), 7.17 (d, $J = 8.0$ Hz, 2H), 7.13 (d, $J = 8.0$ Hz, 2H), 6.97 (m, 2H), 4.27 (d, $J = 5.4$ Hz, 2H), 4.22 (d, $J = 5.4$ Hz, 2H), 3.69 (s, 2H), 3.67 (s, 2H), 2.88 (hept, $J = 7.0$ Hz, 1H), 1.32 (t, $J = 5.4$ Hz, 1H), 1.29 (t, $J = 5.4$ Hz, 1H), 1.24 (d, $J = 7.0$ Hz, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.8 MHz CDCl_3 , δ): 147.1, 140.5, 137.0, 136.8, 136.5, 128.5 (2C), 128.4, 126.9 (2C), 126.1, 121.2, 62.2, 62.0, 35.4, 33.8, 30.8, 24.2 (2C). HRMS (ESI-TOF) (m/z): $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{19}\text{H}_{24}\text{NaO}_2\text{S}$, 339.1389; found, 339.1384.

(E)-2-(4-Methoxybenzyl)-3-(thien-3-ylmethyl)but-2-ene-1,4-diol (12d). Compound **12d** was prepared by a method analogous to that for **12a**, using (Z)-2-iodo-3-(4-methoxybenzyl)but-2-ene-1,4-diol (**10d**) (0.34 g, 1.00 mmol) and (thien-3-ylmethyl)zinc(II) chloride (**11**) (2.30 mL, 0.64 M THF solution 1.50 mmol) to yield **12d** as colorless plates (0.28 g, 0.92 mmol, 92%) after column chromatography (3:2 EtOAc:pentane). R_f (3:2 EtOAc: pentane) 0.46. mp 109–111 °C. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3387, 3324, 3100, 2928, 2834, 1609, 1580, 1508, 1481, 1461, 1432, 1327, 1301, 1247, 1174, 1127, 1062, 1033, 1010, 990, 942, 879, 829, 783, 763, 722, 691, 625, 513. ^1H NMR (500.1 MHz, CDCl_3 , δ): 7.30–7.24 (m, 1H), 7.11 (d, $J = 8.6$ Hz, 2H), 6.94 (m, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 4.27 (s, 2H), 4.19 (s, 2H), 3.78 (s, 3H), 3.68 (s, 2H), 3.63 (s, 2H), overlapped by 1.76 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.8 MHz CDCl_3 , δ): 158.3, 140.4, 137.1, 136.3, 131.6, 129.6 (2 C), 128.3, 126.2, 121.2, 114.3 (2 C), 62.1, 61.8, 55.4, 35.0, 30.9. HRMS (ESI-TOF) (m/z): $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{20}\text{NaO}_3\text{S}$, 327.1025; found, 327.1024.

Homocoupling of (E)-2,3-Diiodobut-2-ene-1,4-diol (20) to the Symmetrical Diol (E)-2,3-Bis(thien-3-ylmethyl)but-2-ene-1,4-diol (21). In a dry Schlenk tube, LiCl (0.12 g, 2.94 mmol, 2.4 equiv) was heated using a heat gun for 5 min under high vacuum at >200 °C until it was free-flowing, and then it was cooled under an argon atmosphere to 25 °C. The diol (**20**) (0.50 g, 1.47 mmol) was added followed by tricyclohexylphosphine (12.3 mg, 44 μmol , 3 mol %), and the solid mixture was held under high vacuum for 30 min. Under an atmosphere of argon, THF (5.6 mL) was added, and the colorless solution was heated to 50 °C. Solid $\text{Pd}(\text{OAc})_2$ (11.6 mg, 55 μmol , 3.5 mol %) was added to the heated mixture to form a dark chocolate-colored mixture. Promptly (thien-2-ylmethyl)zinc(II) chloride (**11**) (0.42 M in THF, 8.8 mL, 3.7 mmol, 2.5 equiv) was added in one portion, forming a clear yellow mixture. After 25 min, the reaction became dark black. TLC analysis (3:2 EtOAc:pentane) showed the starting material was >90% consumed, and new spots appeared due to **21** and $\text{HOCH}_2\text{C}\equiv\text{CCH}_2\text{OH}$. The mixture was cooled to room temperature, quenched with saturated ammonium chloride solution (4 mL), and extracted with EtOAc (3 $\times$ 10 mL). The organic layer was washed immediately with saturated NaHCO_3 (3 $\times$ 4 mL), dried (Na_2SO_4), filtered, and concentrated giving a crude yellow solid. Purification by column chromatography (3:2 EtOAc: pentane) gave **21** as a colorless solid (0.13 g, 0.46 mmol, 31%). [Important note: In our experience, **21** is rather acid sensitive. Concentration of EtOAc its solutions containing even traces of residual NH_4OAc (pK_a 4.8) led to decomposition; washing with hydrogen carbonate avoids this.] TLC (3:2 EtOAc: pentane): R_f 0.35. mp 117–118 °C. IR (diamond-ATR)

$\nu_{\text{max}}/\text{cm}^{-1}$: 3373, 3312, 3099, 2943, 2901, 2850, 1533, 1481, 1433, 1411, 1383, 1337, 1246, 1202, 1127, 1069, 992, 945, 878, 856, 829, 777, 709, 686, 636, 572. ^1H NMR (500.1 MHz, CDCl_3 , δ): 7.28 (dd, $J = 4.8, 3.0$ Hz, 2H), 7.01–6.92 (m, 4H), 4.26 (d, $J = 5.5$ Hz, 4H), 3.68 (s, 4H), 1.24 (t, $J = 5.5$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.6 MHz CDCl_3 , δ): 140.4, 136.5, 128.3, 126.3, 121.2, 62.1, 30.8. HRMS (ESI-TOF) (m/z): $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{14}\text{H}_{16}\text{O}_2\text{S}_2$, 303.0484; found, 303.0476.

2-(4-Methylbenzyl)-3-(thien-2-ylmethyl)fumaraldehyde (16). Diol **15** was oxidized by aerobic oxidation using a modified procedure of Stahl.²⁶ Diol **15** (40.0 mg, 0.138 mmol) was dissolved in DMF (0.8 mL) without any O_2 flowing. The following reagents were promptly added to the mixture sequentially, $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (3.5 mg, 0.01 mmol, 8 mol %), TEMPO (1.7 mg, 0.01 mmol, 8 mol %), and finally *N*-methylimidazole (NMI, 1.76 μL , 1.81 mg, 0.02 mmol, 16 mol %), giving a dark orange/brown solution. Oxygen flow (~5 bubbles per sec) was immediately started. Over 30 min, the reaction became a deep green, and TLC analysis (1:2 EtOAc:pentane) showed consumption of diol **15** (R_f 0.13) and complete formation of **16** (R_f 0.85, yellow, visible to the eye). The O_2 flow was stopped, and the mixture was extracted with EtOAc (3 $\times$ 5 mL). The organic layer was washed with 2 M HCl (3 $\times$ 5 mL) and water (2 $\times$ 5 mL). The organic extracts were dried (MgSO_4) and evaporated to a yellow solid (33.0 mg, 0.15 mmol, 84%). mp 94–96 °C. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3094, 2910, 2872, 2856, 1665 (C = O), 1512, 1446, 1398, 1249, 1130, 1075, 1045, 967, 899, 874, 849, 810, 753, 686, 577, 513, 491, 473. ^1H NMR (400.1 MHz, CDCl_3 , δ): 10.47–10.46 (m, overlapped, 2H), 7.15 (d, $J = 4.4$ Hz, 1H), 7.09 (d, $J = 7.9$ Hz, 2H), 7.03 (d, $J = 7.9$ Hz, 2H), 6.93–6.86 (m, 1H), 6.78 (m, 1H), 4.29 (s, 2H), 4.09 (s, 2H), 2.30 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3 , δ): 193.2, 193.0, 147.7, 146.2, 140.8, 136.6, 134.9, 129.7, 128.3, 127.3, 125.7, 124.7, 28.9, 23.9, 21.1. HRMS (ESI-TOF) (m/z): M^+ Calcd for $\text{C}_{17}\text{H}_{16}\text{O}_2\text{S}$, 284.0866; found, 284.0871.

Preparation of Dialdehydes (13a–13d) by a Modified Swern Oxidation Method: Representative Example, 2-Benzyl-3-(thien-3-ylmethyl)fumaraldehyde (13a). A mixture of dry DMSO (0.25 mL) and CH_2Cl_2 (1.0 mL) was added slowly to oxalyl chloride (0.15 g, 1.20 mmol, 2.5 equiv) in dry CH_2Cl_2 (2.0 mL) at –78 °C, and the mixture was stirred for 30 min at the same temperature. Diol **12a** (132 mg, 0.48 mmol) in dry CH_2Cl_2 (1.2 mL) and DMSO (0.26 mL) was added dropwise over 5 min. The milky mixture was stirred for another 1.5 h. Dry Et_3N (0.37 mL, 2.41 mmol, 5 equiv) was added at –78 °C, and the mixture was allowed to warm to r.t. over 30 min, causing the color to change from milky to yellow. The reaction mixture was concentrated under reduced pressure to provide the crude product. The solid was dissolved in the EtOAc and filtrated to remove trace insoluble compounds. The resultant organic layer was washed with water (10 $\times$ 5 mL) and dried (Na_2SO_4). Concentration at the reduced pressure yielded a yellow solid (100 mg, 0.37 mmol, 77%). mp 100–102 °C. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3329, 3090, 3025, 2940, 2909, 2873, 1755, 1666, 1598, 1495, 1452, 1396, 1231, 1202, 1127, 1075, 1031, 976, 939, 904, 870, 830, 774, 739, 697, 685, 623, 603, 574, 525, 484. ^1H NMR (500.1 MHz, CDCl_3 , δ): 10.49 (s, 1H), 10.46 (s, 1H), 7.33–7.20 (m, 4H), 7.13 (m, 2H), 6.89 (m, 2H), 4.13 (s, 2H), 4.12 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.8 MHz, CDCl_3 , δ): 193.4, 193.3, 147.3, 147.0, 138.4, 138.2, 129.1, 128.4, 127.8, 126.9, 126.6, 121.9, 29.3, 24.4. HRMS (ESI-TOF) (m/z): $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{16}\text{H}_{14}\text{NaO}_2\text{S}$, 293.0607; found, 293.0597.

2-(4-Methylbenzyl)-3-(thien-3-ylmethyl)fumaraldehyde (13b). A mixture of dry DMSO (0.38 mL) and CH_2Cl_2 (1.3 mL) was added slowly to a solution of oxalyl chloride (147 μL , 219 mg, 1.73 mmol, 2.5 equiv) in CH_2Cl_2 (2.5 mL) at –78 °C, and the mixture stirred for 30 min at the same temperature. The diol **12b** (200 mg, 0.69 mmol) in CH_2Cl_2 (1.7 mL) and DMSO (0.4 mL) was added dropwise, and the mixture was stirred for another 1.5 h before the dropwise addition of Et_3N (0.50 mL, 3.46 mmol). The reaction was left to warm to 20 °C for 30 min. The reaction mixture was concentrated under reduced pressure, and the product was purified by flash column chromatography (100% CH_2Cl_2) to yield **13b** (170 mg, 0.60 mmol, 87%) as a yellow solid. TLC: R_f (CH_2Cl_2 100%) 0.75 yellow spot. mp 104–105

°C. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3330, 3093, 2939, 2911, 2875, 2855, 2361, 2091, 1804, 1665, 1511, 1447, 1397, 1202, 1126, 1022, 938, 874, 832, 773, 750, 680, 625, 584, 490, 454, 417. ^1H NMR (400.1 MHz, CDCl_3 , δ): 10.49 (s, 1H), 10.45 (s, 1H), 7.29–7.24 (m, 1H), 7.09 (d, $J = 8.1$ Hz, 2H), 7.02 (d, $J = 8.1$ Hz, 2H), 6.91–6.86 (m, 2H), 4.09 (d, $J = 8.4$ Hz, 4H), 2.30 (s, 3H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (101.6 MHz, CDCl_3 , δ): 193.5, 193.4, 147.5, 146.8, 138.5, 136.6, 135.1, 129.7, 128.3, 127.8, 126.6, 121.8, 28.9, 24.4, 21.1. HRMS (ESI-TOF) (m/z): $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{16}\text{NaO}_2\text{S}$, 307.0763; found, 307.0780.

2-(4-Isopropylbenzyl)-3-(thien-3-ylmethyl)succinaldehyde (13c). Compound 13c was prepared by a method analogous to that for 13a from (E)-2-(4-isopropylbenzyl)-3-(thien-3-ylmethyl)but-2-ene-1,4-diol (12c) (0.25 g, 0.79 mmol). Compound 13c was yielded as a bright yellow solid (0.19 g, 0.61 mmol, 77%). TLC: R_f (100% DCM) 0.73 yellow spot (easily visible to the eye). IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3331, 3091, 2957, 2907, 2767, 1667, 1513, 1465, 1447, 1397, 1192, 1128, 1020, 980, 938, 877, 830, 773, 681, 626, 582, 549, 506. ^1H NMR (500.1 MHz, CDCl_3 , δ): 10.49 (s, 1H), 10.45 (s, 1H), 7.28–7.26 (m, 1H), 7.14 (d, $J = 7.9$ Hz, 2H), 7.05 (d, $J = 7.9$ Hz, 2H), 6.90–6.88 (m, 2H), 4.11 (s, 2H), 4.09 (s, 2H), 2.86 (hept, $J = 6.9$ Hz, 1H), 1.22 (d, $J = 6.9$ Hz, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.8 MHz, CDCl_3 , δ): 193.5, 193.4, 147.6, 147.5, 146.8, 138.5, 135.4, 128.3, 127.8, 127.1, 126.6, 121.9, 33.8, 28.9, 24.4, 24.1. HRMS (ESI-TOF) (m/z): $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{19}\text{H}_{20}\text{O}_2\text{S}$, 312.1178; found, 312.11918.

2-(4-Methoxybenzyl)-3-(thien-3-ylmethyl)fumaraldehyde (13d). Compound 13d was prepared by a method analogous to that for 13a from diol 12d (50 mg, 0.16 mmol). Compound 13d was yielded as a yellow solid (needles on recrystallization from hot isopropanol) (39 mg, 0.13 mmol, 81%). TLC: R_f (EtOAc:pentane, 3:2) 0.84. mp 120–121 °C. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3332, 3091, 2938, 2911, 1751, 1667, 1608, 1582, 1512, 1445, 1397, 1306, 1244, 1179, 1129, 1025, 938, 877, 830, 774, 752, 704, 679, 625, 582, 528, 512, 480, 459. ^1H NMR (500.1 MHz, CDCl_3 , δ): 10.49 (s, 1H), 10.44 (s, 1H), 7.29–7.24 (m, 1H), 7.05 (d, $J = 8.7$ Hz, 2H), 6.90–6.87 (m, 2H), 6.81 (d, $J = 8.7$ Hz, 2H), 4.10 (s, 2H), 4.06 (s, 2H), 3.77 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.8 MHz, CDCl_3 , δ): 193.6, 193.4, 158.6, 147.6, 146.6, 138.5, 130.1, 129.5, 127.7, 126.6, 121.8, 114.5, 55.4, 28.5, 24.4. MS (ESI+): (m/z) 323. HRMS (ESI-TOF) (m/z): $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{16}\text{NaO}_3\text{S}$, 323.0712; found, 323.0721.

2,3-Bis(thien-3-ylmethyl)fumaraldehyde (22). Compound 22 was prepared by a method similar to that for 13a from (E)-2,3-bis(thien-3-ylmethyl)but-2-ene-1,4-diol (21) (50 mg, 0.17 mmol). Compound 22 was yielded as a yellow solid (35 mg, 0.13 mmol, 73%). TLC: R_f (2:1 DCM:pentane) 0.51, crystallized from hot *i*-PrOH on cooling to ambient. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3090, 2976, 2941, 2910, 2873, 1665, 1529, 1446, 1395, 1240, 1194, 1159, 1125, 977, 941, 862, 829, 774, 675, 620, 569, 464, 425. ^1H NMR (500.1 MHz, CDCl_3 , δ): 10.46 (s, 2H), 7.28–7.26 (m, 2H), 6.89–6.88 (m, 4H), 4.11 (s, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.8 MHz, CDCl_3 , δ): 193.2, 146.8, 138.4, 127.7, 126.7, 121.9, 24.4. HRMS (ESI-TOF) (m/z): $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{14}\text{H}_{13}\text{O}_2\text{S}_2$, 277.0351; found, 277.0354.

Cyclisation to Anthra[2,3-*b*]thiophene Using TiCl_4 : Representative Example, Anthra[2,3-*b*]thiophene (1a). Dialdehyde 13a (219 mg, 0.18 mmol) was dissolved in dry dichloroethane (5.4 mL) to form a yellow solution. The solution was cooled to 0 °C, and TiCl_4 (CAUTION! Corrosive, toxic) (0.2 mL, 1.8 mmol, 2.1 equiv) was added over 1 min at 0 °C, forming a brown suspension of the TiCl_4 -aldehyde adduct. The reaction mixture was stirred for 30 min at 0 °C and at r.t. for 4 h. During this time, the reaction mixture became dark brown and viscous. TLC (9:1:1 pentane:EtOAc: CH_2Cl_2) showed the consumption of the starting material 13a, while a shiny yellow precipitate was formed. The reaction was cooled to 0 °C, and 1:1 acetone:MeOH (5 mL) was slowly added forming an immediate yellow precipitation of 1a. The crude mixture was filtered off onto Whatman glass microfiber GF/A on a 47 mm 3-piece (Hartley) filter, washed with 1:1 acetone:MeOH (3 $\times$ 5 mL), and sucked dry under a cushion of argon to provide a yellow powder (138 mg, 0.59 mmol, 73%). The crude material could be further purified by vacuum

sublimation (230–240 °C, 0.02 mbar) (Figure S1) to give shining bright yellow powders. mp > 250 °C. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3440, 2918, 2849, 1400, 1284, 1018, 955, 899, 825, 739, 727, 661, 470, 457. ^1H NMR (500.1 MHz, CDCl_3 , δ): 8.61 (s, 1H), 8.55 (s, 1H), 8.53 (s, 1H), 8.51 (s, 1H), 8.04–8.00 (m, 2H), δ 7.50–7.40 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.8 MHz, CDCl_3 , δ): 139.3, 138.1, 131.5, 131.3, 129.8, 129.7, 128.9, 128.3, 128.2, 126.7, 125.3, 125.1, 123.6, 121.9, 120.7. HRMS (ESI-TOF) (m/z): $[\text{M}^+]$ Calcd for $\text{C}_{16}\text{H}_{10}\text{S}$, 234.0503; found, 234.0500. UV/vis (CH_2Cl_2 , 10^{-4} M) $\lambda_{\text{max}}/\text{nm}$: 435 (log ϵ 4.1), 410 (log ϵ 4.1), 389 (log ϵ 3.8), 368 (log ϵ 3.5). The data of this compound match the published literature values.^{7,17,11}

7-Methylantra[2,3-*b*]thiophene (1b). Compound 1b was prepared by a method equivalent to that for 1a, using 2-(4-methylbenzyl)-3-(thien-3-ylmethyl)fumaraldehyde (13b) (200 mg, 0.7 mmol) and TiCl_4 (0.15 mL, 1.46 mmol, 2.1 equiv) in 1,2-dichloroethane (4.5 mL) at 0 °C for 1 h, warming to r.t., and then stirring for 4 h. Compound 1b was yielded as a brilliant yellow powder (145 mg, 0.58 mmol, 84%). Sublimation (200–210 °C, 0.05 mbar) afforded a brilliant yellow powder. mp > 250 °C. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3065, 3010, 2910, 2851, 1704, 1632, 1469, 1402, 1375, 1287, 1270, 1128, 1080, 1005, 961, 901, 827, 809, 792, 745, 723, 674, 658, 568, 469, 457. ^1H NMR (500.1 MHz, CDCl_3 , δ): 8.59–8.46 (m, 4H), 7.93 (d, $J = 8.7$ Hz, 1H), 7.76 (s, 1H), 7.47 (d, $J = 5.6$ Hz, 1H), 7.40 (d, $J = 5.6$ Hz, 1H), 7.30–7.27 (m, 1H), 2.55 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.8 MHz, CDCl_3 , δ): 139.2, 137.7, 134.7, 131.6, 130.3, 129.9, 129.4, 128.8, 128.3, 128.1, 126.3, 125.5, 125.0, 123.6, 121.8, 120.7, 22.2. UV/vis (CH_2Cl_2 , 10^{-4} M) $\lambda_{\text{max}}/\text{nm}$: 437 (log ϵ 3.6), 412 (log ϵ 3.7), 390 (log ϵ 3.4), 360 (log ϵ 3.1), 343 (log ϵ 3.0). HRMS (ESI-TOF) (m/z): M^+ Calcd for $\text{C}_{17}\text{H}_{12}\text{S}$, 248.0654; found, 248.0650. Anal: Calcd for $\text{C}_{17}\text{H}_{12}\text{S}$ C, 82.22; H, 4.87; found, C, 82.30; H, 4.90%.

7-Isopropylantra[2,3-*b*]thiophene (1c). Compound 1c was prepared by a method analogous to that for 1a, using 2-(4-isopropylbenzyl)-3-(thien-3-ylmethyl)succinaldehyde (13c) (150 mg, 0.48 mmol) and TiCl_4 (0.1 mL, 1.0 mmol, 2.1 equiv) in 1,2-dichloroethane (3.1 mL) at 0 °C for 1.5 h and then warming to 22 °C for 10 min to yield 1c as a shiny yellow powder (130 mg, 0.47 mmol, > 99%). Sublimation (210–220 °C, 0.01 mbar) afforded a brilliant yellow powder. mp > 250 °C. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3070, 3015, 2955, 2926, 2900, 2863, 2100, 1631, 1510, 1470, 1380, 1309, 1284, 1182, 1128, 1081, 1039, 1016, 948, 904, 826, 803, 747, 726, 661, 620, 548, 470, 459. ^1H NMR (500.1 MHz, CDCl_3 , δ): 8.53 (s, 1H), 8.52 (1H), 8.49–8.47 (m, 2H), 7.96 (d, $J = 8.9$ Hz, 1H), 7.78 (s, 1H), 7.47 (d, $J = 5.7$ Hz, 1H), 7.40 (d, $J = 5.7$ Hz, 1H), 7.37 (dd, $J = 8.8$, 1.7 Hz, 1H), 3.10 (hept, $J = 7.0$ Hz, 1H), 1.39 (d, $J = 7.0$ Hz, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.8 MHz, CDCl_3 , δ): 145.3, 139.2, 137.7, 131.6, 130.7, 129.9, 129.5, 128.7, 128.3, 126.1, 126.0, 125.0, 123.6, 123.4, 121.8, 120.7, 34.5, 23.7. UV/vis (CH_2Cl_2 , 10^{-4} M) $\lambda_{\text{max}}/\text{nm}$: 436 (log ϵ 3.5), 410 (log ϵ 3.7), 390 (log ϵ 3.6), 362 (log ϵ 3.4), 343 (log ϵ 3.4). HRMS (ESI-TOF) (m/z): $[\text{M}^+]$ Calcd for $\text{C}_{19}\text{H}_{16}\text{S}$, 276.0967; found, 276.0976; Anal: Calcd for $\text{C}_{19}\text{H}_{16}\text{S}$ C, 82.57; H, 5.84; found, C, 82.26; H, 5.96%.

7-Methoxyantra[2,3-*b*]thiophene (1d). Compound 1d was prepared by a method analogous to that for 1a, using 2-(4-methoxybenzyl)-3-(thien-3-ylmethyl)succinaldehyde (13d) (143 mg, 0.48 mmol) and TiCl_4 (0.1 mL, 1.05 mmol, 2.2 equiv) in 1,2-dichloroethane (4.2 mL) at 0 °C for 2 h and then warming to 22 °C for 1 h to yield 1d as a shiny yellow powder (104 mg, 0.39 mmol, 83%). Sublimation (210–220 °C, 0.02 mbar) afforded a brilliant yellow powder. mp > 250 °C. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3094, 3062, 3005, 2965, 2937, 2836, 1800, 1630, 1585, 1473, 1417, 1346, 1285, 1230, 1218, 1172, 1026, 951, 897, 816, 803, 744, 723, 675, 663, 539, 470, 456. ^1H NMR (500.1 MHz, CDCl_3 , δ): 8.50 (s, 1H), 8.44 (m, 3H), 7.91 (d, $J = 9.2$ Hz, 1H), 7.48 (d, $J = 5.6$ Hz, 1H), 7.40 (d, $J = 5.6$ Hz, 1H), 7.19 (m, 1H), 7.14 (dd, $J = 9.2$, 2.5 Hz, 1H), 3.98 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.8 MHz, CDCl_3 , δ): 157.0, 139.4, 137.1132.1, 130.2, 130, 128.9, 128.6, 128.4, 125.4, 124.3, 123.6, 121.2, 120.9, 120.8, 103.2, 55.4. UV/vis (CH_2Cl_2 , 10^{-4} M) $\lambda_{\text{max}}/\text{nm}$: 443 (log ϵ 3.4), 418 (log ϵ 3.4), 395 (log ϵ 3.2), 378 (log ϵ 3.2), 358 (log ϵ 3.1), 340 (log ϵ 2.9). HRMS (ESI-TOF) (m/z): M^+ Calcd for

C₁₇H₁₂OS, 264.0603; found, 264.0611. Anal: Calcd for C₁₇H₁₂OS C, 77.24; H, 4.58; found, C, 77.27; H, 4.49%.

Cyclisation Using TiCl₄: Representative Example of Byproduct Formation, 6-(4-Methylbenzyl)benzo[*b*]thiophene-5-carbaldehyde. To a solution of 2-(4-methylbenzyl)-3-(thien-3-ylmethyl)-fumaraldehyde (**13b**) (100 mg, 0.35 mmol) in dry dichloroethane (2.3 mL) under argon, titanium tetrachloride (81 μ L, 0.74 mmol, 2.1 equiv) was added slowly at 0 °C. The mixture was stirred at 0 °C for 45 min, during which time it became dark brown-colored and viscous. TLC (10:1:1 pentane:EtOAc:DCM) indicated the complete consumption of the starting material (**13b**) (*R_f* 0.41). The reaction was stopped, and at 0 °C, 1:1 acetone:MeOH (5 mL) was slowly added causing immediate yellow precipitation. The mixture was filtered off onto a Whatman glass microfiber GF/A on a 47 mm 3-piece (Hartley) filter and washed with 1:1 acetone:MeOH, the half closure product was eluted with the 1:1 acetone:MeOH wash. The filtered yellow powder precipitate was 7-methylanthra[2,3-*b*]thiophene (**1b**) which accounted for 57% of the mass balance. The organic wash solution was concentrated by high vacuum and purified by preparative TLC (8:1:1 pentane:EtOAc:DCM) to yield (6-(4-methylbenzyl)-benzo[*b*]thiophene-5-carbaldehyde) (30.0 mg, 0.11 mmol, 32%) as a yellow oil. *R_f* (9:1:1 pentane:DCM:EtOAc) 0.80. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3099, 3018, 2917, 2854, 2724, 2093, 1760, 1683, 1594, 1539, 1512, 1492, 1450, 1404, 1386, 1314, 1227, 1183, 1155, 1125, 1077, 1006, 902, 878, 833, 794, 761, 748, 725, 699, 645, 620, 577, 535, 490, 469, 429. ¹H NMR (500.1 MHz, CDCl₃, δ): 10.29 (s, 1H), 8.31 (s, 1H), 7.70 (s, 1H), 7.48 (d, *J* = 5.5 Hz, 1H), 7.43 (d, *J* = 5.5 Hz, 1H), δ 7.10 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 4.52 (s, 2H), 2.32 (s, 3H). ¹³C{¹H} NMR (125.8 MHz, CDCl₃, δ): 192.4, 145.4, 138.3, 138.2, 137.4, 135.9, 131.3, 129.4, 128.9, 128.8, 127.6, 125.0, 124.5, 38.2, 21.1. HRMS (ESI-TOF) (*m/z*): [M + Na]⁺ Calcd for C₁₇H₁₄NaOS, 289.0658; found, 289.0662.

Naphtho[2,3-*b*:6,7-*b'*]dithiophene (2). The yellow solution of dialdehyde (**18**) (200 mg, 0.72 mmol) in anhydrous dichloroethane (4.5 mL) was cooled to −15 °C and treated under argon with neat TiCl₄ (0.15 mL, 1.6 mmol, 2.2 equiv) over ca. 1 min at −15 °C (CARE! TiCl₄ is a corrosive reactive Lewis acid; quicker additions may cause an uncontrolled reaction). The dark brown thick suspension was allowed to stir at −15 °C for 1 h. After this time, TLC (10:1:1 pentane:EtOAc:DCM) showed that the starting material was consumed. The reaction was stopped, and 1:1 acetone:MeOH (2 mL) was slowly added at −15 °C (CARE! vigorous reaction), leading to a pale yellow precipitate of the target product (**2**). This was filtered off onto a Whatman glass microfiber GF/A using a 47 mm 3-piece (Hartley) filter, washed with 1:1 acetone:MeOH (1 $\times$ 3 mL), and sucked dry under a cushion of argon to provide **2** as a pale yellow powder (140 mg, 0.85 mmol, 81%). This material was pure enough to use directly in further chemistry, but could be further purified by vacuum sublimation (245–250 °C, 0.01 mbar, Figure S2). mp > 250 °C. IR (diamond-ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3094, 3065, 1705, 1505, 1439, 1382, 1311, 1258, 1139, 1078, 1014, 897, 826, 743, 675, 550, 501, 470, 457. ¹H NMR (500.1 MHz, CDCl₃, δ): 8.51 (s, 2H), 8.40 (s, 2H), 7.50 (d, *J* = 5.6 Hz, 2H), 7.43 (d, *J* = 5.6 Hz, 2H). ¹³C{¹H} NMR (125.8 MHz, CDCl₃, δ): 138.9, 137.6, 129.0, 128.5, 123.6, 121.0, 120.9. UV/vis (CH₂Cl₂, 10^{−4} M) $\lambda_{\text{max}}/\text{nm}$: 402 (log ϵ 3.8), 380 (log ϵ 3.7), 360 (log ϵ 3.3), 431 (log ϵ 3.2). HRMS (ESI-TOF) (*m/z*): M⁺ Calcd for C₁₄H₈S₂, 240.0061; found, 240.0054. The data of this compound match the published literature values.⁹

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01770.

Sublimation setup and ¹H, ¹³C{¹H} NMR, and UV–vis spectra (PDF)

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Notes

The authors declare no competing financial interest.

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Efficient synthesis of 2,5-dicarbonyl derivatives of 3,4-ethylenedithiophene (EDTT) via addition-elimination reaction

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ABSTRACT

Derivatives of 3,4-ethylenedithiophene (EDTT) are reported starting from tetrabromothiophene. Selective 2,5-dilithiation followed by reaction with a range of aldehydes gives diols as mixtures of diastereomers. Only the 2 and 5 positions in thiophene react leaving the 3,4-bromides for further elaboration. The diols are oxidised to their corresponding diketones using activated MnO₂. Reaction with 1,2-ethanedithiol, by addition-elimination, provides access to novel monomers for the preparation of conjugated copolymers of 3,4-ethylenedithiophene (EDTT). A range of these monomers can be attained by applying the synthesis of a series of ketones applicable to further synthesis of π -extended thiophene-based organic semiconductors. Finally, this new route was compared to 3,4-ethylenedioxythiophene (EDOT) dialdehyde derivatives synthesised by an alternative to literature chemistry.

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1. Introduction

From their initial mainstream uptake in the early 1980s oligothiophenes have risen to become one of the most privileged structures in the organic semi-conducting materials area.^{1,2} By appropriate choice of thiophene substituents and microstructure (e.g. degree of oligomerisation, connectivity, use of additives, etc.) the resultant materials' (opto)electrical properties can be modulated with a high degree of precision. This ability to tune thiophene-based materials for a specific application has led to their widespread use in organic photovoltaics (OPV),³ organic field effect transistors (OFET),⁴ sensors⁵ and particularly in electrochromic/electroluminescent (OLED)⁶ applications. Such 'modular-materials' approaches have created an insatiable appetite for new thiophene sub-units from materials chemists for their inclusion into oligo(poly)thiophene structures as evidenced by the thousands of papers that have appeared in this area in the last 10 years. In particular, derivatives of 3,4-ethylenedioxythiophene (EDOT) **1** have proved popular targets as this monomer is easily polymerised to PEDOT-based polymers **3**⁷ whose formulation with polymer supported sulfonates (PEDOT-PSS) now forms the backbone of

many transparent electrode technologies. Recently, new thermoelectric (TE) applications for PEDOT-based materials have emerged,⁸ potentially allowing direct conversion of waste heat into electrical power. For optimal TE devices the use of bulk, rather than thin film, configurations would be preferred (to maximise power-from-heat recovery). Although the low band gap of PEDOT-PSS (1.6 eV) favours high electrical conductivity⁹ (vital for TE applications) the physical properties of current PEDOT-PSS co-polymers (solubility, mp) are less favourable for fabrication of bulk (mm) rather than thin film (~100 nm) devices. We considered the possibility that derivatives of the sulfur analogue of EDOT, that is EDTT **2**, might prove of utility in seeking more processible entities. Both EDTT itself and PEDTT are known versatile components in organic materials chemistry.¹⁰ Although the band gap of PEDTT **4** is greater (2.2 eV) than PEDOT, building in functionality to allow the creation of vinyligous linkages at the 2,5-positions of EDTT **2** should allow band gap reduction, as similar synergies have been noted in related structures.¹¹ The positioning of suitable groups to promote solubility and processability of bulk samples is also desirable.

Consequently, two main points are investigated in this paper. Firstly, the synthesis of new polymer precursors based on EDTT **2** that might have lower band gap potentials (essential for organic materials applications) even if these are based on PEDTT-like structures. Secondly, the potential structure of the new polymers should allow for the improved solubility characteristics required for

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many applications. Two general strategies are employed here in to target monomers for new polymers having small HOMO–LUMO energy differences and good solubility in the different solvents. The first involves increasing the conjugation of polymers by inserting an alkenyl unit (C=C) into the structure of the polymers, to attain a lower band gap. The second strategy involves strategic placement of alkyl groups whereby the side chain will increase the polymer solubility and thus improve its processability (see Scheme 1).

2. Results and discussion

2.1. Synthetic routes to derivatives of EDTT

Our initial study focused on methods to quickly and reliably attain 2,5-derivatives of 3,4-ethylenedithiophene (EDTT) **2** starting from the readily available crystalline tetrabromothiophene **5** (Scheme 2).

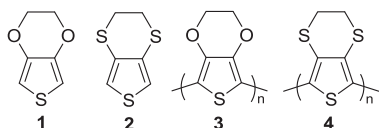
Tetrabromothiophene **5** is easily prepared on large scales by bromination of thiophene in 73% yield, the HBr by-product is conveniently quenched by collecting the off-gas into a suitable water trap. The activated 2,5 positions of **5** are cleanly exchanged with *n*BuLi at -78°C . While rearrangements (the so called “halogen dance”¹²) can take place at higher temperatures, reactive electrophiles are expected to intercept the dilithiated intermediate cleanly. Relatively few investigations have employed this strategy but examples with: chlorotrimethylsilane,¹³ a limited number of aldehydes¹⁴ and acyl chlorides¹⁵ are known. However, the reported yields can be poor in such procedures.

From a practical perspective, addition of the aldehyde at -78°C followed by warming to -20°C affords the maximum yield of **6a–e** (40–82%) by minimising organolithium rearrangement. Compounds **6a–e** are attained as a diastereomeric mixture but the *syn* and *anti* diastereomers could be separated by careful column chromatography. Each of the diastereomeric compounds **6a–e** could be converted into the corresponding ketones **7a–e** using activated MnO_2 , in refluxing dichloromethane. Simple overnight reaction is required to attain complete conversion. Ketones **8** are easily isolated by column chromatography as they appear as bright yellow bands. The resulting micro-crystalline yellow solids show spectra in accord with the proposed formulation. The presence of two keto functions allows potentially many condensation polymers to be accessed related, in part, to EDTT **2** and PEDTT **4**.

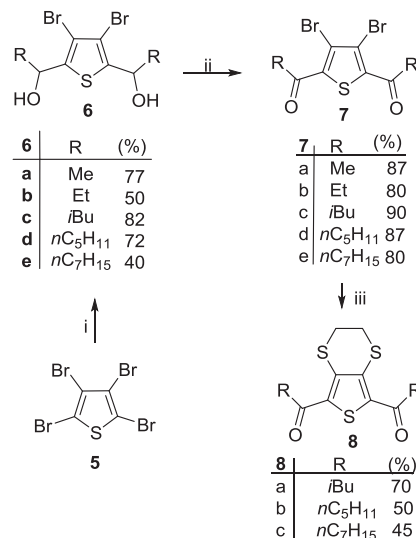
For comparison, the closest literature method for the synthesis of EDTT **2** we could identify is shown in Scheme 3.¹⁶ This approach requires two steps from **9** to add the *bis*-thioether in 86% overall yield. In our approach (Scheme 2), compounds **8a–c** require only one step to install the same thioether. By the reaction of 1,2-ethanedithiol with compounds **7a–c** (in DMF and over 2 days in the presence of Na_2CO_3) more modest yields of 71, 50 and 45% are attained for **8a–c** respectively. For further comparison, the parent **2**, and its *S,O*-analogue, can be also prepared from **9** by the chemistry of Roncali.¹⁷

2.2. Synthetic routes to derivatives of EDOT

In the last few years 3,4-ethylenedioxythiophene (EDOT) **1** and



Scheme 1. The structures of EDOT **1** and EDTT **2** and their derived polymers PEDOT **3** and PEDTT **4**.



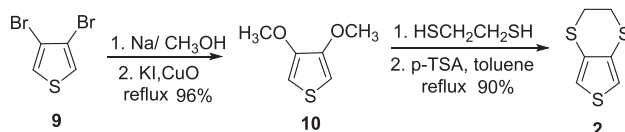
Scheme 2. Synthetic route to ketothiophenes. Reagents and conditions: (i) THF/*n*BuLi, RCHO, -78 to -20°C , 3 h; (ii), MnO_2 (10 equiv.), CH_2Cl_2 , 40°C , 16 h; (iii) 1,2-ethanedithiol (2.2 equiv.), DMF, Na_2CO_3 , 16 h, r.t.

its derivatives have become very important commercial compounds for the preparation of new organic materials.^{7,18} However, most commercial routes to EDOT use $\text{S}(\text{CH}_2\text{CO}_2\text{Me})_2$ and rely on late stage (wasteful) decarboxylation of the ester units. We wondered if a nitrile group was used instead if this could provide access to 2,5-disubstituted aldehydes closely related to our diketo-EDTT species **8**. This new route to derivatives of EDOT has been investigated as shown in Scheme 4.

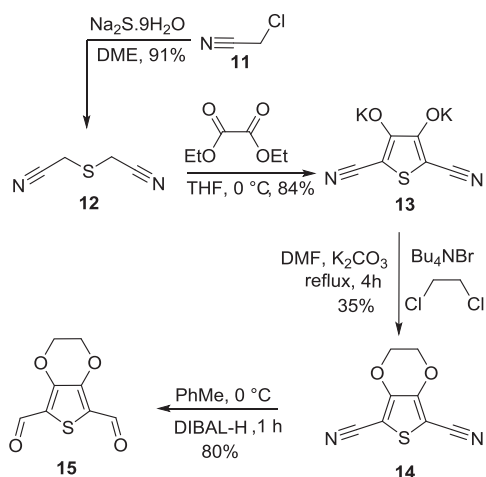
The intermediate **13** is prepared in two steps, the first uses the ultra-cheap starting material $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ for alkylation with chloroacetonitrile **11** in DME to yield compound **12** near quantitatively and in excellent purity which allows its use without purification. Subsequent reaction of **12** and diethyl oxalate prepares the potassium salt **13**, which is also used directly without further purification, to access the dinitrile **14** in modest yield. However, **14** is easily isolated analytically pure after a simple filtration through a silica plug. Finally, **14** was converted to the corresponding aldehyde **15** by its treatment with DIBAL-H at 0°C in anhydrous toluene. Compound **15** is already recognised as an important intermediate in the synthesis of thiophene-based semiconductor polymers.^{19,20}

3. Conclusions

We have successfully found a new route to homologs of 3,4-ethylenedithiophene (EDTT) **2** having ketone functionalities at the 2,5-positions. From tetrabromothiophene **5**, monomers **8a–c** were obtained in three steps. In addition, the monomers **8a–c** are attractive species for the future synthesis of many thiophene-based semiconductor polymers. Additionally, we have reported a new route for the synthesis of the 2,5-diformyl derivative of 3,4-ethylenedioxythiophene (EDOT), the key intermediate **14** is obtained using ultra-cheap $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ in just three steps. Finally,



Scheme 3. One comparative route for EDTT **2**.¹⁶



Scheme 4. Synthetic route for the derivatives of EDOT.

nitrile to formyl conversion proceeds cleanly in near quantitative yield.

4. Experimental

General. All reagents and solvents were purchased from Sigma-Aldrich and were used as supplied unless otherwise stated. Tetrahydrofuran was freshly distilled under argon from sodium/benzophenone. Aldehydes were distilled before use. Evaporation of the solvents was completed by rotary evaporation under reduced pressure. All temperatures refer to those of the cooling and heating baths used. Cooling of the reactions was achieved using a Haake DC50-K75 refrigerated circulator. Thin layer chromatography was performed on foil-backed plates plated with Merck Silica gel 60 F₂₅₄. The plates were visualised using ultraviolet light and basic aqueous KMnO₄. Liquid chromatography was carried out using flash column with specific solvent systems. All proton spectra were referenced to CDCl₃ (δ = 7.27 ppm) or acetone-*d*₆ (δ = 2.05 ppm) as an internal standard. All ¹³C NMR samples were proton-decoupled and referenced to CDCl₃ (δ = 77.0 ppm), acetone-*d*₆ (δ = 29.9 ppm) or DMSO-*d*₆ (δ = 39.5 ppm). Coupling constants (*J*) are quoted in Hertz. Infrared spectra were recorded with a Varian FTS-7000 FT-IR spectrometer using (ATR) operating at room temperature. Mass spectrometry was performed using a Bruker MicroTOF or VG Micromass AutoSpec spectrometers using electrospray (ESI), electron impact (EI) ionization modes; theoretical HRMS molecular weights were determined by these instrument's software. The starting materials tetrabromothiophene **5**, 2,2'-thiodiacetonitrile **12** and activated MnO₂ were prepared by modifications of literature procedures but are described here for clarity. Activated MnO₂ was prepared by a literature method.²¹

4.1. Tetrabromothiophene (**5**)

Compound **5** was prepared by modification of a literature methods.²² Thiophene (10.6 g, 0.127 mol) dissolved in chloroform (8 mL) was treated with a solution of bromine (24 mL, 0.46 mol) in chloroform (8 mL) that was added dropwise over 50 min at 0 °C. The resulting dark mixture was stirred overnight at room temperature, then additional bromine (9.0 mL, 0.17 mol) was then added and the mixture refluxed (70 °C, 57 h). After the reaction had cooled to room temperature, saturated potassium hydroxide solution (100 mL) was added over a 10-min period and the mixture refluxed again (105 °C, 18 h). The reaction was stopped and allowed to cool to room temperature. The 2,3,4,5-tetrabromothiophene **5** was extracted with

dichloromethane, and dried over MgSO₄, and solvent removed. The crude compound was attained as analytically pure colourless crystalline needles (39.6 g, 99.0 mmol, 78%); m.p. 114–115 °C (lit.²² 116–118 °C); ¹³C NMR (100 MHz, CDCl₃) δ _C 117.1, 110.4; MS (EI): *m/z* 400 (M⁺), found 395.6467 C₄SBr₄ requires 395.6448 (⁷⁹Br). These properties were in accord with the literature.²²

4.2. General preparation of the diols (**6**), representative procedure, 1,1'-(3,4-dibromothiophene-2,5-diyl)bis(1-ethanol) (**6a**)

To a solution of tetrabromothiophene **5** (1.10 g, 2.75 mmol) in dry THF (9 mL) under argon, *n*BuLi (3.77 mL, 1.5 M in hexane, 5.66 mmol) was added dropwise at -78 °C. Excess acetaldehyde (0.5 mL) was added at -78 °C. The temperature of the mixture was allowed to warm slowly during 2 h from (-78 to -25 °C). The reaction was quenched with water (8 mL), extracted with EtOAc, dried (MgSO₄) and evaporated to a brown oil. Flash column chromatography (7:3 pentane:EtOAc) yielded a colourless solid (0.696 g, 77%) as a mixture of diastereomers (1:1); *R*_f values 0.37, 0.44 (7:3 pentane:EtOAc); the m.p. for the mixture of diastereomers is 96–110 °C; ¹H NMR (400 MHz, acetone-*d*₆) δ _H 5.16–5.10 (m, 2H, CH₂CH), 4.89–4.88 (m, 2H, OH), 1.46–1.44 (m, 6H, CHCH₃); ¹³C NMR (100 MHz, acetone-*d*₆) δ _C 146.0, 107.9, 66.9, 24.8; IR(ATR) (cm⁻¹) ν _{max} 3285, 2974, 2925, 1436, 1397, 1368, 1329, 1273, 1177, 1088, 1061, 983, 885, 861, 764; MS (ESI): found 329.8747, calcd. for C₈H₁₀Br₂O₂S 329.8748 (⁷⁹Br).

4.3. 1,1'-(3,4-dibromothiophene-2,5-diyl)bis(1-propanol) (**6b**)

Using tetrabromothiophene **5** (0.50 g, 1.25 mmol) in dry THF (3.2 mL) under argon, *n*BuLi (1.8 mL, 1.5 M in hexane, 2.75 mmol) was added dropwise at -78 °C. Then excess propanal (0.27 mL, 3.75 mmol) was added at -78 °C. The temperature of the mixture was warmed slowly during 3 h from (-78 to -65 °C). The reaction was quenched with water (5 mL) extracted with EtOAc, dried (MgSO₄), and evaporated to a brown crude product purified by flash column chromatography (8.5:1.5 light petroleum:EtOAc) yielding a yellow oil (0.215 g, 50%) as mixture of diastereomers (2:1); *R*_f values 0.10, 0.07 (17:3 light petroleum:EtOAc); ¹H NMR (400 MHz, CDCl₃) δ _H 4.89 (m, 2H, CH), 1.73–1.65 (m, 4H, CH₂), 1.00 (t, *J* = 7.3 Hz, 6H), the OH signals were not observed due to exchange; ¹³C NMR (100 MHz, CDCl₃) δ _C 143.9, 108.7, 71.6, 32.0, 10.4; IR(ATR) (cm⁻¹) ν _{max} 3313, 2964, 2930, 2874, 1458, 1378, 1319, 1319, 1171, 1089, 1041, 971, 868; MS (ESI): found 355.9092, calcd. for C₁₀H₁₄Br₂O₂S 355.9075.

4.4. 1,1'-(3,4-dibromothiophene-2,5-diyl)bis(3-methylbutanol) (**6c**)

Preparation from tetrabromothiophene **5** (2.00 g, 5.00 mmol, *n*BuLi (6.9 mL, 1.6 M in hexane, 11.0 mmol) and methylbutyraldehyde (1.29 g, 15.0 mmol). The brown crude product was purified by flash column chromatography (85:15 light petroleum:EtOAc) to yield a pale yellow solid as a (2:1) mixture of diastereomers (1.70 g, 82%); *R*_f values 0.31, 0.15 (85:15 light petroleum:EtOAc); m.p. 112–113 °C; ¹H NMR (400 MHz, CDCl₃) δ _H 5.14–5.13 (m, 2H, 2 × CHOH), 2.22 (br, 2H, 2 × OH), 1.82–1.57 (m, 6H, 2 × CH₂, 2 × CH); 1.04–0.96 (m, 12H, 4 × CH₃); ¹³C NMR (100 MHz, CDCl₃) δ _C 143.1, 110.0, 68.8, 47.2, 24.9, 23.3, 22.1; IR(ATR) (cm⁻¹) ν _{max} 3220, 2955, 2923, 2868, 1743, 1467, 1384, 1367, 1236, 1180, 1108, 1067, 846, 767, 679, 595; MS (ESI): found 413.9688, calcd. for C₁₄H₂₂Br₂O₂S 413.9687 (⁷⁹Br).

4.5. 1,1'-(3,4-dibromothiophene-2,5-diyl)bis(1-hexanol) (**6d**)

Preparation from tetrabromothiophene **5** (1.00 g, 2.50 mmol, *n*BuLi (3.7 mL, 1.5 M in hexane, 5.50 mmol) and *n*-hexanal (0.9 mL,

ca. 0.75 g, 7.5 mmol). The brown crude product was purified by flash column chromatography (85:15 light petroleum:EtOAc) to yield of pale yellow solid as (1:1) mixture of diastereomers (0.80 g, 72%) as colourless solid; R_f 0.66, 0.37 (6:1 pentane:EtOAc); m.p. 82–84 °C; ^1H NMR (400 MHz, CDCl_3) δ_{H} 5.24 (s, 2H, 2 $\times$ OH), 4.93 (m, 2H, 2 $\times$ CH), 1.64–1.36 (m, 16H, 2 $\times$ $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 0.92 (t, J = 7.3 Hz, 6H, 2 $\times$ CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 144.2, 108.0, 70.1, 38.7, 31.5, 25.8, 22.8, 14.2; IR(ATR) (cm^{-1}) ν_{max} 3296, 2954, 2921, 2851, 1642, 1464, 1367, 1316, 1248, 1182, 1164, 1058, 971, 927, 769; MS (ESI): found 442.0007, calcd. for $\text{C}_{16}\text{H}_{26}\text{Br}_2\text{O}_2\text{S}$ (^{79}Br) 442.0000.

4.6. 1,1'-(3,4-dibromothiophene-2,5-diyl)bis(octan-1-ol) (**6e**)

Preparation from tetrabromothiophene **5** (3.00 g, 7.50 mmol, $n\text{BuLi}$ (11.0 mL, 1.5 M in hexane, 16.51 mmol) and n -octanal (2.40 g, 18.76 mmol). The yellow crude product was purified by flash column chromatography (9:1 light petroleum:EtOAc) to yield a yellow oil as a (2:1) mixture of diastereomers (1.46 g, 40%); R_f values 0.30, 0.20 (9:1 light petroleum:EtOAc); ^1H NMR (400 MHz, CDCl_3) δ_{H} 5.06–5.02 (m, 2H, 2 $\times$ CH), 1.83–1.77 (m, 4H, 2 $\times$ CH_2), 1.31 (m, 20H, 2 $\times$ $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 0.88 (t, J = 6.9 Hz, 6H, 2 $\times$ CH_3), the OH signals $\sim\delta_{\text{H}}$ 2.4 were often not clearly observed due to exchange; ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 142.8, 110.1, 70.6, 38.1, 31.9, 29.4, 29.3, 25.7, 22.8, 14.2; IR(ATR) (cm^{-1}) ν_{max} 3331, 2954, 2922, 2853, 1463, 1315, 1168, 1050, 1019, 907, 765; MS (ESI): found 496.0619, calcd. for $\text{C}_{20}\text{H}_{34}\text{Br}_2\text{O}_2\text{S}$ 496.0640.

4.7. General procedure for oxidation of compounds (**6a–e**) to corresponding ketone

Diols **6** (1.41 mmol) were dissolved in dichloromethane (20 mL), and activated MnO_2 ²¹ (10 molar equivalents) added. The dark black suspension was stirred (16 h) at 40–45 °C. Completion of the reaction was determined by TLC. After filtration through Celite, the reaction mixture was concentrated in *vacuo* to afford the corresponding ketone products as pale solids in about 90% yield. These products were >98% pure by ^1H NMR spectroscopy and used without further purification.

4.8. 1,1'-(3,4-dibromothiophene-2,5-diyl)bis(ethan-1-one) (**7a**)

Prepared from diol **6a** (55 mg, 0.16 mmol) to obtain compound **7a** as a colourless solid (47 mg, 87%). R_f 0.84 (7:3 pentane:EtOAc), m.p. 168–170 °C [lit.²⁰ 173–174 °C]; ^1H NMR (400 MHz, CDCl_3) δ_{H} 2.74 (s, 6H, 2 $\times$ CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 189.7, 142.7, 119.4, 29.9; IR(ATR) (cm^{-1}) ν_{max} 2919, 2852, 1649, 1474, 1414, 1353, 1240, 1044, 1029, 949, 870, 802, 666; MS (ESI): found 325.8431, calcd. for $\text{C}_8\text{H}_6\text{Br}_2\text{O}_2\text{S}$ (^{79}Br) 325.8435.

4.9. 1,1'-(3,4-dibromothiophene-2,5-diyl)bis(propan-1-one) (**7b**)

Prepared from diol **6b** (45 mg, 0.12 mmol) to obtain compound **8b** as a colorless solid (35 mg, 0.10 mmol, 82%) R_f 0.70 (17:3 light petroleum:EtOAc); m.p. 118–120 °C; ^1H NMR (400 MHz, CDCl_3) δ_{H} 3.10 (q, J = 7.1, 4H, 2 $\times$ CH_2), 1.24 (t, J = 7.1, 6H, 2 $\times$ CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 192.8, 141.9, 118.9, 35.5, 8.0; IR(ATR) (cm^{-1}) ν_{max} 2983, 2932, 2878, 1651, 1451, 1401, 1379, 1348, 1275, 1184, 1083, 923, 890, 869; MS (ESI): found 351.8751, calcd. for $\text{C}_{10}\text{H}_{10}\text{Br}_2\text{O}_2\text{S}$ (^{79}Br) 351.8762.

4.10. 1,1'-(3,4-dibromothiophene-2,5-diyl)bis(3-methylbutan-1-one) (**7c**)

Prepared from diol **6c** (0.50 g, 1.20 mmol) to obtain compound

7c as a colourless solid (0.44 g, 90%); R_f 0.90 (8.5:1.5 light petroleum:EtOAc); m.p. 97–99 °C; ^1H NMR (400 MHz, CDCl_3) δ_{H} 2.92 (d, J = 6.7 Hz, 4H, 2 $\times$ CH_2), 2.30 (m, 2H, 2 $\times$ CH), 1.01 (d, J = 6.7 Hz, 12H, 4 $\times$ CH_3); ^{13}C NMR (400 MHz, CDCl_3) δ_{C} 192.0, 141.9, 119.0, 50.5, 25.2, 22.7; IR(ATR) (cm^{-1}) ν_{max} 2956, 2930, 2871, 1649, 1470, 1423, 1393, 1362, 1183, 1098, 1120, 1098, 984, 805, 767; MS (ESI): found 407.9384, calcd. for $\text{C}_{14}\text{H}_{18}\text{Br}_2\text{O}_2\text{S}$ (^{79}Br) 407.9388.

4.11. 1,1'-(3,4-dibromothiophene-2,5-diyl)bis(hexan-1-one) (**7d**)

Prepared from diol **6d** (0.52 g, 1.18 mmol) to obtain compound **7c** as a colourless solid (0.45 g, 87%); m.p. 71–72 °C; R_f 0.87 (8:1 light petroleum:EtOAc); ^1H NMR (400 MHz, CDCl_3) δ_{H} 3.05 (t, J = 7.3 Hz, 4H, 2 $\times$ CH_2), 1.75 (m, 4H, 2 $\times$ CH_2), 1.37 (m, 8H, 2 $\times$ CH_2CH_2), 0.91 (t, J = 7.3 Hz, 6H, 2 $\times$ CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 192.5, 141.9, 118.9, 41.9, 31.4, 23.8, 22.6, 14.0. IR(ATR) (cm^{-1}) ν_{max} 2950, 2918, 2867, 1666, 1461, 1426, 1396, 1370, 1246, 1173, 952, 870, 848, 72; MS (ESI): found 435.9707, calcd. for $\text{C}_{16}\text{H}_{22}\text{Br}_2\text{O}_2\text{S}$ (^{79}Br) 435.9700.

4.12. 1,1'-(3,4-dibromothiophene-2,5-diyl)bis(octan-1-one) (**7e**)

Prepared from diol **6e** (0.29 g, 0.58 mmol) to obtain compound **7e** as a faint yellow solid (0.23 g, 0.465 mmol, 80%). R_f 0.74 (9:1 light petroleum:EtOAc); m.p. 48–50 °C; ^1H NMR (500 MHz, CDCl_3) δ_{H} 3.05 (t, J = 6.7 Hz, 4H, 2 $\times$ CH_2), 1.76–1.71 (m, 4H, 2 $\times$ CH_2), 1.38–1.25 (m, 16H, 2 $\times$ $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 0.88 (t, J = 6.7 Hz, 6H, 2 $\times$ CH_3); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 192.6, 141.9, 119.0, 41.9, 31.8, 29.2, 29.2, 24.2, 22.7, 14.2; IR(ATR) (cm^{-1}) ν_{max} 2954, 2916, 2847, 1666, 1559, 1470, 1269, 1222, 1171, 770, 727; MS (ESI): found 492.0300, calcd. for $\text{C}_{20}\text{H}_{30}\text{Br}_2\text{O}_2\text{S}$ (^{79}Br) 492.0300.

4.13. 1,1'-(3,4-(ethylenedithio)thiophene-2,5-diyl)bis(3-methylbutan-1-one) (**8a**)

Neat 1,2-ethanedithiol (0.84 g, 9.01 mmol) was added slowly to a solution of (**7c**) (1.68 g, 4.10 mmol) and Na_2CO_3 (1.00 g, 9.44 mmol) in dry DMF (20.5 mL) and the mixture was stirred at room temperature under an atmosphere of argon. After (64 h) the mixture was extracted with ethyl acetate (3 $\times$ 100 mL). The organic layer was washed with 2 M HCl (3 $\times$ 30 mL) and then dried with MgSO_4 , filtered and concentrated under reduced pressure. Purification was achieved by flash column chromatography (18:1 light petroleum:EtOAc) to afford **8a** (0.991 g, 2.89 mmol, 70%) as yellow microcrystals; R_f 0.26 (18:1 light petroleum:EtOAc); m.p. 99–100 °C; ^1H NMR (400 MHz, CDCl_3) δ_{H} 3.21 (s, 4H, 2 $\times$ CH_2), 2.69 (d, J = 6.7 Hz, 4H, 2 $\times$ CH_2CO), 2.36–2.28 (m, 2H, 2 $\times$ CH), 1.00 (d, J = 6.7 Hz, 12H, 4 $\times$ CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 192.9, 136.4, 133.5, 50.1, 26.5, 25.7, 22.8; IR(ATR) (cm^{-1}) ν_{max} 2951, 2871, 1728, 1654, 1442, 1411, 1398, 1362, 1278, 1183, 1035, 956, 917, 880, 688; MS (EI): found 342.0785, calcd. for $\text{C}_{16}\text{H}_{22}\text{O}_2\text{S}_3$ 342.0782. Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{O}_2\text{S}_3$ C: 56.10; H: 6.47% found C: 55.97, H: 6.78%.

4.14. 1,1'-(3,4-(ethylenedithio)thiophene-2,5-diyl) bis(hexan-1-one) (**8b**)

Neat 1,2-ethanedithiol (83.0 mg, 0.89 mmol) was added to a solution of (**7d**) (156 mg, 0.36 mmol) and Na_2CO_3 (94 mg, 0.89 mmol) in dry DMF (1.8 mL) and the mixture was stirred at room temperature under an atmosphere of argon (40 h). The mixture was extracted with ethyl acetate (3 $\times$ 4 mL) and the organic layer was then washed with (2 M HCl) until DMF free. The organic extracts were dried with MgSO_4 and concentrated in *vacuo*. The crude product was then purified by flash column chromatography (9:1 light petroleum:EtOAc) giving a pale yellow solid (75.0 mg, 57%); R_f

0.47 (9:1 light petroleum:EtOAc); m.p. 59–60 °C; ^1H NMR (400 MHz, CDCl_3) δ_{H} 3.22 (s, 4H, 2 $\times$ CH_2), 2.28 (t, $J = 7.2$ Hz, 4H, 2 $\times$ CH_2), 1.74–1.70 (m, 4H, 2 $\times$ CH_2), 1.34–1.31 (m, 8H, 2 $\times$ CH_2CH_2), 0.91 (t, $J = 7.2$, 6H, 2 $\times$ CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 193.3, 136.4, 133.2, 41.2, 31.5, 26.5, 24.3, 22.6, 14.1; IR (ATR) (cm^{-1}) ν_{max} 2954, 2933, 2859, 1641, 1463, 1447, 1417, 1366, 1315, 1275, 1247, 1184, 1164, 973, 848, 730; MS (EI): m/z found 370.1095, calcd. for $\text{C}_{18}\text{H}_{26}\text{O}_2\text{S}_3$ 370.1086.

4.15. 1,1'-(3,4-(ethylenedithio)thiophene-2,5-diyl)bis(octan-1-one) (**8c**)

Neat 1,2-ethanedithiol (83 mg, 0.9 mmol) was added to a solution of **7e** (194 mg, 0.39 mmol) and Na_2CO_3 (104 mg, 0.98 mmol) in dry DMF (4 mL) at room temperature. The mixture was then stirred for (40 h) until a precipitate formed. The mixture was extracted with ethyl acetate (4 $\times$ 10 mL) and the organic layer was then washed with (2 M HCl) until DMF free. The extracts were dried (MgSO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (9:1 light petroleum:EtOAc) giving a butter cream yellow solid (75 mg, 45%); R_f 0.26 (9:1 light petroleum:EtOAc); m.p. 65–67 °C; ^1H NMR (400 MHz, CDCl_3) δ_{H} 3.20 (s, 4H, 2 $\times$ CH_2), 2.20 (t, $J = 7.4$ Hz, 4H, 2 $\times$ CH_2), 1.76–1.69 (m, 4H, 2 $\times$ CH_2), 1.34–1.29 (m, 16H, 2 $\times$ $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 0.86 (t, $J = 7.4$, 6H, 2 $\times$ CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 193.2, 136.3, 133.1, 41.2, 31.8, 29.3, 29.1, 26.5, 24.5, 22.7, 14.2; IR (ATR) (cm^{-1}) ν_{max} 2953, 2928, 2850, 1646, 1465, 1444, 1418, 1404, 1368, 1354, 1316, 1298, 1250, 1181, 1166, 1099, 1057, 1021, 970; MS (EI): found 426.1721, calcd. for $\text{C}_{22}\text{H}_{34}\text{O}_2\text{S}_3$ 426.1721.

4.16. 2,2'-Thiodiacetonitrile (**12**)

Solid $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ (10.8 g, 45.01 mmol) was dissolved in DME (35 mL), and chloroacetonitrile (4.77 g, 63.2 mmol) was then added. The mixture was allowed to stir at r.t. (16 h). Water was added and the compound was extracted from chloroform (3 $\times$ 40 mL). The organic layer was dried (MgSO_4) and the solvent removed. Elution through a silica plug (1:1 EtOAc:pentane) yielded compound **16** as a colorless oil (3.24 g, 28.9 mmol, 91%); ^1H NMR (400 MHz, CDCl_3) δ_{H} 3.57 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 114.9, 17.5; IR (ATR) (cm^{-1}) ν_{max} 2970, 2929, 2246, 1399, 1174, 922; MS (EI): found 112.0089, calcd. for $\text{C}_4\text{H}_4\text{N}_2\text{S}$ requires 112.0089. The above values are concordant with literature data.²³

4.17. Potassium 2,5-dicyanothiophene-3,4-bis(olate) (**13**)

To dry $t\text{BuOK}$ (8.0 g, 71.3 mmol) in dry THF (95 mL), a solution of **12** (4.00 g, 35.6 mmol) in THF (43 mL) was added dropwise at 0 °C. The mixture was stirred for 5 min and then added a solution of diethyl oxalate (5.21 g, 35.66 mmol) in dry THF (40 mL) at 0 °C. After 30 min stirring at 0 °C the precipitate was collected by vacuum filtration and washed with diethyl ether and THF to obtain **13** as a brown powder (7.26 g, 84%); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ_{C} 174.9, 122.8, 65.7; IR (ATR) (cm^{-1}) ν_{max} 2168, 1712, 1518, 1315, 1229, 1019, 764, 592. The compound was used as obtained directly.

4.18. 3,4-Ethylenedioxythiophene-2,5-dicarbonitrile (**14**)

Under an argon atmosphere potassium salt **13** (0.50 g, 2.06 mmol) was dissolved in anhydrous DMF (1.5 mL) at room temperature, and dry potassium carbonate (0.11 g, 0.83 mmol) added followed by tetrabutylammonium bromide (35 mg, 0.10 mmol). The mixture was heated to 135 °C and 1,2-dichloroethane (0.41 g, 4.13 mmol) added dropwise. After stirring at 135 °C (5 h) the reaction was stopped and allowed to cool down.

The mixture was extracted with ethyl acetate (3 $\times$ 10 mL), washed with 5% w/w LiCl(aq) solution (3 $\times$ 10 mL) and the combined organic extracts dried (MgSO_4) and concentrated *in vacuo* to afford the crude product. Filtering through a silica plug with a dichloroethane wash yielded, on removal of the solvent, **14** (0.13 g, 35%) obtained as a colourless solid, R_f 0.68 (1:1 EtOAc:hexane) ^1H NMR (400 MHz, CDCl_3): δ_{H} 4.42 (s, 4H, 2 $\times$ CH_2), ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 147.8, 110.6, 91.3, 65.2. IR (ATR) (cm^{-1}) ν_{max} 2946, 2215, 1632, 1504, 1449, 1078, 914, 843, 806 cm^{-1} . MS (EI): found 191.9988, calcd. for $\text{C}_8\text{H}_4\text{N}_2\text{O}_2\text{S}$ 191.9993.

4.19. 3,4-Ethylenedioxythiophene-2,5-dicarbaldehyde (**15**)

A solution of DIBAL-H (1.08 mL, 1.2 M, 20% wt. in toluene) was added dropwise at 0 °C to a solution of **14** (100 mg, 0.52 mmol) in dry toluene (5.2 mL). The reaction was stirred (30 min) at 0 °C until the starting material was consumed as judged by TLC analysis. The reaction mixture was quenched with (1 M, HCl) and extracted with ethyl acetate (3 $\times$ 10 mL) and dried (MgSO_4), the solvent was evaporated to yield the desired dialdehyde **15** (83 mg, 80%) as a tan brown solid. R_f 0.64 (EtOAc); ^1H NMR (400 MHz, CDCl_3) δ_{H} 10.04 (s, 2H, 2 $\times$ CHO), 4.45 (s, 4H, 2 $\times$ CH_2); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 181.0, 147.4, 124.2, 65.0; IR (ATR) (cm^{-1}) ν_{max} 2953, 2922, 2851, 1662, 1643, 1260, 1230; MS (EI): found 197.9987, calcd. for $\text{C}_8\text{H}_6\text{O}_4\text{S}$ 197.9987. These values are consistent with published literature.^{11d}

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.tet.2017.08.026>.

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