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Highly Stereoselective Palladium Catalysed Cross-Coupling Approaches to the Total Synthesis of Phthoxazolin A

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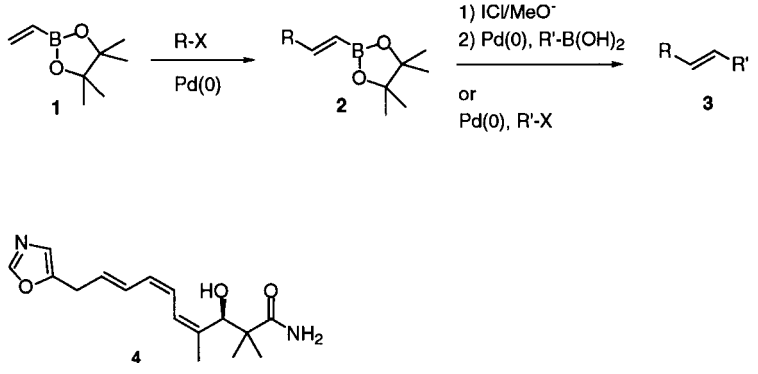
Abstract—The first total synthesis of racemic Phthoxazolin A **4** is described, involving a convergent series of palladium cross-coupling reactions to stereoselectively construct the *Z,Z,E*-trienyl unit. The most important steps involve using vinylboronate pinacol ester **1** as a vinyl dianion equivalent, by employing a Heck coupling of a vinyl iodide **9** with the vinyl boronate **1**, followed by a deboronation–iodination sequence with inversion of alkene stereochemistry to provide a new alkenyl iodide **6**. Final Stille coupling of the vinyl iodide **6** with an oxazolyl alkenyl stannane **40** provided Phthoxazolin A **4**.

Introduction

Conjugated polyenic sub-structures are contained in numerous natural compounds of biological interest, such as modified arachidonic acids and their derivatives,[1] retinoids[2] or macrolide antibiotics[3] and in materials having non-linear optical properties[4] or high conductivity.[5] In order to rapidly build such structures, we have developed a particularly efficient method for the synthesis of polyenes which involves successive use of Heck and Suzuki reactions,[6] in which vinylboronate ester **1** can undergo Heck reactions, with retention of the boronate ester function.[7] In turn, the boronate functionality of the product **2** can take part in subsequent Suzuki cross-coupling reactions to construct polyenes, if R′ is an alkene (Scheme 1). In addition, vinylboronates **2** can be used as precursors of alkenyl iodides, with either retention or inversion of stereochemistry and again be applied in Suzuki coupling reactions.[8] Overall, vinylboronate **1** can be used as a vinyl dianion equivalent to rapidly build up stereodefined polyene systems.

In order to exemplify the application of this methodology and to further develop the coupling protocols, we have studied the synthesis of Phthoxazolin A **4**. Phthoxazolin A **4** was discovered by Omura et al.,[9] and shows potent herbicidal activity against radish seedlings and velvet leaf in pre- and post-emergence treatments. This, in conjunction with its low cytotoxicity to animal cells,[10] makes Phthoxazolin A a potent and attractive herbicide. Phthoxazolin A **4** was chosen as a target molecule to test the reliability of the use of vinylboronate ester **1** as a highly stereoselective



Scheme 1.

Keywords: Phthoxazolin A; Heck and Stille couplings.

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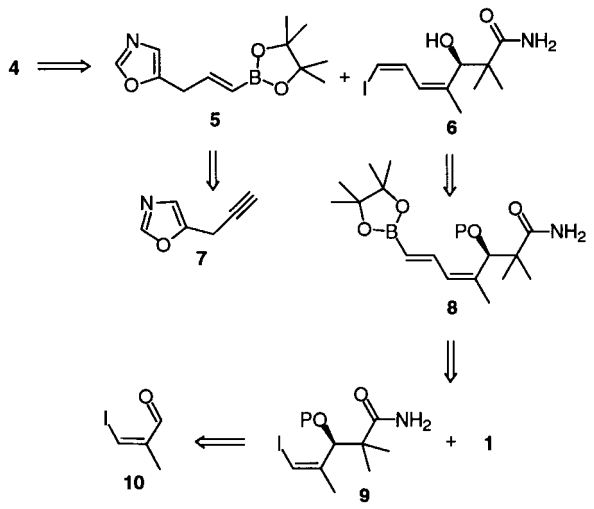


Scheme 2.

vinyl dianion equivalent and, because of the *Z*,*Z*,*E*-triene moiety, is well suited for the demonstration of this methodology. In this paper, we report the full details[11] of the successful application of this chemistry for the total synthesis of racemic Phthoxazolin A **4**.

Results and Discussion

Scheme 2 illustrates a retrosynthetic analysis of Phthoxazolin A **4**, in which the conjugated triene moiety is assembled in a stereoselective manner via two consecutive coupling reactions. Vinyl iodide fragment **9** (available from an aldehyde **10**, via an aldol reaction) could undergo a Heck coupling reaction with vinylboronate ester **1** to stereoselectively generate the *E*,*Z*-dienylboronate **8**. This boronate **8**, on treatment with iodine monochloride, followed by methanolic sodium methoxide, would be transformed into the *Z*-vinyl iodide **6**, a compound now capable of undergoing further coupling reactions with vinylboronate esters. Phthoxazolin A **4** could then be accessed by a Suzuki reaction of **6** with vinylboronate **5**.

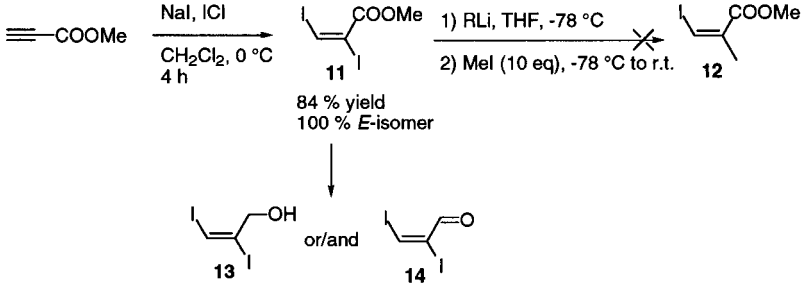
There is no precedent for the preparation of the aldehyde **10**, despite the *E*-isomer (*E*-3-iodo-2-methylprop-2-enal) being known.[12] However, a convenient approach would be the regiospecific introduction of a methyl group into diiodide **11**, using a lithium-halogen exchange procedure, followed by quenching the reaction mixture with methyl iodide to access **12**. Therefore, *E*-2,3-diiodoacrylic acid methyl ester **11** was prepared from methyl propiolate by stereoselective addition of diiodine using iodine monochloride and sodium iodide (Scheme 3).[13] However, attempts to transform diiodide **11** into the corresponding methylated derivative **12**, using a variety of alkyllithiums, were universally unsuccessful. In addition, exposure of **11** to a variety of reducing agents, including sodium and lithium borohydride, lithium aluminium hydride and diisobutylaluminium hydride failed to provide either alcohol **13** or aldehyde **14** in a pure state.

An alternative approach to aldehyde **10** was investigated via iodide **16**, using propargyl acetate which was converted to the corresponding *E*-diiodoalkene **15**[13] (Scheme 4) in good yield and with high stereoselectivity. However, a range of different conditions and reagents (*t*-butyllithium and *n*-butyllithium followed by methyl iodide) failed to effect clean iodide–methyl exchange.

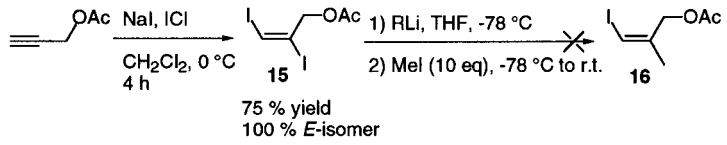
The failure of diiodides **11** and **15** as precursors of aldehyde **10** prompted the application of conditions reported by Negishi et al., for the halo-alkylation of propargyl alcohol[14] to provide iodide **17** (Scheme 5). After considerable experimentation and careful temperature control, it was found that treatment of propargyl alcohol with methylmagnesium bromide in the presence of copper(I), followed by iodinolysis with iodine monochloride, provided *Z*-3-iodo-2-methylprop-2-en-1-ol **17** highly stereoselectively and in good yield. The assignment of the stereochemistry for **17** was achieved by n.O.e. difference spectra (Fig. 1), which differentiates it from the corresponding *E*-isomer.[15,12]

The efficient one-pot synthesis of alcohol **17** was followed by oxidation under Swern conditions[16] to yield the highly unstable aldehyde **10** in 61% crude yield (Scheme 5). Alternative oxidation methods (Sturtz oxidation,[17] PCC in dichloromethane,[18] PDC in THF or dichloromethane,[19] Jones oxidation,[20] and Dess–Martin oxidation[21]) universally lead to decomposition. The high instability and volatility of aldehyde **10** meant that it had to be prepared and used immediately, without further purification. It should be noted that similar properties were reported for its *E*-isomer.[12a]

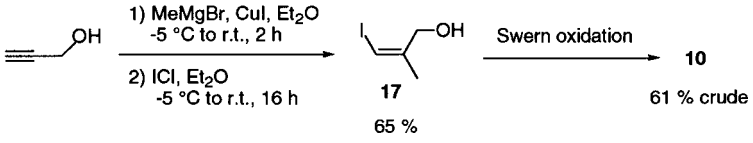
Having accessed aldehyde **10**, the aldol reaction to derive synthon **9** was investigated (Scheme 2). Although chiral oxazolidinones reported by Evans et al. are widely used auxiliaries for a range of asymmetric transformations,[22] the application of isobutyryl systems, such as **19** have not



Scheme 3.



Scheme 4.



Scheme 5.

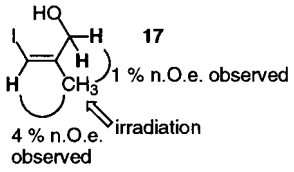


Figure 1.

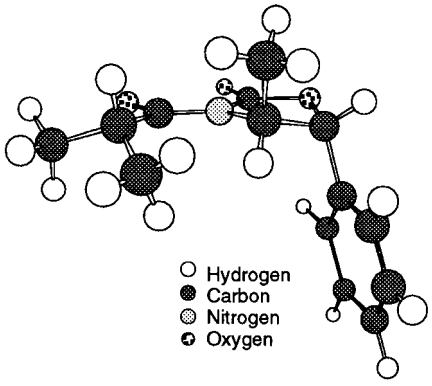
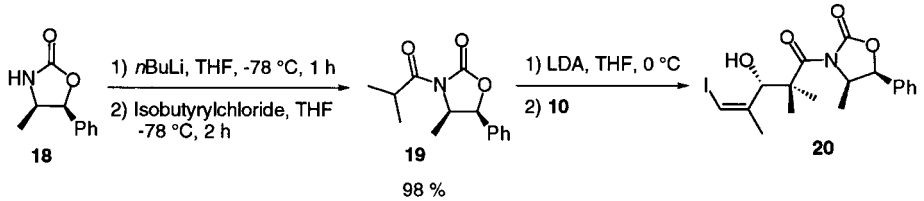


Figure 2.

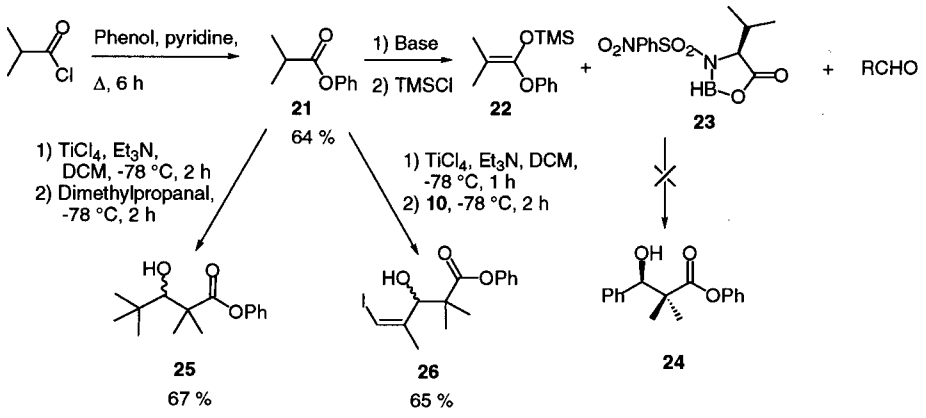
been reported. In order to test whether such disubstituted oxazolidinones could be deprotonated, ephedrine-derived system **19** was prepared (Scheme 6) in 98% yield. However, **19** was resistant to deprotonation with a range of bases (Scheme 6); deprotonation with lithium diisopropylamide at 0°C and subsequent reaction with aldehyde **10** did provide the required aldol adduct **20** but only in 15% yield. Since similar results were also obtained with other, more stable aldehydes than **10**, it can be speculated that the resistance of oxazolidines such as **19** to deprotonation is perhaps not surprising if one considers the likely conformation that is required in order to deprotonate **19**; the CH bond must adopt a 90° dihedral angle relative to the carbonyl function[23] of the butyryl group. Unfortunately, such a dihedral angle is disfavoured due to steric repulsion between the methyl groups of the isobutyryl function and the N·CHMe section of the oxazolidine ring. Examination of the likely lowest energy structure in which the CH does adopt a 90° dihedral angle to the *exo*-carbonyl of the oxazolidine ring is shown in Fig. 2. Even in this orientation, one of butyryl methyl groups clashes with the α-nitrogen CH of the oxazolidine ring and deprotonation is further suppressed by repulsion between any incoming base and the oxazolidinyl methyl group.

The very low yields of the aldol product **20** meant that alternative methods were required for the synthesis of fragment **9**, if the synthesis of Phthoxazolin A **4** was to be realised. Instead of an auxiliary based approach to aldol **9**, a Lewis acid catalysed process using a silyl ketene acetal was considered, similar to that persued by several groups,[24] and the related catalytic aldol reaction.[25] In order to obtain an aldol product, from which one could easily generate the primary amide function of **9**, Kiyooka's methodology was adopted (Scheme 7).[25d] Thus, the ketene acetal **22** was generated in situ using a number of different methods (LDA, triethylamine, potassium hydride etc. followed by trimethylsilyl chloride). The required asymmetric catalyst **23** (also generated in situ as described in the literature[25d]) was directly added to ketene acetal **22** together with various aldehydes (including benzaldehyde), but failed to produce any observable aldol reaction. Attention was therefore turned to the racemic variant, using the titanium(IV) enolate (Scheme 7).

Reaction of pivaldehyde with phenol ester **21**, after formation of the titanium(IV) enolate, resulted in the smooth



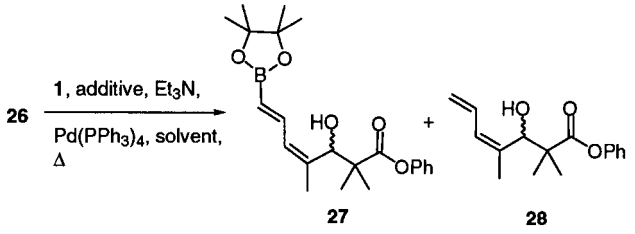
Scheme 6.



Scheme 7.

generation of aldol **25**. Turning to *Z*-3-iodo-2-methylprop-2-enal **10**, reaction under the same conditions produced the required racemic aldol product **26** in 65% yield, when the reaction was quenched overnight with a saturated ammonium chloride solution (yields dropped to 10% if the product titanium complex was only left to hydrolyse for 2 h.

Having accessed aldol product **26**, the use of vinylboronate **1** as a vinyl dianion equivalent via the Heck and Suzuki reactions could now be investigated. The original Heck coupling reactions of boronate **1** for the preparation of polyenes required the use of silver(I) or thallium(I) salts, when using palladium(II) acetate, triphenylphosphine, triethylamine in acetonitrile.[6] However, these reaction conditions proved inadequate for iodide **26** and alternative, milder coupling conditions were required. The use of carefully prepared *tetrakis*(triphenylphosphine)palladium(0)[26] or palladium(II) acetate and triphenylphosphine under rigorously deoxygenated reaction conditions was therefore investigated under different conditions (Scheme 8, Table 1).



Scheme 8.

Entries 1–3 (Table 1) were carried out using DMF as a solvent and these only gave the Suzuki product **28**. However, using acetonitrile immediately resulted in formation of the Heck product **27** and the addition of silver(I) acetate provided the best ratio of Heck to Suzuki product (cf. entries 4 and 7, Table 1). Increasing the reaction temperature also improved the yield (entry 6, Table 2), without affecting the Heck:Suzuki ratio. Replacing silver(I) by thallium(I) acetate decreased the proportion of the Heck product and gave a low yield of 10% (entry 5, Table 1). In addition, it was found that 4 mol% of the catalyst was required; application of just 2 mol% lowered the yield from 42 (entry 6, Table 1) to 20%.

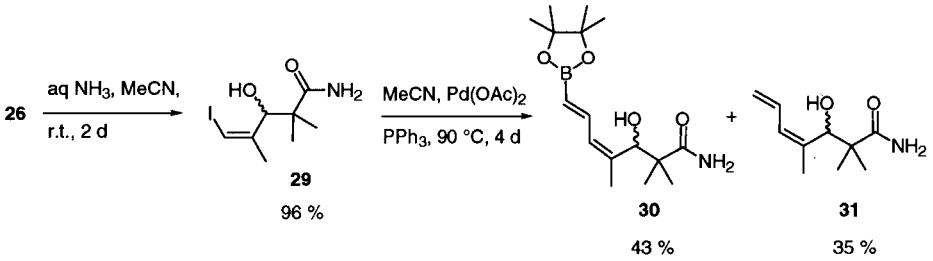
In order to complete the total synthesis of Phthoxazolin A **4**, it was necessary to transform phenol ester **27** into the

Table 1. (A: $Pd(PPh_3)_4$ 4 mol%; B: $Pd(OAc)_2$ 4 mol%, PPh_3 8 mol%)

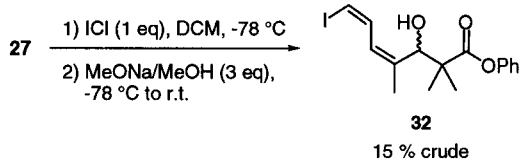
Entry	*T* (°C)	Time (days)	Base	Solvent	Additive	Catalyst	Ratio Heck **27**:Suzuki **28**	Combined yield (%)
1	70	2	Et_3N	DMF	–	A	0:100	35
2	70	5	Et_3N	DMF	–	A	0:100	33
3	70	2	Et_3N	DMF	–	B	0:100	33
4	70	3	Et_3N	CH_3CN	AgOAc	B	65:35	27
5	70	2	Et_3N	CH_3CN	TlOAc	B	45:55	10
6	100	4	Et_3N	CH_3CN	AgOAc	B	65:35	42
7	100	3	Et_3N	CH_3CN	–	B	53:47	22
8	100	4	Et_3N	CH_3CN	AgOAc	A	65:35	40

Table 2.

Entry	Solvent	Catalyst	Base (2 equiv.)	Yield (%)
1	DMF	$Pd(MeCN)_2Cl_2$ 3 mol%	Et_3N	22
2	CH_3CN	$Pd(MeCN)_2Cl_2$ 3 mol%	Et_3N	–
3	THF	$Pd(PPh_3)_4$ 4 mol%	Et_3N	–
4	DMF	$Pd(MeCN)_2Cl_2$ 3 mol%	*i*Pr_2NEt	5
5	THF	$Pd(PPh_3)_4$ 4 mol% and CuI	–	–
6	DMF	$Pd(MeCN)_2Cl_2$ 3 mol%	–	5



Scheme 9.



Scheme 10.

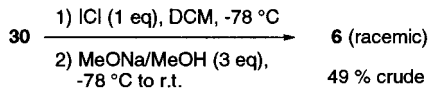
corresponding primary amide. However, it was found more convenient to directly transform the reactive aldol product **26** to the amide **29** prior to the Heck coupling reaction, as shown in Scheme 8. Thus, phenyl ester **27** was first converted to the amide **29** over two days in acetonitrile, with excess aqueous ammonia. For amide **29**, subsequent coupling proved most effective with 2 equiv. of vinylboronate **1**, triethylamine, palladium acetate-triphenylphosphine in acetonitrile and a sealed tube at 90°C. These conditions gave a mixture of Heck/Suzuki products **30** and **31**, respectively, in a ratio of 60:40, with a combined yield of 78% (Scheme 9).

It appears from the coupling of amide **29** (Scheme 9) that use of the amide function, versus the phenyl ester **26**, precludes the necessity to use either silver(I) or thallium(I) salts to effect Heck coupling. Most importantly, however, is the fact that the coupling processes can be carried out in both cases without the need to protect the secondary alcohol, amide or phenyl ester functions. Despite the moderate yield of amide **30**, the coupling was sufficiently efficient to carry on with the synthesis of phthoxazolin A **4**, as outlined in Scheme 2, i.e. via stereoselective iodo-deboronation of the dienyl boronate **30** with inversion of stereochemistry.

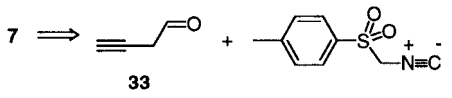
Brown et al.[27] described an efficient method for making vinyl iodides from vinylboronic acids, reactive boronate esters (e.g. catechol) and dibromoboranes. They also reported that it was possible to make both *E*- and *Z*-vinyl iodides[27] from the *E*-vinylboronic acids using iodine and sodium hydroxide; the order of the addition controls the stereochemical course of the process. However, pinacol esters are resistant to such reaction conditions and therefore a stereospecific generation of both *E*- and *Z*-vinyl iodides was developed in our laboratories,[8] using iodine monochloride and sodium methoxide. Thus, treatment of both phenyl ester **27** and amide **30** with iodine monochloride followed by methoxide elimination provided the highly unstable *Z*-iodides **32** and **6**, respectively. Attempts to purify either of these iodides by chromatography lead to complete decomposition, even when chilled (−78°C) eluant was employed. The poor yield of phenol ester **32** (presumably due to the sensitivity of the phenyl ester to strong electrophiles) reinforced the decision to use the primary amides **30** and **6** for the remainder of the synthesis of Phthoxazolin A **4** (Schemes 10 and 11).

Having prepared amide **6**, albeit in crude form, attention was turned to the preparation of oxazole boronate **5**. It was envisaged that boronate **5** would be readily available from oxazole alkyne **7** by hydroboration. Van Leusen et al.[8] reported an efficient method for the synthesis of oxazoles, based on the condensation of tosylmethyl isocyanide (TosMIC) with an aldehyde under basic conditions. Thus, it was hoped that the target molecule **7** could be synthesised from TosMIC and a suitable aldehyde **33** (Scheme 12). However, a wide range of oxidation methods[16–21] failed to transform 3-butyn-1-ol to the corresponding aldehyde **33**; all attempts merely produced a number of unidentifiable products. Therefore, an alternative approach was required, i.e. by preparation of a protected equivalent of aldeyde **7**, such as the acetal **34**. Acetal **34** could be directly accessed from a propargyl metal species generated in situ from propargyl bromide and triethylorthoformate, according a literature method[29] (Scheme 13).

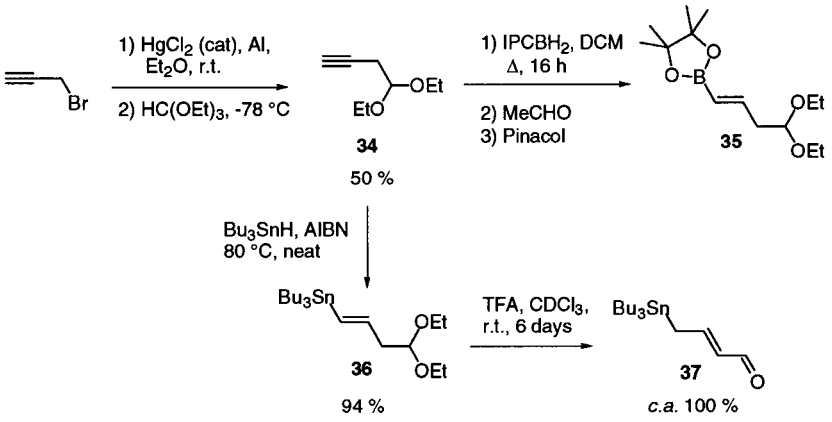
Preparation of acetal **34** proceeded smoothly, however, the aldehyde **33** could not be liberated by a range of acidic conditions, such as *p*-toluenesulfonic acid in acetone or chloroform, 5% aqueous hydrochloric acid, acetic acid in water, Amberlyst 15® in acetone/water, or zeolite Y, producing either unreacted starting material or decomposition products. It was therefore conceived that preparation of vinylboronate **35** (Scheme 9) would act to effectively protect the alkyne of **34**, while providing the required functionality for a Suzuki coupling with iodide **6**. The vinylboronate **35** was therefore prepared in an impure state by hydroboration of the acetylene with $IPCBH_2$ (hydroboration with catecholborane or pinacolborane failed to produce any discernable reaction); attempts to purify further were



Scheme 11.



Scheme 12.



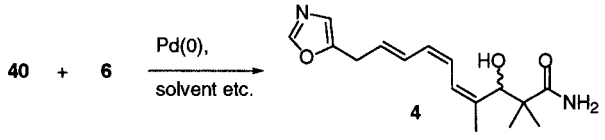
Scheme 13.

unrewarding. Deprotection of the crude vinylboronate **35** was again attempted with the same range of acidic conditions, however, all resulted in complete decomposition, even under mild conditions such as montmorillonite K10 in dichloromethane.[30] In order to avoid the instability inherent in boronate **35**, it was considered that the vinylstannane could provide sufficient stability to allow deprotection of an acetal of structure **36**, which in turn would allow the introduction of a Stille coupling reaction, in place of the Suzuki cross-coupling planned for the final step (Scheme 2). Stannane **36** was prepared from acetal **34** in 94% yield but was once again stable to standard acidic deprotection methods. Eventually TFA was found to effect clean deprotection of the acetal, only to produce the more stable conjugated aldehyde **37** after 6 days at room temperature (Scheme 13).

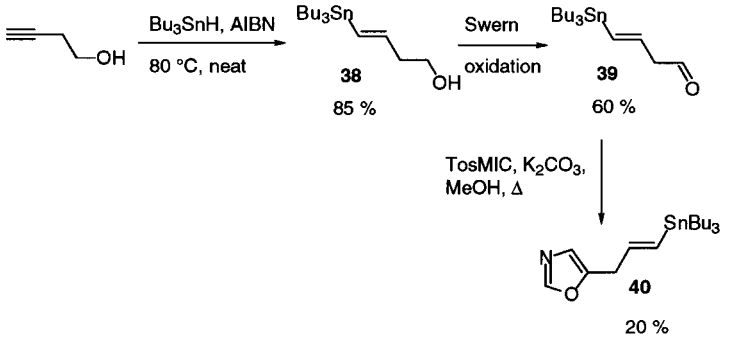
The continued lack of success in accessing a suitable aldehyde precursor to the oxazole of type **5**, lead to the use 3-butyn-1-ol to directly provide stannane **38**. Reaction with tributyltin hydride and AIBN (Scheme 14) gave alcohol **38**, which was then readily oxidised under Swern conditions (a wide range of other oxidants[17–21] caused decomposition), to provide aldehyde **39** in 60% yield. This unstable aldehyde was immediately subjected to reaction with TosMIC[28] to provide the required 5-substituted oxazole **40**, albeit in poor yield (20%) (Scheme 14) despite attempts to optimise the reaction.

In order to complete the synthesis, a range of reaction conditions to accomplish the desired Stille coupling of **40** with **10** (Scheme 15, Table 2) were examined, using conditions that have been frequently described in the literature. These included dichloro*bis*(acetonitrile)palladium(II) and *tetrakis*-(triphenylphosphine)palladium(0) in DMF or acetonitrile and copper(I) acceleration.[31]

In our hands, the best method for the prepartion of Phthoxazolin A **4** from stannane **40** and iodide **6** was catalytic dichloro*bis*(acetonitrile)palladium(II) in DMF, at room temperature (entry 1, Table 2); use of copper(I) and *tetrakis*-(triphenylphosphine)palladium(0) produced little or no product. The poor yield of Phthoxazolin A **4** (entry 1, Table 2) is due to the extreme sensitivity of both starting materials (**40** and **6**) which were both used in a crude form. In addition, Phthoxazolin A **4** is also unstable; even storage as a pure oil at −20°C results in gradual decomposition to produce a complex mixture of products.[32] Storage as a methanolic solution does, however, help to preserve phthoxazolin A for a few weeks.



Scheme 15.



Scheme 14.

Summary

Vinylboronate pinacol ester **1** is a useful two carbon building block, for the stereoselective synthesis of polyenes, as exemplified by the synthesis of the labile molecule Phthoxazolin A **4**. In contrast to earlier work, we have also found the addition of either silver(I) or thallium(I) salts is not necessary to achieve successful Heck coupling with boronate **1** and an alkenyl iodide (for example conversion of iodide **29** to dienylboronate **30**); careful deoxygenation of the reaction mixture appears to be the important factor. Further applications of this type of methodology to the synthesis of more complex polyene structures are underway.

Experimental

All reagents were purchased from Aldrich, Lancaster or Acros and used without further purification unless otherwise stated. Diiodides **11** and **15** were prepared as reported elsewhere[13] and phenyl isobutyrate was prepared according to literature methods.[33] The solvents used were either purchased as anhydrous or distilled before use over either benzophenone/sodium (THF) or calcium hydride (all remaining solvents) under an atmosphere of argon.

Anhydrous reactions were carried out in glassware which was dried prior to use in an oven at 140°C and cooled under a stream of argon. Exhaustive deoxygenation was performed by bubbling argon through the solution via a syringe needle for at least an hour. Concentrations were carried out at 20 mmHg using a Büchi rotary evaporator and evaporation to dryness using the Büchi rotary evaporator followed by drying at pressures <2 mmHg. Column chromatography was achieved under medium pressure using Acros silica gel, pore size 60A. TLC was carried out on either Merck Kieselgel $60F_{254}$ plastic backed plates or Fluka Kieselgel $60F_{254}$ aluminium backed plates.

Melting points were determined using an Electrothermal melting point apparatus. ^{1}H NMR spectra recorded at 200, 300 or 400 MHz on either Bruker AC200, AC300 or AC400 spectrometers. ^{13}C NMR spectra were recorded at 75.5 or 100 MHz on Bruker AC300 or AC400 spectrometers. Electron impact (EI) (70 eV.) and chemical ionisation (CI) mass spectra were recorded on a Kratos MS25. Fast atom bombardment (FAB) spectra were recorded on a Kratos MS50 using a *m*-nitrobenzyl alcohol matrix. Accurate mass determinations were carried out using a Kratos Concept IS spectrometer. IR spectra were recorded on a Perkin–Elmer 29 spectrometer. UV spectra were recorded on a Perkin–Elmer 115 spectrometer.

***Z*-3-Iodo-2-methylprop-2-en-1-ol 17.** Methylmagnesium bromide (8.3 ml of a 2.5 M solution in hexanes, 20.75 mmol) was added to a suspension of copper(I) iodide (1.70 g, 8.92 mmol) in dry diethyl ether (25 ml) under argon at −10°C. Propargyl alcohol (500 mg, 8.93 mmol) was then added and the mixture was stirred for 2 h at room temperature under argon. Then iodine monochloride (1.4 g, 8.62 mmol) was added in solution in dry diethyl ether (10 ml) at −10°C. The reaction mixture was stirred for a further 16 h before being quenched with 10% aqueous ammonium chloride solution (10 ml). The quenched reaction mixture was stirred overnight, extracted with diethyl ether (3×20 ml), washed with water (20 ml), dried ($MgSO_4$), filtered and evaporated to give the crude compound. Purification by silica gel chromatography (hexane/ethyl acetate, 4:1 as eluant) afforded **17** (1.1 g, 65%) as a yellow oil; ν_{max} (film)/cm^{-1} 3300 (OH), 3010 (C:CH), 2980 (aliphatic CH), 2960 (aliphatic CH), 1600 (C:C), 1050 (C·O); δ_H (200 MHz; $CDCl_3$) 1.71 (1H, s, O*H*, disappears upon addition of D_2O), 1.92 (3H, d, *J*=1.5 Hz, CH_3), 4.20 (2H, s, CH_2), 5.95 (1H, d, *J*=1.5 Hz, C:C*H*); δ_C (75.5 MHz; $CDCl_3$) 29.0, 68.3, 75.0, 102.3; *m*/*z* (FAB) 197.9742 (M^+, C_4H_7IO requires *m*/*z*=197.9742, 11%), 181 (M^+-OH, 51), 167 (M^+-CH_2OH, 5).

***Z*-3-Iodo-2-methylprop-2-enal 10.** To a solution of oxalyl chloride (0.10 ml, 1.10 mmol) in dry dichloromethane (5 ml) under argon was added DMSO (0.2 ml, 2.80 mmol) at −78°C. The reaction mixture was stirred for 15 min before adding the alcohol **17** (50 mg, 0.25 mmol) in dichloromethane (2 ml) at −78°C. The mixture was stirred for a further 30 min and then triethylamine (0.05 ml, 0.30 mmol) was added. The reaction was stirred for 5 min at −78°C and then allowed to warm to room temperature. The reaction mixture was partitioned between dichloromethane (10 ml) and water (10 ml). The aqueous layer was separated and extracted with dichloromethane. The combined organic extracts were washed sequentially with 1% hydrochloric acid (5 ml), water (5 ml), 5% aqueous sodium carbonate (5 ml) and water (5 ml). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the crude, unstable product **10** (33 mg, 67%) as a yellow oil; ν_{max} (film)/cm^{-1} 3020 (C:CH), 2940 (aliphatic CH), 2820 (aliphatic CH), 2720 (aldehyde CH), 1680 (C:O), 1660 (C:C); δ_H (200 MHz; $CDCl_3$) 2.52 (3H, d, *J*=1.5 Hz, CH_3), 7.24 (1H, d, *J*=1.5 Hz, *H*C:C), 9.26 (1H, s, C*H*O); *m*/*z* (FAB) 69 (M^+-I, 80%).

(4*R*, 5*S*)-3-Isobutyryl-4-methyl-5-phenyloxazolidin-2-one 19. *n*-Butyllithium (3.6 ml of a 1.7 M solution in hexanes, 6.12 mmol) was added to a solution of (4*R*,5*S*)-4-methyl-5-phenyloxazolidinone **18** (0.9 g, 5.08 mmol) in dry THF (50 ml) at −78°C under argon. The reaction mixture was stirred for 45 min. Then isobutyryl chloride (0.6 ml, 5.53 mmol) was added dropwise under argon at −78°C and stirred for 3 h under argon. The reaction was quenched with 10% aqueous ammonium chloride solution (20 ml). The aqueous layer was extracted with diethyl ether and the combined organic layers were dried ($MgSO_4$) and evaporated to give the crude product which was crystallised from diethyl ether to give a colourless solid **19** (1.23 g, 98%) (found C, 67.9; H, 7.1; N, 5.5; $C_{14}H_{17}NO_3$ requires C, 67.8; H, 6.8; N 5.6%); mp 32–34°C; ν_{max} (nujol)/cm^{-1} 1760 (C:O), 1700 (C:O), 1250 (C·O), 750 (monosubstituted aromatic), 700 (monosubstituted aromatic); δ_H (200 MHz; $CDCl_3$) 0.95 (3H, d, *J*=7.0 Hz, N·CH·CH_3), 1.10 and 1.12 (each 3H, d, *J*=7.0 Hz, CH.*Me*$_2$), 3.85 (1H, m, N·CH), 4.80 (1H, m, C*H*·Me$_2$), 5.65 (1H, d, *J*=7.0 Hz, O·CH), 7.22–7.50 (5H, m, Ph); δ_C (75.5 MHz; $CDCl_3$) 14.6, 19.0, 19.1, 32.8, 55.0, 78.9, 125.8, 128.8, 128.9, 133.6, 177.6, 204.4; *m*/*z* (FAB) 248.1291 (MH^+, $C_{14}H_{18}NO_3$ requires *m*/*z*= 248.1287, 100%), 204 [$MH^+-CH(CH_3)_2$, 31], 178 [$MH^+-C(O)CH(CH_3)_2$, 24].

3-(3-Hydroxy-5-iodo-2,2,4-trimethylpent-4-enoyl)-4-methyl-5-phenyloxazolidin-2-one 20. *n*-Butyllithium (0.08 ml of a 2.5 M solution in hexanes, 0.20 mmol) was added under argon to a solution of dry diisopropylamine (0.023 ml, 0.20 mmol) in THF (5 ml) at 0°C. After stirring for 1 h at 0°C, (4*R*,5*S*)-3-isobutyryl-4-methyl-5-phenyloxazolidin-2-one **19** (40 mg, 0.16 mmol) was added and the reaction mixture was stirred for a further hour. Then *Z*-3-methyl-2-iodoprop-2-enal **10** (30 mg, 0.15 mmol) was added and the reaction was allowed to warm to room temperature. The reaction mixture was quenched with water (3 ml) after 90 min, acidified with 10% aqueous hydrochloric acid solution (5 ml) and extracted with dichloromethane (5 ml). The organic layer was washed with water (5 ml), dried ($MgSO_4$), filtered and evaporated. Purification by silica gel chromatography (petroleum ether 40/60:ethyl acetate, 9:1 as eluant) gave **20** (10 mg, 15%) as a yellow oil; ν_{max} (film)/cm^{-1} 3350 (OH), 3020 (:CH), 1750 (C:O), 1710 (C:O), 1600 (C:C), 1150 (C·O), 750 (monosubstituted aromatic), 700 (monosubstituted aromatic); δ_H (300 MHz; $CDCl_3$) 0.81 (3H, d, *J*=7.0 Hz, N·CH·C*H*$_3$), 1.08 and 1.12 (each 3H, s, CH.*Me*$_2$), 2.17 (3H, s,:CCH_3), 4.15–4.24 (1H, m, N·CH), 3.67 (1H, s, OH, disappears upon addition of D_2O), 5.72 (1H, d, *J*=6.6 Hz, O·CH), 5.80 [1H, s, I·CH], 5.81 (1H, s, HO·C*H*), 7.29–7.43 (5H, m, Ph).

3-Hydroxy-2,2,4,4-tetramethylpentanoic acid phenyl ester 25. Titanium(IV) chloride (0.6 ml in 1.0 M solution in dichloromethane, 0.60 mmol) was added slowly to a solution of isobutyric acid phenyl ester **21** (50 mg, 0.30 mmol) in dichloromethane (5 ml) at −78°C. After 5 min, triethylamine (42 μl, 0.30 mmol) was added and the solution was stirred for 2 h before adding dimethylpropanal (28 mg, 0.33 mmol) in dichloromethane (1 ml). The reaction mixture was stirred at −78°C for 2 h before quenching with saturated aqueous ammoniun chloride (2 ml). The mixture was allowed to warm up to room temperature and stirred for 16 h, acidified with 10% aqueous hydrochloric acid solution (10 ml). The organic layer was washed with water (10 ml), saturated aqueous sodium chloride solution (10 ml), water (10 ml), dried ($MgSO_4$), filtered, evaporated to give the crude product. Purification by silica gel chromatography (petroleum ether 40/60:ethyl acetate, 95:5 as eluant) gave **25** (50 mg, 67%) as a yellow oil whose ^{13}C NMR spectrum matched that quoted in the literature;[34] ν_{max} (film)/cm^{-1} 3440 (OH), 1650 (C:O); δ_H (300 MHz; $CDCl_3$) 1.09 [9H, s, $(CH_3)_3C$], 1.42 [3H, s, $(CH_3)_2C$], 1.46 [3H, s, $(CH_3)_2C$], 2.29 (1H, bs, OH, disappears upon addition of D_2O), 3.75 [1H, s, C(*H*)OH], 7.07–7.44 (5H, m, Ph); *m*/*z* (CI) 268 ($M^+ + NH_4^+$, 100%), 251.1651 (MH^+, $C_{15}H_{22}O_3$ requires *m*/*z*=251.1647, 100), 157 ($M^+ - OPh$, 15).

3-Hydroxy-5-iodo-2,2,4-trimethylpent-4-enoic acid phenyl ester 26. Titanium(IV) chloride (2.4 ml in 1.0 M solution in dichloromethane, 2.40 mmol) was added slowly to a solution of isobutyric acid phenyl ester **21** (200 mg, 1.22 mmol) in dichloromethane (20 ml) at −78°C. After 5 min, triethylamine (0.18 ml, 1.22 mmol) was added and the solution was stirred for 2 h before adding *Z*-3-methyl-2-iodoprop-2-enal **10** (300 mg, 1.53 mmol) in dichloromethane (5 ml) (*the aldehyde was used without any purification due to its volatility and instability*). The reaction mixture was stirred at −78°C for 2 h before quenching with saturated aqueous ammoniun chloride solution (2 ml). The mixture was allowed to warm up to room temperature and stirred for 16 h, acidified with 10% aqueous hydrochloric acid solution (10 ml). The organic layer was washed with water (10 ml), saturated aqueous sodium chloride (10 ml), water (10 ml), dried ($MgSO_4$), filtered, evaporated to give the crude product. Purification by silica gel chromatography (petroleum ether 40/60:ethyl acetate, 9:1 as eluant) gave **26** (285 mg, 65%) as a yellow oil; ν_{max} (film)/cm^{-1} 3400 (OH), 1750 (C:O), 750 (monosubstituted aromatic), 700 (monosubstituted aromatic); δ_H (300 MHz; $CDCl_3$) 1.39 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.95 (3H, d, *J*=1.5 Hz,:CCH_3), 3.60 (1H, s, OH, disappears upon addition of D_2O), 4.81 [1H, s, C*H*(OH)], 6.26 (1H, q, *J*=1.5 Hz,:CH), 7.07–7.45 (5H, m, Ph); δ_C (75.5 MHz; $CDCl_3$) 10.9 (CH_3), 14.0 (CH_3), 28.9 (:C*C*H$_3$), 38.7 [*C*$(CH_3)_2$], 67.1 [(I)C(H)], 75.6 [(H)C(OH)], 120.9 (:*C*CH_3), 128.6, 129.3, 130.7, 132.2 (aromatic carbons), 167.5 (C:O); *m*/*z* (CI) 360.0222 (M^+, $C_{14}H_{17}IO_3$ requires *m*/*z*=360.0221, 15%), 343 ($MH^+ - H_2O$, 50), 233 ($M^+ - I$, 45).

3-Hydroxy-2,2,4-trimethyl-7-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-ylhepta-4,6-dienoic acid phenyl ester 27 and 3-hydroxy-2,2,4-trimethylhepta-4,6-dienoic acid phenyl ester 28. 3-Hydroxy-5-iodo-2,2,4-trimethylpent-4-enoic acid phenyl ester (15 mg, 0.04 mmol), silver(II) acetate (7 mg, 0.04 mmol), palladium(II) acetate (0.3 mg, 1.33 mmol) and triphenylphosphine (0.6 mg, 2.30 mmol) were degassed in acetonitrile (2 ml) for an hour, before adding vinylboronate (12 mg, 0.08 mmol) and triethylamine (8.5 ml, 0.06 mmol). After degassing the solution for a further 1 h, the mixture was heated at 100°C for 4 days in a sealed tube. The solution was then allowed to cool down to room temperature, washed with 10% aqueous hydrochloric acid solution (5 ml), extracted with diethyl ether (3×10 ml). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 ml), dried ($MgSO_4$), filtered and evaporated. Purification by silica gel chromatography (the silica gel used was previously neutralised by addition of one drop of triethylamine to the eluant and the solvent mixture was chilled at 0°C) (petroleum ether 40/60:ethyl acetate, 9:1 as eluant) gave the Heck product **27** (4.3 mg, 27%) and the Suzuki product **28** (1.5 mg, 15%). Boronate **27**; ^1H (300 MHz; $CDCl_3$) 1.57 [12H, s, $(CH_3)_2C$·O], 1.70 (3H, s, CH_3), 1.72 (3H, s, CH_3, 1.82 (1H, bs, OH, disappears upon addition of D_2O), 2.04 (3H, s, CH_3C:), 5.25 [1H, s, C(H)OH], 6.18 [1H, d, *J*=18.5 Hz, B(H)C:], 7.53 [1H, dd, *J*=7.9 and 18.5 Hz, B(H)C:C(H)], 7.19–8.19 [6H, m, Ph+(H)C:(CH_3))]; *m*/*z* (CI) 223.1509 [$C_{22}H_{31}BO_5 - (CH_3)_2CO)OPh^+$, $C_{12}H_{20}BO_3$ requires *m*/*z*= 223.1505, 15%], 193 ($C_{11}H_{18}BO_2^+$, 52). Diene **28**; ν_{max} (film)/cm^{-1} 3415 (OH), 1750 (C:O), 1595 (C:C), 1100 (C·O), 750 (monosubstituted aromatic), 700 (monosubstituted aromatic); δ_H (300 MHz; $CDCl_3$) 1.33 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.87 (3H, s,:CCH_3), 3.55 (1H, bs, OH, disappears upon D_2O addition), 4.94 [1H, s, C*H*(OH)], 5.10 (1H, dd, *J*=1.9 and 10.5 Hz, H_7*cis*), 5.20 (1H, dd, *J*=1.9 and 16.6 Hz, H_7*trans*), 6.12 (1H, d, *J*=10.5 Hz, H_5), 6.66 (1H, dt, *J*=10.5 and 16.6 Hz, H_6), 7.06–7.70 (5H, m, Ph); δ_C (75.5 MHz; $CDCl_3$) 19.7 (CH_3); 20.8 (CH_3); 24.2 (:C*C*H$_3$); 47.6 [*C*$(CH_3)_2$]; 74.8 [(H)C(OH)]; 117.3 (:CH_2);

121.4 (:CH); 126.0 (:CH); 129.4; 132.2; 132.3; 136.2 (CAr); 150.1 (:*C*CH_3); 176.5 (C:O); *m/z* (CI) 279 ($MH^+ + NH_4^+$, 100%), 157 [($MH^+ + NH_4^+$)−PhOCO, 45].

3-Hydroxy-5-iodo-2,2,4-trimethylpent-4-enoic acid amide 29. 3-Hydroxy-5-iodo-2,2,4-trimethylpent-4-enoic acid phenyl ester **26** (15 mg, 0.04 mmol) was stirred at room temperature in acetonitrile (0.2 ml) under argon with aqueous ammonia (0.2 ml) for 48 h. The reaction mixture was then washed with 10% aqueous hydrochloric acid (5 ml), extracted with dichloromethane (3×5 ml), washed with 2 M sodium hydroxide solution (5 ml), water (5 ml), dried ($MgSO_4$), filtered and evaporated. Purification by silica gel chromatography (petroleum ether 40/60: ethyl acetate; 9:1 as eluant) gave **29** (11 mg, 96%) as a yellow oil; δ_H (300 MHz; $CDCl_3$) 1.19 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.89 (3H, d, *J*=1.5 Hz,:CCH_3), 3.22 (1H, bs, OH, disappears upon addition of D_2O), 4.54 [1H, s, C(*H*)OH], 5.46 (1H, bs, NH disappears upon adding D_2O), 6.16 (1H, q, *J*=1.5 Hz, HC:), 6.26 (1H, bs, NH disappears upon adding D_2O); δ_C (75.5 MHz; $CDCl_3$) 19.1 [(CH_3)$_2$C], 21.1 [(CH_3)$_2$C], 26.4 (CH_3C:), 44.1 [(CH_3)$_2$*C*], 79.1 (C·OH), 81.7 (:CI), 145.9 (CH_3*C*:), 180.8 (C:O); *m/z* (CI) 284.0157 (MH^+, $C_8H_{15}NO_2I$ requires *m/z*=284.0149, 100%), 266 (M^+−OH, 35), 156 (M^+−I, 30).

3-Hydroxy-2,2,4-trimethyl-7-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-ylhepta-4,6-dienoic acid amide 30 and 3-hydroxy-2,2,4-trimethylhepta-4,6-dienoic acid amide 31. 3-Hydroxy-5-iodo-2,2,4-trimethylpent-4-enoic acid amide **29** (15 mg, 0.05 mmol), palladium(II) acetate (0.3 mg, 1.30 μmol) and triphenylphosphine (0.8 mg, 3.00 μmol) were degassed in acetonitrile (2 ml) for 1 h before adding vinylboronate **1** (12 mg, 0.08 mmol) and triethylamine (8.5 μl, 0.06 mmol). After degassing the solution for a further 1 h, the mixture was heated at 90°C for 4 days in a sealed tube. The solution was cooled down to room temperature, washed with 10% aqueous hydrochloric acid (5 ml), extracted with diethyl ether (3×10 ml). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 ml), dried ($MgSO_4$), filtered and evaporated. Purification by silica gel chromatography (petroleum ether 40/60:ethyl acetate, 9:1 as eluant) gave the Heck **30** and the Suzuki **31** products (6.6 mg, 43% and 3.2 mg, 35%, respectively) as yellow oils. Boronate **30**; δ_H (300 MHz; $CDCl_3$) 1.26 [12H, s, 2×(CH_3)$_2$C·O], 1.82 [6H, s, (CH_3)$_2$C], 2.03 (3H, s,:CCH_3), 3.58 (1H, bs, OH, disappears upon addition of D_2O), 4.65 [1H, s, C(*H*)OH], 5.17 [1H, d, *J*=16.9 Hz, B(H)C:], 5.41 (1H, bs, NH), 6.04 (1H, d, *J*=10.5 Hz, H_3CC:C*H*), 6.29 (1H, bs, NH), 7.17 [dd, *J*=10.5 and 16.9 Hz, B(H)C:C(*H*)]; *m/z* (CI) 309.2351 ($M^+ + NH_4^+ - H_2O$, $C_{16}H_{28}BNO_4$ requires *m/z*=309.2349, 20%). Diene **31**; δ_H (300 MHz; $CDCl_3$) 1.33 [3H, s, C(CH_3)$_2$], 1.34 [3H, s, C(CH_3)$_2$], 1.78 (1H, s, OH, disappears upon addition of D_2O), 1.80 (3H, s,:CCH_3), 4.64 [1H, s, C(*H*)OH], 5.15 (1H, dd, *J*=1.9 and 10.6 Hz, H_2C:C(H)*cis*), 5.23 [1H, dd, *J*=1.9 and 16.9 Hz, H_2C:C(H)*trans*], 5.55 (1H, bs, NH), 6.02 [1H, d, *J*=10.6 Hz, *H*C:C(CH_3)], 6.28 (1H, bs, NH), 6.56 [1H, dt, *J*=10.6 and 16.9 Hz, H_2C:C(*H*)]; *m/z* (CI) 183 (M^+, 100%).

3-Hydroxy-7-iodo-2,2,4-trimethylhepta-4,6-dienoic acid amide 6. A solution of 3-hydroxy-2,2,4-trimethyl-7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-ylhepta-4,6-dienoic acid amide **30** (25 mg, 0.08 mmol) in dry THF (3.3 ml) under argon was cooled to −78°C. Iodine monochloride (11.7 mg in 1.6 ml of dichloromethane, 0.07 mmol) was slowly added, and the solution was stirred in the absence of light for 2 h. A suspension of sodium methoxide (11.6 mg, 0.21 mmol) in dry methanol (8.3 ml) was added slowly and stirring was continued in the dark for a further 30 min. The cold reaction was then diluted with diethyl ether (10 ml), washed successively with 5% aqueous sodium metabisulphite solution (5 ml), water (10 ml) and saturated aqueous sodium chloride solution (10 ml), dried ($MgSO_4$), filtered and evaporated to give the iodide **6** as a dark red oil (11 mg, 49% crude yield). This material was used without further purification; δ_H (300 MHz; $CDCl_3$) 1.39 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.77 (3H, s,:CCH_3), 3.56 (1H, bs, OH, disappears upon addition of D_2O), 4.02 (1H, bs, NH), 4.23 (1H, bs, NH), 5.08 [1H, s, (*H*)C(OH)], 5.63 [1H, d, *J*=5.3 Hz, (*H*)C:C(CH_3)], 5.70 [1H, dd, *J*=5.3 and 11.3 Hz, I(H)C:(*H*)], 6.01 [1H, d, *J*=11.3 Hz, I(*H*)C:(H)]; *m/z* (CI) 192 ($C_5H_5I^+$, 100%), 87 ($C_4H_8NO^+ + H^+$, 45).

3-Hydroxy-7-iodo-2,2,4-trimethylhepta-4,6-dienoic acid phenyl ester 32. A solution of 3-hydroxy-2,2,4-trimethyl-7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-ylhepta-4,6-dienoic acid phenyl ester **27** (25 mg, 0.07 mmol) in dry THF (3.3 ml) under argon was cooled to −78°C. Iodine monochloride (11.7 mg in 1.6 ml of dichloromethane, 0.07 mmol) was slowly added, and the solution was stirred in the absence of light for 2 h. A suspension of sodium methoxide (11.6 mg, 0.21 mmol) in dry methanol (8.3 ml) was added slowly and stirring was continued in the dark for a further 30 min. The cold reaction was then diluted with diethyl ether (10 ml), washed successively with 5% aqueous sodium metabisulphite solution (5 ml), saturated sodium chloride solution (10 ml) and water (10 ml), dried ($MgSO_4$), filtered and evaporated to give a crude product iodide **32** as a dark red oil (4 mg, 15% crude yield); δ_H (300 MHz; $CDCl_3$) 1.53 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.81 (3H, s,:CCH_3), 2.12 (1H, bs, OH, disappears upon addition of D_2O), 4.79 [1H, s, C(*H*)OH], 5.83 [1H, d, *J*=15.1 Hz, I(H)C:], 6.03 [1H, dd, *J*=7.9 and 15.1 Hz, I(H)C:C(*H*)], 6.04 (1H, d, *J*=7.9 Hz, CH_3C:C*H*), 7.31–7.71 (5H, m, Ph); *m/z* (CI) 278 ($MH^+ - I + NH_4^+$, 95%).

4,4-Diethoxybut-1-yne 34. To aluminium powder (2.32 g, 85.99 mmol) and mercuric chloride (0.3 g, 1.10 mmol) stirred in dry diethyl ether (25 ml) at room temperature, propargyl bromide (8.9 g, 74.85 mmol) was added dropwise. The reaction mixture was then warmed at 45°C for a further 1 h, cooled to −78°C and triethylorthoformate (13.7 ml, 82.50 mmol) was added in small portions. This mixture was kept at −78°C for a further 2 h, then warmed to −40°C for a further 1 h, before being quenched by addition of aqueous saturated ammonium chloride solution. The mixture was diluted with diethyl ether (50 ml), separated, washed with saturated aqueous sodium chloride solution (20 ml), dried ($MgSO_4$), filtered and evaporated. Distillation afforded **34** (5.3 g, 50%) as a yellow oil; bp 50°C (20 mmHg); IR, ^{1}H NMR and ^{13}C NMR matched those quoted in the literature;[35] GC–MS (EI) 141 $[M-H]^+$.

4,4-Diethoxy-1-(3,3,4,4-tetramethyl-1,2,5-dioxaborolane)-but-1-ene 35. 4,4-Diethoxybut-1-yne **34** (0.6 g, 4.22 mmol) was added to a solution of $IPCBH_2$ (1.7 g, 8.40 mmol) in dry dichloromethane (85 ml) under argon at room temperature. The solution was heated at 40°C for 16 h. Acetaldehyde (0.5 ml, 14.40 mmol) was then added and the solution was refluxed for a further 3 h. Pinacol (2.1 g, 17.79 mmol) was then added in solution in dichloromethane (15 ml). The reaction mixture was refluxed for 30 min and, then, was allowed to cool to room temperature before quenching with 5% aqueous sodium hydrogencarbonate solution (50 ml). The organic layer was washed with water, dried ($MgSO_4$), filtered and evaporated. Purification by silica gel chromatography (petroleum ether 40/60:ethyl acetate, 4:1 as eluant) gave the impure **35** (595 mg) as a yellow oil; ν_{max} (film)/cm^{-1} 3030 (:CH), 2960 (CH aliphatic), 2880 (CH aliphatic), 1600 (C:C), 1050 (C·O); δ_H (300 MHz; $CDCl_3$) 1.12–1.25 (6H, m, 2×CH_3CH_2O), 1.20 (12H, s, 4×CH_3·C), 2.25–2.35 and 2.40–2.50 [each 1H, m, CH_2CH(OCH_2CH_3)$_2$], 3.95–4.05 (1H, m, CH_2C*H*), 5.51(1H, dt, *J*=1.5 and 18 Hz, B·CH), 6.56 (1H, dt, *J*=6.7 and 18.0 Hz, B·CH:C*H*); *m/z* (CI) 288.2341 [M^++NH_4^+, ($C_{14}H_{27}BO_4$+NH_4^+) requires *m/z*=288.2346, 57%], 225 (M^+−CH_3CH_2O, 100), 167 (M^+−CH(OEt)$_2$, 25).

Tri-*n*-butyl(4,4-diethoxybut-2-enyl)stannane 36. 4,4-Diethoxybut-1-yne **34** (380 mg, 2.68 mmol), tri-*n*-butyltin hydride (0.9 ml, 3.39 mmol) and AIBN (50 mg, 0.30 mmol) were heated at 80°C for 7 h under argon. The reaction mixture was allowed to cool to room temperature. Purification by silica gel chromatography (petroleum ether 40/60:ethyl acetate, 4:1 as eluant) gave **36** (1.1 g, 94%) as a colourless oil; ν_{max} (film)/cm^{-1} 3010 (:CH), 2940 (CH aliphatic), 2900 (CH aliphatic), 1590 (C:C), 1050 (C·O); δ_H (300 MHz; $CDCl_3$) 0.83 (6H, t, *J*=7.7 Hz, 3×SnCH_2), 0.87 (9H, t, *J*=7.0 Hz, 3×CH_3CH_2CH_2), 1.19 (6H, t, *J*=7.0 Hz, 2×CH_3CH_2O), 1.30 (6H, quintuplet, *J*=7.0 Hz, 3×CH_2CH_2Sn), 1.46 (6H, sextuplet, *J*=7.0 Hz, 3×CH$_3$CH_2CH_2), 2.47 (2H, t, *J*=5.6 Hz,:CHCH_2), 3.45–3.70 (4H, m, 2×OCH_2), 4.52 (1H, t, *J*=5.6 Hz, (*H*)C(OCH_2CH_3)$_2$), 5.91 (1H, dt, *J*=5.6 and 19.0 Hz, HC:C*H*CH_2), 6.02 (1H, d, *J*=19.0 Hz, *H*C: CHCH_2); δ_C (75.5 MHz; $CDCl_3$) 9.2 (SnCH_2), 13.5 (CH_3), 15.5 (*C*H$_3$CH$_2$O), 27.2 (CH_2), 29.1 (CH_2), 42.3 [*C*H$_2$CH(OCH$_2$CH$_3$)$_2$], 60.9 (O*C*H$_2$CH$_3$), 102.4 [H*C*(OCH$_2$CH$_3$)$_2$], 131.0 (:*C*HCH$_2$), 143.6 (H*C*:CHCH$_2$); *m/z* (CI) 435.2289 (MH^+, $C_{20}H_{43}O_2Sn$ requires *m/z*= 435.2285, 10%), 389 ($C_{18}H_{37}O^+$, 35), 331 ($C_{16}H_{32}^+$, 55).

Tri-*n*-butyl(but-2-enal)stannane 37. Tri-*n*-butyl(4,4-diethoxybut-2-enyl)stannane **36** was dissolved in $CDCl_3$ (0.6 ml) and treated with trifluoromethylacetic acid (one drop). The transformation to **37** was followed by ^1H NMR and was complete after 6 days; ν_{max} (film)/cm^{-1} 1680 (C:O); δ_H (300 MHz; $CDCl_3$) 0.91 (6H, t, *J*=7.3 Hz, 3×SnCH_2), 1.27–1.40 (9H, m, 3×CH_3), 1.39 (6H, t, *J*= 7.0 Hz, 3×CH_2CH_2Sn), 1.61 (6H, m, 3×CH$_3$CH_2CH_2CH_2Sn), 2.03 [2H, dd, *J*=1.7 and 6.9 Hz, CH_2(H)C:C(H)], 6.14 [1H, ddt, *J*=1.7, 8.0 and 15.6 Hz, CH$_2$(H)C:C(*H*)CHO], 6.88 [1H, dt, *J*=6.9 and 15.6 Hz, CH$_2$(*H*)C:C(H)CHO], 9.48 (1H, d, *J*=8.0 Hz, CHO); δ_C (75.5 MHz; $CDCl_3$) 13.5 (CH_3), 18.6 (CH_2), 26.9 (CH_2), 27.3 (CH_2), 64.3 (*C*H$_2$C:), 134.6 (:*C*CHO), 154.2 (CH$_2$*C*:), 194.1 (CHO).

Tri-*n*-butyl(4-hydroxybut-3-enyl)stannane 38. 3-Butyn-1-ol (0.5 g, 7.14 mmol), tri-*n*-butyltin hydride (2.4 ml, 9.05 mmol) and AIBN (100 mg, 0.60 mmol) were heated at 80°C for 7 h under argon. The reaction mixture was allowed to cool to room temperature. Purification by silica gel chromatography (petroleum ether 40/60:ethyl acetate, 4:1 as eluant) gave **38** (2.2 g, 85%) as a colourless oil; ν_{max} (film)/cm^{-1} 3320 (OH), 3010 (:CH), 2960 (CH aliphatic), 2880 (CH aliphatic), 1590 (C:C), 1080 (C·O); δ_H (300 MHz; $CDCl_3$) 0.88 (6H, t, *J*=7.2 Hz, 3×SnCH_2), 1.30–1.46 (15H, m, 3×CH_3CH_2CH_2CH_2Sn), 1.48 (6H, t, *J*=7.2 Hz, 3×CH_2CH_2Sn), 1.50 (1H, s, OH, disappears upon addition of D_2O), 2.41 (2H, m,:CCH_2), 3.67 (2H, t, *J*=6.2 Hz,.CH_2OH), 5.93 [1H, dt, *J*=6.2 and 19 Hz,:C(*H*)CH$_2$], 6.12 [1H, dt, *J*=19 Hz, :C(H)Sn]; δ_C (75.5 MHz; $CDCl_3$) 9.7 (SnCH_2), 13.8 (CH_3), 27.6 (CH_2), 29.1 (CH_2), 40.9 (C:C*C*H$_2$), 61.6 (CH_2OH), 132.3 (SnC:*C*H), 145.0 (Sn*C*:CH); *m/z* (EI) 363.1713 (MH^+, $C_{16}H_{35}SnO$ requires *m/z*=363.1709, 10%), 332 (MH^+−CH_2OH, 5), 306 (*n*-$Bu_3SnCH_2^+$, 70).

Tri-*n*-butyl(but-2-enal)stannane 39. To a solution of oxalyl chloride (0.03 ml, 0.30 mmol) in dry dichloromethane (2 ml) under argon was added DMSO (0.04 ml, 0.60 mmol) at −78°C. The reaction mixture was stirred for 15 min before adding tri-*n*-butyl(4-hydroxybut-3-enyl)-stannane **38** (100 mg, 0.28 mmol) in dichloromethane (0.5 ml) at −60°C. The mixture was stirred for a further 15 min, triethylamine (0.20 ml, 1.40 mmol) was added and after 5 min at −78°C, the mixture was allowed to warm to room temperature. The reaction mixture was partitioned between dichloromethane (10 ml) and water (10 ml). The aqueous layer was separated and extracted with dichloromethane. The combined organic extracts were washed sequentially with 1% hydrochloric acid solution (5 ml), water (5 ml), 5% aqueous sodium carbonate solution (5 ml) and water (5 ml). The organic layer was dried ($MgSO_4$), filtered and evaporated to give a brown oil **39** (61 mg, 60%), which was used without further purification; ν_{max} (film)/cm^{-1} 1710 (C:O); δ_H (300 MHz; $CDCl_3$) crude product 0.89 (6H, t, *J*=7.2 Hz, 3×SnCH_2), 1.25–1.60 (21H, m, 3×CH_3CH_2CH_2CH_2Sn), 3.00 [2H, d, *J*=10.9 Hz, (H)C:C(H)CH_2], 5.80 [1H, dd, *J*=10.9 and 17.7 Hz, (H)C:C(*H*)CH$_2$], 6.00 [1H, d, *J*=17.7 Hz, (*H*)C:C(H)CH$_2$], 9.47 (1H, s, CHO); *m/z* (EI) 359.1395 (M − H^+, $C_{16}H_{31}SnO$ requires *m/z*=359.1397, 40%).

5-(3-Tri-*n*-butylstannanylallyl)oxazole 40. Tosylmethyl isocyanide (TosMIC) (38 mg, 0.19 mmol), tri-*n*-butyl(but-2-enal)stannane **39** (100 mg, 0.28 mmol) and potassium carbonate (30 mg, 0.26 mmol) were boiled under reflux in methanol (15 ml) for 6 h under argon. Methanol was evaporated and the residue was partitioned between water (20 ml) and dichloromethane (20 ml). The aqueous layer was extracted with dichloromethane (3×10 ml), the combined organic layers were dried ($MgSO_4$), filtered and evaporated. Purification by silica gel chromatography (petroleum ether 40/60:ethyl acetate, 9:1 as eluant) gave **40** (15 mg, 20%) as a yellow oil; ν_{max} (film)/cm^{-1} 2950 (CH), 2860 (CH), 1600 (C:C), 1080 (C·O); δ_H (300 MHz; $CDCl_3$) 0.90 (6H, t, *J*=7.0 Hz, 3×SnCH_2), 1.05–1.65 (21H, m, 3×CH_3CH_2CH_2CH_2Sn), 3.66 [2H, d, *J*=5.9 Hz, CH_2(H)C:C(H)], 5.96 [1H, A*B*X$_2$, *J*=5.9 and 18.8 Hz,

(*H*)C:C(H)SnBu$_3$], 6.08 [1H, *A*BX$_2$, *J*=18.8 Hz, (H)C:C(*H*)SnBu$_3$], 7.05 [1H, s, N(C:CH)], 7.79 [1H, s, N:C(H)O]; *m/z* (CI) 399 (M^+, 20%), 342.0876 (M^+-n-Bu, $C_{14}H_{24}NOSn$ requires *m/z*=342.0879, 35), 308 ($C_{12}H_{27}Sn^+ + NH_4^+$, 100), 291 ($C_{12}H_{27}Sn^+$, 60).

Phthoxazolin A 4. 3-Hydroxy-7-iodo-2,2,4-trimethylhepta-4,6-dienoic acid amide **6** (2.5 mg, 8.09 μmol), 5-(3-tri-*n*-butylstannanyl-allyl)oxazole **40** (3.2 mg, 8.02 μmol) and diisopropylethylamine (3 μl, 16.88 μl) were degassed in dry DMF (1 ml) at room temperature for 1 h. $Pd(MeCN)_2Cl_2$ (0.1 mg, 0.38 μmol) was then added and the solution was degassed for a further 1 h then stirred for 5 days at room temperature before treating the reaction mixture with aqueous potassium fluoride in acetone at 0°C. After 30 min the reaction mixture was diluted with dichloromethane (10 ml) and washed with 1% aqueous hydrochloric acid solution (5 ml). The aqueous layer was extracted with dichloromethane (2×10 ml), the combined organic layers washed with water, dried ($MgSO_4$), filtered and evaporated. Silica gel chromatography (petroleum ether 40/60:ethyl acetate, 98:2 as eluant) gave a yellow oil which was further purified by silica gel chromatography (dichloromethane: methanol, 10:1 as eluant) to give **4** as a yellow oil (0.5 mg, 22%) whose ^{1}H NMR matched those reported in the literature;[9c] *m/z* (FAB) 291.1702 (MH^+, $C_{16}H_{23}N_2O_3$ requires *m/z*=291.1708, 90%), 183 ($C_{10}H_{17}NO_2$, 55); *m/z* (CI) 308 ($M^+ + NH_4^+$, 45%), 192 ($C_{11}H_{12}NO^+ + NH_4^+$, 30), 116 ($C_5H_{10}NO_2^+$, 25).

Molecular mechanics minimisation of structure 19

Molecular mechanics calculations were carried out on structure **19** using MacSpartan Version 1.0.4, and the Sybyl force field[36], by fixing the dihedral angle of the relevant HC·C═O section to either −90 or −270°. Fig. 2 is a Chem3D[37] representation the lower energy of these two possible CH orientations which could result in deprotonation.[23] The strain energies were as follows: lowest energy conformation (H·C.C:O dihedral −150°), 13 kJmol^{-1}; Fig. 2 conformation (H·C.C:O dihedral −90°), 20 kJmol^{-1}; and the remaining conformation with a H·C.C:O dihedral of −270°, 28 kJmol^{-1}.

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