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Polyenes

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

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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.[1] 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 polyenes.[2–9] 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.[10–21] 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 xanthamonodinic 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

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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.

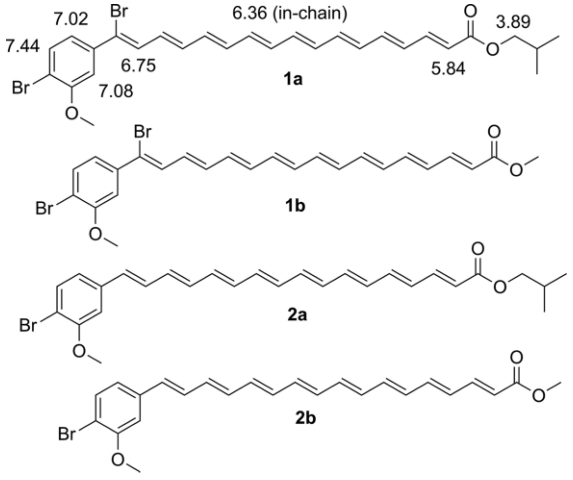
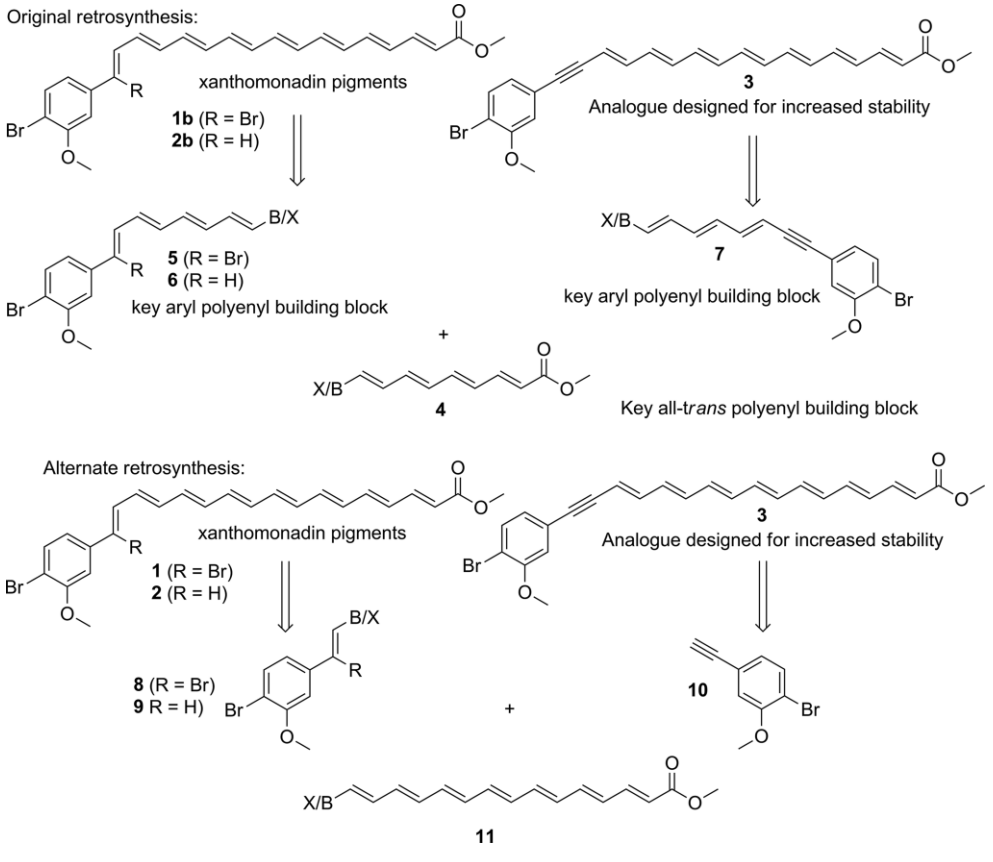


Figure 1. Structures of the various xanthomonadin analogues and ^{1}H NMR spectroscopic data as reported by Andrewes et al. for isobutyl xanthomonadin **1a**.[24]

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 arenyl 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-

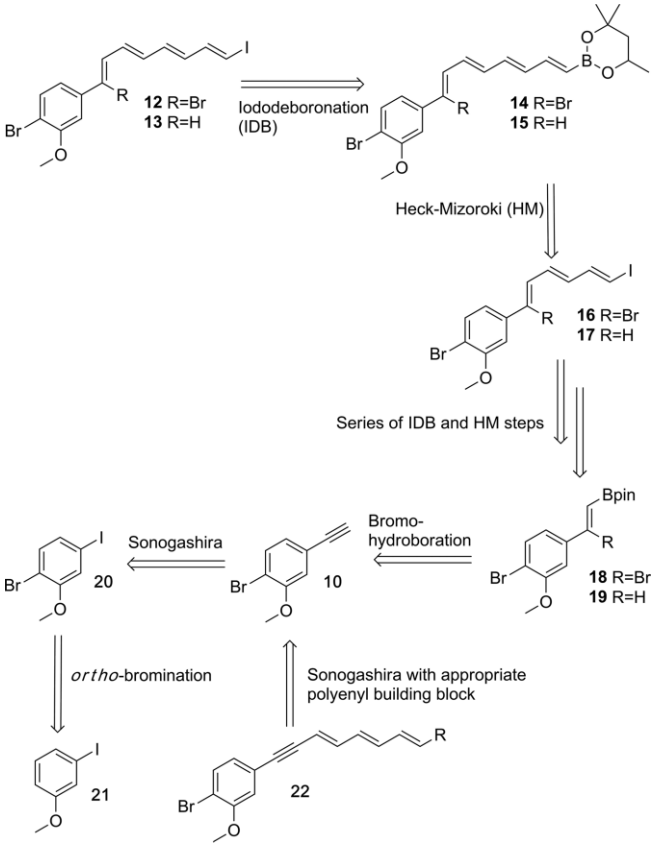


Scheme 1. Retrosynthetic approaches to methyl xanthomonadin and related analogues.

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.

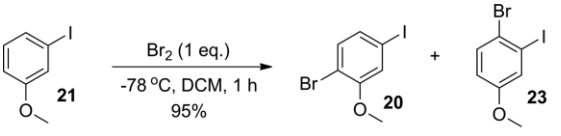
Results and Discussion

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).



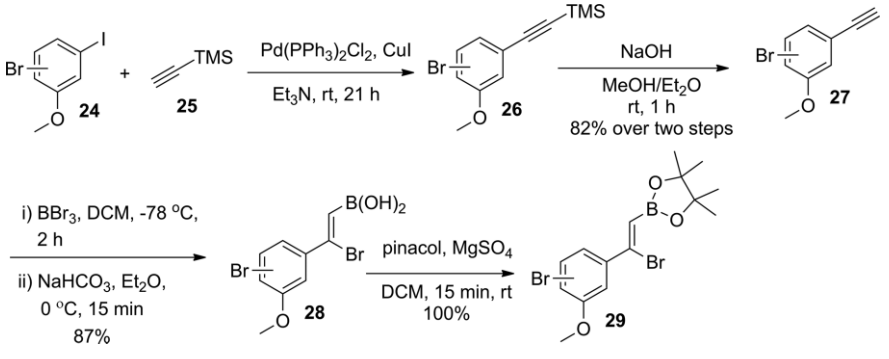
Scheme 2. Retrosynthesis of either tetraene **12** or **13** and alkynyl polyene **22**.

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 Br_2 [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.



regioselectivity 95:5, major isomer not identified (1)

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 SE_{Ar} 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 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.

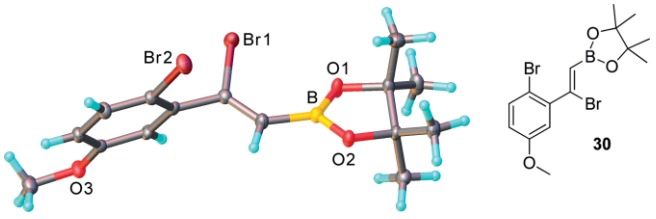
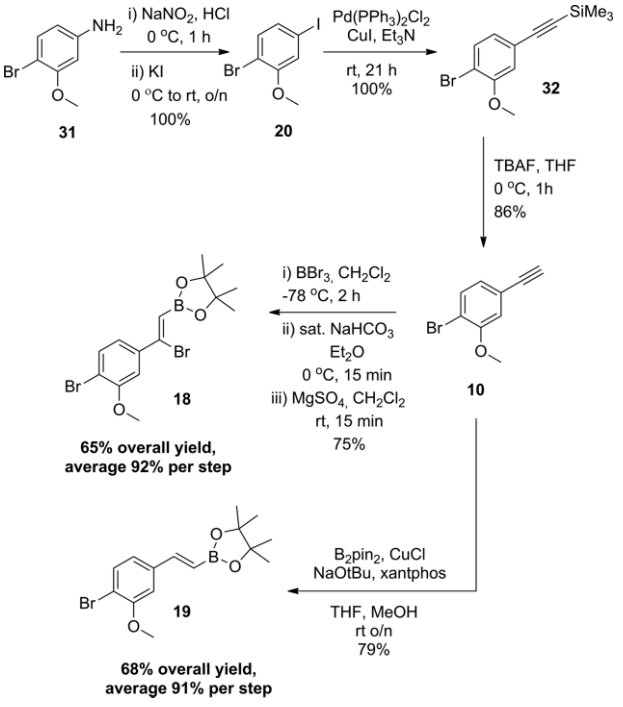


Figure 2. X-ray molecular structure of boronate ester **30** [(CCDC-1537382); thermal ellipsoids shown at 50 % probability].

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**.

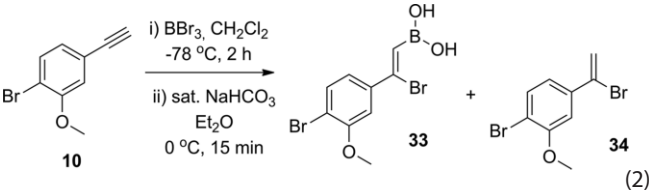
With alkyne building block **10** unambiguously produced, we could develop the synthesis of the two required styrenyl precursors to the different xanthomonadins, i.e. **18** and **19** (Scheme 5). As noted previously, it was envisaged that debrominated styrenyl building block **19** could be synthesised by hydroboration of alkyne **10**. This was achieved using a copper(I)-catalysed borylation with Xantphos, sodium *tert*-butoxide and B_2Pin_2 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**



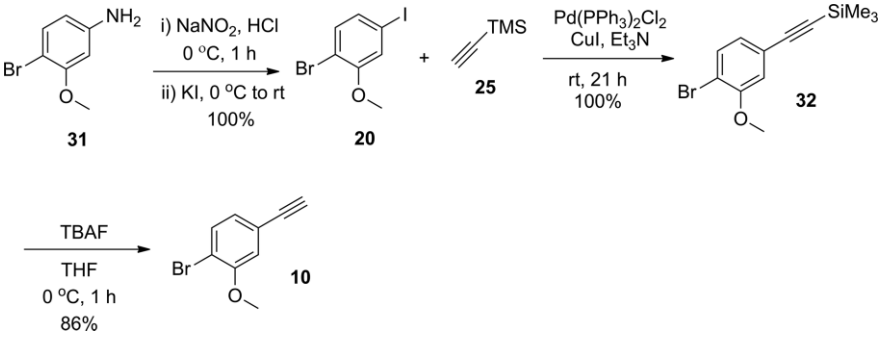
Scheme 5. Current route to key aryl intermediates **10**, **18** and **19**.

was highly dependent upon the quality of the BBr_3 used. Alkene **34** was routinely isolated as a by-product, presumably due to HBr contaminating the BBr_3 reagent [Equation (2)]. Use of a range of HBr scavengers failed to eliminate this issue; however, it was found that use of fresh BBr_3 solution kept this side-reaction to minimal levels.



(2)

Comparison of ^{1}H 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



Scheme 4. Successful route towards alkyne **10**.

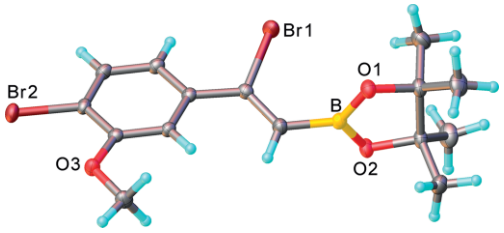
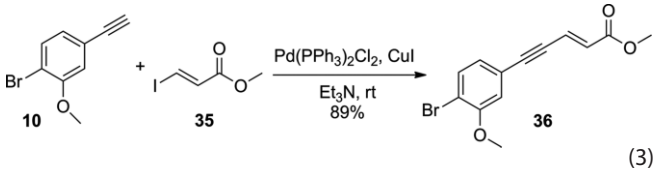


Figure 3. X-ray molecular structure of boronate ester **18** (CCDC-1537383).

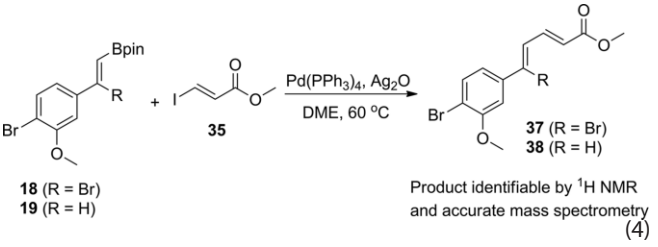
18 and **1a**, something that had not been observed during the synthesis of the incorrect regioisomer **30** (Table 1).

With the desired building blocks in hand, attention turned to the investigation of cross-coupling methods to enable access 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 alkynyl analogue of polyeneyne **3**. This proved successful, giving the resulting enyne **36** in 89 % yield [Equation (3)].



(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, and although it was noted the boronate esters were stable during the course of the SM coupling reaction, the alkenyl iodide partner **35** decomposed. In order to prevent this, cross-coupling of pinacol esters **18** and **19** was attempted using silver(I) oxide as base, which resulted in the desired SM products being be identified in the crude products according to ^{1}H NMR and mass spectrometry. However, isolation of the products **37** and **38** respectively proved difficult to isolate due to their tendency to polymerise [Equation (4)].



(4)

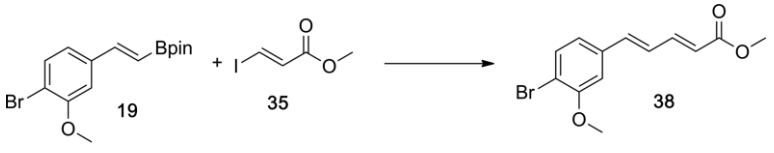
We considered that the temperature used in the cross-coupling reactions above could be a cause of the decomposition of iodide **35**. Hence, optimisation of the cross-coupling conditions between styrenyl boronate **19** and iodoacrylate **35** was carried out in order to develop improved reaction efficiency and allow for lower temperatures, as shown in Table 2.

Examination of Table 2 shows that generally, NMR yields of the model diene product **38** were improved at lower temperatures, particularly perhaps due to its sensitivity to polymerisation. At 60 °C (Table 2, entry 1), product formation was poor, improving significantly both with lower temperature and in-

Table 1. Partial ^{1}H NMR spectroscopic data for xanthomonadin **1a**, the incorrect regioisomer **30** and desired boronate **18**.

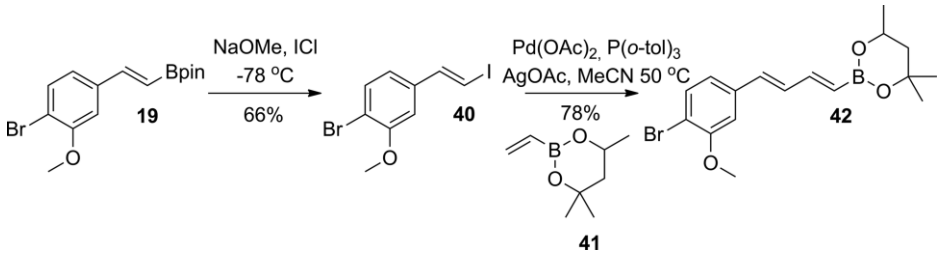
Proton environment type	^{1}H NMR signals Xanthomonadin **1a**	Incorrect regioisomer boronate **30**	Correct regioisomer boronate **18**
Alkene	6.75	6.14	6.43
Aryl	7.02	7.45	7.07
Aryl	7.08	6.72	7.11
Aryl	7.44	6.88	7.48

Table 2. Conditions screen for the Suzuki–Miyaura coupling of styrenyl Bpin **19** with iodoacrylate **35**.



Entry	Catalyst	Catalyst loading [mol-%]	Base	Base [equiv.]	Temp. [°C]	Solvent	NMR yield of **38**[a] after 24 h [%]
1	$Pd(PPh_3)_2Cl_2$	5	Ag_2O	1.2	60	DME	35[b]
2	$Pd(PPh_3)_4$	5	Ag_2O	1.2	40	DME	69
3	$Pd(PPh_3)_4$	10	Ag_2O	1.2	40	DME	92
4	$Pd(PPh_3)_4$	10	Ag_2O	1.2	30	DME	90
5	$Pd(PPh_3)_4$	10	Ag_2O	1.2	r.t.	DME	78
6	$Pd(OAc)_2/PPh_3$ (3 equiv.)	10	Ag_2CO_3	2	r.t.	MeCN	89
7	$Pd(PPh_3)_4$	10	*t*BuOK	2	40	DME	42[c,d]

[a] ^{1}H NMR yields calculated due to product diene **37**'s tendency to polymerise, using characteristic d 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 benefitted from an increase in catalyst loading to improve the reaction rate (Table 2, Entries 2 and 3). Doubling the $Pd(PPh_3)_4$ loading from 5 to 10 mol-% at 40 °C increased the conversion from 69 to 92 %.

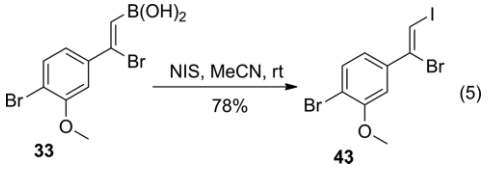


Scheme 6. Iterative cross coupling cycle to furnish aryl dienyl boronate ester **41**.

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 **39** was observed, with ^{1}H 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.

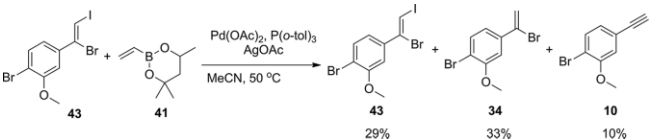
Given our original aim of developing a flexible route to the synthesis of polyenyl intermediates, styrenyl boronate ester **19** was also subjected to an IDB/HM cross-coupling sequence, as an alternative route to the construction of debromo xanthomonadin analogues such as **2**. Indeed, this was successful (Scheme 6), giving pinacol boronate **19** diene **42** in a 51 % yield over the two steps, and interestingly, with diene **42** 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[32] 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.



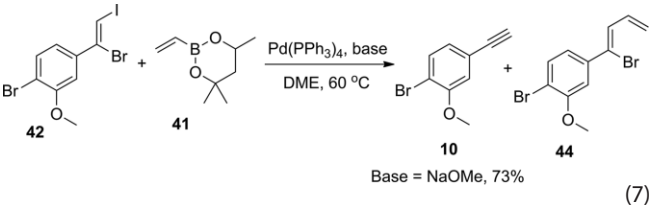
(5)

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.



(6)

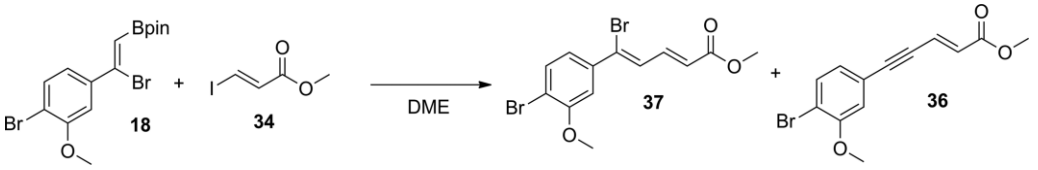
Hence, conditions for the potential SM coupling of the styrenyl bromoiodide **43** was investigated with vinylboronate **41**. Again however, none of the desired cross-coupled product **44** was observed under a range of conditions [see Equation (7)], with alkyne **10** being the major species in most 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 Pd^{II} formed from reaction of Pd^0 with iodide **43**, which could then eliminate to give a dihalo Pd^{II} species.



(7)

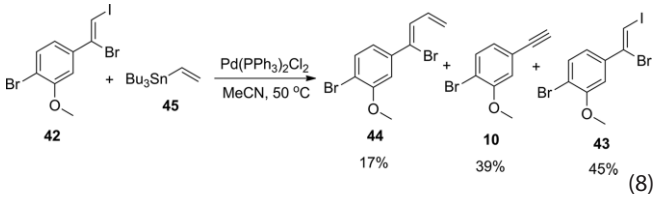
In light of this, other types of cross coupling were considered. Both Stille and Sonogashira couplings were especially appealing, as these could be performed at room temperature. A Stille coupling was therefore attempted on iodide **43** with vinyl stannane **45** [Equation (8)], however, although the 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 reoccuring 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**.

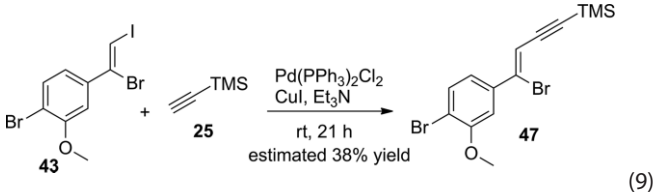


Entry	Catalyst	Loading [mol-%]	Base	Temp [°C]	NMR yields[a] after 24 h [%]	
					37	36
1	$Pd(PPh_3)_2Cl_2$	5	Cs_2CO_3	60	0	43
2	$Pd(PPh_3)_4$	10	Ag_2O	40	0	72[b]
3	$Pd(PPh_3)_2Cl_2$	5	Ag_2O	60	38	62
4	$Pd(PPh_3)_4$	5	Ag_2O	60	37	61
5	$Pd(OAc)_2$	5	Ag_2O	60	0	48
6	$Pd(dppf)Cl_2$	5	Ag_2O	60	34	66

[a] ^{1}H 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.



(8)



(9)

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 ^{1}H NMR were recorded on Bruker Avance-400, Varian V NMR S-600, Varian V NMR S-700 spectrometers. ^{13}C 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. ^{11}B 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 ^{1}H and ^{13}C and to external $BF_3{\cdot}Et_2O$ for ^{11}B. 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 Davisil 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 CH_2Cl_2 was dried by distillation from

CaH_2. Dry Et_3N 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-iodoanisole **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 $NaHCO_3$ (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 $NaHCO_3$ (2 × 25 mL), and dried with $MgSO_4$. The solvent was removed in vacuo to give the desired product (6.33 g, 95 %) as an orange liquid in 95:5 isomeric purity. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.70 (s, 3 H), 6.70 [dd, ^3J(H,H) = 2.8, 8.4 Hz, 1 H], 7.32 [d, ^3J(H,H) = 2.8 Hz, 1 H], 7.40 [d, ^3J(H,H) = 8.4 Hz, 1 H] ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 55.7, 101.0, 116.0, 120.3, 125.4, 132.6, 158.7 ppm. IR (film): $\tilde{\nu}$ (inter alia) = 3002 (w), 2934 (w), 2832 (mw), 1282 (s), 1225 (s), 1031 (s), 592 (s) cm^{-1}. UV/Vis (EtOH) λ_{max} (ε) 542 (317) nm. MS (ASAP) *m/z* 311.9 [M$^+$], 313.9 [M$^+$]. HRMS (ASAP) *m/z* calcd. for $C_7H_6{}^{79}BrIO$ 311.8647 [M$^+$], found 311.8679.

[(4-Bromo-3-methoxyphenyl)ethynyl]trimethylsilane (26)

1-Bromo-2-iodo-4-methoxybenzene (23): (500 mg, 1.60 mmol), $Pd(PPh_3)_2$ (11.23 mg, 0.016 mmol) and CuI (3.05 mg, 0.006 mmol) were added into a Schlenk tube. After evacuating and purging the Schlenk tube with argon (3 times), dry Et_3N (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 solvent (Et_3N) was evaporated and the residue was passed through a short silica gel column (EtOAc/petroleum ether, 90:10 as eluent). The product was concentrated in vacuo to give the crude material as a yellow liquid (541 mg, 119 %). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.09 (s, 9 H), 3.59 (s, 3 H), 6.55 [dd, ^3J(H,H) = 3.2, 8.8 Hz, 1 H], 6.82 [d, ^3J(H,H) = 3.2 Hz, 1 H], 7.23 [d, ^3J(H,H) = 8.8 Hz, 1 H] ppm. MS (EI$^+$) *m/z* 281.9 [M$^+$], 283.9 [M$^+$]; TMS-protected alkyne **26** was taken on for the next step without any further purification or analysis.

1-Bromo-2-ethynyl-4-methoxybenzene (27): To a stirred solution of TMS-protected alkyne **26** (5.94 g, 20.97 mmol) in MeOH (50 mL) and Et_2O (50 mL) was added a solution of NaOH (1 g, 25.17 mmol) in water (20 mL). After stirring at room temp. for 1 h, the aqueous phase was extracted using EtOAc (3 × 20 mL). The combined organic layers were washed with water (3 × 20 mL), and dried with $MgSO_4$. The crude material was concentrated in vacuo to give a brown liquid that was purified by silica gel column chromatography (EtOAc/petroleum ether, 95:5 as eluent) to afford the desired product as a pale yellow liquid (3.52 g, 80 %). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.21 (s, 1 H), 3.64 (s, 3 H), 6.63 [dd, ^3J(H,H) = 3.2, 8.8 Hz, 1 H], 6.90 [d, ^3J(H,H) = 3.2 Hz, 1 H], 7.30 [d, ^3J(H,H) = 8.8 Hz, 1 H] ppm. ^{13}C NMR (176 MHz, $CDCl_3$, 25 °C, TMS): δ = 55.5, 81.5, 81.9, 116.1, 117.1, 118.7, 124.7,133.1, 158.4 ppm. IR (film): $\tilde{\nu}$(inter alia) = 3289 (s), 3076 (w), 2937 (m), 2839 (m) cm^{-1}. UV/Vis (EtOH) λ_{max} (ε) 312 (2561) nm. MS (ASAP) *m/z* 210.0 [M$^+$], 212.0 [M$^+$]. HRMS (ASAP): *m/z*: calcd. for $C_9H_7{}^{79}BrO$ 209.9680 [M$^+$], found 209.9725.

(*Z*)-2-[2-Bromo-2-(2-bromo-5-methoxyphenyl)vinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30): To a well stirred solution of BBr_3 (60 µL, 0.63 mmol) in dry DCM (8 mL) was added alkyne **27** (134 mg, 0.63 mmol) at –78 °C under a positive pressure of argon. The reaction mixture was stirred at this temperature for 2 h and warmed up to 0 °C before adding a saturated aqueous $NaHCO_3$ (2 mL) dropwise and Et_2O (4 mL). After stirring at 0 °C for 15 min, the resulting solution was transferred into a separating funnel and the phases were separated. The aqueous phase was extracted using DCM (2 × 10 mL), and the combined organic layers were washed with water (20 mL), brine (20 mL), and dried with $MgSO_4$. The crude material was concentrated in vacuo to give the boronic acid as a yellow solid. Into a solution of the boronic acid (168.5 mg, 0.50 mmol) in DCM (20 mL) was added $MgSO_4$ (127 mg, 1.05 mmol) and pinacol (59.3 mg, 0.50 mmol). After stirring for 15 min, the resulting solution was filtered and concentrated in vacuo. The crude material was recrystallised by slow evaporation using hexane to give the desired product as a brown solid (155.5 mg, 87 % over the two steps). M.p. 74.4–76.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.34 (s, 9 H), 3.78 (s, 3 H), 6.14 (s, 1 H), 6.72 [dd, ^3J(H,H) = 3.0, 8.4 Hz, 1 H], 6.88 [d, ^3J(H,H) = 3.0 Hz, 1 H], 7.42 [d, ^3J(H,H) = 8.4 Hz, 1 H] ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C, TMS): δ = 23.8, 54.5, 83.1, 110.4, 113.9, 115.4, 132.9, 135.3, 143.3, 157.6 ppm. ^{11}B NMR (128 MHz, $CDCl_3$): δ = 29.3 ppm. IR (KBr disk): $\tilde{\nu}$(inter alia) = 2978 (m), 2942 (m), 1140 (s), 731 (s) cm^{-1}. UV/Vis (EtOH) λ_{max} (ε) 207 (11,254), 297 (2,010), 554 (804) nm. MS (ASAP) *m/z* 417.0 [M + H], 419.0 [M + H], 421.0 [M + H]. HRMS (ASAP) *m/z* calcd. for $C_{15}H_{20}B^{79}Br_2O_3$ 416.9872 [M + H], found 416.9875. Structure determined by X-ray crystallography.

1-Bromo-4-iodo-2-methoxybenzene (20): 4-Bromo-3-methoxyaniline **31** (5.00 g, 24.8 mmol) was stirred in aqueous HCl (37 %, 250 mL) at 80 °C to ensure complete dissolution. This was then cooled to 0 °C and a cold solution of $NaNO_2$ (2.22 g, 32.2 mmol) in H_2O (125 mL) was added dropwise, keeping the temperature constant. The reaction mixture was stirred at 0 °C for 1 h and a cold solution of KI (12.5 g, 74.3 mmol) was carefully added dropwise at 0 °C over a period of 1 h. The resulting dark brown solution was stirred and allowed to reach room temperature overnight. 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 combined and washed sequentially with sat. $NaHCO_3$ (125 mL) and H_2O (125 mL) until neutral pH. The organic layers were then washed with 5 % $Na_2S_2O_3$ (125 mL) and saturated brine (125 mL), dried with $MgSO_4$ and the solvent evaporated to afford a dark brown oil, from with the desired product spontaneously crystallised to give the desired product as dark brown solid (7.8 g, 100 %). M.p. 53.1–55.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.88 (s, 3 H), 7.14–7.18 (m, 2 H), 7.22–7.25 (m, 1 H) ppm. All other spectroscopic data were consistent with those in the literature.[33]

[(4-Bromo-3-methoxyphenyl)ethynyl]trimethylsilane (32): 1-Bromo-4-iodo-2-methoxybenzene **20** (7.71 g, 24.8 mmol), $Pd(PPh_3)_2Cl_2$ (0.173 g, 0.242 mmol) and CuI (47 mg, 0.242 mmol) were added to a dry flask. After purging the flask with argon for 5 min, dry, degassed Et_3N (139 mL) was added to the tube under argon, followed by TMS acetylene **25** (4.0 mL, 29.8 mmol). The reaction mixture was stirred at room temperature in the dark for 16 h. The solvent was then evaporated and the residue was passed through a silica gel column, eluent 5 % EtOAc in petroleum ether. Fractions containing the compound were evaporated to give the desired product as an orange oil (7.11 g, 100 %). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.25 (s, 9 H), 3.89 (s, 3 H), 6.92–6.98 (m, 2 H), 7.45 [d, ^3J(H,H) = 8.1 Hz, 1 H] ppm. ^{29}Si NMR (139 MHz, $CDCl_3$): δ = –17.47 (s) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C, TMS): δ = –0.2, 56.2, 95.0, 104.0, 112.5, 115.0, 123.3, 125.4, 133.1, 155.4 ppm. IR (film): $\tilde{\nu}$(inter alia) = 2157 (w), 2959 (m) cm^{-1}. MS (ASAP) *m/z* 282.0 [M$^+$]. HRMS (ASAP) *m/z* calcd. for $C_{12}H_{15}OSi^{79}Br$ 282.0076 [M$^+$], found 282.0083.

1-Bromo-4-ethynyl-2-methoxybenzene (10): [(4-Bromo-3-methoxyphenyl)ethynyl]trimethylsilane **32** (6.14 g, 21.8 mmol) was dis-

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. Pure fractions were evaporated to give the desired product as an orange solid (3.76 g, 86 %). M.p. 37.4–38.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.12 (s, 1 H), 3.89 (s, 3 H), 6.92–7.01 (m, 2 H), 7.48 [d, ^3J(H,H) = 8.1 Hz, 1 H] ppm. ^{13}C NMR (176 MHz, $CDCl_3$, 25 °C, TMS): δ = 56.2, 77.9, 82.8, 112.9, 115.2, 122.3, 125.5, 133.2, 155.6 ppm. IR (film): $\tilde{\nu}$(inter alia) = 2051 (w), 2939 (w), 3258 (s) cm^{-1}. MS (ASAP) *m/z* 210.0 [M$^+$], 212.0 [M$^+$]. HRMS (ASAP) *m/z* calcd. for $C_9H_7O^{79}Br$, 209.9680 [M$^+$], found 209.9689.

(*Z*)-2-[2-Bromo-2-(4-bromo-3-methoxyphenyl)vinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (18): To a stirred solution of BBr_3 (6.0 mL, 6.0 mmol, 1.0 M in DCM) in DCM (57 mL) was added 1-bromo-4-ethynyl-2-methoxybenzene **10** (1.25 g, 6.0 mmol) in DCM (10 mL) at –78 °C under a positive pressure of argon. The resulting purple solution was stirred at –78 °C for 2 h and warmed to 0 °C before adding sat. $NaHCO_3$ (19 mL). The resulting orange solution was stirred for 10 min, then transferred to a separating funnel. The mixture was extracted with DCM (2 × 114 mL) and the organics washed with H_2O (114 mL) and brine (114 mL), dried with $MgSO_4$, filtered and evaporated to yield a brown oil. This crude residue was then redissolved in DCM (63 mL) and $MgSO_4$ (1.46 g, 12.1 mmol) and pinacol (0.716 g, 6 mmol) were added. The reaction mixture was stirred for 1 h at room temperature, then the solution was filtered and evaporated to give the desired product as a brown solid (1.88 g, 75 %). M.p. 74.8–77.0 °C; ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.35 (s, 12 H), 3.91 (s, 3 H), 6.43 (s, 1 H), 7.07–7.13 (m, 2 H), 7.49 [d, ^3J(H,H) = 8.3 Hz, 1 H] ppm. ^{11}B NMR (128 MHz, $CDCl_3$, 25 °C, TMS): δ = 29.2 ppm. ^{13}C NMR (176 MHz, $CDCl_3$, 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): $\tilde{\nu}$ (inter alia) = 2978 (m), 2942 (m) cm^{-1}. MS (ASAP) *m/z* 415.0 [M$^+$], 417.0 [M$^+$], 419.0 [M$^+$]. HRMS (ASAP) *m/z* calcd. for $C_{15}H_{19}{}^{10}BO_3{}^{79}Br_2$ 414.9830 [M$^+$], found 414.9826. Structure confirmed by X-ray crystallography.

2-[(*E*)-2-(4-Bromo-3-methoxyphenyl)ethenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (19): Copper(I) chloride (16 mg, 0.158 mmol), xantphos (92 mg, 0.158 mmol), sodium *tert*-butoxide (31 mg, 0.32 mmol) and 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.33 g, 5.28 mmol) were added to a dry flask fitted with a Schlenk tap under argon. Dry THF (11 mL) was then added and the reaction mixture stirred for 5 min. 1-bromo-4-ethynyl-2-methoxybenzene **10** (1.11 g, 5.28 mmol) was then added and the reaction mixture stirred for 5 min, then dry MeOH (0.42 mL) was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (110 mL) and washed with H_2O (105 mL) and then saturated brine (105 mL). The organics were dried with $MgSO_4$, filtered and evaporated to yield 2.40 g of a dark yellow oil. The crude product was purified by silica gel chromatography, eluent 0–5 % EtOAc in hexane to yield the desired product as a yellow oil, which became a yellow solid on standing (1.40 g, 79 %). M.p. 66.9–69.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.31 (s, 12 H), 3.90 (s, 3 H), 6.16 [d, ^3J(H,H) = 18.4 Hz, 1 H], 6.91–7.06 (m, 2 H), 7.33 [d, ^3J(H,H) = 18.4 Hz, 1 H], 7.49 [d, ^3J(H,H) = 8.1 Hz, 1 H] ppm. ^{11}B NMR (128 MHz, $CDCl_3$, 25 °C, TMS): δ = 29.7 ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 25.0, 56.2, 83.7, 110.1, 112.5, 120.8, 133.5, 138.4, 148.6, 156.1 ppm. IR (film): $\tilde{\nu}$(inter alia) = 1548 (m), 1620 (m) cm^{-1}. MS (ESI) *m/z* 339.1 [M + H], 341.1 [M + H]. HRMS (ESI) *m/z* calcd. for $C_{15}H_{21}{}^{10}BO_3{}^{79}Br$ 338.0803 [M$^+$], found 338.0814.

[(*Z*)-7-Bromo-7-(4-bromo-3-methoxyphenyl)ethenyl]boronic Acid (33): To a well-stirred solution of BBr_3 (0.19 mL, 1.92 mmol) in DCM (18 mL) was added 1-bromo-4-ethynyl-2-methoxybenzene **10** (0.402 g, 1.92 mmol) at –78 °C under a positive pressure of argon. The resulting purple solution was stirred at –78 °C for 2 h and warmed to 0 °C before adding $NaHCO_3$ (0.323 g, 3.84 mmol) dissolved in H_2O (13 mL). The resulting pale yellow solution was stirred for 25 min, then transferred to a separating funnel. The mixture was extracted with DCM (2 × 20 mL) and the organics washed with H_2O (20 mL) and brine (20 mL), dried with $MgSO_4$, filtered and evaporated to give the desired product as an unstable pale yellow solid (0.522 g, 81 %). M.p. 115.3–118.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.94 (s, 3 H), 6.47 (s, 1 H), 7.03–7.19 (m, 2 H), 7.45–7.60 (m, 1 H) ppm. ^{11}B NMR (128 MHz, $CDCl_3$, 25 °C, TMS): δ = 27.6 ppm. The compound was taken on to the next stage without any further purification or characterisation.

Methyl (2E)-5-(4-Bromo-3-methoxyphenyl)pent-2-en-4-ynoate (36): 1-Bromo-4-ethynyl-2-methoxybenzene **10** (0.175 g, 0.833 mmol), methyl(2*E*)-3-iodoprop-2-enoate **35** (0.147 g, 0.694 mmol), bis(triphenylphosphine)palladium(II) dichloride (49 mg, 0.007 mmol) and copper(I) iodide (1 mg, 0.007 mmol) were added to a flask, which was then purged with argon for 5 min. Dry, degassed Et_3N (3.9 mL) was then added and the reaction mixture stirred in the dark at room temperature for 3 d. The solvent was then evaporated to give 0.347 g of a dark yellow solid. This residue was then purified using silica gel chromatography, eluent 25 % EtOAc in hexane. Pure fractions were evaporated to give the desired product as a yellow solid (0.204 g, 89 %). M.p. 85.8–86.8 °C. ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.78 (s, 3 H), 3.90 (s, 3 H), 6.32 [d, ^3J(H,H) = 15.8 Hz, 1 H], 6.89–6.99 (m, 3 H), 7.50 [d, ^3J(H,H) = 8.0 Hz, 1 H] ppm. ^{13}C NMR (176 MHz, $CDCl_3$, 25 °C, TMS): δ = 51.9, 56.3, 86.8, 97.4, 113.6, 114.8, 122.3, 124.9, 125.4, 130.0, 133.4, 155.7, 166.2 ppm. IR (film): $\tilde{\nu}$ (inter alia) = 1714 (s), 2199 (s), 2947 (w) cm^{-1}. MS (ASAP) *m/z* 295.0 [M + H], 297.0 [M + H]. HRMS (ASAP): *m/z*: calcd. for $C_{13}H_{12}O_3{}^{79}Br$ 294.9969 [M$^+$], found 294.9970. Structure determined by X-ray crystallography.

1-Bromo-4-(1-bromoethenyl)-2-methoxybenzene (34): To a well-stirred solution of BBr_3 (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-ethynyl-2-methoxybenzene **10** (1.0 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 sat. $NaHCO_3$ (15 mL), followed by Et_2O (30 mL), were added dropwise at 0 °C. The now pale yellow reaction mixture was then 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), then the organics was with H_2O (100 mL) and then brine (100 mL). The organics were then dried with $MgSO_4$, filtered and evaporated to yield 1.4 g of a pale yellow solid. The crude solid was then purified by silica gel chromatography, elution gradient 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 %). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.93 (s, 3 H), 5.80 [d, ^3J(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, ^3J(H,H) = 8.2 Hz, 1 H] ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C, TMS): δ = 56.4, 111.2, 112.7, 118.4, 120.5, 129.7, 132.92, 139.2, 156.5 ppm. IR: $\tilde{\nu}$ (inter alia) = 2836 (m), 2943 (m), 2970 (m) cm^{-1}. MS (ASAP) *m/z* 289.9 [M$^+$], 291.9 [M$^+$], 293.9 [M$^+$]. HRMS (ASAP) *m/z* calcd. for $C_9H_8O^{79}Br_2$ 289.8959 [M$^+$], found 289.8942.

Methyl (2E,4Z)-5-Bromo-5-(4-bromo-3-methoxyphenyl)penta-2,4-dienoate (37): 2-[(*Z*)-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 (2*E*)-3-iodoprop-2-enoate (25 mg, 0.12 mmol), $Pd(PPh_3)_2Cl_2$ (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. ^{1}H NMR (400 MHz, $CDCl_3$, 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], 7.46 [d, ^3J(H,H) = 8.0 Hz, 2 H] ppm. MS (ASAP) *m/z* 374.9 [M + H], 376.9 [M + H], 378.9 [M + H]. HRMS (ASAP) *m/z* calcd. for $C_{13}H_{13}O_3{}^{79}Br_2$ 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-methoxyohenyl)penta-2,4-dienoate (38): 2-[(*E*)-2-(4-Bromo-3-methoxyphenyl)ethenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **19** (0.256 g, 0.76 mmol), methyl (2*E*)-3-iodoprop-2-enoate **35** (0.129 g, 0.61 mmol), $Pd(PPh_3)_2Cl_2$ (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 passed through a short Celite/silica plug. The solvent was evaporated to give 0.340 g of a crude green/yellow solid. The crude residue was purified by silica gel chromatography, eluent 0–5 % EtOAc in hexane to give 0.110 g of a bright yellow solid which rapidly polymerised, but from which the desired product could be identified (estimated 41 % I. Y. by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.69 (s, 3 H), 3.86 (s, 3 H), 5.96 [d, ^3J(H,H) = 15.3 Hz, 1 H], 6.85–6.93 (m, 2 H), 7.33 [d, ^3J(H,H) = 10.0 Hz, 1 H], 7.45–7.52 (m, 1 H), 7.55–7.50 (m, 2 H) ppm. MS (ASAP) *m/z* 297.0 [M + H], 299.0 [M + H]. HRMS (ASAP) *m/z* calcd. for $C_{13}H_{14}O_3Br$ 297.0126 [M + H]; found, 297.0128. No further characterisation was performed due to instability.

1-Bromo-4-[(*E*)-2-iodoethenyl]-2-methoxybenzene (40): 2-[(*E*)-2-(4-Bromo-3-methoxyphenyl)ethenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **19** (1.30 g, 3.85 mmol) was dissolved in dry THF (14 mL) and cooled to −78 °C under argon. NaOMe (9.2 mL, 4.62 mmol, 0.5 M in MeOH) was added dropwise and then reaction mixture stirred at −78 °C for 1 h 15 min. Iodine monochloride (0.736 g, 3.95 mmol) in dry DCM (3.9 mL) was then added dropwise at this temperature and the reaction mixture stirred at −78 °C for a further 2 h 10 min. The reaction mixture was warmed to room temperature and diluted with Et_2O (116 mL), then washed with 5 % $Na_2S_2O_5$ (2 × 46 mL), H_2O (46 mL) and brine (46 mL). The organics were dried with $MgSO_4$ under argon, filtered and evaporated to give 1.30 g of a crude yellow solid containing desired product (0.863 g, 66 %). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.90 (s, 3 H), 6.75–6.82 (m, 2 H), 6.88 [d, ^3J(H,H) = 14.9 Hz, 1 H], 7.37 [d, ^3J(H,H) = 14.9 Hz, 1 H], 7.48 [d, ^3J(H,H) = 7.9 Hz, 1 H] ppm. The compound was taken on to the next stage without any further purification or characterisation.

2-[(1E,3E)-4-(4-Bromo-3-methoxyphenyl)buta-1,3-dien-1-yl]-4,4,6-trimethyl-1,3,2-dioxaborinane (42): 1-Bromo-4-[(*E*)-2-iodoethenyl]-2-methoxybenzene **40** (0.863 g, 2.55 mmol) was dissolved in dry, degassed MeCN (15 mL) and added to a dry, argon-purged flask containing $Pd(OAc)_2$ (29 mg, 0.130 mmol), P(*o*-tol)$_3$ (77 mg, 0.255 mmol) and AgOAc (0.458 g, 2.74 mmol). 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (0.50 mL, 2.92 mmol) was then added and the reaction mixture heated to 50 °C for 18 h. The reaction mixture was cooled to room temperature, then diluted with Et_2O containing ≈ 3 ppm BHT (38 mL) and passed through a short Celite/silica plug. The solvent was evaporated to give 1.37 g of crude product as a viscous orange oil. The crude product was purified by silica gel chromatography, elution gradient 0–10 % EtOAc in petroleum ether. Pure fractions were evaporated to give desired product as a viscous yellow oil (0.725 g, 78 %). ^{1}H NMR (600 MHz, $CDCl_3$, 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 [dqd, ^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. ^{11}B NMR (128 MHz, $CDCl_3$, 25 °C, TMS): δ = 25.6 ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 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 (ASAP) *m/z*: 363.1 [M$^+$], 364.1 [M$^+$], 365.1 [M$^+$], 366.1 [M$^+$]. HRMS (ASAP) *m/z* calcd. for $C_{17}H_{23}{}^{10}BO_3Br$ 364.0960 [M$^+$], found 364.0958.

1-[(*Z*)-7-Bromo-8-iodoethenyl]-3-methoxy-4-bromobenzene (43): To a solution of [(*Z*)-7-bromo-7-(4-bromo-3-methoxyphenyl)ethenyl]boronic acid **33** (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 was stirred for 3 h at room temperature. The reaction mixture was diluted with EtOAc (60 mL) and washed with 5 % $Na_2S_2O_5$ (2 × 60 mL), H_2O (2 × 60 mL) and brine (60 mL). The organic layer was dried with $MgSO_4$, 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 5 % EtOAc in petroleum ether. Pure fractions were evaporated to give the desired compound as a pale yellow amorphous powder (0.947 g, 78 %). ^{1}H NMR (400 MHz, $CDCl_3$, 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. ^{13}C NMR (176 MHz, $CDCl_3$, 25 °C, TMS): δ = 56.3, 83.7, 111.4, 113.1, 120.9, 133.1, 136.5, 140.0, 155.7 ppm. IR: $\tilde{\nu}$ (inter alia) = 3044 (w), 2940 (w), 1586 (m), 1582 (m), 1546 (m) cm^{-1}. MS (ASAP) *m/z* 416.8 [M$^+$], 418.8 [M$^+$], 420.8 [M$^+$]. HRMS (ASAP) *m/z* calcd. for $C_9H_7{}^{79}Br_2IO$ 417.8065 [M + H], found 417.7909.

1-Bromo-4-[(1Z)-1-bromobuta-1,3-dien-1-yl]-2-methoxybenzene (44): $Pd(PPh_3)_2Cl_2$ (2 mg, 0.024 mmol) and 1-[(*Z*)-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 %). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.92 (s, 3 H), 5.43 [dd, ^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 (ASAP) *m/z* 315.9 [M$^+$], 317.9 [M$^+$], 319.9 [M$^+$]. HRMS (ASAP) *m/z* calcd. for $C_{11}H_{11}{}^{79}Br_2O$ 316.9177 [M + H], found 316.9188. No further characterisation was performed due to stability issues on purification.

[(3Z)-4-Bromo-4-(4-bromo-3-methoxyphenyl)but-3-en-1-yn-1-yl]trimethylsilane (47): $Pd(PPh_3)_2Cl_2$ (2 mg, 0.024 mmol), copper(I) iodide (1 mg, 0.048 mmol) and 1-[(*Z*)-7-bromo-8-iodoethenyl]-3-methoxy-4-bromobenzene **43** (0.2 g, 0.481 mmol) were added to a dry flask, and the flask sealed and purged with argon for 5 min.

Dry, degassed Et_3N (3.0 mL) was added, followed by ethynyl trimethylsilane **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, ^3J(H,H) = 8.3, 2.0 Hz, 1 H], 7.16 [d, ^3J(H,H) = 2.0 Hz, 1 H], 7.49 [d, ^3J(H,H) = 8.2 Hz, 1 H] ppm. MS (ASAP) *m/z* 385.9 [M^+]. HRMS (ASAP) *m/z* calcd. $C_{14}H_{16}{}^{79}Br_2OSi$ 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 **18**), 1537382 (for **30**), 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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