ON THE SYNTHESIS OF NAPHTHOQUINONES AND ANTHRAQUINONES

A Thesis Submitted to The University of Manchester for the Degree of Doctor of Philosophy (PhD) in Faculty of Science and Engineering

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Abstracts

The serendipitous isolation of 1-chloronaphthalene via a microwave promoted cyclisation of 2-allylphenyl 2,2,2-trichloroacetate during the investigation of catalytic activity of copper (I) complexes has resulted to a synthetically valuable scheme for the preparation of haloarenes. This *Bull Hutching Quayle-Atom Transfer Radical Cyclisation Reaction (BHQ-ATRC)* has herewith enabled the benzannulation of varied 2-allyl-phenyl-2,2,2-tri(bromo/chloro)acetates using a copper(I)chloride complex: chloro[1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene]copper(I), in a conventional thermal cyclisation reaction. The functionalised haloaromatics which were realised from cyclisation of the pivotal precyclised intermediates serve as precursors to the synthesis of plumbagin and juglone and analogues naphthoquinone antibiotics in three synthetic steps.

2-(Cyclohex-1-en-ylmethylphenyl 2’,2’,2’-tribromo/chloro)acetates were also cyclised and the resulting hydroquinone secured a tricyclic core motif found in anthracycline (e.g., γ-cytromycinone), a tetracycline anthraquinone, with an array of bioactivity including, anticancer, antibiotics and antiviral potentials. An application of a palladium-catalysed cross coupling reaction on the resulting haloarenes after the initial ATRC reaction generated intermediate boronic esters as disclosed. Extensive investigation of the optimum reaction conditions with a view of finding a suitable sequence for the formation of intermediate boronic esters which are easily converted to the intended hydroxyanthraquinones is discussed.

Finally, a synthesis of new anthraquinones utilising a Suzuki cross coupling reaction is also reported. It was observed that the one-step cross coupling reaction proceeded efficiently enabling the synthesis of new anthraquinone candidates which themselves are shown to possess an extended π-π stacking coordination. These compounds could be beneficial in molecular recognition, electrical/optical science and possibly, in building up of molecular tweezers when they are evaluated.
Declaration

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The superseding love and wisdom of Jesus Christ my Lord
are limitless in this wooden house—

AMEN
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- Joshua Moore,
- Aduragbemi Adebogun,
- Michael Obi,
- Everyone else who has supported me in any way.
**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Ar</td>
<td>Aryl group</td>
</tr>
<tr>
<td>ATRC</td>
<td>Atom transfer radical cyclisation</td>
</tr>
<tr>
<td>BHQ</td>
<td>Bull-Hutchings-Quayle</td>
</tr>
<tr>
<td>B3LYP</td>
<td>Becke, 3 parameter, Lee-Yang Parr</td>
</tr>
<tr>
<td>Bipy</td>
<td>2, 2’-Bipyridyl</td>
</tr>
<tr>
<td>CAN</td>
<td>Cerium Ammonium Nitrate</td>
</tr>
<tr>
<td>CAS</td>
<td>Cerium Ammonium Sulphate</td>
</tr>
<tr>
<td>Conc.</td>
<td>Concentrated</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation spectroscopy</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical shift</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-Dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DEA</td>
<td>N, N-Diethylaniline</td>
</tr>
<tr>
<td>Diglyme</td>
<td>Bis(2-methoxyethyl) ether</td>
</tr>
<tr>
<td>DMF</td>
<td>N, N-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>EI</td>
<td>Electron impact ionisation</td>
</tr>
<tr>
<td>ES+/−</td>
<td>Electrospray (positive/negative mode)</td>
</tr>
<tr>
<td>GC</td>
<td>Gas chromatography</td>
</tr>
<tr>
<td>GCMS</td>
<td>Gas chromatography mass spectrometry</td>
</tr>
<tr>
<td>HMTA</td>
<td>Hexamethylenetetramine</td>
</tr>
<tr>
<td>HMRS</td>
<td>High Resolution Mass Spectroscopy</td>
</tr>
<tr>
<td>IPr</td>
<td>1,3-Bis-(diisopropyl)imidazolium</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
<tr>
<td>mCPBA</td>
<td>Meta-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>m/z</td>
<td>mass-to-charge ratio</td>
</tr>
<tr>
<td>MW</td>
<td>Microwave</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>Petrol</td>
<td>petroleum ether (40 – 60 °C)</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>Retention factor</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>Trifluoroacetic anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Tetramethylsilane</td>
</tr>
<tr>
<td>X</td>
<td>Leaving group (Cl, Br, I, F etc)</td>
</tr>
</tbody>
</table>
1 Introduction

In 2007, a new Atom Transfer Radical Cyclisation (ATRC)\(^1,2\) reaction was discovered in which 2-allylphenyl 2,2,2-trichloroacetate underwent a regiospecific copper-(I)-catalysed decarboxylative cyclisation, enabling the synthesis of chloroarenes (the BHQ reaction, Scheme 1.1).\(^3\) This reaction sequence was subsequently found to have general application, being compatible with a range of common organic functional groups, and has been utilised in the synthesis of a varied range of poly aromatic hydrocarbon, PAH motifs.\(^4\)

\[
\begin{array}{c}
\text{R} & \text{O} & \text{R} & \text{OH} & \text{R} & \text{O} & \text{CCl}_3 & \text{Cl}
\end{array}
\]

\textbf{Scheme 1.1.} i Ortho-Claisen rearrangement; ii Et\(_3\)N, Cl\(_3\)CCOCl; iii (1,3-bis(2,6-diisopropylphenyl)-2,3-dihydro-1H-imidazol-2-yl)copper(II) chloride; 2 h.

In wishing to pursue further the potential synthetic utility of this reaction, we wished to:

- address the synthesis of relatively simple linear quinones such as juglone and plumbagin whose structures are representative of a range of more complex antibiotics, \(^5-7\) Scheme 1.2;
- apply this methodology to more complex systems such as \(\gamma\)-citromycinone, and
- develop synthetic methodology for the synthesis of molecular PAHs such as 13, 14 and 15 which may have application as molecular sensors, Scheme 1.4.

A four-step (oxidation, alkylation, Claisen and acylation) and a final benzannulation sequence was adopted to the synthesis of aromatics such as 6. C-halogen groups conversion to -OH functionality was successful \textit{via} an intermediate boronate ester.\(^8\) A study carried out to investigate suitable cross-coupling reaction conditions found the \textit{solventless cross coupling borylation} reaction\(^9,10\) to be optimum for the conversion of C-halogen bonds to boronate esters intermediates. Oxidation of the resulting esters with cerium ammonium nitrate (CAN) and a final treatment of those quinones with a mild oxidizing agent (e.g. \(m\)-CBPA) generated the target quinones in good yields. Extension of this basic scheme is demonstrated as a potential route to the synthesis of tricycle
analogues, **Scheme 1.3.** Finally, a synthetic methodology for the preparation of PAFs such as 13 was developed. Anthraquinones have wide applicability. Besides its applications as semiconductor materials, its potential source as biological probes opens a novelty to be tapped. 11-14

**Scheme 1.2.** Proposed Route to Juglone and plumbagin 7a/7b.

**Scheme 1.3.** Proposed synthetic route to 9, the core structure of γ-citromycinone.

**Scheme 1.4.** Anthraquinones 11-15
1.1 Anthraquinones and Naphthoquinones: Origin, Extraction from Nature, Uses and Eventual Synthesis

Anthraquinones and naphthoquinones coincidentally are both families of naturally occurring quinones which have been extensively explored because of their vast applicabilities. Naphthoquinones are commonly found in bacteria, fungi, and other higher plants, anthraquinones occur freely in flowering plants and many others in lichens and fungi. Figure 1.1 shows the basic structure of naphthoquinone and anthraquinone respectively.

![Figure 1.1. Structures 16 and 17.](image)

Although there are many derivatives, the basic view is the term naphthoquinone for 16 (1,4-naphthoquinone) and anthraquinone for 17 (9,10-anthracenedione). 16 (an orange-coloured solid) has a benzophenone structure with an additional benzene ring fused to the left. 17 is a yellow to light red-coloured crystalline solid with two additional benzene rings fused to the benzophenone system on either side. 16 and 17, and their derivatives have found wide applications in food colorants industries, dye, textiles, pharmaceuticals, catalyst for paper industries, biological probes (communication of intracellular signals); and as semiconductors. Medicinally, they are reported as anticancer, antioxidant, immunosuppressive, cathartic, laxative, antifungal, antibacterial, anti-inflammatory, antiviral, neuroprotective, antimalaria, amongst others. With the listed role, 16, 17 and derivatives are expected to proffer continued support to world’s increasing demands in science and technology.
1.2 Discovery of Naphthoquinone and Anthraquinone

Anthraquinones and naphthoquinones have been used over 4000 years but they were not well explored because of inadequate knowledge of their worth.\cite{16, 19, 36-39} Early interest on anthracene chemistry and subsequent discovery of dye from this class of compounds stimulated much research which eventually led to synthesis of 9,10-anthracenedione 17 for the first time by Laurent on treatment of anthracene with nitric acid in 1835.\cite{16, 40} About the same time, Lindley and Hooker working independently on Droseraceous plants observed that the plants have unique colours and they suggested that the plants could be of commercial value if prepared into dye stuff.\cite{41, 42} Droserone 18\cite{37} and hydroxydroserone 19\cite{43} were later reported from the tubers of this plants as the first naphthoquinones by Rennie.\cite{44, 45} Immediately after this development, a very important anthraquinone derivative, alizarin 22, was synthesised by Graebe and Liebermann in 1869.\cite{46-48} Alizarin, 22 (1,2-dihydroxyanthraquinone), a red-coloured crystalline solid, earlier isolated from madder root by a French Chemist, Pierre-Jean,\cite{49} later became commercialised with a name Mordant Red 11 for dyeing of textile fabrics after a successful optimisation of its synthesis and patent by Perkin in the 1870s.\cite{50-52}

This research sparked a great deal of interest into dye chemistry; subsequently in the 1970s research interest in the application of anthraquinones as efficient catalyst in the paper manufacturing industries began to gain momentum.\cite{53, 54} In 1976, Holton reported that the addition of 17 to soda pulping results in improved conversion to products at a
reduced reaction time. His work on this subject culminated in a patent in the US in 1977.\textsuperscript{55, 56} Today, a broad diversity of these compounds with a multitude of applications have emerged, they are either isolated from natural sources or synthesised in the laboratory. For example, anthraquinones have now been reviewed as the largest source of natural pigments having over 700 of its compounds adopted in this relation.\textsuperscript{57} Naphthoquinones on the other hand have evolved with varieties and have continued to find immense applications in dye industry, providing pigment materials such as turkey red, carminic acids and shikonins.\textsuperscript{17}

![Structural formulas of Droserone 18 and Hydroxydroserone 19](image1.png)

![Structural formulas of Shikonins 20 and Carminic acid 21](image2.png)

![Structural formulas of Alizarin 22 and Biramentaceone 23](image3.png)

**Figure 1.3. Pigmented Quinones 18-23.**

Extraction of these compounds from natural sources was next envisaged. These quinones are mostly extracted from natural sources using a range of polar solvents. They typically have relatively poor solubility in non-polar solvents.\textsuperscript{58} Maceration, Soxhlet, super/subcritical fluid extraction, micro-wave assisted, ultrasound-assisted and pressurised liquid extraction methods have been reported.\textsuperscript{57, 59} Duval and Berg, have
listed in their reviews the basic separation techniques which have been successfully adopted for the purification of different anthraquinones, these included counter-current, thin layer, gas, super fluid, column, high performance liquid chromatography and capillary electrophoresis.\textsuperscript{57, 59} Figure 1.4 and 1.5 lists selected napthoquinones and anthqaquinones reviewed in scientific literatures.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Diversity in nature’s napthoquinones and anthraquinones.}
\end{figure}
Figure 1.5. Diversity in nature’s naphthoquinones and anthraquinones.
1.3 Biosynthetic Routes Examples

Studies have shown that many derivatives of naphthoquinone and anthraquinone are a production of acetate-malonate, shikimate or a transformation involving modification of phytochemicals via oxidation processes which may or not require combination of routes.\textsuperscript{17, 18, 59} Most plant-based derivatives of these compounds follow both the shikimate and acetate malonic biosynthesis,\textsuperscript{18, 72} fungi-derived anthraquinones are reportedly generated from the condensation of acetate malonate (via polyketide).\textsuperscript{13, 15, 73} For example, formation of juglone 7a, a member of the naphthoquinone family, proceed through the shikimic pathway; 22 was observed via a shikimate route, otherwise, enzymatic degradation of rhuberythic\textsuperscript{74} acid generates alizarin (Scheme 1.5).\textsuperscript{18}

![Scheme 1.5. Biogenetic route to 7a, 22 and 47.](image)
1.4 Past Synthesis of Naphthoquinones and Anthraquinones

Large scale preparations of anthraquinones and naphthoquinones have been reported. Synthesis of naphthoquinone was originally achieved via a Diels-Alder approach in which a butadiene is coupled to a benzophenone using a pressure vessel at temperature of 70 °C. Most of the reported synthesis of anthraquinones rely on a Diels-Alder reaction, a Friedel-Crafts cyclisation, a direct oxidation of naphthalene/anthracene or related intramolecular cyclisation protocols. Krohn has published an extensive review on the synthesis of these compounds, majority of which employed a modification of the above-listed methodologies.

Scheme 1.6. A Diels-Alder reaction to 16 and 17.

Scheme 1.7. A Friedel Crafts synthesis of 17.
1.5 The Palladium-Catalysed Borylation Reaction of Aryl Halides

Transition-metal catalysed coupling reactions involving aryl halides and a borylating agent have well been reviewed as a source to aryl boronic acids and boronic esters. Some of the borylating sources include tetrahydroxydiboron 57, pinacolborane 56 and bis(pinacolato)diborane 55. Recently, a borylation protocol which utilises photo energy as borylating site activator has also been reported. Previously, aryl boronic esters were prepared from a reaction of aryl lithium or Grignard reagents with aryl halides.

![Scheme 1.8. Borylating agents 55-57.](image)

These organolithium or Grignard reagents however have the disadvantages of non-compatibility with some functional groups, a frequent high level of toxicity and, a reported loss of stereochemistry of starting materials in some cases. Notable metal compounds that have previously been used as catalysts are iron, palladium, copper and cobalt complexes, although palladium complexes have received a significant amount of attention. Solvents play a key role in borylation reactions, reaction rates are facilitated by polar solvents at different temperatures. Common solvents employed are dimethyl sulfoxide (DMSO), dimethylformamide (DMF), acetonitrile (CH$_3$CN), tetrahydrofuran (THF), toluene and 1,4-dioxane. The role of respective ligands have also been reviewed in a recent work published by Kubota.

![Scheme 1.9. Cross coupling reaction of 58 to 59. Reagents and conditions: i. 3 mol % Pd(dppf)Cl$_2$, KOAc, DMSO, 80 °C.](image)

Many bases have been employed for borylation. For example, acetates, carbonates, hydroxides, phosphate and amine of group 1 and 2 metals. Generally, conversions are better when potassium or sodium acetate are used although substrate is a key factor. Recently, it has been published that borylation of aryl halides works well at a
particular pH range, best conversions were observed at pH limit of 6.7–7.7. This finding would therefore eliminate time waste and facilitate direct choice of reaction conditions in future researches. The proposed mechanism is that oxidative addition of the aryl halide 60 to palladium (0) would result in a complex formation 61 and a base replaces the halide in 62. The B-B bond centre of 55 reacts easily with the acetate ion, enhances migration of the boron nucleophile to aryl group in 64 and results in the reductive elimination of the aryl boronic ester 65 and the catalyst is regenerated.\(^8\)

Scheme 1.10. Proposed mechanism for the synthesis of 65.
1.6 Serendipity from a Copper-(I)-Catalysed ATRC Reaction of a 2-allylphenyl 2,2,2-trichloroacetate

During a study of the ATRC reactions of ortho-allylphenyl trichloroacetates Bull et al. observed that ATRC of 66 proceeded smoothly to benzo[b]oxocin-2-one, 67 ([69, 5 mol %, toluene, 110 °C]) with 95% conversion (as monitored by 1HNMR spectroscopy) over a time course of 48 hours. However, allowing this reaction to run for extended reaction times - 120 hours – led, surprisingly, to the production of 1-chloronaphthalene 68.\(^3,96\) Further studies indicated that this unanticipated outcome - the “BHQ” (Bull-Hutching-Quayle) reaction, was found to be general in scope, being compatible with a range of common organic functional groups. This transformation was subsequently optimised using CuCl\(^70\) as catalyst\(^3\) and has been applied to the synthesis of functionalised materials\(^97-100\) and in the modification of bioactive compounds.\(^101\)

![Chemical structures](image)

**Scheme 1.11.** Benzannulation reaction of 66. Reagents and conditions: i 69 (5 mol %); refluxing toluene; 48 h; ii 69 (5 mol %); refluxing toluene; 120 h.
1.6.1 The BHQ–ATRC Sequence Exemplified

As noted above the BHQ reaction is compatible with a range of common functional groups such as –CHO, CH₃, F, CH₃CO enabling the regiocontrolled synthesis of functionalised aromatics (Table 2.1).³ The highest product conversion were observed in the case of ester-substituted aromatics (e.g. R₁ = CO₂Me) although it should be noted that the introduction of a nitro-functional group appears to be deleterious on the yield of the BHQ reaction. These observations suggest that the BHQ reaction could find application in the synthesis of a range of functionalised aromatic intermediates.
Table 1.1. ATRC reaction of 71 to 72. Reagents and conditions: i 69 (5 mol%); 1,2-DCE; Δ (200 °C); μW; 2 h.
In their investigations into the BHQ reaction the Quayle group have shown that even sterically hindered aromatics can be prepared using this methodology, as exemplified by the synthesis of the phenanthrene derivative 74 from trichloroacetate 73 and 4,10-dichlorochrysene 76 from 75.\textsuperscript{97, 98} Extension of this methodology to the synthesis of benzo-fused heterocyclic systems was also possible, as demonstrated by the synthesis of coumarins 78 and 80 from 77 and 79 respectively.\textsuperscript{4, 99}

\textbf{Scheme 1.12.} The BHQ reaction Exemplified. Reagents and conditions. i 69 (5 mol\%); 1,2-DCE; 2h; \(\mu\)W; \(\Delta \) (200 °C).
Further applications of this methodology to the synthesis of the benzannulated steroids 3αS,3βR,11βS,13αS)-7-chloro-3,3α,4,5,11β,12,13,13α-octahydro-13α-methyl-2Hcyclopenta[c]tetraphen-1(3bH)-one, 83a and (3αS,5αS,13αR,13βS)-8-chloro-1,2,3α,4,5,5α,13,13α-octahydro-3α-methyl-12H-cyclopenta[a]chrysen-3(13bH)-one, 83b (1:2 ratio) in 4 synthetic steps was reported. Efforts to separate 83a from 83b was unsuccessful.102

Scheme 1.3. Synthesis of 83a and 83b. Reagents and conditions: i Allyl bromide (1.2 eq.); K₂CO₃ (1.2 eq.); 56 °C; ii µW (215 °C); iii Et₃N (1.2 eq.); Cl₃COCl (1.2 eq.); Et₂O; 0 °C; 80% over three steps; iv 69 (5 mol %); 1,2-DCE; µW (200 °C); 2 h; 67%.
Although azo-aromatics are valuable dye stuffs with numerous applications in industry, academic research methods for the elaboration of the basic azo-dye motif are scarce.\cite{34}

Once again, the BHQ reaction sequence was found to be of use in homologation of these intermediates. Hence, alkylation of phenol 86 (a-i) and Claisen rearrangement of the resulting ethers 87 (a-i) afforded phenol 88 (a-i) which upon esterification with Cl$_3$COCl (1.2 equivalents) in the presence triethylamine (1.2 equivalents), and subsequent thermolysis ([70, 5 mol %, refluxing diglyme, 15 h]) afforded benzo-fused azo-dyes 90 (a-i) in 78 to 96% yield.\cite{100}

Scheme 1.14. The benzannulation reactions of azo-dyes 90 (a-i). Reagents and conditions: i NaNO$_2$; HCl; NaOH; H$_2$O; 0 °C; ii Allyl bromide; KOH (5 eq.); DMSO; 20 °C; 3 h; iii Et$_2$AlCl (2.2 eq.); CH$_2$Cl$_2$; 20 °C; 15 h; iv Cl$_3$COCl (1.2 eq.); Et$_3$N (1.2 eq.); Et$_2$O; 0 °C to r.t.; 3 h; v 70 (5 mol %); refluxing diglyme; 15 h.

a: X, Y, Z = H, H, F; 93%  f: X, Y, Z = H, H, OH; 91%
b: X, Y, Z = H, H, Cl; 87%  g: X, Y, Z = H, H, H; 78%
c: X, Y, Z = H, H, Br; 87%    h: X, Y, Z = H, H, NO$_2$; 94%
d: X, Y, Z = H, H, I; 92%    i: X, Y, Z = i-Pr, H, H; 96%
e: X, Y, Z = H, Me, H; 94%
1.6.2 Proposed mechanism of the BHQ reaction

The mechanism of this reaction presumably follows a cyclisation pathway whereby the initial radical 92 derived from trichloroacetate 91 undergoes an 8-endo-trig-cyclisation affording 93. Subsequent re-formation of a radical centered at Cα- and ring closure, via a 4-exo-trig-reaction in 94 would then result in tricycle intermediate 95, which, upon abstraction of chlorine radical from Cu(II)Cl forms anthracene 96. Retro-[2+2] cycloaddition\(^{103}\) and elimination of CO\(_2\) gas generates trihalide 97\(^{104}\) which on the elimination of hydrogen chloride finally furnishes the observed product 98.

Scheme 1.15. Proposed mechanism of the BHQ reaction leading to 98.
1.7 A Synthesis of Plumbagin and Analogues Using the BHQ Reaction

Plumbagin 7b, 33, 105 a derivative of juglone 7a, is isolated from the Plumbaginaceae, Droseraceae and Ebenaceae families of flowering plants 105-107 and exhibits anticancer, anti-inflammatory, anti-oxidant, antifungal, neuroprotective, hypolipidemic, antibacterial and anti-fungal properties. 23, 24, 108-110 The first synthesis of 7b was reported by Fieser and Dunn in 1936 which also served to confirm its structure. 111 There has been a recent surge of interest in the therapeutic applications of 7b, 7, 33, 112 studies that have been partially fuelled by a greater understanding of its potential mode of action. 113, 114 Unfortunately the isolation of 7b from natural sources generates relatively small amounts of material which are insufficient to fulfil demand from pharmacologists. 115 When coupled with the dearth of literature reports concerning the synthesis of 7b and analogues, 111, 115-123 these observations suggest that the development of generic routes to plumbagin 7b and derivatives is required. 112, 116, 124-134 Moreover, some of the reported synthetic approaches require the use of excess reagents for synthesis, with low conversion, problematic work up, and high process costs reported. Therefore, there is need to develop new and complementary synthetic routes to 7b.

![Figure 1.6. Plumbagin 7b and Juglone 7a.](image-url)
The first recorded synthesis of \(7b\) was accomplished in over 10 steps starting from benzoyl chloride \(99\). The key synthetic step was the cyclisation of acid chloride \(101b\) to ketone \(102\) and subsequent aromatisation of derivative of \(102\) to phenol \(104\). Although \(7b\) was successfully synthesised in this approach, the relatively low overall conversion of the isolated compound poses a setback to this methodology.

Scheme 1.16. The Synthesis of Plumbagin \(7b\) (Fieser and Dunn\(^{111}\)). Reagents and conditions: i Na; Et\(_2\)O; 48 h; KOH; H\(_2\)O; 48 h; 6 M HCl; then HCl (2M); ii mossy Zn; HgCl\(_2\); H\(_2\)O; 6 M HCl; toluene; CH\(_3\)COOH; 11 M HCl; 6 h; iii SOCl\(_2\); \(\Delta\) (100°C); 1 h; iv CS\(_2\) at 0 °C; AlCl\(_3\), 100 °C; ca. 0.5 h; v Br\(_2\); CS\(_2\); 5 °C; 1.5 h; vi DEA; \(\Delta\); I h; 2 M H\(_2\)SO\(_4\); vii Ac\(_2\)O; NaOAc; r.t viii glacial ACOH; CrO\(_3\); 0 °C; 12 h; then 60 h at r.t; ix Zn/NaOAc; Ac\(_2\)O then \(\Delta\); x NaNHMgCl\(_2\); 1 M H\(_2\)SO\(_4\); 0 °C; K\(_2\)Cr\(_2\)O\(_7\).
Later that year, Dieterle and Kruta reported a synthesis of plumbagin 7b from dinitro naphthalene 108 in five synthetic steps. Their approach was to convert 108 to amine 109 via reduction followed by diazotisation and boiling the diazo salt to generate the phenol 110. Reduction of 110 with metallic tin in the presence of hydrochloric acid and subsequent oxidation with hydrogen peroxide in glacial acetic acid furnished 7b after many days. Although this synthetic approach seems somewhat convenient, the reaction exhibited a significant exotherm and took a significant number of days for completion, with, the isolated yield of 7b not reported by the authors.

**Scheme 1.17.** Dieterle and Kruta approach to 7b. Reagents and conditions: i Sn; 11 M HCl; Δ; then NaOH; ii H₂SO₄; NaN₂/H₂O; iii HCl; Sn; iv H₂O₂; CH₃COOH.
Thereafter, several other synthetic approaches have been reported, the major setbacks being overall poor conversion, long synthetic routes and, the use of large quantities of acids and reagents.\textsuperscript{116-122} Recently, a synthesis of 7b (22\% overall yield) utilising 4,8-dihydroxynaphthol-\(\beta\)-D-glucoside 112 has been reported; which the authors isolated from the back of \textit{J. mandshurica}\textsuperscript{133} as the starting material.\textsuperscript{115} Although the synthetic route seems short, the rationale of utilising 7a to obtain 7b may not be immediately justified considering the relative bioactivity of 7a.

**Scheme 1.18.** A Synthesis of 7b from 112. Reagents and conditions: i CAS; MeCN-H\(_2\)O; 0 °C; 78\%; ii \(\text{Na}_2\text{S}_2\text{O}_4\) (saturated solution); 20 °C; 0.5 h then (CH\(_3\))\(_2\text{C}(\text{CH}_3)_2\); BF\(_3\).OEt\(_2\); 3 h; 83\%; iii HMTA; AcOH; SnCl\(_2\).2H\(_2\)O; TsOH; \(\Delta\) (120 °C); 2 h; 49\%; iv Zn(Hg); HCl; ClCH\(_2\)CH\(_2\)Cl; reflux; then CAS; MeCN-H\(_2\)O; 0 °C; 0.5 h; 69\%.
Dimers of 7b, zeylanone 115 and epoxide 116 which employ 7b as a starting material via a cascade Michael addition reactions have recently been reported. Quinone 115 demonstrates remarkable anticancer, antibacterial and antifungal activities. Protection of the OH group in 7b before treatment with potassium hydroxide in CH2Cl2-MeOH solution under an aerobic condition was found to be an optimal condition because direct reaction of 7b with sodium hydroxide was seen to decompose the product. Epoxide 116 was also retrieved in 54% yield after deprotection with acetic acid.

Figure 1.7. Zeylanone 20 and Zeylanone epoxide 21.

Chen et al. have reported the synthesis of 12 novel analogues of 7b with higher inhibitory effects against triple negative breast cancer when compared to 7b by the condensation of substituted furoxans with some analogues of 7b. Current interests are also geared towards the synthesis and applications of metal-based complexes of 7b and analogues for medicinal evaluations.
The first metal complex of 7b was reported in 1983 by Sawhney et al. even though further applications were not evaluated. They found that coordination of 7b to uranyl to furnish UO$_2$(II)-2-methyl-5-hydroxy-1,4-naphthalenedione 117 was achieved on treatment of the nitrate solution of the metal with the sodium salt of the ligand. Complex 117 showed a broad OH band in IR region of 3400 cm$^{-1}$ with a major shift in the C=O from 1634 to 1593 indicating a metal-oxygen complexation (Figure 2.3). Chiniforashan and Tabrizi have reported a synthesis of novel ruthenium (II)$\pi$-Cymene and iridium complexes coordinated to naphthoquinone plumbagin 7b and juglone 7a, and their biological evaluation for human cancer cell lines were accomplished in vitro. In most cases, coordination of metal to these naphthoquinones resulted in compounds of higher bioactivity. Cu$^{2+}$, Cd$^{2+}$, Ca$^{2+}$, Sm$^{3+}$, and others with high affinity for electron pairs have also been reported for complexation with naphthoquinone, their anti-proliferative actions being a result of the induction of oxidative stress enhanced by the lipophilicity of the naphthoquinone ligands.150

![Chemical structure](image)

**Figure 1.8.** UO$_2$(II)-2-methyl-5-hydroxy-1,4-naphthalenedione 117.
2 Results and Discussion

The initial approach to 7b therefore was to prepare the haloaromatics 123-125 via the pivotal pre-cyclization substrates 120-122, a product of acylation of a Claisen phenol 118 and 119. Once haloaromatics 123-125 were formed, then CAN-mediated oxidation reaction could be applied enabling access to quinones 126-128. Application of a palladium-catalysed borylation on 126-128 followed by mild oxidation (e.g. m-CBPA) of the intermediate borane 129/130 would generate the target naphthoquinone 7a and 7b.

![Scheme 2.1](image)

**Scheme 2.1.** Proposed synthetic approach to 7a and Juglone 7b. Reagents and conditions: i Cl₃CCOCl or Br₃CCOCl (1.2 eq.); Et₃N (1.2 eq.); Et₂O; 0 °C to r.t; ii 70 (5 mol %); diglyme Δ (162 °C); 15 h; iii CAN; MeCN; H₂O 1:1; 15 h. iv B₂Pin₂ 55; Pd(dppf)Cl₂; KOAc; v m-CBPA; CH₃CN; 20 °C.
2.1 Preparation of Pre-Cyclisation Substrates

To confirm this assumption, the synthesis of haloaromatics 123 and 124 was undertaken starting from the known aldehyde 5a, Scheme 2.10.\textsuperscript{151}

![Scheme 2.10. Synthesis of Haloaromatics 123 and 124.]

Treatment of 5a with \textit{m}-CBPA (2 equivalents) in dichloromethane followed by saponification of the intermediate formate ester in the work-up furnished phenol 131 in 76\% yield. Alkylation of 131 with allyl bromide (2 equivalents) in the presence of K\textsubscript{2}CO\textsubscript{3} (2 equivalents) followed by Claisen rearrangement furnished ether 132 as a yellow-coloured viscous oil in 76\% yield after purification by column chromatography.

![Scheme 2.3. Etherification of 131. Reagents and conditions: i \textit{m}-CBPA (2 eq.); CH\textsubscript{2}Cl\textsubscript{2}; 15 h; 4 M NaOH in MeOH; 2h then 6 M HCl; 20 °C; ii allyl bromide (1.2 eq.); K\textsubscript{2}CO\textsubscript{3} (1.2 eq.); acetone; 56 °C; 23 h.]

\textbf{Scheme 2.2. Synthesis of Haloaromatics 123 and 124.}

\textbf{Scheme 2.3. Etherification of 131. Reagents and conditions: i \textit{m}-CBPA (2 eq.); CH\textsubscript{2}Cl\textsubscript{2}; 15 h; 4 M NaOH in MeOH; 2h then 6 M HCl; 20 °C; ii allyl bromide (1.2 eq.); K\textsubscript{2}CO\textsubscript{3} (1.2 eq.); acetone; 56 °C; 23 h.}
A similar exposure of aldehyde 5b to m-CBPA (2 equivalents) in dichloromethane at room temperature for 15 hours have also enabled the realisation of phenol 133 (80%) before a subsequent alkylation reaction of the resulting phenol to ether 134 (Scheme 2.4).

Scheme 2.4. Etherification of 133. Reagents and conditions: i m–CBPA (2 eq.); CH₂Cl₂; 15 h; 4 M NaOH in MeOH; 2h then 10 M HCl; 20 °C; 80%; ii allyl bromide (1.2 eq.); K₂CO₃ (1.2 eq.); acetone; 56 °C; 23 h; 94%.

Thermolysis of 132 was attempted using the conditions reported by Otterlo et al.¹⁶⁰ by the (neat, 250 °C, 2 hours). Contrary to Otterlo’s report this rearrangement afforded an almost inseparable mixture of phenols 118a and 118b (118a:118b = 2:1) in 82% together with a much smaller quantity of pure 118a in 8% yield. Similarly, rearrangement of 134 afforded phenol 119 in 90% isolated yield after column chromatography (Scheme 2.5).

Scheme 2.5. ortho-Claisen Rearrangements of 132 and 134 leading to 118a, 118b and 119. Reagents and conditions: Δ, neat (250 °C); 2h.
Figure 2.1. $^1$H NMR (CDCl$_3$) of phenols 118a and 118b
Acylation of the mixture of 118a and 118b (Et$_3$N, 1.2 equivalents, Cl$_3$CCOCl, 1.2 equivalents, Et$_2$O; 0 °C; 118a:118b = 2:1) resulted in the isolation of the trichloroacetates 120a and 120b which were again inseparable by column chromatography, in excellent overall yield (82%; 120a:120b = 2:1). By way of comparison a small quantity of pure 118a furnished acetate 120a in 77% yield under identical acylation conditions. Similarly, an isomeric mixture of phenols 118a/118b (118a:118b = 2:1) was also acylated with tribromoacetyl chloride (Et$_3$N, 1.2 equivalents, Br$_3$CCOCl, 1.2 equivalents, Et$_2$O; 0 °C) which furnished acetates 121a/121b in 74% isolated yield (121a:121b = 2:1) whereas 119 afforded 122 in 88% (Scheme 2.6).

![Scheme 2.6. Generation of pivotal pre-cyclization substrates 120a and 120b, 121a and 121b, 120a and 122. Reagents and conditions: i Et$_3$N (1.2 eq.); Cl$_3$CCOCl (1.2 eq.); Et$_2$O; 0 °C; ii Et$_3$N (1.2 eq.); Br$_3$CCOCl (1.2 eq.); Et$_2$O; 0 °C.](image-url)
2.2 Cyclisation of Chloroacetates/bromoacetates 120-122

With the substrates 120-122 at hand their thermolysis in the presence of catalytic quantities of copper salt 70 under thermal\textsuperscript{152} or microwave\textsuperscript{153} conditions was attempted with a view to the synthesis of 123, 124 and 125. Previous studies within the Quayle group had shown that both methods of activation are possible in these reaction sequences,\textsuperscript{2, 4, 97, 100, 101, 154-159} although there is some substrate dependency in certain cases.\textsuperscript{100, 101, 157-159} Initially, we found that the thermolysis of solutions of trichloroacetates 120a and 120b (120a:120b = 2:1) in DCE in a focussed microwave reactor afforded chloride 123 as a sole regioisomer with a conversion of 84%. However because of the intense pressure build-up during the course of the benzannulation reaction in the enclosed microwave reactor vials classical methods of heating had to be adopted.\textsuperscript{160} Further investigations, under these modified conditions, showed that heating a mixture of 120a and 120b (120a:120b = 2:1) in diglyme at reflux (concentration of 1.5 mmolmL\textsuperscript{-1}) in the presence of 70 (5 mol %) afforded naphthalene 123 in reproducible yields of 38% after chromatography. In a separate experiment a sample of the regioisomerically pure trichloroacetate 120a was also subjected to our standard benzannulation conditions, which afforded 123 in 36% yield after purification, an outcome which suggested that the presence of the unwanted isomer, 120b in the mixture of trichloroacetates originally used in the benzanulation reaction did not have a deleterious effect on the yield of the reaction. (Table 2.1). We presume that 120b undergoes polymerization during the benzannulation sequence which ultimately leads to the formation of an insoluble, intractable, material that can be removed simply by filtration through a silica gel plug upon work-up. Inexplicably, the mixture of bromides 121a/120b underwent benzanlation in the presence of Cu(I)Br, in otherwise identical conditions, but in a much reduced yield of 13% after chromatography. Conducting these reactions in 1,4-dioxane, a lower boiling solvent, resulted in diminished yields in these reactions, Table 2.1.
<table>
<thead>
<tr>
<th>Solvent</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diglyme</td>
<td>38</td>
</tr>
<tr>
<td>Dioxane</td>
<td>27-36</td>
</tr>
</tbody>
</table>

Table 2.1. ATRC of 120-122. Reagents and conditions: 70 (5 mol %); diglyme; 2 h; Δ (162 °C).
The oxidation of 123-125 to quinones 126-128 was also addressed with a view to developing a benzannulation-oxidation sequence to the synthesis of plumbagin 7b and related quinones. Gratifyingly, reaction of 123, 124 and 125 with 2.5 equivalents of cerium ammonium nitrate (CAN) in acetonitrile/water (1:1) at room temperature afforded quinones 126, 127 and 128 in 86%, 86% and 45% yield respectively after purification by column chromatography. It is of note that the regioselective synthesis of halogenated quinones such as 126 has little literature precedent and this approach may therefore have some synthetic utility.

Scheme 2.7. Synthesis of quinones 126-128. Reagents and conditions: i. CAN (2.5 eq.); CH₃CN; 20 °C.
2.3 Synthesis of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene-1,4-diones.

Our planned synthesis of 7b and 7a was to follow the scheme depicted below (Scheme 2.8). It was envisaged that oxidation of the haloaromatics 123-125, derived from the initial BHQ reaction, to the quinones 126-128 followed by palladium-mediated borylation to 129 and 130, and finally chemoselective oxidation of 129 or 130 would lead to the desired target molecules 7a and 7b. The palladium-catalysed borylation of 126, as originally described by Miyaura, was therefore attempted (Scheme 2.8).

Scheme 2.8. Plumbagin 7b and juglone 7a: end-game strategy. Reagents and conditions: i CAN (2.5 eq.); CH₃CN; 20 °C; ii B₂Pin₂ 55 (3 eq.); Pd(dppf)Cl₂ (0.05 eq.); KOAc (3 eq.); DMF; iii m-CBPA; CH₃CN; 20 °C.

Unfortunately reaction of 126 with B₂Pin₂ 55 in the presence of Pd(dppf)Cl₂ (0.05 mol%) in DMF at 90 °C, as indicated in the literature, failed to generate any of the desired boronate esters 129 and 130 even after extended reaction times of 44 hours.

As our aim to access 7b and 7a via boronate ester 129/130 was daunted, we recoursed to the synthesis of boronate ester 135 and 136 in which their accessibility and a subsequent oxidation with cerium ammonium nitrate would afford the ester 129 and 130 before chemoselective, oxidative, unmasking of the C-B functionality to 7b and 7a (Scheme 2.9).
Scheme 2.9. Plumbagin 7b and juglone 7a: end-game strategy. Reagents and conditions: i B$_2$Pin$_2$ 55 (3 eq.); Pd(dppf)Cl$_2$ (0.05 eq.); KOAc (3 eq.); DMF; ii CAN (2.5 eq.); CH$_3$CN; 20 °C; iii $m$-CBPA; CH$_3$CN; 20 °C.

Conducting the reaction of of 124 with B$_2$pin$_2$ 55 in the presence of PdCl$_2$(dppf) (5 mol%) in DMF at 90 °C, (see Scheme 2.9 above),$^8$ failed to generate the desired boronate esters 135 even after extended reaction times of 44 hours (table 2.2; entry 1 below). The use of tetrakis(triphenylphosphine)palladium(0), Pd(PPh$_3$)$_4$, 161 as catalyst in toluene at reflux also failed to generate any of the desired product. In all cases the generation of palladium black was observed without product formation (entry 2). Buchwald et al. have recently disclosed that the Pd(dba)$_2$-SPhos catalyst system is capable of promoting coupling of aryl chlorides and heteroaryl chlorides 162 however, the application of these modified reaction conditions failed to afford the desired product 135 in this case (entry 5).
Table 2.2. Palladium-catalysed borylation of 124 with 55. Reagents and conditions: 124 (1 eq.); 55 (3 eq.); Pd catalyst (0.05 eq.); KOAc (3 eq.); Δ (90-110 °C); 15-44 h.
2.3.1 Optimisation of the Miyaura borylation reaction

In view of the failure to effect a palladium-catalyzed cross-coupling reaction between aryl halides 123 with 124 we decided to use 1-bromonaphthalene 137 as a readily available model substrate in order to generate an optimum set of conditions for this reaction (Table 2.3).
2.3.1.1 Effect of catalyst on the Miyaura borylation reaction

Exposure of bromide 137 to Pd(dppf)Cl$_2$ using KOAc as base in degassed 1,4-dioxane at 90 ºC resulted in no conversion after 20 hours (Table 2.3; entry 1). However, treatment of 137 with 55 in degassed toluene in the presence of Pd(dba)$_2$-SPhos furnished boronate ester 138 albeit with 5% conversion (as monitored by $^1$H NMR spectroscopy of the crude product) (entry 2). Replacing toluene with DMF in this particular reaction resulted in a very slow conversion to product (5% of 138 after 44 hours). Similarly the use of “base-free” conditions, as reported by Matsubara and Yorimitsu,\textsuperscript{163} also proved to be ineffective. Recently, the Miyaura borylation of aryl halides, such as 137, under “solventless” reaction conditions was reported to be more effective than reactions carried out in the presence of solvents.\textsuperscript{10} Utilising these conditions (Table 2.3; entry 8) we noted that bis[(2-diphenylphosphino)phenyl]ether, DPEphos,\textsuperscript{164} promoted the borylation of 137 to 138 with modest levels of conversion (ca. 10%). Although this was a poor conversion it did warrant further scrutiny. Surprisingly increasing the reaction time from 12 to 15 hours for this coupling reaction resulted in a four-fold increase in the extent of conversion (Table 2.3; entry 9). Furthermore, the use of Pd(dba)$_2$-Sphos and Pd(dba)$_2$-Xphos as catalyst,\textsuperscript{162,165} under a standard set of “solventless” reaction conditions (1 mmol 137; 1 mmol Pd(dba)$_2$-Sphos or Pd(dba)$_2$-Xphos; 2 mmol KOAc, 2.5 mmol B$_2$pin$_2$; neat; 12 hours;]), resulted in conversions of 67% and 68% respectively (Table 2.3; entry 4 and entry 6), whereas the use of Pd(dba)$_2$-dppf (Table 2.3; entry 11) as catalyst failed to promote cross coupling. Finally we observed that PdCl$_2$(PPh$_3$)$_2$,\textsuperscript{166} proved to be just as effective as the more exotic catalyst systems for this coupling reaction. Under our standard conditions we found that reaction of 137 with 55 in the presence of PdCl$_2$(PPh$_3$)$_2$ and KOAc (3 equivalents) for 12 hours resulted in a 67% conversion to ester 138 (Table 2.3; entry 12). Reducing the reaction time to 3 hours resulted in an increase in the conversion to 70% and afforded 138 in 46% yield after chromatography (Table 2.3; entry 13).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent (mL)</th>
<th>Reaction time (h)</th>
<th>Conversion (%)&amp;</th>
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<td>1</td>
<td>Pd(dppf)Cl₂</td>
<td>1,4-dioxane</td>
<td>20</td>
<td>none</td>
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<tr>
<td>2</td>
<td>Pd(dba)₂-SPhos</td>
<td>Toluene</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>Pd(dba)₂-SPhos</td>
<td>DMF</td>
<td>44</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
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<td>12</td>
<td>67</td>
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<td>3</td>
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</table>

Table 2.3. Effect of pre-catalyst on the conversion of 137 and 55. Reagents and conditions: i catalyst (5 mol%); KOAc (3 eq.); Δ (50-120 °C); 3-44 h; (% conversion by ^1H NMR; *isolated yield after chromatography).
2.3.1.2 Effect of base on the Miyaura borylation reaction

The outcomes of the Miyaura borylation reactions are responsive to the base used,\(^\text{10, 167}\) which prompted screening of a variety of bases in the optimised, Pd(PPh\(_3\))\(_2\)Cl\(_2\)-catalysed borylation reactions of 1-bromonaphthalene \(\text{137}\). The use of potassium acetate and other bases (e.g. Na\(_2\)CO\(_3\), K\(_2\)CO\(_3\), Cs\(_2\)CO\(_3\) and Et\(_3\)N) \(^\text{10, 93, 168}\) has been reported in Pd-catalysed cross-coupling reactions with mixed outcomes.\(^\text{93, 95}\) In our study we noted that the use of an organic base (Et\(_3\)N) inhibited the cross coupling reaction leading to \(\text{138}\). Trace of amounts of coupled product were observed when sodium acetate or sodium bicarbonate were employed whereas reactions conducted in the presence of potassium acetate resulted in conversions ranging from 22-93\%,\(^\text{93}\) a finding which mirrors reports in the literature.\(^\text{92, 169}\) Based upon these findings, subsequent borylation reactions in this report were therefore carried out in the presence of potassium acetate.
<table>
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<th>Entry</th>
<th>Base</th>
<th>Reaction time</th>
<th>Conversion (%)&lt;sup&gt;£&lt;/sup&gt;</th>
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<td>1</td>
<td>KOAc</td>
<td>3</td>
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<td>NaOAc</td>
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<td>68</td>
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<tr>
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<td>49</td>
</tr>
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<td>24</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>(n-Bu)&lt;sub&gt;4&lt;/sub&gt;NOAc</td>
<td>15-24</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>KOAc</td>
<td>15-24</td>
<td>65-77%</td>
</tr>
</tbody>
</table>

**Table 2.4.** Effect of base on the palladium–catalysed reaction of 137 and 55. Reagents and conditions: 137 (1 eq.); 55 (3 eq.); Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (0.05 eq.); Δ (100-120 °C); 20 h; (*by 1H NMR; # isolated yield after column chromatography).  

As can be seen from **Table 2.4** those reactions that were conducted in the presence of either sodium acetate and potassium acetate afforded roughly comparable conversions to product (67-68%). Reactions involving the use of potassium carbonate and caesium carbonate proved to be inefficient and proceeded to 3% product conversion after 24 hours, which was an identical outcome to the case where no base was added (**Table 2.4**: entry 7). The use of tetrabutylammonium acetate, Bu<sub>4</sub>NAc as base resulted in poor conversion (15%) to 138 (**Table 2.4**: entry 8) whereas triethylamine, which has been
widely employed in such reactions\textsuperscript{169} resulted in the moderate conversion (49\%) to \textbf{138} over a 3 hour reaction time (\textbf{Table 2.4}; entry 3). Increasing the reaction time to 12 hours in this particular case only resulted in marginally higher conversions (49–55\%) to product. The use of caesium acetate in the Miyaura borylation reaction is not well documented but again resulted in moderate conversions (30\%) over extended reaction times (12 hours), entry 4. The results depicted in \textbf{Table 2.4} indicate a general trend where it appears that the presence of an acetate counterion results in higher conversions whereas carbonate bases prove to be poor promoters of this coupling reaction. Interestingly Zernickel \textit{et al.} have recently disclosed that a threshold pH of 6.7–7.7 is optimum for the borylation of aryl halides such as \textbf{137} with tetrahydroxydiboron, where sodium and potassium acetates proved to be optimal.\textsuperscript{95}
2.3.1.3 Solvent Effects on the Miyaura borylation reaction

In order to complete this survey, the effect of solvent on the course of the Miyaura borylation reaction was also studied briefly. The initial borylation reaction of 137 with bis(pinacolato)diboron 55, when conducted in DMF, was largely unsuccessful (5% conversion) and merely deposited palladium black from solution. Replacing the solvent, DMF, with either toluene or 1,4-dioxane did not have any significant effect, in most cases, a similar outcome was observed. Finally, reaction of 137 with B₂Pin₂ 55 under a solvent-free condition at 118 °C for 24 hours enabled the conversion of 137 to 138 in 71–75%. On completion of this investigation we were able to define optimum conditions for the coupling of 124 with 55. These coupling reactions were best achieved in a sealed Reacti-Vial™ charged with the 123/124 (0.8 mmol), B₂Pin₂ 55 (2.0 mmol), palladium catalyst (PdCl₂(PPh₃)₂ (0.01–0.02 mmol) in the presence of anhydrous potassium acetate (2.0 mmol) when heated, without solvent, to 118 °C for 20–24 hours. Surprisingly conversions were higher when chlorides such as 123 rather than the corresponding bromide 124 were employed in the coupling reaction, Scheme 2.10.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conversion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF</td>
<td>5%</td>
</tr>
<tr>
<td>Toluene</td>
<td>5%</td>
</tr>
<tr>
<td>dioxane</td>
<td>none</td>
</tr>
<tr>
<td>Neat</td>
<td>71-75 (%46)</td>
</tr>
</tbody>
</table>

Table 2.5. Solvent effects on the Miyaura borylation coupling reaction of 137 leading to 138. Reagents and conditions: i 137 (1eq.); 55 (3 eq.); Pd(PPh₃)₂Cl₂ (0.05 eq.); KOAc (3 eq.); Δ (50-118 °C); 20 h. (*by 1H NMR; *isolated yield after column chromatography).
Employing these modified reaction conditions [123/124 (0.8 mmol), B$_2$pin$_2$ 55 (2.0 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.01–0.02 mmol) anhydrous KOAc (2.0 mmol), Δ (118 °C), 20–24 hr] enabled the isolation of ester 135, from 5-bromo-1,4-dimethoxynaphthalene 124 in 68% yield after chromatography. Similarly subjection of chloride 123 to these reaction conditions afforded the boronate ester 135 in 68–75% isolated yields after chromatography.

Scheme 2.10. Optimized Miyaura borylation of 123 and 124. Reagents and conditions: i chloride 123 (1 eq.) 55 (3 eq.); PdCl$_2$(PPh$_3$)$_2$ (0.05 eq.); KOAc (3 eq.); Δ (118-130 °C); 24 h; 68-75%; ii bromide 124/123 (1 eq.) 55 (3 eq.); PdCl$_2$(PPh$_3$)$_2$ (0.05 eq.); KOAc (3 eq.); Δ (118-130 °C); 24 h; 65-68%.
2.3.2 Towards juglone and plumbagin: oxidation of the boronate ester

The final step of our planned synthesis entailed chemoselective oxidation of the ethers 135/136 to quinones 129/130 followed by conversion of the boronate ester moiety to a phenolic hydroxyl group. We found that oxidation of 135/136 with cerium ammonium nitrate (2.5 equivalents) in acetonitrile/water (2:1 mL) at room temperature for 1 hour afforded the quinones 129/130 in good yield after chromatography. Finally, oxidation of the quinones 129/130 with m-CBPA (1.5 equivalent, DCM, r.t, 6 h) efficiently led to the naphthoquinones 7a and 7b in 54% and 94% isolated yields respectively whose spectral data were identical to that of authentic materials.

![Diagram](image)

**Scheme 2.11.** Synthesis of 7b and 7a: the end game. Reagents and conditions: i 124 or 125 (1 eq.); 55 (3 eq.); Pd catalyst (0.05 eq.); KOAc (3 eq.); Δ (118-130 °C); 24 h; 53-68%; ii CAN (2.5 eq.); MeCN:H₂O (1:1); 20 °C; 2 h-6h; 53-66%; iii m-CBPA (1.5 eq.); CH₃CN:H₂O or CH₂Cl₂; 6 h; 20 °C; 54% and 94%.
2.3.3 Plumbagin and juglone: conclusion

In summary, we have developed a 8 step synthesis of plumbagin 7b starting from readily available 2,5-dimethoxy-4-methylbenzaldehyde 5b. The key steps of this synthesis included the application of a new benzannulation reaction for the regioselective synthesis of 5-chloro-1,4-dimethoxy-2-methylnaphthalene 125 and its conversion to 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene-1,4-dione 130 using a solventless Miyaura borylation reaction. Chemoselective oxidation of this intermediate using m-CPBA afforded plumbagin 7b in high yields, Scheme 2.12.

Scheme 2.12. Benzannulation sequence leading to the synthesis of 7b. Reagents and conditions: i m-CPBA (1.4 eq.), CH₂Cl₂, 15 h, 4 M NaOH in MeOH, 2 h, then 10 M HCl; 79%; ii Allylbromide (1.2 eq.), K₂CO₃ (1.2 eq.), acetone, reflux; 94%; iii Δ (162 °C), 1 h; 100% iv Cl₃CCOCl (1.2 eq.) or Br₃CCOCl (1.2 eq.), NET₃ (1.2 eq.), pyridine, 0 °C to r.t.; 91% and 64%; v 70 (5 mol %); 1,2-DCE (1 mL); Δ (165 °C); 2 h; 30%; vi 55 (3 eq.); Pd(dpdpf)Cl₂ (0.05 eq.); KOAc (3 eq.); 1,4-dioxane; 90 °C; 24 h; 54%; vii CAN (2.5 eq.); MeCN-H₂O; 20 °C; 12 h; 53%; viii m-CPBA; MeCN:H₂O; 20 °C; 3 h; 94%.
A similar sequence as above has enabled the synthesis of juglone, 7a, in 50% yield (Scheme 2.13)

Scheme 2.13. Initial benzannulation sequence leading to the synthesis of 7a. Reagents and conditions: i m-CBPA (2 eq.); CH₂Cl₂; 15 h; 4 M NaOH in MeOH; 2 h; then 6 M HCl; 76%; ii allylbromide (1.2 eq.); K₂CO₃ (1.2 eq.); acetone; reflux; 76%; iii Δ (162 °C); 1 h; 82%; iv Cl₃CCOCl (1.2 eq.); NEt₃ (1.2 eq.); Et₂O; 0 °C to r.t.; 62%; v Br₃CCOCl (1.2 eq.); NEt₃ (1.2 eq.); Et₂O; 0 °C to r.t.; 74%; vi 70 (5 mol %); diglyme (1 mL); 165 °C; 2 h; 36%; vii 70 (5 mol %); diglyme (1 mL); 165 °C; 2 h; 12%; viii 55 (3 eq.); Pd(PPh₃)₂Cl₂ (0.05 eq.); KOAc (3 eq.); 118 °C; 24 h; 71%; ix CAN (2.5 eq.); MeCN-H₂O; 20 °C; 1 h; 66%; x m-CBPA (1.5 eq.); MeCN:H₂O; 20 °C; 1 h; 50%.
2.3.4 UV-vis Absorption Spectra

UV-vis absorption spectra of 16, 123, 129, 135 and 7a were measured in chloroform. Absorption spectra of naphthoquinone 16 was obtained as standard for comparison. Figure 2.2 shows that bathochromic shifts of all but 135 were higher than that of the naphthoquinone 16. A shift of 5.7 cm\(^{-1}\) was observed for 123 with reference to 16, whereas, juglone 7a, with an additional OH- group at C1 showed a noticeable energy transition in the visible region. This observed bathochromic shift is a result of a strong intramolecular hydrogen bonding of the OH- group in solution.\(^{170}\)

![UV-vis absorption spectra of 7a, 16, 123, and 129.](image)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>(\lambda_{\text{max}})</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="16" /></td>
<td>337</td>
</tr>
<tr>
<td><img src="image" alt="123" /></td>
<td>342</td>
</tr>
<tr>
<td><img src="image" alt="129" /></td>
<td>356</td>
</tr>
<tr>
<td><img src="image" alt="7a" /></td>
<td>432</td>
</tr>
</tbody>
</table>

Figure 2.2. UV-vis absorption of 7a, 16, 123, and 129.
Given the paucity of borylated quinones related to 129 and 130 in the literature we investigated the physical origins of the absorption spectra of 1,4-naphthaquinone 16, juglone 7a and 123, 129 and 135 using time dependent density functional theory (TD-DFT). Each molecule was fully optimised at the B3LYP\textsuperscript{171-173}/6-311G(d,p)\textsuperscript{174-176} level. No treatment for solvent interaction was included. All calculations were carried out using the GAUSSIAN 09\textsuperscript{177} suite of programs. Where appropriate the global conformational minimum was obtained by calculating rotational potentials for all rotatable groups.

Figure 2.3 shows the computed UV-vis spectra, where in each case the intensities have been normalised by the highest absorption in the range 270 – 600 nm. Table 2.6 compares the calculated peaks with those observed and provides a breakdown of the electronic excitations involved.

We note that the spectra of 1,4-naphthaquinone 16 and juglone 7a are dominated by bands of charge transfer type character in which electron density is transferred from an orbital (HOMO or HOMO-1) centred on the phenyl /phenol unit to an orbital (LUMO) centred on the quinone unit, see Figure 2.4. 129 also shows some similar characteristics but the absorption band is brought about by a more complex mix of excitations, see Table 2.6. The strong shift to longest wavelength in 7a appears to be due to the hydrogen bonding between the phenolic H atom and a quinoid O atom. The conformation of 7a in which the phenolic H is rotated through 180° such that no hydrogen bonding is possible shifts the band back to significantly shorter wavelengths. The absorption bands of 123 and 135 do not show the charge transfer character but rather a $\pi^* \leftarrow \pi$ character with correspondingly higher absorption energies.
Figure 2.3. Computed absorption spectra obtained at the B3LYP/6-311G(d,p) level for 16, 7a, 123, 129 and 135.
<table>
<thead>
<tr>
<th></th>
<th>Experimental $\lambda$ / nm</th>
<th>Computed $\lambda$ / nm</th>
<th>Oscillator Strength</th>
<th>Electronic Character and Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,4-Naphthaquinone 16</td>
<td>337</td>
<td>339</td>
<td>0.050</td>
<td>HOMO $\rightarrow$ LUMO 97%</td>
</tr>
<tr>
<td>Juglone 7a</td>
<td>432</td>
<td>437</td>
<td>0.079</td>
<td>HOMO $\rightarrow$ LUMO 99%</td>
</tr>
<tr>
<td>129</td>
<td>356</td>
<td>361</td>
<td>0.022</td>
<td>HOMO $\rightarrow$ LUMO 96%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>353</td>
<td>0.021</td>
<td>HOMO $\rightarrow$ LUMO 37%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>347</td>
<td>0.022</td>
<td>HOMO-3 $\rightarrow$ LUMO 61%</td>
</tr>
<tr>
<td></td>
<td>135</td>
<td>320/332</td>
<td>0.111</td>
<td>HOMO $\rightarrow$ LUMO 96%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>295</td>
<td>0.057</td>
<td>HOMO $\rightarrow$ LUMO+1 79%</td>
</tr>
<tr>
<td></td>
<td>123</td>
<td>342</td>
<td>0.100</td>
<td>HOMO $\rightarrow$ LUMO 96%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>306</td>
<td>0.089</td>
<td>HOMO $\rightarrow$ LUMO+1 84%</td>
</tr>
</tbody>
</table>

Table 2.6. Computed absorption spectra properties of 16, 7a, 123, 129 and 135 corresponding to Figure 2.5. See Figures 2.4-2.7 for orbitals referred to.
Figure 2.4. Frontier orbitals (isovalue 0.04 au) responsible for key absorption bands in 16 and 7a.
<table>
<thead>
<tr>
<th>HOMO-3</th>
<th>HOMO-2</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>HOMO-1</td>
<td>HOMO</td>
</tr>
<tr>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
</tbody>
</table>
Figure 2.5. Frontier orbitals (isovalue 0.04 au) responsible for key absorption bands in 129
Figure 2.6. Frontier orbitals (isovalue 0.04 au) responsible for key absorption bands in 135.
Figure 2.7. Frontier orbitals (isovalue 0.04 au) responsible for key absorption bands in 123.
2.4 Studies Towards the Synthesis of γ-citromycinone, 141

Anthracyclines\textsuperscript{83, 178, 179} are a large group of red to orange-coloured linear polyketides comprising the aglycone unit and the supported sugar component(s). The aglycons are generally referred to as anthracyclinones.\textsuperscript{180, 181} The attractiveness of anthracycline chemistry developed due to the remarkable and unique responses they demonstrated when applied as antitumor agents in the early 1960s; therefore they are among the most actively researched areas of chemistry.\textsuperscript{83, 182} With the discovery of β-rhodomycine\textsuperscript{183, 184} in 1950 by the research group of Brockmann,\textsuperscript{185} it was consequently possible for other groups to envisage analogues and generate variants through functional group manipulation either around the aglycone system or sugar component.\textsuperscript{82, 186} Of these compounds, Daunomycin\textsuperscript{187} and Doxorubicin (14-hydroxydaunomycin\textsuperscript{188}) 140 have been most extensively studied owing to their broad spectrum biological activities. While 139 is broadly applied to treatment of leukaemia; 140 is used for the treatment of varieties of solid tumours, including breast cancers.\textsuperscript{189-191} The major challenge associated with administration of these compounds is a lack of selectivity in cells causing reported cardiotoxicity,\textsuperscript{192-194} resulting in a continuous search for better analogues which could surpass existing or known antibiotics. One of the early discovered anthracyclines was γ-citromycinone\textsuperscript{195-197} 141, a 4,11-dihydroxyanthracyclinone antibiotic, isolated from Streptomyces purpurascens\textsuperscript{198} by Niemeyer, a doctoral student of Brockmann Hans in 1967.\textsuperscript{197} The general structure of these class of compounds contains the 7,8,9,10-tetracene-5,12-quinone chromophore.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{Anthracyclines 139-143.}
\end{figure}
Previous attempts to isolate 141 from natural sources\textsuperscript{197} have met with limited success, likewise, reported syntheses\textsuperscript{195,196} of 141 have also been problematic. The reported syntheses have either furnished related compounds or very low yields, presumably reason why most authors have yet to report the percentage conversion of 141. This chapter therefore describes the author’s effort in synthesising “141” ABC ring, using the BHQ reaction as a key step.

The first synthesis of quinone 141 was reported by Kende et. al. in 1981.\textsuperscript{199} Unfortunately, the result of structural elucidation proved that diol 155\textsuperscript{197} was synthesised instead. The hydroxy group at position C-10 was wrongly placed at C-9 and therefore led to the synthesis of 155, Scheme 2.14. The initial synthetic step involved the aromatisation of ketone 144 using 2,3-Dichloro-5,6-dicyano-p-benzoquinone, DDQ and the subsequent treatment with trimethyl orthoformate (HC(OCH\textsubscript{3})\textsubscript{3}) furnishing aldehyde 145 (65%). Alkylation of 145 using Emmons reagent (EtO\textsubscript{2}POCH\textsubscript{2}CO\textsubscript{2}Et) in the presence of NaH (1.5 eq.) in benzene followed by hydrogenation with catalytic Pd-C (5%) in ethanol afforded ester 146 in 92% yield. Claisen condensation of 146 with diethyl oxalate (NaH in C\textsubscript{6}H\textsubscript{6}) supplied ester 147 in 68% after 20 hours. Alkylation of the diester 147 with methyl vinyl ketone (MVK) in refluxing C\textsubscript{6}H\textsubscript{6}-ethanol and Et\textsubscript{3}N (1:1) gave the Michael adduct 148 in 80% after 20 hours. Treatment of 148 with pyrrolidine (reflux with benzene) resulted in spontaneous cyclisation to furnish the tricycle 149 in 87%. Enone 149 then subjected to alkaline hydrolysis using KOH (5 equivalents) in refluxing EtOH furnished the acid derivative 150 in 95% after a period of 24 hours. Cyclodehydration (TFA in TFAA (2:1) for 2 hours) afforded tetracycle 151 in 63% which upon oxidation (AgO, Me\textsubscript{2}CO, HNO\textsubscript{3}, r.t, 3 h) generated the naphthoquinone 152 which immediately underwent isomerisation on treatment with HCl (few drops) at r.t to afford quinone 153 in 93%. Quinone 153 was demethylated (AlCl\textsubscript{3}, DCM, 18 h, 20 °C) to ketone 154, ethynylation\textsuperscript{200} of 154 and subsequent reduction using di-imide (generated in situ from KO\textsubscript{2}CN=NCO\textsubscript{2}K, pyridine and alcohol) resulted in the isolation of 155 in 63%. Aside from the reported rigorous synthetic route, most reaction steps went to completion after a very long duration to furnish the desired products.
Scheme 2.14. Synthesis of 150. i DDQ (3.2 eq.); HC(OCH₃)₃/EtOH; 24 h; ii (EtO)₂POCH₂CO₂Et (1.2 eq.); NaH (1.5 eq.); C₆H₆; 20 °C; 4 h; iii H₂; 5% Pd-C; EtOH; 20 °C; iv (Et₂O)C₂ (1.2 eq.); NaH (2.0 eq.); C₆H₆; 2 h; v cat; Et₃N; EtOH:C₆H₆ (1:1); Δ; 20 h; vi pyrrolidine; C₆H₆; catalytic AcOH; 5 h; vii KOH (5 eq.); EtOH; Δ; 24 h; viii TFA-TFAA (2:1); 2 h; ix AgO (4 eq.); Me₂CO; HNO₃; 20 °C; 3 min; x acetone; HCl; 20 °C; xi AlCl₃; CH₂Cl₂; 20 °C; 18 h; m-CBPA; CH₂Cl₂; 20 °C; then NaOH; H₂O-THF; 20 °C; 18 h.
A frequently used approach to the synthesis of the linear, tetracyclic framework present in the anthracyclines utilizes a Diels Alder intermolecular cyclisation approach, between diones such as 157 which exist in tautomeric equilibria with diols 156. For example, for the addition of anthracene example 157, to diene 49 after a slow tautomeric interconversion of 156 to 157 furnishing naphthacenequinone 158 at 120 °C (Scheme 2.15).  

Scheme 2.15. Synthesis of 158 by Diels Alder reaction
Hauser and Mai reported the first total synthesis of 141 in 1984. In this synthesis an intermolecular ene reaction was adopted as a key step in the conversion of aldehyde 159 to the exo-methylene alcohol 160. Treatment of 159 with a Lewis acid (SnCl₄) in dichloromethane at room temperature promoted cyclisation affording olefin 160 in 93% yield.

Scheme 2.16. Cyclisation of 159 to 160. Reagents and conditions: i SnCl₄.5H₂O (0.5 eq.); CH₂Cl₂; 20 °C.

Sharpless epoxidation of 160 (VO(acac)₂; t-BuO₂H) afforded the cis-epoxide 161 as sole stereoisomer in 66 % yield. Methylation of 161 (Me₂SO₄; K₂CO₃) in acetone furnished epoxide 162, which, on treatment with excess organocuprate reagents (2 eq. CuCN, 12 eq. CH₃Li, THF, 0 °C) enabled access to diol 163. Finally, demethylation of 163 to the desired product 141 was cleanly accomplished, in 86% yield, using BCl₃ in dichloromethane at 0° C.

Scheme 2.17. Synthesis of γ-citromycinone 141 from 160. Reagents and conditions: i t-BuO₂H; VO(acac)₂; CH₂Cl₂; 66%; ii Me₂SO₄; K₂CO₃; acetone; 91% iii CuCN; MeLi; THF; 0° C; 84%; iv BCl₃; CH₂Cl₂; 86%.
Thereafter, Umezawa et al\textsuperscript{196} reported a short synthesis of \textbf{141} following the degradation of antitumour serirubicin\textsuperscript{205} \textbf{164}. Treatment of \textbf{164} with catalytic amount of Pd/BaSO\textsubscript{4} (5\%) in methanol afforded \textbf{141} in a rather unreported conversion. The initial sugar \textbf{164}, was isolated from the culture filtrate of Streptomyces cyaneus MG344-hF49.\textsuperscript{206}

\begin{equation*}
\begin{align*}
\textbf{164} & \quad \xrightarrow{i} \quad \textbf{141} \\
& \quad \text{Reagents and conditions: i H}_2; 5\% \text{ Pd/BaSO}_4; \text{MeOH; 65 °C.}
\end{align*}
\end{equation*}

\textbf{Scheme 2.18}. Degradation of \textbf{164} to \textbf{141}. Reagents and conditions: i H\textsubscript{2}; 5\% Pd/BaSO\textsubscript{4}; MeOH; 65 °C.
2.4.1 Model studies directed toward the synthesis of γ-citromycinone 141

This chapter describes how the BHQ reaction was to be applied to the synthesis of 172, a model compound related to the ABC ring system of γ-citromycinone 141. The key question to be posed here was whether the radical 166, derived from trichloroacetate 165, would undergo an 8-endo-trig cyclization reaction to 167 in order to trigger a benzannulation pathway 168. Subsequent to the formation of 168, a formal 4-exo-trig radical closure onto the aromatic ring and retro-[2+2] cycloaddition of CO₂ and rearomatisation by loss of two molecules of HCl would ultimately lead to the tetrahydroanthracene 172, Scheme 2.19.

Scheme 2.19. The benzannulation of trihaloacetate 165 leading to 9-chloro-5,8-dimethoxy-1,2,3,4-tetrahydroanthracene, 172.
In planning a route to 9 it was envisaged that Dakin oxidation of aldehyde 5a, as above, would afford phenol 131, which on alkylation with 2-chlorocyclohexan-1-one 178, Wittig olefination and ortho-Claisen rearrangement would generate the key intermediate 175. Acylation of 175 would be expected to afford the pre-cyclisation substrates 176a or 176b respectively. Benzannulation of 176a/176b to 8a/8b and oxidation to quinone 177a/177b would then enable introduction of the C9-hydroxyl group via a Miyaura borylation–oxidation sequence as previously utilised in the synthesis of plumbagin 7b (Scheme 2.20).

Scheme 2.20. Proposed synthetic route to 9. Reagents and conditions: i m-CBPA (2 eq.); CH₂Cl₂; 15 h; 4 M NaOH; 4 h then 6 M HCl; ii α-chlorocyclohexanone 178; K₂CO₃; refluxing acetone; iii MePPh₃Br; KO'Bu; THF; 15 h; iv Δ (162 °C); 2 h; v Cl₃CCl/Br₃CCl, Et₃N, Et₂O, 0 °C to r.t.; vi 70 (5 mol %); refluxing diglyme; 3 h; vii CAN; MeCN: H₂O (1:1); 15h.
Dakin oxidation of 5a leading to phenol 131 was achieved in 69-80% and was amenable to scale-up on a 6 g scale (section 2.1). Attempted etherification of 178 with phenol 131, as suggested by Zhou207 afforded 173 in 21% yield when conducted in acetone as solvent. After optimisation which included replacing acetone with DMF while employing 1.5 to 2 equivalents of 2-chlorocyclohexan-1-one 178, over a reaction time of 48 hours, resulted in vastly improved yields of the isolated product (80% isolated yield) after chromatography (Table 2.7).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent (mL)</th>
<th>Reaction Time (h)</th>
<th>131 (eq.)</th>
<th>178 (eq.)</th>
<th>% Conversion</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>Acetone</td>
<td>24</td>
<td>1.0</td>
<td>1.0</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
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<td>1.0</td>
<td>70</td>
</tr>
<tr>
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<td>1.5</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
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<td>2.0</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>48</td>
<td>1.0</td>
<td>2.0</td>
<td>95 (80)</td>
</tr>
</tbody>
</table>

Table 2.7. Results of etherification of 131 with 178 (%Isolated yield after chromatography). Reagents and conditions: i K₂CO₃; refluxing acetone/DMF.
Wittig reaction of 173 proceeded without incident and furnished alkene 174 in 72-74% isolated yield on a 6 g scale using a slightly modified literature procedure.\(^{208, 209}\) We noted in this sequence that the addition of 2-(2,5-dimethoxyphenoxy)cyclohexa-1-one to a pre-formed solution of the Wittig reagent at 0 °C afforded slightly higher yields (72-74\%) when compared to yields obtained (of 66-68\%) when methyltriphenylphosphonium bromide was added to a mixture of KO\textsubscript{t}Bu (1.2 equivalents) and ketone 173 (1 equivalent) in THF at 0 °C. (Scheme 2.21).

\[ \text{Scheme 2.21. Synthesis of alkene 174. Reagents and conditions: } \text{MePPh}_3\text{Br (1.2 eq.); KO}^\text{t}\text{Bu (1.2 eq.); THF; 0-20 °C; 5 h.} \]

Thermolysis of neat 174 for 3 hours at 250 °C under an atmosphere of nitrogen afforded the Claisen rearranged product 175. Further experiments indicated that this rearrangement reaction had gone to completion after 60 minutes at 250 °C and that the product 175 was stable to these reaction conditions for up to 16 hours.

\[ \text{Scheme 2.22. Claisen rearrangement of 174. Reagents and conditions: } 24 \text{ (1eq.); Δ (240-250 °C); 1 h.} \]
Acylation of 175 with either trichloroacetyl chloride (1.2 equivalents) or tribromoacetyl chloride (1.2 equivalents) in diethyl ether for 15 hours at 0°C to room temperature also afforded 176a and 176b in 82% and 69% yield respectively after chromatography. TLC analysis indicated that this reaction was relatively sluggish and was incomplete after 10 hours and the use of prolonged reaction times (20 h) resulted in low isolated yields of the desired products, presumably due to product decomposition. These reactions were therefore conducted for 15 hours at 0°C to room temperature and afforded 176a and 176b in yields of 82% and 69% respectively after purification by column chromatography, Scheme 2.23.

Scheme 2.23. Acylation of phenol 175 to 176a and 176b. Reagents and conditions: i. 175 (1 eq.); Cl$_3$CCOCl/Br$_3$CCOCl (1.2 eq.); NEt$_3$ (1.2 eq.), Et$_2$O, 0 °C to 25 °C; 69%/82%.
With the trichloroacetate \(176a\) and bromoacetate \(176b\) to hand they were subjected to the BHQ reaction using a standard set of reaction conditions (162 °C in diglyme for 2 hours in the presence of 70, Scheme 2.24). Fortunately, these reactions proceeded without incident and furnished anthracenes \(8a\) and \(8b\) in yields of 27% and 43% respectively. Further efforts to optimise these reactions, either by increasing catalyst loading or conducting the reaction at higher temperatures (200 °C) failed to generate in an improvement in isolated yield of the desired benzannulated products. In the case of \(176b\) the use of Cu(I)Br (10 mol %) resulted in the isolation of bromide \(8b\) in diminished yield (15%). This substrate was also found to suffer thermal decomposition at temperatures in excess of 162 °C.

![Scheme 2.24. Benzannulation sequence leading to 8a and 8b. Reagents and conditions: i 70 (5 mol%); diglyme; Δ (162 °C); 3 h.](image)

\[\text{Scheme 2.24. Benzannulation sequence leading to 8a and 8b. Reagents and conditions: i 70 (5 mol%); diglyme; Δ (162 °C); 3 h.}\]
2.4.2 Elaboration of 9-chloro-5,8-dimethoxy-1,2,3,4-tetrahydroanthracene, 8a and 9-bromo-5,8-dimethoxy-1,2,3,4-tetrahydroanthracene, 8b

The synthesis of the model compound 9 required conversion of either 8a or 8b into 181 using the Miyaura borylation reaction followed by oxidation to the phenol 9, as previously described for 135 (section 2.3.1.3). Unfortunately attempted borylation of chloride 8a with B₂Pin₂ 55, using these optimised conditions ²¹⁰ [8a, 1 equivalent; 55, 3 equivalents; PdCl₂(PPh₃)₂, 0.05 equivalents; anhydrous KOAc, 3 equivalents; 118 °C-130°C, 20–24 h], proved to be unsuccessful. In contrast the palladium-catalysed borylation of bromide 8b, under a similar set of reaction conditions, furnished two products after purification by column chromatography. The first, relatively non-polar product (Rf 0.7; petroleum ether/ethyl acetate, 9:1), proved to be the symmetrical, dehalogenated, aromatic 183²¹¹ (24%), while the more polar material (Rf 0.4; petroleum ether/ethyl acetate, 9:1), a cream-coloured solid, was shown to be the desired boronate ester 181, which was isolated in 60% yield (Scheme 2.25).

Scheme 2.25. Miyaura borylation of 8b to 181 and 183. Reagents and conditions: i. 8b (1 eq.); 55 (3 eq.); PdCl₂(PPh₃)₂ (0.05 eq.); anhydrous KOAc (3 eq.); Δ (120 °C); 20–24 h.
Unfortunately, oxidation of ester 181 was irreproducible and marred by a competing protodeboronation reaction. Hence slow addition of a solution of cerium ammonium nitrate, CAN (0.83 g, 1.51 mmol) in acetonitrile-water (3:1, 4 mL) to a solution of 181 at 20 °C afforded quinone 182 in 27% yield after purification by chromatography. Repeating the reaction for a longer reaction time (24 hours) led to the isolation of the symmetrical quinone 184 in 38% yield as the only identifiable product after chromatography.

Scheme 2.26. CAN-mediated oxidation of 179 to 180 and 182. Reagents and conditions: i. 179 (1 eq.); CAN (2.5 eq.); CH$_3$CN-H$_2$O (1:1); 20 °C.
Finally, oxidation of quinone 182 with *m*-CBPA also proved to be problematic. Whereas reaction of 182 with *m*-CPBA (1.5 equivalents) in DCM for 6 hours resulted in no reaction, increasing the amount of *m*-CBPA to a 3-fold excess resulted in the isolation of quinone 184 (40%) together with only trace quantities of the desired hydroxyquinone 9.

Scheme 2.27. Synthesis of 184 and 9. Reagents and conditions: 181 (1 eq.); *m*-CBPA (1.5 eq.); CH₂Cl₂; 20 °C; 6 h.

Figure 2.9. Aromatic region of the ¹HNMR (CDCl₃) spectrum of hydroxyquinone 9.
2.5 The synthesis of 1,8-difunctionalised anthraquinones.

This section comprises two short projects which were concerned with the use of 1,8-dichloroanthraquinone as a readily available scaffold for the synthesis of anthraquinone derivatives:

1. The Miyaura borylation of readily available 1,8-dichloroanthraquinone, 12 was investigated as a model study for the synthesis of 1,8-dihydroxyanthraquinones 11, a structural motif that is common to a number of natural products.

2. The synthesis of 1,8-di-arylanthraquinones was investigated with a view to the synthesis of molecules such as 13 (Ar = pyrenyl), as shown in (Scheme 2.28). These systems may have interesting molecular recognition properties.

![Scheme 2.28. Coupling reactions of 1,8-dichloroanthraquinone 12.](image)

Incorporation of a polycyclic aromatic such as pyrene into constructs such as 12 via Suzuki cross-coupling reaction has little precedent in the literature but could lead to the synthesis of “molecular tweezers” which may have applications in the development of sensors and enzyme models. Pyrene and its derivatives have commonly found applications as sensors, light emitting diodes (LEDs), laser dye, optoelectronic materials and biomedical probes.\(^\text{213-222}\) Their desirable charge carrier ability is attributed to \(\pi\) stacking interface because of the way the four benzene rings are fused in the plane; most especially, when these compounds are coupled to substituent groups which enabled extended \(\pi\)-\(\pi\) conjugation in the new scaffold.\(^\text{213, 223}\)
In 2005, Inouye et al reported that pyrene-based derivatives, alkynyl pyrenes, demonstrated photochemical properties by acting as fluorochrome probe on DNA system. Interestingly, increasing the number of the alkynyl substituents attached to the pyrene core also effectively enhanced the photosensitivity of the system. Among the most studied class include the thiophene-substituted derivatives, they have found significant applications in organic-semiconductor-based field effect transistors (OFETs) and have shown interesting optical properties.

![Figure 2.10.](image)

**Figure 2.10.** 1,8-Bis(5-octythiophen-2-yl)pyrene 185 and 1,8-bis(5'-octyl-[2,2'-bithiophen]-5-yl)pyrene 186 as potential OFETs.

Cheng et al in 2007 synthesised dipyrenylbenzenes which displayed remarkable charge mobility. Zhen et al reported the photophysical properties of pyrene derivatives 187-189. Very recently it has been shown that 1-(pyrene-1-yl)-3-(5-chlorothiophene-2-yl)acrylic ketone 190 and 1-(pyrene-1-yl)-3-(5-phenylthiophene-2-yl)acrylic ketone 191 possesses nonlinear optical properties (NLO).

![Figure 2.11.](image)

**Figure 2.11.** Pyrene derivatives 187-191 exhibiting photophysical properties.
Anthracenes on the other hand have a wide variety of scientific applications.\textsuperscript{226-228} They have been employed as semiconductors, many being employed in organic light emitting devices (OLEDs).\textsuperscript{228} Some have been developed as chiral reagents and applied in catalysis.\textsuperscript{229-231} Synergistic effects in terms of $\pi$ stacking interactions could be enhanced if pyrene is successfully coupled to anthracene, they may result also in new scaffold with improved electrochemical properties. These systems could be enrichment for important chemical reactions such as molecular sensing, stereo-controlled reactions and in drug discovery.\textsuperscript{232-233} Examples of these cross coupling involves the Suzuki reaction\textsuperscript{8, 234} where notably; a palladium catalyst is employed, with or without solvents.\textsuperscript{10, 95} Past studies have relied on aryl bromide or iodide as precursors for this Suzuki cross coupling, possibly because of their reactivities.\textsuperscript{89, 163, 168, 235} A study which employed 1,8-dichloroanthraquinone and 1-methyl benzene as precursors in their reaction also afforded cross-coupled products 192-194 in a rather unreported yields.\textsuperscript{236, 237} In this study, a chloride, 1,8-dichloroanthraquinone 12, has been employed as starting material for the generation of new anthraquinones via a Suzuki cross coupling reaction.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure212.png}
\caption{Outcome of a previous cross-coupling\textsuperscript{236, 237}}
\end{figure}
2.5.1 The synthesis of 1,8-dihydroxyanthraquinone 11

As noted above (Section 2.4.2) oxidation of arylboronate esters to their respective phenols in substrates such as 8a is difficult in certain cases, Scheme 2.26. Although the Miyaura reaction to the intermediate boronic acid 181 was successful, final oxidation of 182 with m-CBPA proceeded inefficiently and afforded trace quantities of the desired phenol, 9, Scheme 2.29.

![Scheme 2.29](image)

**Scheme 2.29.** Synthesis of 9-hydroxy-5,6,7,8-tetrahydroanthracene-1,4-dione 9. Reagents and conditions: i 8a (1 eq.); 55 (3 eq.); PdCl₂(PPh₃)₂ (0.05 eq.); anhydrous KOAc (3 eq.); Δ (120 °C); 20–24 h; ii m-CBPA (2.5 eq.); CH₂Cl₂; 6 h.

In order to delineate the effect of substrate on this series of transformations the synthesis of 10 and its oxidation to 1,8-dihydroxyanthraquinone was next investigated. At the start of this project the preparation of 10 was unknown, but during the writing of this thesis its preparation was disclosed using a modified Miyaura reaction. In our hands exposure of 12 to B₂Pin₂ 55 and Pd(PPh₃)₂Cl₂, in the presence of potassium acetate at 160 °C for 24 hours, without solvent, afforded two major components, the more polar of which was ester 10, which was isolated in 28% yield after purification by column chromatography on silica. A less polar fraction, determined to be anthraquinone 17, was also isolated from this reaction (Scheme 2.30).

![Scheme 2.30](image)

**Scheme 2.30.** Miyaura coupling of 12 and 55 leading to 10 and 17. Reagents and conditions: 12 (1 eq.); 55 (3 eq.); [Pd(PPh₃)Cl₂ (0.1 eq.); KOAc (7 eq.); Δ (140 °C-160 °C); 20 h.
Given the poor yield in this borylation reaction its optimisation was next attempted. Reduction of temperature from 160 °C to 130 °C did not have any noticeable effect on the isolated yield or rate of reaction in this case. Conducting the reaction at temperatures below 100 °C resulted in the formation of 10 in lower overall conversion. Solvent effects on the course of this borylation reaction were also briefly investigated. Performing the reaction in DMF as solvent at 130 °C afforded 10 in 15% yield after chromatography, which diminished to 6% isolated yield when conducted in THF at reflux. Reaction with dioxane or toluene at 85 °C and 100 °C respectively failed to improve the overall conversion and led to the isolation of only trace amounts of 10, as indicated by $^1$H NMR spectra of the crude products, Table 2.8).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF</td>
<td>16%</td>
</tr>
<tr>
<td>Toluene</td>
<td>Trace</td>
</tr>
<tr>
<td>1,4-Dioxane</td>
<td>Trace</td>
</tr>
<tr>
<td>THF</td>
<td>5%</td>
</tr>
<tr>
<td>Neat</td>
<td>28%</td>
</tr>
</tbody>
</table>

Table 2.8. Optimisation reaction for the synthesis of 10. Reagents and conditions: 12 (1 eq.); 55 (4 eq.); Pd(PPh$_3$)$_2$Cl$_2$ (0.1 eq); KOAc (7 eq.); Δ (90-130 °C); 20 h.
At this stage we wished to determine whether dibromide 12b would participate more effectively than dichloride 12a in this palladium-catalyzed transformation. Unfortunately repeating the borylation reaction with 12b, under otherwise identical conditions afforded 10 in 10% yield after chromatography. GCMS analysis of the crude reaction mixture from this reaction also indicated the presence 1-bromoanthracene-9,10-dione,\textsuperscript{239} 1-hydroxyanthracene-9,10-dione,\textsuperscript{240} and anthracene-9,10-dione 17\textsuperscript{241}

\begin{equation}
\begin{align*}
\text{12b} & \xrightarrow{\text{i}} \text{10} \\
\text{10} & \xrightarrow{\text{ii}} \text{11}
\end{align*}
\end{equation}

**Scheme 2.31.** Synthesis of 11. Reagents and conditions: i dibromide 12b (0.13 g; 0.36 mmol; 1 eq.); 55 (0.37 g; 1.5 mmol); Pd(PPPh\textsubscript{3})Cl\textsubscript{2} (0.04 g; 0.05 mmol); KOAc (0.25 g; 2.55 mmol); Δ (140 °C); 20 h; 10% ii m-CBPA (2.5 eq.); CH\textsubscript{2}Cl\textsubscript{2}; 6 h; 20 °C; 81%.
Finally, oxidation of 10 with m-CBPA (2.5 equivalents) in dichloromethane for 6 hours at ambient temperature afforded chrysazin, 11 in 81% yield after purification by column chromatography. This result indicates that aryl boronate esters such as 10 can be efficiently converted to their respective phenols, which suggests that further optimisation of this reaction on substrates such as 182 is merited.

![Figure 2.13. $^1$HNMR (CDCl$_3$) spectrum of chrysazin, 11.](image)
2.5.2 Functionalization of 1,8-dichloronaphthaquinone using the Suzuki reaction

This short study was concerned with the synthesis of model compounds 13 and 197, a class of molecules which may find application as molecular probes.

Scheme 2.32. Suzuki coupling of 12a leading to 13 and 197. Reagents and conditions: i 12a (1 eq.); 194 (3 eq.); Pd(PPh₃)₄ (0.2 eq.); K₂CO₃ (2 M); Δ (90 °C); 6 h; ii 12a (1 eq.); 196 (3 eq.); Pd(PPh₃)₄ (0.2 eq.); K₂CO₃ (2 M); Δ (90 °C); 6 h.

Although the Suzuki cross-coupling reactions of 1,8-dihaloanthraquinones with arylboronic acids was reported some time ago this reaction has received scant attention in the literature.²³⁶, ²³⁷ In an initial series of experiments we observed that reaction of 1,8-dichloroanthraquinone 12a (1 equivalent) with pyren-1-ylboronic acid 195 (3 equivalents) in the presence of a catalytic quantity of Pd(PPh₃)₄ (0.3 mol equivalents) and an excess of K₂CO₃ (2M solution) in toluene at 90 °C generated a dirty-red coloured reaction mixture after 3 hours. Chromatography of the resulting reaction mixture on silica gel seemingly afforded two major products by TLC. The less polar of these, an orange-coloured solid, proved to be anthraquinone 14 which was isolated in low yield (17 %). Although we were able to obtain an ¹H NMR spectrum of 14,
acquisition of its HSQC $^1$H NMR spectrum was not possible, which meant that only a tentative assignment, based upon inspection and coupling constant data was possible (Figure 2.14).

Fortunately, we were able to obtain both the $^1$H- and $^1$H-HSQC NMR spectra of 13 (Figures 2.15a and b) which indicated that bulk sample to be slightly impure (impurities denoted by “x” in the $^1$H NMR spectrum). Most notably, the $^1$H NMR spectrum of 13 reveals that $H_i$ is shielded considerably when compared to $H_d$. Examination of the single crystal X-ray structure for this compound reveals (Figure 2.18) that if 13 adopts an anti-conformation, then $H_i$ lies over shielding region of the neighbouring pyrene ring which presumably causes $H_i$ to be observed at $\delta$ 6.9 ppm. This data suggests therefore that in solution at ambient temperature the anti-conformation appears to be favoured.

![Figure 2.14. $^1$H NMR spectrum of 14.](image-url)
Figure 2.15a. $^1$HNMR spectrum of 13 (assignments for $H_e/H_i$ and $H_d/H_j$ may be interchanged).
Interestingly X-ray analysis of a crystal picked from the bulk sample of 14 was of diffraction quality and was shown to be a mixture of 14 and 15 by X-ray crystallography, **Figure 2.17**. Analysis of this material by single crystal X-ray crystallography again confirmed that carbon-carbon bond formation had occurred at one of the C-Cl bonds, but partial reduction or hydrolysis had proceeded at the second C-Cl. Unfortunately, recrystallization had not enabled separation of these two impurities, as evidenced by the X-ray structure (**Figure 2.17**).

![Figure 2.15b. COSY spectrum of 13.](image)

**Figure 2.15b. COSY spectrum of 13.**

![Figure 2.16. Anthraquinones 13 and 14.](image)

**Figure 2.16. Anthraquinones 13 and 14.**
Figure 2.17. Single crystal X-ray structure of 15 showing multiple occupancy of -H and –OH at C3.
The single crystal X-ray structure of 13 (Figure 2.18) clearly reveals that, in the solid state at least, the molecule is present as the anti-atropisomer (torsion angles about C14-C13-C9-C10 of 68.20° and C38-C33-C32-C31 of -54.82° respectively). Further examination of this crystal structure indicates that the mean planes containing the pyrene residues are not parallel but sustain an angle of 60.35° with respect to each other. In addition, the tricyclic core of the anthraquinone residue is substantially distorted, and adopts a half-chair conformation, such that O1 lies 0.967 Å above the plane containing the anthraquinone core thereby minimizing steric interactions between O1, C13 and C33.

Figure 2.18. The single crystal X-ray structure of 13.
Repeating this reaction on a slightly larger scale (1 equivalent of 12a; 3 equivalents of 195; Pd(PPh₃)₄, 0.3 mol equivalents) over a longer time course (a total of 12 hours) afforded dark red-coloured crude material. TLC analysis of this crude material seemingly indicated the presence of two components. Chromatography of this material on silica led to the isolation of pyrene 198 in 50% yield and 13 (< 45%) which, again was isolated as slightly impure material. Encouragingly the formation of anthraquinone 14 or phenol 15 were not observed under these reaction conditions (Scheme 2.33).

Scheme 2.33. Suzuki coupling of 12a and 195. Reagents and conditions: 12a (1 eq.); 55 (3 eq.); Pd(PPh₃)₄ (0.2 eq.); K₂CO₃ (2 M); Aliquat® 336; Δ (90 °C); 6 h.
Although the structure of 13 has been confirmed by single crystal X-ray crystallography, $^1$H NMR (DMSO) spectra of 13 was not fully resolved because of impurities. This observation was initially suggestive of atropisomerism$^{242-244}$ and therefore led to conduction of a Variable-temperature (VT) NMR experiment. (Figure 2.19).

Figure 2.19. VT-$^1$HNMR (DMSO) of 13 within region of detected impurities 7.5-8.5 ppm.

The results of the VT-NMR experiments at 328 K shows distinctive resonances for each peak and indicates that additional peaks suspected to be impurities have not been resolved even at higher temperature. This observation has thus assuaged our doubt of any possibility of atropisomers of 13 in DMSO, as was earlier anticipated.
A repeat of this procedure [anthraquinone \(12c\) (0.184 g; 1 equivalent; \(195\) (0.296 g; 3 equivalents; \(\text{Pd(PPh}_3\text{)}_4\) (0.3 mol equivalents) in toluene in the presence of excess \(\text{K}_2\text{CO}_3\) (2M solution) at 90 °C-110 °C] (Scheme 2.34), afforded a dirty red-coloured crude product. Purification of the crude material by column chromatography afforded only one fraction. Examination of the \(^1\text{HNMR (CDCl}_3\) of this component shows it to be \(13\) albeit contaminated with impurities.

\[
\begin{align*}
&\text{B(OH)}_2 \\
&195 \\
&\text{O} \\
&12c \\
&\rightarrow \\
&\text{O} \\
&13
\end{align*}
\]

Scheme 2.34. Suzuki coupling reaction of \(195\) and \(12c\). Reagents and conditions: \(12c\) (1 eq.); \(193\) (3 eq.); \(\text{Pd(PPh}_3\text{)}_4\) (0.3 eq.); \(\text{K}_2\text{CO}_3\) (2 M); \(\text{Aliquat}^{\text{©}}\) 336; toluene; \(\Delta\) (90 °C); 6 h.
In a similar vein the synthesis of anthraquinone 197 was also investigated, as outlined below (Scheme 2.35).

![Scheme 2.35. Suzuki coupling of 12a and 196. Reagents and conditions: 12a (1 eq.); 196 (1.3 eq.); Pd(PPh₃)₄ (0.2 eq.); K₂CO₃ (2 M); Aliquat® 336; Δ (90 °C); 6 h.]

Reagents and conditions:
- 12a (1 eq.)
- 196 (1.3 eq.)
- Pd(PPh₃)₄ (0.2 eq.)
- K₂CO₃ (2 M)
- Aliquat® 336
- Δ (90 °C)
- 6 h.

Reaction of 198 (1 equivalent) with 199 (1.2 equivalents) in the presence of AlCl₃ (0.5 equivalents) in dichloromethane at 0 °C to room temperature afforded a beige-coloured solid as product after 3 hours. TLC of the crude material reveals two spots. Purification of this material by column chromatography on silica gel afforded 200 in ca. 90% purity (Scheme 2.36).²⁴⁵

![Scheme 2.36. Synthesis of 187 and 200. Reagents and conditions: 198 (1 eq.); CH₂Cl₂; 0 °C-20 °C.]

Reagents and conditions:
- 198 (1 eq.)
- CH₂Cl₂
- 0 °C-20 °C.

Repeating the above reaction with a slight excess of 199 (1.49 equivalents) with respect to 198 (5.0 g) in DCM for 16 hours followed by recrystallisation (50/50 hexane/methanol) of the crude product afforded 187 (0.997 g; 3.17 mmol; 13%). Further recrystallisation of the mother liquors from the initial recrystallization afforded additional quantities of 187 (1.571 g; 5.00 mmol; 20%). Concentration of the filtrates
from this recrystallisation afforded a yellow-coloured solid which was found to be mainy 200 (2.47 g; ca. 90% purity) by $^1$H NMR analysis, Scheme 2.36.

**Figure 2.20.** Aromatic region of the $^1$H NMR spectrum of 200 (in CDCl$_3$).

**Figure 2.21.** Aromatic region of the 1H NMR spectrum of 187 (in CDCl$_3$).
Borylation of 200 (ca. 90% purity) using B$_2$pin$_2$ 55 in the presence of [Ir(COD)OMe]$_2$ (1 mol%) in hexane at 80 °C for 24 hours afforded a brown-coloured crude product. Column chromatography of this material on silica gel followed by further purification by recrystallisation from hexane furnished boronic ester 196 as a colourless crystalline solid in 25% isolated yield (Scheme 2.37).

Scheme 2.37. Iridium-catalysed borylation of 200. Reagents and conditions: [Ir(OMe(COD))]$_2$ (0.051 mmol); dtbpy (0.10 mmol); 200 (1.94 mmol); 55 (5.2 mmol); refluxing hexane; 16 h.
Finally, coupling of 196 with anthraquinone 12a in toluene using a catalytic quantity of Pd(PPh$_3$)$_4$ and excess K$_2$CO$_3$ (see Scheme 2.35) resulted in the formation of a complex mixture of products as indicated by the $^1$H NMR spectra of the crude reaction mixture. Purification of this mixture proved to be unsuccessful although the formation of 197 was apparent from an analysis of the mass spectral data of this mixture (HRMS (APCI) of 721.3097 corresponding to C$_{54}$H$_{41}$O$_2$ ([M+H]$^+$)).

![197]

**Figure 2.22.** 1,8-Bis(7-(tert-butyl)pyren-2-yl)anthracene-9,10-dione 197.
2.6 Concluding Remarks and Future Work

The cyclisation of 2-allylphenyl 2,2,2-trichloroacetate 66 to 1-chloronaphthalene 68 via an extrusion of CO₂ from lactone 67 is a potentially remarkable reaction in the formation of naphthalene- and chrysazen derivatives, Scheme 2.38. Within the group, this methodology has been exemplified in the synthesis of organic materials, functionalised azo-dyes and in the modification of bioactive compounds.

Scheme 2.38. Cyclisation of 66 to 67 and 68.

In this thesis, the scope of the BHQ reaction has further been extended to accommodate substrates bearing oxygen functionality in the parent aromatic system. These highly oxygenated aromatics then serve as precursors for the synthesis of anthraquinone and naphthoquinone derivatives.

In some cases, low yields of the benzannulation products were observed. This is however an area for further research even though a previous study on related systems had suggested a formation of intractable extracts during column chromatography. New ligands and catalysts other than the frequently adopted 1,3-bis(2,6-diisopropylphenyl) imidazolium copper(I)chloride complex 70 should be evaluated for improved conversion.
In an initial model study, it was found that treatment of the resulting haloaromatics with a boron nucleophile (B<sub>2</sub>pin<sub>2</sub>) before oxidation of the intermediate boronic esters with cerium ammonium nitrate (CAN) and further treatment of the resulting quinones with <i>m</i>-CBPA enabled the synthesis of plumbagin 7b, juglone 7a and other analogues in 54-86% conversion.

Unfortunately, the interconversion of hydroquinone 8a to hydroxyquinone 9 proved to be problematic. The synthetic sequence which commences from 2-chlorocyclohexan-1-one 178 to 9-hydroxy-5,6,7,8-tetrahydroanthracene-1,4-dione 182 utilising a similar procedure as above, was unsatisfactory. The key intermediate boronic ester was successfully isolated in 60% conversion, treatment with CAN and further oxidation of the ester with <i>m</i>-CBPA saw a slow formation of the product in trace quantity. In this case, the tricyclic is suggested to be unstable to treatment with <i>m</i>-CBPA. Revaluation of oxidising agents is a new challenge to be undertaken. Further screening of oxidising reagents for a possible realisation of this goal is a great asset considering that 9 is core in most anthracycline antibiotics.

Scheme 2.39. i 70 (5 mol%); refluxing diglyme; 2 h.

A palladium-catalysed cross coupling reaction was undertaken in a way to install the boronic ester nucleophile. An extensive study of the optimum reaction conditions enabling cross coupling of the haloaromatics with a borylating agent, B<sub>2</sub>pin<sub>2</sub> 55, shows that a temperature threshold of 118-130 °C at reaction time of 20-24 h with at least 0.05 equivalents of catalyst, Pd(PPh<sub>3</sub>)<sub>4</sub>, neat, was optimum for the coupling reaction. Anthraquinone 10 was converted to hydroxyquinone 11 in 81%.

![Scheme 2.41](image)

**Scheme 2.41.** Synthesis of 1,8-dihydroxyanthraquinone 11.

Finally, a one-step synthesis of the new anthraquinone derivative, 1,8-di(pyren-1-yl)anthracene-9,10-dione 13, was attempted using a Suzuki cross-coupling reaction of 1,8-dichloroanthraquinone 12a and 1-pyrenyllboronic acid 195. Formation of 13 was hampered by the concomitant formation of 14 and 15. Compound 13 may find relevant applications in the development of molecular tweezer and in molecular recognition. 13 has extended π-π stacking geometry, feature which makes it applicable in this regard.246

![Scheme 2.42](image)

**Scheme 2.42.** 195 (3 eq.); Pd(PPh<sub>3</sub>)<sub>4</sub>; K<sub>2</sub>CO<sub>3</sub>; Aliquat® 336; 16 h.
An ongoing programme is the optimisation of 13 starting from 1,8-diiodoanthraquinone 12c because preparation of 13 from 12a afforded product contaminated with impurities despite side products. Further studies would be, evaluation of 13 as a molecular tweezer. The scope of the coupling should be expanded to accommodate substrates with substituents groups so that electronic effect may be studied.

Scheme 2.43. Pd(PPh₃)₄ (3 mol %); K₂CO₃ (2M); aliquat® 336; refluxing toluene; 16 h.
3 Experimental

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3.2 General Experimental

Chemicals and reagents were usually obtained from Sigma Aldrich, Fisher Scientific and, Fluorochem and were used without further purification (unless otherwise stated). 1, 2-DCE was degassed under an atmosphere of nitrogen prior to use; DCM was used without further drying. Dried solvent refers to solvent either purchased as ‘labelled’ or solvent stored over oven-dried 4 Å molecular sieves and redistilled before use. ‘Petrol’ refers to the fraction of petroleum ether that boils between 40 ºC and 60 ºC under atmospheric pressure. Temperatures are quoted in degrees Celsius (ºC) and remain uncorrected. Melting points were performed using a Sanyo Gallenkamp (MPD 350.BM 3.5) melting point apparatus and are uncorrected. Microwave irradiation was conducted in a Biotage Initiator microwave reactor (maximum power output of 300 W; operating frequency 2450 MHz). Infrared (IR) analysis was recorded via a BRUKER ALPHA FT-IR (G1003613) as evaporated films and absorption peaks measured in wave numbers (cm⁻¹). UV-Vis analysis was conducted with a Cary 5000 UV-Vis-NIR spectrophotometer. Thin layer chromatography (TLC) was performed on a 0.2 mm precoated POLYGRAM® SIL G/UV254 silica gel plates manufactured in Germany by MACHERE-NAGEL GmbH and Co and visualisation done under UV absorption (254 nm), or with potassium permanganate. Flash column chromatography was carried out on Merck (60Å, 230 – 400 mesh, 40 – 60 µm) silica gel purchased from Sigma Aldrich. Low-resolution mass spectra were recorded on Water SQO2 (electrospray) and Agilent 6120 (APCI) spectrometer. High-resolution mass spectra were recorded on a Thermo Exactive plus EMR (APCI and ES scan) and Agilent 5975C MSD or Agilent 5973N MSD (GCMS) spectrometer. Modes of ionisation were electron impact (EI), chemical ionisation (CI) using ammonia or electrospray in positive mode (ES⁺). ASAP (Atomic Solids Analysis Probe) mass spectra were obtained using a Thermal Exactive Plus EMR Orbitrap instrument (positive ion mode). Proton NMR spectra (¹H NMR) were recorded on either AVANCE III HD PRODIGY Ascend™ 500 (500 MHz) spectrometer or an AVANCE III HD PRODIGY Ascend™ 400 (400 MHz) spectrometer. Reference frequency was used as standard in both cases. Chemical shifts (δ) are quoted in ppm from higher and lower frequency. Signal splitting patterns are described as singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), broad singlet (bs) or multiplet (m). Coupling constants (J) are quoted in Hz. Carbon NMR spectra (¹³C
NMR) were recorded on either AVANCE III HD PRODIGY Ascend™ 500 (125 MHz) spectrometer or an AVANCE III HD PRODIGY Ascend™ 400 (100 MHz) spectrometer, again using a reference frequency as standard in both cases. Chemical shifts (δ) are quoted in ppm from higher and lower frequency. Microanalyses were determined in the University of Manchester Microanalysis Laboratory and were conducted on a flash 2000 Thermal Scientific Analyser for detection of % levels of carbon and hydrogen.
3.3 Experimental Procedures

3.3.1 Procedure for the Preparation of Phenols

2,5-Dimethoxyphenol,\textsuperscript{15} 131

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{HO} & \quad \text{O}
\end{align*}
\]

An ice-cold solution of \(m\)-CBPA (12.0 g of ca. 77\% w/w, ca. 53 mmol) in \(\text{CH}_2\text{Cl}_2\) (30 mL) was added, drop-wise, to a solution of 2,5-dimethoxybenzaldehyde \(5\text{a}\) (6.0 g, 36.10 mmol) while maintaining the reaction temperature at ca. 5 °C. On completion of the addition the reaction mixture was allowed to warm up to room temperature and the reaction continued for 24 hours. The reaction then was quenched by the addition of saturated aqueous \(\text{NaHCO}_3\) (250 mL), followed by addition of aqueous sodium sulphite solution (50 mL of a 10\% w/v solution) in order to decompose residual peroxides. The organic layer was separated and the aqueous layer re-extracted with DCM (3 × 20 mL). The combined organic layers were dried (\(\text{MgSO}_4\)) and concentrated \textit{in vacuo} to afford the crude formate ester, a dark yellow coloured solid, which was then re-dissolved in methanol (10 mL) and reacted with \(\text{NaOH}\) solution (80 mL of a 4M solution) for 2 hours. The reaction mixture was then acidified to pH 1 by the addition of 6 M HCl and extracted with \(\text{CH}_2\text{Cl}_2\) (3 × 20 mL). The combined organic extracts were dried over \(\text{MgSO}_4\) and concentrated \textit{in vacuo} to obtain the \textit{title compound} \textbf{131}, a red-coloured viscous oil. Yield 5.03 g (76\%). \textsuperscript{1}H NMR: (400 MHz, \(\text{CDCl}_3\)) \(\delta\) 3.77 (3H, s), 3.87 (3H, s), 5.67 (1H, s), 6.40 (1H, dd, \(J = 8.8, 2.7\) Hz), 6.59 (1H, d, \(J = 2.7\) Hz), 6.80 (1H, d, \(J = 8.8\) Hz) ppm. \textsuperscript{13}C NMR: (100 MHz, \(\text{CDCl}_3\)) \(\delta\) 55.64, 56.54, 101.69, 104.20, 111.41, 140.91, 146.38, 154.51 ppm. IR: \(\nu_{\text{max}}\) 1131, 1148, 1232, 1506, 2836, 2938, 3413 cm\textsuperscript{-1}. MS: (APCI): m/z 155.1 ([M+H\textsuperscript{+}]). HRMS: (APCI\textsuperscript{+}) \(\text{C}_8\text{H}_{10}\text{O}_3\text{H}\) ([M+H\textsuperscript{+}]) requires 155.0703; found 155.0697.
m-CPBA (1.72 g of ca. 77% material, ca. 7.7 mmol) was added to a solution of 2,5-Dimethoxy-4-methylbenzaldehyde (1.0 g, 5.6 mmol) in CH$_2$Cl$_2$ (20 mL) while maintaining the internal temperature at 0 °C. Once the addition was complete, the reaction mixture was brought to reflux for one hour and then allowed to cool to ambient temperature. The reaction mixture was extracted with saturated aqueous NaHCO$_3$ solution (40 mL) and the organic extracts washed (NaHCO$_3$, 2 × 20 mL; sodium sulphite, 2 × 20 mL and then water, 2 × 20 mL), dried (MgSO$_4$) and concentrated in vacuo to afford the crude formate ester as a viscous oil. This oil was then re-dissolved in CH$_2$Cl$_2$ (20 mL) and stirred with aqueous NaOH (10 mL, 50% w/v) for 1 h. At this stage conc. HCl (10 M) was added, with cooling, in order to adjust the aqueous phase to pH 1. The organic layer was separated, washed (water, 7 × 20 mL), dried (MgSO$_4$) and concentrated in vacuo to afford the title compound as a dark brown-coloured crystalline solid. Yield 747 mg (80%). Repeating this reaction on a 10 g scale afforded 7.4 g of title compound 133 (79%); m.p 77-79 °C (lit.$^{247}$ m.p. 78.3-78.6 °C). This material was of sufficient purity to be used in the next step without any additional purification. $^1$H NMR: (400 MHz; CDCl$_3$) δ 2.07 (3H, s), 3.67 (3H, s), 3.78 (3H, s) 5.45 (1H, s), 6.43 (1H, s), 6.62 (1H, s) ppm. $^{13}$C NMR: (100 MHz; CDCl$_3$) 15.7, 55.9, 56.7, 99.1, 114.0, 117.1, 139.7, 144.0, 152.1 ppm. IR: $\nu_{\text{max}}$ 1148, 1223, 1516, 2958, 3004, 3397 cm$^{-1}$. MS: (ES$^-$): m/z 167.0 ([M-H]).
3.3.2 Procedure for the Preparation of Ethers

2-(Allyloxy)-1, 4-dimethoxybenzene,\textsuperscript{160}132

To a solution of phenol 131 (5.32 g, 34.5 mmol) in acetone (300 mL) was added K$_2$CO$_3$ (11.0 g; 79.6 mmol) and the mixture stirred for 10 minutes under an atmosphere of nitrogen. Allyl bromide (5.9 mL, 159.2 mmol) was then added via syringe; when this addition was complete the reaction mixture was brought to reflux for 23 hours under an atmosphere of nitrogen. On cooling to room temperature inorganic material was removed by filtration and the filtrate was reduced \textit{in vacuo} to obtain the crude product. Flash chromatography of this material (silica; eluent ethyl acetate-hexane, 15% v/v) afforded the \textit{title compound} 132, a yellow-coloured oil. Yield 5.00 g (76 %). \textsuperscript{1}H NMR: (400 MHz; CDCl$_3$) δ 3.77 (3H, s), 3.84 (3H, s), 4.60-4.64 (2H, dt, $J = 5.5$, 1.4 Hz), 5.28-5.33 (1H, dq, $J = 10.5$, 1.4), 5.40-5.46 (1H, dq, $J = 17.2$, 1.4 Hz), 6.02-6.15 (1H, m), 6.39-6.44 (1H, dd, $J = 8.7$, 2.9 Hz), 6.53 (1H, d, $J = 2.9$ Hz), 6.81 (1H, d, $J = 8.7$ Hz) ppm. \textsuperscript{13}C NMR: (100 Hz; CDCl$_3$) δ 55.7, 56.6, 69.8, 102.1, 103.5, 112.3, 118.1, 133.2, 143.8, 148.8, 154.1 ppm. IR: $\nu_{\text{max}}$ 831, 1160, 1608, 2934, 3079 cm$^{-1}$. MS (ES?): m/z 217 ([M+Na]$^+$), 195.0 ([M+H]). HRMS (ES$^+$) C$_{11}$H$_{15}$O$_3$ ([M+H]$^+$) requires 195.1016; found 195.1009.
2,5-Dimethoxy-4-methylphenol, 133 (1.0 g, 6 mmol) was added to a suspension of potassium carbonate (1.7 g, 12 mmol) in dry acetone (30 mL) and the resultant mixture stirred for five minutes under an atmosphere of nitrogen. Allyl bromide (1 mL, 12 mmol) was then added drop-wise to the reaction mixture and then brought to a gentle reflux for a period of 8 h. After allowing to cool to ambient temperature the reaction mixture was filtered through a celite® pad to remove any inorganic material and the filtrate was then concentrated in vacuo. The residue was then re-dissolved in DCM, washed with water (5 × 20 mL) and then saturated NaHCO₃ solution (5 × 20 mL), dried over anhydrous MgSO₄ and concentrated in vacuo. Purification of the residue by column chromatography (ethyl acetate-petroleum ether, 10% v/v) afforded the title compound, a yellow-coloured oil. Yield 1.16 g (94%). Repeating this reaction on an 8 g afforded 9 g of the title compound (91% yield). \(^1\)H NMR: (400 MHz; CDCl₃) δ 2.06 (3H, s), 3.67 (3H, s), 3.72 (3H, s), 4.52 (2H, dt, J = 5.5, 1.5 Hz), 5.17 (1H, dq, J = 10.4, 1.5 Hz, =CH₂), 5.30 (1H, dq, J = 17.3, 1.5 Hz), 6.10 (1H, ddt, J = 17.3, 10.4, 1.5 Hz), 6.42 (1H, s), 6.61 (1H, s) ppm. \(^1\)C NMR: (100 MHz; CDCl₃) δ 15.6, 56.3, 56.8, 70.6, 100.3, 115.7, 117.7, 118.7, 133.7, 143.2, 146.4, 151.4 ppm. IR: \(\nu_{\text{max}}\) 854, 1262, 1511, 1611, 2991, 3081 cm\(^{-1}\). MS (ES\(^+\)): m/z 209.2 ([M+H]\(^+\)), 231.2 ([M+Na]\(^+\)). HRMS: (ES\(^+\)) \(\text{C}_{12}\text{H}_{17}\text{O}_3\) ([M+H]\(^+\)) requires 209.1187; found 209.1178.
A standard literature procedure was adopted, and modification was applied where necessary and are well documented. To a solution of 2,5-dimethoxyphenol (5.00 g, 32.43 mmol, 1 equivalent) in DMF (50 mL) in a round bottom flask was added potassium carbonate (15.0 g, 108.53 mmol, 3 equivalents) and the mixture was stirred for 1 hour at 65 °C in an inert atmosphere of nitrogen. 2-chlorocyclohexanone (6.6 g, 49.77 mmol, 1.5 equivalents) was dissolved in degassed DMF (20 mL) and the solution was added portion-wise over 10 minutes to the reaction mixture and the solution allowed to stir at 65°C. After 36 hours, the reaction mixture was cooled to room temperature and diethyl ether (25 mL) was added to separate the organic phase. Freshly prepared brine (20 mL) was then added to the mixture via a separatory funnel and extracted with further diethyl ether (10 mL × 5 times) followed by washing with water (20 mL × 5 times). The combined organic extract was dried (MgSO₄), filtered and concentrated under reduced pressure to afford a dense yellow oil as the crude product. Flash chromatography of this material (silica; eluent petroleum ether-ethyl acetate, 80% v/v) afforded the title compound as bright yellow-coloured viscous oil. Yield 5.85 g (80%). ¹H NMR: (400 MHz; CDCl₃) δ 1.69-1.85 (3H, br. s), 1.97-2.12 (3H, br. s), 2.32-2.42 (2H, s), 3.74 (3H, s), 3.83 (3H, s), 4.63-4.69 (1H, ddd, J = 11.0 Hz, 6.5 Hz, 1.0 Hz), 6.43-6.51 (2H, m), 6.82 (1H, d, J = 9.3 Hz) ppm. ¹³C NMR: (100 MHz; CDCl₃) δ 23.0, 27.7, 34.4, 40.7, 55.6, 56.9, 82.1, 105.0, 105.7, 113.5, 144.5, 147.8, 154.0, 207.7 ppm. IR: νmax 1127, 1260, 1505, 2834, 2938 cm⁻¹. MS (ES): m/z 249.2 ([M-H]⁻ 100%), 273.2 ([M+Na]+, 100%) 151.0 ([M-(C₉H₁₂O₂)-H]⁻, 60%). HRMS (HESI-POS): C₁₄H₁₈O₄Na ([M+Na]^+) requires 273.1086, found 273.1097. Microanalysis: C₁₄H₁₈O₄ requires: C, 66.90; H, 7.25%; found: C, 67.18 H, 7.34%.
3.3.3 Procedure for the Preparation of Alkene

1,4-dimethoxy-2-((2-methylene cyclohexyl)oxy)benzene, 174

A slight modification was made to a known synthetic procedure. A round bottom flask equipped with a magnetic stirrer bar was placed in an ice bath and the temperature was maintained at 0 °C. Methylphenylphosphonium bromide (10.000 g, 27.993 mmol) and potassium t-butoxide (3.144 g, 28.019 mmol) was placed in the flask followed by the addition of anhydrous THF (40 mL) and the resulting solution was stirred for 45 minutes. The reaction mixture was warmed up to room temperature and allowed to stir for an additional 30 minutes before adding in portion-wise to a stirring solution of 2-(2,5-dimethoxyphenoxy)cyclohexan-1-one 173 (5.85 g, 23.37 mmol in 20 mL THF) and the reaction was left to stir for 3 hours. The mixture was quenched by the slow addition of brine (20 mL) and the organic phase was separated by extraction with diethyl ether, washed with brine (20 mL × 5 times), dried (MgSO₄), filtered and concentrated in vacuo to afford a dense yellow-coloured crude product. Flash chromatography of this material (silica; eluent: petroleum ether-ethyl acetate, 90% v/v) afforded the title compound as a bright yellow-coloured viscous oil. Yield 4.15 g (72%). H NMR: (400 MHz; CDCl₃) δ 1.48-1.69 (4H, m) 1.83-2.10 (4H, m), 2.40-2.47 (1H, br. s), 3.75 (3H, s), 3.83 (3H, s), 4.58 (1H, dd, J = 8.0 Hz, 3.8 Hz), 4.84 (1H, s), 4.91 (1H, s), 6.44 (1H, dd, J = 8.8, 3.0 Hz), 6.53 (1H, d, J = 2.8 Hz), 6.82 (1H, d, J = 8.8 Hz) ppm. 13C NMR: (100 MHz; CDCl₃) δ 23.4, 27.8, 33.3, 34.0, 55.8, 57.0, 79.7, 104.0, 104.4, 108.3, 113.4, 144.6, 147.2, 148.6, 154.1 ppm. IR: νmax 1117, 1258, 1503, 1653, 2832, 2932 cm⁻¹. MS (ES⁺): m/z 271.1 ([M+Na]+, 100%). HRMS (HESI-POS): C₁₅H₂₂O₃Na ([M+Na]+) requires 271.1292, found 271.1305. Microanalysis: C₁₅H₂₀O₃ requires C, 72.55; H, 8.12%; found: C, 72.44; H, 8.17%.
3.3.4 Procedure for the ortho-Claisen Rearrangements

4-Allyl-3, 6-dimethoxyphenol and 2-allyl-3,6-dimethoxyphenol, \textbf{118a} and \textbf{118b}\textsuperscript{160}

The title compound was prepared by a slight modification to that reported by Otterlo\textsuperscript{160}. Thermolysis of \textbf{132} (7.16 g, 36.9 mmol), heated in the absence of solvent, under an atmosphere of nitrogen at 240-250 °C for 60 minutes afforded a dark brown-coloured residue which on cooling to ambient temperature was purified by column chromatography (silica; eluent hexane-ethyl acetate, 8:2 v/v) to afford an almost inseparable mixture of 4-allyl-3,6-dimethoxyphenol and 2-allyl-3,6-dimethoxyphenol, \textbf{118a} and \textbf{118b} (\textbf{118a}:\textbf{118b} = 2:1), a bright yellow-coloured viscous oil. Yield 5.87 g (82%). \textsuperscript{1}H NMR: (500 MHz; CDCl\textsubscript{3}) \(\delta\) 3.33 (2/3H, d, \(J = 6.6\) Hz), 3.46 (4/3H, d, \(J = 6.1\) Hz), 3.78 (1H, s), 3.79 (2H, s), 3.86 (1H, s), 3.87 (2H, s), 4.94-5.12 (2H, m, minor + major), 5.56 (1/3H, s), 5.75 (2/3H, s), 5.97-6.13 (1H, m), 6.38 (2/3H, d, \(J = 8.9\)), 6.58 (1/3H, s), 6.66-6.75 (1H, m) ppm. \textsuperscript{13}C NMR: (105 MHz, CDCl\textsubscript{3}) \(\delta\) 27.6 (major), 33.7 (minor), 56.0 (major), 56.2 (minor), 56.4 (major), 56.8 (minor), 99.4 (minor), 101.1 (major), 108.2 (minor + major), 113.1 (minor), 114.3 (major), 114.96 (major), 114.5 (minor), 136.4 (major), 137.44 (minor), 140.17 (minor), 141.1 (major), 144.3 (major), 144.5 (minor), 151.7 (minor), 152.6 (major) ppm. IR: \(\nu_{\text{max}}\) 1062, 1040, 1439, 2939, 3076, 3493 cm\textsuperscript{-1}. MS: (ES\textsuperscript{+}) \textquoteright m/z 195.0 ([M+H]\textsuperscript{+}). HRMS: (ES\textsuperscript{+}) \textsuperscript{C}_{11}H_{14}O_{3}Na ([M+Na]\textsuperscript{+}) requires 217.0835; found 217.0856.
2-Allyl-3,6-dimethoxyphenol,\textsuperscript{160} \textbf{118a}

Purification of the above material by column chromatography (as above) afforded a pure sample of \textit{2-allyl-3,6-dimethoxyphenol}, \textbf{118a}. Yield 590 mg (8\%) which had the following analytical data: \textsuperscript{1}H NMR: (500 MHz, CDCl\textsubscript{3}) \(\delta\) 3.66 (2H, dt, \(J = 6.1, 1.4\ \text{Hz}\)), 3.70 (3H, s), 3.77 (3H, s), 4.83-5.01 (2H, m), 5.65 (1H, s), 5.83-6.00 (1H, m), 6.28 (1H, d, \(J = 8.9\)), 6.6 (1H, d, \(J = 8.9\)) ppm. \textsuperscript{13}C NMR: (125 MHz; CDCl\textsubscript{3}) \(\delta\) 27.6, 56.2, 56.0, 101.1, 108.2, 114.3, 114.9, 136.4, 141.2, 144.3, 152.6 ppm. IR: \(\nu_{\text{max}}\) 1062, 1040, 1439, 1511, 2939, 3076, 3493 cm\textsuperscript{-1}. MS: (ES\textsuperscript{+}) m/z 195.0 ([M+H]\textsuperscript{+}), (ES\textsuperscript{-}) m/z 193.0 ([M-H\textsuperscript{-}]). HRMS: (ES\textsuperscript{+}) [C\textsubscript{11}H\textsubscript{13}O\textsubscript{3}]\textsuperscript{+} ([M-H\textsuperscript{-}]) requires 193.0870; found 193.0865. The spectroscopic properties of \textbf{118a} were as reported by Otterlo.\textsuperscript{160}
2- Allyl-3,6-dimethoxy-4-methylphenol, 119

The ether 134 (5.34 g; 25.7 mmol) was heated, in the absence of solvent under an atmosphere of nitrogen at 240-250 °C for 60 minutes. On cooling to room temperature, the dark brown-coloured residue was purified by column chromatography (silica; eluent hexane-ethyl acetate; 8:2 v/v) to afford the title compound, 119, a yellow-coloured oil. Yield 5.34 g (ca. 100%). ¹H NMR: (400 MHz; CDCl₃) δ 2.26 (3 H, s), 3.47 (2H, d, J = 6.1 Hz), 3.71 (3H, s), 3.87 (3H, s), 4.90-5.05 (2H, m), 5.57 (1H, bs), 6.02 - 6.12 (1H, m), 6.59 (1H, s) ppm. ¹³C NMR: (100 MHz; CDCl₃) δ 15.9, 28.5, 56.2, 61.1, 110.7, 114.7, 119.2, 121.0, 136.8, 142.1, 142.7, 150.7 ppm. IR: νmax 1053, 1219, 1412, 1488, 2939, 3074, 3527 cm⁻¹. MS: (ES⁺): m/z 209 ([M+H]⁺). HRMS: (ES⁺) C₁₂H₁₇O₃ ([M+H]⁺) requires 209.1187; found 209.1179.
The title compound was prepared by a slight modification to a known synthetic procedure. A solution of I,4-dimethoxy-2-(2-methylenecyclohexyl)oxybenzene (1.36 g, 5.48 mmol, 1 equivalent) was heated without solvent, under an atmosphere of nitrogen at 240-250 °C for 60 minutes. On cooling to room temperature, the title compound was recovered as a dark brown–coloured viscous oil. Yield 1.36 g (100%). ¹H NMR: (400 MHz; CDCl₃) δ 1.59 (4H, m), 1.99 (4H, m), 3.33 (2H, s), 3.77 (3H, s), 3.87 (3H, s), 5.31 (1H, br., s), 5.74 (1H, s), 6.38 (1H, d, J = 8.8 Hz), 6.70 (1H, d, J = 9.1 Hz) ppm. ¹³C NMR: (100 MHz; CDCl₃) δ 22.4, 23.0, 25.2, 28.7, 31.2, 56.2, 56.3, 101.2, 108.1, 115.5, 120.5, 136.2, 141.2, 144.7, 152.9 ppm. IR: υ_max 1131, 1247, 1468, 2833, 2926, 3539 cm⁻¹. MS (ES): m/z 247.1 ([M-H]⁻, 100%). HRMS (HESI-POS): C₁₅H₂₀O₃Na ([M+Na]⁺), requires 271.1305; found 271.1303. Microanalysis: C₁₅H₂₀O₃Na requires: C, 72.55; H, 8.12%; found: C, 72.26; H, 7.99%. 

2-(cyclohex-1-en-1-ylmethyl)-3,6-dimethoxyphenol, 175
3.3.5 Procedure for the Preparation of Chloroacetates and Bromoacetates

2-Allyl-3, 6-dimethoxyphenyl 2,2,2-trichloroacetate and 4-allyl-3,6-dimethoxyphenyl 2,2-trichloroacetate, 120a and 120b

A solution of an isomeric mixture of phenols 118a and 118b (3.0 g; 15.5 mmol; 118a:118b = 2:1) and triethylamine (2.6 mL, 18.5 mmol) in dry diethyl ether (50 mL) was cooled to 0 °C under nitrogen. To this solution was added trichloroacetyl chloride (3.37 g, 2.1 mL, 18.5 mmol), drop-wise, via syringe. The reaction mixture was stirred for 3 hours at 0 °C and then quenched by the slow addition of sodium bicarbonate (50 mL of a saturated solution). The organic layer was separated, washed with water (3 × 50 mL), dried (MgSO₄) and concentrated in vacuo to afford the title compound 2-allyl-3,6-dimethoxyphenyl 2',2',2'-trichloroacetate, 120a together with 4-allyl-3,6-dimethoxyphenyl 2',2',2'-trichloroacetate 120b, a pale yellow oil which was used directly in the benzannulation reaction. Yield 3.25 g (62%; 120a:120b = 2:1). ¹H NMR: 500 MHz, CDCl₃ δ 3.32 (2/3H, br. d, J = 6.3 Hz), 3.37-3.42 (4/3H, m), 3.80 (2/3H, s), 3.81 (2H, s), 3.82 (2/3H, s), 3.83 (2H, s), 4.98 (2/3H, br. dq, J = 10, 1.6Hz), 5.03 (2/3 H, br. q, J = 17.0, 1.6 Hz), 5.08 (1/3H, br. dq, J = 17.0, 1.6 Hz), 5.09 (1/3H, br. dq, J = 11.0, 1.6 Hz), 5.87 (2/3H, ddt, J = 17.0, 11.0, 6.3 Hz) 5.93-6.02 (1/3H, m), 6.70 (1/3H, s), 6.77-6.81 (4/3H, m), 6.85 (2/3H, d, J = 9.0 Hz) ppm. ¹³C NMR: (125 MHz, CDCl₃) δ 28.2 (major), 34.0 (minor), 56.2 (minor), 56.3 (major), 56.6 (major), 56.9 (minor), 105.1 (minor) 109.1 (minor), 110.4 (major), 115.2 (major), 115.6 (major), 116.07 (minor ), 122.5 (major), 128.0 (minor), 138.53, 137.7, 136.27, 134.95 (minor + major), 144.22 minor), 145.07 (major), 151.22 (minor), 151.78 (major), 159.58 (major), 160.2 (minor) ppm (CCl₃ carbon not observed). IR: vₘₐₓ 675, 1161, 1491, 1781, 2837, 2940 cm⁻¹. MS: (ES+) m/z 360.9 ([M{³⁵Cl}+Na]⁺); 363.0 ([M{³⁷Cl}+Na]⁺). HRMS: (ES+) C₁₃H₁₃²³⁵Cl₃O₄Na [M{³⁵Cl}+Na]⁺ requires 360.9772; found 360.9764.
2-Allyl-3,6-dimethoxyphenyl 2,2,2-trichloroacetate, 120a

Repeating the reaction as above using a pure sample of 118a (0.59 g, 3.00 mmol) afforded the title compound, 120a, a green-coloured semi solid. Yield 800 mg (77%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 3.39 (2H, br. dt, $J = 6.3, 1.5$ Hz), 3.81 (3H, s), 3.82 (3H, s), 4.99 (1H, dq, $J = 11.0, 1.5$ Hz), 5.03 (1H, dq, $J = 17.0, 1.5$ Hz), 5.89 (1H, ddt, $J = 17.1, 11.0, 6.3$ Hz), 6.78 (1H, d, $J = 9.0$ Hz), 6.84 (1H, d, $J = 9.0$ Hz) ppm. $^{13}$C NMR: (125 MHz, CDCl$_3$) δ 28.2, 56.3, 115.6, 123.3, 134.9, 138.4, 145.3, 151.8, 159.0, 163.3 (CCl$_3$ carbon not observed) ppm. IR: $\nu_{\text{max}}$ 675, 1491, 1780, 2846, 2921 cm$^{-1}$. MS: (EI) m/z: 338.1 C$_{13}$H$_{13}^{35}$Cl$_3$O$_4$ ([M$^{35}$Cl]$^+$), 340.1 C$_{13}$H$_{13}^{37}$Cl$_3$O$_4$ ([M$^{37}$Cl]$^+$). HRMS (HESI$^+$) C$_{13}$H$_{13}^{35}$Cl$_3$O$_4$Na ([M$^{35}$Cl]+Na$^+$) requires 360.9772; found 360.9764.
To a mixture of 118a/118b (2.60 g, 5.6 mmol; 118a:118b = 2:1) and trimethylamine (0.9 mL, 680 mg, 6.72 mmol) in dry diethyl ether at 0 °C was added dropwise, via syringe a solution of tribromoacetyl chloride (2.11 g, 6.72 mmol) in dry diethyl ether (5 mL). After 3 hours at 0 °C the reaction mixture was poured into ice-cold water (50 mL) and diethyl ether (50 mL) was added. The organic layer was collected, and the aqueous layer extracted with diethyl ether (2 × 20 mL). The combined organic extracts were dried (MgSO₄) and concentrated to 20 mL and passed through a pad of celite®. The celite was washed with diethyl ether (20 mL) and the combined organic extracts were concentrated in vacuo to afford 2-allyl-3,6-dimethoxyphenyl 2',2',2'-tribromoacetate, 121a together with 2-allyl-3,6-dimethoxyphenyl 2',2',2'-tribromoacetate 121b, a yellow coloured semi-solid. Yield 4.7 g (74%; 121a:121b = 2:1). ¹H NMR: (400 MHz; CDCl₃) δ 3.40 (2/3H, d, J = 6.6, minor), 3.45 (4/3H, d, J = 6.0, major), 3.8-3.85 (6H, m, minor + major), 4.98-5.14 (2H, m, minor + major), 5.92-6.01 (1H, m, minor + major), 6.71 (1/3H, s, minor), 6.79-6.81 (1H, m, minor + major), 6.84-6.91 (2/3H, d, J = 9.0, major) ppm. ¹³C NMR: (125 MHz, CDCl₃) δ 27.5 (major), 27.5 (minor), 28.2 (major), 34.0 (minor), 56.2 (minor), 56.3 (major), 56.6 (major), 57.0 (minor), 105.1 (minor), 109.0 (minor), 110.5 (major), 115.3 (major), 115.6 (major), 116.2 (minor), 122.6 (major), 128.0 (minor), 138.7, 136.2, 135.1 (minor + major), 144.4 (minor), 145.2 (major), 151.2 (minor), 152.0 (major), 159.5 (minor + major) ppm. IR: ν max 646, 1179, 1409, 1490, 1759, 2839, 2969 cm⁻¹. MS: (EI⁺) m/z 469.8 ([M{79}Br]⁺); 471.9 ([M{81}Br]⁺, 96%). HRMS: (ES⁺) C₁₃H₁₃⁸¹Br₃O₄K ([M{81}Br]+K)⁺ requires 508.7996; found 508.7982.
To a solution of 2-allyl-3,6-dimethoxy-4-methylphenol, 119 (700 mg, 3.4 mmol) and pyridine (0.4 mL, 5.04 mmol) in anhydrous diethyl ether (10 mL) at 0 °C was added, drop-wise, tribromoacetyl chloride (1.0 mL, 5.04 mmol). On completion of the addition the reaction mixture was left to reach ambient temperature over the course of 3 hours and was then quenched by the addition of saturated aqueous NaHCO₃ (30 mL). The reaction mixture was extracted with diethyl ether (2 × 20 mL) and the combined organic extracts were washed with additional quantities of saturated aqueous NaHCO₃ (4 × 10 mL), water (3 × 10 mL), dried (MgSO₄) and concentrated in vacuo. Purification of the residue by column chromatography (silica; eluent Ethyl acetate-petroleum ether, 10% v/v) afforded the title compound 122, a yellow-coloured crystalline solid. Yield 1.05 g (64%); m.p. 52-54 °C. ¹H NMR: (400 MHz; CDCl₃) δ 2.33 (3H, s), 3.45 (2H, d, J = 5.9), 3.72 (3H, s), 3.83 (3H, s), 5.05 (2H, m), 5.91 – 6.01 (1H, m), 6.72 (1H, s). ¹³C NMR: (100 MHz; CDCl₃) δ 16.5, 27.7, 28.9, 56.3, 61.2, 112.7, 115.8, 126.6, 130.1, 135.6, 136.3, 147.1, 150.2, 159.6 ppm. IR: νmax 1190, 1407, 1483, 1761, 2840, 2938 cm⁻¹. MS: (APCI⁺) m/z 486.8 ([M{⁷⁹Br}+H]⁺), 488.8 ([M{⁸¹Br}+H]⁺).
The following compounds were prepared by employing standard procedure previously adopted. To a stirred solution of freshly prepared 2-(cyclohex-1-en-1-ylmethyl)-3,6-dimethoxyphenol 175 (1.76 g, 7.09 mmol) was added dropwise anhydrous trimethylamine (1.2 mL, 8.5 mmol, 1.2 equivalents) under an atmosphere of nitrogen at 0 °C followed by the slow dropwise addition of trichloroacetyl chloride (1 mL, 8.5 mmol, 1.2 equivalents) and the reaction was allowed to warm up to room temperature and then stirred for 15 hours. The mixture was quenched with the slow addition of saturated solution of NaHCO$_3$ (40 mL) and the separated organic phase was extracted with diethyl ether (10 mL × 3 times). The resulting organic extract was wash with water (20 mL × 2 times), dried (MgSO$_4$), filtered and concentrated under reduced pressure to afford the title compound 176a as beige–coloured solid. Yield 2.29 g (82%); m.p. 75.6-77.6 °C. $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ 1.47-1.63 (4H, m), 1.91-1.98 (4H, m), 3.32 (2H, s), 3.82 (3H, s), 3.83 (3H, s), 5.24-5.30 (1H, m), 6.79 (1H, d, $J = 9.0$ Hz), 6.85 (1H, d, $J = 8.8$ Hz) ppm. $^{13}$C NMR: (100 MHz; CDCl$_3$) $\delta$ 22.3, 22.9, 25.1, 28.1, 28.5, 31.7 56.45, 56.47, 109.0, 110.1, 121.7, 122.8, 134.7, 139.1, 145.2, 152.1, 159.2 ppm. IR: $\nu_{\text{max}}$ 676, 1163, 1262, 1492, 1579, 1776, 2935, 3013 cm$^{-1}$. MS (ES$^+$): m/z 433.1 ([M$^{35+}$K$^+$], 100%), 431.1 ([M$^{37+}$K$^+$], 90%). HRMS (HESI-POS): $C_{17}H_{19}O_4Cl_3K$ ([M$^{35+}$K$^+$]) requires 430.9981; found 430.9979. Microanalysis: $C_{17}H_{19}O_4Cl_3$ requires: C, 52.32; H, 4.99%; found: C 51.87 H 4.86%.
To a stirred solution of freshly prepared 2-(cyclohex-1-en-1-ylmethyl)-3,6-dimethoxyphenol 175 (1.36 g, 5.5 mmol) was added dropwise anhydrous trimethylamine (0.92 mL, 9.09 mmol, 1.2 equivalents) in an atmosphere of nitrogen at 0 °C followed by the slow addition of dropwise portion of tribromoacetyl chloride (1.3 mL, 6.6 mmol, 1.2 equivalents) and the reaction was allowed to warm up to room temperature and stirred for 15 hours. The reaction mixture was quenched with saturated solution of NaHCO₃ (40 mL) and then extraction with diethyl ether (10 mL × 3 times). The resulting organic extract was wash with water (20 mL × 2 times), dried (MgSO₄), filtered and concentrated under reduced pressure to afford the crude product. Flash chromatography of this material (silica; eluent: petroleum ether-ethyl acetate, 85% v/v) afforded the title compound 176b as an orange-coloured solid. Yield 1.98 g (69%); m.p. 86.9-88.9 °C. ¹H NMR: (400 MHz; CDCl₃) δ 1.48-1.63 (4H, m), 1.89-1.96 (4H, m), 3.31 (2H, s), 3.82 (6H, s), 5.25-5.29 (1H, m), 6.80 (1H, d, J = 9.0 Hz), 6.85 (1H, d, J = 9.0 Hz) ppm. ¹³C NMR: (100 MHz; CDCl₃), δ 22.3, 22.9, 25.1, 28.3, 31.7, 56.44, 56.49, 109.1, 110.2, 121.8, 122.8, 134.7, 139.0, 145.0, 152.2, 159.3 ppm. IR: υmax 599, 1178, 1261, 1492, 1654, 1764, 2926, 3009 cm⁻¹. MS (ES⁺): m/z 548.9 ([M⁺+Na]⁺, 52%), 546.9 ([M⁺⁺+Na]⁺, 40%). HRMS (HESI-POS): C₁₇H₁₉O₄Br₃Na [M⁺+Na]⁺ requires 546.8726; found 546.8726.
3.3.6 Procedure for Cyclisation of ortho-Allyl Trichloroacetates and Tribromoacetates

5-chloro-1,4-dimethoxynaphthalene, 123

A solution of 120a and 120b (3.95 g, 11.6 mmol; 120a:120b = 2:1) and Cu(I)Cl 70 (143 mg, 5 mol%) in anhydrous diglyme (8 mL) was brought to reflux under nitrogen for 2 hours. On cooling to ambient temperature, the reaction mixture was applied to a silica gel column (pet. ether slurry) eluting with petroleum ether-dichloromethane (7:3 v/v). Under these conditions diglyme eluted first followed by the title compound 123, a colourless solid. Yield 940 mg (36%); m.p. 81.4-82.0 °C. 1H NMR: (400 MHz; CDCl₃) δ 3.93 (1H, s), 3.97 (1H, s), 6.77 (1H, d, J = 8.3 Hz), 6.87 (1H, d, J = 8.5 Hz), 7.34 (1H, t, J = 7.8 Hz), 7.55 (1H, d, J = 7.3 Hz), 8.20 (1H, d, J = 8.5 Hz) ppm. 13C NMR: (100 MHz; CDCl₃) δ ppm 157.2, 133.7, 125.4, 129.7, 128.8, 129.4, 121.2, 108.3, 105.4, 57.2, 55.9. IR: υmax 755, 1059, 1359, 1450, 2956, 3078 cm⁻¹. MS: (ES⁺) m/z: 223.0 ([35ClM+H]⁺). HRMS: (ES⁺) [C_{12}H_{11}ClO_2] ([35ClM]⁺) requires 222.0442; found 222.0442. Microanalysis: C_{12}H_{11}ClO_2 requires: C, 64.73; H, 4.98%; found: C, 64.57; H, 4.97%.
A solution containing CuBr (31 mg, 0.2 mmol) and the crude tribromoacetates 121a and 121b (1.0 g, 2.2 mmol; 121a:121b = 2:1) in diglyme (5 mL) was heated to reflux for 2 h under an atmosphere of nitrogen. On cooling to ambient temperature, the reaction mixture was purified, without any additional work-up, by direct application to a silica column (eluent CH$_2$Cl$_2$-pet. ether, 7:11 v/v). In this way diglyme eluted first followed by the title compound 124, a beige-coloured crystalline solid. Yield 70 mg (12%); m.p. 78.0-81.0 °C (no reported m.p.). $^1$H NMR: (400 MHz; CDCl$_3$) δ 8.18 (1H, dd, $J$ = 8.3, 1.3 Hz), 7.74 (1H, dd, $J$ = 7.5, 1.3 Hz), 7.17 (1H, dd, $J$ = 8.3, 7.5 Hz), 6.81 (1H, d, $J$ = 8.5 Hz), 6.69 (1H, d, $J$ = 8.5 Hz), 3.98 (3H, s), 3.83 (3H, s) ppm. $^{13}$C NMR: (100 MHz; CDCl$_3$) δ 149.7, 133.7, 128.7, 125.8, 124.5, 121.9, 116.4, 108.3, 104.3, 56.9, 55.8 ppm. IR: $\nu_{\text{max}}$ 754, 1055, 1357, 1453, 2956, 3545 cm$^{-1}$. MS: (ES$^+$) m/z 265.9 ([M$^{79}$Br]$^+$), 267.9 ([M$^{81}$Br]$^+$). HRMS: (ES$^+$) C$_{12}$H$_{11}$BrO$_2$ ([M$^{79}$Br]$^+$) requires 265.9937; found 265.9938. Microanalysis: C$_{12}$H$_{11}$BrO$_2$ requires: C, 53.96; H, 4.15%; found: C, 53.86; H: 4.31%.
A solution of tribromoacetate, 122 (1.0 g, 2.1 mmol) and copper(I) bromide (30 mg, 10 mol%) in anhydrous diglyme (1.5 mL) was brought to reflux for 2 hours under an atmosphere of nitrogen. On cooling to ambient temperature, the reaction mixture was purified by column chromatography (silica; eluent ethyl acetate-petroleum ether, 12 % v/v). Use of this solvent system enabled initial elution of diglyme followed by the title compound, 125 which was isolated as a pale yellow-coloured crystalline solid. Yield 260 mg (45%); m.p. 62–64 °C. \(^1\)H NMR: (400 MHz; CDCl\(_3\)) \(\delta\) 2.45 (3H, s), 3.84 (3H, s), 3.93 (3H, s), 6.74 (1H, s), 7.26 (1H, dd, \(J = 7.3, 8.3 \) Hz), 7.75 (1H, d, \(J = 7.3 \) Hz), 8.06 (1H, d, \(J = 8.3 \) Hz) ppm. \(^{13}\)C NMR: (100 MHz; CDCl\(_3\)) \(\delta\) 16.2, 56.2, 61.1, 110.8, 116.9, 121.5, 123.1, 126.3, 126.9, 131.1, 132.2, 147.2, 151.8 ppm. IR: \(\nu_{\text{max}}\) 757, 1062, 1357, 1454, 2929, 3070 cm\(^{-1}\). MS: GCMS \(m/z\) 265.0 ([M\(^{79}\)Br]-CH\(_3\))^\(+\), 100%), 267.0 ([M\(^{81}\)Br]-CH\(_3\))^\(+\), 97%), 280.0 ([M\(^{79}\)Br])^\(+\), 63%), 282.0 ([M\(^{81}\)Br])^\(+\), 61%); HRMS: (EI^+) C\(_{13}\)H\(_{13}\)O\(_2\)Br ([M\(^{79}\)Br])^\(+\) requires 280.0093; found 280.0098.
9-chloro-5,8-dimethoxy-1,2,3,4-tetrahydroanthracene, 8a

A solution of trichloroacetate 176a (0.35 g, 1.26 mmol) was placed in a one neck round bottom flask (50 mL) which was equipped with a magnetic stirrer bar and thoroughly degassed for 10 minutes before the addition of anhydrous diglyme (1 mL, 8.35 mmol) and Cu(I)Cl 70 (0.03 g, 0.0614 mmol, 5 mol%). The reaction mixture was then heated to a temperature of 162 °C for 2 hours under an atmosphere of nitrogen. On completion (monitored by TLC), the resulting crude was left to cool, and the resulting crude product was purified by flash chromatography (eluent: petroleum ether-ethyl acetate, 80% v/v) to afford the title compound 8a as yellow-coloured oil. Yield 0.07 g; (28%).

$^1$H NMR: (400 MHz; CDCl$_3$) δ 1.66-1.87 (4H, m), 2.84-2.98 (4H, m), 3.82 (3H, s), 3.87 (3H, s), 6.50 (1H, d, $J = 8.3$ Hz), 6.71 (1H, d, $J = 8.3$ Hz), 7.85 (1H, s). $^{13}$C NMR: (100 MHz; CDCl$_3$) δ 22.6, 23.5, 28.6, 30.8, 55.7, 57.8, 103.1, 108.3, 120.1, 122.8, 126.5, 128.8, 135.9, 136.6, 149.3, 150.0 ppm. IR: $\nu_{\text{max}}$ 614, 1157, 1253, 1573, 1678, 2834, 2932 cm$^{-1}$. MS (GCMS): m/z 276.1 ([M$^{35}$], 75%), 279.1 ([M$^{37}$], 25%). HRMS (ASAP-POS): C$_{16}$H$_{18}$O$_2^{35}$Cl ([M$^{35}$]+H$^+$) requires 277.0990; found 277.0996.
A solution of 2-(cyclohex-1-en-1-ylmethyl)-3,6-dimethoxyphenyl 2,2,2-tribromoacetate 176b (0.82 g, 1.56 mmol) was placed in a one neck round bottom flask (50 mL) which was equipped with a magnetic stirrer bar and thoroughly degassed for 10 minutes before addition of anhydrous diglyme (1 mL, 8.35 mmol) and Cu(I)Cl 70 (ca. 0.04 g, 0.0818 mmol, 5 mol%). The reaction mixture was then heated to a temperature of 155-159 °C for 3 hours under an atmosphere of nitrogen. On completion (monitored by TLC), the resulting crude product was left to cool before it was purified on a silica gel column (eluent: petroleum ether-ethyl acetate, 80% v/v). This enabled the isolation of the title compound 8b as bright yellow-coloured crystalline solid. Yield 0.215 g (43%); m.p. 96-97 °C. ¹H NMR: (400 MHz; CDCl₃) δ 1.66-1.87 (4H, m), 2.84-2.95 (4H, m), 3.81 (3H), 3.86 (3H, s), 6.58 (1H, d, J = 8.3 Hz), 6.74 (1H, d, J = 8.5 Hz), 7.90 (1H, s) ppm. ¹³C NMR: (100 MHz; CDCl₃) δ 22.6, 24.0, 31.0, 32.3, 55.7, 57.3, 103.2, 108.5, 119.4, 121.1, 123.9, 126.7, 136.8, 138.0, 149.2, 149.7 ppm. IR: υmax 579, 1151, 1252, 1447, 1621, 2832, 2933 cm⁻¹. MS (ES⁺): m/z 361.0 ([M⁺]+K⁺, 100%), 359.0 ([M⁺]+K⁺, 90%); 345.0 ([M⁺-(CH₃)]⁺, 35%), 343.0 ([M⁺-(CH₃)]⁺, 33%). HRMS (HESI-POS): C₁₆H₁₁O₂⁺BrK ([M⁺]+K⁺) requires 359.0044; found 359.0040.
3.3.7 Procedure for the Preparation of Boronic Esters

\[4,4,5,5-Tetramethyl-2-(naphthalen-1-yl)-1,3,2-dioxaborolane,^{249}\]

A 10 cm screwcap vial equipped with magnetic stirrer bar was charged with 1-bromonaphthalene 137 (0.2 g; 1 mmol; 1 eq.), B\(_2\)Pin\(_2\) 55 (0.26 g; 1.0 mmol; 1 eq.), Pd(PPh\(_3\))\(_2\)Cl\(_2\) (0.01 g; 0.014 mmol; 0.01 eq.), and anhydrous potassium acetate (0.2 g; 2 mmol; 2 eq.). The vial was transferred to a preheated oil bath (100-120 °C). After 3 hours, the reaction mixture was cooled to room temperature, dissolved in EtOAc-H\(_2\)O (10 mL, 1:1) and the organic phase was extracted with ethyl acetate (10 mL × 3 times), washed with water (20 ml × 5 times) and dried over MgSO\(_4\). The solvent was removed in vacuo and the title compound 138 was isolated after elution of the crude product on a silica gel column (eluent: petroleum ether/ethyl acetate; 90% v/v) colourless crystalline solid. Yield 0.091 g (46%); m.p. 56.6˗58.8 °C lit.\(^{93}\) m.p. 54–55 °C. \(^1\)H NMR: (400 MHz; CDCl\(_3\)) δ 1.44 (12H, s), 7.46˗7.58 (3H, m), 7.85 (1H, dd, \(J = 8, 1.3\)Hz), 7.94 (1H, d, \(J = 8.1\)Hz), 8.10 (1H, dd, \(J = 7.23, 1\)Hz), 8.78 (1H, d, \(J = 8.4\)Hz) ppm. \(^{13}\)C NMR: (100 MHz; CDCl\(_3\)) δ 24.98, 83.74, 124.98, 125.48, 126.33, 128.35, 128.41, 131.60, 133.21, 135.64, 136.92 ppm. IR: \(\upsilon_{ma}\) 1057, 1143, 1333, 1462, 1507, 2974, 3044 cm\(^{-1}\). MS (GCMS): m/z 254.2 ([M]\(^+\), 64%). HRMS (ES\(^+\)): C\(_{16}\)H\(_{19}\)O\(_2\)BH\(_4\) \([M+NH_4]^+\) requires 272.1816; found 272.1828.
A 10 mL reacti-vial™ was charged with 123 (132 mg, 0.59 mmol), B₂Pin₂ 55 (455 mg, 1.8 mmol), Pd(PPh₃)₂Cl₂ (20 mg, 5 mol%), anhydrous potassium acetate (177 mg, 1.8 mmol) and then sealed under an atmosphere of nitrogen and transferred to a preheated oil bath (100-120 °C). After 20 hours the reaction mixture was cooled to room temperature and partitioned between water (10 mL) and ethyl acetate (10 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts washed (water, 20 mL), dried (MgSO₄) and concentrated in vacuo. Purification of the residue by column chromatography (silica; eluent petroleum ether-ethyl acetate, 9:1 v/v) afforded the title compound, a colourless crystalline powder. Yield 235 mg (71%); m.p. 99.7-101.7 °C. ¹H NMR: (400 MHz; CDCl₃) δ 1.46 (12H, s), 3.95 (3H, s), 3.97 (3H, s), 6.70 (1H, d, J = 8.4 Hz), 6.72 (1H, d, J = 8.4 Hz), 7.49 (1H, dd, J = 8.5, 6.8 Hz), 7.55 (1H, dd, J = 6.8, 1.3 Hz), 8.23 (1H, dd, J = 8.5, 1.3 Hz) ppm. ¹³C NMR: (100 MHz; CDCl₃) δ 25.1, 55.7, 55.9, 83.5, 103.0, 103.9, 122.6, 125.1, 125.8, 128.21, 130.5, 149.7, 149.8, (one aromatic resonance not apparent due to quadrupole broadening) ppm. IR: δmax 1052 (B-C), 1141 (C-O), 1328 (-C-H), 1466 (-C-H), 1516 (C₆-C₂), 2976 (C-H), 3076 (Ar-H) cm⁻¹. MS: (ES⁺) m/z 314.2 ([M]⁺, 25%), 315.2 ([M+H]⁺, 50%), 337.2 ([M+Na]⁺, 65%). HRMS: (EI⁺) C₁₈H₂₃O₄BNa ([M+Na]⁺) requires 337.1582; found 337.1571.
Bromonaphthalene 125 (200 mg, 0.71 mmol), $\text{B}_2\text{pin}_2$ 55 (217 mg, 0.85 mmol), Pd(dppf)Cl$_2$ (10 mg, 14.2 mmol) and KOAc (210 mg, 2.13 mmol) were added to a Schlenk tube under an atmosphere of nitrogen. 1,4-Dioxane (10 mL) was then added and the mixture heated to 90 °C for 20 hours under an atmosphere of nitrogen. On cooling to room temperature, the reaction mixture was poured into water (10 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL), dried (MgSO$_4$) and concentrated in vacuo. Purification of the residue by column chromatography (silica; eluent ethyl acetate-petroleum ether, 15% v/v) afforded the title compound 136, a colourless solid Yield 130 mg (54%); m.p. 146–148 °C. $^1$H NMR: (400 MHz, CDCl$_3$) $\delta$ 1.45 (12H, s, 12 H), 2.43 (3H, s,), 3.83 (3H, s), 3.98 (3H, s), 6.63 (1H, s), 7.48 (2H, m), 8.04 (1H, m) ppm. $^{13}$C NMR: (101 MHz, CDCl$_3$) $\delta$ 16.3, 25.1, 55.7, 61.3, 83.6, 107.5, 122.4, 125.3, 125.7, 127.0, 128.2, 129.4, 147.5, 151.8 (one aromatic resonance not apparent due to quadrupole broadening) ppm. IR: $\nu_{\text{max}}$ 1232, 2846, 2975 cm$^{-1}$. MS: (ES$^+$) m/z 329.4 ([M$^{11}$B]+H$^+$, 100%); HRMS: (ESI$^+$) C$_{19}$H$_{26}$O$_4$B([M$^{11}$B]+H$^+$) requires 329.19119, found 329.1923. Microanalysis: C$_{19}$H$_{25}$BO$_4$ requires: C, 69.53; H, 7.68%; found: C, 69.50; H, 7.60%.
A 10 mL reacti-vial™ equipped with magnetic stirrer bar was charged with aryl bromide 8b (0.088 g, 0.239 mmol, 1 equivalent), B2Pin2 55 (0.3 g, 1.18 mmol, 3 mol equivalents), Pd(PPh3)2Cl2 (0.03g, 2.03 mmol, 0.05 equivalents), and anhydrous potassium acetate (0.2g, 2.03 mmol, 3 mol equivalents). The vial was transferred to a preheated oil bath (100 °C–120 °C). After 20 hours, the reaction mixture was cooled to room temperature, dissolved in EtOAc-H2O (10 mL, 1:1) and the organic phase was extracted with ethyl acetate (10 mL × 3 times), washed with water (20 ml × 5 times) and dried over MgSO4. The solvent was removed in vacuo and the product was isolated after elution of the crude product on a silica gel column (eluent: petroleum ether-ethyl acetate; 90% v/v) to furnish the title compound 181 as a cream-coloured crystalline solid. Yield 0.146 g (60%); m.p. 107.5-108.9 °C. 1H NMR: (400 MHz; CDCl3) δ 1.39 (12H, s), 1.64-1.84 (4H, m), 2.82- 3.01 (4H, m), 3.84 (3H, s), 3.86 (3H, s), 6.48 (1H, d, J = 8.3 Hz), 6.55 (1H, d, J = 8.3 Hz), 7.81 (1H, s) ppm. 13C NMR: (100 MHz; CDCl3) δ 23.0, 23.6, 25.0, 26.1, 29.1, 30.6, 55.5, 56.5, 83.4, 101.7, 103.6, 121.9, 124.4, 127.8, 135.3, 140.0, 149.5, 149.7 ppm. IR: νmax 1040, 1120, 1252, 1461, 1654, 1764, 2926, 2976 ppm. MS (ES+): m/z 407.2 ([M+K]+, 70%), 285.2 ([M-(C6H10)-H]+, 100%) cm⁻¹. HRMS (HESI-POS): C22H29O4BK ([M+K]+) requires 407.1790; found 407.1791.
Synthesis of 5,8-dimethoxy-1,2,3,4-tetrahydroanthracene, 183

The above-mentioned procedure also afforded the title compound 183 as colourless semi-solid oil. Yield. 36 mg (24%). $^{1}$H NMR: (400 MHz; CDCl$_3$) $\delta$ 1.80-1.93 (4H, m), 2.92-3.07 (4H, m), 3.95 (6H, s), 6.60 (2H, s), 7.90 (2H, s) ppm. $^{13}$C NMR: (100 MHz; CDCl$_3$) $\delta$ 23.4, 29.9, 55.6, 120.8, 128.3, 129.4, 136.2, 149.1 ppm. MS (APCI$^+$): m/z 243.2 ([M+H]$^+$, 100%). HRMS (APCI-POS): C$_{16}$H$_{19}$O$_2$ (M+H$^+$) requires 243.1380; found 243.1378.
3.3.8 Procedure for the Preparation of Quinones

5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene-1,4-dione, 129

To a solution of 135 (110 mg; 0.35 mmol) in acetonitrile (4 mL) was added a solution of cerium ammonium nitrate (CAN) (480 mg; 0.88 mmol) in acetonitrile-water (4 mL; 3:1 v/v). After one hour at ambient temperature, water (50 mL) was added and the aqueous phase extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. Purification of the residue by column chromatography (silica; eluent petroleum ether-ethyl acetate, 9:1 v/v) afforded the title compound 129, a yellow-coloured crystalline solid. Yield 70 mg (66%); m.p. 131-132 °C. ¹H NMR: (400 MHz, CDCl₃) δ 1.49 (12H, s), 6.98 (1H, d, J = 10.0 Hz), 7.02 (1H, d, J = 10.0 Hz), 7.75 (1H, t, J = 7.2 Hz), 7.77 (1H, dd, J = 7.2, 1.7 Hz), 8.09 (1H, dd, J = 7.2, 1.7 Hz) ppm. ¹³C NMR: (100 MHz, CDCl₃) δ 24.8, 84.8, 126.9, 131.5, 133.1, 135.4, 137.3, 138.1, 139.2, 185.1, 186.3 (one aromatic resonance not observed due to quadrupole broadening) ppm. IR: v_max 1032, 1193, 1322, 1474, 1663, 2932, 2977 cm⁻¹. MS: (ES⁺) m/z 283.1 ([M-H]⁺, 12%), 307.1 ([M+Na]⁺, 100%). HRMS: (EI⁺) C₁₆H₁₇BO₄+Na ([M+Na]⁺) requires 307.1112; found 307.1105. Microanalysis: C₁₆H₁₇BO₄ requires: C, 67.64; H, 6.03%; found: C, 67.95; H, 5.95%.
A solution of cerium (IV) ammonium nitrate (840 mg, 0.23 mmol) in water (1.0 mL) was added drop wise to 3.0 g of flash silica gel in a round bottom flask and the contents were stirred until the silica was evenly coated. A solution of 136 (200 mg, 0.6 mmol) in DCM (5 mL) was then added and the reaction mixture stirred for 12 hours. The reaction was then quenched by the addition of (10 mL) and the slurry extracted with DCM (2 × 10 mL) and the combined organic extracts dried (MgSO\(_4\)) and concentrated in vacuo. Purification of the residue by column chromatography (silica; eluent ethyl acetate-petroleum ether, 1:4 v/v) afforded naphthoquinone 130, a yellow-coloured solid. Yield 95 mg (53%); m.p. 98-100 °C. \(^1\)H NMR: (400 MHz, CDCl\(_3\)) \(\delta\) 1.41 (12 H, s), 2.13 (3H, d, \(J = 1.5\) Hz), 6.79 (1H, q, \(J = 1.5\) Hz), 7.62 (1H, t, \(J = 7.2\) Hz), 7.65 (1H, dd, \(J = 7.2, 1.8\) Hz), 8.00 (1H, dd, \(J = 7.2, 1.8\) Hz) ppm. \(^{13}\)C NMR: (100 MHz, CDCl\(_3\)) \(\delta\) 16.7, 84.3, 127.0, 131.6, 132.9, 134.9, 135.8, 136.9, 148.8, 185.6, 186.3 (one carbon not observed due to quadrupole broadening) ppm. IR: \(\nu_{\text{max}}\) 1035, 1171, 1311, 1474, 1658, 2932, 2980 cm\(^{-1}\). MS: (ES\(^+\)) m/z 172.8 ([M-B(O-iPr)\(_2\)]\(^-\), 100%), 296.9 ([M-H\(^-\)], 5%).
This compound was made after slight modification of a known procedure. A 50 mL RBF equipped with a magnetic stirrer bar was added 2-(5,8-dimethoxy-1,2,3,4-tetrahydroanthracen-9-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolan 181 (0.22 g: 0.59 mmol) before the addition of acetonitrile (4 mL). A solution of cerium ammonium nitrate, CAN (0.83 g; 1.51 mmol in acetonitrile/water; 3:1 mL) was slowly added in dropwise manner and the reaction mixture was stirred at room temperature. After 1h 30 minutes, the solution was poured into water (20 mL), extracted with ethyl acetate (10 mL × 2 times) and the combined extracts was dried over MgSO₄. The solvent was removed in vacuo and the product was isolated after elution of the crude product on a silica gel column (eluent: petroleum ether/ethyl acetate; 80% v/v) afforded the title compound 182 as an orange-coloured solid. Yield 0.055 g (27%); m.p. 112.0 °C–114.0 °C. ¹H NMR: (400 MHz; CDCl₃) δ 1.51 (12H, s), 1.75-1.92 (4H, m), 2.83-2.97 (4H, m), 6.93 (1H, d (distorted), J_app = 10.3 Hz), 6.95 (1H, d (distorted), J_app = 10.3 Hz), 7.74 (1H, s) ppm. ¹³C NMR (100 MHz, CDCl₃), δ 22.1, 22.7, 24.5, 29.2, 30.3, 84.1, 127.9, 128.9, 133.3, 137.9, 139.1, 143.5, 147.3, 185.5, 186.7 Ar⁻B is unresolved on spectrum due to quadrupole broadening) ppm. IR: ν_max 1027, 1165, 1282, 1574, 1661, 2920, 2975 cm⁻¹. MS (APCI): m/z 339.2 ([M+H]⁺, 100%). HRMS (APCI-POS): C₂₀H₂₄O₄B ([M+H]⁺) requires 339.1762; found 339.1762.
Anthracene-9,10-dione\textsuperscript{250} 17 and 1,8-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anthracene-9,10-dione\textsuperscript{238} 10

A 10 mL reacti-vial\textsuperscript{TM} equipped with magnetic stirrer bar was charged with 1,8-dichloroanthracene-9,10-dione 12a (0.1 g; 0.36 mmol), B\textsubscript{2}Pin\textsubscript{2} 55 (0.37 g; 1.5 mmol), catalyst Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} (0.04 g; 0.05 mmol) and anhydrous potassium acetate (0.25 g; 2.55 mmol) which has been thoroughly grounded together to fine particles using a mortar and pestle. The vial was transferred to a preheated oil bath (140 °C). After 20 hours, the reaction mixture was cooled to room temperature, dissolved in EtOAc-H\textsubscript{2}O (10 mL, 1:1) and the organic phase was extracted with ethyl acetate (10 mL × 3 times). This was further washed with water (20 ml × 5 times) and dried over MgSO\textsubscript{4}. The solvent was removed in vacuo and the product was isolated after elution of the crude product on a silica gel column (eluent: petroleum ether-ethyl acetate; 75% v/v) afforded compounds 17 and 10 respectively.

Anthracene-9,10-dione\textsuperscript{250} 17

![anthracene-9,10-dione](image)

Light yellow-coloured crystalline solid. Yield 10 mg; 0.05 mmol (10%); m.p. 284.0-286.0 °C (Lit.\textsuperscript{250} m.p. 284–285 °C). \textsuperscript{1}H NMR: (400 MHz; CDCl\textsubscript{3}) δ 7.80-7.85 (4H, m), 8.32-8.36 (4H, m) ppm. \textsuperscript{13}C NMR: (100 MHz; CDCl\textsubscript{3}) δ 127.2, 133.5, 134.1, 183.2 ppm. IR: \textit{v}\textsubscript{max} (film) 1246, 1468, 1673, 2854, 2977 cm\textsuperscript{-1}. MS (GCMS): m/z 208.0 ([M]\textsuperscript{+}; 100%). HRMS (ASAP-POS): C\textsubscript{14}H\textsubscript{8}O\textsubscript{2} requires 208.0519; found 208.0524.
1,8-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anthracene-9,10-dione,\textsuperscript{238} 10

The *title compound* 10 was isolated from the above procedure as cream-coloured crystalline solid. Yield 0.047 g (28%); m.p. 230.0-232.5 °C (no reported m.p.\textsuperscript{238}). \textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}) δ 1.49 (24H, s), 7.74-7.80 (4H, m), 8.29-8.33 (2H, dd, J = 6.52 2.8 Hz) ppm. \textsuperscript{13}C NMR: (100 MHz; CDCl\textsubscript{3}) δ 25.0, 84.1, 127.8, 133.2, 133.3, 136.2, 137.6, 139.8, 183.4, 185.1 ppm. IR: $\nu_{\text{max}}$ (film) 1057, 1181, 1314, 1468, 2941, 2979 cm$^{-1}$. MS (ASAP): m/z 461.2 ([M+H]$^+$, 100%). HRMS (ASAP-POS): C$_{26}$H$_{31}$O$_4$B$_2$ ([M+H]$^+$) requires 461.2301; found 461.2305.
3.3.9 Procedure for the Preparation of Hydroxyquinones

5-hydroxynaphthalene-1,4-dione,$^{251}$7a

To a solution of quinone 129 (40 mg; 0.14 mmol) in DCM (1.0 mL) at ambient temperature was added m-CBPA (46 mg of ca. 77% w/w; ca. 0.21 mmol). After six hours at ambient temperature the reaction was diluted by the addition of ethyl acetate (20 mL) and quenched by the addition of saturated solution of sodium sulphite (20 mL). The organic phase was separated, and the aqueous phase extracted with ethyl acetate (3 × 30 mL). The combined organic extracts washed once more with saturated sodium sulphite solution (3 × 20 mL), dried (MgSO₄) and concentrated \textit{in vacuo}. Chromatography of the residue (silica; eluent: petroleum ether-ethyl acetate, 7:3 v/v) afforded the \textit{title compound}, 5-hydroxynaphthalene-1,4-dione 7a, \textit{(juglone)}, an orange-coloured solid. Yield 10 mg (50%); m.p. 163–165 °C (Lit.$^{7}$ m.p. 163–165 °C). $^{1}$H NMR: (400 MHz, CDCl$_3$) δ 6.89 (2H, s), 7.22 (1H, dd, $J = 7.4$, 2.1 Hz), 7.54-7.61 (2H, m), 11.84 (1H, s) ppm. $^{13}$C NMR: (100 MHz, CDCl$_3$) δ 115.0, 119.2, 124.5, 131.7, 136.6, 138.7, 139.6, 184.3, 190.3 ppm. IR: $\nu_{\text{max}}$ 1217, 1361, 1447, 1636, 2925, 3062, 3622-2500 cm$^{-1}$. MS: (ASAP): m/z 175.0 ([M+H]$^+$, 100%). HRMS: (ASAP$^+$) C$_{10}$H$_7$O$_3$ ([M+H]$^+$) requires 175.0390; found 175.0389. Microanalysis: C$_{10}$H$_6$O$_3$ requires: C, 68.97; H: 3.47%; found: C, 68.70; H, 3.53
5-hydroxy-2-methyl-1,4-naphthoquinone,\textsuperscript{7b} m-CPBA (35 mg of ca. 77\% w/w; ca. 0.16 mmol) was added to a solution of boronate ester \textbf{130} (40 mg, 0.13 mmol) in MeCN-H\textsubscript{2}O (3 mL, 2:1 v/v) and the reaction mixture stirred at ambient temperature for 3 hours. After this time TLC analysis indicated complete consumption of starting material. The reaction was partitioned between satd. aqueous NaHCO\textsubscript{3} (10 mL) and ethyl acetate (20 mL). The aqueous layer was extracted with EtOAc (3 x 3 mL) and the combined organic extracts washed (water, brine and then Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3}), dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo} to afford 5-hydroxy-2-methyl-1,4-naphthoquinone \textbf{7b}, \textit{plumbagin}, an orange-coloured solid, which was essentially pure by spectroscopic analysis. Yield 24 mg (94\%); m.p. 72-74 °C (Lit.\textsuperscript{7} 76-78 °C). \textsuperscript{1}H NMR: (400 MHz, CDCl\textsubscript{3}) \(\delta\) 2.13 (3H, d, \(J = 1.6\) Hz), 6.75 (1H, q, \(J = 1.6\) Hz), 7.19 (1H, dd, \(J = 7.7, 1.6\) Hz), 7.54 (1H, t, \(J = 7.7\) Hz), 7.57 (1H, dd, \(J = 7.7, 1.6\) Hz), 11.92 (1H, s, OH) ppm. \textsuperscript{13}C NMR: (100 MHz, CDCl\textsubscript{3}) \(\delta\) 16.5, 115.1, 119.2, 124.2, 132.0, 135.5 136.1, 149.6, 161.2, 184.8, 190.3 ppm. IR: \(\nu_{\text{max}}\) 1227, 1359, 1452, 1639, 2920, 2961, 3618 cm\textsuperscript{-1}. MS: (APCI): m/z 187.8 ([M+H]\textsuperscript{+}, 20\%).
Synthesis of 5,6,7,8-tetrahydroanthracene-1,4-dione,\textsuperscript{212}184

A 50 mL RBF equipped with a magnetic stirrer bar was added 9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6,7,8-tetrahydroanthracene-1,4-dione \textbf{182} (0.048 g; 0.14 mmol) followed by addition of DCM (3 mL). \textit{m}-CBPA (0.165 g; 0.96 mmol) was added to the stirring mixture and the reaction left to stir for 6 hours. On completion (monitored by \textit{^1}H NMR), the reaction was quenched with the addition of saturated solution of sodium sulphate (20 mL) and the organic phase was separated, extracted with ethyl acetate (30 mL × 3), re-washed with 3 portions of saturated sodium sulphate solution (20 mL × 3 times) to remove the unreacted peroxide. The filtrate was dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo} to afford an orange-coloured solid as crude product. Flash column chromatography (silica; eluent petroleum ether-ethyl acetate; 70% v/v) furnished the \textit{title compound} \textbf{184} as an orange-coloured solid. Yield 0.012 g (38%); m.p. 112-114 °C. \textit{^1}H NMR: (400 MHz; CDCl\textsubscript{3}) δ 1.78−1.90 (4H, m), 2.85−2.95 (4H, m), 6.91 (2H, s) 7.78 (2H, s). \textit{^13}C NMR: (100 MHz; CDCl\textsubscript{3}), δ 22.5, 29.8, 127.2, 129.4, 138.6, 144.4, 185.3 ppm. IR: \(\nu_{\text{max}}\) 1246, 1374, 1457, 1665, 2853, 3029 cm\textsuperscript{-1}. MS (APCI): m/z 213.1 ([M-H]\textsuperscript{+}, 66%).
A 50 mL RBF equipped with a magnetic stirrer bar was added 9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6,7,8-tetrahydroanthracene-1,4-dione 10 (0.048 g; 0.14 mmol) followed by addition of DCM (3 mL). m-CBPA (0.165 g; 0.96 mmol) was added to the stirring mixture and the reaction left for 6 hours. On completion (monitored by $^1$H NMR), the reaction was quenched with the addition of saturated solution of sodium sulphate ($\text{Na}_2\text{SO}_4$) and the organic phase was separated and extracted with ethyl acetate (30 mL × 3), re-washed with 3 portions of saturated sodium sulphate solution to remove the unreacted peroxide. The filtrate was dried over MgSO$_4$, concentrated in vacuo to afford an orange-coloured solid which upon purification by column chromatography on silica (eluent petroleum ether-ethyl acetate; 70% v/v) afforded the title compound 11 as a brilliant orange-coloured solid. Yield 14 mg (81%); m.p. 185.0-187.0 °C, Lit.$^{252}$ m.p. 191-192 °C. $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ 7.32 (2H, d, $J = 8.5$ Hz), 7.66-7.74 (2H, t, $J = 7.8$ Hz), 7.85 (2H, d, $J = 7.5$ Hz), 12.09 (2H, s) ppm. $^{13}$C NMR: (100 MHz; CDCl$_3$) $\delta$ 115.8, 120.0, 124.6, 133.6, 137.3, 162.5, 181.7, 193.1 ppm. IR: $\nu_{\max}$ (film) 1261, 1356, 1620, 2250-3600 cm$^{-1}$. MS (GCMS): m/z 240.0 ([M]$^+$, 100%), 223.0 (6%), 212 (17%), 184 (20%), 155 (9%), 92 (9%). HRMS (ASAP-POS): C$_{14}$H$_8$O$_4$ requires 240.0417; found 240.0421.
3.3.10 Procedure for the Preparation of Halo-quinones

5-chloronaphthalene-1,4-dione,\textsuperscript{253} \textbf{126}

![Chemical structure of 5-chloronaphthalene-1,4-dione]

To a solution of \textbf{123} (230 mg, 1.0 mmol) in acetonitrile (4 mL) was added cerium (IV) ammonium nitrate (1.37 g, 2.5 mmol) in acetonitrile-water (3 mL of a 2:1 v/v mixture) at ambient temperature. After 1 hour the reaction was partitioned between water (50 mL) and ethyl acetate (20 mL) and the aqueous phase extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried (MgSO\textsubscript{4}), concentrated \textit{in vacuo} and the residue purified by column chromatography (silica; eluent ethyl acetate) to afford the title compound \textbf{126}, an orange–coloured crystalline solid. Yield 170 mg (86%); m.p. 163.6–165 °C (Lit.\textsuperscript{253} m.p. 164–165 °C). \textsuperscript{1}H NMR: (400 MHz; CDCl\textsubscript{3}) δ 6.96 (1 H, d, \textit{J} = 10.5 Hz), 6.99 (1 H, d, \textit{J} = 10.5 Hz), 7.66 (1H, t, \textit{J} = 7.8 Hz), 7.78 (1H, dd, \textit{J} = 8.0, 1.0 Hz), 8.10 (1H, dd, \textit{J} = 7.8, 1.0 Hz) ppm. \textsuperscript{13}C NMR: (100 MHz, CDCl\textsubscript{3}) δ 126.1, 133.7, 134.4, 134.6, 136.8, 137.5, 140.4 ppm. IR: \textit{\textnu}\textsubscript{max} 780, 1317, 1444, 1661, 2923, 3054 cm\textsuperscript{-1}. MS: (EI\textsuperscript{+}) m/z 192.0 ([M\textsuperscript{[35Cl]}], 100%). HRMS: (EI\textsuperscript{+}) C\textsubscript{10}H\textsubscript{5}ClO\textsubscript{2} ([M\textsuperscript{[35Cl]}]\textsuperscript{+}) requires 191.9973, found 191.9982. Microanalysis: C\textsubscript{10}H\textsubscript{5}ClO\textsubscript{2} requires: C: 62.36, H: 2.62%; found C: 62.64, H: 2.89%.

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5-bromonaphthalene-1,4-dione,\textsuperscript{254} \textsuperscript{127}

Oxidation of \textsuperscript{124} (100 mg, 0.38 mmol) as above afforded the title compound, an orange-coloured crystalline solid. Yield 50 mg (55\%); m.p. 163.8–165 °C (Lit.\textsuperscript{254} m.p. 159–160 °C). \textsuperscript{1}H NMR: (400 MHz, CDCl\textsubscript{3}) (400 MHz, CDCl\textsubscript{3}) δ 6.96 (1H, d, \(J = 10.3\) Hz), 7.01 (1H, d, \(J = 10.3\) Hz), 7.57 (1H, t, \(J = 8.0\) Hz), 7.94 (1H, dd, \(J = 8.0, 1.3\) Hz), 8.07 (1H, dd, \(J = 8.0, 1.3\) Hz) ppm. \textsuperscript{13}C NMR: (100 MHz, CDCl\textsubscript{3}) δ 122.0, 126.7, 129.1, 133.7, 134.6, 136.8 (Ar\textsubscript{3}), 140.2, 141.0, 183.3, 184.5 ppm. IR: \(\nu\textsubscript{max}\) 780 (C-Br), 1315, 1441, 1660, 2920, 3053 cm\textsuperscript{-1}. MS: (APCI) m/z 236.9 ([M{\textsuperscript{79}Br}]\textsuperscript{+}, 100\%), 238.9 ([M{\textsuperscript{81}Br}]+H\textsuperscript{+}, 90\%); (ES\textsuperscript{−}) 237.0 ([M{\textsuperscript{79}Br}]+H\textsuperscript{−}, 60\%), 239.0 ([M{\textsuperscript{81}Br}]+H\textsuperscript{−}, 50\%). HRMS: (APCI\textsuperscript{+}) C\textsubscript{10}H\textsubscript{15}{\textsuperscript{79}BrO\textsubscript{2}} ([M{\textsuperscript{79}Br}]\textsuperscript{+}) requires 236.9546, found 236.9544.
5-bromo-2-methyl-1,4-naphthoquinone, 128

![Chemical structure of 5-bromo-2-methyl-1,4-naphthoquinone](image)

CAN (290 mg, 0.54 mmol) was added to a solution of bromonaphthalene 125 (75 mg, 0.27 mmol) in MeCN:H₂O (4 mL, 1:1 v/v) and the reaction was stirred overnight at room temperature. Ethyl acetate (6 mL) was then added and the organic extract was collected, washed with water (3 x 4 mL), dried (MgSO₄) and concentrated in vacuo. Purification of the residue by column chromatography (silica gel: eluent 10% ethyl acetate-petroleum ether, 10% v/v) afforded the title compound, 128 as a yellow-coloured crystalline solid. Yield 30 mg (45%); m.p 103-105 °C. ¹H NMR: (400 MHz, CDCl₃) δ 2.11 (3H, d, J = 1.5 Hz), 6.79 (1H, q, J = 1.5 Hz), 7.45 (1H, t, J = 8.0 Hz), 7.90 (1H, dd, J = 8.0, 1.3 Hz), 8.09 (1H, dd, J = 8.0, 1.3 Hz) ppm. ¹³C NMR: (100 MHz, CDCl₃) δ 15.9, 121.6, 126.9, 129.3, 133.4, 134.9, 137.1, 140.6, 146.4, 183.3, 184.5 ppm. IR: υₘₐₓ 772, 1318, 1444, 1659, 2990, 3052 cm⁻¹. MS: (ES⁻) m/z 249.0 ([M{⁷⁹Br}-H]⁻, 15%), 249.2 ([M{⁸¹Br}-H]⁻, 4%).
3.3.11 Procedure for Synthesis of Pyrene Derivatives

Pyren-1-ylboronic acid \(195\) (0.148 g, 0.6 mmol), \(\text{Pd(PPh}_3\text{)}_4\) (0.046 g, 0.04 mmol), and aliquot \(336^\circ\) (ca. 3 drops) were added to a stirring solution of 1,8-dichloroanthraquinone \(12a\) (0.056 g, 0.202 mmol) in toluene (3 mL) over an excess of \(\text{K}_2\text{CO}_3\) (1 mL, 2M) and the solution was thoroughly degassed before it was brought to reflux. After 3 hours, the solution was cooled to room temperature, and a second portion of \(195\) (0.6 mmol), \(\text{P(PPh}_3\text{)}_4\) (0.04 mmol), and \(\text{K}_2\text{CO}_3\) (1 mL, 2M) were added, this mixture was again heated to reflux for another 3 hours. The crude mixture was poured into a beaker of water, extracted with chloroform, and washed with brine (3×15 mL). The combined organic extract was dried over \(\text{MgSO}_4\), concentrated \textit{in vacuo} to obtain a dirty red-coloured crude product. Flash column chromatography of the material (silica: eluent hexane-ethyl acetate 80% v/v) afforded 1-(pyren-1-yl)anthracene-9,10-dione, \(14\), together with a slightly impure sample of 1,8-di(pyren-1-yl)anthracene-9,10-dione, \(13\) and 1-hydroxy-8-(pyren-1-yl)anthracene-9,10-dione, \(15\) respectively.
Orange-coloured crystals. Yield 40 mg (17%); m.p. 245-255 °C. $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ ppm. 7.64 (1H, d, $J = 9.23$ Hz), 7.68 (1H, td, $J = 7.55$, 1.3 Hz), 7.77 (1H, t, $J = 7.4$ Hz), 7.78 (1H, t, $J = 7.4$ Hz), 7.90 (1H, d, $J = 7.8$ Hz), 7.93 (1H, d, $J = 9.6$ Hz), 7.94 (1H, dd, $J = 7.75$, 1.09 Hz), 7.95 (1H, t, $J = 7.73$ Hz), 8.02 (1H, t, $J = 7.64$ Hz), 8.14 (1H, d, $J = 8.87$ Hz), 8.15 (1H, d, $J = 7.54$ Hz), 8.19 (1H, d, $J = 8.91$ Hz), 8.24 (1H, brd, d, $J = 7.6$ Hz), 8.30 (1H, d, $J = 7.88$ Hz), 8.36 (1H, dd, $J = 7.8$ Hz, 1.0), 8.60 (1H, dd, $J = 7.9$, 1.5 Hz). $^{13}$C NMR: (100 MHz; CDCl$_3$) $\delta$ 124.57, 124.62, 124.75, 124.95, 124.99, 125.22, 125.78, 125.97, 126.83, 127.33, 127.42, 127.65, 127.73, 128.40, 130.67, 131.01, 131.55, 131.98, 132.92, 133.13, 133.77, 134.25, 134.31, 134.88, 137.34, 138.76, 142.85, 182.92, 183.53 ppm. IR: $\nu_{\text{max}}$ (film) 1247, 1313, 1677, 2957, 3036 cm$^{-1}$. MS (MALDI): m/z (408.2 [M]$^+$, 100%), 409.2 [M+H]$^+$, 30%). 431.1 [M+Na]$^+$, 10%). HRMS (APCI-POS): C$_{30}$H$_{16}$O$_3$ (M+H)$^+$ requires 409.1223; found 409.1220.
1,8-di(pyren-1-yl)anthracene-9,10-dione, 13

Red-coloured crystalline solid (107 mg) isolated in a slightly impure state. M.p. 352-353 °C. $^1$H NMR: (400 MHz; CDCl$_3$) δ 6.89 (1H, d, $J = 7.6$ Hz) 7.25 (1H, d, $J = 7.6$ Hz) 7.36 (1H, d, $J = 9.0$ Hz) 7.60 (1H, d, $J = 9.0$ Hz) 7.65 (1H, dd, $J = 7.4$ Hz, 1.2 Hz) 7.78 (1H, d, $J = 6.7$ Hz), 7.80 (1H, d, $J = 8.8$ Hz), 7.90 (1H, d, $J = 8.7$ Hz), 7.97 (1H, d, $J = 9.3$ Hz) 8.04 (2H, t, $J = 7.6$ Hz) 8.46-8.52 (1H, dd, $J = 7.8$Hz, 1.4Hz) ppm. $^{13}$C NMR: (100 MHz; CDCl$_3$) δ 123.1, 124.1, 124.3, 124.5, 124.6, 124.8, 125.0, 125.5, 125.8, 126.2, 126.75, 126.78, 127.0, 127.30, 127.36, 127.5, 127.9, 130.0, 130.9, 131.3, 132.0, 132.3, 134.2, 135.5, 135.7, 138.1, 138.9, 141.8, 183.9, 185.1 ppm. IR: $\nu_{\text{max}}$ (film) 1243, 1310, 1671, 2910, 3035 cm$^{-1}$. MS (ES+): m/z (631.4 [M+Na]$^+$, 100%). HRMS (APCI): C$_{46}$H$_{24}$O$_2$ (M$^+$) requires 608.1782; found 6.81782.
Scale-up of the this reaction (as described below) afforded pyrene, 198 and 1,8-di(pyren-1-yl)anthracene-9,10-dione, 13 after column chromatography:

Pyren-1-ylboronic acid 195 (0.296 g, 1.2 mmol), Pd(PPh₃)₄ (0.092 g, 0.08 mmol), and aliquot 336° (ca. 3 drops) were added to a stirring solution of 1,8-dichloroanthraquinone 12a (0.112 g, 0.404 mmol) in toluene (3 mL) over an excess of K₂CO₃ (1 mL, 2M) and the solution was thoroughly degassed before it was brought to reflux. After 3 hours, the solution was cooled to room temperature, and a second portion of 195 (1.2 mmol), P(PPh₃)₄ (0.08 mmol), and K₂CO₃ (1 mL, 2M) were added, this mixture was again heated to reflux for another 3 hours. The crude mixture was poured into a beaker of water, extracted with chloroform, and washed with brine (3×15 mL). The combined organic extract was dried over MgSO₄, concentrated in vacuo to obtain a dirty red-coloured crude product. Chromatography of the material (silica: eluent hexane-ethyl acetate 80% v/v) afforded compound two components, which proved to be pyrene, 198 (50% yield) followed by slightly impure 1,8-di(pyren-1-yl)anthracene-9,10-dione, 13 (110 mg).

Pyrene,²⁵⁷ 198

As ayellow-coloured solid. Yield 0.045 g (50%); m.p. 156-158 °C. ¹H NMR (400 MHz; CDCl₃) δ 8.03 (2H, t, J = 7.2 Hz) 8.10 (4H, s) 8.20 (2H, s) 8.22 (2H, s) ppm. ¹³C NMR: (100 MHz; CDCl₃) δ 124.6, 124.9, 125.6, 127.4, 131.1 ppm. IR: υmax (film) 1623, 2921, 3030 cm⁻¹. MS (APCI⁺): m/z (203.1 [M+H]⁺, 100%). Spectroscopic data identical to an authentic sample.
2-tert-Butylpyrene,\textsuperscript{255} 200

Pyrene 198 (2.5 g, 12.3 mmol) was dissolved in dichloromethane (10 mL) and the solution was brought to 0 °C before slow addition of 2-chloro-2-methylpropane 199 (1.38 g, 14.9 mmol). Aluminium chloride, AlCl\(_3\), (1.76 g, 7.29 mmol) was subsequently added and the mixture was stirred at room temperature for 3 hours, poured into a large excess beaker of ice water, filtered and the organic extract was separated, dried over MgSO\(_4\), and the solvent was removed by concentration \textit{in vacuo}. Column chromatography of the residue (elucent: hexane-ethyl acetate 90% v/v) afforded the title compound 200 (ca. 90%) which was contaminated with a small amount of 187 (ca. 10%) as a colourless crystalline solid. Yield 2.188 g (ca. 90% purity), m.p. 116-117 °C (Lit.\textsuperscript{255} m.p. 110-112 °C). \(^1\)H NMR: (400 MHz; CDCl\(_3\)) \(\delta\) 1.60 (9 H, s) 7.96-8.00 (1H, t, \(J = 7.5\) Hz) 8.07 (4H, s) 8.16 (2H, d, \(J = 7.7\) Hz), 8.24 (2H, s) ppm. \(^{13}\)C NMR: (100 MHz; CDCl\(_3\)) \(\delta\) 31.9, 122.2, 124.7, 125.5, 127.2, 127.5, 130.9, 149.0 ppm. IR: \(\nu_{\text{max}}\) (film) 1618, 2957, 3047 cm\(^{-1}\). MS (GCMS): \(m/z\) (259.1 [M+H]\(^+\), 100%). HRMS (APCI-POS): C\(_{20}\)H\(_{19}\) (M+H\(^+\)) requires 259.1481; found 259.1485.
Pyrene 198 (5.0 g; 24.7 mmol; 1 equivalent) was dissolved in dichloromethane (30 mL) and to this stirring solution 2-chloro-2-methylpropane 199 (4 mL, 36.7 mmol; 1.49 equivalents) was added and the solution brought to 0 °C before the slow addition of aluminum chloride, AlCl₃ (3.5 g, 14.5 mmol; 0.5 equivalents), the solution was stirred at room temperature for 16 hours before it was poured into a large beaker of ice-water. The mixture was vacuum-filtered, the organic extract separated, dried over MgSO₄ and the solvent was removed in vacuo which was shown by ¹H NMR analysis to be a mixture of 187 and 200. Recrystallisation (× 2) of the mixture (methanol and hexane; 50% v/v) afforded the title compound as colorless solid. Yield 2.564 g (33%); m.p. 206-208 °C (Lit.²⁵⁶ m.p. 208 °C). ¹H NMR: (400 MHz; CDCl₃) δ 1.59 (18H, s) 8.03 (4 H, s) 8.19 (4H, s) ppm. ¹³C NMR: (100 MHz; CDCl₃) δ 31.9, 122.0, 127.4, 130.7, 148.7 ppm. IR: νmax (film) 1600, 2951, 3039 cm⁻¹. MS (APCI⁺): m/z (315.2 [M+H]⁺, 100%). HRMS (APCI-POS): C₂₄H₂₇ requires 315.2107; found 315.2108.
1,5-cyclooctadiene(methoxy)iridium(I) dimer [Ir(OMe)(COD)]$_2$ (0.034 g, 0.051 mmol) and 4,4’-di-tert-butyl-2,2’dipyridyl (dtbpy) (0.027 g, 0.10 mmol) were added to a stirring solution of 200 (1 g, 3.86 mmol) in hexane (30 mL) followed by the addition of bis(pinacolato)diboron, B$_2$Pin$_2$ 55 (1.32 g, 5.2 mmol) and this solution was thoroughly degassed before it was refluxed for 16 hours. The resulting solution was reduced (in vacuo) and the crude product was loaded onto a silica gel column (eluent; hexane-ethyl acetate, 90% v/v). Recrystallisation from hexane afforded the title compound, 196 as colourless, crystalline, solid. Yield 0.376 g; (25%); m.p. 240-242 °C (Lit. 245 m.p. 240-241 °C). $^1$H NMR: (400 MHz; CDCl$_3$) δ 1.47 (12H, s) 1.59 (9H, s) 8.04 (2H, d, $J$ = 9.0 Hz) 8.08 (2H, d, $J$ = 9.0 Hz) 8.21 (2H, s) 8.61 (2H, s) ppm. $^{13}$C NMR: (100 MHz; CDCl$_3$) δ 25.0, 31.9, 35.2, 84.1, 122.1, 122.8, 126.3, 127.4, 127.6, 130.2, 131.1, 131.4, 149.5 ppm. IR: $\nu_{\text{max}}$ (film) 1234, 1634, 2955, 3039 cm$^{-1}$. MS (ES$^+$): m/z (385.2 [M+H]$^+$, 80%). HRMS (HESI): C$_{26}$H$_{29}$O$_2$BNa (M+Na$^+$) requires 407.2153; found 407.2151.
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166


Appendix

Datablock: s5404l_twin1_hklf4

Bond precision:  C-C = 0.0030 Å  Wavelength=1.54184

Cell:  
a=9.2072(9)  b=16.8137(16)  c=12.2511(8)
alpha=90  beta=92.214(7)  gamma=90
Temperature:  100 K

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R(reflections)= 0.0486( 4628)  wR2(reflections)= 0.1325( 6921)
S = 0.954  Npar= 301
### Datablock: s53971

**Bond precision:** C-C = 0.0022 Å  
**Wavelength:** 0.71073 Å

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- \( a = 11.3263(6) \) Å  
- \( b = 11.7239(4) \) Å  
- \( c = 12.8756(7) \) Å  
- \( \alpha = 82.700(4) \) °  
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**Temperature:** 100 K

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**wR2(reflections):** 0.1252 (7485)

**S:** 1.089  
**Npar:** 460