Polyenes

Approaches to Styrenyl Building Blocks for the Synthesis of Polyene Xanthomonadin and its Analogues


Abstract: A number of aryl building blocks for the synthesis of two xanthomonadin natural product pigments, as well as a related analogue, were accessed using a divergent hydroboration/bromoboration approach from a key alkynyl intermediate. A new approach towards substitution patterns around the ring was adopted following the isolation of an unexpected regioisomer from the bromination reaction. Potential coupling reactions onto these building blocks were explored, with a successful Sonogashira coupling performed on the key alkynyl intermediate, and with the key debrominated styrenyl boronate ester intermediate functionalised both by preliminary Suzuki–Miyaura coupling and by iododeboronation/Heck–Mizoroki coupling. Coupling reactions with brominated styrenyl intermediates proved much more challenging due to the instability of the intermediates to cross-coupling, but some studies have shown promise.

Introduction

Polyene natural products are ubiquitous in nature, and a wide variety of synthetic methods for their construction have been developed. Cross-coupling, and iterative cross-coupling in particular, represents an extremely powerful methodology in this respect, and has consequently seen widespread use in natural product total synthesis. One drawback of such methodology is that the conditions for cross-coupling are frequently more forcing than desirable for the synthesis of such intrinsically unstable products. We have shown that Heck–Mizoroki (HM) reactions can often perform well at lower temperatures than is common for Suzuki–Miyaura cross-couplings, making this reaction potentially better suited to the construction of complex polynes. With this in mind, we envisaged the total synthesis of xanthomonadin 1, and its derivatives, would be an ideal test for the development of mild, polyene-compatible methodology; more especially because we have frequently found electron deficient alkenyl coupling partners to be challenging, with extended chain lengths doing little to aid stability.

Xanthomonadin _campestris_ (black rot of crucifers) and members of the genus _Xanthomonas_ are the cause of a number of plant diseases. These bacteria form characteristic yellow colonies due to the yellow, membrane-bound pigments they produce. Andrewes and Starr pioneered investigations into these yellow pigments, first proposing the combination of arylated, polyenic and halogenated structures in 1973.[22] Andrewes then reported an attempted total synthesis of one of the proposed structures later that year, although the characteristics of this compound did not match those of any previously isolated pigments.[23] The first of these pigments, isobutyl xanthomonadin 1a, was successfully isolated and characterised from _Xanthomonas juglandis_ strain XJ103 in 1976, and the micro- and resonance Raman spectroscopic characteristics obtained by Sharma et al. in 2012.[24,25] Interestingly, it has been postulated that these bacteria produce such compounds as biological, photo-protective agents. However, despite the similarity of such polyene compounds to the carotenoids, no efforts have been reported to synthesise this general class of compounds in order to test this photoprotective hypothesis. It is also interesting to observe that the nature of the ester function seems to depend upon the alcohol used in the extraction procedure, suggesting either that the ester itself is highly labile or that the free carboxylic acid is in fact the natural product; this would make xanthamonodic acid a potentially more appropriate name, and allow the compound to be better incorporated into biological membranes.

During their investigations, Andrewes and Starr identified a number of different pigments in addition to xanthomonadin 1a by mass spectrometry, the most common of these being the putative debrominated xanthomonadin pigment 2.[22,26] This raises questions about the purpose of the bromine in xanthomonadin 1 and its relatives, specifically whether it provides an improvement in the activity or of stability to the pigment. However, a lack of complete spectroscopic data is a challenge in the synthesis of these pigments, particularly the lack of detailed NMR spectroscopic data. Indeed, the extent of the NMR spectroscopic data available for xanthomonadin 1a is detailed in...
Figure 1, with only mass spectrometry and UV data available for isobutyl debrominated xanthomonadin 2a (UV data was obtained on a mixture of pigments containing 2a). Therefore, one aim of our work was also to corroborate the characterisation data for all the xanthomonadins and build a full spectroscopic profile of the pigments.

Figure 1. Structures of the various xanthomonadin analogues and $^1$H NMR spectroscopic data as reported by Andrewes et al. for isobutyl xanthomonadin 1a.[24]

With our experience in highly stereoselective polyene construction,[6,27] we anticipated stability issues in the construction of these pigments and therefore envisaged that an alkynyl analogue such as 3 might be useful, not only in terms of an interesting derivative for assessing biological activity (note that such an alkynyl function is a useful addition in synthetic retinoids, such as EC23 and related structures, having previously shown that such analogues can have the desired beneficial effects whilst retaining biological activity[28–30]), but also because of the potential for imparting increased stability to the structure as a whole and making it more likely that useful stable analogues could be accessed.[28–30]

Our original retrosynthesis involved the synthesis of tetraenyl building blocks, employing a Suzuki–Miyaura (SM) coupling to complete the synthesis. As a result, we would require one key polyenyl intermediate, which could then be coupled with the appropriate polyenyl aryl intermediates to furnish each of the three target pigments. With this in mind, we considered the synthesis of all-trans polyene unit 4 using our Heck–Mizoroki (HM)/iododeboronation (IDB) iterative cross-coupling (ICC) methodology (Scheme 1) which we had previously applied in the synthesis of other polyene natural products.[2–9,31] Alternatively, if an all-trans heptaene 11 could be accessed, then this could be coupled directly onto suitable styrenyl and alkynyl aryl building blocks 8–10.

Given the planned use of the HM/IDB methodology, the exact nature of the alkenyl iodide-boronic acid coupling partners in the construction reaction could remain flexible. We anticipated that aryl building blocks 8–10 could be used to access fragments 5–7 via palladium-catalysed cross-coupling, and therefore, these represented the key first targets for our in-
tended approach, allowing us to choose the most appropriate route to access the desired pigments once we understood more about the stability and reactivity of the various intermediates. Herein, we report our approaches to the synthesis of these key building blocks, and their application in cross-coupling protocols to access polyene natural products systems and their polyenyl analogues.

Results and Discussion

Access to the ideal aryl tetraenyl iodide intermediates 12 and 13 from styrenyl building blocks 18 and 19 was envisioned from either a bromoboration or hydroboration reaction of Sonogashira phenylacetylene analogue 10 (Scheme 2). Sonogashira coupling onto building block 10 could also furnish a key polyenyl intermediate such as 22, or provide direct access to desired analogue 3. In turn, access to phenylacetylene analogue 10 was envisaged to be readily achievable from meta-iodoanisole 21 (Scheme 2).

The initially desired bromination of 3-iodoanisole 21 proved more challenging than expected, with elemental bromine giving a mixture of regioisomers and NBS proving unreactive. Fortunately, lowering of the reaction temperature was found to give adequate regiocontrol (95:5) for the reaction employing Br₂ [Equation (1)], however, the two isomers could not be readily separated. The identity of the major regioisomer could not be unambiguously determined at this stage. Hence, the mixture was carried forward through the next synthetic steps with the intention of determining the major regioisomer at a later stage.

The subsequent Sonogashira coupling and alkyne deprotection sequence was found to be successful under standard conditions (Scheme 3), furnishing the desired building block 27 for the key stereoselective bromoboration reaction. Attempts to perform a direct conversion were unsuccessful; however, after screening several conditions, a two-step process involving initial formation of a boronic acid 28 was developed. This involved initial reaction with boron tribromide followed by hydrolysis and esterification to give pinacol ester 29 as the desired Z-alkene stereoisomer. Whilst the boronic acid 28 proved difficult to handle, as the corresponding pinacol ester 29 it was readily handled and had the advantage of providing crystalline material. Subsequent single-crystal X-ray crystallography provided proof of both the regiochemical outcome of the bromination and stereocontrol in the bromoboration reactions (Scheme 3). However, as can be seen from Figure 2, although the bromoboration of 27 gave the desired stereochemical result, the outcome of the SEAr reaction to derive the starting bromide 24 was not that anticipated. Indeed, X-ray crystallography showed the bromine atom was in fact located ortho to the alkene, i.e. forming structure 30 (see Figure 2) and showing that the major

Scheme 2. Retrosynthesis of either tetraene 12 or 13 and alkylnyl polyene 22.

Scheme 3. Formation of alkyne 27 and the key bromoboration step.
regioisomer formed in the original bromination of 3-iodoanisole was in fact 23. As a result of these results and having uncovered the actual regioisomeric control, the rest of the route towards a key arenyl intermediate was now established and hence, a new selective entry to the required building block 20 was required.

Figure 2. X-ray molecular structure of boronate ester 30 ([CCDC-1537382]; thermal ellipsoids shown at 50 % probability).

We next examined an alternative synthesis of the desired iodide 20 utilizing a Sandmeyer approach from aniline 31 which proceeded readily to give the iodide 20 in quantitative yield (Scheme 4). Iodide 20 was then taken through the previously developed series of reactions to give alkyne 10 in excellent overall yield (Scheme 4); the only deviation from the previous route being use of TBAF rather than NaOH to cleanly convert TMS-alkyne 32 to required alkyne 10.

With alkyne building block 10 unambiguously produced, we could develop the synthesis of the two required styrenyl precursors to the different xanthomonadins, i.e. 18 and 19 (Scheme 5). As noted previously, it was envisaged that debrominated styrenyl building block 19 could be synthesised by hydroboration of alkyne 10. This was achieved using a copper(I)-catalysed borylation with Xantphos, sodium tert-butoxide and B₂Pin₂ in THF/methanol, and with some optimisation the styrenyl pinacolate ester 19 was isolated in a 79 % yield and an overall 68 % yield from aniline 31 (Scheme 5).

Turning to bromo-analogue 18, application of the bromoboration conditions previously discussed (vide supra) and subsequent pinacol ester formation gave key brominated styrenyl boronate ester 18 in a 75 % yield over the two steps. This ester was also successfully recrystallized and the structure confirmed by X-ray crystallography (Figure 3). This route gave key boronate ester 18 from aniline 31 in an overall 65 % yield (Scheme 5). It was found that the bromoboration step converting 10 to 18 was highly dependent upon the quality of the BBr₃ used. Alkene 34 was routinely isolated as a by-product, presumably due to HBr contaminating the BBr₃ reagent [Equation (2)]. Use of a range of HBr scavengers failed to eliminate this issue; however, it was found that use of fresh BBr₃ solution kept this side-reaction to minimal levels.

Comparison of ¹H NMR spectroscopic data obtained for styrenyl units 18 and 30 with those obtained by Andrewes et al. for the corresponding section of isobutyl xanthomonadin 1a, showed a good agreement between the correct regioisomer.
**Figure 3.** X-ray molecular structure of boronate ester 18 (CCDC-1537383).

18 and 1a, something that had not been observed during the synthesis of the incorrect regioisomer 30 (Table 1).

With the desired building blocks in hand, attention turned to the investigation of cross-coupling methods to enable access to the required natural product pigments and analogue 3. A Sonogashira coupling was attempted on alkyne 10 [Equation (3)] as a model cross-coupling reaction allowing access to a simplified alkylnyl analogue of polyeneyne 3. This proved successful, giving the resulting enyne 36 in 89 % yield [Equation (3)].

Attention was then turned to Suzuki–Miyaura cross-coupling of styrenyl boronate analogues 18 and 19. Initially, these cross-couplings [Equation (4) and Equation (5)] were unsuccessful.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst loading [mol-%]</th>
<th>Base</th>
<th>Base [equiv.]</th>
<th>Temp. [°C]</th>
<th>Solvent</th>
<th>NMR yield of 38[a] after 24 h [%]</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)₂Cl₂</td>
<td>5</td>
<td>Ag₂O</td>
<td>1.2</td>
<td>60</td>
<td>DME</td>
<td>35[b]</td>
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<td>2</td>
<td>Pd(PPh₃)₄</td>
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<td>Ag₂O</td>
<td>1.2</td>
<td>40</td>
<td>DME</td>
<td>69</td>
</tr>
<tr>
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<td>Pd(PPh₃)₄</td>
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<td>Ag₂O</td>
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<td>40</td>
<td>DME</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh₃)₄</td>
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<td>Ag₂O</td>
<td>1.2</td>
<td>30</td>
<td>DME</td>
<td>90</td>
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<tr>
<td>5</td>
<td>Pd(PPh₃)₄</td>
<td>10</td>
<td>Ag₂O</td>
<td>1.2</td>
<td>r.t.</td>
<td>DME</td>
<td>78</td>
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<td>6</td>
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<td>Ag₂CO₃</td>
<td>2</td>
<td>r.t.</td>
<td>MeCN</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>Pd(PPh₃)₄</td>
<td>10</td>
<td>tBuOK</td>
<td>1.2</td>
<td>40</td>
<td>DME</td>
<td>42[c,d]</td>
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</table>

[a] ¹H NMR yields calculated due to product diene 37’s tendency to polymerise, using characteristic δ at δ = 5.96 ppm for the diene (easily identifiable) vs. doublets appearing at either δ = 6.16 or 7.33 ppm for pinacolate ester 19. [b] Multiple side-products observed. [c] Major product was the minor side-product observed in all other reactions. [d] Conversion after 14.5 h. The SM tolerated lower temperatures, but benefited from an increase in catalyst loading to improve the reaction rate (Table 2, Entries 2 and 3). Doubling the Pd(PPh₃)₄ loading from 5 to 10 mol-% at 40 °C increased the conversion from 69 to 92 %.
creased palladium loading (Table 2, Entries 2 and 3). Further reduction in temperature (Table 2, Entries 4 and 5) made little difference at 30 °C but reduced product formation at room temperature. Changing bases also had an impact with silver carbonate improving the room temperature reaction (Table 2, Entry 6) and tert-butoxide causing significant by-product formation (Table 2, Entry 7); a by-product that was generally observed in all reactions. This generally minor side-product was observed, with 1H NMR signals at δ = 6.12 (d, 1 H, J = 18.3 Hz), 6.55–6.60 (m, 1 H) and 7.90 (dd, 1 H, J = 12.4, 7.8 Hz) inter alia, but remained elusive to isolation due to its high susceptibility towards polymerisation and hence, was not fully structurally identified.

Given our original aim of developing a flexible route to the synthesis of polyenyl intermediates, styrenyl boronate ester was also subjected to an IDB/HM cross-coupling sequence, as an alternative route to the construction of debromo xanthomonadin analogues such as 2. Indeed, this was successful (Scheme 6), giving pinacol boronate diene in a 51 % yield over the two steps, and interestingly, with diene showing good stability and especially compared with the more electron deficient system 38.

Attention was then turned to reaction of the brominated styrenyl boronate analogues to give an alkenyl iodide as an alternative building block. Our standard iododeboronation conditions (NaOMe, ICl at –78 °C) were found to have limited success when applied to boronate ester 18. A literature procedure was found which could affect the conversion of boronic acids to halides using N-halosuccinimides at room temperature in acetonitrile which, when attempted using N-iodosuccinimide (NIS) on pinacol ester 18 gave only unreacted starting material and alkyne 10. These conditions were, however, successfully applied to convert styrenyl boronic acid 33 to styrenyl iodide 43 in a 78 % yield [Equation (5)]. Indeed, iodide 43 proved to be quite stable, and perhaps surprisingly so given the dihalogenated alkene moiety; our previous observations of related compounds showed instability despite storage at –18 °C under argon in the dark, whereas 43 proved stable for several months in these conditions.

The HM cross-coupling potential of styrenyl iodide 43 was then explored with vinylboronate 41 [Equation (6)], which unfortunately proved unsuccessful, with starting material, alkyne 34 and alkyne 10 observed.

Hence, conditions for the potential SM coupling of the styrenyl bromoiodide 43 was investigated with vinylboronate 41. Again however, none of the desired cross-coupled product was observed under a range of conditions [see Equation (7)], with alkyne 10 being the major species in most cases. Indeed, use of sodium methoxide as base yielded alkyne 10 as sole product in 73 % yield [Equation (7)], suggesting a possible route in which the boronate ester functions as a reducing agent for the PdII formed from reaction of Pd0 with iodide 43, which could then eliminate to give a dihalo PdII species.

In light of this, other types of cross coupling were considered. Both Stille and Sonogashira couplings were especially appealing, as these could be performed at room temperature. A Stille coupling was therefore attempted on iodide 43 with vinyl stannane 45 [Equation (8)], however, although the desired product 44 was obtained, it was produced in an inseparable mixture of products, including alkyne 10 and starting material. A range of conditions were explored (see ESI for details), which improved the conversion to an extent, but not sufficiently to allow for isolation of the pure product. A Sonogashira reaction of iodobromostyrene 43 with TMS acetylene 25 under standard conditions [Equation (9)] was attempted, with similar results to the previous Stille coupling. The desired product 47 was again produced, but could not be isolated pure. We anticipate that this recurring theme of challenging purification of cross-coupling products may be something that improves when using longer polyene systems.
Table 3. Attempted Suzuki–Miyaura couplings onto brominated styrenyl pinacol ester 18.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst Loading [mol-%]</th>
<th>Base</th>
<th>Temp [°C]</th>
<th>NMR yields[a] after 24 h [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)₂Cl₂ 5</td>
<td>Cs₂CO₃</td>
<td>60</td>
<td>0 43</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh₃)₄ 10</td>
<td>Ag₂O</td>
<td>40</td>
<td>0 72[b]</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh₃)₂Cl₂ 5</td>
<td>Ag₂O</td>
<td>60</td>
<td>38 62</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh₃)₄ 5</td>
<td>Ag₂O</td>
<td>60</td>
<td>37 61</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)₂ 5</td>
<td>Ag₂O</td>
<td>60</td>
<td>0 48</td>
</tr>
<tr>
<td>6</td>
<td>Pd(dppf)Cl₂ 5</td>
<td>Ag₂O</td>
<td>60</td>
<td>34 66</td>
</tr>
</tbody>
</table>

[a] ¹H NMR yields calculated due to product diene 37’s tendency to polymerise, using characteristic dd at δ = 6.12 ppm for the diene (easily identifiable) vs. the singlet appearing at δ = 6.43 ppm or the doublet appearing at δ = 6.32 ppm for pinacolate ester 18 and enyne 35, respectively. [b] After 14.5 h.

The difficulties associated with iodide 43 meant attention was then turned to SM coupling of the more stable 1,2-boro-bromo styrene system 18, to endeavour to access bromo diene 37. This approach proved more successful (see Table 3) and while enyne 36 proved to be the major product under all conditions, careful choice of catalyst and base did result in formation of the desired product 37. It was clear that further work was needed if conditions suitable for a total synthesis of the brominated xanthomonadins were to be developed.

Conclusions

A number of key styrenyl building blocks for the synthesis of brominated xanthomonadin 1, debrominated xanthomonadin 2 and desired alkynyl analogue 3 were successfully synthesised, and their reactivity in several model cross-couplings for the construction of the xanthomonadins and their analogues were examined. Regioselective hydroboration and stereoselective bromoboration proved to be robust and efficient routes to the desired styrenyl boronate esters 18 and 19, using desired alkynyl building block 10 as their key intermediate, representing an efficient way to access these systems. The reactivity of these building blocks proved to be as anticipated, with the Sonogashira onto alkynyl building block 10 proving extremely facile.

The successful Suzuki–Miyaura cross-coupling onto debrominated styrenyl boronate ester 19 along with the demonstrated reactivity towards iterative cross-coupling does indeed provide the intended flexible route to debrominated xanthomonadin 2. Whilst the brominated styrenyl analogues proved to be as challenging to cross-couple as expected, the unexpected stability of iodide 43, combined with a number of promising results across a number of different cross-coupling reactions provides encouragement that suitable conditions for reacting onto these intermediates will be found, thus allowing access to brominated xanthomonadin 1. Should this prove not to be the case, the successful Sonogashira coupling of alkyne 10 also opens up the possibility of functionalising the alkyne at a later stage in the synthesis via a hydrobromination reaction. This body of work therefore represents considerable progress towards the total synthesis of xanthomonadin, with our own HM/IDB iterative cross-coupling methodology envisioned to furnish the polyenyl building block required to complete the synthesis.

Experimental Section

General Experimental: Except where specified, all reagents were purchased from commercial sources and were used without further purification. All ¹H NMR were recorded on Bruker Avance-400, Varian V NMR S-600, Varian V NMR S-700 spectrometers. ¹³C NMR were recorded on the Bruker Avance-400, Varian V NMR S-600, Varian V NMR S-700 instruments at frequencies of 101 MHz, 151 MHz or 176 MHz respectively. ¹¹B NMR were recorded on the Bruker Avance-400 instrument at a frequency of 128 MHz. Chemical shifts are expressed as parts per million downfield from the internal standard TMS for ¹H and ¹³C and to external BF₃·Et₂O or ¹¹B. ASAP mass spectrometry was performed on Waters Xevo QTOF. EI mass spectrometry was performed on a Thermo-Finnigan Trace GC–MS. IR spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrometer. UV/Vis spectra were recorded on a Unicam UV2 spectrometer. Column chromatography was performed on Davissil Silica gel, 60 meshes. TLC was performed on Polygram SIL G/UV254 plastic backed silica gel plates with visualization achieved using a UV lamp. Melting points were determined using a Büchi Electrothermal melting point apparatus. Dry CH₂Cl₂ was dried by distillation from...
CaH₂. Dry Et₂N was dried from KOH pellets. Brine refers to saturated aqueous sodium chloride.

**Specific Experimental Procedures**

1-Bromo-2-iodo-4-methoxybenzene (23): To a stirred solution of 3-idoanisole 21 (2.55 mL, 21.4 mmol) in dry DCM (100 mL) under a positive pressure of argon was added bromine (1.1 mL, 21.4 mmol) dropwise at –78 °C. The resulting solution was stirred at –78 °C for 1 h. The reaction mixture was quenched by the slow addition of saturated aqueous NaHCO₃ (20 mL), and warmed to room temperature. Further DCM (25 mL) was added and the layers were separated. The organic phase was washed with saturated aqueous Na₂CO₃ (2 × 25 mL), and dried with MgSO₄. The solvent was removed in vacuo and the resulting solution was transferred into a separating funnel and conc. H₂SO₄ (20 mL) was added. The mixture was washed with 10% Na₂S₂O₃ solution and H₂O (3 × 20 mL), and then dried over anhydrous MgSO₄. The solvent was removed in vacuo to give the desired product (2.65 g, 76% as an orange oil. The product was recrystallised to give a brown solid (2.12 g, 60%).

1-Bromo-4-iodo-2-methoxybenzene (20): A 10% solution of TMS-protected alkyne 26 (5.94 g, 20.97 mmol) in MeOH (50 mL) was stirred in aqueous HCl (37% 20 mL) at 0 °C. The resulting solution was filtered and concentrated in vacuo. The crude material was recrystallised to give the desired product as a brown solid (155.5 mg, 87% over the two steps). M.p. 74.4–74.6 °C. 

HRMS (ASAP) m/z 417.0 [M + H], 419.0 [M + H], 421.0 [M + H]. HRMS (ASAP) m/z calc. for C₁₅H₂₀B₇₉Br₂O₃ 416.9872 [M + H], found 416.9875. Structure determined by X-ray crystallography.

1-Bromo-4-ido-2-methoxybenzene (20): 4-Bromo-3-methoxyaniline 31 (500 mg, 2.48 mmol) was stirred in aqueous HCl (37% 250 mL) at 80 °C to ensure complete dissolution. The reaction mixture was diluted with EtOAc (250 mL) and the layers separated. The aqueous layer was extracted using EtOAc (2 × 250 mL). The organic layers were washed sequentially with sat. NaHCO₃ (125 mL) and H₂O (125 mL) until neutral pH. The organic layers were then washed with 5% Na₂S₂O₃ (125 mL) and saturated brine (125 mL), dried with MgSO₄ and the solvent evaporated to afford a brown oil, from with the desired product was isolated. The resulting solution was stirred at room temperature in the dark for 16 h. The solvent was then evaporated and the residue was passed through a short silica gel column (pentane/ethyl acetate 1:1 as eluent). The product was concentrated in vacuo to give a dark brown solid (7.8 g, 100%). M.p. 53.1–55.6 °C. 

HRMS (ASAP) m/z calc. for C₁₅H₂₀B₇₉Br₂O₃ 416.9875 [M + H], found 416.9875. Structure determined by X-ray crystallography.

1-Bromo-2-iodo-4-methoxybenzene (23): (500 mg, 1.66 mmol), Pd(PPh₃)₂Cl₂ (11.23 mg, 0.016 mmol) and CuI (3.05 mg, 0.006 mmol) were added into a Schlenk tube. After purging the flask with argon for 3 times, dry Et₃N (25 mL) was added via cannula under argon, followed by TMS acetylene (272 µL, 1.92 mmol). The reaction mixture was stirred at room temp. in the dark for 21 h. Then solution (Et₂N) was evaporated and the residue was passed through a short silica gel column (pentane/ethyl acetate 1:1 as eluent). The product was concentrated in vacuo to give the crude material as a yellow liquid (541 mg, 119%). 

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1-Bromo-4-iodo-2-methoxybenzene (20): A 10% solution of TMS-protected alkyne 26 (5.94 g, 20.97 mmol) in MeOH (50 mL) and Et₂O (50 mL) was added as a solution of NaOH (1 g, 25.17 mmol) in dry DCM (50 mL) under a positive pressure of argon. After stirring for 21 h, the reaction mixture was quenched by the slow addition of saturated aqueous NaHCO₃ (20 mL), and warmed to room temperature. Further DCM (25 mL) was added and the layers were separated. The organic phase was washed with saturated aqueous Na₂CO₃ (2 × 25 mL), and dried with MgSO₄. The solvent was removed in vacuo and the resulting solution was transferred into a separating funnel and conc. H₂SO₄ (20 mL) was added. The mixture was washed with 10% Na₂S₂O₃ solution and H₂O (3 × 20 mL), and then dried over anhydrous MgSO₄. The solvent was removed in vacuo to give the desired product (2.65 g, 76% as an orange oil. The product was recrystallised to give a brown solid (2.12 g, 60%). 

1-Bromo-4-iodo-2-methoxybenzene (20): A 10% solution of TMS-protected alkyne 26 (5.94 g, 20.97 mmol) in MeOH (50 mL) and Et₂O (50 mL) was added as a solution of NaOH (1 g, 25.17 mmol) in dry DCM (50 mL) under a positive pressure of argon. After stirring for 21 h, the reaction mixture was quenched by the slow addition of saturated aqueous NaHCO₃ (20 mL) and warmed to room temperature. Further DCM (25 mL) was added and the layers were separated. The organic phase was washed with saturated aqueous Na₂CO₃ (2 × 25 mL), and dried with MgSO₄. The solvent was removed in vacuo and the resulting solution was transferred into a separating funnel and conc. H₂SO₄ (20 mL) was added. The mixture was washed with 10% Na₂S₂O₃ solution and H₂O (3 × 20 mL), and then dried over anhydrous MgSO₄. The solvent was removed in vacuo to give the desired product (2.65 g, 76% as an orange oil. The product was recrystallised to give a brown solid (2.12 g, 60%).
solved in THF (307 mL) and cooled to 0 °C under argon. TBAF (21.8 mL, 21.8 mmol) was then added dropwise at 0 °C. The reaction mixture was warmed to room temperature, then stirred at this temperature for 3 d. This mixture was then evaporated to give a dark brown oil. The crude product was purified by silica gel chromatography, eluent 0–5 % EtOAc in hexane. Partial fractions were evaporated to give the desired product as an orange solid (3.76 g, 86 %). M.p. 74.8–77.0 °C. 1H NMR (700 MHz, CDCl3, 25 °C, TMS): δ = 3.93 (s, 3 H), 5.80 [d, J(H,H) = 2.1 Hz, 1 H], 6.12 (d, J = 2.1 Hz, 1 H), 7.02–7.12 [m, 2 H], 7.50 [d, J(H,H) = 8.2 Hz, 1 H] ppm. 13C NMR (176 MHz, CDCl3, 25 °C, TMS): δ = 25.0, 56.4, 84.2, 111.3, 113.2, 120.9, 133.1, 138.9, 141.8, 155.6 ppm. IR (KBr disk): ν(=CH) = 2978 (m), 2942 (m) cm–1. [M]+. HRMS (ASAP): m/z 289.9 [M]+, found 289.9492.

1-Bromo-4-(1-bromoethyl)-2-methoxymethane (34): To a well-stirred solution of BBr3 (4.8 mL, 4.78 mmol, 1.0 M solution in DCM) in DCM (45 mL) at –78 °C was added a solution of 1-bromo-4-ethyl-2-methoxymethane (10 g, 4.78 mmol) dropwise. The resulting deep pink solution was then stirred at –78 °C for 3 h. The reaction mixture was then warmed to 0 °C and stirred at this temperature for 2 h. The reaction mixture was then transferred to a separating funnel and the layers separated. The aqueous layer was then washed with DCM (2 × 100 mL) and then brine (100 mL). The organics were then dried with MgSO4, filtered and evaporated to yield 1.4 g of a pale yellow solid. The crude solid was then purified by silica gel chromatography, eluent 0 % to 10 % to 50 % EtOAc in hexane. Pure fractions were evaporated to give 0.411 g of a pale yellow solid containing 41 % desired product (0.173 g, 13 %). 1H NMR (600 MHz, CDCl3, 25 °C, TMS): δ = 3.93 (s, 3 H), 5.80 [d, J(H,H) = 2.1 Hz, 1 H], 6.12 (d, J = 2.1 Hz, 1 H), 7.02–7.12 [m, 2 H], 7.50 [d, J(H,H) = 8.2 Hz, 1 H] ppm. 13C NMR (151 MHz, CDCl3, 25 °C, TMS): δ = 25.0, 56.4, 84.2, 111.3, 113.2, 120.9, 133.1, 138.8, 141.8, 155.6 ppm. IR (film): ν(=CH) = 2978 (m), 2942 (m) cm–1. MS (ASAP) m/z 289.9 [M]+, 291.9 [M]+, 293.9 [M]+. HRMS (ASAP): m/z calc. for C13H10O2Br2 289.8959 [M]+, found 289.8942.

(Methyl (2E,4Z)-5-Bromo-5-(4-bromo-3-methoxyphenyl)penta-2,4-dienoate (37): 2-(1Z)-2-Bromo-2-(4-bromo-3-methoxy-
phenyl)[ethenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 18 (60 mg, 0.144 mmol), methyl (2E)-3-isodoprop-2-enoate (25 mg, 0.12 mmol), Pd(PPh3)2Cl2 (4.2 mg, 0.006 mmol) and silver oxide (33 mg, 0.144 mmol) were added to a dry flask and the flask sealed and purged with argon. Dry, degassed DME (1.1 mL) was then added and the reaction mixture stirred at 60 °C for 2 d 15 h. The reaction mixture was then diluted with EtOAc (10 mL), passed through a short plug of Celite and the solvent evaporated to give 57 mg of a crude brown oil from which the desired product could be identified. 1H NMR (400 MHz, CDCl3, 25 °C, TMS): δ = 3.74 (s, 3 H), 3.90 (s, 3 H), 6.12 [dd, 3J(H,H) = 15.4, 0.9 Hz, 1 H], 7.03–7.12 (m, 2 H), 7.35 [dd, 3J(H,H) = 8.1, 2.0 Hz, 1 H]. 13C NMR (100 MHz, CDCl3, 25 °C, TMS): δ = 25.6 ppm. 11B NMR (128 MHz, CDCl3, 25 °C, TMS): δ = 39.0 ppm. MS (APPI) m/z 374.9 [M + H]+, 376.9 [M + H]+, 378.9 [M + H]+. HRMS (APPI) m/z calculc. for C15H17BO3Br2 374.9231 [M+H]+, found 374.9247. No further characterisation was performed due to stability issues on purification.

Methyl (2E,4E)-5-(4-Bromo-3-methoxyphenyl)pent-2-4-dienoate (38): 2-[(E)-2-(4-Bromo-3-methoxyphenyl)ethenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 19 (0.325 g, 0.76 mmol), methyl (2E)-3-isodoprop-2-enoate 35 (0.129 g, 0.61 mmol), Pd(PPh3)2Cl2 (22 mg, 0.031 mmol) and silver oxide (0.174 g, 0.76 mmol) were added to a dry flask and the flask sealed and purged with argon. Dry, degassed DME (4.6 mL) was then added and the reaction mixture stirred at 60 °C for 2 d 17 h. The reaction mixture was then diluted with EtOAc (50 mL) and purified by silica gel chromatography at 0 °C, eluent 0–5 % EtOAc in petroleum ether. Fractions containing product were evaporated to give 0.408 g of a dark yellow oil. The crude product was purified by silica gel chromatography to 0 °C, eluent 5 % EtOAc in petroleum ether. Pure fractions were evaporated to give the desired compound as a pale yellow oil (0.725 g, 78 %). 1H NMR (400 MHz, CDCl3, 25 °C, TMS): δ = 1.23–1.33 (m, 9 H), 1.46–1.53 (m, 1 H), 1.80 (ddd, 3J(H,H) = 14.0, 11.2, 2.9 Hz, 1 H), 3.92 (s, 3 H), 4.24 (ddd, 3J(H,H) = 14.8, 6.1, 3.1 Hz, 1 H), 5.64 [d, 3J(H,H) = 17.4 Hz, 1 H], 6.59 [d, 3J(H,H) = 15.6 Hz, 1 H], 6.77–6.84 (m, 1 H), 6.87–6.94 (m, 2 H), 7.06 [dd, 3J(H,H) = 17.3, 10.5 Hz, 1 H], 7.42–7.47 (m, 1 H) ppm. 13C NMR (128 MHz, CDCl3, 25 °C, TMS): δ = 25.6 ppm. 11B NMR (151 MHz, CDCl3, 25 °C, TMS): δ = 23.1, 28.1, 31.2, 46.0, 64.8, 70.8, 109.7, 111.3, 120.3, 131.7, 133.3, 133.6, 134.9, 137.9, 146.3, 155.9 ppm. MS (APPI) m/z: 363.1 [M]+, 364.1 [M]+, 365.1 [M]+, 366.1 [M]+. HRMS (APPI) m/z calculc. for C15H17BO3Br2 364.0960 [M]+, found 364.0958.

1-(1Z)-7-Bromo-8-iodoethenyl]-3-methoxy-4-bromobenzene (43): To a solution of 1-(1Z)-7-bromo-7-(4-bromo-3-methoxyphenyl)ethenyl|boronic acid (30) (0.972 g, 2.90 mmol) in MeCN (17 mL), protected from light, was added N-iodosuccinimide (0.780 g, 3.48 mmol) and the reaction mixture stirred for 3 h at room temperature. The reaction mixture was diluted with EtOAc (60 mL) and washed with 5 % Na2S2O5 (2 × 60 mL), H2O (2 × 60 mL) and brine (60 mL). The organic layer was dried with MgSO4 filtered and evaporated to yield 1.05 g of a crude orange oil. The crude product was purified by silica gel chromatography at 0 °C, eluent 2 % EtOAc in petroleum ether. Pure fractions were evaporated to give the desired compound as a pale yellow amorphous powder (0.947 g, 78 %). 1H NMR (400 MHz, CDCl3, 25 °C, TMS): δ = 3.92 (s, 3 H), 6.98 [dd, 3J(H,H) = 8.3, 2.1 Hz, 1 H], 7.03 [d, 3J(H,H) = 2.1 Hz, 1 H], 7.44 (s, 1 H), 7.50 [d, 3J(H,H) = 8.2 Hz, 1 H] ppm. 13C NMR (176 MHz, CDCl3, 25 °C, TMS): δ = 56.3, 83.7, 111.4, 113.1, 120.9, 133.1, 136.3, 140.0, 155.7 ppm. IR: ν (inter alia) = 3044 (w), 2940 (w), 1586 (m), 1582 (m), 1546 (m) cm–1. MS (APPI) m/z: 416.8 [M]+, 418.8 [M]+, 420.8 [M]+. HRMS (APPI) m/z calculc. for C17H12BrO2 417.8065 [M]+, found 417.7909.

1-Bromo-4-[(1E,3E)-4-(4-Bromo-3-methoxyphenyl)buta-1,3-dien-1-yl]-2-methoxybenzene (44): Pd(PPh3)2Cl2 (2 mg, 0.024 mmol) and 1-[(1Z)-7-bromo-8-iodoethenyl]-3-methoxy-4-bromobenzene 43 (0.20 g, 0.481 mmol) were added to a dry flask, and the flask purged with argon for 5 min. Dry, degassed MeCN (5.0 mL) was added, followed tributyl(vinyl)tin (0.14 mL, 0.481 mmol). The reaction mixture was then stirred at room temperature for 16 h, then at 50 °C for 2 d. The reaction mixture was diluted with EtOAc containing 3 ppm BHT (20 mL) and passed through a Celite/silica plug, then the solvent evaporated to give 0.408 g of a dark yellow oil. The crude product mixture was purified by silica gel chromatography, elution gradient 0–5 % EtOAc in petroleum ether. Fractions containing product were evaporated to give 0.185 g of a dark yellow oil as a mixture containing the desired product (26 mg, 17 %). 1H NMR (600 MHz, CDCl3, 25 °C, TMS): δ = 3.92 (s, 3 H), 5.43 [d, 3J(H,H) = 9.6, 1.5 Hz, 1 H], 5.49–5.61 (m, 1 H), 6.75–6.84 (m, 2 H), 7.04–7.12 (m, 3 H) ppm. MS (APPI) m/z: 315.9 [M]+, 317.9 [M]+, 319.9 [M]+. HRMS (APPI) m/z calculc. for C17H11BrO3 316.9177 [M]+, found 316.9188. No further characterisation was performed due to stability issues on purification.
Dry, degassed Et$_3$N (3.0 mL) was added, followed by ethynyl tri-methylsilane 25 (0.08 mL, 0.577 mmol). The reaction mixture was then stirred at room temperature for 3 d. The solvent was evaporated to give 0.353 g of a dark brown residue, which was subjected to silica gel chromatography, eluent 5 % ETOAc in hexane. Fractions containing product were evaporated to give 0.202 g of a light brown solid which was a mixture containing desired product (estimated 38 % yield). $^1$H NMR (400 MHz, CDCl$_3$, 25 °C, TMS): δ = 0.19 (s, 9 H), 3.91 (s, 3 H), 6.32 (s, 1 H), 7.07 (dd, $^3$J(H,H) = 8.3, 2.0 Hz, 1 H), 7.16 (dd, $^3$J(H,H) = 2.0 Hz, 1 H), 7.49 (d, $^3$J(H,H) = 8.2 Hz, 1 H) ppm. MS (ASAP) m/z 385.9 [M$^+$]. HRMS (ASAP) m/z calc'd C$_{14}$H$_{16}$Br$_2$OSi 385.9337 [M$^+$], found 385.9349. No further characterisation was performed.

Supporting Information (see footnote on the first page of this article): All relevant $^1$H, $^{13}$C and $^{11}$B spectra and crystal data are detailed in the supporting information. CCDC 1537383 (for 30), 1537382 (for 18), and 1819789 (for 35) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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