JOC Article

Mechanistic Studies on the Heck−Mizoroki Cross-Coupling Reaction of a Hindered Vinylboronate Ester as a Key Approach to Developing a Highly Stereoselective Synthesis of a C1−C7 *Z,Z,E*-Triene Synthon for Viridenomycin

Andrei S. Batsanov, Jonathan P. Knowles, and Andrew Whiting*

University of Durham, Department of Chemistry, Sciences Laboratories South Road DH1 3LE, Durham, United Kingdom

andy.whiting@durham.ac.uk

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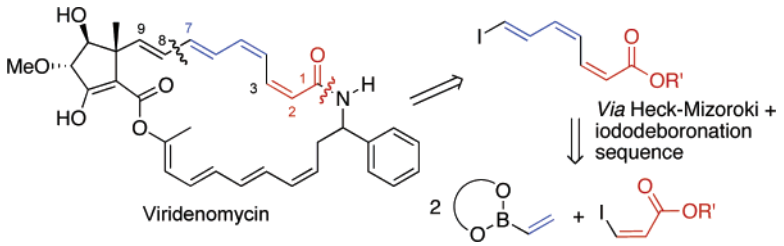

Mechanistic studies of the Heck−Mizoroki reaction of a vinylboronate ester with electronically different (four-substituted) aryl iodides shows that electron donors accelerate the cross-coupling, demonstrating that the oxidative addition step is not rate determining and that there is development of some degree of positive charge in the rate determining step. These results were used as a basis to allow the development of reaction conditions for the Heck−Mizoroki coupling of a hindered vinylboronate ester with electron deficient methyl *cis*-2-iodoacrylate. The resulting dienylboronate ester was converted through a series of highly stereoselective iodo-deboronations and Heck−Mizoroki reactions into a trienyl iodide precursor for further application in the total synthesis of viridenomycin.

Introduction

The Heck−Mizoroki (HM) coupling of hindered vinylboronate esters with aryl[1] and alkenyl iodides[2] is of considerable synthetic utility, especially in the latter case for the stereocontrolled synthesis of polyenes[3] due to its ability to act as a vinyl dianion equivalent by combination with a highly stereoselective iodo-deboronation process.[4] Viridenomycin **1**[5] has yet to succumb to total synthesis,[6] and as part of a program concerned with its synthesis using this type of methodology,[7] the retrosynthetic analysis (Scheme 1) suggested the need for a trienyl iodide of type **3** to construct the C7−C8 bond in viridenomycin **1**. The triene **3** could in turn be accessed from the corresponding boronate **4** via a series of HM couplings[2] with a vinylboronate ester of type **6**, followed by stereoselective iodo-deboronations.[4] However, initial investigations into the

TABLE 1. σ and k Values for each Aryl Iodide Reacted as in Eq 2 Using Ph_3P and $(4\text{-MeOPh})_3P$

entry	aryl iodide **7**	k_{obs} for PPh_3 (10^{-5} mmol dm^{-3} s^{-1})	k_{obs} for P (*p*-MeOPh)$_3$ (10^{-5} mmol dm^{-3} s^{-1})	δ
1	**a**	160	390	0.268
2	**b**	130	300	0.170
3	**c**	120	220	0
4	**d**	120	*a*	0.062
5	**e**	80	*a*	0.227
6	**f**	28	55	0.788

[a] These reactions showed significant curvature in their conversion vs time plots very early in the reactions preventing the initial rates being obtained.

* Corresponding author. Tel: +44 191 334 2081. Fax: +44 191 384 4737.

(1) (a) Hunt, A. R.; Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1993**, *34*, 3599−3602. (b) Stewart, S. K.; Whiting, A. *J. Organomet. Chem.* **1994**, *482*, 293−300. (c) Lightfoot, A. P.; Maw, G.; Thirsk, C.; Twiddle, S.; Whiting, A. *Tetrahedron Lett.* **2003**, *44*, 7645−7648.

(2) Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1995**, *36*, 3925−3928.

(3) (a) Hénaff, N.; Whiting, A. *Org. Lett.* **1999**, *1*, 1137−1139. (b) Hénaff, N.; Whiting, A. *Tetrahedron* **2000**, *56*, 5193−5204. (c) Lightfoot, A. P.; Twiddle, S. J. R.; Whiting, A. *Org. Biomol. Chem.* **2005**, *3*, 3167−3172.

(4) (a) Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1995**, *36*, 3929−3932. (b) Lightfoot, A. P.; Twiddle, S. J. R.; Whiting, A. *Tetrahedron Lett.* **2004**, *45*, 8557−8861. (c) Batsanov, A.; Howard, J. A. K.; Lightfoot, A. P.; Twiddle, S. J. R.; Whiting, A. *Eur. J. Org. Chem.* **2005**, 1876−1883.

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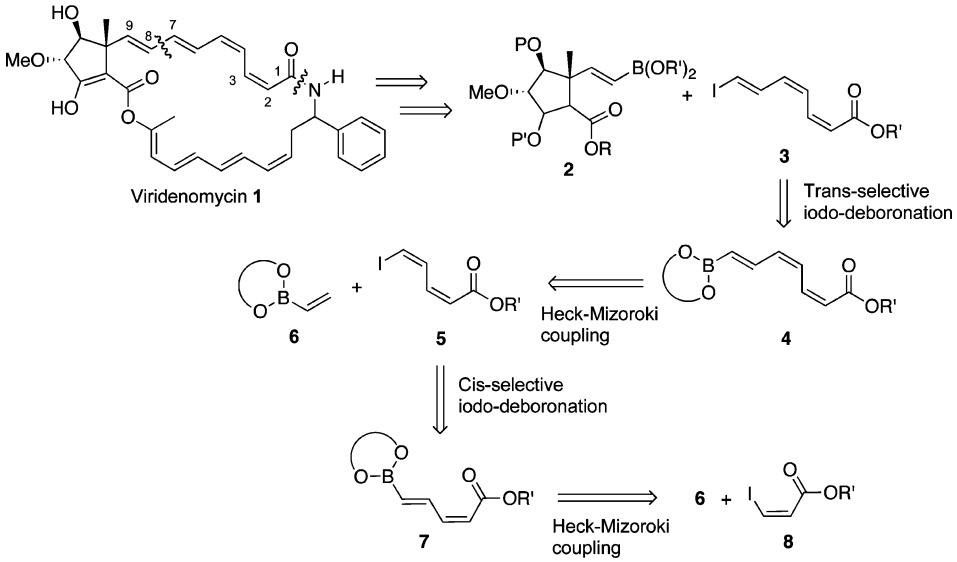
SCHEME 1. Retrosynthetic Scheme for the Synthesis of the Northern Tetraene Section of Viridenomycin

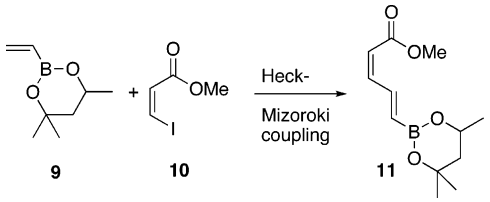


coupling of a hindered vinylboronate ester with methyl *cis*-iodoacrylate led to a series of unexpected amine−acrylate Michael addition products or the formation of the Suzuki−Miyaura (SM) product.[8]

In this paper, we present mechanistic investigations into the factors that affect the HM coupling of a hindered boronate ester with aryl and alkenyl iodides and the application of this information in solving the problem controlling HM versus SM coupling of such systems to allow the selective synthesis of products of type **7** and, hence, systems of type **3**.

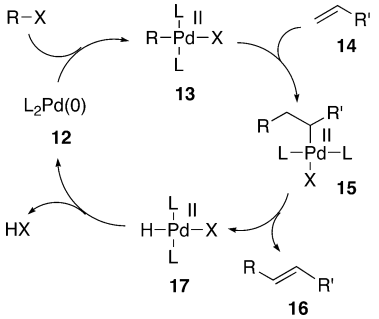
Results and Discussion

Our starting point was an investigation into the coupling of methylpentanediol boronate ester **9** (a vinylboronate ester with superior shelf stability and ease of preparation as compared to other hindered vinylboronate esters[1c]) with iodoacrylate **10**,[8] which despite carrying out screening of a range of conditions (solvents, phosphines, amines, etc.), failed to provide the HM product **11**. To solve this problem, involving a reactive electron deficient alkenyl iodide and a seemingly rather unreactive vinyl system, it was realized that an improved understanding of the mechanism operating in this attempted HM reaction was required. While vinylboronate esters, such as **9**, may at first appear to be electronically similar to acrylates, we note that (a) boron is electropositive and thus is a σ-donor and (b) B−O π-bonding drastically reduces the π-acceptor properties of the boronate moiety in alkyl-substituted boronates. Hence, to obtain a better understanding of the effects influencing the process outlined in eq 1, and to try and solve the problem of the synthesis of dienylboronate **11**, mechanistic studies were required. However, these experiments would be easier to carryout on a series of readily available, and directly comparable, aryl iodides in place of the acrylate **10**.



Hammett Studies on the Reaction of Boronate Ester 9 with Four-Substituted Aryl Iodides. An often reproduced representation of the HM mechanism[9] is shown in Scheme 2. This process has been investigated by several groups[10] and portrays the HM reaction as a process that is accelerated by electron-withdrawing substituents on the aryl halide, yet not necessarily having the oxidative addition as rate determining. However, recently, Dupont et al.[11] have shown that electron-withdrawing substituents on the aryl group (Scheme 2, R = aryl) increase the rate of reaction, as demonstrated by a clear positive Hammett correlation,[11] which suggests that oxidative addition of R−X to the Pd(0) complex **12** providing palladium(II) complex **13** is

SCHEME 2. General Mechanistic Scheme for the HM Cross-Coupling Reaction



(5) (a) Nakagawa, M.; Toda, Y.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Antibiot.* **1992**, *45*, 1133−1138. (b) Nakagawa, M.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1991**, *32*, 659−662. (c) Hasegawa, T.; Kamiya, T.; Henmi, T.; Iwasaki, H.; Yamatodani, S. *J. Antibiot.* **1975**, *28*, 167−175.

(6) (a) Pattenden, G.; Blake, A. J.; Constandinos, L. *Tetrahedron Lett.* **2005**, *46*, 1913−1915. (b) Mulholland, N. P.; Pattenden, G. *Tetrahedron Lett.* **2005**, *46*, 937−939. (c) Kruger, A. W.; Meyers, A. I. *Tetrahedron Lett.* **2001**, *42*, 4301−4304. (d) Waterson, A. G.; Kruger, A. W.; Meyers, A. I. *Tetrahedron Lett.* **2001**, *42*, 4305−4308. (e) Ishihara, J.; Hagihara, K.; Chiba, H.; Ito, K.; Yanagisawa, Y.; Totani, K.; Tadano, K.-I. *Tetrahedron Lett.* **2000**, *41*, 1771−1774. (f) Arrington, M. P; Meyers, A. I. *Chem. Commun*. **1999**, 1371−1372. (g) Trost, B. M; Jiang, C. *Org. Lett.* **2003**, *5*, 1563−1565.

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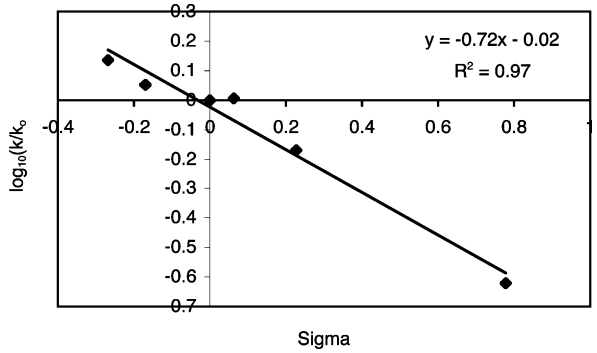
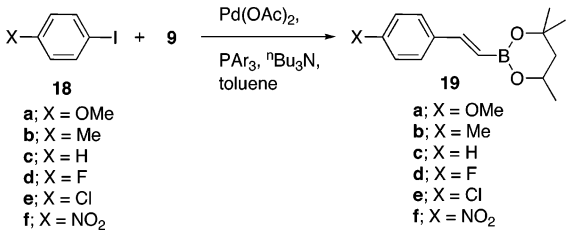
(8) Maw, G.; Thirsk, C.; Whiting, A. *Tetrahedron Lett.* **2001**, *42*, 8387−8390.

CHART 1. Hammett Plot Resulting from the Reaction Shown in Eq 2 with Ph_3P

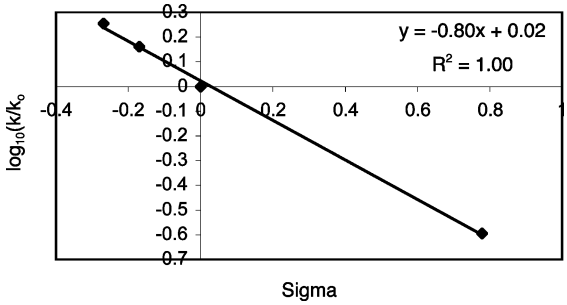


rate determining. Clearly, to exercise control over processes such as the coupling outlined in eq 1, one needs to understand both the nature of the rate determining step and the nature of the probable type of palladium complex involved that determines which mechanism predominates and, hence, which product may be obtained. To this end, a Hammett study of the reaction of boronate ester **9** with a range of four-substituted aryl iodides was undertaken, as outlined in eq 2.



Our standard HM conditions (1.2 equiv of tributylamine, 5 mol % $Pd(OAc)_2$, 15 mol % PPh_3) were investigated, and the reactions were followed by GC-MS. Unfortunately, in the cases of **18a** and **18b**, considerable aryl−aryl exchange between the aryl halide and the phosphine[12] complicated the kinetics, leading to the formation of both the expected product and the unsubstituted styrylboronate **19c**. However, combination of the two product concentrations to give a total product concentration allowed the direct comparison of all six reactions. Using initial rates, the Hammett plot shown in Chart 1 was generated, and the negative correlation indicated that there was formation of some degree of a positive charge in the rate determining step. In an attempt to stabilize any forming positive charge while also reducing the aryl−aryl exchange, the study was repeated using tris(4-methoxyphenyl)phosphine instead of triphenylphosphine. This was initially found to give no reaction with **18f**; however, reducing the amount of phosphine from 15 to 10 mol % was found to give an active catalyst. Instead of reducing the aryl−aryl exchange as hoped (with triphenylphosphine, the exchange was only seen when the aryl group of the iodide was more electron rich than that of the phosphine), the exchange was now seen to some extent in all reactions. Combination of the product concentrations was again employed, and this resulted in the Hammett plot shown in Chart 2.

CHART 2. Hammett Plot Resulting from the Reaction Shown in Eq 2 with $(4\text{-MeOPh})_3P$



The similar, negative Hammett parameters seen for the two reactions suggests that the same rate determining step is involved in both cases. It also appears, from the case using 15 mol % tris(4-methoxyphenyl)phosphine, that an excess of an electron rich phosphine can saturate palladium and render it unreactive. This also implies that the active palladium catalyst contains at most two phosphine ligands, which is entirely consistent with the results of a recent theoretical study that suggested that the active catalytic species in such reactions contained only one phosphine ligand.[13]

Since studies of reactions involving only the oxidative addition step of aryl halides to palladium has been shown to give a positive Hammett parameter,[10f,14] it therefore shows that in the present case, oxidative addition is not rate determining. This is not unexpected, as other studies[15] have also suggested that oxidative addition is not rate limiting for related HM reactions involving aryl iodides. A recent study also showed that the rate determining step in the oxidative addition of iodobenzene to $Pd(dba)L_2$ complexes is the dissociation of dba,[16] proving how facile the oxidative addition can be. Interestingly, a Hammett parameter of −1.6 has been reported to the HM couplings of allylic alcohols with aryl iodides, although the rate determining step in this case is unclear.[17] It is also interesting to note that the Hammett parameters obtained when the olefin component is electronically varied in the HM reaction of

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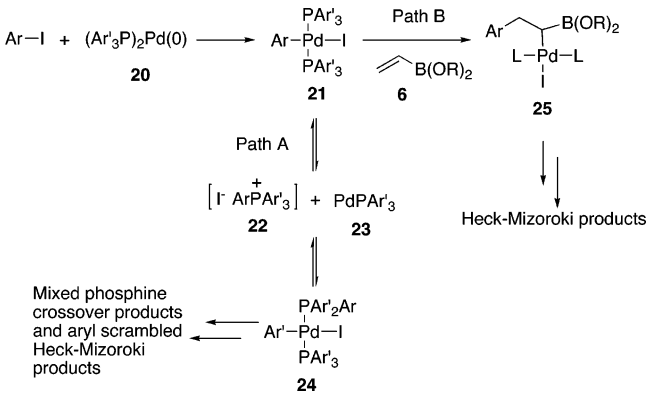
(16) Mace, Y.; Kapdi, A. R.; Fairlamb, I. J. S.; Jutand, A. *Organometallics* **2006**, *25*, 1795−1800.

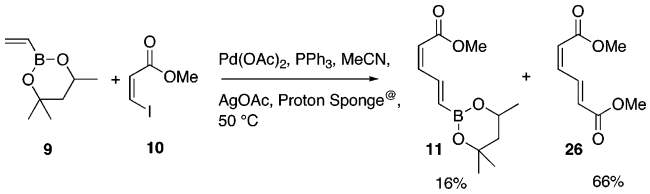
(17) Benhaddou, R.; Czernecki, S.; Ville, G.; Zegar, A. *Organometallics* **1988**, *7*, 2435−2439.

iodobenzene with four-substituted styrenes[18] matches closely with the results reported here. This related study also suggested[18] that the electrophilic attack of palladium on the double bond gave rise to the negative Hammett parameter, although only in the case of α-substitution. In the case of *β*-substitution, the forming positive charge at the non-benzylic position was not stabilized by an electron-donating aryl substituent. In the present case, the observed products are due only to *β*-substitution of the boronate **9** (see Scheme 3, path B, via intermediate **25**), and because the electronically varied group is on the iodide, it is able to stabilize a developing positive charge at the forming benzylic position. Hence, it appears that the rate determining step in the HM coupling of vinylboronate **9** with aryl iodides is the electrophilic attack of palladium on the olefin double bond of vinylboronate **6** after an initial rapid oxidative addition, via **21** to give **25**. Our current view of the HM process involving the vinylboronate ester system with an aryl iodide is outlined in Scheme 3, which also explains the origin of the competing aryl crossover reaction.[12] It should be noted that an equivalent reactive entity to the iodo−palladium(II) complex **25** may also be the corresponding acetate complex resulting from iodide−acetate exchange on complex **21**.[10g]

SCHEME 3. Postulated Mechanism Scheme for the HM versus Aryl Crossover Reaction



Synthetic Approaches to the Viridenomycin Triene Synthon 3. With this piece of mechanistic knowledge in hand, attention was turned to the seemingly intractable HM coupling of vinylboronate ester **9** with iodoacrylate **10**. Since in this case, the forming positive charge would not be at a benzyl but on an allyl position, which would be additionally destabilized by the strong electron-withdrawing ester function (presumably explaining the previous lack of reactivity), it appeared that a polar solvent would be necessary to stabilize the transition state. Since use of standard amine bases was not possible due to reaction with the acrylate[8] and inorganic bases appeared to force the SM reaction,[8,19] *N*,*N*-diethylaniline was used as base [as in eq 1, HM conditions: 5% $Pd(OAc)_2$, 10% P(*p*-MeOPh)$_3$, *N*,*N*-diethylaniline, MeCN, 70 °C] since this had been shown to be unreactive in the Michael addition to acrylate **10**.[8] Although this gave rise to a detectable level of dienylboronate **11** (GC-MS), the conversion was insufficient to allow isolation. In addition, concerns that *N*,*N*-diethylaniline possessed insufficient basicity to effectively regenerate the palladium(0) catalyst led to the investigation of Proton Sponge as the base [as in eq 1, HM conditions: 5% $Pd(OAc)_2$, 10% P(*p*-MeOPh)$_3$, Proton Sponge, MeCN, 70 °C] since this aniline-type base was also ineffective in the Michael addition to acrylate **10**. This improved the level of conversion to the dienylboronate **11**, but again, the product remained impossible to isolate from the crude reaction mixture. Reduction of the reaction temperature from 70 to 50 °C due to concerns over product stability led to the isolation of dienylboronate **11**, but only in 1.6% yield, whereas use of *N*,*N*-diethylaniline under the same conditions proved unsuccessful. Although the SM reaction of boronate **9** with iodide **10** was not competing under these conditions,[8] the addition of silver(I) acetate to the reaction was investigated to try and improve the HM selectivity in these reactions.[2,3] This led to a dramatic increase in the overall conversion, with dienylboronate **11** being isolated in 16% yield; however, the major product was identified as dienyldiester **26** (eq 3).



Nickel catalyzed reductive dimerization of iodide **10** has previously been reported;[20] however, this involved the use of stoichiometric zinc reductant and the isomeric purity of the product was poor, which is characteristic of nickel catalyzed homocouplings.[21] In this case, only silver(I) is present as a potential reductant; however, since the reaction mixture turned purple (presumably due to the generation of elemental iodine), the reaction with silver(I) is either slow or does not contribute to the formation of the observed product **26**. It may be that vinylboronate **9** is responsible for the reduction of any palladium(II) iodide complex that could result from any oxidative addition of iodine to palladium(0).[22] The isomeric purity of the isolated diene **26** was notably high (13:1, *E*,*Z*/*Z*,*Z*; no *E*,*E* detectable), and this stereochemistry suggests that the product is formed in a Michael addition−elimination process, as shown in Scheme 4, with reductive elimination of elemental iodine occurring from the palladium species eliminated from **28** leading to regeneration of the active catalyst.

Although slow addition of iodide **10** to the reaction shown in eq 3 proved to be successful in increasing the ratio of dienes **11** to **26**, the reactions failed to reach completion, and the highest yield of dienylboronate **11** achieved using this method was still only 5%. Increasing the steric bulk around the palladium seemed to be another possibility for reducing the competing Michael addition process; hence, tri(*o*-tolyl)phosphine was investigated due to both its steric bulk and its increased basicity relative to triphenylphosphine. This proved highly successful in preventing

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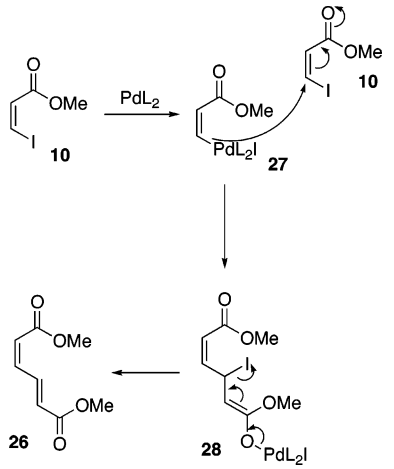
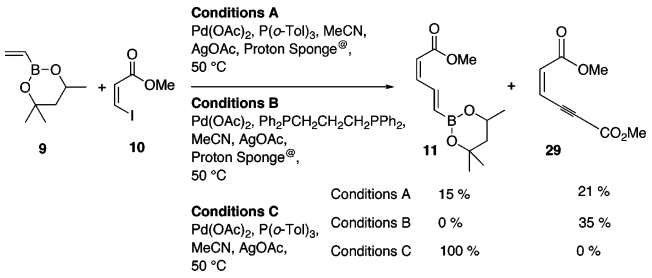
SCHEME 4. Proposed Mechanistic Explanation for the Origin of Diene 26



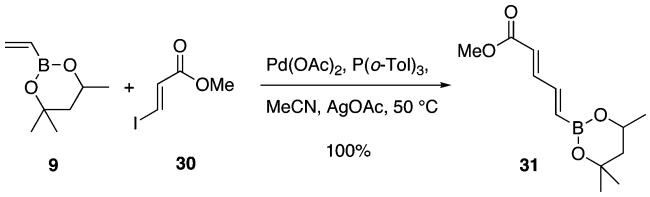
the formation of the unwanted diene **26**; however, a new unwanted byproduct was observed. Purification gave dienylboronate **11** in 15% yield and the new species **29** in 21% yield (eq 4, Conditions A). Given the virtually identical Tolman electronic parameters[23] of tris(4-methoxyphenyl)phosphine and tri(*o*-tolyl)phosphine (2066.1 and 2066.6 cm^{-1}, respectively) this seems to be an entirely steric effect, the bulk around palladium preventing the organometallic intermediate from behaving as a nucleophile in the case of tri(*o*-tolyl)phosphine.



The formation of enyne **29** is assumed to arise from elimination of HI from palladium(II) complex **27** (Scheme 4) to give methyl propiolate, which then undergoes Sonogashira coupling[24] with acrylate **10**, which may well require silver(I) to be present to promote this reaction. It is noteworthy that elimination of HI from acrylate **10** appears to occur only when tri(*o*-tolyl)phosphine is used as the palladium ligand. In addition, the reaction of acrylate **10** with Proton Sponge shows no detectable methyl propiolate generation even over several weeks. It also seems that the presence of vinylboronate **9** is essential for this reaction to occur, possibly acting as a reactant to remove HI from the reaction; in the absence of the boronate **9**, yields of the enyne **29** are low.

Use of 1,3-bis(diphenylphosphino)propane (eq 4, Conditions B) was also investigated as a palladium ligand. This gave a mixture of unreacted acrylate **10**, together with enyne **29**, the desired dienylboronate **11** being virtually undetectable. Since the combination of bidentate phosphine, alkenyl iodide, and silver(I) salt is recognized to promote a cationic reaction pathway,[25] this result is perhaps not surprising since the generation of methyl propiolate results from facile deprotonation of a cationic organo−palladium species [presumably not dissimilar to the palladium(II) complex **27** (Scheme 4)].

In an effort to reduce the elimination of HI in the reaction involving tri(*o*-tolyl)phosphine, as in eq 4, Conditions A, Proton Sponge was removed, and the reaction was run using stoichiometric silver(I) acetate as sole base (eq 4, Conditions C). This not only significantly increased the pH of the reaction but also produced the desired dienylboronate **11** in quantitative yield. The successful Conditions C (eq 4) also work well with the corresponding *E*-iodoacrylate,[26] as in eq 5, producing the all-*trans*-dienylboronate **31** in essentially quantitative yield. It is interesting to note that silver(I) is ideal for both *cis*- and *trans*-iodoalkenes in this case (eqs 4 and 5), which contrasts with earlier findings that suggested that thallium(I) and silver(I) salts were best applied to *cis*- and *trans*-iodoalkenes, respectively; however, the current conditions are vastly improved in terms of efficiency and selectivity.[2]



Thus, with dienylboronate **11** in hand, the iododeboronation reaction was investigated with inversion of the stereochemistry at the boronate double bond[4] being necessary for the formation of dienyl iodide **32** (Scheme 5).

This reaction proved successful, with the light and seemingly heat sensitive dienyl iodide **32** being isolated in 49% yield initially. Samples of dienyl iodide **32** in chloroform were completely degraded after several days of standing; however, larger scale reactions led to an improved 69% yield by using chilled solvent in the chromatographic purification (Scheme 5) and a 94:6 isomeric purity [minor isomer appears to be the (2*E*,4*Z*,6*E*) isomer]. The sensitivity of dienyl iodide **32** meant that it was used immediately in the HM coupling with vinylboronate **9**, and since the potential for Michael addition was still present, the amine-free HM conditions (vide supra) were again utilized. This gave trienylboronate **33** in 81% yield as a major stereoisomer (i.e., 90:10 isomeric purity), with the minor isomer appearing to be the (2*E*,4*Z*,6*E*) isomer carried over from dienyliodide **32**. This was then exposed to the iododeboronation reaction, this time with retention of the alkenylboronate geometry, which gratifyingly provided trienyl

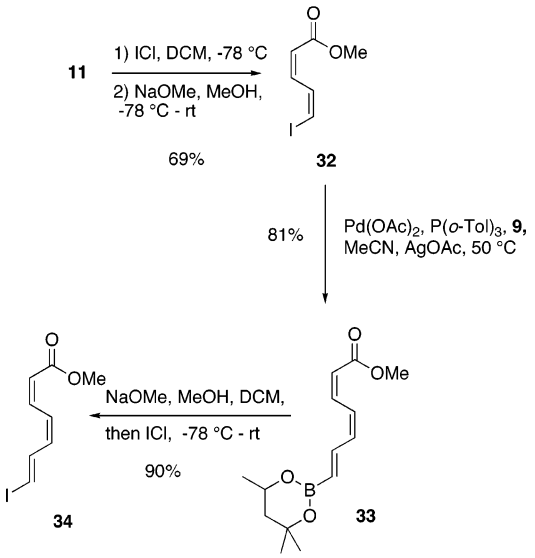
(23) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313−348.

(24) (a) Although it is known that Sonogashira reactions involving alkynes bearing electron-withdrawing groups can be problematic (see ref 23b), we have found that the coupling of methyl propiolate and **10** can be performed in reasonable yield (see Experimental Section). (b) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, 1979−2018.

(25) (a) Moritani, I.; Fujiwara, Y.; Danno, S. *J. Organomet. Chem.* **1971**, *27*, 279−282. (b) Stang, P. J.; Kowalski, M. H.; Schiavelli, M. D.; Longford, D. *J. Am. Chem. Soc.* **1989**, *111*, 3347−3356. (c) Stang, P. J.; Kowalski, M. H. *J. Am. Chem. Soc.* **1989**, *111*, 3356−3362. (d) Hinkle, R. J.; Stang, P. J.; Kowalski, M. H. *J. Org. Chem.* **1990**, *55*, 5033−5036. (e) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417−1419. (f) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481−1486. (g) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1992**, *57*, 3558−3563. (h) Portnoy, M.; Ben-David, Y.; Milstein, D.; *Organometallics* **1994**, *13*, 3465−3479.

(26) Methyl *E*-iodoacrylate is prepared from the corresponding *Z*-iodoacrylic acid by an HI-mediated isomerization−methylation sequence (see Experimental Section), which needs to be carried out under carefully controlled conditions, otherwise 3,3-diiodopropionic acid is produced (see single-crystal X-ray structure, Figure 1, ESI).

SCHEME 5. Conversion of Dienylboronate 11 to Trienyl Iodide 34



iodide **34** in 90% yield with high stereochemical purity (90:10 isomeric purity [minor isomer again appears to be the (2*E*,4*Z*,6*E*) isomer]).

Conclusion

Although it is difficult to be sure of the latter parts of the HM reaction mechanism involving aryl iodides and a hindered vinylboronate ester, it is clear that the rate determining step is not oxidative addition. Indeed, there is a need for a more detailed kinetic study to determine actual reaction orders and hence reveal the mechanism operating in such systems. However, with knowledge that oxidative addition is not rate determining at hand, it is possible to make suitable choices about catalyst, ligand, and reaction conditions, which provide the required control in subsequent coupling reactions involving systems that formerly did not produce any of the desired HM products. Hence, it becomes possible to use iodoacrylates for HM reactions to develop an approach toward carboxylate-substituted polyenes, such as that required for an attempted synthesis of viridenomycin **1**. Thus, this approach can be usefully employed for the synthesis of building block **34**, which is required for the northern tetraene section of viridenomycin **1**. This has been achieved in a promising overall 50% yield from methyl propiolate. In the process, new conditions for the selective HM coupling of vinyl iodides with vinylboronates have been developed. These conditions are not only of potential use for the further application of vinylboronates as vinyl dianion equivalents in synthesis but have also provided further insight into the HM coupling of seemingly low reactivity vinylboronate esters.

Experimental Section

Synthesis of 4,4,6-Trimethyl-2-[(*E*)-2-(4-chlorophenyl)ethenyl]-1,3,2-dioxaborinane 19e. To a dried Schlenk tube under a positive pressure of argon was added $Pd(OAc)_2$ (19 mg, 0.085 mmol), PPh_3 (63 mg, 0.24 mmol), 4-iodo-chlorobenzene (390 mg, 1.64 mmol), and AgOAc (308 mg, 1.85 mmol). Syringe addition of toluene (20 mL), $^nBu_3N$ (0.46 mL, 1.9 mmol), and vinylboronate[26] **9** (300 mg, 1.95 mmol) was followed by degassing using the freeze−pump−thaw method (3×), and the stirred mixture was heated to 110 °C. After 24 h, the reaction mixture was cooled, diluted with Et_2O (80 mL), and passed through Celite before washing with 10% HCl (40 mL), water (40 mL), and saturated aqueous sodium chloride (40 mL). Drying ($MgSO_4$) and solvent removal provided the crude product as a yellow oil that was purified by silica gel chromatography (hexane/Et_2O, 96:4 as eluent) to afford styrylboronate 1**9e** (376 mg, 87%) as a clear oil. ν_{max}/cm^{-1} (film): 1623 (m), 1490 (m), 1391 (vs), 1303 (vs), 1270 (vs), 1206 (vs), 1160 (vs), 1090 (vs); UV ($CHCl_3$, nm): 216 (ϵ 7990), 232 (ϵ 6380), 272 (ϵ 15700); δ_H (400 MHz, $CDCl_3$) 1.31 (d, J = 6.0 Hz, 3H), 1.34 (s, 6H), 1.56 (t, J = 6.0 Hz, 1H), 1.83 (dd, J = 13.8 and 3.2 Hz, 1H), 4.22−4.32 (m, 1H), 6.07 (d, J = 18.0 Hz, 1H) 7.20−7.30 (m, 3H), 7.40 (d, J = 8.4 Hz, 2H); δ_C (101 MHz, $CDCl_3$) 23.3, 28.3, 31.4, 46.1, 65.1, 71.1, 128.3, 128.8, 134.1, 136.6, 145.2; δ_B (128 MHz, $CDCl_3$) 26.8; *m*/*z* (EI^+) 264.1084 (M^+, $C_{14}H_{18}BO_2Cl^+$ 264.1083), 266, 251, 249, 164 (100%).

4,4,6-Trimethyl-2-[(*E*)-2-(4-fluorophenyl)ethenyl]-1,3,2-dioxaborinane 19d. To a dried Schlenk tube under a positive pressure of argon was added $Pd(OAc)_2$ (19 mg, 0.085 mmol), tri(2-furyl)-phosphine (58 mg, 0.25 mmol), 4-iodo-fluorobenzene (0.184 cm^3, 1.6 mmol), $^nBu_3N$ (0.46 mL, 1.9 mmol), and vinylboronate[27] **9** (300 mg, 1.95 mmol). Syringe addition of toluene (20 mL) was followed by degassing using the freeze−pump−thaw method (3×), and the stirred mixture was heated to 110 °C. After 24 h, the reaction mixture was cooled, diluted with Et_2O (80 mL), and passed through Celite before washing with 10% HCl (40 mL), water (40 mL), and saturated aqueous sodium chloride (40 mL). Drying ($MgSO_4$) and solvent removal provided the crude product as a red−brown oil that was purified by silica gel chromatography (hexane/Et_2O, 96:4 as eluent) to afford **19d** (210 mg, 53%) as a pale yellow oil. IR (film, cm^{-1}): 1625 (m), 1599 (m), 1505 (m), 1389 (vs), 1304 (vs), (C−B) 1269 (vs), 1205 (vs), 1156 (vs), 1093 (m). UV ($CHCl_3$, nm): 203 (ϵ 6000), 228 (ϵ 6030), 264 (ϵ 8810); δ_H (400 MHz, $CDCl_3$) 1.31 (d, *J* 6.0, 3H), 1.34 (s, 6H), 1.57 (t, *J* 6.0, 1H), 1.83 (dd, *J* 13.8 and 3.2, 1H), 4.22−4.32 (m, 1H), 6.07 (dd, *J* 18.2 and 0.8, 1H) 6.96−7.15 (m, 2H), 7.25 (d, *J* 18.4, 1H), 7.41−7.44 (m, 2H). δ_C (101 MHz, $CDCl_3$) 23.3, 28.3, 31.4, 46.1, 65.0, 71.1, 115.6 (d, J_{C-F} 22), 128.7 (d, J_{C-F} 7.9), 134.3 (d, J_{C-F} 3.4), 145.3, 161.7, 164.2; δ_F (376 MHz, $CDCl_3$) −113.9 (m); δ_B (128 MHz, $CDCl_3$) 26.4 (br); *m*/*z* (EI^+) 248.1378 (M^+, $C_{14}H_{18}BO_2F^+$ 248.1378), 233, 148 (100%).

Methyl 3-*Z*-Iodoacrylate[28] 10. A stirred solution of methyl propiolate (5.3 mL, 59.6 mmol) and sodium iodide (14.4 g, 96 mmol) in acetic acid (22 mL) under argon was heated to 115 °C. After 1 h, the hot mixture was poured onto water (100 mL), extracted with Et_2O (3 × 100 mL), washed with saturated aq $NaHCO_3$ (4 × 50 mL), saturated aq sodium metabisulphate (50 mL), and brine (50 mL), dried ($MgSO_4$), and evaporated to give **10** as a yellow oil (12.49 g, 99%). All spectral and analytical properties were as reported.[28]

(2*Z*,4*E*)-Hexa-2,4-dienoic Acid Dimethyl Ester 26. To a dried Schlenk tube under a positive pressure of argon was added AgOAc (140 mg, 0.84 mmol), $Pd(OAc)_2$ (9 mg, 0.040 mmol), tris(4-methoxyphenyl)phosphine (27.5 mg, 0.078 mmol), and dry MeCN (5 mL). The mixture was degassed using the freeze−pump−thaw method (1×), and Proton Sponge (200 mg, 0.93 mmol), vinylboronate[27] **9** (0.16 mL, 0.95 mmol), and **10** (0.090 mL, 0.80 mmol) were added. The mixture was degassed using the freeze−pump−thaw method (2×) and heated to 50 °C. After 21 h, the mixture was cooled, diluted with Et_2O (60 mL), passed through Celite, washed with 5% HCl (20 mL) and brine (20 mL), dried ($MgSO_4$), concentrated, and purified by silica gel chromatography (EtOAc/petroleum ether, 1:9 as eluent) to give **11** (28 mg, 16%) as a clear

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(28) Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. *Can. J. Chem.* **1994**, *72*, 1816−1819.

oil and **26** (45 mg, 66%) as a white solid. Mp 72.4−73.2 °C (lit.[29] 72−73 °C). All spectral properties were identical to those reported in the literature.[29]

***Z*-Hex-2-en-4-ynedioic Acid Dimethyl Ester 29. Conditions A.** To a dried Schlenk tube under a positive pressure of argon was added silver(I) acetate (140 mg, 0.84 mmol), $Pd(OAc)_2$ (9 mg, 0.040 mmol), tri(*o*-tolyl)phosphine (24.5 mg, 0.081 mmol), and dry MeCN (5 mL). The mixture was degassed using the freeze−pump−thaw method (2×), and Proton Sponge (198 mg, 0.92 mmol), vinylboronate[27] **9** (0.160 mL, 0.95 mmol), and **10** (0.090 mL, 0.80 mmol) were added. The mixture was degassed using the freeze−pump−thaw method (3×), and the stirred mixture was heated to 50 °C. After 26 h, the mixture was cooled, diluted with Et_2O (60 mL), passed through Celite, washed with 5% HCl (20 mL), water (20 mL) and brine (20 mL), dried ($MgSO_4$), and evaporated to give a brown oil. Purification by silica gel chromatography (gradient elution, EtOAc/petroleum ether, 5:95 to 20:80 as eluent) gave **11** (28 mg, 15%) as a pale yellow oil and **29** (14 mg, 21%) as a pale yellow oil; **29**: ν_{max}/cm^{-1} (film) 2950 (w), 2160 (w), 1710 (vs), 1434 (m), 1260 (s), 1220 (s), 1180 (s), 1070 (m); δ_H ($CDCl_3$, 400 MHz) 3.80 (3H, s), 3.83 (3H, s), 6.21 (1H, d, *J* 11.6), 6.35 (1H, d, *J* 11.6); δ_C ($CDCl_3$, 101 MHz) 52.1, 53.1, 81.6, 89.9, 119.9, 133.4, 153.9, 164.3; *m*/*z* (EI^+) 168.0417 (M^+, $C_8H_8O_4^+$ 168.0417) and 153 (100%, M − Me^+).

Conditions B. To a dried Schlenk tube under a positive pressure of argon was added silver(I) acetate (280 mg, 1.68 mmol), $Pd(OAc)_2$ (18 mg, 0.080 mmol), 1,3-bis(diphenylphosphino)propane (33 mg, 0.081 mmol), and dry MeCN (10 mL). The mixture was degassed using the freeze−pump−thaw method (2×), and Proton Sponge (400 mg, 0.92 mmol), vinylboronate[27] **9** (0.080 mL, 0.48 mmol), and **10** (0.180 mL, 1.60 mmol) were added. The mixture was degassed using the freeze−pump−thaw method (2×), and the stirred mixture was heated to 50 °C. After 26 h, the mixture was cooled, diluted with Et_2O (80 mL), passed through Celite, washed with 5% HCl (40 mL), water (40 mL), and brine (40 mL), dried ($MgSO_4$), and evaporated to give a brown oil. Purification by silica gel chromatography (gradient elution, EtOAc/petroleum ether, 10:90 to 100:0) yielded **29** (39 mg, 28%) as a pale yellow oil.

Sonogashira Method. To a dried Schlenk tube under a positive pressure of argon was added K_2CO_3 (290 mg, 2.1 mmol), $Pd(OAc)_2$ (16 mg, 0.071 mmol), triphenylphosphine (38 mg, 0.055 mmol), copper(I) iodide (28 mg, 0.15 mmol), and dry DMF (10 mL). The mixture was degassed using the freeze−pump−thaw method (2×), methylpropiolate (0.17 mL, 1.9 mmol) and **10** (348 mg, 1.6 mmol) were added, followed by a further degassing (3×) and heating to 50 °C. After 5 h, the mixture was cooled, diluted with Et_2O (80 mL), passed through Celite, and washed with 5% HCl (20 mL), water (40 mL), and brine (40 mL), dried ($MgSO_4$), and evaporated to give the crude product as a brown oil. Purification by silica gel chromatography (EtOAc/petroleum ether, 1:9 to 1:4 as eluent) gave **29** (85 mg, 32%) as a pale yellow oil. All spectroscopic and analytical properties were identical to those reported previously.

(2*Z*,4*E*)-5-(4,4,6-Trimethyl-[1,3,2-dioxaborinan-2-yl])-penta-2,4-dienoic Acid Methyl Ester 11. To a dried Schlenk tube under a positive pressure of argon was added silver(I) acetate (150 mg, 0.90 mmol), $Pd(OAc)_2$ (9 mg, 0.040 mmol), tri(*o*-tolyl)phosphine (25 mg, 0.082 mmol), and dry MeCN (5 mL). The mixture degassed using the freeze−pump−thaw method (2×), and vinylboronate[27] **9** (0.16 mL, 0.95 mmol) and **10** (175 mg, 0.83 mmol) were added, and then the mixture was degassed using the freeze−pump−thaw method (2×) and heated to 50 °C with vigorous stirring. After 23 h, the mixture was cooled, diluted with Et_2O (70 mL), passed through Celtite, washed with 5% HCl (10 mL), water (20 mL), and brine (20 mL), dried ($MgSO_4$), and evaporated to give crude product as a yellow oil. Purification by silica gel chromatography (EtOAc/petroleum ether, 1:9 as eluent) gave **11** (197 mg, 100%) as a pale yellow oil in >99:1 isomeric purity; ν_{max}/cm^{-1} (film) 2980 (weak, various C−H), 1720 (s, C═O), 1590 (s, C═C), 1390 (s), 1300 (vs), 1270 (s), 1200 (vs), 1160 (vs), 1020 (s); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6), 1.30 (3H, s), 1.31 (3H, s), 1.48−1.55 (m, 1H), 1.78−1.82 (1H, m), 3.74 (3H, s), 4.19−4.28 (1H, m), 5.71 (1H, d, *J* 11), 5.83 (1H, d, *J* 17.5), 6.59 (1H, dt, *J* 11, 1), 8.04 (1H, ddd, *J* 17.5, 11, 1); δ_C (101 MHz, $CDCl_3$) 23.2 (CH*Me*), 28.3, 31.3, 46.1, 51.4, 65.1, 71.2, 118.8, 125.9, 141.4, 146.5, 166.6; δ_B (128 MHz, $CDCl_3$) 26.0; *m*/*z* (CI^+) 256 (M + NH_4^+, 100%), 239, 162, 136; HRMS (ES^+) 256.1717 ($C_{12}H_{23}NBO_4^+$, M + NH_4^+ 256.1715).

***Z*-Iodoacrylic Acid.**[28,30] A stirred mixture of acetic acid (22 mL), propiolic acid (3.7 mL, 60 mmol), and sodium iodide (14.3 g, 95 mmol) was heated to 115 °C under Ar. After 90 h, the hot mixture was poured onto water (150 mL), extracted with Et_2O (100 mL), separated, and re-extracted with Et_2O (2 × 50 mL), and the combined organic phase was washed with saturated aqueous $Na_2S_2O_3$ (75 mL) and brine (75 mL) and dried ($MgSO_4$). Evaporation gave *Z*-iodoacrylic acid[28,30] as a pale yellow solid (9.76 g, 82%). Mp 64−66 °C (lit.[28] 62−64 °C). All spectral properties were identical to those reported in the literature.[28]

3,3-Diiodopropanoic Acid.[31] *Z*-Iodoacrylic acid (4.00 g, 20.2 mmol) was dissolved in 57% aqueous HI (5.3 mL, 40 mmol), and the stirred mixture was heated to 90 °C under argon. After 24 h, the mixture was cooled, diluted with 5% HCl (50 mL) and Et_2O (50 mL), separated, and re-extracted with Et_2O (4 × 25 mL), and the combined organic phases were washed with saturated aq $Na_2S_2O_3$ (10 mL) and brine (10 mL) and dried ($MgSO_4$), and evaporation gave the crude product as an orange solid. Recrystallization from DCM/hexane gave a white crystalline solid (3.87 g). Further purification by repeated crystallization from DCM/hexane (4×) gave 3,3-diiodopropanoic acid (0.879 g, 18%) as a white crystalline solid. Mp 85.0−86.1 °C (lit.[31] 87 °C) δ_H (500 MHz, $CDCl_3$) 3.80 (2H, d, *J* 7) and 5.24 (1H, t, *J* 7); δ_C (126 MHz, $CDCl_3$) −45.8, 53.0, 175.2; ν_{max}/cm^{-1} (neat) 3000 (broad, acid O−H), 1690 (vs), 1430 (s), 1320, 1250 (s), 1140; *m*/*z* (EI^+) 325.8291 (M^+, $C_3H_4I_2O_2^+$ 325.8295), 199, 127 (100%), 71. $C_3H_2I_2O_2$ C, 11.06; H, 1.24; found C, 10.89; H, 1.22%.

The structure was characterized by a single-crystal X-ray diffraction study, using a Siemens SMART 1K CCD area detector, graphite-monochromated Mo Kα radiation ($\bar{\lambda}$ = 0.71073 Å) and SHELXTL 6.14 programs.[33] Crystal data: $C_3H_4I_2O_2$, *M* = 325.86, *T* = 130 K, monoclinic, space group $P2_1/c$ (No. 14), *a* = 12.724(2) Å, *b* = 6.5787(9) Å, *c* = 8.808(1) Å, α = 102.61(1)°, *U* = 719.5(2) Å,^{3} *Z* = 4, D_c = 3.008 g cm^{-3}, μ = 8.65 mm^{-1}, 8140 reflections with $2\theta \leq 58°$, absorption correction by numerical integration (transmission max. 0.6394, min. 0.3387, R_{int} = 8.0% before and 2.6% after correction), final R(*F*) = 1.8% on 1739 data with $I \geq 2\sigma(I)$, wR(F^2) = 4.5% on all 1898 unique data. Crystallographic file in CIF format is available as Supporting Information.

***E*-Iodoacrylic Acid.**[32] *Z*-Iodoacrylic acid (3.10 g, 15.7 mmol) was added to a solution of 57% aqueous HI (0.300 mL, 2.3 mmol) in benzene (8 mL), and the stirred mixture was heated to 80 °C under argon. After 18 h, the mixture was cooled, diluted with Et_2O (40 mL) and water (1.5 mL), and re-extracted with Et_2O (20 mL), and the combined organic phase was washed with dilute aqueous $Na_2S_2O_3$ (10 mL) and dried ($MgSO_4$), and the solvent evaporated to give the crude product, which was washed with hexane (100 mL) to give *E*-iodoacrylic acid[30] (2.76 g, 89%) as a white crystalline solid: Mp. 142−144 °C (lit.[32] 140−141 °C). All spectral properties were identical to those reported in the literature.[32]

(29) Martin, M.-E.; Planchenault, D.; Huetl, F. *Tetrahedron* **1995**, *51*, 4985−4990.

(30) Jung, M. E.; Hagenah, J. A.; Long-Mei, Z. *Tetrahedron Lett.* **1983**, *24*, 3973−3974.

(31) (a) Masuda, E.; Nishida, K. *J. Pharm. Soc. Jpn.* **1934**, *54*, 1091−1100. (b) Ibid, *Chem. Abstr.* **1935**, *29*, 3305.

(32) Takeuchi, R.; Tanabe, K.; Tanaka, S. *J. Org. Chem.* **2000**, *65*, 1558−1561.

(33) SHELXTL 6.14; Bruker AXS: Madison, WI, 2003.

Methyl *E*-Iodoacrylate 30. *E*-Iodoacrylic acid (671 mg, 3.39 mmol) was dissolved in MeOH (8 mL), H_2SO_4 (0.205 mL, 3.69 mmol) was added, and the stirred mixture was heated to 85 °C under argon. After 4.25 h, the mixture was cooled, evaporated, and redissolved in a mixture of Et_2O and chloroform (150 mL, 4:1, respectively). Washing with water (40 mL), 5% aq sodium metabisulphite (40 mL), saturated aq $NaHCO_3$ (40 mL) and brine (40 mL), drying ($MgSO_4$), and evaporation gave **30** (532 mg, 74%) as a pale yellow solid; Mp 41−44 °C; δ_H (500 MHz, $CDCl_3$) 3.75 (3H, s), 6.88 (1H, d, *J* 15), 7.89 (1H, d, *J* 15); δ_C (126 MHz, $CDCl_3$) 52.1, 99.8, 136.3, 164.8; ν_{max}/cm^{-1} (neat) 2900 (w), 1721 (vs), 1589 (s), 1434 (s), 1350 (s), 1262 (s), 1216 (s); *m*/*z* (EI^+) 211.9327 (M^+, $C_4H_5IO_2^+$ 211.9329), 181, 153, 127, 85 (100%).

(2*E*,4*E*)-5-(4,4,6-Trimethyl-[1,3,2-dioxaborinan-2-yl])-penta-2,4-dienoic Acid Methyl Ester 31. To a dried Schlenk tube under a positive pressure of argon was added silver(I) acetate (430 mg, 2.58 mmol), $Pd(OAc)_2$ (26 mg, 0.12 mmol), tri(*o*-tolyl)phosphine (70 mg, 0.23 mmol), and a solution of methyl *E*-iodoacrylate **30** (500 mg, 2.36 mmol) in dry MeCN (14.5 mL). The mixture was degassed using the freeze−pump−thaw method (2×), vinylboronate[27] **9** (0.46 mL, 2.76 mmol) was added, and the mixture was degassed using the freeze−pump−thaw method (1×) and heated to 50 °C with vigorous stirring. After 22 h, the mixture was cooled, diluted with Et_2O (80 mL), passed through Celite, and washed with 5% HCl (20 mL), water (40 mL), and brine (40 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow oil. Purification by silica gel chromatography (EtOAc/petroleum ether, 1:9 as eluent) gave product **31** (560 mg, 100%) as a pale yellow oil in >99:1 isomeric purity; ν_{max}/cm^{-1} (film) 2980 (w, C−H), 1710 (s, C═O), 1600 (s, C═C), 1425 (w), 1395 (s), 1305 (s), 1245 (vs), 1155 (vs), 1120 (s), 1010 (s); δ_H (500 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6), 1.30 (3H, s), 1.31 (3H, s), 1.48−1.55 (m, 1H, CH*H*), 1.78−1.82 (1H, m), 3.74 (3H, s), 4.19−4.28 (1H, m), 5.91 (1H, d, *J* 17.5), 5.96 (1H, d, *J* 15), 6.96 (1H, dd, *J* 17.5, 11), 7.27 (1H, dd, *J* 15, 11); δ_C (126 MHz, $CDCl_3$) 23.2, 28.2, 31.3, 46.0, 51.8, 65.1, 71.3, 122.8, 143.5, 146.2, 167.6; δ_B (128 MHz, $CDCl_3$) 26; *m*/*z* (CI^+) 256 (M + NH_4^+, 100%), 239, 162, 136; HRMS (ES^+) 256.1717 ($C_{12}H_{23}NBO_4^+$, M + NH_4^+ 256.1715).

(2*Z*,4*Z*)-5-Iodo-penta-2,4-dienoic Acid Methyl Ester 32. A solution of **11** (385 mg, 1.46 mmol) in dry DCM (10 mL) was degassed using the freeze−pump−thaw method (3×) and cooled to −78 °C under argon. Iodine monochloride (1.9 mL of a 1.0 M solution in DCM, 1.9 mmol) was added dropwise, the mixture stirred for 4 h, NaOMe (3.8 mL of a 0.5 M solution in MeOH, 1.9 mmol) was added dropwise, and the mixture was allowed to warm to room temperature. After 30 min, the mixture was diluted with Et_2O (80 mL), washed with 5% aq sodium metabisulphite (40 mL), water (40 mL), and brine (40 mL), dried ($MgSO_4$), and evaporated to give the crude product as a yellow oil. Purification by silica gel chromatography (EtOAc/petroleum ether, 5:95 as eluent, cooled to 0 °C) gave **32** (267 mg, 69%) as a yellow oil in 94:6 isomeric purity [minor isomer appears to be the (2*E*,4*Z*) isomer]; ν_{max}/cm^{-1} (film) 3030 (w, C−H), 2950 (w), 1710 (vs), 1620 (s), 1430 (m), 1400 (m), 1280 (m), 1200 (vs), 1160 (vs), 1050 (m); δ_H ($CDCl_3$, 500 MHz) 3.75 (3H, s), 5.91 (1H, dt, *J* 11 and 1), 6.74 (1H, ddd, *J* 11, 8, 1), 6.86 (1H, dt, *J* 8, 1), 8.02 (1H, ddd, *J* 11, 8, 1); δ_C ($CDCl_3$, 126 MHz) 51.5, 94.0, 121.2, 134.6, 143.0, 166.2; *m*/*z* (EI^+) 238 (M^+), 207, 179, 127, 111; HRMS (ES^+) 260.9385 ($C_6H_7O_2INa^+$, M + Na^+ 260.9383).

(2*Z*,4*Z*,6*E*)-7-(4,4,6-Trimethyl-[1,3,2-dioxaborinan-2-yl)-hepta-2,4,6-trienoic Acid Methyl Ester 33. To a dried Schlenk tube under a positive pressure of argon was added silver(I) acetate (190 mg, 1.14 mmol), $Pd(OAc)_2$ (11.5 mg, 0.051 mmol), tri(*o*-tolyl)phosphine (31 mg, 0.10 mmol), and a solution of **33** (250 mg, 1.05 mmol) in dry MeCN (6 mL). The mixture was degassed using the freeze−pump−thaw method (2×), **9** (0.20 mL, 1.2 mmol) was added, and the mixture was further degassed (2×) and heated to 50 °C with vigorous stirring. After 21 h, the mixture was cooled, diluted with Et_2O (80 mL), washed with 5% HCl (20 mL), water (40 mL), and brine (40 mL), dried ($MgSO_4$), and evaporated to give the crude product as an orange oil. Purification by silica gel chromatography (EtOAc/petroleum ether, 1:9 as eluent) gave **33** (225 mg, 81%) as a viscous pale yellow oil in 90:10 isomeric purity [minor isomer appears be to the (2*E*,4*Z*,6*E*) isomer]; ν_{max}/cm^{-1} (film) 2970 (w), 1720 (s), 1610 (s), 1440 (m), 1390 (m), 1290 (s), 1160 (vs), 1020 (m); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6), 1.30 (3H, s), 1.31 (3H, s), 1.48−1.55 (m, 1H), 1.80 (1H, dd, J 11.2, 3.2, CHH), 3.73 (3H, s), 4.20−4.28 (1H, m), 5.66−5.78 (2H, m), 6.39 (1H, t, *J* 10), 7.19−7.25 (1H, m), 7.32 (1H, m), 7.44 (1H, dd, *J* 17, 11); δ_C (101 MHz, $CDCl_3$) 23.3, 28.3, 31.4, 46.2, 51.3, 65.1, 71.2 (*C*Me_2), 118.1, 126.0, 138.9, 139.3, 139.7, 166.9; δ_B (128 MHz, $CDCl_3$) 26 (brs); *m*/*z* (EI^+) 264 (M^+), 164, 106 (100%), 83; HRMS (ES^+) 287.1428 (M + Na^+, $C_{14}H_{21}BO_4Na^+$ 287.1425).

(2*Z*,4*Z*,6*E*)-7-Iodo-hepta-2,4,6-trienoic Acid Methyl Ester 34. A solution of **33** (233 mg, 0.87 mmol) in dry THF (5 mL) was cooled to −78 °C under argon in the absence of light. NaOMe (2.1 mL of a 0.5 M solution in MeOH, 1.05 mmol) was added dropwise, the mixture was stirred for 30 min, and iodine monochloride (0.90 mL of a 1.0 M solution in DCM, 0.90 mmol) was added dropwise. The mixture was stirred for 1 h, warmed to room temperature, diluted with Et_2O (60 mL), and washed with 5% aq sodium metabisulphite (30 mL), water (30 mL), and brine (30 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow oil that was immediately purified by silica gel chromatography (EtOAc/petroleum ether, 5:95 as eluent, cooled to 0 °C) to give **34** (209 mg, 90%) as a pale yellow oil in 90:10 isomeric purity [minor isomer appears to be the (2*E*,4*Z*,6*E*) isomer]; ν_{max}/cm^{-1} (film) 3050 (w, C−H), 2950 (w), 1710 (vs), 1610 (s), 1540 (s), 1440 (m), 1290 (w), 1230 (m), 1200 (vs), 1160 (vs), 1020 (w); δ_H (500 MHz, $CDCl_3$) 3.74 (3H, s), 5.81 (1H, d, *J* 11.5), 6.24 (1H, t, *J* 11.5), 6.68 (1H, d, *J* 14), 7.02 (1H, t, *J* 11.5), 7.30 (1H, t, *J* 11.5), 7.58 (1H, dd, *J* 14, 11.5); δ_C (126 MHz, $CDCl_3$) 51.5, 85.8, 119.1, 124.3, 135.8, 137.9, 139.9, 166.9; *m*/*z* (CI^+) 264.9721 ($C_8H_{10}IO_2^+$, MH^+ 264.9720), 252, 239, 156, 139.

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Supporting Information Available: General experimental methods, all kinetic data and analyses, ^1H and ^{13}C NMR spectra for compounds **19e**, **19d**, **29**, **11**, **30**, **31**, **32**, **33**, and **34**, ^{19}F NMR spectrum for **19d**, and crystallographic data for 3,3-diiodopropanoic acid. This material is available free of charge via the Internet at http://pubs.acs.org.

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