The Stereoselective synthesis of polyene natural products

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The Stereoselective Synthesis of Polyene Natural Products

A thesis submitted to the University of Durham for the degree of Ph.D.

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2005

Declaration:

I confirm that no part of the material offered has previously been submitted for a degree or qualification at this or any other University or institute of learning.

To my parents and sister

Acknowledgements

In producing this work I must firstly thank my supervisor Dr. Andy Whiting for numerous ideas, continued assistance and the opportunity to conduct this work. Also my industrial supervisor Dr. Andrew P. Lightfoot who has highlighted an alternative approach to specific problems and this work in general. Furthermore both have been very supportive and demonstrated a high level of confidence in me and my work which has been of great benefit professionally and personally.

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Abbreviations

Ac	acetyl
AIBN	2,2'-azobis(2-methylpropionitrile)
aq.	aqueous
Ar	aromatic
9-BBN	9-borabicyclo[3.3.1]nonane
Boc	*tert*-butoxycarbonyl
bp	boiling point
Bu	butyl
CAN	ceric ammonium nitrate
CI^+	chemical ionisation
Cy	cyclohexyl
d	doublet
dba	dibenzylidene acetone
DCE	1,2-dichloroethane
DCM	dichloromethane
DEAD	diethylazodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	dimethylaminopyridine
DMF	*N,N'*-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dt	doublet of triplets
EI	electron ionisation
ES^+	electrospray (positive ion)
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
GC	gas chromatograghy
GC-MS	gas chromatography – mass spectrometry
HMDS	hexamethyldisilazane
LDA	lithium diisopropylamine

LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
M	molar
mp	melting point
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MS	mass spectrometry
NHC	*N*-heterocyclic carbene
NMP	1-methyl-2-pyrrolidinone
nmr	nuclear magnetic resonance
Ph	phenyl
Piv	pivaloyl
Pr	propyl
*i*PrOH	isopropyl alcohol
Py	pyridine
q	quartet
s	singlet
Sia	siamyl (1,2-dimethylpropyl)
t	triplet
TBAF	tetrabutyl ammonium fluoride
TBS	*tert*-butyl-dimethylsilyl
TES	triethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	tetramethylsilyl
Ts	tosyl

Abstract

A strategy for the stereocontrolled synthesis of polyene units was developed which centred around the chemistry of the vinyl boronate ester 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane **123**. Reaction conditions have been developed to allow the Heck coupling of **123** with a range of aryl and alkenyl electrophiles. The reaction is promoted by cationic palladium species which can be generated through the addition of metal salts to the reaction mixture. Conversely conditions have also been developed which allows **123** to react exclusively at the boron functionality along the Suzuki-Miyaura pathway, the syntheses of a range of styrene and diene systems being demonstrated. Vinyl boronate **123** demonstrates complete chemoselectivity which is controlled by the reaction conditions employed.

The alkenyl boronate esters, products of the Heck coupling of **123**, can be converted to alkenyl iodides to produce the *E*- or *Z*-isomer with extremely high geometrical purity. This is done through an iododeboronation reaction involving ICl and NaOMe where the order of reagent addition determines the stereochemical outcome. Presented within is a detailed insight into the mechanistic intricacies of the transformations and the use of alternative and novel reagents such as pyridine-ICl for stereoselective iodo- and chlorodeboronation reactions is also demonstrated.

This strategy was successfully applied to the syntheses of 1,6-diphenyl-1,3,5-hexatrienes of varying alkene geometries **205-207**, which were prepared from just iodobenzene and vinyl boronate **123** using those three key reactions. The use of this strategy also went some way to preparing the tetraene-containing natural product ixoric acid **124**, although a total synthesis was not achieved during these studies.

Research towards the first total synthesis of the natural product viridenomycin **125** was also conducted, especially towards the cyclopentenol core **246**. An advanced intermediate cyclopentenone **248**, was prepared from readily available starting materials along a succinct synthetic pathway to provide **248** in a good yield whilst expressing high diastereo- and enantioselectivity. Thus, a route was demonstrated which appears superior to those already existing in the literature.

1 Introduction

Polyene natural products appear widely in nature and as such many show biological effects on a range of organisms. In the continued quest for potential drug molecules and the development and advancement of synthetic strategies, a large number of these natural products have been synthesised.[1] The key issues surrounding the construction of conjugated systems is the ability to control the geometry of each alkene function, the major obstacle being that (*Z*)-alkene units are less thermodynamically stable then the (*E*)-form and, as a consequence, are susceptible to isomerisation to the favoured isomer. Thus, the more (*Z*)-double bonds in any polyene system, the more difficult it is to construct.

The utilisation of traditional synthetic methods for alkene construction has in many cases proven successful; however, most possess a number of disadvantages. The use of strong bases and harsh conditions to induce elimination reactions is not always applicable in the preparation of highly sensitive and elaborate natural products. The Wittig reaction and its variant, the Horner-Wadsworth-Emmons reaction, suffer from the fact that they generally produce mixtures of isomers and, although selectivity in favour of the (*Z*)-alkene can be obtained, the reactions appear inherently (*E*)-selective.[2] Again, the Julia and modified Julia protocols can, in certain instances, favour the formation of (*Z*)-alkene units, but the reaction generally provides mixtures which favour the thermodynamically more stable (*E*)-form.[3,4] The reagent-controlled reduction of alkynes to generate (*E*)- or (*Z*)-alkenes is, however, highly useful and can be used as an integral part of a strategy to construct polyenes which is based around the use of the Sonogashira[5] coupling reaction to introduce the alkyne function, which can therefore be considered as a masked alkene motif.[6,7]

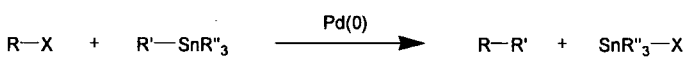
Increasingly, palladium catalysed coupling reactions, such as the Heck, Suzuki-Miyaura and Stille reactions, have been employed as key reactions when building polyene moieties in natural product total syntheses. The advantage of using these cross-coupling reactions to construct such systems is that the alkene geometries are already predefined in the coupling partners and the units are merely connected together in a carbon-carbon single bond forming reaction unlike methods such as the Wittig where the double bond is actually formed in the reaction. As long as there is retention of alkene geometry under the reaction conditions employed, this strategy provides a solution to the difficulty involved in the construction of polyene units.

This review will explore the details of each of the three aforementioned palladium catalysed coupling reactions before moving on to discuss examples of how each has been applied to the syntheses of a number of polyene-containing natural products.

1.1 Stille Coupling Reactions

1.1.1 Introduction

The palladium catalysed coupling of an organotin reagent with an organic electrophile was first reported in the late 1970s by a number of different groups.[8-10] However, it was the extensive synthetic and mechanistic studies performed by Stille that gave rise to the naming of the reaction.[11] A generalised reaction is outlined below (Equation 1); both R and R' are commonly sp^2 hybridised such as alkenyl, aryl and heteroaryl (to avoid the problem of β-hydride elimination). The leaving group, X, is usually triflate or one of the halides, most commonly iodide or bromide, but occasionally chloride. Originally performed using tin as the organometallic reagent, related couplings using organomagnesium[12] and organozinc[13] compounds have also proceeded successfully.



R and R' = usually sp^2 hybridised
X = halide or triflate
R'' = usually *n*Bu or Me

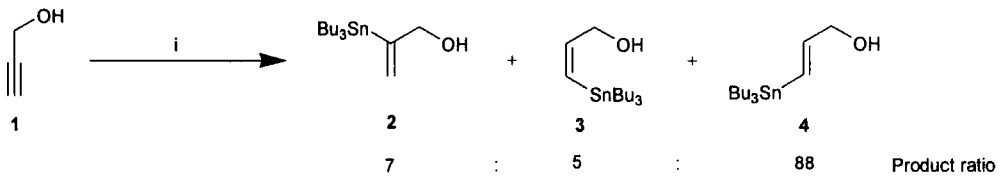
Equation 1

1.1.2 Preparation of Alkenyl Tin Reagents

There are number of ways by which the alkenyl tin reagent can be prepared with a large degree of control over the geometry of the system formed.

1.1.2.1 Tin Hydride Additions to Alkynes

The radical addition of a trialkyl tin hydride reagent to a terminal alkyne substrate can be employed to synthesise a substituted alkenyl tin reagent. The reaction can be initiated either by light or thermally in the presence of an initiator such as AIBN. These reactions are highly regioselective with the tin adding preferentially to the terminal carbon and (*E*)-alkenes being the favoured geometrical isomer although the (*Z*)-form is often observed.[14,15]



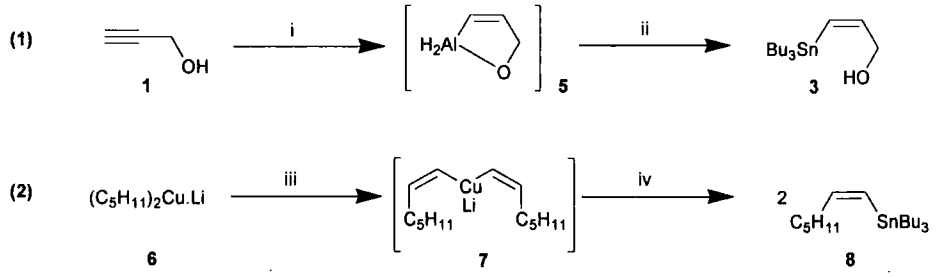
(i) AIBN, nBu$_3$SnH, 80°C, 2 h, 89%.

Equation 2

The hydrostannylation of alkynes can also be catalysed by a range of transition metal systems.[16] These reactions are subject to a large number of variables such as the metal, ligand, and substrate (in particular the electronic and steric effects of groups surrounding the alkyne). Each variable can dramatically effect the product distribution so that a mixture of regio- and geometrical isomers is usually obtained. If using this method of preparation, the conditions employed need to be chosen precisely depending on the nature of the substrate.

1.1.2.2 Electrophilic and Nucleophilic Tin Compounds

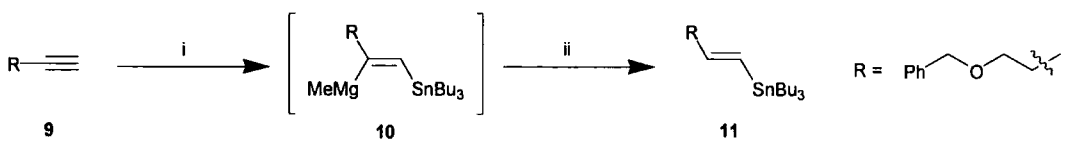
Electrophilic or nucleophilic tin reagents can also be used to generate alkenyl tin substrates for Stille couplings; a particular advantage of these methods over the use of tin hydrides is that if desired, (*Z*)-alkene systems can be prepared with high if not complete selectivity. Attack of a nucleophile, such as an organometallic compound, on an electrophilic tin reagent, such as a tin halide or triflates, can be used to generate the desired coupling agent. The examples overleaf (Equation 3) from the Corey group show two reactions of organometallic nucleophiles with tri-*n*-butyltin triflate to generate (*Z*)-alkenyl-tin products. In (1), the aluminium nucleophile is generated by the reaction of the substrate with $LiAlH_4$ before quenching with the triflate to give the terminal (*Z*)-alkene **3** with greater than 98% selectivity.[17] However, this example is substrate specific. Reaction (2) shows a synthesis which is much more applicable to a variety of systems as it does not require the assistance of a neighbouring functional group to install the alkene geometry.[18] The bis-(*Z*)-alkenyl-copper lithium intermediate **7** is generated from reaction of **6** with acetylene before addition of the tri-*n*-butyltin triflate and nucleophilic capture of the tin with retention of alkene geometry.



(i) $LiAlH_4$, THF, 23°C, 23 h. (ii) nBu$_3$SnOTf, Et_2O, -78°C, 5 h, 80%. (iii) Acetylene, Et_2O, -30°C, 20 min. (iv) nBu$_3$SnOTf, 90%.

Equation 3

The use of nucleophilic tin reagents to prepare functionalised alkenes tends to involve the substitution of a halide or triflate from a substrate. Tin cuprates can be reacted with β-chloroacrylates giving substitution; the reaction proceeds with retention of alkene geometry so either form can be prepared depending on the nature of the starting material.[19] A less substrate specific method involves the addition of an organotin-magnesium complex across a terminal alkene in the presence of copper(I) cyanide resulting in a single geometric and regioisomer. The reaction can be quenched with a range of electrophiles to provide a plethora of different alkenyl tin reagents.[20]

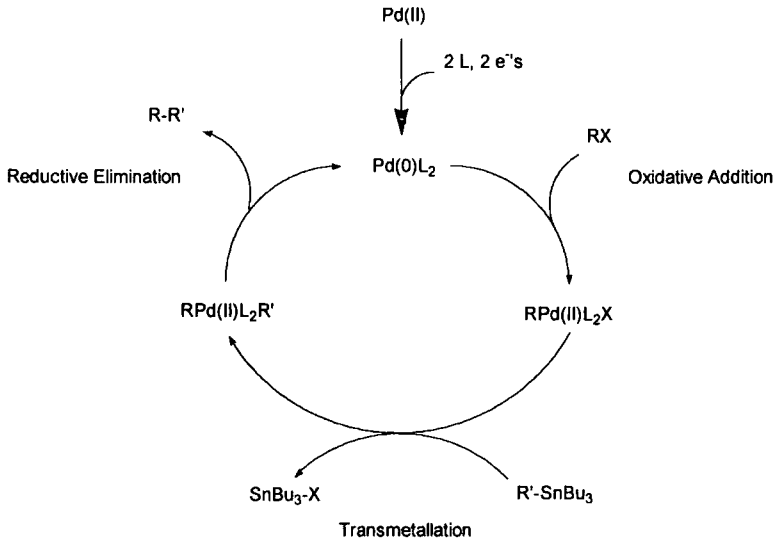


(i) nBu$_3$SnMgMe, CuCN, THF, 0°C, 30 min. (ii) H_3O^+, 0°C, 10 min, 88%.

Equation 4

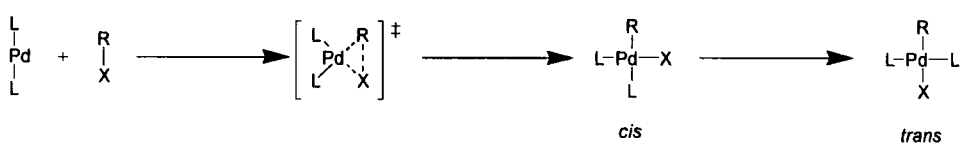
1.1.3 Mechanistic Details

The generalised catalytic cycle (scheme 1 - tri-*n*-butyltin moiety illustrated) presents the three main steps of oxidative addition, transmetallation and reductive elimination involved in the Stille coupling reaction. This cycle was proposed by Stille[11] as a working model and is an oversimplification due to the intricacies surrounding each of the three steps, which will be discussed in further detail.



Scheme 1

The process of oxidative addition sees the organic electrophile (R-X) added to the active palladium(0) species (coordinated by two ligands) resulting in the oxidation of the palladium centre to Pd(II). The mechanism can be considered as a nucleophilic attack by the Pd(0) centre on the electrophile, a process whose rate is increased by the presence of electron rich ligands and electronically deficient substrates.[21,22] It was widely believed that the direct product of the oxidative addition was the *trans*-product; however, mechanistic studies using a range of conditions have allowed the isolation and characterisation of the *cis*-product.[23-25] The addition process involves a concerted interaction of the $Pd(0)L_2$ centre with R-X generating a three-centred transition state which leads to the *cis*-addition product (scheme 2).[24,26] Under standard reaction conditions, the isomerisation of the addition product to the thermodynamically more stable *trans*-form is much more rapid than the transmetallation process and, as a consequence, the *cis*-form is rarely observed.

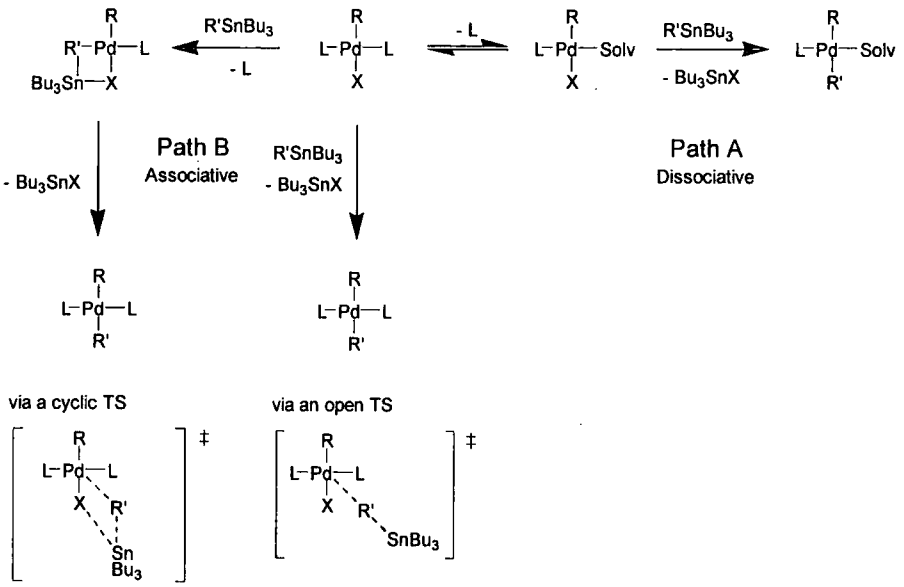


Scheme 2

The coupling of iodide and bromide substrates has always been possible and even trivial and, although the coupling of chlorides had been limited to certain systems, conditions have now been developed by Fu and co-workers which allow the coupling of a range of

chloride substrates in high yields.[27] Triflates also participate in Stille coupling reactions; however, it is important to note that the successful coupling of triflates requires the use of either a highly polar solvent or the addition of LiCl.[28-30] Nonetheless, the coupling of vinyl triflates has become particularly useful as these can be easily prepared from ketones utilizing enolate chemistry to generate the kinetic or thermodynamic product.[30]

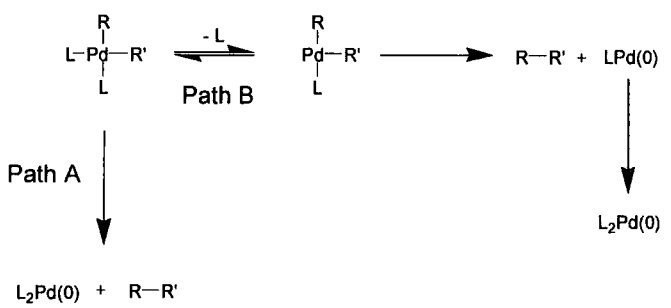
The transmetallation step, which sees the overall addition of R' to the Pd(II) centre at the expense of X, is generally the rate-determining step of the cycle. It is a highly intricate and complex process with each variable in the reaction mixture appearing to be able to change dramatically the process, which led to the proposal of a number of different mechanisms (scheme 3).



Scheme 3

Path A, postulated independently by both Farina and Hartwig, follows a dissociative mechanism by which a ligand is lost from the palladium centre before transmetallation in which R' is exchanged for X.[28,31] Later, Espinet presented the concept of an associative mechanism (Path B) in which two different processes are discussed involving either a cyclic or open transition state. Firstly, transmetallation through the formation of a Pd-X-Sn bridge. This passes through a cyclic transition state and results in the exchange of a ligand not X for the incoming organic fragment R'. Secondly, an associative mechanism passing through an open transition state (which is also discussed for the dissociative mechanism) by which R' does exchange with X.[32,33]

The final process of reductive elimination not only produces the desired coupled product but also regenerates the active catalyst species [Pd(0)L_2] which then re-enters the catalytic cycle. The carbon-carbon bond is formed from the carbon-palladium bonds with a concomitant elimination of the organic product. The elimination process can only occur from the *cis*-complex and so isomerisation of the *trans*-form must first occur. This may be achieved *via* dissociation and re-association of a ligand, a process which is facilitated by the presence of polar solvents. The *cis*-complex can then eliminate following two different pathways as presented by Stille and depicted below (scheme 4).[34,35] As shown in path A, the product can eliminate directly from the 4-coordinate centre. Alternatively, there can be an initial dissociation of a ligand to form a T-shaped[36] intermediate which then undergoes elimination, association of a ligand re-generates the active catalyst.



Scheme 4

1.1.4 Reaction Conditions

The reaction employs commercially available sources of palladium(0) or (II), examples of which include $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd(MeCN)_2Cl_2$ and $Pd(OAc)_2$. When using Pd(II), it must be reduced *in situ* to the active species, which is usually achieved by the homocoupling of two carbon units. However, it is also possible to pre-reduce the metal before its addition to the reaction mixture using DIBAL-H.[37] The Pd is used in conjunction with a ligand, such as the traditional triphenylphosphine. A whole range of phosphine ligands have been developed, and of particular utility was tri-*tert*-butylphosphine, which allowed the coupling of chloride substrates.[27] Vastly enhanced reaction rates over triphenylphosphine (10^2-10^3) have been demonstrated when using the weaker electron donating ligands tri-2-furylphosphine and triphenylarsine attributed to the fact they could easily dissociate from the metal facilitating the rate-determining

transmetallation step. These Farina conditions have been applied widely in Stille coupling reactions.[38]

The majority of reactions tend to be performed in ethereal solvents such as THF and dioxane or polar solvents such as DMF, NMP and DMSO (which assist the steps involved in the reaction as discussed above). The robust nature of the reaction has been demonstrated by the fact that it is possible to employ a wide range of solvents.

Additives, particularly copper(I) salts, have been shown to have a co-catalytic effect. The copper is able to coordinate free ligands which are not bound to the palladium centre, which facilitates the rate determining transmetallation step or reductive elimination where ligand dissociation may be required.[39] As stated earlier, the presence of LiCl (or polar solvent) is required for the coupling of triflates to take place; this is because the palladium-triflate addition product cannot undergo transmetallation with organo-tin species. The addition of chloride ions allows exchange with the triflate functionality at the metal centre and transmetallation can proceed (for polar solvent systems the solvent itself can perform this role).

1.1.5 Application to Natural Product Synthesis

Of all the palladium(0)-catalysed coupling reactions, the Stille reaction has become the most applicable to natural product synthesis. The organotin reagents and the reaction itself are air- and moisture stable. That allied with the fact that the reaction is able to proceed under mild conditions with high functional group tolerance makes it particularly advantageous.[10] With respect to the construction of polyenes, the fact the coupling of alkenyl units gives negligible isomerisation provides great assistance when building conjugated systems.[40-42] The Stille reaction tends to be incorporated as a final step in a natural product synthesis, often coupling two fragments together through the creation of a diene or triene system. Intramolecular Stille reactions have evolved into a powerful tool when employed in the cyclisation step of many macrocyclic polyene total syntheses.

1.1.5.1 Syntheses of Manumycins

The actinomyces soil bacteria (genus: *Streptomyces*) have given rise to the manumycin group of polyene metabolites. Manumycin A **12** was the first to be isolated in 1963 from *Streptomyces parvulus*,[43] but structural determination, including a full

stereochemical assignment, took a number of years to complete.[44,45] Further related structures have since been discovered including manumycin B[46] **13**, alisamycin[47,48] **14**, colabomycin A[49,50] **15** and colabomycin D[51] **16**. At the present time, the group consists of 23 members, all of which possess the same basic structural features but with slight modifications. At their centre exists a 2-amino-4-hydroxycyclohex-2-enone ring with either an epoxyketone (see **12**) or β-hydroxy ketone function (see **16**). There is a 'lower' polyene chain extending to what is usually a 2'-amino-3'-hydroxycyclopent-2'-enone unit. Some variation is observed in the 'lower' chain, but it is the 'upper' polyene chains that differ significantly in both length and functionalities giving most family members their distinction.

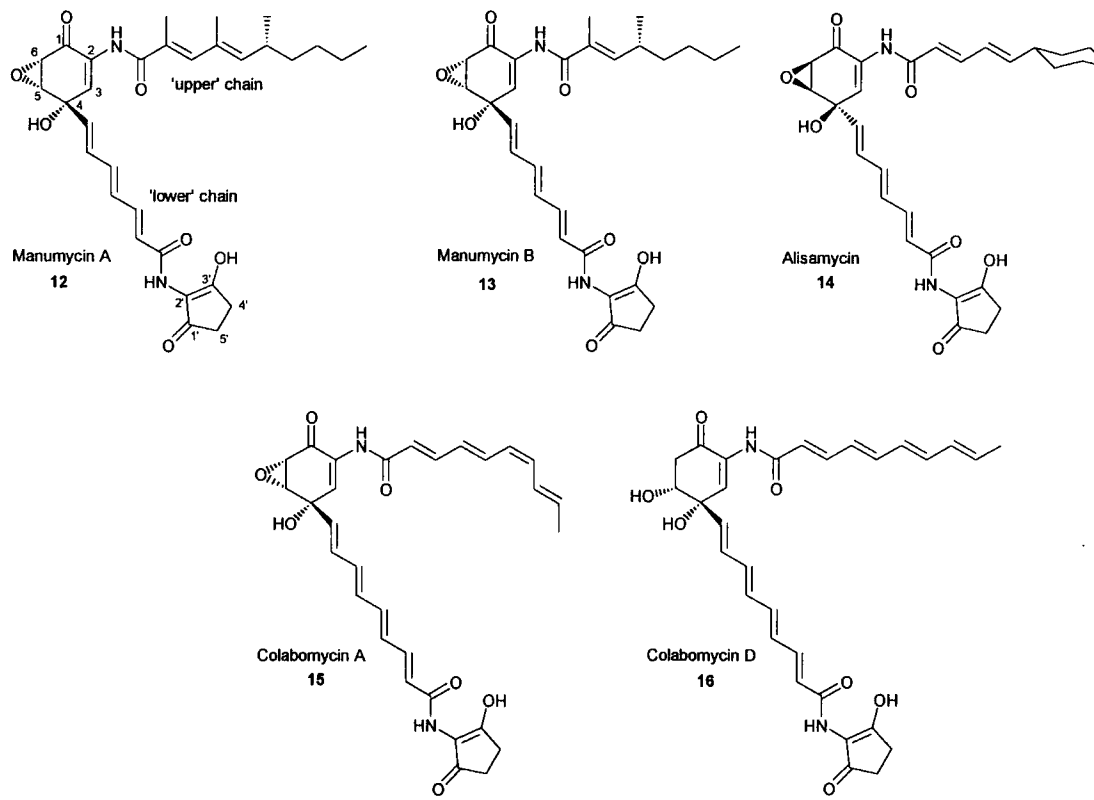
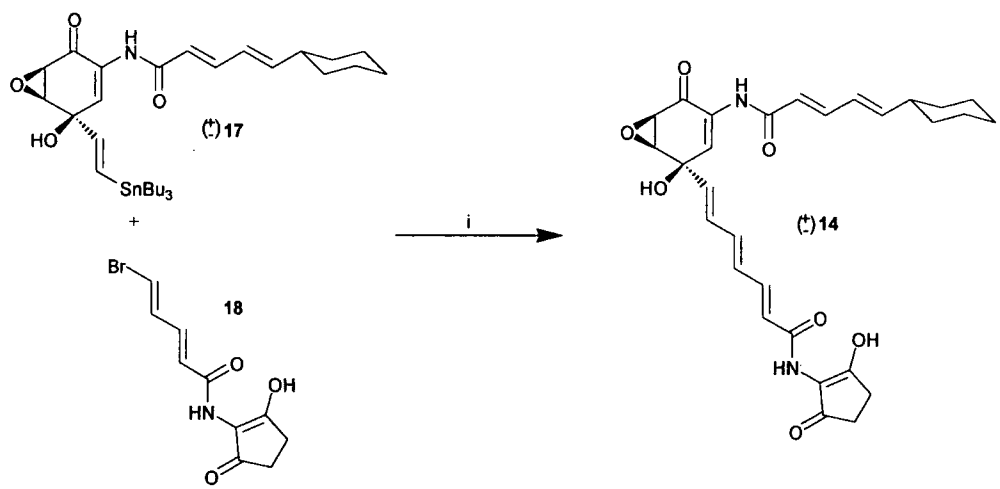


Figure 1

Across the group, the manumycins show a range of biological activities such as antibiotic, antifungal and insecticidal effects.[52] Most interesting is the inhibitory effect of manumycins A, B and C on the enzyme Ras farnesyltransferase,[53] which is a key component in the cellular growth pathway and as such is a potential target when inhibiting the abnormal cell growth and differentiation found in tumours. In more advanced studies, manumycin A **12** was found to regress tumour growth significantly *in*

vivo when using mice models.[53] It has been shown by structure-activity relationships that the origin of the inhibition arises through the enzyme binding the 'upper' side chain; structural variations in the 'lower' chain have little effect.[54,55] These demonstrations of the potential of certain manumycins as anti-cancer agents has propelled work on their syntheses.

A significant volume of work performed by the Taylor group has resulted in the syntheses of a number of the manumycins.[45,56-58] The key strategy applied to the syntheses of these family members is the Stille cross coupling reaction as a means of attaching the 'lower' polyene chain to the central unit. The first total synthesis of a member of the manumycin family (albeit as a racemate) was that of alisamycin **14** reported by them as recently as 1996.[56] The final coupling step of the synthesis between the stannane **17** and dienyl bromide **18** was performed using pre-reduced catalyst at ambient temperature to afford the target molecule in a 64% yield (equation 5).



(i) ($PdCl_2(PPh_3)_2$/DIBAL-H), DMF/THF, 25°C, 12 h, 64%.

Equation 5

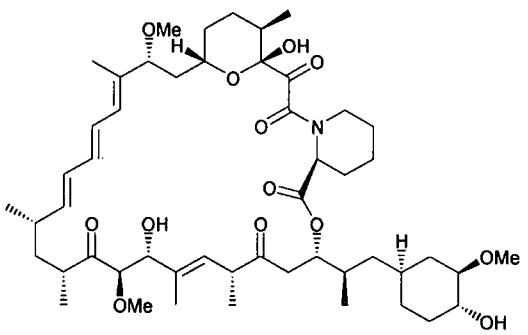
Following this the group also provided the first total synthesis of manumycin A utilising the same strategy of linking the 'lower' chain through a Stille reaction again using pre-reduced catalyst.[45] The synthetic route gave (+)-manumycin A, the enantiomer of the naturally occurring form **12**, but in doing so confirmed the stereochemistry of the natural form and demonstrated the *syn*-hydroxy epoxide relationship of the central ring.

An interesting feature of colabomycin A **15** is the presence of a (*E,E,Z,E*)-tetraene within the 'upper' polyene chain. As discussed earlier, the sensitivity of the

thermodynamically unfavourable (*Z*)-alkene makes the stereocontrolled synthesis of such systems extremely complex. As yet, colabomycin A has not been synthesised; however, in a route to the synthesis of racemic colabomycin D, the all (*E*)-alkene version was prepared in racemic form.[58]

1.1.5.2 Synthesis of Rapamycin

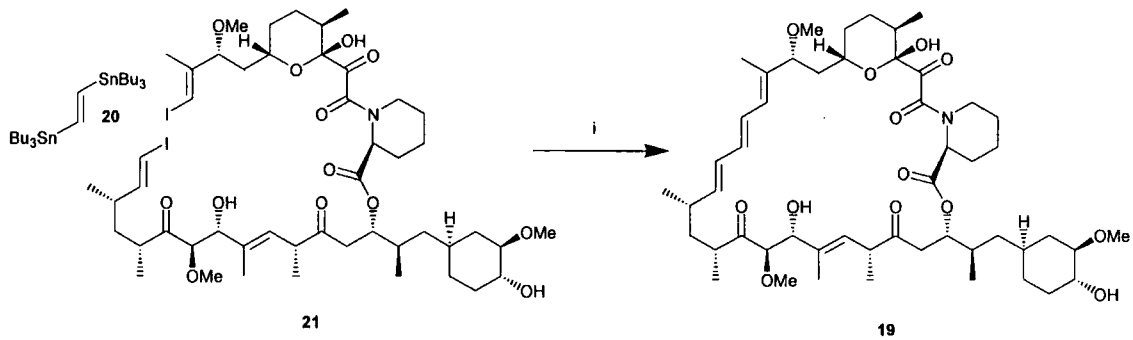
Rapamycin **19** is a metabolite of the soil bacteria *Streptomyces hygroscopicus*.[59] It exhibits potent antibiotic, cytotoxic and, in particular, significant immunosuppressive activity which has led to it being the subject of a comprehensive study as a potential rival to other immunosuppressive agents.[60] Its structure and stereochemical assignment was fully elucidated through crystallographic and nmr studies which have shown rapamycin to be a 29-membered macrocycle possessing a number of stereogenic centres and an all (*E*)-triene unit.[61,62]



19

Figure 2

The first total synthesis of rapamycin was reported by Nicolaou and contained a novel 'double' Stille coupling reaction.[63] This key reaction in the strategy was incorporated as the final synthetic step and involved the construction of the triene unit whilst simultaneously performing the cyclisation (equation 6). The 1,2-di(tri-*n*-butyl)tin-(*E*)-vinyl fragment **20** was coupled with the two terminal (*E*)-iodoalkenes of **21** to introduce the central alkene unit of the triene with complete retention of alkenyl geometry to yield the target molecule **19** possessing the desired (*E,E,E*)-alkene geometries. It is important to note that the mild conditions and high functional group tolerance of the reaction meant that no protecting groups were required in this final coupling reaction. This is a fine example of the potential of using the Stille reaction in polyene synthesis.

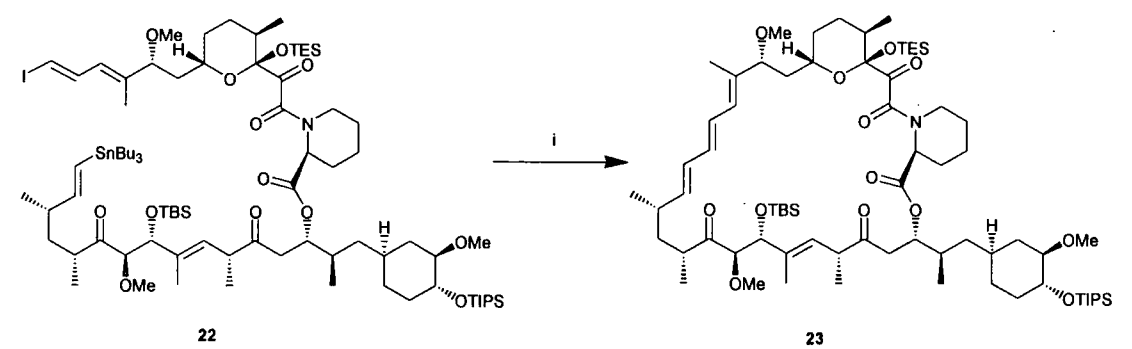


(i) $Pd(MeCN)_2Cl_2$, DIPEA, DMF/THF (1:1), 25°C, 24 h, 28%.

Equation 6

The coupling step itself was performed using a standard palladium(II) source in the presence of DIPEA in a polar solvent mixture of DMF and THF. After 24 hours at room temperature, a 28% yield of rapamycin was obtained along with a 30% yield of an iodo-stannane intermediate (believed to be from the reaction at the less substituted alkenyl iodide). Under similar conditions this was converted to **19** in a 60% yield increasing the overall yield to 46%.

Later, Smith published an alternative synthesis of rapamycin, which also utilised a Stille coupling as means of constructing the polyene and performing the cyclisation.[64] However, it used a single Stille reaction between an (*E*,*E*)-dienyl iodide and (*E*)-alkenyl tin functionality. In addition, the alcohol groups were all protected as silyl ethers rather than the 'naked' substrate used by Nicolaou. The catalyst used for this reaction was $Pd(P(2\text{-furyl})_3)_2Cl_2$ which was pre-prepared following a literature procedure[65] and is an interesting variation of the Farina conditions.[38] Again, the reaction was performed at ambient temperature but with a much shorter reaction time of 7 hours. The result was more successful than the 'double' Stille with the cyclised product being obtained in a 74% yield before deprotection to give the natural product.



(i) $Pd(P(2\text{-furyl})_3)_2Cl_2$, DIPEA, DMF/THF (1:1), 25°C, 7 h, 74%.

Equation 7

1.1.5.3 Syntheses of Mycotrienin I and Mycotrienol I

Isolated from a number of *Streptomyces* species are the (+)-mycotrienins I **24** and II **25** and (+)-mycotrienols I **26** and II **27**,[66-68] which have been shown to be potent antifungal agents.[69-71] Their basic structure consists of a macrocyclic amide which possesses a number of interesting features such as a quinone based subunit, an all (*E*)-triene and four or five asymmetric centres.[72]

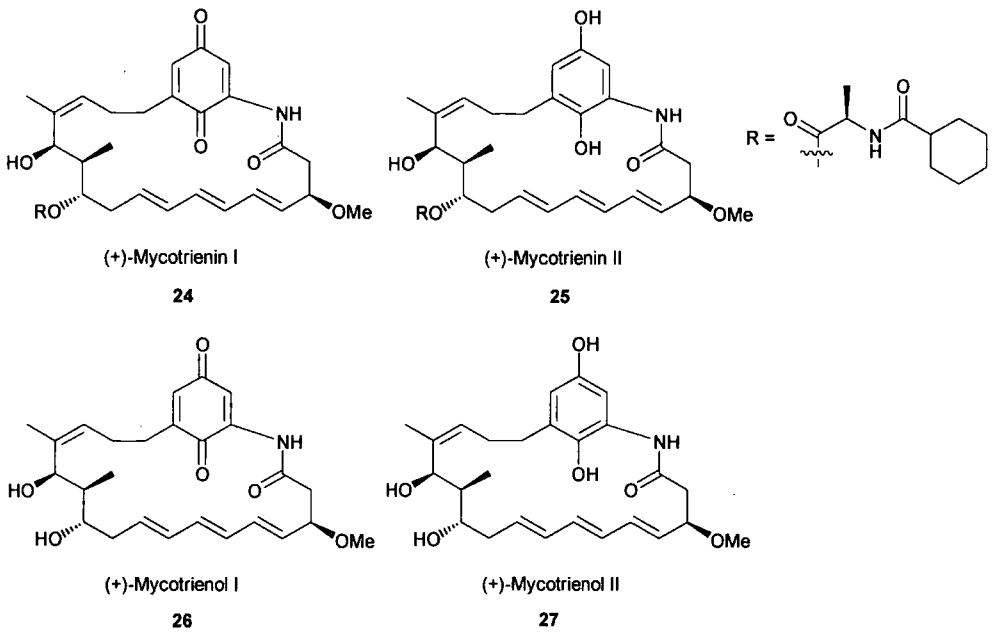
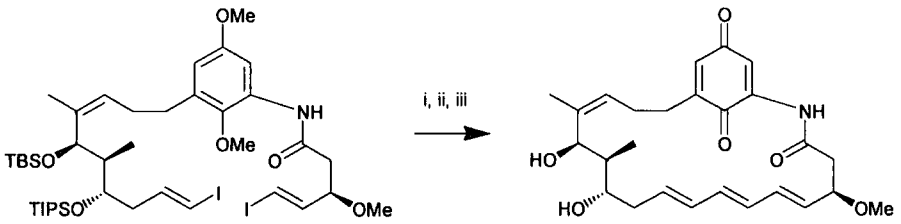


Figure 3

The tandem Stille strategy pioneered by Nicolaou during the synthesis of rapamycin was later applied by Panek to the syntheses of (+)-mycotrienin I **24** and (+)-mycotrienol I **26** to perform the same function of triene formation and macrocyclisation, the example shown (equation 8) is that of **26**.[73] The reaction conditions used for the coupling were identical to those employed by Nicolaou. The product of the Stille reaction was not isolated but carried through two further steps, oxidation to give the quinone and deprotection of the alcohol groups, furnishing the target molecule (+)-mycotrienol I **26**. The yield over these three steps was 54% showing that the coupling reaction proceeded much more efficiently for this system than during the rapamycin synthesis although performed under the same conditions.



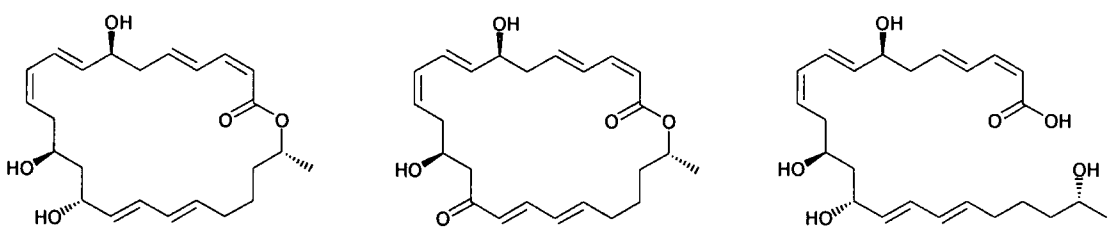
28 26

(i) $Pd(MeCN)_2Cl_2$, DIPEA, **20**, DMF/THF (1:1), 25°C, 24 h. (ii) CAN, THF/H_2O (10:1), 0°C, 30 min. (iii) aq. HF, MeCN, 25°C, 48 h, 54% (3 steps).

Equation 8

1.1.5.4 Synthesis of Macrolactin A

Isolated from taxonomically unclassifiable marine bacteria were 8 metabolites with closely related structures known as the macrolactins.[74] Macrolactins A-F are 24-membered lactones with either 3 or 4 defined stereogenic centres; A-E also contain three 1,3-diene units of defined (*E,E*)-, (*Z,E*)- and (*E,Z*)- geometry.[75] The final members of the group are the open-chain variants macrolactinic acid **31** and isomacrolactinic acid. Macrolactin A **29** has demonstrated a range of biological activities such as antibiotic, antiviral and cancer cell cytotoxicity properties.[74] A recent report presented the extension of the family through isolation of seven new macrolactins (G-M) from the culture broth of *Bacillus* sp. isolated from the red algae *Schizymenia dubyi*.[76]

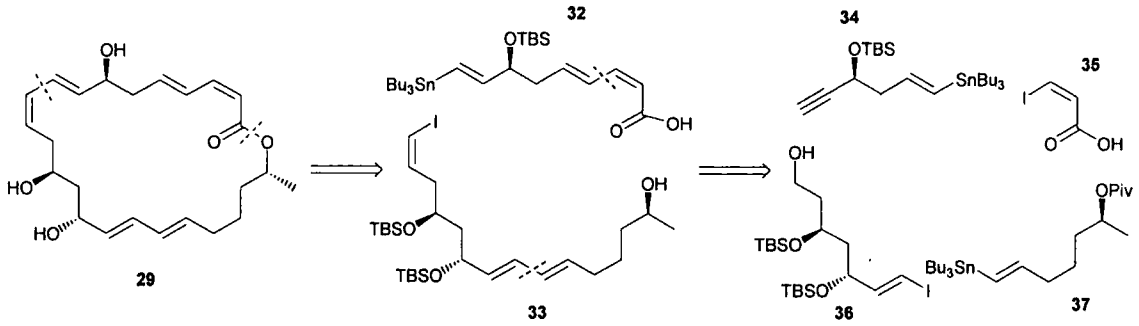


Macrolactin A **29** | Macrolactin E **30** | Macrolactinic Acid **31**

Figure 4

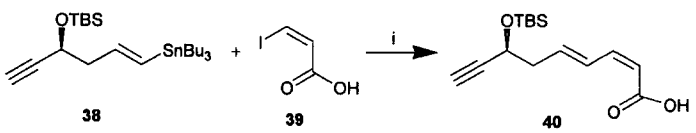
Retrosynthetic analysis of the macrolactins dividing the molecule into two and then four major fragments shows that the macrocycle, and in particular each diene, can be assembled via a series of Stille coupling reactions. In addition, the high stereochemical integrity of the reaction allows the preparation of conjugated (*Z*)-alkene units. The strategy was applied by Smith to the synthesis of macrolactin A **29** (Scheme 5). This example demonstrates the use of palladium catalysed coupling reactions throughout a

synthesis rather than following traditional methods and only using the Stille reaction in a final coupling step.[77] Following this success it was applied to the syntheses of macrolactin E **30** and macrolactinic acid **31**.[78]



Scheme 5

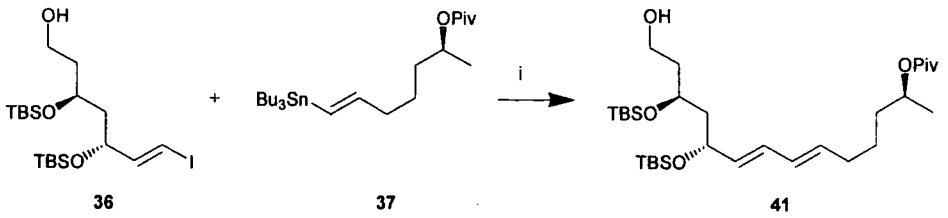
The upper fragment **32** was the first section prepared with the (*E*,*Z*)-diene function constructed *via* a Stille coupling reaction between the (*E*)-alkenyl stannane **38** (prepared from propargyl aldehyde) and (*Z*)-3-iodopropenoic acid **39** under standard conditions with the addition of $Ph_2PO_2NBu_4$ to remove the residual tin. The reaction proceeded with retention of alkene geometry giving the (*Z*,*E*)-diene fragment in a 64% yield (Equation 9). A palladium catalysed hydrostannylation of the alkyne furnished the (*E*)-alkenyl stannane **32** to allow the Stille coupling as a means of attaching the upper and lower portions of the molecule.



(i) $Pd(MeCN)_2Cl_2$, $Ph_2PO_2NBu_4$, DMF, 25°C, 18 h, 64%.

Equation 9

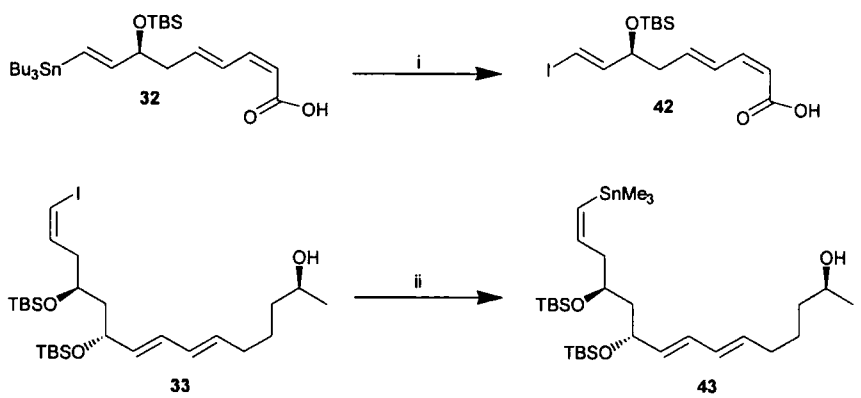
Synthesis of the lower fragment **33** involved the Stille coupling of **36** (again prepared from propargyl aldehyde) and **37** [derived from (*S*)-1-heptyn-6-ol] under similar conditions. On this occasion however, the catalyst was used in the absence of $Ph_2PO_2NBu_4$ giving a 63% yield of the coupled product. Conversion to the (*Z*)-iodoalkene coupling fragment **33** was achieved through Wittig chemistry.



(i) $Pd(MeCN)_2Cl_2$, DMF, 25°C, 14 h, 63%.

Equation 10

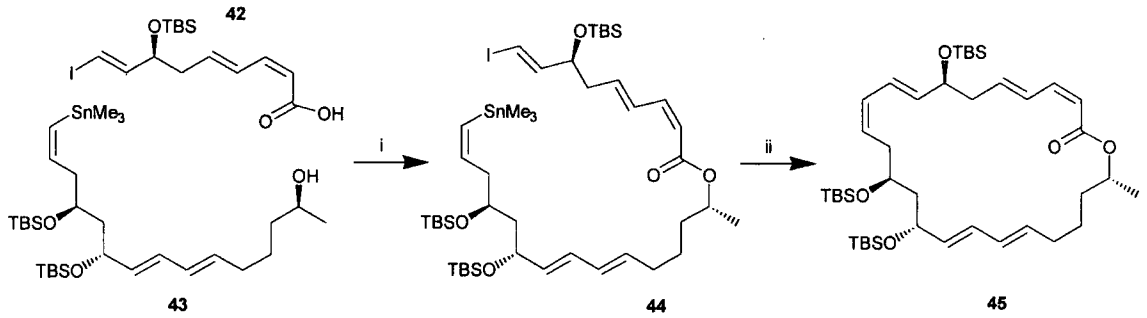
Macrocycle assembly was performed in a two-step process, involving a Mitsunobu esterification followed by a cyclisation again utilising a Stille coupling. Initial attempts at the coupling proceeded extremely slowly and in low yields so the alkenic functionalities were exchanged and the more reactive trimethyl tin used to replace the tri-*n*-butyl form. A tin-halogen exchange was employed to convert **32** to the alkenyl iodide **42**, whilst a palladium catalysed stannylation brought about the conversion of **33** to the (*Z*)-alkenyl tin fragment **43** with the complete preservation of alkenyl geometry.



(i) I_2, DCM, 77%. (ii) $Pd_2(dba)_3$, $(Me_3Sn)_2$, NMP, 25°C, 30 min, 64%.

Scheme 6

With the new fragments the esterification proceeded smoothly providing **44** in a 74% yield. Repetition of the coupling using $Pd_2(dba)_3$ in the presence diisopropylethylamine provided a 50% yield in just 5 hours; alcohol deprotection using TBAF provided the first synthesis of macrolactin A **29**. Macrolactinic acid **31** was prepared from the lactone in a 69% yield by treatment with KOH/MeOH.



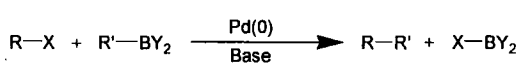
(i) PPh_3, DEAD, benzene, 10°C, 30 min, 74%. (ii) $Pd_2(dba)_3$, DIPEA, NMP, 25°C, 5 h, 50%.

Scheme 7

1.2 Suzuki-Miyaura Coupling Reactions

1.2.1 Introduction

Since first being reported, the palladium catalysed coupling of organoboron compounds with organic electrophiles in the presence of a base has become known as the Suzuki or Suzuki-Miyaura reaction.[79,80] A generalised Suzuki-Miyaura reaction is outlined below (Equation 11). Both R and R' are commonly sp^2 hybridised such as alkenyl, aryl and heteroaryl; however, the coupling of alkylboron species has also been reported.[81] The boron function itself can be a boronic acid, boronate ester, borane[81] or even a trifluoroborate salt.[82,83] The organic electrophile is, as with the Stille, usually an iodide, bromide or triflates; however, conditions for the room temperature coupling of aryl chlorides have also been developed.[84]



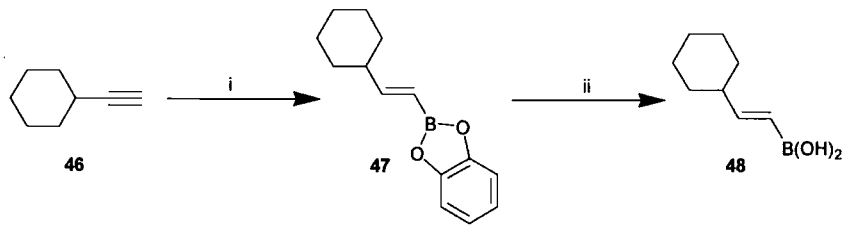
R and R' = usually sp^2 hybridised
X = halide or triflate
Y = OH, OR, R, F (as $R'BF_3K$)

Equation 11

1.2.2 Preparation of Alkenyl Boron Reagents

The most common starting point in the preparation of alkenyl boron species is the corresponding alkyne with the introduction of the boron functionality through a hydroboration reaction. The thermally induced hydroboration of a wide range of terminal alkynes can be performed with a number of different hydroborating agents giving *cis*-addition and hence the (*E*)-alkenyl boronate. There is however, the issue of the regioselectivity of addition, which is controlled by the steric nature of the alkyne

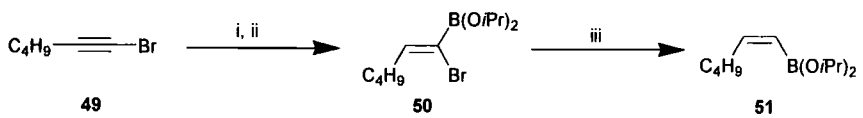
substituent and hydroborating agent so consequently can be increased through the use of reagents such as catecholborane[85,86] and 9-BBN[87] which promote the addition of the boron function to the less sterically hindered carbon. In the example shown in Scheme 8, the hydroboration gives 98% of the terminal addition product with complete (*E*)-alkene selectivity. Hydrolysis of the boronate ester to the boronic acid can be achieved through stirring in the presence of water and re-esterification, can be performed, in the presence of an alcohol.[88]



(i) Catecholborane, 70°C, 1 h, 82%. (ii) H_2O, 25°C, 1 h, 97%.

Scheme 8

Interestingly, (*Z*)-alkenyl boron coupling reagents can be prepared using a hydroboration reaction, but in a slightly different process being prepared from 1-halo-1-alkynyl substrates. Hydroboration of **49** using $HBBr_2.SMe_2$[89] again gives *cis*-addition with 98% regioselectivity before treatment with an *i*-propanol to yield the (*Z*)-haloalkenyl boronate ester **50**. Reaction with a nucleophile such as the hydride ion gives an S_N2 substitution reaction of the halide with the corresponding inversion of stereochemistry to form the (*Z*)-alkenyl boronate ester **51** in greater then 99% (*Z*)-selectivity. Alternative organic nucleophiles such as a Grignard reagent can generate 1,2-diorganosubstituted alkenyl boronates.[90,91]

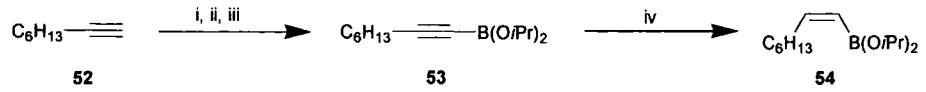


(i) $HBBr_2.SMe_2$, DCM, 25°C, 8 h. (ii) *i*PrOH, pentane, -10°C, 15 min, 87%. (iii) $KHB(OiPr)_3$, Et_2O, 0°C, 30 min, 89%.

Scheme 9

Another interesting and widely applicable method for the preparation of (*Z*)-alkenyl boronate esters is outlined in Scheme 10. Starting from a terminal alkyne, the alkynyl boronate ester **53** is prepared through reaction of the corresponding lithium reagent with a trialkyl borate.[92] A Lindlar reduction of the alkyne then generates the (*Z*)-alkenyl

boronate ester **54**, the selectivity of this reaction (scheme 10) is 95:5 in favour of the desired (*Z*)-form.[93]



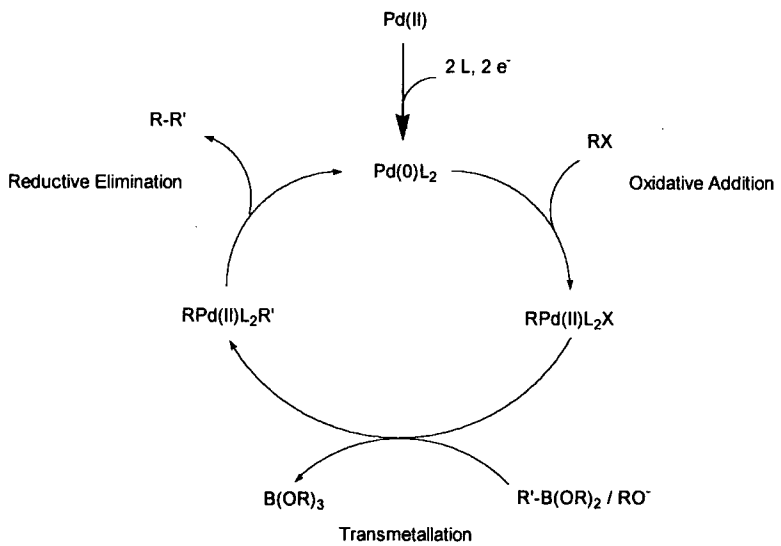
52 **53** **54**

(i) BuLi, Et_2O, -78°C. (ii) $B(OiPr)_3$, -78°C, 2 h. (iii) HCl, Et_2O, -78°C to 25°C, 95%. (iv) Lindlar catalyst, pyridine, 1,4-dioxane, H_2, 25°C, 82%.

Scheme 10

1.2.3 Mechanistic Details

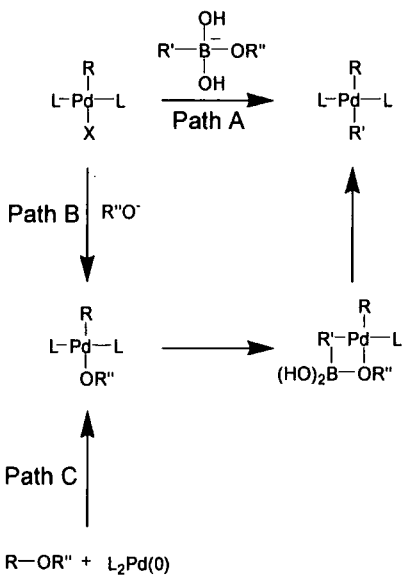
The mechanism outlined below (Scheme 11 – boronate acid/ester illustrated) follows the general process for palladium catalysed cross coupling reactions. The mechanistic intricacies of the oxidative addition and reductive elimination steps are as discussed for the Stille coupling reaction (1.1.3); however, unlike in the Stille coupling, the oxidative addition is usually the rate-determining step. As the reaction involves the coupling of an alternative organometallic reagent the key step of transmetallation is very different.



Scheme 11

As stated earlier, the reaction is performed in the presence of a base (usually hydroxide or alkoxide), and it is the base that plays a major role in the process of transmetallation. Scheme 12 depicts the three proposed mechanisms of base-assisted transmetallation.[94] The presence of a hard nucleophilic base can result in quaternisation of the boron centre through the formation of the 'ate' complex, which increases the nucleophilicity of R' allowing direct attack of the palladium centre following path A. Note that 'ate' complexes, such as the trifluoroborate salts, probably undergo direct transmetallation

through path A.[95] Alternatively substitution at the palladium centre can occur with the base replacing the halide or triflate to generate alkoxo- or hydroxo-palladium(II) species as shown in path B. Quaternisation of the boron function can then occur with the palladium bound base allowing transmetallation to occur *via* 4-membered ring transition state. Finally, in certain instances, the base has been shown to react directly with the organic electrophile which then undergoes oxidative addition to give the alkoxo- or hydroxo-palladium(II) species (path C). This can then undergo 'ate' complex formation as discussed in path B. The mechanism the reaction follows is dependent on the nature of the substrates, the reaction conditions employed and the base used.



Scheme 12

1.2.4 Reaction Conditions

A wide range of palladium sources have been employed, the most common being $Pd(PPh_3)_4$, but palladium(II) species such as $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$ have also been shown to be effective. More recently, palladacycle catalyst systems have been applied to many of the different cross-coupling reactions which includes the Suzuki-Miyaura reaction.[96] Their structure consists of a palladium metallated carbon which acts as a linker supporting donor groups (usually PR_2, NR_2 or SR) which can bind to the metal; some generalised structures are depicted in Figure 5. As a consequence of the organic linker and the donor groups, the use of additional ligand is not required as the palladacycle itself can catalyse the reaction.[97]

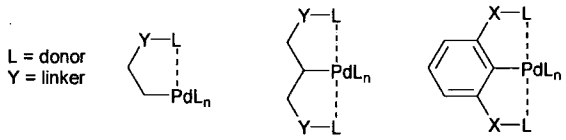


Figure 5

The use of $Pd(PPh_3)_4$ doesn't require the further addition of ligands; however, the difficulty in coupling chloride and sterically hindered substrates has led to the development of a wide range of ligands such as those discussed below. Used in conjunction with $Pd_2(dba)_3$ and $Pd(OAc)_2$, Buchwald has developed a range of bulky phosphine ligands such as **55** and **56** which can catalyse the aforementioned couplings and, in the case of **55**, are effective at room temperature.[84,98,99] Beller has shown that the phosphite ligands **57** and **58** can be used for Suzuki-Miyaura couplings in conjunction with $Pd(OAc)_2$ and a hydroxide or carbonate base.[100] Further development resulted in the synthesis of the bulky diadamantyl-*n*-butylphosphane **59**, an extremely reactive ligand for the coupling of aryl chlorides.[101] *N*-heterocyclic carbene ligands (NHC's) have evolved as alternatives to phosphines in a number of cross-coupling reactions[102] and those employed in these couplings have recently reached comparable levels of reactivity. Hermann reported a bis-adamantyl NHC **60** and demonstrated the coupling of aryl chlorides to give biaryls at room temperature.[103] Organ has demonstrated the use of the NHC **61** which can, produce biaryls in extremely impressive yields with some examples being almost quantitative.[104] The development of these ligands has increased the scope of the Suzuki-Miyaura reaction by increasing the range of possible substrates. Continued development should allow the coupling of further substrates such as alkenyl chlorides.

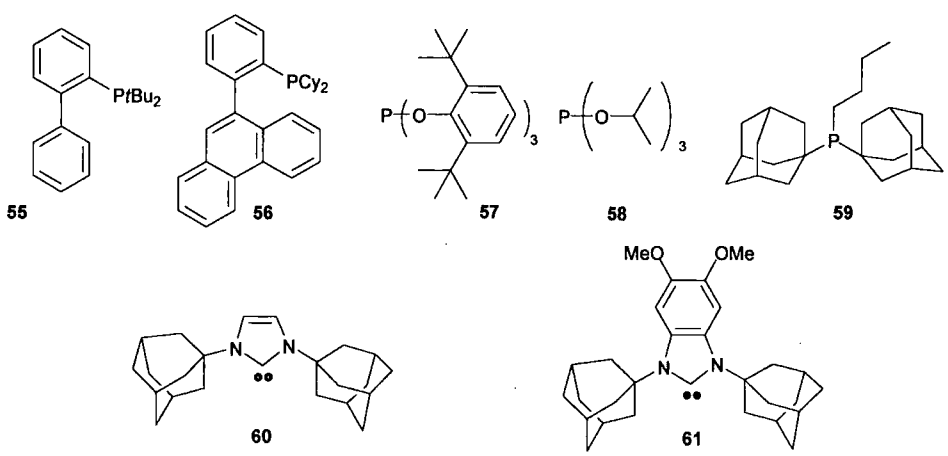


Figure 6

As discussed briefly already, the Suzuki-Miyaura reaction proceeds in the presence of a base commonly a hydroxide, alkoxide or carbonate but a range of bases have been examined. During the total synthesis of the natural product palytoxin, Kishi examined the effect of the bases TlOH and Ag_2O on the rate of coupling in comparison to KOH. A 30 fold rate enhancement was found for Ag_2O and, when using TlOH, the rate enhancement was 10^3. [105] The increased reaction rate has allowed coupling reactions to be performed successfully at room temperature, thus protecting sensitive functional groups which is particularly advantageous in natural product synthesis and has become known as Kishi conditions.

The reaction can, depending on the nature of the substrates, be performed in a wide variety of solvent systems which can be organic, biphasic or aqueous.

1.2.5 Application to Natural Product Synthesis

In natural product syntheses, the Suzuki-Miyaura reaction is commonly employed to bring about the stereocontrolled coupling of two alkenyl fragments to form a diene system. The reaction, however, does have the limitation of requiring the presence of a base to assist the transmetallation step and thus can limit its applicability to sensitive natural product systems.

1.2.5.1 Syntheses of Retinoids

The classification, retinoids **62-67**, refers to the natural and synthetic analogs of retinal (vitamin A) and there exists a large range of these polyenes.[106] Retinal **64** is required for mammalian cell growth and is an essential factor in embryonic and postnatal life.[107] In fact, retinoic acids and analogues can control the differentiation of cells along a number of different pathways.[108] The basic structure of the retinoids consists of a tri-methyl substituted cyclohexene unit possessing a functionalised polyene arm which can contain different alkene geometries and a variety of terminal functional groups.

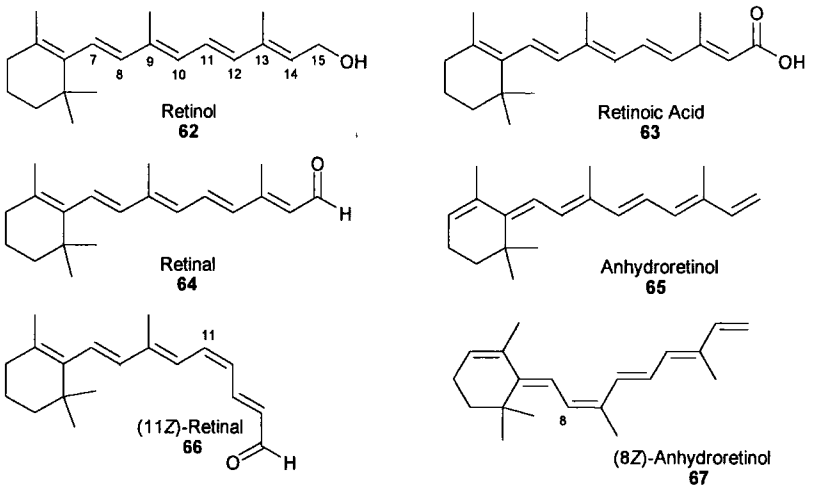
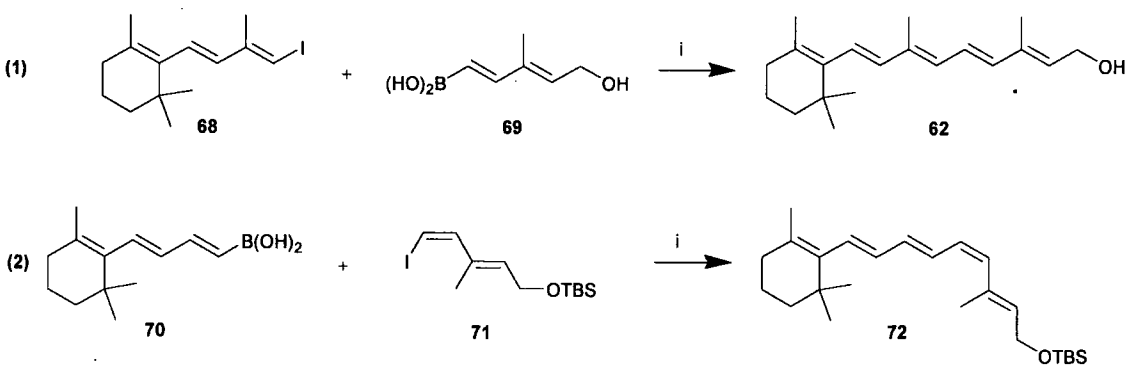


Figure 7

The research of de Lera *et al.* has resulted in the syntheses of a number of retinoids and analogues utilising both the Stille[109] and Suzuki-Miyaura coupling reactions.[110,111] In the majority of cases, the general strategy involved using these reactions for the preparation of tetraenes through the coupling of two diene units. When employing the Suzuki-Miyaura method, a dienyl iodide was coupled with a dienyl boronic acid under the conditions developed by Kishi.[105] These conditions, using TlOH, allowed the reaction to be performed at room temperature, a major advantage in the synthesis of the thermally unstable vitamin A and analogues. The coupling step in the synthesis of retinol is outlined in Scheme 13 (1), the reaction proceeded rapidly to give a high yield (83%) of the desired product.[110]



(i) $Pd(PPh_3)_4$, 10% aq TlOH, THF, 25°C, 30 min, **62** 83%, **72** 63%.

Scheme 13

Continued development resulted in the synthesis of further retinoid analogues which were demethylated at the 9-position.[110] Equation (2) in Scheme 13 shows the key coupling step in the syntheses of 11-(*Z*)-9-demethylretinol and 11-(*Z*)-9-demethylretinal

which possess a (*Z*)-alkene unit at carbon 11 within the polyene. The (*Z*)-alkene was introduced by the iodide coupling partner and prepared using Wittig chemistry to give a 16:1 ratio of geometrical isomers in favour of the (*Z*)-form **71**. The coupling with boronic acid **70** was again performed successfully under Kishi conditions to give the coupled product in a 63% yield but, more importantly, with complete retention of alkene geometry, i.e. no isomerisation to the favoured (*E*)-form. Alcohol deprotection of **72** generated the retinol analogue; oxidation to the retinal was performed with manganese dioxide.

1.2.5.2 Syntheses of Eicosanoids

Arachidonic acid **73** is the key precursor in the human biosyntheses of the eicosanoids. Arachidonic acid itself is one of the essential dietary fatty acids that the body is unable to manufacture.

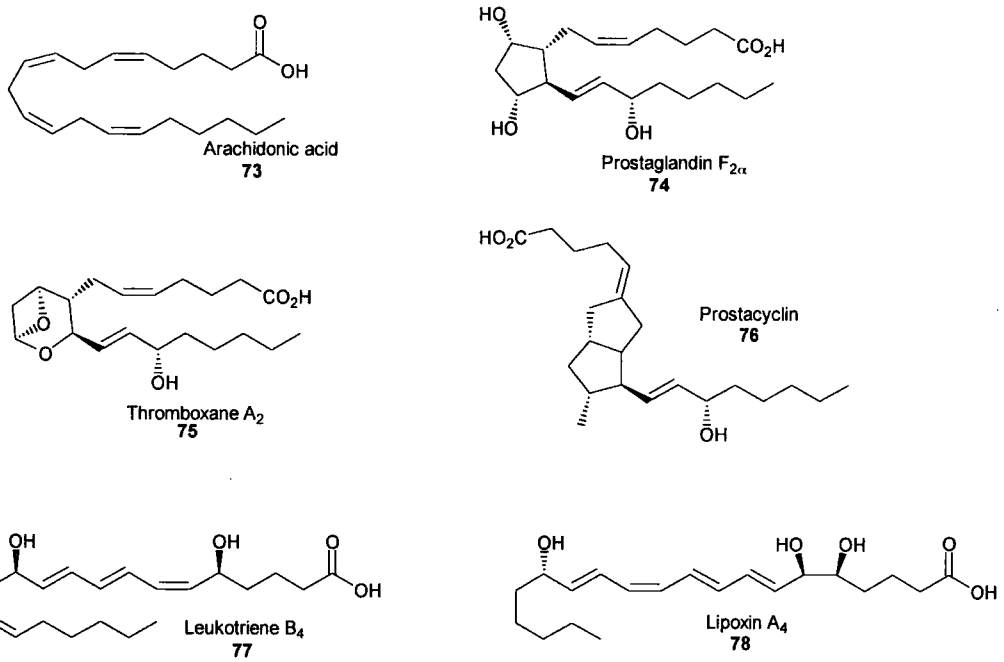
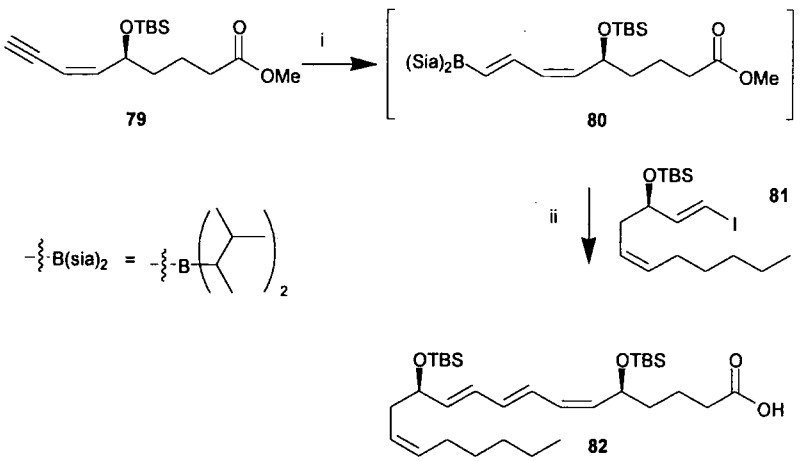


Figure 8

The metabolites, the eicosanoids, have been divided into families of related structures, the prostaglandins, thromboxanes, prostacyclins, leukotrienes and the lipoxins. All contain double bonds but it is the leukotrienes and lipoxins that contain conjugated polyenic systems and are of interest to this review. These compounds are involved in mediation of inflammation, allergies and asthma and as such have long been the subject of intense investigations.[112]

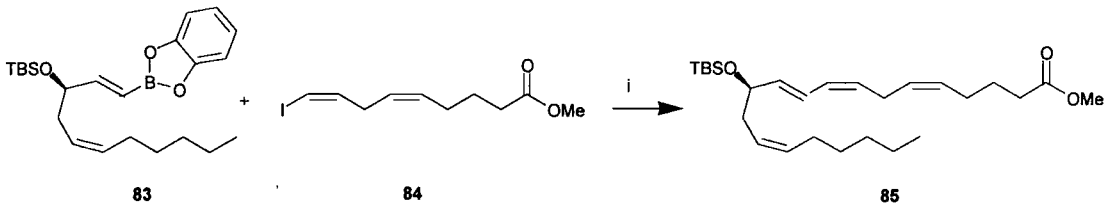
Leukotriene B_4 was synthesised by Sato and coworkers using a Suzuki-Miyaura coupling to construct the (*Z*,*E*,*E*)-triene system.[113] The reaction involved the coupling of the boronate substituted diene **80**, containing the internal (*Z*)-alkene, with the alkenyl iodide **81**. The boronate was prepared *in situ via* a hydroboration of the alkyne **79** with disiamyl borane and then coupled directly to the iodide in a one pot procedure. The reaction utilised $Pd(PPh_3)_4$ in the presence lithium hydroxide; the coupling of the borane proceeded well at a relatively low temperature to give the desired product with retention of all alkene geometries in an average yield of 72% for the two step process. Deprotection of the alcohol groups with tetra-*n*-butyl ammonium fluoride generated the target molecule.



(i) $HBSia_2$, THF, 0°C, 1 h. (ii) $Pd(PPh_3)_4$, 2 N aq. LiOH, 40°C, 18 h, 72%.

Scheme 14

Further arachidonic acid metabolites include the monohydroxyicosatetraenoic acids (HETE's) and have been the subject of synthetic investigation by Nicolaou.[112] Of particular interest is the synthesis of 12(*R*)-HETE as it possesses an (*E*,*Z*)-diene which was constructed through a Suzuki-Miyaura coupling.[114] On this occasion, the catechol ester of the (*E*)-alkenyl boronate **83** was coupled to the (*Z*)-alkenyl iodide **84**. Kishi conditions were applied and a rapid reaction gave a 55% yield with retention of the (*Z*)-alkene geometry. Interestingly, the use of TlOH and the lower temperature left the methyl ester intact unlike Sato's leukotriene B4 synthesis where the basic conditions of the Suzuki-Miyaura reaction (aq. LiOH) resulted in ester hydrolysis. Completion of the 12(*R*)-HETE synthesis thus required saponification of the ester (LiOH) and alcohol deprotection.



83 84 85

(i) $Pd(PPh_3)_4$, aq. TlOH, Hexane/THF, 25°C, 30 min, 55%.

Equation 12

1.2.5.3 Syntheses of Mollusc Pheromones

Isolated from the sea slug *Navanax inermis* were the alarm pheromones navenones A-C. These bright yellow highly conjugated systems are secreted when the slug is endangered and they induce an immediate escape response by any other *Navanax* in the vicinity.[115] These unsaturated ketones all possess the same basic structure, an all (*E*)-tetraene substituted at one end with a methyl ketone and at the other with either a pyridine (**86**), phenyl (**87**) or phenolic group (**88**). Subsequently a number of other related compounds with similar basic structures were isolated from a range of marine molluscs, these include lignarenones A and B (**89** & **90**) and the haminols A and B (**91** & **92**).[116,117]

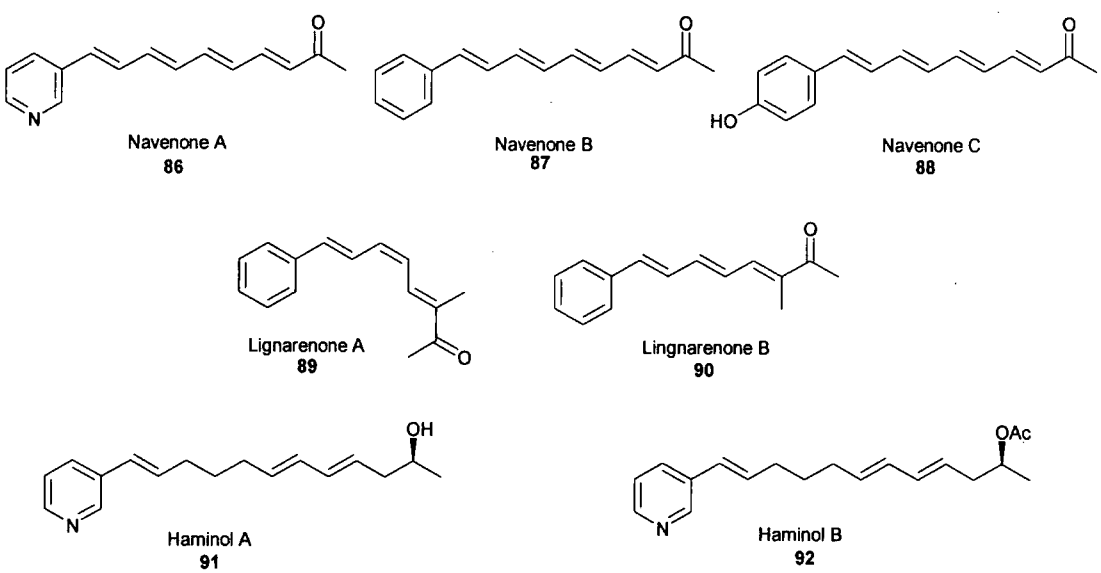
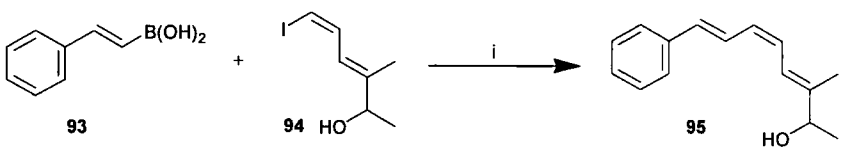


Figure 9

As in the synthesis of the retinoid tetraenes (1.2.5.1), de Lera has utilised the Suzuki-Miyaura reaction to couple alkenyl fragments producing polyenes. This has resulted in the syntheses of all of the products depicted in Figure 9.[118,119] As was the case in the syntheses of the retinoid polyene tetraenes, the navanone tetraenes were prepared via

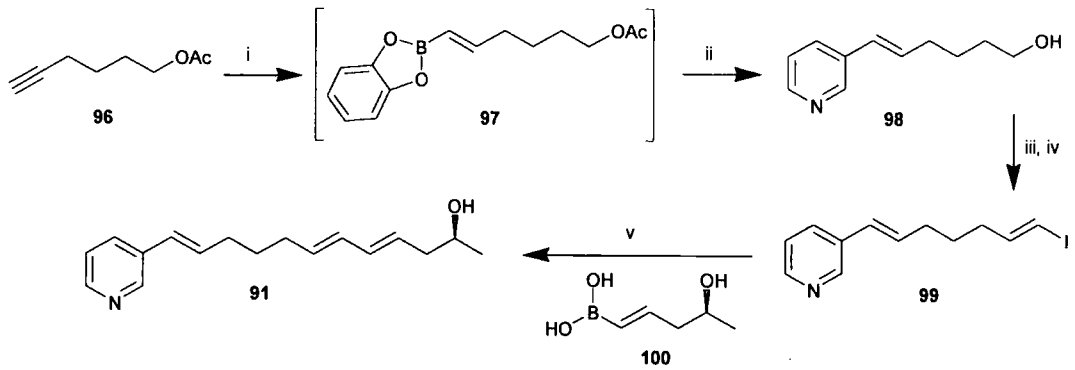
the coupling of two diene fragments, again under Kishi conditions.[118] The only one of the pheromones to possess a (*Z*)-alkene, which is positioned at the centre of a triene, is lignarenone A, and it was successfully synthesised.[118] The key coupling step was performed between the (*Z*)-alkenyl iodide **94** and the boronic acid **93** (Equation 13); the iodide was prepared using Wittig chemistry with a *Z*:*E* selectivity of greater than 20:1. Again, the Suzuki-Miyaura coupling was performed in the presence of TlOH at room temperature to generate the coupled product **95** in a 80% yield with retention of alkene geometry. A number of conditions were examined to bring about the oxidation of the secondary alcohol; however, all resulted in some isomerisation of the (*Z*)-alkene producing mixtures of lignarenone A and B. In fact, the best method (Dess-Martin) still resulted in a mixture of products which favoured the thermodynamically more stable lignarenone B in a 2:1 ratio. This highlights the sensitivity of such systems and the difficulty involved in their syntheses. The use of the Suzuki-Miyaura reaction with Kishi's mild reaction conditions allowed the construction of the polyene with the desired geometry. However, the conditions required to bring about a remote functional group interconversion still led to the isomerisation of the already established system.



(i) $Pd(Ph_3)_4$, 10% aq TlOH, THF, 25°C, 80%.

Equation 13

Syntheses of the related haminols A and B employed two Suzuki-Miyaura reactions to bring about their construction (Scheme 15).[119] The initial Suzuki-Miyaura reaction was employed to couple 3-bromopyridine with the alkenyl catechol boronate ester **97** which was prepared *in situ* through the hydroboration of the corresponding alkyne **96** thus attaching the arm to the heteroaromatic. Standard conditions were used to give the coupled product **98** in a 64% yield. Conversion of the arm group functionality to give an alkenyl iodide allowed the second coupling to the boronic acid **100** under Kishi conditions to give haminol A in a 72% yield; reaction of haminol A with acetic anhydride in pyridine afforded haminol B.



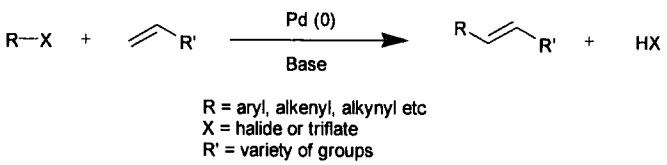
(i) Catecholborane, 80°C, 3 h. (ii) 3-Bromopyridine, $Pd(PPh_3)_4$, 3N NaOH, THF, 85°C, 1 h, 64%. (iii) a) $(COCl)_2$, DMSO, DCM, -60°C. b) Et_3N, -60°C to 25°C, 72%. (iv) $CrCl_2$, CHI_3, THF, 0°C, 30 min, 72%. (v) $Pd(PPh_3)_4$, 10% aq TlOH, THF, 25°C, 2 h, 72%.

Scheme 15

1.3 Heck Coupling Reactions

1.3.1 Introduction

The palladium(0) catalysed cross coupling of an organic electrophile with an alkene in the presence of a base has become known as the Heck reaction since initial reports over 30 years ago.[120] In the generalised reaction depicted below, R is limited to alkenyl, aromatic, heteroaromatic or alkynyl with X being either a halide or triflate. As with the reactions discussed earlier, the organic electrophiles were limited to iodides and bromides but conditions have now been developed for the coupling of aryl chlorides.[121]

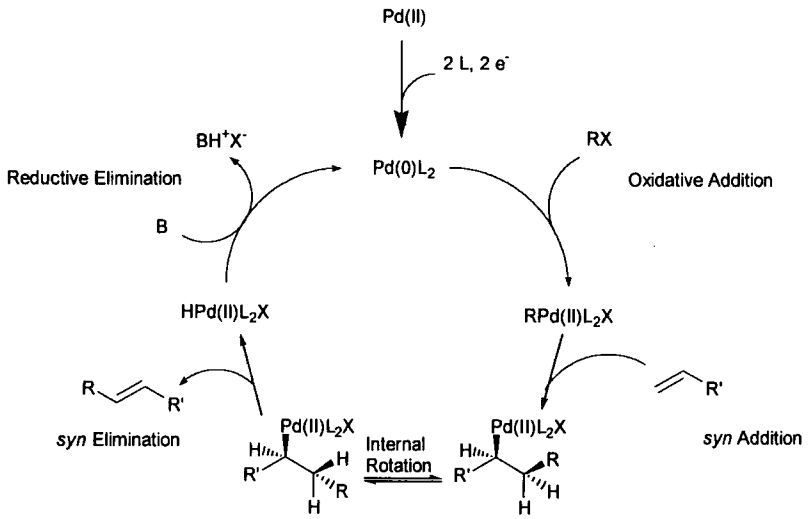


Equation 14

1.3.2 Mechanistic Details

From the nature of the reactants it is clear that the Heck coupling differs significantly from the Stille and Suzuki-Miyaura coupling reactions discussed. The reaction does not contain an organometallic reagent, so consequently the mechanistic details of the process are quite different and the transmetallation and reductive elimination processes discussed previously do not apply. A general catalytic cycle is outlined overleaf (Scheme 16) and follows an oxidative addition (as discussed, 1.1.3) before an addition-

elimination process to the alkene substrate to generate the coupled product allowing catalyst regeneration.

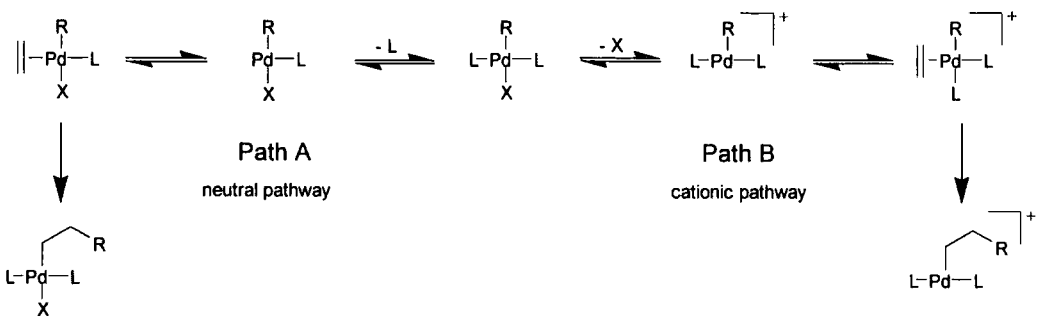


Scheme 16

After oxidative addition, the alkene inserts into the resultant Pd(II)R bond in a *syn*-process; internal rotation occurs to then allow a β-hydride elimination again in a *syn* manner. The geometry of the alkene product is determined by the nature of the alkenic substrate, but for mono-substituted alkenes, the thermodynamically more stable (*E*)-alkene is preferentially formed.[122] After elimination, the palladium(II) product must be reduced to the active Pd(0) species. The role of the base is to assist this through the abstraction of HX from the palladium forming the protonated halide salt.

There are two proposed mechanisms for the insertion process which involve neutral and cationic palladium species (Scheme 17). Before insertion can occur, the palladium needs to coordinate the incoming alkene. To do this it must become coordinatively unsaturated in one of two ways. As shown in path A the metal centre can lose a ligand to allow coordination followed by insertion, the neutral pathway.[123] The reaction tends to follow path A when using labile ligands such as phosphines and with the halides which form strong bonds to the palladium. Alternatively, as in path B, the metal centre can lose the anionic ligand, thus forming a cationic catalyst specie. Path B has been invoked when coupling triflates, due to the weak Pd-triflate bond and its potency as a leaving group, and when using bidentate ligands which are not as labile.[124,125] In fact, the cationic pathway can be generated by performing the Heck reaction in the presence of metal salts, particularly those of silver(I)[126-128] and thallium(I).[128-130] The metal additives can abstract the halide ion from the palladium centre after the oxidative

addition step thus forming a cationic palladium species that exists throughout the cycle.[131]



Scheme 17

The nature of the palladium species, i.e. neutral or cationic, has a profound effect on the regiochemistry of the insertion product formed. For neutral Pd systems, the regiochemistry is governed primarily by the sterics of the alkene substrate with the organic group adding to the least hindered end of the alkene. When following the cationic pathway, the regiochemistry of addition is determined largely by electronic factors as the Pd complex increases the polarisation of the alkene. As a consequence the organic group adds to the end of least electron density. Thus, depending on the mechanism of insertion the nature and selectivity of the product formed can vary dramatically (figure 10).[132] To summarise, variation of the reaction conditions and hence the mechanism the reaction follows can impart a level of control on the reaction to generate the desired product.

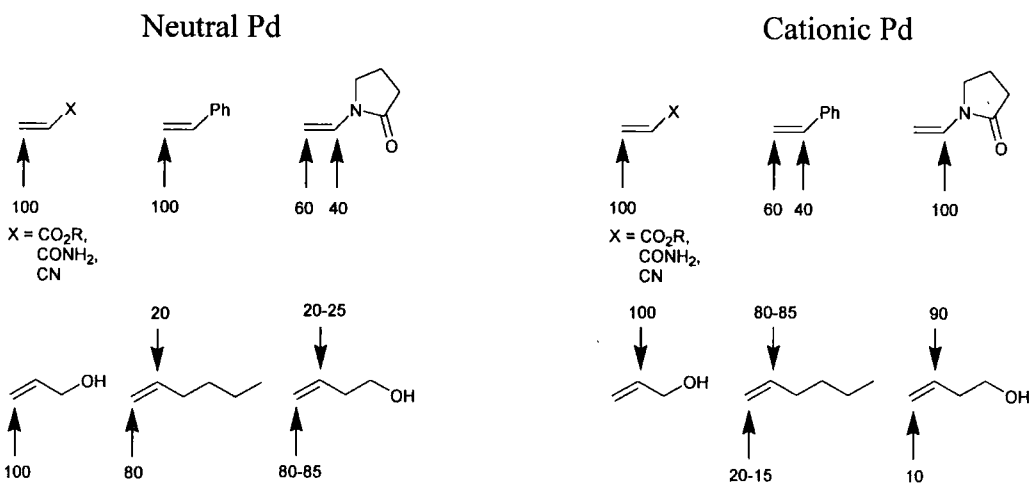


Figure 10

1.3.3 Reaction Conditions

Common catalysts employed are again commercial sources of Pd(II) or Pd(0) such as $Pd(OAc)_2$ and Pd_2dba_3 with added ligands such as the phosphines (PR_3) to stabilise the Pd(0) species. The active Pd(0) species is generated by the reduction of the Pd(II) by a phosphine ligand which itself is oxidised to the phosphine oxide.[133] As was discussed for the Suzuki-Miyaura reaction, the development of conditions for the efficient coupling of aryl chloride electrophiles has resulted in a range of different ligands and many are applicable to the Heck reaction such as phosphite ligands (1.2.4).[134] In addition, bulky ligands have been investigated such as thiourea based systems[135] and palladacycle catalysts.[97,136]

The base required to assist catalyst regeneration is usually a tertiary amine although inorganic bases such as sodium or potassium acetate, carbonate or bicarbonate have also been employed. The reaction has been performed in a number of solvents covering a range of polarities depending on the specific reaction but they are commonly aprotic.

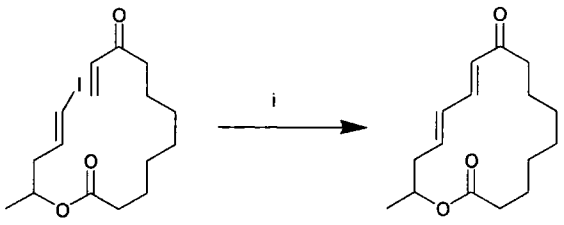
As discussed, additives such as silver(I)[126-128] and thallium(I)[128-130] salts can increase the rate of reaction through abstraction of a halide from the Pd(II) complex resulting in a cationic catalyst centre. This can increase the rate of insertion but also changes the regioselectivity of the process.

1.3.4 Application to Natural Product Synthesis

Although one of the most synthetically useful Pd catalysed reactions, there are few examples of its use in this area of polyene synthesis as it is in many ways inferior to the Stille and Suzuki-Miyaura coupling reactions. Due to the variability in the products obtained and the lack of control over what is formed, particularly with more complex alkenes, the use of the reaction in polyene natural product synthesis has been limited. The Heck reaction has, however, proved to be a valuable carbon-carbon single bond forming tool in a range of other natural product syntheses.[137]

Investigations into the potential use of the Heck reaction in intramolecular cyclisations of macrocyclic lactones through the formation of a diene was performed some time ago.[138] Cyclisation of the model system **101** was successfully induced using a stoichiometric amount of $Pd(MeCN)_2Cl_2$ in acetonitrile at room temperature giving a 55% yield of the (*E,E*)-diene. The use of a stoichiomeric amount of palladium and the

disappointing yield demonstrates the inferiority when compared to the Stille intramolecular cyclisations outlined previously.

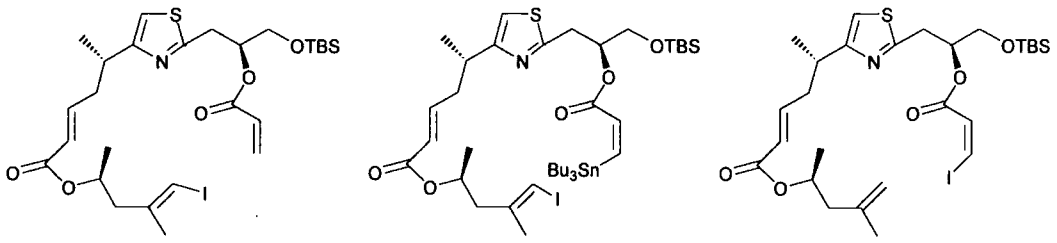


101 102

(i) $Pd(MeCN)_2Cl_2$, Et_3N, HCO_2H, MeCN, 25°C, 11 h, 55%.

Equation 15

As part of the work on the total synthesis of (-)-pateamine (a potent cytotoxin from the marine sponge *Mycale* sp.[139]), Pattenden and co-workers compared the use of the Heck and Stille reactions to bring about the cyclisation of a number of substituted compounds to form the (*Z,E*)-diene.[140] Under various Heck conditions, good yields were observed; however, the (*E,E*)-diene was always formed and, in many cases, was favoured over the desired (*Z,E*)-diene. However, in the presence of the CH_2OTBS substituent, substrate **103**, the desired (*Z,E*)-system was formed with greater than 75% selectivity in a 60% yield. The Stille reaction was then examined for structure **104** and gave exclusively the desired (*Z,E*)-diene in a 72% yield. In the case of the Stille reaction, as the (*Z*)-alkene geometry was already installed with the (*Z*)-alkenyl stannane, coupling with retention of stereochemistry would yield the desired system. In the case of the Heck reaction, the (*Z*)-alkene was not preformed, and any selectivity would have to occur in the Heck coupling. As discussed, the (*E*)-isomer of the alkene formed in the Heck reaction is usually the major product so the results were to be expected. A more successful Heck transformation may have been possible using **105**, coupling the (*Z*)-iodoalkene; as a direct comparison of the two reactions the study may do the Heck reaction an injustice.

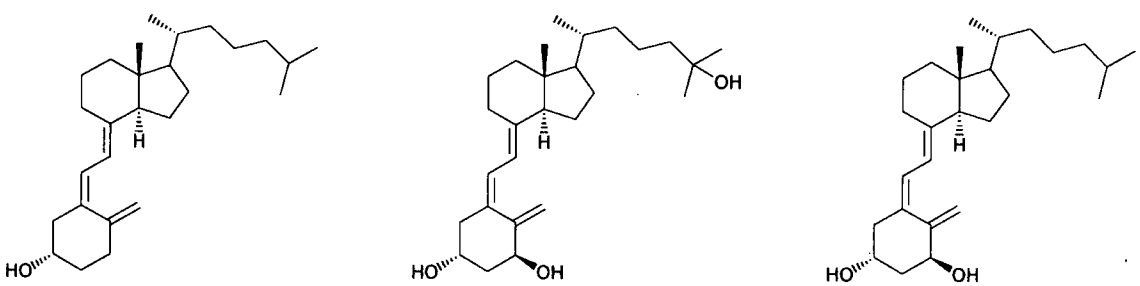


103 104 105

Figure 11

1.3.4.1 Syntheses of Vitamin D Metabolites

Derived from cholesterol are the vitamin D metabolites which occur in a wide range of animals.[141] In humans, the metabolite calcitriol **107** is the main active form and plays an essential role in calcium and phosphorus metabolism. A number of metabolites have been isolated which effect the proliferation and differentiation of a range of cell types, which has resulted in research into their potential as anti-cancer agents. Within their structures exists a triene unit with one of the alkene units being doubly substituted and terminal, and it is this system that is of interest for this review.

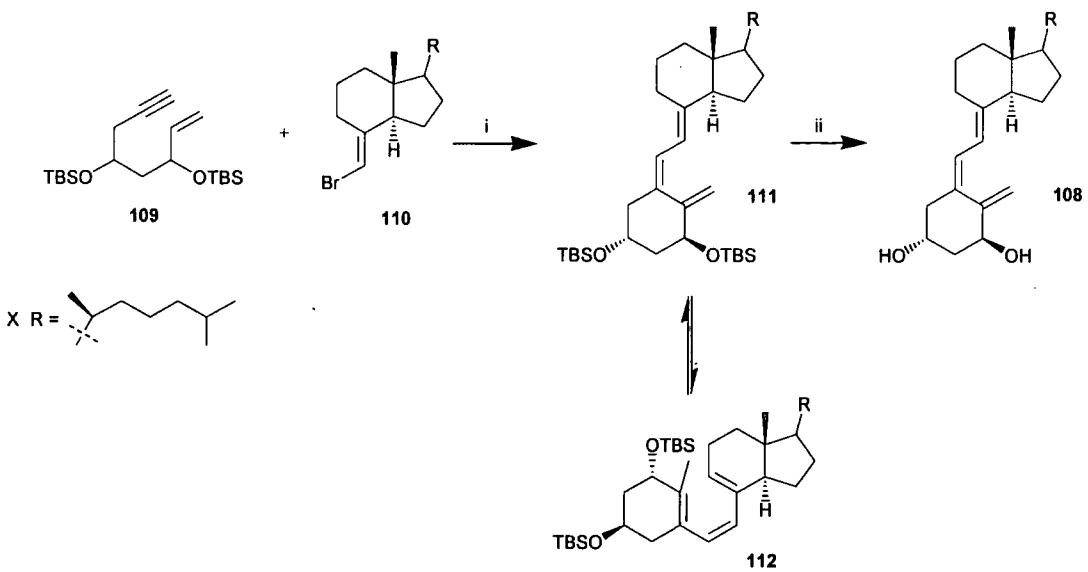


Vitamin D_3 **106** Calcitriol **107** Alphacalcidol **108**

Figure 12

Trost and coworkers applied a novel Heck coupling strategy to the synthesis of some of the vitamin D metabolites. The synthesis involved an intermolecular coupling of an alkyne **109** and bromoalkene **110** before an intramolecular Heck cyclisation involving a terminal alkene to set up a triene system.[142] The target molecules calcitrol **107** and alphacalcidol **108** differ only in the R groups they possess so the key Heck reactions are the same in both cases. The reaction of the acyclic 1,7-enyne **109** with the vinyl bromide **110** is shown below. The reaction used a Pd(0) source, the triphenylphosphine ligand and the triethylamine base as a component of the solvent mixture and was

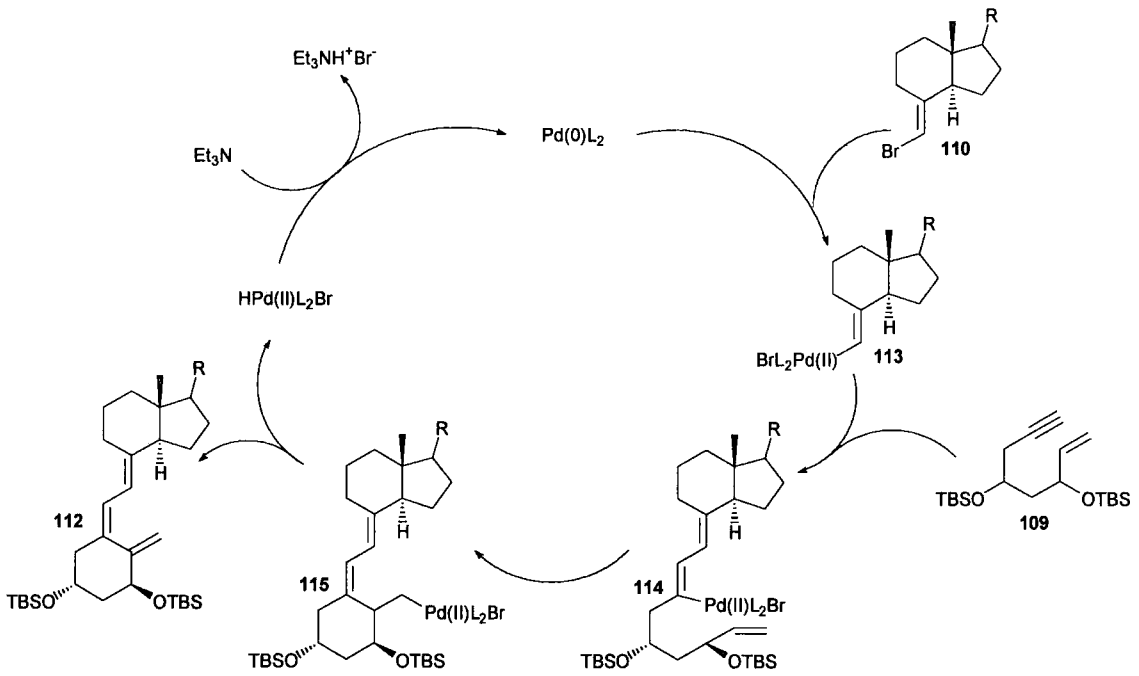
refluxed. In each case a small amount of the tautomer **112** was formed (no other geometrical isomers were observed) which on isolation and heating equilibrated to the desired form; yields of 52% (calcitrol **107**) and 76% (alphacalcidiol **108**) were obtained. Deprotection of the alcohols using TBAF generated the target molecules.



(i) Pd_2dba_3, PPh_3, Toluene/Et_3N (1:1), reflux, 1.5 h, 76%. (ii) TBAF, THF, 25°C, 40 h, 79%.

Scheme 18

The postulated catalytic cycle is outlined in Scheme 19. After oxidative addition the initial intermolecular coupling to the alkyne is favoured over the alkene. Following this, the intramolecular reaction occurs with the terminal alkene to give **115** rather than reductive elimination which would have resulted in the formation of the ene-yne. This second Heck process results in the cyclisation to give the substituted cyclohexane, *syn*-β-hydride elimination from **115** then generates the desired triene product.



Scheme 19

In this instance the successful application of the Heck reaction in the synthesis has been achieved as it is ideally suited to the target system. Consequently, this success may be limited and not necessarily transferred readily to other systems that differ greatly in structure.

1.3.4.2 Synthesis of Phthoxazolin A

Isolated from the fermentation broth of *Streptomyces griseoauranticus* was the metabolite phthoxazolin A **116**.[143] Studies showed it to display potent herbicidal activity against certain plant species allied with a low toxicity towards animal cells providing it with two extremely attractive properties.[144] Its structure consists of an oxazole head group connected to a functionalised tail unit which contains a triene unit of (*E,Z,Z*)-geometry.

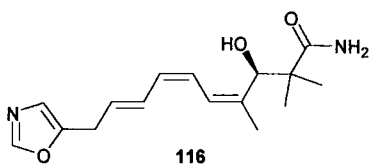
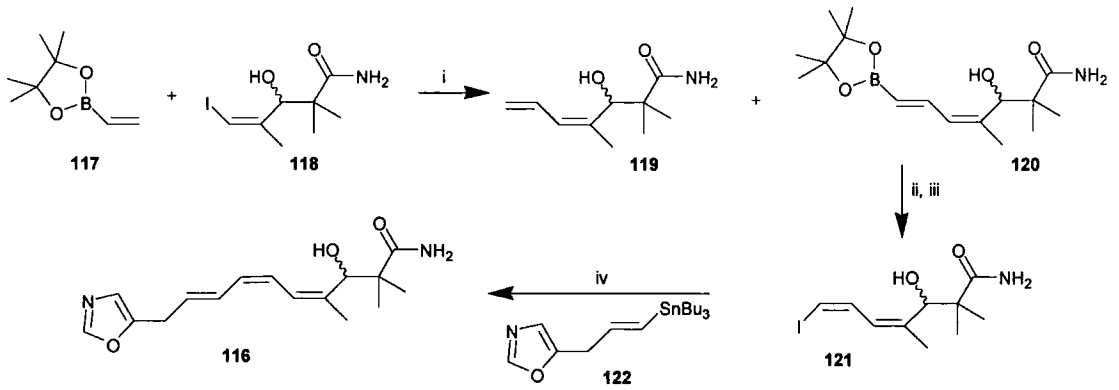


Figure 13

The first total synthesis of racemic phthoxazolin A by Henaff and Whiting demonstrated a new strategy of building polyene chains through the Heck coupling of a vinyl boronate ester with an alkenyl iodide.[145,146] The vinylboronate ester **117** was

employed to undergo Heck coupling to an iodide which could be followed by the stereocontrolled conversion of the boronate ester to the iodoalkene to allow a further Heck reaction thus building the polyene. However, as the vinylboronate can also react at the other end and participate in Suzuki-Miyaura coupling, conditions were developed to maximise the overall yield of the reaction and increase the ratio of Heck coupled product.



(i) $Pd(OAc)_2$, PPh_3, Et_3N, MeCN, 90°C, 4 days, 43%. (ii) ICl in DCM, THF, -78°C, 2 h. (iii) NaOMe in MeOH, -78°C, 30 min, 49%. (iv) $Pd(MeCN)_2Cl_2$, DIPEA, DMF, 25°C, 5 days, 20%.

Scheme 20

The initial coupling reaction gave a reasonable 78% yield but the mixture of Heck and Suzuki-Miyaura couplings meant that the yield of the desired product was just 43%. In both the Heck **120** and Suzuki-Miyaura **119** products there was retention of iodoalkene stereochemistry. Conversion of the dienyl boronate ester to the (*Z*)-iodide **121** was performed utilising conditions developed by the group[147] providing a crude yield of 49% (attempts at purification led to decomposition). To accomplish the final coupling step to yield phthoxazolin A, a Stille coupling reaction was utilised. The reaction proceeded with retention of stereochemistry giving a low 20% yield which can be accounted for by the instability of the product and the fact that both starting materials were used in crude form. Nevertheless, this synthesis, and in particular that of the (*E,Z,Z*)-triene system, demonstrates the potential of this strategy and is one of the more successful applications of Heck coupling in polyene natural product synthesis.

2 Results and Discussion

2.1 Aims and Overview

As was shown in the Introduction, there are a number of different methods by which polyene systems can be constructed but as yet there is no reliable and widely applicable method for their stereocontrolled syntheses. As discussed (1.3.4.2), research performed in this group has led to a strategy for the synthesis of polyene systems which culminated in the total synthesis of phthoxazolin A.[145,146] The strategy was based around the pinacol vinyl boronate ester, 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane **117**, which can be employed to introduce an ethylene unit into a specific substrate using a Heck coupling protocol. Stereocontrolled iododeboronations can be employed to convert the resultant alkenyl boronate ester into either an (*E*)- or (*Z*)-alkenyl iodide with very high levels of stereocontrol depending on the reaction conditions.[147] The preparation of these (*E*)- or (*Z*)-alkenyl iodides then allows further Heck couplings and an extension of the polyene chain to be achieved.

Later work involved the application of this strategy to the synthesis of the southern hemisphere of the natural product viridenomycin **125**.[148] During this research, a number of problems were identified with the use of **117**. Its synthesis can be compromised by low yields since it tends to azeotrope with THF during purification by distillation. In addition, upon storage, even at reduced temperatures, it converts slowly to a thick gel like substance over a period of a few weeks. Its practical application in reactions is also compromised due to its relatively high volatility, meaning that it was often lost to some extent during degassing and argon sparging of reaction vessels. Consequently, alternatives to the pinacol ester were investigated leading to the use of racemic 2-methyl-2,4-pentane diol to prepare the vinyl boronate 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane **123** which was largely free of the problems associated with the pinacol form.

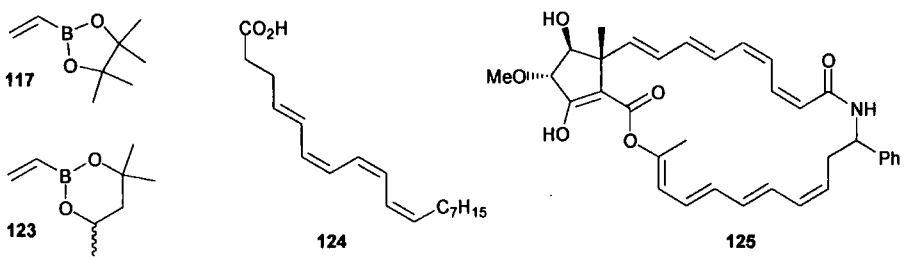


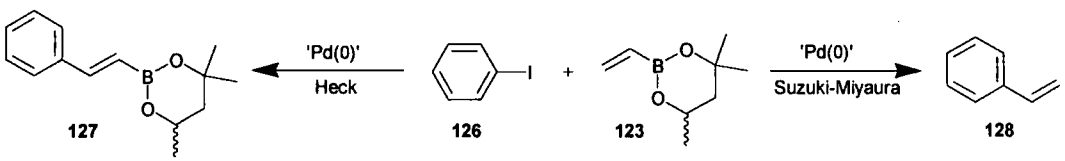
Figure 14

It is at this point the project commenced. The initial aim was to take the newly identified vinyl boronate ester **123** and examine its potential as the key alkenyl building block in this strategy of polyene construction. This involved development of conditions for the aforementioned Heck and iododeboronation reactions which could be applied to a range of systems providing high levels of both chemo- and stereocontrol. This would be facilitated by identifying the mechanistic issues surrounding each reaction which could then be controlled depending on the specific requirements of a particular system. Once done, the aim was to test the strategy on model systems before its application to the synthesis of the natural product ixoric acid **124** and continuation of the work towards the first total synthesis of viridenomycin **125**.

2.2 Heck Coupling Reactions

2.2.1 Introduction

One of the key reactions in this strategy is the Heck coupling of the vinyl boronate ester **123**. It can be regarded as a vinyl dianion equivalent as, under palladium catalysed coupling conditions, it is able to react at either end along the Heck or Suzuki-Miyaura pathways. The vital aspect of the Heck coupling is being able to control the reaction so that complete chemoselectivity is obtained. A large volume of preliminary work involved the Heck coupling of **117** with aryl halides paying particular attention to the product ratio,[149-151] thus, conditions for the efficient coupling of **123** were quickly established.[152]

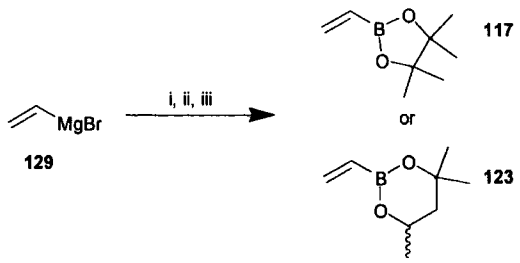


Scheme 21

The specific aim of the work undertaken here was initially to compare the Heck couplings of the two vinyl boronate esters **117** and **123** with aryl halides and then, to develop the strategy for polyene synthesis by coupling the 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane **123** with alkenyl iodides of defined geometry. Variation of the reaction conditions to assess their impact on the ratio of Heck and Suzuki-Miyaura products formed would provide an insight into the mechanism of the reaction and assist in controlling the selectivity of the process.

2.2.2 Syntheses of the Vinyl Boronate Esters

The starting point was the preparation of both vinyl boronate esters **117** and **123**; the syntheses followed the same protocol with the diol used being the only difference. A one pot reaction is performed and involves the nucleophilic attack of the vinyl Grignard reagent on trimethyl borate. Hydrolysis under acidic conditions and re-esterification with the desired diol affords the vinyl boronate ester (Equation 16).



i) $B(OMe)_3$ (1 eqv), THF, -78°C, 2 h. ii) 20% HCl, 25°C, 10 min.
iii) Pinacol or *rac*-2-methyl-2,4-pentane diol (1 eqv.), 1 h, **117** 32%, **123**, 82%.

Equation 16

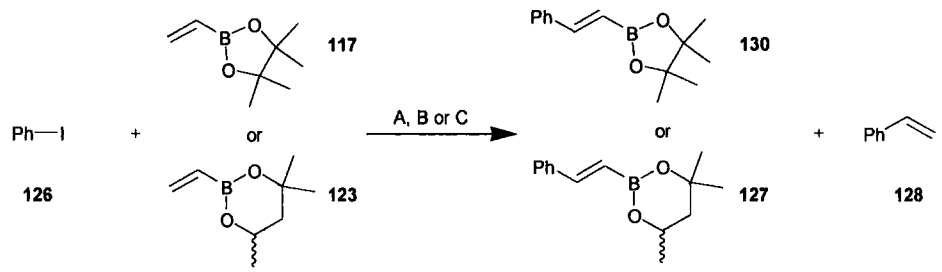
The synthesis of **117** gave, as expected, a disappointing yield due to the reasons identified previously, i.e. the difficulty in its purification. During distillation, an initial fraction containing a mixture is obtained as the vinyl boronate azeotropes with the residual THF; pure **117** then follows but as a consequence it is obtained in reduced quantities, hence, the 32% yield illustrated above. It must be noted that the reaction is performed in THF as the vinyl magnesium bromide is commercially available as a solution in this solvent only. The purification of **123** is much more straightforward due to its higher boiling point allowing its synthesis in consistently high yields (82%) after distillation. The robust procedure and the improved ease of isolation allows its preparation on a multi-gram scale.

2.2.3 Heck Coupling Reactions

2.2.2.1 Coupling of Aryl Halides

2.2.2.1.1 Iodobenzene

As a direct comparison of vinyl boronates **117** and **123**, both were coupled with iodobenzene (Equation 17) to generate either 4,4,5,5-tetramethyl-2-((*E*)-styryl)-1,3,2-dioxaborolane **130** or 4,4,6-trimethyl-2-((*E*)-styryl)-1,3,2-dioxaborinane **127**. As eluded to, the vinyl boronate **123** can react at either end under palladium catalysed coupling conditions and as a consequence the formal Suzuki-Miyaura product (in this case styrene **128**) is often observed in the crude product material. Standard conditions which had been developed in the group were initially used for the coupling reactions,[152] these involved the use of $Pd(OAc)_2$ (5 mol%) and triphenylphosphine as the catalyst in the presence of tri-*n*-butylamine in refluxing toluene. The results are shown in Table 1. Note that the vessel in which the reaction is performed must be rigorously degassed before heating to obtain efficient coupling, and this was done using the freeze-pump-thaw method.



A) $Pd(OAc)_2$ (5 mol%), PPh_3 (12-15 mol%), nBu_3N (1.2 eqv.), Toluene, 110°C, 24 h. B) Conditions A, TlOAc (1.2 eq). C) Conditions A, AgOAc (1.2 eq).

Equation 17

Entry	Vinyl Boronate	Conditions	H:S-M Ratio[a]	Yield/%[b]
1	**117**	A	85:15	38
2	**123**	A	91:9	73
3	**123**	B	100:0	86
4	**123**	C	100:0	88

[a] Determined from the ^1H nmr of the crude product. [b] Isolated yield after purification by SiO_2 column chromatography.

Table 1

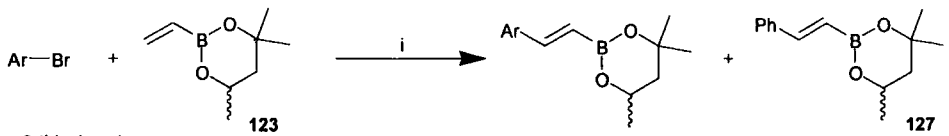
In all cases the Heck coupled product was obtained exclusively with (*E*)-alkenyl geometry. In these systems there is a very large *J* coupling across the alkene of ~18 Hz. Entries 1 and 2 (Table 1) give a direct comparison of the Heck coupling of the two vinyl boronates with both reacting under the same conditions (A). The coupling of the pinacol boronate gave a very low yield (38%) of the product **130** which may be attributed to loss of the reagent on during the freeze-pump-thaw process or possibly increased sensitivity of the system. Coupling of the more robust 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane **123** allowed isolation of the product in a much greater yield (73%). There is a marked difference in the selectivity of the two reactions with the vinyl boronate ester **123** being more selective for the Heck pathway than the pinacol form **117** (91:9 compared to 85:15). The origin of the difference in selectivity may be due to the sterics of the two boronate esters. The ester of 2-methyl-2,4-pentane diol could possibly be a more hindered system and as such reduce the rate of reaction at that end of the alkene. In addition this may account for the increased stability it demonstrates over the pinacol equivalent. This is supported when examining the outcome of a competition reaction between the two vinyl boronates. The Heck coupling reaction with iodobenzene was repeated (conditions A) but with both **117** and **123**

present in the reaction mixture and the crude product examined for its constituents by ^{1}H nmr. Three products were obtained from the reaction; both of the Heck coupled products **130** and **127** and the formal Suzuki-Miyaura product, styrene **128**. The ratio of the Heck coupled products was 54:46 in favour of the pinacol boronate ester **130**, which suggests a slightly slower reaction rate of **123** due to its increased steric hindrance. Interestingly the Heck:Suzuki-Miyaura product ratio was 88:12, a value that is an average of the values obtained when coupling the vinyl boronate esters in isolation. To conclude, not only is 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane **123** free of the physical problems associated with the pinacol form **117**, it also demonstrates superior selectivity and gives higher isolated yields when employed in the Heck coupling reaction and is the reagent of choice in this strategy for polyene synthesis.

As discussed in the Introduction (1.3), the use of metal additives such as silver(I)[126-128] and thallium(I) salts[128-130] can increase the rate of the Heck reaction. The effect of the acetate salts of each were examined on the coupling of **123** with iodobenzene (Table 1, entries 3 and 4) with all other reaction conditions remaining constant. As can be observed, the addition of these salts led to an increase in chemoselectivity to the point that the Heck product was obtained exclusively. As a consequence, this allowed the isolation of the desired coupled product in greater yields. There appeared to be little difference between the two metal additives, although the reaction showed high selectivity under the standard conditions (A), so only a slight increase in the selectivity was required. A higher yield was obtained when using AgOAc (88%), but the difference of 2% is negligible.

2.2.2.1.2 Heteroaromatic Bromides

To complete a study started prior to the commencement of this project the coupling of the vinyl boronate **123** was attempted with a small number of heteroaromatic bromides.[152] The standard conditions employed for the coupling of iodobenzene were again used but with 10 mol% catalyst and an extended reaction time to overcome the sluggish nature of the reaction when compared to iodobenzene. The substrates investigated were 2-bromothiophene, 3-bromofuran, 2-bromopyridine and 3-bromopyridine. The results are shown in Table 2.



131 Ar = 2-thiophenyl
132 Ar = 3-furyl
133 Ar = 2-pyridyl
134 Ar = 3-pyridyl

135 Ar = 2-thiophenyl
136 Ar = 3-furyl
137 Ar = 2-pyridyl
138 Ar = 3-pyridyl

i) $Pd(OAc)_2$ (10 mol%), PPh_3 (22 mol%), nBu$_3$N (1.2 eq), Toluene, 110°C, 4 days.

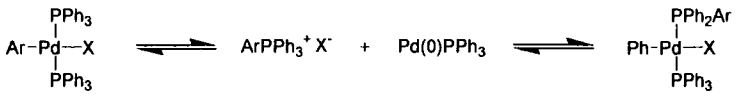
Equation 18

Entry	Bromide	Ratio 135-138:127[a]	Yield/%[b]
1	**131**	91:9	31
2	**132**	60:40	28
3	**133**	-	-
4	**134**	0:100[c]	-

[a] Determined from ^{1}H nmr of the crude product. [b] Isolated yield after purification by SiO_2 column chromatography. [c] The only detectable coupled product but in trace amounts.

Table 2

These coupling reactions did show complete Heck selectivity; none of the Suzuki-Miyaura product was observed in any of the reactions. However, the presence of a major by-product, 4,4,6-trimethyl-2-((*E*)-styryl)-1,3,2-dioxaborinane **127**, was observed, where the phenyl group is derived from the triphenylphosphine ligand through an aryl ligand crossover reaction. There are a number of examples of aryl-aryl exchange between the palladium centre and phosphine ligands for Pd(II) complexes which has been studied using substituted and deuterated labelled systems.[153,154] Further investigations into the mechanistic intricacies of the exchange have postulated a simplified general mechanism (Scheme 22) by which the Pd(II) oxidative addition product undergoes reductive elimination to give the phosphonium salt and a Pd(0) species. Oxidative addition of the phosphonium salt can then occur involving a different carbon phosphorous bond to generate the phenyl palladium(II) species.[155-157] With respect to the Heck couplings of the aryl bromides it may be assumed that after oxidative addition the coordination-insertion process involving the alkene is the rate determining step and sufficiently slow that it allows the phenyl transfer to occur at a competitive rate. This interchange then allows the palladium bound phenyl group to participate in the catalytic cycle in place of the heteroaromatic to generate the coupled product **127**.



Scheme 22

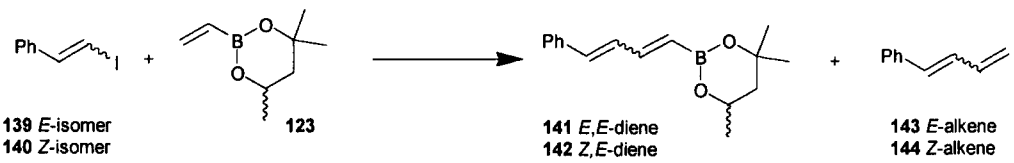
The only successful couplings obtained with these heteroaromatic bromides were for 2-bromothiophene **131** and 3-bromofuran **132** (Table 2, entries 1 and 2). Coupling of 2-bromothiophene allowed isolation of the desired product in a 31% yield, which may appear disappointing; however, previous work involving the pinacol boronate **117** and the corresponding iodide produced only a 5% conversion to the Suzuki-Miyaura product. The result obtained in this study is relatively impressive and again demonstrates the superiority of **123**.[150] The coupling of 3-bromofuran **132** generated a reasonable yield (28%) of the desired product, again better than anything observed for the pinacol form, but there was considerable by-product **127** formation. The observed ratio of 60:40 suggests that the alkene coordination-insertion step is much slower for the furyl system than that of the thiophenyl resulting in increased amounts of phenyl-aryl exchange.

All attempts at the coupling of the pyridines **133** and **134** (Table 2, entries 3 and 4) failed to deliver any of the desired Heck coupled product. The reaction with 2-bromopyridine **133** failed to proceed at all, and when reacting **134**, the only detectable coupled product was the ligand exchange product **127**. These results suggest that the oxidative addition product, pyridyl-Pd(II)$(PPh_3)_2Br$, is, in fact, highly stable and hence does not undergo addition across the alkenyl boronate. Furthermore, little pyridyl-phenyl exchange occurs. These results also reinforce the findings from previous studies involving **117**, where no coupling of the pyridine occurred and only the crossover styryl boronate was formed in trace amounts.

2.2.2.2 Coupling of Alkenyl Halides

To date, the vast majority of research on the Heck coupling of either of the vinyl boronate esters has taken place with aryl substrates. The main aim of this project was to develop a strategy for the stereocontrolled construction of polyene units. With that in mind, the Heck coupling of vinyl boronate **123** with (*E*)- and (*Z*)-alkenyl iodides was examined. The iodide substrates were (*E*)-2-iodo-vinylbenzene **139** and (*Z*)-2-iodo-vinylbenzene **140**, prepared with high selectivity from 4,4,6-trimethyl-2-(*E*)-styryl-

1,3,2-dioxaborinane **127** using an iododeboronation reaction as will be discussed in 2.3.2.1.



139 *E*-isomer
140 *Z*-isomer
123
141 *E,E*-diene
142 *Z,E*-diene
143 *E*-alkene
144 *Z*-alkene

Equation 19

Entry	Iodide	Ligand	Base	Solvent	Additive	Temp/°C	%Conv.[a]	H:S-M[a]
1	**140**	-	nBu$_3$N	Toluene	-	110	100	58:42[b]
2	**140**	PPh$_3$	nBu$_3$N	Toluene	-	110	100	53:47
3	**140**	P(*o*-tolyl)$_3$	nBu$_3$N	Toluene	-	110	100	32:68
4	**140**	PtBu$_3$	nBu$_3$N	Toluene	-	110	100	58:42
5	**140**	P(2-furyl)$_3$	nBu$_3$N	Toluene	-	110	100	54:46
6	**140**	1,10-Phenanthroline	nBu$_3$N	Toluene	-	110	13	100:0
7	**140**	PPh$_3$	nBu$_3$N	Toluene	TlOAc	110	100	65:35
8	**140**	PPh$_3$	nBu$_3$N	Toluene	AgOAc	110	100	100:0
9	**139**	PPh$_3$	nBu$_3$N	Toluene	-	110	100	34:66
10	**139**	DUPHOS[c]	nBu$_3$N	Toluene	-	110	0	-
11	**139**	BINAP[d]	nBu$_3$N	Toluene	-	110	63	29:71
12	**139**	XANTHPHOS[e]	nBu$_3$N	Toluene	-	110	36	43:57
13	**139**	PPh$_3$	nBu$_3$N	Toluene	-	78	15	30:70
14	**139**	PPh$_3$	nBu$_3$N	Acetonitrile	-	78	49	35:65
15	**139**	PPh$_3$	nBu$_2$NH	Acetonitrile	-	78	37	35:65
16	**139**	PPh$_3$	nBuNH$_2$	Acetonitrile	-	78	84	26:74
17	**139**	PPh$_3$	nBu$_3$N	Toluene	TlOAc	110	100	84:16
18	**139**	PPh$_3$	nBu$_3$N	Toluene	AgOAc	110	100	88:12

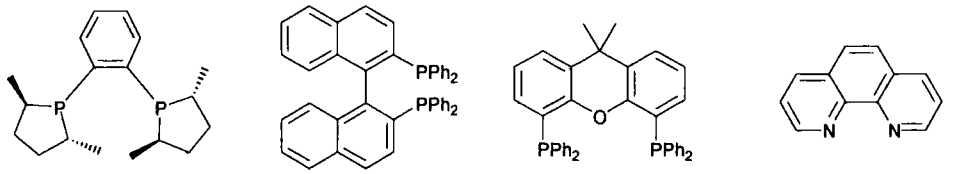
[a] Determined by ^{1}H nmr of the crude product. [b] Isomerisation of the (*Z*)-alkene to the (*E*)-form occurred for both products. [c] (-)-1,2-Bis[(2*R*,5*R*)-2,5-dimethylphospholano)benzene **145**. [d] 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl **146**. [e] 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene **147**.

Table 3

The initial conditions used were the standard ones which had proven successful for the Heck couplings with iodobenzene generating high chemoselectivity and good yields. These preliminary couplings (Table 3, entries 1 and 9) gave very disappointing results, although the reaction gave full conversion. The Heck:Suzuki-Miyaura selectivity was poor and in the case of **139**, favoured the Suzuki-Miyaura product. However, this

established the 'natural' selectivity of the couplings. This led to a series of screening reactions to establish which variables played a significant role in controlling the chemoselectivity of the reaction, and to allow the identification of the ideal coupling conditions for alkenyl systems. The results are shown in Table 3 [note: all reactions employed 5 mol% $Pd(OAc)_2$].

Initially, and most obviously, the choice of palladium ligand was examined. Changing the phosphine ligands had a minimal effect on the product ratio (Table 3, entries 2-5) which produced similar results. The only significant variation in the selectivity arose when using tri-*ortho*-tolylphosphine, which resulted in a shift in selectivity towards the Suzuki-Miyaura product. It was expected that the use of bulky bidentate ligands would have a dramatic effect on the selectivity of the reaction (Table 3, entries 10-12); these ligands were chosen with a deliberate increase in the distance between the two phosphorus donor atoms (Figure 15). However, there was a dramatic reduction in the level of conversion shown by the reaction. Indeed, in the case of the DUPHOS ligand **145**, the reaction failed altogether. The use of *rac*-BINAP **146** and XANTHPHOS **147** did give some conversion, but this was low in comparison to the monodentate ligands. It is interesting to note that as the distance between the two phosphorus donor atoms increased on going from BINAP to XANTHPHOS, the Heck selectivity also increased. The use of the diamine ligand 1,10-phenanthroline **148** (Table 3, entry 6) resulted in a dramatic increase in selectivity, so that the Heck coupled product was formed exclusively; however, there was very low conversion under these conditions, *i.e.* only 13%. This was an interesting result, particularly when considering the failed attempts at the Heck coupling of the bromopyridines. It suggests that aromatic amine binding to the palladium is sufficiently strong and the catalyst sufficiently stable as to seriously retard the reaction. The coupling was also performed in the absence of any ligand (Table 3, entry 1). Surprisingly, this gave complete conversion and a product ratio comparable to those obtained previously; however, isomerisation of the (*Z*)-alkene occurred, so that both the Heck and Suzuki-Miyaura products possessed an internal (*E*)-alkene. The isomerisation of the (*Z*)-alkene most likely occurred in the coupled products rather than during the reaction. The lack of an added ligand would result in stabilisation of the palladium(0) species through π-coordination of the products. Any allyl-cation formation, however, would lead to the isomerisation to give the all (*E*)-alkenyl product.



145 DUPHOS | **146** *rac*-BINAP | **147** XANTHPHOS | **148** 1,10-Phenanthroline

Figure 15

Changing the solvent from toluene to acetonitrile, both at reflux, resulted in a reduction in conversion (entries 9 and 14). However, this can most likely be attributed to the lower temperature of the reaction, rather than any significant solvent effect. In fact when using toluene, but at a lower temperature, a lower conversion was induced (Table 3, entry 13). There was no significant difference in the ratio of products formed.

Three different bases were also tested in this reaction (Table 3, entries 14-16), tri-*n*-butylamine, di-*n*-butylamine and *n*-butylamine. It was hoped that the different steric effects would perhaps alter the selectivity obtained when using tri-*n*-butylamine. As identified above, the low levels of conversion obtained can be attributed to performing the reaction in refluxing acetonitrile (due to the low boiling *n*-butylamine), although a reasonable conversion was demonstrated when using *n*-butylamine. No significant change in chemoselectivity was obtained when using di-*n*-butylamine; however, a slight increase in the selectivity favouring the formation of the Suzuki-Miyaura product was observed for *n*-butylamine.

The use of the metal additives, *i.e.* thallium(I) and silver(I) acetate (Table 3, entries 7, 8, 17 and 18) was the only variable that resulted in a dramatic change in product selectivity. The Heck selectivity of the (*E*)-styryl iodide **139** coupling swung dramatically in favour of the Heck product when using both additives (Table 3, entries 17 and 18) in comparison to the 'natural' Suzuki-Miyaura preference. There was little difference between using either thallium(I) or silver(I), both additives being suitable for scale up and isolation of the product dienyl boronate **141** in good yields under the optimised conditions (Table 4, entries 1 and 2). There was a more marked difference when using the two different metal additives in the coupling of (*Z*)-styryl iodide **140** (Table 3, entries 7 and 8). Although both thallium(I) and silver(I) acetate increased the Heck selectivity compared to those without additives (Table 3, entry 2), the increase in selectivity was more modest using the thallium(I) salt compared to silver(I), which gave

complete Heck selectivity. This was further demonstrated by reaction scale up under the optimised conditions and isolation of the desired (*Z*,*E*)-dienyl boronate **142** (Table 4, entries 3 and 4). In all cases, the expected retention of alkenyl iodide geometry was observed, with no isomerisation under these reaction conditions.

An overall survey of Table 3 shows that the only really significant factor in boosting Heck selectivity is the presence of the metal additives, thallium(I) or silver(I) acetate. If the use of these salts is required, AgOAc is advisable due to superior results (table 4) and the higher toxicity of thallium compounds. To achieve high conversions, the reactions should be performed in refluxing toluene and the preferred palladium ligand and base (Table 3) are triphenylphosphine and tri-*n*-butylamine respectively. These conditions were scaled up and applied to the syntheses of the aforementioned dienyl boronates **141** and **142** to obtain the isolated products after purification by silica gel chromatography.

Entry	Iodide	Additive	H:S-M Ratio[a]	Yield/%[b]
1	**139**	TlOAc	84:16	51
2	**139**	AgOAc	88:12	55
3	**140**	TlOAc	65:35	46
4	**140**	AgOAc	100:0	58

[a] Determined by ^{1}H nmr of the crude product. [b] Isolated yield after purification by SiO_2 column chromatography. Conditions: $Pd(OAc)_2$ (5 mol%), PPh_3 (15 mol%), TlOAc or AgOAc (1.2 eq), nBu_3N (1.2 eq), **123** (1.2 eq), Toluene, 110°C, 24 h.

Table 4

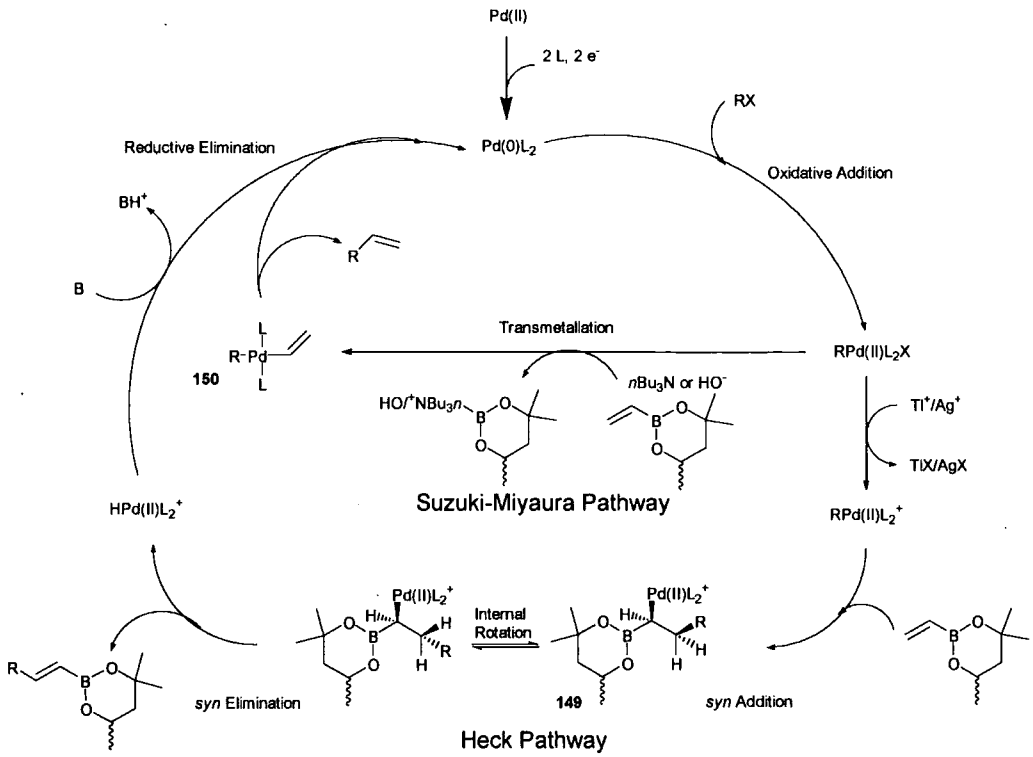
2.2.2.3 Mechanistic Discussion

There are two main mechanistic details which need to be discussed regarding the coupling of vinyl boronate **123**. Firstly, how the use of the thallium(I) and silver(I) acetate additives increases Heck selectivity, and secondly, the actual mechanism of the formation of the formal Suzuki-Miyaura product. A general discussion of the mechanism of Heck coupling reactions appeared in section (1.3.2) and the proposed mechanisms behind the key process of alkene coordination and insertion into the palladium-carbon bond was presented. This process can follow either a neutral or cationic pathway, with the latter being promoted when thallium(I) and silver(I) salts are present in the reaction mixture. It can be inferred that the successful Heck coupling of the vinyl boronate ester **123** follows a process of coordination and insertion involving a

cationic palladium species, hence, the addition of the aforementioned additives promotes this.

As discussed previously (1.3.2), when the coupling follows a neutral pathway, the regioselectivity of addition is governed by sterics and the organic group tends to add to the least substituted carbon which, in the case of **123**, is the terminal carbon. When a cationic catalyst is involved, the regioselectivity of addition is governed by electronic factors and the organic group adds to the alkenyl carbon of least electron density which, in this system, could again be considered to be the terminal carbon of the alkene. Either way the desired product is formed. This suggests that the increased Heck selectivity obtained when using metal additives is due to a rate increase of the Heck coupling over the Suzuki-Miyaura coupling by promoting the formation of the required cationic catalyst species.

As discussed previously (1.2.3), Suzuki-Miyaura reactions require the presence of a base to induce the transmetallation process and these are commonly hydroxides, alkoxides or carbonates. In this system, if the formation of the Suzuki-Miyaura product follows this pathway, the amine (commonly tri-*n*-butylamine) would have to form the 'ate'-complex with the boronate ester, allowing transmetallation. An alternative explanation for the formation of the Suzuki-Miyaura product is that the presence of water in the reaction mixture can result in the formation of hydroxide ions that can facilitate transmetallation.



Scheme 23

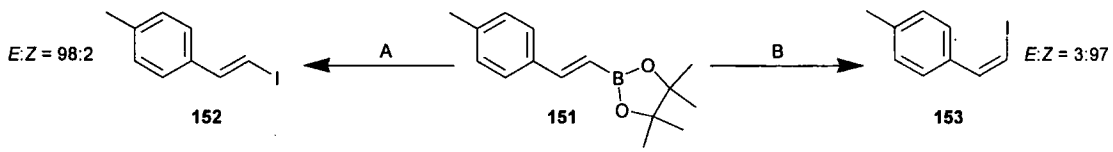
2.2.3 Conclusion

Conditions have been developed to allow the Heck coupling of 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane **123**. The reaction proceeds *via* a cationic palladium catalyst pathway, so to increase the Heck selectivity of the process, the reaction can be performed in the presence of thallium(I) or silver(I) acetate. The coupling of aryl iodides proceeds to give good yields and high Heck selectivity, even without the metal salts. Coupling of alkenyl iodides requires the presence the additives and even then, complete Heck selectivity is not guaranteed, resulting in reduced yields when compared to the aryl system. Nonetheless, this process is a reliable and valid way of introducing a functionalised alkenyl unit into an aryl or alkenyl system.

2.3 Iododeboronation Reactions

2.3.1 Introduction

Brown had demonstrated the conversion of alkenyl boronic acids into alkenyl iodides using an iododeboronation reaction; however, those conditions were not applicable to the pinacol substrate **151**.[158] Research performed within the group led to the development of conditions to transform substituted alkenyl boronate pinacol esters, products of the Heck reaction, into either (*E*)- or (*Z*)-iodoalkenes.[147] The transformations are induced through reaction with iodine monochloride and sodium methoxide where the order of reagent addition determines the stereochemical outcome. Initial treatment with NaOMe followed by ICl generates the (*E*)-alkenyl iodide, whereas initial reaction with ICl before NaOMe addition yields the (*Z*)-alkenyl iodide.



A) i) NaOMe/MeOH (2.0 eq), THF, -78°C, 20 min. ii) ICl/DCM (1.0 eq), -78°C, 2.5 h, 87%, *E*:*Z* 98:2.
B) i) ICl/DCM (1.0 eq), DCM, -78°C, 2.5 h. ii) NaOMe/MeOH (2.0 eq), -78°C, 25 min, 79%, *E*:*Z* 3:97.

Scheme 24

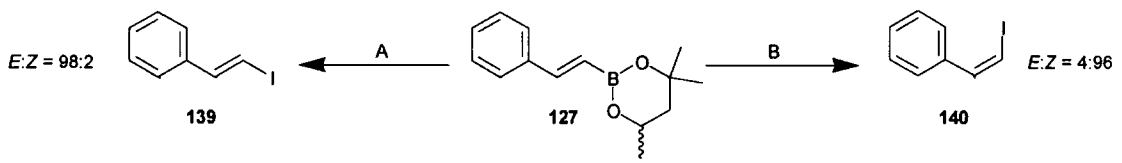
The specific aims of this area of research were to test, and if necessary modify, the established iododeboronation procedures when using the 2-methyl-2,4-pentane diol derived boronate ester. Again, probing the mechanistic details of the transformations would provide more information on the reactions and allow a wider applicability in terms of substrates but also identify potential and superior reagents.

2.3.2 Phenyl Substituted Alkenyl Boronate Esters

2.3.2.1 Examination of the Conditions

The conditions outlined above for the pinacol ester were initially examined on 4,4,6-trimethyl-2-((*E*)-styryl)-1,3,2-dioxaborinane **127** before some modifications in an attempt to increase both yields and selectivity. Both transformations were performed using 1.2 equivalents of each reagent, ICl as a 1.0M solution in DCM and NaOMe as a 0.5M solution in MeOH. It was found that the during synthesis of (*E*)-2-iodo-vinylbenzene **139**, warming to room temperature after the ICl addition generated greater yields and had no adverse influence on the isomer ratio. The isomer ratio obtained was consistently 98:2 in favour of the desired form, identical to that obtained for the pinacol

system; in addition the yield was similar at 86%. Note that the isomers were inseparable but the ratio of the two was the same before and after purification. The conditions for the synthesis of (*Z*)-2-iodo-vinylbenzene **140** were again based on those developed previously; however, extension of the reaction time of the ICl resulted in greater yields. For this system, again, the isolated yield was much greater at 95% albeit with almost the same level of selectivity (96:4). It is important to note that the quality of the ICl reagent has a significant effect on the yields of these reactions resulting in reduced levels of conversion.

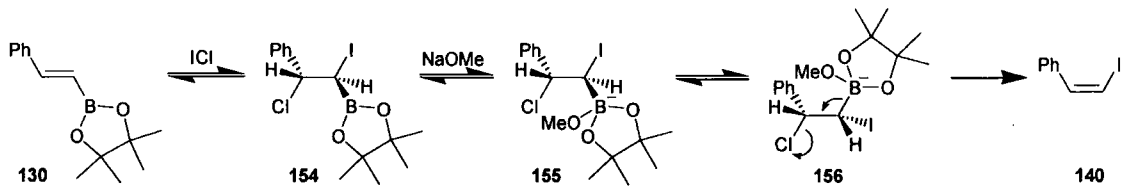


A) i) NaOMe/MeOH (1.2 eq), THF, -78°C, 30 min. ii) ICl/DCM (1.2 eq), -78°C to 25°C, 2 h, 86%, *E*:*Z* 98:2. B) i) ICl/DCM (1.2 eq), DCM, -78°C, 4 h. ii) NaOMe/MeOH (1.2 eq), -78°C, 30 min, 95%, *E*:*Z* 4:96.

Scheme 25

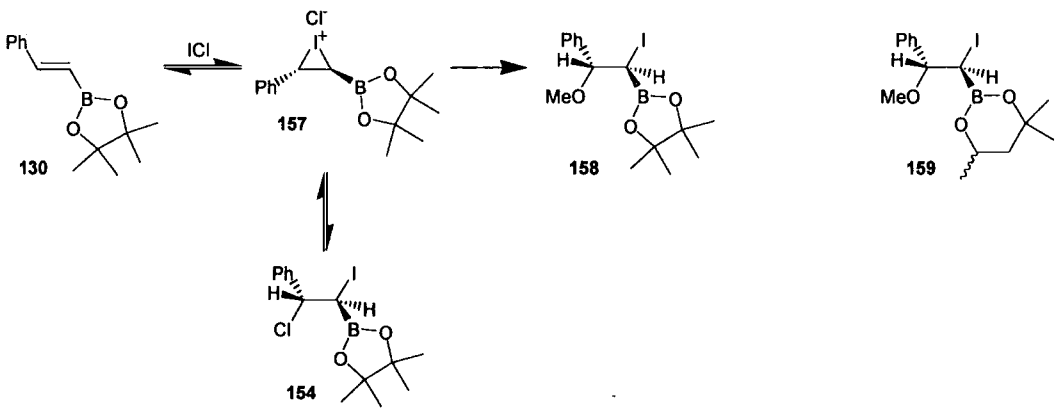
2.3.2.2 Mechanistic Discussion

The mechanisms involved in these transformations were examined through following the reaction by nmr with the observation, and if possible, isolation of any intermediates formed. The substrate used was 4,4,5,5-tetramethyl-2-(*E*)-styryl-1,3,2-dioxaborolane **130** as the ^{1}H nmr spectrum is less complex than the 2-methyl-2,4-pentane diol form. The reaction of **130** with ICl results in the formation of an intermediate believed to be the addition product **154**, which could be isolated. Indeed, treatment of this intermediate with NaOMe results in the rapid conversion to the (*Z*)-alkenyl iodide **140**. Hence, it is believed that the mechanism for the iododeboronation with inversion of stereochemistry initially involves an *anti*-addition of ICl, *via* an iodonium species, across the alkenyl substrate to give **154** (Scheme 26). Subsequent addition of NaOMe results in 'ate'-complex formation **155**, before rotation around the central bond **156** to allow *anti*-periplanar elimination of the boronate chloride, thus yielding the (*Z*)-alkenyl iodide. These conclusions are in accord with the ideas postulated by Brown for related reactions.[159]



Scheme 26

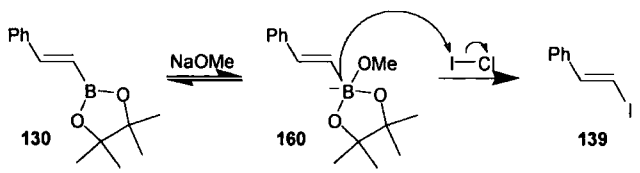
Evidence for the intervention of an iodonium species comes from performing these reactions in methanol, and indeed, suggests that the iodonium species and the chloride form a relatively stable ion pair. Thus, when the substrate **130** is treated with ICl in methanol, two products are formed; the ICl addition product **154**, formed from ring opening of the iodonium by the chloride ion, and **158**, formed when methanol opens the iodonium species. The ratio of these products was 92:8 in favour of the methoxy containing product. In the case of **127**, there was a single product formed which was the methoxy addition product **159**. Thus, the iodonium species is stabilised through ion pairing with the chloride. This is sufficiently strong that the chloride can only ring open, if at all, in minimal amounts when a suitable alternative nucleophile is present. In each case, only one addition regioisomer is formed which results from nucleophilic ring opening at the benzylic centre. Interestingly, the low ability of the methoxy group as a leaving group is demonstrated by the fact addition of NaOMe to the substrates **158** and **159** gave no elimination products.



Scheme 27

The reaction to generate the (*E*)-alkenyl iodide was much too rapid to follow accurately by nmr. Addition of NaOMe showed no significant change in the ^{1}H nmr spectrum. However, ^{11}B nmr showed the presence of two different boron species, one being the starting material and the other, the minor peak present at a much lower shift (2 ppm), is

likely to be due to 'ate'-complex formation. Addition of ICl saw instantaneous conversion to the (*E*)-alkenyl iodide and no intermediates could be observed. It is believed that this process follows the same mechanism as that proposed by Brown,[158] by which the addition of the NaOMe results in 'ate'-complex formation with the methoxide coordinating to the boron centre. Addition of the polarised ICl causes nucleophilic capture of the electropositive iodine with retention of alkene geometry.

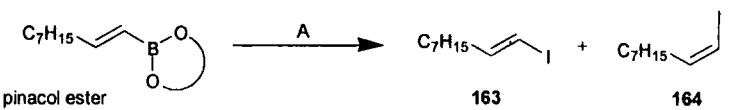


Scheme 28

2.3.3 Alkyl Substituted Alkenyl Boronate Esters

2.3.3.1 Examination of the Conditions

It was desirable to examine the newly developed protocols on different substrates, particularly those that did not posses a benzylic centre. The alkyl substituted alkenyl boronate esters, 4,4,5,5-tetramethyl-2-(*E*)-non-1-enyl-1,3,2-dioxaborolane **161** and 4,4,6-trimethyl-2-(*E*)-non-1-enyl-1,3,2-dioxaborinane **162** were selected, both of which can be prepared from the corresponding alkyne *via* a hydroboration-transesterification procedure (2.5.2.3.2). First to be examined was the iododeboronation with retention of stereochemistry to give (*E*)-1-iodo-non-1-ene **163** through treatment with NaOMe followed by ICl. The results obtained are shown in Table 5.



A) i) NaOMe/MeOH (1.2 eq), THF, T1°C, 30 min. ii) ICl/DCM (1.2 eq), T2°C, 2 h.

Equation 20

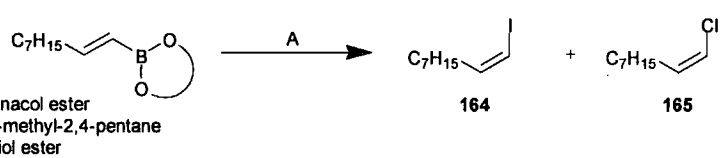
Entry	Substrate	Temperatures/°C	Conversion/%[a]	163:164[a]	Yield/%[b]
1	**161**	T1 -78, T2 -78 to 25	25	100:0	-
2	**161**	T1 25, T2 25	79	94:6	46
3	**162**	T1 -78, T2 -78 to 25	73	100:0	44
4	**162**	T1 25, T2 25	100	93:7	47

[a] Determined by ^{1}H nmr of the crude product. [b] Isolated yield after purification by SiO_2 column chromatography.

Table 5

Application of the standard conditions to each substrate (Table 5, entries 1 and 3) gave complete (*E*)-selectivity of the product. Unfortunately, the reactions did not go to completion and a reduced conversion was obtained. In the case of **161**, the conversion was very low at 25%. Conversely, for **162**, the level of reaction was much greater allowing isolation of the product in a reasonable yield (44%). To overcome these problems, the reaction was performed at approximately room temperature (Table 5, entries 2 and 4). The effect of the temperature change was two-fold: (1) as expected, it increased the conversion of each reaction which, in the case of **162**, went to completion; and (2) it decreased the selectivity so that some of the (*Z*)-product **164** was also formed. The use of these conditions did allow the isolation of the desired product but with disappointingly low yields. Through the course of these studies, it was discovered that 1-iodo-non-1-ene, of either geometry, was much more sensitive than 2-iodo-vinylbenzene upon purification and storage which accounts for the lower yields obtained in the example above. The best overall result was obtained using the original conditions (Table 5, entry 3).

The next logical step was to explore the transformation with inversion of stereochemistry to generate (*Z*)-1-iodo-non-1-ene **164** through reaction with ICl followed by NaOMe. Again, both substrates were examined, initially using the standard conditions and the results are shown in Table 6.



161 = pinacol ester
162 = 2-methyl-2,4-pentane diol ester

164 **165**

A i) ICl/DCM (1.2 eq), DCM, T1°C, 4 h. ii) NaOMe/MeOH (1.2 eq), T2°C, 30 min.

Equation 21

Entry	Substrate	Temperatures/°C	Conversion/%[a]	164:165[a]	Yield/%[b]
1	**161**	T1 -78, T2 -78	100	16:84	-
2	**161**	T1 -78, T2 25	100	69:31	-
3	**161**	T1 25, T2 25	100	94:6	65
4	**162**	T1 -78, T2 -78	100	17:83	-
5	**162**	T1 25, T2 25	100	37:63	-
6	**162**	T1 40, T2 40	100	60:40	-
7	**162**	T1 70, T2 70[c]	100	76:24	64

[a] Determined by ^{1}H nmr of the crude product. [b] Isolated yield after purification by SiO_2 column chromatography. [c] 1,2-dichloroethane used as solvent.

Table 6

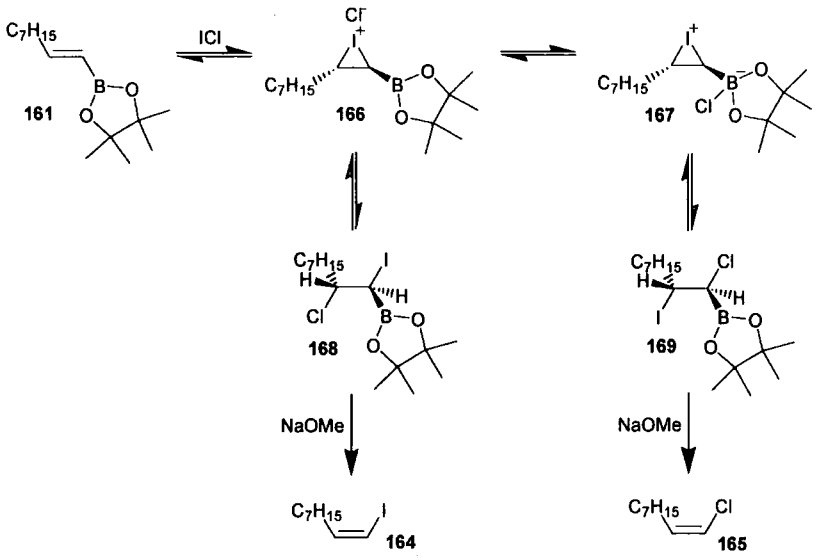
The initial reactions performed (Table 6, entries 1 and 4) provided startling results. The formation of (*Z*)-1-chloro-non-1-ene **165** competes substantially with iodide **164** formation. In fact, for those two examples, it is formed preferentially. Although this problem had never been observed in the aryl substituted systems, early work by Brown using mixed halogen systems had suffered from this problem.[159] There is no issue surrounding the level of conversion as all reactions went to completion and, in addition, no formation of (*E*)-isomers of any kind. Following from the investigations into (*E*)-alkenyl iodide synthesis, the temperatures at which each step was performed were varied. For substrate **162**, as the temperature increases (Table 6, entries 4-7), the selectivity of the reaction changes towards the desired iodide product **164** allowing its isolation in a good yield (64%) when performed at 70°C. The same is also true of the pinacol ester **161** (Table 6, entries 1 and 3); however, the temperature threshold at which the iodide becomes the favoured product is much lower in this case allowing greater selectivity and yield at room temperature (65%). It was important to discover how the temperature affected the reaction, so the initial addition of ICl was performed at -78°C before warming to room temperature and adding the NaOMe (Table 6, entry 2). The result was a selectivity value closer to that obtained when performing both steps at room temperature. This indicates that there is a temperature controlled equilibrium of the two potential addition products which only eliminate on the addition of base.

It is clear that the use of the alkyl substituted substrates had a significant effect on the reaction and led to the modification of the reaction conditions. In addition, and unlike the styryl system, there was a discernable difference between the two ester functionalities. Nonetheless, the use of these protocols allows the preparation of the desired iodo-alkenes in good yields and high, if not complete, geometrical purity.

2.3.3.2 Mechanistic Discussion

From these results, it appears synthesis of (*E*)-1-iodo-non-1-ene **163** follows the same mechanism as discussed earlier (Scheme 28). The formation of the (*Z*)-isomer at higher temperatures will be due to that process being able to proceed at a competitive rate at elevated temperatures.

The formation of the chloride product **165** when synthesising (*Z*)-1-iodo-non-1-ene **164**, provides increased support to the mechanism outlined above (2.3.2.2) but the different substrate adds a further complication. The origin of the chloride product arises from the ring opening of the iodonium species **166**. The chloride ion can obviously attack either carbon centre to give a mixture of addition products. Attack of the chloride ion on the alkyl substituted carbon generates the desired addition product **168**; this occurs preferentially at elevated temperatures and is the thermodynamically favoured addition product. Following the mechanism through, the base mediated *anti*-periplanar elimination step generates (*Z*)-1-iodo-non-1-ene **164**. However, if the chloride ion attacks the carbon bound to the boron, the resulting addition product is **169**. This process is favoured at low temperatures and the addition product may be formed through an intermediate which involves boron 'ate'-complex formation with the chloride ion **167**. Formation of this complex may provide a boron assisted delivery of the chloride to the *alpha*-position generating **169** and consequently (*Z*)-1-chloro-non-1-ene. As discussed earlier, the addition reaction is an equilibrium process, hence, the temperature at which the ICl addition reaction occurs is not as important as the temperature of the NaOMe mediated elimination which is irreversible. Thus, the ratio of **168** to **169** will be governed by that temperature.



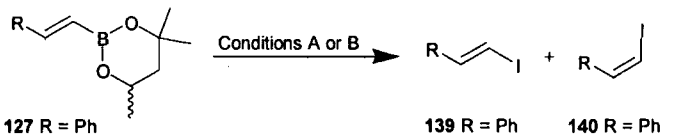
Scheme 29

2.3.4 Alternative Reagents

Further reagents were examined for their effect on the iododeboronation reactions. It was hoped that the development of a number of different conditions by which to induce these transformations would allow tailored conditions to be applied to particular substrates. This would provide more options in a complex total synthesis involving sensitive substrates expanding the scope of this strategy for the stereocontrolled synthesis of polyenes.

2.3.4.1 Sodium Hydroxide and Iodine

A recent publication by Grubbs demonstrated the iododeboronation of alkenyl pinacol boronates using modified Brown conditions.[160] A number of reactions were conducted on different substrates using sodium hydroxide and iodine but performed in THF at room temperature rather than ether at 0°C as tested by Brown.[158] The reactions showed *E*:*Z* selectivity of the iodide products in the ranges of 8-20:1, but always in favour of the (*E*)-alkene. The procedure only involved initial addition of NaOH followed by I_2, rather than the other way round and hence, no (*Z*)-alkene selectivity was reported. It was decided to test these conditions on the substrates 4,4,6-trimethyl-2-(*E*)-styryl-1,3,2-dioxaborinane **127** and 4,4,6-trimethyl-2-(*E*)-non-1-enyl-1,3,2-dioxaborinane **162** and vary the order of reagent addition to examine the possibility of using these conditions to prepare (*Z*)-iodo alkenes. The results are shown in Table 7.



127 R = Ph
162 R = C_7H_{15}

139 R = Ph **140** R = Ph
163 R = C_7H_{15} **164** R = C_7H_{15}

A) i) $NaOH/H_2O$ (3 eq), THF, 25°C, 10 min. ii) I_2/THF (2 eq), 25°C, 2 h.

B) i) I_2/THF (2 eq), THF, 25°C, 2 h. ii) $NaOH/H_2O$ (3 eq), 25°C, 10 min.

Equation 22

Entry	Substrate	Conditions	*E*:*Z* Ratio[a]	Yield/%[b]
1	**127**	A	97:3	78
2	**127**	B	100:0	52
3	**162**	A	100:0	56
4	**162**	B	100:0	58

[a] Determined by ^1H nmr of the crude product. [b] Isolated yield after purification by SiO_2 column chromatography.

Table 7

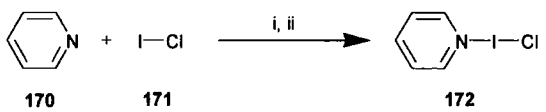
The first and most important point to note is that the order of reagent addition had no effect on the stereochemical outcome. For both substrates the use of conditions B, initial addition of iodine, generated only the (*E*)-alkenyl iodide. In fact, it was only entry 1, which involved the use of conditions A and the phenyl substituted alkenyl boronate, that actually provided any of the (*Z*)-isomer. These conditions cannot be used to prepare (*Z*)-iodoalkenes, only the (*E*)-isomer. For substrate **127**, although the selectivity was approximately equal to, or greater than, that obtained when using NaOMe/ICl, the lower yields mean that this does not provide a worthwhile alternative in this instance. In the case of the alkyl substituted substrate **162**, the selectivity and yields obtained were slightly higher than when performed using NaOMe/ICl. This suggests that these milder reaction conditions may be useful when preparing (*E*)-alkenyl iodides involving sensitive substrates.

These results confirm previous findings that the use of I_2/NaOH cannot give conversion of the alkenyl pinacol ester into the (*Z*)-alkenyl iodide.[147] From a mechanistic viewpoint, it appears that the lack of polarisation in the iodine molecule (compared to ICl) means that it is unable to add across the double bond. As discussed earlier, the transformation with inversion of stereochemistry involves an *anti*-addition, *anti*-elimination process and so the (*Z*)-alkene is not formed. This lack of addition reaction

means that even when NaOH is added second, the reaction still follows 'ate'-complex formation and nucleophilic capture of the iodine with retention of stereochemistry, generating the (*E*)-iodo alkene.

2.3.4.2 Substituted Pyridine-Iodinemonochloride Complexes

A survey of the literature to identify potential alternative electropositive sources of iodine had led to the identification of the novel system, pyridine-iodinemonochloride **172**.[161-163] This compound had been demonstrated to be a highly efficient source of iodine to induce the iodination of a range of aromatic compounds.[164] Consequently, it was examined as an iodine source for the iododeboronation reactions. Pyridine-iodinemonochloride was easily prepared in consistently high yields from a simple reaction of pyridine and ICl in DCM. Treatment with hexane results in precipitation of the product as a yellow solid which is stable and easy to handle. Again, the age and quality of the ICl solution has a significant influence on the yield of the reaction in terms of yield.



170 **171** **172**

i) DCM, 0°C, 30 min. ii) 0°C-25°C, 30 min, hexane, 90%.

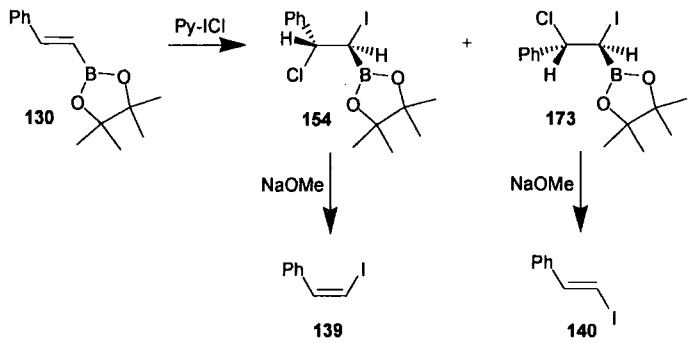
Equation 23

Pyridine-iodinemonochloride was used as an iododeboronating agent on the phenyl and alkyl substituted alkenyl boronate systems discussed above. The effects of using this reagent were striking and the results between the two systems very different, leading to further elucidation of the mechanistic issues involved in these transformations.

2.3.4.2.1 Phenyl Substituted Alkenyl Boronate Esters

The pinacol ester 4,4,5,5-tetramethyl-2-(*E*)-styryl-1,3,2-dioxaborolane **130** was examined and the reaction followed by ^{1}H nmr; the results were very different when compared to using ICl. The addition of pyridine-ICl to a solution containing **130** resulted in the formation of two addition products in a 1:1 ratio. Note that for complete conversion of the starting material, two equivalents of the complex were required. One addition product was identical to that assigned as the *anti*-addition product of ICl across the alkene **154**. The other was presumed to be the diastereoisomer, *i.e.* the formal-*syn*-addition product **173**. Treatment of this mixture with NaOMe gave the expected

elimination, again, through an *anti*-periplanar mechanism, to give a 1:1 mixture of the (*E*)-and (*Z*)-styryl iodides **139** and **140**.

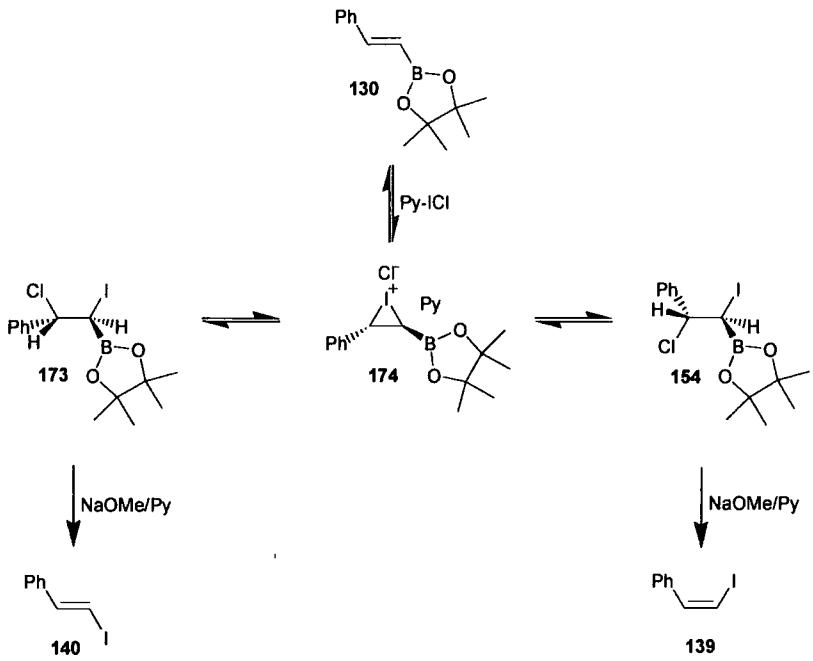


Scheme 30

Although there is a precedent for the *syn*-addition of dihalogen species to carbon multiple bonds,[165,166] it is doubtful that such a process is occurring in the present case. It is interesting that two equivalents of the complex are required in order to bring about the ICl addition reaction. This suggests that under these conditions, an excess of either chloride ion or pyridine is essential to assist the addition step.

The major difference in the reaction compared to using ICl alone, is the presence of the pyridine base. The effect of pyridine on the reaction was thus probed by treating the addition product **154** with two equivalents of pyridine. A mixture of three products was obtained: the starting material **130**; and the iodides **139** and **140**, present in a ratio of 2:1:1. Hence, pyridine can attack the iodine resulting in elimination, re-formation of the pyridine-ICl complex and production of the starting alkenyl boronate **130**. The reaction can then proceed as previously, resulting in a 1:1 mixture of the *syn*- and *anti*-addition products. Hence, pyridine is directly responsible for the formation of two addition products. In this example, pyridine was also able to mediate the elimination reaction through boron 'ate'-complex formation, resulting in the preparation of iodides **139** and **140**. The reaction gave only 50% conversion of boronate **130**, suggesting that the excess of chloride ions was in some way required to assist the addition step. Chloride ion must coordinate the iodonium species, forming a stable ion pair which is further stabilised by the pyridine, either through coordination to the boron or the ion pair itself, since ICl alone adds across the double bond. The presence of a nucleophile such as the chloride ion or pyridine results in both ring opening of the iodonium species and S_N2-mediated epimerisation at the chloride substituted benzylic position resulting in a 1:1

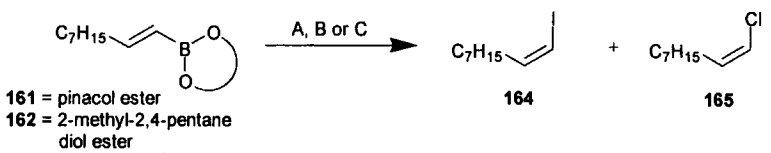
mixture of addition products **154** and **173**. This stable ion pair effect was also inferred when discussing the methanol opening of the iodonium species of **130** (2.3.2.2).



Scheme 31

2.3.4.2.2 Alkyl Substituted Alkenyl Boronate Esters

The use of pyridine-ICl in the iododeboronation of the alkyl substituted alkenyl boronate esters was examined. As with the reactions involving ICl and NaOMe the same two products were obtained, (*Z*)-1-chloro-non-1-ene **165** as well as the desired (*Z*)-1-iodo-non-1-ene **164**. Importantly, the use of pyridine-ICl gave direct conversion to these products; no addition intermediates could be observed and there was no requirement for additional base. As with the phenyl system, the use of two equivalents was required to bring about complete conversion.



A) i) ICl/DCM (1.2 eq), DCM, 25°C, 4 h. ii) NaOMe/MeOH (1.2 eq), 25°C, 30 min. B) Py-ICl (2 eq), DCM, 25°C, 4 h. C) i) Py-ICl (1.0 eq), $BF_3.Et_2O$, DCM, 25°C, 4 h. ii) NaOMe/MeOH (4 eq), 25°C, 30 min.

Equation 24

Entry	Substrate	Conditions	Conversion/%[a]	164:165[a]
1	**162**	A	100	37:63
2	**161**	B	100	7:93
3	**162**	B	100	5:95
4	**162**	C	100	34:66

[a] Determined by ^{1}H nmr of the crude product.

Table 8

The result of performing the reaction under the standard conditions at the same temperature is presented as a reference (Table 8, entry 1). The reaction of both substrates with Py-ICl (Table 8, entries 2 and 3) show that the reaction is extremely selective, albeit generating the chloride product **165**, with much greater selectivity than when using ICl/NaOMe. With reference to the mechanistic details discussed for that process (Scheme 29), the presence of pyridine results in the attack of chloride ion on the iodonium ion at the boron-bound carbon. It can be suggested that the iodonium species can be stabilised by pyridine, rather than ion pairing with the chloride, thus allowing chloride-boron 'ate'-complex formation (Figure 16) and *alpha*-delivery of the chloride. This addition product then undergoes base assisted *anti*-periplanar elimination mediated by pyridine itself to generate the (*Z*)-alkenyl chloride **164**.

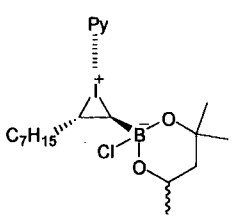


Figure 16

Interestingly, pyridine-ICl can be used as a 'clean' shelf-stable source of ICl. Addition of the Lewis acid, BF_3, to the reaction resulted in coordination to the pyridine and *in situ* formation of ICl. This then reacted as expected, and as a result, after treatment with NaOMe, gave a product ratio almost identical to that obtained using ICl/NaOMe alone (Table 8, entry 4). This adds further support to the fact that the pyridine plays an essential role in controlling the chemoselectivity of iodonium ring opening.

2.3.4.2.3 Synthesis and Structural Evaluation of a Range of Substituted Pyridine Iodinemonochloride Complexes

Following on from the highly selective chlorodeboronation reactions performed with pyridine-ICl, a number of other analogues of this interesting charge transfer complex were prepared involving different substituted pyridine units to examine their effect on the reaction. All were prepared in the same fashion as pyridine-ICl, again in high yields.

176 3-Bromopyridine
170 Pyridine
177 2,2-Bipyridine
178 2,6-Lutidine
179 2,4,6-Collidine
180 DMAP

171

181 3-Bromopyridine-ICl
172 Pyridine-ICl
182 2,2-Bipyridine-ICl
183 2,6-Lutidine-ICl
184 2,4,6-Collidine-ICl
185 DMAP-ICl

i) DCM, 0°C, 30 min. ii) 0°C-25°C, 30 min, hexane, **181** 73%, **172** 90%, **182** 94%, **183** 82%, **184** 75%, **185** 87 %.

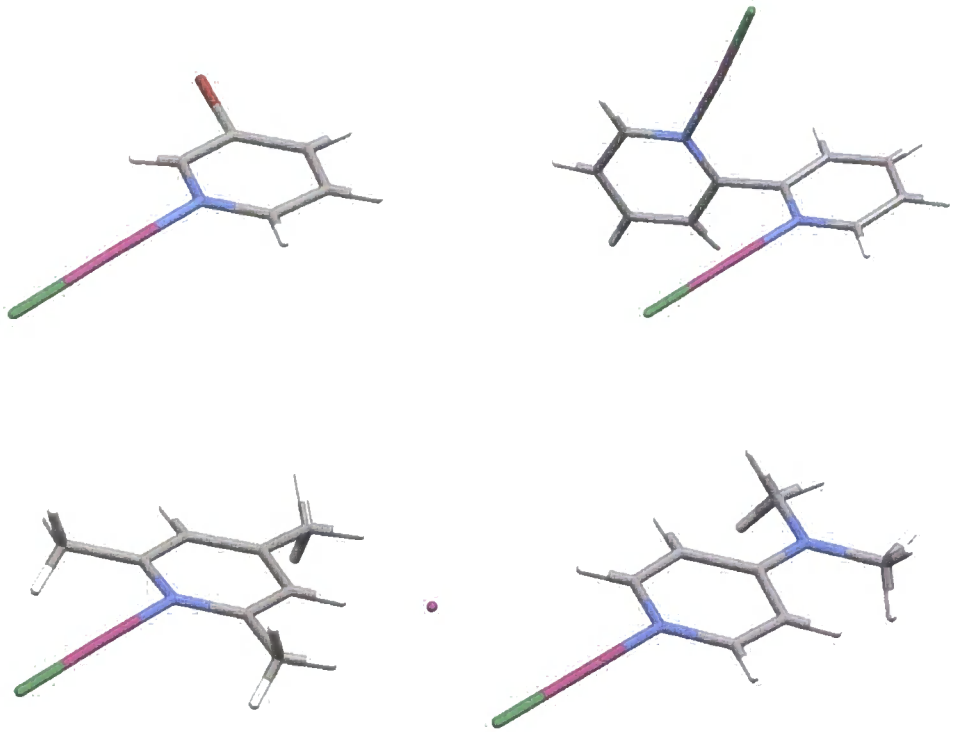
Equation 25

Once prepared, a slow recrystallisation from DCM/hexane produced yellow crystalline materials which were identical by characterisation to the powdered form but allowed crystallographic studies to be performed. The X-ray structures of 3-bromopyridine-ICl **181**, 2,2-bipyridine-$(ICl)_2$ **182**, 2,6-lutidine-ICl **183**, 2,4,6-collidine-ICl **184** and DMAP-ICl **185** have been determined to complement the existing information on that of pyridine-ICl **172**.[167] The structures of **181**, **182**, **184**, **185** and that of pyridine-ICl **172** are all similar and are charge transfer complexes between the nitrogen donor and the ICl molecule (Figure 17). The N-I-Cl moieties are linear and nearly coplanar with the pyridine ring. The more important structural parameters are displayed in Table 9.

Entry	Compound	N-I/Å	I-Cl/Å	ave.N-C/Å	N-I-Cl/°	C-N-C/°	φ^a
1	**181**	2.344(2)	2.4734(7)	1.341(3)	178.43(5)	120.0(2)	5.2
2	**172**[b]	2.29(1)	2.510(4)	1.33(2)	178.7(3)	120(1)	0.1
3	**182**	2.321(2)	2.4974(7)	1.344(3)	179.41(5)	119.8(2)	4.5
		2.337(2)	2.4878(9)		175.33(5)	119.6(2)	6.6
4	**183**	2.300(1)	2.5421(5)	1.358(2)	-	120.9(1)	7.1
5	**184**	2.294(5)	2.531(2)	1.367(8)	179.05(14)	119.8(5)	1.5
6	**185**	2.246(2)	2.5615(7)	1.351(3)	179.24(5)	117.9(2)	0.4

[a] φ is the angle between the N-I bond and the heterocycle plane. [b] Data from literature.[167]

Table 9



181 **182**

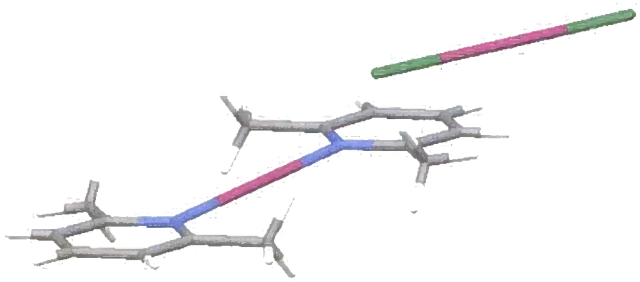
184 **185**

Figure 17

The key N-I-Cl moiety can be described as a three-centred four-electron bond involving one bonding and one non-bonding electron pair.[168] In the above cases the N-I bond lengths are longer than the sum of the covalent radii (2.03 Å) but much shorter than the sum of the van der Waals radii (3.67 Å).[169] It must be noted that as the electron donating properties of the pyridine substituents increase there is a significant shortening of the N-I bond with a concomitant increase in the I-Cl bond length (Table 9, entries 1-3, 5 and 6). The I-Cl bond lengths are much greater than that in the gas phase ICl molecule (2.321 Å), which is practically equal to the sum of the covalent radii, and in crystal structures of ICl (2.353 and 2.450 Å) in the α-phase[170] and (2.35 and 2.44 Å) in the β-phase[171] which are both characterised by strong intermolecular I-I and I-Cl interactions. Note that the molecule **184** displays a 3% level of disorder, hence the additional iodine on Figure 17 above, all data refers to the major form.

The structure of 2,6-lutidine-iodinemonochloride **183** (Figure 18), is distinct from the examples discussed previously. It comprises bis(2,6-lutidino)iodonium cations charge balanced by ICl_2^- anions where in both cases the iodine lies at a crystallographic inversion centre, hence the N-I-N and Cl-I-Cl bond angles are 180°. The N-I bond lengths (2.300 Å) are comparable with those of the cations bis(pyridine)iodonium (2.259 Å)[172] and bis(2,4,6-collidine)iodonium (2.29 Å)[173] as well as the other

complexes. The I-Cl bond length in the anion (2.542 Å) lies in the observed range for such systems (2.53-2.57 Å).[174]

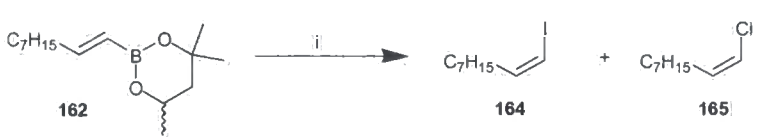


183

Figure 18

2.3.4.2.4 Chlorodeboronation Reactions

Each of the above complexes were used to perform the chlorodeboronation of the substrate 4,4,6-trimethyl-2-non-1-enyl-1,3,2-dioxaborinane **162**. The procedure used was identical to that outlined above when using pyridine-iodinemonochloride, which gave direct conversion to the alkenyl iodide **164** and chloride **165** products with high selectivity for the latter. The postulated mechanism involves initial addition of ICl across the alkene, which is influenced by the pyridine, before base-assisted elimination of the iodoboronate, again mediated by the pyridine. The key aspect was to examine the effect the different pyridine substituents would have on the overall conversion and chemoselectivity of the reaction. The results of the reaction depicted in Equation 26 are shown in Table 10. Note: in the case of 2,2-bipy-$(ICl)_2$, only one molar equivalent was used.



162 **164** **165**

i) ArN-ICl (2 eq), DCM, 25°C, 4 h.

Equation 26

		Product ratio[a] (yield%)[b]		
Entry	**Reagent**	**162**	**164**	**165**
1	**181**	0	16	84
2	**172**	0	5	95 (48)
3	**182**	0	6	94
4	**183**	0	0	100 (69)
5	**184**	0	0	100 (60)
6	**185**	38	23	39

[a] Determined from the ^{1}H nmr of the crude reaction product. [b] Isolated yield after purification by SiO_2 column chromatography.

Table 10

With the exception of DMAP-ICl (Table 10, entry 6), all of the complexes gave complete conversion of the starting alkenyl boronate with greater selectivity than the ICl/NaOMe protocol. As can be seen, the product ratio is significantly affected by the nature the pyridine present, further supporting the theory that it has a major influence on the regioselectivity of the ICl addition step. This selectivity increases with the electron-donating strength of the pyridine substituents (Table 10, entries 1-5), the more electron rich and stronger donor pyridines favour addition of the chloride to the boron substituted end of the alkene. Indeed, the 2,6-lutidine and 2,4,6-collidine-iodinemonochloride complexes **183** and **184** produced exclusively (*Z*)-1-chloro-non-1-ene **165**, allowing its isolation in good yields (69% and 60% respectively, Table 10, entries 4 and 5) and are, therefore, the reagents of choice for this transformation. In contrast, it was surprising, that DMAP-ICl **185** resulted in such a low conversion and low selectivity (Table 10, entry 6), considering it possessed the most electron rich pyridine (indicated by having the shortest N-I bond and longest I-Cl bond).

To probe further the mechanism of iodo/chloro-deboronation the reaction was performed with a single equivalent of bipyridine-ICl_2 **182** (Table 10 entry 3). It was anticipated that the comparison of the results between this reaction and that of pyridine-ICl would indicate why two equivalents of pyridine-ICl are needed for complete consumption of the boronate and whether they worked in tandem. The bipyridine-$(ICl)_2$ provides the correct molar ratio required for the reaction but the bipyridyl structure effectively locks the two units into close proximity preventing potential intermolecular interactions between the pyridine rings. However, the reaction of **182** gave virtually the same result as for pyridine-ICl showing that the predefined orientation of the bipyridine system has no effect on the conversion or selectivity of the reaction.

Regarding the mechanism of the reaction, the results reinforce the ideas postulated in 2.3.4.2.2, *i.e.* that the iodonium species is stabilised by the pyridine allowing chloride-boron 'ate'-complex formation and *alpha*-delivery of the chloride to the boron bound carbon. The more strongly electron-donating the pyridine is, the greater the stabilisation of the iodonium species allowing increased 'ate'-complex formation and selectivity for this pathway.

2.3.5 Conclusion

The original conditions for the stereoselective iododeboronation of alkenyl boronate esters have been examined and new conditions developed to allow the successful reaction of a wider range of substrates. In addition, the steps taken in this development have highlighted the mechanistic issues involved in the transformations which appear to be much more complex then first envisaged and are somewhat substrate dependent.

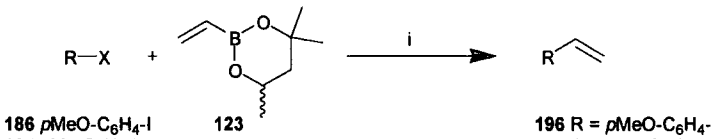
2.4 Suzuki-Miyaura Coupling Reactions

2.4.1 Introduction

As stated previously, 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane **123** is a vinyl dianion equivalent that can, under palladium catalysed coupling conditions, react at either end following the Heck or Suzuki-Miyaura pathways. As described here (2.2) and in previous work, conditions have been developed to maximise the selectivity of the Heck pathway as this suited the strategy towards the syntheses of certain target molecules. However, the development of conditions to allow a vinyl boronate ester, either the pinacol **117** or 2-methyl-2,4-penatane diol form **123**, to selectively undergo Suzuki-Miyaura couplings had never previously been fully investigated. Not only would the development of this reaction add another dimension to the versatility of the vinylboronate ester as a reagent, but in addition, provide further options when applied to the synthesis of specific polyene functions such as those present in certain natural products. Consequently, a study was performed to explore the potential of this reaction paying particular attention to the Suzuki-Miyaura to Heck product selectivity and reaction yields, as was the case when examining the Heck coupling. The vinylboronate ester **123** was coupled with a number of aryl halides with the aim of producing styrenes and, as a natural progression to link this to the synthesis of polyenes, with the (*E*)- and (*Z*)-styryl iodides **139** and **140** to produce dienes.

2.4.2 Coupling of Aryl Halides

The coupling reactions of 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane **123** were attempted with a number of *para*-substituted aryl halides to vary the electronics of the ring systems, whilst exploring the reactivity of iodides, bromides and chlorides. Standard coupling conditions were employed with palladium(0)-tetrakistriphenylphosphine ($Pd(PPh_3)_4$) as the catalyst in refluxing THF. Three different bases were examined for their effect on the reaction, potassium *tert*-butoxide (KO*t*Bu), potassium hydroxide (KOH) and silver(I) oxide (Ag_2O) all of which have been shown to promote the Suzuki-Miyaura reaction. The use of these conditions allowed a robust set-up (degassing of reaction vessels was not necessary) and a minimal work up (filtration through celite and solvent removal) before analysis of the crude product and purification.



186 *p*MeO-C_6H_4-I
187 *p*Me-C_6H_4-I
126 C_6H_5-I
188 *p*CF_3-C_6H_4-I
189 1-naphthyl-I
190 *p*MeO-C_6H_4-Br
191 *p*Me-C_6H_4-Br
192 C_6H_5-Br
193 *p*CF_3-C_6H_4-Br
194 1-naphthyl-Br
133 2-pyridyl-Br
195 C_6H_5-Cl

123

196 R = *p*MeO-C_6H_4-
197 R = *p*Me-C_6H_4-
128 R = C_6H_5-
198 R = *p*CF_3-C_6H_4-
199 R = 1-naphthyl
137 R = 2-pyridyl

i) $Pd(PPh_3)_4$ (5 mol%), base (1.2 eq), THF, 67°C, 24 h.

Equation 27

		Base / Yield %		
Entry	**Substrate**	**KO*t*Bu**[a]	**KOH**[a]	**Ag_2O**[b]
1	**186**	95	66	90
2	**187**	75	68	82
3	**126**	62	73	51
4	**188**	87	75	76
5	**189**	65	74	96
6	**190**	65	28	0
7	**191**	52	35	0
8	**192**	56	36	0
9	**193**	71	50	11[c]
10	**194**	60	58	0
11	**133**	41	31	39[a]
12	**195**	0	0	0

[a] GC yield determined through calibration with undecane as the internal standard. [b] Isolated yield after purification by SiO_2 column chromatography. [c] Determined by ^1H nmr of the crude product.

Table 11

The most significant result involving these reactions is that the vinyl boronate showed complete chemoselectivity for the Suzuki-Miyaura pathway, none of the Heck product was generated in any of the reactions performed, despite the hindered boronate ester. This is a vital finding and highly impressive; during the Heck couplings, complete selectivity was achievable but dependent on the substrate in question with the reaction conditions modified accordingly. Here, however, under a number of different conditions and with a range of substrates, the reaction follows a single pathway. This demonstrates that the vinyl boronate **123** can be used to add a two carbon ethene fragment to a substrate with complete selectivity. The use of nucleophilic oxygen bases

results in the catalytic cycle following exclusively the Suzuki-Miyaura and not the Heck pathway. The base obviously facilitates the formation of the boron 'ate' complex thus driving the transmetallation process rather than addition of the organo-palladium complex across the alkene which would be the case when following the Heck pathway. The specific intricacies of the transmetallation step are unknown, but will follow either of the mechanisms discussed previously (1.2.3): base-halide exchange before 'ate'-complex formation and nucleophilic substitution at the palladium centre or initial quaternerization of the boronate ester, followed by the nucleophilic substitution.

When examining the yields of the desired products the levels of reactivity displayed by each of the three different halides investigated is significantly different. They follow the established trend of iodides being more reactive than bromides which in turn are much more reactive than the chlorides, this is indicative of a rate determining oxidative addition step. The aryl iodides (Table 11, entries 1-5) generally show impressive yields across all of the reaction conditions examined (51-96%). The presence of the substituent group in the *para*-position does seem to have a slight effect. This is best demonstrated when examining the results obtained when employing KOH as the base. (the others show some anomalies). They show an increasing level of reactivity with an increase in the electron withdrawing nature of the substituent, this again is in accord with a rate-determining oxidative addition step in the catalytic cycle. When comparing the effect of the base used in each reaction the results show that the use of KO*t*Bu and Ag_2O generally provide slightly higher yields.

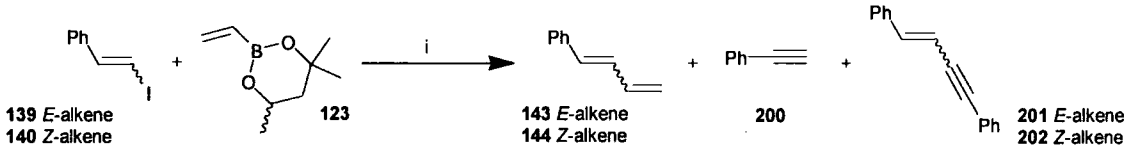
The yields obtained for the coupling of the bromides were much lower than for the corresponding iodides (Table 11, entries 6-11), again for the coupling of the substituted aryls, yields generally increased with electron withdrawing strength of the substituent (most accurately demonstrated when using KOH). There was, however, a much more pronounced effect when comparing the base used in each reaction. The use of KO*t*Bu gave good yields (52-71%) and KOH gave the desired coupled products but in reduced yields (28-50%). When using Ag_2O, only the most electron deficient bromide, the *para*-trifluoro methyl substrate **193** (Table 11, entry 9), showed any coupling at all and with a very poor 11% yield (as determined by ^{1}H nmr). This was most unexpected after its successful application to the coupling of the aryl iodides. As a comparison to the unsuccessful Heck studies performed on 2-bromopyridine **133** outlined earlier, coupling was attempted under the Suzuki-Miyaura conditions (Table 11, entry 13). The reaction

proceeded moderately well under all the conditions tested. The difference in the Heck and Suzuki-Miyaura coupling of this substrate must centre on the difference between the coordination-insertion and transmetallation steps. As discussed earlier the oxidative addition product of the Heck reaction must be so stable that insertion of the alkene into the organo-palladium bond does not occur at any appreciable rate. However, under these basic Suzuki-Miyaura conditions, the addition product is able to undergo transmetallation with the boronate ester **123** generating 2-vinyl pyridine **137**.

As can be seen, all attempts at the coupling of chlorobenzene proved to be unsuccessful (Table 11, entry 12). A number of conditions have been devised to couple aryl chlorides in palladium catalysed reactions, which could be applied to this reaction, but this was beyond the scope of this investigation and was felt to deviate from the specific targets.[84,98-104]

2.4.3 Coupling of Alkenyl Iodides

To develop the Suzuki-Miyaura reaction of **123** towards the preparation of polyenes, coupling with the (*E*)- and (*Z*)-styryl iodides **139** and **140** was attempted. The conditions used for these reactions were based on those that had been successfully applied to the coupling of aryls; however, some unexpected results were obtained generating in some cases a mixture of products.



139 *E*-alkene
140 *Z*-alkene

123

143 *E*-alkene
144 *Z*-alkene

200

201 *E*-alkene
202 *Z*-alkene

i) $Pd(PPh_3)_4$ (5 mol%), base (1.2 eq), THF, 67°C, 24 h.

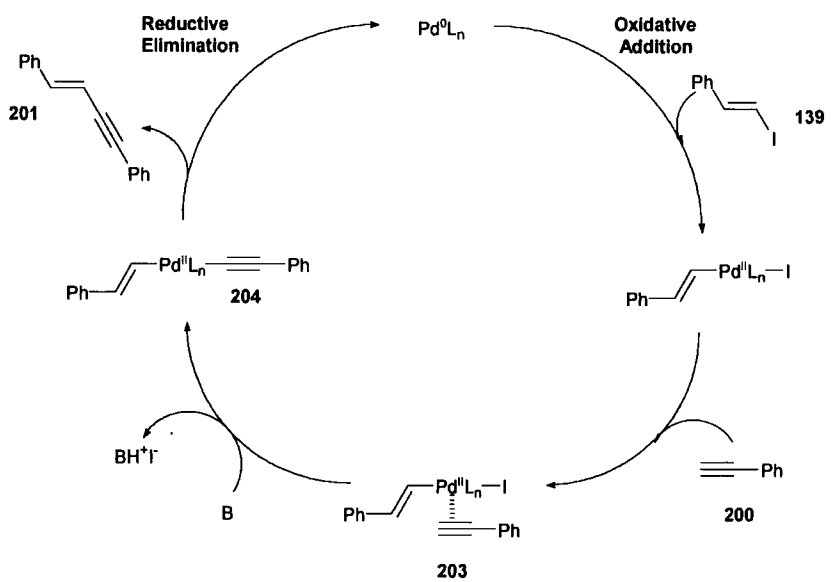
Equation 28

			Product Ratio[a] (yield %[b])		
Entry	**Substrate**	**Base**	**143 or 144**	**200**	**201 or 202**
1	**139**	KO*t*Bu	47 (26)	0	53
2	**139**	KOH	100 (63)	0	0
3	**139**	Ag_2O	100 (56)	0	0
4	**140**	KO*t*Bu	0	68	32
5	**140**	KOH	90 (46)	10	0
6	**140**	Ag_2O	100 (51)	0	0

[a] Determined by ^1H nmr of the crude product. [b] Isolated yield after purification by SiO_2 column chromatography.

Table 12

The coupling of (*E*)-styryl iodide using KO*t*Bu resulted in the formation of two products in a 47:53 ratio and as a consequence gave a low yield of the desired product (26%, table 12, entry 1). The major product formed in the reaction was the ene-yne, 1-(*E*)-4-phenyl-1-buten-3-ynyl **201**. Under these reaction conditions, the *tert*-butoxide ion facilitates the elimination of HI from the substrate **139** to generate phenylacetylene **200**, which can participate in the coupling process to generate the aforementioned ene-yne. The mechanism of ene-yne formation is likely to be akin to that of the Sonagashira coupling reaction.[175] Although there is no copper(I) co-catalyst, there are a number of literature examples in which conditions have been developed to avoid the use of a copper which employ carbonate bases and allow the syntheses of ene-yne units.[176,177] The mechanism outlined in Scheme 32 has been postulated for the coupling in the absence of copper(I),[178] initial oxidative addition occurs as expected, the key difference is in the transmetallation step, obviously the alkyne cuprate cannot be formed. Activation of the alkyne C-H bond is achieved *via* an initial π-coordination of the alkyne to the palladium centre **203**, thus weakening the C-H bond allowing the base assisted removal of HI to afford the vinyl-alkynyl palladium species **204**. A reductive elimination process then regenerates the active catalyst producing the ene-yne **201**.



Scheme 32

When the (*Z*)-isomer **140** was reacted in the presence of KO*t*Bu (Table 12, entry 4), the reaction yielded only phenylacetylene **200** and ene-yne **202**, with none of the desired

diene. It appears that the increased sensitivity of the (*Z*)-form results in rapid elimination of HI and as a consequence, there is less of the electrophile to undergo oxidative addition and therefore, reduced amounts of any coupled product are formed. The fact that the only coupled product is the ene-yne suggests that the Sonogashira coupling proceeds at a greater rate than the Suzuki-Miyaura. This may be due to the fact that after the elimination of HI from the electrophile **140**, the base exists as the protonated iodide salt and, as a result, it cannot promote transmetallation as it is unable to quaternarise the boron centre.

This elimination problem is not so severe when using KOH and is, as expected, dependent on the nature of the base employed in the reaction. The (*E*)-iodide **139** coupled successfully (Table 12, entry 2) to give exclusively the desired diene with no elimination products allowing the isolation of **143** in a much improved yield (63%). Coupling of the more sensitive (*Z*)-isomer **140** resulted in a small amount of elimination to the alkyne, but no Sonogashira coupling, to give **144** in a reasonable yield (46%) (table 12, entry 5). The use of Ag_2O provided a solution to the problem of elimination from the substrate; no HI elimination from the electrophile was observed for either substrate. This allowed the successful coupling of the iodides (Table 12, entries 3 and 6) to generate solely the desired dienes **143** and **144**. The yields of the reactions (56% and 51%) are lower than those obtained for the aryl couplings. As expected all of the coupled products, either the dienes or ene-ynes showed complete retention of alkene geometry.

2.4.4 Conclusion

The Suzuki-Miyaura reaction of the vinyl boronate ester **123** is an efficient and reliable reaction which proceeds with complete selectivity over the potential Heck pathway. The coupling can occur with both aryl and alkenyl substrates in good yields with complete retention of alkenyl geometry although the choice of base in such reactions is of considerable importance. This reaction is one that can be easily encompassed as a further tool in developing this vinyl boronate based strategy towards the stereoselective synthesis of polyene natural products.

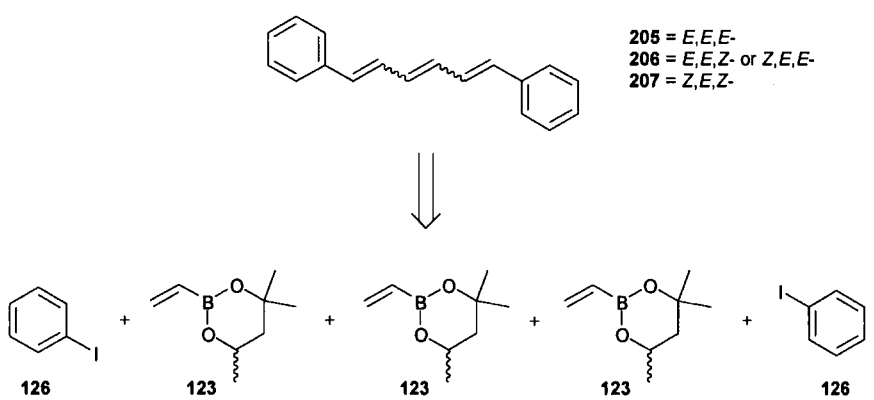
2.5 Application of the Strategy to the Synthesis of Polyenes

As discussed previously, the three reactions: Heck coupling; iododeboronation; and Suzuki-Miyaura coupling, are the key processes in our strategy for the construction of polyene units. The palladium catalysed coupling reactions are employed to link the alkene units together with the geometry of each installed through the stereocontrolled iododeboronations. Having examined each of the aforementioned reactions individually, they were used in combination to prepare a number of 1,6-diphenyl-1,3,5-hexatrienes of varying geometries before attempting the synthesis of the tetraene-containing natural product ixoric acid **124**.

2.5.1 1,6-Diphenyl-1,3,5-hexatriene Syntheses

2.5.1.1 Introduction

Having already investigated each of the key reactions with aromatic containing substrates, the 1,6-diphenyl-1,3,5-hexatrienes were chosen as target molecules to test the strategy, as in fact, many of the reactions had been performed previously. It was envisaged that the structures could be prepared from just two starting materials, 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane **123** and iodobenzene **126** (Scheme 33). Two molecules of iodobenzene **126** would provide each aromatic unit but, more importantly, the three vinyl boronate ester units **123** would be used to provide each alkene unit and be regarded as a genuine two-carbon alkenyl building block.

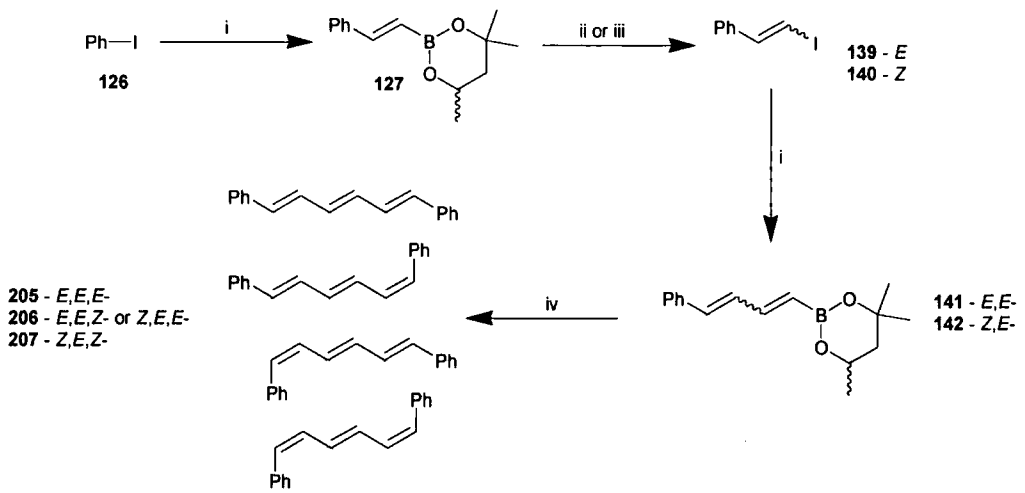


Scheme 33

2.5.1.2 Synthetic Route

The initial reaction along the proposed synthetic route to the trienes was the Heck coupling of iodobenzene **126** with 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane **123**.

This reaction links the phenyl unit with the first alkene to generate 4,4,6-trimethyl-2-(*E*)-styryl-1,3,2-dioxaborinane **127**. As discussed (2.2.3), the reaction was performed under standard conditions but with the addition of AgOAc to induce complete Heck selectivity, allowing the isolation of **127** in an 88% yield.



i) $Pd(OAc)_2$ (5 mol%), PPh_3 (15 mol%), nBu$_3$N (1.2 eq), AgOAc (1.2 eq), **123** (1.2 eq), Toluene, 110°C, 24 h, **127** 88%, **141** 55%, **142** 58%. ii) a) NaOMe/MeOH (1.2 eq), THF, -78°C, 30 min. b) ICl/DCM (1.2 eq), -78°C to 25°C, 2 h, **139** 86%. iii) a) ICl/DCM (1.2 eq), DCM, -78°C, 4 h. b) NaOMe/MeOH (1.2 eq), -78°C to 25°C, 30 min, **140** 95%. iv) $Pd(PPh_3)_4$ (5 mol%), Ag_2O (1.2 eq), **139** or **140** (1.0 eq), THF, 65°C, 24 h, **205** 67%, **206** 48%, **206** 49%, **207** 64%.

Scheme 34

With the desired Heck product in hand the next step was conversion to either of the alkenyl iodides **139** and **140**. These transformations were performed using ICl and NaOMe with the modified conditions discussed earlier (2.3.2) to afford the iodides in high yields (**139** 86% and **140** 95%) and with what is of greater significance very high geometrical purity (**139** 98% and **140** 96%). These reactions allowed control over the geometry of the initial alkene unit of the system. The second alkenyl unit was introduced through the Heck coupling of the alkenyl iodides with the vinyl boronate ester **123**. As discussed (2.2.2.2), the use of metal additives, particularly silver(I) acetate, was necessary to increase the Heck selectivity of the process. The couplings proceeded as expected to provide **141** and **142** in good yields (55% and 58% respectively) with complete retention of alkene geometry. No coupled products of the minor iodide isomer present in each starting material could be observed.

Completion of the syntheses of the 1,6-diphenyl-1,3,5-hexatrienes required Suzuki-Miyaura couplings of the dienyl boronate esters **141** and **142** with the alkenyl iodides

139 and **140**. The conditions used were based on those developed during the study on the coupling of the vinyl boronate **123** with the alkenyl iodides (2.4.3). As was concluded, the choice of base in the reactions of such substrates is of vital importance, and so, following the success of its use in those coupling reactions, silver(I) oxide was employed for the syntheses of the trienes. Each dienyl boronate was coupled with both iodides to generate the trienes of (*E*,*E*,*E*)-, (*E*,*E*,*Z*)-, (*Z*,*E*,*E*)- and (*Z*,*E*,*Z*)-geometries. Obviously the products containing the one (*Z*)-alkene unit are identical but they differ in the order in which the alkenes were constructed. Overall, the reactions proceeded in good yields (48-67%) and as with the previous Suzuki-Miyaura couplings of **139** and **140** with the boronate **123**, the use of Ag_2O allowed coupling with no phenylacetylene formation. The dienyl boronate esters **141** and **142** show similar levels of reactivity to the vinyl boronate systems; significantly, the reaction of the boronate ester of 2-methyl-2,4-pentane diol is independent of the rest of the structure. In addition, and of vital importance to the strategy of polyene synthesis, no alkene isomerisation was observed under the reactions conditions developed. However, the triene products **206** and **207** are susceptible to isomerisation to the all-(*E*)-form **205**, either under heating above the reaction temperature of 65°C (e.g. during drying or melting point determination) or even upon storage at room temperature over a few months. It is important to note that the order in which the polyenes are constructed has little effect on the yields and geometrical purity. This is demonstrated when examining the preparation of the (*E*,*E*,*Z*)- and (*Z*,*E*,*E*)-trienes. The point in the reaction sequence at which the (*Z*)-alkene unit is introduced has little effect on the end result, showing that the sensitive (*Z*)-alkene is stable to the conditions required to perform each of the key reactions of the strategy.

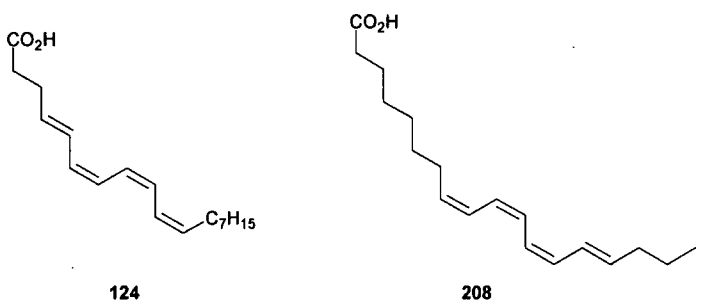
2.5.1.3 Conclusion

The successful syntheses of these 1,6-diphenyl-1,3,5-hexatriene model systems using just three key reactions demonstrates the strength of this strategy in the preparation of polyenes with full control over the alkene geometries. The ability to control the iododeboronation reactions to give either (*E*)- or (*Z*)-iodoalkenes and the coupling of the alkenyl boronates to give either the Heck and Suzuki-Miyaura products simply through variation of the reaction conditions has been demonstrated and is the backbone of the strategy.

2.5.2 Synthesis of Ixoric Acid

2.5.2.1 Introduction

Having sucessfully applied our strategy to the syntheses of the 1,6-diphenyl-1,3,5-hexatriene model systems **205-207**, attention turned to natural product targets. Ixoric acid was identified as an ideal target. Isolated from the *ixora chinensis* shrub, it is the major component of the seed oil.[179] The structure of the molecule is relatively simple. There is a carboxylic acid functional group at one end and an alkyl chain at the other; however, it is the (*E,Z,Z,Z*)-tetraene moiety linking the two that provides the major synthetic challenge. There are some discrepancies regarding the actual structure of ixoric acid in the literature. Both **124** and the alternative structure **208** have been depicted, hence, in order to solve this and further develop the polyene construction strategy, the synthesis of **124** was attempted.

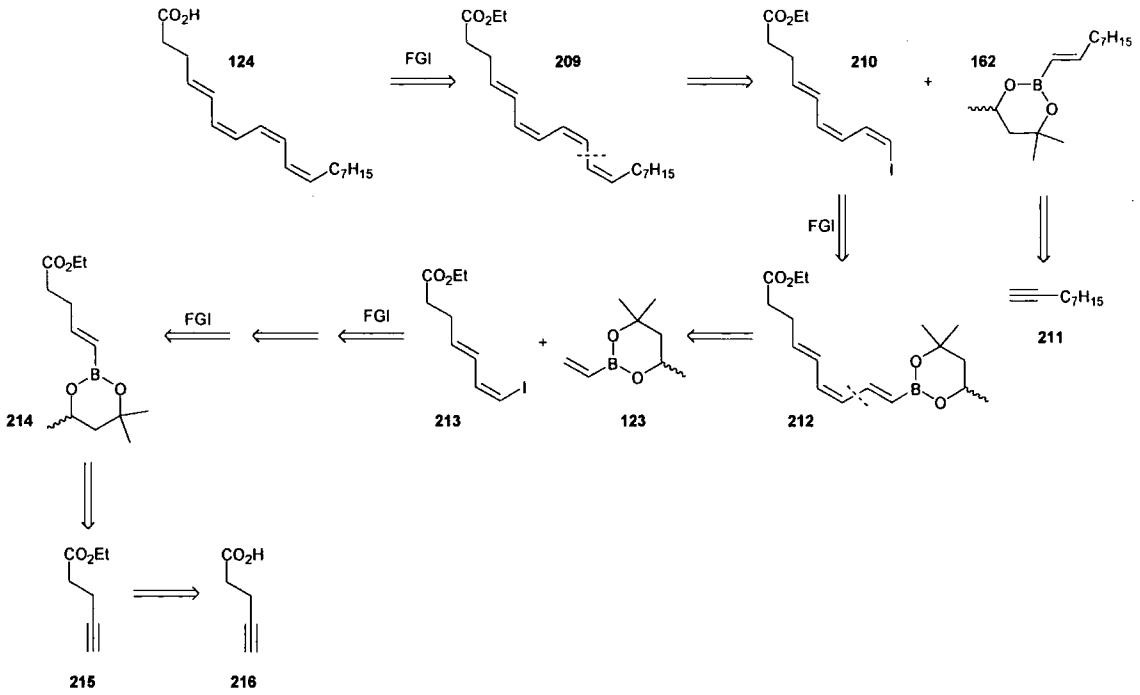


124 208

Figure 19

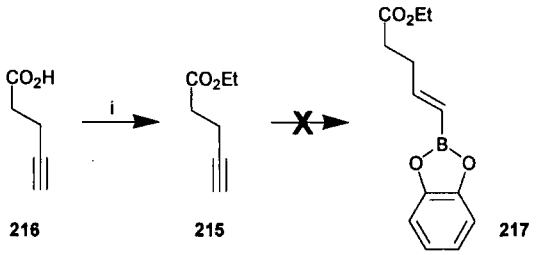
2.5.2.2 The Initial Route

The retrosynthetic scheme below depicts the first proposed route to the synthesis. The structure was divided into two main fragments **210** and **162** to be linked *via* a Suzuki-Miyaura reaction as in the preparation of the 1,6-diphenyl-1,3,5-hexatrienes. The triene **210** was to be constructed from 4-pentynoic acid **216** (protected as the ethyl ester) using a series of iododeboronation and Heck coupling reactions.



Scheme 35

Starting from 4-pentynoic acid **216**, the acid catalysed esterification to provide the ethyl ester was performed following a literature procedure.[180] The reaction proceeded consistently well allowing the isolation of **215** albeit in a moderate yield (71%) considering the process (Scheme 36); however, this reflects the high volatility of the product **215** and the difficulty this caused when removing the ethanol. The next step was the hydroboration of alkyne **215** before transesterification to generate the alkenyl boronate **214**. The reaction was attempted under standard conditions using both neat catecholborane and as a solution in THF.[85,86] None of the desired product could be observed in any of the reactions performed and all attempts led to decomposition of the molecule involving the ester group. As this problem occurred at such an early stage in the reaction sequence, alternative routes were identified.

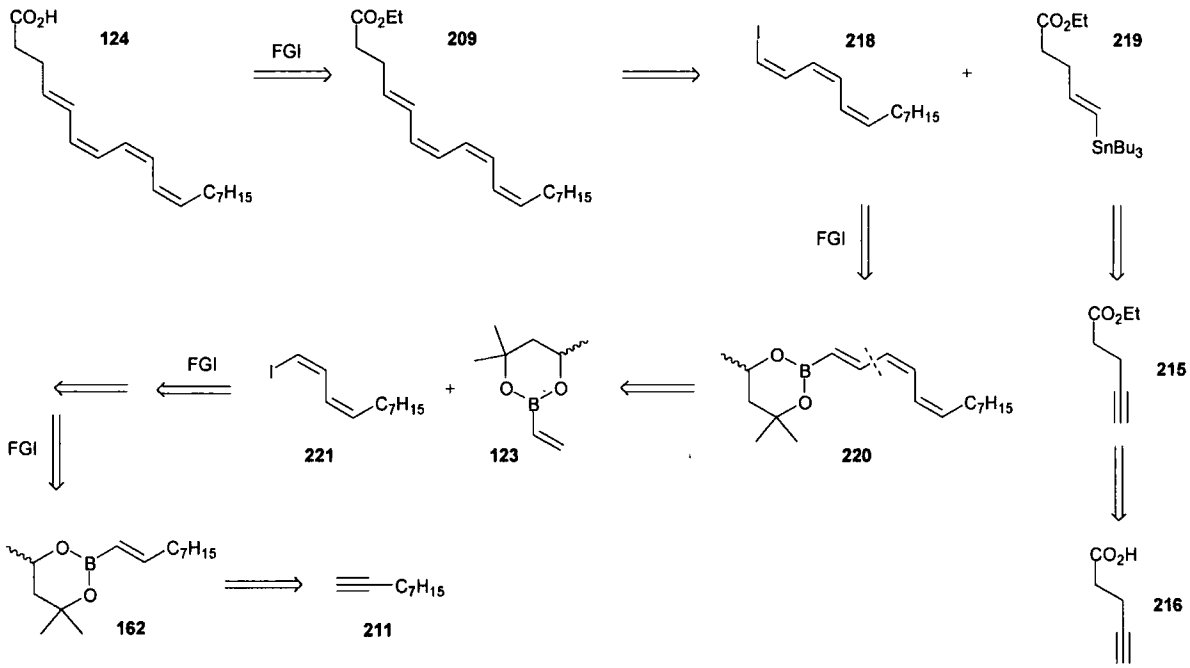


i) H_2SO_4 (5 mol%), $HC(OEt)_3$ (2.2 eq), EtOH, 50°C, 24 h, 71%.

Scheme 36

2.5.2.3 The Revised Route

Following the failure of the hydroboration reaction in the initial route a modified synthesis was devised (Scheme 37). This circumvented the problematic hydroboration step by constructing the polyene from the opposite end and, as a result, the sensitive ethyl ester functionality was not present throughout the synthesis. The target molecule was again divided into two major fragments; the alkenyl tin head group **219** and the alkenyl iodide tail unit **218**. In this revised synthesis, it was envisaged that the two could be connected through a Stille coupling reaction to generate the esterified product before saponification to yield the acid **124**. The head group **219** was again to be prepared from 4-pentynoic acid, and the polyene tail group **218** from 1-nonyne **211**.

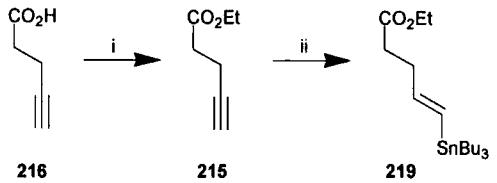


Scheme 37

2.5.2.3.1 Synthesis of the Head Group

The synthesis of the head group was similar to the preliminary steps of the initial synthesis, but with a hydrostannylation replacing the hydroboration. As stated previously, the esterification of the 4-pentynoic acid proceeded smoothly (Scheme 38). Conversion to the alkenyl tin head group **219** was achieved through the addition of tri-*n*-butyltin-hydride to the alkyne. The reaction was performed under the usual type of thermal radical conditions, using AIBN as the initiator. A single regioisomer was obtained with addition of the tin to the terminal position only. The ratio of geometrical

isomers could not be determined from the ^{1}H nmr but is expected to favour the (*E*)-alkene if it is not formed exclusively.



i) H_2SO_4 (5 mol%), $HC(OEt)_3$ (2.2 eq), EtOH, 50°C, 24 h, 71%. ii) nBu$_3$SnH (1.3 eq), AIBN (10 mol%), 80°C, 6 h, 88%.

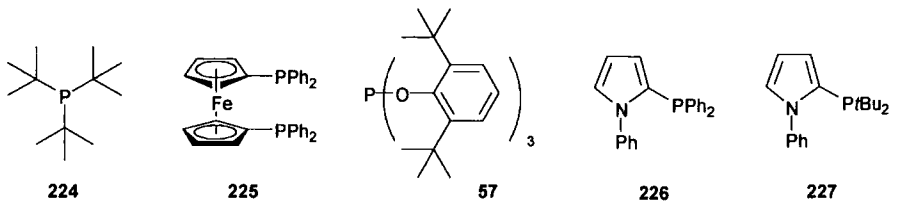
Scheme 38

2.5.2.3.2 Synthesis of the Tail Group

With the head group in hand the next, and most difficult process, was to construct the all-(*Z*)-triene containing iodide tail unit **218**. Commencing from 1-nonyne **211** a hydroboration-transesterification protocol generated the desired alkenyl boronate ester **162** (Scheme 39). The procedure that proved to be successful here was identical to that which resulted in decomposition of the substrate during the attempted synthesis of the head group. The esters of both 2-methyl-2,4-pentane diol and pinacol were prepared, again with the pinacol ester giving a slightly lower yield (**161** 57%, **162** 77%). In fact, this procedure was also used to prepare 4,4,5,5-tetramethyl-2-(*E*)-styryl-1,3,2-dioxaborolane **130** (53%), 4,4,6-trimethyl-2-(*E*)-styryl-1,3,2-dioxaborinane **127** (66%), 2-(*E*)-hept-1-enyl-4,4,6-trimethyl-1,3,2-dioxaborinane **222** (71%) and 4,4,6-trimethyl-2-(*E*)-pent-1-enyl-1,3,2-dioxaborinane **223** (57%). In all cases, only a single regio- and geometrical isomer was obtained with the distinctive coupling of J~18 Hz.

The second step along the reaction sequence (Scheme 37) was a (*Z*)-selective iododeboronation of the alkenyl boronate ester to yield (*Z*)-1-iodo-non-1-ene **164**. This step not only installed the geometry of the initial alkene unit but primed the system to allow a Heck coupling of the vinylboronate ester **123**. The details of the iododeboronation reactions are discussed in section 2.3.3. Initial studies on the iododeboronation provided the corresponding alkenyl chloride **165**. A number of attempts were made to Heck couple **165** with **123** under standard conditions but using a range of ligands that had allowed the coupling of aryl chlorides. These included tri-*t*-butyl phosphine **224**, 1,1'-bis(diphenylphosphino) ferrocene **225**, tri-(2,6-di-*t*-butylphenyl)phosphite **57**, 2-(diphenylphosphanyl)1-phenyl-1*H*-pyrrole **226** and 2-(di-t-butylphosphanyl)-1-phenyl-1*H*-pyrrole **227**. A reaction was also performed in the

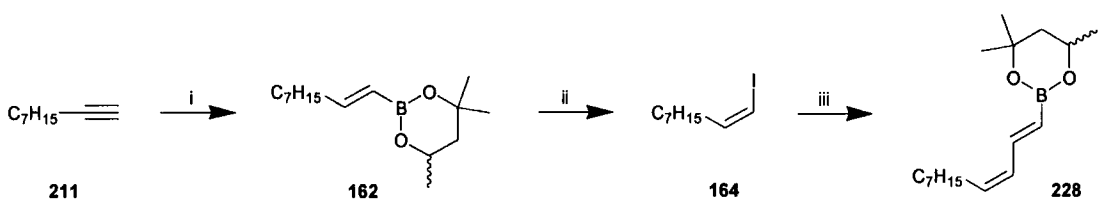
presence of silver(I) acetate; however, all reactions failed resulting in recovery of the starting material.



224 225 57 226 227

Figure 20

With the development of conditions for the successful iododeboronation, the iodide (*Z*)-1-iodo-non-1-ene **164** was available and so its Heck coupling to **123** was examined. The conditions used were those developed previously for the coupling of (*Z*)-2-iodo-vinylbenzene **140**, i.e. standard conditions but performed in the presence of AgOAc to boost Heck selectivity. Initially, the reaction gave low yields, which was due to the sensitivity of the iodide and under the reaction conditions resulted in decomposition. The iodide appeared stable to the presence of the silver(I) acetate but decomposed at the high reflux temperature (110°C). But, as was discussed earlier (2.2.2.2), performing the reaction at lower temperatures results in reduced and in fact poor conversions. To circumvent this problem, the reaction mixture was set up in the absence of the iodide which was drip-fed to the refluxing catalyst mixture over two hours. This, in conjunction with a reduced reaction time, allowed the successful isolation of the desired dienyl boronate 4,4,6-trimethyl-(1*E*,3*Z*)-1,3-undecadienyl-1,3,2-dioxaborinane **228** in a moderate, but improved, 40% yield with complete retention of alkene geometry.



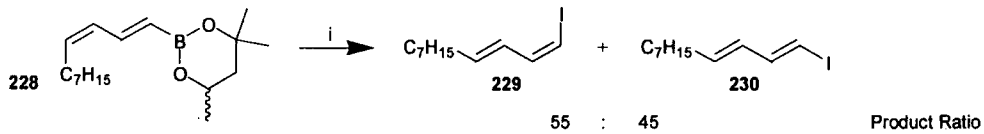
211 162 164 228

i) a) Catecholborane (1.0 eq), 0°C then 70°C for 2 h. b) *rac*-2-methyl-2,4-pentane diol (1.0 eq), $NaHCO_3$, DCM, 25°C, 2 h, 77%. ii) a) ICl/DCM (1.2 eq), DCE, 70°C, 4 h. b) NaOMe/MeOH (1.2 eq), 70°C, 30 min, 64%. iii) $Pd(OAc)_2$ (10 mol%), PPh_3 (30 mol%), AgOAc (1.2 eq), **123** (1.2 eq), Toluene, 6 h, 40%.

Scheme 39

The next procedure along the synthetic route was a second (*Z*)-selective iododeboronation, but this time on the (*Z*,*E*)-dienyl boronate system **228**. Again, the initial conditions explored were those that had been used to prepare (*Z*)-2-iodo-

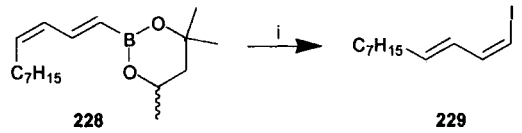
vinylbenzene **140** performing the reaction at -78°C. The reaction gave rise to two products, (1*Z*,3*E*)-1-iodo-1,3-undecadiene **229** and (1*E*,3*E*)-1-iodo-1,3-undecadiene **230** which were obtained in a ratio of 55:45 with the isomers being inseparable by silica gel column chromatography giving a combined yield of 26% (Equation 29). The most significant factor is that in both products, the internal alkene, which was in the (*Z*)-orientation in the starting diene, isomerised to the (*E*)-form during the reaction. With regards to the actual iododeboronation of the terminal alkenyl boronate, the reaction showed very poor (*Z*)-selectivity indicating that both the (*E*)-selective and (*Z*)-selective mechanisms (as discussed previously, 2.3) were in operation.



i) a) ICl/DCM (1.2 eqv.), -78°C, 4 h. b) NaOMe/ MeOH (1.2 eqv.), -78°C to 25°C, 30 min, 26%.

Equation 29

As the temperature of previous iododeboronation reactions (2.3.3) had such a significant impact on the products formed it was varied in this instance. The initial problem here was not competing chloride formation but the different (*Z*)- and (*E*)-selective reaction pathways. To 'switch-off' the iododeboronation reaction with retention of alkene geometry, the reaction was performed at an even lower temperature using a liquid nitrogen/methanol ice bath. In addition, it was hoped that this would also reduce the level of isomerisation observed for the internal double bond. The reaction was performed with a slight deficiency of both ICl and NaOMe rather than an excess, so that no ICl addition to the internal double bond could occur (Equation 30). The use of these reactions did significantly affect the outcome of the reaction. A single product was obtained, (1*Z*,3*E*)-1-iodo-1,3-undecadiene **229**, showing that the iododeboronation of the alkenyl boronate proceeded with complete selectivity for the (*Z*)-pathway. Unfortunatley, as was the case previously, all of the material had isomerised to give the internal (*E*)-alkene. Attempts at the purification of the iodide resulted in a dramatic loss in material and some isomerisation to the all (*E*)-form so that again a mixture of **229** and **230** was obtained.

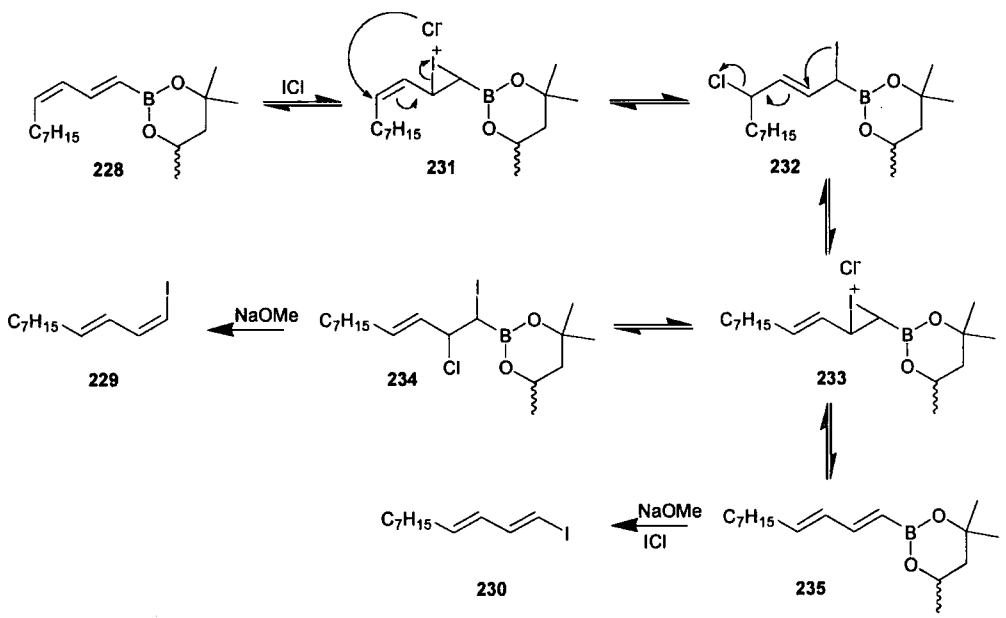


228 229

i) a) ICl/DCM (0.95 eq), -93°C, 30 min. b) NaOMe/ MeOH (0.95 eq), -93°C to 25°C, 30 min.

Equation 30

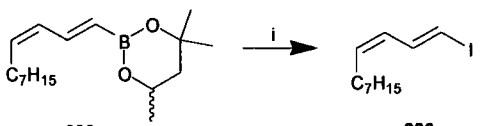
Scheme 40 depicts the process of product formation that appears to be in operation for the (*Z*)-selective iododeboronation of **228**. There is the initial iodonium formation existing as the stable ion pair with the chloride **231**. Unlike in previous systems, in the case of the diene the chloride can either open the iodonium ring, or as it appears is favoured here, attack the internal double bond which results in rearrangment and iodonium ring opening **232**. This process is in equilibrium so the iodonium can re-form eliminating the chloride, but in doing so results in isomerisation of the internal alkene to the thermodynamically favoured (*E*)-form **233**. The chloride can then ring open the iodonium species to form the expected *anti*-addition product **234** before treatment with NaOMe and mediation of the elimination reaction generating the iodide product **229**. When the reaction was performed at the higher temperature (-78°C) (1*E*,3*E*)-1-iodo-1,3-undecadiene **230** was produced, this must be derived from elimination of ICl from addition product **234** after the isomerisation process (it is known that the ICl addition step to the alkenyl boronates is reversible). If this occurs after the addition of NaOMe the reaction can follow the mechansim of 'ate'-complex formation and nucleophilic capture of the iodine with retention of stereochemistry. Thus, it appears that the isomerisation is inherent to the reaction mechanism and an inevitable aspect of the (*Z*)-selective iododeboronation of this particular substrate.



228 231 232 229 234 233 230 235

Scheme 40

Consequently this problematic iododeboronation was attempted using alternative reagents. In the example below, using iodine and sodium acetate (equation 31). The two reagents were premixed and cooled to -90°C before the addition of substrate **228** and warming to room temperature. It was envisaged that the acetate anion would be able to ring open the iodonium species and the isomerisation process which occurs with the chloride ions may have been avoided. A single product was obtained from the reaction, unfortunately, it was (1*E*,3*Z*)-1-iodo-1,3-undecadiene **236**. Again attempts at purification resulted in decomposition of the product. This result does, however, support earlier findings and our proposed mechanisms of iododeboronation and, for this particular system, isomerisation. Due to its lack of polarisation, the iodine is unable to form the iodonium species and add across the double bond. As a result the isomerisation process is unable to occur and the internal alkene remains in the (*Z*)-configuration. However, this also means that the reaction to give the (*Z*)-iodoalkene cannot occur. As a result, the acetate forms the 'ate'-complex with the boronate ester before nucleophilic capture of the iodine to generate exclusively the external (*E*)-iodoalkene product **236**.



228 **236**

i) a) I_2 (0.95 eq), NaOAc (0.95 eq), -90°C to 25°C, 20 min.

Equation 31

It was at this point that the synthesis ceased due to the inability to generate the desired (*Z*,*Z*)-dienyl iodide **221**. It appears that not only is the isomerisation of the (*Z*)-alkene favoured thermodynamically but also occurs as a consequence of the mechansim of the (*Z*)-selective iododeboronation reaction which is key to this strategy of polyene construction. To complete the synthesis of the tail unit, once this problematic reaction had been mastered, a further (*Z*)-selective iododeboronation would be required sandwiched between two Heck couplings with the vinyl boronate **123**; all of which would probably require development of specific conditions.

2.5.2.4 Conclusion

Unfortunately, the total synthesis of ixoric acid was not achieved. The head group **219** was sucessfully prepared in a good yield from commercially available 4-pentynoic acid.

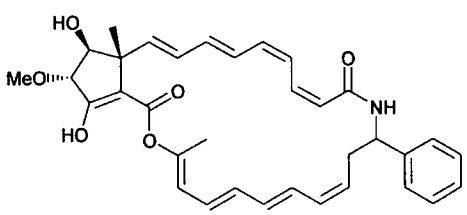
The problems which led to the termination of the synthesis arose during the construction of the all (*Z*)-containing triene tail unit **218**. The major obstacle in its synthesis was the isomerisation of the (*Z*)-alkene unit to the thermodynamicaly favoured (*E*)-form. This process did not occur during the Heck coupling reactions but was the result of a side reaction during the iododeboronation of the dienyl boronate 4,4,6-trimethyl-(1*E*,3*Z*)-1,3-undecadienyl-1,3,2-dioxaborinane **228** to generate further (*Z*)-alkene units and could not be solved. As this reaction was key to our strategy, and it was the mechanism of the desired transformation that had an adverse effect on the system, the synthesis was terminated.

The strategy could easily be used to prepare the all (*E*)-analogue of ixoric acid **124** but this would defeat the object of developing the process which was to be able to control the stereochemistry of any polyene system. It was aslo felt that using other methods to construct the target molecule again deviated from the objective of its synthesis when commissioned.

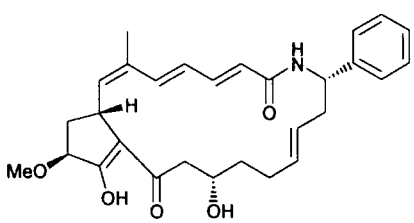
2.6 Synthesis of Viridenomycin

2.6.1 Introduction

Viridenomycin **125** is a bacterial metabolite which has been isolated on different occasions from a number of *streptomyces* strains.[181,182] Studies have shown **125** to be highly bioactive against gram-positive bacteria and some fungi. In addition, it has shown activity against murine tumours, prolonging the survival periods of mice bearing leukemia and melanoma. The reported structure[183] of viridenomycin is shown below and, as can be seen, the stereochemistry at the benzylic centre is unknown. However, analogy to the related *streptomyces* metabolite hitachimycin **237**, and the fact it is likely to derive from an amino acid building block, suggests that it will be (*S*).[184,185] The molecule contains a further three chiral centres all of which are situated on the cyclopentenol core unit which exists in the enol form. The cyclopentenol consitutes part of the greater 24-membered macrocycle connected through a lactam and an enol lactone linkage. Of particular interest to this study are the two tetraene units contained within the macrocycle, the (*E*,*E*,*Z*,*Z*)-moeity contained in the northern portion of the molecule and the (*E*,*E*,*E*,*Z*)-polyene contained within the southern hemisphere.



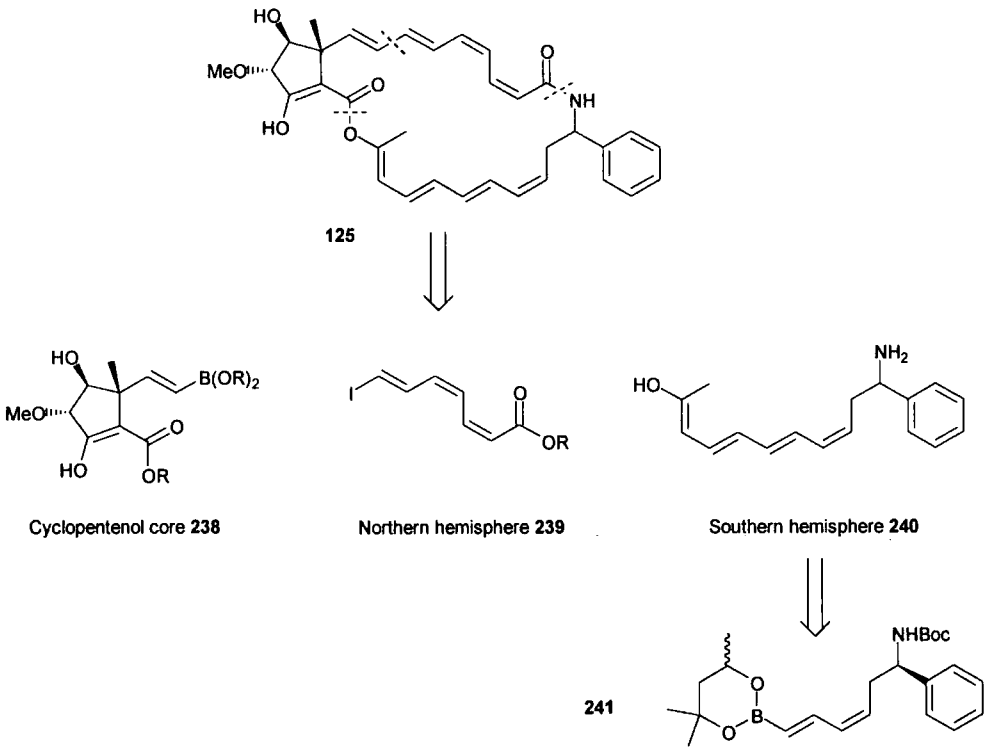
Viridenomycin **125**



Hitachimycin **237**

Figure 20

The total synthesis of viridenomycin has been an ongoing project in this group and work has gone some way towards its synthesis. Scheme 41 below depicts our retrosynthetic strategy for the synthesis of **125**. It divides the molecule into three major fragments, the northern **239** and southern **240** polyene containing hemispheres and the cyclopentenol core **238**. The bulk of the work undertaken has focussed on the construction of the southern hemisphere **240**, with the advanced intermediate **241** being prepared from (*S*)-phenylglycine in just six steps.[148] Consequently, the work undertaken and reported here is towards the synthesis of the cyclopentenol core **238**.



Scheme 41

2.6.2 Synthesis of the Cyclopentenol Core

2.6.2.1 Introduction

A number of different groups have published their research towards the synthesis of the cyclopentenol core, particularly when compared to that involving the other fragments of the target molecule. Research has led to the development of routes which have decreasing numbers of steps and as a consequence increasing yields. Meyers has gone some way to synthesising viridenomycin[186,187] and the group has published some of the earlier work on the synthesis of the cyclopentenol core. Intermediate **242** was prepared by the group from a chiral bicyclic lactam through a 20 step sequence giving a 9% yield.[188] Around a similar time, Japanese workers published a synthesis which provided **243** albeit in a 26 step route from an advanced intermediate derived from D-glucose affording a 10% yield.[189] Trost's synthesis of intermediate **244** dramatically reduced the number of steps required to prepare the key core fragment thus allowing a slight increase in the overall yield.[190] The most recent, and by far most efficient synthesis of an intermediate, was that of **245** reported by Pattenden and coworkers in 2005. The route is very succinct at just 7 steps providing the target in a 25% yield and employs an Evans asymmetric aldol reaction to introduce the stereochemistry to the system.[191]

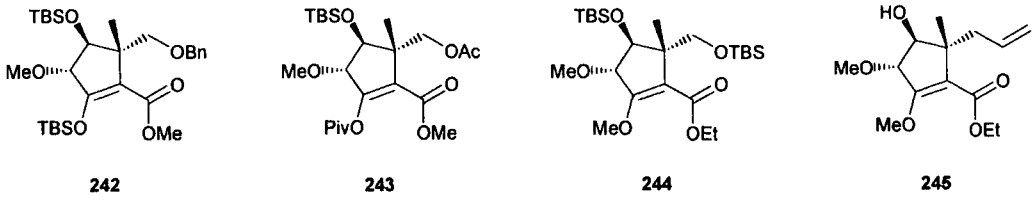
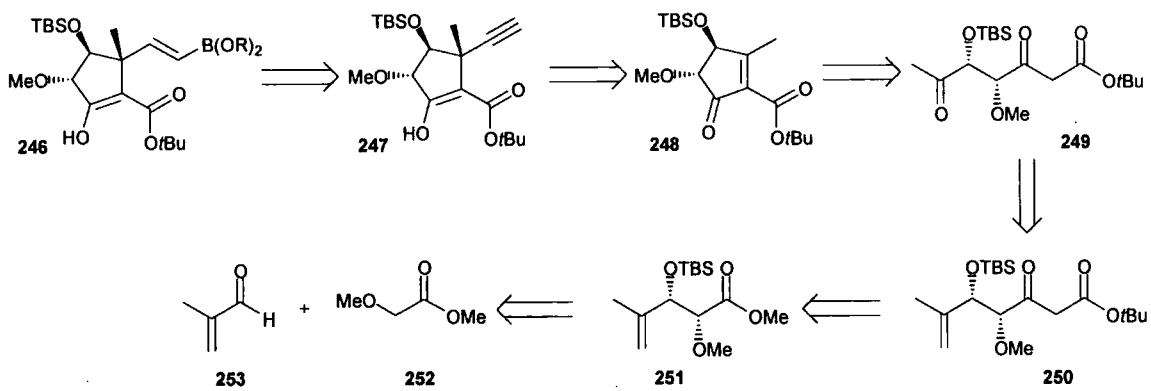


Figure 21

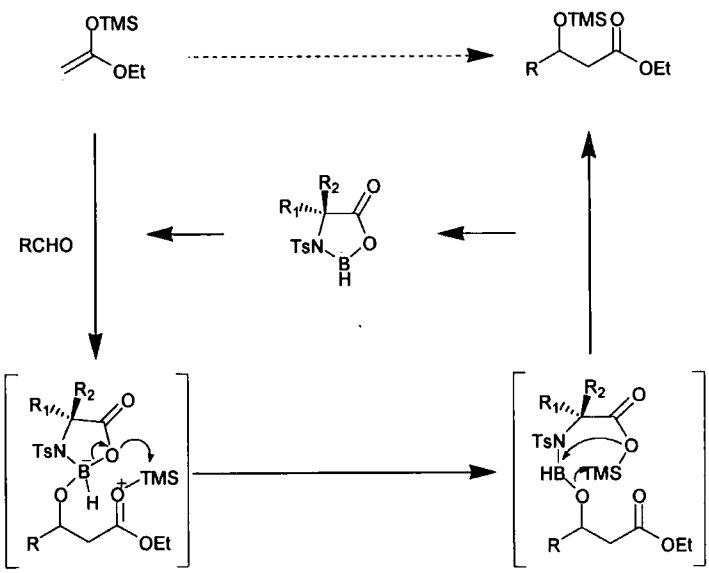
The increasing momentum of the research towards this target led us to explore and develop our proposed route to viridenomycin's cyclopentenone core. The retrosynthetic Scheme 42 shows that route, which is much shorter than the majority of those published and hence posseses the potential to be higher yielding. There are two main issues surrounding the synthesis of the core unit. Firstly, the introduction of the sterochemistry to the system, and secondly the method of cyclisation used to prepare the five-membered ring. In this route, the stereochemistry was due to be installed using an initial aldol reaction between the ester **252** and methacrolein **253**. The advantage of performing this reaction first is that a number of different types of asymmetic aldol reactions can be easily examined with no detriment to the progress of the synthesis. Once performed, the free alcohol group of the aldol product will be protected before conversion of **251** to the β-keto ester **250**. This, in conjunction with the oxidation of the alkene to the ketone **249**, prepares the system for cyclisation of the molecule by means of a Knoevenagel condensation to give the cyclopentenone **248**. A nucleophilic 1,4-addition of an alkyne unit should allow preparation of **247**. The steric constraints of the system should give the desired stereochemistry at the addition centre. Alcohol trapping may not be needed if the system exists in the enol form. A hydroboration of the alkyne function would generate the alkenyl boronate **246** to allow a Suzuki-Miyaura coupling reaction to the northern hemisphere fragment.



Scheme 42

2.6.2.2 Route 1

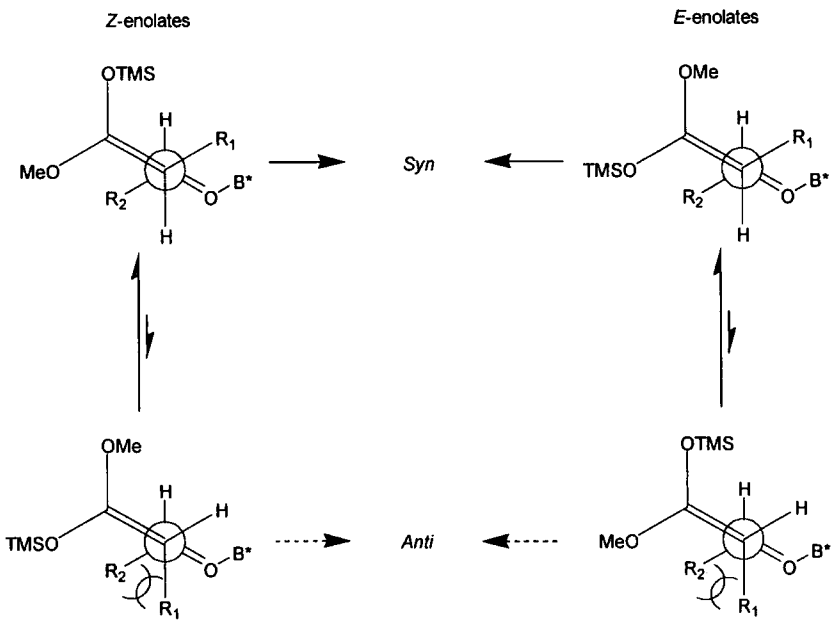
As eluded to above, the initial plan was to use the readily available starting materials methylmethoxy acetate **252** and methacrolein **253** for the key aldol process. It was decided to employ a Mukaiyama aldol reaction, as this allows enolate formation as a separate step and avoids over complication of the aldol reaction itself. In addition, silylated enolates possess significant nucleophilic character and there are a wide variety of chiral Lewis acid systems that can mediate the reaction and induce the desired stereochemistry to the system.[192] Following a literature survey, the oxazaborolidine mediated approach was chosen as the method which would best allow us to generate the desired stereoisomer. A major advantage this method has over many others is that the oxazaborolidine complexes scavange electrophilic silicon species formed during the reaction, which has been reported as being essential to provide efficient asymmetric induction (Scheme 43). The product formed after the initial nucleophilic addition situates the boron carboxylate in a position to effect intramolecular silicon transfer. Regeneration of the boron heterocycle induces the transfer of the silicon to the adolate oxygen liberating both the oxazaborolidine catalyst and silylated aldol product thus preventing any silicon catalysis which would be achiral.



Scheme 43

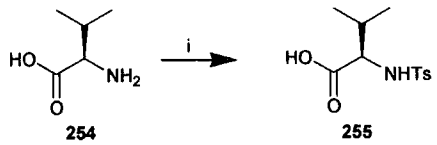
The oxazaborolidine itself is prepared *in situ* from a reaction between borane and an amino acid derivative which is usually sulfonated. This provides a route to either enantiomer of the product simply by changing the form of the amino acid used which is

highly useful when developing syntheses of natural product targets. In terms of diastereomeric control these reactions are also inherently *syn*-selective regardless of the geometry of the silyl enol ether (Scheme 44). The reactions proceed through an open, extended transition state. The attempt to minimise the steric interaction between the enolate substituent R_1 and the aldehyde alkyl substituent R_2 results in the preferential formation of the *syn*-product.[192,193]



Scheme 44

The *syn*-selectivity and the enantiocontrol demonstrated by these oxazaborolidine systems were ideal properites when considering synthesis of **251**. Derivatives of valine have been reported in the literature as the amino acid precursor of choice when applying the reaction to some natural product syntheses albeit when generating a single stereocentre.[194-196] The oxazaborolidine generates the new stereocentre in the product with the opposite stereochemistry to that which it possesses itself. It was envisaged that the use of tosylated (*R*)-valine would generate the desired stereochemistry at the newly formed alcohol centre and the *syn*-selective nature of the reaction would assist in generating the single product **251**. Thus, *N*-tosyl-(*R*)-valine **255** or (*R*)-3-methyl-2-toluene-4-sulfonylamino-butyric acid **255** was prepared from the amino acid through reaction with *para*-toluene sulfonyl chloride (tosyl chloride) under basic conditions, a reaction which could be performed on multigram scale and in good yields.

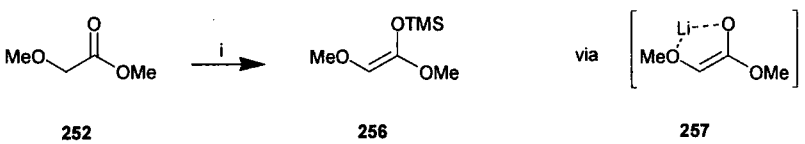


254 255

i) NaOH (1.0 eq), TsCl (1.0 eq), H_2O, 25°C, 5 h, 66%.

Equation 32

The preparation of the required silyl enol ether **256** for the Mukaiyama aldol reaction was done from methoxymethyl acetate **252** following a literature procedure through reaction with lithium hexamethyldisilazide (LiHMDS) and trimethylsilyl chloride (TMSCl).[197] Consistent with the literature, a single product was obtained, believed to be **256** in the (*Z*)-configuration. The rationale for its formation is that the enolate formed can be stablised by coordination to the lithium through two oxygen atoms; trapping as the silyl enol ether thus generates the (*Z*)-O-enolate **256**. As outlined above, in this instance, the geometry of the enolate does not affect the outcome of the reaction.



252 256 257

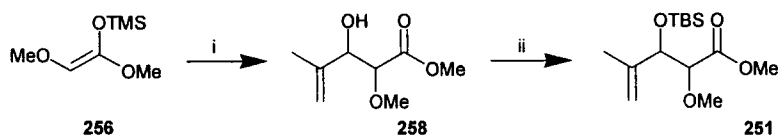
i) LiHMDS (1.2 eq), TMSCl (1.5 eq), THF, -78°C, 1.5 h, 71%.

Equation 33

With all the reagents prepared, the oxazaborolidine mediated Mukaiyama aldol reaction step could be performed. Again, the protocol used was a general procedure demonstrated on numerous occasions in the literature.[194-196] This involved the initial preparation of the oxazaborolidine through the reaction of *N*-tosyl-(*R*)-valine **255** and borane before cooling to allow the addition of the methacrolein **253** and enolate **256**. The direct product of the reaction was the TMS-silylated alcohol, formed as outlined in Scheme 43. The material was de-silylated following a procedure developed by Carreira which involved treatment with aq. TFA at a reduced temperature before purification.[198] Initial reactions involving catalytic amounts of the oxazaborolidine (25%) generated extremely poor yields which were often in single figures. Employing a stoichiometric amount of the oxazaborolidine brought about a significant increase in the yield but this was again very disappointing (21%). During the experimental process there was a dramatic loss in material after the de-silylation procedure. This may be due, in addition to removal of the silyl species, to the formation of retro-aldol products which were sufficiently volatile as not to be detected. Material loss may also be due to

decomposition of the product when purifying through silica gel column chromatography. Rather disappointing was the diastereoselectivity demonstrated by the reaction. The ^{1}H nmr spectrum showed two distinct products in a ratio of 60:40, presumably in favour of the *syn*-product. The value was much lower than had been expected on the basis of related reactions in the literature. The isomer ratio was consistent before and after purification showing that there was no preferential loss of a diastereoisomer accounting for the loss of material.

Although the aldol reaction failed to deliver the desired results, to assess the viability of the proposed route, the synthesis was continued. If the remaining steps were satisfactory the aldol reaction could be reassessed with a plethora of different procedures available to generate the desired stereochemistry. The product **258** obtained from the aldol reaction was protected as the *tert*-butyl-dimethylsilyl ether (TBS), it being much more robust than the TMS group which had previously been removed. The reaction was performed using standard conditions of TBS-Cl and imidazole in the presence of a catalytic amount of DMAP. An impressive yield (89%) of the desired product **251** was obtained; however, the reaction was very sluggish and needed a longer than expected reaction time.



256 **258** **251**

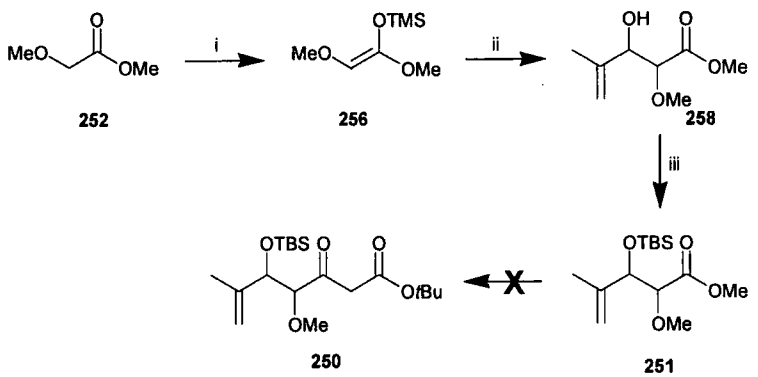
i) **255** (1.1 eq), BH_3/THF (1.0 eq), **253** (1.1 eq), DCM, -78°C, 6 h, 21%. ii) Imidazole (2.0 eq), DMAP (5 mol%), TBSCl (1.8 eq), DCM, 25°C, 18 h, 89%.

Scheme 45

The condensation reaction to transform **251** into **250** was then investigated. It was hoped that the methyl ester would react with the enolate of *tert*-butyl acetate. The reaction was attempted with two different bases, lithium diisopropylamine (LDA), both prepared *in situ* and as a commercially available solution, and LiHMDS. The reactions were performed using either 1.0 or 1.2 equivalents of each reagent, but in all cases the reaction failed to proceed and the starting material **251** was recovered. In fact, a literature search highlighted an example of the same reaction but with a different substrate which required the use of 15 equivalents of LDA and 17 equivalents of *t*-butyl acetate.[199] This demonstrates that this reaction is inherently difficult to induce and, with

respect to substrate **251**, the use of such an excess of base may result in scrambling of the stereocentres installed through the aldol reaction.

To summarise, this initial route was hampered in two steps, the aldol reaction, which gave a low yield of the desired product and with poor selectivity, and the condensation reaction which failed to proceed (Scheme 46). Both failures may be a consequence of the presence of the methyl ester group. The lack of steric bulk may reduce the selectivity of the aldol reaction, and the poor ability of the methoxy anion as a leaving group may inhibit the condensation reaction. The failure of the condensation reaction is one that appeared to be not easily overcome and so the proposed synthetic route was modified to account for this.



i) LiHMDS (1.2 eq), TMSCl (1.5 eq), THF, -78°C, 1.5 h, 71%. ii) **255** (1.1 eq), BH_3/THF (1.0 eq), **253** (1.1 eq), DCM, -78°C, 6 h, 21%. iii) Imidazole (2.0 eq), DMAP (5 mol%), TBSCl (1.8 eq), DCM, 25°C, 18 h, 89%.

Scheme 46

2.6.2.3 Route 2

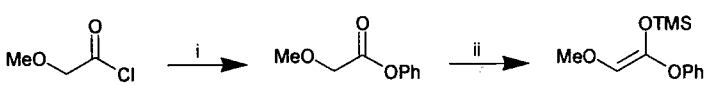
As a solution to the problems discovered with the use of the methyl ester identified above, an alternative route was created which replaced the methyl ester with the phenyl equivalent. The expected advantage was two-fold; hopefully the increased bulk of the group would induce a higher level of diastereoselectivity in the aldol reaction and the condensation step would be achieveable under mild reaction conditions.

2.6.2.3.1 Synthesis of the Silyl-enol Ether

Unfortunately, the analogue of methylmethoxy acetate, methoxy-acetic acid phenyl ester **260**, was not commercially available. However, it could be simply prepared on a multigram scale in high yield (96%) from methoxyacetal chloride **259** (Scheme 47).

The protocol simply involved reaction of the acid chloride with phenol under mildly basic conditions in an ethereal solvent.

Before proceeding with the synthesis, the effect of having the phenyl ester present was examined with respect to the condensation reaction. Methoxy-acetic acid phenyl ester **260** was, as attempted previously for substrate **251**, reacted with the enolate of *tert*-butyl acetate generated through reaction with LiHMDS. The reaction did give conversion to the desired product; however, it was the level of conversion which was interesting. The use of 1.2 equivalents of the enolate resulted in a conversion of approximately 60%, which indicated that two equivalents would be required to achieve complete conversion which was found to be the case. In either test reaction, none of the product was actually isolated. So the changing of the ester group had solved the problem of the failed condensation reaction, its effect on the aldol reaction needed to be investigated. The silyl enol ether **260** was prepared following the protocol that had been shown to be successful earlier generating the desired product in quantitative yields when performed on large scales (scheme 47).



259 **260** **261**

i) Phenol (1.0 eq), Et_3N (1.0 eq), Et_2O, 25°C, 3 h, 96%. ii) LiHMDS/THF (1.2 eq), TMSCl (1.5 eq), -78°C, 1.5 h, 100%.

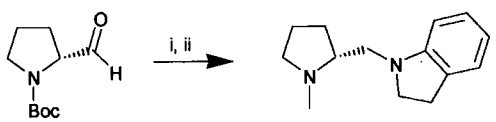
Scheme 47

2.6.2.3.2 The Mukaiyama Aldol Reaction

After the disapointing outcome of the Mukaiyama aldol reaction demonstrated in the initial route, a detailed exploration of the conditions was performed to increase both selectivity and yields. Three methods were used to mediate the aldol reaction. Initially, a Lewis acid-mediated approach employing tin(II) triflate [$Sn(OTf)_2$] was attempted. This method would indicate any change in diastereoselectivity induced by having the phenyl group present but also provide a racemic product to assist in developing conditions for enantiomer separation by chiral HPLC.

Second was a $Sn(OTf)_2$/chiral diamine mediated approach which had been successfully used in the reaction of the enolate **261** with a range of substrates to give the desired products with extremely high dia- and enantioselectivity.[200] In fact, Kobayashi has

published a vast amount of material on this strategy for controlling the Mukaiyama aldol reaction.[201,202] The chiral diamines are all derived from (*S*)-proline with the substituents determining the stereochemical outcome. After studying the published examples, the chiral diamine 1-(2*R*)-1-methyl-pyrrolidin-2-ylmethyl-2,3-dihydro-1*H*-indole **263** was prepared as it should generate the desired enantiomer with high selectivity. Chiral diamine **263** was prepared from the commercially available *N*-Boc-(*R*)-prolinal **262** in a two step process. The first step involved a reductive amination of the aldehyde with indoline in the presence of the reducing agent triacetoxyborohydride;[203] the crude product was not isolated but used directly in the next step. Conversion of the *N*-Boc functionality to the methylated form was achieved through a reduction using an excess of $LiAlH_4$ to produce the desired product **263** in a respectable 82% yield over the two steps (Equation 34).[204]

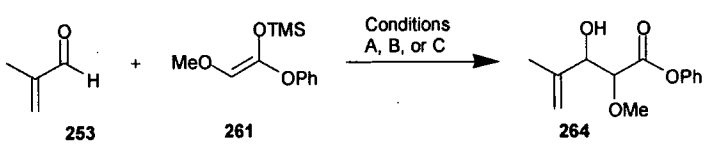


262 **263**

i) Indoline (1.0 eq), $Na(AcO)_3BH$ (2.0 eq), DCE, 25°C, 20 h. ii) $LiAlH_4/Et_2O$ (5.7 eq), 25°C, 72 h, 82%.

Equation 34

The third and final strategy to be explored was again the oxazaborolidine-mediated approach which had been used in the initial synthesis and again, the reagent had to be employed in a stoichiometric quantity (Equation 35). All of the aforementioned methods were employed for the key Mukaiyama aldol reaction, and the results are displayed in Table 13.



253 **261** **264**

A) $Sn(OTf)_2$ (1.0 eq), DCM, -78°C, 5 h. B) $Sn(OTf)_2$ (1.5 eq), **263** (1.8 eq), $nBu_2Sn(OAc)_2$ (1.6 eq), DCM, -78°C, 20 h. C) **255** (1.1 eq), BH_3/THF (1.0 eq), DCM, -78°C, 5 h.

Equation 35

Entry	Conditions	Yield/%[a]	*syn*:*anti*[b,c]	ee[d]
1	**A**	32	83:17	0
2	**B**	30	82:18	0
3	**C**	18	79:21	81

[a] Isolated yield after purification by SiO_2 column chromatography. [b] Determined by ^1H nmr of the crude product. [c] Assignment confirmed through crystallographic studies see 2.6.2.3.3 [d] Determined by chiral HPLC, chiralcel OD column, 90:10 hexane:IPA, 1ml/min.

Table 13

Each of the methods investigated generated the desired products albeit with varying degrees of success. In all cases a disappointing yield was obtained, as occurred for **258**, this suggests that the product **264** is indeed sensitive to purification by silica gel column chromatography. The lowest yield obtained under conditions C (Table 13, entry 3), the oxazaborolidine method, is most likely due to the fact that the initial aldol product is partially TMS-silylated (Scheme 43), the products of conditions A and B do not suffer from this problem and allow a more straightforward isolation procedure.

The diastereoselectivity demonstrated by the silyl enol ether **261** is much greater than that observed for the methyl ester equivalent **256**, showing that the phenyl group does indeed influence the selectivity of the reaction. The values are all approximately the same level of 80:20 compared to 60:40 for **258**. The selectivity favours the *syn*-product as predicted above (Scheme 44) with the reaction proceeding through an open, extended transition state. However, the nature and, more importantly, the sterics of the ester group, do appear to impart a significant effect on the diastereoselectivity of the reaction. The *syn*-relationship between the alcohol and methoxy groups was confirmed through crystallographic studies of futher advanced intermediates (2.6.2.3.3).

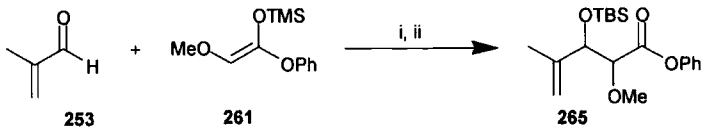
Of even greater importance and significance, was the enantioselectivity displayed under each of the reaction conditions. As expected the conditions A (Table 13, entry 1) gave no asymmetric induction, a fact demonstrated through chiral HPLC and optical rotation studies of the product. Most surprisingly, and in contradiction to literature reports, the tin/chiral diamine approach (conditions B, Table 13, entry 2) imparted no asymmetric induction on the system, generating a racemic product. It can only be concluded that the $Sn(OTf)_2$, which is present in an excess, is able to promote the reaction without coordination to the chiral diamine as was purported to account for the enantioselectivity demonstrated in these reactions. Hence, the results obtained were almost identical to

those when using $Sn(OTf)_2$ alone (conditions A, Table 13, entry 1). The oxazaborolidine method did generate a good degree of enantioselectivity in the reaction to give the favoured product with an enantiomeric excess of 81 (Table 13, entry 3). Although the major aldol product is the *syn*-diastereoisomer, the absolute stereochemistry of the enantiomer is as yet not proved conclusively.

Overall, the original oxazaborolidine approach gave the most promising results, particularly being the only enantioselective reaction. The only major problem was the yield obtained when using this reaction due to the need to desilylate the direct product and the sensitivity of **264** to purification by silica column chromatography, and attempts were made to counteract this.

Initially, the problem of desilylation of the direct aldol product was examined. Quenching the reaction with sat. aq. $NaHCO_3$ resulted in some desilylation, and stirring of this mixture for extended periods of the time resulted in increased amounts of alcohol liberation but only to a maximum of approximately 50%. The Carreira procedure,[198] which involved treatment with aq. TFA at a reduced temperature, resulted in a dramatic loss of material when applied to the synthesis of **258**; however, this process was re-examined. It was feared that an excess of the TFA may facilitate the formation of retro aldol products, as only ~50% of the material required desilylation 0.5 eq. of TFA was employed. Fortunately, this provided a solution to the problem, and high yields of the desired product, albeit in the crude form, were obtained. Again, with reference to route 1, the TBS protected aldol product **251** appeared stable to the conditions of purification being isolated in an 89% yield (Scheme 45). As **264** in the crude form was relatively clean, it was converted directly to the TBS protected product **265** to allow isolation of this more stable form and an overall superior yield. The same reaction conditions were employed to protect the aldol product (i.e. TBSCl, imidazole and catalytic DMAP), although a high yield was obtained previously, the reaction was very sluggish. On this system (using purified **264**), the reaction only reached completion after 3 days albeit in a reasonable, 75% yield. More forcing conditions were used to bring about the protection of the crude secondary alcohol which involved the use of TBSOTf and 2,6-lutidine as the base. This reaction was much more rapid, proceeding in just a few hours. The crude material was then purified by silica gel column chromatography with no observable degradation of the product **265** to provide a 71% yield over the two steps. This is a significant increase on the 14% overall yield when isolating the alcohol and

protecting using TBSCl. In addition, silica column purification of **265** allows some separation of the diastereoisomers so that a ratio of 92:8 could be obtained in favour of the *syn*-form.



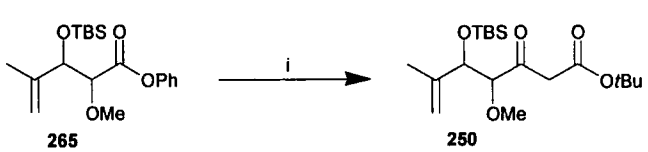
i) **255** (1.1 eq), BH_3/THF (1.0 eq), DCM, -78°C, 5 h. ii) 2,6-lutidine (2.5 eq), TBSOTf (1.3 eq), DCM, 25°C, 4 h, 71%.

Equation 36

Thus, conditions had been developed to generate the intermediate **265** in high diastereomeric and enantiomeric purity from methoxyacetal chloride in just three steps with an overall yield of 68%, utilising the oxazaborolidine mediated Mukaiyama aldol reaction (Equation 36).

2.6.2.3.3 Cyclisation to the Cyclopentenone

The second major challenge in the synthesis of the viridenomycin cyclopentenol core was the installation of the various funtionalities which were intended to allow the Knoevenagel cyclisation reaction (Scheme 42). This involved creation of the β-keto ester **250**, through reaction of intermediate **265** with the enolate of *t*-butyl acetate, and subsequent oxidative cleavage of the alkene to generate the ketone **249**. As discussed, a small test reaction was performed on the phenyl ester of substrate **260** to generate the β-keto ester. This reaction proceeded well and showed that two equivalents of the *t*-butyl acetate enolate were required for complete conversion of the substrate. These conditions were applied to **265** and the reaction worked extremely well allowing isolation of the desired product in an impressive 80% yield (Equation 37).



i) LiHMDS/THF (2.0 eq), *t*-butyl acetate (2.0 eq), THF, -78°C, 2 h, 80%.

Equation 37

Again, on purification by silica gel column chromatography, some separation of the diastereoisomers could be achieved so that the major *syn*-product could be obtained

exclusively. This major isomer was obtained as a clear oil but slowly solidified on storage to afford a white solid. Thermal recrystallisation generated material which was suitable for X-ray crystallographic studies in order to determine the absolute stereochemistry. The major diastereoisomer was indeed the *syn*-product as predicted; however, the only material that generated crystals which allowed diffraction studies was that derived from the tin triflate/chiral diamine approach to the Mukaiyama aldol reaction which gave a racemic product. Unfortunatley, product **250** derived from the enatioselective oxazaborolidine mediated aldol route did not provide material suitable for such studies and the absolute stereochemistry was not determined. Figure 22 shows the obtained structure of **250**, and as stated above, the *syn*-relationship between the OTBS and OMe is presented. Furthermore, the β-keto ester exists in the ketone form; there is no keto-enol tautomerisation.

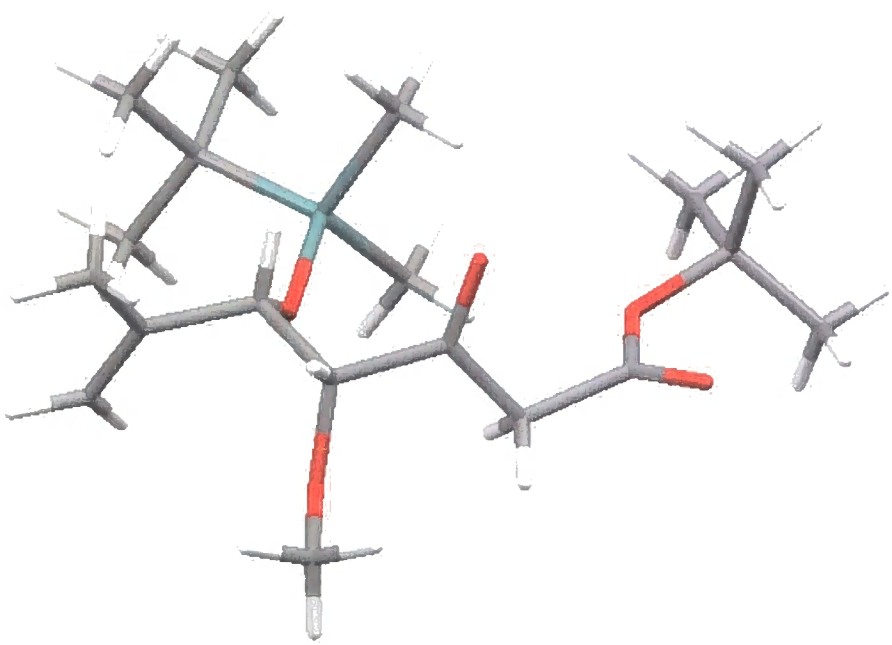


Figure 22

The next step was oxidative cleavage of the alkene functionality of **250** to generate the ketone containg **249** (Scheme 42). Two approaches were examined for this transformation: an osmium tetroxide (OsO_4) method involving oxidation to the 1,2-diol before bond cleavage; and ozonolysis to give the ketone directly.

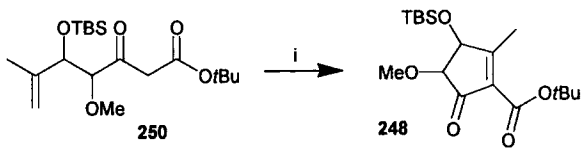
An initial OsO_4 reaction was performed with oxidative cleavage of the alcohol induced by the addition of sodium periodate ($NaIO_4$). Study of the ^1H nmr of the crude reaction

material showed little reaction of the alkene itself but a number of products which appeared to involve desilylation and scrambling of the installed stereochemistry. With that in mind, a literature procedure was followed which involved the addition of 2,6-lutidine to the reaction which was purported to suppress side reactions and hence, improve yields.[205] Unfortunately, the result obtained differed little from the initial reaction and so further conditions were explored. There are a number of different co-oxidants that can be used in this reaction so in a final attempt Oxone® was used to replace $NaIO_4$.[206] Again the reaction provided similar results to those already obtained and so the ozonolysis of the alkene was examined.

A small study was carried out to identify rapidly the best potential conditions for the transformation by varying the solvent and reducing agent used. The ozonlysis reactions themselves were performed in both dichloromethane and methanol, and the reducing agents dimethyl sulfide (DMS), triphenylphosphine (PPh_3) and zinc dust were each used in conjunction with both solvents. The crude products were analysed by ^1H nmr spectroscopy. All of the reactions showed complete conversion of the alkene however they differed in the levels of byproduct formation. The use of PPh_3 demonstrated superior results producing clean material particularly when performing the reaction in MeOH. These conditions were used to scale up the reaction. Unfortunately, **249** appeared to be sensitive to purification by silica gel column chromatography and after a dramatic loss of material the major component consisted of a mixture of what appeared to be **249** and the cyclised product **248**. In the case of the aldol product **264**, the problem of its sensitivity was overcome by using the crude material in the subsequent reaction along the sequence and isolating the more stable product; this ideology was applied to **249**. It was believed that the addition of base to the reaction mixture would induce cyclisation to **248**, particularly after cyclisation was observed on the column. In addition, the experimental procedure could be made much simpler by using solid-supported PPh_3. After the reduction step, the reagent could be removed by filtration thus assisting the tricky removal of triphenylphosphine oxide and leaving just **249** in solution before base addition.

This one-pot procedure for ozonolysis and Knoevenagel cyclisation was then examined using a range of bases, both nitrogen derived (2,6-lutidine and LiHMDS) and inorganic (Na_2CO_3, K_2CO_3, Cs_2CO_3). Surprisingly, the nitrogen containing bases failed to induce a cyclisation which had appeared to proceed readily due to the sensitive nature of **249**.

However, each of the inorganic carbonate bases gave rise to the desired transformation with complete conversion (Equation 38). There was little, if any by-product formation, and no discernible difference between each reaction depending on the group I counter-ions present. The only problem was the isolation of the cyclised product **248** in rather disapointing yields (32%), which again appears to be a problem with the purification of a sensitive substrate.

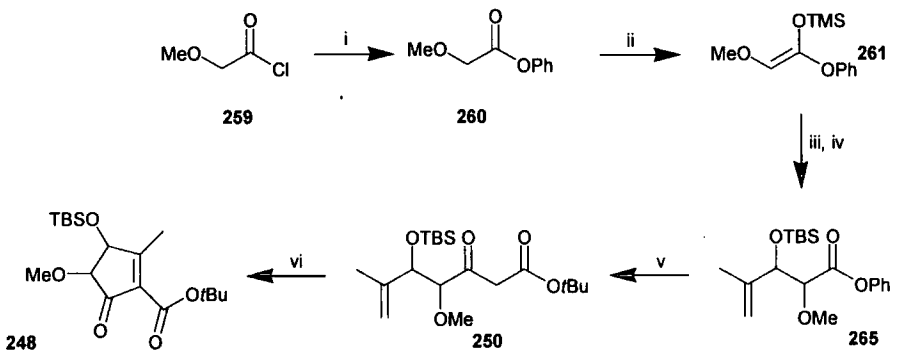


i) O_3, PPh_3 (1.7 eq), MeOH, -78°C, 30 min, then K_2CO_3 (2.0 eq), 0°C, 1 h, 32%.

Equation 38

2.6.2.4 Conclusion

This is where the synthesis of the cyclopentenol core of viridenomycin currently lies, Scheme 48 below depicts the synthesis achieved in this study.



i) Phenol (1.0 eq), Et_3N (1.0 eq), Et_2O, 25°C, 3 h, 96%. ii) LiHMDS/THF (1.2 eq), TMSCl (1.5 eq), -78°C, 1.5 h, 100%. iii) **255** (1.1 eq), BH_3/THF (1.0 eq), methacrolein **253** (1.0 eq), DCM, -78°C, 5 h. iv) 2,6-lutidine (2.5 eq), TBSOTf (1.3 eq), DCM, 25°C, 4 h, 71% (2 steps). v) LiHMDS/THF (2.0 eq), *t*-butyl acetate (2.0 eq), THF, -78°C, 2 h, 80%. vi) O_3, PPh_3 (1.7 eq), MeOH, -78°C, 30 min, then K_2CO_3 (2.0 eq), 0°C, 1 h, 32%.

Scheme 48

All of the reaction steps to **250** proceed with impressive yields and can be performed on a range of scales. The key aldol reaction demonstrates high levels of diastereo- and enantioselectivity, although the absolute stereochemistry of this system is as yet unknown with certainty. One of the advantages of using the oxazaborolidine-mediated Mukaiyama aldol reaction is that either enantiomer of valine can be used so that if the

absolute stereochemistry of our system is not that of viridenomycin, the correct one can be easily prepared.

The final transformation to generate the cyclopentenone **248** is the major limiting factor of this synthetic route as it proceeds in what can only be described as a low yield and this needs to be improved. Nonetheless this route provides an advanced intermediate of the central core of viridenomycin in a very short sequence (5 steps) from readily available starting materials. This compares favourably with many of the published routes highlighted above (2.6.2.1) which employ a much greater number of steps and hence overall low yields.

2.7 Future Work

2.7.1 Vinyl Boronate Strategy for Polyene Synthesis

Work is currently underway to further develop and address the remaining issues regarding the vinyl boronate **123** Heck coupling aspect of this strategy. Kinetic studies are being performed to establish more accurately our proposed theory that the Heck coupling requires a cationic palladium catalyst species and efficient Heck selectivity is obtained by promoting its formation. In addition, the problematic formation of the ligand crossover product which occurred when coupling bromides is also being addressed. This may be overcome by increasing the reaction rate of the desired coupling, i.e. through promotion of the cationic palladium species, or by using alternative ligands which may not participate as readily in the crossover process such as tri(2-furyl)phosphine.

Although a number of problematic issues surrounding the stereoselective iododeboronations of the alkenyl boronate esters were resolved, the reaction appears to be very substrate sensitive. Consequently, when applied in the future, conditions may need to be developed when necessary for a particular synthesis. However, the insight gained during this research into the mechanistic intricacies of the reactions will assist the development of successful reaction conditions.

The Suzuki-Miyaura coupling of vinyl boronate **123** has been shown to proceed with complete selectivity with a range of substrates. In fact, this reaction needs no further development unless problems arise at a later stage of use.

2.7.2 Viridenomycin Synthesis

The work performed and discussed here has focussed on the synthesis of viridenomycin's cyclopentenol core, and the cyclopentenone intermediate **248** has been prepared. As discussed, the yield for the final step is very low and may limit this synthetic route. Further development of these conditions may be required to boost this. As yet, the absolute stereochemistry has not been determined. If samples of the β-keto ester **250** derived from the oxazaborolidine mediated aldol reaction fail to provide material suitable for crystallographic determination, then derivatisation of various intermediates may do. Alternatively, once the cyclopentenol unit is prepared, the nmr data, particularly the coupling constants around the ring, may be compared with both the natural product and the core units published in the literature of known

stereochemistry. Depending on the absolute chemistry obtained here, the valine enantiomer used in the aldol reaction may need to be changed.

From **248**, two more steps are required to generate our desired cyclopentenol core unit **246**, a 1,4-addition of an alkyne unit to the enone before its hydroboration to generate the alkenyl boronate ester. The introduction of the alkyne may be done via the cuprate[207] or Grignard reagent of TMS-acetylene. Trapping of the alcohol may not be required as viridenomycin exists in the enol form. With regard to the stereochemistry of the chiral centre that this process creates, the steric bulk of the neighbouring OTBS group should force the alkyne to approach from the opposite side and thus the OTBS and methyl groups end up on the same side of the ring. After desilylation, a catecholborane mediated hydroboration and transesterification procedure should provide the alkenyl boronate ester, as has been the case for a number of compounds in this study. This would allow attachment of the core to the northern hemisphere fragment through a Suzuki-Miyaura coupling protocol as developed here.

3 Experimental

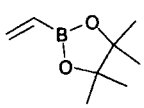
3.1 General Experimental Information

All ^{1}H nmr were recorded on Varian Unity-300, Varian Mercury-400, Bruker Avance-400 or Varian Inova-500 spectrometers. ^{13}C nmr spectra were recorded on Varian Mercury-400, Bruker Avance-400 and Varian Inova-500 instruments at frequencies of 100 or 126 MHz. ^{11}B nmr were recorded on either the Bruker Avance-400 at a frequency of 128 MHz or Varian Inova-500 at a frequency of 160 MHz. Chemical shifts are expressed as parts per million downfield from the internal standard TMS for ^{1}H and ^{13}C and to external $BF_3.Et_2O$ for ^{11}B. EI mass spectrometry was performed on a Micromass Autospec, Finnigan MAT 900XLT or Finnigan MAT 95XP with electrospray methods, both +ve and –ve, conducted on a VG platform. GC-MS was performed on either a Thermoquest Trace or VG Trio. IR spectra were recorded on a Perkin-Elmer 298 spectrometer employing NaCl plates or KBr discs. Elemental analysis was performed using an Exeter Analytical E-440 Elemental Analyser. Melting points were determined using an Electrothermal melting point apparatus. $[\alpha]_D$ values are given in deg $cm^2\ g^{-1}$ and were recorded at the D line of sodium (589 nm) in a 0.05 dm cell using an AA10 Automatic polarimeter. Column chromatography was performed on Davisil Silica gel, 60 mesh. TLC was performed on Polygram SIL G/UV_{254} plastic backed silica gel plates with visualization achieved using a UV lamp, or by staining with $KMnO_4$ or vanillin.

All glassware was oven dried (130°C) before use and cooled under a positive pressure of argon. Solvents were dried by distillation from CaH_2 (DCM, hydrocarbons) or sodium-benzophenone ketyl (THF). All reactions were performed at room temperature unless otherwise stated. All other materials were purchased from either Aldrich or Lancaster and used without further purification, unless stated otherwise.

3.2 Specific Experimental Procedures

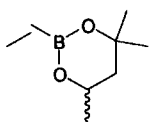
4,4,5,5-Tetramethyl-2-vinyl-1,3,2-dioxaborolane 117



Vinylmagnesium bromide (20 cm^3 of a 1.0M solution in THF, 20 mmol) was added dropwise over 1 h to a stirred solution of anhydrous trimethylborate (2.04 cm^3, 18 mmol) in dry THF (34 cm^3) at -78°C under argon. The reaction was left to stir for a

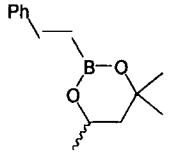
further hour before warming to room temperature, followed by the addition of 20% HCl (8.8 cm^3). After 10 min, pinacol (2.13 g, 18 mmol) was added and the reaction was stirred for another hour. The two phases were separated and the aqueous phase extracted with Et_2O (20 cm^3), the combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 x 20 cm^3) and water (2 x 20 cm^3). Drying ($MgSO_4$) and solvent removal afforded the crude product which was purified by Kugelröhr distillation to yield **117** (0.87 g, 32%) as a clear oil, bp 115-120°C (760 mm Hg) (lit[208] 35-40°C (20 mm Hg)). Characterisation data was consistent with literature values.[160]

4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane 123



Vinylmagnesium bromide (100 cm^3 of a 1.0M solution in THF, 100 mmol) was added dropwise over 1 h to a stirred solution of anhydrous trimethylborate (10.2 cm^3, 90 mmol) in dry THF (100 cm^3) at -78°C under argon. The reaction was left to stir for a further hour before warming to room temperature allowing the addition of 20% HCl (44 cm^3). After 10 min, a solution of 2-methyl-2,4-pentanediol (11.34 cm^3, 90 mmol) in Et_2O (9 cm^3) was added and the reaction was stirred for a further hour. The two phases were separated and the aqueous phase extracted with Et_2O (100 cm^3), the combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 x 100 cm^3) and water (2 x 100 cm^3). Drying ($MgSO_4$) and solvent removal afforded the crude product as a yellow oil. Kugelröhr distillation yielded **123** (11.3 g, 82%) as a clear oil, bp 50-55°C (0.46 mm Hg) (lit[209] 57-58°C 22 mm Hg). ν_{max}(film)/cm^{-1} 3064, 2974, 1616, 1419, 1391, 1299 and 1239; δ_H (500 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.0, boronate OCH(C*H*$_3$)), 1.31 (6H, s, boronate OC(C*H*$_3$)$_2$), 1.52 (1H, t, *J* 13.8, boronate C*H*H), 1.80 (1H, dd, *J* 13.8 & 3.0, boronate CH*H*), 4.19-4.24 (1H, m, boronate OC*H*(CH$_3$)), 5.78 (1H, dd, *J* 19.0 & 13.3, CHH=C*H*B) 5.87 (1H, dd, *J* 13.3 & 4.5, C*H*H=CHB) and 6.05 (1H, dd, *J* 19.0 & 4.5, CH*H*=CHB); δ_C (125 MHz, $CDCl_3$) 23.4 (boronate OCH(*C*H$_3$)), 28.3 (boronate OC(*C*H$_3$)(CH$_3$)), 31.4 (boronate OC(CH$_3$)(*C*H$_3$)), 46.1 (boronate *C*H$_2$), 65.0 (boronate O*C*H(CH$_3$)), 71.0 (boronate O*C*(CH$_3$)$_2$), 134.1 (alkenic); δ_B (128 MHz, $CDCl_3$) 25.7; *m/z* (EI) 154.1156 (M^+, $C_8H_{15}O_2B^+$ requires 154.1160), 103, 85, 59 (100) and 43.

4,4,6-Trimethyl-2-((*E*)-styryl)-1,3,2-dioxaborinane 127



Heck Procedure

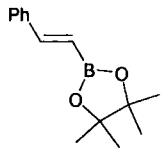
Dry toluene (10 cm^3) was added to a Schlenk-like tube with stirring under a positive pressure of argon containing $Pd(OAc)_2$ (9 mg, 0.04 mmol), PPh_3 (31 mg, 0.12 mmol) and AgOAc (0.16 g, 0.96 mmol) forming a suspension. Tri-*n*-butylamine (0.23 cm^3, 0.96 mmol), iodobenzene (0.09 cm^3, 0.8 mmol) and the vinylboronate **123** (0.15 g, 0.96 mmol) were added and the solution was degassed using the freeze-pump-thaw method (x 3) before heating to 110°C. After 24 h the reaction mixture was cooled, diluted with Et_2O (40 cm^3) and passed through Celite before washing with 10% HCl (20 cm^3), water (20 cm^3) and brine (20 cm^3). Drying ($MgSO_4$) and solvent removal provided the crude product as a brown oil which was purified by silica column chromatography (hexane:Et_2O, 96:4) to afford **127** (0.16 g, 88%) as a clear oil. ν_{max}(film)/cm^{-1} 3023, 2973, 1624, 1449, 1392, 1306 and 1210; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.4, boronate OCH(C*H*$_3$)), 1.34 (3H, m, boronate OC(C*H*$_3$)$_2$), 1.35 (3H, m, boronate OC(C*H*$_3$)$_2$), 1.52-1.59 (1H, m, boronate C*H*H), 1.83 (1H, dd, *J* 13.6 & 2.8, boronate CH*H*), 4.24-4.32 (1H, m, boronate OC*H*(CH$_3$)), 6.11 (1H, d, *J* 18.0, alkenic), 7.23-7.33 (4H, m, 3Ar-*H* & 1 alkenic) and 7.48 (2H, d, *J* 8.0, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 23.2 (boronate OCH(*C*H$_3$)), 28.2 (boronate OC(*C*H$_3$)(CH$_3$)), 31.3 (boronate OC(CH$_3$)(*C*H$_3$)), 46.0 (boronate *C*H$_2$), 64.8 (boronate O*C*H(CH$_3$)), 70.9 (boronate O*C*(CH$_3$)$_2$), 126.9 (2C, Ar), 128.3 (Ar), 128.4 (2C, Ar), 138.0 (Ar) and 146.5 (alkenic); δ_B (128 MHz, $CDCl_3$) 26.9; *m/z* (EI) 230.1478 (M^+, $C_{14}H_{19}O_2B^+$ requires 230.1482), 215, 130 (100), 91, 77, 51 and 43.

Hydroboration Procedure

Catecholborane (6.40 cm^3, 60 mmol) was added dropwise to phenylacetylene (6.58 cm^3, 60 mmol) stirring at 0°C under argon. After the subsidence of exotherms the reaction was heated at 70°C for 2 h before cooling to room temperature and diluting with DCM (60 cm^3). Saturated aq. $NaHCO_3$ (50 cm^3) and 2-methyl-2,4-pentane diol (7.61 cm^3, 60 mmol) were then added and the mixture vigorously stirred for a further 2 h. The two phases were separated and the organic phase washed with saturated aq. $NaHCO_3$ (40 cm^3) and water (40 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude

product which was purified by Kugelröhr distillation to give **127** (9.11 g, 66%) as a clear oil, bp 95-100°C (0.38 mm Hg) (lit[210] 101-104°C 0.2 mm Hg).

4,4,5,5-Tetramethyl-2-((*E*)-styryl)-1,3,2-dioxaborolane 130



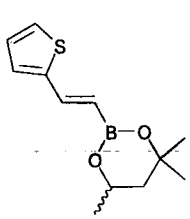
Heck Procedure

Dry toluene (10 cm^3) was added to a Schlenk-like tube with stirring under a positive pressure of argon containing $Pd(OAc)_2$ (28.1 mg, 0.125 mmol) and PPh_3 (78.5 mg, 0.30 mmol). Tri-*n*-butylamine (0.72 cm^3, 3.0 mmol), iodobenzene (0.28 cm^3, 2.5 mmol) and the vinyl boronate **117** (0.69 g, 3.0 mmol) were added and the solution was degassed using the freeze-pump-thaw method (x 3) before heating to 110°C. After 24 h the reaction was cooled and diluted with EtOAc (25 cm^3) before washing with 10% HCl (2 x 20 cm^3) and brine (2 x 20 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product which was purified by silica column chromatography (hexane:Et_2O, 95:5) to furnish **130** as a clear oil (0.22 g, 38%). Characterisation data was consistent with literature values.[211]

Hydroboration Procedure

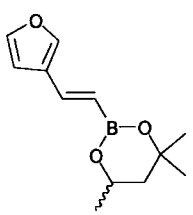
Catecholborane (4.18 cm^3, 39.2 mmol) was added dropwise to phenylacetylene (4.30 cm^3, 39.2 mmol) stirring at 0°C under argon. After the subsidence of exotherms the reaction was heated at 70°C for 2 h before cooling to room temperature and diluting with DCM (40 cm^3). Saturated aq. $NaHCO_3$ (32 cm^3) and pinacol (4.63 g, 39.2 mmol) were then added and the mixture vigorously stirred for a further 2 h. The two phases were separated and the organic layer washed with saturated aq. $NaHCO_3$ (40 cm^3) and water (40 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product which was purified by Kugelröhr distillation to give **130** (4.73 g, 53%) as a clear oil, bp 90-95°C/0.12 mm Hg. Characterisation data was consistent with literature values.[211]

4,4,6-Trimethyl-2-((*E*)-2-thiophen-2-yl-vinyl)-1,3,2-dioxaborinane 135



Dry toluene (10 cm^3) was added to a Schlenk-like tube with stirring under a positive pressure of argon containing $Pd(OAc)_2$ (28.1 mg, 0.125 mmol) and PPh_3 (72 mg, 0.275 mmol). Tri-*n*-butylamine (0.60 cm^3, 2.50 mmol), 2-bromothiophene (0.12 cm^3, 1.25 mmol) and vinylboronate **123** (0.23 g, 1.50 mmol) were added and the solution was degassed using the freeze-pump-thaw method (x 3), before heating to 110°C. After 4 d the reaction mixture was cooled, diluted with Et_2O (40 cm^3) and passed through Celite before washing with 10% HCl (20 cm^3), water (20 cm^3) and brine (20 cm^3). Drying ($MgSO_4$) and solvent removal provided the crude product as a brown oil. Kugelröhr distillation afforded **135** (92 mg, 31%) as a yellow oil, bp 90-95°C (0.12 mm Hg). ν_{max}(film)/cm^{-1} 3069, 2971, 1613, 1418, 1392, 1303 and 1231; δ_H (400 MHz, $CDCl_3$) 1.22-1.26 (9H, m, boronate 3 x C*H*$_3$), 1.44-1.50 (1H, m, boronate C*H*H), 1.74 (1H, dd, *J* 11.2 & 3.2, boronate CH*H*), 4.18-4.22 (1H, m, boronate OC*H*(CH_3)), 5.79 (1H, d, *J* 17.8, alkenic), 6.89-6.91 (1H, m, Ar-*H*), 6.97-6.98 (1H, m, Ar-*H*), 7.12-7.13 (1H, m, Ar-*H*) and 7.31 (1H, d, *J* 17.8, alkenic); δ_C (100 MHz, $CDCl_3$) 23.2 (boronate OCH(*C*H_3)), 28.1 (boronate OC(*C*H_3)(CH_3)), 31.2 (boronate OC(CH_3)(*C*H_3)), 46.0 (boronate *C*H_2), 64.8 (boronate OCH(CH_3)), 70.9 (boronate O*C*(CH_3)$_2$), 125.5 (Ar), 126.8 (Ar), 127.5 (Ar), 138.9 (Ar) and 144.6 (alkenic); δ_B (128 MHz, $CDCl_3$) 26.2; *m/z* (EI) 236.1043 (M^+ 100%, $C_{12}H_{17}BO_2S^+$ requires 236.1042), 221, 136 (100), 111, 85 and 43.

2-((*E*)-2-Furan-3-yl-vinyl)-4,4,6-trimethyl-1,3,2-dioxaborinane 136



Dry toluene (10 cm^3) was added to a Schlenk-like tube with stirring under a positive pressure of argon containing $Pd(OAc)_2$ (28.1 mg, 0.125 mmol) and PPh_3 (72 mg, 0.275 mmol). Tri-*n*-butylamine (0.60 cm^3, 2.50 mmol), 2-bromofuran (0.11 cm^3, 1.25 mmol) and vinylboronate **123** (0.23 g, 1.50 mmol) were added and the solution was degassed using the freeze-pump-thaw method (x 3), before heating to 110°C. After 4 d the reaction mixture was cooled, diluted with Et_2O (40 cm^3) and passed through Celite before washing with 10% HCl (20 cm^3), water (20 cm^3) and brine (20 cm^3). Drying ($MgSO_4$) and solvent removal provided the crude product as a brown oil. Kugelröhr distillation afforded **136** (76 mg, 28%) as a yellow oil, bp 65-75°C (0.19 mm Hg). ν_{max}(film)/cm^{-1} 2973, 1635, 1418, 1391, 1305 and 1231; δ_H (400 MHz, $CDCl_3$) 1.23-

1.33 (9H, m, boronate 3 x C*H*$_3$), 1.50-1.57 (1H, m, boronate C*H*H), 1.81 (1H, dd, *J* 14.0 & 2.4, boronate CH*H*), 4.22-4.28 (1H, m, boronate OC*H*(CH$_3$)), 5.77 (1H, d, *J* 18.0, alkenic), 6.59 (1H, s, Ar-*H*), 7.18 (1H, d, *J* 18.0, alkenic), 7.34 (1H, s, Ar-*H*), 7.47 (1H, s, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 22.2 (boronate OCH(*C*H$_3$)), 27.2 (boronate OC(*C*H$_3$)(CH$_3$)), 30.3 (boronate OC(CH$_3$)(*C*H$_3$)), 45.0 (boronate *C*H$_2$), 63.8 (boronate O*C*H(CH$_3$)), 69.8 (boronate O*C*(CH$_3$)$_2$), 106.6 (Ar), 135.2 (Ar), 140.6 (Ar), 142.5 (Ar) and 145.5 (alkenic); δ_B (128 MHz, $CDCl_3$) 26.6; *m/z* (EI) 220 (M^+), 205, 130 (100), 120 and 43. Accurate mass could not be obtained as largest molecular ion was due to contamination with by-product **127**.

((*E*)-2-Iodo-vinyl)-benzene 139

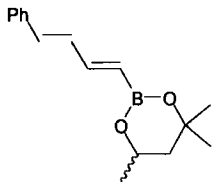
To a stirred solution of boronate **127** (2.0 g, 8.70 mmol) in dry THF (25 cm^3) under argon at -78°C in the absence of light, was added NaOMe (20.9 cm^3 of a 0.5M solution in MeOH, 10.44 mmol) dropwise and the reaction allowed to stir for 30 min. ICl (10.4 cm^3 of a 1.0M soln. in DCM, 10.4 mmol) was added over 5 min and the reaction was allowed to warm to room temperature. After 2 h, the solution was diluted with Et_2O (60 cm^3) before washing with 5% aq. $Na_2S_2O_5$ (70 cm^3), water (70 cm^3) and brine (70 cm^3). Drying ($MgSO_4$) and solvent removal afforded the crude product as a brown oil. Purification by silica column chromatography (petroleum ether:Et_2O, 90:10) provided **139** (1.7 g, 86%) as a yellow oil. Characterisation data was consistent with literature values.[212]

((*Z*)-2-Iodo-vinyl)-benzene 140

To a stirred solution of boronate **127** (1.5 g, 6.52 mmol) in dry DCM (20 cm^3) under argon, in the absence of light at -78°C was added ICl (7.83 cm^3 of a 1.0M solution in DCM, 7.83 mmol) dropwise over a period of 5 min. After stirring for 4 h NaOMe (15.65 cm^3 of a 0.5M solution in MeOH, 7.83mol) was added and the reaction left for a further 30 min before warming to room temperature. The reaction mixture was diluted with Et_2O (60 cm^3), washed with 5% aq. $Na_2S_2O_5$ (50 cm^3), water (50 cm^3) and brine (50 cm^3) before drying ($MgSO_4$) and solvent removal to afford the crude product. Purification by silica column chromatography (petroleum ether:Et_2O, 90:10) provided

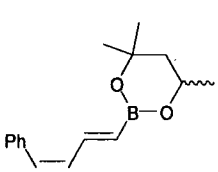
140 (1.4 g, 95%) as a yellow oil. Characterisation data was consistent with literature values.[213]

4,4,6-Trimethyl-2-((1*E*,3*E*)-4-phenyl-buta-1,3-dienyl)-1,3,2-dioxaborinane 141



To a dried Schlenk-like tube under a positive pressure of argon was added $Pd(OAc)_2$ (9 mg, 0.04 mmol), PPh_3 (31 mg, 0.12 mmol) and AgOAc (0.16 g, 0.96 mmol). Syringe addition of toluene (5 cm^3), iodide **139** (0.18 g, 0.80 mmol) and vinyl boronate **123** (0.15 g, 0.96 mmol) was followed by degassing using the freeze-pump-thaw method (x 3) before heating to 110°C. After 24 hours the reaction was cooled and diluted with Et_2O (40 cm^3) before passing through Celite and washing with 10% HCl (20 cm^3) and brine (20 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product as a brown oil. Purification by silica column chromatography (hexane:Et_2O, 95:5) afforded **141** (0.11 g, 55%) as a yellow oil. ν_{max}(film)/cm^{-1} 3058, 3023, 2973, 1622, 1602, 1391, 1301 and 1249; δ_H (500 MHz, $CDCl_3$) 1.31-1.34 (9H, m, boronate 3 x C*H*$_3$), 1.52-1.57 (1H, m, boronate C*H*H), 1.82 (1H, dd, *J* 14.0 & 3.0, boronate CH*H*), 4.23-4.30 (1H, m, boronate OC*H*(CH_3)), 5.64 (1H, d, *J* 17.3, Ph-CH=CH-CH=C*H*B), 6.69 (1H, d, *J* 15.5, Ph-C*H*=CH-CH=CHB), 6.85 (1H, dd, *J* 15.5 & 10.5, Ph-CH=C*H*-CH=CHB, 7.11 (1H, dd, *J* 17.3 & 10.5, Ph-CH=CH-C*H*=CHB), 7.25 (1H, t, *J* 7.5, Ar-*H*), 7.33 (2H, t, *J* 7.5, Ar-*H*) and 7.44 (2H, d, *J* 7.5, Ar-H); δ_C (126 MHz, $CDCl_3$) 23.4 (boronate OCH(*C*H_3)), 28.4 (boronate OC(*C*H_3)(CH_3)), 31.5 (boronate OC(CH_3)(*C*H_3)), 46.2 (boronate *C*H_2), 65.0 (boronate O*C*H(CH_3)), 71.1 (boronate O*C*(CH_3)$_2$), 126.9 (2C, Ar), 128.1 (Ar), 128.8 (2C, Ar), 131.3 (alkenic), 135.0 (alkenic), 137.4 (Ar) and 147.1 (alkenic); δ_B (160 MHz, $CDCl_3$) 26.0; *m/z* (EI) 256 (M^+), 241, 156, 128 (100), 91, 77, 55 and 43; (ES$^+$ found: MH^+ 257.1708; $C_{16}H_{22}O_2B^+$ requires 257.1707).

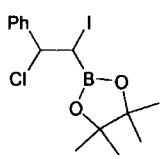
4,4,6-Trimethyl-2-((1*E*,3*Z*)-4-phenyl-buta-1,3-dienyl)-1,3,2-dioxaborinane 142



To a dried Schlenk-like tube under a positive pressure of argon was added $Pd(OAc)_2$ (74.1 mg, 0.33 mmol), PPh_3 (260 mg, 0.99 mmol) and AgOAc (1.31 g, 7.82 mmol).

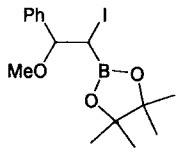
Syringe addition of toluene (10 cm^3), iodide **140** (1.50 g, 6.52 mmol) and vinyl boronate **123** (1.20 g, 7.82 mmol) was followed by degassing using the freeze-pump-thaw method (x 3) before heating to 110°C. After 24 h the reaction was cooled and diluted with EtOAc (50 cm^3) before passing through Celite and washing with 10% HCl (50 cm^3) and brine (50 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product as a brown oil. Purification by silica column chromatography (hexane:Et_2O, 98:2) afforded **142** (0.98 g, 58%) as a thick orange oil. ν_{max}(film)/cm^{-1} 3057, 3023, 2973, 1623, 1599, 1408, 1390 and 1209; δ_H (400 MHz, $CDCl_3$) 1.24-1.35 (9H, m, 3 x C*H*$_3$), 1.47-1.53 (1H, m, boronate C*H*H), 1.78 (1H, dd, *J* 14.4 & 3.2, boronate CH*H*), 4.17-4.24 (1H, m, boronate OC*H* (CH_3)), 5.67 (1H, d, *J* 17.2, =C*H*B), 6.30 (1H, t, *J* 11.6, PhCH=C*H*-CH=CHB), 6.49 (1H, d, *J* 11.6, PhC*H*=CH-CH=CHB), 7.32-7.37 (5H, m, Ar-*H*) and 7.45 (1H, dd, *J* 17.2 & 11.6, PhCH=CH-C*H*=CHB); δ_C (100 MHz, $CDCl_3$) 23.1 (boronate OCH(*C*H_3)), 28.1 (boronate OC(*C*H_3)(CH_3)), 31.2 (boronate OC(CH_3)(*C*H_3)), 46.0 (boronate *C*H_2), 64.7 (boronate O*C*H(CH_3)), 70.8 (boronate O*C*(CH_3)$_2$), 127.1 (2C, Ar), 128.2 (Ar), 129.2 (2C, Ar), 131.7 (alkenic), 132.5 (alkenic), 137.5 (Ar) and 142.5 (alkenic); δ_B (128 MHz, $CDCl_3$) 25.7; *m/z* (EI) 256 (M^+), 241, 156, 128 (100), 91, 77, 55 and 43; (ES^+ found: MH^+ 257.1705; $C_{16}H_{22}O_2B^+$ requires 257.1707).

2-(2-Chloro-1-iodo-2-phenyl-ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 154



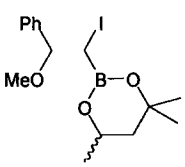
To a stirred solution of styryl boronate **130** (0.63 g, 2.49 mmol) in dry THF (20 cm^3) under argon was added ICl (0.44 g, 2.74 mmol). The reaction was allowed to stir for 90 min before solvent removal to afford the crude product. Attempts at purification resulted in decomposition of the product, consequently it was characterised crude by nmr. δ_H (400 MHz, $CDCl_3$) 1.28-1.37 (12H, m, 4 x C*H*$_3$), 3.82 (1H, d, *J* 12.6, C*H*IB), 5.21 (1H, d, *J* 12.6, PhC*H*Cl), 7.34-7.39 (5H, m, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.1 (*C*H_3), 24.3 (*C*H_3), 24.6 (*C*H_3), 24.8 (*C*H_3), 62.2 (*C*-I), 83.4 (O*C*(CH_3)$_2$), 84.6 (*C*-Cl), 127.4 (2C, Ar), 128.6 (2C, Ar), 129.0 (Ar) and 140.2 (Ar); δ_B (128 MHz, $CDCl_3$) 31.3.

2-(1-Iodo-2-methoxy-2-phenyl-ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 158



In the absence of light ICl (0.37 g, 2.29 mmol) was dissolved with stirring under argon in dry MeOH (12 cm^3) before the addition of the styryl boronate **130** (0.44 g, 1.90 mmol). After 1 h the reaction was diluted with Et_2O (75 cm^3) and washed with 5% $Na_2S_2O_5$ (75 cm^3) and brine (75 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product (0.53 g, 72%) as a pale orange oil. Attempts at purification resulted in decomposition of the product, consequently it was characterised crude. ν_{max}(film)/cm^{-1} 3062, 2977, 2931, 2820, 1493, 1405 and 1380; δ_H (400 MHz, $CDCl_3$) 1.19 (6H, s, 2 x C*H*$_3$), 1.21 (6H, s, 2 x C*H*$_3$), 3.14 (3H, s, O*Me*), 3.17 (1H, d, *J* 10.0, C*H*IB), 4.29 (1H, d, *J* 10.0, PhC*H*OMe), 7.17-7.27 (5H, m, Ar-*H*); δ_C (126 MHz, $CDCl_3$) 24.3 (*C*H$_3$), 24.7 (*C*H$_3$), 57.8 (O*Me*), 84.3 (O*C*(CH$_3$)$_2$), 85.6 (PhCHOMe), 127.8 (2C, Ar), 128.5 (2C, Ar), 128.6 (Ar) and 139.9 (Ar); δ_B (128 MHz, $CDCl_3$) 32.0; *m/z* (ES^+) 411.0616 (MNa^+, 100%; $C_{15}H_{22}O_3BNaI^+$ requires 411.0604), 410, 357 and 222.

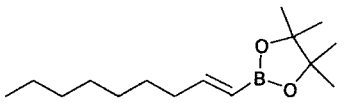
2-(1-Iodo-2-methoxy-2-phenyl-ethyl)-4,4,6-trimethyl-1,3,2-dioxaborinane 159



In the absence of light, ICl (0.25 g, 1.53 mmol) was dissolved with stirring under argon in dry MeOH (8 cm^3) before the addition of the styryl boronate **127** (0.29 g, 1.28 mmol). After 1 h the reaction was diluted with Et_2O (60 cm^3) and washed with 5% $Na_2S_2O_5$ (60 cm^3) and brine (60 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product (0.31 g, 63%) as a pale yellow oil. Attempts at purification resulted in decomposition of the product, consequently it was characterised crude. ν_{max}(film)/cm^{-1} 3061, 2972, 2931, 2819, 1493, 1453 and 1209; δ_H (400 MHz, $CDCl_3$) 1.28-1.33 (9H, m, 3 x C*H*$_3$), 1.52-1.58 (1H, m, boronate C*H*H), 1.79 (1H, d, *J* 14.0, boronate CH*H*), 3.15 (1H, t, *J* 10.6, C*H*IB), 3.20-3.22 (3H, m, O*Me*), 4.25-4.35 (1H, m, boronate OC*H*(CH$_3$)), 4.32 (1H, d, *J* 10.6, PhC*H*OMe), 7.29-7.35 (5H, m, Ar-*H*); δ_C (126 MHz, $CDCl_3$) 23.3 (boronate OCH(C*H*$_3$)), 27.6 (boronate OC(*C*H$_3$)(CH$_3$)), 31.1 (boronate OC(CH$_3$)(*C*H$_3$)), 46.0 (boronate *C*H$_2$), 57.8 (O*Me*), 65.7 (boronate O*C*H(CH$_3$)), 71.5 (O*C*(CH$_3$)$_2$), 85.5 (PhCHOMe), 128.0 (2C, Ar), 128.3 (2C, Ar), 128.3 (Ar) and 140.5

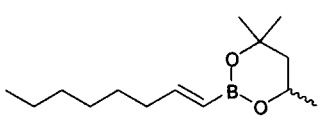
(Ar); δ_B (128 MHz, $CDCl_3$) 28.4; *m/z* (ES^+) 411.0607 (MNa^+, 100%; $C_{15}H_{22}O_3BNaI^+$ requires 411.0604), 410, 357, 261, 230 and 205.

4,4,5,5-Tetramethyl-2-((*E*)-non-1-enyl)-1,3,2-dioxaborolane 161



Catecholborane (2.58 cm^3, 24.2 mmol) was added dropwise to 1-nonyne (3.96 cm^3, 24.2 mmol) with stirring under argon at 0°C. The reaction was then heated to 70°C for 2 h before cooling to room temperature and diluting with DCM (24 cm^3) allowing the addition of pinacol (2.86 g, 24.2 mmol) and saturated aq. $NaHCO_3$ (20 cm^3). After vigorous stirring at room temperature for 2 h the phases were separated and the organic layer washed with saturated aq. $NaHCO_3$ (18 cm^3) and water (18 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product as a yellow oil. Purification by silica column chromatography (petroleum ether:EtOAc, 91:9) furnished **161** as a pale yellow oil (3.47 g, 57%). ν_{max}(film)/cm^{-1} 2977, 2927, 1639, 1466, 1398, 1363 and 1319; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.2, CH_3CH_2), 1.24-1.42 (22H, m, 4 x CH_3 & 5 x CH_2), 2.11-2.17 (2H, m, CH_2=CH), 5.42 (1H, dt, *J* 18.0 & 1.6, =CHB) and 6.63 (1H, dt, *J* 18.0 & 6.4, CH_2CH=); δ_C (100 MHz, $CDCl_3$) 14.4 (CH_3CH_2), 22.9 (CH_2), 25.0 (boronate CH_3), 28.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 32.0 (CH_2), 36.1 (CH_2), 83.2 (boronate $OC(CH_3)_2$) and 155.1 (CH_2CH=); δ_B (128 MHz, $CDCl_3$) 30.1; *m/z* (EI) (M^+, $C_{15}H_{29}BO_2^+$ requires 252.2261, obtained 252.2269), 237, 166, 153 (100), 85, 55 and 43.

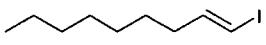
4,4,6-Trimethyl-2-((*E*)-non-1-enyl)-1,3,2 dioxaborinane 162



Catecholborane (0.86 cm^3, 8.05 mmol) was added dropwise to 1-nonyne (1.32 cm^3, 8.05 mmol) with stirring under argon at 0°C. The reaction was then heated to 70°C for 2 h before cooling to room temperature and diluting with DCM (8 cm^3) allowing the addition of 2-methyl-2,4-pentane diol (1.03 cm^3, 8.05 mmol) and saturated aq. $NaHCO_3$ (6 cm^3). After vigorous stirring over 2 h the phases were separated and the organic layer washed with saturated aq. $NaHCO_3$ (6 cm^3) and water (6 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product as a yellow oil. Purification by SiO_2 column chromatography (petroleum ether:EtOAc, 91:9) furnished **162** as a clear oil

(1.57 g, 77%). ν_{max}(film)/cm^{-1} 2972, 2925, 1639, 1413, 1387 and 1302; δ_H (500 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.0, C*H*$_3$CH$_2$-), 1.26-1.29 (17H, m, boronate 3 x C*H*$_3$ & 4 x C*H*$_2$), 1.40 (2H, t, *J* 7.0, C*H*$_2$), 1.47-1.52 (1H, m, boronate C*H*H), 1.77 (1H, dd, *J* 13.5 & 2.5, boronate CH*H*), 2.08-2.12 (2H, m, C*H*$_2$-CH=), 4.17-4.24 (1H, m, boronate OC*H*(CH$_3$)), 5.33 (1H, d, *J* 17.8, =C*H*B) and 6.53 (1H, dt, *J* 17.8 & 6.5, C*H*$_2$CH=); δ_C (126 MHz, $CDCl_3$) 14.4 (*C*H$_3$CH$_2$), 22.9 (*C*H$_2$), 23.5 (boronate OCH(C*H*$_3$)), 28.4 (*C*H$_2$), 28.7 (boronate OC(*C*H$_3$)(CH$_3$)), 29.5 (*C*H$_2$), 29.5 (*C*H$_2$), 31.5 (boronate OC(CH$_3$)(*C*H$_3$)), 32.1 (*C*H$_2$), 35.8 (*C*H$_2$), 46.2 (boronate *C*H$_2$), 64.8 (boronate OCH(CH$_3$)), 70.8 (boronate O*C*(CH$_3$)$_2$) and 151.5 (CH$_2$*C*H=); δ_B (128 MHz, $CDCl_3$) 25.7; *m/z* (EI) 252.2259 (M^+, $C_{15}H_{29}BO_2^+$ requires 252.2261), 237, 168, 153, 83, 55 and 43 (100%).

(*E*)-1-Iodo-non-1-ene 163



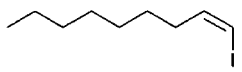
Iodine Monochloride/Sodium Methoxide Procedure

Boronate **161** (0.25 g, 0.99 mmol) was dissolved in THF (7 cm^3) with stirring under argon and cooled to -78°C before the addition of NaOMe (2.38 cm^3 of a 0.5M soln. in MeOH, 1.19 mmol). After stirring for 30 min ICl (1.19 cm^3 of a 1.0M soln. in DCM, 1.19 mmol) was added and the reaction allowed to warm to room temperature over 2 h. The reaction was diluted with Et_2O (35 cm^3) before washing with 5% $Na_2S_2O_5$ (50 cm^3), water (50 cm^3) and brine (50 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product as a yellow oil. Purification by silica column chromatography (hexane) afforded **163** (0.12 g, 47%) as a clear oil. Characterisation data was consistent with literature values.[212]

Iodine/Sodium Hydroxide Procedure

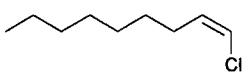
Boronate **162** (2.0 g, 7.94 mmol) was dissolved with stirring in THF (20 cm^3) before the addition of NaOH (0.95 g, 23.8 mmol) in water (5 cm^3). After 30 min of vigorous stirring the portionwise addition of I_2 (4.03 g, 15.9 mmol) commenced and was added over 2 h. The reaction was then diluted with Et_2O (100 cm^3) before washing with 5% $Na_2S_2O_5$ (100 cm^3) and brine (100 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product as a brown oil. Purification by silica column chromatography (hexane) afforded **163** (1.35 g, 67%) as a clear oil. Characterisation data was consistent with literature values.[212]

(*Z*)-1-Iodo-non-1-ene 164



Boronate **161** (0.50 g, 1.98 mmol) was dissolved with stirring under argon in dry DCM (15 cm^3) before the dropwise addition of ICl (2.38 cm^3 of a 1.0M soln. in DCM, 2.38 mmol), the reaction was then left to stir for 4 h. NaOMe (4.75 cm^3 of a 0.5M soln. in MeOH, 2.38 mmol) was then added dropwise and the reaction left for a further 30 min. The reaction was diluted with Et_2O (35 cm^3) before washing with 5% $Na_2S_2O_5$ (50 cm^3), water (50 cm^3) and brine (50 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product as a yellow oil. Purification by silica column chromatography (hexane) afforded **164** (0.33 g, 65%) as a clear oil. Characterisation data was consistent with literature values.[214]

(*Z*)-1-Chloro-non-1-ene 165

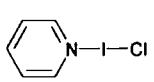


2,6-Lutidine-ICl (1.07 g, 3.97 mmol) was dissolved with stirring under argon in dry DCM (15 cm^3). Boronate **162** (0.50 g, 1.98 mmol) was then added and the reaction was left to stir for 4 h. Dilution with Et_2O (35 cm^3) allowed washing with 5% $Na_2S_2O_5$ (50 cm^3), water (50 cm^3) and brine (50 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product as a yellow oil. Purification by silica column chromatography (hexane) afforded **165** (0.22 g, 69%) as a clear oil. Characterisation data was consistent with literature values.[214]

General procedure for the preparation of substituted pyridine iodinemonochloride complexes 172, 181-185

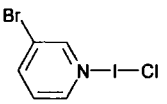
The appropriate pyridine derivative (30 mmol) was dissolved with stirring under argon in freshly distilled DCM (10 cm^3) before cooling to 0°C. The dropwise addition of ICl (30 cm^3 of a 1.0M soln. in DCM, 30 mmol) was performed over 30 min before warming to room temperature and stirring for a further 30 min. Hexane was added until the product precipitated out of solution allowing filtration, isolation and drying of the product.

Pyridine Iodinemonochloride complex 172



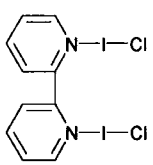
Obtained **172** as a yellow solid (6.55 g, 90%). Characterisation data was consistent with literature values.[164]

3-Bromopyridine Iodinemonochloride Complex 181



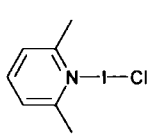
Obtained **181** as a yellow solid (7.05 g, 73%). Mp 95-96°C; ν_{max}(KBr disc)/cm^{-1} 2961, 1411, 1260, 1094, 1021 and 800; δ_H (400 MHz, $CDCl_3$) 7.36 (1H, ddd, *J* 8.0, 5.2 & 0.4, Ar*H*), 8.11 (1H, ddd, *J* 8.0, 2.0 & 1.2, Ar*H*), 8.58 (1H, dd, *J* 5.2 & 1.2, Ar*H*) and 8.73 (1H, dd, *J* 2.0 & 0.4, Ar*H*); δ_C (100 MHz, $CDCl_3$) 123.1 (Ar), 127.6 (Ar), 142.7 (Ar), 146.8 (Ar) and 149.8 (Ar); Elemental Analysis, found C, 18.85; H, 1.24; N, 4.31. $C_5H_4NBrClI$ requires C, 18.75; H, 1.26; N, 4.37. Crystallographic data can be found in appendix A.

2,2-Bipyridine-Diiodinemonochloride Complex 182



Obtained **182** as a yellow solid (6.75 g, 94%). Mp 130-131°C; ν_{max}(KBr disc)/cm^{-1} 3092, 3071, 1589, 1463, 1297, 1074 and 794; δ_H (500 MHz, $CDCl_3$) 7.60 (2H, t, *J* 5.5, Ar*H*), 7.80 (2H, d, *J* 8.0, Ar*H*), 8.17 (2H, t, *J* 8.0, Ar*H*) and 8.95 (2H, d, *J* 5.5, Ar*H*); δ_C (126 MHz, $CDCl_3$) 126.2 (Ar), 127.1 (Ar), 140.6 (Ar), 150.2 (Ar) and 154 (Ar); Elemental Analysis, found C, 25.28; H, 1.71; N, 5.84; $C_{10}H_8N_2Cl_2I_2$ requires C, 24.98; H, 1.68; N, 5.83. Crystallographic data can be found in appendix A.

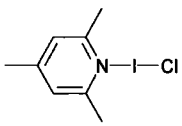
2,6-Lutidine Iodinemonochloride Complex 183



Obtained **183** as a yellow solid (6.12 g, 76%). Mp 103-105°C; ν_{max}(KBr disc)/cm^{-1} 2974, 1601, 1465, 1377, 1161 and 792; δ_H (500 MHz, $CDCl_3$) 2.81 (6H, s, 2 x Me), 7.17 (2H, d, *J* 8.0, Ar*H*) and 7.66 (1H, t, *J* 8.0, Ar*H*); δ_C (126 MHz, $CDCl_3$) 29.1 (2C, Me), 123.6 (2C, Ar), 140.0 (Ar) and 158.3 (Ar); Elemental Analysis, found C, 31.21;

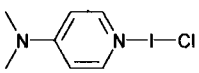
H, 3.38; N, 5.09; C_7H_9NClI requires C, 31.20; H, 3.37; N, 5.20. Crystallographic data can be found in appendix A.

2,4,6-Collidine Iodinemonochloride Complex 184



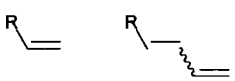
Obtained **184** as a yellow solid (5.80 g, 68%). Mp 110-111°C; ν_{max}(KBr disc)/cm^{-1} 3050, 2962, 1613, 1457, 1378 and 849; δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s, Me), 2.77 (6H, s, 2 x Me) and 7.00 (2H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.1 (2C, Me), 27.5 (Me), 124.4 (2C, Ar) and 156.8 (Ar); Elemental Analysis, found C, 33.69; H, 3.90; N, 4.94; $C_8H_{11}NClI$ requires C, 33.89; H, 3.91; N, 4.94. Crystallographic data can be found in appendix A.

DMAP Iodinemonochloride Complex 185



Obtained **185** as a yellow solid (7.41 g, 87%). Mp 140-141°C; ν_{max}(KBr disc)/cm^{-1} 3072, 2918, 1607, 1458, 1389, 1215 and 811; δ_H (400 MHz, $CDCl_3$) 3.10 (6H, s, 2 x Me), 6.44 (2H, d, *J* 7.2, Ar*H*) and 8.08 (2H, d, *J* 7.2, Ar*H*); δ_C (100 MHz, $CDCl_3$) 39.8 (2C, Me), 108.6 (2C, Ar), 147.9 (2C, Ar) and 155.3 (Ar); Elemental Analysis, found C, 29.58; H, 3.53; N, 9.75; $C_7H_{10}N_2ClI$ requires C, 29.55; H, 3.55; N, 9.84. Crystallographic data can be found in appendix A.

General Procedures for the Preparation of Styrenes and Dienes 128, 137, 143, 144, 196-199



Characterisation data for the styrenes **128**, **137**, **196-199** was consistent with commercial samples. Characterisation data for dienes **143** and **144** was consistent with literature values.[215,216]

Method A

To a Schlenk-like tube under a positive pressure of argon was added $Pd(PPh_3)_4$ (39 mg, 33.8 μmol) and *t*BuOK (91 mg, 0.81 mmol). This was followed by freshly distilled THF (6 cm^3), the halide substrate (0.675 mmol) and vinyl boronate **123** (0.13 g, 0.81 mmol). The tube was then heated at 67°C for 24 h before cooling, dilution with Et_2O (30 cm^3) and filtration through Celite. This solution was treated with undecane (0.05 cm^3, 37.5 mmol) and a sample was analysed by GC. Drying ($MgSO_4$) and solvent removal afforded the crude product from which the Heck:Suzuki ratio could be determined by ^1H nmr. If performed, purification was carried out by silica column chromatography (hexane). Characterisation data for **201** was consistent with literature data.[217]

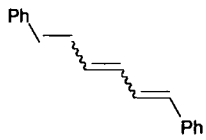
Method B

To a Schlenk-like tube under a positive pressure of argon was added $Pd(PPh_3)_4$ (39 mg, 33.8 μmol) and KOH (45 mg, 0.81 mmol). This was followed by freshly distilled THF (6 cm^3), the halide substrate (0.675 mmol) and vinyl boronate **123** (0.13 g, 0.81 mmol). The tube was then heated at 67°C for 24 h before cooling, dilution with Et_2O (30 cm^3) and filtration through Celite. This solution was treated with undecane (0.05 cm^3, 37.5 mmol) and a sample was analysed by GC. Drying ($MgSO_4$) and solvent removal afforded the crude product from which the Heck:Suzuki ratio could be determined by ^1H nmr. If performed, purification was carried out by silica column chromatography (hexane).

Method C

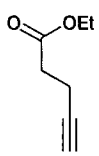
To a Schlenk-like tube under a positive pressure of argon was added $Pd(PPh_3)_4$ (39 mg, 33.8 μmol) and Ag_2O (0.29 g, 1.35 mmol). This was followed by freshly distilled THF (6 cm^3), the halide substrate (0.675 mmol) and vinyl boronate **123** (0.13 g, 0.81 mmol). The tube was then heated at 67°C for 24 h before cooling, dilution with Et_2O (30 cm^3) and filtration through Celite. This solution was treated with undecane (0.05 cm^3, 37.5 mmol) and a sample was analysed by GC. Drying ($MgSO_4$) and solvent removal afforded the crude product from which the Heck:Suzuki ratio could be determined by ^1H nmr. If performed, purification was carried out by silica column chromatography (hexane).

1,6-Diphenyl-1,3,5-hexatrienes 205-207



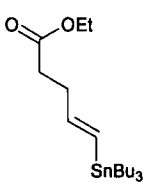
In a Schlenk-like tube $Pd(PPh_3)_4$ (42 mg, 0.36 μmol) and Ag_2O (0.34 g, 1.45 mmol) were dissolved with stirring under argon in freshly distilled THF (8 cm^3). To this was added the iodide **139** or **140** (0.17 g, 0.72 mmol) and the boronate **141** or **142** (0.19 g 0.72 mmol). The reaction was then heated at reflux for 24 h before cooling and diluting with Et_2O (40 cm^3) followed by washing through celite. Solvent removal yielded the crude product which could be purified by silica gel chromatography (hexane:Et_2O, 96:4). The characterisation data for all products **205-207** are consistent with literature values.[217]

Pent-4-ynoic acid ethyl ester 215



A stirred mixture of $HC(OEt)_3$ (33.9 cm^3, 67.8 mmol), absolute EtOH (36 cm^3, 203 mmol) and 4-pentynoic acid (3.0 g, 30.6 mmol) under a positive pressure of argon was treated with a catalytic amount of 18.8 M H_2SO_4 (0.107 cm^3, 1.65 mmol) followed by heating at 50°C for 24 h. The reaction mixture was then concentrated *in vacuo* and the resulting oil re-dissolved in EtOAc (18 cm^3) before washing with 1M $NaHCO_3$ (3 x 18 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product as a yellow oil. Purification by silica column chromatography (petroleum ether:Et_2O, 50:50) afforded **215** (2.72 g, 71%) as a clear oil. Characterisation data was consistent with literature values.[180]

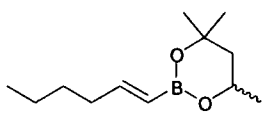
(*E*)-5-Tributylstannanyl-pent-4-enoic acid ethyl ester 219



With stirring under argon Bu_3SnH (2.78 cm^3, 10.31 mmol) was added dropwise to the alkyne **215** (1.0 g, 7.93 mmol) followed by AIBN (0.13 g, 0.79 mmol). After heating at 80°C for 6 h the reaction was cooled and flushed through a pad of silica. Excess Bu_3SnH was removed through distillation leaving the desired product **219** as a clear oil (2.91 g, 88%). ν_{max}(film)/cm^{-1} 2957, 2925, 1740, 1648, 1599, 1459 and 1375; δ_H (400

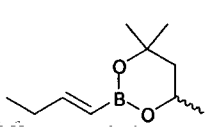
MHz, $CDCl_3$) 0.83-0.91 (15H, m, 3x($CH_2CH_2CH_2CH_3$) & 3x($CH_2CH_2CH_2CH_3$)), 1.23-1.32 (9H, m, OCH_2CH_3 & 3x($CH_2CH_2CH_2CH_3$)), 1.43-1.51 (6H, m, 3x($CH_2CH_2CH_2CH_3$) 2.35-2.44 (4H, m, 2xCH_2), 4.13 (2H, q, *J* 6.8, OCH_2CH_3) and 5.86-6.04 (2H, m, alkenic); δ_C (100 MHz, $CDCl_3$) 9.6 ($SnCH_2CH_2CH_2CH_3$), 13.9 ($SnCH_2CH_2CH_2CH_3$), 14.5 (OCH_2CH_3), 27.5 ($SnCH_2CH_2CH_2CH_3$), 29.3 ($SnCH_2CH_2CH_2CH_3$), 32.9 (CH_2), 33.9 (CH_2), 60.5 (OCH_2CH_3), 128.9 (Alkenic), 147.0 (Alkenic) and 173.5 (CO_2Et); *m/z* (ES^+) 441.1787 (MNa^+ 100%, $C_{19}H_{38}O_2{}^{120}SnNa^+$ requires 441.1786), 323 and 267.

2-((*E*)-Hept-1-enyl)-4,4,6-trimethyl-1,3,2-dioxaborinane 222



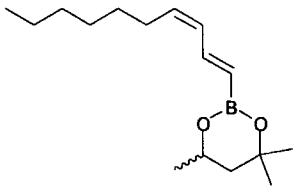
Catecholborane (2.22 cm^3, 20.8 mmol) was added dropwise to 1-heptyne (2.73 cm^3, 20.8 mmol) with stirring under argon at 0°C. The reaction was heated at 70°C for 2 h, after cooling to room temperature the reaction was diluted with DCM (20 cm^3) allowing the addition of 2-methyl-2,4-pentane diol (2.66 cm^3, 20.8 mmol) and saturated aq. $NaHCO_3$ (17 cm^3). After vigorous stirring over 2 h the phases were separated and the organic layer washed with saturated aq. $NaHCO_3$ (20 cm^3) and water (40 cm^3). Drying ($MgSO_4$) and solvent removal afforded the crude product as a pale yellow oil. Purification by silica column chromatography (petroleum ether:Et_2O, 91:9) provided **222** as clear oil (3.33 g, 71%). ν_{max}(film)/cm^{-1} 2972, 2927, 1638, 1413, 1387 and 1303; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.2, CH_3CH_2), 1.25-1.55 (16H, m, 3 x CH_3, 3 x CH_2 and boronate CHH), 1.76 (1H, d, *J* 13.6, boronate CHH), 2.07-2.13 (2H, m, CH_2-CH=), 4.18-4.23 (1H, m, boronate $OCH(CH_3)$), 5.33 (1H, d, *J* 17.8, C=CHB) and 6.53 (1H, dt, *J* 17.8 & 5.2, CH_2-CH=); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3CH_2), 22.5 (CH_2) 23.2 (boronate $OCH(CH_3)$), 28.1 (boronate $OC(CH_3)(CH_3)$), 31.3 (boronate $OC(CH_3)(CH_3)$), 31.5 (CH_2), 35.5 (CH_2), 46.0 (boronate CH_2), 64.6 (boronate $OCH(CH_3)$), 70.5 ($OC(CH_3)_2$) and 151.2 (CH_2CH=); δ_B (128 MHz, $CDCl_3$) 25.2; *m/z* (EI) 224.1943 (M^+, $C_{13}H_{25}BO_2{}^+$ requires 224.1948), 209, 168 (100), 153, 83, 55 and 43.

4,4,6-Trimethyl-2-((*E*)-pent-1-enyl)-1,3,2-dioxaborinane 223



Catecholborane (3.91 cm^3, 36.7 mmol) was added dropwise to 1-pentyne (3.62 cm^3, 36.7 mmol) with stirring under argon at 0°C. The reaction was heated at 70°C for 2 h, after cooling to room temperature the reaction was diluted with DCM (36 cm^3) allowing the addition of 2-methyl-2,4-pentane diol (4.65 cm^3, 36.7 mmol) and saturated aq. $NaHCO_3$ (30 cm^3). After vigorous stirring over 2 h the phases were separated and the organic layer washed with saturated aq. $NaHCO_3$ (30 cm^3) and water (30 cm^3). Drying ($MgSO_4$) and solvent removal afforded the crude product as a pale yellow oil. Purification by silica column chromatography (petroleum ether:Et_2O, 91:9) provided **223** as clear oil (4.14 g, 57%). ν_{max}(film)/cm^{-1} 2973, 2934, 1639, 1416, 1388 and 1310; δ_H (300 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.2, CH_3CH_2), 1.25-1.29 (9H, m, 3 x CH_3), 1.37-1.56 (3H, m, boronate CHH and CH_3CH_2), 1.77 (1H, d, *J* 13.8, boronate CHH), 2.05-2.13 (2H, m, CH_2-CH=), 4.12-4.24 (1H, m, boronate OCH(CH_3)), 5.34 (1H, dd, *J* 17.7 & 1.5, C=CHB) and 6.52 (1H, dt, *J* 17.7 & 6.3, CH_2-CH=); δ_C (100 MHz, $CDCl_3$) 13.8 (CH_3CH_2), 21.6 (CH_2), 23.2 (boronate OCH(CH_3)), 28.1 (boronate OC(CH_3)(CH_3)), 31.3 (boronate OC(CH_3)(CH_3)), 37.6 (CH_2), 46.0 (boronate CH_2), 64.6 (boronate OCH(CH_3)), 70.5 (boronate OC(CH_3)$_2$) and 150.9 (CH_2-CH=); δ_B (128 MHz, $CDCl_3$) 26.7; *m/z* (EI) 196.1632 (M^+, $C_{11}H_{21}BO_2^+$ requires 196.1635), 181, 153, 96, 83, 55 and 43 (100).

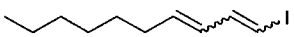
4,4,6-Trimethyl-((1*E*,3*Z*)-1,3-undecadienyl)-1,3,2-dioxaborinane 228



To a dried Schlenk-like tube under a positive pressure of argon was added $Pd(OAc)_2$ (44 mg, 0.20 mmol), PPh_3 (160 mg, 0.60 mmol) and AgOAc (0.40 g, 2.38 mmol). Syringe addition of toluene (6 cm^3) and vinyl boronate **123** (0.36 g, 2.38 mmol) was followed by degassing using the freeze-pump-thaw method (x 3) before heating to 110°C. The iodide **164** (0.50 g, 1.98 mmol) was added dropwise to the refluxing mixture over 2 h. After 6 h of total reaction the solution was cooled to room temperature and diluted with Et_2O (30 cm^3) before passing through Celite and washing with 10% HCl (25 cm^3) and brine (25 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product as a brown oil. Purification by silica column chromatography (hexane:Et_2O, 98:2) afforded **228** (0.22 g, 40%) as a yellow oil. ν_{max}(film)/cm^{-1} 3017, 2971, 2926, 1634, 1595, 1405, 1387 and 1303; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.2, CH_3CH_2), 1.27-1.39 (19H, m,

3 x boronate C*H*$_3$ & 5 x C*H*$_2$), 1.50 (1H, dd, *J* 14.0 & 11.6, boronate C*H*H), 1.79 (1H, dd, *J* 14.0 & 2.8, boronate CH*H*), 2.26 (2H, q, *J* 7.6 Hz, C*H*$_2$C=), 4.20-4.26 (1H, m, boronate OC*H*(CH$_3$)), 5.46 (1H, d, *J* 17.6, -CH=CH-CH=C*H*B), 5.51 (1H, dt, *J* 10.6 & 7.6, -C*H*=CH-CH=CHB), 6.04 (1H, t, *J* 10.6, -CH=C*H*-CH=CHB) and 7.22 (1H, dd, *J* 17.6 & 10.6, -CH=CH-C*H*=CHB); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*H$_3$CH$_2$), 22.7 (*C*H$_2$), 23.2 (boronate OCH(*C*H$_3$)), 28.0 (*C*H$_2$), 28.1 (boronate OC(*C*H$_3$)(CH$_3$)), 29.2 (*C*H$_2$), 29.2 (*C*H$_2$), 29.6 (*C*H$_2$), 31.3 (boronate OC(CH$_3$)(*C*H$_3$)), 31.8 (*C*H$_2$), 46.1 (boronate *C*H$_2$), 64.7 (boronate O*C*H(CH$_3$)), 70.7 (boronate O*C*(CH$_3$)$_2$), 130.8 (alkenic), 135.2 (alkenic) and 141.8 (alkenic); δ_B (128 MHz, $CDCl_3$) 26.4; *m/z* (EI) 278 (M^+), 263, 222, 178, 83, 55 and 43 (100); (ES^+ found: MH^+ 279.2494; $C_{17}H_{32}O_2B^+$ requires 279.2490).

1-Iodo-undeca-1,3-diene



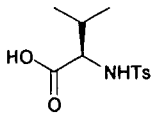
Iodine Monochloride/Sodium Methoxide Procedure

The substrate **228** (0.10 g, 0.36 mmol) was dissolved in THF (2 cm^3) with stirring under argon and cooled to -93°C. ICl (0.34 cm^3 of a 1.0M soln. in DCM, 0.34 mmol) was added dropwise and the reaction left to stir for 30 min before the addition of NaOMe (0.68 cm^3 of a 0.5M soln. in MeOH, 0.34 mmol), after 30 min the reaction was allowed to warm to room temperature. The reaction was diluted with Et_2O (20 cm^3) before washing with 5% $Na_2S_2O_5$ (20 cm^3), water (20 cm^3) and brine (20 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product **229**, exclusively the internal (*E*), external (*Z*)-isomer as a brown oil. Attempts at purification by silica column chromatography led to decomposition of the product.

Iodine/Sodium Acetate Procedure

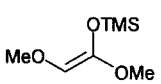
NaOAc (17.2 mg, 0.21 mmol) and I_2 (53 mg, 0.21 mmol) were dissolved with stirring under argon in dry DCM (2 cm^3) and cooled to -90°C. To this was added the substrate **228** (61 mg, 0.22 mmol) in DCM (1 cm^3) dropwise and the reaction was allowed to warm to room temperature over 20 min. The reaction was diluted with Et_2O (20 cm^3) before washing with 5% $Na_2S_2O_5$ (20 cm^3), water (20 cm^3) and brine (20 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product **236**, exclusively the internal (*Z*), external (*E*)-isomer as a brown oil. Attempts at purification by silica column chromatography led to decomposition of the product.

(*R*)-3-Methyl-2-(toluene-4-sulfonylamino)-butyric acid 255



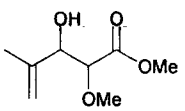
To a suspension of (*R*)-Valine (10.0 g, 85 mmol) in water (100 cm^3) cooled to 0°C was added sodium hydroxide (3.50 g, 85 mmol) portionwise with stirring over 1 h. After stirring for a further 30 min *p*-toluenesulfonyl chloride (16.3 g, 85 mmol) was added and the reaction stirred at room temperature for 5 h, 50% aq. NaOH was added to maintain the pH above 9. The reaction was filtered and the filtrate acidified until the product formed as a milky precipitate. Filtration and subsequent drying afforded the desired product **255** (15.3 g, 66%) as a white solid, mp 146°C (lit[219] 144-146°C). ν_{max}(KBr disc)/cm^{-1} 3278, 2970, 1703, 1598, 1329, 1159 and 1089; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, d, *J* 7.2 Hz, CH(C*H*$_3$)(CH$_3$)), 0.96 (3H, d, *J* 6.8 Hz, CH(CH$_3$)(C*H*$_3$)), 2.08-2.12 (1H, m, C*H*(CH$_3$)$_2$), 2.41 (3H, s, *pMe*-Ar), 3.79 (1H, dd, *J* 9.8 & 4.4 Hz, C*H*^{i}Pr), 5.09 (1H, d, *J* 9.8 Hz, N*H*), 7.28 (2H, d, *J* 8.0 Hz, Ar-*H*) and 7.72 (2H, d, *J* 8.0 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 17.1 (*C*H$_3$), 19.0 (*C*H$_3$), 21.5 (*C*H$_3$), 31.4 (*C*H(CH$_3$)$_2$), 60.5 (*C*H^{i}Pr), 127.3 (2C, Ar), 129.7 (2C, Ar), 136.6 (Ar), 143.9 (Ar) and 175.5 (*C*O$_2$H); *m/z* (ES^+) 294.0766 (MNa^+ 100%, $C_{12}H_{15}O_4NSNa^+$ requires 294.0771), 279 and 226; Elemental Analysis, found C, 52.64; H, 6.28; N, 5.16; $C_{12}H_{15}O_4NS$ requires C, 53.12; H, 6.32; N, 5.16.

((*Z*)-1,2-Dimethoxy-vinyloxy)-trimethyl-silane 256



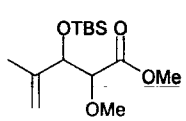
A solution of LiHMDS in THF (45 cm^3 of a 1.0M soln. in THF, 45 mmol) was cooled to -78°C with stirring under argon before the dropwise addition of methyl methoxyacetate (3.75 cm^3, 37.5 mmol) over 30 min. The reaction was then stirred for a further 30 min before the dropwise addition of TMSCl (7.34 cm^3, 56.3 mmol) over 10 min. The solution was then allowed to warm to room temperature before dilution with petroleum ether (30 cm^3), filtration and solvent removal. Repetition of this process afforded the crude product which was purified by Kugelröhr distillation, bp 120-125°C (~200 mm Hg) (lit[197] 68-71°C 35 mm Hg), to give the desired product **256** (4.72 g, 71%) as a yellow oil. Characterisation data was consistent with literature values.[198]

3-Hydroxy-2-methoxy-4-methyl-pent-4-enoic acid methyl ester 258



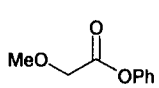
N-Ts-(*R*)-Valine **255** (4.88 g, 18.0 mmol) was dissolved with stirring under argon in DCM (100 cm^3) before cooling to 0°C allowing the dropwise addition of borane (16.4 cm^3 of a 1.0M soln. in THF, 16.4 mmol). After stirring at room temperature for 30 min the reaction was cooled to -78°C before the dropwise addition of methacrolein (1.56 cm^3, 16.4 mmol). After 15 min silyl enol ether **256** (3.18 g, 18 mmol) was also added dropwise and the reaction stirred at -78°C for 6 h. The reaction was quenched with saturated aq. $NaHCO_3$ (18 cm^3) before warming to room temperature over 30 min. The solution was diluted with Et_2O (100 cm^3) and the two phases were separated, the organic layer was washed with saturated aq. $NaHCO_3$ (120 cm^3) and brine (120 cm^3). Drying ($MgSO_4$) afforded the part-silylated crude product as a pale yellow oil. The material was redissolved in THF (120 cm^3) and cooled to -78°C before the dropwise addition of 10% aq. TFA solution (30 cm^3, 39 mmol) and the reaction left to stir for 2 h. After warming to room temperature the reaction was partitioned between Et_2O (100 cm^3) and water (100 cm^3), after phase separation the organic layer was washed with saturated aq. $NaHCO_3$ (120 cm^3) and brine (120 cm^3). Drying ($MgSO_4$) and solvent removal afforded the crude product as a yellow oil. Purification by silica column chromatography (hexane:EtOAc, 80:20) provided **258** (0.61 g, 21%) as a pale yellow oil. $[\alpha]^{23}_D$= +25.7 (*c* 0.52, $CHCl_3$); ν_{max}(film)/cm^{-1} 3493, 3078, 2953, 2833, 1747, 1650, 1438, and 1269; Major δ_H (400 MHz, $CDCl_3$); 1.80 (3H, s, C*H*$_3$), 2.57 (1H, d, *J* 5.6, O*H*), 3.46 (3H, s, O*Me*), 3.77 (3H, s, CO_2*Me*), 3.88 (1H, d, *J* 5.6, C*H*OMe), 4.29 (1H, t, *J* 5.6 , C*H*OH), 4.96-4.97 (1H, m, C=C*H*H) and 5.01-5.03 (1H, m, C=CH*H*); δ_C (100 MHz, $CDCl_3$) 18.2 (*C*H$_3$), 52.0 (CO_2*Me*), 58.9 (O*Me*), 76.2 (*C*HOMe), 82.7 (*C*HOH), 113.6 (C=*C*H$_2$), 142.9 (*C*=CH$_2$) and 170.9 (*C*O$_2$Me); Minor δ_H (400 MHz, $CDCl_3$); 1.79 (3H, s, C*H*$_3$), 2.53 (1H, d, *J* 5.4, O*H*), 3.45 (3H, s, O*Me*), 3.76 (3H, s, CO_2*Me*), 3.95 (1H, d, *J* 5.4, C*H*OMe), 4.38 (1H, t, *J* 5.4, C*H*OH), 4.96-4.97 (1H, m, C=C*H*H) and 5.01-5.03 (1H, m, C=CH*H*); δ_C (100 MHz, $CDCl_3$) 18.6 (*C*H$_3$), 51.9 (CO_2*Me*), 58.8 (O*Me*), 75.3 (*C*HOMe), 82.7 (*C*HOH), 113.4 (C=*C*H$_2$), 143.0 (*C*=CH$_2$) and 170.7 (*C*O$_2$Me); *m/z* (ES^+) 197.0782 (MNa^+ 100%, $C_8H_{14}O_4Na^+$ requires 197.0784).

3-(*tert*-Butyl-dimethyl-silanyl-oxy)-2-methoxy-4-methyl-pent-4-enoic acid methyl ester 251



The alcohol **258** (0.61 g, 3.52 mmol) was dissolved with stirring in DCM (20 cm^3) and cooled to 0°C before the addition of imidazole (0.48 g, 7.04 mmol), DMAP (22 mg, 0.18 mmol) and TBSCl (0.69 g, 4.58 mmol). The reaction was allowed to stir for 16 h before the addition of further TBSCl (0.27 g, 1.76 mmol) and left to stir for a further 2 h before quenching with saturated aq. NH_4Cl (5 cm^3). The phases were separated and the organic layer washed with saturated aq. $NaHCO_3$ (20 cm^3) and brine (20 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product as a pale yellow oil. Purification by silica column chromatography (hexane:Et_2O, 80:20) provided the product **251** (0.91 g, 89%) as a clear oil. $[\alpha]^{23}_D$= +26.1 (*c* 0.51, $CHCl_3$); ν_{max}(film)/cm^{-1} 3078, 2954, 2858, 1751, 1463, and 1256; Major δ_H (400 MHz, $CDCl_3$) 0.10 (6H, s, $OSi(CH_3)_2C(CH_3)_3$), 0.92 (9H, s, $OSi(CH_3)_2C(CH_3)_3$), 1.76 (3H, t, *J* 1.2, CH_3), 3.40 (3H, s, O*Me*), 3.70 (3H, s, CO_2Me), 3.78 (1H, d, *J* 6.3, C*H*OMe), 4.29 (1H, d, *J* 6.3, C*H*OTBS), 4.84-4.86 (1H, m, C=C*H*H) and 4.88-4.89 (1H, m, C=CH*H*); δ_C (100 MHz, $CDCl_3$) -4.9 ($OSi(CH_3)(CH_3)C(CH_3)_3$), -3.7 ($OSi(CH_3)(CH_3)C(CH_3)_3$), 17.6 (CH_3), 18.0 ($OSi(CH_3)(CH_3)C(CH_3)_3$), 25.7 ($OSi(CH_3)_2C(CH_3)_3$), 51.7 (CO_2Me), 59.1 (O*Me*), 78.4 (*C*HOMe), 85.5 (*C*HOTBS), 113.3 ($C=CH_2$), 144.3 ($C=CH_2$) and 171.7 (CO_2Me); Minor δ_H (400 MHz, $CDCl_3$) 0.10 (6H, s, $OSi(CH_3)_2C(CH_3)_3$), 0.92 (9H, s, $OSi(CH_3)_2C(CH_3)_3$), 1.75 (3H, t, *J* 1.2, CH_3), 3.35 (3H, s, O*Me*), 3.74 (1H, d, *J* 7.9, C*H*OMe), 3.76 (3H, s, CO_2Me), 4.27 (1H, d, *J* 7.9, C*H*OTBS), 4.96-4.97 (1H, m, C=C*H*H) and 5.01-5.02 (1H, m, C=CH*H*); δ_C (100 MHz, $CDCl_3$) -4.8 ($OSi(CH_3)(CH_3)C(CH_3)_3$), -2.9 ($OSi(CH_3)(CH_3)C(CH_3)_3$), 17.0 (CH_3), 18.2 ($OSi(CH_3)(CH_3)C(CH_3)_3$), 25.6 ($OSi(CH_3)_2C(CH_3)_3$), 51.8 (CO_2Me), 58.5 (O*Me*), 77.2 (*C*HOMe), 83.4 (*C*HOTBS), 114.8 ($C=CH_2$), 144.2 ($C=CH_2$) and 171.1 (CO_2Me); *m/z* (ES^+) 311.1645 (MNa^+ 100%, $C_{14}H_{28}O_4SiNa^+$ requires 311.1649).

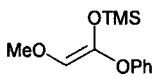
Methoxy-acetic acid phenyl ester 260



Phenol (13.0 g, 138 mmol) was dissolved with stirring under argon in dry Et_2O (150 cm^3) before the addition of Et_3N (19.0 cm^3, 138 mmol). Methoxyacetyl chloride (12.6 cm^3, 138 mmol) was added dropwise over 1 h (exotherms) resulting in the formation of a white precipitate. The reaction was stirred at room temperature for a further 3 h before being partitioned between Et_2O (150 cm^3) and water (150 cm^3), the phases were separated and the organic layer washed with brine (150 cm^3). Drying ($MgSO_4$) and solvent removal produced **260** (22.0 g, 96%) as a pale yellow oil. Further purification

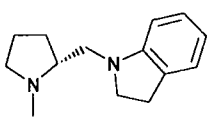
was not necessary. ν_{max}(film)/cm^{-1} 3068, 2935, 2832, 1778, 1593, 1493 and 1197; δ_H (400 MHz, $CDCl_3$) 3.54 (3H, s, O*Me*), 4.29 (2H, s, CH_2), 7.13 (2H, dd, *J* 8.4 & 0.9, Ar-*H*), 7.23-7.27 (1H, m, Ar-*H*) and 7.39 (2H, t, *J* 8.4, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 59.6 (O*Me*), 69.2 (*C*H_2), 121.4 (2C, Ar), 126.1 (Ar), 129.5 (2C, Ar), 150.2 (Ar) and 168.8 (*C*O_2Ph); *m/z* (ES^+) 166, 138, 108, 77, 65 and 45 (100); (CI^+ found: MNH_4^+ 184.0968, $C_9H_{14}O_3N^+$ requires 184.0968).

((*Z*)-2-Methoxy-1-phenoxy-vinyloxy)-trimethyl-silane 261



A solution of LiHMDS in THF (101.6 cm^3 of a 1.0M soln. in THF, 101.6 mmol) was cooled to -78°C before the dropwise addition of the ester **260** (14.1 g, 84.7 mmol) over 30 min. After stirring for a further 45 min TMSCl (16.2 cm^3, 127.1 mmol) was added dropwise, after 10 minutes the solution was warmed to room temperature before diluting with petroleum ether (60 cm^3), filtration and solvent removal. Addition of petroleum ether (60 cm^3) followed by a second filtration and removal of the solvent afforded the crude product as a yellow oil. Kugelröhr distillation yielded **261** (20.2 g, 100%) as a clear oil, bp 100-105°C (0.51 mm Hg). ν_{max}(film)/cm^{-1} 3073, 2959, 2832, 1716, 1594, 1491 and 1253; δ_H (400 MHz, $CDCl_3$) 0.18 (9H, s, OSi(CH_3)$_3$), 3.56 (3H, s, O*Me*), 5.67 (1H, s, *H*C=), 7.00-7.04 (3H, m, Ar-*H*) and 7.26-7.30 (2H, m, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 5.3 (OSi(*C*H_3)$_3$), 59.9 (O*Me*) 116.2 (2C, Ar), 120.8 (Ar), 122.3 (*C*H=), 129.2 (2C, Ar), 142.7 (Ar) and 156.8 (=*C*O_2); *m/z* (ES^+) 261, 221(100) and 189. Attempts to obtain an accurate mass value led to fragmentation so severe that only the molecular ion of ester **260** could be observed.

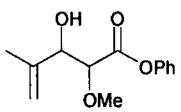
1-((2*R*)-1-Methyl-pyrrolidin-2-ylmethyl)-2,3-dihydro-1*H*-indole 263



N-Boc-(*R*)-Prolinal (8.0 g, 40.2 mmol) was dissolved with stirring under argon in DCE (160 cm^3) before the addition of indoline (4.48 cm^3, 40.2 mmol,) and the portionwise addition of sodium triacetoxyborohydride (17.0 g, 80.3 mmol). The reaction was stirred at room temperature for 20 h before quenching through the addition of saturated aq. $NaHCO_3$ (80 cm^3). The two phases were separated and the aqueous phase extracted with EtOAc (2 x 80 cm^3). Drying ($MgSO_4$) and solvent removal afforded the crude

product as light brown oil. The material was then re-dissolved with stirring under argon in dry Et_2O (100 cm^3) before cooling to 0°C. $LiAlH_4$ (223 cm^3 of a 1.0M soln. in Et_2O, 230 mmol) was added and the reaction was allowed to stir at room temperature for 3 d. The reaction was quenched through the addition of water (8.7 cm^3) followed by 3M NaOH solution (8.7 cm^3) and water (26.1 cm^3). The solution was filtered before drying ($MgSO_4$) and solvent removed to yield the product **263** (7.11 g, 82%) as a pale yellow oil. Further purification was not necessary. Characterisation data was consistent with literature values for the (*S*) enantiomer.[202] $[\alpha]^{22}_D$= +49.4 (*c* 0.5, EtOH) (lit[202] (*S*)-$[\alpha]^{28}_D$= -82.5 (*c* 1.6, EtOH)).

3-Hydroxy-2-methoxy-4-methyl-pent-4-enoic acid phenyl ester 264



Lewis Acid Mediated Approach - $Sn(OTf)_2$

A suspension of $Sn(OTf)_2$ (0.71 g, 1.71 mmol) in DCM (10 cm^3) was cooled to -78°C with stirring under argon before the dropwise addition of methacrolein (0.15 cm^3, 1.71 mmol) and silyl enol ether **261** (0.49 g, 2.05 mmol). After 5 h the reaction was warmed to room temperature before quenching with saturated aq. $NaHCO_3$ (3 cm^3) and stirring for a further 2 h. The reaction was then diluted with Et_2O (20 cm^3) and passed through celite before washing of the organic layer with brine (20 cm^3). Drying ($MgSO_4$) and solvent removal afforded the crude product as a clear oil. Purification by silica column chromatography (hexane:EtOAc, 80:20) afforded **264** (0.13 g, 32%) as a clear oil.

$Sn(OTf)_2$/Chiral Diamine Mediated Approach

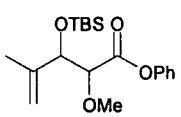
To a suspension of $Sn(OTf)_2$ (10.1 g, 24.1 mmol) in DCM (32 cm^3) stirring under argon was added the chiral amine **263** (6.3 g, 28.9 mmol) in DCM (32 cm^3) followed by dibutyltin diacetate (6.94 cm^3, 25.7 mmol). The solution was then cooled to -78°C before the dropwise addition of the silyl enol ether **261** (5.7 g, 24.1 mmol) in DCM (32 cm^3) and methacrolein (1.42 cm^3, 16.1 mmol). After stirring for 20 h the reaction was allowed to warm to room temperature before quenching with saturated aq. $NaHCO_3$ (45 cm^3). The phases were separated and the aqueous phase extracted with DCM (3 x 50 cm^3). To the combined organic extracts was added water (300 cm^3), filtration and phase separation allowed drying of the organic layer (Na_2SO_4) before solvent removal to afford the crude product as an orange oil. Washing the crude product through 40g SCX

(DCM) removed the chiral amine (recovery 82%) before solvent removal to afford the crude product as an orange oil. Purification of the product by silica column chromatography (hexane:EtOAc, 80:20) yielded the desired product **264** (1.15 g, 30%) as a pale yellow oil.

Oxazaborolidine Mediated Approach

N-Ts-(*R*)-Valine **255** (1.60 g, 6.0 mmol) was partially dissolved with stirring under argon in freshly distilled DCM (20 cm^3) and cooled to 0°C. Borane (6.0 cm^3 of a 1.0M soln. in THF, 6.0 mmol) was added dropwise and the reaction left to stir for a further 15 min before cooling to -78°C. Methacrolein (0.52 cm^3, 6.0 mmol) and the silyl-enol ether **261** (1.71 g, 7.2 mmol) were then added dropwise and the reaction was allowed to stir for 5 h at -78°C. The reaction was warmed to room temperature before quenching with saturated aq. $NaHCO_3$ (6 cm^3) and the reaction left for a further 45 min. The reaction was diluted with petroleum ether (100 cm^3) and the sample was filtered to remove the *N*-Ts-(*R*)-valine. The two phases were separated and the organic phase dried ($MgSO_4$) before solvent removal to produced the crude product as a pale yellow oil. Purification of the product by silica column chromatography (hexane:EtOAc, 80:20) yielded the desired product **264** (0.26 g, 18%) as a clear oil. $[\alpha]^{23}_D$ = +26.1 (c = 0.51 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3488, 3075, 2930, 2833, 1767, 1650, 1592, 1489 and 1192; δ_H (400 MHz, $CDCl_3$) 1.89 (3H, s, C*H*$_3$), 2.62 (1H, bs, O*H*), 3.57 (3H, s, O*Me*), 4.10 (1H, d, *J* 5.6, C*H*OMe), 4.48 (1H, t, *J* 5.6, C*H*OH), 5.05-5.07 (1H, m, =C*H*H), 5.13 (1H, s, =CH*H*), 7.10 (2H, dt, *J* 7.6 & 1.2, Ar-*H*), 7.25 (1H, tt, *J* 7.6 &1.2, Ar-*H*) and 7.37-7.41 (2H, m, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 18.2 (*C*H$_3$), 59.0 (O*Me*), 76.4 (*C*HOMe), 82.6 (*C*HOH), 114.3 (=*C*H$_2$), 121.4 (2C, Ar), 126.2 (Ar), 129.5 (2C, Ar), 142.8 (*C*=CH$_2$), 150.3 (Ar) and 169.0 (*C*O$_2$Ph); *m/z* (ES^+) 259.0939 (MNa^+ 100%, $C_{13}H_{16}O_4Na^+$ requires 259.0941), 237, 219, 187, 177 and 137; HPLC; (Daicel Chiracel OD, hexane:IPA, 90:10, 1 cm^3/min) τ_{minor} = 11.46 (9.5%), τ_{major} = 12.57 (90.5%).

3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methoxy-4-methyl-pent-4-enoic acid phenyl ester 265



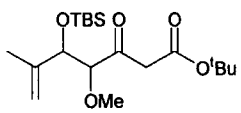
Oxazaborolidine Aldol and Direct Protection Approach

N-Ts-(R)-Valine **255** (1.60 g, 6.0 mmol) was partially dissolved with stirring under argon in freshly distilled DCM (20 cm^3) and cooled to 0°C. Borane (6.0 cm^3 of a 1.0M soln in THF, 6.0 mmol) was added dropwise and the reaction left to stir for a further 15 min before cooling to -78°C. Methacrolein (0.52 cm^3, 6.0 mmol) and the silyl-enol ether **261** (1.71 g, 7.2 mmol) were then added dropwise and the reaction was allowed to stir for 5 h at -78°C. The reaction was warmed to room temperature before quenching with saturated aq. $NaHCO_3$ (6 cm^3) and the reaction left for a further 1.5 h. The two phases were separated and the organic phase diluted with petroleum ether (200 cm^3) and washed with brine (40 cm^3). Drying ($MgSO_4$) and solvent removal afforded the part-silylated crude product, this was then redissolved in THF (15 cm^3) and cooled to -78°C. A 10% aq. TFA solution (2.3 cm^3, 3 mmol) was then added dropwise and the reaction left to stir for 1 h before warming to room temperature. The reaction mixture was partitioned between Et_2O (50 cm^3) and water (50 cm^3) before phase separation and washing of the organic layer with saturated aq. $NaHCO_3$ (40 cm^3) and brine (40 cm^3). Drying ($MgSO_4$) and solvent removal afforded the desilylated aldol product, this was redissolved with stirring under argon in dry DCM (20 cm^3) before the dropwise addition of 2,6-lutidine (1.75 cm^3, 15 mmol). The reaction was then cooled to -10°C to allow the dropwise addition of TBSOTf (1.77 cm^3, 7.8 mmol) before again warming to room temperature were it was allowed to stir for 4 h. The reaction was partitioned between Et_2O (20 cm^3) and water (40 cm^3), after phase separation the organic layer was washed with 10% HCl (25 cm^3), water (25 cm^3) and brine (25 cm^3). Drying ($MgSO_4$) and solvent removal gave the crude product as a pale yellow oil. Purification by silica column chromatography (hexane:Et_2O, 95:5) gave the protected aldol product **265** (1.49 g, 71%) as a clear oil. $[\alpha]^{23}_D$ = +35.7 (c = 0.56 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3076, 2954, 2857, 1770, 1590, 1492, 1252 and 1194; δ_H (500 MHz, $CDCl_3$) 0.08 (3H, s, $OSi(CH_3)(CH_3)C(CH_3)_3$), 0.11 (3H, s, $OSi(CH_3)(CH_3)C(CH_3)_3$), 0.91 (9H, s, $OSi(CH_3)_2C(CH_3)_3$), 1.85 (3H, s, CH_3), 3.52 (3H, s, O*Me*), 3.99 (1H, d, *J* 6.5, C*H*OMe), 4.40 (1H, d, *J* 6.5, C*H*OTBS), 4.95-4.96 (1H, m, =C*H*H), 5.01 (1H, s, =CH*H*), 7.07 (2H, dd, *J* 7.5 & 1.0, Ar-*H*), 7.23 (1H, tt, *J* 7.5 & 1.0, Ar-*H*) and 7.37 (2H, td, *J* 7.5 & 1.0, Ar-*H*); δ_C (126 MHz, $CDCl_3$) 0.2 ($OSi(CH_3)(CH_3)C(CH_3)_3$), 0.4 ($OSi(CH_3)(CH_3)C(CH_3)_3$), 22.6 (CH_3), 23.4 ($OSi(CH_3)(CH_3)C(CH_3)_3$), 30.9 ($OSi(CH_3)(CH_3)C(CH_3)_3$), 64.2 (O*Me*), 83.9 (*C*HOTBS), 90.5 (*C*HOMe), 119.4 ($C=CH_2$), 126.5 (2C, Ar), 131.1 (Ar), 134.6 (2C, Ar), 149.4 ($C=CH_2$), 155.6 (Ar) and 174.3 (CO_2Ph); *m/z* (ES^+) 373.1806 (MNa^+, $C_{19}H_{30}O_4SiNa^+$ requires 373.1806), 368, 352, 351 (100%) and 319.

Protection of the Alcohol ***264***

The alcohol **264** (1.0 g, 4.24 mmol) was dissolved with stirring under argon in DCM (25 cm^3) before the addition of imidazole (0.58 g, 8.47 mmol), DMAP (52 mg, 0.42 mmol) and TBSCl (1.27 g, 8.47 mmol). The reaction was left to proceed at room temperature for 3 d before quenching with the addition of saturated aq. NH_4Cl (5 cm^3). The phases were separated and the organic layer washed with saturated aq. $NaHCO_3$ (30 cm^3) and brine (30 cm^3). Drying ($MgSO_4$) and solvent removal yielded the crude product as yellow oil. Purification was performed by silica column chromatography (hexane:Et_2O, 90:10) to afford the desired product **265** (1.11 g, 75%) as a clear oil.

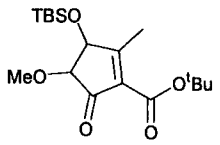
5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-6-methyl-3-oxo-hept-6-enoic acid *tert*-butyl ester 250



A solution of LiHMDS in THF (5.71 cm^3 of a 1.0M soln. in THF, 5.71 mmol,) was cooled to -78°C with stirring under argon before the dropwise addition of *tert*-butyl acetate (0.76 cm^3, 5.71 mmol). The reaction was left to stir for 15 min before the dropwise addition of the phenyl ester **265** (1.0 g, 2.85 mmol) and the reaction was left to stir for 2 h. The reaction was warmed to room temperature before quenching with 5% HCl (5 cm^3). Dilution with Et_2O (40 cm^3) allowed washing with 5% HCl (20 cm^3), saturated aq. $NaHCO_3$ (20 cm^3) and brine (20 cm^3). Drying ($MgSO_4$) and solvent removal afforded the crude product which was purified by silica column chromatography (hexane:Et_2O, 95:5) to give the desired product **250** (0.85 g, 80%) as a clear liquid. $[\alpha]^{23}_D$ = +50.3 (c = 0.53 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3075, 2955, 2857, 1742, 1721, 1651, 1472, 1252 and 1159; δ_H (400 MHz, $CDCl_3$) 0.01 (3H, s, $OSi(CH_3)(CH_3)C(CH_3)_3$), 0.03 (3H, $OSi(CH_3)(CH_3)C(CH_3)_3$), 0.89 (9H, s, $OSi(CH_3)(CH_3)C(CH_3)_3$), 1.46 (9H, s, $OC(CH_3)_3$), 1.74 (3H, s, CH_3), 3.37 (1H, d, *J* 16.2, CHH), 3.40 (3H, s, O*Me*), 3.64 (1H, d, *J* 16.2, CHH), 3.71 (1H, d, *J* 4.4, CHOMe), 4.29 (1H, d, *J* 4.4, CHOTBS), 4.91-4.92 (1H, m, C=CHH) and 5.01-5.02 (1H, m, C=CHH); δ_C (100 MHz, $CDCl_3$) 0.0 ($OSi(CH_3)(CH_3)C(CH_3)_3$), 0.2 ($OSi(CH_3)(CH_3)C(CH_3)_3$), 23.4 ($OSi(CH_3)(CH_3)C(CH_3)_3$), 23.9 (CH_3), 31.1 ($OSi(CH_3)(CH_3)C(CH_3)_3$), 33.3 ($OC(CH_3)_3$), 53.3 (CH_2), 65.2 (O*Me*), 82.6 (CHOMe), 86.9 ($OC(CH_3)_3$), 95.2 (CHOTBS), 118.7 ($C=CH_2$), 149.0 ($C=CH_2$), 171.9 (CO_2tBu)

and 210.2 (*C*=O); *m/z* (ES^+) 395.2229 (MNa^+, $C_{19}H_{36}O_5SiNa^+$ requires 395.2224), 390, 377, 359, 317, 247 and 185 (100%). For the racemic solid form, mp 37-38°C; Elemental Analysis, found C, 61.22; H, 9.86; $C_{19}H_{36}O_5Si$ requires C, 61.25; H, 9.74.

3-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-2-methyl-5-oxo-cyclopent-1-enecarboxylic acid *tert*-butyl ester 248



The substrate **250** (0.10 g, 0.27 mmol) was dissolved in MeOH (3 cm^3) and cooled to -78°C. Ozone was bubbled through the solution until a blue/purple colour persisted, at which point oxygen was passed through to remove the excess ozone. Solid supported PPh_3 (0.15 g of 3 mmol/g, 0.45 mmol) was then added and the reaction allowed to warm to room temperature with stirring over 30 min. The reaction was filtered and the solution cooled to 0°C before the addition of K_2CO_3 (75 mg, 0.54 mmol), the solution was left to stir for 1 h. The reaction was quenched through the addition of water (4 cm^3) before extracting with DCM (3 x 10 cm^3). Drying ($MgSO_4$) and solvent removal afforded the crude product as a yellow/orange oil. Purification was performed by silica column chromatography (hexane:Et_2O, 85:15) to afford the desired product **248** (31 mg, 32%) as a clear oil. $[\alpha]^{23}_D$ = +62.8 (c = 0.53 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2956, 2858, 1731, 1713, 1637, 1472, 1368, 1254 and 1156; δ_H (500 MHz, $CDCl_3$) 0.15 (3H, s, OSi(C*H*$_3$)(CH_3)C(CH_3)$_3$), 0.16 (3H, s, OSi(CH_3)(C*H*$_3$)C(CH_3)$_3$), 0.93 (9H, s, OSi(CH_3)(CH_3)C(C*H*$_3$)$_3$), 1.53 (9H, s, OC(C*H*$_3$)$_3$), 2.28 (3H, d, *J* 1.0, C*H*$_3$), 3.67 (3H, s, O*Me*), 3.75 (1H, d, *J* 3.5, C*H*OMe) and 4.49 (1H, dd, *J* 3.5 & 1.0, C*H*OTBS); δ_C (126 MHz, $CDCl_3$) 0.00 (OSi(*C*H$_3$)(CH_3)C(CH_3)$_3$), 0.6 (OSi(CH_3)(*C*H$_3$)C(CH_3)$_3$), 20.3 (*C*H$_3$), 23.3 (OSi(CH_3)(CH_3)*C*(CH_3)$_3$), 30.9 (OSi(CH_3)(CH_3)C(*C*H$_3$)$_3$), 33.4 (OC(*C*H$_3$)$_3$), 64.4 (O*Me*), 81.7 (*C*HOTBS), 87.5 (O*C*(CH_3)$_3$), 94.1 (*C*HOMe), 137.1 (alkenic), 166.9 (alkenic), 181.5 (*C*O$_2$*t*Bu) and 202.6 (*C*=O); *m/z* (ES^+) 379.1911 (MNa^+100%, $C_{18}H_{32}O_5SiNa^+$ requires 379.1911), 349, 323 and 245.

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Appendix A – Crystallographic Data

3-Bromopyridine-iodinemonochloride 181 (04srv082)

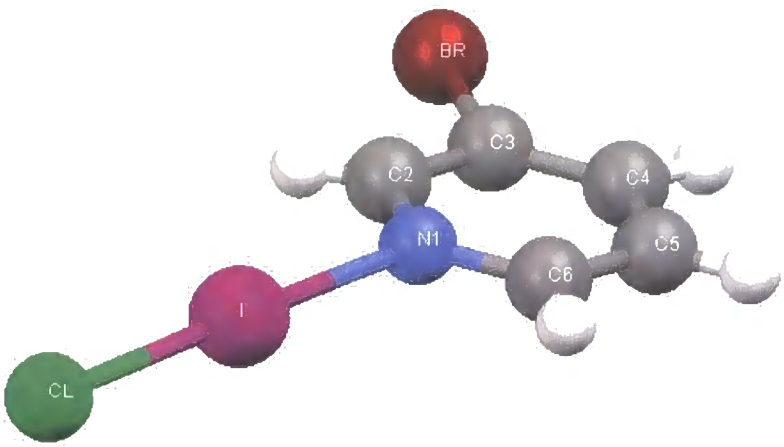

Table 1. Crystal data and structure refinement for **181**.

Empirical formula	C5 H4 Br Cl I N	
Formula weight	320.35	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*C*2/*c* (No. 15)	
Unit cell dimensions	a = 21.337(3) Å	α= 90°
	b = 4.174(1) Å	β= 94.38(1)°
	c = 18.384(3) Å	γ = 90°
Volume	1632.5(5) Å^3	
Z	8	
Density (calculated)	2.607 g/cm^3	
Absorption coefficient	9.060 mm^{-1}	
F(000)	1168	
Crystal size	0.28 × 0.05 × 0.03 mm^3	
θ range for data collection	2.82 to 30.00°.	
Index ranges	$-30 \leq h \leq 30$, $-5 \leq k \leq 5$, $-25 \leq l \leq 25$	
Reflections collected	9303	
Independent reflections	2372 [R(int) = 0.0537]	
Reflections with I>2σ(I)	2054	
Completeness to θ = 30.00°	99.8 %	

Absorption correction	Integration
Max. and min. transmission	0.8181 and 0.1702
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2372 / 0 / 98
Largest final shift/e.s.d. ratio	0.003
Goodness-of-fit on F^2	0.928
Final R indices [I>2σ(I)]	R1 = 0.0202, wR2 = 0.0378
R indices (all data)	R1 = 0.0254, wR2 = 0.0387
Largest diff. peak and hole	0.858 and -0.688 e.$Å^{-3}$

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^4$) for **181**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
I	4084.86(7)	8591.4(3)	5554.18(7)	161.9(5)
Br	2273.6(1)	1679.3(6)	3469.6(1)	274.7(7)
Cl	4360.5(3)	11023.2(1)	6763.3(3)	216(1)
N(1)	3828(1)	6148(4)	4423(1)	171(4)
C(2)	3249(1)	4972(6)	4273(1)	184(5)
C(3)	3100(1)	3259(5)	3639(1)	181(5)
C(4)	3552(1)	2734(6)	3150(1)	201(5)
C(5)	4148(1)	3986(6)	3312(1)	211(5)
C(6)	4272(1)	5685(6)	3953(1)	198(5)

Table 3. Bond lengths [Å] and angles [°] for **181**.

I-N(1)	2.3437(18)	C(3)-C(4)	1.386(3)
I-Cl	2.4734(7)	C(4)-C(5)	1.387(3)
Br-C(3)	1.886(2)	C(4)-H(4)	0.99(2)
N(1)-C(2)	1.339(3)	C(5)-C(6)	1.384(3)
N(1)-C(6)	1.342(3)	C(5)-H(5)	0.97(3)
C(2)-C(3)	1.383(3)	C(6)-H(6)	0.95(3)
C(2)-H(2)	0.88(3)		
N(1)-I-Cl	178.43(5)	C(3)-C(4)-C(5)	118.3(2)
C(2)-N(1)-C(6)	120.0(2)	C(3)-C(4)-H(4)	123.9(16)
C(2)-N(1)-I	119.42(15)	C(5)-C(4)-H(4)	117.9(16)
C(6)-N(1)-I	120.34(16)	C(6)-C(5)-C(4)	119.2(2)
N(1)-C(2)-C(3)	120.8(2)	C(6)-C(5)-H(5)	122.6(16)
N(1)-C(2)-H(2)	114.4(17)	C(4)-C(5)-H(5)	118.2(16)
C(3)-C(2)-H(2)	124.5(17)	N(1)-C(6)-C(5)	121.6(2)
C(2)-C(3)-C(4)	120.1(2)	N(1)-C(6)-C(6)	117.6(15)
C(2)-C(3)-Br	118.18(17)	C(5)-C(6)-H(6)	120.8(15)
C(4)-C(3)-Br	121.67(18)		

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for **181**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\, h^2\, a^{*2}U_{11} + \ldots + 2\, h\, k\, a^*\, b^*\, U_{12}\,]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
I	15.33(8)	16.46(8)	16.74(8)	2.06(5)	1.01(5)	-0.62(6)
Br	16.0(1)	31.8(1)	34.4(1)	-7.4(1)	0.4(1)	-3.3(1)
Cl	21.8(3)	26.3(3)	16.5(3)	0.3(2)	1.0(2)	-4.3(2)
N(1)	17(1)	18(1)	17(1)	2(1)	1(1)	2(1)
C(2)	18(1)	19(1)	19(1)	1(1)	5(1)	2(1)
C(3)	15(1)	16(1)	22(1)	2(1)	-1(1)	1(1)
C(4)	20(1)	21(1)	19(1)	-1(1)	-1(1)	3(1)
C(5)	18(1)	26(1)	20(1)	2(1)	6(1)	3(1)
C(6)	16(1)	20(1)	23(1)	4(1)	1(1)	0(1)

Table 5. Hydrogen coordinates ($\times 10^3$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **181**.

	x	y	z	U(iso)
H(2)	300(1)	522(6)	462(1)	20(7)
H(4)	347(1)	151(6)	269(1)	24(7)
H(5)	446(1)	366(6)	296(1)	30(7)
H(6)	468(1)	659(6)	408(1)	19(7)

2,2'-Bipyridine-diiodinemonochloride 182 (04srv083)

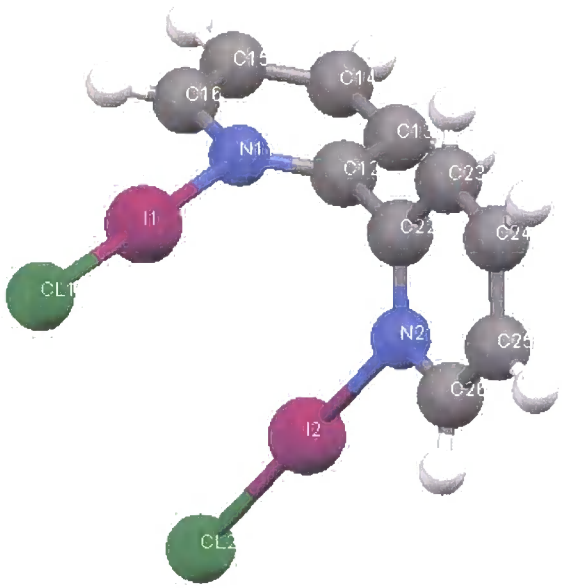

Table 1. Crystal data and structure refinement for **182**.

Empirical formula	C10 H8 Cl2 I2 N2	
Formula weight	480.88	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$ (No. 14, non-standard setting)	
Unit cell dimensions	a = 10.073(1) Å	α= 90°
	b = 12.141(7) Å	β= 101.67(1)°
	c = 11.859(1) Å	γ = 90°
Volume	1420.3(8) $Å^3$	
Z	4	
Density (calculated)	2.249 g/cm^3	
Absorption coefficient	4.781 mm^{-1}	
F(000)	888	

Crystal size	0.50 × 0.16 × 0.07 mm^3
θ range for data collection	2.42 to 30.00°.
Index ranges	$-13 \leq h \leq 14, -17 \leq k \leq 17, -16 \leq l \leq 16$
Reflections collected	19301
Independent reflections	4128 [R(int) = 0.0942]
Reflections with I>2σ(I)	3867
Completeness to θ = 30.00°	99.7 %
Absorption correction	Integration
Max. and min. transmission	0.7597 and 0.1521
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4128 / 0 / 177
Largest final shift/e.s.d. ratio	0.001
Goodness-of-fit on F^2	1.067
Final R indices [I>2σ(I)]	R1 = 0.0244, wR2 = 0.0607
R indices (all data)	R1 = 0.0261, wR2 = 0.0616
Largest diff. peak and hole	1.192 and -0.726 e.$Å^{-3}$

Table 2. Atomic coordinates (×10^4) and equivalent isotropic displacement parameters ($Å^2$ ×10^4) for **182**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
I(1)	1681(1)	1233(1)	5448(1)	190(1)
I(2)	2880(1)	4577(1)	5698(1)	188(1)
Cl(1)	1835(1)	183(1)	3668(1)	288(1)
Cl(2)	1409(1)	5947(1)	4478(1)	256(1)
N(11)	1529(2)	2192(2)	7111(2)	191(3)
N(21)	4310(2)	3236(2)	6708(2)	195(3)
C(12)	2603(2)	2691(2)	7774(2)	172(4)
C(13)	2461(2)	3318(2)	8715(2)	229(4)
C(14)	1167(3)	3456(2)	8959(2)	248(4)
C(15)	79(2)	2936(2)	8281(2)	247(4)
C(16)	298(2)	2293(2)	7369(2)	237(4)
C(22)	3956(2)	2530(2)	7467(2)	180(4)
C(23)	4803(2)	1675(2)	7943(2)	243(4)
C(24)	6033(3)	1535(2)	7599(2)	257(5)
C(25)	6393(2)	2273(2)	6824(2)	251(5)
C(26)	5519(2)	3122(2)	6398(2)	241(4)

Table 3. Bond lengths [Å] and angles [°] for **182**.

I(1)-N(11)	2.3214(18)	C(12)-C(22)	1.493(3)
I(1)-Cl(1)	2.4974(7)	C(13)-C(14)	1.401(3)
I(2)-N(21)	2.337(2)	C(14)-C(15)	1.375(4)
I(2)-Cl(2)	2.4878(9)	C(15)-C(16)	1.387(3)
N(11)-C(16)	1.342(3)	C(22)-C(23)	1.390(3)
N(11)-C(12)	1.346(3)	C(23)-C(24)	1.390(3)
N(21)-C(22)	1.343(3)	C(24)-C(25)	1.384(4)
N(21)-C(26)	1.349(3)	C(25)-C(26)	1.382(3)
C(12-C(13)	1.382(3)		
N(11)-I(1)-Cl(1)	179.41(5)	C(12)-C(13)-C(14)	119.0(2)
N(21)-I(2)-Cl(2)	175.33(5)	C(15)-C(14)-C(13)	119.3(2)
C(16)-N(11)-C(12)	119.77(19)	C(14)-C(15)-C(16)	118.8(2)
C(16)-N(11)-I(1)	117.52(16)	N(11)-C(16)-C(15)	121.9(2)
C(12)-N(11)-I(1)	122.61(14)	N(21)-C(22)-C(23)	121.6(2)
C(22)-N(21)-C(26)	119.6(2)	N(21)-C(22)-C(12)	117.38(19)
C(22)-N(21)-I(2)	124.65(14)	C(23)-C(22)-C(12)	120.98(19)
C(26)-N(21)-I(2)	115.44(15)	C(22)-C(23)-C(24)	118.9(2)
N(11)-C(12)-C(13)	121.2(2)	C(25)-C(24)-C(23)	119.0(2)
N(11)-C(12)-C(22)	117.67(18)	C(26)-C(25)-C(24)	119.5(2)
C(13)-C(12)-C(22)	121.1(2)	N(21)-C(26)-C(25)	121.4(2)

Table 3a. Torsion angles [°] for **182**.

I(2)-N(21)-C(22)-C(12)	-6.5(3)
N(21)-C(22)-C(12)-N(11)	88.0(2)
C(22)-C(12)-N(11)-I(1)	-5.2(3)

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^4$) for **182**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
I(1)	188(1)	178(1)	194(1)	-18(1)	17(1)	5(1)
I(2)	206(1)	162(1)	203(1)	9(1)	62(1)	-13(1)
Cl(1)	391(3)	260(3)	214(2)	-49(2)	64(2)	13(2)
Cl(2)	296(3)	216(3)	268(3)	63(2)	84(2)	47(2)
N(11)	175(9)	185(8)	209(8)	-26(6)	29(7)	2(6)
N(21)	162(9)	196(9)	221(8)	6(7)	27(7)	-13(6)
C(12)	168(10)	172(9)	178(9)	23(7)	38(8)	13(7)
C(13)	234(11)	239(11)	214(10)	-31(8)	45(9)	-10(8)
C(14)	273(12)	262(11)	222(10)	-18(9)	79(9)	38(9)
C(15)	193(11)	296(12)	263(11)	8(9)	70(9)	34(8)
C(16)	164(10)	273(11)	268(11)	-39(9)	26(9)	1(8)
C(22)	166(10)	188(9)	184(9)	-25(7)	34(8)	-5(7)
C(23)	231(11)	276(12)	225(10)	44(9)	54(9)	34(9)
C(24)	223(11)	314(12)	231(11)	19(9)	43(9)	72(9)
C(25)	168(11)	322(12)	262(11)	-8(9)	41(9)	27(8)
C(26)	197(11)	261(11)	280(11)	4(9)	84(9)	-19(8)

Table 5. Hydrogen coordinates ($\times 10^3$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **182**.

	x	y	z	U(iso)
H(13)	323(4)	372(3)	918(3)	41(9)
H(14)	103(4)	386(3)	957(3)	33(8)
H(15)	-89(3)	300(3)	843(3)	29(8)
H(16)	-48(3)	188(3)	689(3)	28(8)
H(23)	454(3)	130(3)	852(3)	30(8)
H(24)	659(3)	98(2)	792(2)	15(6)
H(25)	725(4)	227(3)	663(3)	40(9)
H(26)	568(3)	362(3)	578(3)	26(7)

2,6-Lutidine-iodinemonochloride 183 (04srv159)

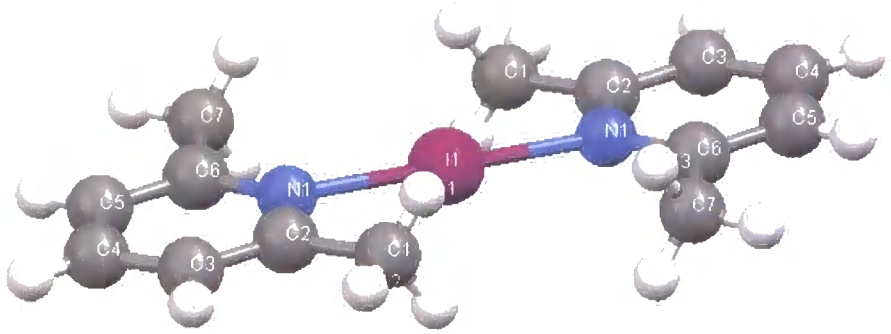

Table 1. Crystal data and structure refinement for **183**.

Empirical formula	C7 H9 Cl I N	
Formula weight	269.50	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$ (No. 2)	
Unit cell dimensions	a = 7.3067(12) Å	α= 98.436(3)°
	b = 8.2529(13) Å	β= 103.498(3)°
	c = 8.5370(14) Å	γ = 111.922(3)°
Volume	448.50(13) Å^3	
Z	2	
Density (calculated)	1.996 g/cm^3	
Absorption coefficient	3.796 mm^{-1}	
F(000)	256	
Crystal size	0.24 × 0.23 × 0.13 mm^3	
θ range for data collection	2.54 to 30.53°.	
Index ranges	$-10 \leq h \leq 10, -11 \leq k \leq 11, -12 \leq l \leq 12$	
Reflections collected	5502	
Independent reflections	2699 [R(int) = 0.0135]	
Reflections with I>2σ(I)	2498	
Completeness to θ = 30.53°	98.2 %	
Absorption correction	Integration	
Max. and min. transmission	0.6772 and 0.4862	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2699 / 0 / 130
Largest final shift/e.s.d. ratio	0.001
Goodness-of-fit on F^2	1.071
Final R indices [I>2σ(I)]	R1 = 0.0158, wR2 = 0.0384
R indices (all data)	R1 = 0.0174, wR2 = 0.0392
Largest diff. peak and hole	0.376 and -0.663 e.Å^{-3}

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å^2 $\times 10^4$) for **183**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
I(1)	5000	5000	5000	149(1)
I(2)	10000	10000	5000	165(1)
Cl	8599(1)	8423(1)	6991(1)	283(1)
N(1)	3463(2)	4875(2)	2280(2)	150(2)
C(1)	3169(3)	1768(2)	1517(2)	227(3)
C(2)	2965(2)	3389(2)	1054(2)	170(3)
C(3)	2274(3)	3383(2)	-606(2)	215(3)
C(4)	2106(3)	4901(2)	-1015(2)	228(3)
C(5)	2580(2)	6384(2)	255(2)	209(3)
C(6)	3239(2)	6349(2)	1909(2)	169(3)
C(7)	3680(3)	7915(2)	3307(2)	222(3)

Table 3. Bond lengths [Å] and angles [°] for **183**.

I(1)-N(1)	2.9997(12)	C(3)-C(4)	1.390(2)
I(1)-N(1)#1	2.2997(12)	C(3)-H(3)	0.97(3)
I(2)-Cl#2	2.5421(5)	C(4)-C(5)	1.383(2)
I(2)-Cl	2.5421(5)	C(4)-H(4)	0.97(2)
N(1)-C(2)	1.3583(19)	C(5)-C(6)	1.390(2)
N(1)-C(6)	1.3583(18)	C(5)-H(5)	0.925(18)
C(1)-C(2)	1.498(2)	C(6)-C(7)	1.501(2)
C(1)-H(11)	0.91(2)	C(7)-H(71)	0.98(2)
C(1)-H(12)	1.12(3)	C(7)-H(72)	0.96(2)
C(1)-H(13)	0.97(2)	C(7)-H(73)	0.98(2)
C(2)-C(3)	1.387(2)		
N(1)-I(1)-N(1)#1	180.0	C(4)-C(3)-H(3)	121.0(16)
Cl#2-I(2)-Cl	180.0	C(5)-C(4)-C(3)	118.88(15)
C(2)-N(1)-C(6)	120.88(13)	C(5)-C(4)-H(4)	121.1(13)
C(2)-N(1)-I(1)	119.39(9)	C(3)-C(4)-H(4)	120.0(13)
C(6)-N(1)-I(1)	119.46(10)	C(4)-C(5)-C(6)	120.04(15)
C(2)-C(1)-H(11)	112.3(13)	C(4)-C(5)-H(5)	122.1(11)
C(2)-C(1)-H(12)	105.6(15)	C(6)-C(5)-H(5)	117.9(11)
H(11)-C(1)-H(12)	108.1(19)	N(1)-C(6)-C(5)	120.07(14)
C(2)-C(1)-H(13)	113.7(13)	N(1)-C(6)-C(7)	119.03(13)
H(11)-C(1)-H(13)	109.3(17)	C(5)-C(6)-C(7)	120.90(14)
H(12)-C(1)-H(13)	107.5(19)	C(6)-C(7)-H(71)	112.1(14)
N(1)-C(2)-C(3)	120.00(14)	C(6)-C(7)-H(72)	110.6(13)
N(1)-C(2)-C(1)	119.25(13)	H(71)-C(7)-H(72)	105.3(18)
C(3)-C(2)-C(1)	120.75(14)	C(6)-C(7)-H(73)	111.5(13)
C(2)-C(3)-C(4)	120.07(15)	H(71)-C(7)-H(73)	108.1(18)
C(2)-C(3)-H(3)	118.9(16)	H(72)-C(7)-H(73)	108.9(18)

Symmetry transformations used to generate equivalent atoms: #1 -x+1,-y+1,-z+1 #2 -x,-y+2,-z+1

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^4$) for **183**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U_{11} + \ldots + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
I(1)	173(1)	154(1)	124(1)	47(1)	42(1)	74(1)
I(2)	178(1)	208(1)	116(1)	42(1)	37(1)	94(1)
Cl	331(2)	391(2)	239(2)	178(2)	99(2)	232(2)
N(1)	165(6)	163(6)	131(5)	52(4)	45(4)	75(5)
C(1)	314(9)	174(7)	204(7)	40(6)	80(6)	118(6)
C(2)	174(6)	175(6)	158(6)	33(5)	54(5)	73(5)
C(3)	222(7)	246(8)	146(7)	15(6)	36(6)	91(6)
C(4)	219(7)	321(9)	154(7)	98(6)	49(6)	116(7)
C(5)	206(7)	265(8)	210(7)	125(6)	75(6)	129(6)
C(6)	163(6)	171(6)	196(7)	70(5)	65(5)	82(5)
C(7)	294(8)	184(7)	214(7)	53(6)	70(6)	136(6)

Table 5. Hydrogen coordinates ($\times 10^3$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **183**.

	x	y	z	U(iso)
H(11)	237(3)	132(3)	216(2)	21(5)
H(12)	258(4)	71(4)	31(4)	60(8)
H(13)	460(3)	198(3)	206(3)	32(6)
H(3)	199(4)	233(4)	-147(3)	57(8)
H(4)	164(3)	490(3)	-218(3)	30(5)
H(5)	246(3)	741(2)	5(2)	31(8)
H(71)	286(4)	755(3)	405(3)	38(6)
H(72)	329(3)	880(3)	288(3)	34(6)
H(73)	515(4)	850(3)	397(3)	37(6)

2,4,6-Collidine-iodinemonochloride 184 (04srv175)

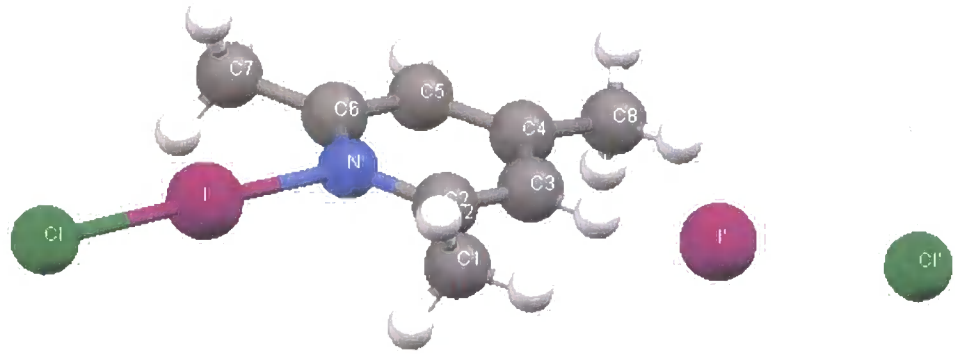

Table 1. Crystal data and structure refinement for **184**.

Empirical formula	C8 H11 Cl I N	
Formula weight	283.53	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Hexagonal	
Space group	$P6_1$ (No. 161)	
Unit cell dimensions	a = 9.1915(12) Å	α= 90°
	b = 9.1915(12) Å	β= 90°
	c = 21.005(3) Å	γ = 120°
Volume	1536.8(4) Å^3	
Z	6	
Density (calculated)	1.838 g/cm^3	
Absorption coefficient	3.329 mm^{-1}	
F(000)	816	
Crystal size	0.29 × 0.10 × 0.03 mm^3	
θ range for data collection	2.56 to 30.51°.	
Index ranges	$-13 \leq h \leq 13$, $-13 \leq k \leq 12$, $-30 \leq l \leq 29$	
Reflections collected	18238	
Independent reflections	3120 [R(int) = 0.0855]	
Reflections with I>2σ(I)	3015	
Completeness to θ = 30.51°	100.0 %	
Absorption correction	Integration	
Max. and min. transmission	0.9107 and 0.5352	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	3120 / 1 / 111
Largest final shift/e.s.d. ratio	0.010
Goodness-of-fit on F^2	1.207
Final R indices [I>2σ(I)]	R1 = 0.0453, wR2 = 0.0998
R indices (all data)	R1 = 0.0481, wR2 = 0.1011
Absolute structure parameter	0.03(4)
Largest diff. peak and hole	1.406 and -1.330 e.Å^{-3}

Disorder: The molecule shows minor disorder by a 120\% rotation in its plane, the alternative positions of the ICl group (I'Cl', occupancy 3%) nearly overlaps with the major positions of the ICl group of the adjacent molecule, related by the *a* translation.

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å^2 $\times 10^4$) for **184**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
I	4386.0(4)	3440.7(5)	3650	196(1)
Cl	7564(2)	5004(2)	3606(1)	343(4)
I'	-2660(20)	3690(20)	3547(8)	380(30)
Cl'	-5030(50)	4380(60)	3545(18)	150(70)
N	1505(6)	2025(6)	3671(2)	219(8)
C(1)	1631(9)	4749(7)	3499(3)	253(12)
C(2)	647(6)	2863(7)	3583(3)	188(10)
C(3)	-1044(7)	2052(8)	3584(2)	223(10)
C(4)	-2006(7)	289(8)	3660(3)	248(11)
C(5)	-1102(8)	-567(8)	3739(2)	218(11)
C(6)	641(7)	313(8)	3742(2)	213(10)
C(7)	1591(9)	-587(8)	3836(3)	251(12)
C(8)	-3871(7)	-652(9)	3615(4)	298(12)

Table 3. Bond lengths [Å] and angles [°] for **184**.

I-N	2.294(5)	C(2)-C(3)	1.347(8)
I-Cl	2.5312(16)	C(3)-C(4)	1.415(8)
I'-Cl'	2.55(4)	C(4)-C(5)	1.411(8)
I'-C(3)	2.588(17)	C(4)-C(8)	1.488(7)
N-C(2)	1.363(7)	C(5)-C(6)	1.387(8)
N-C(6)	1.371(8)	C(6)-C(7)	1.486(8)
C(1)-C(2)	1.512(8)		
N-I-Cl	179.05(14)	C(2)-C(3)-I'	121.1(6)
Cl'-I'-C(3)	162.1(13)	C(4)-C(3)-I'	117.2(5)
C(2)-N-C(6)	119.8(5)	C(5)-C(4)-C(3)	116.5(5)
C(2)-N-I	120.5(4)	C(5)-C(4)-C(8)	120.8(6)
C(6)-N-I	119.7(4)	C(3)-C(4)-C(8)	122.5(5)
C(3)-C(2)-N	121.4(6)	C(6)-C(5)-C(4)	120.4(6)
C(3)-C(2)-C(1)	119.9(5)	N-C(6)-C(5)	120.4(5)
N-C(2)-C(1)	118.7(5)	N-C(6)-C(7)	119.2(5)
C(2)-C(3)-C(4)	121.4(6)	C(5)-C(6)-C(7)	120.3(6)

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for **184**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U_{11} + \ldots + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
I	21.8(2)	18.3(2)	18.0(1)	-0.1(1)	1.6(2)	9.4(2)
Cl	22.8(7)	20.5(6)	61(1)	1.3(8)	8.4(8)	12.0(5)
N	23(2)	29(2)	15(2)	-1(2)	-1(2)	14(2)
C(1)	33(3)	17(2)	30(3)	0(2)	1(2)	15(2)
C(2)	16(2)	24(2)	19(2)	-9(2)	-9(2)	12(2)
C(3)	31(3)	33(3)	9(2)	5(2)	2(2)	20(3)
C(4)	28(3)	35(3)	17(2)	-9(2)	-8(3)	20(2)
C(5)	27(3)	25(3)	15(2)	-4(2)	-1(2)	14(2)
C(6)	27(3)	29(3)	10(2)	-1(2)	-4(2)	15(2)
C(7)	33(3)	24(3)	23(3)	-2(2)	-2(2)	18(3)
C(8)	20(3)	41(3)	29(3)	4(3)	0(3)	16(3)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **184**.

	x	y	z	U(iso)
H(11)	2386	5040	3132	38
H(12)	2293	5262	3884	38
H(13)	852	5170	3430	38
H(3)	-1597	2682	3527	27
H(5)	-1694	-1752	3792	26
H(71)	2402	-297	3488	38
H(72)	820	-1803	3839	38
H(73)	2191	-240	4243	38
H(81)	-4201	-1271	3211	45
H(82)	-4305	130	3630	45
H(83)	-4345	-1449	3970	45

DMAP-iodinemonochloride 185 (04srv160)

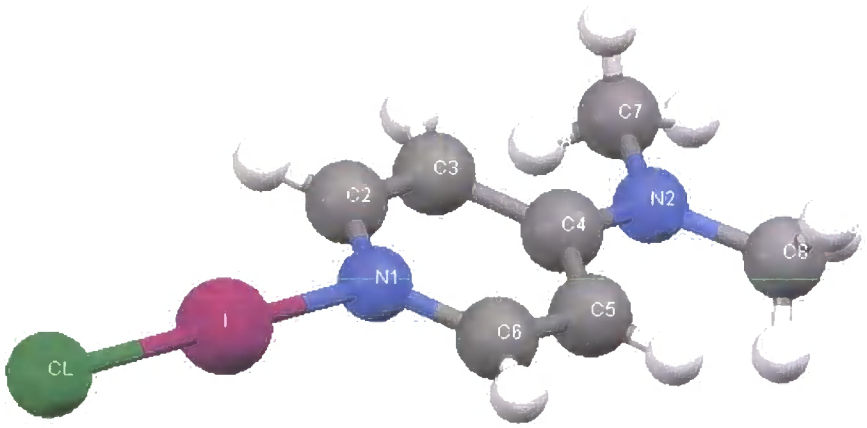

Table 1. Crystal data and structure refinement for **185**.

Empirical formula	C7 H10 Cl I N2	
Formula weight	284.52	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$ (No. 14)	
Unit cell dimensions	a = 8.4864(9) Å	α= 90°

	b = 7.4207(7) Å	β= 105.19(2)°
	c = 15.8671(16) Å	γ = 90°
Volume	964.32(17) Å^3	
Z	4	
Density (calculated)	1.960 g/cm^3	
Absorption coefficient	3.540 mm^{-1}	
F(000)	544	
Crystal size	0.50 × 0.11 × 0.03 mm^3	
θ range for data collection	2.49 to 29.99°.	
Index ranges	$-11 \leq h \leq 11, -10 \leq k \leq 10, -22 \leq l \leq 22$	
Reflections collected	16640	
Independent reflections	2813 [R(int) = 0.0250]	
Reflections with I>2σ(I)	2541	
Completeness to θ = 29.99°	100.0 %	
Absorption correction	Integration	
Max. and min. transmission	0.8957 and 0.2356	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2813 / 0 / 104	
Largest final shift/e.s.d. ratio	0.003	
Goodness-of-fit on F^2	1.056	
Final R indices [I>2σ(I)]	R1 = 0.0219, wR2 = 0.0544	
R indices (all data)	R1 = 0.0245, wR2 = 0.0557	
Largest diff. peak and hole	1.538 and -0.656 e.Å^{-3}	

Table 2. Atomic coordinates (×10^4) and equivalent isotropic displacement parameters (Å^2 ×10^4) for **185**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
I	-1471.8(2)	3410.9(2)	3830.43(8)	225.6(5)
Cl	-3412.4(7)	3233.6(8)	4821.8(4)	300(1)
N(1)	215(2)	3533(2)	2952(1)	228(3)
N(2)	3295(2)	3700(3)	1300(1)	244(4)
C(2)	-362(3)	3251(3)	2084(1)	232(4)
C(3)	613(3)	3293(3)	1519(1)	222(4)
C(4)	2305(3)	3656(3)	1836(1)	215(4)
C(5)	2876(3)	3967(3)	2749(1)	244(4)
C(6)	1820(3)	3904(3)	3266(1)	260(4)
C(7)	2664(3)	3384(3)	365(2)	281(5)
C(8)	5012(3)	4188(4)	1627(2)	349(5)

Table 3. Bond lengths [Å] and angles [°] for **185**.

I-N(1)	2.2462(19)	N(2)-C(7)	1.459(3)
I-Cl	2.5615(7)	C(2)-C(3)	1.370(3)
N(1)-C(6)	1.350(3)	C(3)-C(4)	1.417(3)
N(1)-C(2)	1.351(3)	C(4)-C(5)	1.421(3)
N(2)-C(4)	1.343(3)	C(5)-C(6)	1.365(3)
N(2)-C(8)	1.458(3)		
N(1)-I-Cl	179.24(5)	N(1)-C(2)-C(3)	122.9(2)
C(6)-N(1)-C(2)	117.91(19)	C(2)-C(3)-C(4)	120.1(2)
C(6)-N(1)-I	121.65(15)	N(2)-C(4)-C(3)	121.6(2)
C(2)-N(1)-I	120.44(14)	N(2)-C(4)-C(5)	122.55(19)
C(4)-N(2)-C(8)	120.90(19)	C(3)-C(4)-C(5)	115.84(19)
C(4)-N(2)-C(7)	121.07(18)	C(6)-C(5)-C(4)	120.3(2)
C(8)-N(2)-C(7)	117.90(19)	N(1)-C(6)-C(5)	122.9(2)

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^4$) for **185**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U_{11} + \ldots + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
I	248.3(8)	226.8(8)	209.6(8)	-15.5(5)	74.0(5)	-4.8(4)
Cl	302(3)	357(3)	278(3)	-48(2)	142(2)	-35(2)
N(1)	238(8)	229(8)	219(8)	0(6)	67(7)	-27(6)
N(2)	197(8)	320(9)	216(8)	-8(7)	56(7)	10(7)
C(2)	220(9)	245(10)	231(10)	-23(8)	59(8)	-7(7)
C(3)	224(9)	256(10)	184(9)	-20(7)	51(7)	2(7)
C(4)	213(9)	197(9)	232(9)	-3(7)	54(7)	23(7)
C(5)	227(9)	277(10)	211(9)	9(8)	27(8)	-7(8)
C(6)	300(10)	280(10)	190(9)	-1(8)	46(8)	-10(8)
C(7)	298(11)	350(12)	209(10)	-29(8)	92(8)	-26(8)
C(8)	204(10)	531(15)	308(12)	21(11)	58(9)	-26(10)

Table 5. Hydrogen coordinates ($\times 10^3$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **185**.

	x	y	z	U(iso)
H(2)	-149	301	186	28
H(3)	15	308	91	27
H(5)	400	422	300	29
H(6)	223	413	387	31
H(7A)	207	224	27	36(5)
H(7B)	358	333	9	36(5)
H(7C)	193	437	11	36(5)
H(8A)	510	543	185	55(6)
H(8B)	555	410	115	55(6)
H(8C)	554	336	210	55(6)

5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-6-methyl-3-oxo-hept-6-enoic acid *tert*-butyl ester 250 (05srv155)

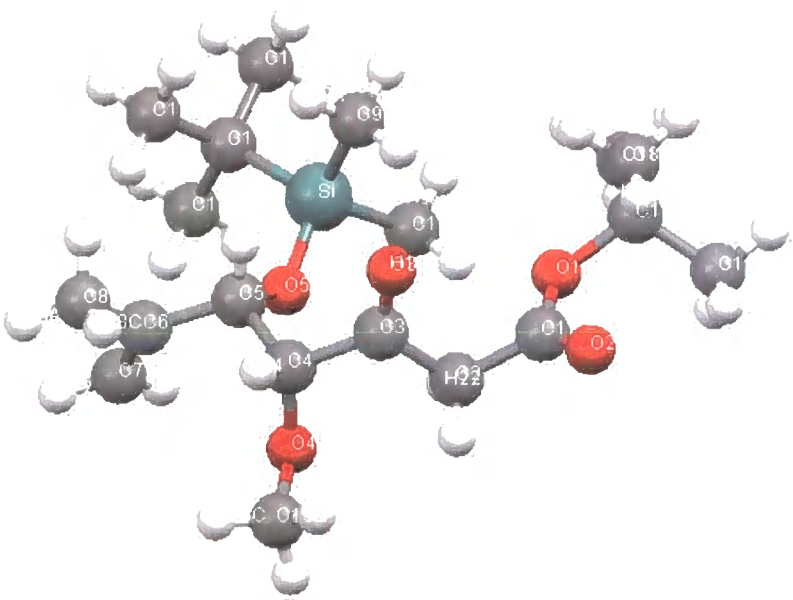

Table 1. Crystal data and structure refinement for **250**.

Empirical formula	C16 H30 O5 Si	
Formula weight	372.6	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Space group	*P* -1	
Unit cell dimensions	*a* = 6.0668 Å	α= 110.62°
	b = 12.1376 Å	β= 94.1°

	c = 16.237 Å	γ = 100.51°
Volume	1088.23 Å^3	

Table 2. Atomic coordinates (×10^4) for **250**.

	x	y	z
Si	2842	3751	1351
O(1)	6111	6993	3393
O(2)	7208	7509	4861
O(3)	3292	5012	4081
O(4)	7127	3113	3367
O(5)	4241	3185	1963
C(1)	6844	6785	4107
C(2)	7127	5509	3840
H(21)	8250	5431	4227
H(22)	7550	5244	3280
C(3)	4957	4657	3830
C(4)	4930	3313	3478
H(4)	4280	3004	3907
C(5)	3353	2690	2578
H(5)	1860	2871	2701
C(6)	3117	1335	2256
C(7)	4479	783	1723
H(71)	5490	1230	1470
H(72)	4300	-100	1537
C(8)	1361	692	2619
H(8a)	1315	-175	2372
H(8b)	-120	832	2457
H(8c)	1729	995	3268
C(9)	838	4573	1992
H(9a)	-370	4007	2074
H(9b)	223	5005	1673
H(9c)	1624	5131	2561
C(10)	5076	4817	1119
H(10a)	5973	5407	1687
H(10b)	4365	5250	796
H(10c)	6084	4364	749
C(11)	1272	2527	279
C(12)	-640	1686	484
H(12a)	-1480	1034	-90

H(12b)	-1725	2168	803
H(12c)	28	1304	874
C(13)	2883	1783	-277
H(13a)	3544	1403	144
H(13b)	4100	2316	-365
H(13c)	2036	1155	-782
C(14)	224	3101	-314
H(14a)	-670	2453	-864
H(14b)	1452	3618	-476
H(14c)	-790	3604	15
C(15)	5591	8174	3478
C(16)	7707	9159	3864
H(16a)	8145	9275	4487
H(16b)	7420	9911	3831
H(16c)	8933	8930	3526
C(17)	3693	8392	4023
H(17a)	2420	7709	3772
H(17b)	3240	9112	4018
H(17c)	4206	8494	4627
C(18)	4833	7984	2518
H(18a)	6040	7793	2176
H(18b)	4460	8708	2491
H(18c)	3520	7329	2280
C(19)	8166	2875	4079
H(19a)	8050	3500	4650
H(19b)	9780	2885	4022
H(19c)	7394	2075	4060

Table 3. Bond lengths [Å] for **250**.

Si-O(5)	1.66	C(19)-H(19c)	0.987
Si-C(9)	1.857	C(19)-H(19a)	0.986
Si-C(10)	1.852	C(18)-H(18a)	0.963
Si-C(11)	1.89	C(18)-H(18c)	0.962
O(5)-C(5)	1.424	C(18)-H(18b)	0.961
O(4)-C(19)	1.419	C(17)-H(17a)	0.966
O(4)-C(4)	1.411	C(17)-H(17b)	0.965
O(3)-C(3)	1.211	C(17)-H(17c)	0.965
O(2)-C(1)	1.206	C(16)-H(16c)	0.979
O(1)-C(1)	1.333	C(16)-H(16b)	0.979
O(1)-C(15)	1.485	C(16)-H(16a)	0.98
C(9)-H(9c)	0.958	C(15)-C(17)	1.507
C(9)-H(9a)	0.96	C(15)-C(18)	1.516
C(9)-H(9b)	0.958	C(15)-C(16)	1.506
C(8)-H(8c)	0.979	C(14)-H(14a)	0.995
C(8)-H(8b)	0.979	C(14)-H(14b)	0.996
C(8)-H(8a)	0.98	C(14)-H(14c)	0.995
C(7)-H(71)	0.955	C(13)-H(13c)	0.982
C(7)-H(72)	0.988	C(13)-H(13b)	0.983
C(6)-C(8)	1.484	C(13)-H(13a)	0.982
C(6)-C(7)	1.333	C(12)-H(12b)	1.01
C(5)-H(5)	0.988	C(12)-H(12c)	1.01
C(5)-C(6)	1.515	C(12)-H(12a)	1.01
C(4)-H(4)	0.976	C(11)-C(14)	1.536
C(4)-C(5)	1.542	C(11)-C(13)	1.536
C(3)-C(4)	1.523	C(11)-C(12)	1.537
C(2)-H(21)	0.934	C(10)-H(10a)	0.991
C(2)-C(3)	1.514	C(10)-H(10c)	0.989
C(2)-H(22)	0.924	C(10)-H(10b)	0.991
C(19)-H(19b)	0.988	C(1)-C(2)	1.5