Approaches to the total synthesis of viridenomycin

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Declaration

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Abstract

Viridenomycin is a polyene macrolide possessing considerable biological activity. Much work has been performed previously within the Whiting group on the development of methodology for the stereoselective synthesis of polyenes and this project builds on this work.

New conditions have been developed to allow the HM reactions of electron-poor vinyl iodides with vinylboronate esters. This, combined with previously developed methodology involving the use of iodine monochloride and sodium methoxide to substitute the boronate ester function with an iodide group in a stereoslective manner, allowed the stereoselective synthesis of the *Z*,*Z*,*E*-triene northern hemisphere of viridenomycin. Conditions have been developed to allow further HM reactions and amide couplings of this fragment.

In developing conditions for the HM reactions of electron-poor vinyl iodides, a number of side reactions were observed, often in competition with the desired processes. Presented within is a study of these reactions with regard to their generality and mechanism.

A number of routes to the highly substituted cyclopentenone fragment of viridenomycin have been developed with the most successful of these showing high yield as well as enantio- and diastereo-selectivity. In this process, a number of unusual cross-ozomides have been isolated in which two new chiral centres were formed with complete diastereoselectivity.

Conditions to permit diastereoselective conjugate additions to the cyclopentenones synthesised have been developed. The yields and diastereoselectivites of these reactions were somewhat variable, however, in the best case both proved to be high.

Thus, one of the three fragments of viridenomycin have been synthesised whilst another is at a very advanced stage. In addition, some work has been performed on the conditions required for the final assembly.

Abbreviations

Ac	acetate
acac	acetoacetate
ACCN	1,1'-azobis(cyclohexanecarbonitrile)
AIBN	2,2'-azobis(2-methylpropiononitrile)
aq.	aqueous
Ar	aryl
BINAP	1,1'-binaphthalene-2,2'-diylbis(diphenylphosphine)
Boc	tert-butyloxycarbonyl
BOXAX	2,2'-bis(oxazolin-2-yl)-1,1'-binaphthyl
brs	broad singlet
C	Celsius
CDI	carbonyl diimidazole
CI^+	chemical ionisation (positive)
CI^-	chemical ionisation (negative)
cm	centimetre
Cy	cyclohexyl
d	doublet
dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEA	*N*,*N*-diethylaniline
DIBAL-H	di-iso-butylaluminium hydride
dippb	1,4-bis(diisopropylphosphino)butane
dippe	1,2-bis(diisopropylphosphino)ethane
dippp	1,3-bis(diisopropylphosphino)propane
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMS	dimethylsulphide
DMSO	dimethylsulphoxide

dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dt	doublet of triplets
EI	electron ionisation
ES^-	electrospray (negative)
ES^+	electrospray (positive)
Et	ethyl
g	gram
GC-MS	gas chromatography-mass spectrometry
HM	Heck-Mizoroki
HMDS	hexamethyldisilylamide
HMPA	hexamethyl phosphoramide
HPLC	high performance liquid chromatography
hr	hour
HRMS	high resolution mass spectrometry
Hz	Hertz
Ile	isoleucine
iPr	*iso*-propyl
LAH	lithium aluminium hydride
LDA	lithium di*iso*propylamide
m	multiplet
M	molar
Me	methyl
mg	milligram
min	minute
MHz	megahertz
mmol	millimole
mol	mole
Mpt	melting point
nBu	*n*-butyl
NMR	nuclear magnetic resonance
o	*ortho*

Oct	octyl
OMs	mesyl
OTf	triflyl
P	in scheme, protecting group
p	*para*
pet.	petroleum
Ph	phenyl
Phe	phenylalanine
PMP	1,2,2,6,6-pentamethylpiperidine
Pr	propyl
PS	Proton Sponge
Py	pyridine
PyBOP	benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
q	quartet
R	any group, generally alkyl
RCM	ring-closing metathesis
s	singlet
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
t	triplet
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluroride
TBS	tert-butyldimethylsilyl
tBu	*tert*-butyl
TFA	trifluoroacetic acid
TFP	tri(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMPP	tris(4-methoxyphenyl)phosphine
TMS	trimethylsilyl
TMSA	trimethylsilylacetylene
Tol	tolyl

TPP	triphenylphosphine
Ts	tosyl
Val	valine
X	generally, any halide

1 Introduction

1.1 Heck-Mizoroki reaction mechanism

1.1.1 Background

Palladium catalysed cross-coupling reactions have proved extremely powerful synthetic tools and their scope continues to increase year on year. Alongside the well-established Heck-Mizoroki,[1,2] Kumada,[3,4] Negishi,[5,6] Sonogashira-Hagihara,[7,8] Stille[9,10] and Suzuki-Miyaura[11,12] reactions, palladium catalysis of aryl and vinyl hydroamination,[13] sulphination,[14] dechlorination,[15] dialkoxylation[16] and intramolecular arylation[17] has more recently been discovered. Other palladium catalysed reactions include the conversion of saturated ketones into α,β-unsaturated ketones[18] (eliminating the need for the use of selenium and sulphur chemistry) and carbon-hydrogen bond alkenylation.[19]

Although the mechanisms of many of these reactions are thought to be relatively well understood, their nature often prevents easy observation of the highly reactive intermediates often associated with homogeneous catalysis. Whilst accurate knowledge of the mechanism in operation is not necessarily a prerequisite for the application of these reactions to organic synthesis, knowledge of the mechanism may assist the optimisation of reaction conditions and improve regio-, stereo- and chemo-selectivity, with a concomitant reduction of side-reactions.

The majority of the palladium catalysed cross-couplings are thought to share a similar mechanism.[20] For the Suzuki-Miyaura, Sonogashira, Stille, Negishi, Hayama[21] and Kumada reactions, the proposed mechanism involves initial oxidative addition of the halide to a palladium(0) catalytic species to form a palladium(II) species, transmetallation of the organometallic reagent by palladium and reductive elimination of the product from this species to regenerate the active palladium(0) catalyst (Scheme 1).

The Heck-Mizoroki (HM) reaction has evolved significantly from its original guise as the arylation of olefins with arylmercury compounds.[22-24] Whilst it was possible to use catalytic palladium in this reaction through the use of copper salts with dioxygen as a reoxidant,[25] the use of aryl mercury compounds has a number of drawbacks. The independent discovery by both Mizoroki[1] and Heck[2] that aryl iodides could be used as a substitute for aryl mercury compounds, and that this modification maintained the oxidation state of palladium, allowing for the use of catalytic palladium in the absence of reoxidants, was particularly significant. The reaction has been further developed over the years to allow the coupling of less reactive halides, such as bromides,[26] chlorides,[27] pseudo-halides such as triflates,[28] tosylates,[29] mesylates,[30] aryl diazonium salts[31] and even phosphates.[32] In addition, the reaction is not limited to arylation; it can be used to add vinyl halides to olefins[33] and can involve the use of chiral ligands on palladium for the generation of chiral centres with a high degree of enantiocontrol for certain substrates.[34-36] Recent developments involve the replacement of the halide with an organoboron reagent in the presence of stoichiometric reoxidant,[37,38] although this is closely related to the original use of aryl mercury compounds.

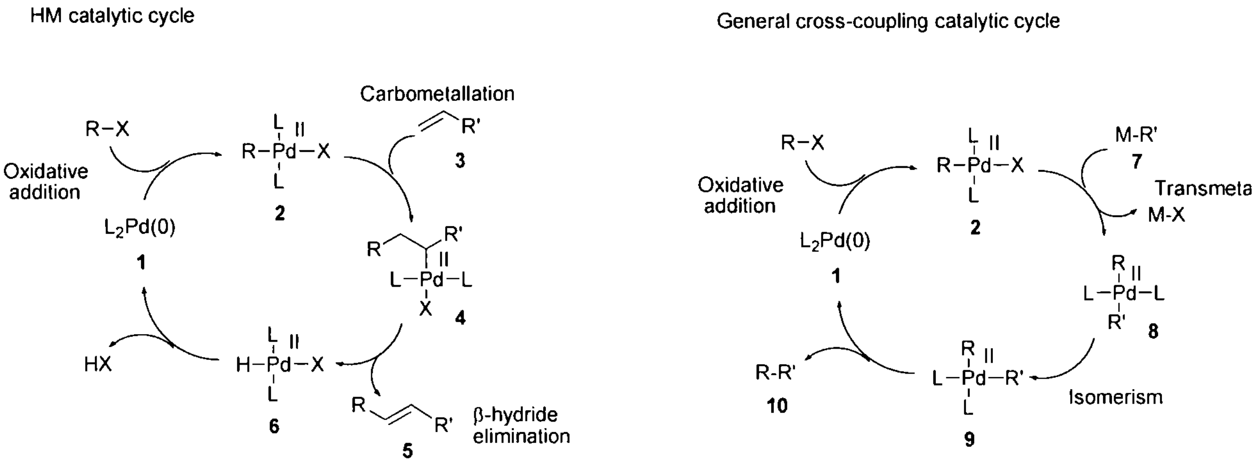
In contrast to the previously mentioned cross-couplings reactions, the HM reaction, having no organometallic reagent, does not include a transmetallation step in its mechanism. This introduction will examine the current mechanistic view of the HM reaction and factors which impact upon it.

1.1.2 Basic mechanism

There has been a broadly accepted understanding of the mechanism operating in the HM reaction for many years,[39] involving an initial oxidative addition of the halide to a palladium(0) catalyst. Despite various claims for a possible palladium(II/IV) cycle in the mechanism,[40,41] the evidence for this is poor, since it has been shown that in the majority of cases that the palladacycles involved act as reservoirs of palladium,[42-48] some of which is reduced to palladium(0). Although palladium(II/IV) cycles do appear to operate for certain other reactions involving the use of strong oxidants,[49,50] such reactions presumably promote the palladium(IV) oxidation state. Further evidence against this mechanism comes from gas phase computational studies which indicate that the rate determining step in a palladium(II/IV) cycle involving iodobenzene would be the oxidative addition of iodobenzene to palladium.[51] Since the actual rate determining step in the HM reaction of aryl iodides is not oxidative addition,[52] (*vide infra*) this suggests that a palladium(II/IV) cycle is not in operation. Hence, the mechanism of the HM process can be represented by

Scheme 1, involving a palladium(0) species **1** undergoing oxidative addition to generate a palladium(II) species **2**, which reacts with the olefin component **3**, possibly following initial η^2-coordination to the palladium atom. This results in a carbometallation reaction to generate palladium(II) alkyl complex **4**. Elimination of palladium hydride from complex **4** furnishes the product **5** and base assisted elimination of HX from palladium(II) complex **6** regenerates the active palladium(0) catalyst **1**.

Scheme 1; comparison of HM mechanism with that of a generalised palladium catalysed cross-coupling reaction



HM-type mechanisms have also been suggested for certain other reactions, for instance the recently reported arylation of arenes.[53]

1.1.3 Reaction conditions

A number of palladium sources are used in the HM reaction, which are either sources of palladium(0) such as $Pd(PPh_3)_4$, $Pd(dba)_2$ and $Pd_2(dba)_3$, or sources of palladium(II) such as $Pd(OAc)_2$, and $PdCl_2(MeCN)_2$. A wide range of solvents can be also used in the HM reaction and elevated temperatures compared with other cross coupling reactions are frequently required (compared with Sonogashira reactions, for example, which often proceed rapidly at room temperature[8]). High boiling point solvents such as DMF, DMA and toluene are often used. Additionally, inorganic bases such as NaOAc are often used and polar solvents can be preferred to achieve homogeneity.[54,55] The use of non-polar solvents also becomes convenient when organic bases, such as trialkylamines, are used. Recently, ionic liquids have also have been shown to be useful solvents in HM reactions.[56]

The use of ligand free HM reactions is possible, and indeed, the early examples of HM reactions were performed under these conditions.[2] However, it is more generally found that the addition of palladium-stabilising ligands is highly beneficial in terms of providing increased reactivity, stability and selectivity of the catalyst.[26] The most widely used ligands are phosphines, such as triphenylphosphine and tri(*o*-tolyl)phosphine,[57] however, nitrogen,[58] arsine,[59] sulphur[60] and carbene[61] derived ligands can be used. A wide variety of bidentate ligands have also been developed for palladium, these including P,P, P,N,[62-66] N,N,[67-76] N,S[77] and P,S[78,79] ligands as well as tridentate ligands which can switch to bidentate coordination to allow a substrate to bind.[80] Tetradentate phosphines have even been synthesised and used successfully.[81] Tridentate, bis-phosphine mono-nitrogen ligands that can switch between phosphorus and nitrogen coordination have also been developed.[82,83] The use of chiral, chelating ligands can give rise to high levels of asymmetric induction for certain substrates (*vide infra*).

In addition to the use of palladium-stabilising ligands, HM reactions have often been subjected to empirical treatment with various additives, generally claimed to promote selectivity or reactivity. These have included saturation of the reaction with chloride ion[33,84] (Jeffery protocol), addition of phase transfer catalysts,[85] and the addition of either silver[86] or thallium[87] salts. Whilst this approach is often successful in terms of achieving the desired product, the exact mode of action of these additives is not always well understood.

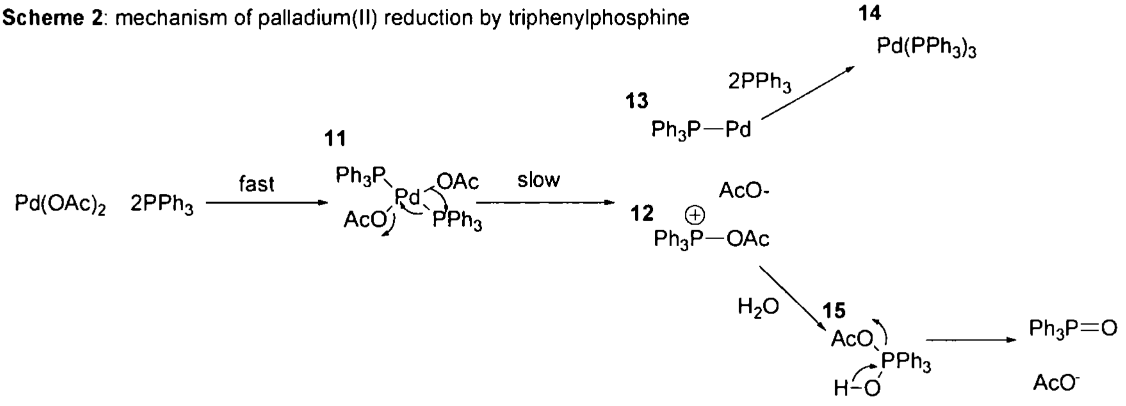
Choice of reaction conditions can also have a marked effect on the regioselectivity of the reaction; control over α-substitution and β-substitution often being possible (*vide infra*).

1.1.4 Catalyst generation

In most cases, the catalyst used in the HM reaction is generated *in situ*, which effectively means that the first step of the reaction has to be the reduction of the palladium(II) precursor to provide the active palladium(0) catalytic species. Although there have been various claims made for palladium(II/IV) catalytic cycles,[41,42] and indeed, some palladium(IV) species have been isolated,[88] all current evidence seems to point to a palladium(0/II) cycle, and this necessarily requires the reduction to the active palladium(0) catalyst.

There is a range of methods for the *in situ* reduction of palladium(II) salts to palladium(0) species, including treatment with sodium borohydride,[89] hydrazine,[90] phenyl or methyl lithium (to give biphenyl or ethane (and lithium chloride) respectively),[91] n-butyllithium (to give butane, butene, octane and lithium chloride)[91] and electrochemical methods.[92] However, the most common procedure is the use of triphenylphosphine as the reducing agent and the mechanism of this reduction has been investigated independently by the groups of Jutand[93] and Hayashi,[94] both of which propose the mechanism shown in Scheme 2. This involves initial ligation of palladium(II) acetate to give complex **11**, which can eliminate acetoxytriphenylphosphonium acetate to generate a monotriphenylphosphinylpalladium(0) complex, which can coordinate further phosphines.

Scheme 2: mechanism of palladium(II) reduction by triphenylphosphine



This mechanism explains the isotopic labelling observed by Hayashi[94] and the independence of the rate of reaction on phosphine concentration observed by Jutand.[93] It has been demonstrated that the presence of one equivalent of water is necessary for the reduction step to proceed (causing hydrolysis of acetoxytriphenylphosphonium acetate **12**, see Scheme 2),[94] however, given the low catalyst loadings used, this is rarely a problem even under rigorously anhydrous conditions! Further evidence for this mechanism comes from the observation of similar behaviour of analogues of Pd(OAc)$_2$, such as Pd(TFA)$_2$[95] and related, sulphur bridged species.[96]

Given that this method of reduction only works for $Pd(OAc)_2$ and related species, and not for palladium(II) halide salts,[93] it appears that the thermodynamic driving force for this reaction is the formation of the strong phosphorus-oxygen bond in triphenylphosphine oxide. This reduction is faster for electron poor phosphines, as demonstrated by a positive Hammett parameter for *para*-substituted tri-aryl phosphines.[97] This is also in agreement with the proposed mechanism of reduction. In certain cases, such as when using tri(*o*-tolyl)phosphine, reduction of palladium by this mechanism (Scheme 2) does not operate. Indeed, this led to the initial proposal of palladium(II/IV) cycles[40,41] (*vide supra*) for the resulting palladacycle catalysts. However, other methods for the reduction of such species, including reaction with olefins and *via* a palladium amide species can account for a reductive catalyst generation process.[98] Indeed, for the majority of palladacycles, and other supported palladium species, it is usually found that the active species involved in catalysis are palladium(0) species,[42,43] often resulting from degradation of the ligand.[44-48] The formation of active catalytic species from palladacycle 'reservoirs' can give rise to complicated kinetics.[99]

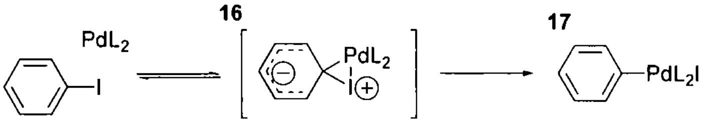
In cases where none of these potential reducing agents are present, it is possible for organic amine bases to perform the reduction of palladium(II) to palladium(0),[100] although this has been found to be slow compared to reduction by triphenylphosphine.[97] In addition, the olefin may reduce the palladium(II) species, either by a Heck-type reaction for palladacycle,[98] or by a Wacker-type process.[101] In addition, another process that may be involved in catalyst generation is the dissociation of dimeric catalysts. This is responsible for the induction period observed in certain cases.[102,103] EXAFS studies have shown that the active catalytic species in these systems are monomeric and that the equilibrium favours these species at high dilution.[104] It could be argued that this is not a true catalyst generation step, but part of an equilibrium governing the oxidative addition step.

1.1.5 Oxidative addition

Despite being perhaps the easiest step to investigate due to it being the first step in the catalytic cycle (and having received the most attention), the mechanism of the oxidative addition step of aryl and vinyl halides and tosylates to palladium(0) species is still under investigation. Early studies of the mechanism of oxidative addition involved the reaction of alkyl and aryl iodides with iridium complexes,[105-107] aryl iodides, bromides and chlorides with $Ni(PEt_3)_4$,[108] and the oxidative addition of benzyl chlorides to $Pd(PPh_3)_4$.[109] Although these studies, particularly those involving nickel, shed some light on the oxidative addition process involved, it became clear that studies on palladium systems were required.

The first such study[110] was the oxidative addition of aryl iodides to $Pd(PPh_3)_4$, which proved that electron withdrawing groups on the aryl iodide accelerated the reaction with a clear positive Hammett correlation ($\rho = +2.0$). In contrast to this behaviour, electron donating substituents on the aryl ring of the phosphine have been shown to increase the rate of HM reaction.[82] The oxidative addition step has been found to be first order in both palladium and aryl iodide, but negative first order in added triphenylphosphine. Since at this time it was known that in solution, $Pd(PPh_3)_4$ dissociates to PPh_3 and $Pd(PPh_3)_3$,[111,112] it was proposed that the active species in the oxidative addition was probably $Pd(PPh_3)_2$, formed from an unfavourable equilibrium dissociation of a further PPh_3 from $Pd(PPh_3)_3$, which has actually been isolated as a solid. The build-up of negative charge on the aryl ring in the transition state of the oxidative addition process (demonstrated by the positive Hammett parameter) has been explained by a three centre transition state **16** (Scheme 3), which collapses to the oxidative addition product **17**.[110]

Scheme 3: oxidative addition of palladium(0) to aryl iodide



This study also explained the relative lack of reactivity of aryl bromides and chlorides, suggesting that the electropositive iodine is a better ligand for palladium than either bromine or chlorine.[110] It has also been suggested that a transition state such as **16** occurs following initial η^2-coordination of the aryl ring to palladium.[113] This study also observed the disappearance of the palladium(0) starting material, but did not isolate the resulting product or provide information on the structure of oxidative addition species. However, based on the proposed transition state **16**, the *cis*-isomer would be expected for product **17**.

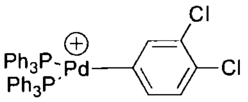
It has been found that co-ordinately unsaturated palladium (*i.e.* one triphenylphosphine per palladium) is unstable in solution and reacts readily with aryl iodides.[93] This provides further support for the suggestion that the active species is co-ordinately unsaturated and that it is in equilibrium with the inactive, saturated species. A subsequent study of oxidative addition of aryl iodides to $Pd(PPh_3)_4$ in less polar solvents[114] (toluene) gave a similar Hammett parameter ($\rho = +2.3$) and kinetics, the lack of effect of the change in solvent polarity indicating little charge development in the transition state. Because of this it was suggested that transition state **16** was unlikely due to the development of charge[114] but a similar three centre transition state must occur as the alternative is an S_NAr mechanism which involves the generation of formal charges.

In contrast, the oxidative addition of aryl chlorides to palladium(0) species has been found to proceed through a highly charged transition state;[115] a Hammett parameter of +5.2 being found for the addition of aryl chlorides to $Pd(dippp)_2$. Again, oxidative addition is predicted to proceed through an unsaturated palladium(0) species [*i.e.* Pd(dippp)] and involves a three-centre late-transition state charged species, which is essentially analogous to structure **16** (Scheme 3), but involving chloride ion.

Although oxidative addition to palladium(0) is generally accepted to be an irreversible process, it has been shown that for sterically crowded systems the process is reversible; reductive elimination can be induced by the addition of bulky, electron-rich phosphines.[116] Thus, reaction of tri-*tert*-butylphosphine with a palladium(II) oxidative addition product of mono-ligated tri-*ortho*-tolylphosphinyl complex produces reversal of the oxidative addition, regenerating the aryl halide and producing a bis(tri-*tert*-butylphosphinyl)palladium(0) complex.[116] Reductive elimination of aryl halides from platinum(IV) complexes has been reported,[117] but given the aforementioned lack of palladium(IV) species in HM chemistry, this is probably of little significance.

As mentioned previously, the catalysts employed in the HM reaction are typically generated *in situ* from palladium(II) precursors. The investigation of the oxidative addition process involving $Pd(PPh_3)_4$ has tended to ignore the possible influences of any associated anions. When using $Pd(OAc)_2$ as the catalyst precursor, two equivalents of acetic acid are generated during the palladium reduction process, however, since HM reactions are performed in the presence of stoichiometric bases, this results in the formation of two equivalents of acetate anion, and, in addition, two equivalents of the trialkylammonium cation are also generated (for example). It had been found using ^{31}P NMR spectroscopy that there are signals present for palladium-phosphine complexes in solution, that their chemical shift depends on the anions present,[91] and that their reactivity is dependent upon the palladium(II) precursor used. Additional investigations have shown that only one equivalent of acetic acid per palladium is actually generated,[97] and investigation into the effect of added chloride ion on the rate and mechanism of oxidative addition has shown that the reaction is far more complex than previously thought.[118] It appears that in the presence of chloride ions, a number of palladium(0) species are present in solution, all of which disappear to give a single oxidative addition product upon addition of iodobenzene.[118] This shows that either all species are active in the oxidative addition, or they are in rapid equilibrium with each other (or both). Although various anionic palladium species with chloride ligands have been proposed, there is little chemical evidence for the existence of any of them, and indeed, they have been proposed on the basis of 'general chemical expectations' rather than hard evidence.[118] That said, it has been demonstrated that the transition state that occurs in the oxidative addition step involving iodobenzene and palladium(0) in the presence of chloride ions is different to the one that occurs in their absence. This has been clearly demonstrated by comparison of the Hammett parameters for two processes, which produced Hammett parameters of $\rho = +2.7$ and $\rho = 2.0$ respectively. This indicates that there is a greater degree of negative charge in the transition state when chloride is added and is consistent with a chloride ligated anionic palladium species being involved. It is interesting to note that studies of similar reactions by electrospray mass spectrometry found no evidence of anionic palladium species in negative mode, the only species being observed being cations such as **18** in positive mode.[119]

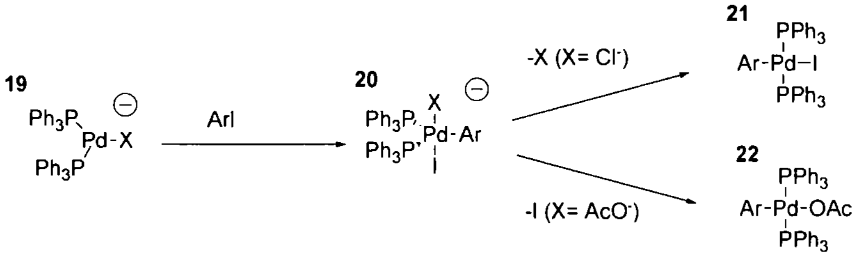
18



The presence of chloride was found to accelerate the rate of oxidative addition; two equivalents per palladium giving the greatest level of acceleration compared to the absence of chloride.[92] A further addition of chloride ion was also shown to retard the reaction.[118]

The acceleration of the oxidative addition step by increasing the negative charge on palladium is in some ways unsurprising, especially in the light of the fact that more electron donating phosphines also increase the rate of oxidative addition[97] or the overall reaction[82] in HM reactions. It has also been found that the nature of the palladium(0) species changes upon the addition of acetate anions to the solution.[120] This was again rationalised by the suggestion of anionic, acetate-ligated palladium species, however, in this case, a substantial increase in rate of oxidative addition was not observed.[120] It was also found that the final product of the oxidative addition reaction, in the presence of acetate, was *trans*-$ArPdL_2OAc$ and not the expected *trans*-$ArPdL_2I$, and that the acetate was reactive towards olefins whilst the iodide was not.[120] These results led to the proposal of five-coordinate, anionic palladium intermediates in the oxidative addition step.[120,121] Hence, the HM process could be represented as proceeding through the mechanism outlined in Scheme 4. An anionic complex of type **19** can react by oxidative addition in the presence of, for example, chloride, resulting in the formation of the proposed *trans*-$ArXPdL_2I$ five-coordinate species **20**. This structure is consistent with the observation of two equivalent phosphines by ^{31}P NMR spectroscopy, and also accounts for the reported release of a second equivalent of chloride upon formation of the product.[121] A similar five coordinate intermediate has been proposed involving acetate,[97,120] and therefore, in both chloride and acetate cases, a revised mechanism of oxidative addition can be proposed, in which a three coordinate palladium anion adds to the aryl iodide to give a five coordinate palladium anion (as outlined in Scheme 4).

Scheme 4: mechanism involving proposed five-coordinate palladium species



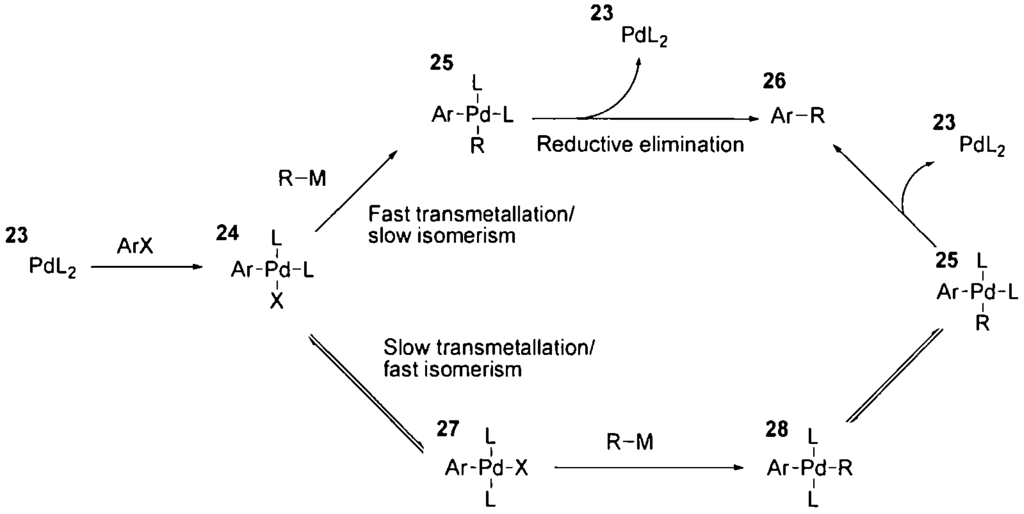
In contrast to the preceding discussion, the proposed five coordinate intermediates such as **20** seem unlikely since the reluctance of palladium to form five coordinate complexes is documented,[122,123] five coordinate species only being isolated when polydentate ligands are used. This reluctance of palladium to be five-coordinate can also be inferred from the lack of reactivity of chelated palladium(II) aryl halide complexes in the carbometallation step of the HM reaction (*vide infra*), where dissociation is necessary for the olefin to bind. Additionally, for the previously observed intermediates, these species were seen to be relatively stable, having a lifetime of over one hour (observed using electrochemical methods). This is clearly not consistent with a five coordinate palladium anion such as **20**, because if such a species were to form, it would be expected to rapidly dissociate to restore the preferred square planar geometry.

Curiously, it has also been claimed that an acetate ligated, three coordinate anion is less reactive than $Pd(PPh_3)_2$ and that this reduction in the rate of the oxidative addition step is responsible for the overall acceleration of the reaction by bringing the rates of the fastest and slowest steps closer together.[124] However, the addition of acetate has variously been shown either to have no effect on the rate of oxidative addition[120] or even to increase it,[125] therefore, if its presence does accelerate the reaction, this is clearly not the reason.

It is interesting that recent DFT studies[126-128] which included solvation effects on the anionic HM reaction mechanism have reached similar conclusions on the overall mechanism. A previous DFT study including solvation effects had suggested that three coordinate palladium anions were stable species in solution.[129] These calculations also suggested that the addition of acetate to palladium to form a three coordinate anion should increase the rate of oxidative addition.[126] However, it is known that oxidative addition of aryl iodides is not rate limiting.[52] Indeed, such reactions occur rapidly at room temperature[110] and it has been shown that it is often not rate limiting for aryl bromides.[130] Whilst some claims for rate limiting oxidative addition for aryl bromides have been made,[131] such reactions have been found to occur at room temperature.[132] More importantly, both studies showed that oxidative addition of the three coordinate anion to an aryl halide did not give the expected five coordinate anionic palladium species, rather a four coordinate anionic species was produced involving the halide of the aryl halide.[126,127] This species undergoes an oxidative addition reaction with concurrent loss of halide to form a neutral four coordinate product,[126,127] with the dissociated halide electrostatically bound to a phosphine ligand.[128] This mechanism rationalises some of the experimental observations, for example an intermediate that undergoes slow release of chloride, without resorting to less plausible five coordinate palladium species.

Another point of interest is the geometry of the product obtained in the oxidative addition process. From the proposed three centre transition state (*i.e.* **16**, Scheme 3), the expected geometry of the resulting palladium(II) complex should be *cis* with respect to the Ar and X groups on palladium, and indeed this is observed in solution.[133] However, the product that is invariably isolated when using monodentate phosphines is the *trans*-isomer; the *cis* product only having been found once for addition of aryl halides[134] although a number of *cis*-oxidative addition products have been characterised from the oxidative addition of halogen-nitrogen bonds.[135] A clue as to the reason for this comes from the observation that the isolated products of oxidative addition from stoichiometric reactions often react more slowly in subsequent steps than the apparently identical species under catalytic conditions.[136] It was noted that if the isomerisation of a *cis*-oxidative addition product, *i.e.* **24** (Scheme 5), was slower than transmetallation (traditional cross-coupling reactions such as Suzuki-Miyaura and Negishi being discussed), then the reaction could proceed directly *via* a reductive elimination from **25**.[42] However, if isomerisation is fast, transmetallation yields the *trans*-palladium species **27** and a second isomerisation is required before reductive elimination can occur (Scheme 5). For stoichiometric reactions in which the product of oxidative addition is isolated, isomerisation to the *trans*-product **27** is ensured because this is the thermodynamically favoured product.[42] Whilst a reductive elimination step is not present in the HM reaction, the reactivity of the *cis* and *trans* oxidative addition products[137] are unlikely to be the same and hence isomerisation is likely to be significant. Such effects have also been noted in the Negishi reaction.[138]

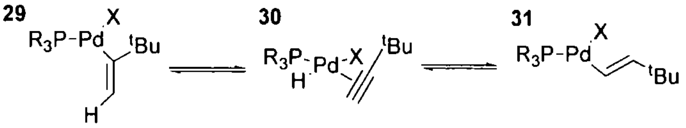
Scheme 5: competition between transmetallation and isomerisation



The mechanism of the isomerisation of the *cis*-products of oxidative addition has been investigated.[139] Although the mechanistic details are complex, after isolating an oxidative addition product, it was possible to study the rearrangement process. Four separate pathways were proposed to be in operation; two dependant on triphenylphosphine concentration and involving associative replacement of phosphines with iodide, either THF mediated, or iodide bridged species; and two independent of triphenylphosphine concentration, with both dissociative and associative pathways proposed, depending on the solvent and involving Berry pseudorotation processes.[139]

Suggestions have been made of regiochemical scrambling following the oxidative addition step. The proposed mechanism is shown in Scheme 6.[32] Although potentially important, this phenomenon does not appear to be common.

Scheme 6: proposed mechanism of isomerisation

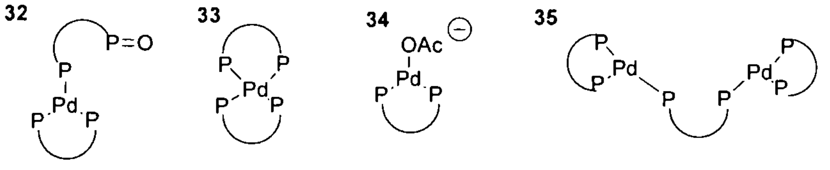


The oxidative addition of aryl triflates has also been investigated and appears to occur by a similar mechanism to that of the corresponding halides. Again, the oxidative addition step is accelerated by the presence of electron withdrawing groups on the aryl group; a Hammett parameter of $\rho = +2.55$ being found in the reaction of aryl triflates with $Pd(PPh_3)_4$.[28] As previously established,[78,140-148] the product of oxidative addition was found to be ionic with the palladium triflate bond fully dissociated in moderately polar solvents.[28] In non-polar solvents, however, although no covalent bonding is present (IR spectroscopy), the ions exist in the form of tight ion pairs.[28] Again, addition of chloride ion was found to accelerate the reaction although only when large excesses (150 fold) were added,[28] while other systems show severely inhibited activity.[149] It was also observed that the addition of chloride could enable regeneration of a neutral palladium halide species.[91] This has subsequently been verified and applied synthetically.[150]

The magnitude of the Hammett parameter found for the oxidative addition of aryl electrophiles to palladium(0) species can be related to the reactivity of the aryl species towards oxidative addition. The experimentally observed order of reactivity is: I > OTf > Br > Cl, and the Hammett parameters found for iodides, triflates and chlorides are 2.0,[110] 2.55[28] and 5.6[115] respectively. Although the Hammett parameter for the oxidative addition of aryl bromides to palladium(0) has not been determined, the Hammett parameters for the oxidative additions of aryl iodides, bromides and chlorides to $Ni(PEt_3)_4$ are 2.0, 4.4 and 5.4 respectively.[108] It appears therefore, that the smaller the Hammett parameter found for the oxidative addition of a group of aryl electrophiles, the more facile the process. This is not entirely unexpected since a lower Hammett parameter indicates a less charged transition state, which may consequently need less stabilisation by the solvent.

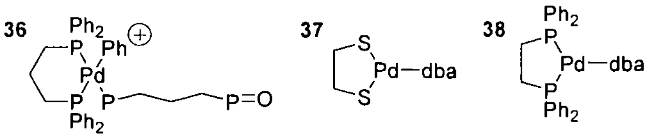
So far in this review, only monodentate phosphines have been discussed. Whilst the majority of phosphines used in HM reactions are monodentate, bidentate (or chelating) phosphines are important because of their ability to activate unreactive halides, particularly chlorides,[27] and for their ability, when chiral, to impart enantioselectivity in certain HM reactions.[151] The use of bidentate phosphines has several implications for the oxidative addition step, *i.e:* i) that the product of oxidative addition is necessarily *cis*; ii) that the chelating ligand does not permit the formation of *trans*-complexes;[42] and iii) that the bite angle of the phosphine has a significant impact on the reactivity of the palladium(0) species.[152,153] The first issue surrounding the use of bidentate phosphines arises when the catalyst is being formed *in situ* by reduction of a palladium(II) precursor. Since the mono-oxidation of the bidentate phosphine effectively yields a monodentate phosphine (phosphine oxides not generally being coordinating), this gives rise to a scenario that is somewhat more complex than that found for the monodentate systems. Since it is clearly necessary to use at least two equivalents of the bidentate phosphine, species such as triphosphine ligated system **32** tend to result[154] with predictable mechanistic complications. This situation can be avoided in several ways: firstly the use of three equivalents of the bidentate ligand forces the formation of **33**[94,154] by means of the chelate effect; secondly, palladium(II) precursors can be avoided by the use of palladium(0) sources such as $Pd_2(dba)_3$, however, dba can coordinate palladium and impede oxidative addition;[155,156] and thirdly, addition of acetate promotes the formation of three coordinate species such as **34**.[154] The situation may be somewhat simplified in circumstances where the mono-oxidised phosphine can be displaced by the olefin.[157]

Figure 1



When three equivalents of bidentate phosphine are used the rate determining step is found to be dissociative; a dimeric palladium species such as **35** losing a phosphine to give a reactive di-coordinate palladium species.[158] Oxidative addition of the halide to complex **35** gives the expected *cis*-product with dissociation of the monodentate phosphine: one theoretical study which included solvation effects suggested that this occurred following initial η^2-complexation of the iodo-arene to palladium.[158] When the catalyst is generated from a palladium(0) dba species, dba dissociation is generally required prior to oxidative addition although the dba coordinated species apparently show some activity in oxidative addition.[155] Three coordinate anionic palladium species with bidentate phosphines have been 'characterised' in solution by DFT calculations[129] and have been shown to be active catalysts, giving either the *cis*-aryl acetate product or cationic species such as **36**.

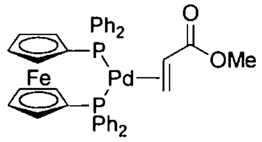
Figure 2



As well as the bite angle, the nature of the coordinating atom in bidentate ligands can have a marked effect, the reactivity of **37** to iodobenzene being considerably greater than that of **38**.[159]

Another interesting feature of chelated palladium catalysts is that in some cases they allow the isolation of palladium-olefin complexes.[160] The complex (dppf)Pd(methylacrylate) **39** has been isolated and characterised, and the complex was stable to dissociation of methylacrylate, although this process could be promoted by the addition of Lewis acids.[160] Addition of PhI or PhOTf led to oxidative addition with displacement of the alkene.[160]

39



As alluded to in the last section, the generation of palladium catalysts from palladium(0) precursors can have effects on the oxidative addition step. Such palladium(0) species often incorporate dba and this has been found to impact the reactivity of the active catalysts. Despite the common assumption that dba is a weak ligand for palladium, the presence of dba has been found to inhibit the oxidative addition of PhI to $Pd(PPh_3)_4$.[161] Comparison of the rate constants for oxidative addition of PhI to preformed $Pd(PPh_3)_4$ and $Pd(PPh_3)_n$ generated from $Pd(dba)_2$ showed that the presence of dba decreases the rate of reaction by a factor of ten,[161] and the oxidative addition to chelated palladium catalysts is similarly inhibited.[155] Studies involving substituted dba analogues have shown that the dissociation of dba can govern the rate of oxidative addition to aryl iodides[162,163] and in some cases the presence of dba can completely inhibit reaction by preventing oxidative addition taking place.[156]

The nature of the olefin coordinating palladium can have a considerable impact on the reactivity of the metal to aryl halides. For similar species, small changes such as fluorination can switch the kinetic preference of a system between η^2-coordination and oxidative addition.[164,165]

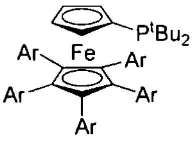
Oxidative addition to amine ligated palladium-phosphine complexes has also been proposed,[166] however, subsequent studies have shown that amine decomplexation is required before oxidative addition can take place.[167,168] DFT studies have added support to this hypothesis by suggesting that the amine binds to palladium after oxidative addition has taken place.[169] Despite claims that oxidative addition is rate limiting in these amination reactions,[168] some doubts have been cast over this by the observation of large differences between the stoichiometric and catalytic behaviour of the systems in question.[170]

The coordination number of the active palladium species has also received recent attention, with two theoretical studies which included solvation effects suggesting that palladium-monophosphine species are involved.[113,171] It was also suggested that whilst oxidative addition of PhI to $Pd(PPh_3)_2$ occurs with an energy barrier, oxidative addition to $PdPPh_3$ required no activation. Although the dissociation of PPh_3 from $Pd(PPh_3)_2$ is endothermic, it was suggested that in solution, a favourable entropic contribution gives a sufficient concentration of the active catalytic species.[92] Further evidence for this mechanism comes from a recent investigation of the oxidative addition of aryl iodides, bromides and chlorides to a palladium diphosphine complex with a bulky monodentate phosphine (Q-phos derivative **40**).[172] This investigation claimed that three distinct mechanisms were in operation depending on the identity of the halide.[172] Aryl iodides reacted by oxidative addition with concurrent dissociation of a ligand, whereas aryl bromides were found to follow a mechanism involving rate determining ligand dissociation followed by rapid oxidative addition, and aryl chlorides were found to react by reversible dissociation of a phosphine followed by rate limiting oxidative addition.[172] Three-coordinate products, consistent with this mechanism, have been isolated and characterised.[173] It should be noted that this actually involves *two* different mechanisms; one for aryl iodides and one for aryl bromides and chlorides, with the bromides and chlorides having different rate determining steps.[170] Although these results are in agreement with those of the DFT studies, it should be noted that the great steric bulk of the ligand involved is likely to promote reaction by ligand dissociation. However, another experimental study has implied the participation of monoligated palladium triphenylphosphine species.[174] Another DFT study has suggested that the mechanism can depend on the aryl halide; both chlorobenzene and bromobenzene proceeding through monoligated palladium routes (albeit with different rate determining steps) whilst iodobenzene reacted by both mono- and bis-ligated palladium routes.[175] DFT studies also suggest that the unsaturated palladium(II) monochloride anion can be active.[176] For bulky monodentate phosphines, different rotameric forms may be involved in the oxidative addition,[177] with stabilisation by η^2-coordination from the second aryl ring.[178]

It is interesting to note that subtle changes to the phosphine ligand can have marked effects on the mechanism and hence reactivity. Studies on bis(trialkylphosphine)palladium complexes **41**-**44** found that for iodobenzene, **41** and **42** react *via* an associative mechanism whilst **43** and **44** react *via* a dissociative mechanism (initial loss of phosphine).[132] Whilst **41** and **42** react rapidly with iodobenzene, the same reaction with **43** and **44** is slow. In contrast, **43** and **44** are active catalysts of the Heck reaction of chlorobenzene with butyl acrylate whilst **41** and **42** are virtually inactive.[132]

Figure 3

40



Ar = 4-MeC_6H_4

$R_3P-Pd-PR_3$

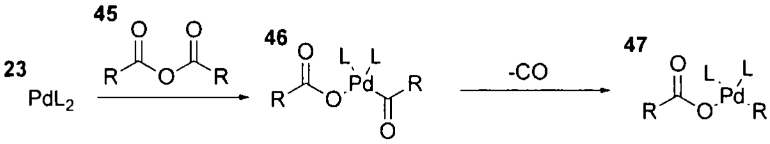
41 $PR_3 = Cx_3P$
42 $PR_3 = Cx_2P^tBu$
43 $PR_3 = CxP^tBu_2$
44 $PR_3 = P^tBu_3$

Oxidative addition of alkyne ligated palladium complexes in solution has also been investigated theoretically.[179] It has been suggested that acetylene is an excellent ligand for palladium and that oxidative addition of aryl iodides to such species is a favourable process. The addition occurs with initial coordination of iodine, followed by concerted iodide dissociation/ metal-carbon bond formation.[179] Such a mechanism has also received investigation in the context of the hydroarylation of alkynes, in this case the oxidative addition being proposed to occur through a mono-ligated palladium(0) alkyne species with prior dissociation of another ligand.[180]

Oxidative addition of alkyl halides to palladium has been investigated using DFT calculations.[181] Although this study suggested that the barriers to oxidative addition were markedly higher than for corresponding aryl and vinyl halides, the real problem with the use of such species is their inherent instability due to *β*-hydride elimination.

Finally, the oxidative additions of a number of other species have been investigated, including benzoic anhydride[182] and acetic anhydride[183] Although rare, these species can be used as electrophiles in the HM reaction if a decarbonylation step is added between the oxidative addition and carbometallation steps.[182] The mechanism of oxidative addition of these species involves insertion of palladium into one of the carbon-oxygen single bonds of **45** to generate species **46** from which loss of carbon monoxide generates a palladium alkyl or aryl acetate or benzoate **47** (Scheme 7).[171,182] It has been suggested that the presence of chloride is necessary for this reaction as palladium benzoates are unreactive.[100]

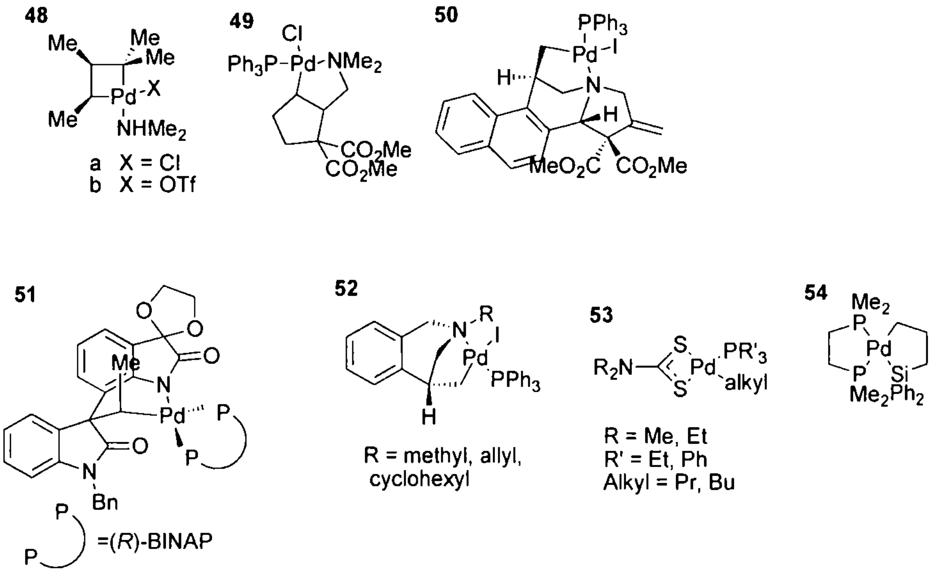
Scheme 7: HM reactions of anhydrides



1.1.6 Carbometallation, β-hydride elimination and HX elimination

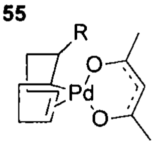
Since these steps follow oxidative addition they are significantly more difficult to investigate and are best discussed together rather than as separate steps. Although the products of oxidative addition are sometimes isolable, it has often been found that they show different reactivity to those generated under catalytic conditions.[136] This has been ascribed to *cis*/*trans*-isomerisation (*vide supra*) and makes experimental studies of carbometallation both difficult and potentially meaningless. Additionally, palladium alkyl compounds with β-hydrogens are generally too unstable to allow their isolation.[55,183] Whilst palladium alkyl species lacking β-hydrogens are relatively easily prepared,[184,185] those possessing β-hydrogens are much less stable[186,187] due to β-hydride elimination. Indeed, even when β-hydrogen are absent, reductive elimination reactions have been noted,[188] presumably through bimolecular reactions. In the few instances where palladium σ-alkyl species possessing β-hydrogens have been isolated, the species are either poorly characterised[189,190] or have general structural features that stabilise such intermediates.[191-197] It seems that for intermediates in which the palladium atom is locked in a small (four or five membered) ring and is coordinated by an intramolecular hereroatom[198-201] (species **48** to **54**), the β-hydride elimination process is sluggish, this being ascribed to the palladium atom having an enforced geometry that disfavours *β*-hydride elimination.[191,192] Such behaviour is also seen for platinum alkyl species possessing *β*-hydrogens.[202]

Figure 4: stable palladium-alkyl species



Some of these palladium(II) complexes demonstrate remarkable thermal stability.[195,197] Stable *σ*-alkyl palladium species lacking intramolecular heteroatom coordination have only been found in one instance[203] (species **55**), in this case the *β*-hydrogens are in positions such that they can never adopt the cisoid geometry relative to palladium necessary for *β*-hydride elimination. Interestingly, although it may be expected that unsaturated palladium would destabilise such species by promoting *β*-hydride elimination, cationic triflate **48b** (no covalent bonding is seen for such triflate species) was found to be more stable than the neutral chloride **48a**.[191] In the case of compound **53**, *β*-hydride elimination/carbometallation sequences occur on warming such that when the starting alkyl group is *iso*-propyl or *sec*-butyl, the resulting species contains mainly the primary alkyl group.[193] For compound **54**, it is difficult to know whether the stabilisation owes to coordination by silicon or to geometrical constraints in the cyclic structure.[201]

55



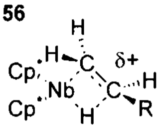
R = OMe, OEt, Ar, NEt_2, OAc, NO_2

Because of the highly specialised structures of these σ-alkyl palladium species, it is likely that even if the study of stoichiometric β-hydride eliminations from these species is undertaken, the results will not be representative of the more general case.

The study of β-hydride elimination from bis(phosphine) dialkyl palladium species has suggested that β-hydride elimination occurs by a non-dissociative pathway.[204,205] However, it has been shown that for amino-iridium complexes, β-hydride elimination occurs following phosphine dissociation.[206]

Before investigations of carbometallation, studies on the mechanism of insertion of various species into transition metal carbon σ-bond served as a model for the carbometallation step. Investigation of the insertion of *para*-substituted styrenes into a rhodium hydride bond[207] showed that the process produced a negative Hammett parameter, $\rho = -0.9$. This shows that electron donating substituents on the olefin accelerate the migratory insertion. The same study also demonstrated that the migration is accelerated by electron donating phosphine ligands.[207] Interestingly, a second study on the kinetics and mechanism of the insertion of a range of olefins into a niobium hydride bond showed an identical Hammett parameter ($\rho = -0.90$), suggesting that this effect may be more general as the two hydride bonds involved are very different electronically.[208] The postulated mechanism to explain these results involves a cyclic transition state **56** in which there is build up of positive charge on the olefin being stabilised by electron donating groups.[208]

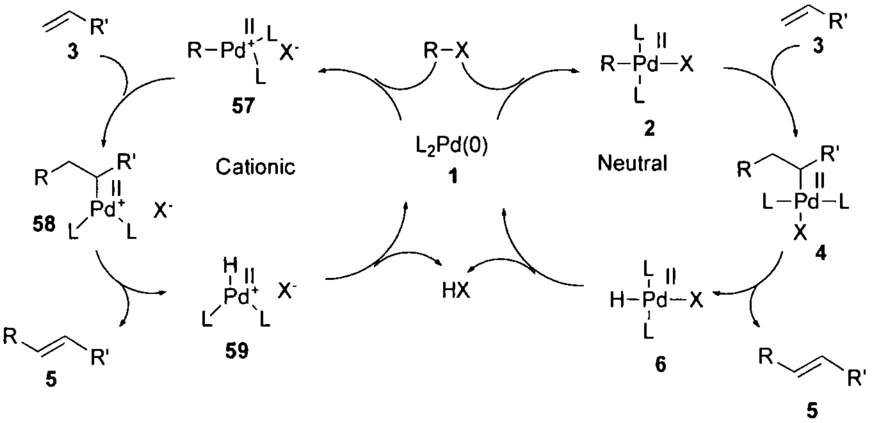
56



The bond breaking/forming process was suggested to be concerted,[208] however, the electronic effects in these reactions appear to be complex. In another system it was found that electron withdrawing groups accelerated the migration;[209] this being ascribed to stabilisation of the ground state with the effect of increasing the olefin binding constant. The migratory insertion of olefins into palladium alkyl bonds has also been investigated and it was found that electron poor olefins underwent a faster insertion process although electron rich olefins bound to the metal more strongly.[210] It was found that *syn* insertion occurred for the insertion of olefins into palladium(II) acyl bonds; these reactions being faster for cationic palladium species than for neutral. The mechanism of insertion was suggested to involve the dissociation of either solvent (cationic pathway) or phosphine (neutral pathway), to allow the coordination of the olefin.[211] Also, the investigation of the intramolecular insertion of alkynes and olefins into palladium acyl bonds showed a dissociative equilibrium existed between a phosphine ligated species and the less coordinately saturated active species. The existence of five coordinate intermediates in the reaction was disproved.[212] Carbopalladation reactions of benzynes have been reported,[213] in these cases the resulting sp^2 carbon coordinated palladium intermediates are able to undergo further coupling reactions.

The nature of the product obtained from the oxidative addition step has a great influence on the rest of the catalytic cycle (see Scheme 8). Cationic palladium species formed from the oxidative addition of triflates[148] and diazonium salts[214] behave differently to the neutral species generated from halides.[147] Additionally, the nature of the phosphine (monodentate or bidentate) has a marked effect on subsequent steps, some bidentate phosphines chelating so strongly that they render the oxidative addition product unreactive.[27] Some phosphines can also produce dimeric, halide-bridged oxidative addition products.[133] It is possible to move from a neutral system to a cationic system through the addition of a halide scavenger such as silver(I) triflate,[144] equally, it is possible to move in the opposite direction by the addition of a halide source such as lithium chloride.[91]

Scheme 8; Comparison of cationic and neutral HM cycles



For a long time there has been considerable evidence that oxidative addition is not rate limiting in HM reactions. The observation of a reversal of the expected reactivity for aryl iodides[101,215] is noteworthy, and the unexpectedly low reactivity of aryl chlorides in HM reactions, when compared to their rates of oxidative addition, suggests that even for these species, other steps may limit the reaction rate.[216]

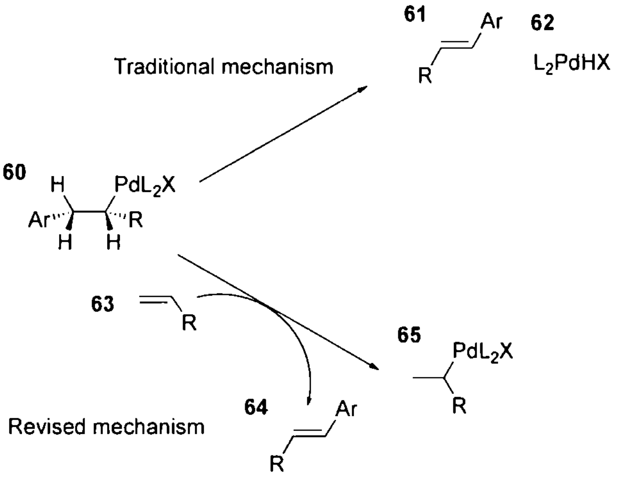
It has been proposed that for the reaction of aryl iodides with acrylates using triphenylphosphine as ligand, the rate determining step depends on the phosphine/palladium ratio. Olefin coordination being rate limiting when the ratio is 2:1 or more whilst migratory insertion being rate limiting for ratios of 1:1.[215] Strong effects of the phosphine/palladium ratio have also been observed in other systems,[217,218] although mechanistic reasoning was not given.

1.1.6.1 Neutral monodentate intermediates

For monodentate ligands and ligand free systems, various suggestions for the rate determining step have been put forward. These include β-hydride elimination,[219] coordination/insertion of the olefin[220] and halide dissociation.[221]

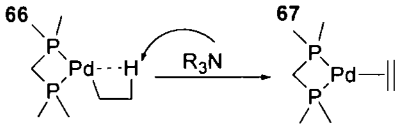
An interesting observation came in an investigation of a ligand free HM reaction. It was found that for certain combinations, addition of one olefin to a HM reaction accelerated the arylation of another olefin.[222] This was rationalised by a modification of the β-hydride elimination step; the elimination of palladium hydride **62** being replaced by the transfer of the palladium hydride species **62** to another olefin **63** furnishing the product and unsubstituted palladium(II) alkyl species **65** (Scheme 9). This palladium hydride transfer was suggested to be the rate determining step,[222] although a traditional β-hydride elimination step, followed by an elimination of HX, would still be required to generate an active catalyst. The study also proposed that both revised and traditional mechanisms could occur at the same time.[222]

Scheme 9: competing mechanisms for β-hydride elimination



Although this is an interesting suggestion and explains the behaviour observed, such interception of palladium hydride species by olefins is normally seen under conditions where no base is employed, for example, when stoichiometric palladium is used.[223-225] This suggests that base normally reacts with palladium hydride species considerably faster than olefins. Such observations support the results of a theoretical study which suggested that in the presence of base, β-hydride elimination was base assisted with the base deprotonating the agostic hydrogen in intermediate **66** (Equation 1).[226]

Equation 1

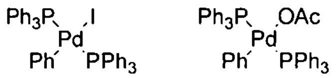


The olefin insertion step has been shown to be irreversible in the ligand free palladium system in a study which also found β-hydride elimination to be rate determining.[219] High pressure experiments have shown that olefin coordination or insertion is rate determining when triphenylphosphine is the ligand and also prove the presence of a polar transition state.[220] Gas phase DFT studies have suggested that for carbene ligands, halide dissociation is required before the olefin can bind to the resulting cationic intermediate.[221]

Another interesting suggestion was that the aryl iodide species **68**, resulting from the oxidative addition of PhI to $Pd(PPh_3)_4$, was unreactive to olefins, whilst the corresponding aryl acetate species **69** (arising from the proposed oxidative addition to palladium anions, *vide supra*) was the active species.[120] However, the problem with this suggestion is that HM reactions of aryl iodides are frequently performed in the absence of acetate,[1,227] showing that aryl acetate **69** is not the only possible reactive intermediate. This appears to be another case of stoichiometric reactions being unrepresentative of those taking place under catalytic conditions,[136] and presumably can be explained by several factors, including isomerisation.[139] Hence, it appears likely that the increase in reactivity observed upon the addition of, for example, acetate anions to aryl iodide **68** is due to an increased rate of isomerisation to the reactive *cis*-form,[139] or that the *cis*/*trans* equilibrium for aryl acetate **69** lies more on the side of *cis*-form than the equivalent equilibrium for aryl iodide **68**.

Figure 5

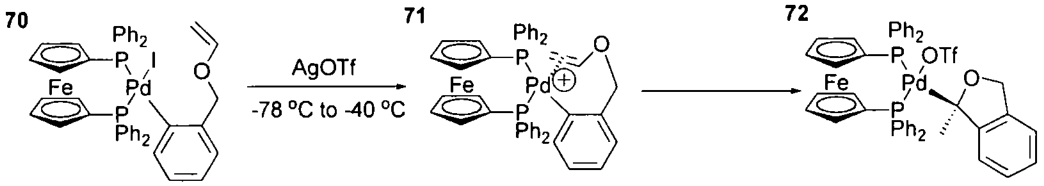
68 **69**



1.1.6.2 Cationic intermediates

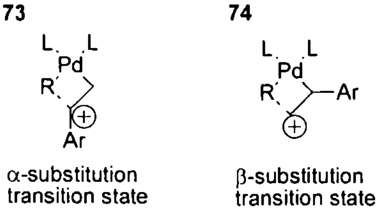
Although one study has suggested that the reaction of cationic palladium aryl species with olefins is slow,[120] this does not appear to be a general phenomenon since it has been shown that insertion reactions of olefins into palladium carbon σ-bonds is faster for cationic species.[211] Indeed, the carbopalladation of olefins by cationic palladium species has been followed at -60 °C.[223] It has also been found that the addition of chloride to cationic systems, to form the neutral chloride species, can completely inhibit the reaction with olefins.[149] Cationic palladium systems have also been used to great success in the asymmetric HM reaction.[151] In these systems, reactions are accelerated by electron donating groups on the aryl moiety, which is the reverse order of reactivity observed for oxidative addition and this behaviour can be ascribed to rate limiting olefin coordination or carbometallation.[144] The high enantiomeric excesses observed in the asymmetric HM reactions under cationic conditions are thought to be due to the olefin being able to bind to palladium without partial dissociation of the bidenatate phosphine.[142,145] This observation has led to the proposal of some sort of dissociation from a four coordinate palladium(II) complex in order for the olefin to coordinate.[146] In cationic systems, the availability of a free site for an olefin to bind is due to the dissociation of an anion, whilst in neutral systems phosphine dissociation is necessary.[144] Because dissociation of many chelated phosphines is slow,[27] HM reactions using aryl halides and bidentate phosphines often do not occur.[147,148] The olefin insertion reaction can be facile in cationic systems; in the intramolecular HM reaction shown in Scheme 10, this occurs rapidly at -40 °C.[147]

Scheme 10: acceleration of HM reactions through halide abstraction



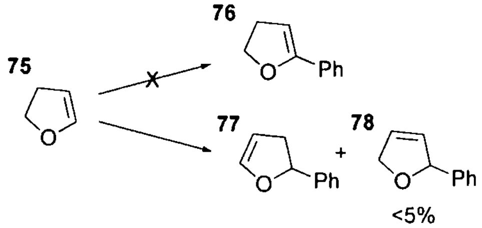
There has been most work done on styrene-related systems, which has provided information on the olefin insertion step in the cationic HM reaction of PhOTf with a range of *para*-substituted styrenes.[228] A negative Hammett parameter ($\rho = -0.74$) was obtained for α-substituted products only, notably no correlation being found for β-substituted products. This observation was rationalised by the transition states **73** and **74**. For α-substitution, the build-up of positive charge occurs at the α-carbon and is stabilised by electron donating groups on the aryl ring of the styrene. For β-substitution, the build-up of positive charge occurs at the β-carbon and no stabilisation from groups on the styrene is possible.[228]

Figure 6



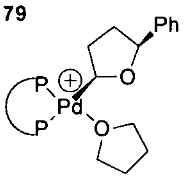
Other studies have focussed on using NMR spectroscopy to follow the reactions of olefins with cationic palladiums species.[223] This allowed the observation of a number of intermediates, albeit under stoichiometric conditions. As noted previously, in the absence of base the eliminated palladium hydride species was seen to react with further olefin which was present in excess.[223-225] In certain circumstances, isomerisation can occur to give unexpected products (Scheme 11). This is most noteable in the case of 2,3-dihydrofuran **75**, a common substrate in the asymmetric HM reaction.

Scheme 11: potential products from dihydrofuran



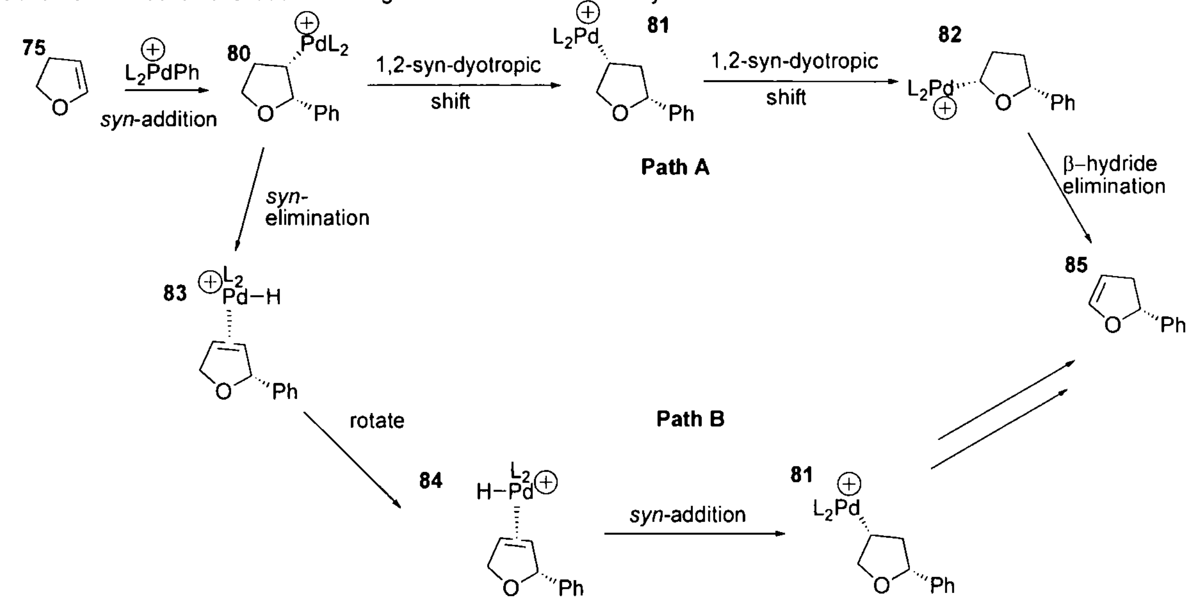
This isomerisation is in fact of considerable importance to these reactions as it permits the formation of a chiral centre where none would be expected. Observation by NMR spectroscopy has shown that this isomerisation is extremely rapid, only intermediate **79** being seen prior to the formation of product 77.[224]

79



Deuterium labelling experiments have demonstrated that this isomerisation occurs either by a two consecutive 1,2-*syn*-dyotropic shifts (Scheme 12, path A) or by a *syn* chain-walking mechanism (Scheme 12, path B). *Anti*-1,2-dyotropic shifts and *anti*-β-hydride elimination pathways were ruled out.[229]

Scheme 12: mechanistic rationale of regiochemical outcome for dihydrofuran



Given that these reactions were carried out in the presence of base and that *β*-hydride elimination in the presence of base has been proposed to involve direct deprotonation of an agostic palladium-hydride bond,[226] path A may appear more likely as no such intermediate is inferred.

Carbene ligated palladium catalysts have also been used with some success under cationic conditions ($AgBF_4$). These strong donor ligand systems presumably assist in stabilising the positive metal centre.[61]

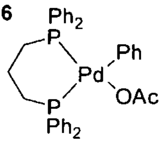
The use of cationic catalysts has also been shown to have a pronounced effect on the regioselectivity of the HM reaction. Typically, in the neutral manifold, steric effects have a large impact upon regiocontrol and tend to favour *β*-substitution, however, by using a cationic catalyst, electronic effects can be made to dominate.[146] For electron rich olefins, coordination to the cationic palladium atom favours migration to the *α*-carbon,[144] acrylates, however, always show complete *β*-selectivity.[146] Interestingly, it has been reported that it is possible to achieve highly selective *α*-substitution using a neutral catalyst through careful choice of ligand and solvent.[230,231] It was postulated that this may be due to these conditions giving rise to transient cationic catalysts.[231]

Regioselectivity has been shown to depend strongly on the palladium counterion, solvent polarity and phosphine bite angle.[232] Careful choice of conditions has allowed remarkably selective arylation of butyl vinyl ether, complete β-selectivity being seen for a substrate that tends to give substantial α-substitution.[233]

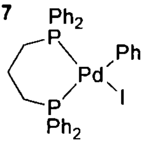
Cationic intermediates have been found under conditions where neutral species would be expected. When acetate is used as base, displacement of the halide on palladium is possible due to the acetate being present in large excess. For palladium-acetate bonds, dissociation is preferred when compared with iodine-palladium bonds.[157] It has been shown that acetate **86** reacts with both methyl acrylate and styrene *via* a cationic mechanism, dissociation of acetate being rate determining. The corresponding iodide **87** reacts with styrene by the same mechanism, albeit more slowly, but when methyl acrylate is used both neutral and cationic pathways are involved.[157] Similar results have been seen in the reactions of **86** and **87** with *iso*-butyl vinyl ether.[234]

Figure 7

86



87

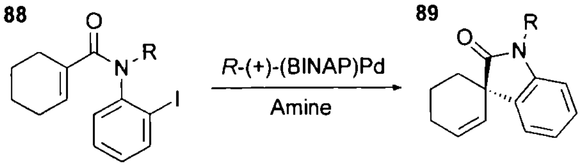


DFT studies including solvation have been used to generate a selectivity index for α/β-selectivities of a variety of olefins, in both neutral and cationic pathways, and the results appear to be quite accurate.[235]

1.1.6.3 Neutral bidentate intermediates

As previously noted, reactions involving this sort of species tend to be sluggish due to the reluctance of both chelated phosphines and halides to dissociate from palladium to give a coordinately unsaturated species.[27] However, it appears that under certain circumstances, the olefin can displace the halide to give a reactive species. This was suggested as being the mechanism operating in the neutral asymmetric HM reaction shown in Equation 2.[150]

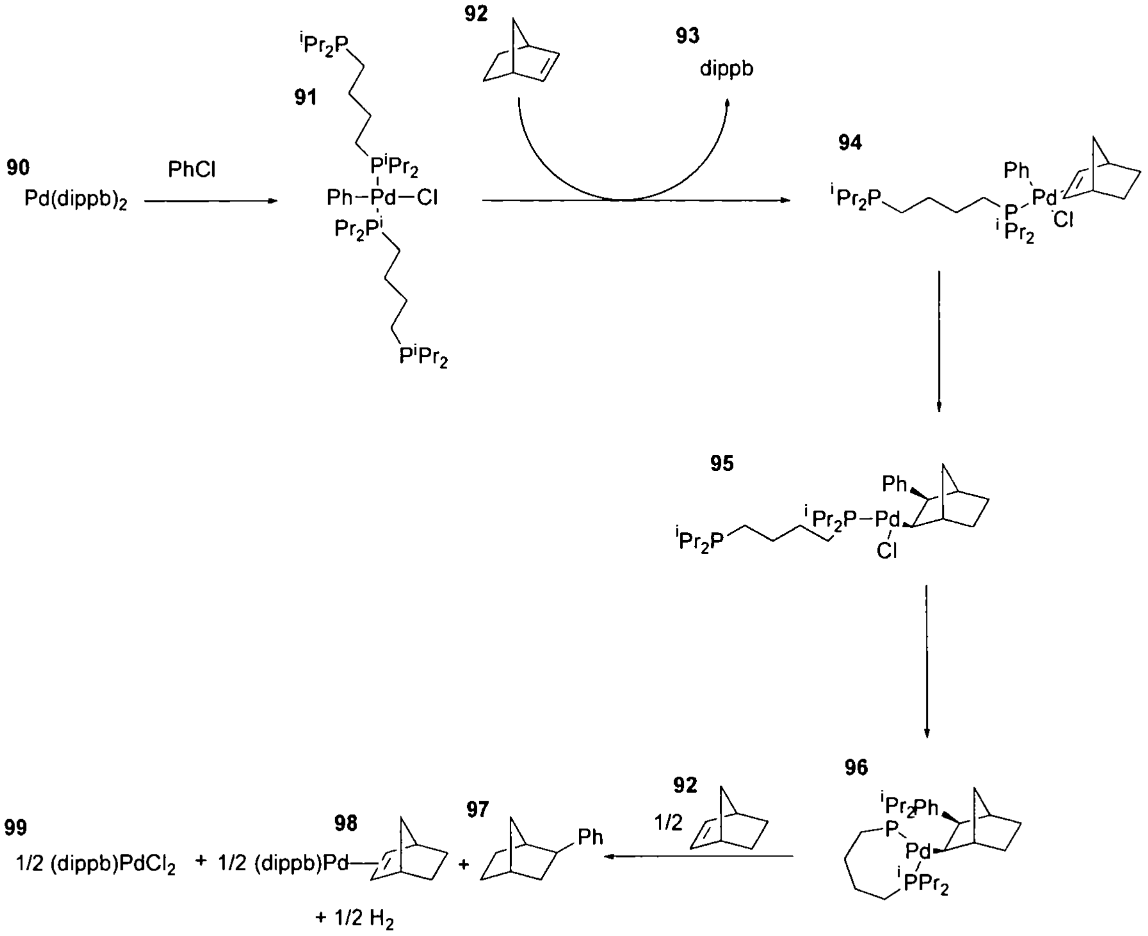
Equation 2



High e.e.s were obtained in the absence of added halide scavengers, indicating that phosphine dissociation was not occurring. The proposed mechanism involved associative displacement of halide by the olefin to give a reactive cationic species.[150] In this case, the five coordinate palladium transition state required contains two bidentate ligands which makes it less disfavoured than the five coordinate palladium intermediates discussed previously. Another interesting observation to come from this study was the reversal of enantioselectivity upon the addition of AgOTf to the reaction,[150] thus forming a cationic species upon oxidative addition.

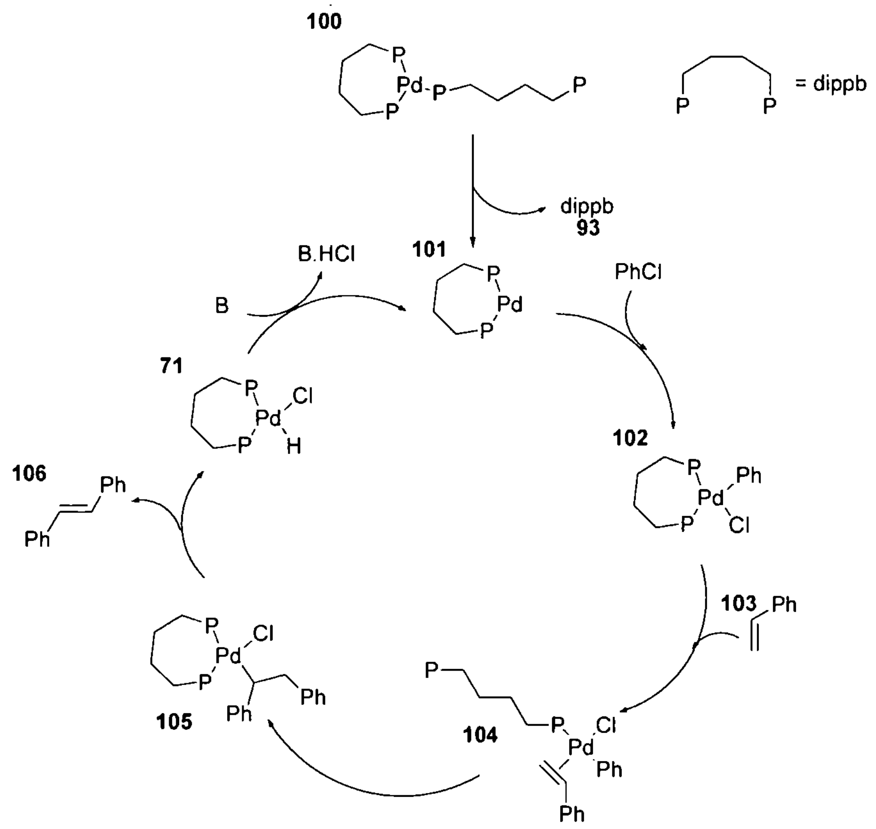
More generally, however, small ring chelated palladium species seem to be poor catalysts of the HM reaction. Although the oxidative addition can occur, the resulting palladium species is unreactive towards olefins due to its coordination saturation and lack of labile groups.[27,216] For some chelated species, the poor catalytic activity observed is due to disproportionation of the catalyst. For the reaction shown in Scheme 13, evolution of hydrogen occurs and the catalyst is oxidised to palladium(II) chloride in two catalytic cycles.[103]

Scheme 13: disproportionation of chelated palladium catalysts



Whilst the small ring chelates from phosphines such as dippe and dippp generally give poor catalysts, increasing the size of the ring tends to increase activity.[27,216] The use of dippb as a ligand allows the coupling of aryl chlorides;[27] the increased ring size apparently increasing the lability of the phosphine and causing it to behave more like a monodentate ligand[236] (Scheme 14).

Scheme 14: revised mechanism of HM reactions using chelated catalysts



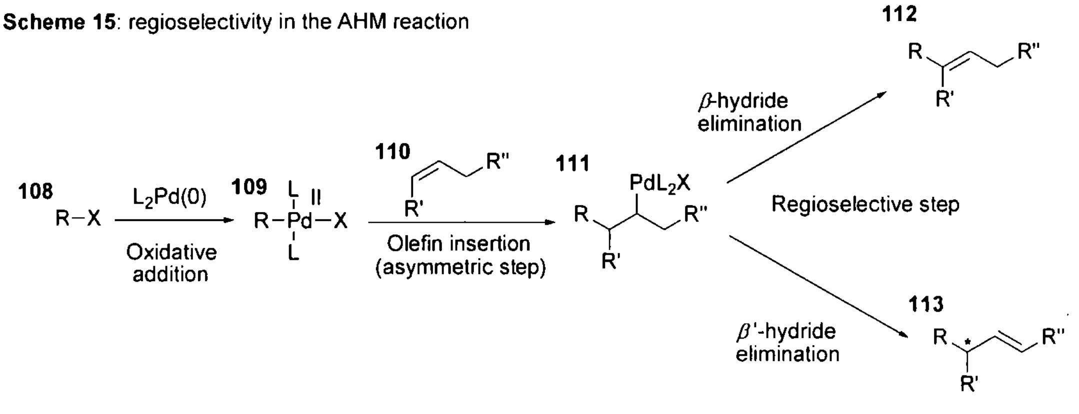
The kinetics of the HM reaction catalysed by chelated neutral species have been investigated.[41] Use of a range of *para*-substituted iodides gave a Hammett parameter ρ = +1.39, and although the positive sign of this value is consistent with oxidative addition, its magnitude is not and rate limiting olefin insertion was proposed.[41]

Bidentate carbene-phosphine ligands have also been investigated by gas phase DFT studies and a mechanism involving rate limiting phosphine dissociation (*i.e.* chelate opening) has been proposed.[221]

1.1.7 Asymmetric HM (AHM) reactions

The HM reaction discussed hereto is concerned with the generation of an sp^2 hybridised centre and consequently, induction of chirality is generally not possible. However, if the incoming group is added to a di- or tri-substituted carbon and a *β*'-proton is present, the competing *β*'-hydride elimination can give rise to a chiral centre (Scheme 15). In this case, the use of chiral ligands on palladium can give asymmetric induction.

Scheme 15: regioselectivity in the AHM reaction



The discovery of this reaction came considerably later than that of the achiral variant, Shibasaki[34] and Overman[35] independently discovering the intramolecular version and Hayashi[142,145] subsequently developing an intermolecular variant. The importance of this variant of the HM reaction is demonstrated by its extensive application to natural product total synthesis.[237] Although the mechanism of this variant of the HM reaction is the same, the greater complexity introduced by the required enantioselective and regioselective steps merits further discussion.

Good control over both the enantioselectivity of the olefin insertion and the regioselectivity of the subsequent *β*-hydride elimination from **111** are essential to the AHM reaction. Even if good enantioselectivity can be achieved in the first step, the induced chirality will be lost if poor control of the *β*-hydride elimination step yields achiral product. Additionally, the reinsertion of olefin **113** into the palladium hydride bond can lead to an equilibrium between the two products with consequent loss of chirality.[238]

1.1.7.1 Enantioselectivity

This requires a chiral palladium catalyst and hence the use of a chiral ligand. Bidentate ligands are required to achieve good asymmetric induction and a huge number of different ligands have been used. These include homochiral chelating P,P, P,N and N,N ligands.[151] It is important to note that the enantioselective step in such reactions is necessarily either olefin coordination step (coordination to one pro-chiral face) or carbometallation, no selectivity being possible in the oxidative addition step due to the achiral nature of aryl halides.

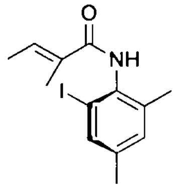
Another important point relating to the enantioselectivity of the olefin insertion is whether the palladium(II) species is neutral or cationic. As a rule, the cationic pathway is found to give much greater asymmetric induction, this being ascribed to the requirement for ligand dissociation in the neutral pathway (*vide supra*). Whilst in the neutral pathway, partial dissociation of the bidentate chiral ligand reduces the influence of the ligand and thus e.e., in the cationic pathway the olefin can bind without ligand dissociation and thus high e.e. can be achieved.

Important exceptions to this rule have been observed in which high e.e.s have been found using the neutral pathway.[239] Indeed, in some cases it has been found that the addition of silver additives to promote the cationic pathway can be detrimental to asymmetric induction.[240] Also, the observed stereochemistry is generally reversed on moving from a cationic catalyst to a neutral catalyst.[240] It has been shown that in these cases, phosphine dissociation does not occur and although halide dissociation to yield a cationic intermediate has been postulated, this would not explain the change in configuration, the lack of selectivity for aryl triflates or the lack of solvent effects.[150] Two other potential mechanisms have been suggested, involving associative displacement of halide by the olefin and insertion from a five coordinate palladium(II) intermediate.[240]

As noted earlier, the reluctance to form five coordinate intermediates is documented,[122,123] however, in this case with both the phosphine and the halide/olefin being bidentate, and thus having an enforced bite angle, such intermediates seem more plausible than in the case where all substituents are monodentate. Both mechanisms have the potential to explain the reversal in product configuration over the cationic pathway and thus without further studies it is not possible to say which occurs although the authors favour the associative displacement process.[150]

An intriguing recent study suggested that certain AHM reactions may be a dynamic kinetic resolution. As AHM reactions are often intramolecular, systems such as **114** are relatively common. Iodide **114** possesses axial chirality and such systems can have considerable barriers to rotation depending on the nature of the aryl substituents; for this reason it is possible to prepare such species in enantiopure form.[241]

114



It has been observed that in cases such as this, the oxidative addition step can be enantioselective, the catalyst preferentially adding to one enantiomer of a slowly racemising mixture. Strong evidence for such a proposal comes from the HM reaction of **114** using an achiral catalyst; use of starting material of 99% e.e. provides the expected product with 71% e.e.[241] Although some loss of chirality is seen, such losses may not be seen when racemic starting material and chiral catalysts are used since following enantioselective oxidative addition, the rotation required for racemisation becomes less likely due to increased bulk of palladium-phosphine complexes *versus* iodine. An interesting upshot of this form of enantioselectivity would be that such reactions could give reduced e.e., or only 50% conversion, should the temperature be insufficient for racemisation to occur.

1.1.7.2 Regioselectivity

Regiocontrol in HM reactions requires a way to favour *β*'-hydride elimination over *β*-hydride elimination. The most obvious way to achieve this is through the generation of a quaternary chiral centre since in this way no *β*-hydride elimination is possible. Unfortunately, the formation of asymmetric quaternary centres is rather less well documented than for tertiary centres although it has been known to be possible for some time. Presumably, the tri-substituted olefins required for this tend to be less reactive due to steric hinderance and although possible, this reaction remains a challenge.

A number of other, more common ways of favouring *β*'-hydride elimination include: i) Use of intramolecular AMH reactions since when the product is an endocyclic alkene, the rotation required around the alkene σ-bond for β-hydride elimination to occur is not possible; ii) Use of a thermodynamic driving force for β'-elimination through choice of the group R''. For instance, R''= OH gives an enol which tautomerises to the corresponding aldehyde or ketone, R''= OR gives an enol ether or R''= alkenyl gives a conjugated diene; iii) Use of an allylsilane as the olefin component has also allowed controlled β'-hydride elimination under AMH reaction conditions.[242] Additionally, it may be expected that β'-hydride elimination would be favoured kinetically since the rotation around the alkene σ-bond necessary for β-hydride elimination is not necessary for β'-hydride elimination.

In certain cases, most notably in that of 2,3-dihydrofuran (*vide supra*), isomerisation to unexpected products may allow the formation of chiral centres.

These points explain why the AMH reaction is most often used in intramolecular reactions to form endocyclic alkenes, another drive for β'-hydride elimination often also being present.[238]

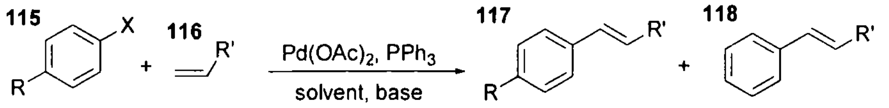
1.1.7.3 Product isomerisation

In order to prevent the loss of chirality associated with isomerisation by reinsertion of products back into the palladium(II) hydride bond, it is often necessary to add chemicals to suppress this, these typically being thallium or silver salts.[86,87,243]

1.1.8 Aryl-aryl exchange

The observation of the formation of unexpected products in HM reactions using triaryphosphine ligands has been known for some time.[57,244] Typically, when triphenylphosphine is used, the alkenylated benzene product **118** is found as one of the products (Equation 3).

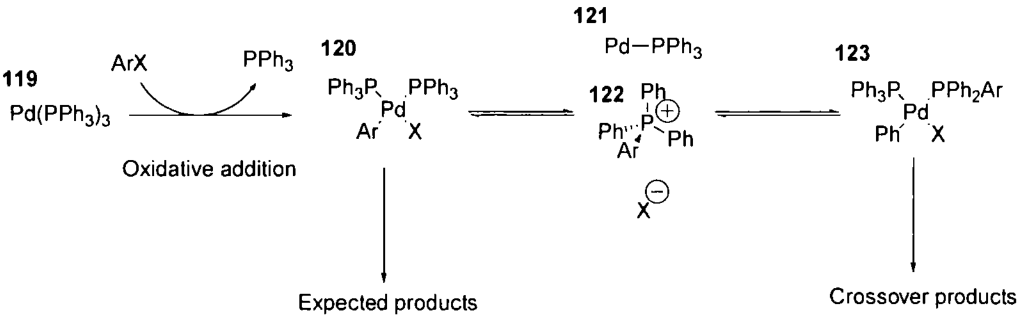
Equation 3



In addition, the phosphine resulting from exchange of one of the aryl groups of the phosphine with one of those from the halide can be observed.[244] This problem tends to occur in systems which generally show poor reactivity, such as deactivated bromides, possibly because of the temperatures required to achieve coupling in such systems.[216] It has been found that addition of stoichiometric $Pd(PPh_3)_4$ to vinyl triflates and aryl halides gives rise to vinylphosphonium[141,245] and tetra-aryl phosphonium salts.[246] This process can also be performed with catalytic palladium as a useful method to generate mixed aryl triarylphosphines.[247]

The mechanism for this scrambling involves the oxidative addition of the aryl halide to palladium(0) phosphine ligated catalyst **119** and subsequent reductive elimination to generate phosphonium salt **122** (Scheme 16).[248,249] The eliminated phosphonium salt can then undergo oxidative addition to the palladium(0) species **121** generated in this process. However, the phosphorus-carbon bond undergoing the oxidative addition may not be the same as that formed in the reductive elimination species **123** can form, and hence aryl-aryl exchange can occur.[248,249] It has been demonstrated that the selection of the phosphorus-carbon bonds that undergo oxidative addition is entirely random, allowing the statistical modelling of product distributions.[248]

Scheme 16: mechanistic rationale for observed cross-over products



Various attempts have been made to eliminate these reactions, mainly by varying the phosphine ligand employed,[216,250] however, the only way to eliminate such side reactions is through the use of *ortho*-substituted phosphines, such as tri(*o*-tolyl)phosphine[250] and tri(mesityl)phosphine,[216] or by using trialkylphosphines.[250] The reaction also appears to be promoted by electron donating substituents, either on the phosphine or the aryl group of the halide.[248] This is presumably due to the promotion of the reductive elimination step by stabilisation of the positive charge on phosphorus in aryl phosphonium salt **122**.

1.1.9 Summary and conclusions

At best it can be said that the mechanism of the oxidative addition is strongly dependant on conditions, particularly depending on whether the reaction is saturated with halide. However, as the reaction proceeds, assuming aryl or vinyl halides are involved, the mechanism of the oxidative addition may well change as the halide generated saturates the reaction mixture. Clearly, no one proposed mechanism for the oxidative addition explains all the phenomena observed and it seems likely that several mechanisms may be in operation, either independently or in parallel, depending on the reaction conditions.

For subsequent steps, the mechanism is more poorly understood due to difficulties of investigations. It seems that even for aryl chlorides, the rate determining step is often after the oxidative addition step, since the rates of reaction of such species are lower than those seen for the oxidative addition reactions. This may be due to the electron rich, chelating nature of the phosphines required to activate aryl chlorides, which in turn disfavours carbometallation or dissociation. For iodides, and some other activated leaving groups, it seems to be generally accepted that the rate determining step comes after initial oxidative addition. However, the nature of this step is unclear and has a strong dependence on the nature of the species produced in the oxidative addition step.

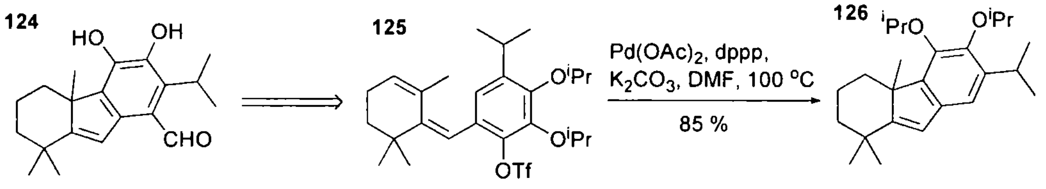
Clearly, for a full understanding of the mechanism in operation, further studies are required, although it may well be the case that due to the reactive nature of the intermediates involved and the complexity of the reaction conditions, a comprehensive understanding will be challenging to achieve.

1.2 HM reactions in total synthesis

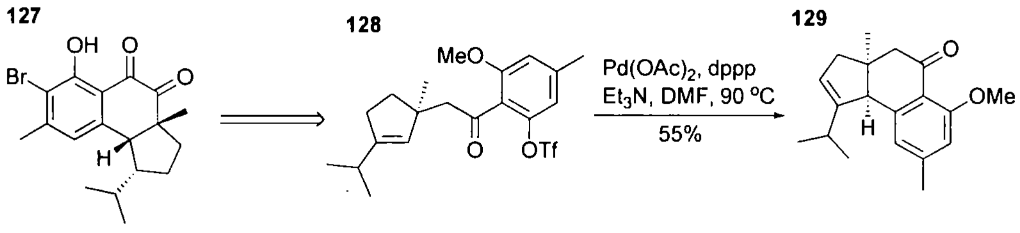
In recent years the HM reaction has seen extensive use in total synthesis; a quick literature search reveals over two hundred and thirty articles since 1991 that cite the use of a HM reaction in total synthesis and this is unlikely to be exhaustive. These articles mainly involve the construction of natural products although drugs have also been synthesised. In this context, the asymmetric HM reaction has seen considerable use[251] due to its potential to construct tertiary and even quaternary stereocentres which would prove challenging by other methods. The non-asymmetric HM reaction has also seen considerable use in this area and the following examples are illustrative.

The total synthesis of (±)-dichroanal B **124** (Scheme 17) uses a HM reaction for the key cyclisation step of triflate **125**, the desired tricyclic **126** being formed in an impressive 85% yield.[252] A similar strategy was employed in the total synthesis of 6-*epi*-(-)-hamigeran B **127** (Scheme 18), triflate **128** cyclising to give intermediate **129** in reasonable yield.[253]

Scheme 17: key HM reaction in the total synthesis of **124**

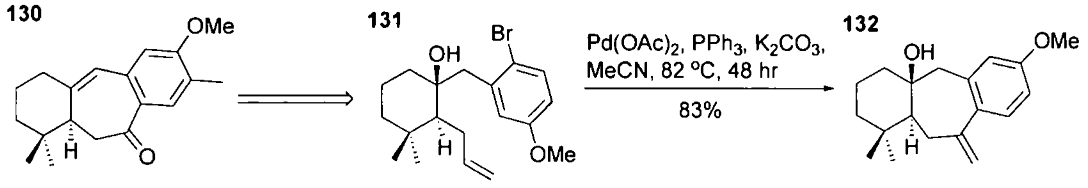


Scheme 18: key HM reaction in the total synthesis of **127**



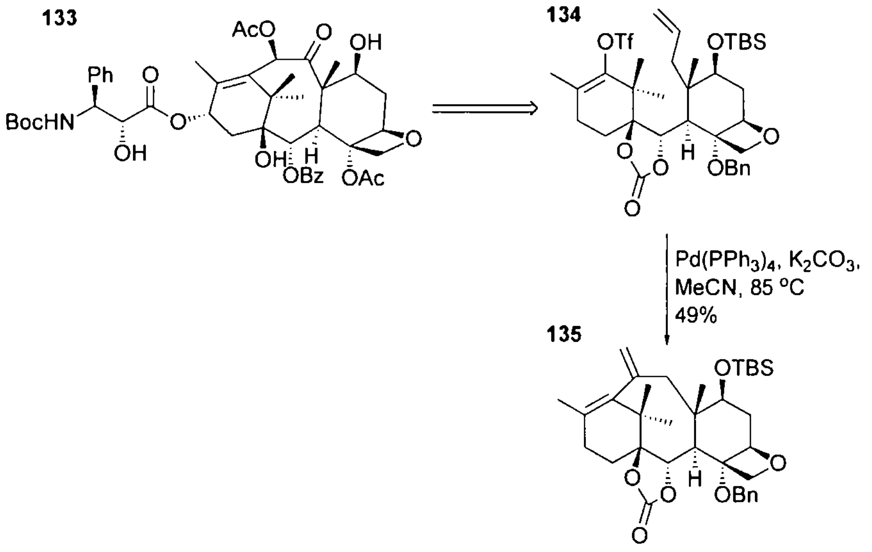
HM cyclisations have also been used to produce larger ring sizes, for instance in the total synthesis of faveline methyl ether **130** (Scheme 19), HM reaction of bromide **131** gave preferentially the seven-membered ring and hence intermediate **132**.[254]

Scheme 19: construction of a medium ring using a HM reaction



Taxol derivative **133**, the subject of much synthetic and medicinal interest, has been synthesised numerous times and indeed one route utilised a HM reaction. Reaction of triflate **134** under HM conditions gave eight membered intermediate **135** for elaboration to taxol.[255] An interesting feature of this approach was the early introduction of the four-membered oxygen containing ring.

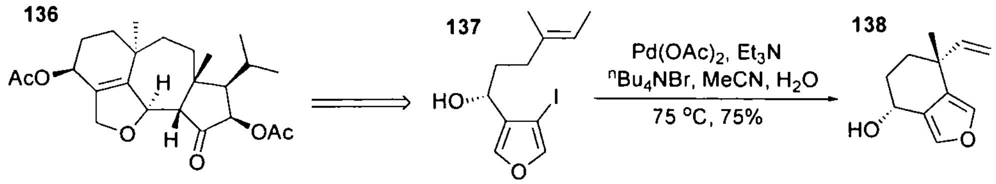
Scheme 20: key HM ring-closing reaction in the total synthesis of taxol



As the previous two examples demonstrate, when used for cyclisations, HM reactions tend to give the smaller of two possible ring sizes.

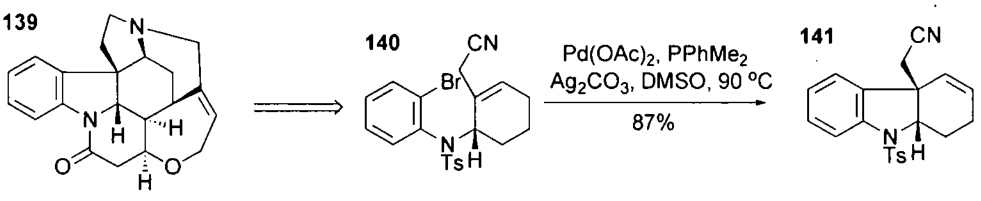
HM cyclisations of chiral substrates can occur with impressive diastereoselectivity as demonstrated in the total synthesis of heptemerone B **136** (Scheme 21). In this case the chiral alcohol centre controls which face of olefin **137** reacts, producing 5:1 diastereoselectivity for isomer **138** shown.[256]

Scheme 21: diastereoselective HM cyclisation

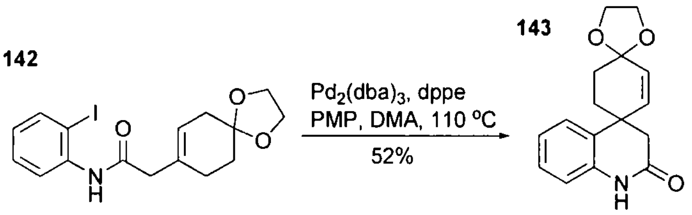


The elaborate strychnine ring system **139** has also been accessed *via* a diastereoselective HM reaction; bromide **140** cyclising to **141**, apparently with complete diastereoselectivity.[257] Another route to the strychnine system came from reaction of iodide **142** to produce the spiro-cyclic system **143** which subsequently underwent a conjugate addition/basic cyclisation sequence to produce a tetracyclic system for derivatisation to strychnine.[258]

Scheme 22: diastereoselective HM cyclisation

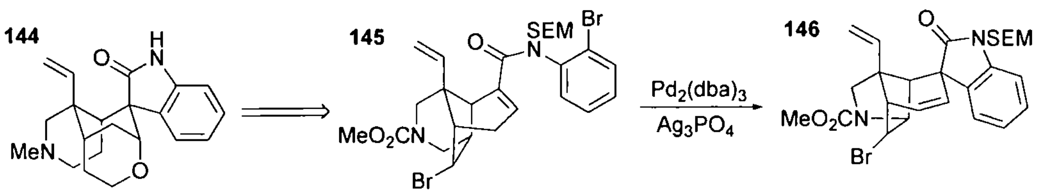


Scheme 23: construction of a spiro-centre using a HM reaction



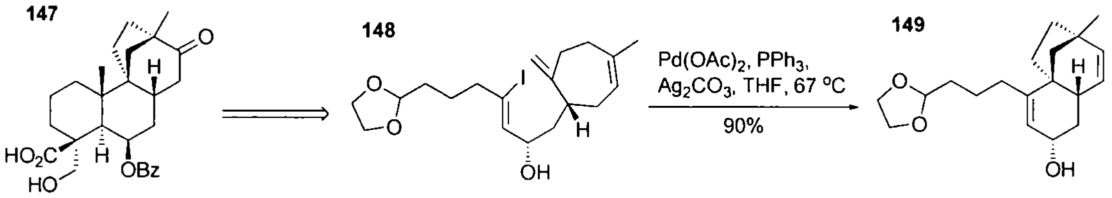
Other spiro-cyclic centres have been formed through HM reactions; for example, in the synthesis of gelsemine **144**, reasonable selectivity for the desired diastereoisomer was achieved through the HM reaction shown in Scheme 24.[259]

Scheme 24: construction of a spiro-centre using a HM reaction



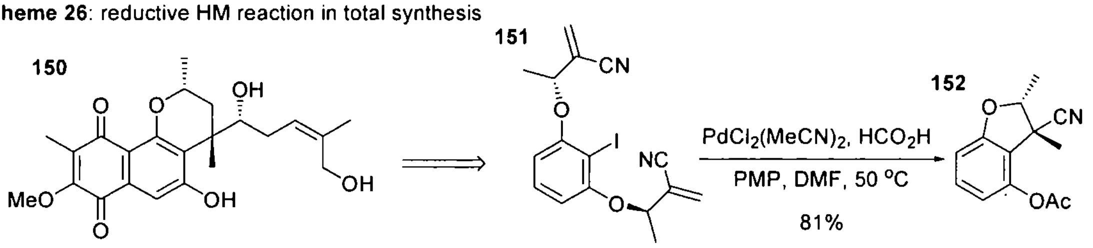
HM cascade reactions have also been seen to proceed with impressive diastereoselectivity. In the total synthesis of scopadulcic acid **147**, such a cascade was performed on iodide **148** to set up two new chiral centres in intermediate **149**.[260]

Scheme 25: diastereoselective HM cascade reaction

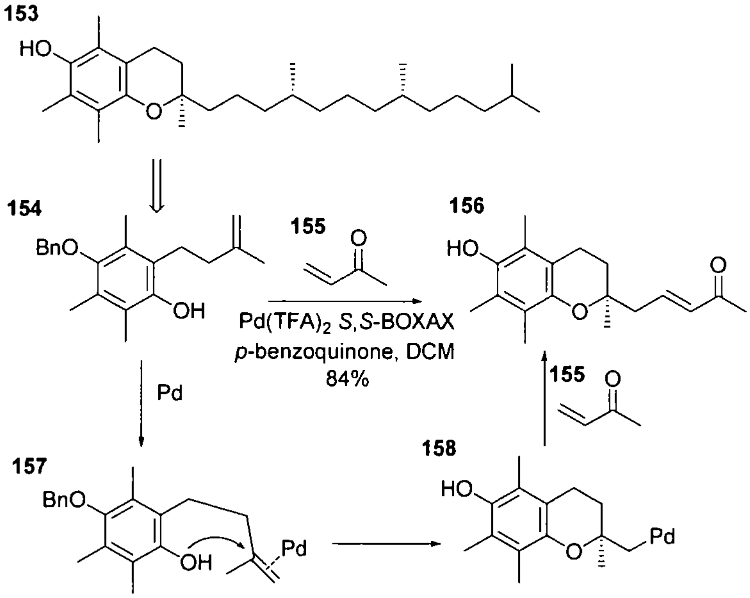


Variants of the HM reaction have also seen use in the area of total synthesis. These include reductive HM reactions (Scheme 26) and oxidative HM reactions ('Wacker-Heck' reactions, Scheme 27). For the synthesis of vitamin E **153** shown in Scheme 27, an initial oxidative step sets up a reactive alkyl palladium intermediate which is intercepted by an olefin.[261] The use of formic acid in Scheme 26 allows a HM reaction to proceed without the isolation of an olefin, direct reduction of the palladium alkyl intermediate occurring in this situation in which *β*-hydride elimination cannot occur in this synthesis of furaquinocin A **150**.[262]

Scheme 26: reductive HM reaction in total synthesis

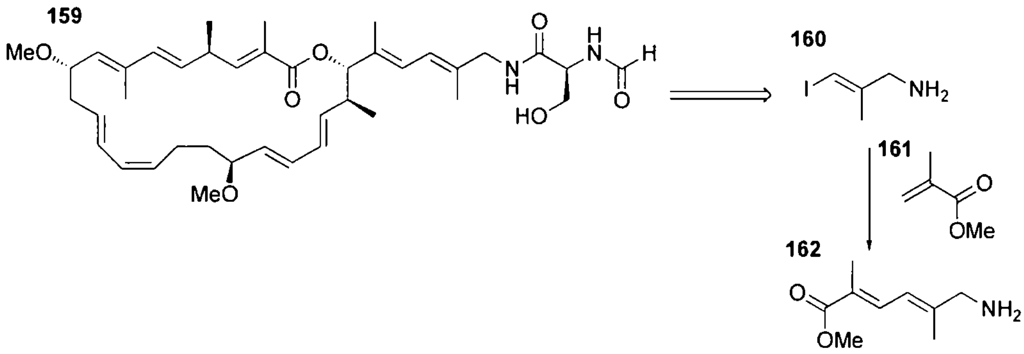


Scheme 27: mechanism of an oxidative HM reaction for total synthesis of **153**



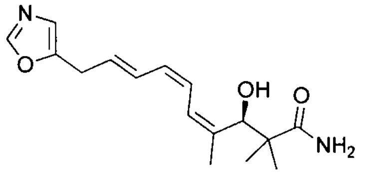
Given their use in total synthesis, it is interesting to note that HM reactions have been applied relatively little to the construction of polyenes whilst other palladium catalysed reactions, most notably the Suzuki-Miyaura and Stille reactions, have enjoyed considerable use. A HM reaction was employed in the total synthesis of iejimalide B **159**, however, as shown in Scheme 28, this was hardly a key step.[263]

Scheme 28: use of HM reaction in the total synthesis of polyene **159**



One notable use of HM chemistry in the total synthesis of polyenes comes in the total synthesis of phthoxazolin A (*aka* inthomycin, **163**) by Hénaff and Whiting.[264,265] The method employed in this synthesis involved the HM reactions of vinylboronate esters which had been found to function as vinyl-dianion equivalents.[266,267]

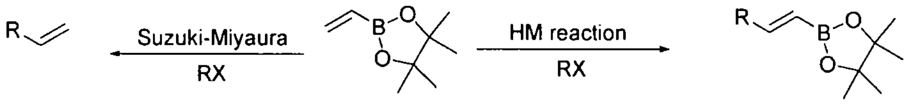
163



Vinylboronates such as pinacol ester **165** can react with aryl or vinyl halides either by HM or Suzuki-Miyaura [268] reactions, the ratio between the two products depending on the choice of base, solvent, temperature and additives present.[269]

Scheme 29: chemo-selectivity in the reaction of vinyl boronates with aryl halides

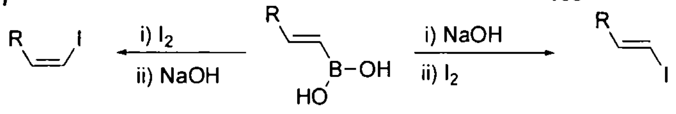
164 **165** **166**



Brown had previously shown that vinyl boronic acids could be converted to vinyl iodides by reaction with iodine and sodium hydroxide. The stereochemical outcome of this reaction was found to depend on the order of addition of the two reagents; initial addition of sodium hydroxide retaining the initial geometry of the olefin[270] and initial addition of iodine giving inversion of the initial geometry (Scheme 30).[271]

Scheme 30: stereoselectivity in the iododeboronation of vinyl boronic acids

167 **168** **169**



Although vinyl boronate esters were initially found to be stable to these conditions,[270] subsequent studies showed that these too could be converted to vinyl iodides through the use of iodine monochloride and sodium methoxide.[267] Through a sequence of HM selective reactions of vinyl boronates and stereoselective iododeboronation of the resulting boronate product, an iterative approach to building up polyene structures was achieved.[266] The power of this methodology was demonstrated by the total synthesis of racemic Phthoxazolin A.[264,265]

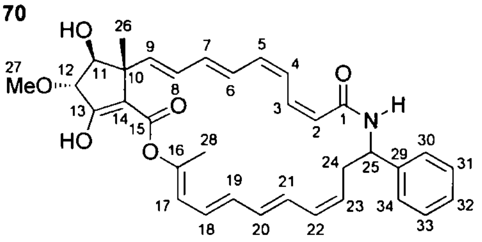
2 Results and Discussion

2.1 Aims and overview

Following the impressive demonstration of the HM/iododeboronation chemistry in the total synthesis of phthoxazolin A, a yet more challenging target was sought. This was found in polyene macrolide viridenomycin **170** (Figure 15, shown with the numbering system used by the first paper reporting its structure), which shows considerably more varied geometry than the single (*Z*,*Z*,*E*)-triene section of phthoxazolin A. An approach to the stereoselective synthesis of viridenomycin will be presented in this thesis.

Figure 7: structure of viridenomycin

170



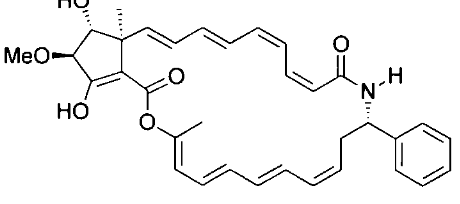
2.2 Structure and biological activity of viridenomycin

The 24-membered macrocyclic polyene lactam viridenomycin was first isolated from a culture broth of a strain of *Streptomyces viridochromogenes* in 1975.[272] The molecule was found to have extremely high antiprotozoal activity as well as being an antibiotic, however, the structure was not identified. A subsequent study searching for new antitumour antibiotics rediscovered the molecule, this time from a culture of *Streptomyces gannmycicus*.[273] The study found that viridenomycin prolonged the survival of mice bearing B16 melanoma and reported the structure. In this case the structure was assigned based on NMR spectroscopy,[274] hence only the relative stereochemistry of the cyclopentene ring was assigned; the absolute configuration of these and the remote benzylic centre remain unknown.

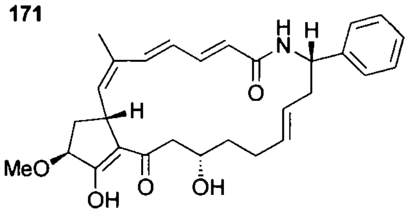
Viridenomycin is related to hitachimycin (*aka* stubomycin, **171**) which has been synthesised and the absolute stereochemistry determined.[275] Given the similarity, it may be expected that the stereochemistry of viridenomycin will reflect that of hitachimycin and hence be that shown in Figure 8.

Figure 8: Comparison of viridenomycin **170** and hitachimycin **171**

170



171

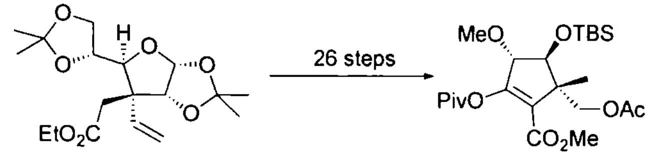


Structurally remarkable features of viridenomycin include the two tetraene sections; the (*Z,Z,E,E*) northern (C_2-C_9) and (*E,E,E,Z*) southern (C_{16}-C_{23}) hemispheres; the highly substituted cyclopentene ring with the ketone present in its enol form; and the enol lactone function at the C_{17} end of the southern hemisphere.

2.3 Previous attempts at synthesis by other groups

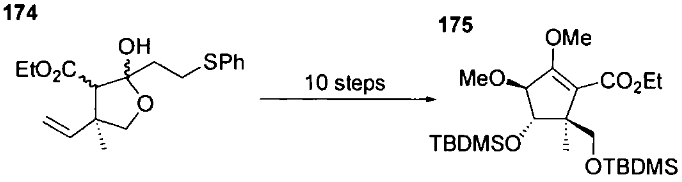
Given the wealth of structural features and biological activity present in viridenomycin, it is unsurprising that a number of attempts have been made towards its total synthesis. Most synthetic effort has focused on the highly functionalised cyclopentene core, the first such example being that of Ishihara *et al.* who outlined a 26 step synthesis of enantiopure cyclopentene equivalent **173** starting from glucose derivative **172** (Equation 4).[276] Although the yields of each step were generally high, the longwinded nature of the synthesis contributed to the poor overall yield (9.6%) which ultimately makes this route undesirable.

Equation 4



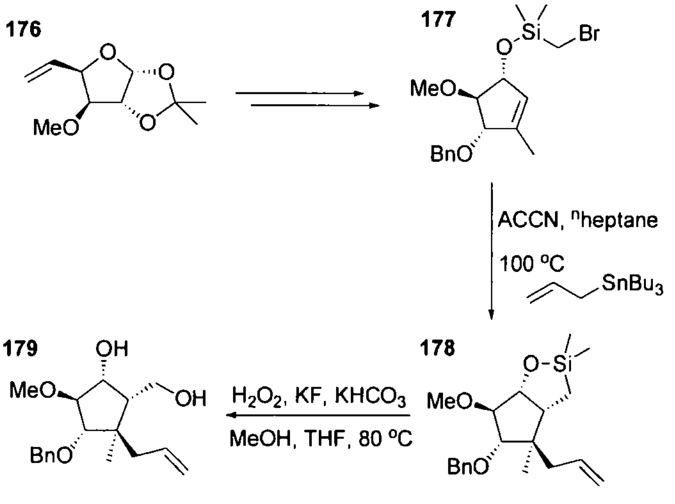
Trost and co-workers produced a more efficient (14% overall yield) and much more concise (10 step) synthesis of cyclopentene **175**, starting from tetrahydrofuran **174**, itself accessed though an enantioselective palladium catalysed alkylation.[277]

Equation 5



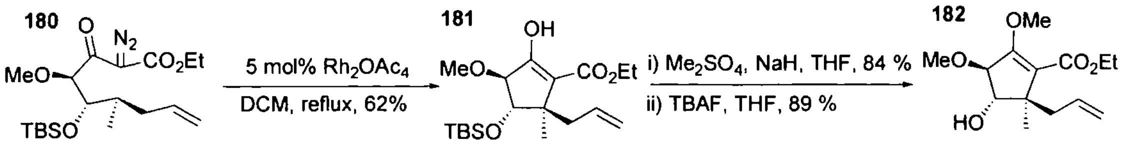
More recently, Pattenden has produced two syntheses of the cyclopentene core. The first involved a tandem radical cyclisation-trapping strategy (Scheme 31), **177** being accessed *via* a route involving a Grubbs ring closing metathesis from commercial compound **176**.[278] This lengthy synthesis constitutes the least efficient route to the cyclopentene core to date with an overall yield of 4.3% over 20 steps.

Scheme 31: recent route to cyclopentanone **179**



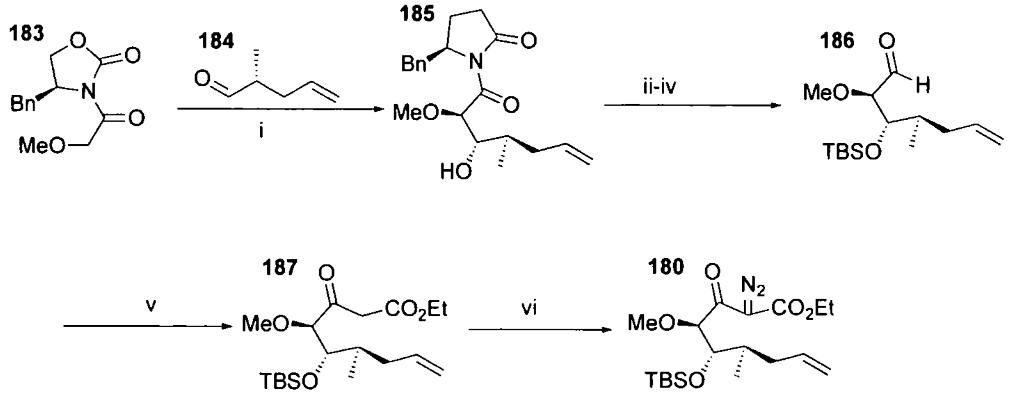
Conversely, Pattenden's second strategy is the most efficient synthesis to date (25% overall yield over 9 steps) and involves the rhodium catalysed intramolecular C-H insertion reaction shown in Scheme 32.[279]

Scheme 32: efficient synthesis of cyclopentene **182**



The preparation of **180** involved the use of a chiral auxiliary as shown in Scheme 33. A chiral auxillary controlled asymmetric aldol reaction is used to set up the required stereocentres. Following removal of the auxiliary and oxidation to the corresponding aldehyde, conversion to a *β*-keto-ester by treatment with tin(II) chloride and ethyl diazoacetate allowed diazo-transfer to form **180**.

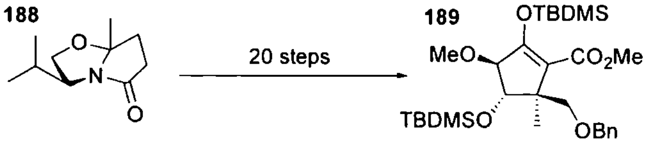
Scheme 33: enantioselective route to diazoketone **180**



i) Bu_2BOTf, Et_3N, PhMe, -50 °C, 89 % ii) TBSOTf, 2,6-lutidine, DCM, 0 °C, 80 % iii) $LiBH_4$, THF, 0 °C – rt then H_2O iv) $(COCl)_2$, DMSO, DCM, -78 °C then Et_3N and H_2O v) $SnCl_2$, EtO_2CCHN_2, DCM, rt, 89 % three steps vi) *p*-acetamidobenzenesulphonylazide, 84 %.

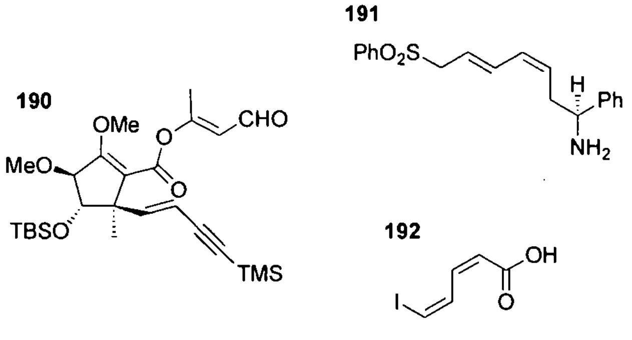
The efforts that have come closest to the synthesis of viridenomycin have been those of Meyers. The reported synthesis of the cyclopentenol equivalent **189** is rather lengthy and inefficient (8.9% overall yield, Equation 6),[280] however, no other group has reported such progress towards the northern and southern hemispheres.

Equation 6



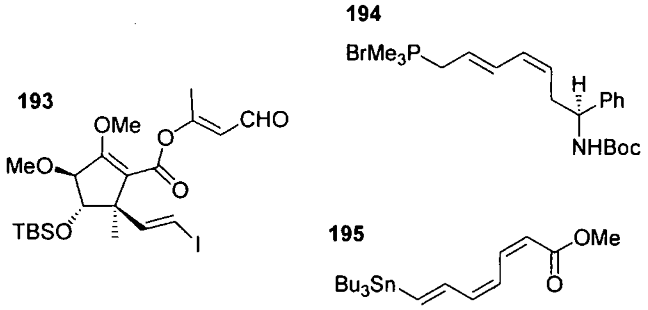
Intermediates **190**, **191** and **192** were prepared and their coupling to form viridenomycin attempted.[281]

Figure 9


190 **191** **192**

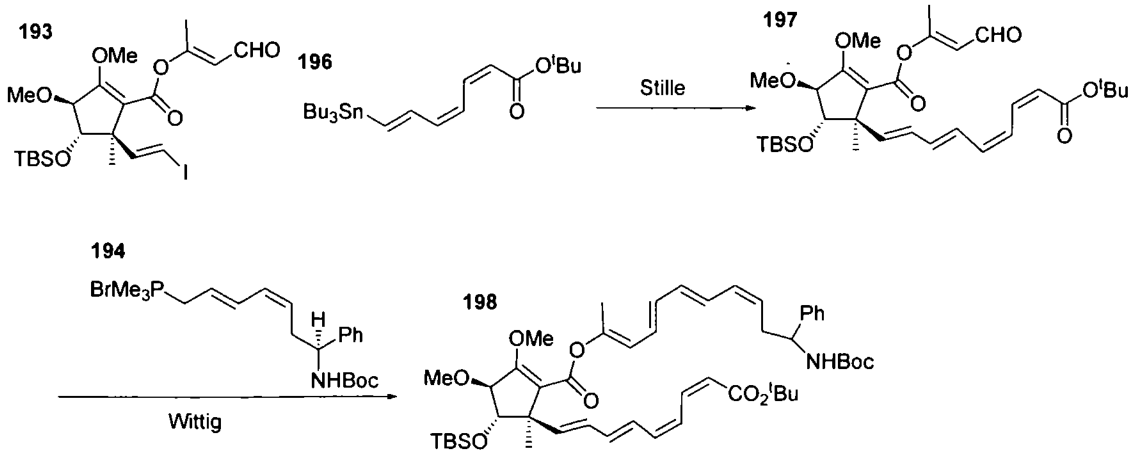
Ultimately, the required Julia olefination between fragments **190** and **191** was not achieved and second generation intermediates **193**, **194** and **195** were prepared.[282]

Figure 10


193 **194** **195**

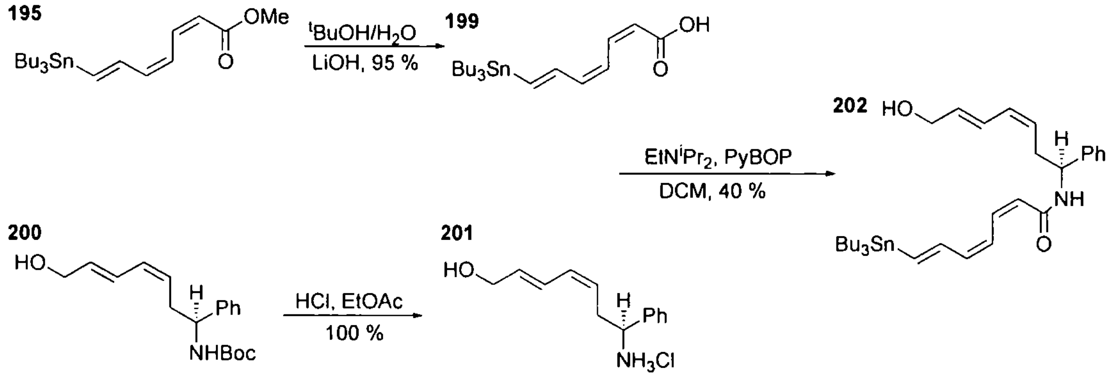
The Stille coupling of **193** and **196** proved successful as was the subsequent Wittig reaction to generate **198** (Scheme 34). Unfortunately, all attempts to deprotect **198** led to decomposition.[282]

Scheme 34: Meyers' attempted construction of viridenomycin


193 **196** **197** **194** **198**

The amide bond formation between organostannane **199** and allylic alcohol **201** was also performed to generate **202** (Scheme 35). Attempts to form an ylide from this allylic alcohol also proved unsuccessful; the attempts at bromination and tosylation of **202** leading to destruction of the molecule.[282]

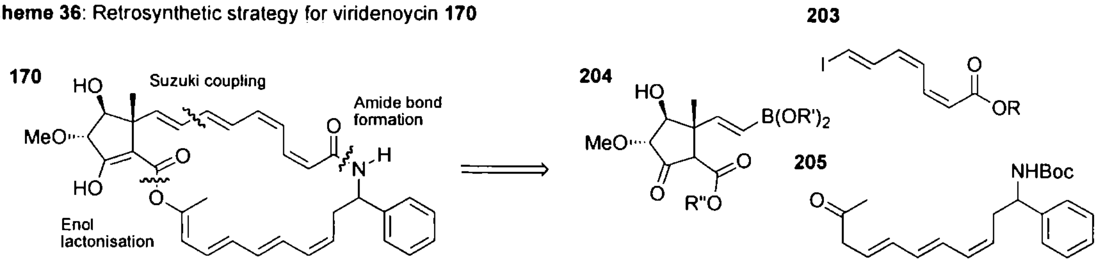
Scheme 35: Meyers' second generation attempt to construct viridenomycin



2.4 Retrosynthetic strategy

Prior to the start of this project, work was already underway within the Whiting group towards the total synthesis of viridenomycin. The retrosynthetic strategy employed is outlined in Scheme 36 and involves the division of viridenomycin into three synthons; northern triene **203**, cyclopentanone core **204** and southern triene **205**. The disconnections involve a Suzuki-Miyaura cross-coupling between fragments **203** and **204**, an amide bond formation between fragments **203** and **205** and an enol-lactonisation between fragments **204** and **205**.

Scheme 36: Retrosynthetic strategy for viridenoycin **170**

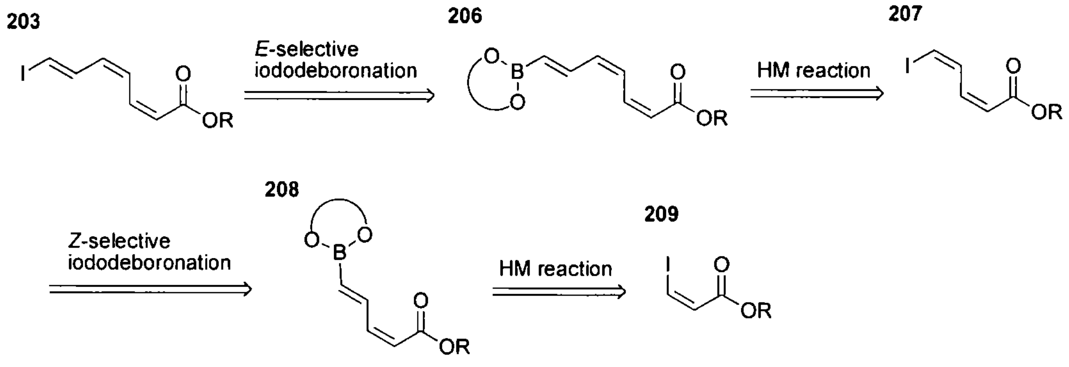


This approach in many ways mirrors that of Meyers and appears the most logical in that it allows the potentially unstable polyene sections to be assembled separately, minimising the number of reactions which they would be subjected to. In addition, this strategy allows a flexible approach to the final assembly of the three fragments; the three reactions described above can be performed in any order depending on the relative stabilities of fragments **203**, **204** and **205**.

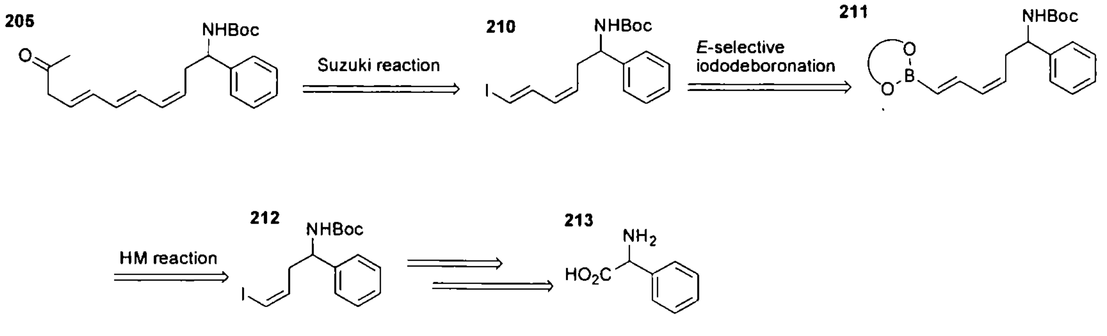
2.4.1 Approaches to the major fragments

Further disconnections for the two polyene fragments **203** and **205** involve the use of the aforementioned HM/iododeboronation methodology, **203** being obtained from a *cis*-haloacrylate of type **209** (Scheme 37) and **205** being obtained from vinyl iodide **212**, itself a derivative of phenylglycine (Scheme 38).

Scheme 37: Retrosynthetic strategy for fragment **203**

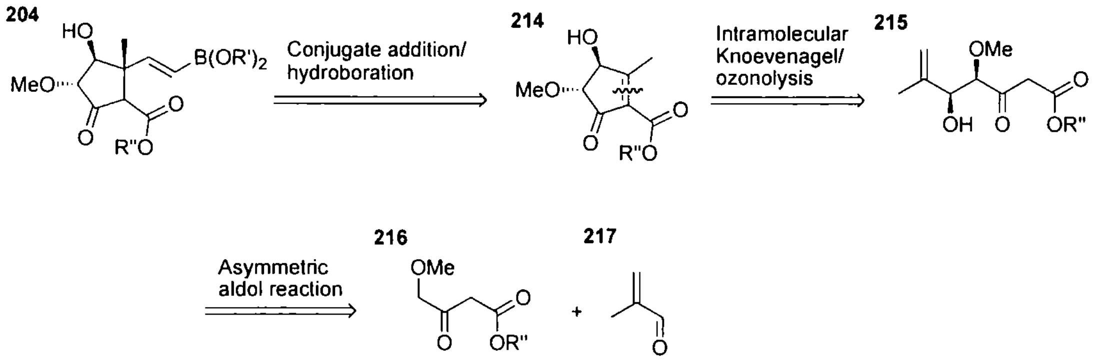


Scheme 38: Retrosynthetic strategy for fragment **205**



The retrosynthesis of core fragment **204** was performed as shown in Scheme 39; conjugate addition of a metallic acetylide and subsequent hydroboration providing boronate **204** from cyclopentenone **214**. Disconnection of cyclopentenone **214** through an intramolecular aldol reaction giving a diketone, itself accessed through the ozonolysis of alkene **215**. It was envisioned that **215** could be accessed through an asymmetric aldol reaction of *β*-keto ester **216** with methacrolein.

Scheme 39: Retrosynthetic strategy for fragment **204**

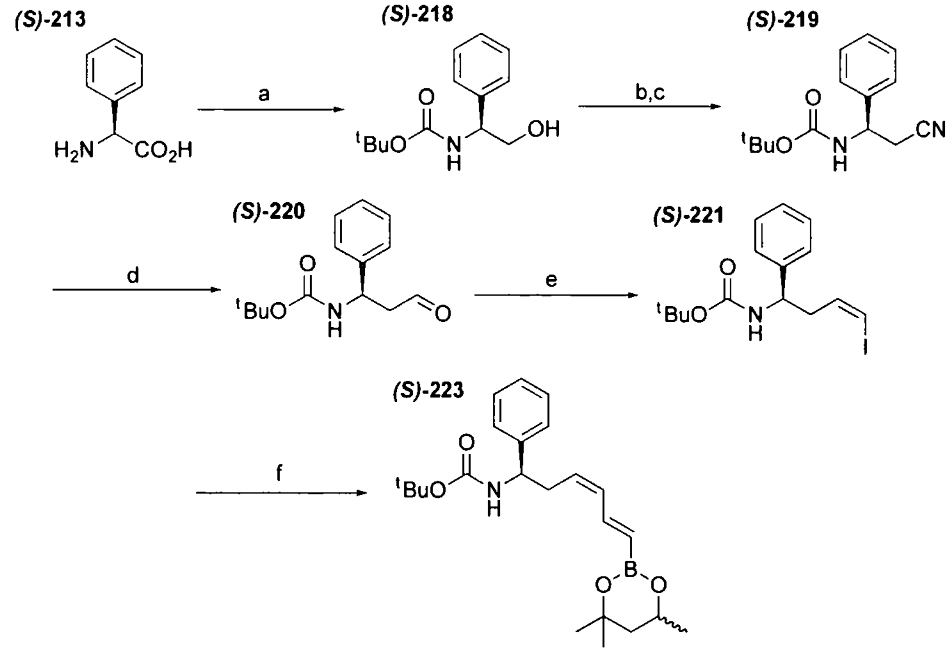


A more detailed retrosynthetic analysis of fragment **204** will be discussed in the relevant section relating to the synthesis of the cyclopentanone core.

2.5 Synthetic work within the Whiting group

As already mentioned, considerable effort had already been expended on this synthesis prior to the start of this project. Details of this work will be discussed in the appropriate section, however, as none of the work presented here contributes to the southern fragment **205**, the synthetic route to advanced intermediate **223** is detailed here. As shown in Scheme 40, reduction and protection of phenylglycine was followed by tosylation to allow displacement with cyanide. DIBAL-H reduction afforded aldehyde **220** which underwent a kinetic Wittig reaction to provide vinyl iodide **221** with high *Z*-selectivity. The HM selective reaction of vinylboronate **222** also proved successful, however, the required iododeboronation led to decomposition of the substrate. This decomposition appears to owe to the instability of the Boc-group to the strongly electrophilic nature of iodine monochloride.[283]

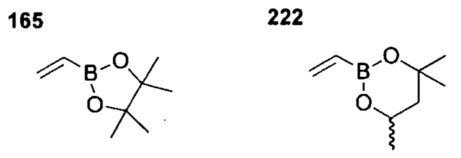
Scheme 40



a) $NaBH_4$, I_2, THF, reflux, 24 hr then MeOH then $(Boc)_2O$, Et_3N, 96%; b) TsCl, Et_3N, DCM, 16 hr, 87 %; c) NaCN, DMF, rt, 24 hr, 96%; d) DIBAL-H, Et_2O, -40 °C, 71%; e) (Iodomethyl)trimethylphosphonium iodide, KHMDS, THF, HMPA, -78 °C, 47%, *Z*/*E* > 10:1; f) **222**, Bu_3N, $Pd(OAc)_2$, PPh_3, toluene, 120 °C, 20 hr, 70%, HM:Suzuki-Miyaura > 95:5.

In addition, it should be noted that due to the instability and volatility of pinacol ester **165**, hexalene glycol analogue **222** had been developed which showed neither of these problems.[284]

Figure 11



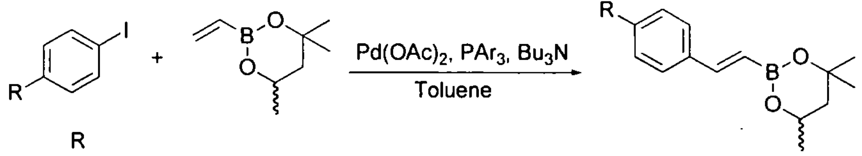
2.6 Kinetic studies of HM reactions of vinylboronate 222

As already mentioned, the HM reactions of vinylboronates **165** and **222** have been used extensively within the Whiting group. Prior to the start of this project, some purely empirical evidence suggested that the reactivity of aryl halides in these reactions was atypical when compared with more typical HM reactions involving, for example, acrylates.[284,285] Particular difficulties were found for the HM reactions of halothiophenes, halopyridines[285] and nitro-substituted aryl iodides. It was noted in the introduction to this thesis that HM reactions tend to proceed faster when electron deficient aryl halides are involved, whether or not oxidative addition is rate limiting.

This unusual behaviour was felt to merit further investigation, especially because of the electron deficient nature of halo-acrylate **209** in the HM reaction needed for the synthesis of the northern hemisphere of viridenomycin (*vide infra*). To this end, a small kinetic study was undertaken with the aim of generating a Hammett plot.[286] It was hoped that as well as providing some quantitative evidence for the order of reactivity in these reactions, the magnitude of the Hammett parameter obtained would shed some light on the nature of the rate limiting step in these reactions and hence facilitate their optimisation. With this in mind, the HM reactions of vinylboronate **222** with a range of *para*-substituted aryl iodides **223a-f** were investigated.

Equation 7

223a-f **222** **224a-f**



	R
a	OMe
b	Me
c	H
d	F
e	Cl
f	NO$_2$

2.6.1 Triphenylphosphine/palladium(II) acetate catalysis

Since this system was that typically employed by the group, it appeared logical to use this as the system with which to generate the required data. The reactions were performed in toluene at 100 °C using tributylamine as base. GC-MS was used to follow the reaction progress and the calculation of response factors using purified product and an internal standard allowed quantitative data to be obtained. Using this method, conversion *versus* time plots were obtained for the six substrates of interest. Interestingly, all such plots proved to be linear over the time period investigated (see Appendix 1) which allowed simple comparison of the reaction rates. The main problem encountered was that for substrates **223a** and **223b**, considerable aryl-aryl exchange was observed, giving rise to the unexpected formation of **224c**. This "scrambling" was most significant for **223a**, in this case a ratio of **224a**:**224c** of 3:1 was observed by ^{1}H NMR spectroscopy at the end of the reaction. Taking into account the number of equivalents of phosphine used, the maximum possible ratio of these two products should every aryl ring exchange would be 55:45.

The formation of this unwanted product posed a considerable problem to the kinetics. Clearly, ignoring the formation of this product was not possible as this would give artificially lower rates for the electron rich substrates. Not wanting to discard the data obtained, the concentrations of the two products obtained for the reactions of **223a** and **223b** were added to give a total product concentration; this gave the observed rate constants shown in Table 1.

Table 1: observed rate constants for PPh_3 catalysis

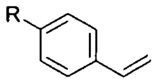
R	$k_{obs}/10^{-6}$ M s^{-1}	σ
MeO	1.6	-0.268
Me	1.3	-0.170
H	1.2	0
F	1.2	0.062
Cl	0.80	0.227
NO_2	0.25	0.778

2.6.2 Tri(2-furyl)phosphine/ palladium(II) acetate catalysis

This ligand was investigated in the hope that it would prevent the observed aryl group scrambling. This met with some success: the concentration of cross-over product was seen to be minimal in all reactions. Unfortunately, it also became apparent that all reactions produced considerable amounts of the Suzuki-Miyaura coupled product (ie. *para*-substituted styrenes **225a-f**). Due to the completely different nature of the HM and Suzuki-Miyaura reactions, accounting for this competition was impossible and the data obtained was of no use for kinetic purposes.

Figure 12

225a-f



	R
a	OMe
b	Me
c	H
d	F
e	Cl
f	NO_2

2.6.3 Tris(4-methoxyphenyl)phosphine/ palladium(II) acetate catalysis

This electron-rich ligand was investigated with the intention of accelerating the slightly sluggish reactions to allow the kinetics to be followed to a greater conversion. The reaction temperature was also increased to 110 °C for the same reason.

Somewhat surprisingly, initial investigations into a catalytic system derived from palladium(II) acetate and three equivalents of phosphine showed that no reaction took place over 7 hr. Reducing the number of equivalents of phosphine to two was found to give an active catalyst and this system was employed for the HM reactions of the six substrates.

Unfortunately, products deriving from aryl-aryl exchange were seen to be present in all reactions from an early stage. Amazingly, in the reaction of **223b**, the ratio of **223b**:**223a** obtained following the reaction was 7:3 compared to the maximum calculated ratio of

71:29. Clearly, the aryl groups of the phosphine ligand all exchanged under these conditions. Whilst the linear behaviour in the conversion *versus* time plots seen in the use of triphenylphosphine was seen for three substrates (**223b**, **c** and **f**), the remaining three substrates showed significant curvature. In the case of **223a** an initial linear period allowed the extraction of a rate constant but for **223d** and **223e** curvature was seen from the beginning. The rate constants obtained are shown in Table 2.

Table 2: observed rate constants for TMPP catalysis

R	$K_{obs}/10^{-6}$ M s^{-1}	Sigma
MeO	3.9	-0.268
Me	3.0	-0.170
H	2.2	0
NO_2	0.55	0.778

2.6.4 Discussion

The rate constants shown in Tables 1 and 2 were used to generate the Hammett plots shown in Charts 1 and 2. The virtually identical Hammett parameters obtained for the two cases are strongly suggestive that the same mechanism and rate limiting step operate in both cases. As can be seen, both provide quantitative evidence for the atypical order of reactivity in the HM reactions of vinylboronate **222**.

Chart 1: Hammett plot for triphenylphosphine catalysis.

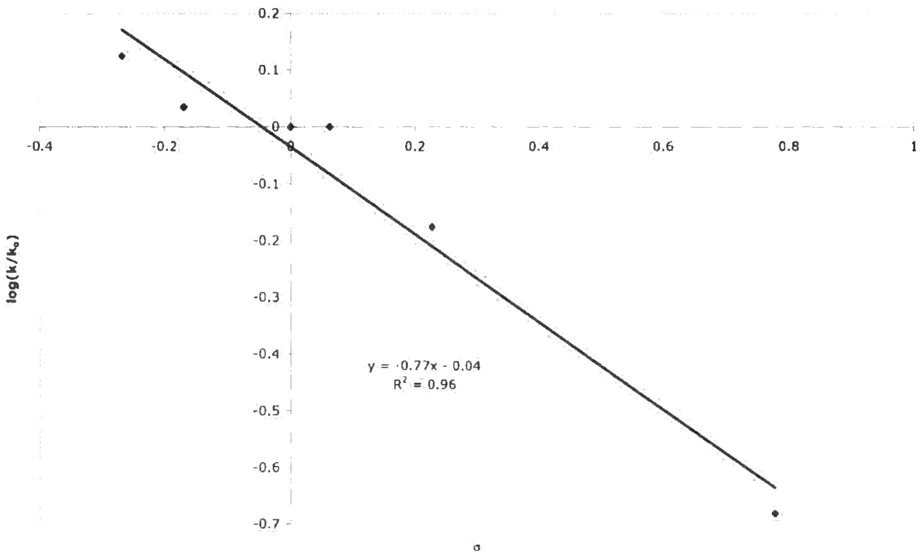
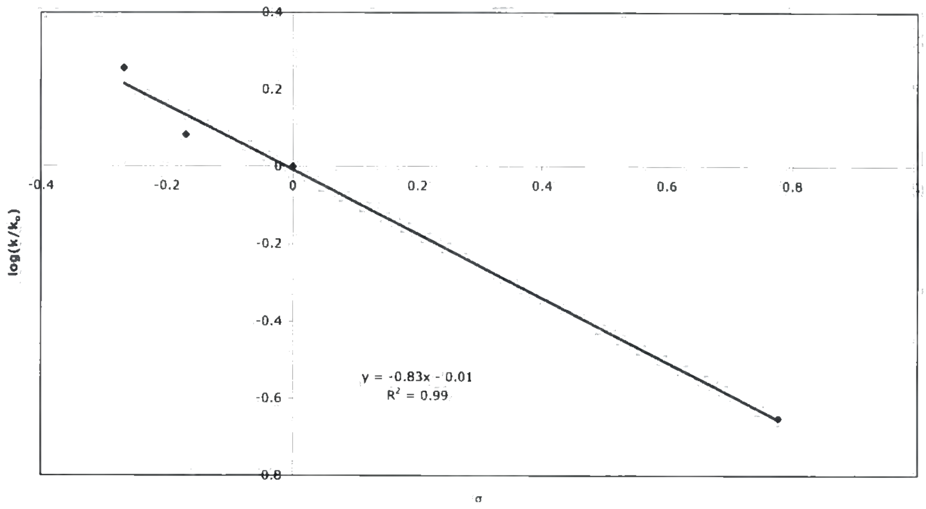


Chart 2: Hammett plot for tris(4-methoxyphenyl)phosphine catalysis.



The sign and magnitude of the Hammett parameters obtained lead to a number of conclusions: i) that oxidative addition is not rate limiting in these reactions as the sign of the Hammett parameters obtained are opposite to those obtained for the oxidative addition reaction;[110] ii) that cationic species are not involved in the rate limiting step due to the relatively small magnitude of the Hammett parameter, however, some build-up of positive charge is present in the transition state; and iii) that the rate limiting step in these reactions is different to that in the reactions of more usual HM substrates such as acrylates.

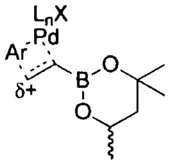
Unfortunately, the data obtained in both cases was somewhat spoilt by the occurrence of aryl-aryl exchange. Although dealt with through the addition of the two product concentrations, this must necessarily have had some effect on the observed rate constants. As it has been demonstrated that electron-rich substrates react faster (Table 1, entries 3-6 which were unaffected by aryl-aryl exchange demonstrate this), it would be expected that when triphenylphosphine was used as ligand, the exchange observed with substrates **223a** and **223b** would slow these two reactions by means of converting them to the less reactive substrate **223c**. Thus, the rate constants for substrates **223a** and **223b** in Table 1 should be lower than expected and hence the magnitude of the Hammett parameter obtained should be lower than that expected. In contrast, when tris(4-methoxyphenyl)phosphine was used as ligand, in all cases when aryl-aryl exchange was observed the rate of the reactions should have been accelerated by means of replacing the intended aryl iodide with **223a**; the most reactive iodide. The effect of this should be most pronounced in the less reactive electron-poor systems, however, this is countered by the fact that the aryl-aryl exchange became less significant as the electron density of the aryl halide decreased. Assuming that these two effects roughly cancel each other out, the expected outcome would be that the reactions of the five substrates **223b-d** were accelerated to a similar extent whilst that of **223a** was not accelerated at all. This would result in the observed rate constant for **223a** being anomalously low.

It would appear that problems with the two catalytic systems discussed above are not particularly significant: that the two Hammett parameters obtained are roughly equal in sign and magnitude suggests that the parameter from triphenylphosphine catalysis is not markedly reduced whilst the good fit seen for the point from substrate **223a** in Table 2 suggests that the acceleration of the other five substrates is fairly insignificant. It could be however, that the curvature seen for substrates **223d** and **223e** owes something to the aryl-aryl exchange.

Another potential issue surrounding the aryl-aryl exchange is the effect on the phosphine ligand. It has been demonstrated that HM reactions proceed faster in the presence of electron-rich phosphines as compared with their electron-poor analogues.[82] It would hence be expected that the aryl-aryl exchange of the aryl groups of the phosphine ligands throughout the reactions should have two effects: i) that the reactions should show curvature in their conversion *versus* time plots as the nature of the catalyst changed throughout the reaction; and ii) that the Hammett plots obtained should show some curvature as the reactions of the electron-deficient aryl iodides would be further retarded by the conversion of the phosphine to a less efficient catalyst whilst those of the electron-rich aryl iodides would be accelerated by the conversion of the phosphine to a more efficient catalyst. Again, it would appear that this effect is minimal as the majority of the conversion *versus* time plots were found to be linear, as were the two Hammett plots.

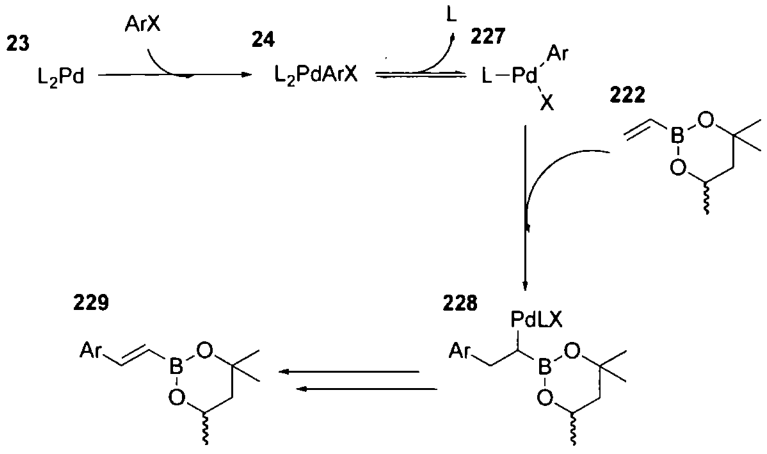
It is noteworthy that the Hammett parameters obtained match closely with those obtained in a study of the HM reaction of iodobenzene with a range of 4-substituted styrenes.[228] The conclusion of this study was that the electrophilic attack of the aryl palladium species on the olefin double bond was responsible for the observed Hammett parameter. The Hammett parameter was only seen in the case of *α*-substitution, in the case of *β*-substitution the forming positive charge was not at the benzylic position of the olefin and so could not be stabilised by the aryl substituent. In the present case, the product is due exclusively to *β*-substitution, however, as the electronically varied group is on the iodide, a negative Hammett parameter would be observed for *β*-substitution. Hence, it appears possible that the rate limiting step in the HM reactions of **222** is the carbometallation of **222** itself, proceding *via* a transition state such as **226**.

226



Another point to note is the linear nature of the conversion *versus* time plots obtained. Although no attempt was made to prove this, such behaviour is indicative of a zero order reaction. Combining this possibility with the observation that using an excess of an electron rich phosphine inhibits the reaction raises the possibility that the rate limiting step could be dissociative. Hence, another suggestion for the rate limiting step in the HM reactions of vinylboronate **222** is that following the oxidative addition step, a slow dissociation of a phosphine ligand is required in order for vinylboronate **222** to coordinate palladium, five-coordinate palladium species being disfavoured (Scheme 41). This process could be expected to produce a negative Hammett parameter as more electron-donating aryl groups on palladium in oxidative addition product **24** should promote phosphine dissociation by further stabilising the resulting co-ordinately unsaturated palladium product.

Scheme 41



Hence, two possibilities exist for the rate limiting step of HM reactions of vinylboronate **222**. With the current data, it is not possible to say whether carbometallation of **222** or phosphine dissociation from **24** is rate limiting. Clearly, rate limiting carbometallation would not be consistent with a zero-order reaction, however, linear conversion *versus* time plots are not conclusive proof of zero-order reactions.

Given the dramatic increase in aryl-aryl exchange observed on changing the ligand from triphenylphosphine to tris(4-methoxyphenyl)phosphine, it appears that the main factor in determining whether the exchange occurs is the stability of the tetraarylphosphonium salt intermediate. Electron donating substituents on any of the aryl rings facilitate the exchange by stabilising the positive charge in this species; this observation is consistent with the accepted mechanism.[248,249] In contrast, the re-insertion of palladium into the phosphorus-carbon bond has been suggested to be entirely random, giving a product distribution which could be modelled statistically. In this case, however, the re-insertion appears to occur preferentially into the more electron rich phosphorus carbon bond giving the complete aryl-aryl exchange seen using tris(4-methoxyphenyl)phosphine as ligand with substrate **223b**.

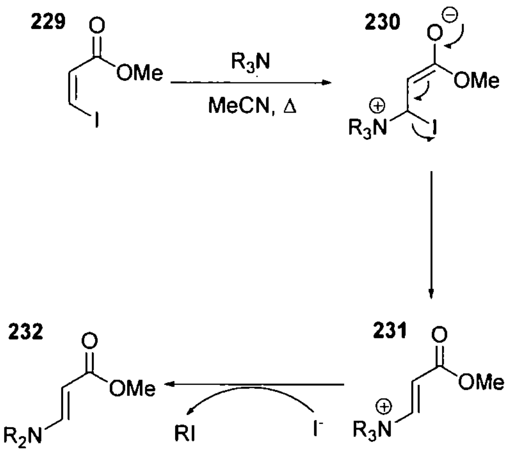
In conclusion, the rate limiting step in the HM reaction of vinylboronate **222** is different from that of, for example, acrylates. This is interesting because it may be expected that the two should behave in a similar manner as both could be regarded as having an electron-withdrawing group bonded to the olefin, indeed, ^{1}H NMR spectroscopy shows the olefinic protons of the two species to have similar chemical shifts. However, it should be noted that boron is electropositive and thus a σ-donor which apparently has a dramatic effect on the reactivity of olefinic groups bonded to it. Clearly, further studies are required for a full understanding of the mechanism operating in these reactions, however, it has been possible to suggest why electron deficient aryl iodides are rather less reactive in HM reactions with vinylboronate **222**.

2.7 Northern Hemisphere

This chapter concerns the synthesis of a range of polyenes, the geometry of which were assigned on the basis of their ^{1}H NMR spectra. For a detailed discussion on how such assignments were made see Appendix 3.

As already noted, some considerable work had been performed with the aim of the total synthesis of viridenomycin by the Whiting group prior to the start of this project. As part of this work, attempts at the HM reaction of a haloacrylate of type **209** were made. Use of methyl ester **229**, synthesised by the addition of hydroiodic acid across methyl propiolate,[287] met with abject failure; use of standard conditions developed for HM selective reactions of vinylboronates led to the formation of *β*-amino-acrylates of type **232**. This product was found to arise through the unprecedented Michael-addition/dealkylation sequence shown in Scheme 42.[288]

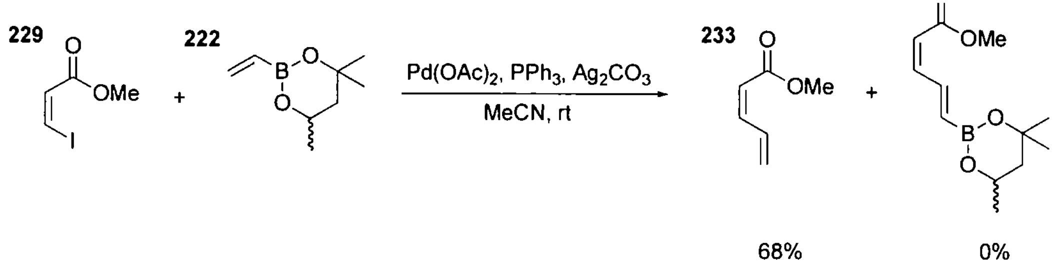
Scheme 42: proposed mechanism for amino-acrylate formation



It was found that this was a general phenomenon for iodide **229** with a range of alkylamine bases. The only type of amine found not to undergo this type of reaction were aniline derivatives. Given the careful choice of conditions required in order to achieve selective HM reaction as opposed to Suzuki-Miyaura coupling in these reactions, and also that inorganic bases tended to promote the latter, this did not bode well for this reaction.

Non-Michael accepting alternatives to methyl ester **229** were investigated, however, the desired *ortho*-esters proved impossible to form under standard conditions. Hence, a screen of reaction conditions using methyl ester **229** was performed with a range of palladium sources, ligands, additives, bases solvents and temperatures. Despite considerable work, none of the desired HM reaction product was detected. The only product identified from these reactions was Suzuki-Miyaura product **233** when silver(I) carbonate was used as base (Equation 7).[288]

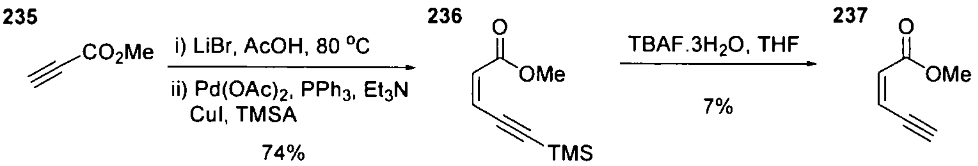
Equation 7



In a final attempt to produce a HM product from iodide **229**, its reaction with styrene was investigated. Despite the known reactivity of styrene in HM reactions, no product from its reaction with **229** was ever detected, suggesting that the plan for the synthesis of northern fragment **203** shown in Scheme 37 would fall at the first hurdle. Another observation which did not bode well for the reaction was that the only HM reaction of iodide **229** in the literature required silver(I) carbonate as base,[289] which in this instance promoted the Suzuki-Miyaura coupling.

It was at this point that this project began and it was initially proposed to approach the desired diene **207** by a different route. To this end, a Sonogashira reaction was employed to provide eneyne **236** in good yield (Scheme 43).[290,291] It was envisioned that following alkyne deprotection, the desired dienyl iodide could be obtained through the conjugate addition of iodide. Unfortunately, the attempted deprotection of **236** gave very poor yields of **237** despite literature claims to the contrary.[292] In addition, the attempted addition of HI to **237** gave rise to a complex mixture of products. Whilst it would conceivably have been possible to have accessed the desired iodide through a hydroboration/iododeboronation sequence, it was felt that this would defeat the point of the project and attention returned to the apparently intractable HM reaction.

Scheme 43: Sonogashira route to eneyne **237**

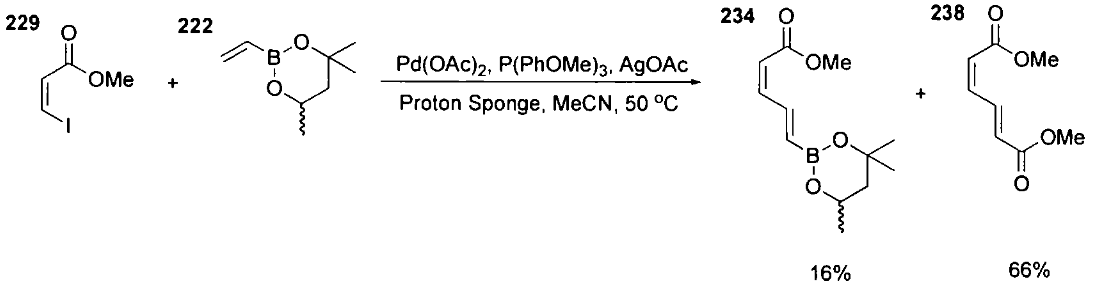


It was hoped that some of the information gained through the kinetic study (*vide supra*) could be of use in achieving the HM reaction of iodide **229** with boronate **222**. Although the use of tris(4-methoxyphenyl)phosphine had been shown to promote aryl-aryl exchange during the kinetic study, its use was investigated in this reaction because: i) electron rich ligands have been shown to accelerate HM reactions; ii) the lower reaction temperatures permitted by a more active catalyst would be expected to disfavour aryl-aryl exchange; and iii) the ligand screen performed earlier had not used it.

Initial results were somewhat disappointing; reaction of **222** with **229** in the presence of N,N-diethylaniline in toluene at 110 °C gave a level of product **234** detectable by GC-MS (ca. 1%) , however, the amount was seen to decrease to zero over 70 hr. Repeating the reaction at room temperature gave an improved level of conversion as shown by GC-MS (<5%), however, the amount of product **234** precluded observation by ^{1}H NMR spectroscopy let alone isolation. Use of another aniline-type base, Proton Sponge®, proved more successful and after considerable experimentation it proved possible to isolate the desired diene **234** in an uninspiring 1.6% yield using MeCN as solvent at 50 °C.

Previous work within the group had shown that the addition of silver and thallium salts could improve these reactions with regard to both rate and HM selectivity.[293] Hence the addition of silver(I) acetate was investigated and it was found that diene **234** was formed in an improved 16% yield. Intriguingly, the main product of this reaction was identified as dienyl diester **238**. The initially inexplicable formation of this product was felt to merit further investigation (*vide infra*).

Equation 8

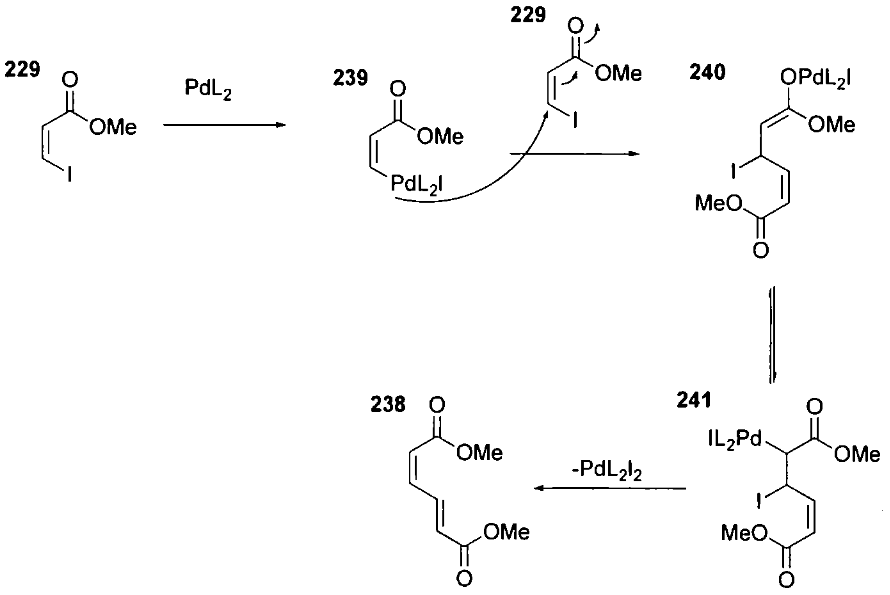


2.7.1 Optimisation of HM reaction to 234

The high combined yield of **234** and **238** suggested that it would be possible to obtain **234** in good yield if a way of preventing the reductive dimerisation to form **238** could be found. The most obvious way appeared to rely on the fact that the reaction to form **238** was bimolecular in **229** whilst the reaction to form **234** was unimolecular in **229**. Hence, it would be reasonable to expect that if the concentration of **229** could be minimised, improved selectivity for **234** should result. This was investigated through the slow addition of iodide **229** to the reaction, however, although the ratio of **234** to **238** was much improved (5:1), this was found to be at the expense of yield (5%). The reason for this drop in yield remains unknown, however, given the sensitivity of palladium-catalysed reactions to oxygen, it could be that the set-up required for such a slow addition allowed the ingress of sufficient oxygen to render the catalyst inactive.

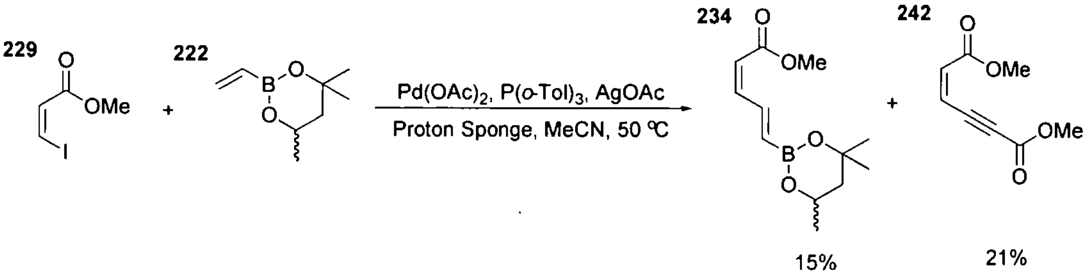
Clearly another way of preventing the undesired reductive dimerisation process was required. At this stage the reductive dimerisation process was proposed to proceed through an initial 1,4-addition of vinyl palladium **239** to iodide **229** followed by elimination of palladium(II) iodide to produce diene **238** (Scheme 44).

Scheme 44: proposed mechanism for reductive dimerisation process



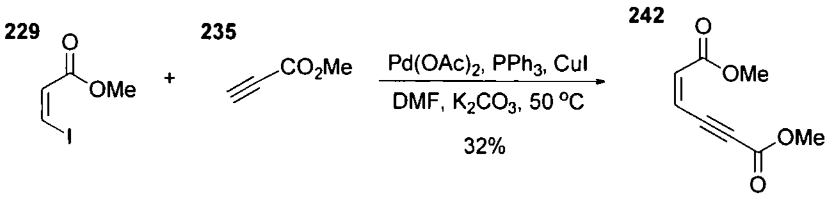
Given this mechanistic view, it was hoped that increasing the bulk of the ligands on palladium would disfavour the reaction and consequently promote the desired HM reaction, hence tri(*o*-tolyl)phosphine was investigated. This approach proved successful in terms of preventing the reductive dimerisation, and indeed, no diester **238** was detectable. Unfortunately, the yield of diene **234** remained low (15%) and the main product was found to be eneyne **242** (21%).

Equation 9



Doubts about the identity of eneyne **242** were dispelled by its independent synthesis by a Sonogashira reaction. Whilst the use of the same method as used for TMS acetylene (Scheme 43) failed due to the instability of methyl propiolate to triethylamine, use of potassium carbonate in DMF gave **242** in moderate yield. Both routes to **242** are of note because the difficulty of effecting Sonogashira reactions on electron-deficient alkynes is well documented.[294]

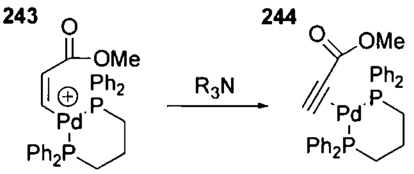
Equation 10



The formation of eneyne **242** in Equation 9 appears to arise from initial elimination of HI from iodide **229** followed by a Sonogashira coupling with another molecule of iodide **229**. This elimination appears to be palladium mediated; no methyl propiolate was seen by ^{1}H NMR spectroscopy in its absence. Palladium could presumably mediate such a process by means of an oxidative addition followed by a β-hydride elimination. The role of base in this reaction would, therefore, be to regenerate a palladium(0) catalyst by removal of HX.

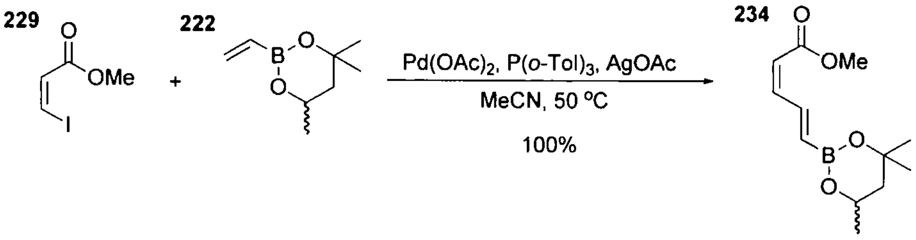
Further ligand screening failed to solve the dual problems of the reductive dimerisation and the HI elimination. In fact, use of dppp was found to give complete selectivity for the elimination/Sonogashira sequence; eneyne **242** being isolated in 35% yield. The increased elimination seen for the use of this ligand is perhaps unsurprising given that the combination of bidentate ligands and silver salts in HM reactions is known to produce cationic palladium intermediates.[157] Hence, cation **243** would be expected to be present and the electron-withdrawing nature of palladium in this species could promote β-hydride elimination by increasing the acidity of the β-hydrogen.

Equation 11



Given that elimination of HI was clearly a key step in the formation of eneyne **242**, it appeared logical to investigate the removal of the amine base. Hence, the reaction was performed using tri(*o*-tolyl)phosphine as ligand with silver(I) acetate as sole base. Gratifyingly, this was found to give dienyl boronate **234** in quantitative yield.

Equation 12

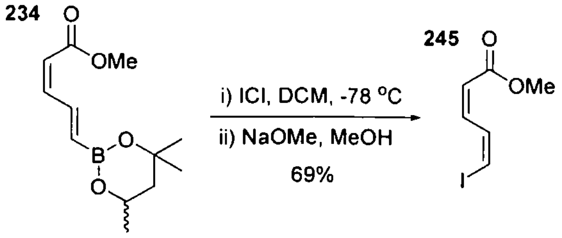


It is interesting to note that the removal of the amine from the reaction prevented the apparent *β*-hydride elimination from species **243** and subsequent Sonogashira coupling of the resulting alkyne. Based on the common depiction of the HM reaction it would be expected that elimination of palladium(II)-HX from **243** would occur regardless, the only effect of the lack of amine being the inability to regenerate an active catalyst. The fact that the lack of amine prevents this process is consistent with the proposal that *β*-hydride elimination is amine-assisted, following the formation of an agostic palladium-hydrogen bond.[226] Clearly, however, *β*-hydride elimination from palladium alkyl species is a rather more facile process as the less basic acetate anion is able to regenerate an active catalyst in the HM cycle.

2.7.2 Route to triene iodide 254

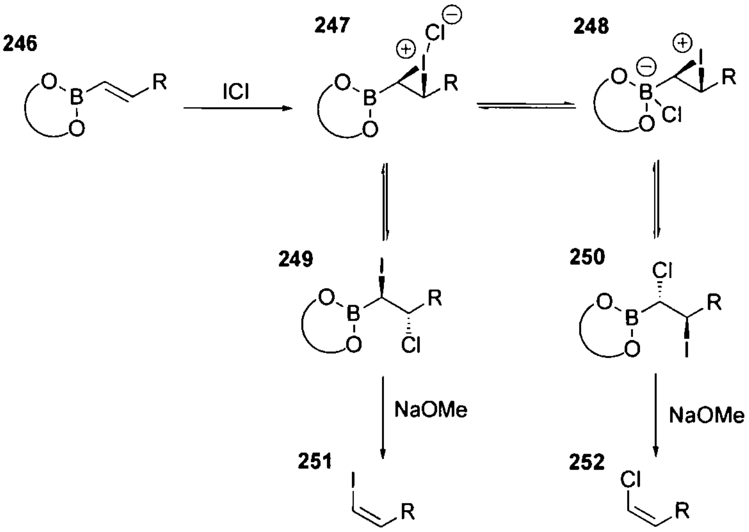
As shown in Scheme 37, the next reaction required of boronate **234** was an iododeboronation, inversion of the *trans*-geometry of the boronate double bond being required. Initial attempts on a small scale proved slightly disappointing; *Z*,*Z*-diene **245** was formed in a moderate 49% yield with the product being somewhat unstable. Fortunately, on repeating the reaction on a larger scale with chilled solvent for the chromatographic purification, the yield was improved to an acceptable 69%.

Equation 13



The stereoselectivity of this reaction was found to be high; the desired 2*Z*,4*Z*-isomer being present in a ratio of 94:6 to a second isomer. Based on ^{1}H NMR spectroscopy, this second isomer was identified as being 2*E*,4*Z*. The stereochemical outcome of this iododeboronation can be explained by the mechanism shown in Scheme 45[295] and proceeds by initial reaction of olefin **246** with iodine monochloride to produce iodonium ion **247**, stabilised as an ion-pair with chloride anion. This species can undergo collapse either to saturated derivative **249**, effecting overall *anti*-addition of iodine monochloride, or to zwitterion **248** in which case chlorine is directed to the *β*-position of the molecule to derive **250**. The two pathways described are in competition and lead to the formation of the corresponding vinyl iodide or vinyl chloride respectively, upon treatment with sodium methoxide.

Scheme 45: mechanistic rationalisation for iododeboronation with inversion

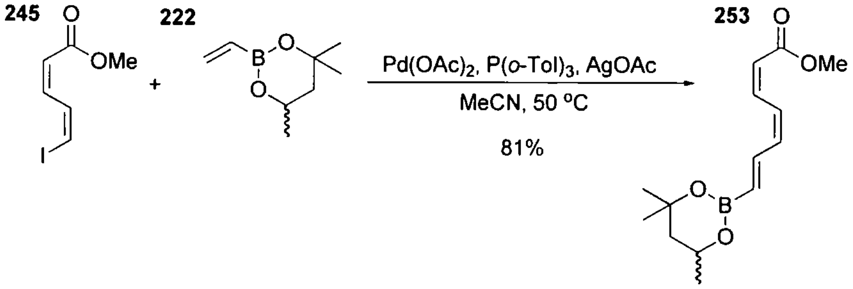


Previous work had shown that the competing pathway to produce vinyl chloride **252** occurred mainly when the R-group was electron-rich (e.g. alkyl) or when pyridine was present in the reaction,[296] this being thought to displace chloride from ion-pair **247** and thus promote the formation of zwitterion **248**. In the present case, the strongly electron-withdrawing nature of the R-group and lack of pyridine was expected to disfavour the formation of vinyl chloride **252** and, indeed, none was detected.

The cause of the apparent isomerisation to produce small quantities of the the 2*E*,4*Z*-isomer is unclear. Clearly, lack of selectivity in the iododeboronation is not the cause as this would lead to an isomeric mixture at the other double bond, in fact, this reaction appears to have proceeded with complete stereospecificity. A possible explanation is that an acid-catalysed isomerisation occurred; acid potentially resulting from the ingress of water into the reaction or from impurities within the iodine monochloride. Such an isomerisation could presumably occur at any stage of the reaction before addition of the sodium methoxide and could potentially be accelerated by the reactive nature of some of the intermediates of the iododeboronation reaction. Another possible cause is the reversible conjugate addition of iodide anion. This would explain the selective isomerisation of the internal olefin.

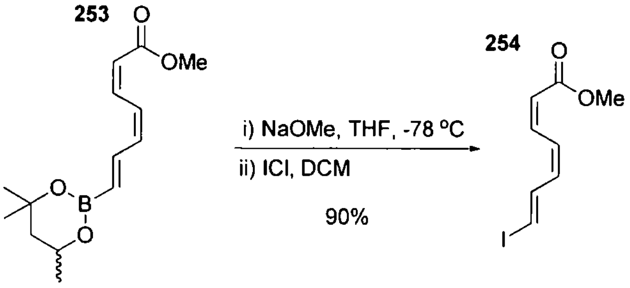
With iodide **245** in hand, a second HM reaction was required to access the desired trienyl system. Since this molecule was still rather electron-deficient and also potentially a Michael acceptor, the HM conditions developed for iodide **229** were again employed. These were again found to be successful, with trienyl boronate **253** being isolated in an impressive 81% yield. The remaining material from this reaction was not identified, however, given its less polar nature, it seems likely that the competing Suzuki-Miyaura coupling claimed at least some of the starting material.

Equation 14



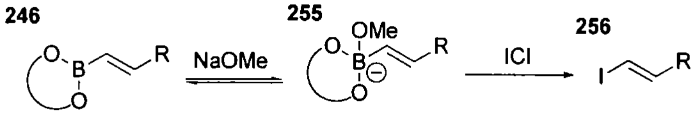
Iododeboronation of boronate **253** was required to proceed with retention of geometry to produce the synthon for the northern hemisphere of viridenomycin. As expected, reversal of the order of the addition of the iodine monochloride and sodium methoxide produced the desired 2*Z*,4*Z*,6*E*-triene **254**. The isomeric impurity arising from the previous iododeboronation reaction was in fact slightly enriched by this process; the 2*E*,4*Z*,6*E*-isomer being present in a 1:9 ratio to **254**. The high yield of this product does not reflect its stability; chilled solvent had to be used in the chromatographic purification, light had to be rigorously excluded from both reactions and purified product, and storage for more than a few days led to decomposition as evidenced by ^{1}H NMR spectroscopy. On exposure to light for just a few hours, chloroform solutions of **254** acquired a purple colour, presumably due to the formation of diiodine by decomposition of **254**.

Equation 15



The opposing stereoselectivity resulting from the reversal of the order of addition of the two reagents can be explained by the mechanism shown in Scheme 46.[295] Addition of sodium methoxide to boronate **246** leads to the formation of "ate"-complex **255** which behaves as a nucleophile upon the addition of the strongly electrophilic iodine monochloride, the geometry of the double bond of this nucleophile being retained.

Scheme 46: mechanistic rationalisation for iododeboronation with retention

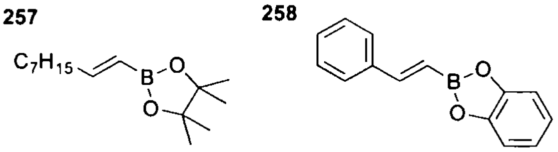


2.7.3 Coupling reactions of triene 254

As the required coupling partner for the elaboration of **254** to viridenomycin had yet to be synthesised, its coupling with a number of model compounds was investigated. It was hoped that as well as demonstrating the viability of **254** in such reactions, it would also ensure that future efforts were directed toward a cyclopentanone derivative capable of undergoing coupling.

To this end, the Suzuki-Miyaura couplings of **254** with boronates **257** and **258** were investigated.[271,297] Although neither are structurally similar to the intended cyclopentanone reagent, it was initially hoped simply to demonstrate that **254** was capable of participating in Suzuki-Miyaura couplings.

Figure 13

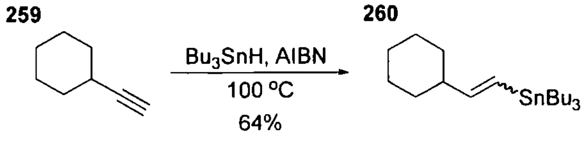


Unfortunately, although trace amounts of what appeared to be the Suzuki-Miyaura product was seen under certain conditions, the product was never separated from a number of unidentified by-products. In addition, the expected unreacted **254** was not recovered from the reaction mixture, apparently showing that decomposition of **254** occurred under the reaction conditions.

It was thought that the instability of **254** in the Suzuki-Miyaura reactions was in part be due to the elevated temperatures required for such reactions to occur. It was realised that it would be preferable for the coupling reaction to occur under ambient conditions. Due to the mild conditions employed in many Stille couplings, it was hoped that this reaction might provide the key to cross-coupling iodide **254**.

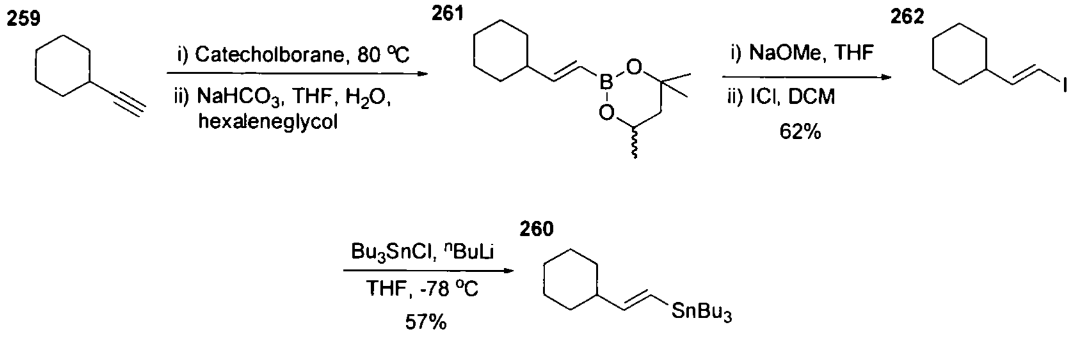
Organostannane **260** was identified as an ideal model compound; the bulky cyclohexyl group mimicking the desired cyclopentane ring. The most obvious route to **260** apparently involved the hydrostannylation of cyclohexylacetylene, and indeed, this did prove successful, however, the yield of the desired compound was disappointing (Equation 16) and ^{1}H NMR spectroscopy showed a complex mixture of isomers, possible including regioisomeric products.

Equation 16



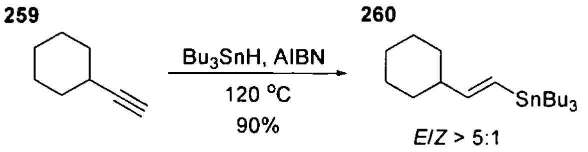
Seeking a more stereoselective route to **260**, the lithium halogen exchange on vinyl iodide **262** (prepared by iododeboronation of boronate **261**, Scheme 47) followed by quenching with tri-*n*-butyltin chloride was performed. This approach was found to be almost stereospecific, however, the overall efficiency of the route was poor and the formation of the corresponding vinyl chloride competed in the iododeboronation reaction.

Scheme 47: hydroboration/iododeboronation route to organostannane **260**



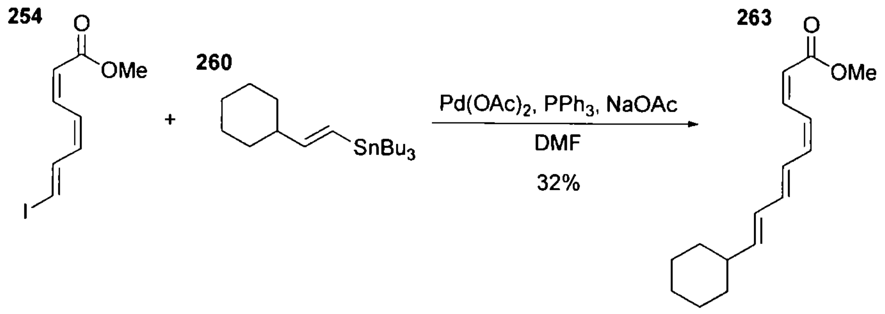
Returning to the hydrostannylation reaction, it was found that simply increasing the temperature by 20 °C increased the stereoselectivity to an acceptable level, apparently suggesting that the reaction at lower temperature was to some degree under kinetic control.

Equation 17



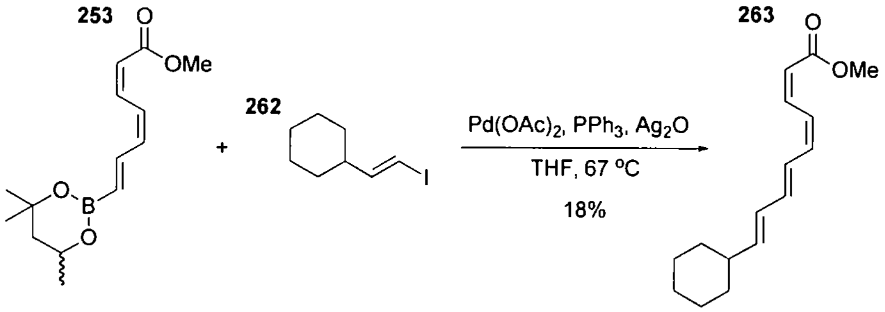
The Stille couping of **254** and **260** was found to proceed at room temperature as had been hoped. However, the yield of tetraene **263** was low, this being in part due to the challenge of purifying the rather non-polar product from the equally non-polar organostannane. Following purification, it rapidly became apparent that the isomeric purity of the isolated product was poor. The complex olefinic region in the ^{1}H NMR spectrum did not allow an estimate of purity to be made, however, ^{13}C NMR spectroscopy suggested two major isomers in an approximately 1:1 ratio.

Equation 18



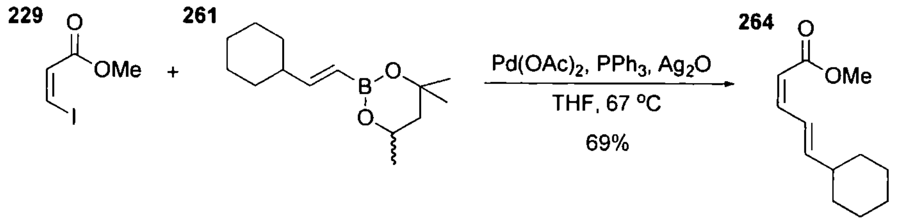
It was unclear whether the observed isomerisation was occurring on iodide **254** before coupling or on tetraene **263** after coupling occured. Hence, the Suzuki-Miyaura coupling of triene boronate **253** with vinyl iodide **262** was investigated. In this case, the Suzuki-Miyaura coupling was successful, however, the yield was poor and the isomeric purity appeared identical to that obtained from the Stille coupling. This appears to suggest that the observed isomerisation in the two cases is largely due to the instability of tetraene **263** to the reaction conditions whilst the lack of product formation in Suzuki-Miyaura couplings of iodide **254** is due to the instability of this material.

Equation 19



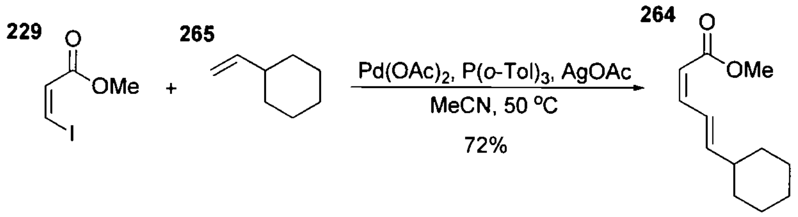
This latter supposition was reinforced by the discovery that the Suzuki-Miyaura coupling of iodide **229** with boronate **261** proceeded in good yield although it was found that an excess of the iodide was required to achieve complete consumption of the boronate. This behaviour was found to be due to competition by the previously seen reductive dimerisation reaction, leading to formation of diester **238**.

Equation 20



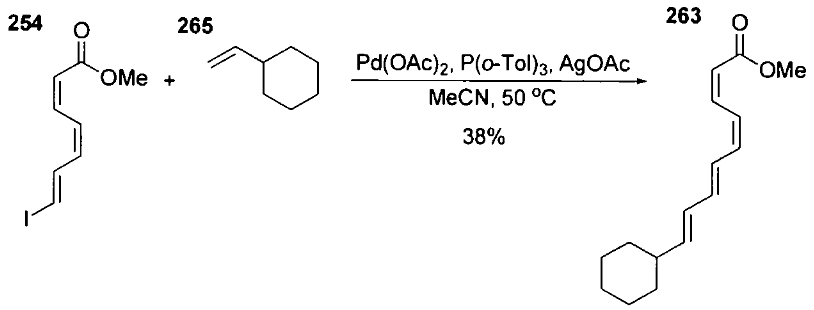
Slightly surprisingly, it was discovered that Suzuki-Miyaura product **264** could also be accessed by means of the HM reaction of iodide **229** with vinylcyclohexane. The yield of this reaction was in fact found to be marginally greater than that achieved using the Suzuki-Miyaura coupling route and this led to the investigation of a HM reaction for the conversion of triene iodide **254** to the desired tetraene.

Equation 21



The HM reaction of iodide **254** with vinylcyclohexane was found to be the most successful synthesis of tetraene **263**. Although the yield is far from outstanding (Equation 22), the isomeric purity of **263** appeared to be improved; ^{13}C NMR spectroscopy suggesting 2:1 ratio of the desired 2*Z*,4*Z*,6*E*,8*E*-isomer to another, unknown, isomer.

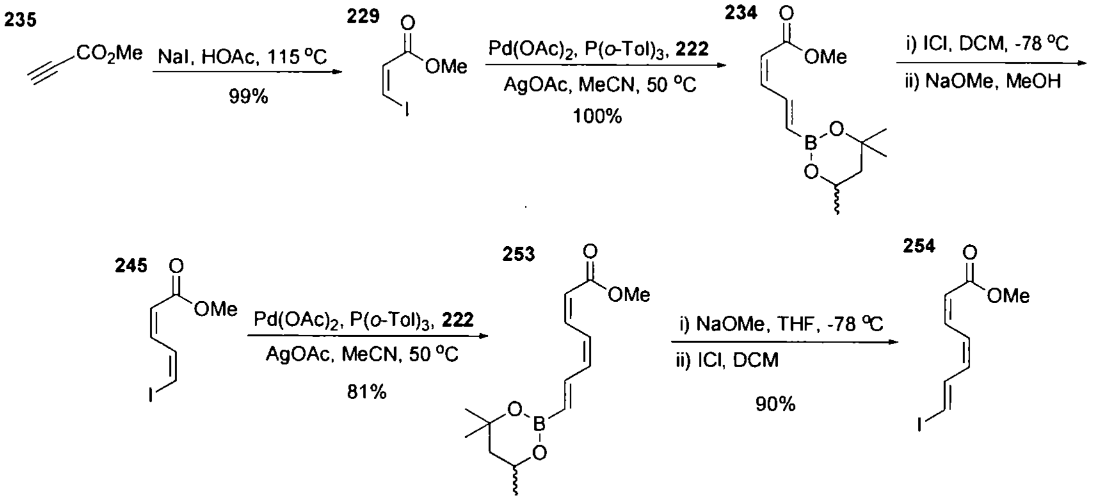
Equation 22



At this point, the screening of coupling reactions of iodide **254** was halted, largely due to the amount of time being taken in producing the unstable iodide. Two potential coupling reactions had been identified and it was felt that any further optimisation should be performed on the cyclopentanone once synthesised. It seemed likely that optimisation on the actual cyclopentanone would be easier as its more polar nature would facilitate chromatographic purification. In addition, it was thought that reaction conditions obtained from further optimisation on a model compound would not necessarily be transferable to the cyclopentanone.

In conclusion to this section, the desired triene iodide **254** has been formed in 5 steps in 50% overall yield from methyl propiolate, an impressive demonstration of the power of the HM reaction/iododeboronation methodology for rapid and stereoselective polyene synthesis. In addition, the viability of iodide **254** in both HM reactions and Stille couplings has been demonstrated although isomeric purity remains an issue.

Scheme 48: optimised route to trienyl iodide **254**

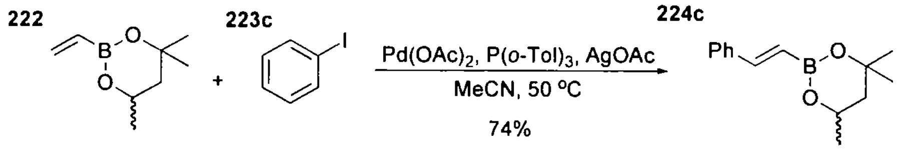


2.7.4 Application of new HM conditions

Following the success of the new conditions for the HM reaction of iodide **229**, a small study was made to investigate the generality of these conditions to other substrates. Although clearly highly successful for coupling iodide **229**, such conditions could be expected to lead to the formation of Suzuki-Miyaura coupled products for other substrates.

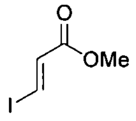
Returning to the standard reaction of iodobenzene with vinylboronate **222**, the new conditions were found to be somewhat disappointing. Whilst yields of 88% were obtained using tri-*n*-butylamine in toluene with triphenylphosphine as ligand,[293] the new conditions gave a yield of only 74% with the presence of Suzuki-Miyaura coupled product being evident from the crude ^{1}H NMR spectrum.

Equation 23



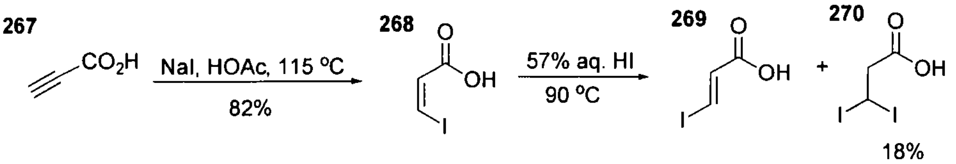
With this result apparently suggesting that the new conditions were better suited to electron-deficient vinyl iodides, it was decided to investigate the effect of both geometry and sterics on the HM reactions of systems of type **209**. To this end, it was decided to synthesise the corresponding *trans*-iodide **266**. Consulting the literature revealed that the corresponding carboxylic acid could be obtained by isomerisation of *cis*-acid **268**,[298,299] itself obtained by addition of hydroiodic acid across propiolic acid.[287]

266



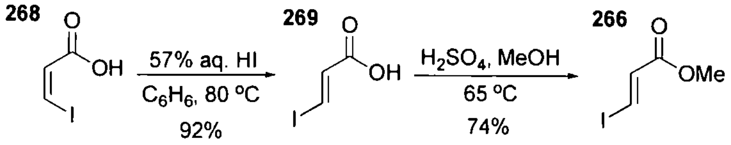
Trans-addition of HI across propiolic acid proceeded smoothly under the same conditions used for methyl propiolate to afford *cis*-acid **268** in good yield.[287] The isomerisation of this species has been reported several times and some confusion exists over the conditions required.[300] Procedures in the literature generally involve stoichiometric amounts of strong acid although the temperatures employed vary considerably. In my hands, the use of stoichiometric HI was found to give a saturated species as the major product, albeit contaminated with the desired *trans*-acid **269**. This saturated species was eventually purified by repeated crystallisation and identified as the hydrogen iodide adduct **270**.[301]

Scheme 49: addition/isomerisation route to acid **269**



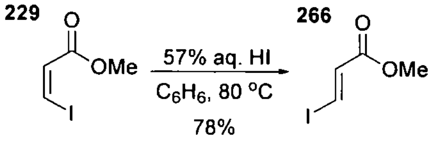
Diiodide **270** had been reported but not characterised by Takeuchi *et al* as they attempted the isomerisation of *cis*-acid **268**.[302] This paper also reported that through the use of catalytic HI, the formation of this compound could be avoided. This was found to be the case; use of 5 mol% of HI afforded the desired *trans*-acid **269** in excellent yield and subsequent acid-catalysed esterification provided methyl ester **266** in good yield. The yield of **266** was reduced by the compounds volatility, this being discovered after the loss of a substantial amount of material whilst drying *in vacuo*. This behaviour by **266**, which is a crystalline material, is somewhat surprising given that **229**, which is an oil, shows no such volatility.

Scheme 50: isomerisation/methylation route to iodide **266**



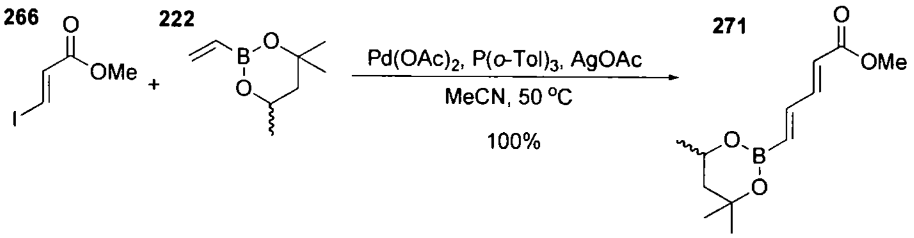
Large quantities of **266** were required for another project and owing to the slightly indirect nature of the route to **266**, the direct isomerisation of methyl ester **229** was investigated. This route proved successful although trace amounts of the corresponding diodide could be detected by ^{1}H NMR spectroscopy and the yield still suffers slightly from the volatility of the product.

Equation 24



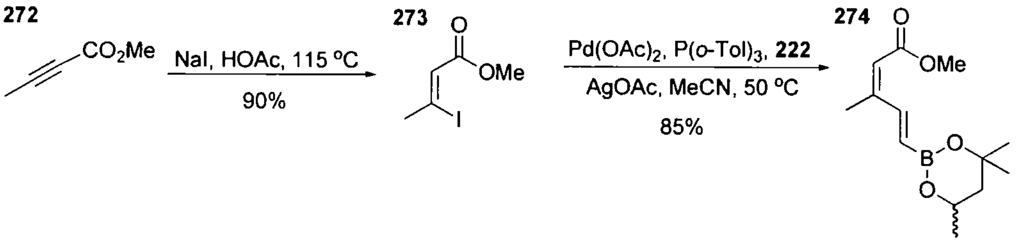
With **266** in hand, attention was turned to its HM reaction with vinylboronate **222**. Using the same conditions employed for *cis*-iodide **229**, all-*trans* diene **271** was obtained in quantitative yield. Following the reaction by TLC suggested it to be rather slower than that of **229**; whilst *cis*-iodide **229** reacted relatively rapidly and reactions were only left overnight out of convenience, *trans*-iodide **266** required the full reaction time and reduction of this led to reduced yields.

Equation 25



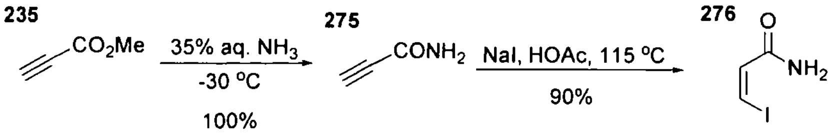
Having showed that the geometry of the olefin had little effect on the HM reaction, investigation of the effect of sterics was required. Iodide **273**, prepared in an analogous fashion to **229**[287] but from methyl tetrolate **272**,[303] appeared an ideal candidate and was placed under the aforementioned conditions. Again, the desired HM product **274** was isolated in high yield (Scheme 51). This HM reaction is of considerable interest as it allows entry to the highly biologically active retinoid framework,[304] with the potential for selectively forming stereo-isomeric compounds.

Scheme 51: route to methyl-substituted derivative **274**



Seeking to move away from iodo-acrylate derivatives, amide **276** was synthesised from methyl propiolate (Scheme 52).[290,305] Disappointingly, under the HM conditions shown to be so successful for acrylate derivatives, amide **276** underwent no reaction with only starting material being recovered.

Scheme 52: route to amide **276**

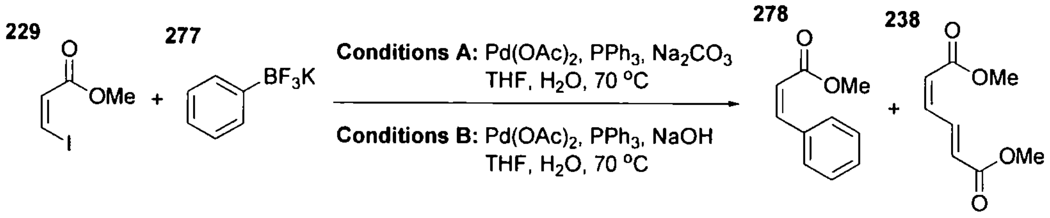


This small study demonstrates that the newly developed conditions for HM reactions of vinylboronate **222** are more generally applicable, however, they are rather better suited to the highly electron-deficient nature of iodo-acrylate derivatives. Clearly, for a full picture of the utility of such conditions, a far more comprehensive study would be required. Sadly, time did not permit such a study to be performed with the construction of the cyclopentanone core demanding attention.

2.8 Reductive dimerisation process

As mentioned previously, the reductive dimerisation reaction of iodide **229** to produce diester **238** was observed several times during attempted coupling reactions of this iodide. This process was again observed during the attempted Suzuki-Miyaura couplings of **229** with potassium vinyltrifluoroborate **277** to produce methyl *cis*-cinnamate **278**. In this reaction, it was found that the nature of the base used controlled the chemical outcome; use of sodium carbonate gave exclusively diester **238** whilst use of sodium hydroxide gave only Suzuki-Miyaura coupled product **278** (Equation 26).

Equation 26



Conditions A:	0%	11%
Conditions B:	25%	0%

This behaviour was rationalised by the suggestion that the observed effect was a measure of the rate of the Suzuki-Miyaura coupling relative to the fixed rate of the reductive coupling process and that the nucleophilicity of the base controlled the rate of the Suzuki-Miyaura coupling. Hence, the nucleophilic hydroxide anion readily displaced fluoride from boron, resulting in a rapid Suzuki-Miyaura coupling[306] and no reductive dimerisation reaction, whilst for the less nucleophilic sodium carbonate, the equilibrium disfavoured displacement of fluoride and the resulting sluggish Suzuki-Miyaura coupling permitted the reductive dimerisation to dominate.

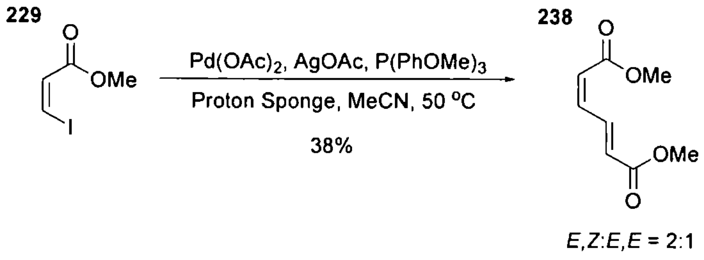
The reductive dimerisation process was intriguing for several reasons; partly due to the novelty of the process involved as no obvious reducing reagent was present, partly due to the unusual stereoselectivity demonstrated by the reaction and partly because of a lack of efficient ways to perform such reductive coupling of vinyl halides.

Three general methods have been reported for the reductive homocoupling of aryl and vinyl halides: i) transformation of into the corresponding organo-lithium[307] or Grignard[308,309] and subsequent palladium-catalysed homo-coupling; ii) copper-catalysed Ullmann coupling;[310,311] and iii) nickel[312-316] or palladium[317,318]-catalysed homo-coupling in the presence of a stoichiometric reductant such as zinc metal. All three methods possess significant drawbacks to their use, for instance, the metal-halogen exchange/cross-coupling route is not feasible for substrates possessing a number of functional groups, for example, esters, because of the incompatibility of Grignard reagents. The copper-catalysed Ullmann coupling frequently requires extremely high temperatures to effect the desired reaction although recent work has done much bring the conditions closer to ambient. In addition, the stereo-control of Ullmann couplings is often poor, leading to mixtures of all possible isomers. Nickel and palladium catalysed homo-coupling reactions also often show poor stereoselectivity[319-321] and the requirement to use stoichiometric zinc makes these reactions unappealing.

Because of this lack of efficient methods in the literature, it was decided to investigate this novel process with the hope of optimising the yield, finding its generality and explaining the origin of the curious stereochemistry of the product.

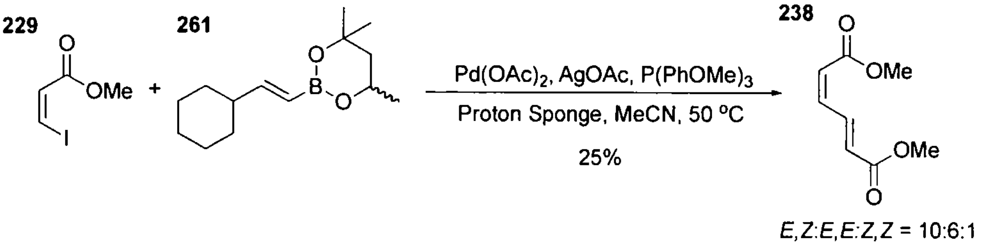
The first reaction undertaken in this study was that shown in Equation 8 but with vinylboronate **222** removed. Due to the high combined yield of **234** and **238** in Equation 8, it was expected that by removing the competing HM reaction, a high yield of reductive dimer **238** would result. This was not found to be the case, in fact, removal of **222** resulted in a decreased yield of **238** (Equation 27) and very poor stereoselectivity.

Equation 27



This suggested that vinylboronate **222** reacted in some way to remove the iodine necessarily produced by such a process, potentially by an iodo-deboronation reaction as seen with iodine monochloride. To test this hypothesis, the reaction was rerun, this time in the presence of substituted vinylboronate **261**, it being hoped that should iodo-deboronation occur, the resulting iodide could be isolated as proof of this. Inexplicably, the addition of this reagent in fact resulted in a decrease in the yield of **238** despite the apparent lack of any product from the potentially competing Suzuki-Miyaura coupling.

Equation 28



A range of conditions were screened, the results being shown in Table 3. It can be seen that both Proton Sponge® and silver(I) acetate are required to achieve a reasonable yield of diester **238**, the presence of the silver salt being more critical than the Proton Sponge® (Entries 1 and 2). Screening of ligands revealed that whilst the reaction with tris(4-methoxyphenyl)phosphine was more efficient than with triphenylphosphine, the greatest yield was achieved in the absence of any ligand.

It was investigated whether another aniline type base other than Proton Sponge® could promote the reaction through the use of *N*,*N*-diethylaniline (DEA) (Entry 5). This was not found to give the desired product, however, a new species was isolated and identified as vinyl acetate **279**.[322] It was demonstrated that the presence of silver(I) was required for this exchange to occur; the use of sodium acetate gave only a poor yield of diester **238** (Entry 6).

279

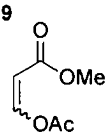


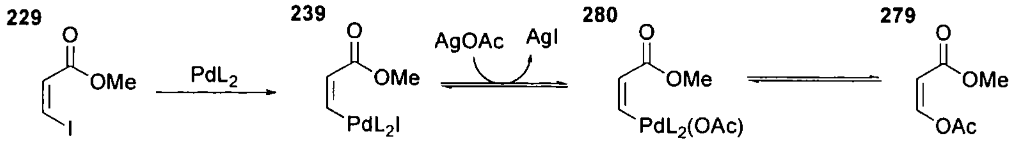
Table 3: initial screen of conditions in the reductive dimerisation process

Entry	Solvent	Ligand	Conditions[a] (equivalents)	Product (yield)	Selectivity (*E,Z*:*E,E*:*Z,Z*)
1	MeCN	TMPP	AgOAc (1.05), 50 °C	**238** (22 %)	6:7:1
2	MeCN	TMPP	Proton Sponge® (1.2), 50 °C	0	
3	MeCN	TPP	Proton Sponge® (1.2), AgOAc (1.05), 50 °C	**238** (21 %)	10:1:3
4	MeCN	-	Proton Sponge® (1.2), AgOAc (1.05), 50 °C	**238** (44 %)	24:1:0
5	MeCN	-	DEA (1.1), AgOAc (1.05), 50 °C	**279** (36 %)	*E*:*Z* = 9:8[b]
6	MeCN	-	DEA (1.1), NaOAc (1.05), 50 °C	**238** (12 %)	5:1:0
7	THF	-	Proton Sponge® (1.6), AgOAc (1.5), 50 °C	**279** (32 %) and **238** (9 %)	6.5:1.6:1
8	DMF	-	Proton Sponge® (1.6), AgOAc (1.5), 50 °C	**238** (23 %)	55:1:0
9	THF/H_2O (9:1)	TPP	Na_2CO_3 (3.5), 70 °C	**238** (30 %)	12:1:0
10	THF/H_2O (9:1)	TPP	70 °C	**238** (8 %)	
11	THF/H_2O (9:1)	-	Na_2CO_3 (3.5), 70 °C	**238** (13 %)	50:1:0

[a] All reactions use 5 mol% $Pd(OAc)_2$
[b] 2:1 after silica gel chromatography

It was demonstrated that both the reductive dimerisation reaction and the iodine/acetate exchange process were palladium catalysed; removal of palladium acetate returning only starting material in both cases. The mechanism of the iodide/acetate exchange is expected to proceed through the mechanism shown in Scheme 53. Following initial oxidative addition, exchange of the halide on palladium with the excess of acetate can occur and the subsequent reversal of the oxidative addition reaction provides vinyl acetate **279**. The lack of stereoselectivity of this reaction appears to be a function of the stability of the product to isomerisation rather than the selectivity of the reaction as judged by the change in isomeric purity after silica gel chromatography. Similar halide-exchange processes have bee reported previously.[323]

Scheme 53: proposed mechanism for iodine/acetate exchange



This reaction is unusual for a number of reasons. Firstly, it apparently demonstrates that the oxidative addition reaction is reversible which is not usually thought to be the case unless very bulky ligands are involved. Secondly, it has been shown that iodide is far less prone to dissociate from palladium(II) species than acetate.[157] In view of this, it might be expected that in the first equilibrium shown in Scheme 53, reductive elimination of the starting iodide might be preferred despite the excess of acetate present, however, the crude ^{1}H NMR spectrum of the reaction indicated that all of iodide **229** was consumed. Thirdly, it is not clear why silver(I) acetate causes the exchange to occur whilst sodium acetate does not.

A possible explanation for the final two points above is that the driving force for the exchange of iodide is the formation of silver(I) iodide. Assuming that this salt is insoluble in acetonitrile at 50 °C this would ensure that the first equilibrium in Scheme 53 is driven to the right and also explain the lack of exchange seen with sodium acetate which would be expected to show some solubility.

Changing the solvent in the reductive dimerisation reaction revealed a marked effect. Use of THF proved relatively unsuccessful, the main product being acetate **279** (Entry 7). With DMF the result was more interesting; although the yield was reduced as compared to the same conditions in MeCN, the stereoselectivity was significantly improved for the *E*,*Z*-isomer (Entry 8). The results of the solvent screen appear to show that the stereoselectivity is dependent on solvent polarity; the stereoselectivity increasing in the order DMF > MeCN > THF.

Having seen that the reductive dimerisation reaction could occur under conditions used for Suzuki-Miyaura reactions, these conditions were employed in the absence of a boronate coupling partner (Entry 9). Indeed, this was found to work; although the yield was not as high as those found under the Proton Sponge®/silver(I) acetate conditions, the lack of these reagents makes it far more economical. The role of base in this reaction was unclear and its removal was investigated (Entry 10), however, this led to a dramatic drop in yield. This apparently demonstrates that an acidic by-product is formed and base its necessary for its neutralisation. As the only expected by-product of the reaction is iodine, this suggests that iodine is eliminated from palladium and subsequently hydrolysed to produce HI and IOH, both of which can be neutralised by sodium carbonate. Although this would explain the observed behaviour, it would mean that an equivalent of sodium hypoiodite is generated by the reaction and this redox active species could be expected to interfere with palladium catalysis.

Removal of the phosphine ligand was also investigated under these "Suzuki-Miyaura" conditions due to the success seen under the other conditions (Entry 11). Although this was found to dramatically improve the stereoselectivity to a level only previously seen using DMF, the yield was reduced to an unacceptable level. This may be due to better stabilisation of ligand free palladium under the other conditions by ligation by species such as Proton Sponge® and MeCN.

These experiments, designed to give an insight into the reductive dimerisation process, left us more confused by the process than we were to start with! It appeared that Proton Sponge® functioned as some sort of reducing agent for the expected palladium(II) iodide by-product whilst *N*,*N*-diethylaniline did not, however, the reaction could proceed to some degree in the absence of any reducing agent. The role of silver was also unclear, it was apparently necessary for the reaction in MeCN but not in THF/water although the difference in temperature between these two conditions suggested that silver could simply function to reduce the temperature required for the reaction to occur. The observed iodide exchange also posed unanswered questions, particularly why the presence of Proton Sponge® apparently prevented this process. With these issues in mind, a second batch of experiments were devised, the results of which are shown in Table 4.

The use of catalytic Proton Sponge® was investigated (Entry 1), it being thought that this molecule may function as a ligand for palladium, thus explaining its impact on the reaction. This was found to be detrimental to the yield of the reaction and in addition, a considerable quantity of acetate **279** was isolated. This showed that stoichiometric Proton Sponge® was required for both the reductive dimerisation to occur and for the prevention of the formation of acetate **279**, hence neither appear to be the result of Proton Sponge® functioning as a ligand for palladium.

Table 4: second generation of experiments

Entry	Solvent	Ligand	Conditions[a] (equivalents)	Product (yield)	Selectivity (*E,Z*:*E,E*:*Z,Z*)
1	MeCN	-	Proton Sponge® (0.1), AgOAc (1.05), 50 °C	**238** (7 %) and **279** (17 %)	3:1:0 (**238**)
2	MeCN	-	Proton Sponge® (1.2), Ag_2O (0.55), 50 °C	**238** (19 %)	8:2:1
3	MeCN	-	Proton Sponge® (1.2), AgOTf (1.05), 50 °C	0	
4	MeCN	-	Proton Sponge® (1.2), $AgNO_3$ (1.05), 50 °C	**238** (6 %)	3:1:0
5	MeCN	-	Proton Sponge® (1.2), AgTFA (1.05), 50 °C	0	
6	MeCN	-	Proton Sponge® (1.2), AgOTf (1.05), Bu_4NOAc (1.05), 50 °C	**238** (35 %)	28:1:0
7	MeCN	-	Proton Sponge® (1.2), AgOTf (1.05), Bu_4NBr, 50 °C	0	
8	MeCN	-	Proton Sponge® (1.6), AgOAc (1.5), 50 °C	**238** (51 %)	21:1:0
9[b]	MeCN	-	Proton Sponge® (2.4), AgOAc (2.4), 50 °C	**238** (57 %)	17:1:0
10	MeCN	-	DEA (1.05), AgTFA (1.05), 50 °C	0	
11	MeCN	-	Proton Sponge® (1.2), **222** (1.2), AgOAc (1.05), 50 °C	**234** (61 %)	
12[c]	MeCN	-	Proton Sponge® (1.5), AgOAc (1.4), 50 °C	**238** (21 %) and **242** (4 %)	50:1:0 (**238**)

[a] All reactions use 5 mol% $Pd(OAc)_2$ unless otherwise stated
[b] Used 10 mol% $Pd(OAc)_2$
[c] Used 5 mol% PdI_2

With the role of silver salts in the reaction being unknown, a range of silver salts were investigated (Entries 2 to 5). It was found that silver(I) acetate was optimal although silver(I) oxide also gave some reaction. Interestingly, silver(I) triflate gave no reaction, providing evidence that the reaction does not proceed by a cationic mechanism. This view gained more support when it was found that the addition of tetrabutylammonium acetate to the silver(I) triflate reaction gave diester in comparable yield to the use of silver(I) acetate alone. Intriguingly, addition of tetrabutylammonium bromide in the same manner did not result in reductive dimerisation, showing that acetate plays some role other that just an anion.

A surprising result came with the use of silver(I) trifluoroacetate (Entry 5). It was expected that this should give similar results to silver(I) acetate, however, no reaction was found with its use. The difference between silver(I) acetate and silver(I) trifluoroacetate was underlined by the discovery that under the conditions found to afford vinyl acetate **279** with silver(I) acetate, no such reaction was observed with silver(I) trifluoroacetate (Entry 10). The reason behind this difference is unknown, although less basic than acetate due to the electron withdrawing nature of the three fluorine atoms, the trifluoroacetate anion has been found to participate in palladium-catalysed reactions,[324] indeed, palladium(II) trifluoroacetate is a commercially available palladium salt.

Due to a lack of success in optimising the conditions and a lack of knowledge of the stoichiometry of the reaction, increasing the number of equivalents of the reagents was investigated. It was discovered that the use of 1.5 equivalents of both silver(I) acetate and Proton Sponge® increased the yield of diester **238** to an acceptable level (Entry 8) and that a further increase combined with the use of 10 mol% palladium acetate gave a further small increase, albeit with a slight reduction in stereoslectivity (Entry 9).

Given the decrease in yield observed on the removal of vinylboronate **222** from the reaction in Equation 8, its addition to the ligand-free conditions was investigated (Entry 11). Most surprisingly, this was found to give clean dienyl boronate **234** in moderate yield. Whatever the reason behind this, it is a relief that the use of tri(*o*-tolyl)phosphine with removal of Proton Sponge® was discovered before this, otherwise a far less efficient reaction to diene **234** may have been settled for.

Given that the reaction to form diester **238** had to be expected to eliminate palladium(II) iodide at some point, the use of palladium(II) iodide as the catalyst was investigated. As can be seen (Entries 8 *vs* 12), changing from palladium(II) acetate to palladium(II) iodide results in a dramatic reduction in yield of diester **238**. In addition, some elimination and Sonogashira coupling apparently occurs as evidenced by the formation of small amounts of eneyne **242**. Curiously, the stereoselectivity of the reductive dimerisation reaction improved under these conditions.

This last result suggested that palladium(II) iodide was not on the catalytic cycle as if it were, identical behaviour to the use of palladium(II) acetate should have been observed. In order to probe the mechanism, particularly with regard to the role of Proton Sponge® in the reaction, a number of NMR spectroscopy experiments were undertaken. Initial studies focussed on the reaction of Proton Sponge® with palladium(II) iodide, the expected by-product of the reaction which would require reduction to permit catalysis to occur. It was found that reaction of Proton Sponge® with one equivalent of palladium(II) iodide in D_3-

MeCN at room temperature gave very slow conversion to another species. The rate of conversion to this species was found to be increased at 50 °C, ultimately giving a 1:1 mixture of Proton Sponge® and an unknown, asymmetric (ie. with two distinct aryl rings) Proton Sponge® derivative with the aryl protons being significantly downfield of those of Proton Sponge®. This new species also showed a singlet at 4.8 ppm and two broad singlets at 3.2 ppm and 3.6 ppm in the ^1H NMR spectrum. Upon heating to 70 °C, this species was seen to convert to a symmetric species over a period of 48 hr, this new species also possessing aryl protons downfield of those of Proton Sponge® but missing the broad peaks between 3 and 4 ppm as well as the singlet at 4.8 ppm. Due to the 50% conversion seen using one equivalent of palladium(II) iodide relative to Proton Sponge, the reaction was repeated using two equivalents of palladium(II) iodide in the hope of forcing the reaction to completion. Unfortunately, no further reaction was seen and consequently, assignment of the structure of the newly formed species proved impossible. This was compounded by the finding that purification of the reaction, when performed on a larger scale, was made impossible by the high water solubility of Proton Sponge® preventing aqueous washing and its high polarity preventing silica gel chromatography.

It was eventually discovered that through the use of 2.4 equivalents of palladium(II) iodide, complete conversion of Proton Sponge® to the initial product at 50 °C could be achieved in 7 days. The NMR spectra of this species are shown in Figures 14 and 15. With the Proton Sponge® removed, it appears that the apparent single species is in fact two species; one symmetric and one asymmetric in a 1:1 ratio. Intriguingly, on heating to 70 °C, this product did not convert to that seen previously when Proton Sponge® remained in the mixture, however, a new peak did appear at 18.6 ppm in the ^1H NMR spectrum. The ^1H NMR spectrum of the apparently symmetric Proton Sponge® derivative and that of Proton Sponge® itself are shown in Figures 16 and 17 respectively.

Figure 14: ^1H NMR spectrum of 'asymmetric' Proton Sponge derivative

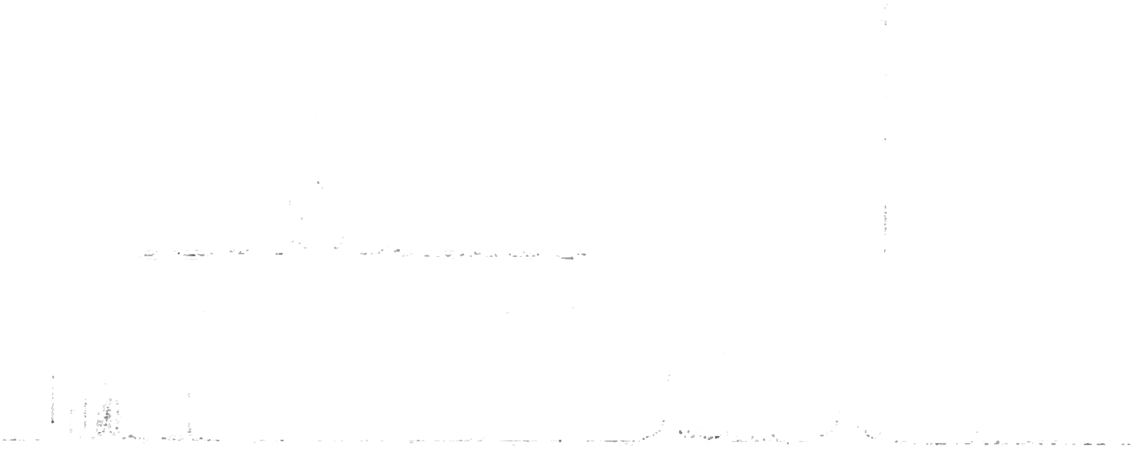


Figure 15: ^{13}C NMR spectrum of 'asymmetric' Proton Sponge derivative

Figure 16: ^{1}H NMR spectrum of 'symmetric' Proton Sponge derivative

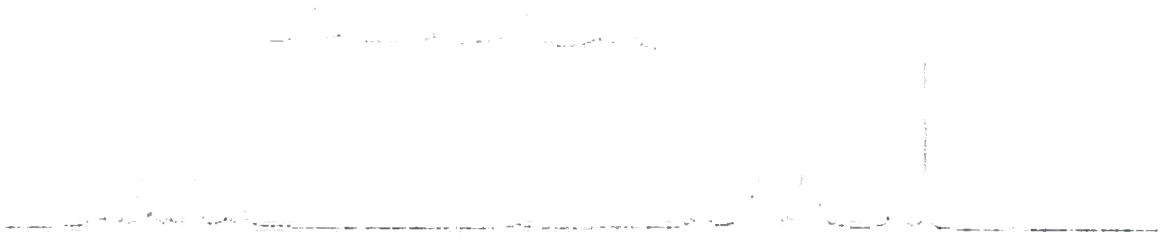
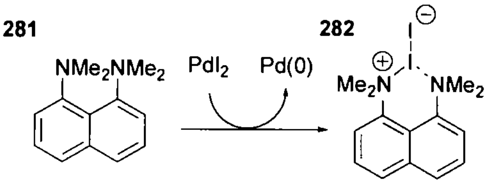


Figure 17: ^{1}H NMR spectrum of Proton Sponge

The NMR data obtained are not sufficient to assign the structures of the products formed although several points, most notably the peak at 4.8 ppm in the ^1H NMR spectrum and 80.1 ppm in the ^{13}C NMR spectrum, are intriguing. Analysis of the first species by mass spectrometry showed only Proton Sponge® by positive electrospray and iodide by negative electrospray. This appears to suggest that the reaction of Proton Sponge® is reversible which would be consistent with iodine complexation of Proton Sponge®, iodine complexes of such amines being documented.[325] Such complexation could also explain the symmetric and asymmetric species observed with complexation of one or both nitrogen atoms possible as well as the downfield shifts seen in the NMR spectra. Hence it appears possible that following reductive elimination of iodine from palladium iodide to derive a palladium(0) species, the iodine could be trapped by complexation to Proton Sponge® to give a species of type **282** (Equation 29).

Equation 29



Whilst interesting, it was thought that the above observations may not have been related to the effect of Proton Sponge® on the reductive dimerisation reaction as the reductive dimerisation was complete within 24 hr at 50 °C whilst the reaction of Proton Sponge® with palladium(II) iodide at the same temperature took considerably longer to reach completion. Given the effect of silver salts on much palladium chemistry, it was thought to investigate the effect of the addition of silver(I) acetate on the reaction of Proton Sponge® with palladium(II) iodide. This was found to increase the rate of conversion to the asymmetric species at 50 °C; a considerable amount of this species was seen to be present after 4 hr (20% conversion). In addition, the ^1H chemical shifts for the remaining Proton Sponge® were seen to be broadened and shifted downfield. On increasing the temperature to 70 °C, all remaining Proton Sponge® was consumed as was the asymmetric species formed at 50 °C, however, the species formed was not the same as that seen in the absence of silver(I) acetate. This new species showed broad ^1H NMR signals in the aryl region and the peak at 4.8 ppm was still present.

The above results clearly showed that a combination of Proton Sponge® and silver(I) acetate could react with palladium(II) iodide on the timescale required to be the reducing agents in the reductive dimerisation reaction, however, the product of this reaction remained unknown as did whether this reaction actually reduced palladium(II) to palladium(0). Since it was not possible to purify the resulting products, the investigation of the reaction of Proton Sponge® with iodine was examined as if Proton Sponge® were to react to reduce palladium(II) iodide, the product of the two reactions could be expected to be the same. Although the reaction in Et_2O was seen to give little conversion, use of MeCN as solvent gave conversion to a new species, however, this was not the same as any of the species observed in the reaction with palladium(II) iodide.

Frustrated by the inability to identify the products of the above reactions, it was decided to perform a reductive dimerisation reaction in D_3-MeCN so that the reaction could be followed by ^{1}H NMR spectroscopy. The catalyst loading for this reaction was increased in the hope that catalytic intermediates could be observed. Unfortunately, the increase in the catalyst loading resulted in the initial rapid formation of significant amounts of vinyl acetate **279** and dimer **238** was only seen to form significantly after this stopped. This increased iodine-acetate exchange presumably results from the increased concentration of acetate due to the increased amount of palladium(II) acetate. Surprisingly, no conversion of Proton Sponge® to one of the previously seen products was seen although the peaks aryl peaks of Proton Sponge® were all seen to shift downfield and broaden slightly from the start of the reaction as had been seen when silver(I) acetate was used previously. This effect is presumed to arise from the ligation of silver by Proton Sponge®. The reason for the lack of reaction of Proton Sponge® under these conditions was unclear but the reduced amount of product formed due to competition from the iodine-acetate exchange reaction combined with the high catalyst loading meant that reduction of palladium was less critical as fewer catalyst turnovers were needed. For this reason, the reaction was re-run on a normal scale without the use of a deuterated solvent and the crude product analysed by ^{1}H NMR spectroscopy without an aqueous work-up, only a Celite filtration being performed. Although the majority of the expected mass was lost as had been seen on previous attempts at handling the products from the reactions of Proton Sponge®, sufficient Proton Sponge®-derived material was present to allow observation by ^{1}H NMR spectroscopy. None of the previously observed, unidentified species were seen in this spectrum, the only Proton Sponge®-derived product being the downfield shifted and broadened species observed every time silver(I) acetate had been used. This result appears to indicate that this shifting does not result from ligation of silver since such a complex would be unlikely to pass through a Celite pad, and therefore may be the result of a chemical reaction. However, even if this were to be the case, this reaction could not be responsible for the reduction of palladium under these conditions as it had been seen to occur prior to the formation of any dimer **238** in the NMR reaction. For this reason, as well as the complete failure of chromatography to separate these species, further investigation of this product was not performed.

Due to the failure of the above reactions to shed any light on the mechanism of the reduction of palladium in this process, a number of other reactions (Table 5) were performed with the hope of identifying other reagents which could effect this reduction.

Table 5: investigation of potential reducing agents

Entry	Solvent	Ligand	Conditions[a] (equivalents)	Product (yield)	Selectivity (*E,Z*:*E,E*:*Z,Z*)
1	MeCN	-	Phenol (1.5), Et_3N (1.5), AgOAc (1.5), 50 °C	**238** (7 %)	3:1:0
2	MeCN	-	Proton Sponge® (1.6), 80 °C	**238** (14 %)	7:1:0
3	THF/H_2O (9:1)	TPP	Na_2CO_3 (3.5), $Na_2S_2O_3$ (1.0), 70 °C	**238** (12 %)	2:1:0
4	THF/H_2O (9:1)	TPP	Starch (700 g mol^{-1}), Na_2CO_3 (3.4), 70 °C	**238** (50 %)	1:2:3.7
5	MeCN	-	Proton Sponge® (0.7), AgOAc (0.7), CuOAc (0.7), 50 °C	**238** (78%)	5:1:1.3
6	MeCN	-	Proton Sponge® (0.7) CuOAc (0.7), 50 °C	**238** (19%)	26:1:0

[a] All reactions use 5 mol% $Pd(OAc)_2$ unless otherwise stated

The replacement of Proton Sponge® with phenol (Entry 1) was investigated as it was though that this might effect the required reduction through a electrophilc aromatic substitution with iodine. As can be seen, this did not prove successful.

The use of Proton Sponge® in the absence of silver(I) acetate at an increased temperature was investigated as the NMR experiments had shown that silver(I) acetate allowed the reaction of Proton Sponge® to occur more rapidly. Although this did give rise to reductive dimerisation, the reaction was far less efficient than that seen in the presence of silver(I) acetate (Entry 2).

Given that no reducing agent was present in the reactions performed in THF, it was investigated whether the presence of a reducing agent could improve the yield under these conditions. Sodium thiosulphate was used due its efficiency in reducing iodine (some reactions had been seen to turn purple) and its water solubility. This was in fact found to give a reduced yield as compared to the use of only sodium carbonate (Entry 3) and may reflect poisoning of palladium by the sulphur-containing anion.

Given the propensity of starch for absorption of iodine and the purple colour seen in some of the reactions, the addition of starch was investigated. Although it was difficult to determine the amount of starch required to absorb the expected amount of iodine, one report[326] suggested typical absorption levels of up to 30% and this value was used. This experiment proved relatively successful with the isolated yield being increased from 30% to 50%, however, the stereochemical outcome of the reaction was altered considerably (Entry 4). In the presence of starch, the previously always dominant *E*,*Z*-isomer became the minor product with the major isomer being the *Z*,*Z*. Although this result apparently shows that elemental iodine is released by the reaction, albeit potentially in equilibrium with palladium(II) iodide, the reason behind the marked change in stereoselectivity was unclear. There was a suggestion that perhaps the adsorption of palladium onto the starch in some way altered the sterics around palladium such that the all-*cis* product became favoured, however, there was no way to test this. Another proposition was that the preferred product of all reductive dimerisation reactions was all-*cis* **238**, that a subsequent palladium mediated isomerisation gave rise to the other isomers and that the addition of starch sequestered the palladium and reduced this isomerisation. This was disproved by a number of NMR spectrscopy experiments which demonstrated that: i) both *E*,*Z* and *Z*,*Z* isomers are thermally stable up to 80 °C; ii) the *E*,*Z*-isomer is stable to palladium acetate at 70 °C in MeCN; and iii) the *Z*,*Z*-isomer is isomerised directly to the *E*,*E*-isomer by palladium acetate at 50 °C in MeCN, no *E*,*Z*-isomer being detectable. Consequently, although the addition of starch improves the yield of this reaction, its use in these reactions is of limited synthetic interest due to the lack of stereochemical control. In addition, the lack of understanding of the change in stereoselectivity made it difficult to suggest ways to improve this.

Another reducing agent was sought with the hope of retaining the increased yield seen with starch whilst not inducing a loss of stereochemical control. Following a personal communication with Dr John Brown (Oxford), copper(I) acetate was investigated as the use of copper(II) acetate had been found successful in oxidative Suzuki-Miyaura couplings, hence the idea of the reverse process. Gratifyingly, this gave a dramatic increase in yield (Entry 5), however, the stereochemical control was reduced although the *E*,*Z*-isomer still dominated. The role of copper(I) acetate in the reaction fell into doubt when it was found that the expected oxidation product, copper(II) iodide, was unstable to disproportionation to copper(I) iodide and iodine, and hence, it appears unlikely that copper(I) acetate behaves as a reducing agent for the iodine formed. Another possible way for the copper salt to increase the yield was for it to catalyse an Ullmann coupling. This would explain the increase in yield (the two reactions would give the same product) as well as the decrease in stereoselectivity with the high stereoselectivity of the palladium catalysed reaction being eroded by the poor stereoselectivity of an Ullmann coupling. This hypothesis appears to be incorrect based on the reactivity seen in the absence of silver(I) acetate (Entry 6); it can be seen that the yield is reduced but the stereoselectivity is increased. Were an Ullmann reaction contributing to the yield in Entry 5, removal of silver would be expected to give a decrease in both yield and stereoselectivity as the poor stereochemical control of an Ullmann coupling would override that of the palladium catalysed reaction.

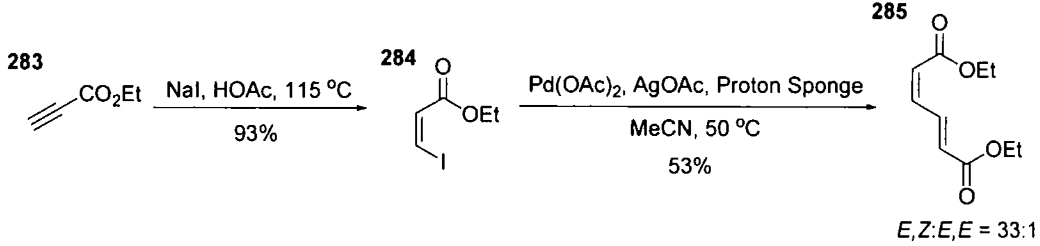
The reactivity in entries 5 and 6 also show that the optimal conditions for the palladium-catalysed reductive dimerisation of iodide **229** apparently involve three metals as well as Proton Sponge®. This is far from ideal for use in synthetic chemistry and clearly, further optimisation of the reaction conditions would be required for the reaction to be used in this context.

Despite a considerable amount of effort, the studies described above ultimately failed in identifying the mechanism of reduction of palladium in this reaction although a reasonable degree of optimisation of the yield was achieved. To be of serious synthetic use this reaction would require further optimisation, preferably simplifying the conditions and gaining some mechanistic insight into the reduction of palladium. However, at this point it was decided to investigate the more general application of this reaction with the use of a number of other substrates.

2.8.1 Screening of other substrates

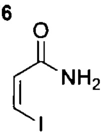
The first reaction investigated in this small study was the simple substitution of the ester group of iodide **229** by the synthesis of ethyl ester **284** in an analogous fashion. Under the conditions shown in Scheme 54 (these conditions were employed throughout the substrate screen due to the moderate yield and high stereoselectivity), ethyl ester **284** was found to undergo the reductive dimerisation in comparable yield to the corresponding methyl ester.

Scheme 54: synthesis and reductive dimerisation of ethyl analogue **284**

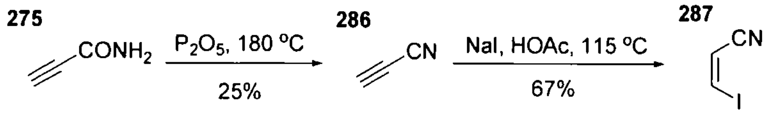


Following this success, other electron deficient vinyl halides were sought and amide **276** and nitrile **287** appeared suitable. Amide **276** had already been synthesised for use in a HM reaction (Scheme 52) and nitrile **287** was synthesised by a literature method involving dehydration of propiolamide **275** and subsequent conjugate addition of iodide (Scheme 55).[290,305]

276

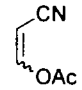


Scheme 55: dehydration/1,4-addition to form iodide **287**



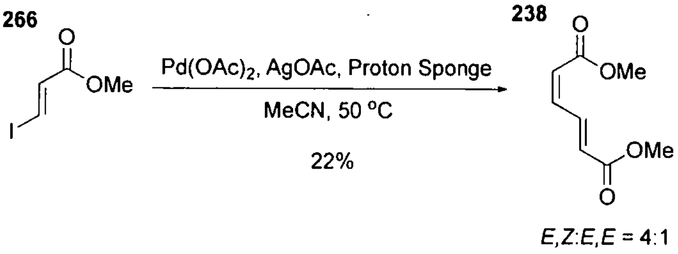
Unfortunately, both substrates failed to show any sign of reductive coupling under the standard conditions, demonstrating the sensitivity of this reaction to the electronics of the vinyl halide. The only product seen in these reactions was what appeared to be vinyl acetate **288** resulting from iodine-acetate exchange on nitrile **287**. In the case of amide **276**, although all starting material was consumed, no recognisable products were seen by ^{1}H NMR spectroscopy.

288



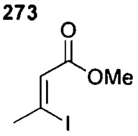
The effect of the geometry of the vinyl halide on the stereochemical outcome of the reaction was investigated through the use of from *trans*-methyl acrylate **266**. Remarkably, this was found to give the same *E*,*Z*-isomer as seen previously, albeit with lower yield and stereoselectivity (Equation 30). Increasing the temperature to try to improve conversion in this sluggish reaction was found to give a decreased yield, potentially due to the instability of the product under these conditions. Interestingly, the higher temperature reaction was seen to give slightly greater stereoselectivity.

Equation 30



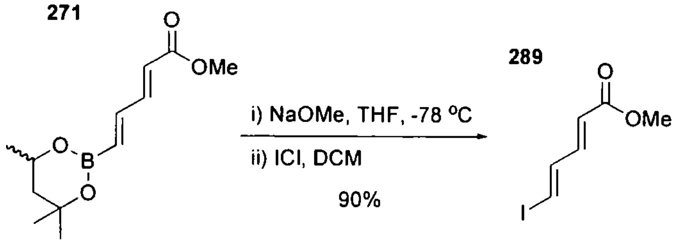
Further investigation of the stereocontrol of the reaction was attempted through the use of methyl-substituted iodide **273**. Disappointingly, no conversion of this substrate was seen under the standard conditions, suggesting that steric bulk on the vinyl halide strongly disfavours the reductive dimerisation.

273



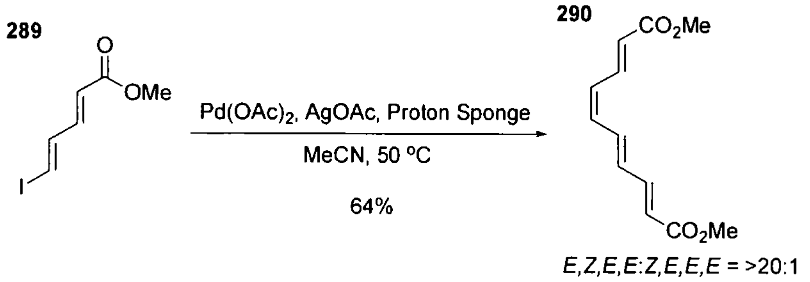
Having investigated vinyl iodides in the reductive dimerisation reaction, attention was turned to dienyl iodides in the hope that polyene systems could be constructed. Two dienes were investigated; all-*cis* diene **245**, already synthesised for the construction of the northern hemisphere, and the all-*trans* analogue **289**, synthesised by an analogous route (Equation 31) starting from dienyl boronate **271**.[327]

Equation 31

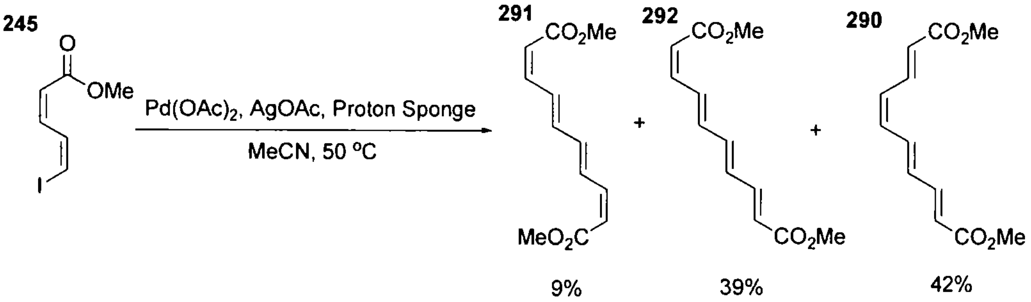


Both **245** and **289** were found to be reactive under these conditions and the yields were in fact found to be higher than those seen for the simple vinyl systems (Equations 32 and 33).

Equation 32



Equation 33



The stereoselectivity of these reactions is of considerable interest as in the case of all *trans*-iodide **289**, the stereoselectivity is extremely high, hence this reaction gives access to polyenes with geometries which would otherwise be very difficult to obtain. As was seen for both **229** and **266**, inversion of the geometry of only one double bond was seen, however, in this case, the fact that the geometry of the internal double bonds remains unchanged gives some mechanistic insight. In the case of all *cis*-iodide **245**, the stereoselectivity of the reaction is rather less impressive with three isomers being obtained. Some difficulties were encountered in determining the geometry of **291** by ^{1}H NMR spectroscopy due to the symmetry of the molecule generating an AA'BB' system for the protons of interest which meant that no coupling constants could be calculated. The geometry of **291** was finally proven by means of a crystal structure. Interestingly, the major isomer is the same as that resulting from the corresponding *trans*-iodide.

Moving to a triene by applying the conditions to iodide **254** met with failure; although some reductive dimerisation product could be seen by ^{1}H NMR spectroscopy, the main products appeared to be two isomeric vinyl acetates and the fact that none of the products could be separated by silica gel chromatography meant that the geometries and yields of these products were not established.

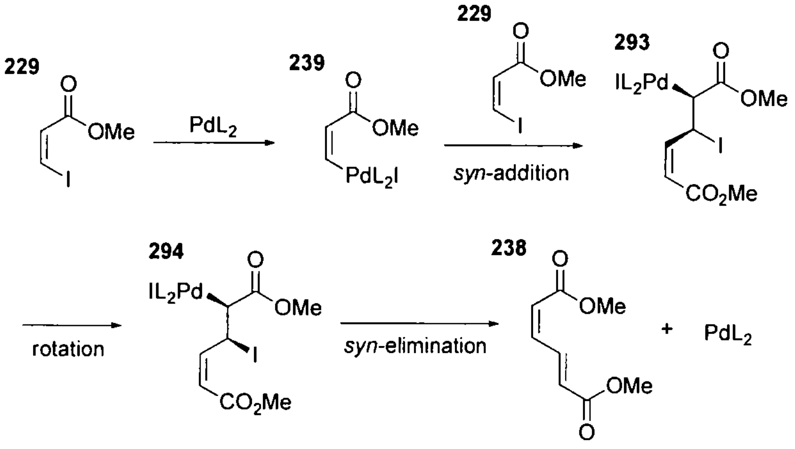
2.8.2 Mechanistic considerations

The reductive dimerisation of the two dienyl iodides **245** and **289** gave further insight into the mechanism of the reductive dimerisation reaction. Given the inversion of only one double bond seen in the reaction of *trans*-iodide **289**, the previously proposed conjugate addition of a palladium-alkenyl species to another iodide molecule seemed unlikely as in the case of a dienyl substrate, such a 1,6-conjugate addition might be expected to isomerise both double bonds of the Michael-acceptor. Further evidence against this conjugate addition mechanism comes from the stereoselectivity seen in the reductive dimerisation of *trans*-iodide **266**, the *E*,*E*-isomer would be expected based on this mechanism but the major product was found to be the *E*,*Z*-isomer.

With this mechanism apparently ruled out, the next suggestion involved an initial carbopalladation of the iodide by a palladium-alkenyl species (Schemes 56 and 57), this seeming particularly likely for vinyl iodides **229**, **266** and **284** given the reactivity of acrylates in HM reactions. Following carbopalladation, reductive elimination of palladium(II) iodide would provide the observed product.

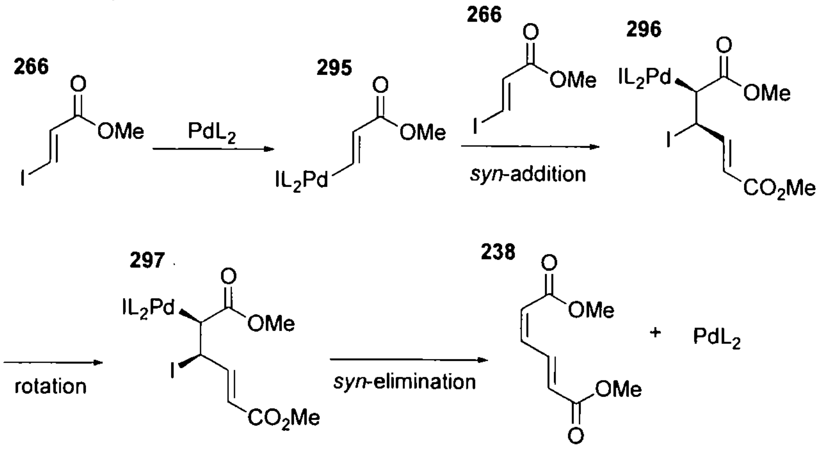
This mechanism also explains the stereoselectivity seen in the majority of these reactions. For *cis*-olefins, following oxidative addition of a palladium(0) species to one molecule of iodide **229**, *syn*-addition to a second molecule of **229** derives palladium-alkyl species **293**. Until this point, the mechanism is identical to that of a HM reaction, however, in this case, elimination of palladium(II) iodide may occur to provide the observed reductive dimerisation. In order for *syn*-elimination of palladium(II) iodide to occur, rotation around the carbon–carbon sigma bond to generate intermediate **294** is necessary and this causes the *trans*-geometry of the resulting double bond.

Scheme 56: Proposed mechanism for *cis*-iodides.



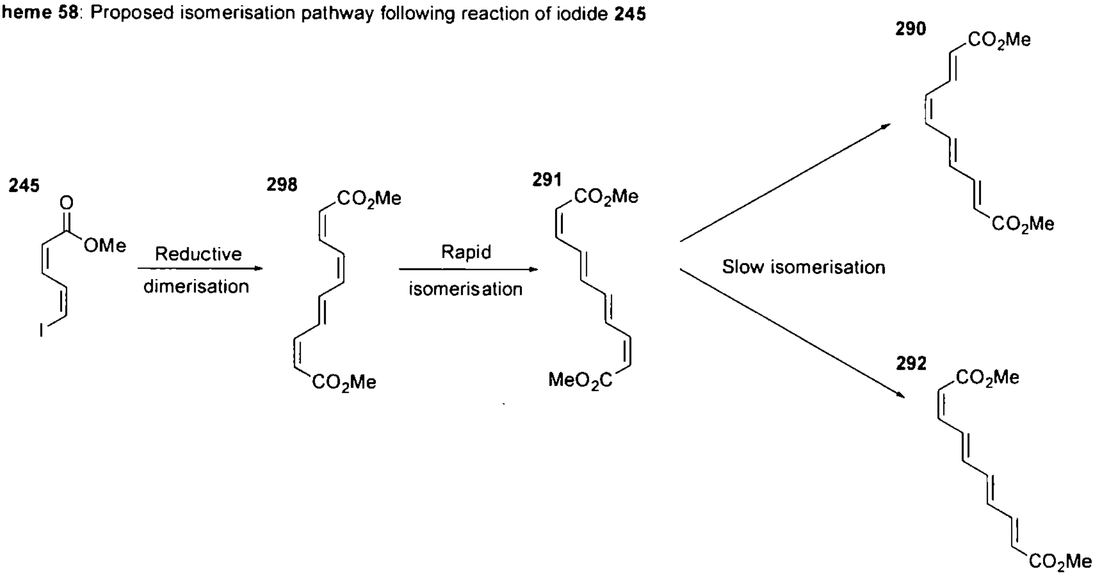
In the case of *trans*-olefins, the oxidative addition derives *trans*-palladium vinyl species **295** which also undergoes *syn*-addition to a second molecule of **266** to provide palladium alkyl species **296**. In this case, the rotation required to achieve *syn*-elimination generates intermediate **297** which provides the *cis*-geometry of the resulting double bond.

Scheme 57: Proposed mechanism for *trans*-iodides.



This mechanism does not explain the mixture of isomers found for *Z,Z*-iodide **245**, however, it should be noted that in contrast to *E,Z,E,E*-isomer **290** resulting from the coupling of *E,E*-diene **289**, the *Z,E,E,Z*-isomer **291** was found to be highly unstable to both heat and light, isomerising to give the *Z,E,E,E*-isomer **292**. *Z,E,E,E*-isomer **292** was also found to be unstable, albeit it less so than *Z,E,E,Z*-isomer **291**, slowly isomerising to produce the thermodynamic *E,E,E,E*-isomer. In light of these results, it seems likely that the initial product of the reductive dimerisation of *Z,Z*-diene **245** is in fact the *Z,E,Z,Z*-isomer **298** expected based on the mechanism shown in Scheme 56 and that this is highly unstable and isomerises under the reaction conditions. A possible pathway for this isomerisation is outlined in Scheme 58 with initial rapid isomerisation of the kinetic product **298** to *Z,E,E,Z*-isomer **291** which isomerises more slowly to produce the two main products of the reaction.

Scheme 58: Proposed isomerisation pathway following reaction of iodide **245**



One question which remains unanswered is the reason for the lower reactivity of *E*-iodide **266** compared with *Z*-iodide **229**. Assuming that the mechanism outlined in Schemes 56 and 57 holds true, two explanations appear possible: i) that the *syn*-addition of the palladium vinyl species across the iodide is slower for the *trans*-isomer, such effects being well documented for the addition of other organometallics across double bonds;[328-330] and ii) that the rotation required to achieve *syn*-elimination of palladium iodide is disfavoured for the *trans*-isomer as in this case it involves an increase in the steric interactions between the substituents, whilst in the case of the *cis*-isomer, the same rotation results in a decrease in the same steric interactions. With no evidence to support either hypothesis, it cannot be said which of these is the more likely and it could even be that the two effects work together.

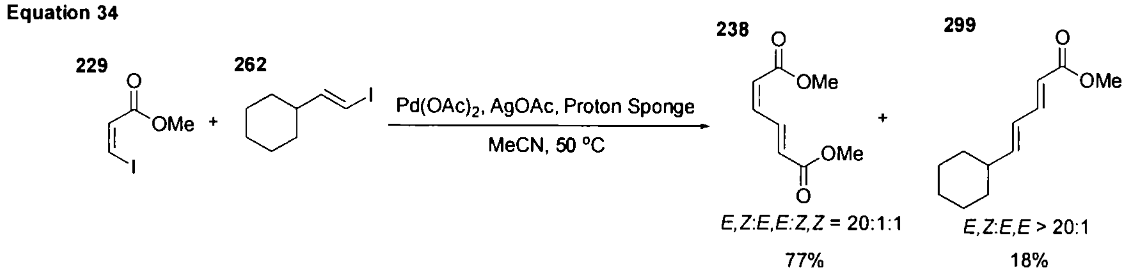
Another point of interest regarding the reactivities of iodides **229** and **266** is the marked difference in stereocontrol; although both favour the *E,Z*-isomer, *cis*-iodide **229** shows much greater stereoselectivity. Leakage to provide the *E,E*-isomer could arise from a palladium promoted isomerisation of another isomer however, this cannot be the reason in this case because such an effect would not be substrate dependent and also, it has been demonstrated that the *E,Z*-isomer is not isomerised under the reaction conditions. However, it should be noted that the *Z,Z*-isomer is isomerised directly to the *E,E*-isomer under the reaction conditions and hence, apparent leakage to the *E,E*-isomer may in fact reflect leakage to the *Z,Z*-isomer. The fact that isomeric leakage is more apparent for *E*-iodide **266** could perhaps be taken as support for the second argument in the previous paragraph by suggesting that by disfavouring rotation to allow *syn*-elimination of palladium iodide, palladium alkyl species **296** is longer lived and can undergo for example *anti*-elimination to derive a different isomer. However, this is far from conclusive since another process, for instance an *anti*-addition, could also produce unexpected isomers.

There appear to be two problems with the mechanism detailed above: i) that the HM reaction should always be in competition (i.e. elimination of PdHI instead of PdI_2), especially if *syn*-elimination of PdI_2 is disfavoured for *trans*-iodides; and ii) that there is no obvious reason for the complete selectivity seen for the terminal double bond in the diene systems investigated, *syn*-addition across the internal double bond could equally be expected and this would result in a HM reaction to produce a branched product. Regarding the first point, given that no HM derived products were isolated under any circumstances, it seems that elimination of PdI_2 must be significantly faster than that of PdHI. There is no clear answer for the second point, due to the size of iodine a steric argument seems unlikely and due to conjugation, the electronics of the two bonds would be expected to be similar.

2.8.3 Cross dimerisation reactions

In order to both test the mechanism suggested above and assess the scope of these reactions in accessing structurally unusual polyene derivatives, it was decided to investigate cross-dimerisation reaction (i.e. reductive coupling of two different vinyl halides). This clearly could result in a complex mixture of products with both the intended heterodimer as well as two homodimers potentially being present. With this in mind, it was decided to attempt to match the reactivity of the two vinyl halides; choosing an electron-rich substrate that it was hoped would preferentially be added across a double bond, and an electron-poor substrate with the hope that *syn*-addition across such a species would be faster. Hence, the reaction of iodides **229** and **262** was performed (Equation 34).

Equation 34

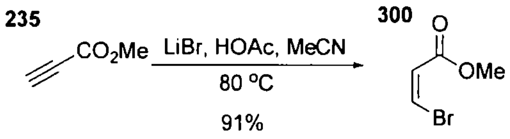


As can be seen, some of the expected heterodimer **299** is formed, the geometry of which is that expected based on the proposed mechanism, however, the yield is low and the major product is clearly homodimerised product **238**. It is interesting to note that in this reaction the yield of homodimer **238** is considerably higher than that seen in the absence of iodide **262** and the combined yield of the two products is nearly quantitative. This appears to be another case where addition of another substrate dramatically increases the yield of the reductive dimerisation process. It should be noted that no homodimerisation of iodide **262** was observed and the majority (61%) of this starting material was recovered.

Although it might be expected that the more electron-rich vinyl palladium species resulting from iodide **262** would add across electron-poor double bonds more rapidly, it was quickly realised that the electron-poor iodide **229** would be expected to undergo a faster oxidative addition reaction. Hence, the majority of the palladium would be expected to react with iodide **229** and given the expected faster *syn*-addition to acrylate **229** as compared with cyclohexane **262**, homodimerisation of would be expected to dominate as was observed.

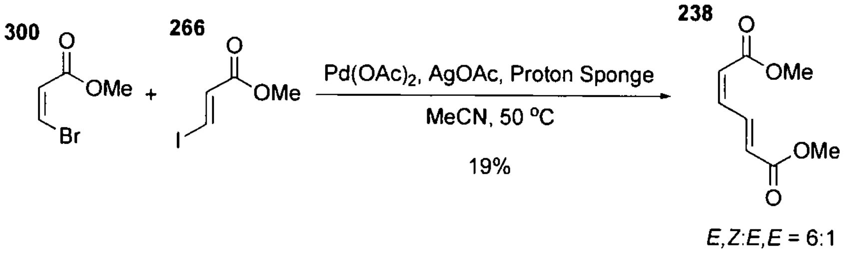
In order to avoid this problem, bromo-acrylate derivative **300** was synthesised in a similar manner to that used for the corresponding iodide[290] (Equation 35). Since it is well documented that oxidative addition to bromides is considerably slower than the equivalent addition to iodides, it was expected that in the reaction with **262**, the majority of the palladium should react with **262** and following *syn*-addition to bromide **300** and elimination of PdIBr, heterodimer **299** should be the major product. Unfortunately, when the reaction was performed, no heterodimer was found; although trace amounts of the homodimerisation product **238** were seen, the major product was an unidentified derivative of cyclohexylvinyliodide **262**.

Equation 35



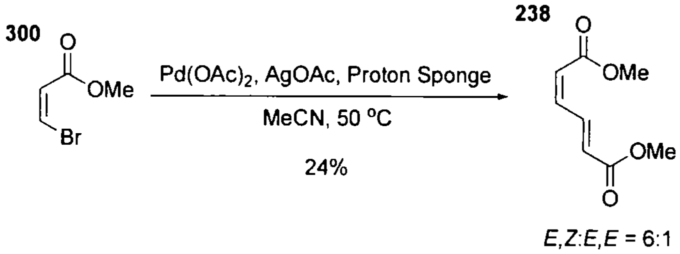
Another heterodimerisation reaction was attempted, this time involving two electron-poor vinyl halides. The reaction of *trans*-iodide **266** with *cis*-bromide **300** was expected to produce the *E,E*-dimer because following preferential oxidative addition to the iodide, *syn*-addition could be expected to occur faster across the *cis*-bromide which would produce a *trans*-double bond following rotation and *syn*-elimination. Once again, the expected result was not observed, the majority of the vinyl bromide was recovered and the major product was the *E,Z*-dimer, this being in slightly higher yield than would have been expected using the iodide alone which suggests that bromide **300** does participate in the reaction. The observed stereoselectivity was in fact an improvement compared to that seen using only *trans*-iodide **266**.

Equation 36



Due to the apparent lack of reactivity of bromide **300** in these reactions, the reaction of **300** alone was run. This showed that although bromide **300** did participate under the conditions employed, its reactivity was similar to that of *trans*-iodide **266** (Equation 37).

Equation 37



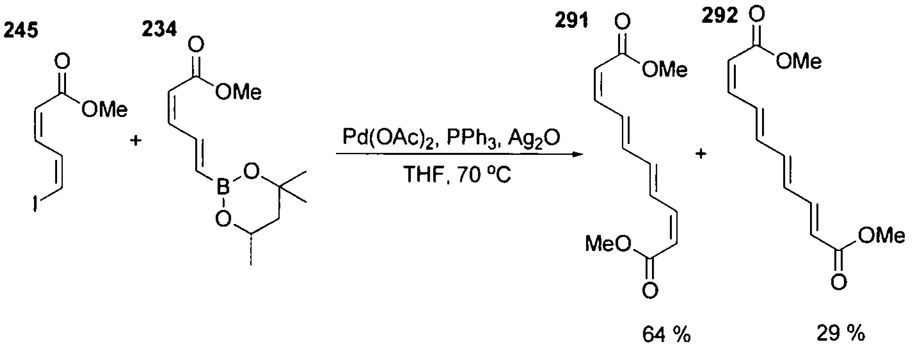
The reason for the lack of reactivity of bromide **300** might be expected to be due to a reduced rate of oxidative addition compared with the corresponding iodide, however, Sonogashira reactions of this substrate occur at room temperature which makes this seem unlikely. The only other obvious explanation for the lack of reactivity is that elimination of $PdIBr$ or $PdBr_2$ is less favourable than that of PdI_2, however, if this is the case the reason for it is unclear.

Due to a lack of success at achieving the desired cross-dimerisation and an increasing amount of confusion about what was occurring in these reactions, no further examination of the cross-dimerisation was performed.

2.8.4 Competition with Suzuki-Miyaura couplings

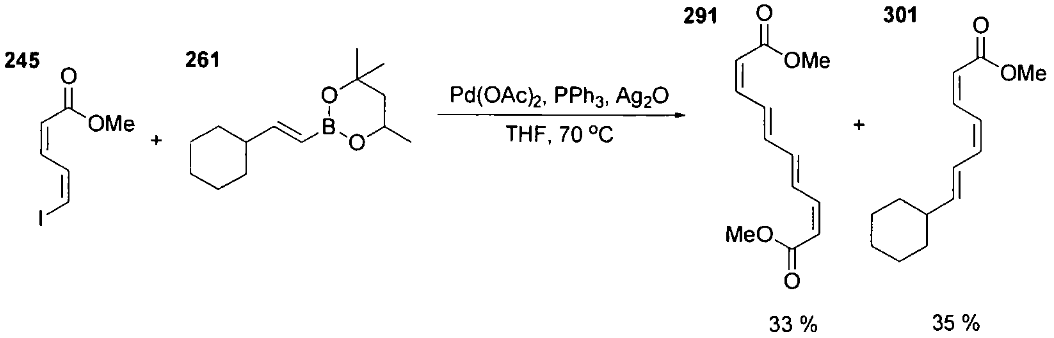
At the time of this study, it was discovered that the Suzuki-Miyaura coupling of *Z,Z*-iodide **245** with dienyl boronate **234** gave two products, neither of which were the expected isomers (Equation 38).

Equation 38



At first glance, this behaviour might appear to be due simply to the reductive dimerisation reaction proceeding faster than the Suzuki-Miyaura coupling, however, when the yields are taken into consideration, it becomes clear that boronate **234** must be involved. Another explanation for the formation of these two unexpected isomers was that following the Suzuki-Miyaura coupling, isomerisation of the product under the reaction conditions provided the isomers observed. This hypothesis could not easily be tested on this system and the Suzuki-Miyaura coupling in Equation 39 was performed.

Equation 39



This result clearly demonstrates that both the Suzuki-Miyaura coupling and reductive dimerisation reaction occur under these conditions and that for the reagents involved in

Equation 39, their rates are comparable. It is interesting to note that in the presence of boronate **261**, the reductive dimerisation reaction gives a single stereoisomer and this isomer gives some support to the suggested isomerisation pathway in Scheme 58.

Although the results in Equation 39 cannot be directly related to those in Equation 38, it does strongly suggest that at least some product occurs as a result of the reductive dimerisation, however, the majority must arise by a Suzuki-Miyaura coupling for the yield to be as high as it is. As suggested in Scheme 58, the expected *Z,Z,E,Z*-isomer produced by both the Suzuki-Miyaura coupling and the reductive dimerisation reaction appears to isomerise under the reaction conditions. These results, and others within the group,[327] have shown that achieving Suzuki-Miyaura couplings on electron-deficient dienes can be challenging.

2.8.5 Conclusions

The work above shows that the reductive dimerisation process discovered has the potential to access geometrically interesting polyenes which would otherwise be difficult to synthesise[331] and underlines the importance of carefully selecting conditions for the Suzuki-Miyaura reactions of these electron-poor vinyl iodides.

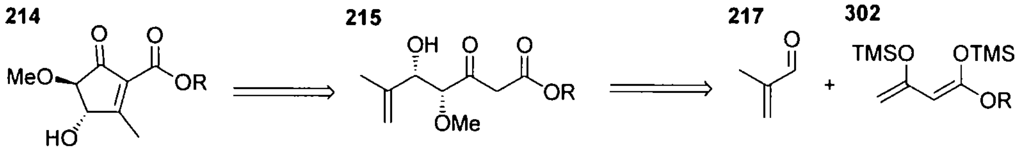
Despite a wealth of results, this reductive dimerisation process remains poorly understood, indeed, this study has probably produced more questions than answers. Although the mechanisms shown in Schemes 56 and 57 explain the majority of the results observed, they do not explain the behaviour seen when heterodimerisation reactions were attempted. Although other mechanisms are possible, there is insufficient evidence at present to speculate as to what might be happening and it seems likely that a fully dedicated project on this area would be necessary in order to achieve the desired level of understanding.

2.9 Cyclopentanone core

2.9.1 Retrosynthetic strategy and previous work

As previously shown in Scheme 39, the retrosynthetic approach adopted towards the cyclopentanone core involved a diastereoselective conjugate addition of an acetylide unit to a cyclopentenone of type **214**, itself accessed by an ozonolysis/Knoevenagel sequence from a β-keto-ester such as **215**. Several approaches to β-keto-esters of type **215** could be conceived and it was initially decided to access such a species directly by means of an enantio- and diastereo-selective Mukaiyama aldol reaction of a bis(trimethylsilyl) enol ether of type **302**.

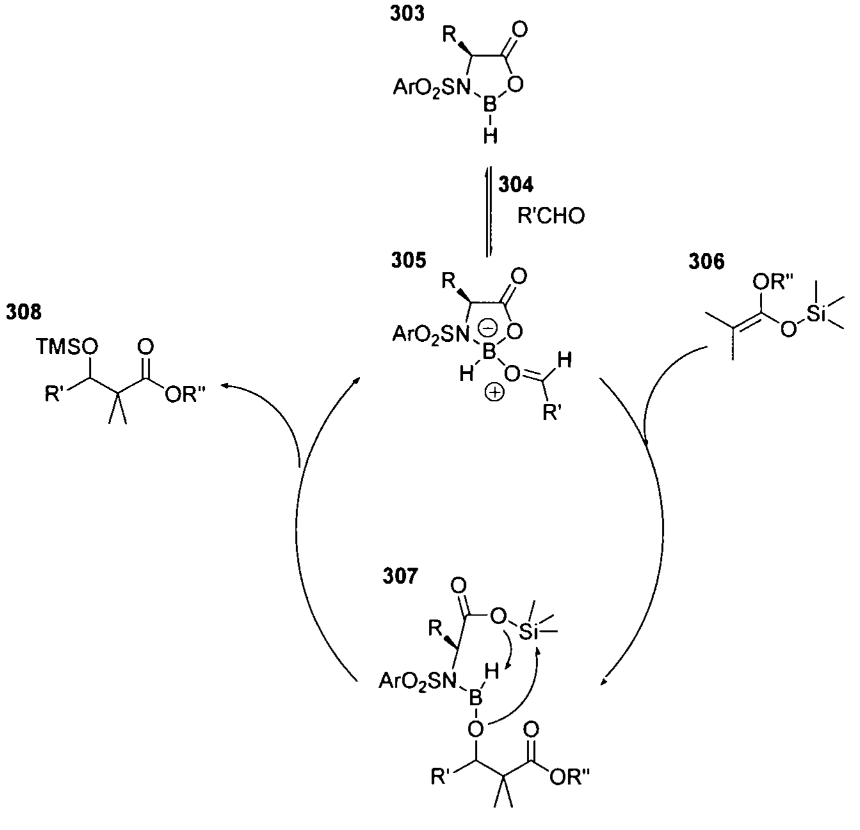
Scheme 59: retrosynthetic approach to cyclopentenone **214**



Since the discovery by Mukaiyama that silyl enol ethers and silyl ketene acetals could react with aldehydes in an aldol-type reaction in the presence of Lewis acids,[332] considerable work has been performed on the asymmetric variant.[333] A large number of chiral Lewis acids have been developed with the aim of achieving asymmetric induction in these reactions and a number of categories of Lewis acid are in common usage including: titanium(IV) complexes bearing chiral ligands such as binol;[334,335] boron based systems, particularly oxazaborolidinone systems developed independently by Masamune,[336] Corey[337] and Kiyooka[338] but also the chiral acyl-oxy boron systems developed by Yamamoto;[339] tin complexes bearing chiral amine ligands from the work started by Mukaiyama[340] and continued by Kobayashi;[341] and the more recently developed copper based systems.[342,343] All systems have been shown to give high enantioselectivity with a wide range of substrates and their application to total synthesis is well documented.[344,345] These systems are all reported to give preferentially the required *syn*-aldol products meaning that any could be chosen on this basis. Since all four possible diastereoisomers of viridenomycin had to be synthesised, it was necessary to choose a system which was available in both enantiomeric forms and hence an oxazaborolidinone system was chosen owing to the commercial availability of both enantiomers of a wide range of amino acids.

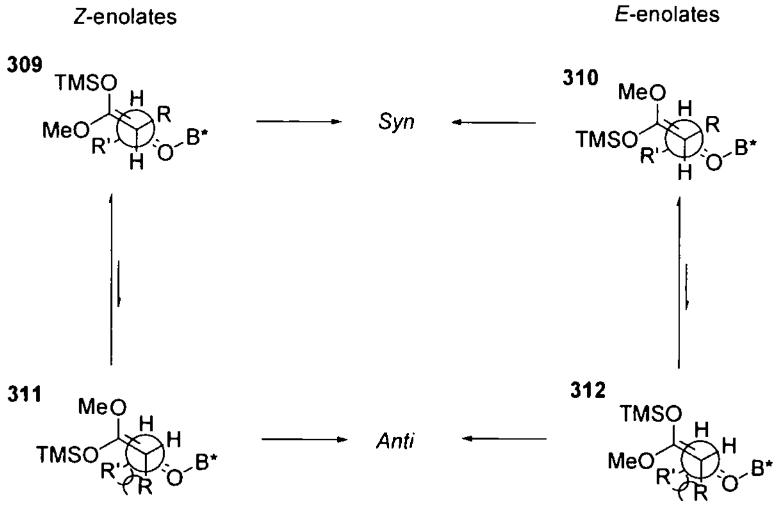
Systems of this type have the advantage that the mechanism necessarily prevents catalysis of the racemic background reaction by enforcing silicon transfer to the alcohol function of the newly formed product in the ring-opened intermediate **307** (Scheme 60).[336]

Scheme 60: mechanism of oxazaborolidinone catalysis



Another advantage of this type of system is that the diastereoselectivity of the aldol product is not influenced by the geometry of the double bond in the silyl enol ether; both *Z*- and *E*-isomers give the *syn* product through the open, extended transition states shown in Scheme 61.[346,347] This behaviour is in contrast with that of aldol reactions of metal enolates where the geometry of the enolate controls the diastereoselectivity.[348] For this reason, there was less concern over producing a single stereoisomer when generating the required silyl enol ethers.

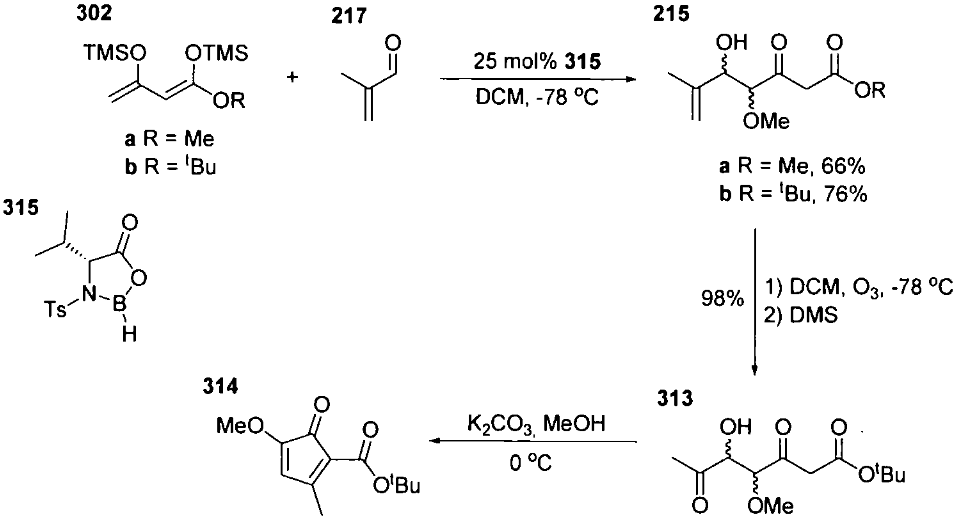
Scheme 61: origin of *syn*-selectivity in Mukaiyama aldol reactions



Although synthetic routes to dienes of type **302** were well documented in the literature because of their use in Diels-Alder reactions,[349] they had seen little use in Mukaiyama aldol reactions. Reports of their use in asymmetric Mukaiyama aldol reactions were not promising; e.e.s tended to be poor and there were no reports of performing these reactions on substrates which would create two chiral centres, hence no information on diastereoselectivity was available.[350,351]

Some considerable work (see Scheme 62) was performed on this approach prior to the start of the present work, however, although the desired Mukaiyama aldol reaction was found to be successful using 25 mol% of oxazaborolidinone **315**, it quickly became apparent that the products existed as mixtures of keto- and enol-tautomers and that this prevented the determination of both diastereo- and enantio-selectivity. Despite the synthesis of a large number of derivatives with the aim of eliminating keto-enol tautomerism, the selectivity of the reaction to give **215** could not be determined and the absolute stereochemistry remained unproven.[352]

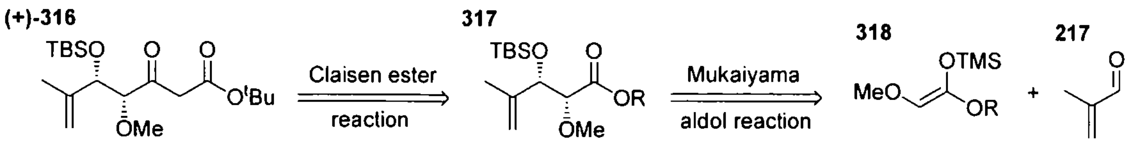
Scheme 62: attempted route to cyclopentenone



Another problem with this route was found when attempting to perform the Knoevenagel cyclisation; although the ozonolysis reaction proceeded smoothly, the product identified following the attempted condensation was proposed to be elimination product **314**. It was not found to be possible to purify this product due to its instability, but all analytical data was consistent with the structure drawn.[352] Whilst this unexpected elimination could presumably be prevented by protection of the alcohol function prior to ozonolysis, such a protection on a molecule such as **215b** was thought likely to be difficult to achieve selectively given the aforementioned contribution from the enol tautomer.

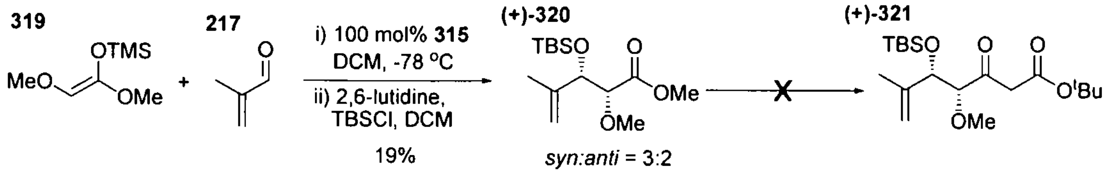
Because of these difficulties, the retrosynthetic strategy was modified to allow the characterisation and protection of the aldol product. In the approach shown in Scheme 63, following the asymmetric Mukaiyama aldol reaction of the more typical type of substrate silyl ketene acetal **318** with methacrolein, and protection of the alcohol group, a Claisen ester reaction was expected to provide the desired *β*-keto-ester which could then be returned to the initial retrosynthetic strategy.

Scheme 63: revised retrosynthetic approach



Some problems were initially found with this route; use of methyl silyl ketene acetal **319** gave poor diastereoselectivity in the Mukaiyama aldol reaction and the product **(+)-320** showed no reactivity in the subsequent Claisen ester reaction (Scheme 64).[297]

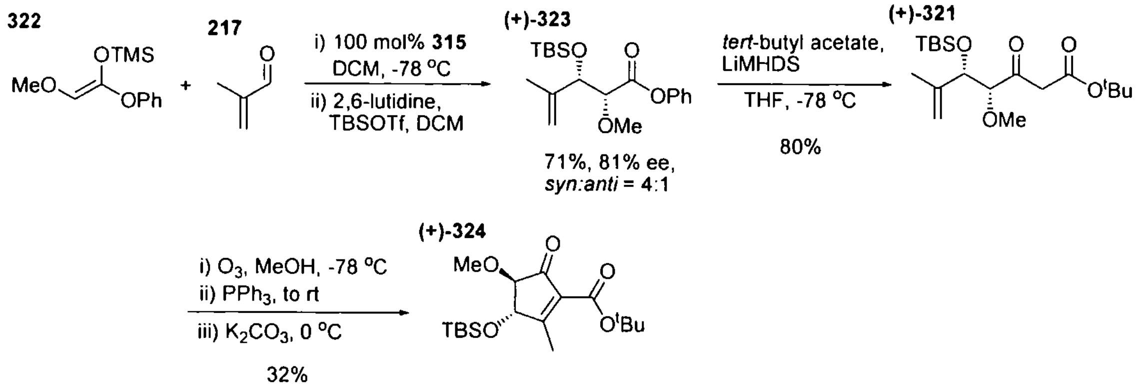
Scheme 64: initial use of methyl ester



Both of these problems were solved through the use of phenyl analogue **322** (Scheme 65), which gave high yields in the Mukaiyama aldol reaction and subsequent protection using TBSOTf, and reacted smoothly with the lithium enolate of *tert*-butyl acetate to give the protected *β*-keto-ester **(+)-321** in an efficient manner. The only problems found in the Mukaiyama aldol reaction was the need to use stoichiometric amounts of the oxazaborolidinone "catalyst" to achieve a reasonable yield, presumably indicating that the catalyst does not turn over, and the need to employ a desilylation of the crude aldol intermediate (Carreira procedure[342]) prior to the TBS protection.[297] This impressive reactivity was all the more gratifying given that such phenoxyl ketene acetals are considered to be rather less reactive than their alkoxy analogues.[353]

^{1}H NMR spectroscopy showed the major diastereoisomer from the Mukaiyama aldol reaction to be the expected *syn*-isomer. In addition, the enantiomers of the free aldol product were found to be separable by chiral HPLC which showed an e.e. of 81% although the absolute stereochemistry of the major enantiomer, predicted to be that drawn, could not be ascertained. Although the absolute stereochemistry of viridenomycin is unknown, the commercial availability of both enantiomers of valine meant that both enantiomers of **323** could be readily available.

Scheme 65: route to cyclopentenone **324**



Unfortunately, this approach encountered problems at the ozonolysis/Knoevenagel condensation stage and although some of the desired product was isolated, the best yield was found to be 32% following extensive optimisation. In addition, a number of literature procedures failed to effect the desired 1,4-addition of an acetylide unit to cyclopentenone (+)-**324**.[297]

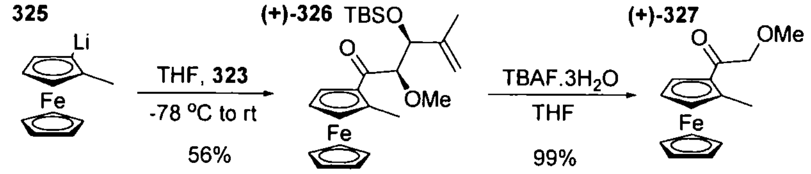
It was at this point that the current project began and the initial aims were determination of the absolute stereochemistry of aldol product (+)-**323**, optimisation of the route to cyclopentenone (+)-**324** and development of conditions to allow a conjugate addition to this molecule.

2.9.2 Determination of the absolute stereochemistry

It should be noted at the start of this section that both enantiomeric series have been used for much of the project. This has the potential to cause some confusion and to clarify matters, each substrate synthesised is labelled (+) or (-) according to its optical rotation. This is generally straightforward as derivitisation of the *syn*-aldol product does not generally give a product of different rotation, however, it should be noted that for four substrates (**418**, **425**, **427** and **431**) the measured rotations are *opposite* to that expected based on the starting enantiomer of **323**.

The most effective way to prove the absolute stereochemistry of aldol product (+)-**323** was clearly derivatisation to a crystalline material to permit X-ray diffraction studies to be performed. Initial investigations into this approach were not promising; although reaction with lithiated ferrocene derivative[354] **325** gave a solid material, this was found to be amorphous and attempts to induce crystallisation were not rewarding.

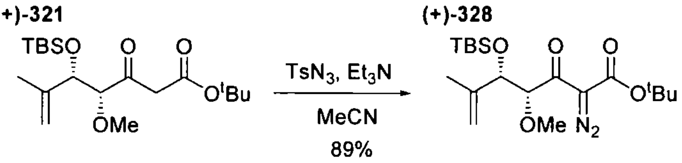
Scheme 66: synthesis of ferrocene **326**



This lack of crystallinity was felt to be at least in part due to the apolar nature of the TBS protecting group and deprotection of this function was investigated, however, use of TBAF gave exclusively retro-aldol product (+)-**327**.

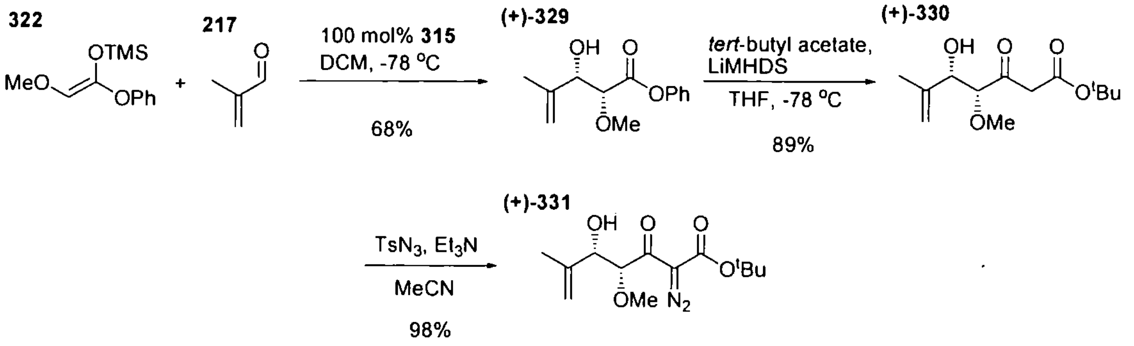
Turning attention to the β-keto-ester system (+)-**321**, derivitisation in such a way as to prevent keto-enol tautomerism was investigated. Whilst reaction with 2,4-dinitrophenylhydrazine proved extremely sluggish, reaction with tosyl azide was found to be rapid and afforded the expected diazoketone (+)-**328** in high yield. Unfortunately, this product also proved to be an oil in non-racemic form, although the racemic compound was found to be a low melting point solid.

Equation 40



This lack of crystallinity was again ascribed to the TBS group, however, removal of this group was not attempted as it was expected that this would again induce the retro-aldol reaction as seen for ferrocene-derivative (+)-**326**. Gratifyingly, it was found that the Claisen ester reaction could be performed on free alcohol (+)-**329** through the use of an extra equivalent of base, and that this product also reacted efficiently with tosyl azide to produce diazoketone (+)-**331**.

Scheme 67: synthesis of free alcohol **331**



Disappointingly, this product was again found to be an oil, however, it was found that all four diastereoisomers of this compound could be separated by chiral HPLC which allowed comparison with the product of the initial retrosynthetic strategy shown in Scheme 59 (*vide infra*).

Thinking to use the keto-enol tautomerism to our advantage, *β*-keto ester **(+)-330** was treated with triethylamine and iron(III) chloride in the hope of crystallising the iron enolate. Unfortunately, although IR spectroscopy clearly showed complexation had occurred by the disappearance of the carbonyl stretches at 1737 and 1717 cm^{-1}, it did not prove possible to grow crystals of the complex.

Returning to the displacement of phenol from **(+)-323** as the method of derivatisation, it was found that through the use of 2,4-dinitroaniline, amide **(+)-332** could be produced and this was found to be crystalline. X-ray diffraction studies proved the absolute stereochemistry of amide **(+)-332** (and thus phenyl ester **(+)-323**) to be that shown in Figure 18, which is that expected based on the transition states proposed for oxazaborolidinone catalysis in the literature.

Equation 41

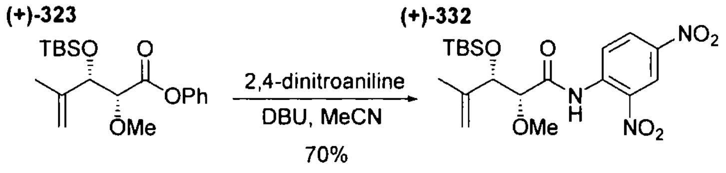
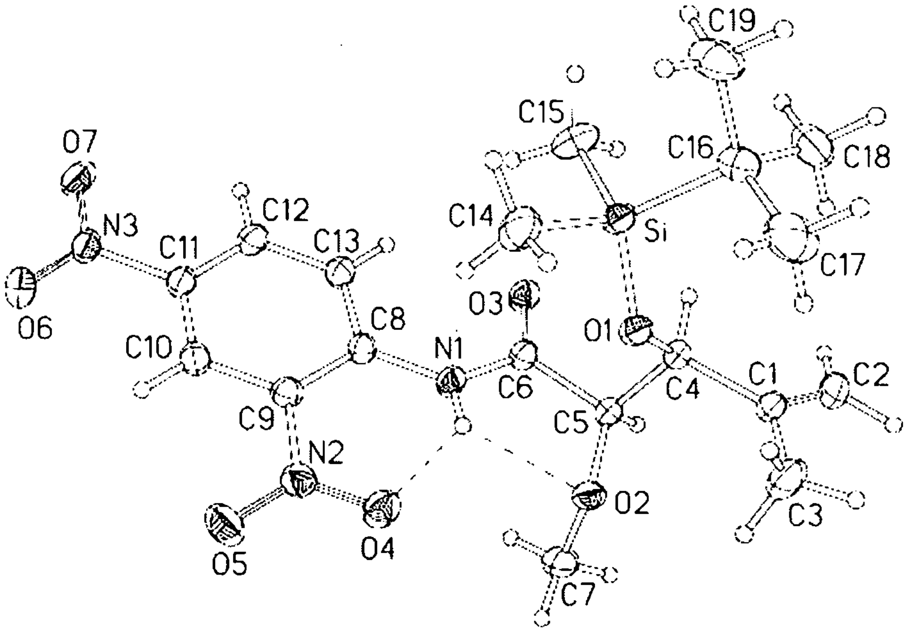
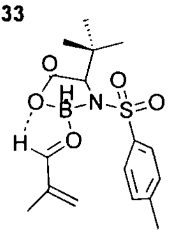


Figure 18: crystal structure of **332**



The work performed by Corey *et al.* on the complexation of aldehydes with a range of catalysts suggested the likely transition state when oxazaborolidinones are used is that shown in structure **333**.[355] It can be seen that the hydrogen bond between the oxygen of the oxazaborolidinone ring and the formyl hydrogen, combined with the complexation of the aldehyde oxygen to boron, locks the conformation of the aldehyde.[356] Whilst complexed in this fashion, the α-substituent of the amino acid directs the aryl group of the tosyl function such that it blocks one face of the aldehyde. Hence, the approach of the reacting silyl ketene acetal must occur from the front face as drawn and this, combined with the open extended transition state discussed above, produces the isomer shown.

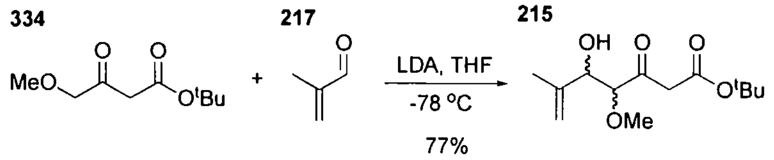
333



2.9.2.1 Stereochemical outcome of the initial approach

Returning to the retrosynthetic strategy of Scheme 59, the Mukaiyama aldol reaction of diene **302b** with methacrolein was performed and the product reacted with tosyl azide to produce diazoketone **331** in order that the diastereo- and enantio-selectivity of this reaction could be established. Racemic **215** was prepared by reaction of the bis(lithium enolate) of **334** with methacrolein and subsequent reaction of the aldol product with tosyl azide. For the purposes of comparison, the asymmetric Mukaiyama aldol reaction of diene **302b** was performed using a stoichiometric amount of oxazaborolidinone **315**.

Equation 42



An HPLC method was developed which separated all four stereoisomers and this allowed the determination of both the diastereo- and enantio-selectivity of the Mukaiyama aldol reaction shown in Scheme 59. The results were somewhat surprising (Table 6); despite all literature results for the use of oxazaborolidinone catalysts in Mukaiyama aldol reactions showing strong preferences for the *syn*-diastereoisomer, it was seen that the major diastereoisomer in this reaction was in fact the *anti*-diastereoisomer. This seems to show that the presence of a second TMS enol ether function in the molecule changes the preferered transition state although it is hard to suggest why this should be. It should be noted that although the diastereoselectivity is poor, the absolute stereochemistry of the major enantiomer of the minor *syn*-diastereomer is the same as that obtained *via* the revised route suggesting that some of the reaction does proceed through the expected transition state **333**. The lack of enantio- and diastereo-selectivity was somewhat surprising and suggests that a number of competing transition states possess similar energy, thus producing a mixture of all possible products. This perhaps explains why no reports of diastereoselective Mukaiyama aldol reactions on substrates of this type can be found in the literature.

Table 6: comparison of the three methods used in the synthesis of **(+)-331**

Entry	Method[a]	d.r. (*syn*:*anti*)	e.e. (*syn*)	e.e. (*anti*)
1	A	2:1	NA	NA
2	B	1:2	40	20
3	C	7:1	88	26

[a] Method A: use of bis(lithium) enolate
Method B: use of bis(trimethylsilyl) enol ether
Method C: Claisen ester reaction approach

Having ascertained the selectivity of the reaction, it could be clearly seen that it was of little use for the desired total synthesis and no further work was performed on this reaction.

2.9.3 Optimistion of the route in Scheme 65

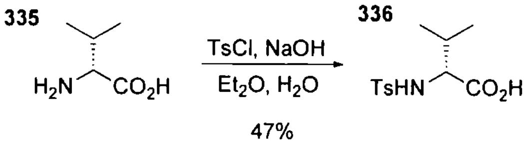
2.9.3.1 Mukaiyama aldol reaction

Although the Mukaiyama aldol reaction shown in Scheme 65 was clearly relatively efficient, it was decided at the start of the current project that further optimisation would be desirable. The diastereoselectivity showed room for improvement and although silica gel chromatography could increase the *syn*:*anti* ratio to 92:8, it was thought that by further increasing the d.e., complete separation might be possible. In addition, the level of asymmetric induction was somewhat lower than might be expected based on examples in the literature and the necessity to use a stoichiometric amount of the oxazaborolidinone was disappointing.

At the start of the optimisation study it was noticed that the yield of the Mukaiyama aldol reaction was somewhat variable and conversion was occasionally seen to drop to as low as 50% depending on the batch of *N*-tosyl-D-valine used. Elemental analysis suggested the presence of varying amounts of water and this appeared to explain the varying yields. Given that the method used for the preparation of *N*-tosyl-D-valine involved precipitation from water,[352] another method, this time involving using organic solvents, was sought. Another literature procedure was found and this was found to give improved yields using a combination of sodium hydroxide and Hünig's base,[357] however, yields of the Mukaiyama aldol reaction were found to be extremely low when this material was used to generate the oxazaborolidinone catalyst. Another procedure was found in a recent publication by Li and

Zhao[358] and despite a considerable decrease in yield of **326**, elemental analysis showed this product to be pure.

Equation 43



Use of this pure compound in the Mukaiyama aldol reaction gave improved results; the yield was found to increase to an impressive 89% over the two steps and the e.e. also increased to 91% although the diastereoselectivity remained unchanged. This sensitivity of the Mukaiyama aldol reaction to the source of the sulphonamide is intriguing and does not appear to be reported elsewhere.

Following this initial success, two further amino acids were investigated in order to see what effect changing the substituent had on the reaction. L-isoleucine and L-phenylalanine were chosen and both were *N*-tosylated using a literature method[358] before being reacted with borane to generate oxazaborolidinones **337** and **338** respectively. The results for the use of these species are shown in Table 7 and it can be seen that whilst **337** is less efficient in terms of yield (Entry 2), **338** gave an increase in yield and a large improvement in diastereoselectivity (Entry 3). The similar steric bulk of oxazaborolidinone **338** to systems **315** and **337** suggests that this large increase in diastereoselectivity may be due to another factor, for instance, π-stacking effects, as suggested for similar systems.[359]

Scheme 68: catalyst screening for Mukaiyama aldol reaction

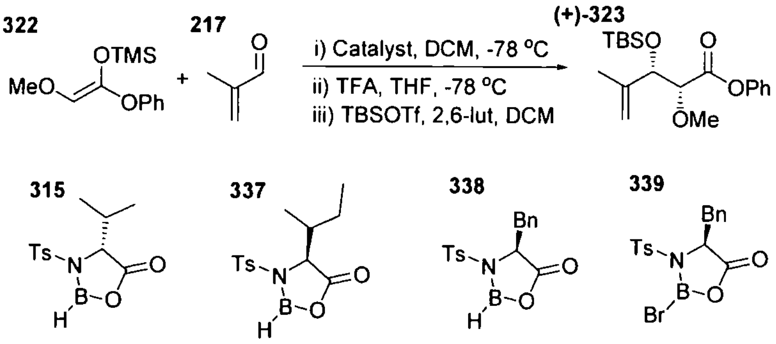


Table 7: catalyst screen for the reaction in Scheme 68

Entry	Catalyst	Loading/%	Yield **332**/%	d.r. (*syn*:*anti*)	e.e./%
1	**315**	100	89	4.0:1	91
2	**337**	100	52	4.5:1	93
3	**338**	100	95	8.3:1	91
4	**338**	24	51*	4.6:1	51
5	**339**	100	33 (+49% **340**)	8.3:1	99
6	**339**	20	18*	7.2:1	83

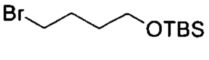
*Yield of free-alcohol without TBS protection.

With the success seen using oxazaborolidinone **338** it was attempted to perform a catalytic rather than stoichiometric reaction, however, the yield, diastereoselectivity and enantioselectivity dropped markedly (Entry 4), showing that the catalyst did not turn over.

This lack of catalyst turn over was thought to be due to a failure of the silicon transfer step in Scheme 60, thus leaving an inactive boronate species together with a silicon Lewis acid which could catalyse a racemic reaction. It was hoped to avoid this problem by increasing both the Lewis acidity of, and the steric bulk around, the boron atom of the catalyst. To this end, bromo-oxazaborolidinone **339** was generated by the reaction of monobromoborane with *N*-tosyl-L-phenylalanine.

Using a stoichiometric amount of this species, identical diastereoselectivity to that seen using **338** was observed together with improved e.e. (Entry 5), however, the yield was poor due to the formation of by-product **340**. Under catalytic conditions the yield was seen to drop even further although less of by-product **340** was observed (Entry 6).

340



By-product **340** is likely to come about through a Lewis acid-induced ring opening reaction of THF in which following coordination of THF to boron, nucleophilic attack of bromide anion opens the ring to form an alkoxy-boron species which is convered to the corresponding alcohol during aqueous work up. The effect of this side reaction is both to reduce the amount of catalyst available to catalyse the Mukaiyama aldol reaction, and to compete with TBSOTf in the final protection step, thus further reducing the amount of product produced. Although this problem could presumably be avoided by choosing a source of borane that did not contain THF, this was not investigated as it was thought that if the catalyst was able to induce this side-reaction, other side reactions were likely for other commercial borane complexes.

Optimisation efforts on the Mukaiyama aldol reaction were stopped at this point as it was becoming clear that achieving a catalytic reaction was going to be time-consuming. Given the relatively low cost of amino acids and tosyl chloride, the need to use stoichiometric amounts of species **338** was not seen to be a significant problem and the increase in diastereoselectivity achieved by this study did allow separation of the diastereoisomers such that large amounts of the *syn*-diastereoisomer could be produced.

2.9.3.2 Knoevenagel/ozonolysis sequence in Scheme 65

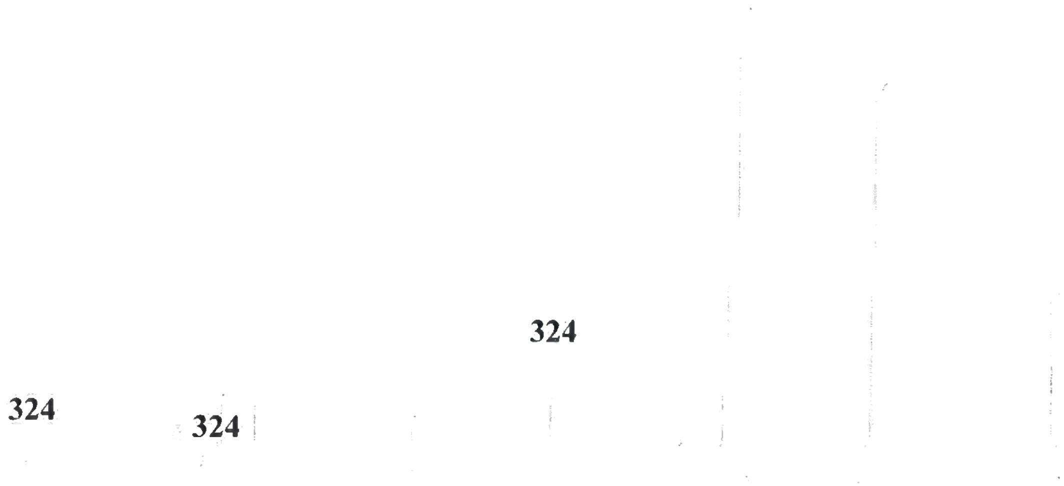
Although some considerable effort had been spent on optimising the combined ozonolysis/Knoevenagel step prior to the start of this project, it was decided to continue this study because the yield for the two steps remained poor. Previous work had involved performing a solvent screen as well as the use of a range of bases which gave the conclusions that methanol was by far the best solvent and that only inorganic bases such as potassium carbonate were effective at inducing the desired Knoevenagel condensation. In addition, replacing the intended ozonolysis reaction with a two step bis-hydroxylation/oxidative cleavage sequence had been investigated and found to be ineffective; only decomposition of starting material being observed.

Re-examination of the conversion of **(+)-321** to **(+)-324** (Scheme 65) in the present project began with the isolation of what was expected to be the secondary ozonide by performing the ozonolysis reaction in DCM and evaporating the resulting solution without performing a reductive quench. ^{1}H NMR spectroscopy showed the resulting species to be more complex than expected and it was clear that the expected secondary ozonide was not being formed as a single species. Although this type of behaviour might be expected in alcoholic solvents where protonation of the intermediate carbonyl oxide can induce side reactions through the formation of hydroperoxides,[360] the use of DCM was expected to give no such problems. GC-MS of the crude reaction mixture showed a number of peaks, one of which appeared to result from the loss of the *tert*-butyl group.

It was found that using the optimised conditions shown in Scheme 65, the main problem was a poor mass recovery following the aqueous work-up rather than loss of the material on the column as might have been suspected for a potentially sensitive substrate. ^1H NMR spectroscopy of the crude reaction mixture showed an extremely complicated region between 2.5 and 3.5 ppm, however, flushing the column with more polar solvents following elution of the desired product failed to provide any further material.

Given that the crude product from the reaction in DCM looked less complicated by ^1H NMR spectroscopy that that from methanol, this reaction was run and purified by silica gel chromatography. In this case the vast majority of the mass was lost on the column, however, a single fraction was collected which was seen to contain two species; cyclopentenone **(+)-324**, the Knoevenagel cyclisation having occurred during chromatography, and another, unknown compound with ^1H NMR signals for the CH groups at significantly lower frequency than those of the cyclopenteneone (Figure 19). In addition, an intriguing AB quartet integrating for two hydrogen atoms can be seen at 2.8 ppm. Following ^{13}C NMR spectroscopy, it was seen that the unidentified compound possessed no ketone function, only the carbonyl group of the ester remaining, and that a methylene group was still present. Unfortunately, the fact that this compound could not be separated from cyclopentenone **(+)-324** meant that the use of further analytical techniques was limited and the unknown compound was not identified at this stage.

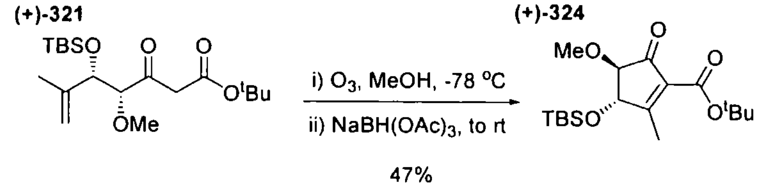
Figure 19: ^{1}H NMR spectrum of **324** and unidentified by-product



Following this result, further attempts were made to improve the yield of this reaction. Changing the catalyst to pyrrolidinium acetate following reaction in DCM had no effect on the formation of the unknown species and again, a mixture of two compounds was obtained following silica gel chromatography. Returning to methanol as solvent, it was found that increasing the temperature of the ozonolysis reaction from -78 °C to -42 °C gave a fractional increase in the mass recovered following silica gel chromatography, however, the resulting product was seen to contain ^{1}H NMR signals in the aromatic region.

It was eventually discovered that changing the reducing agent from DMS or triphenylphosphine to sodium triacetoxyborohydride gave an increase in yield (47%). Another advantage of this procedure was that no base had to be added to effect the Knoevenagel condensation, this occurred spontaneously on warming to room temperature.

Equation 44



Despite this increase in yield, the major problem remained a poor crude mass recovery from the aqueous work-up following the reaction. It was found that under the potassium carbonate Knoevenagel conditions, acidification of the aqueous phase prior to organic extraction greatly increased the mass recovery (70% *versus* 50%), however, a mixture of the expected product and an unidentified by-product possessing an exchangeable proton was isolated after chromatography.

Elimination of the potassium carbonate mediated Knoevenagel step whilst retaining methanol as solvent and solid-supported triphenylphosphine as reductive quench further improved the mass recovery and it proved possible to isolate 80% of the mass following chromatography, however, this same by-product remained.

Given the exchangeable proton seen at 6.3 ppm in the ^{1}H NMR spectrum of this by-product, it seemed likely that the loss of this species seen when extracting from aqueous base owed to the solubility of this species in the aqueous base. Unfortunately, attempts to remove this by-product by washing an organic solution of the mixture with a number of aqueous bases proved unsuccessful. Ultimately, it did not prove possible to determine the identity of this species or to prevent its formation by changing the reaction conditions and hence it did not prove possible to increase the yield beyond the moderate 47% above and further effort was directed towards achieving a conjugate addition to this substrate.

2.9.3.3 Conjugate addition reaction

Whilst looking through the literature for suitable methods for performing the desired reaction of **204** into **214** (Scheme 39), it was quickly realised that a considerable number of methods have been developed for achieving conjugate additions to 1,4-enones, most notably through the work of Lipshutz on organocuprates.[361] Although much work has been done on the asymmetric version of this reaction,[362] in particular, through the use of chiral phosphines as ligands, in this case it was intended to control the desired stereochemistry of the forming quaternary chiral centre by ensuring approach to cyclopentenone **324** from the front face as shown in Equation 44 through the bulky TBS protecting group on oxygen. Such direction of organometallic reagents by substituents of cyclopentenones has some precedent in the literature.[363] Given the importance of this reaction to the total synthesis of viridenomycin, a brief discussion of the available methods for achieving such reactions is merited.

Probably the most commonly used and well known method for achieving conjugate addition reactions is the use of organocuprates, Although considerable work was required in order to understand the structure and solution state behaviour of these often poorly defined systems, they are now used routinely. Whilst the formation of quaternary centres has received considerably less attention than the corresponding tertiary centres, presumably owing to the reduced reactivity of these systems because of increased steric hinderance, conditions for effecting such reactions have been known for some time.[364]

The behaviour of organocuprates in solution is complicated and their reactivity has often been tuned by the empirical use of various additives, particularly lithium halides and trimethylsilyl chloride. The effect of these additives is generally regarded as being to change the order of the cuprate into one more suited to the required reaction[365] although it has been argued that trimethylsilyl chloride can function to activate the ketone and indeed the product under such conditions is the silyl enol ether. Recent work has suggested the mechanism to be more complex than previously thought and it appears possible that the formation of higher order cuprates (more than three alkyl groups) may not in fact be responsible for the changes in reactivity seen when these additives are used.[366] Given the complex solution state behaviour of organocuprates, it is unsurprising that pronounced solvent effects are often seen; addition of relatively small amounts of more coordinating solvents can have dramatic effects on reactivity.[367]

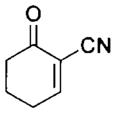
Significant substrate dependence is often seen for the conjugate addition of organocuprates and it is common to find that apparently similar enones react in different manners with the same cuprate.[368] Factors affecting the reactivity of enones include whether the enone is cyclic or acyclic, the number of substituents on the double bond and the ring size for cyclic substituents.[369] It is noteworthy that cyclopentenones are regarded as one of the most challenging classes of substrate in the conjugate addition of organocuprates.[370]

The use of non-transferable organic groups has been seen in the use of organocuprates and this allows the use of only one equivalent of a potentially expensive organic group to be used.[371] Non-transferable organic groups typically used are alkynes, which show poor reactivity as cuprates.

In a similar manner to that discussed above, Grignard reagents can be made to add to enones in a conjugate manner through the use of copper(I) salts as catalysts. This reaction relies on the uncatalysed 1,2-addition reaction being significantly slower than the conjugate addition of the cuprate formed in low concentration.[362] Again, use of chiral ligands has been used to produce high enantioselectivity and this area has received much work in recent years, most notably by Feringa.[372,373] As is the case for stoichiometric organocuprates, quaternary centres are considerably harder to form than tertiary centres, however, recent work has made some progress in addressing this issue.[374]

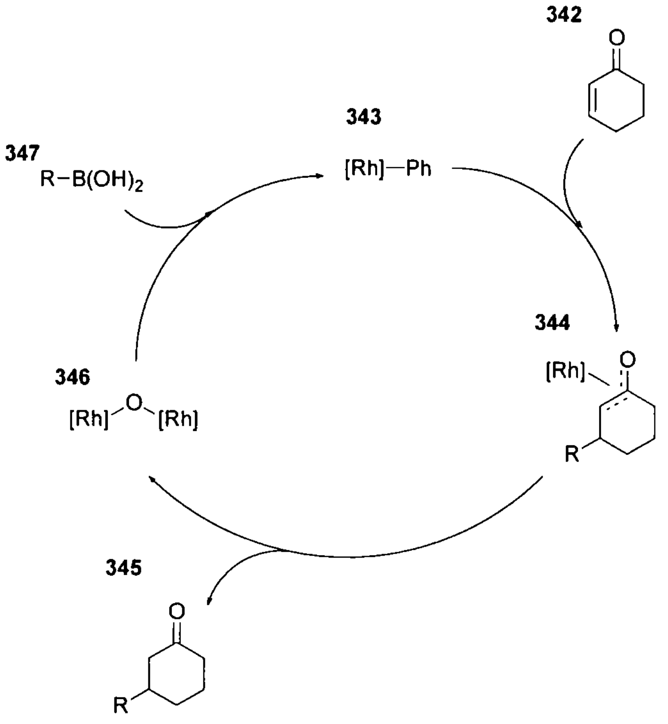
Other methods for the conjugate addition of Grignard reagents involves the use of stoichiometric cerium(III) salts to form a "softer" nucleophile[375] and it has even been found that for certain substrates, Grignard reagents undergo preferential conjugate addition in the absence of catalysts.[376] Of particular interest to the present synthesis, doubly activated cyclohexenone **341** was found to undergo this reaction in good yield with a number of different Grignard reagents.[377]

341



The addition of organoboronates and organotrifluoroborates to enones has also become an efficient method for effecting this reaction since first being reported by Miyaura[378] and subsequent work by Hayashi.[379] This reaction employs rhodium salts as a catalyst and more recent work using chiral ligands for this metal has allowed the formation of chiral centres at the *β*-position of enones with impressive enantioselectivity.[379] The mechanism is thought to proceed through initial transmetallation of the organoboron species by rhodium, subsequent coordination of the enone permits the conjugate addition to take place to yield the product coordinated to rhodium in an η^3-fashion. Hydrolysis of this species provides the free product and oxygen bridged rhodium dimer **346** which reacts with the organoboron species to restart the cycle (Scheme 69).[380]

Scheme 69: mechanistic scheme for rhodium-catalysed conjugate addition



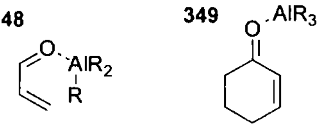
The mechanism of this reaction limits substrate choice as nucleophiles possessing *β*-hydrogens undergo *β*-hydride elimination faster than conjugate addition upon transmetallation to rhodium. For this reason, the reaction has mainly been used to add arylboronates although there has been success using both vinyl- and alkynyl-boronates.[381] Another problem is the need to use an excess of the nucleophile since proto-deboronation is frequently a competing reaction.

The major limitation of this reaction is the effect of the steric bulk of the enone on the reaction. Although one *β*-substituent is well tolerated and cyclic systems are good substrates, the addition of a second *β*-substituent hinders the reaction to such an extent that no such examples have been reported.

Another method for the conjugate addition of organic groups to enones is the use of alanes. Given that alanes possess three transferable organic groups, it is necessary to either make all three groups the desired one, or to use two non-tranferable groups; in this case alkynyl or vinyl groups are transferred in preference to alkyl groups[382] and this permits the facile generation of suitable alanes from dimethylaluminium chloride. This method for conjugate addition is generally limited to acyclic enones and it has been suggested that this owes to the requirement for the enone to adopt an s-*trans* conformation in order to accept the incoming nucleophile whilst the oxygen is activated by coordination to aluminium (Figure 20).[383]

Figure 20

348 **349**



Reactive conformation

Unreactive cyclic substrate

This lack of reactivity of cyclic enones has been overcome by the introduction of transition metal catalysts, particularly nickel salts.[384] The yields of these reactions have often been found to be high, however, they cannot be regarded as particularly efficient because the catalyst loadings used are high.[385] In addition, the nature of the catalytic species is something of a mystery; treatment of nickel(II) acetylacetonate with one equivalent of DIBAL-H being required to generate the active species. These issues have not prevented the application of this methodology to a range of substrates.[385]

Another type of organometallic which can undergo conjugate addition to activated double bonds are organozinc reagents. Because these reagents are softer than the corresponding Grignard reagents, competing 1,2-addition is much less of a problem. Although these additions can be performed in the absence of a catalyst,[386] the use of copper salts has allowed the formation of quaternary centres in high yield.[387]

Certain soft nucleophiles, in particular enolates of *β*-keto esters, can add to enones in a conjugate manner. This reaction has been known for considerably longer than the addition of organometallic nucleophiles and is generally limited to substrates possessing two electron-withdrawing groups which allow the facile deprotonation of an adjacent carbon-hydrogen bond.[388] Although quaternary centres can be formed using this reaction, the steric hinderance disfavours this process and forcing conditions are often required.[389] Asymmetric variants of this reaction have been achieved through the use of chiral catalysts, particularly amine bases.[388]

Silyl enol ethers and silyl ketene acetals can undergo conjugate addition to enones in the presence of Lewis acids.[390] This reaction is essentially a development of the aforementioned Mukaiyama aldol reaction and indeed is often refered to as the Mukaiyama-Michael reaction. The catalysts employed in this reaction are generally similar to those used in the Mukaiyama aldol reaction and the use of chiral oxazaborolidinone catalysts in particular has allowed the generation of chiral centres with high enantiocontrol.[391] It should be noted that most work has been directed towards the formation of tertiary centres and the formation of quarternary centres is not well reported.

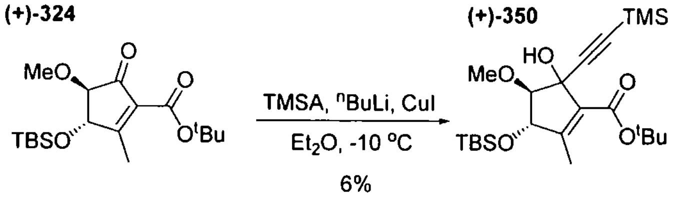
Other miscellaneous methods to achieve conjugate additions to enones have been reported, for instance, a palladium-catalysed addition of acetylene nucleophiles has recently been reported[392] and the TBAF-promoted addition of allylsilanes to enones offers a mild method for the addition of allyl groups.[393]

For the synthesis of viridenomycin, the addition of an alkynyl group to cyclopentenone **(+)-324** was required. The nature of this nucleophile ruled out a number of the methods discussed above, in particular, the Michael reaction of a doubly activated organic nucleophile and the Mukaiyama-Michael reaction. Hence, it appeared that the addition of an organometallic reagent would be required, most likely a cuprate or an alane.

Based on the above discussion, cyclopentenone **(+)-324** might appear to be a poor substrate due to the forming quaternary centre and the cyclic nature of the substrate. In addition, additions to five-membered ring substrates are considered much more challenging than their six-membered homologues. In its favour, cyclopentenone **(+)-324** could be expected to be more active than other substrates due to the conjugation of two electron-withdrawing groups to the reacting double bond.

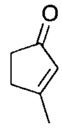
Initial attempts at a diastereoselective conjugate addition reaction to (+)-**324** were not promising. Prior to the start of this project the addition of the lithium cuprate of trimethylsilylacetylene using a literature procedure involving the use of trimethylsilyl iodide as an activating agent[394] failed to give any conversion of the starting material. At the start of this project a number of other approaches also met with failure, these included the uncatalysed addition of alkynyl alanes, the addition of a number of alkynylcuprates[395] and the palladium-catalysed addition of trimethylsilyl acetylene.[392] Due to the documented lack of reactivity of alkynylcuprates,[371] the use of a vinylcuprate was investigated but again no reaction was observed. The only product isolated in this study was the formation of small amounts of 1,2-addition of an alkynyl group under one set of reaction conditions (Equation 45). This result is consistent with another study which suggested that alkynyl nucleophiles tend to undergo 1,2-additions to such systems.[396]

Equation 45



Due to the poor yield of the ozonolysis/Knoevenagel condensation sequence limiting the availability of cyclopentenone (+)-**324**, it was necessary to optimise conditions for the conjugate addition reaction to this substrate on a model compound. Cyclopentenone **351** was chosen for this purpose as it possessed the two problems associated with system (+)-**324**; namely the forming quaternary centre and five-membered ring, without the expected activation of possessing two electron-withdrawing groups. Thus, it was expected that any conditions which could effect conjugate additions to cyclopentenone **351** should be more successful on the actual system (+)-**324**.

351



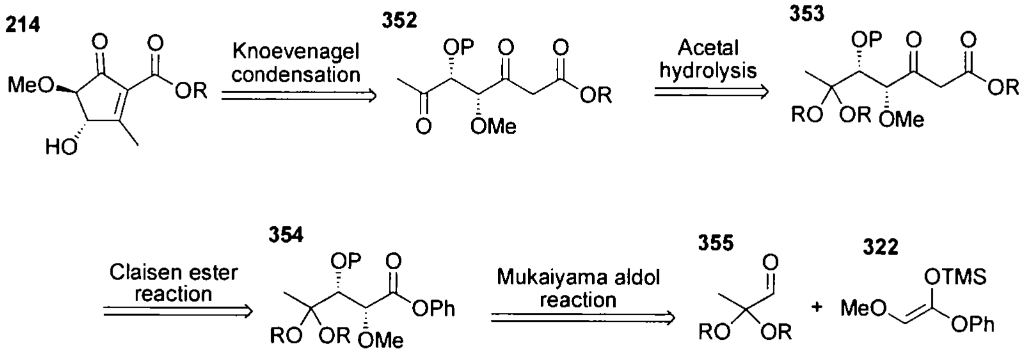
Perhaps unsurprisingly, model compound **351** proved equally unreactive under the aforementioned conditions, and after a small screen it was decided to find a more efficient route to *tert*-butyl ester **(+)-324** in order that optimisation studies could be performed on this substrate.

2.10 Alternative approaches to the cyclopentenone system

2.10.1 Acetal protection route

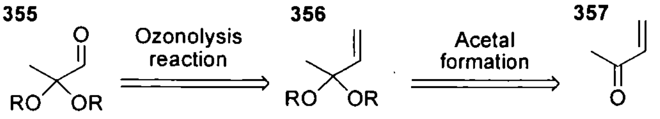
Given that the major issue with the synthetic route outlined in Scheme 63 appeared involve side-reactions occurring during the ozonolysis reaction, a simple modification appeared to involve the masking of the desired methyl ketone in a different fashion. Thus, the revised retrosynthetic strategy in Scheme 70 was devised, in which the ketone is protected as an acetal rather than masked as an alkene. This modification removed the need for the ozonolysis reaction, replacing it instead with an acetal hydrolysis reaction under which conditions the subsequent Knoevenagel reaction might be expected to occur. One issue which was immediately noted about this route was that a chemo-selectivity issue might arise in the initial Mukiayama aldol reaction as the reactivity of acetals under such conditions is documented.[397,398]

Scheme 70: revised retrosynthetic approach to cyclopentenone **214**



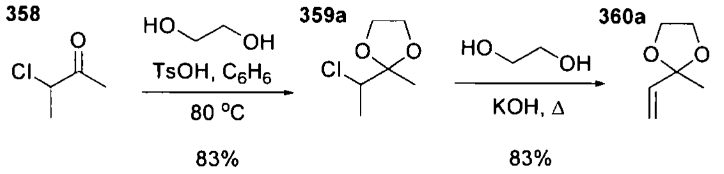
Another issue surrounding the use of an acetal of type **355** was generating such a species in the first place. It was decided that the use of a cyclic acetal was required owing to their greater hydrolytic stability, and although routes to similar species have been reported, they were generally seen to be complex and low yielding,[399] potentially due to the volatility of the product. For this project it was decided to devise a new route to these species, involving unmasking the desired aldehyde by ozonolysis of the corresponding alkene (Scheme 71).

Scheme 71: retrosynthetic approach to aldehyde **355**



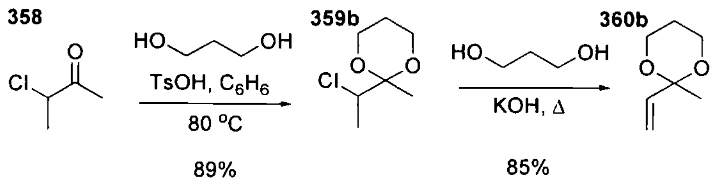
Hence, following preparation of vinyl acetal **360a** through a literature method,[400] ozonolysis of this substrate was performed. Following quenching with DMS, evaporation led to substantial loss of material, owing to the expected volatility of the product. In addition to this problem, it was seen by ^{1}H NMR spectroscopy that the product was not clean and showed a substantial peak at 8 ppm in addition to the expected peak for DMSO.

Scheme 72: route to five-membered ring vinyl acetal **360a**



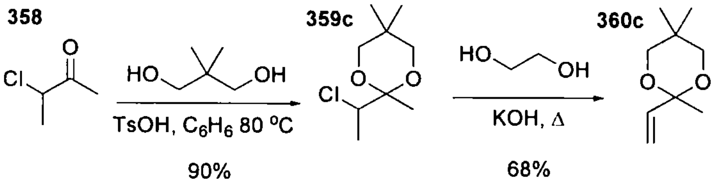
In an effort to reduce the volatility of the acetal, it was decided to increase the ring size from five to six. Acetal **360b** was prepared using an analogous method to that used for five-membered ring analogue **360a** and again the ozonolysis was performed using DMS as a quench. Although this product was somewhat less volatile and therefore the mass recovery was improved, ^{1}H NMR spectroscopy again showed the same peak of unknown origin and the product remained impossible to separate from the DCM solvent. In addition, it was discovered that vinyl acetal **360b** showed a great instability to hydrolysis; samples left in chloroform overnight were found to be completely hydrolysed. This behaviour was in marked contrast to that of five-membered analogue **360a** which had been seen to be indefinitely stable under the same conditions.

Scheme 73: route to six-membered ring vinyl acetal **360b**



In order to further reduce the volatility of the ozonolysis product and hopefully increase the hydrolytic stability of the alkene precursor, dimethyl-substituted analogue **359c** was investigated. This was found to reduce the volatility of vinyl-acetal **360c** to such an extent that the product could no longer be distilled from the reaction mixture and an aqueous work-up was required, this presumably being responsible for the marked decrease in yield. In addition, the hydrolytic stability of vinyl acetal **360b** was seen to be greatly improved and this curious difference in hydrolytic stability between apparently similar acetals was felt to merit further investigation (*vide infra*).

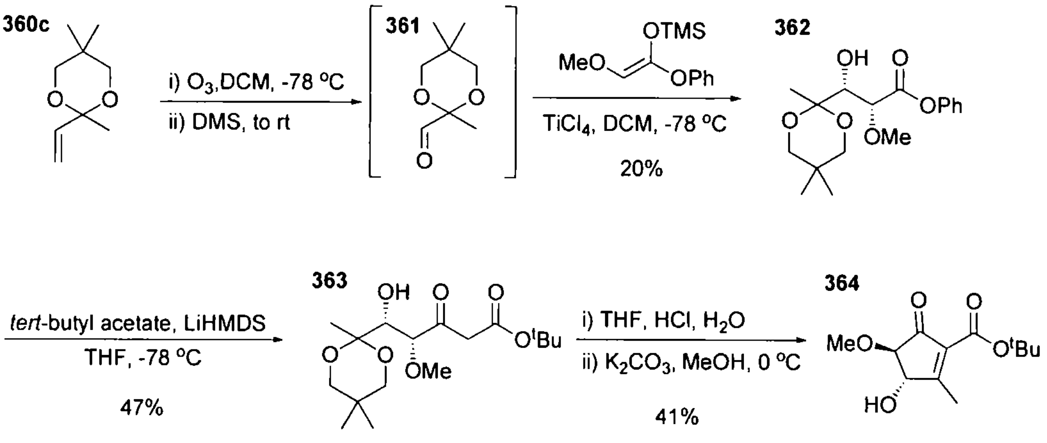
Scheme 74: route to six-membered ring vinyl acetal **360c**



The ozonolysis reaction gave mixed results; although the reduced volatility of the product meant that no material was lost during evaporation, the ^{1}H NMR spectrum of the product again showed a strong unassignable peak at 8 ppm. Distillation and chromatography both failed to produce the desired aldehyde in pure form and it was decided to generate the aldehyde *in situ*.

Hence, following ozonolysis of a DCM solution of **360c** and quenching with DMS, the mixture was re-cooled to -78 °C and treated with silyl ketene acetal **322** in the presence of titanium(IV) chloride. No attempt was made to induce asymmetry because owing to the novelty of the reaction, it was felt that it would be best to observe the reaction under standard conditions prior to investigating the use of asymmetric catalysts should the racemic reaction prove successful. The ^{1}H NMR spectrum of the crude reaction mixture was seen to be extremely complex and did not offer much hope of isolating a clean product. Surprisingly, following careful chromatographic purification it was found that the expected product could be isolated as a pure compound, albeit in poor yield. Somewhat surprisingly, the diastereoselectivity of this reaction was seen to be impressive with a *syn:anti* ratio of 8:1 being found following chromatographic purification. Whilst is would be preferable to report this ratio prior to purification in order to avoid partial separation of the diastereoisomers, this was precluded by the complexity of the crude reaction mixture. Analysis of the ^{1}H NMR spectra of the other fractions recovered following chromatography did not appear to show signals corresponding to the *anti* diastereoisomer and thus it would appear that the ratio seen following chromatography is a good reflection of the diastereoselectivity of the reaction. This level of diastereoselectivity is impressive, particularly when compared to the ratio of 2:1 obtained when titanium(IV) chloride was used for the reaction shown in Scheme 65. Presumably, this dramatic increase in selectivity owes to the considerable increase in steric bulk of the aldehyde (methacrolein *versus* aldehyde **360c**) which would be expected to favour the *syn* diastereoisomer by increasing the unfavourable interactions in the transition state required to produce the *anti* diastereomer. Again, the geometry of the silyl enol ether would not be expected to influence the geometry of the product as open, extended transition states similar to those shown in Scheme 61 have been proposed for titanium(IV) chloride catalysis of the Mukaiyama aldol reaction.

Scheme 75: route to cyclopentenone **364**



The chemo-selectivity of the reaction was poor as had been expected, however, it was not possible to identify the majority of the other products. One by-product which was readily identified was phenol, this presumably coming about through the reaction of aldol product **362** with a further molecule of silyl ketene acetal **322**. This result suggests that aldehyde **361c** is a relatively poor electrophile in this reaction, possibly owing to its great steric bulk, and that the yield of aldol product **362** might be expected to be increased if the side reactions could be controlled.

Turning attention to the subsequent Claisen ester reaction, three equivalents of base were employed as had been used for free alcohol (+)-**329** (Scheme 67) and this was found to give the expected *β*-keto ester **363** in reasonable yield. The hydrolysis of the acetal function of

363 was initially investigated in an NMR tube which showed that the reaction took fourteen days and that the Knoevenagel reaction did not in fact occur under the same conditions. Thus, having stirred the acetal on a larger scale in a mixture of THF and 20% HCl for fourteen days, the reaction was worked-up and the crude ketone subjected to a basic condensation reaction.

This produced cyclopentenone **364** in moderate yield and good diastereoselectivity (Scheme 75). It is interesting to note that none of cyclopentadienone **314** was seen to form under these conditions whilst apparently identical conditions gave this as the only identifiable product when the route in Scheme 62 was employed. This appears to suggest that the presence of the remaining diol, which was not removed following the hydrolysis reaction, somehow prevents the over-elimination reaction to derive **314**.

Given the disappointing yields of all three steps in Scheme 75, it was decided that optimising the reaction would be time consuming, not least because of the difficulty in altering the observed chemo-selectivity of the Mukaiyama aldol reaction. In addition, no asymmetric Mukaiyama aldol reactions have been reported for aldehydes such as **360** and given the large number of potential catalysts previously discussed, it was decided to proceed with a more conventional approach.

2.10.1.1 Acetal hydrolysis studies

As mentioned earlier, the marked difference in rates of hydrolysis between the various acetals caused some intrigue and it was intended to perform a kinetic study in order to quantify these observations. Initial studies involved the addition of D_2O to solutions of the acetals in $CDCl_3$, however, this gave complicated kinetic behaviour, presumably due to the heterogeneous nature of the system.

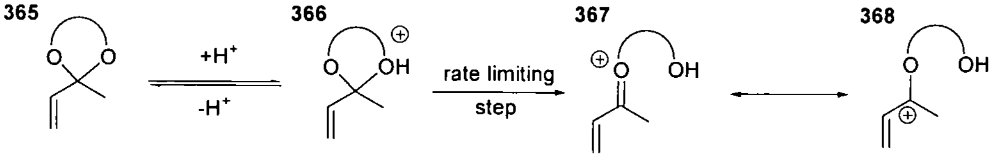
Running the reactions in D_8-THF using a large excess of D_2O (with catalytic amounts of DCl) to ensure pseudo-first order behaviour simplified the reactions considerably and allowed the pseudo-first order rate constants to be determined from plots of ln[product] *versus* time (see Appendix 1). The results are shown in Table 8.

Table 8: rate constants of the acetal hydrolysis study

Entry	Acetal	Acid (loading/mol%)	k_I/s^{-1}
1	**359a**	DCl (50)	0
2	**360a**	DCl (50)	$8.8\pm0.3\times10^{-4}$
3	**360a**	DCl (5)	$6.4\pm0.1\times10^{-5}$
4	**360a**	HCl (50)	$4.7\pm0.1\times10^{-4}$
5	**359b**	DCl (50)	$2.25\pm0.03\times10^{-6}$
6	**360b**	DCl (50)	$9.9\pm0.6\times10^{-3}$
7	**360b**	DCl (5)	$6.2\pm0.1\times10^{-4}$
8	**359c**	DCl (50)	0
9	**360c**	DCl (50)	$7.33\pm0.08\times10^{-4}$

It can immediately be seen that substitution of the chloroalkyl group for a vinyl group greatly increases the rate of hydrolysis; in the case of the five-membered ring system, the system goes from being indefinitely stable to hydrolysis to one that is slowly hydrolysed (Entries 1 and 2), whilst for the six-membered ring system, the slowly hydrolysed chloroalkyl system is rapidly hydrolysed following elimination (Entries 5 and 6). Similar behaviour is also seen for the disubstituted system (Entries 8 and 9). Such behaviour is well documented and provided strong support for the mechanism of hydrolysis occurring via the A1 mechanism[401,402] shown in Scheme 76, the vinyl group serving to stabilise the positive charge in canonical form **368** and thus accelerating the hydrolysis.[403]

Scheme 76: A1 mechanism for acetal hydrolysis



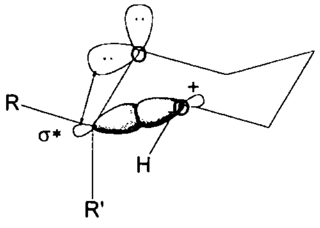
A kinetic isotope experiment was performed in order to gain further support for this mechanism and it can be seen from Entries 2 and 4 that use of H_2O rather than D_2O (together with HCl rather than DCl) leads to a substantially slower hydrolysis. The value of k_H/k_D obtained (0.53) is a good match for those previously reported for hydrolysis by the A1 mechanism.[404,405] This kinetic isotope effect is clearly too small in magnitude to be a primary kinetic isotope effect and is unlikely to be a secondary kinetic isotope effect because of the lack of change in hybridisation at the oxygen centre in the rate determining step. Hence it would appear likely that this is a solvent isotope effect which comes about because of the poorer solvation of deuterium-protonated species as compared to hydrogen-protonated species. This effect is consitent with the specific acid catalysis that would be expected from the proposed rate limiting step.

Whilst all these results mirrored those of previous studies,[406] it can also be seen that the size of the ring as well as the presence of substituents, has a marked effect on the rate of hydrolysis. On moving from the five-membered chloroalkyl acetal **359a** to its six-membered homologue, it can be seen that a stable system becomes a system which is hydrolysed, albeit very slowly (Entries 1 and 5). More dramatically, the same pattern can be seen for the vinyl-substituted system **360** (Entries 2 and 6 and 3 and 7) with a factor of ten being seen between the two rate constants at both acid loadings.

It can also be seen that upon the addition of the two methyl substituents to the six-membered ring, the hydrolytic stability is increased considerably, both for the chloroalkyl systems (Entries 5 and 8) and for the vinyl systems (Entries 6 and 9).

These results confirmed the previous qualitative observations regarding the stability of these systems to hydrolysis by giving some quantitative data. Although the results do not provide the reason for these marked differences in stability, it appears likely that the differences arise because of the relative orientations of the oxygen lone pairs in the protonated forms of the acetals. In order for rapid hydrolysis to occur in the A1 mechanism, it is necessary for the equitorial lone pair of the non-protonated oxygen to overlap with the σ^* orbital of the adjacent carbon-oxygen bond (Figure 21), indeed, in rigid bicyclic systems, no hydrolysis occurs when the conformation is such that this overlap cannot occur.[407]

Figure 21: orbital interactions in protonated cyclic acetal



In the present case, it seems plausible that there is relatively poor overlap between these two orbitals when a five-membered ring is present making these species stable to hydrolysis. On increasing the ring size to a six-membered ring, substantial overlap becomes possible and hydrolytic stability is reduced. Hence, it appears that the effect of the two methyl substituents is to flatten the ring from the preferred chair conformation such that the overlap between the two orbitals is reduced, so increasing hydrolytic stability.

Another possible explanation for the observed differences in stability comes from an entropic argument. It would be expected that on moving from a five-membered ring system to a six-membered ring system, hydrolysis would become more entropically favourable because of the greater amount of freedom of the longer alkyl chain. In the case of the dimethyl-substituted system, the gem-dialyl effect reduces the available conformations for the ring opened hydrolysis product and thus it might be expected that this hydrolysis would be less entropically favoured than the unsubstituted analogue.

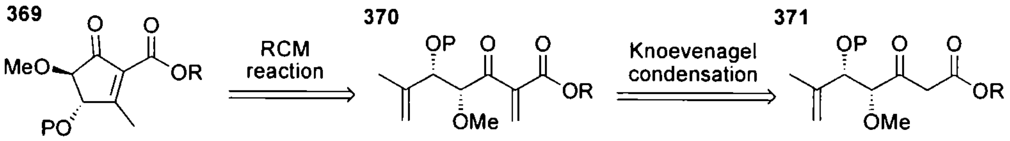
Whatever the reason for the differences in hydrolytic stability, these results are interesting in that nothing similar has previously been reported and underline the importance of choosing a diol with the correct balance of hydrolytic stability and ease of removal when protecting ketones.

2.10.2 Ring closing metathesis approach

Since the development of olefin metathesis by Schrock and Grubbs,[408,409] huge progress has been made in applying this methodology to synthetic organic chemistry. Of particular interest to total synthesis are cross-metathesis reactions where two electronically different olefins are selectively coupled with the loss of a two-carbon unit (ethene).[410] In a similar fashion, when a molecule contains two electronically different olefin functions, it is possible to effect the same reaction to produce a cyclic product with one double bond within the ring, the ring-closing metathesis (RCM) reaction.[411] Although the majority of the double bonds produced by metathesis reactions possess *trans*-geometry, in RCM reactions the geometry of the olefin is controlled to some extent by the forming ring and thus for small rings, only *cis* double bonds can be formed.

Applying this reaction to the retrosynthesis of fragment **369**, it was envisioned that rather than using an intramolecular Knoevenagel condensation to close the ring, a RCM reaction of a diene of type **370** should provide the same product (Scheme 77). Further disconnection of diene **370** could be performed by means of an intermolecular Knoevenagel condensation with formaldehyde to return to a *β*-keto ester of type **371** which had already been produced in good yield as discussed previously. This approach required no further steps over the route outlined in Scheme 59 and had the added advantages that it removed the troublesome ozonolysis step whilst retaining the successful Knoevenagel condensation, albeit in intermolecular form in the revised retrosynthesis.

Scheme 77: RCM-based retrosynthetic approach to cyclopentenone **369**



Initial reaction of *β*-keto ester **(+)-321** with paraformaldehyde was initially found to give no product, only starting material being recovered. This result came as a surprise given the reactivity of *β*-keto ester **(+)-321** in the previous intramolecular Knoevenagel reaction and after trying several other conditions, it was thought that this problem might be due to a lack of reactivity of paraformaldehyde. To overcome this problem, two other sources of formaldehyde were investigated; aqueous formaldehyde and trioxane (formaldehyde trimer). Under a range of conditions, these reagents also failed to produce the desired product (Table 9).

Table 9: conditions employed in the attempted Knoevenagel reaction of **321**

Entry	CH_2O source	Base	Solvent	Temperature/ °C	Outcome[1]
1	Paraformaldehyde	NaOAc	MeOH	0	A
2	Paraformaldehyde	NaOAc	MeOH	60	B
3	Paraformaldehyde	Py/HOAc	DCM	0	A
4	37% aq. CH_2O[412]	NaOAc	MeOH	0	A
5	37% aq. CH_2O	NaOAc	DMSO	80	B
6	Trioxane	Et_3N	MeCN	20	A
7	Trioxane	Et_3N	MeCN	50	A
8	Trioxane	Et_3N	DMSO	80	A
9[2]	Trioxane	Et_3N	DMSO	80	A
10	Eschenmoser's salt[413]	Et_3N	DCM	20	A
11	Eschenmoser's salt	NaH	THF	60	B
12	Bromochloromethane	Et_3N	MeCN	20	A

[1] A: starting material recovered
B: starting material decomposed
[2] $Sc(OTf)_3$ employed as Lewis acid

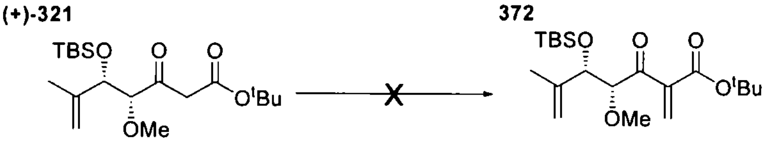
It can be seen that under the majority of reaction conditions, the starting *β*-keto ester was recovered unchanged and that under the more forcing conditions investigated to attempt to induce some reaction, only decomposition of this starting material was observed. What is not clear from this result is whether the observed decomposition occurred on the starting material or whether initial diene formation occurred and this potentially unstable substrate subsequently decomposed.

Eschenmoser's salt was investigated as another potentially more reactive source of formaldehyde, however, under literature conditions[413] (Entry 10) no reaction was seen and even generating the sodium enolate of **(+)-321** and reacting this with Eschenmoser's salt at elevated temperature (Entry 11) failed to provide the desired product.

An attempt to perform the desired Knoevenagel reaction in a stepwise manner using bromochloromethane as the electrophile again returned only starting material (Entry 12).

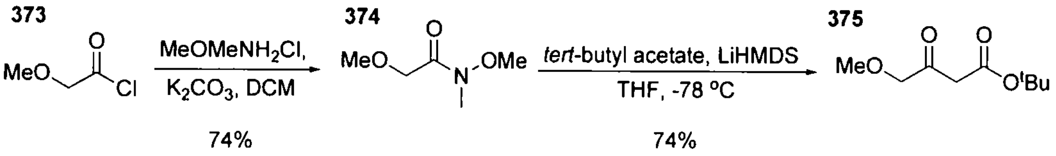
In an effort to determine whether the lack of reactivity seen was due to β-keto ester (+)-**321** or to some issue regarding the use of formaldehyde as an electrophile, the reaction between (+)-**321** and benzaldehyde was investigated. Again, under a number of conditions no reaction was observed and this behaviour appeared to show that whilst the methylene group of (+)-**321** is activated enough to undergo intramolecular reactions, steric bulk disfavours intermolecular reactions.

Equation 46



In order to test this hypothesis as well as further screen conditions for performing Knoevenagel reactions on this type of substrate, model compound **375** was synthesised from the acid chloride via the corresponding Weinreb amide[414] (Scheme 78). It was also noted that should this Knoevenagel reaction prove successful, conversion of this product to the corresponding silyl enol ether and subsequent Mukaiyama aldol reaction with methacrolein would generate the desired substrate.

Scheme 78: synthesis of model compound **375**

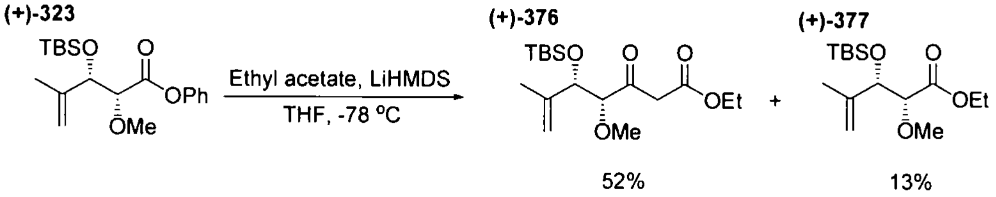


Under the conditions used in Table 9, it was again found that this substrate would not participate in the desired Knoevenagel reaction and this appeared to suggest that the steric bulk of (+)-**321** was not the issue. Again, although starting material was recovered under mild conditions, more forcing conditions led to decomposition.

It was demonstrated that the β-protons of β-keto ester **375** were easily deprotonated by running an NMR experiment; under basic conditions in D_8-THF, the two protons of the methylene carbon were found to exchange with D_2O faster than the sample could be run. Given the acidic nature of these protons, it was far from clear why such a substrate would be unreactive in a Knoevenagel condensation and it was speculated that the *tert*-butyl function might disfavour the reaction by means of steric bulk, In order to test this hypothesis, it was decided to synthesise the ethyl analogue of **(+)-321** by replacing *tert*-butyl acetate with ethyl acetate in the Claisen ester reaction.

This approach met with a somewhat surprising result; although the product was clearly formed, it was apparent from the ^{1}H NMR spectrum that another species was present and this was found to be inseparable by silica gel chromatography. Given the similar chemical shifts of the two species which both possessed ethyl groups, it was at first thought that some degree of epimerisation had occurred during the reaction and that the second component was the *anti* diastereoisomer. On closer inspection however, the second component did not appear possess a methylene group and mass spectrometry revealed that this second species was in fact ethyl ester **(+)-377**.

Equation 47



The formation of this species appears to be due to elimination of ethoxide from the lithium enolate of ethyl acetate prior to this species reacting with phenyl ester **(+)-323**. The fate of the ketene which must be formed in this process remains a mystery; no sign of a product deriving from this presumably reactive species was ever isolated.

The fact that elimination of ethoxide was a relatively minor side reaction suggested that under suitably optimised conditions this process could be prevented. With this in mind, a screen of reaction temperatures was undertaken and it was found that running the reaction for longer at lower temperatures before warming to room temperature resulted in an increased level of by-product **(+)-377** (1:1). Hence, the reaction was performed at a higher temperature by adding a cold solution of the lithium enolate to a room temperature solution of phenyl ester **(+)-323**. Disappointingly, this was found to result in an identical level of by-product formation to that found initially which suggested that temperature variation was unlikely to solve this problem.

In order to overcome this problem, a change of nucleophile was sought and given the nature of this species, organozinc chemistry appeared ideal. Unfortunately, use of ethyl bromoacetate in the Reformatsky reaction with phenyl ester **(+)-323** proved unsuccessful with only starting material being recovered. The reason for this lack of reactivity is unclear, indeed, such reactions are well documented in the literature.[415]

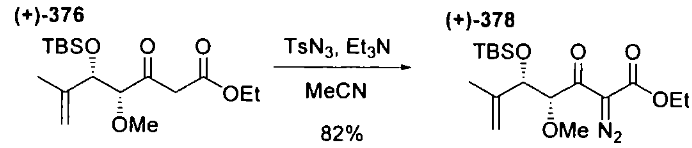
The use of *iso*-propyl acetate and phenyl acetate in the Claisen ester reaction was also investigated. *Iso*-propyl acetate was found to give similar results to that seen for ethyl acetate whilst phenyl acetate was found to give no conversion of the starting material, presumably due to rapid elimination of lithium phenoxide. Although this behaviour had been expected for phenyl acetate, it had been hoped that some degree of nucleophilic displacement of phenol would occur so that the use of an excess of phenyl acetate would allow quantitative formation of the *β*-keto phenyl ester whereon treatment with another alkoxide would yield the ester of choice.

Although it would presumably have been possible to access the desired ethyl ester by a saponification and subsequent re-esterification of *tert*-butyl ester **(+)-321**, this approach was thought to be rather inefficient and was not investigated.

Despite not having access to ethyl ester **(+)-376** in a pure form, a number of reactions were attempted on the available mixture in order to determine whether the *tert*-butyl ester function of **(+)-321** was responsible for its lack of reactivity.

Initial reaction of this mixture with tosyl azide proved highly successful, producing diazoketone **(+)-378** in impressive yield, this being effectively quantitative given the level of impurity present in the starting material.

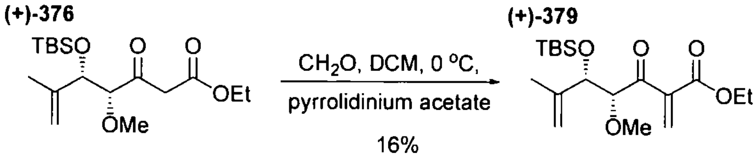
Equation 48



Following this success, it was attempted to perform the desired Knoevenagel reaction with formaldehyde, however, again no product was isolated. In order to overcome this lack of reactivity, it was decided to generate anhydrous, monomeric formaldehyde in solution. This was achieved through the vacuum pyrolysis of paraformaldehyde and collecting the product in a liquid nitrogen trap. Subsequent evaporation of DCM into the trap gave an anhydrous solution which was used immediately as rapid polymerisation was observed following warming to room temperature.

Use of this reagent with ethyl ester **(+)-376** was found to give the desired diene, albeit in low yield, when pyrrolidinium acetate was used as catalyst. This low yield appeared to be due to the instability of diene **(+)-379** to silica gel chromatography as the conversion was seen to be high and indeed, the instability of related species had already been reported.[416]

Equation 49



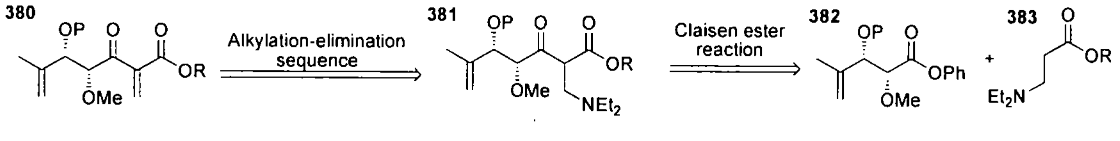
On applying these conditions to *tert*-butyl esters **(+)-321** and **375**, it was found that no conversion occurred and all starting material was recovered in both cases. This behaviour appears to show that the presence of the *tert*-butyl ester function of **(+)-321** is detrimental to its reactivity in Knoevenagel reactions.

In order to see if this effect extended to the ozonolysis/Knoevenagel reaction sequence, this sequence was performed on the mixture of ethyl esters **(+)-376** and **(+)-377**. Although this substrate gave a considerable improvement in mass recovery following silica gel chromatography, it was immediately apparent that a number of inseparable species were formed in the reaction, most likely due to the presence of impurity **(+)-377**. Although the major species did appear to be the desired cyclopentenone, the complex nature of the mixture combined with an inability to purify the starting material meant that this approach was abandoned.

2.10.2.1 Alternative approach

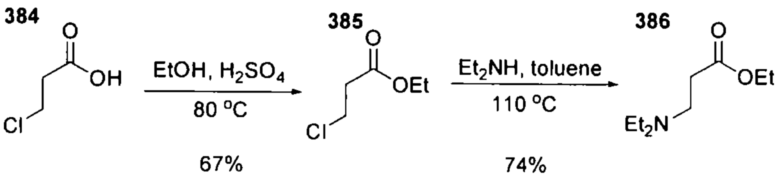
This inability to access the desired ethyl ester (+)-**376** in pure form, combined with the problems encountered in performing the subsequent Knoevenagel reaction, led to an adjustment of the retrosynthetic strategy. Scheme 79 shows this new approach in which following an initial Claisen ester reaction between *β*-amino ester **383** and phenyl ester **382**, alkylation of the nitrogen to generate the quaternary ammonium salt allows an elimination to occur to generate the required double bond. Although this approach might appear to possess one of the same problems as seen previously, namely the potential for the elimination of ethoxide, it was felt that any ethyl ester (+)-**377** formed should in this case be easily separated from the desired product. Another potential problem was seen to be competing *β*-elimination of lithium diethylamide from the lithium enolate species formed.

Scheme 79: revised retrosynthetic approach to diene **380**



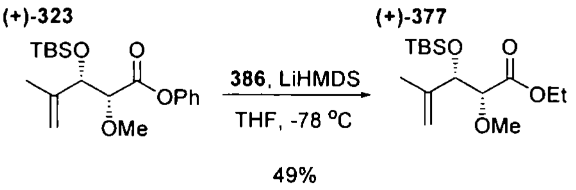
Amine **386** was synthesised in a simple and relatively efficient manner from 3-chloropropionic acid as shown in Scheme 80 in which following esterification, nucleophilic displacement using an excess of diethylamine provided the desired product.[417]

Scheme 80: synthesis of *β*-amino ester **386**



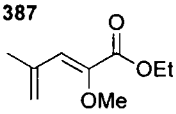
Application of amine **386** to the Claisen ester reaction proved rather less successful with use of LiHMDS as base providing only ethyl ester (+)-**377** in poor yield.

Equation 50



Changing the base to butyl lithium did not yield any improvement, in fact in this case considerable quantities of elimination product **387** were observed together with previously seen ethyl ester (+)-**377**.

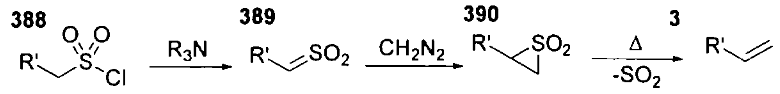
387



This behaviour clearly showed that the lithium enolate of **386** was a poor nucleophile in this reaction with elimination of ethoxide from the lithium enolate being preferred. It is interesting to note that the fate of the ketene generated in this process again remains unknown. Although it was possible that this problem could be overcome through a change of ester to one less easily elimination, particularly a *tert*-butyl ester, it was felt that given the complete lack of reactivity of ethyl ester **386** in this reaction, such an exercise was likely to be a waste of time.

As a final attempt to generate the desired diene, it was decided to investigate whether the double bond could be introduced starting from diazoketone (+)-**328**. Although the conversion of diazoalkanes to olefins is documented,[418] only one report of such a reaction was found in the literature for diazoketones and this method involved four low yielding steps.[419] Scheme 81 shows the proposed mechanism for the conversion of diazoalkanes into olefins, in which sulphene **389**, generated in situ from the corresponding sulphonyl chloride and triethylamine, reacts with diazomethane to produce episulphone **390**. Heating of this species causes the elimination of sulphur dioxide which produces olefin **3**.[418]

Scheme 81: proposed mechanism for the conversion of diazoalkanes to alkenes



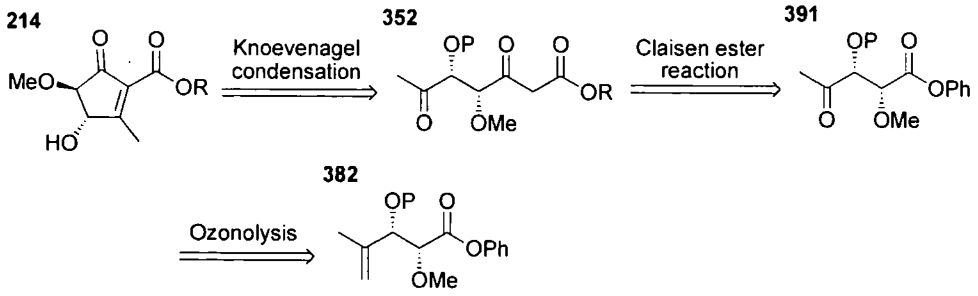
Unfortunately, with diazoketones (+)-**328** and (+)-**378**, no reaction was seen under the conditions described in the literature and increasing the temperature failed to effect any reaction. This lack of reactivity is not greatly surprising given the much greater stability of diazoketones compared with diazoalkanes.

With this failure, the attempt to synthesise cyclopentenone (+)-**324** by means of an RCM reaction was abandoned as no other possibilities for the synthesis of the required diene could be conceived.

2.10.3 Ozonolysis/Claisen ester reaction approach

Following the previously described failure to effect the desired RCM reaction to produce cyclopentenone (+)-**324**, another route was conceived starting again with phenyl ester (+)-**323**. In this approach, shown in Scheme 82, initial ozonolysis of this substrate to derive ketone **391** precedes a Claisen ester reaction to afford diketone **352** which would be expected to undergo the subsequent Knoevenagel condensation under the reaction conditions given that the initial product of the Claisen ester reaction is the lithium enolate.

Scheme 82: retrosynthetic approach to cyclopentenone **214** involving an initial ozonolysis reaction

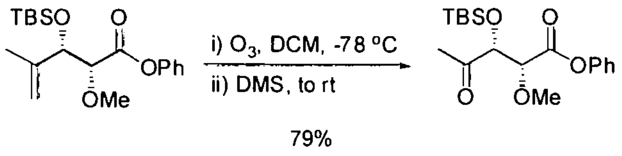


Although it was immediately seen that one potential problem with this route was the competing reaction of the lithium enolate with the ketone function of **391** rather than the phenyl ester function, it was hoped that the great steric bulk α to the ketone, combined with the reactivity of a phenyl ester, might favour the desired reaction.

The ozonolysis reaction was initially performed on a mixture a diastereoisomers (*syn:anti* 1.4:1) and was found to be relatively successful with the expected ketone being isolated in good yield. Interestingly, it was seen that some enrichment of the *anti*-diastereoisomer (*syn:anti* 1.1:1) was observed in this reaction.

Equation 51

(+)-323 **(+)-392**



Following this success, the reaction was scaled up using pure *syn*-diastereoisomer and although the yield was found to decrease slightly, the increased scale permitted observation and isolation of a second, less polar fraction during silica gel chromatography. This second fraction accounted for the majority of the remaining mass, however, its identify proved elusive. ^{1}H NMR spectroscopy showed the CH signals to be at lower frequency than those of ketone **392** (Figure 22) whilst ^{13}C NMR spectroscopy showed there to be no ketone to be present, the carbonyl group of the phenyl ester group also having disappeared.

Figure 22: ^{1}H NMR spectrum of by-product from ozonolysis of phenyl ester **(+)-323**

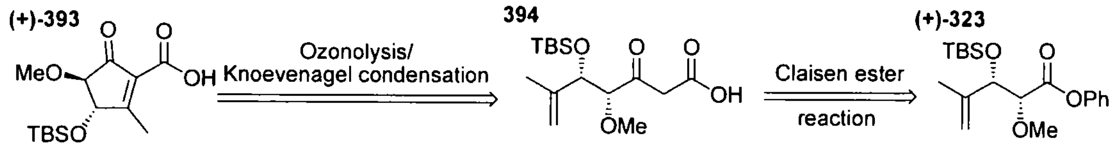
It was noted that a similar species had been observed but not purified following the ozonolysis of *tert*-butyl ester **(+)-321** under the same conditions and this led to the conclusion that the two products were most likely related. In this case, the advantage was that the unknown compound was present as a single species which was expected to make characterisation easier. Unfortunately, this species was found to be *meta*-stable, samples in chloroform converting to the expected ketone product **(+)-392** over several days. This hindered characterisation and whilst the IR spectrometry was unremarkable, mass spectrometry led to substantial decomposition which prevented an accurate mass measurement from being performed. Of the major peaks present in the mass spectrum, one which stood out was at *m/z* = 368 which suggested addition of ozone and subsequent loss of formaldehyde, however, it was difficult to see what the resulting product could be as the implied carbonyl oxide structure was expected to be highly unstable.

Regardless of the identity of the minor by-product, with the ketone available in good yield, attention was turned to the Claisen ester reaction. Unfortunately, but not unexpectedly, the crude reaction mixture was seen to be extremely complex by ^{1}H NMR spectroscopy and TLC. It could be seen that none of the desired cyclopenteneone **(+)-324** was present and nothing resembling the expected intermediate ketone was be seen to be present. For this reason this approach was abandoned.

2.10.4 Acetic acid addition approach

The approach outlined in Scheme 83 was investigated briefly because it required minimal changes to the synthetic scheme. Also, since it appeared that the presence of a *tert*-butyl ester in some way disfavoured the ozonolysis/Knoevenagel condensation step, the absence of this group might be beneficial. Hence, by replacing *tert*-butyl acetate with acetic acid in the Claisen ester reaction, acid **394** could be derived directly and used in the subsequent ozonolysis step.

Scheme 83: retrosynthetic appraoch using the bis(lithium) salt of acetic acid

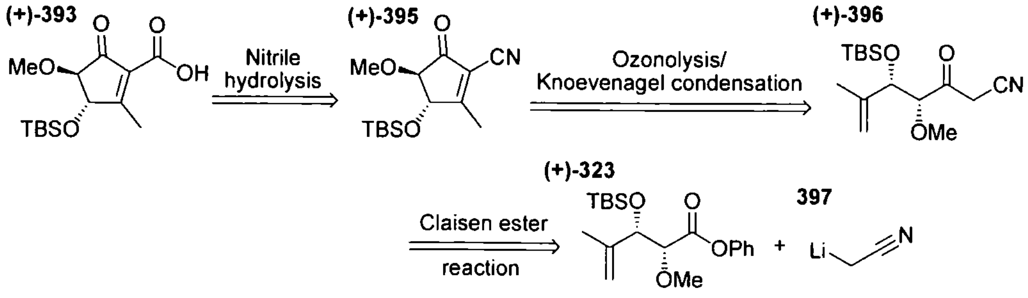


The bis(lithium) salt of acetic acid has been used before as a nucleophile with some success, particularly in the addition to ketones.[420] In this case, following its generation using the literature method,[421] it was reacted with phenyl ester (+)-**323** at room temperature. Unfortunately, no reaction was seen to occur and phenyl ester (+)-**323** was recovered unchanged. It was thought that this might owe to the relatively poor solubility of the salt in the reaction, however, increasing the temperature to 50 °C in order to overcome this issue did not result in reaction.

2.10.5 Nitrile approach

Since it had been shown that the free acid could not be introduced in a Claisen ester reaction, that the *tert*-butyl ester interfered with the ozonolysis/Knoevenagel condensation step and that other esters were difficult to produce, another protecting group for carboxylic acids was sought. Nitriles have been used to mask carboxylic acids in a number of cases where esters proved unsuitable[422] and it was decided to use this approach in this instance. It was thought that following a Claisen ester reaction and the subsequent ozonolysis/Knoevenagel condensation sequence, hydrolysis of the nitrile would provide the desired carboxylic acid, ready to be activated for enol lactonisation (Scheme 84).

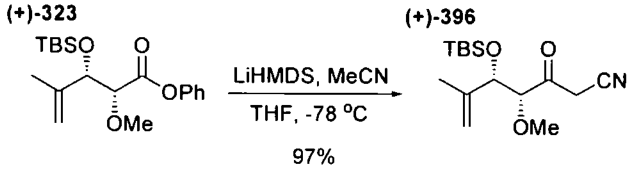
Scheme 84: retrosynthetic approach to cyclopentenone using acetonitrile as a masked carboxylic acid



The use of acetonitrile in Claisen ester reactions is documented, however, the yields have often been found to be poor and strong bases such as sodium amide have been employed.[423]

Given the high yield using LiHMDS for the Claisen ester reaction of *tert*-butyl acetate, this base was investigated with acetonitrile in the hope of achieving a good yield. The reaction was seen to be successful and ^{1}H NMR showed complete conversion to nitrile (+)-**396** when two equivalents of base were used, however, the product was found to be difficult to separate from the phenol by-product. It was found that by running two consecutive silica gel columns very carefully, the product could be isolated in almost quantitative yield (Equation 52), however, on scaling the reaction up, more and more columns were needed and this became extremely time consuming.

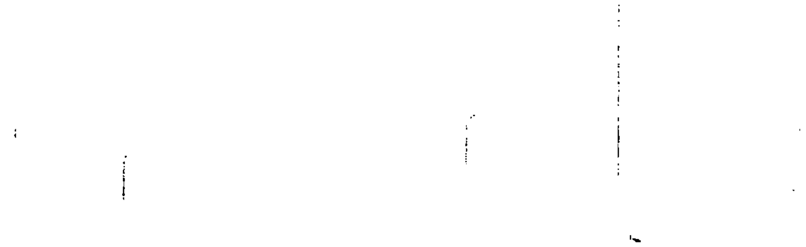
Equation 52



It was found that by washing the crude reaction with aqueous sodium hydroxide following an acidic quench, that the majority of the phenol could be removed. This permitted complete separation to be achieved using only one column with only a small reduction in yield of nitrile (+)-**396**.

Following this success, attention was turned to the ozonolysis/Knoevenagel condensation step (Scheme 84, conversion of (+)-**396** to (+)-**395**). It was initially decided to perform this in a stepwise manner, isolating and characterising the ketone before attempting the intramolecular condensation and the ozonolysis was performed in DCM using DMS as a quench. Although the reaction was seen to be far cleaner than that of *tert*-butyl analogue (+)-**321**, ^{1}H NMR clearly showed two products to be present in the crude product, one of which was clearly the intermediate ketone and the other of which was unknown. It was observed that the unknown material possessed an AB quartet similar to that seen for the first unknown by-product produced in the ozonolysis reaction of *tert*-butyl ester (+)-**321** (Figure 23).

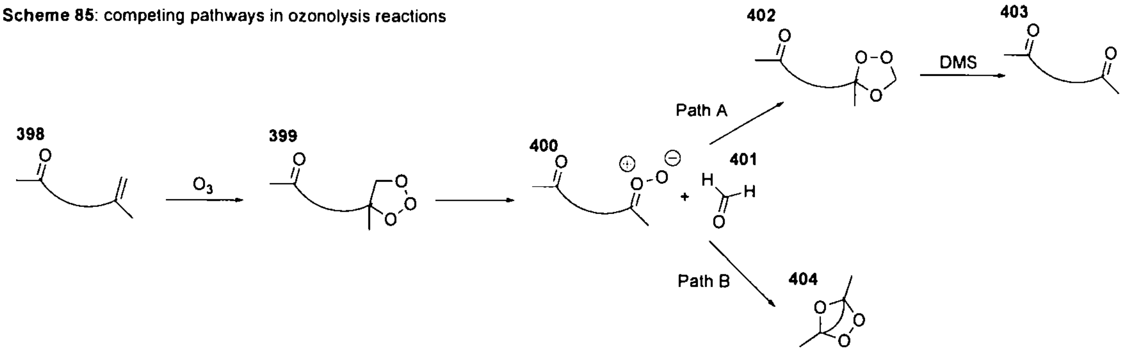
Figure 23: ^{1}H NMR spectrum ozonolysis by-product following purification



In this case, TLC showed the two well separated spots and silica gel chromatography was performed with the hope of separating the ketone and this unknown compound. Interestingly, following chromatography it was found that the less polar fraction was cyclopentenone **(+)-395** and not the expected ketone, showing that silica gel chromatography caused the desired Knoevenagel condensation. The yield of this reaction was reasonable and certainly an improvement over that seen for *tert*-butyl ester **(+)-321**. The second, more polar fraction was isolated and characterisation revealed no ketone group to be present, that the nitrile remained, and that the molecular mass was 315. This again indicated addition of ozone to the alkene and subsequent loss of formaldehyde, which leads to the suggestion of an unstable carbonyl oxide structure.

At this stage it was realised that carbonyl oxides can react with other ketones, both intra- and inter-molecularly, to produce so called cross-ozonides.[424] Hence, as shown in Scheme 85, following addition of ozone across the double bond of the alkene, this primary ozonide collapses by loss of formaldehyde to produce highly unstable carbonyl oxide **400**. Normally, in the absence of a ketone function, this would add formaldehyde with reversed regioselectivity to derive secondary ozonide **402** which is quenched with a reducing agent such as DMS to derive the expected ketone together with formaldehyde (Path A).

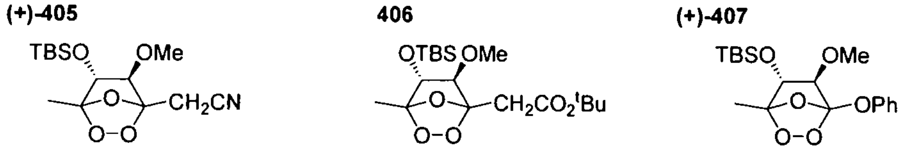
Scheme 85: competing pathways in ozonolysis reactions



In the case where a ketone function is present within the molecule, intramolecular trapping of the carbonyl oxide may compete with the re-addition to formaldehyde and this process produces cross-ozonides of type **404** (Path B). A similar process can also occur in an intermolecular fashion when a ketone is used as solvent and a solvent molecule traps the intermediate carbonyl oxide.[425]

Given this known process, it was suggested that the three unknown species derived from the ozonolysis reactions of **(+)-396**, **(+)-321** and **(+)-323** were in fact cross-ozonides **(+)-405**, **406** and **(+)-407** respectively. In the case of phenyl ester **(+)-323**, it can be seen that the intermediate carbonyl oxide is in fact trapped by the carbonyl group of the phenol ester rather than a ketone as in the other two cases. This perhaps explains the meta-stable nature of cross-ozonide **(+)-407** as the carbon centre possessing the phenoxy group looks susceptible to hydrolysis.

Figure 24: structures of cross-ozonides



Unfortunately, two of the cross-ozonides could not be fully characterised; in the case of **(+)-407** the meta-stable nature of the product interfered with mass spectrometry and in the case of **406**, the compound could not be separated from cyclopenteneone **(+)-324**. Another interesting point regarding this reaction is its stereospecific nature; when a single diastereoisomer was used in the ozonolysis reaction, in all three cases a single diastereoisomer was produced showing that two new chiral centres were formed with complete selectivity.

It was of interest to know the configuration of the two new chiral centres, however, this would require X-ray diffraction studies and hence crystalline material. Such a study would also prove conclusively the identity of the product. Unfortunately, *tert*-butyl ozonide **406** could not be purified and phenyl ozonide (+)-**407** was an oil. Gratifyingly, following further silica gel chromatography to remove traces of cyclopentenone (+)-**395**, nitrile (+)-**405** was found to be a crystalline solid and recrystallisation from petroleum ether gave material suitable for X-ray diffraction. This confirmed the identity to be cross-ozonide (+)-**405** and demonstrated the configuration of the two newly-formed chiral centres to be that shown.

Equation 53

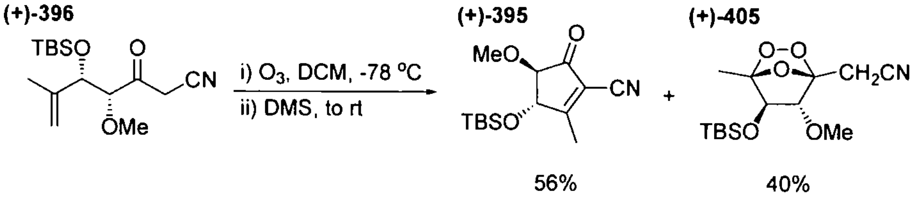
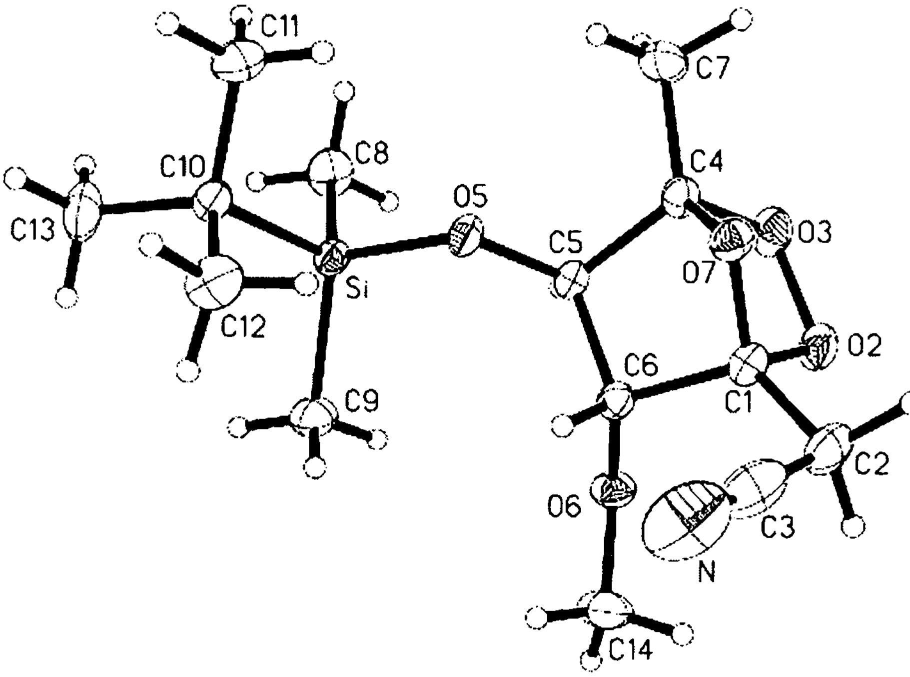


Figure 25: crystal structure of ozonide **405**



The transition state controlling the stereochemistry of the forming ozonide remains unknown, however, given the highly reactive nature of carbonyl oxides it is expected that the stereochemistry is controlled at the stage in which the primary ozonide collapses to form the carbonyl oxide as this would be expected to react rapidly with whichever face of the ketone is closest.[426]

Cross-ozonide **(+)-405** was found to be remarkably stable, no decomposition was observed up to its melting point of 80 °C and even during the high temperatures involved during elemental analysis, no sign of decomposition was seen. More surprisingly, the compound showed no sign of decomposition on storage for over one year. Despite this, the nature of the structure caused some concern for the crystallographer! A number of similar structures have been reported[427-429] although few crystal structures exist,[430] and the stability of such materials appears to depend on the bulk of the molecule; highly crowded, sterically hindered systems generally being relatively stable.[427] Hence, in this case, the high stability is likely to be due to the bulky nature of the TBSO function.

Although interesting, cross-ozonide **(+)-405** was of no use for this synthesis and its formation limited the yield of the desired cyclopentenone. Given the virtually quantitative nature of the combined yield, it was hoped that through changing the reaction conditions, improved selectivity for cyclopentenone **(+)-395** could be achieved in the ozonolysis reaction.

It was initially thought to disfavour the formation of the intramolecular cross-ozonide by promoting the formation of an intermolecular cross-ozonide which could be subsequently reduced. Given that aldehydes were reported to be more reactive than ketones in the addition to carbonyl oxides,[424] the reaction was performed in DCM using acetaldehyde as a cosolvent. Although this proved successful in terms of preventing the formation of cross-ozonide **(+)-405**, no increase in the yield of cyclopentenone **(+)-395** was found and the fate of the remaining material remains unknown.

In another attempt at reducing the formation of **(+)-405**, a solvent screen was performed. Given the polar nature of the carbonyl oxide, it was expected that a change in solvent polarity would have a marked effect on the selectivity of the reaction. Four solvents (other than DCM) were chosen as the choice of solvents for performing such reactions is somewhat limited. These reactions were performed with no quench; the reactions were warmed to room temperature following ozonolysis and evaporated. The results are shown in Table 10.

Table 10: conditions used for the ozonolysis of **396**

Entry	Solvent	Ratio ketone:**405**	Yield **395**/%
1	MeOH	ND	ND
2	DCM	1.4:1	56
3	Chloroform*	1.2:1	30
4	Hexane	>9:1	36
5	Acetone	5:1	31

*reaction performed at -60 °C.

Methanol (Entry 1) was found to give little or none of the desired product; the crude reaction was extremely complex by both ^{1}H NMR spectroscopy and TLC (five spots) and no attempt was made to purify the reaction.

DCM (Entry 2) and chloroform (Entry 3) can be seen to give similar results in terms of the ratio between the two products although the yield was considerably higher in DCM. This difference may reflect the difference in reaction temperature necessitated by the melting point of chloroform rather than a true solvent effect. It is interesting to note that the ratio between the ketone and the cross-ozonide is largely unchanged by the removal of DMS. This appears to show that for both DCM and chloroform, reduction of the secondary ozonide occurs prior to the addition of DMS although the mechanism of this reaction remains unknown. This result also underlines the stability of cross-ozonide (+)-**405** to DMS; it is clear that at room temperature this reagent does not effect the reduction of the cross-ozonide to the desired ketone.

It is clear that hexane (Entry 4) substantially reduces the competing formation of cross-ozonide (+)-**405**, however, the ^{1}H NMR spectrum of the crude material showed that a number of side reactions were occurring. Although in this case the addition of DMS did simplify the spectrum somewhat with concomitant conversion of the DMS to DMSO, the material remained a complex mixture as evidenced by the low yield.

It is interesting to see that acetone (Entry 5) also improves the ratio of ketone to ozonide although the yield remains poor. Although it was possible that this reduction was due to the intermolecular trapping of the intermediate carbonyl by acetone, it did not prove possible to isolate such a cross-ozonide from the reaction.[425]

Due to this lack of success, it was attempted to perform the desired ozonolysis reaction in a stepwise manner through the use of a bis-hydroxylation/oxidative cleavage sequence. Unfortunately, use of AD mix (both α and β) gave complete consumption of the starting β-keto nitrile without producing any apparent product.

Without the possibility of avoiding the formation of cross-ozonide (+)-**405**, a method was sought to reduce the compound to the desired ketone. As already noted, DMS was not an efficient reductant for this compound at room temperature, and it was found that even in refluxing THF, no reduction took place.

A number of other conditions were screened for the reduction of cross-ozonide (+)-**405**: lithium aluminium hydride proved ineffective giving a mixture of products; aqueous sodium sulphite gave no reaction; and sodium borohydride gave a mixture of products.

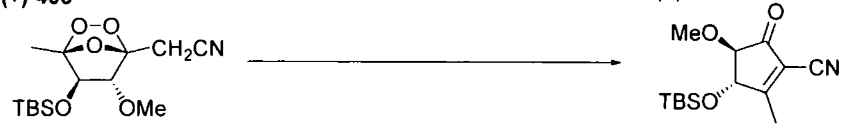
A reported reagent for the reduction of peroxides in ethereal solvents, namely acidic iron(II) sulphate solution,[431] was investigated and found to give conversion to an unknown material in relatively poor yield (39% based on proposed formula). The ^{1}H NMR spectrum of this material, shown in Figure 26, shows what could be an alkene resonance whilst the ^{13}C NMR spectrum shows both olefin and ester functions to be present. IR spectroscopy showed that the nitrile remained and confirmed the presence of a carbonyl group with the stretch at 1738 cm^{-1} although no olefin stretch could be seen. Mass spectrometry of this material indicated the molecular weight to be 297, consistent with elimination of water from cross-ozonide (+)-**405**, however, the structure of this compound remains unclear.

Figure 26: ^{1}H NMR spectrum of product from attempted iron(II) sulphate reduction

Returning to more conventional methods for the reduction of ozonides, the use of triphenylphosphine was investigated. Although no reaction was seen at room temperature, it was found that elevating the temperature to 67 °C (refluxing THF) gave slow reduction of the ozonide. After three days, the reaction was seen to be complete and silica gel chromatography provided cyclopentenone **(+)-395** in a reasonable 56% yield.

Despite the fact that there was not any great difficulty separating the desired product from triphenylphosphine oxide, solid supported triphenylphosphine was investigated. Although it was expected that this reaction would be slower than that of triphenylphosphine, remarkably it was found that under the same conditions the reaction was complete in under six hours. In addition, the yield was seen to be fractionally improved.

Equation 54



(+)-405

(+)-395

Conditions A: PPh_3, THF, 67 °C	56%
Conditions B: solid-supported PPh_3, THF, 67 °C	60%
Conditions C: Zn, aq. HCl, THF	65%

Finally, it was found that through the use of zinc dust and aqueous hydrochloric acid in THF, cross-ozonide **(+)-405** could be reduced to the desired cyclopenteneone in reasonable yield. The fate of the remaining material is unknown although it is possible that it may owe to the instability of the TBS group to the acidic reaction conditions. Attempts to reduce the acidity of the reaction by substituting hydrochloric acid with acetic acid did not give any reaction.

Although the yield for the reduction of cross-ozonide **(+)-405** was not outstanding, it was realised that a reasonably efficient route to cyclopenteone **(+)-395** had been devised (50% overall yield over 6 steps) and it was decided that further optimisation was not necessary. Instead, attention was turned to the conjugate addition reaction.

2.11 Conjugate addition reactions

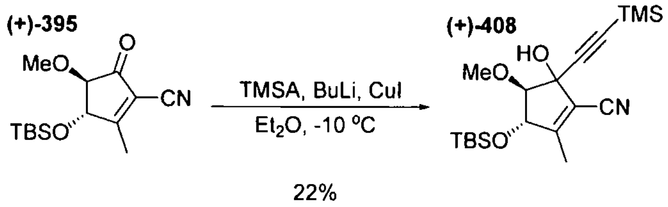
2.11.1 Conjugate addition to nitrile (+)-395

It should be noted that from this stage onwards, both enantiomers of phenyl ester **323** were in use and the structures shown are those used for each particular reaction.

As discussed previously, it had not proved possible to effect a conjugate addition reaction to *tert*-butyl cyclopentenone (+)-**324** under a range of conditions. More hope was held for nitrile analogue (+)-**395**, both because of the reported facile conjugate addition reactions to similar substrates in the literature, and because the nitrile function is a better electron withdrawing group than an ester function and as such might be expected to further activate the double bond. In addition, ^{13}C NMR spectroscopy appeared to show that the carbonyl carbon was rather less electron deficient in this substrate (195 ppm *vs* 203 ppm for nitrile (+)-**395** and ester (+)-**324** respectively) suggesting that competing 1,2-addition might be less of an issue.

Despite this optimism, initial results for the addition of vinyl and alkynyl groups using organocuprate chemistry were not promising; in most cases no conversion was seen except in one case, when, using a cuprate derived from TMS acetylene, small amounts of 1,2-addition product (+)-**408** was isolated.

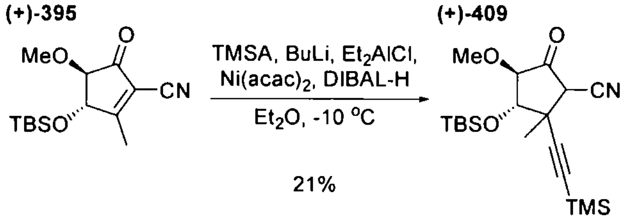
Equation 55



This lack of success with vinyl and alkynyl nucleophiles led to the examination of the addition of allyl nucleophiles. Unfortunately, under literature conditions,[393] TBAF promoted addition of allyltrimethylsilane gave no reaction and attempts with allylcuprates were similarly unrewarding.

Due to this lack of success with organocuprates, attention was turned to the use of organoalanes. Although, as previously discussed, no reaction would be expected on this type of substrate in the absence of a catalyst, it was hoped that the use of a nickel catalyst would promote the desired reaction.[385] Initial results showed some promise and after a little experimentation it was found that an alkynyl group could be added in a conjugate fashion, albeit in poor yield.

Equation 56

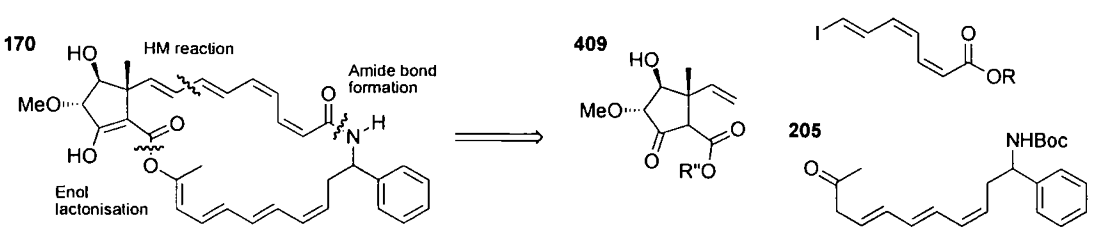


Whilst promising, this reaction showed a number of disadvantages, in particular its complexity and the difficulty in purifying products from the crude black tar which was invariably produced. Despite extremely careful chromatographic purification, the product invariably retained some degree of brown colouration.

Due to the expense of cyclopentenone **(+)-395**, it was decided to further optimise this reaction by returning to model compound **351**. For this less activated substrate, the addition of an alkynyl group under identical conditions proved rather less successful; although it was apparent that some product had been formed, the level of conversion was so low as to make isolation impossible.

Given the consistently poor results seen for alkynyl nucleophiles and the lack of literature methods for effecting such reactions, it was decided to modify the retrosynthetic approach slightly from that shown in Scheme 36.

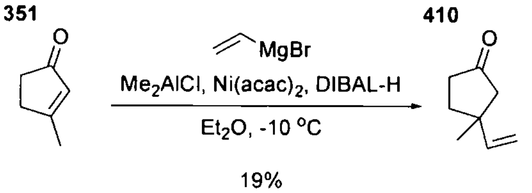
Scheme 86: Revised retrosynthetic strategy for viridenomycin **170**



Scheme 86 shows the revised retrosynthetic strategy in which following the conjugate addition of a vinyl unit to cyclopentenone (+)-**395**, a HM reaction couples the resulting cyclopentanone core to the northern triene. It was possible to make this modification as it had been shown previously that iodide **254** did react in a HM reaction with vinylcyclohexane, and that this reaction was more selective and better yielding that the Suzuki-Miyaura or Stille alternatives. In addition, this modification shortened the overall synthetic route as it was no longer necessary to perform a TMS-deprotection/hydroboration reaction sequence to obtain the necessary coupling partner.

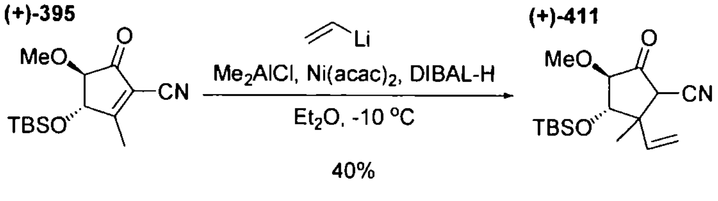
Thus, following a change to a vinylalane reagent, it was found that under the previously used conditions, conjugate addition did occur to model compound **351**, although again the yield was rather poor.

Equation 57



It was expected that the yield of this reaction would improve when applied to the more activated substrate (+)-**395** and this was indeed found to be the case with cyclopentanone (+)-**411** being formed in moderate yield.

Equation 58

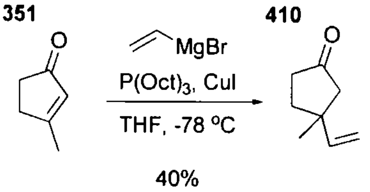


Unfortunately, it did not prove possible to optimise this yield any further and the product again proved difficult to purify from the crude mixture. Because of these issues, the reaction was not considered acceptable and an alternative was sought.

Gratifyingly, it was discovered that the addition of a vinyl unit to model compound **351** had been performed previously under different conditions involving the use of a trialkylphosphine together with copper(I) iodide and a Grignard reagent. This approach was investigated, albeit using trioctylphosphine rather than the reported tributylphosphine, and the approach was found to be quite successful.

Equation 59

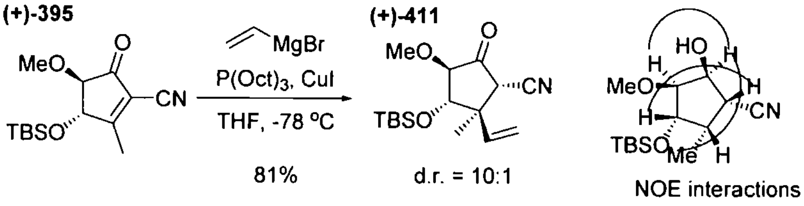
351 **410**



On applying the reaction to actual substrate **(+)-395**, not only did the product prove to be much easier to purify than that obtained by the previous route, but the yield was much improved. ^{1}H NMR spectroscopy showed the diastereomeric ratio to be an impressive 10:1. The stereochemistry of this molecule was assigned based on interactions in its ^{1}H NOESY spectrum from the known stereochemistries of the CHOMe and CHOTBS centres. The stereochemistry of the CHCN centre was assigned from the cross-ring interaction between C*H*OTBS and C*H*CN and that of the CMe(CHCH$_2$) centre was assigned from the cross-ring interaction between C*Me*(CHCH$_2$) and C*H*OMe.

Equation 60

(+)-395 **(+)-411**

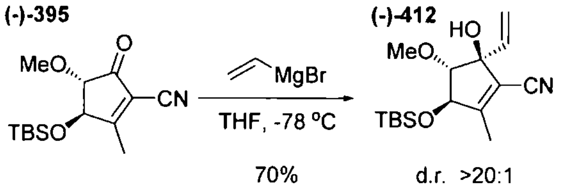


It is interesting to note that good diastereoselectivity was also achieved for the chiral centre formed α to the nitrile and indeed it is possible that the minor isomer produced may be a diastereoisomer at this position. Although not relevant to the synthesis of viridenomycin, little or no control of this centre was expected as such a centre is easily epimerised. For this reason, it is likely that selective formation of the diastereoisomer shown is due to it being the thermodynamic product following rapid epimerisation under the reaction conditions, rather than it being formed by selective protonation of one face of the expected copper or magnesium enolate.

On a related matter, it was seen by ^1H NMR spectroscopy that cyclopentanone (+)-**411** existed entirely in the keto-form in chloroform, no sign of the enol form being detectable. This was slightly surprising, not only because viridenomycin exists entirely in the enol form, but also because significant enol contributions have been reported for similar molecules.[433] Although it is clear that the enol form of (+)-**411** would be less favoured than in viridenomycin due to the absence of an adjacent hydrogen bond acceptor, the reason why the contribution is not the same as similar, albeit less substituted species, is unclear.[434]

Given that it had been reported that Grignard reagents added to similar species to (-)-**395** in the absence of copper,[377] this was investigated in case the copper and phosphine served no useful purpose. Under these conditions, the only product found was 1,2-addition product (-)-**412** showing that a cuprate is needed to effect a conjugate addition to this substrate. The diastereoselectivity of this reaction was found to be extremely high, so high in fact that the other diastereoisomer formed could not be detected.

Equation 61



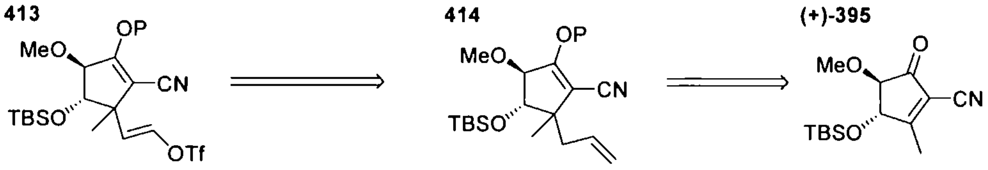
In order to see whether the nature of the phosphine had a marked effect on the reaction, tributylphosphine was investigated. This resulted in a decrease in both yield (60%) and diastereoselectivity (4:1), possibly owing to the reduced solubility of the copper-phosphine complex necessitating an increased reaction temperature. Whatever the reason, it is fortunate that trioctylphosphine and not tributylphosphine was present in the laboratory when the reaction shown in Equation 60 was attempted.

It was investigated whether the reaction could be made catalytic in copper with the hope of minimising waste and aiding purification. Although use of 20 mol% of both copper(I) iodide and trioctylphosphine did not produce any 1,2-addition product **(-)-412**, it was found that the desired product was contaminated with an unknown material and could not be purified. All further reactions were therefore performed using stoichiometric amounts of both copper(I) iodide and trioctylphosphine.

It was investigated whether an alkynyl group could be added using the same conditions as used for the addition of the vinyl group. Hence, following deprotonation of TMS acetylene using butyl lithium, copper(I) iodide and trioctylphosphine were added and the resulting cuprate reacted with cyclopentenone **(+)-395**. Unfortunately, no reaction was seen, even on warming to room temperature, further demonstrating the difficulty in achieving conjugate additions of alkynyl nucleophiles.[396]

It was hoped that the addition of an allyl group to cyclopentenone **(+)-395** could be performed in case the HM reaction of the vinyl group failed. Through the addition of an allyl unit and subsequent trapping on the copper enolate with a suitable protecting group, oxidative cleavage of the double bond to the corresponding aldehyde followed by conversion to vinyl triflate **413** would provide a suitable coupling partner for trienyl boronate **253**, thus providing an alternative route to the northern hemisphere of viridenomycin.

Scheme 87: retrosynthetic approach to vinyl triflate **413**

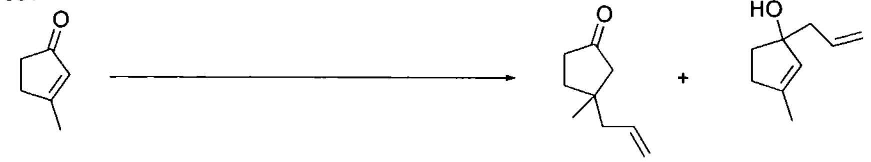


Under the same conditions as used for the addition of a vinyl unit to **(+)-395**, no reaction was seen whilst for model compound **351**, only 1,2-addition was observed. Consulting the literature revealed conditions involving the generation of a higher order cuprate through the addition of an equivalent of a lithium halide salt for additions of allyl Grignard reagents[435] and these were applied to the model compound.

Under these conditions, only 1,4-addition product **415** was observed, although the yield was poor and significant quantities of starting material were recovered.

Equation 62

351 **415** **416**



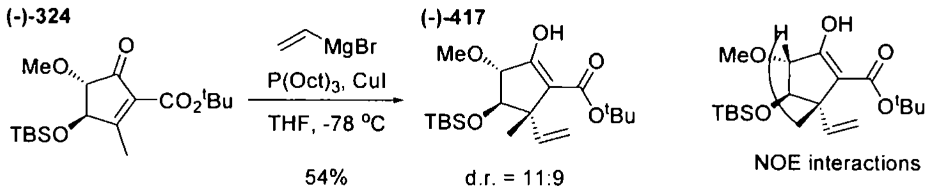
Conditions A: AllylMgBr, CuI, P(Oct)$_3$, THF, -78 °C	7%	85%
Conditions B: AllylMgBr, CuBr.DMS, LiCl, TMSCl, THF, -78 °C	33%	0%

These same conditions were applied to nitrile **(+)-395** and although conversion reached only 50%, it was apparent that a significant amount of the desired product was formed as judged by the methine and methyl ^{1}H NMR chemical shifts. Unfortunately, although this product could easily be separated from the starting material, it did not prove possible to separate this species from a number of other unidentified by-products. When all efforts to overcome this behaviour met with failure, all further efforts were focussed on vinyl system **(+)-411**.

2.11.2 Conjugate addition to *tert*-butyl ester (-)-324

Having developed conditions suitable for performing conjugate additions to nitrile **395**, it was of interest to know whether the same conditions would effect the same reaction to the previously synthesised substrate **(-)-324**. The reaction proved successful, however, it was apparent that two diastereoisomers were produced in approximately one to one ratio. It was initially hoped that these would prove to be epimers at the newly formed α-chiral centre, however, it became clear that both isomers existed entirely as their enol tautomers and consequently the two isomers had to be epimers at the forming quaternary centre. The stereochemistry of the major isomer was assigned based on interactions in its ^{1}H NOESY spectrum from the known stereochemistries of the CHOMe and CHOTBS centres. The stereochemistry of the single new CMe(CHCH$_2$) centre was assigned from the cross-ring interaction between C*H*OMe and C*Me*(CHCH$_2$).

Equation 63



This difference in selectivity between nitrile **(+)-395** and *tert*-butyl ester **(-)-324** is somewhat surprising as the steric bulk at this position would not be expected to influence the diastereoselectivity and neither would electronic effects. More surprisingly still, product **(-)-417** was found to epimerise upon standing in chloroform to give a further two diastereoisomers. Although unproven, it is expected that this epimerisation occurs at the α-methoxy chiral centre by means of the reprotonation of trace amounts of the less stablised enol form of the molecule. Such behaviour was not observed for nitrile **(+)-411** and this may reflect the difference in stability of the enol tautomers of the two species; the potential for hydrogen-bonding in *tert*-butyl system **(-)-417** allowing sufficient concentration of the less stabilised enol to give slow epimerisation.

Although useful to know that such a reaction could be performed, the low yields, poor selectivity and isomeric instability of the resulting product meant that further efforts were directed towards the more stable nitrile-substituted cyclopentenone **(+)-395**.

2.12 Hydrolysis of the nitrile function

Following the successful conjugate addition of a vinyl unit to cyclopentenone **(+)-395**, hydrolysis of the nitrile function of this molecule to the corresponding carboxylic acid was required in order that this species could be activated for the subsequent enol lactontonisation reaction.

The hydrolysis of nitriles generally occurs under acidic or basic conditions and forcing conditions are often required.[436-438] In this case, use of mildly acidic and basic conditions at ambient temperature gave no reaction with cyclopentanone **(+)-411** whilst under more forcing conditions, rapid decomposition of the starting material was observed. The use of the extremely mild method involving sodium peroxide[439] failed to induce any reaction with this substrate.

Application of the same conditions to the more stable cyclopentenone **(+)-395** was also found to be ineffective; at room temperature no reaction occurred whilst at elevated temperatures, loss of the TBS group was observed under both acidic and basic conditions. No such loss was observed for cyclopentanone **(+)-411** and this difference presumably reflects the more labile nature of the allylic alcohol compared with its non-allylic counterpart.

Following the screening of a number of conditions, it was realised that a standard hydrolysis reaction was unlikely to succeed on substrate **(+)-411** owing to its inherent instability. Enzymatic hydrolysis was also investigated using a range of commercial nitrilases[440] and found to give no reaction, possibly because of the bulky nature of the substrate. For this reason, it was decided to use a slightly less direct but much milder approach to the hydrolysis of nitriles, namely reduction to the corresponding aldehyde and reoxidation to the desired oxidation state.

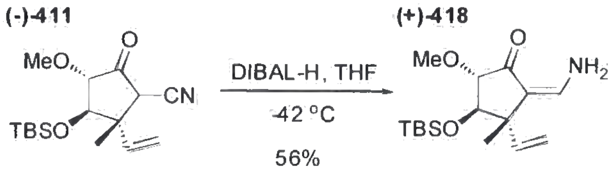
2.12.1 Reductive approach

DIBAL-H is most commonly used for the reduction of nitriles to aldehydes and has been found to be selective for nitriles in the presence of carbonyl groups.[441] In addition, the reaction tends to stop at the aldehyde provided the reaction is quenched at low temperature because under these conditions, the intermediate tetrahedral intermediate does not collapse to permit further reduction of the resulting imine.[442] Following an acidic work-up, the imine is hydrolysed to the aldehyde. In the present case, there was some concern over the presence of the free ketone function and more particularly, that its potential to enolise might quench an equivalent of DIBAL-H through the formation of the diisopropylaluminium enolate. For this reason, an excess of DIBAL-H was employed in the reaction with **(-)-411** and the reaction quenched at low temperature to avoid over-reduction. This yielded a product with a clear single olefinic proton at 6.5 ppm in its ^{1}H NMR spectrum, the multiplicity of which was rather unusual (Figure 27). In addition, it was apparent that two distinct exchangeable protons were present at 6 ppm and 8.5 ppm.

Figure 27: ^{1}H NMR spectrum of DIBAL-H reduction product at room temperature

This led to some confusion as the product was neither the expected aldehyde nor the intermediate imine. Mass spectrometry showed the product to have gained two mass units indicating a single reduction to have taken place without loss of nitrogen whilst IR spectroscopy showed the nitrile function to have disappeared and the carbonyl stretch to have moved to a lower frequency. At this point it was quickly realised that the product from the reaction of DIBAL-H with **(-)-411** was in fact enamine **(+)-418** and although primary enamines are not generally considered stable,[443] in this case such behaviour could perhaps have been anticipated as both conjugative and hydrogen bonding effects are present to stabilise such a species.

Equation 64

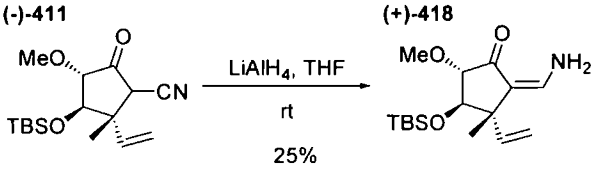


Enamine **(+)-418** was found to be stable to further reduction by DIBAL-H; warming to room temperature before quenching the reaction gave the best yield of this species. The relatively poor yield of this species does not owe to any side reactions but appears to be due to difficulty recovering all of the mass from the initial reaction work-up, most likely because of the presence of the enamine function.

Stephen's reduction[444] of cyclopentanone **(+)-411** was also investigated which involved the treatment of the substrate with anhydrous hydrogen chloride and tin(II) chloride in ether.[445] Surprisingly, despite these rather forcing conditions, only starting material was recovered from the reaction.

Incredibly, it was found that cyclopentanone **(-)-411** was again reduced to enamine **(+)-418** by lithium aluminium hydride (Equation 65); no further reduction taking place even when a large excess of this reagent was used. This was not the expected result as lithium aluminium hydride normally reduces ketones and imines rapidly,[446] hence this result appears to reinforce the initial expectation that following initial formation of a metal enolate, the ketone is protected from reduction.

Equation 65



Further interest in enamine **(+)-418** came from the unusual multiplicity of the olefinic proton in the ^1H NMR spectrum. It was speculated that this was due to a slowed rate of rotation around the carbon-nitrogen bond due to the hydrogen bonding present and that this made the two protons on nitrogen inequivalent to the olefinic proton. This hypothesis was tested by performing a variable temperature ^1H NMR spectroscopy study and it can be seen that at 50 °C a clear triplet appears (Figure 28) whilst at -50 °C a doublet of doublets is seen (Figure 29).

Figure 28: enamine **(+)-418** at 50 °C

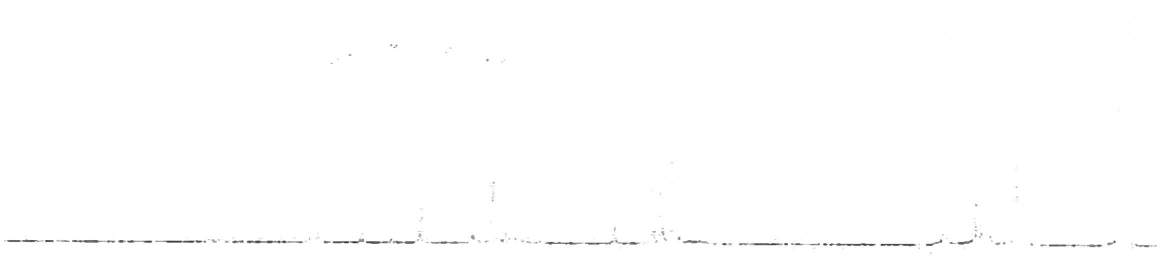
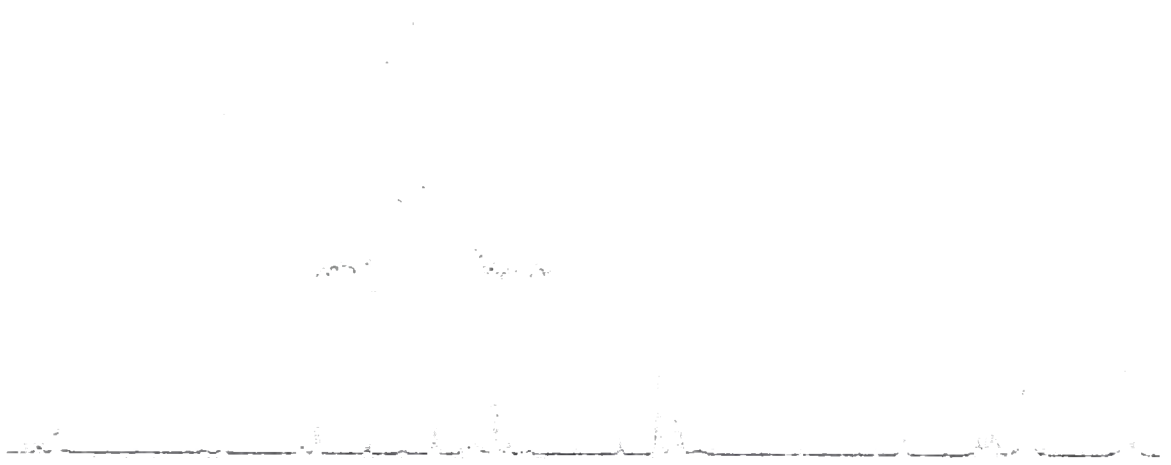
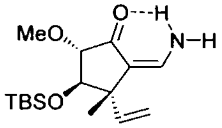


Figure 29: enamine **(+)-418** at -50 °C



This behaviour shows that at higher temperatures, rotation around the carbon-nitrogen bond becomes rapid causing the two enamine protons to become equivalent, whilst at low temperatures, rotation slows to such an extent that they become completely inequivalent. At the coalescence temperature, which in this case happens to be at around room temperature, the rate of rotation is comparable with the NMR time scale and an intermediate peak is seen. The coalescence temperature of 25 °C combined with the 500 MHz spectrometer used suggests the rate of rotation to be approximately 14 Hz at this temperature. As would be expected, increasing the solvent polarity by changing to DMSO disrupts the hydrogen bonding to such an extent that rapid rotation is seen at room temperature.

418



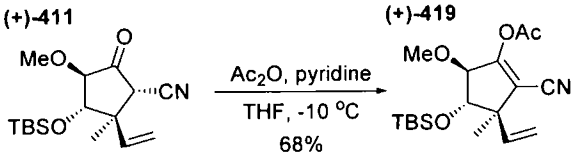
Returning to the synthetic work, it appeared that since the enamine was in the desired oxidation state, a simple hydrolysis should provide the desired aldehyde. A number of conditions were employed, both acidic and basic, and although under certain circumstances small aldehyde peaks were seen by ^{1}H NMR spectroscopy, under no circumstances was anything clean ever obtained. It thus appears that decomposition of this molecule is again faster than the desired hydrolysis.

In another approach, it was attempted to methylate enamine **(+)-418** in the hope that this would occur on oxygen and thus prevent the hydrogen bonding and conjugation effects responsible for the stability of the enamine. Unfortunately, treatment with Meerwein's reagent led to rapid decomposition of the starting material.

2.12.2 Protection of the ketone function

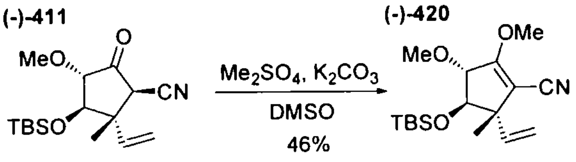
In order to prevent the tautomerisation of the intermediate imine to enamine **(-)-418** following reduction of cyclopentanone **(+)-411**, a number of methods for protecting the ketone in its enol form were investigated. Initial use of acetic anhydride with triethylamine as base gave moderate yields of the desired enol acetate, however, the best conditions found involved the use of pyridine (Equation 66).

Equation 66



Methylation of the enol could be achieved through the use of methyl sulphate with potassium carbonate in DMSO although the yields in this case were moderate.

Equation 67

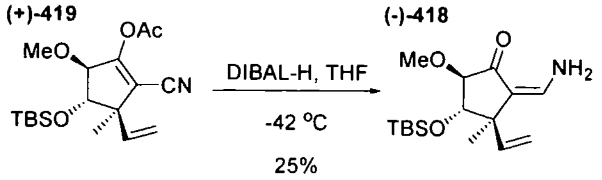


Attempts were also made to directly quench the metal enolate resulting from the conjugate addition reaction with a suitable electrophile, however, these did not prove particularly successful. Although in some cases small amounts of the expected protected enol were obtained, the majority of the material obtained in all cases was cyclopentanone **(-)-411**. Attempts to overcome this issue through transmetallation to other, potentially more reactive, metal enolates also proved unsuccessful.

Hydrolysis of these protected species was investigated but proved to be ineffective; in the case of enol acetate **(+)-419**, deprotection was particularly facile whilst methyl enol ether **(-)-420** proved stable to all but the most forcing conditions. Because of this, attention was turned to the alternative reduction/reoxidation approach.

Treatment of enol acetate **(+)-419** with an excess of DIBAL-H was again found to produce enamine **(-)-418**, albeit in poor yield. The competing reaction of DIBAL-H with the enol acetate did not come as a great surprise and it did not prove possible to prevent this reaction by quenching the reaction at low temperature.

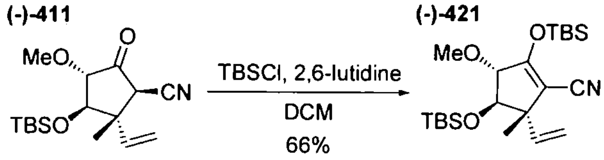
Equation 68



Turning attention to methyl enol ether **(-)-420**, initial reaction with DIBAL-H at -42 °C was found to give no reaction. Even on warming to room temperature and stirring for several hours with multiple equivalents of DIBAL-H failed to effect any reduction of the starting material. The material even proved resistant to two equivalents of DIBAL-H in refluxing THF whilst use of multiple equivalents of DIBAL-H under these conditions gave complete conversion to a complex mixture of products and although traces of aldehyde were apparent, the major product appeared to result from loss of the methyl enol ether function.

Given the curious lack of reactivity of methyl enol ether **(-)-420**, attention was turned to preparing a silyl enol ether. Use of TMSCl and triphenylsilyl chloride was unsuccessful, however, it was found that TBS enol ether **(-)-421** could be prepared in good yield using TBSCl and 2,6-lutidine.

Equation 69



Initial reaction of this species with a large excess DIBAL-H at -40 °C gave little conversion although it was seen that hydrolysis of the TBS enol ether did not occur under the work up conditions. Despite this lack of conversion, a small peak at 9.6 ppm was apparent in the ^{1}H NMR spectrum of the crude product suggesting that the reaction was possible.

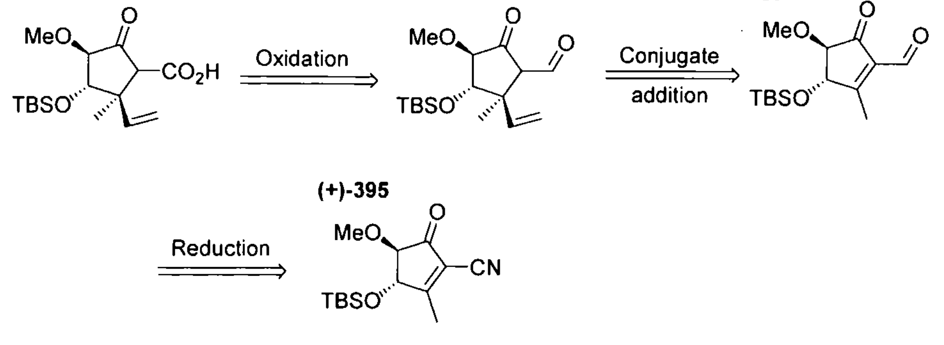
On increasing the temperature in order to improve the conversion, no aldehyde peak was observed following an aqueous work up although small amounts of enamine **(+)-418** were apparent suggesting that the lower temperature aqueous quench favoured imine hydrolysis over enol ether hydrolysis. Unfortunately, despite the use of elevated temperatures and large excesses of DIBAL-H, it did not prove possible to achieve a reasonable conversion in this reaction. This behaviour mimics that seen for methyl enol ether **(-)-420** and is most unusual as nitriles typically react rapidly with DIBAL-H even at reduced temperatures, as was seen for cyclopentanone **(-)-411**. It is far from clear why the presence of an alkyl or silyl group group on the oxygen atom adjacent to the nitrile function should have such a detrimental effect on its reactivity.

One point of interest regarding the protection of the ketone function was that in all three cases, varying levels of a second diastereoisomer were seen. It proved possible to limit the level of this epimerisation by keeping the reaction temperatures as low as possible and in all cases levels of approximately 5:1 were obtained. Given that the quaternary chiral centre does not seem susceptible to epimerisation, it seems probable that this epimerisation is occurring at the α-methoxy chiral centre as was seen for *tert*-butyl analogue **(-)-417** (*vide supra*). Although no evidence of enol tautomers was seen for nitrile system **(+)-411**, an increased contribution from the enolate tautomer could be expected under the basic reaction conditions used in all three protection reactions.

2.12.3 Reduction of cyclopentenone (+)-395

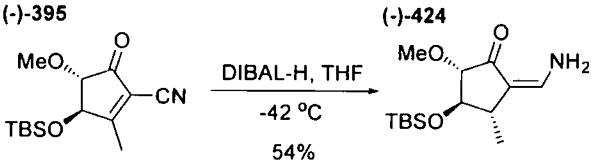
In an alternative approach, it was envisaged that a conjugate addition could be performed on cyclopentenone-aldehyde **423**, itself derived by reduction of cyclopentenone nitrile **395** (Scheme 88). Again, oxidation of aldehyde **422** would be expected to produce the required carboxylic acid and in this case, tautomerisation of the intermediate imine resulting from a DIBAL-H reduction would not be possible because of the intervening sp^2-carbon atom.

Scheme 88: retrosynthetic approach involving initial reduction of nitrile **395**



That treatment of cyclopentenone **(-)-395** with DIBAL-H did not give the expected product by this point came as no great surprise! Indeed, a product possessing what again appeared to be an enamine proton in the olefinic region of the ^{1}H NMR spectrum was seen and it quickly became apparent that as well as reducing the nitrile function, the excess of DIBAL-H employed had also effected a conjugate addition of hydride, thus reducing the double bond to give **(-)-424**.

Equation 70



It was attempted to avoid this problem by using only one equivalent of DIBAL-H, however, it was seen that the preferred reaction of DIBAL-H with this substrate is a conjugate addition reaction as the only product seen was the intermediate cyclopentanone.

The conjugate addition reaction of hydride to cyclopentenone **(-)-395** is of particular interest due to the high level of stereocontrol observed (>20:1 d.r.). The stereochemistry shown is that of the major isomer as determined by ^{1}H NOESY experiments, interactions being seen between C*H*OMe and C*H*Me to confirm the stereochemistry of the new centre and shows that the hydride is delivered from the front face as drawn. This is in contrast to the behaviour seen for the addition of vinyl units to **(+)-395** in which attack occured from the opposite face to avoid steric interactions with the TBS group.

The mechanism of DIBAL-H reductions is thought to involve initial coordination of the reacting nitrile to aluminium in order to provide a nucleophilic “ate”-complex as aluminium hydride complexes are not efficient nucleophiles.[442] In this case it seems reasonable to suggest that the oxygen of the TBSO group serves to activate DIBAL-H to nucleophilic attack and thus delivers it from the same face.

Another unusual feature of this reaction is that DIBAL-H does not generally perform such conjugate reductions unless additives such as copper(I) alkyl species are present.[447]

Enamine **(-)-424** showed similar solution-state effects in its ^{1}H NMR spectrum to those seen for analogue **(+)-418** with a triplet seen at higher temperature (Figure 30) and a doublet of doublets seen at low temperature (Figure 31).

Figure 30: ^{1}H NMR spectrum of enamine **(-)-424** at 20 °C

Figure 31: ^{1}H NMR spectrum of enamine **(-)-424** at -20 °C

One notable difference between enamines **(+)-418** and **(-)-424** is their different coalescence point; whilst this was seen at room temperature for **(+)-418**, the temperature had to be reduced to -10 °C to see the same effect in **(-)-424** (Figure 32)

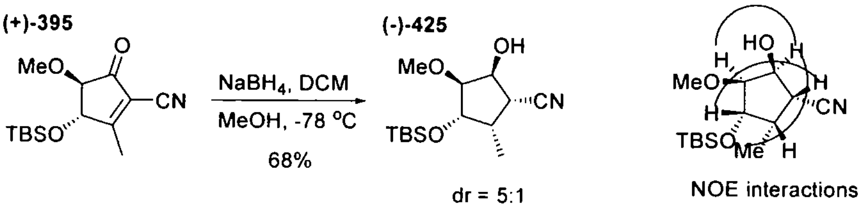
Figure 32: ^{1}H NMR spectrum of enamine **(-)-424** at -10 °C

This difference in temperature means that in order to achieve the same 14 Hz rate of rotation around the carbon-nitrogen single bond, more substituted enamine **(+)-418** has to be heated some 30 °C higher. This effect can only be steric in origin, presumably owing to some conformational difference resulting from the change from quaternary to tertiary centre.

In an effort to overcome the competing conjugate reduction of cyclopentenone **(+)-395**, a Luche reduction of the ketone function was investigated. It was hoped that this would prevent the conjugate reduction from occurring and that the resulting alcohol could be reoxidised at a later stage.

Under literature conditions for a somewhat similar substrate,[448] reduction occurred to derive a product which was seen to contain six single hydrogen environments. This was identified as doubly reduced cyclopentanone **(-)-425**, showing again that conjugate addition of hydride to this substrate it remarkably facile. Again, reasonable diastereoselectivity was seen for the formation of the isomer shown. The stereochemistry of this molecule was assigned based on interactions in its ^{1}H NOESY spectrum from the known stereochemistries of the CHOMe and CHOTBS centres. The stereochemistry of the CHOH centre was assigned from the interactions between C*H*OMe and C*H*OH which allowed the assignment of the CHMe centre from the cross-ring interaction between C*H*OH and CH*Me*. The stereochemistry of the CHCN centre was assigned from the cross-ring interaction between C*H*OTBS and C*H*CN.

Equation 71



In this case, it would appear that as the nucleophile is already an "ate"-complex, attack at the double bond occurs from the opposite face from the TBS group in order to minimise steric interactions. The explanation for the selectivity seen for the reduction of the ketone appears to involve the approach of the nucleophile from the opposite face to the α-methoxy group which is notably different for that seen in the 1,2-addition of a vinyl group in which the addition to the ketone appeared to be controlled by the OTBS function.

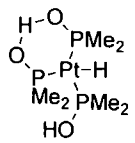
Following these failures at hydrolysis and reduction of the nitrile function, the alcoholysis (i.e. addition of ROH) of the nitrile function was also investigated as saponification of the resulting ester was expected to be more facile than hydrolysis. Although there are a number of reports of such reactions in the literature,[449,450] the conditions employed were seen to be extremely forcing and it was expected that such conditions would result in the rapid decomposition of the starting material. A transition metal-catalysed method had been reported[451] and although the conditions were still rather forcing, no acid was employed and so it was felt that decomposition was less likely.

The reported ruthenium catalysed alcoholysis was applied to cyclopentenone **(+)-395**, cyclopentanone **(+)-411** and methyl enol ether **(-)-420**. No ester was produced in any of these reactions and although some decomposition of cyclopentanone **(+)-411** was observed, the other two substrates were recovered unchanged.

2.12.4 Hydration of the nitrile function

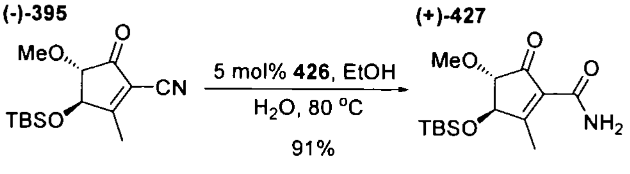
Following a personal communication with Frazer Fleming (Duquesne University, Pittsburgh, USA) suggesting an approach involving effecting the desired hydrolysis by an initial hydration and subsequent hydrolysis of the resulting amide, a transition metal catalysed hydration was investigated. Although a number of catalysts and conditions had been reported,[452] the most mild and efficient catalyst appeared to be platinum complex **426** developed by Parkins.[453] Typical catalyst loadings were as low as 0.5 mol% and the conditions simply involved heating an aqueous solution of the substrate to 80 °C.

426



The conditions were initially applied to cyclopentenone **(-)-395** and this was found to be extremely successful with the desired amide being isolated in excellent yield, however, a comparatively high catalyst loading was required in order for the reaction to reach completion.

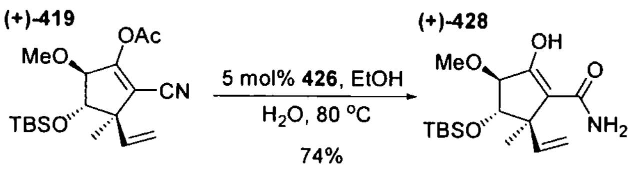
Equation 72



Cyclopentanone **(+)-411** was found to give only starting material under identical conditions. This suggested either that conjugation of the nitrile to the olefin double bond in cyclopentenone **(-)-395** activated it in some way, or that the presence of some structural feature of cyclopentanone **(+)-411**, such as the minor enol tautomer, inhibited the catalyst.

Application of these conditions to enol acetate (+)-**419** was found to be rather more successful with β-keto amide (+)-**428** being isolated in high yield. The hydrolysis of the enol acetate was not expected under these conditions as the catalyst was reported to be selective for nitriles, however, it is fortunate that this hydrolysis is markedly slower than the competing hydration otherwise the cyclopentanone formed would not undergo hydration at all.

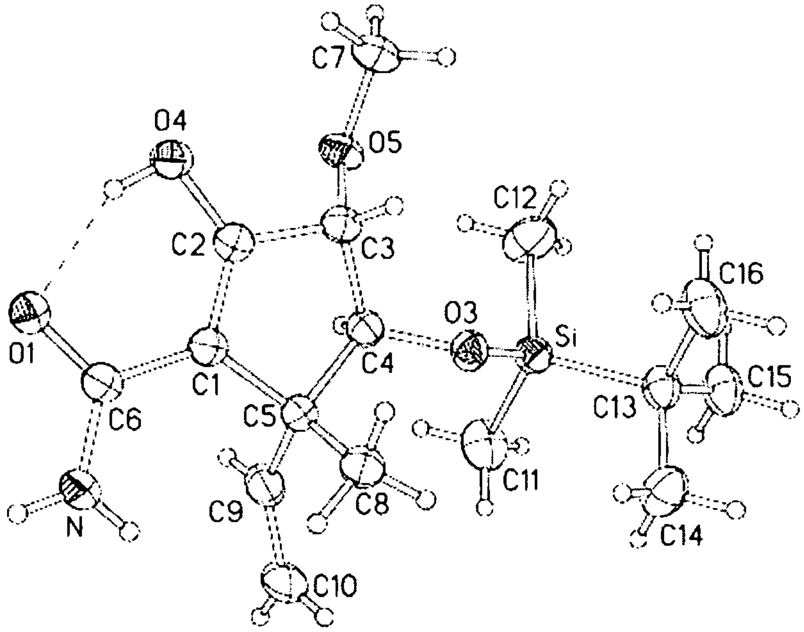
Equation 73



It is interesting to note that amide (+)-**428** exists entirely as the enol tautomer in solution with no level of the keto-form being detectable. This markedly different behaviour to that seen for nitrile (+)-**411** presumably reflects the stabilisation of this form achieved from the intramolecular hydrogen bond of the enol proton to the carbonyl group of the amide.

Amide (+)-**428** was found to be a solid and recrystallisation from petroleum ether gave material suitable for X-ray diffraction studies. Although some co-crystallisation with the minor diastereoisomer occurred, it proved possible to confirm the stereochemistry of the quaternary centre to be that assigned by ^{1}H NMR spectroscopy. Again, it was seen that this molecule exists entirely as the enol tautomer in the solid state.

Figure 33: crystal structure of enol amide **(+)-428**

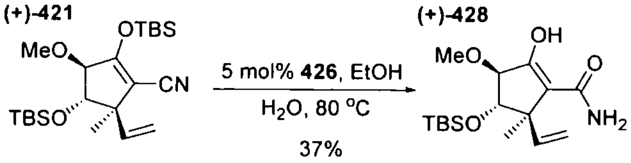


With the wish to keep the ketone protected in the enol form throughout the hydration, reaction of methyl enol ether **(-)-420** was investigated. Surprisingly, under the same conditions as used previously, no reaction was observed and even using elevated temperatures and longer reaction times, only starting material was recovered.

This appears to show that the nitrile is not activated by having a double bond conjugated to it and that the deactivation seen in this substrate and cyclopentanone **(+)-411** is due to the oxygen lone pair interfering with the catalyst. In the case of enol acetate **(+)-419**, the reduced accessibility of the oxygen lone pair appears to prevent this behaviour and allows normal catalysis to occur.

Hydration of TBS enol ether **(+)-421** was attempted in the hope that the steric bulk on the enol oxygen atom might overcome the deactivation seen with methyl enol **(-)-420**. This was found to be the case and hydration of the nitrile function did proceed, however, the product was found to again be free enol **(+)-428**. Although unexpected, the hydrolysis of the TBS protecting group appears to be due to its instability to the hot, aqueous reaction conditions rather than any effect of the catalyst as hydrolysis was observed for this species under similar conditions in the absence of catalyst **426**.

Equation 74



2.12.5 Amide hydrolysis

Following the synthesis of amides **(+)-427** and **(+)-428**, attempts were made to effect their hydrolyses. Initial attempts using standard acidic and basic conditions led only to decomposition which was unsurprising given the previously seen behaviour. More mild conditions for the hydrolysis of amides were seen to involve the generation of the corresponding diazonium species, either through direct reaction with a nitrosonium salt[454,455] or through the use of a nitrite salt under acidic conditions.[456]

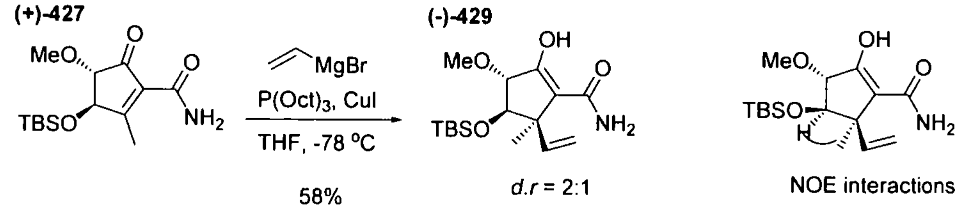
Both methods were applied to amides **(+)-427** and **(+)-428**, however, although conversion to a more polar species was seen in some cases, it proved impossible to isolate any clean material.

Attempts to reduce the two amides to the corresponding aldehydes using Schwartz' reagent[457] were similarly unsuccessful with multiple products being seen in both cases.

2.12.5.1 Conjugate addition to amide (+)-427

The conjugate addition of a vinyl unit to cyclopentenone amide **(+)-427** was investigated as this would provide a more direct route to *β*-keto amide **(-)-428**. This was found to be successful provided that another equivalent of vinylmagnesium bromide was employed, presumably in order to deprotonate one of the amide protons. Although the yield was somewhat lower than seen for nitrile **(+)-395**, this is a more efficient route to the *β*-keto amide system as it avoids the moderately efficient enol protection step, however, it can be seen that this reaction produces the wrong configuration at the quaternary centre. In addition, the diastereoselectivity with which this centre was formed was considerably lower than that seen for nitrile **(+)-395** with a ratio of 2:1. The stereochemistry of the major isomer was assigned based on interactions in its ^{1}H NOESY spectrum from the known stereochemistries of the CHOMe and CHOTBS centres. The stereochemistry of the single new CMe(CHCH$_2$) centre was assigned from the interaction between C*H*OTBS and C*Me*(CHCH$_2$).

Equation 75



The reason for this change in selectivity remains unknown; the involvement of dimeric amide complexes was proposed, however, the addition of HMPA to the reaction had no effect on yield or selectivity which makes this explanation seem less likely.

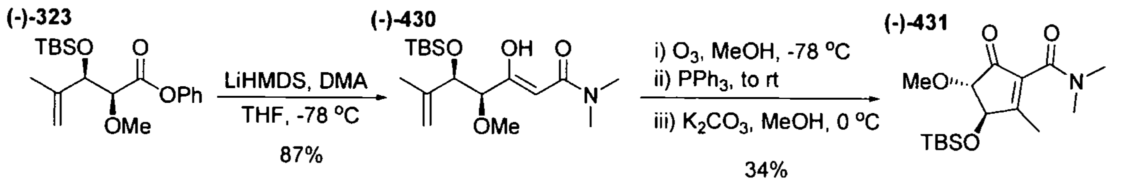
2.13 Direct route to amide-substituted cyclopentenone

In order to further investigate the effect of the amide function on the conjugate addition reaction, a tertiary amide was desired in order to see whether the unusual diastereoselectivity seen for primary amide (+)-**427** owed to the deprotonation of the amide function. In addition, it was hoped that a tertiary amide might prove more amenable to hydrolysis.

Although a double alkylation of the nitrogen atom of (+)-**427** could conceivably have been performed, this would have added further steps to the overall synthesis and in order to avoid this the direct addition of the lithium enolate of DMA to phenol ester (+)-**323** was investigated.

This reaction proved successful with the desired *β*-keto amide being isolated in high yield, however, the ^{1}H NMR spectrum showed the molecule to exist predominantly in the enol form (1:1.8 keto:enol). This was not particularly surprising given the behaviour seen for amides (+)-**428** and (-)-**429**, however, ^{1}H NMR spectroscopy indicated that the enol form remained favoured, albeit to a lesser extent, when DMSO was employed as a solvent (keto:enol, 1:1.1) which was expected prevent the hydrogen bonding stabilising this tautomer. The level of enol tautomer seen caused some concern as ozonolysis could presumably cleave both the intended double bond and that of the enol. Indeed, the ozonolysis of *tert*-butyl ester **(+)-321** which existed as a mixture of tautomers had proved rather problematic whilst that of nitrile **(+)-396**, which existed entirely in the keto form, proceeded relatively smoothly.

Scheme 89: route to dimethylamide **431**



Initial attempts at the ozonolysis of *β*-keto amide **(-)-430** met with even less success than seen for *β*-keto ester **(+)-321**, indeed, using DCM as solvent, no identifiable products were obtained apparently justifying concerns over the level of keto-enol tautomerism. Fortunately, use of the conditions initially developed for *β*-keto ester **(+)-321** proved rather more successful, giving the desired cyclopentenone, albeit in poor yield.

This improvement in yield was at first thought to owe to reducing the level of the enol tautomer by the increase in solvent polarity, however, ^{1}H NMR spectroscopy studies showed that the contribution of the enol tautomer was in fact increased by the use of methanol (keto:enol 1:2). In addition, variable temperature NMR spectroscopy studies showed that the temperature had little impact on the keto/enol ratio and that at the reaction temperature this ratio was 1:2.2. This appears to suggest that the improvements seen in the yield of the ozonolysis reactions of both *tert*-butyl ester **(+)-321** and dimethylamide **(-)-430** when using methanol instead of DCM are due to protonation of the carbonyl oxide intermediate rather than to any reduction in the oxidative cleavage of the enol cabon-carbon double bond. Protonation of the carbonyl oxide intermediate has the effect of changing the ozonolysis mechanistic pathway such that cross-ozonides as isolated for nitrile **(+)-396** and observed for esters **(+)-321** and **(+)-323** cannot form. Although the formation of such a cross-ozonide did not prove a major problem for nitrile **(+)-396**, it may be that the presence of a second carbonyl group in substrates **(+)-321** and **(-)-430** leads to the formation of less stable cross-ozonides which decompose to produce the range of products observed.

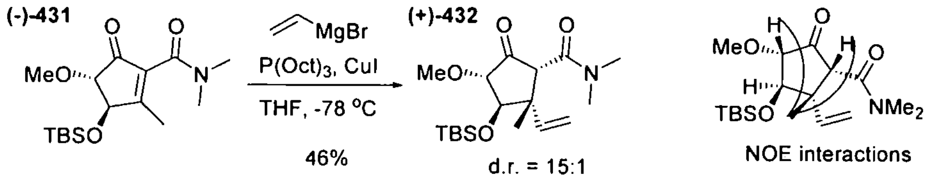
Despite this improvement in yield, the main problem with the use of the above conditions for the ozonolysis/Knoevenagel reaction of *β*-keto amide was a poor mass recovery following the aqueous work-up. With this in mind, the final addition of potassium carbonate was omitted and the solvent evaporated following filtration of the solid-supported triphenylphosphine. ^{1}H NMR spectroscopy showed the resulting material to be almost exclusively the intermediate methyl ketone although the spectrum was again complicated by the keto-enol tautomerisation. Attempts at chromatographic purification of this material led to cyclisation to cyclopentenone, the reaction presumably being mediated by the silica gel as had been observed for both *β*-keto nitrile **(+)-396** and *tert*-butyl ester **(+)-321**. It became apparent that some insoluble material was produced but despite this, the approach led to an increase in yield (40%) of cyclopentenone **(-)-431**.

Unfortunately, attempts to scale up both methods for the ozonolysis/Knoevenagel sequence met with limited success. Although a change in the work-up procedure for the route using potassium carbonate led to an increase in mass recovery, scaling up led to increasing amounts of material being lost during chromatography whilst for the second approach, on an increased scale it proved difficult to achieve complete cyclisation. Despite this, two reactions of cyclopentenone **(-)-431** were investigated: the conjugate addition of a vinyl group and the reduction of the amide function to an aldehyde.

The reduction of amide **(-)-431** using Schwartz' reagent proved unsuccessful with only starting material being recovered. This may reflect the increased steric bulk as compared with unsubstituted amide **(+)-427** and indeed it has been noted that hindered substrates are challenging substrates for this reaction.[457]

The conjugate addition to cyclopentenone **(-)-431** proved successful, albeit in low yield. It was clear from the crude ^{1}H NMR spectrum that two diastereoisomers were formed in similar amounts, however, only one of these two diastereoisomers (**(+)-432**) was isolated following silica gel chromatography as one diastereoisomer converted to the other during this process. This epimerisation demonstrates that the two diastereoisomers were epimers at the α-position and it is interesting to note that the geometry of this centre was opposite to that found for nitrile **(+)-411**. The level of diastereoselectivity observed at the forming quaternary centre was the most impressive of all the examples in this project with the minor diastereoisomer being almost undetectable. The stereochemistry of this molecule was assigned based on interactions in its ^{1}H NOESY spectrum from the known stereochemistries of the CHOMe and CHOTBS centres. The stereochemistry of the CMe(CHCH$_2$) centre was assigned from the cross-ring interaction between C*H*OMe and C*Me*(CHCH$_2$) and that of the CHCONMe$_2$ centre was assigned from the interaction between C*Me*(CHCH$_2$) and C*H*CONMe$_2$.

Equation 76



It was most surprising that in contrast to primary amides **(+)-428** and **(-)-429**, no evidence of the enol tautomer was detectable by NMR spectroscopy. This may owe to the increased steric bulk on the nitrogen atom disfavouring the hydrogen bonding required to stabilise this tautomer.

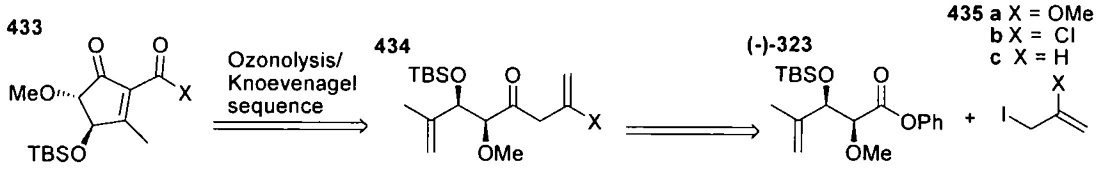
In contrast with amide **(+)-427**, the stereochemistry obtained at the forming quaternary centre was that desired for viridenomycin with the nucleophile being delivered form the opposite face to the OTBS group. This difference in selectivity suggests that the stereoselectivity observed for primary amide **(+)-427** owes in some way to the deprotonation of one of the amide protons.

Unfortunately, because of the low yields of the ozonolysis and conjugate addition steps in this series, further investigation of this system was not undertaken.

2.14 Other methods for masking the carboxylic acid group of 393

Due the inability to achieve the hydrolysis of the nitrile group of cyclopentanone (+)-**411** and with the other methods of protecting the required carboxylic acid moiety proving less than successful it was investigated whether this group could be masked in some other way. It was decided to attempt to unmask this function without introducing another step by using the ozonolysis step, which already unmasked the ketone function, to also reveal the carbonyl group of the carboxylic acid (Scheme 90).

Scheme 90: retrosynthetic approach involving an oxidative unmasking of the acid function



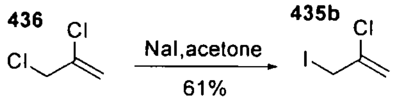
Although use of a vinyl ether (**435a**) seemed to meet these requirements, a search of the literature revealed few reports of such compounds and their syntheses appeared troublesome.[458] For this reason, the use of vinyl chloride **435b** was chosen as this maintained the oxidation state whilst removing the problematic vinyl ether function. In addition, this approach was expected to produce the acid chloride upon ozonolysis which could be converted to the desired ester by performing the ozonolysis reaction in an alcoholic solvent. Several reports of the synthesis of vinyl chloride **435b** appeared in the literature, however, the compound had always been used as an electrophile[459] and metal halogen exchange on such a compound might be expected to be troublesome owing both to the strongly electrophilic nature of the starting material and in terms of achieving selective exchange of the iodide.

At the same time it was decided to introduce an allyl group to phenyl ester (-)-**323** such that the ozonolysis would unmask aldehyde **433c**. This approach was felt to avoid the issues described above however, one possible issue with this approach was felt to be the problem of effecting an intramolecular Knoevenagel reaction on a methyl ketone in the presence of an aldehyde which could undergo intermolecular aldol reactions. Another issue was seen to be that if the Knoevenagel reaction proved successful, problems might arise in achieving selective conjugate addition in the presence of such a reactive group.

Another issue regarding the use of both routes discussed above was the introduction of a second carbonyl oxide function into the molecule following the ozonolysis reaction. Given that one such function had proven capable of reacting with the ketone function to an appreciable extent, the introduction of a second such function caused some concern.

Iodide **435b** was synthesised from the commercially available chloride **436** using a literature procedure.[459] Given that there were no reports of metal-iodine exchange in this compound, a number of conditions were investigated and phenyl acetate used as an electrophile in order to avoid wasting phenyl ester **(-)-323**.

Equation 77

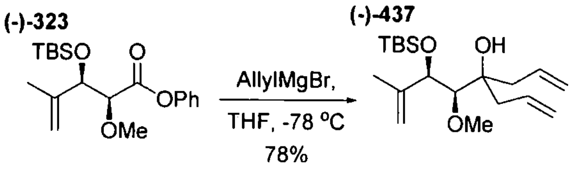


Use of *n*- and *sec*- butyllithium was avoided as both compounds might be expected to perform nucleophilic substitution reactions faster than the desired metal-halogen exchange. Use of *tert*-butyllithium was investigated and although complete consumption of iodide **435b** was observed, none of the expected product was obtained.

Zinc-iodine exchange was investigated as the competing exchange with the chloride was expected to be slow, however, although the metal-halogen exchange appeared to proceed smoothly, it did not prove possible to perform a nucleophilic displacement on phenyl acetate.

Introduction of an allyl rather than a 2-chloro-allyl group was expected to be rather more facile and use of allylmagnesium bromide was investigated. Unfortunately, when a single equivalent of the Grignard reagent was employed, the only species recovered from the reaction (Equation 78) were phenol, phenyl ester **(-)-323** and double addition product **(-)-437** which was subsequently isolated in good yield through the use of an excess of the Grignard reagent.

Equation 78



Ultimately it did not prove possible to stop the addition at the intermediate allyl ketone as this species proved to be rather more reactive than the starting material to nucleophilic attack. This fact led to this approach being abandoned.

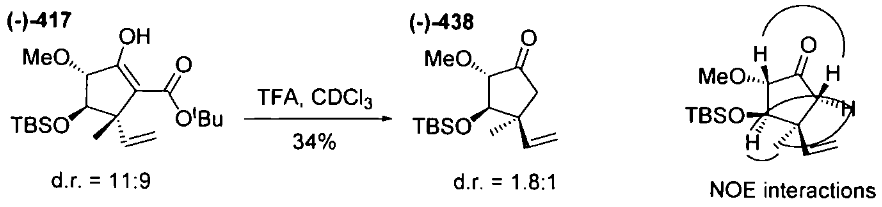
2.15 Return to *tert*-butyl cyclopentenone 324

Having apparently exhausted all methods for achieving the required hydrolysis of the nitrile function of **(+)-411** and with other methods for masking the carboxylic acid group proving unsuccessful, attention was returned to the previously abandoned system **(+)-324**.

Although the conjugate addition of a vinyl group to this substrate had proved successful (*vide supra*), the diastereoselectivity had been poor with almost no selectivity for the desired diastereoisomer. Despite this, it was attempted to perform the de-*tert*-butylation of this substrate in the hope that the two isomers could be separated at a later stage.

This met with limited success; although the de-*tert*-butylation reaction proceeded readily at room temperature, it was clear that a considerable amount of the decarboxylated product **(-)-438** was being produced. This result did not come as a great surprise as decarboxylation of such substrates is well documented under acid conditions. Although the majority of the material was not decarboxylated, it did not prove possible to isolate the desired acid in clean form although some evidence of it was seen by ^{1}H NMR spectroscopy.

Equation 79



An interesting point regarding the decarboxylation reaction of **(-)-417** is the diastereoselectivity shown (Equation 79); starting from a 11:9 mixture of diastereoisomers, it can be seen that the product **(-)-438** is produced with a diastereomeric ratio of 1.8:1 in favour of the *opposite* diastereoisomer. The stereochemistry of this molecule was assigned based on interactions in its ^{1}H NOESY spectrum from the known stereochemistries of the CHOMe and CHOTBS centres. The two signals of the CH_2 group were assigned from their interactions with the C*H*OMe and C*H*OTBS protons. The stereochemistry of the C*Me*($CHCH_2$) centre was assigned from the interactions between C*Me*($CHCH_2$) and both C*H*OTBS and a single proton of the CH_2 group.

Since decarboxylation is known to proceed through a cyclic transition state with assistance from the *β*-keto group,[460] this result perhaps reflects some difference in conformation between the two diastereoisomers. It is also possible that this difference in stability to decarboxylation explains the observed stereochemistry in viridenomycin.

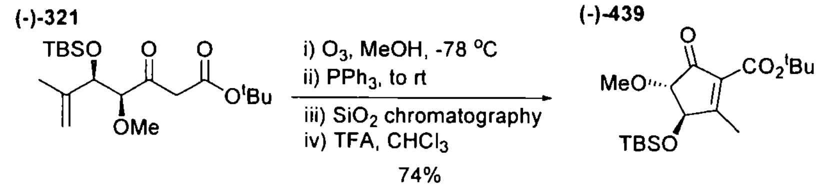
Although reduction of both the reaction time and acid loading proved somewhat effective in reducing the level of decarboxylation, it did not prove possible to isolate the desired acid in a clean form. This problem appeared to be due to a combination of the high polarity of the substrate and some level of sensitivity of the material to silica gel.

2.15.1 Conjugate addition to the free carboxylic acid (-)-439

Given that conjugate additions to carboxylic acids have been reported,[461] this approach was explored. De-*tert*-butylation of cyclopentenone **(-)-324** proved successful using TFA, however, the poor yield of the starting material made this route less desireable.

As noted earlier, eliminating the potassium carbonate cyclisation step following the ozonolyis of *β*-keto ester **(-)-321** led to a marked increase in the mass of the material recovered at the expense of the appearance of an unidentified impurity. Gratifyingly, it was found that treating this material with TFA provided the desired acid **(-)-439** in high overall yield as the impurity could be removed during this sequence of reactions.

Equation 80



Conjugate addition to acid **(-)-439** substrate without protection of the acid group did not prove successful; although all of the starting material was consumed no material was recovered following silica gel chromatography.

Temporary protection of the carboxylic acid group of **(-)-439** was attempted using a method used for singly activated systems;[462] formation of the TMS carboxylate. Hence, following deprotonation of the acid function using sodium hydride, TMSCl was added and the resulting solution added to a solution of the cuprate.

Again, all starting material **(-)-439** was seen to be consumed and in this case a small amount of material was isolated following silica gel chromatography. Unfortunately, although some of this material resembled the expected acid, it was again seen to be contaminated by a number of impurities. This behaviour appears to suggest that the TMS protection of the acid function was at least partly successful, however, it may be that the presence of TMSCl or sodium chloride interfered in some way with the order of the organocuprate as the reaction behaved rather differently to previous reactions upon work up. Whether this effect is responsible for the poor mass recovery and level of impurity observed or whether this owes to the sensitivity of the product is unclear.

2.16 Conjugate additions to 3-methyl cyclopentenones

The difference in the reactivities of the various cyclopentenones synthesised in this project merits some discussion. In most cases (e.g. **(+)-395** and **(-)-431**) the desired diastereoisomer was obtained, however, the selectivity was rather variable and in one instance (i.e. **(+)-427**), the opposite diastereoisomer was the major product.

Studies have shown that the diastereoselectivity of the addition to substituted cyclopentenones is dependent on a number of factors and in particular, nucleophiles are often added *trans* to the 5-substituent.[363] Given that in the current project the 4-substituent (OTBS) and 5-substituent (OMe) appear to direct to opposite faces, it appears that the variable selectivity may owe to these competing effect with perhaps subtle conformational effects determining which substituent effect dominates for each substrate. In any case, it is fortunate that in two cases, high selectivity was obtained for the desired diastereoisomer.

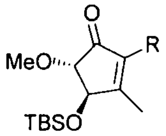
The variation in yield obtained from these conjugate addition reactions (Table 11) is also interesting, particularly in relation to the ^{13}C NMR spectroscopy data. ^{13}C NMR spectroscopy data has been used in the past as a measure of the electron density on a substrate with a greater chemical shift showing decreased electron density around that particular atom.[463] Hence, the polarisation of a chemical bond could be inferred from the difference in the shifts of the two atoms. In this case, the variation shown in the ^{13}C NMR peaks of the olefin carbons drew some attention.

As can be seen in Table 11, the polarisation across the double bonds varies considerably between the substrates. The most notable observation is that whilst nitrile **(+)-395** and primary amide **(+)-427** show a large degree of polarisation, *tert*-butyl ester **(+)-324** and tertiary amide **(-)-431** show considerably less. Such high polarisation might be expected for **(+)-395** given the electon-withdrawing nature of nitrile, however, the high polarisation of primary amide **(+)-427** is intriguing. Although differences in double bond polarisation might be expected to be determined purely by electronics, the greater polarisation of primary amide **(+)-427** compared with that of *tert*-butyl ester **(+)-324** demonstrates that another factor must be involved. It therefore seem likely that steric effects have some impact on the bond polarisation, presumably by dictating the orientation of the *exo*-

carbonyl group thus changing its level of conjugation to the alkene. Hence, when the substituent is small (Entries 2, 3 and 5), there is little steric hinderance to achieving good conjugation with the olefin π-system and the double bond is strongly polarised. For bulky substituents, (Entries 1 and 4), steric interactions might be expected to force some degree of rotation of the substituent group such that conjugation to the olefin is reduced, resulting in a less polarised double bond.

Table 11: NMR data for 3-methyl cyclopentenones

Entry	Substrate/R	δ_C (α)/ppm	δ_C (β)/ppm	$\Delta\delta_C$ /ppm	Yield /%
1	**324**, $CO_2{}^tBu$	132	176	44	54
2	**395**, CN	116	184	68	81
3	**427**, $CONH_2$	129	183	54	58
4	**431**, $CONMe_2$	137	172	35	46
5	**439**, CO_2H	126	188	62	-



It is interesting to note that the yields obtained in the conjugate addition of a vinyl group to these molecules correlates well with the measured polarisation of the double bond. The exception to this is acid **(-)-439**, however, it seems likely that this owes more to a difficulty in isolating the product than to a lack of reactivity.

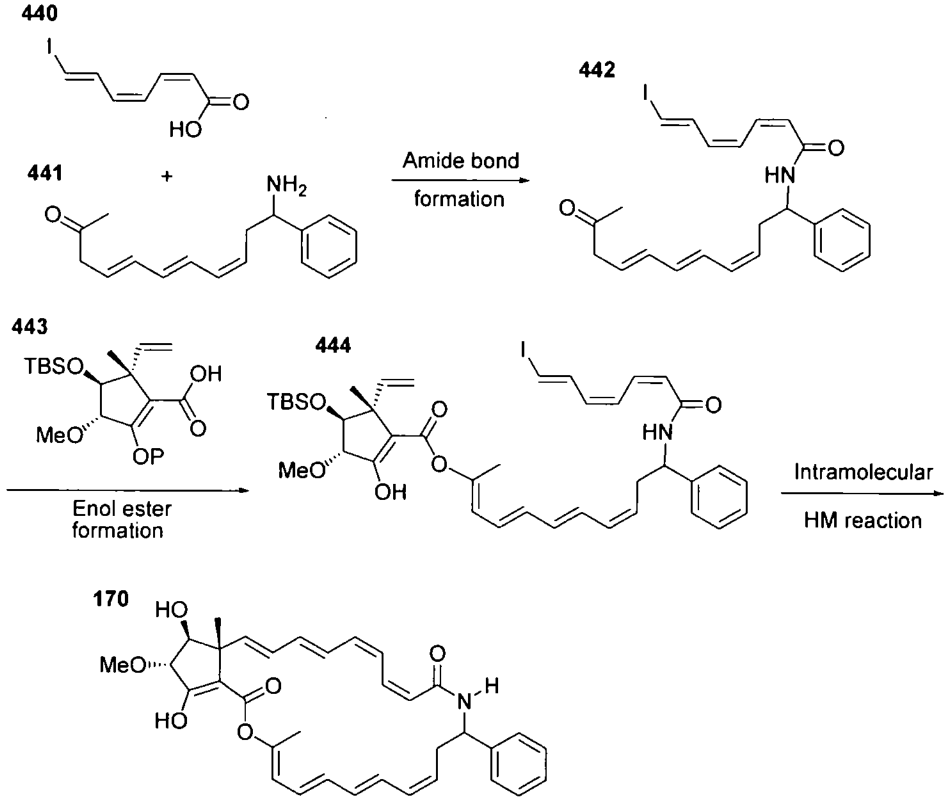
This correlation between NMR spectroscopy data and reactivity may prove useful in predicting the reactivity of other cyclopentenones to conjugate addition, at least under these conditions.

2.17 Assembly of the major fragments

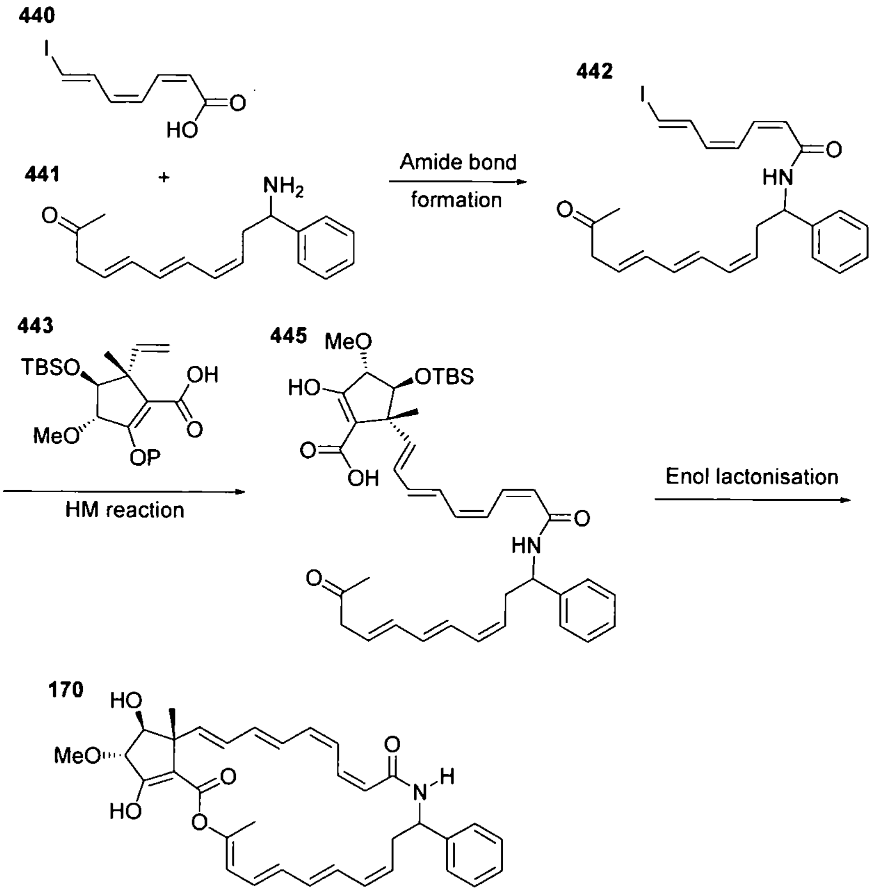
2.17.1 Order of assembly

With one of the desired fragments assembled and another apparently close to being finished, some thought was given to the final assembly to viridenomycin. Clearly, the order of the three couplings would be critical to maximise both yields and the stability of the product in subsequent steps and two plausible routes are shown in Schemes 90 and 91.

Scheme 90: construction of viridenomycin involving a final HM reaction



Scheme 91: construction of viridenomycin involving a final enol lactonisation

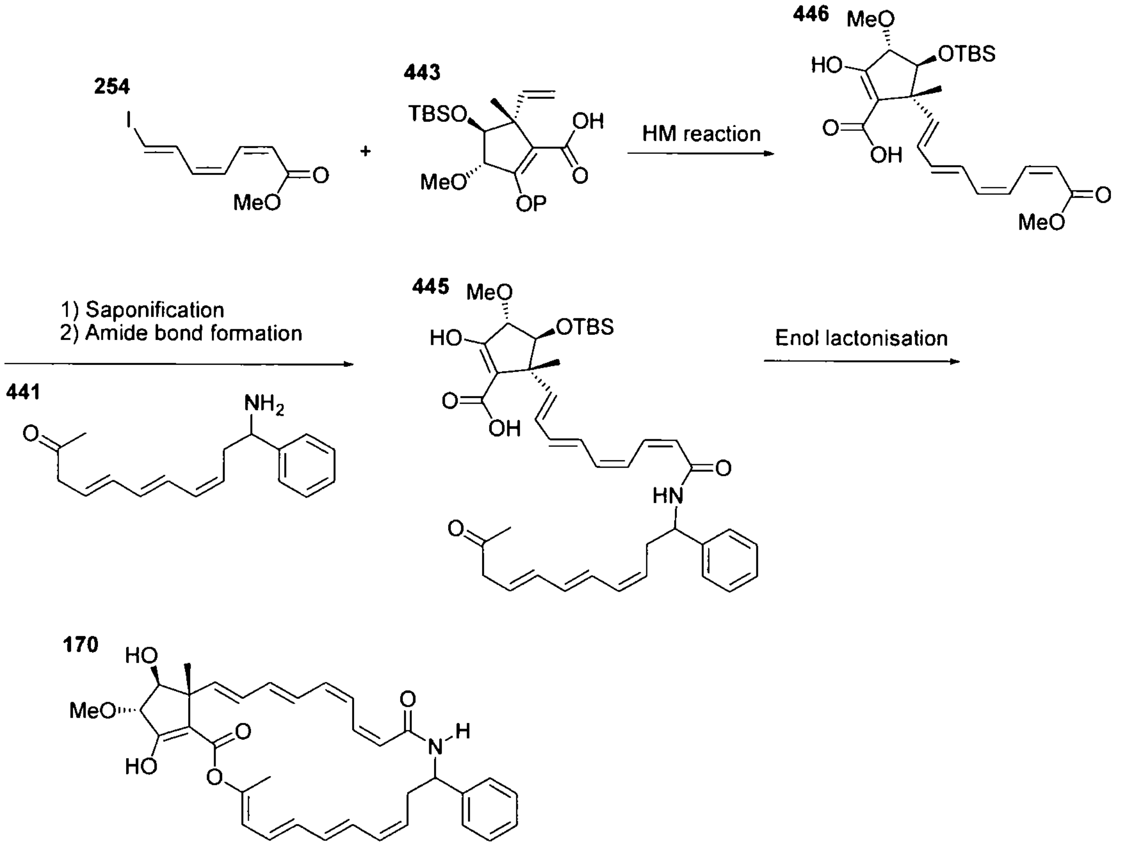


Both routes have a number of advantages and disadvantages, the merits of which would have to be determined following examination of the stability and reactivity of the intermediates. The route shown in Scheme 90 with a final HM reaction has the advantages that such a HM reaction is likely to be favoured by making the reaction intramolecular which might be expected to improve on the yields seen previously in similar reactions. In addition, this route avoids performing an intramolecular enol ester formation which might be expected to simplify the reaction by allowing the separate generation of the required active ester and enolate. In contrast, the route shown in Scheme 91 with a final enol lactonisation reaction has the advantage that the presumably unstable enol lactone **444** is exposed to the minimum of further reactions.

A third possibility, shown in Scheme 92, with an initial HM reaction could also be conceived but has the additional disadvantage that the saponification of **446** the must be performed on the relatively unstable cyclopentanone core together with the required triene.

Another disadvantage of this approach is that a regioselective amide bond formation would have to be achieved because of the presence of the two carboxylic acid functions following saponification of **446**.

Scheme 92: construction of viridenomycin involving an initial HM reaction



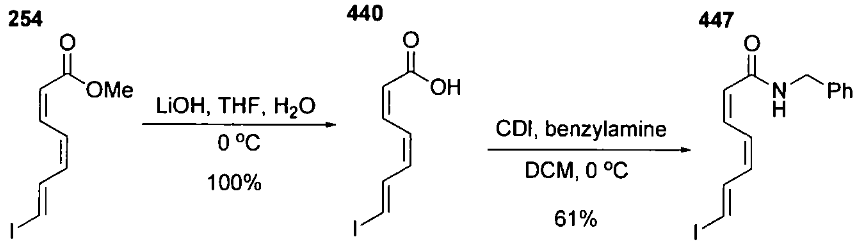
After some consideration, the route outlined in Scheme 90 was decided upon as being the most promising and some work was undertaken to develop conditions for this approach.

2.17.2 Amide coupling of the northern hemisphere

With this in mind, saponification of methyl ester **254** was investigated. There was some considerable concern over the stability of this system to the conditions required, particularly with regard to isomeric purity, however, it was found that the reaction could be performed at 0 °C to provide the desired isomer **440** in quantitative yield. Gratifyingly, the isomeric purity was little changed from that seen for the starting methyl ester.

In the absence of the desired amine coupling partner, a test reaction using benzylamine was performed in order to test the viability of acid **440** in such reactions. Under conditions found to be successful within the group,[464] the desired amide **447** was formed in good yield. Although some isomerisation occurred at the start of the reaction, it was found that the other isomer produced could be separated by chromatography allowing the product to be isolated in high isomeric purity.

Scheme 93: developed conditions for amide coupling of triene fragment



It was hoped that by reducing the electron-deficiency of the triene by replacing the ester function with an amide, the stability of the species would be increased since more electron-rich systems had previously been seen to be more stable than diene **245** and triene **254**. Unfortunately, this was not found to be the case and in fact the stability of amide **447** to UV light was found to be markedly less than either methyl ester **254** or acid **440**. For acid **440**, after standing in fluorescent light for 4 hr only 30% of the starting material was consumed to another isomer, complete consumption occurring within 24 hr, whilst for methyl ester **254**, complete consumption required several days. In contrast, amide **447** was completely converted to a number of isomers in only 80 minutes. This behaviour did not provide much optimism for the assembly of viridenomycin as intermediate **442** might be expected to show a similar level of stability.

Despite this lack of stability, it was clear that suitable conditions had been found for coupling acid **440** with a model amine.

2.17.3 HM coupling of the northern hemisphere

Initial results for this reaction were not promising and indeed, a successful HM reaction between the vinyl function of the cyclopentanone system (+)-**411** and methyl ester **254** has yet to be achieved.

Given the high yields in the nitrile series, all work focussed on the use of nitrile (+)-**411** and its protected derivatives as models required cyclopentanone fragment, however, couplings with triene **254** and acrylate **229** met with failure. This may reflect an increased amount of steric hinderance on moving from the model compound vinylcyclohexane to nitrile (+)-**411** with the methyl group of the quaternary centre disfavouring the carbometallation step. Another possibility is that the nitrile function of (+)-**411** functions as a ligand for palladium and that this in some way disfavours the reaction, in which case the problem will resolve itself when the corresponding acid or ester is synthesised.

2.18 Concluding remarks

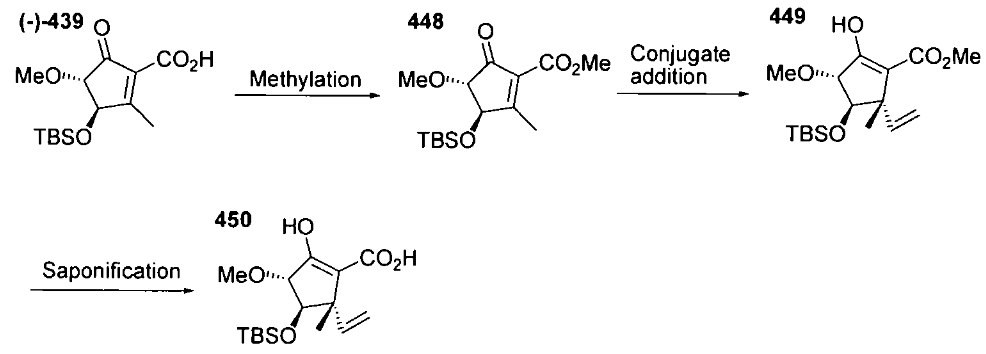
As previous synthetic efforts have shown, viridenomycin remains a challenging synthetic target and further work will be required in order to achieve this goal. However, there is reason to be optimistic with one fragment synthesised and another apparently close to being finished. Indeed, two issues of considerable concern have been overcome in this project with the HM reaction of iodoacrylate **229** and the success at the diastereoselective conjugate addition reaction. Assuming a route to the southern hemisphere can be found, and given the greater stability of this system compared with the northern fragment there is no obvious reason why it could not, the main challenge is likely to be the assembly of the three fragments.

It is interesting that the northern hemisphere, which was expected to be the most challenging fragment, proved to be considerably more simple to synthesise than the cyclopentanone core which has continued to show unusual reactivity throughout this project. The instability and facile epimerisation of some of the cyclopentanone systems made in this project perhaps provides another reason for the observed instability of viridenomycin.

2.19 Future work

The two obvious areas in need of further work are the southern fragment **205** and the unmasking of the acid function of the cyclopentanone core. Assuming that hydrolysis of the nitrile function is not achieved, the most sensible way to proceed appears to be using the *tert*-butyl system **(-)-321** to access the cyclopentenone carboxylic acid **(-)-439**. Methylation of this substrate should allow a conjugate addition to be performed (Scheme 94), hopefully with better diastereoselectivity than observed for *tert*-butyl analogue **(+)-324**. Although this provides a slightly indirect route to the desired system it has the advantages that the overall yield to acid **(-)-439** is high, it relies on the conjugate addition methodology which has proved successful for most of the cyclopentenones synthesised and that the final saponification of the methyl ester is likely to allow more easy isolation of the free acid than the conditions used for *tert*-butyl ester **(-)-384**.

Scheme 94: plan for future work on the cyclopentanone core



With regard to the final assembly, given the great instability seen for amide **447** it seems wise to attach this fragment at as late a stage as possible. Hence, as seen from the present perspective, the logical route of assembly involves initial enol lactonisation between fragments **441** and **443** followed by the required amide bond formation and HM reactions in whichever order proves most convenient. Given the problems encountered in achieving the HM reaction of the vinyl group of **(+)-411**, it may be that leaving this reaction until last may promote it somewhat by means of making it an intramolecular reaction.

In the event of the HM reaction of this vinyl group proving impossible, it may be that conjugate addition of a dienyl function could be performed as a route to dienyl lithium is present in the literature.[465] In this way, steric hinderance would be less likely to disfavour the HM reaction, in this case with dienyl iodide **245**.

In any event, it seems sure that the final assembly is likely to be as challenging as the routes to the syntheses of the fragments.

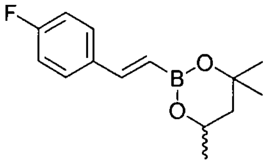
3 Experimental section

3.1 General experimental procedures

All ^1H NMR spectra were recorded on either Varian Mercury-400, Varian-Mercury 500 or Varian VNMRS 700 MHz spectrometers. ^{13}C NMR spectra were recorded on Varian Mercury-400, Varian Mercury-500 or Varian VNMRS 700 instruments at frequencies of 101, 126 or 176 MHz. ^{11}B NMR spectra were recorded on a Bruker Avance-400 instrument at a frequency of 128 MHz. Chemical shifts are expressed as parts per million downfield from the internal standard TMS except in ^{11}B NMR spectroscopy where shifts are expressed as parts per million downfield shift from external $BF_3.OEt_2$. GC-MS analysis was carried out on an Agilent 6890N GC equipped with a 5973N MSD Performance Turbo CI running in EI mode, and an Anatune Focus Autosampler/liquid handler. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. UV-Vis spectra were recorded on a Unicam UV2 spectrometer. Column chromatography was performed on Davisil Silica gel, 60 mesh. TLC was performed on Polygram SIL G/UV254 plastic backed silica gel plates with visualization achieved using a UV lamp or staining with basic $KMnO_4$. All glassware was oven dried (130 °C) before use and cooled under a positive pressure of argon. Dry solvents were dried by distillation (from CaH_2 for DCM and hydrocarbons or sodium-benzophenone ketyl for THF) or through the use of a commercial drying system. All other reagents were purchased from Acros, Aldrich, Lancaster or Strem and used without further purification unless otherwise stated. Syntheses of stryrylboronates **225a**, **b** and **f**[297] and *β*-keto ester **(+)-321**,[297] and the preparation of *β*-keto ester **330** by the bis-(silyl enol ether) route,[352] were performed using literature procedures. Some assignment of the olefinic peaks in the ^1H NMR spectra are presented here, for a more detailed assignment for all such structures as well as how the assignment was performed see Appendix 3. For operational reasons, both enantiomers of phenyl ester **323** were in use at various stages of the synthesis and consequently both possible configurations are present in the compounds subsequently produced. The measured rotations relate to the structure shown in the specific experimental section, as do the signs associated with the structures in the text, however, it should be noted that for four substrates (**418**, **425**, **427** and **431**) the measured rotations are *opposite* to that expected based on the starting enantiomer of **323**.

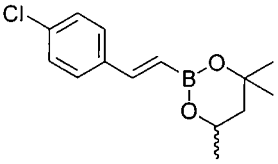
3.2 Specific experimental procedures

2-(4-Fluorostyryl)-4,4,6-trimethyl-1,3,2-dioxaborinane 225d



To a dried Schlenk tube under a positive pressure of argon was added Pd(OAc)$_2$ (19 mg, 0.085 mmol), tri(2-furyl)phosphine (58 mg, 0.25 mmol), 4-iodo-fluorobenzene **223d** (0.184 cm^3, 1.6 mmol), tributylamine (0.46 mL, 1.9 mmol) and vinylboronate **222** (300 mg, 1.95 mmol). Syringe addition of toluene (20 mL) was followed by degassing using the freeze-pump-thaw method (3 ×) and the stirred mixture was heated to 110 °C. After 24 hr the reaction mixture was cooled, diluted with Et$_2$O (80 mL) and passed through Celite before washing with 10% HCl (40 mL), water (40 mL) and saturated aqueous sodium chloride (40 mL). Drying (MgSO$_4$) and solvent removal provided the crude product as a red/brown oil which was purified by silica gel chromatography (hexane:Et$_2$O, 96:4 as eluent) to afford the title compound as a pale yellow oil (210 mg, 53 %). ν_{max} /cm^{-1} (film): 1625, 1599, 1505, 1389, 1304, 1269, 1205, 1156 and 1093; δ_H (400 MHz, CDCl$_3$) 1.31 (d, *J* 6.0, 3H, -CH$_3$), 1.34 (d, *J* 3.0, 6H, 2x-CH$_3$), 1.57 (t, *J* 6.0, 1H, -CH), 1.83 (dd, *J* 13.8 and 3.2, 1H, -CH), 4.22-4.32 (m, 1H, -OCH), 6.07 (dd, *J* 18.2 and 0.8, 1H, =CH-) 6.96-7.15 (m, 2H, Ph), 7.25 (d, *J* 18.4, 1H, =CH-), 7.41-7.44 (m, 2H, Ph). δ_C (101 MHz, CDCl$_3$) 23.3 (CH*Me*), 28.3 (C*Me*$_2$), 31.4 (C*Me*$_2$), 46.1 (*C*H$_2$), 65.0 (*C*HMe), 71.1 (s, *C*Me$_2$), 115.6 (d, $J_{C\text{-}F}$ 22, Ph), 128.7 (d, $J_{C\text{-}F}$ 7.9, Ph), 134.3 (d, $J_{C\text{-}F}$ 3.4, Ph), 145.3(=*C*-), 161.7, 164.2; δ_F (376 MHz, CDCl$_3$) -113.9 (m); δ_B (128 MHz, CDCl$_3$) 26.4 (br). *m/z* (EI) 247.1413 ($C_{14}H_{18}BO_2F^+$, M$^+$, requires 247.1415), 233 (M$^+$-CH$_3$), 148 (100 %). λ_{max} /nm (CHCl$_3$): 203 (ε = 6000), 228 (ε = 6030), 264 (ε = 8810).

2-(4-Chlorostyryl)-4,4,6-trimethyl-1,3,2-dioxaborinane 225e



To a dried Schlenk tube under a positive pressure of argon was added Pd(OAc)$_2$ (19 mg, 0.085 mmol), triphenylphosphine (63 mg, 0.24 mmol), 4-iodo-chlorobenzene **223e** (390 mg, 1.64 mmol) and AgOAc (308 mg, 1.85 mmol). Syringe addition of toluene (20 mL), tributylamine (0.46 mL, 1.9 mmol) and vinylboronate **222** (300 mg, 1.95 mmol) was followed by degassing using the freeze-pump-thaw method (3 ×) and the stirred mixture was heated to 110 °C. After 24 hr the reaction mixture was cooled, diluted with Et_2O (80 mL) and passed through Celite before washing with 10% HCl (40 mL), water (40 mL) and saturated aqueous sodium chloride (40 mL). Drying ($MgSO_4$) and solvent removal provided the crude product as a yellow oil which was purified by silica gel chromatography (hexane:Et_2O, 96:4 as eluent) to afford the title compound as a clear oil. Yield: 376 mg (87 %). ν_{max}/ cm^{-1} (film) 1623, 1490, 1391, 1303, 1270, 1206, 1160 and 1090; δ_H (400 MHz, $CDCl_3$) 1.31 (d, J = 6.0 Hz, 3H, -CH_3), 1.34 (d, J = 2.0 Hz, 6H, 2x-CH_3), 1.56 (t, J = 6.0 Hz, 1H, -CH), 1.83 (dd, J = 13.8 and 3.2 Hz, 1H, -CH), 4.22-4.32 (m, 1H, -OCH), 6.07 (d, J = 18.0 Hz, 1H, =CH-) 7.20-7.30 (m, 3H), 7.40 (d, J = 8.4 Hz, 2H, Ph); δ_C (101 MHz, $CDCl_3$) 23.3 (CH*Me*), 28.3 (C*Me*$_2$), 31.4 (C*Me*$_2$), 46.1 (*C*H_2), 65.1 (*C*HMe), 71.1 (*C*Me_2), 128.3 (Ph), 128.8 (Ph), 134.1 (Ph), 136.6 (Ph), 145.2 (=*C*-); δ_B (128 MHz, $CDCl_3$) 26.8; *m/z* (EI) 264.1084 (M^+, $C_{14}H_{18}BO_2Cl^+$ requires 264.1083), 266 (^{37}Cl M^+), 251 (^{37}Cl M^+-CH_3), 249 (^{35}Cl M^+-CH_3) and 164 (^{35}Cl M^+-$C_6H_{12}O$); λ_{max} /nm ($CHCl_3$): 216 (ε = 7990), 232 (ε = 6380), 272 (ε = 15700).

General procedure; triphenylphosphine catalysis

To a dried Schlenk tube under a positive pressure of argon was added palladium(II) acetate (9 mg, 0.04 mmol), triphenylphosphine (31.5 mg, 0.12 mmol), hexamethylbenzene (48 mg, 0.30 mmol), aryl iodide **223** (0.80 mmol), tributylamine (0.23 mL, 0.96 mmol) and vinylboronate **222** (0.12 mL, 0.72 mmol). Syringe addition of toluene (10 mL) was followed by degassing using the freeze-pump-thaw method (3×) and the stirred mixture was heated to 100 °C. The progress of the reaction was followed over a period of 5 hr by the removal of an aliquot of the reaction mixture using a dry, argon flushed syringe. Of this aliquot, 200 μL were diluted with toluene (800 μL) and the resulting solution analyzed by GC-MS. Manual integration of the product peak areas relative to hexamethylbenzene internal standard allowed the calculation of product concentration using predetermined response factors. The rate constants for each data set were obtained by multiplying the gradient of each graph by a factor of five to account for the five-fold dilution.

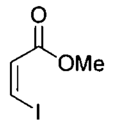
General procedure; tri(2-furyl)phosphine catalysis

To a dried Schlenk-type tube under a positive pressure of argon was added palladium(II) acetate (9.5 mg, 0.042 mmol), tri(2-furyl)phosphine (29 mg, 0.13 mmol), hexamethylbenzene (48mg, 0.30mmol), aryl iodide **223** (0.80mmol), tributylamine (0.23 mL, 0.96 mmol). Syringe addition of toluene (10 mL) and vinylboronate **222** (170 mg, 1.1 mmol) was followed by degassing using the freeze-pump-thaw method (3×) and the stirred mixture was heated to 110 °C. The progress of the reaction was followed over a period of 8 hr by the removal of an aliquot of the reaction mixture using a dry, argon flushed syringe. Of this aliquot, 200 μL were diluted with toluene (800 μL) and the resulting solution run on GC-MS.

General procedure; tris(4-methoxyphenyl)phosphine catalysis

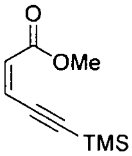
To a dried Schlenk tube under a positive pressure of argon was added palladium(II) acetate (9 mg, 0.04 mmol), tris(4-methoxyphenyl)phosphine (27.5 mg, 0.078 mmol), tributylamine (0.23 mL, 0.96 mmol), hexamethylbenzene (49 mg, 0.30 mmol) and aryl iodide **223** (0.82 mmol). Syringe addition of toluene (10 mL) and vinylboronate **222** (0.13 mL, 0.78 mmol) was followed by degassing using the freeze-pump-thaw method (3×) and the stirred mixture was heated to 110 °C. The progress of the reaction was followed by the removal of an aliquot of the reaction mixture using a dry, argon flushed syringe. Of this aliquot, 200 μL were diluted with toluene (800 μL) and the resulting solution analyzed by GC-MS. Manual integration of the product peak areas relative to hexamethylbenzene internal standard allowed the calculation of product concentration using predetermined response factors. The rate constants for each data set were obtained by multiplying the gradient of each graph by a factor of five to account for the five-fold dilution.

(Z)-methyl 3-iodoacrylate 229



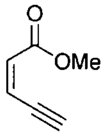
A stirred solution of methyl propiolate (5.3 mL, 59.6 mmol) and sodium iodide (14.4 g, 96 mmol) in acetic acid (22 mL) under argon was heated to 115°C. After 1 hr the hot mixture was poured onto water (100 mL), extracted with Et_2O (3 × 100 mL), washed with sat. aq. $NaHCO_3$ (4 × 50 mL), sat. aq. sodium metabisulphate (50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated to give the title compound as a yellow oil (12.49 g, 99 %). All spectral properties were identical to those reported.[352]

(Z)-methyl 5-(trimethylsilyl)pent-2-en-4-ynoate 236



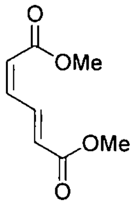
To a dried Schlenk tube under a positive pressure of argon was added acetic acid (0.135 ml, 2.36 mmol), methyl propiolate (0.168 mL, 1.89 mmol), anhydrous MeCN (2 mL) and lithium bromide (208 mg, 2.40 mmol), the mixture degassed using the freeze-pump-thaw method (3 ×) and heated to 85 °C. After 23 hr the mixture was cooled, triethylamine (8 mL) and TMS acetylene (0.30 mL, 2.1 mmol) added, the mixture degassed using the freeze-pump-thaw method (3 ×), palladium(II) acetate (9 mg, 0.040 mmol), triphenylphosphine (21 mg, 0.080 mmol) and copper(I) iodide (15.5 mg, 0.81 mmol) added, the mixture degassed using the freeze-pump-thaw method (3 ×) and stirred at room temperature under argon. After 5.5 hr the mixture was diluted with Et_2O (60 mL), passed through Celite, washed with water (2 × 10 mL), 3% HCl (10 mL) and brine (10 mL), dried ($MgSO_4$), concentrated and purified by silica gel chromatography (EtOAc: petroleum ether, 5:95 as eluent) to give the title compound (255 mg, 74 %) as a yellow oil. All spectral properties were identical to those reported in the literature.[291]

(Z)-methyl pent-2-en-4-ynoate 237



TBAF.3H_2O (100 mg, 0.32 mmol) was added to a stirred solution of eneyne **236** (230 mg, 1.26 mmol) in THF/Et_2O (4:1, 5 mL) and after 5 min the mixture diluted with Et_2O (5 mL) and water (5 mL). The mixture was separated, re-extracted with Et_2O (2 × 5 mL) and the combined organic phase dried ($MgSO_4$) and evaporated. Purification by silica gel chromatography (EtOAc: pet. ether, 5:95 as eluent) gave the title compound (10 mg, 7 %) as a yellow oil. All spectral properties were identical to those reported.[292b]

(2Z,4E)-dimethyl hexa-2,4-dienedioate 238



Aqueous base method.

To a dried Schlenk tube under a positive pressure of argon was added palladium(II) acetate (9 mg, 0.040 mmol), triphenylphosphine (22 mg, 0.084 mmol) and THF (1 mL), the mixture stirred for 2 min, Na_2CO_3 (300 mg, 2.8 mmol), water (1 mL), THF (8 mL) and *cis*-iodoacrylate **229** (0.090 mL, 0.81 mmol) added, the mixture degassed using the freeze-pump-thaw method (3 ×) and heated to 70 °C. After 70 hr the mixture was cooled, diluted with EtOAc (100 mL) and water (20 mL), passed through Celite, washed with sat. aq. sodium thiosulphate (30 mL), 5% HCl (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated to give crude product as a brown oil. Purification by silica gel chromatography (EtOAc: petroleum ether 1:19 then 1:9 as eluent) gave the title compound (20.4 mg, 30 %) as a white solid. Mpt 72.4-73.2 °C (lit.[205] 72-73 °C). All spectral properties were identical to those reported in the literature.[205] *m/z* (ES^+) 171.0653 ($C_8H_{11}O_4^+$, $M+H^+$, requires 171.0652), EI^+ 170, 155, 139, 123 and 111 (100 %)

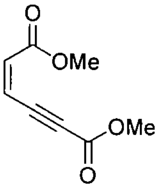
Proton Sponge method.

To a dried Schlenk tube under a positive pressure of argon was added **229** (267 mg, 1.25 mmol) and dry MeCN (7 mL), the mixture degassed using the freeze-pump-thaw method (1 ×), palladium(II) acetate (27.5 mg, 0.12 mmol), Proton Sponge (650 mg, 3 mmol) and silver(I) acetate (500 mg, 3 mmol) added, the mixture further degassed using the freeze-pump-thaw method (2 ×) and heated to 50 °C under argon. After 20 hr the reaction was cooled, diluted with Et_2O (70 mL), passed through Celite and washed with 5% HCl (30 mL) and brine (30 mL). Drying ($MgSO_4$) gave crude product as a brown solid. Purification by silica gel chromatography (EtOAc: petroleum ether, 1:4 as eluent) gave the title compound (61 mg, 57%). All spectroscopic and analytical properties for *E,E*-,[5] *Z*,-,*Z*[5] and *E,Z*-isomers[1] were identical to those reported.

Copper(I) acetate method.

To a dried Schlenk tube under a positive pressure of argon was added palladium(II) acetate (12 mg, 0.05 mmol), copper(I) acetate (155 mg, 1.3 mmol), silver(I) acetate (200 mg, 1.2 mmol), Proton Sponge (280 mg, 1.3 mmol), dry MeCN (9 mL) and iodide **229** (393 mg, 1.85 mmol), the mixture degassed using the freeze-pump-thaw method (3 ×) and heated to 50 °C with vigorous stirring. After 20 hr the mixture was cooled, diluted with Et_2O (80 mL), passed through Celite and washed with 5% HCl (30 mL) and brine (30 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a brown solid. Purification by silica gel chromatography (EtOAc: pet. ether, 1:19 then 1:9 as eluent) gave: iodide **229** (35 mg, 9 % recovery), *cis,cis* **238** (22 mg, 14 %) as a white solid and a mixture of *cis,trans* and *trans,trans*-**238** (101 mg, 64 %) as a white solid. 78 % combined yield of **238** plus 9% recovery of starting material.

(Z)-dimethyl hex-2-en-4-ynedioate 242



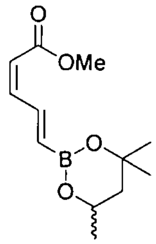
Method 1

To a dried Schlenk tube under a positive pressure of argon was added silver(I) acetate (140 mg, 0.84 mmol), $Pd(OAc)_2$ (9 mg, 0.040 mmol), tri(*o*-tolyl)phosphine (24.5 mg, 0.081 mmol) and dry MeCN (5 mL), the mixture degassed using the freeze-pump-thaw method (2 ×), Proton Sponge® (198 mg, 0.92 mmol), vinylboronate **222** (0.160 mL, 0.95 mmol) and iodide **229** (0.090 mL, 0.80 mmol) added, the mixture degassed using the freeze-pump-thaw method (3 ×) and the stirred mixture heated to 50 °C. After 26 hr the mixture was cooled, diluted with Et_2O (60 mL), passed through Celite, washed with 5% HCl (20 mL), water (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated to give a brown oil. Purification by silica gel chromatography (gradient elution, EtOAc: petroleum ether, 5:95 to 20:80 as eluent) gave boronate **234** (28 mg, 15 %) as a pale yellow oil and the title compound (14 mg, 21 %) as a pale yellow oil; ν_{max} /cm^{-1} (film) 2950 (w, C-H), 2160 (w, C≡C), 1710 (vs, C=O), 1434 (m), 1260 (s), 1220 (s), 1180 (s) and 1070 (m); δ_H ($CDCl_3$, 400 MHz) 3.80 (3H, s, OMe), 3.83 (3H, s, OMe), 6.21 (1H, d, *J* 11.6, CH) and 6.35 (1H, d, *J* 11.6, CH); δ_C ($CDCl_3$, 101 MHz) 52.1 (Me), 53.1 (Me), 81.6 (C≡C), 89.9 (C≡C), 119.9 (C=C), 133.4 (C=C), 153.9 (CO_2Me) and 164.3 (CO_2Me); *m/z* (ES^+) 191.03157 ($C_8H_8O_4Na^+$, $M+Na^+$, requires 191.03148), 171, 130 (100 %) and 121.

Method 2

To a dried Schlenk tube under a positive pressure of argon was added K_2CO_3 (290 mg, 2.1 mmol), palladium(II) acetate (16 mg, 0.071 mmol), triphenylphosphine (38 mg, 0.055 mmol), copper(I) iodide (28 mg, 0.15 mmol) and dry DMF (10 mL), the mixture degassed using the freeze-pump-thaw method (2 ×), methylpropiolate (0.17 mL, 1.9 mmol) and iodoacrylate **229** (348 mg, 1.6 mmol) added, the mixture further degassed (3 ×) and heated to 50 °C under argon. After 5 hr the mixture was cooled, diluted with Et_2O (80 mL), passed through Celite and washed with 5% HCl (20 mL), water (40 mL) and brine (40 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a brown oil. Purification by silica gel chromatography (EtOAc: pet. ether, 1:9 to 1:4 as eluent) gave the title compound (85 mg, 32 %) as a pale yellow oil.

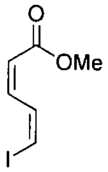
(2Z,4E)-methyl 5-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)penta-2,4-dienoate 234



To a dried Schlenk tube under a positive pressure of argon was added silver(I) acetate (150 mg, 0.90 mmol), palladium(II) acetate (9 mg, 0.04 mmol) and tri(*o*-tolyl)phosphine (25 mg, 0.082 mmol) and dry MeCN (5 mL), the mixture degassed using the freeze-pump-thaw method (2 ×), vinylboronate **222** (0.16 mL, 0.95 mmol) and iodide **229** (175 mg, 0.83 mmol), the mixture degassed using the freeze-pump-thaw method (2 ×) and heated to 50 °C with vigorous stirring. After 23 hr the mixture was cooled, diluted with Et_2O (70 mL), passed through Celtite, washed with 5% HCl (10 mL), water (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated to give crude product as a yellow oil. Purification by silica gel chromatography (EtOAc: petroleum ether, 1:9 as eluent) gave the title compound (197 mg, 100 %) as a pale yellow oil. ν_{max} /cm^{-1} (film) 2980 (weak, various C-H), 1720 (s, C=O), 1590 (s, C=C), 1390 (s) 1300 (vs), 1270 (s), 1200 (vs), 1160 (vs), 1020 (s); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6, CH*Me*), 1.30 (3H, s, C*Me*$_2$), 1.31 (3H, s, C*Me*$_2$), 1.48-1.55 (m, 1H, CH*H*), 1.78-1.82 (1H, m, C*H*H), 3.74 (3H, s, OMe), 4.19-4.28 (1H, m, -OCH), 5.71 (1H, d, *J* 11, =CH), 5.83 (1H, d, *J* 17.5), 6.59 (1H, td, *J* 11, 1, =CH) and 8.04 (1H, ddd, *J* 17.5, 11, 1, =CH); δ_C (101 MHz, $CDCl_3$) 23.2 (CH*Me*), 28.3 (C*Me*$_2$), 31.3 (C*Me*$_2$), 46.1 (CH_2), 51.4 (OMe), 65.1 (*C*HMe), 71.2 (*C*Me$_2$), 118.8 (C=C), 125.9 (C=C), 141.4 (C=C), 146.5

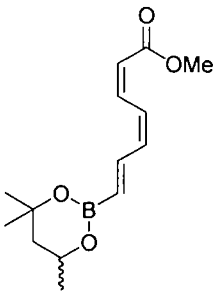
(C=C) and 166.6 (CO_2Me); δ_B (128 MHz, $CDCl_3$) 26.0; *m/z* (CI^+) 256 ($M+NH_4^+$, 100 %), 239, 162 and 136; HRMS (ES^+) 256.1717 ($C_{12}H_{23}NBO_4^+$, $M+NH_4^+$ requires 256.1715).

(2Z,4Z)-methyl 5-iodopenta-2,4-dienoate 245



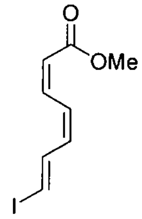
A solution of boronate **234** (385 mg, mmol) in dry DCM (10 mL) was degassed using the freeze-pump-thaw method (3 ×) and cooled to -78 °C under argon. Iodine monochoride (1.9 mL of a 1.0 M solution in DCM, 1.9 mmol) was added dropwise, the mixture stirred for 4 hr, NaOMe (3.8 mL of a 0.5 M solution in MeOH, 1.9 mmol) added dropwise and the mixture allowed to warm to room temperature. After 30 min the mixture was diluted with Et_2O (80 mL), washed with 5% aq. sodium metabisulphite (40 mL), water (40 mL) and brine (40 mL), dried ($MgSO_4$) and evaporated to give the crude product as a yellow oil. Purification by silica gel chromatography (EtOAc: petroleum ether, 5:95 as eluent, cooled to 0 °C) gave the title compound (267 mg, 69 %) as a yellow oil. ν_{max} /cm^{-1} (film) 3030, 2950, 1710, 1620, 1430, 1400, 1280, 1200, 1160 and 1050; δ_H ($CDCl_3$, 500 MHz) 3.75 (3H, s, OMe), 5.91 (1H, t, *J* 11.6), 6.74 (1H, t, *J* 7.6), 6.86 (1H, d, *J* 7.6) and 8.02 (1H, dd, *J* 11.6 and 7.6); δ_C ($CDCl_3$, 126 MHz) 51.5 (OMe), 94.0 (CHI), 121.2 (CH), 134.6 (CH), 143.0 (CH) and 166.2 (CO_2Me); *m/z* (EI) 238 (M^+), 207 ($M-CH_3O^+$), 179 ($M-C_2H_3O_2^+$), 127 (I^+) and 111 ($M-I^+$); HRMS (ES^+) 260.9385 ($C_6H_7O_2INa^+$, $M+Na^+$, requires 260.9383).

(2Z,4Z,6E)-methyl 7-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)hepta-2,4,6-trienoate 253



To a dried Schlenk tube under a positive pressure of argon was added silver(I) acetate (190 mg, 1.14 mmol), palladium(II) acetate (11.5 mg, 0.051 mmol), tri(*o*-tolyl)phosphine (31 mg, 0.10 mmol) and a solution of iodide **245** (250 mg, 1.05 mmol) in dry MeCN (6 mL), the mixture degassed using the freeze-pump-thaw method (1 ×), vinylboronate **222** (0.20 mL, 1.2 mmol) added, the mixture further degassed (2 ×) and heated to 50 °C with vigorous stirring. After 21 hr the mixture was cooled, diluted with Et_2O (80 mL), washed with 5% HCl (20 mL), water (40 mL) and brine (40 mL), dried ($MgSO_4$) and evaporated to give crude product as a orange oil. Purification by silica gel chromatography (EtOAc: petroleum ether, 1:9 as eluent) gave the title compound (225 mg, 81 %) as a viscous pale yellow oil. ν_{max} /cm^{-1} (film) 2970, 1720, 1610, 1440, 1390, 1290, 1160 and 1020; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6, CH*Me*), 1.30 (3H, s, C*Me*$_2$), 1.31 (3H, s, C*Me*$_2$), 1.48-1.55 (m, 1H, CH*H*), 1.80 (1H, dd, J 11.2, 3.2, CHH), 3.73 (3H, s, OMe), 4.20-4.28 (1H, m, OCH), 5.71 (1H, d, *J* 17.5, alkene), 5.74 (1H, d, *J* 10, alkene), 6.39 (1H, t, *J* 10, alkene), 7.23 (1H, t, *J* 12, alkene), 7.32 (1H, t, *J* 11 alkene) and 7.44 (1H, dd, *J* 17 and 12, alkene); δ_C (101 MHz, $CDCl_3$) 23.3 (CH*Me*), 28.3 (C*Me*$_2$), 31.4 (C*Me*$_2$), 46.2 (CH_2), 51.3 (OMe), 65.1 (*C*HMe), 71.2 (*C*Me$_2$), 118.1 (C=C), 126.0 (C=C), 138.9 (C=C), 139.3 (C=C), 139.7 (C=C) and 166.9 (*C*O$_2$Me); δ_B (128 MHz, $CDCl_3$) 26.0 (brs); ν_{max} /cm^{-1} (film) 2970 (w, C-H), 1720 (s, C=O), 1610 (s, C=C), 1440 (m), 1390 (m), 1290 (s), 1160 (vs) and 1020 (m); HRMS (ES$^+$) 287.1428 ($C_{14}H_{21}BO_4Na^+$, M+Na$^+$, requires 287.1425; *m/z* (EI) 264 (M$^+$), 164 (M-$C_6H_{12}O^+$), 106 ($C_6H_7BO^+$, 100 %) and 83 ($C_3H_3CO_2^+$).

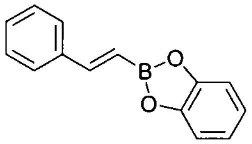
(2Z,4Z,6E)-methyl 7-iodohepta-2,4,6-trienoate 254



A solution of boronate **253** (233 mg, 0.87 mmol) in dry THF (5 mL) was cooled to -78 °C under argon in the absence of light. NaOMe (2.1 mL of a 0.5 M solution in MeOH, 1.05 mmol) was added dropwise, the mixture stirred for 30 min and iodine monochloride (0.90 mL of a 1.0 M solution in DCM, 0.90 mmol) added dropwise. The mixture was stirred for 1 hr, warmed to room temperature, diluted with Et_2O (60 mL) and washed with 5% aq. sodium metabisulphite (30 mL), water (30 mL) and brine (30 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow oil which was immediately purified by silica gel chromatography (EtOAc: petroleum ether, 5:95 as eluent, cooled to 0 °C) to give the title compound (209 mg, 90 %) as a pale yellow oil. δ_H (500 MHz, $CDCl_3$) 3.74 (3H, s, OMe), 5.81 (1H, d, *J* 11.5, alkene), 6.24 (1H, t, *J*

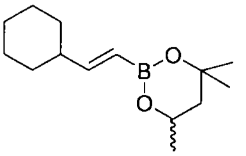
11.5, alkene), 6.68 (1H, d, *J* 14, CHI), 7.02 (1H, t, *J* 11.5, alkene), 7.30 (1H, t, *J* 11.5, alkene) and 7.58 (1H, dd, *J* 14, 11.5, CHIC*H*); δ_C (126 MHz, $CDCl_3$) 51.5 (OMe), 85.8 (CHI), 119.1 (alkene), 124.3 (alkene), 135.8 (alkene), 137.9 (alkene), 139.9 (alkene) and 166.9 (CO_2Me); ν_{max}/cm^{-1} (film) 3050 (w, C-H), 2950 (w, C-H), 1710 (vs, C=O), 1610 (s, C=C), 1540 (s, C=C), 1440 (m), 1290 (w), 1230 (m), 1200 (vs, C-O), 1160 (vs, C-O) and 1020 (w); *m/z* (CI$^+$) 264.9721 ($C_8H_{10}IO_2^+$, MH$^+$, requires 264.9720), 252, 239, 156 and 139.

2-styrylbenzo[d][1,3,2]dioxaborole 258



Phenylacetylene (2.0 mL, 18.2 mmol) was cooled to 0 °C under argon, catecholborane (1.95 mL, 18.3 mmol) added dropwise and the stirred mixture heated to 70 °C. After 2 hr the mixture was cooled and Kugelrohr distillation of the thick orange oil afforded the title compound (2.06 g, 51 %) as a white solid. All spectral properties were identical to those reported.[466]

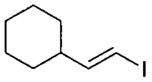
2-((E)-2-cyclohexylvinyl)-4,4,6-trimethyl-1,3,2-dioxaborinane 261



Stirred cyclohexylacetylene (3 mL, 23 mmol) was cooled to 0 °C under argon, catecholborane (2.55 mL, 26 mmol) added dropwise and the mixture heated to 70 °C. After 2 hr the mixture was cooled to room temperature, diluted with water (5 mL) and stirred for 30 min before the addition of sat. aq. $NaHCO_3$ (20 mL) and a solution of 2-methyl pentane-2,4-diol (3.3 mL, 26 mmol) in Et_2O (10 mL). The solution was stirred vigorously for 100 min, diluted with Et_2O (50 mL) and water (25 mL), separated, washed with sat. aq. $NaHCO_3$ (40 mL), water (40 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated to give crude product as a pale brown oil. Cooling to -15 °C caused precipitation and the mixture was extracted with Et_2O/pet. ether (5:95, 3 × 5 mL) and the solution purified by silica gel chromatography (Et_2O/pet. ether, 5:95 as eluent) to give the title compound (4.33 g, 89%) as a pale yellow oil. δ_H (400 MHz, $CDCl_3$) 1.00-1.29 (14H, m), 1.49 (1H, dd, *J* 14, 12,), 1.59-1.78 (6H, m), 1.92-2.02 (1H, m, C*H*-CH=CH), 4.15-4.24 (1H, m, C*H*Me), 5.28 (1H, dd, *J* 18, 1.6, C*H*B) and 6.47 (1H, dd, *J*

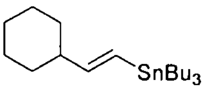
18, 6, C*H*=CHB); δ_C (101 MHz, $CDCl_3$) 23.3 (CH*Me*), 26.2, 26.4, 28.3 (C*Me*$_2$), 31.4 (C*Me*$_2$), 32.3, 43.0, 46.1 (*C*H$_2$), 64.7 (*C*HMe), 70.7 (*C*Me$_2$), 120.6 (brs, *C*HB) and 156.6 (*CH*=CHB); δ_B (128 MHz, $CDCl_3$) 26 (brs); ν_{max} /cm^{-1} (film) 2925, 1635, 1448, 1388, 1303, 1237, 1209, 1190 and 1165; *m/z* (EI) 235.1981 (M$^+$, $C_{14}H_{25}{}^{10}BO_2$ requires 235.1978), 180, 153, 136 and 108 (100%).

((E)-2-iodovinyl)cyclohexane 262



To a solution of boronate **261** (274 mg, 1.30 mmol) in THF (7 mL) was added NaOMe (3.0 mL of a 0.5 M solution in MeOH, 1.5 mmol) dropwise, the mixture stirred for 15 min prior to the addition of iodine monochloride (1.5 mL of a 1.0 M solution in DCM, 1.5 mmol) and the mixture stirred at room temperature in the absence of light. After 1 hr the mixture was diluted with Et_2O (60 mL), washed with 5% aq. sodium metabisulphite (20 mL), water (40 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated to give the crude product as a yellow oil. Purification by silica gel chromatography (pet. ether as eluent) gave the title compound (174 mg, 62%) as a clear oil. ν_{max}/cm^{-1} (film) 2925, 1635, 1448, 1388, 1303, 1237, 1209, 1190 and 1165; δ_H ($CDCl_3$, 400 MHz) 1.04-1.32 (5H, m), 1.60-1.66 (1H, m), 1.68-1.76 (4H, m), 1.96-2.06 (1H, m), 5.95 (1H, dd, *J* 14, 1.2, CHI) and 6.47 (1H, dd, *J* 14, 6.8, CHI=C*H*); δ_C ($CDCl_3$, 101 MHz) 25.9, 26.0, 32.1, 44.7, 73.4, 152.3; *m/z* (EI) 236.0055 (M$^+$, $C_8H_{13}I^+$ requires 236.0056), 180, 167, 127 and 109 (100%).

Tributyl((E)-2-cyclohexylvinyl)stannane 260



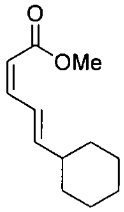
Hydrostannylation method

To a dried Schlenk tube under a positive pressure of argon was added AIBN (226 mg, 1.4 mmol), tributyltin hydride (2.3 mL, 8.6 mmol) and cyclohexylacetylene (1.0 mL, 7.8 mmol) and the stirred mixture heated to 120 °C under argon. After 3.5 hr the mixture was cooled and purified by silica gel chromatography (pet. ether as eluent) to give the title compound (2.80 g, 90 %) as a clear oil. ν_{max} (film)/cm^{-1} 1376 (w), 1449 (s), 1597 (s) and 2851 (s); δ_H (400 MHz, $CDCl_3$) 0.8-0.9 (14H, m), 1.05-1.34 (12H, m), 1.44-1.54 (6H, m), 1.60-1.76 (5H, m), 1.92-2.02 (1H, m, C*H*-CH=CH) and 5.77-5.93 (2H, m, Alkene); δ_C (101 MHz, $CDCl_3$) 9.5, 13.9, 26.2, 26.4, 27.4, 29.3, 32.7, 45.2, 123.6 (*C*H=CH-Sn) and 155.6 (Sn-*C*H=CH); HRMS (ES$^+$) 401.2229 ($C_{20}H_{41}Sn^+$, M+H$^+$, requires 401.2225).

Lithium halogen exchange method

A solution of iodide **262** (216 mg, 1.02 mmol) and Bu_3SnCl (0.30 mL, 1.1 mmol) in dry THF (10 mL) was cooled to -78 °C under argon in the absence of light. ^{n}BuLi (0.83 mL of a 1.6 M solution in hexane, 1.3 mmol) was added dropwise and the mixture stirred at -78 °C. After 1 hr the mixture was allowed to warm to room temperature, stirred for a further 1 hr and quenched by the addition of sat. aq. NH_4Cl (10 mL). The mixture was diluted with water (20 mL) and Et_2O (70 mL), separated, reextracted with Et_2O (20 mL) and the combined organic phase washed with water (20 mL) and brine (20 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a pale yellow oil. Purification by silica gel chromatography (pet. ether as eluent) gave the title compound (234 mg, 57 %) as a clear oil.

(2Z,4E)-methyl 5-cyclohexylpenta-2,4-dienoate 264



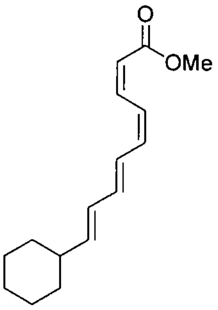
Heck method

To a dried Schlenk tube under a positive pressure of argon was added palladium(II) acetate (36 mg, 0.16 mmol), tri(*o*-tolyl)phosphine (98 mg, 0.32 mmol), silver acetate (600 mg, 3.6 mmol) and dry MeCN (20 mL), the mixture degassed using the freeze-pump-thaw method (2 ×), vinylcyclohexane (0.550 mL, 4.0 mmol) and iodide **229** (0.364 mL, 3.3 mmol) added, the mixture further degassed (2 ×) and heated to 50 °C with vigorous stirring. After 25 hr the mixture was cooled, diluted with Et_2O (150 mL) and passed through Celite. Washing with 5 % HCl (40 mL), water (50 mL) and brine (50 mL), drying ($MgSO_4$) and evaporating gave crude product as a brown oil. Purification by silica gel chromatography (EtOAc: pet ether, 1:39 as eluent) gave the title compound (316 mg, 49 %) as a clear oil. ν_{max} /cm^{-1} (film) 2927, 1719, 1637, 1601, 1438, 1173; δ_H ($CDCl_3$, 500 MHz) 1.10-1.18 (3H, m), 1.24-1.30 (3H, m), 1.64-1.69 (1H, m), 1.71-1.80 (3H, m), 2.11-2.19 (1H, m), 3.72 (3H, s, OMe), 5.57 (1H, d, *J* 11.5, C*H*CO_2Me), 6.01 (1H, dd, *J* 15.5, 7, CH=C*H*-CH), 6.55 (1H, t, *J* 11.5, C*H*=CH-CH) and 7.32 (1H, dd, *J* 15.5, 11.5, C*H*=CH-CO_2Me); δ_C ($CDCl_3$, 126 MHz) 26.0, 26.2, 32.4, 41.3, 51.2, 115.2, 124.6, 146.2, 151.5 and 167.2; *m/z* (CI$^+$) 195 (100 %); HRMS (ES$^+$) 195.1378 (M+H$^+$, $C_{12}H_{19}O_2^+$, requires 195.1380).

Suzuki-Miyaura method

To a dried Schlenk tube under a positive pressure of argon was added palladium(II) acetate (10 mg, 0.045 mmol), triphenylphosphine (85 mg, 0.32 mmol), silver(I) oxide (750 mg, 3.2 mmol), dry THF (20 mL), boronate **261** (369 mg, 1.56 mmol) and iodide **229** (0.300 mL, 2.7 mmol) and the stirred mixture heated to reflux under argon. After 21 hr the mixture was cooled, diluted with Et_2O (80 mL), passed through Celite and washed with 5% HCl (30 mL), water (30 mL) and brine (30 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a brown oil. Purification by silica gel chromatography (EtOAc: pet. ether, 1:49 as eluent) gave the title compound (209 mg, 69 %) as a clear oil.

(2Z,4Z,6E,8E)-methyl 9-cyclohexylnona-2,4,6,8-tetraenoate 263



Stille method

A solution of iodide **254** (120 mg, 0.45 mmol) and stannane **260** (280 mg, 0.70 mmol) in dry DMF (10 mL) was degassed using the freeze-pump-thaw method (2 ×), NaOAc (115 mg, 1.40 mmol), palladium(II) acetate (5.9 mg, 0.026 mmol), triphenylphosphine (21 mg, 0.080 mmol) and copper(I) iodide (6 mg, 0.03 mmol) added and the mixture further degassed (2 ×) and stirred at room temperarure in the absence of light. After 280 hr the mixture was diluted with Et_2O (60 mL) and passed through Celite. Washing with 5% HCl (10 mL), water (20 mL) and brine (20 mL), drying ($MgSO_4$) and evaporating gave the crude product as a yellow oil. Purification twice by silica gel chromatography (EtOAc: pet ether, 5:95 as eluent) gave the title compound (36 mg, 32 %) as a pale yellow oil.

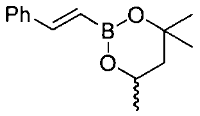
Suzuki-Miyaura method

To a dried Schlenk tube under a positive pressure of argon was added palladium(II) acetate (5.5 mg, 0.024 mmol), triphenylphosphine (27 mg, 0.10 mmol) and dry THF (2 mL), the mixture degassed using the freeze-pump-thaw method (1 ×), a solution of boronate **253** (150 mg, 0.57 mmol) in dry THF (2 mL) added, the mixture further degassed (1×), a solution of iodide **262** (108 mg, 0.46 mmol) in dry THF (2 mL) and silver(I) oxide (210 mg, 0.91 mmol) added, the mixture further degassed (2 ×) and heated to 65 °C with vigorous stirring in the absence of light. After 22 hr the mixture was cooled, diluted with Et_2O (40 mL), passed through Celite and washed with 5% HCl (20 mL) and brine (20 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow oil. Purification by silica gel chromatography (Et_2O: pet. ether, 2:98 to 5:95 as eluent) gave the title compound (29 mg, 18 %) as a pale yellow oil.

Heck method

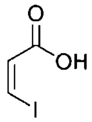
To a dried Schlenk tube under a positive pressure of argon was added $Pd(OAc)_2$ (4 mg, 0.018 mmol), P(*o*-tol)$_3$ (11 mg, 0.036 mmol), AgOAc (70 mg, 0.42 mmol) and a solution of iodide **254** (100 mg, 0.38 mmol) in dry MeCN (3 mL), the mixture degassed using the freeze-pump-thaw method (1 ×), vinylcyclohexane (0.075 mL, 0.56 mmol) was added, the mixture further degassed (2 ×) and heated to 50 °C with vigorous stirring. After 21 hr the mixture was cooled, diluted with Et_2O (60 mL), passed through Celite and washed with water (30 mL) and brine (30 mL). Drying ($MgSO_4$) and evaporation gave the crude product as an orange oil. Purification by silica gel chromatography (EtOAc: pet ether, 3:197 as eluent) gave the title compound (34 mg, 36 %) as a pale yellow oil. ν_{max} (film)/cm^{-1} 1007 (w), 1173 (vs), 1448 (s), 1596 (s), 1717 (vs) and 2925 (s); δ_H (500 MHz, $CDCl_3$) 0.88 (2H, m, aliphatic), 1.0-1.4 (4H, m, aliphatic), 1.5-1.8 (4H, m, aliphatic), 2.0-2.1 (1H, m, C*H*(CH_2)$_2$, 3.74 (3H, s, OMe), 5.70 (1H, d, *J* 11, C*H*CO_2Me), 5.83 (1H, dd, *J* 14.5, 7, C*H*-CH(CH_2)$_2$), 6.14 (1H, dd, *J* 15.5, 10.5, C*H*=CH-CH(CH_2)$_2$), 6.37-6.41 (2H, m, C*H*=CH-CH=CH-CO_2Me and C*H*-CH=CH-CH(CH_2)$_2$), 6.65 (1H, dd, *J* 15, 12 C*H*=CH-CH=CH-CH(CH_2)$_2$), 7.12 (1H, t, *J* 12, C*H*=CH-CO_2Me) and 7.25 (1H, t, *J* 12, CH-CH=CH-CO_2Me); δ_C (126 MHz, $CDCl_3$) 26.2 (CH_2(*C*H_2)$_2$), 26.3 (*C*H_2(CH_2)$_2$), 32.9 (CH(*C*H_2)$_2$), 41.3 (*C*H(CH_2)$_2$), 51.4 (OMe), 116.8, 123.7, 124.8, 127.9, 138.1, 138.5, 139.0, 144.8 and 167.2; *m/z* (EI) 246 (M^+), 131, 105 and 91 (100%); HRMS (ES+) 247.1692 ($M+H^+$, $C_{16}H_{23}O_2^+$ requires 247.1693).

4,4,6-trimethyl-2-styryl-1,3,2-dioxaborinane 225c



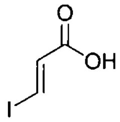
To a dried Schlenk tube under a positive pressure of argon was added silver(I) acetate (150 mg, 0.90 mmol), palladium(II) acetate (9 mg, 0.040 mmol), tri(o-tolyl)phosphine (24.5 mg, 0.081 mmol) and dry MeCN (5 mL), the mixture degassed using the freeze-pump-thaw method (2 ×), iodobenzene **223c** (0.090 mL, 0.80 mmol) and vinylboronate **222** (0.16 mL, 0.95 mmol) added, the mixture degassed using the freeze-pump-thaw method (2 ×) and heated to 50 °C under argon. After 22 hr the mixture was cooled, diluted with Et_2O (80 mL), passed through Celite and washed with 5% HCl (30 mL), water (30 mL) and brine (30 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow oil. Purification by silica gel chromatography (Et_2O: pet. ether, 5:95 as eluent) gave the title compound (137 mg, 74 %) as a clear oil. All spectral properties were as those reported.[297]

(Z)-3-iodoacrylic acid 268



A stirred mixture of acetic acid (22 mL), propiolic acid (3.7 mL, 60 mmol) and sodium iodide (14.3 g, 95 mmol) were heated to 115 °C under argon. After 90 min the hot mixture was poured onto water (150 mL), extracted with Et_2O (100 mL), separated, re-extracted with Et_2O (2 × 50 mL) and the combined organic phase washed with saturated aqueous $Na_2S_2O_3$ (75 mL) and brine (75 mL), drying ($MgSO_4$) and evaporation gave the title compound as a pale yellow solid (9.76 g, 82 %). Mpt; 64-66 °C (lit.[287] 63-65 °C). All spectral properties were identical to those reported in the literature.[287]

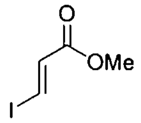
(E)-3-iodoacrylic acid 269



Iodide **268** (3.10 g, 15.7 mmol) was added to a solution of 57 % aqueous HI (0.300 mL, 2.3 mmol) in benzene (8 mL) and the stirred mixture heated to 80 °C under argon. After 18 hr the mixture was cooled, diluted with Et_2O (40 mL) and water (15 mL), re-extracted with Et_2O (20 mL), the combined organic phase washed with dilute aqueous

$Na_2S_2O_3$ (10 mL), dried ($MgSO_4$) and solvent evaporated to give the crude product which was washed with hexane (100 mL) to give the title compound (2.76 g, 89 %) as a white crystalline solid. Mpt. 142-144 °C (Lit.[302] 140-141 °C). All spectral properties were identical to those reported in the literature.[302]

(*E*)-methyl 3-iodoacrylate 266



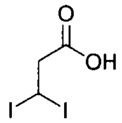
From acid

Iodide **269** (671 mg, 3.39 mmol) was dissolved in MeOH (8 mL), H_2SO_4 (0.205 mL, 3.69 mmol) added and the stirred mixture heated to 85 °C under argon. After 4.25 hr the mixture was cooled, evaporated and redissolved in a mixture of Et_2O and chloroform (150 mL, 4:1). Washing with water (40 mL), 5% aq. sodium metabisulphite (40 mL), sat. aq. $NaHCO_3$ (40 mL) and brine (40 mL), drying ($MgSO_4$) and evaporation gave the title compound (532 mg, 74 %) as a pale yellow solid. Mpt. 41-44°C; δ_H (500 MHz, $CDCl_3$) 3.75 (3H, s, Me), 6.88 (1H, d, *J* 15, CHI=C*H*) and 7.89 (1H, d, *J* 15, CHI); δ_C (126 MHz, $CDCl_3$) 52.1 (Me), 99.8 (CHI), 136.3 (CHI=*C*H) and 164.8 (*C*O_2Me); ν_{max}/cm^{-1} (neat) 2900 (weak, various C-H), 1721 (vs, C=O), 1589 (s, C=C), 1434 (s), 1350 (s), 1262 (s) and 1216 (s); *m/z* (EI) 211.9327 (M^+, $C_4H_5IO_2^+$, requires 211.9329), 181, 153, 127 and 85 (100 %).

Direct isomerisation

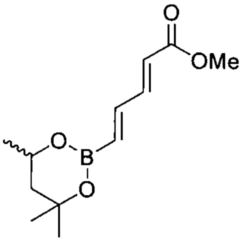
Iodide **229** (3.36 g, 15.8 mmol) was added to a stirred solution of 57% HI (0.30 mL, 2.3 mmol) in benzene (8 mL) and the mixture heated to 80 °C under argon. After 18 hr the mixture was cooled and partitioned between water (20 mL) and Et_2O (25 mL). The aqueous phase was extracted with Et_2O and the combined organic phase washed with sat. aq. $NaHCO_3$ (25 mL), 5% aq. sodium metabisulphite (25 mL) and brine (25 mL). Drying ($MgSO_4$) and evaporation gave the title compound (2.62 g, 78%) as a white solid.

Methyl 3,3-diiodopropanoic acid.



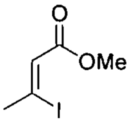
Iodide **268** (4.00 g, 20.2 mmol) was dissolved in 57 % aqueous HI (5.3 mL, 40 mmol) and the stirred mixture heated to 90 °C under argon. After 24 hr the mixture was cooled, diluted with 5% HCl (50 mL) and Et_2O (50 mL), separated, re-extracted with Et_2O (4 × 25 mL), the combined organic phases washed with sat. aq. $Na_2S_2O_3$ (10 mL) and brine (10 mL), drying ($MgSO_4$) and evaporation gave the crude product as an orange solid. Recrystalisation from DCM/hexane gave a white crystalline solid (3.87 g). 2.86 g were further purified by repeated crystallisation from DCM/hexane (4 ×) to give the title compound (0.879 g, 18 %) as a white crystalline solid. Structure identified by X-ray crystallography. Mpt 85-86 °C (lit.[301] 87 °C) δ_H (500 MHz, $CDCl_3$) 3.80 (2H, d, *J* 7, CH_2) and 5.24 (1H, t, *J* 7, CHI_2); δ_C (126 MHz, $CDCl_3$) -45.8 (CHI_2), 53.0 (CH_2) and 175.2 (CO_2H); ν_{max}/cm^{-1} (neat) 3000 (broad, acid O-H), 1690 (vs, C=O), 1430 (s), 1320, 1250 (s, two bands, C-O) and 1140; *m/z* (EI) 325.8291 (M^+, $C_3H_4I_2O_2$, requires 325.8295), 199, 127 (100%) and 71.

(2*E*,4*E*)-methyl 5-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)penta-2,4-dienoate 271



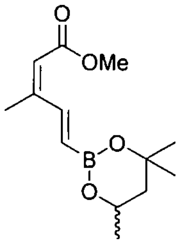
To a dried Schlenk tube under a positive pressure of argon was added silver(I) acetate (430 mg, 2.58 mmol), palladium(II) acetate (26 mg, 0.12 mmol), tri(o-tolyl)phosphine (70 mg, 0.23 mmol) and a solution of iodide **266** (500 mg, 2.36 mmol) in dry MeCN (14.5 mL), the mixture degassed using the freeze-pump-thaw method (2 ×), vinylboronate **222** (0.46 mL, 2.76 mmol) added, the mixture degassed using the freeze-pump-thaw method (1 ×) and heated to 50 °C with vigorous stirring. After 22 hr the mixture was cooled, diluted with Et_2O (80 mL), passed through Celite and washed with 5 % HCl (20 mL), water (40 mL) and brine (40 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow oil. Purification by silica gel chromatography (EtOAc: petroleum ether, 1:9 as eluent) gave the title compound (560 mg, 99.5 %) as a pale yellow oil. ν_{max} /cm^{-1} (film) 2980 (w, C-H), 1710 (s, C=O)), 1600 (s, C=C), 1425 (w), 1395 (s), 1305 (s), 1245 (vs), 1155 (vs), 1120 (s) and 1010 (s); δ_H (500 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6, CH*Me*), 1.30 (3H, s, C*Me*$_2$), 1.31 (3H, s, C*Me*$_2$), 1.48-1.55 (m, 1H, CH*H*), 1.78-1.82 (1H, m, C*H*H), 3.74 (3H, s, OMe), 4.19-4.28 (1H, m, -OCH), 5.91 (1H, d, *J* 17.5, CHB), 5.96 (1H, d, *J* 15, C*H*CO_2Me), 6.96 (1H, dd, *J* 17.5, 11, C*H*=CHB) and 7.27 (1H, dd, *J* 15, 11, C*H*=$CHCO_2Me$); δ_C (126 MHz, $CDCl_3$) 23.2 (CH*Me*), 28.2 (C*Me*$_2$), 31.3 (C*Me*$_2$), 46.0 (CH_2), 51.8 (OMe), 65.1 (*C*HMe), 71.3 (*C*Me_2), 122.8 (C=C), 143.5 (C=C), 146.2 (C=C) and 167.6 (*C*O_2Me); δ_B (128 MHz, $CDCl_3$) 26; *m/z* (EI) 238.1368 ($C_{12}H_{19}BO_4$, M^+ requires 238.1371), 223, 207, 179, 138 and 107 (100%).

(*Z*)-methyl 3-iodobut-2-enoate 273



A stirred mixture of acetic acid (6 mL), sodium iodide (2.4 g, 16 mmol) and methyl tetrolate **272** (900 mg, 9.2 mmol) was heated to 115 °C under argon, stirred for 90 min and poured onto water (20 mL). The mixture was extracted with Et_2O (2 × 30 mL) and the combined organic phase washed with sat. aq. $NaHCO_3$ (3 × 20 mL), 5% aq. sodium metabisulphite (20 mL) and brine (20 mL). Drying ($MgSO_4$) and evaporation gave the title compound (1.87 g, 90 %) as a clear oil. Further purification was not necessary. ν_{max} /cm^{-1} (film) 2951, 2914, 2839, 1731, 1629, 1435, 1375, 1313, 1275, 1174, 1079 and 1044; δ_H (500 MHz, $CDCl_3$) 2.73 (3H, d, *J* 1.6, Me), 3.74 (3H, s, OMe) and 6.30 (1H, q, *J* 1.6, CH); δ_C (126 MHz, $CDCl_3$) 36.7, 51.7, 114.0, 125.3 and 164.9; *m/z* (EI) 226 (M^+), 195, 167, 127 and 99; HRMS (ES^+) 243.9830 ($M+NH_4^+$, $C_5H_{11}O_2IN^+$, requires 243.9829).

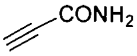
(2*Z*,4*E*)-methyl 3-methyl-5-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)penta-2,4-dienoate 274



To a dried Schlenk tube under a positive pressure of argon was added iodide **273** (324 mg, 1.43 mmol), dry MeCN (9 mL), palladium(II) acetate (16 mg, 0.07 mmol), tri(*o*-

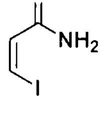
tolyl)phosphine (43 mg, 0.14 mmol), silver(I) acetate (280 mg, 1.56 mmol) and vinylboronate **222** (0.28 mL, 1.7 mmol), the mixture degassed using the freeze-pump-thaw method (3 ×) and heated to 55 °C with vigorous stirring. After 21 hr the mixture was cooled, diluted with Et_2O (80 mL), passed through Celite and washed with 5% HCl (25 mL), water (25 mL) and brine (25 mL). Drying ($MgSO_4$) and evaporation gave the crude product as an orange oil. Purification by silica gel chromatography (EtOAc:pet. ether, 1:11 as eluent) gave the title compound (305 mg, 85 %) as a clear oil. ν_{max} /cm^{-1} (film) 2978, 2945, 1717, 1624, 1588, 1426, 1396, 1325, 1300, 1237 and 1155; δ_H (500 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.5, CH*Me*), 1.30 (3H, s, C*Me*Me), 1.32 (3H, s, CMe*Me*), 1.52 (1H, t, *J* 13, C*H*H), 1.80 (1H, dd, *J* 13 and 2.5), 1.98 (3H, d, *J* 1.5, MeC=), 3.71 (3H, s, OMe), 4.22-4.27 (1H, m, C*H*Me), 5.75 (1H, s, C*H*CO_2Me), 5.92 (1H, d, *J* 18, C*H*B) and 8.25 (1H, d, *J* 18, CHB=C*H*); δ_C (126 MHz, $CDCl_3$) 20.9 (C*Me*H), 23.2 (CMe*Me*), 28.2 (C*Me*Me), 31.3 (CH=C*Me*), 46.0 (CH_2), 51.2 (OMe), 65.1 (*C*HMe), 71.2 (*C*Me_2), 118.5 (alkene), 129-131 (*C*HB), 142.5 (alkene), 151.8 (alkene) and 166.5 (*C*O_2Me); δ_B (128 MHz, $CDCl_3$) 26 (brs); *m/z* (EI) 252 (M+H$^+$, 100%), 237 and 152; HRMS (ES$^+$) 269.1902 (M+NH4$^+$, $C_{13}H_{21}BO_2$ requires 269.1907).

Propiolamide 275[305]



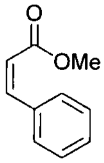
A vigorously stirred aqueous solution of ammonia (28 mL of a 35% solution, 0.48 mol) was cooled to -30 °C under argon, methylpropiolate (8.3 g, 99 mmol) added dropwise, the reaction stirred for 20 min and concentrated to 20 mL in vacuo. The mixture was partitioned between brine (20 mL) and Et_2O (40 mL), reextracted with Et_2O (40 mL) and EtOAc (2 × 40 mL), dried ($MgSO_4$) and evaporated to give the title compund (6.8 g, 100%) as a white solid. Mpt. 55-57 °C (lit. 55-56 °C); δ_H (500 MHz, DMSO) 4.08 (1H, s, CH), 7.62 (1H, brs, NH) and 8.07 (1H, brs, NH); δ_C (126 MHz, DMSO) 75.5 (alkyne), 78.6 (alkyne) and 153.3 (*C*ONH_2); All other spectral properties were identical to those reported in the literature.[305]

(*Z*)-3-iodoacrylamide 276



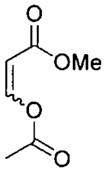
A stirred solution of propiolamide **275** (550 mg, 8.0 mmol) and sodium iodide (1.8 g, 12 mmol) in acetic acid (10 mL) was heated to 115 °C under argon, stirred for 75 min and diluted with water (40 mL). Solid $NaHCO_3$ was added until no further CO_2 was evolved and the mixture extracted with EtOAc (4 × 40 mL). The combined organic phase was washed with 5% aq. sodium metabisulphite (20 mL), reextracted with EtOAc (20 mL) and the combined organic phase dried ($MgSO_4$) and evaporated to give the title compound (1.42 g, 90 %). Mpt. 97-99 °C (lit.[290] 98-102 °C) δ_H (500 MHz, DMSO) 6.93 (1H, d, *J* 8.5, CH), 7.19 (1H, d, *J* 8.5, CH), 7.26 (1H, brs, NH) and 7.54 (1H, brs, NH); δ_C (126 MHz, DMSO) 90.0 (*C*HI), 132.6 (*C*H) and 165.6 (*C*ONH$_2$); All other spectral properties were as reported in the literature.[290]

(*Z*)-methyl cinnamate 278



To a dried Schlenk tube under a positive pressure of argon was added palladium(II) acetate (9 mg, 0.04 mmol), triphenylphosphine (22 mg, 0.084 mmol) and THF (1 mL), the mixture stirred for 2 min, sodium hydroxide (170 mg, 4.25 mmol), THF (8 mL), water (1 mL), potassium phenyltrifluoroborate **277** (200 mg, 1.09 mmol) and iodide **229** (0.100 mL, 0.90 mmol) added, the mixture degassed using the freeze-pump-thaw method (3 ×) and heated to 70 °C. After 4 hr the mixture was cooled, diluted with EtOAc (60 mL) and water (5 mL), passed through Celite, separated, washed with 5% HCl (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated to give crude product as a brown solid. Purification by silica gel chromatography (EtOAc: petroleum ether, 2:98 as eluent) gave the title compound (37 mg, 25 %) as a clear oil. All spectral properties were identical to those reported in the literature.[467]

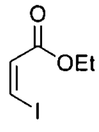
Methyl 3-acetoxyacrylate 42



To a dried Schlenk tube under a positive pressure of argon was added palladium(II) acetate, silver (I) acetate (140 mg, 0.84 mmol), dry MeCN (5 mL), *N*,*N*-diethylaniline (0.135 mL, 0.85 mmol) and iodide **229** (0.090 mL, 0.80 mmol), the mixture degassed using the freeze-pump-thaw method (3 ×) and the heated to 50 °C. After 20 hr the mixture was cooled, diluted with Et_2O (60 mL), passed through Celite and washed with

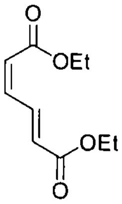
5% HCl (20 mL) and brine (20 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a brown oil. Purification by silica gel chromatography (EtOAc; hexane, 1:4 as eluent) gave the title compound (41 mg, 36 %) as a yellow oil. All spectral properties were identical to those reported in the literature.[322c]

(*Z*)-ethyl 3-iodoacrylate 284



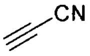
To a stirred solution of ethyl propiolate (5.08 g, 51.8 mmol) in acetic acid (20 mL) under argon was added sodium iodide (11.5 g, 77 mmol) and the mixture heated to 115 °C. After 90 min the reaction was poured into water (60 mL), solid $NaHCO_3$ added until no further CO_2 was evolved and the mixture extracted with Et_2O (3 × 60 mL). The combined organic phase was washed with sat. aq. $NaHCO_3$ (50 mL), 5% aq. sodium metabisulphite (50 mL) and brine (50 mL). Drying ($MgSO_4$) and evaporation gave the title compound (10.9 g, 93 %) as a yellow oil. Further purification was not necessary. All spectral properties were identical to those reported in the literature.[287]

(2*Z*,4*E*)-diethyl hexa-2,4-dienedioate



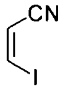
To a dried Schlenk tube under a positive pressure of argon was added iodide **284** (400 mg, 1.77 mmol) and dry MeCN (15 mL), the mixture degassed using the freeze-pump-thaw method (1 ×), palladium(II) acetate (27 mg, 0.12 mmol), silver(I) acetate (387 mg, 2.3 mmol) and Proton Sponge (585 mg, 2.7 mmol) added, the mixture further degassed (2 ×) and heated to 50 °C. After 20 hr the mixture was cooled, diluted with Et_2O (100 mL), passed through Celite and washed with 5% HCl (35 mL) and brine (35 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a brown oil. Purification by silica gel chromatography (EtOAc: pet. ether, 1:9 as eluent) gave the title compound (92 mg, 53%) as a pale yellow oil. ν_{max} /cm^{-1} (film) 2984, 2940, 1720, 1601, 1368, 1308, 1265, 1191 and 1097; δ_H (500 MHz, $CDCl_3$) 1.29-1.33 (6H, m, 2xCH_3), 4.21-4.25 (4H, m, 2xCH_2), 5.95 (1H, d, *J* 11.5, CH), 6.09 (1H, d, *J* 16, CH), 6.63 (1H, t, *J* 11.5, CH) and 8.38 (1H, dd, *J* 16, 11.5, CH); δ_C (126 MHz, $CDCl_3$) 14.3, 14.4, 60.8, 60.9, 124.8, 129.2, 138.6, 140.6, 165.5 and 166.2; *m/z* (EI) 198.0889 (M^+, $C_{10}H_{14}O_4^+$, requires 198.0887), 169 and 153 (100%).

Propiolonitrile 286



A mixture of propiolamide **275** (1.5 g, 21 mmol) and phosphorus pentoxide (7.5 g, 53 mmol) were heated to 180 °C and the product collected at -78 °C as it distilled to give the title compound (270 mg, 25%) as a clear oil. δ_H (500 MHz, $CDCl_3$) 2.53 (1H, s, CH); δ_C (126 MHz, $CDCl_3$) 57.8 (alkyne), 73.1 (alkyne) and 104.6 (*C*≡N). All other spectral properties were identical to those reported in the literature.[305]

(Z)-3-iodoacrylonitrile 287

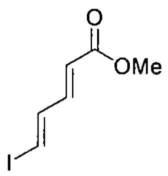


To a stirred solution of propiolonitrile **286** (240 mg, 4.7 mmol) in acetic acid (10 mL) under argon was added sodium iodide (1.04 g, 7 mmol) and the mixture heated to 115 °C. After 80 min the reaction was diluted with water (40 mL), $NaHCO_3$ added until no more CO_2 was evolved and the mixture extracted with Et_2O (3x30 mL). The combined organic phase was washed with 5% sodium metabisulphite (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated to give the title compound (566 mg, 67%) as a yellow oil. δ_H (500 MHz, $CDCl_3$) 6.75 (1H, d, *J* 9) and 7.67 (1H, d, *J* 9); δ_C (126 MHz, $CDCl_3$) 104.0 (*C*HI), 114.4 (*C*H) and 117.4 (*C*N). All other spectral properties were as reported in the literature.[290]

Reductive dimerisation of iodide 245

To a dried Schlenk tube under a positive pressure of argon was added palladium(II) acetate (7.5 mg, 0.033 mmol), silver(I) acetate (168 mg, 1.0 mmol), Proton Sponge (229 mg, 1.1 mmol) and a solution of iodide **245** (160 mg, 0.67 mmol) in dry MeCN (6 mL), the mixture degassed using the freeze-pump-thaw method (3 ×) and heated to 50 °C with vigorous stirring. After 19.5 hr the mixture was cooled, diluted with Et_2O (60 mL), passed through Celite and washed with 5% HCl (20 mL) and brine (20 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a brown solid. Purification by silica gel chromatography (EtOAc: pet. ether, 1:19 then 1:9 as eluent) gave *Z,E,E,Z*-**291** (7 mg, 9 %), *Z,E,E,E*-**292** (29 mg, 39 %) and *E,Z,E,E*-**290** (31 mg, 42 %), all pale yellow solids: *Z,E,E,Z*-**291**; Mpt. 110-112 °C; ν_{max} /cm^{-1} 3020, 2952, 1711, 1620, 1438, 1215 and 1174; δ_H (700 MHz, CDCl$_3$) 3.74 (6H, s, 2×OMe), 5.74 (2H, d, *J* 11, 2xC*H*CO$_2$Me), 6.64 (2H, m, C*H*$_{internal}$), 6.69 (2H, t, *J* 11, C*H*=CHCO$_2$Me) and 7.68 (2H, m, C*H*-CH=CHCO$_2$Me); δ_C (101 MHz, CDCl$_3$) 51.4 (2×CO$_2$*Me*), 118.5 (alkene), 132.3 (alkene), 140.6 (alkene), 144.0 (alkene) and 166.8 (2×*C*O$_2$Me); *m/z* (EI) 222, 158, 131 (100 %) and 103; HRMS (ES$^+$) 240.1233 (M+NH$_4^+$, C$_{12}$H$_{18}$NO$_4^+$, requires 240.1230); elemental analysis, found C, 64.59; H, 6.34; C$_{12}$H$_{14}$O$_4$ requires C, 64.86; H, 6.31; λ_{max}/nm (DCM) 327 (ε = 7500), 340 (ε = 11000) and 357 (ε =9500). *E,Z,E,E*-**290**: δ_H (500 MHz, CDCl$_3$) 3.77 (3H, s, OMe), 3.78 (3H, s, OMe), 5.97 (1H, d, *J* 15), 5.98 (1H, d, *J* 15), 6.26 (1H, t, *J* 12), 6.39 (1H, t, *J* 12), 6.46 (1H, dd, *J* 15, 12), 7.11 (1H, dd, *J* 15, 12), 7.38 (1H, dd, *J* 15, 12) and 7.76 (1H, dd, *J* 15, 12); δ_C (126 MHz, CDCl$_3$) 51.8 (OMe), 51.9 (OMe), 123.0, 123.2, 130.2, 134.0, 134.3, 135.7, 138.4, 143.8, 167.2 and 167.3; *m/z* (EI) 222, 131 and 103 (100 %); HRMS (ES$^+$) 240.1232 (M+NH$_4^+$, C$_{12}$H$_{18}$NO$_4^+$ requires 240.1230). *Z,E,E,E*-**292**: Mpt. 98 – 100 °C; ν_{max}/cm^{-1} 3022, 2951, 1712, 1621, 1438, 1268, 1213, 1177 and 1139; δ_H (500 MHz, CDCl$_3$) 5.75 (1H, d, *J* 11, MeO$_2$C$_{cis}$C*H*), 5.96 (1H, d, *J* 15, MeO$_2$C$_{trans}$C*H*), 6.48 (1H, dd, *J* 15, 12 MeO$_2$C$_{trans}$-CH=CH-C*H*), 6.52 (1H, dd, *J* 15, 12, MeO$_2$C$_{cis}$-CH=CH-CH=C*H*), 6.63 (1H, t, *J* 11.5, MeO$_2$C$_{cis}$-CH=C*H*), 6.70 (1H, dd, *J* 15, 11, MeO$_2$C$_{trans}$-CH=CH-CH=C*H*), 7.34 (1H, dd, *J* 15, 12, MeO$_2$C$_{trans}$CH=C*H*) and 7.68 (1H, dd, *J* 15, 12, MeO$_2$C$_{cis}$-CH=CH-C*H*); δ_C (126 MHz, CDCl$_3$) 51.5 (CO$_2$*Me*), 51.8 (CO$_2$*Me*), 118.8 (alkene), 122.4 (alkene), 132.4 (alkene), 133.7 (alkene), 139.8 (alkene), 140.0 (alkene), 143.8 (alkene), 144.0 (alkene), 166.8 (*C*O$_2$Me) and 167.4 (*C*O$_2$Me); *m/z* (EI) 222, 158, 131 (100 %) and 103; HRMS (ES$^+$) 223.0969 (M+H$^+$, C$_{12}$H$_{15}$O$_4^+$, requires 223.0965).

(2*E*,4*E*)-5-Iodo-penta-2,4-dienoic acid methyl ester 289[327]

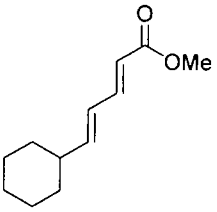


To a dried Schlenk tube under a positive pressure of argon was added a solution of boronate **271**, (980 mg, 4.1 mmol) in dry THF (20 mL), and the tube cooled to -78 °C in the absence of light. NaOMe (9.9 mL of a 0.5 M solution in MeOH, 5.0 mmol) was added dropwise, the mixture stirred for 30 minutes and iodine monochloride (4.9 mL of a 1.0 M solution in DCM, 4.9 mmol) added dropwise. The mixture was stirred for 1 hr, warmed to room temperature, diluted with Et$_2$O (65 mL) and washed with 5 % aqueous sodium metabisulphite (35 mL), water (35 mL), and brine (35 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow solid which was purified by silica gel chromatography (EtOAc:petroleum ether, 5:95 as eluent) to give the title compound (883 mg, 90 %) as a white powder. All spectral properties were identical to those reported.[327]

Reductive dimerisation of iodide 289

To a dried Schlenk tube under a positive pressure of argon was added iodide **289** (100 mg, 0.42 mmol), palladium(II) acetate (5 mg, 0.02 mmol), silver(I) acetate (105 mg, 0.63 mmol), Proton Sponge (143 mg, 0.67 mmol) and dry MeCN (4 mL), the mixture degassed using the freeze-pump-thaw method (3 ×) and heated to 50 °C with vigorous stirring. After 20 hr the mixture was cooled, diluted with Et_2O (30 mL), passed through Celite and washed with 5% HCl (10 mL), water (10 mL) and brine (10 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow solid. Purification by silica gel chromatography (EtOAc:petroleum ether, 5:95 then 1:9 as eluent) gave **290** (30 mg, 64 %) as a white solid.

(2*E*,4*E*)-methyl 5-cyclohexylpenta-2,4-dienoate 299



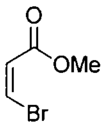
Cross-dimerisation method

To a dried Schlenk tube under a positive pressure of argon was added palladium(II) acetate (18 mg, 0.08 mmol), silver(I) acetate (280 mg, 1.6 mmol), Proton Sponge (390 mg, 1.8 mmol), dry MeCN (10 mL), iodide **262** (184 mg, 0.78 mmol) and iodide **229** (236 mg, 1.1 mmol), the mixture degassed using the freeze-pump-thaw method (3 ×) and heated to 50 °C under argon. After 20 hr the reaction was cooled, diluted with Et_2O (80 mL), passed through Celite and washed with 5% HCl (30 mL) and brine (30 mL). Drying ($MgSO_4$) gave the crude product as a brown oil. Purification by silica gel chromatography (gradient elution, EtOAc:pet. ether, 0:1 to 15:85 as eluent) gave **262** (113 mg), **299** (38 mg, 25%) and **238** (72 mg, 77%).

Heck method

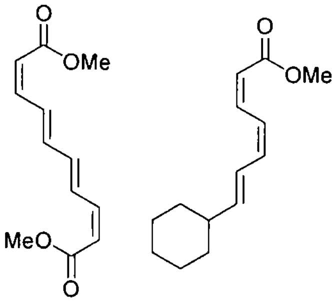
To a dried Sclenk tube under a positive pressure of argon was added palladium(II) acetate (36 mg, 0.16 mmol), tri(*o*-tolyl)phosphine (98 mg, 0.32 mmol), silver(I) acetate (600 mg, 3.6 mmol) and dry MeCN (20 mL), the mixture degassed using the freeze-pump-thaw method (1 ×), iodide **266** (700 mg, 3.3 mmol) and vinylcyclohexane (0.55 mL, 4.0 mmol) added, the mixture further degassed (2 ×) and heated to 50 °C. After 25 hr the reaction was cooled, diluted with Et_2O (150 mL), passed through Celite and washed with 5% HCl (40 mL) and brine (40 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a brown oil. Purification by silica gel chromatography (EtOAc:pet. ether, 1:25 as eluent) followed by extensive evaporation in vacuo gave the title compound (87 mg, 13%) as a clear oil. ν_{max} (film) /cm^{-1} 2925, 2852, 1720, 1641, 1613, 1435, 1336, 1263 and 1144; δ_H (700 MHz, $CDCl_3$) 1.06-1.34 (5H, m), 1.60-1.80 (5H, m), 2.09 (1H, m, C*H*(CH$_2$)$_2$), 5.79 (1H, d, *J* 15, C*H*CO$_2$Me), 6.06 (1H, dd, *J* 15, 6, C*H*-CH(CH$_2$)$_2$), 6.12 (1H, dd, *J* 15, 10.4, C*H*-CH=CHCO$_2$Me) and 7.26 (1H, dd, *J* 15, 10.4, C*H*=CHCO$_2$Me); δ_C (176 MHz, $CDCl_3$) 26.0 (2xCH$_2$), 26.1 (CH$_2$), 32.4 (2xCH$_2$), 41.2 (CH(CH$_2$)$_2$), 51.5 (CO$_2$*Me*), 118.9 (alkene), 126.0 (alkene), 145.9 (alkene), 150.4 (alkene) and 167.8 (*C*O$_2$Me); *m/z* (EI) 194.1301 (M$^+$, $C_{12}H_{18}O_2^+$ requires 194.1301), 113 and 67 (100 %).

(*Z*)-3-Bromo-acrylic acid methyl ester 300[291]



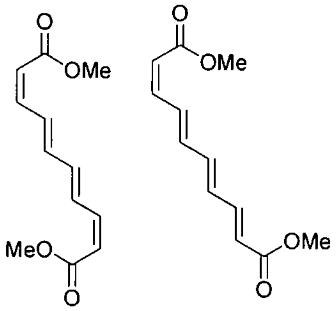
To a stirred solution of lithium bromide (2.5 g, 29 mmol) in dry MeCN (20 mL) was added glacial acetic acid (1.6 mL, 28 mmol) and methyl propiolate (2.0 mL, 22 mmol) and the mixture heated to 85 °C. After 18 hr the mixture was cooled, diluted with water (100 mL) and extracted with Et_2O (2 × 75 mL). The combined organic phase was washed with sat. aq. $NaHCO_3$ (40 mL) and brine (40 mL), dried ($MgSO_4$) and evaporated to give the title compound (3.37 g, 91%) as a pale yellow oil. ν_{max} /cm^{-1} (film) 3080, 2952, 1727, 1611, 1434, 1336, 1210 and 1164; δ_H (500 MHz, $CDCl_3$) 3.77 (3H, s, OMe), 6.63 (1H, d, *J* 8.5) and 7.00 (1H, d, *J* 8.5); δ_C (126 MHz, $CDCl_3$) 51.8 (OMe), 121.8 (alkene), 124.2 (alkene) and 164.5 (*C*O$_2$Me); *m/z* (EI$^+$) 166, 164, 135 and 133 (100%); HRMS (EI) 163.9467 ($C_4H_5BrO_2^+$, M$^+$, requires 163.9467).

(2*Z*,4*E*,6*E*,8*Z*)-dimethyl deca-2,4,6,8-tetraenedioate 291 and (2*Z*,4*Z*,6*E*)-methyl 7-cyclohexylhepta-2,4,6-trienoate 301



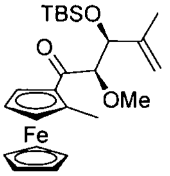
To a dried Schlenk tube under a positive pressure of argon was added palladium(II) acetate (6 mg, 0.03 mmol), triphenylphosphine (36 mg, 0.14 mmol), silver(I) oxide (155 mg, 0.67 mmol) and a solution of iodide **245** (131 mg, 0.55 mmol) in dry THF (5 mL), the mixture degassed using the freeze-pump-thaw method (1 ×), boronate **261** (160 mg, 0.68 mmol) added, the mixture further degassed (2 ×) and heated to 70 °C with vigorous stirring. After 17 hr the mixture was cooled, diluted with Et_2O (35 mL), passed through Celite and washed with 5% HCl (20 mL) and brine (20 mL). Drying ($MgSO_4$) and evaporation gave the crude product as an orange oil. Purification by silica gel chromatography (EtOAc: pet. ether, 3:97 then 5:95 then 10:90 as eluent) gave a mixture of **301** and **261**, 134 mg, 1:2 ratio, ~35 % triene) as a pale yellow oil and tetraene **291** (20 mg) as a pale yellow solid.

(2*Z*,4*E*,6*E*,8*Z*)-dimethyl deca-2,4,6,8-tetraenedioate 291 and (2*Z*,4*E*,6*E*,8*E*)-dimethyl deca-2,4,6,8-tetraenedioate 292



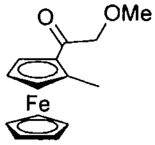
To a dried Schlenk tube under a positive pressure of argon was added palladium(II) acetate (6 mg, 0.03 mmol), triphenylphosphine (36 mg, 0.14 mmol), silver(I) oxide (155 mg, 0.67 mmol) and a solution of iodide **245** (131 mg, 0.55 mmol) in dry THF (5 mL), the mixture degassed using the freeze-pump-thaw method (1 ×), boronate **234** (170 mg, 0.71 mmol) added, the mixture further degassed (2 ×) and heated to 70 °C with vigorous stirring. After 17 hr the mixture was cooled, diluted with Et_2O (35 mL), passed through Celite and washed with 5% HCl (20 mL) and brine (20 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a bright yellow oil. Purification by silica gel chromatography (EtOAc: pet. ether, 5:95 then 10:90 then 20:80 as eluent) gave **291** (78 mg, 64%) and **292** (35 mg, 29 %), both pale yellow solids (93 % combined yield).

3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methoxy-4-methyl-1-(2-methyl-ferrocenyl)-pent-4-en-1-one 326



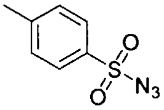
A solution of bromomethylferrocene (455 mg, 1.6 mmol) in dry THF (7 mL) was cooled to -78 °C under argon., ^{n}BuLi (1.1 mL of a 1.6 M solution in hexane, 1.76 mmol) added dropwise and the solution stirred for 20 min. Phenyl ester **323** (650 mg, 1.85 mmol) was added dropwise, the mixture stirred at -78 °C for 1 hr, warmed to room temperature and stirred for a further 2 hr. The reaction was quenched by the addition of sat. aq. NH_4Cl (3.5 mL), partitioned between water (40 mL) and Et_2O (40 mL), separated and the organic phase washed with brine (40 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a red oil. Purification by silica gel chromatography (EtOAc: pet ether, 5:95 then 10:90 as eluent) gave the title compound (407 mg, 56 %) as a deep red oil which solidified after extensive drying in vacuo. Mpt. 52 – 54 °C; $[\alpha]_D^{23}$ = + 308 (c=0.26 in DCM); ν_{max} cm^{-1} (film) 2954, 2929, 2857, 1671, 1472, 1422, 1265, 1118, 1107 and 1094; δ_H (400 MHz, $CDCl_3$) -0.03 (3H, s, SiMe*Me*), -0.02 (3H, s, Si*Me*Me), 0.86 (9H, s, SiC(*Me*)$_3$), 1.68 (3H, s, Me), 2.28 (3H, s, Cp*Me*), 4.12 (1H, d, *J* 5.6, C*H*OMe), 4.15 (5H, s, Cp), 4.29 (1H, t, *J* 2.4), 4.36 (1H, d, *J* 5.6, C*H*OTBS), 4.45 (1H, m), 4.52 (1H, m), 4.76 (1H, m) and 4.87 (1H, m); δ_C (101 MHz, $CDCl_3$) -4.88 (SiMe*Me*), -4.83 (Si*Me*Me), 15.0 (Me), 18.4 (CpMe), 18.7 (Si*C*(Me)$_3$), 26.0 (C(*Me*)$_3$), 59.4 (MeO), 69.2, 69.4, 70.1 (Fe*C*Me), 70.5 (5x Cp), 74.9, 78.6 (CHOMe), 86.7 *C*HOTBS), 88.5 (Fe*C*C=O), 113.6 (C=*C*H$_2$), 144.4 (*C*=CH$_2$) and 203.7 (C=O); *m*/z (ES$^+$) 457.1858 ($C_{24}H_{37}O_3FeSi^+$, M+H$^+$, requires 457.1856, 100%).

2-Methoxy-1-(2-methyl-ferrocenyl)-ethanone 327



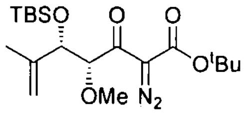
A solution of **326** (135 mg, 0.296 mmol) in acetone (15 mL) was cooled to 0 °C, TBAF.3H_2O (100 mg, 0.32 mmol) added and the mixture stirred for 45 min before warming to room temperature and stirring for 30 min. TLC showed no reaction, the solvent was evaporated and the mixture redissolved in THF (15 mL). Further TBAF.3H_2O (100 mg, 0.32 mmol) was added, the mixture stirred for 16 hr and partitioned between Et_2O (60 mL) and water (30 mL). The phases were separated and the organic phase washed wth brine (30 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a red oil. Purifcation by silica gel chromatography (EtOAc:pet. ether, 1:3 as eluent) gave the title compound (80 mg, 99 %). ν_{max}/cm^{-1} (film) 3092, 2924, 2821, 1682, 1461, 1424, 1378, 1342, 1260, 1196, 1129 and 1061; δ_H ($CDCl_3$, 400MHz) 2.32 (3H, s, Me), 3.52 (3H, s, OMe), 4.14 (5H, s, FeCp), 4.33 (1H, t, *J* 2.8, FeCH), 4.36 (1H, d, *J* 16, CH*H*), 4.43-4.45 (1H, m, FeCH), 4.52 (1H, d, *J 16, C*HH) and 4.58 (1H, dd, *J* 2.4, 1.2, FeCH); δ_C ($CDCl_3$, 101MHz) 15.2 (Me), 59.6 (OMe), 69.1 (FeCH), 70.0 (FeCH), 70.7 (5C, FeCp), 73.8 (FeCMe), 74.7 (FeCH), 75.7 (CH_2), 87.4 (Fe*C*CO) and 202.0 (C=O); *m/z* (ES^+) 272.04958 (M^+, $C_{14}H_{16}O_2{}^{56}Fe^+$, requires 272.04942, 100 %).

4-Methyl-benzenesulphonyl azide[468]



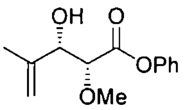
To a stirred solution/suspension of sodium azide (7.15 g, 0.11 mol) in ethanol (30 mL) was added a solution of *para*-toluenesulphonyl chloride (19.0 g, 0.10 mol) in acetone (80 mL). The mixture was stirred at room temperature for 16 hr and filtered. The mixture was diluted with DCM (40 mL) and washed with water (3×40 mL). Drying ($MgSO_4$) and evaporation gave the title compound (19.1 g, 97%) as a clear oil. All spectral properties were identical to those reported.[468]

(4*R*,5*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-6-methyl-3-oxo-2-diazo-hept-6-enoic acid *tert*-butyl ester 328



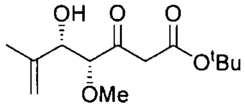
To a stirred solution of **321** (265 mg, 0.72 mmol) in MeCN (10 mL) was added tosyl azide (200 mg, 1.02 mmol) and triethylamine (0.114 mL, 0.82 mmol). The reaction was stirred for 105 min, the solvent evaporated and the resulting solid purified by silica gel chromatography (DCM as eluent) to give the title compound (255 mg, 89 %) as a pale yellow oil. $[\alpha]_D^{23}$ = +34.0 (c = 0.5, DCM); ν_{max}/cm^{-1} (film) 3019, 2931, 2858, 2138, 1710, 1652, 1472, 1371, 1258, 1216, 1134 and 1087; δ_H ($CDCl_3$, 500 MHz) 0.00 (3H, s, SiMe*Me*), 0.01 (3H, s, Si*Me*Me), 0.87 (9H, s, SiC(Me)$_3$), 1.52 (9H, s, O^{t}Bu), 1.76 (3H, s, CH$_3$C=), 3.41 (3H, s, OMe), 4.41 (1H, d, *J* 4.5, CHOTBS), 4.46-4.72 (1H, brm, CHOMe), 4.90 (1H, s, CH*H*) and 4.96 (1H, s, C*H*H); δ_C ($CDCl_3$, 126 MHz) -5.2 (SiMe*Me*), -4.8 (Si*Me*Me), 18.4 (Si*C*Me$_3$) 18.7 (Me), 25.9 (SiC*Me*$_3$), 28.4 (OC*Me*$_3$), 58.3 (CN$_2$), 59.6 (OMe), 77.5 (*C*OMe), 78.3 (COTBS), 83.4 (O*C*Me$_3$), 113.4 (C=*C*H$_2$), 144.4 (*C*=CH$_2$), 160.4 (*C*O$_2$^{t}Bu) and 190.9 (C=O); Anal. Calc. for $C_{19}H_{34}SiO_5N_2$ C 57.29, H 8.54, N 7.03; found C 57.07, H 8.69, N 6.80; *m/z* (ES$^+$) 819 (2M+Na$^+$, 100%), 421 (M+Na$^+$) and 343. For the solid, racemic form, Mpt 41-42 °C.

(2R,3S)-phenyl 3-hydroxy-2-methoxy-4-methylpent-4-enoate 329



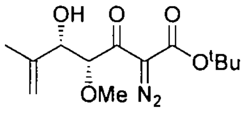
A solution/suspension of N-tosyl-D-valine (3.20 g, 12.0 mmol) in dry DCM (40 mL) under argon was stirred for 2 hr before cooling to 0 °C to allow the dropwise addition of borane (12.0 mL of a 1.0 M solution in THF, 12.0 mmol). After stirring for a further 15 min the mixture was cooled to -78 °C and methacrolein (1.04 mL, 12.0 mmol) and silyl enol ether **322** (4.0 g, 17 mmol) added dropwise. The mixture was stirred at -78 °C for 3.75 hr, warmed to room temperature over 20 min and quenched by the slow addition of sat. aq. $NaHCO_3$ (12 mL). The reaction was stirred for a further 30 min before separating, diluting with pet. ether (300 mL) and washing with brine (100 mL). Drying ($MgSO_4$) and evaporation gave the part-desilylated product as a clear oil which was dissolved in THF (30 mL) and cooled to -78 °C under argon. 10 % aq. TFA (4.6 mL, 6.0 mmol) was added dropwise, the mixture stirred for 55 min and warmed to room temperature over 15 min. The reaction was partitioned between water (100 mL) and ether (100 mL), separated, extracted with ether (50 mL) and the combined organic phase washed with sat. aq. $NaHCO_3$ (80 mL) and brine (40 mL). Drying ($MgSO_4$) and evaporation gave crude product as a clear oil. Purification by silica gel chromatography (EtOAc: hexane, 1:3 then 3:7) gave the title compound (1.92 g, 68 %) as a clear oil. All spectral properties were identical to those reported.[297]

(4*R*,5*S*)-*tert*-butyl 5-hydroxy-4-methoxy-6-methyl-3-oxohept-6-enoate 330



A stirred solution of LiHMDS (6.4 mL of 1.0 M in THF, 6.4 mmol) was cooled to -78 °C under argon, *tert*-butyl acetate (0.86 mL, 6.4 mmol) added dropwise and the mixture stirred for 15 min before the dropise addition of phenyl ester **329** (485 mg, 2.06 mmol). The mixture was stirred at -78 °C for 90 min, warmed to room temperature over 10 min and quenched by the addition of 5% HCl (10 mL). The mixture was diluted with Et_2O (70 mL), separated and washed with 5% HCl (15 mL), sat. aq. $NaHCO_3$ (30 mL), water (30 mL) and brine (30 mL). Drying ($MgSO_4$) and evaporation gave crude product as a yellow oil. Purification by silica gel chromatography (EtOAc: pet. ether, 1:4 as eluent) gave the title compound (471 mg, 89 %) as a pale yellow oil. $[\alpha]_D^{23}$ = +80.0 (c = 0.35 in DCM) ν_{max} /cm^{-1} (film) 3469 (br, OH), 2980, 2933, 1737, 1717, 1653, 1455, 1394, 1369, 1324, 1249 and 1158; δ_H (500 MHz, $CDCl_3$) 1.47 (9H, s, O^{t}Bu), 1.80 (3H, s, Me), 2.57 (1H, brs, OH), 3.41 (1H, d, *J* 16, CH*H*), 3.46 (3H, s, OMe), 3.60 (1H, d, *J* 16, C*H*H), 3.82 (1H, d, *J* 3.5, C*H*OMe), 4.29 (1H, m, C*H*OH), 5.00 (1H, s, =C*H*H) and 5.07 (1H, s, =CH*H*); δ_C (126 MHz, $CDCl_3$) 19.0 (Me), 28.1 (C*Me*$_3$), 47.5 (CH_2), 60.1 (OMe), 75.5 (*C*HOMe), 82.2 (OC*Me*$_3$), 87.7 (*C*HOH), 113.3 (C=*C*H$_2$), 143.3 (*C*=CH$_2$), 166.7 (CO_2^{t}Bu) and 205.1 (C=O); *m/z* (CI$^+$) 276 (M+NH_4^+), 220, 206 (100%) and 150; HRMS (ES$^+$) 276.1806 (M+NH_4^+, $C_{13}H_{26}O_5N^+$, requires 276.12805.

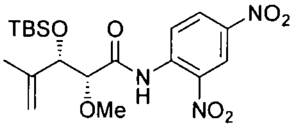
(4*R*,5*S*)-5-Hydroxy-4-methoxy-6-methyl-3-oxo-2-diazo-hept-6-enoic acid *tert*-butyl ester 331



To a stirred solution of **330** (260 mg, 1.0 mmol) in MeCN (10 mL) under argon was added tosyl azide (199 mg, 1.0 mmol) and Et_3N (0.153 mL, 1.10 mmol). The reaction was stirred at room temperature for 90 min before evaporation gave a yellow oil.

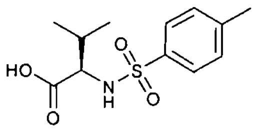
Purification by silica gel chromatography (EtOAc: pet. ether, 1:3 as eluent) gave the title compound (280 mg, 98 %) as a pale yellow oil. $[\alpha]_D^{23}$ = +60.0 (c = 0.20 in DCM); ν_{max} /cm^{-1} (film) 3480 (br), 2980, 2933, 2833, 2136, 1709, 1659, 1478, 1456, 1370, 1316, 1258, 1213, 1135 and 1076; δ_H (500 MHz, $CDCl_3$) 1.52 (9H, s, O^{t}Bu), 1.85 (3H, s, Me), 2.51 (1H, brs, OH), 3.41 (3H, s, OMe), 4.33 (1H, m, C*H*OH), 4.92 (1H, d, *J* 2.5, C*H*OMe), 4.98 (1H, m, =C*H*H) and 5.06 (1H, m, CH*H*); δ_C (126 MHz, $CDCl_3$) 19.1 (Me), 28.4 (OC*Me*$_3$), 58.9 (OMe), 74.9 (*C*HOMe), 83.6 (), 83.8 (), 112.4 (C=*C*H$_2$), 144.1 (*C*=CH$_2$), 160.3 (*C*O$_2$^{t}Bu) and 190.5 (C=O); *m/z* (ES$^+$) 307.1267 (M+Na$^+$, $C_{13}H_{20}O_5N_2Na^+$, requires 307.1265), 285 (M+H$^+$) and 229.

(2*R*,3*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methoxy-4-methyl-pent-4-enoic acid (2,4-dinitro-phenyl)-amide 332



To a stirred solution of 2,4-dinitroaniline (157 mg, 0.86 mmol) in dry MeCN (6 mL) under argon was added DBU (0.12 mL, 0.81 mmol), stirred for 2 min and a solution of phenyl ester **323** (335 mg, 0.96 mmol) in dry MeCN (1 mL) added dropwise. The reaction was stirred for 6.5 hr, quenched by the addition of 5% HCl (0.9 mL), diluted with Et_2O (60 mL) and washed with 5% HCl (30 mL), sat. aq. $NaHCO_3$ (30 mL) and brine (30 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow oil. Purification by silica gel chromatography (chloroform as eluent then a second column with EtOAc: pet. ether, 1:9 as eluent) gave the title compound (254 mg, 70 %) as a pale yellow solid. $[\alpha]_D^{23}$ = +104 (c = 0.68, DCM); Mpt. 97 – 98 °C; ν_{max} /cm^{-1} ($CHCl_3$) 3306 (br), 3020, 2932, 1711 (m), 1600 (s), 1507 (vs), 1441 (m), 1342 (vs), 1216 (vs) and 1088 (s); δ_H (500 MHz, $CDCl_3$) -0.11 (3H, s, SiMe*Me*), -0.02 (3H, s, Si*Me*Me), 0.75 (9H, s, C*Me*$_3$), 1.85 (3H, s, Me), 3.55 (3H, s, OMe), 3.84 (1H, d, *J* 2.5, C*H*OMe), 4.45 (1H, d, *J* 2.5, CHOTBS), 5.00 (1H, s, C*H*H), 5.11 (1H, s, CH*H*), 8.49 (1H, dd, *J* 9, 3, aryl), 9.15 (1H, d, *J* 3, aryl), 9.17 (1H, d, *J* 9, aryl) and 11.7 (1H, brs, exchanges slowly with D_2O, NH); δ_C (126 MHz, $CDCl_3$) -5.3 (Si*Me*Me), -4.8 (SiMe*Me*), 18.1 (*C*Me$_3$), 19.2, (Me), 25.6 (C*Me*$_3$), 60.8 (OMe), 77.0 (*C*HOMe), 86.4 (*C*HOTBS), 113.7 (*C*H$_2$), 122.0 (aryl), 122.3 (aryl), 130.2 (aryl), 135.3 (aryl), 139.1 (aryl), 142.0 (aryl), 144.0 (*C*=CH$_2$) and 171.8 (C=O); *m/z* (ES$^+$) 440 (M+H$^+$); Elemental Analysis, found C, 51.99; H, 6.72; N, 9.47; $C_{19}H_{29}N_3O_7Si$ requires C, 51.92; H, 6.65; N 9.56. Characterised by X-ray crystallography.

(*R*)-3-methyl-2-(tosylamino)butanoic acid 336



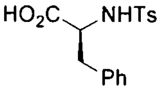
Method 1.

D-Valine (15 g, 128 mmol) was dissolved with vigorous stirring in 2M aqueous sodium hydroxide (64 mL, 128 mmol) and the solution cooled to 0 °C. Tosyl chloride (25.5 g, 134 mmol) was added followed by EtN^iPr_2 (24.4 mL, 140 mol) and acetone (64 mL). The reaction was stirred at 0 °C for 10 min before warming to room temperature. After a further 17 hr the mixture was washed with Et_2O (2 x 150 mL) and the combined organic phase reextracted with 2 M sodium hydroxide (50 mL). The combined aqueous phase was cooled to 0 °C, acidified to pH 1 by the careful addition of 37 % HCl and the mixture extracted with EtOAc (3 x 150 mL). The combined organic phase was washed with brine (3 x 100 mL), dried ($MgSO_4$) and evaporated to give the title compound (27.5 g, 80 %) as a white solid. All spectral and analytical data was identical to those reported.[297]

Method 2.

To a stirred suspension of D-valine (10.7 g, 91 mmol) in water (110 mL) was added sodium hydroxide (3.75 g, 91 mmol) in one portion, the mixture stirred for 15 min and tosyl chloride (17.5 g, 91 mmol) added in one portion. The reaction was stirred for 1 hr, 5% aq. sodium hydroxide (30 mL) and Et_2O (175 mL) added, stirred for a further 5 hr, acidified with 20% HCl, separated and the aqueous phase extracted with Et_2O (150 mL). The combined organic phase was with brine (80 mL), dried ($MgSO_4$) and concentrated to ca. 50 mL. Dilution with pet. ether (50 mL), cooling and filtration gave N-TsD-Val (11.7 g, 47 %) as a white solid. All spectra and analytical data was identical to that reported.[297]

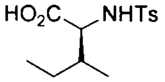
(*S*)-3-Phenyl-2-(toluene-4-sulfonylamino)-propionic acid



To a stirred suspension of *S*-phenylalanine (15 g, 91 mmol) in water (110 mL) at 0 °C was added NaOH (3.75 g, 91 mmol) portionwise over 1 hr, TsCl (17.5 g, 91 mmol) added in one portion, warmed to room temperature and stirred for 3.5 hr. Further NaOH (10 mL of a 20 % aq. solution) and water (70 mL) were added, stirred for 30 min, Et_2O

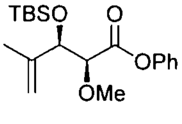
(300 mL) was added and the mixture stirred vigorously for 2 hr before adjusting the pH to 1 with 20 % HCl. The phases were separated, the aqueous phase extracted with Et_2O (150 mL) and the combined organic phase washed with water (100 mL) and brine (100 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a white solid which was recrystalised from Et_2O/acetone to give the title compound (16.0 g, 55 %) as a white solid. All analytical data was identical to that reported.[358]

(*S*)-3-Methyl-2-(toluene-4-sulfonylamino)-pentanoic acid



A stirred suspension of L-isoleucine (6.65 g, 50 mmol) in water (60 mL) was cooled to 0 °C, sodium hydroxide (2.06 g, 50 mmol) added portionwise over 45 min, tosyl chloride (9.6 g, 50 mmol) added in one portion and the mixture warmed to room temperature. After stirring for 2 hr, 5% aq. sodium hydroxide (30 mL) was added, the mixture stirred for 30 min, Et_2O (100 mL) added, the mixture stirred for a further 2 hr, acidified with 20% HCl and separated. The aqueous phase was extracted with Et_2O (100 mL) and the combined organic phase washed with brine (80 mL). Drying ($MgSO_4$), concentration to ca. 30 mL, dilution with pet. ether (30 mL), cooling and filtration gave the title compound (7.45 g, 52 %) as a white solid. $[\alpha]_D^{23}$ = +19.1 (c = 3.5, acetone); Mpt. 134 – 135 °C; Anal. Calc. for $C_{13}H_{19}NSO_4$ C 54.74, H 6.67, N 4.91, found C 54.69, H 6.69, N 4.99. All other analytical data was identical to that reported.[358]

(2*S*,3*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methoxy-4-methyl-pent-4-enoic acid phenyl ester 323



TiCl$_4$ promoted method.

A stirred solution of titanium(IV) chloride (0.66 mL, 6 mmol) in dry DCM (20 mL) was cooled to -78 °C under argon, methacrolein (0.55 mL, 6 mmol) and silyl enol ether **322** (1.95 g, 8.2 mmol) added dropwise and the mixture stirred for 2 hr before warming to room temperature. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (10 mL) and the mixture stirred for a further 15 min before phase separation. The aqueous phase was extracted with pet. ether (100 mL) and the combined organic phase dried ($MgSO_4$) and evaporated to give crude desilylated product as a white solid. The crude product was dissolved in dry DCM (20 mL) under argon, 2,6-lutidine (1.75 mL, 15 mmol) added dropwise and the mixture cooled to -10 °C. TBSOTf (1.8 mL, 7.8 mmol) was added dropwise, the mixture warmed and stirred at room temperature. After 3.75 hr the mixture was partitioned between Et_2O (40 mL) and water (40 mL), the phases separated and the organic phase washed with 5% HCl (25 mL), water (25 mL) and brine (25 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a pale orange oil. Purification by silica gel chromatography (Et_2O:pet ether, 5:95 as eluent) gave the title compound (1.36 g, 65 %) as a clear oil. *Syn:anti* = 2:1. All spectral and analytical data was identical to those reported.[297]

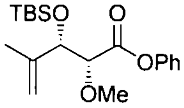
N-Ts-Phenylalanine promoted Mukaiyama aldol.

A stirred suspension of N-Ts-L-Phe (1.91 g, 6.0 mmol) in dry DCM (30 mL) was cooled to 0 °C under argon, borane (6.0 mL of a 1.0 M solution in THF, 6 mmol) added dropwise, the mixture warmed to room temperature, stirred for 20 min and cooled to -78 °C to allow the dropwise addition of methacrolein (0.52 mL, 6.0 mmol) and silyl enol ether **322** (1.7 g, 7 mmol). The reaction was stirred at -78 °C for 3.5 hr, warmed to room temperature, quenched by the careful addition of sat. aq. $NaHCO_3$ (6 mL), stirred for 15 min, diluted with pet. ether (250 mL), separated and washed with brine (80 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a clear oil which was redissolved in THF (20 mL) and cooled to -78 °C with stirring under argon, 10 % aq. TFA (2.3 mL) was added dropwise and the mixture stirred for 45 min before warming to room temperature. The mixture was partitioned between water (50 mL) and Et_2O (50 mL), separated and the organic phase washed with sat. aq. $NaHCO_3$ (40 mL), water (20 mL) and brine (40 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a clear oil which was redissolved in dry DCM (20 mL) with stirring under argon, 2,6-lutidine (1.75 mL, 15 mmol) added dropwise and the mixture cooled to -10 °C to allow the dropwise addition of TBSOTf (1.77 mL, 7.8 mmol). The reaction was warmed to room temperature, stirred for 4 hr, partitioned between water (40 mL) and Et_2O (40 mL), separated and the organic phase washed with 5% HCl (25 mL), water (25 mL) and brine (25 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow oil. Purification by silica gel chromatography (Et_2O: pet. ether, 5:95 as eluent) gave *syn* diastereoisomer (1.49 g, 71 %) as a clear oil and a mixture of diastereoisomers (500 mg) as a clear oil. Combined yield: 1.99 g, 95 %. All spectral and analytical data was identical to those reported.[297]

N-Ts-Isoleucine promoted Mukaiyama aldol.

A stirred suspension of N-Ts-L-Ile (1.71 g, 6.0 mmol) in dry DCM (30 mL) was cooled to 0 °C under argon, borane (6.0 mL of a 1.0 M solution in THF, 6 mmol) added dropwise, the mixture warmed to room temperature, stirred for 20 min and cooled to -78 °C to allow the dropwise addition of methacrolein (0.52 mL, 6.0 mmol) and silyl enol ether **322** (1.7 g, 7 mmol). The reaction was stirred at -78 °C for 3.5 hr, warmed to room temperature, quenched by the careful addition of sat. aq. $NaHCO_3$ (6 mL), stirred for 55 min, diluted with pet. ether (250 mL), separated and washed with brine (80 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a clear oil which was redissolved in THF (20 mL) and cooled to -78 °C with stirring under argon, 10 % aq. TFA (2.3 mL) was added dropwise and the mixture stirred for 55 min before warming to room temperature. The mixture was partitioned between water (50 mL) and Et_2O (50 mL), separated and the organic phase washed with sat. aq. $NaHCO_3$ (40 mL), water (20 mL) and brine (40 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a clear oil which was redissolved in dry DCM (20 mL) with stirring under argon, 2,6-lutidine (1.75 mL, 15 mmol) added dropwise and the mixture cooled to -10 °C to allow the dropwise addition of TBSOTf (1.77 mL, 7.8 mmol). The reaction was warmed to room temperature, stirred for 4 hr, partitioned between water (40 mL) and Et_2O (40 mL), separated and the organic phase washed with 5% HCl (25 mL), water (25 mL) and brine (25 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow oil. Purification by silica gel chromatography (Et_2O: pet. ether, 5:95 as eluent) gave *syn* diastereoisomer (1.10 g, 52 %) as a clear oil.

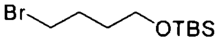
(2*R*,3*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methoxy-4-methyl-pent-4-enoic acid phenyl ester 323



N-Ts-Valine promoted Mukaiyama aldol.

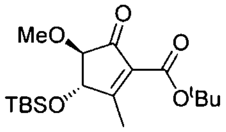
To a stirred solution/suspension of N-Ts-D-Val (1.60 g, 6 mmol) in dry DCM (20 mL) at 0 °C under argon was added borane (6.0 mL of a 1.0 M solutionin THF, 6.0 mmol) dropwise, the mixture warmed to room temperature, stirred for 15 min and cooled to -78 °C to allow the dropwise addition of methacrolein (0.52 mL, 6.0 mmol) and silyl enol ether **322** (1.7 g, 7 mmol). The reaction was stirred at -78 °C for 4 hr, warmed to room temperature and quenched by the addition of sat. aq. $NaHCO_3$ (6 mL). The mixture was stirred for 15 min, diluted with pet. ether (250 mL), separated and washed with brine (80 mL). Drying ($MgSO_4$) and evaporation gave the crude product which was redissolved in THF (20 mL) and cooled to -78 °C to allow the dropwise addition of 10% aq. TFA (2.3 mL, 3 mmol). The mixture was stirred for 45 min, warmed to room temperature, partitioned between Et_2O (50 mL) and water (50 mL), separated and washed with sat. aq. $NaHCO_3$ (40 mL) and brine (40 mL). Drying ($MgSO_4$) and evaporation gave the crude product (2.06 g) as a clear oil, 1.90 g of which was redissolved in dry DCM (20 mL) with stirring under argon. 2,6-lutidine (1.75 mL, 15 mmol) was added dropwise and the mixture cooled to -10 °C to allow the dropwise addition of TBSOTf (1.77 mL, 7.8 mmol). The reaction was warmed to room temperature, stirred for 4 hr, partitioned between Et_2O (40 mL) and water (40 mL), separated and washed with 5% HCl (40 mL) and brine (40 mL). Drying ($MgSO_4$) and evaporation gave the crude product as an orange oil. Purification by silica gel chromatography (Et_2O:pet. ether, 5:95 as eluent) gave *syn*-product (1.38 g) and a mixture of diastereoisomers (335 mg), both clear oils. 89 % combined yield based on amount of crude alcohol used in protection step. All spectral and analytical data was identical to those reported.[297]

(4-Bromo-butoxy)-*tert*-butyl-dimethyl-silane 340



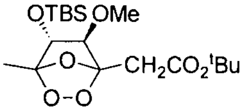
To a stirred solution of borane (4.0 mL of a 1.0 M solution in THF, 4.0 mmol) under argon was added boron tribromide (2.0 mL of a 1.0 M solution in DCM, 2.0 mmol) dropwise, the mixture stirred for 10 min and an aliquot (3.0 mL, 3.0 mmol) added dropwise to a stirred solution/suspension of N-Ts-L-Phe (0.96 g, 3.0 mmol) in dry DCM (15 mL) at 0 °C under argon. The mixture was warmed to room temperature, stirred for 10 min and cooled to -78 °C to allow the dropwise of methacrolein (0.35 mL, 4.0 mmol) and silyl enol ether (0.8 g, 3.4 mmol). The reaction was stirred for 3 hr, warmed to room temperature, quenched by the addition of sat. aq. $NaHCO_3$ (3 mL), stirred for 30 min, diluted with pet. ether (125 mL) and washed with brine (40 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a clear oil which was redissolved in THF (10 mL) and cooled to -78 °C to allow the dropwise addition of 10% aq. TFA (1.1 mL). The mixture was stirred for 1 hr, warmed to room temperature, diluted with Et_2O (40 mL) and washed with water (10 mL), sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a clear oil which was redissolved in dry DCM (10 mL) with stirring under argon, 2,6-lutidine (0.90 mL, 7.7 mmol) added dropwise and the mixture cooled to -10 °C to allow the dropwise addition of TBSOTf (0.90 mL, 4.0 mmol). The reaction was warmed to room temperature, stirred for 3.5 hr, diluted with Et_2O (50 mL) and washed with water (20 mL), 5% HCl (20 mL) and brine (20 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a clear oil. Purification by silica gel chromatography gave the title compound (524 mg, 49%) and aldol product **323** (350 mg, 33%), both clear oils. All spectral properties of **340** were identical to those reported.[469]

(3*S*,4*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-2-methyl-5-oxo-cyclopent-1-enecarboxylic acid *tert*-butyl ester 324



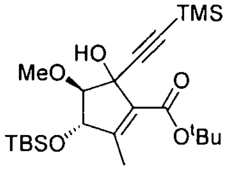
A solution of **321** (200 mg, 0.54 mmol) in dry MeOH (6 mL) was cooled to -78 °C under argon. Ozone was passed through until a blue colour persisted at which point oxygen was passed through to remove the excess ozone. Sodium triacetoxyborohydride (145 mg, 0.68 mmol) was added, the mixture stirred at -78 °C for 15 min and warmed to room temperature. After stirring for a further 45 min the reaction was quenched by the addition of 5% HCl (5 mL) and extracted with DCM (3×20 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a brown oil. Purification by silica gel chromatography (Et_2O: pet. ether, 5:95 then 15:85 as eluent) gave the title compound (89 mg, 47 %) as a pale yellow oil. All spectral properties were identical to those reported.[297]

[(5*R*,6*R*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-6-methoxy-4-methyl-2,3,7-trioxa-bicyclo[2.2.1]hept-1-yl]-acetic acid *tert*-butyl ester 406



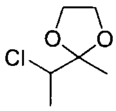
A stirred solution of *β*-keto ester **321** (214 mg, 0.58 mmol) in dry DCM (20 mL) was cooled to -78 °C under argon, ozone passed through until a blue colour was seen, oxygen passed through to remove the excess ozone and DMS (0.26 mL, 3.5 mmol) added dropwise. The mixture was stirred for 15 min, warmed to room temperature, stirred for 25 min and evaporated to afford the crude product as a pale yellow oil. Purification by silica gel chromatography (Et_2O: pet. ether, 1:9 then 1:5 as eluent) gave a mixture of cyclopentenone **324** and cross-ozonide **406** (1:1.4, 72 mg, 33%) as a clear oil. NMR data for cross-ozonide: δ_H (500 MHz, $CDCl_3$) 0.09 (3H, s, Si*Me*Me), 0.12 (3H, s, SiMe*Me*), 0.90 (9H, s, SiC*Me*$_3$), 1.47 (9H, s, OC*Me*$_3$), 1.54 (3H, s, Me), 2.85 (2H, ABq, CH_2), 3.51 (3H, s, OMe), 3.82 (1H, d, *J* 1.5, C*H*OMe) and 3.86 (1H, d, *J* 1.5, C*H*OTBS); δ_C (126 MHz, $CDCl_3$) -4.6 (Si*Me*$_2$), 12.1 (Me), 18.0 (Si*C*Me$_3$), 25.8 (SiC*Me*$_3$), 28.1 (OC*Me*$_3$), 34.3 (CH_2), 59.7 (OMe), 77.6 (*C*HOTBS), 82.3 (*C*HOMe), 91.3 (O*C*Me$_3$), 107.1 (O*C*Me), 113.0 (O*C*CH$_2$) and 166.2 (*C*O$_2{}^t$Bu).

(3*S*,4*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-hydroxy-4-methoxy-2-methyl-5-trimethylsilanylethynyl-cyclopent-1-enecarboxylic acid *tert*-butyl ester 350



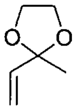
To a solution of TMS-acetylene (0.056 mL, 0.40 mmol) in anhydrous Et_2O (2 mL) at -78 °C under argon was added nBuLi dropwise (0.25 mL of a 1.6 M solution in hexane, 0.40 mmol) and the solution stirred at -78 °C. After 30 min the solution was warmed to -10 °C and added to a stirred suspension of CuI (38 mg, 0.20 mmol) in anhydrous Et_2O (2 mL) at -10 °C under argon. After 1 hr a solution of cyclopentenone **324** (72 mg, 0.20 mmol) in anhydrous Et_2O (1 mL) was added dropwise and the mixture stirred under argon at -10 °C for 80 min before being quenched by the addition of 5% HCl (2 mL). The mixture was diluted with Et_2O (25 mL), water (10 mL) and 5% HCl (8 mL), separated, re-extracted with Et_2O (25 mL), the combined organic phase dried ($MgSO_4$) and evaporated to give the crude product as a clear oil. Purification by silica gel chromatography (EtOAc/hexanes 2:98 then 5:95 as eluent) gave the title compound (5.5mg, 6%) as a clear oil. δ_H (500MHz, $CDCl_3$) 0.07 (9H, s, Me$_3$SiC), 0.16 (6H, s, *Me*$_2{}^t$BuSi), 0.90 (9H, s, ^{t}BuSi), 1.54 (9H, s, ^{t}BuO), 2.05 (3H, m, MeC), 2.09 (1H, s, OH), 3.56 (3H, s, MeO), 3.61 (1H, d, *J* 6.4, MeOC*H*) and 4.30 (1H, s, C*H*OTBS); δ_C (126MHz, $CDCl_3$) -4.2 (*Me*$_2{}^t$BuSiO), 0.1 (Me$_3$Si), 13.7 (*Me*CCOSi), 18.2 (Me$_3$*C*Si), 25.9 (*Me*$_3$CSi), 28.4 (*Me*$_3$CO), 58.5 (MeO), 80.0 (*C*HOMe); 82.2 (*C*HOTBS), 95.5 (O*C*Me$_3$), 98.9 (alkyne), 103.3 (alkyne), 128.7 (*C*OH), 129.9 (alkene), 155.9 (alkene) and 164.1 (*C*O$_2{}^t$Bu); m/z (ES$^+$) 477.2463 (MNa$^+$ 100%, $C_{23}H_{42}O_5NaSi_2{}^+$ requires 477.2463), 447, 437, 403 and 373.

2-(1-Chloroethyl)-2-methyl-1,3-dioxolane 359a



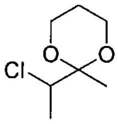
A solution of 3-chloro—2-butanone (23.2 mL, 0.23 mol), ethylene glycol (12.4 mL, 0.22 mol) and TsOH (170 mg, 0.89 mmol) in benzene (330 mL) was heated to reflux in a flask equipped with a Dean Stark system. After 21 hr the mixture was cooled, the benzene evaporated and the crude product purified by Kugelrohr distillation to give the title compound (27.4 g, 83 %) as a clear oil. All spectral properties were as those reported.[400]

2-Methyl-2-vinyl-1,3-dioxolane 360a



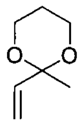
To a solution of potassium hydroxide (24 g, 0.43 mol) in ethylene glycol (50 mL) at 130 °C was added **359a** (10.5 g, 70 mmol) and the mixture stirred at 125 °C under argon. After 3 hr the temperature was increased to 160 °C and product distilled from the reaction mixture to give the title compound (6.62 g, 83 %) as a clear oil. All spectral properties were identical to those reported.[400]

2-(1-Chloroethyl)-2-methyl-1,3-dioxane 359b



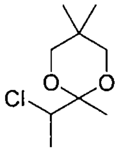
A solution of 3-chloro—2-butanone (23.2 mL, 0.23 mol), 1,3-propanediol (16.5 mL, 0.23 mol) and TsOH (1.0 g, 5.2 mmol) in benzene (330 mL) was heated to reflux in a flask equipped with a Dean Stark system. After 20 hr the mixture was cooled, the benzene evaporated and the crude product purified by Kugelrohr distillation to give the title compound (33.2 g, 89 %) as a clear oil. ν_{max} /cm^{-1} (film) 2960, 2872, 1480, 1449, 1372, 1247, 1153 and 1057; δ_H (CDCl$_3$, 400 MHz) 1.43 (3H, s, Me), 1.45 (3H, d, *J* 6.8, Me), 1.48-1.57 (1H, m, CH$_2$), 1.76-1.86 (1H, m, CH$_2$), 3.77-3.97 (4H, m, 2xCH$_2$O) and 4.12 (1H, q, *J* 6.8, CHCl); δ_C (CDCl$_3$, 101MHz) 15.7, 19.2, 25.2, 59.9, 60.2 and 99.4; *m/z* (ES$^+$) 167 (M+H$^+$, ^{37}Cl) and 165.0677 (M+H$^+$, C$_7$H$_{14}$O$_2$^{35}Cl$^+$, requires 165.0677, 100%).

2-Methyl-2-vinyl-1,3-dioxane 360b



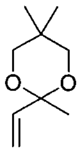
To a stirred solution of potassium hydroxide (14.4 g, 0.26 mol) in 1,3-propanediol (30 mL) at 125 °C was added **359b** (7.10 g, 43.2 mmol) and the mixture stirred at 125 °C. After 2 hr the temperature was increased to 165 °C and the product distilled from the reaction mixture and separated from water to give the title compound (4.73 g, 85 %) as a clear oil. Bpt. 123 °C at 760 Torr; ν_{max} /cm^{-1} (film) 2962, 1645, 1403, 1369, 1249, 1191, 1143, 1086; 1.38 (3H, s, Me), 1.94-2.06 (2H, m, CH_2), 3.78-3.98 (4H, m, $2xCH_2$), 5.36 (1H, dd, *J* 10.8, 1.2), 5.39 (1H, dd, *J* 17.6, 1.2) and 5.80 (1H, dd, *J* 17.6, 10.8); δ_C ($CDCl_3$, 101 MHz) 25.8, 29.0, 61.2, 99.2, 118.1 and 138.9; *m/z* (ES$^+$) 129.0911 (M+H$^+$, $C_7H_{13}O_2^+$, requires 129.0910), 99, 79 and 60 (100%).

2-(1-Chloroethyl)-2,5,5-trimethyl-1,3-dioxane 359c



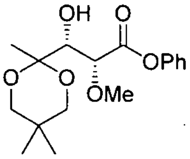
A stirred solution of 3-chlorobutanone (23.2 mL, 0.23 mol), 2,2-dimethyl-1,3-propanediol (24 g, 0.23 mol) and $TsOH.H_2O$ (1.0 g, 5.2 mmol) in benzene (330 mL) was heated to reflux in a round bottomed flask equipped with a Dean-Stark apparatus. After 23 hr the mixture was cooled, the benzene evaporated and the resulting oil dissolved in Et_2O (250 mL). The solution was washed with sat. aq. $NaHCO_3$ (150 mL), water (150 mL) and brine (150 mL), dried ($MgSO_4$) and evaporated to give the title compound (40.3 g, 90 %) as a yellow oil. ν_{max} (film)/ cm^{-1} 2980, 1473, 1396, 1329, 1311, 1213 and 1080; δ_H ($CDCl_3$, 500 MHz) 0.83 (3H, s, CMe*Me*), 1.06 (3H, s, C*Me*Me), 1.43 (3H, s, $MeCO_2$), 1.51 (3H, d, *J* 7, *Me*CH), 3.44 (1H, d, *J* 11.5, CH*H*), 3.46 (1H, d, *J* 11.5, C*H*H), 3.59 (2H, t, *J* 12, C*H*$_2$) and 4.11 (1H, q, *J* 7, CHCl); δ_C ($CDCl_3$, 126 MHz) 15.2 (CMe*Me*), 19.3 (C*Me*Me), 22.4 (*Me*CO_2) 22.9 (*Me*CHCl), 30.1 (CMe_2), 60.5 (CHCl), 70.6 (CH_2), 70.8 (CH_2) and 99.3 (CO_2); *m/z* (CI$^+$) 195, (M$^+$, ^{37}Cl), 193 (M$^+$, ^{35}Cl, 100%), 159 and 129; HRMS (ES$^+$) 193.0989 (M+H$^+$, $C_9H_{18}ClO_2^+$, requires 193.0990.

2,5,5-Trimethyl-2-vinyl-1,3-dioxane 360c



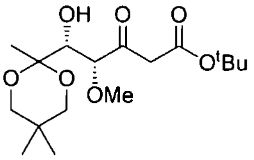
To a stirred solution of potassium hydroxide (28.8 g, 0.50 mol) in ethylene glycol (60 mL) at 120 °C was added **359c** (8.63 g, 44.4 mmol) and the temperature increased to 160 °C. After 23 hr the mixture was cooled, diluted with water (300 mL) and extracted with Et_2O (3×150 mL). The combined organic phase was washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated to give the title compound (4.79 g, 68 %) as a pale yellow oil. ν_{max} (film)/ cm^{-1} 2689, 1645, 1472, 1396, 1369, 1239 and 1089; δ_H ($CDCl_3$, 400 MHz) 0.70 (3H, s, CMe*Me*), 1.16 (3H, s, C*Me*Me), 1.40 (3H, s, *Me*CO_2), 3.32 (2H, d, *J* 11, 2xCH*H*), 3.58 (2H, d, *J* 11, 2xC*H*H), 5.32-5.39 (2H, m, CH_2) and 5.75 (1H, dd, *J* 17.6, 10.8, C*H*=CH_2); δ_C ($CDCl_3$, 101 MHz) 22.1 (CMe*Me*), 22.8 (C*Me*Me), 28.7 (*Me*CO_2), 30.2 (*C*Me_2), 71.6 (2xCH_2), 98.8 (CO_2), 118.0 (*C*H_2=CH) and 138.6 (CH_2=*C*H); *m/z* (EI) 157, 141, 129, 71 and 43; HRMS (ES^+) 157.1222 ($C_9H_{17}O_2^+$, M+H^+, requires 157.1223).

(±)-Phenyl-3-hydroxy-2-methoxy-3-(2,5,5-trimethyl-1,3-dioxan-2-yl)propanoate 362



A solution of **360c** (640 mg, 4.05 mmol) in dry DCM (20 mL) was cooled to -78 °C under argon, ozone passed through until a blue colour persisted, oxygen passed through to remove the excess ozone and DMS (0.44 mL, 6.0 mmol) added dropwise. The mixture was stirred at -78 °C for 30 min, warmed to 0 °C and stirred for 1 hr. After warming to room temperature the mixture was cooled to -78 °C and $TiCl_4$ (0.60 mL, 5.5 mmol) and silyl enol ether **322** (2.05 g, 8.6 mmol) added dropwise. The mixture was stirred at -78 °C for 2.5 hr, warmed to room temperature over 30 min and the mixture quenched by the addition of sat. aq. $NaHCO_3$ (40 mL). The mixture was diluted with water (20 mL) and DCM (20 mL), separated, the aqueous phase extracted with DCM (2x 40 mL) and the combined organic phase washed with brine (40 mL). Drying ($MgSO_4$) and evaporation gave crude product as a yellow oil. The mixture was purified by silica gel chromatography (gradient elution, EtOAc: hexane, 1:4 to 2:3 as eluent then a second column EtOAc: hexane, 3:7 as eluent) to give the title compound (260 mg, 20 %) as a clear oil. ν_{max}/cm^{-1} (film) 3487, 2955, 2871, 1771, 1592, 1492, 1397, 1375, 1237, 1194, 1165, 1133 and 1090; δ_H (400 MHz, CDCl$_3$) 0.85 (3H, s, CMe*Me*), 1.11 (3H, s, C*Me*Me), 1.54 (3H, s, Me), 2.81 (1H, brs, OH), 3.42-3.49 (2H, m, 2x CH*H*), 3.58 (3H, s, OMe), 3.62-3.72 (2H, m, 2xC*H*H), 4.17 (1H, brm, C*H*OH), 4.27 (1H, t, *J* 6.8, C*H*OMe), 7.08-7.13 (2H, m, Ar), 7.21-7.26 (1H, m, Ar) and 7.35-7.41 (2H, m, Ar); δ_C (101 MHz CDCl$_3$) 15.9 (CMe*Me*), 22.6 (C*Me*Me), 23.3 (Me), 30.4 (*C*Me$_2$), 58.7 (OMe), 70.3 (CH$_2$O), 70.7 (CH$_2$O), 75.2 (CHOH), 79.8 (*C*HOMe), 98.8 (Me*C*O$_2$), 121.5 (2xArC), 126.1 (1xArC), 129.6 (2xArC), 150.7 (ArCO) and 169.5 (*C*O$_2$Ph); *m/z* (CI$^+$) 342 (M+NH$_4^+$), 248 and 129 (100%); HRMS (ES$^+$) 342.1910 (M+NH$_4^+$, $C_{17}H_{28}NO_6^+$ requires 342.1911).

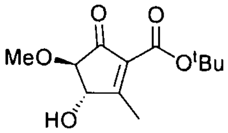
(±)-*tert*-butyl 5-hydroxy-4-methoxy-5-(2,5,5-trimethyl-1,3-dioxan-2-yl)-3-oxopentanoate 363



LiHMDS (1.27 mL of a 1.0 M solution in THF, 1.27 mmol) was cooled to -78 °C with stirring under argon, *tert*-butyl acetate (0.17 mL, 1.3 mmol) added dropwise and the mixture stirred for 15 min. A solution of phenyl ester **362** (140 mg, 0.43 mmol) in dry THF (2 mL) was added dropwise, the mixture stirred for 90 min, warmed to room temperature over 15 min and stirred for a further 15 min. The reaction was quenched by the addition of 5% HCl (2 mL), the mixture partitioned between water (10 mL) and ether (30 mL), separated and washed with 5% HCl (10 mL), sat. aq. NaHCO$_3$ (10 mL), water (10 mL) and brine (10 mL). Drying (MgSO$_4$) and evaporation gave crude product as a yellow oil. Purification by silica gel chromatography (EtOAc: pet. ether, 15:85 then 30:70 as eluent) gave the title compound (70 mg, 47 %) as a pale yellow oil. ν_{max} /cm^{-1} (film) 3469 (br), 2955, 2871, 1740, 1718, 1459, 1395, 1369, 1321, 1257 and 1145; δ_H (500 MHz, CDCl$_3$) 0.79 (3H, s, CMe*Me*), 1.11 (3H, s, C*Me*Me), 1.46 (3H, s, *Me*CO$_2$), 1.47 (9H, s, C(*Me*)$_3$), 2.80 (1H, brs, OH), 3.38-3.45 (3H, m, 2xOCH*H* and CH*H*), 3.48 (3H, s, OMe), 3.58-3.69 (3H, m, 2xOC*H*H and C*H*H), 3.80 (1H, d, *J* 4, C*H*OH) and 3.99 (1H, d, *J* 4, C*H*OMe); δ_C (126 MHz, CDCl$_3$) 14.7 (CMe*Me*), 22.5 (C*Me*Me), 23.4 (*Me*CO$_2$), 28.2 (C*Me*$_3$), 30.3 (*C*Me$_2$), 46.9 (*C*H$_2$CO), 59.2 (OMe), 70.2 (CH$_2$O), 70.5 (CH$_2$O), 75.6 (COH), 81.9 (*C*OMe), 85.1 (*C*Me$_3$), 98.9 (*C*(OCH$_2$), 166.8 (*C*O$_2$^{t}Bu) and

204.2 (C=O); *m/z* (CI^+) 364 ($M+NH_4^+$), 308, 206, 176, 150 and 129 (100%); HRMS (ES^+) 364.2328 ($M+NH_4^+$, $C_{17}H_{34}NO_7^+$ requires 364.2330).

(±)-*tert*-butyl 3-hydroxy-4-methoxy-2-methyl-5-oxocyclopent-1-enecarboxylate 364

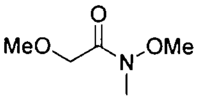


To a solution of **363** (50 mg, 0.14 mmol) in THF (5 mL) was added 37% HCl (0.030 mL, 0.36 mmol) and water (0.5 mL). The mixture was stirred at room temperature for 14 days, diluted with Et_2O (40 mL) and washed with sat. aq. $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL). Drying ($MgSO_4$) and evaporation gave the crude ketone which was redissolved in MeOH (3 mL) and cooled to 0 °C to allow the addition of K_2CO_3 (39 mg, 0.28 mmol). The reaction was stirred for 1 hr, quenched by the addition of water (3 mL) and partitioned between water (20 mL) and DCM (20 mL), separated, the aqueous phase extracted with DCM (20 mL) and the combined organic phase dried ($MgSO_4$) and evaporated to give the crude product as a pale yellow oil. Purification by silica gel chromatography (EtOAc: pet. ether, 2:3 then 1:1 as eluent) gave the title compound (14 mg, 41 %) as a pale yellow oil. ν_{max} /cm^{-1} (film) 3468 (br), 3020, 2928, 2855, 1740, 1627, 1457, 1370, 1259, 1216 and 1156; δ_H (500 MHz, $CDCl_3$) 1.55 (9H, s, O^{t}Bu), 2.36 (3H, s, Me), 2.46 (1H, brs, OH), 3.70 (3H, s, OMe), 3.90 (1H, d, *J* 3.5, C*H*OH) and 4.62 (1H, d, *J* 3.5, C*H*OMe); δ_C (126 MHz, $CDCl_3$) 14.9 (Me), 28.3 ($OC(CH_3)_3$), 59.3 (OMe), 76.5 (CHOH), 82.7 (*C*HOMe), 88.6 (O*C*(CH_3)$_3$), 132.5 (alkene), 161.6 (alkene), 174.7 (*C*O$_2$^{t}Bu) and 195.9 (C=O); *m/z* (ES^+) 265.1049 ($C_{12}H_{18}O_5Na^+$, $M+Na^+$, requires 265.1047, 100%).

General procedure for acetal hydrolysis

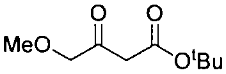
The appropriate acetal (0.23 mmol) was dissolved in 0.75 mL of D_8-THF and observed by ^1H NMR. D_2O (0.100 mL) and the appropriate amount of acid in D_2O (0.010 mL) were added, the mixture shaken and the hydrolysis followed over time by ^1H NMR spectroscopy.

N,2-dimethoxy-N-methylacetamide 374



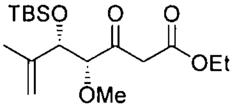
A stirred solution of methoxyacetylchloride (6.2 mL, 67 mmol) in dry DCM (100 mL) was cooled to 0 °C under argon, N, O-dimethyl hydroxylamine hydrochloride (7.4 g, 76 mmol) and K_2CO_3 (23.0 g, 167 mmol) added, the mixture allowed to warm and stirred at room temperature for 25 hr. The mixture was filtered and the filtrate evaporated to give the title compound (6.59 g, 74 %) as a clear oil. ν_{max} /cm^{-1} (film) 2940, 2823, 1684, 1449, 1390, 1331, 1200 and 1139; δ_H (400 MHz, $CDCl_3$) 3.03 (3H, s, NMe), 3.30 (3H, s, OMe), 3.55 (3H, s, OMe) and 4.06 (2H, s, CH_2); δ_C (101 MHz, $CDCl_3$) 32.0 (NMe), 59.1 (OMe), 61.2 (OMe), 69.5 (CH_2) and 170.6 (C=O); *m/z* (CI$^+$) 134 (M+H$^+$), 121 and 104 (100%); HRMS (ES$^+$) 134.0812 (M+H$^+$, $C_5H_{12}NO_3^+$ requires 134.0812).

tert-butyl 4-methoxy-3-oxobutanoate 375



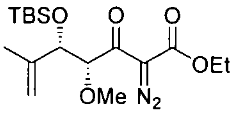
To a stirred solution of LiHMDS (10 mL of a 1.0M solution in THF, 10 mmol) at -78 °C under argon was added *tert*-butyl acetate (1.35 mL, 10 mmol) dropwise, the mixture stirred for 15 min and Weinreb amide **374** (700 mg, 5.3 mmol) added dropwise. The reaction was gradually warmed to room temperature over 3 hr, quenched by the addition of 5% HCl (8 mL), diluted with Et_2O (80 mL), separated and washed with 5% HCl (2x 40 mL), water (40 mL) and brine (40 mL). Drying ($MgSO_4$) and evaporation gave crude product as a pale yellow oil. Purification by silica gel chromatography (Et_2O: pet. ether, 2:3 as eluent) gave the title compound (700 mg, 74 %) as a pale yellow oil. ν_{max} /cm^{-1} (film) 2981, 2935, 1722, 1652, 1456, 1394, 1369, 1325, 1251, 1155 and 1112; δ_H (500 MHz, $CDCl_3$) 1.45 (9H, s, C(C*H*$_3$)$_3$), 3.40 (2H, s, C*H*$_2$), 3.41 (3H, s, OMe) and 4.07 (2H, s, C*H*$_2$OMe); δ_C (126 MHz, $CDCl_3$) 28.1 (C(*C*H$_3$)$_3$), 47.3 (*C*H$_2$), 59.5 (OMe), 77.4 (*C*H$_2$OMe), 82.2 (*C*(CH$_3$)$_3$), 166.2 (*C*O$_2$^{t}Bu) and 202.1 (C=O); *m/z* (CI$^+$) 206 (M+NH$_4^+$), 176, 150, 120 and 106 (100%); HRMS (ES$^+$) 206.1388 (M+NH$_4^+$, $C_9H_{20}NO_4^+$, requires 206.1387).

(4R,5S)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-6-methyl-3-oxo-hept-6-enoic acid ethyl ester 376



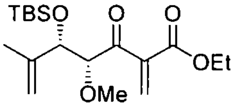
To a stirred solution of LiHMDS (12.0 mL of a 1.0 M solution in THF, 12.0 mmol) at -78 °C under argon was added EtOAc (1.2 mL, 12 mmol) dropwise, the mixture stirred for 15 min and phenyl ester **323** (1.89 g, 5.4 mmol) added dropwise. The reaction was stirred for 2 hr, warmed to room temperature, quenched with 5% HCl (10 mL), diluted with Et_2O (80 mL), separated and washed with 5% HCl (40 mL), sat. aq. $NaHCO_3$ (40 mL) and brine (40 mL). Drying ($MgSO_4$) and evaporation gave crude product as a yellow oil. Purification by silica gel chromatography (Et_2O: pet. ether, 7:93 as eluent) gave a mixture of **376** and **377** (4:1) (1.20 g, 65 %) as a clear oil. **376**; ν_{max} /cm^{-1} (film) 2931, 2858, 1750, 1657, 1468, 1369, 1317, 1255, 1218, 1095 and 1034; δ_H (500 MHz, $CDCl_3$) 0.02 (3H, s, SiMe*Me*), 0.04 (3H, s, Si*Me*Me), 0.90 (9H, s, SiC*Me*$_3$), 1.28 (3H, t, *J* 7, $C\mathit{H}_3CH_2$), 1.76 (3H, s, Me), 3.41 (3H, s, OMe), 3.48 (1H, d, *J* 16, CH*H*), 3.72 (1H, d, *J* 16, C*H*H), 3.73 (1H, d, *J* 4), 4.20 (2H, q, *J* 7, $C\mathit{H}_2CH_3$), 4.31 (1H, d, *J* 4), 4.94 (1H, s, =C*H*H) and 5.04 (1H, s, =CH*H*); δ_C (126 MHz, $CDCl_3$) -5.1 (SiMe*Me*), -5.0 (Si*Me*Me), 14.3 ($\mathit{C}H_3CH_2$), 18.3 (Si*C*Me$_3$), 18.8 (Me), 25.9 (SiC*Me*$_3$), 47.0 ($\mathit{C}H_2$), 60.2 (O*Me*), 61.3 ($\mathit{C}H_2O$), 77.5 (*C*HOMe), 90.2 (*C*HOTBS), 113.7 ($C{=}\mathit{C}H_2$), 143.9 ($\mathit{C}{=}CH_2$), 167.6 (*C*O$_2$Et) and 204.8 (*C*=O); *m/z* (ES$^+$) 367.1911 (M+Na$^+$, $C_{17}H_{32}O_5NaSi^+$ requires 367.1911), 345 and 303 (100%).

(4R,5S)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-6-methyl-3-oxo-2-diazo-hept-6-enoic acid ethyl ester 378



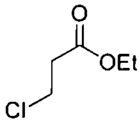
To a stirred solution of **376** (129 mg, 0.375 mmol) in MeCN (2.5 mL) under argon was added Et_3N (0.058 mL, 0.42 mmol) and tosyl azide (90 mg, 0.46 mmol), the mixture stirred for 2 hr and evaporated to give an off-white solid. Purification by silica gel chromatography (EtOAc: pet. ether, 1:9) gave a mixture of product and tosyl azide which was further purified by silica gel chromatograpy (DCM then EtOAc: pet ether, 15:85 as eluent) to give the title compound (114 mg, 82 %) as a clear oil. $[\alpha]_D^{23}$ = +22.8 (c=1.7, DCM); ν_{max} /cm^{-1} (film) 2930, 2134, 1718, 1665, 1465, 1369, 1303, 1253, 1218 and 1089; δ_H (500 MHZ, $CDCl_3$) 0.01 (6H, s, Si*Me*$_2$), 0.87 (9H, s, SiC(*Me*)$_3$), 1.33 (3H, t, *J* 7, C*H*$_3$CH$_2$O), 1.77 (3H, s, Me), 3.42 (3H, s, OMe), 4.32 (2H, q, *J* 7, C*H*$_2$CH$_3$), 4.42 (1H, d, *J* 5, C*H*OTBS), 4.55 (1H, brs, C*H*OMe), 4.90 (1H, s, =CH*H*) and 4.97 (1H, s, =C*H*H); δ_C (126 MHz, CDCl$_3$) -5.1 (SiMe*Me*), -4.9 (Si*Me*Me), 14.5 (*C*H$_3$CH$_2$), 18.4 (Si*C*Me$_3$), 18.7 (Me), 25.9 (SiC*Me*$_3$), 59.6 (OMe), 61.8 (*C*H$_2$O), 77.3 (*C*HOTBS), 113.5 (alkene), 144.3 (alkene), 161.4 (*C*O$_2$Et) and 190.4 (*C*=O); *m/z* (ES$^+$) 393.1814 (M+Na$^+$, $C_{17}H_{30}O_5N_2NaSi^+$ requires 393.1816.

(4*R*,5*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-6-methyl-2-methylene-3-oxo-hept-6-enoic acid ethyl ester 379



To a stirred solution of *β*-keto ester **376** (180 mg, 0.52 mmol) in DCM (5 mL) was added AcOH (0.050 mL, 0.88 mmol), pyrrolidine (0.070 mL, 0.84 mmol) and formaldehyde (1.0 mL of a 1.6 M solution in DCM, 1.6 mmol), the mixture stirred for 2.5 hr, diluted with Et$_2$O and washed with 5% HCl (15 mL), water (15 mL) and brine (15 mL). Drying (MgSO$_4$) and evaporation gave crude product as a pale yellow oil. Purification by silica gel chromatography (Et$_2$O: pet. ether, 1:9 then 1:4 as eluent) gave ethoxyaldol **377** (54 mg) as a clear oil and the title compound (30 mg, 16%) as a clear oil. δ_H (400 MHz, CDCl$_3$) 0.02 (3H, s, Si*Me*Me), 0.03 (3H, s, SiMe*Me*), 0.87 (9H, s, C*Me*$_3$), 1.33 (3H, t, *J* 7, C*H*$_3$CH$_2$), 1.75 (3H, s, Me), 3.39 (3H, s, OMe), 4.16 (1H, d, *J* 5, C*H*OMe), 4.29 (2H, q, *J* 7, CH$_3$C*H*$_2$), 4.43 (1H, d, *J* 5, C*H*OTBS), 4.88 (1H, s, C*H*H), 4.95 (1H, s, CH*H*), 6.36 (1H, s, C*H*H) and 6.39 (1H, s, CH*H*); δ_C (101 MHz, CDCl$_3$) -4.8 (Si*Me*$_2$), 14.3 (CH$_2$*C*H$_3$), 18.5 (*C*H$_3$), 22.8 (*C*Me$_3$), 26.0 (C*Me*$_3$), 59.7 (OMe), 61.4 (*C*H$_2$CH$_3$), 77.8 (*C*HOMe), 89.5 (*C*HOTBS), 114.0 (*C*H$_2$), 132.6 (*C*H$_2$), 141.8 (alkene), 144.2 (alkene), 165.0 (*C*O$_2$Et) and 199.7 (*C*=O); *m/z* (ES$^+$) 357 (M+H$^+$), 303, 231 and 156 (100 %).

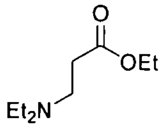
Ethyl 3-chloropropanoate 385



To a stirred solution of 3-chloropropionic acid (10.0 g, 92.6 mmol) in ethanol (100 mL) was added H$_2$SO$_4$ (5.0 mL, 90 mmol) dropwise and the mixture heated to reflux under argon . After 17 hr the mixture was cooled, concentrated to ca. 50 mL and partitioned between water (150 mL) and Et$_2$O (200 mL). The organic phase was washed with sat.

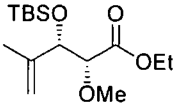
aq. $NaHCO_3$ (60 mL) and brine (60 mL), dried ($MgSO_4$) and evaporated to give the title compound (8.51 g, 67 %) as a very pale yellow oil. ν_{max} /cm^{-1} (film) 2983, 1736, 1375, 1206 and 1019; δ_H (500 MHz, $CDCl_3$) 1.25 (3H, t, *J* 7, CH_3), 2.75 (2H, t, *J* 6.5, CH_2CO_2), 3.73 (2H, t, *J* 6.5, CH_2Cl) and 4.16 (2H, q, *J* 7, CH_2O); δ_C (126 MHz, $CDCl_3$) 14.2 (CH_3), 37.6 (CH_2), 39.1 (CH_2), 61.0 (CH_2O) and 170.3 (CO_2); *m/z* (EI$^+$) 136.0288 (M$^+$, $C_5H_9O_2Cl^+$ requires 136.0286, 100%).

Ethyl 3-(diethylamino)propanoate 386



To a stirred solution of diethylamine (13.1 g, 0.18 mmol) in dry toluene under argon was added **385** (6.5 g, 47.6 mmol) and the mixture heated to 110 °C. After 1 hr the mixture was cooled, concentrated, partitioned between water (150 mL) and Et_2O (150 mL) and the organic phase washed with water (100 mL) and brine (50 mL). Drying ($MgSO_4$) and evaporation gave the title compound (5.95 g, 74 %) as an orange oil. ν_{max} /cm^{-1} (film) 2973, 2808, 1737, 1466, 1371, 1201 and 1050; δ_H (500 MHz, $CDCl_3$) 1.01 (6H, t, *J* 7, $(CH_3CH_2)_2N$), 1.24 (3H, t, *J* 7, CH_3CH_2O), 2.43 (2H, t, *J* 7.5, CH_2CO_2), 2.50 (4H, q, *J* 7, $(CH_3CH_2)_2N$), 2.78 (2H, t, *J* 7.5, CH_2CH_2N) and 4.12 (2H, q, *J* 7, CH_2O); δ_C (126 MHz, $CDCl_3$) 12.0 ($(CH_3CH_2)_2N$), 14.3 (CH_3CH_2O), 32.4 (CH_2CO_2), 46.6 ($(CH_3CH_2)_2N$), 48.1 (CH_2CH_2N), 60.4 (CH_2O) and 173.0 (CO_2); *m/z* (EI$^+$) 173.1409 (M$^+$, $C_9H_{19}NO_2$ requires 173.1410, 100%).

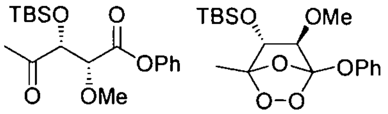
(2*R*,3*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methoxy-4-methyl-pent-4-enoic acid ethyl ester 377



To a stirred solution of **386** (173 mg, 1.02 mmol) in dry THF (5 mL) at -78 °C under argon was added ^{t}BuLi (0.82 mL of a 1.5 M solution in pentane, 1.2 mmol) dropwise and the mixture stirred for 5 min before the dropwise addition of **55** (236 mg, 0.67 mmol). The reaction was stirred at -78 °C for 2 hr, warmed to room temperature, stirred for 30 min and quenched by the dropwise addition of sat. aq. NH_4Cl (1 mL). The mixture was partitioned between Et_2O (30 mL) and water (20 mL), separated and the organic phase washed with brine (20 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow oil. Purification by silica gel chromatography (EtOAc: pet.

ether, 2:98 to 5:95 as eluent) gave the title compound (99 mg, 49 %) as a pale yellow oil. $[\alpha]_D^{23}$ = +42.2° (c=0.45, DCM). ν_{max} /cm^{-1} (film) 2929, 2903, 1749, 1650, 1472, 1463, 1370, 1291, 1196, 1123 and 1096; δ_H (400 MHz, $CDCl_3$) 0.06 (3H, s), 0.07 (3H, s), 0.88 (9H, s), 1.26 (3H, t, *J* 7.2), 1.76 (3H, s), 3.40 (3H, s), 3.75 (1H, d, *J* 6.2), 4.16 (2H, q, *J* 7.2), 4.27 (1H, d, *J* 6.2), 4.83 (1H, m) and 4.88 (1H, m); δ_C (101 MHz, $CDCl_3$,) -4.9, -4.8, 14.3, 17.7, 18.4, 25.9, 59.1, 60.9, 78.7, 85.5, 113.6, 144.4 and 164.7; *m/z* (ES^+) 325.1805 ($M+Na^+$,$C_{15}H_{30}O_4NaSi^+$ requires 325.1806), 303 and 271.

(2*R*,3*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methoxy-4-oxo-pentanoic acid phenyl ester 392 and *tert*-Butyl-((5*R*,6*R*)-6-methoxy-4-methyl-1-phenoxy-2,3,7-trioxa-bicyclo[2.2.1]hept-5-yloxy)-dimethyl-silane 407



Mixture of diastereoisomers.

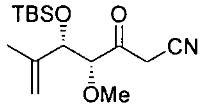
A stirred solution of phenyl ester **323** (120 mg, 0.34 mmol, 1.4:1 *syn*:*anti*) in dry DCM (4 mL) under argon was cooled to -78 °C, ozone bubbled though until a blue colour appeared, O_2 passed through to remove the excess ozone and DMS (0.050 mL, 0.68 mmol) added dropwise. The mixture was stirred at -78 °C for 10 min, warmed to room temperature, stirred for 15 min and evaporated to give crude product as a clear oil. Purification by silica gel chromatography (Et_2O: pet. ether, 15:85 as eluent) gave **392** (95 mg, 79 %, 1.16:1 *syn*:*anti*) as a clear oil.

Single diastereoisomer

A stirred solution of phenyl ester **323** (147 mg, 0.42 mmol) in dry DCM (5 mL) under argon was cooled to -78 °C, ozone bubbled though until a blue colour appeared, O_2 passed through to remove the excess ozone and DMS (0.060 mL, 0.82 mmol) added dropwise. The mixture was stirred at -78 °C for 10 min, warmed to room temperature, stirred for 15 min and evaporated to give crude product as a clear oil. Purification by silica gel chromatography (Et_2O: pet. ether, 12:88 as eluent) gave **392** (90 mg, 61 %) as a clear oil and cross-ozonide (20 mg, 13%) as a clear oil. **392**: $[\alpha]_D^{23}$ = +58.3 (c = 1.2, DCM); ν_{max} /cm^{-1} (film) 2955, 2931, 1780, 1720, 1593, 1493, 1464, 1352, 1254, 1192, 1163, 1139 and 1113; δ_H (500 MHz, $CDCl_3$) 0.07 (3H, s, SiMe*Me*), 0.10 (3H, s, Si*Me*Me), 0.94 (9H, s, C*Me*$_3$), 2.31 (3H, s, MeCO), 3.50 (3H, s, OMe), 4.22 (1H, d, *J* 4, C*H*OMe), 4.51 (1H, d, *J* 4, C*H*OTBS), 7.18 (2H, d, *J* 8, aryl), 7.24 (1H, t, *J* 8, aryl) and

7.39 (1H, t, *J* 8, aryl); δ_C (126 MHz, $CDCl_3$) -4.75 (Si*Me*$_2$), 18.3 (Si*C*Me$_3$), 25.9 (C*Me*$_3$), 27.2 (*Me*CO), 59.6 (OMe), 79.7 (*C*HOMe), 83.4 (*C*HOTBS), 121.3 (2C, aryl), 126.2 (1C, aryl), 129.6 (2C, aryl), 150.5 (1C, aryl), 168.0 (*C*O$_2$Ph) and 210.0 (*C*=O); *m/z* (CI^+) 370 ($M+NH_4^+$), 278 and 276 (100%); HRMS (ES^+) 370.2045 ($M+NH_4^+$, $C_{18}H_{32}NO_5Si^+$ requires 370.2044). **407**: $[\alpha]_D^{23}$ = + 19 (c = 0.26, DCM); ν_{max}/cm^{-1} (film) 2955, 2931, 2858, 1593, 1492, 1472, 1349, 1225, 1160 and 1106; δ_H (500 MHz, $CDCl_3$) 0.14 (3H, s, Si*Me*Me), 0.17 (3H, s, SiMe*Me*), 0.95 (9H, s, CMe$_3$), 1.52 (3H, s, Me), 3.65 (3H, s, OMe), 3.84 (1H, d, *J* 2, C*H*OMe), 4.06 (1H, d, *J* 2, C*H*OTBS), 7.20 (1H, tt, *J* 5,1, *para*-aromatic CH) and 7.27-7.36 (4H, m, aromatic CH); δ_C (126 MHz, $CDCl_3$) -4.9 (Si*Me*Me), -4.6 (SiMe*Me*), 12.5 (Me), 18.1 (*C*Me$_3$), 25.8 (C*Me*$_3$), 59.5 (OMe), 79.4 (*C*HOTBS), 90.4 (*C*HOMe), 111.1 (O*C*Me), 121.2 (O*C*OPh), 121.4 (aromatic), 125.5 (aromatic), 129.3 (aromatic) and 152.2 (aromatic); *m/z* (CI^+) 370 (100%); HRMS not obtained due to decomposition resulting peaks of greater molecular weight.

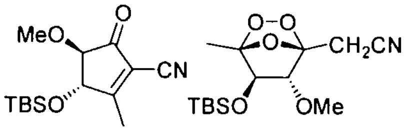
(4*R*,5*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-6-methyl-3-oxo-hept-6-enenitrile 396



A stirred solution of LiHMDS (6.0 mL of a 1.0 M solution in THF, 6.0 mmol) was cooled to -78 °C under argon, MeCN (0.35 mL, 6.7 mmol) added dropwise and the mixture stirred for 30 min before the dropwise addition of phenyl ester **323** (1.00 g, 2.86 mmol). The reaction was stirred for 2 hr, warmed to room temperature and quenched by the addition of 5% HCl (5 mL). The mixture was diluted with Et_2O (70 mL) and washed with 5% HCl (30 mL), water (30 mL) and brine (30 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow oil. Purification by silica gel chromatography (two columns, Et_2O: pet. ether, 1:4 then 1:1 as eluent) gave the title compound (820 mg, 97 %) as a clear oil which subsequently crystalised. Mpt. 41-44 °C; $[\alpha]_D^{23}$ = +62.3 (c = 0.43, DCM); ν_{max} /cm^{-1} (film) 2951, 2929, 2857, 2258, 1737, 1652, 1471, 1388, 1311, 1254 and 1081; δ_H (500 MHz, $CDCl_3$) 0.00 (3H, s, Si*Me*Me), 0.02 (3H, s, SiMe*Me*), 0.89 (9H, s, C*Me*$_3$), 1.76 (3H, s, Me), 3.42 (3H, s, OMe), 3.71 (1H, abq, CH_2CN), 3.74 (1H, d, *J* 3.6, C*H*OMe), 4.31 (1H, d, *J* 3.6, C*H*OTBS), 4.98 (1H, s, =C*H*H) and 5.06 (1H, s, =CH*H*); δ_C (126 MHz, $CDCl_3$) -5.2 (Si*Me*Me), -4.9 (SiMe*Me*), 18.3 (*C*Me$_3$), 18.8 (Me), 25.9 (C*Me*$_3$), 30.6 (*C*H$_2$CN), 60.5 (OMe), 77.5 (*C*HOMe), 89.9 (*C*HOTBS), 113.7 (*C*N), 114.1 (=*C*H$_2$), 143.6 (*C*=CH$_2$) and 199.9 (*C*=O); *m/z* (CI^+) 315

($M+NH_4^+$), 187, 132 and 91; HRMS (ES$^+$) 315.2099 ($C_{12}H_{31}SiN_2O_3^+$, $M+NH_4^+$, requires 315.2098); elemental anal. $C_{12}H_{27}SiNO_3$ requires C, 60.61; H 9.09; N 4.71; found C, 60.52; H, 9.28; N, 4.46.

(3*S*,4*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-2-methyl-5-oxo-cyclopent-1-enecarbonitrile 395 and [(1*R*,4*S*,5*R*,6*R*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-6-methoxy-4-methyl-2,3,7-trioxa-bicyclo[2.2.1]hept-1-yl]-acetonitrile 405



A stirred solution of nitrile **396** (576 mg, 1.94 mmol) in dry DCM (50 mL) was cooled to -78 °C under argon, ozone bubbled through until a blue colour appeared, oxygen passed through to remove the excess ozone and DMS (0.90 mL, 12 mmol) added dropwise. The reaction was stirred for 15 min, warmed to room temperature over 30 min and evaporated to give the crude product as a pale yellow oil. Purification by silica gel chromatography (Et_2O:pet. ether, 15:85 then 1:4 then 1:1 as eluent) gave **395** (305 mg, 56 %) as a clear oil and **405** (242 mg, 40 %), as a white solid. **395**: $[\alpha]_D^{23}$ = +48.0 (c=0.5, DCM); ν_{max}/cm^{-1} (film) 2959, 2932, 2860, 2255, 1742, 1629, 1472, 1363, 1261, 1119, 1078 and 1023; δ_H (500 MHz, $CDCl_3$) 0.17 (3H, s, Si*Me*Me), 0.17 (3H, s, SiMe*Me*), 0.93 (9H, s, C*Me*$_3$), 2.33 (3H, d, *J* 1, Me), 3.68 (3H, s, OMe), 3.79 (1H, d, *J* 3, C*H*OMe) and 4.60 (1H, dd, *J* 3, 1, C*H*OTBS); δ_C (126 MHz, $CDCl_3$) -5.1 (Si*Me*Me), -4.6 (SiMe*Me*), 16.6 (Me), 18.1 (*C*Me$_3$), 25.7 (C*Me*$_3$), 59.6 (OMe), 77.0 (*C*HOTBS), 88.2 (*C*HOMe), 111.0 (=*C*-CN), 115.8 (CN), 184.4 (Me-*C*=) and 195.3 (C=O); *m/z* (CI$^+$) 299 ($M+NH_4^+$, 100%); HRMS (ES$^+$) 299.1788 ($M+NH_4^+$, $C_{14}H_{27}SiO_3N_2^+$, requires 299.1785). **405**: Mpt. 52-55 °C; $[\alpha]_D^{23}$ = -23.3 (c = 0.43, DCM); ν_{max} /cm^{-1} (film) 3016, 2934, 2857, 2264, 1471, 1462, 1358, 1257, 1215 and 1111; δ_H (500 MHz, $CDCl_3$) 0.12 (3H, s, SiMe*Me*), 0.15 (3H, s, Si*Me*Me), 0.92 (9H, s, SiC(*Me*)$_3$), 1.58 (3H, s, Me), 3.08 (2H, m, CH_2), 3.55 (3H, s, OMe), 3.67 (1H, d, *J* = 1.5, C*H*OMe) and 3.94 (1H, d, *J* = 1.5, C*H*OTBS); δ_C (126 MHz, $CDCl_3$) -4.42 (SiMe*Me*), -4.38 (Si*Me*Me), 11.9 (Me), 17.8 (CH_2), 18.0 (Si*C*Me$_3$), 25.8 (SiC*Me*$_3$) 59.8 (OMe), 77.3 (*C*OMe), 92.0 (COTBS), 105.2 (*C*MeO$_2$), 113.3 (CH$_2$*C*O$_2$) and 114.1 (CN); Elemental analysis, anal. calc. for $C_{14}H_{25}NO_5Si$; C, 53.33; H, 7.94; N, 4.44; found C, 53.51; H, 8.04; N, 4.34; *m/z* (ES$^+$) 333 ($M+NH_4^+$) and 316 ($M+H^+$).

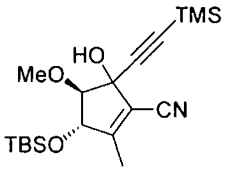
*Reduction of ozonide **405**.*

To a stirred solution of ozonide **405** (260 mg, 0.83 mmol) in THF (25 mL) was added zinc powder (160 mg, 2.0 mmol) then 20% HCl (0.50 mmol, 3.2 mmol) dropwise, stirred vigorously for 40 min, partitioned between Et_2O (50 mL) and water (20 mL), the aqueous phase extracted with Et_2O (10 mL) and the combined organic phase washed with brine (20 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a pale yellow oil. Purification by silica gel chromatography (Et_2O: pet. ether, 15:85 then 1:4 then 1:1 as eluent) gave cyclopentenone **395** (156 mg, 67 %) as a pale yellow oil.

Iron(II) sulphate mediated ozonide reduction.

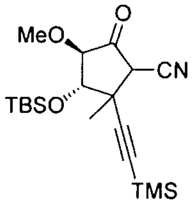
To a stirred solution of ozonide **405** (40 mg, 0.13 mmol) in THF (4 mL) was added an aqueous solution of $FeSO_4$ (1.2 mL of 3.5 M, 4.3 mmol containing 5% H_2SO_4) and the mixture stirred vigorously for 2 hr before diluting with Et_2O (30 mL) and washing with water (15 mL) and brine (15 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a clear oil. Purification by silica gel chromatography (Et_2O: pet. ether, 1:4 then 1:1 as eluent) gave a clear oil (15 mg, 39%). ν_{max}/cm^{-1} (film) 1212, 1262, 1398, 1426, 1473, 1738, 2400, 2961 and 3019; δ_H (500 MHz, $CDCl_3$) 0.16 (3H, s), 0.16 (3H, s), 0.91 (9H, s), 2.33 (3H, s), 3.58 (3H, s), 4.22 (1H, d, *J* 4.5) and 5.04 (1H, d, *J* 4.5); -4.7, -4.3, 18.3, 20.7, 25.7, 57.6, 69.0, 104.4, 106.6 (q), 112.6 (q), 157.3 (q) and 170.0 (q); *m/z* (ES^+) 315.1729 ($M+NH_4^+$, $C_{14}H_{23}O_4N_2Si^+$ requires 315.1735).

(3*S*,4*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-hydroxy-4-methoxy-2-methyl-5-trimethylsilanylethynyl-cyclopent-1-enecarbonitrile 408



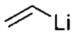
A stirred solution of TMS acetylene (162 mg, 1.66 mmol) in dry Et_2O (8 mL) was cooled to -78 °C under argon, *n*-BuLi (0.76 mL of a 2.5 M solution in hexanes, 1.9 mmol) added dropwise and the mixture stirred for 30 min. The mixture was warmed to -10 °C and 5.8 mL of the resulting solution added to a stirred solution/suspension of copper(I) iodide (104 mg, 0.55 mmol) in dry Et_2O (4 mL) at -10 °C under argon. The mixture was stirred for 1 hr before the dropwise addition of a solution of cyclopentenone **395** (150 mg, 0.53 mmol) in dry Et_2O (5 mmol) and the mixture stirred at -10 °C. After 90 min the mixture was warmed to room temperature, quenched by the dropwise addition of 5% HCl (2 mL), diluted with Et_2O (30 mL) and water (10 mL), separated and the organic phase washed with brine (10 mL). Drying ($MgSO_4$) and evaporation gave the crude product as an orange oil. Purification by silica gel chromatography (EtOAc: pet. ether, 5:95 as eluent) gave the title compound (45 mg, 22 %) as a colourless wax. $[\alpha]_D^{23}$ = +111 (c = 1.8, DCM); ν_{max} /cm^{-1} (film) 3049, 2956, 2302, 2220, 1720, 1652, 1605, 1462, 1421, 1265, 1128 and 1100; δ_H (500 MHz, $CDCl_3$) 0.07 (3H, s, Si*Me*Me), 0.12 (3H, s, SiMe*Me*), 0.20 (9H, s, Si*Me*$_3$), 0.90 (9H, s, ^{t}Bu), 1.97 (3H, d, *J* 1.5, Me), 2.68 (1H, s, OH, exchanges with D_2O), 3.57 (3H, s, OMe), 3.65 (1H, d, *J* 6, C*H*OMe) and 4.35 (1H, dd, *J* 6, 1.5, C*H*OTBS); δ_C (126 MHz, $CDCl_3$) -5.0 (Si*Me*Me), -4.4 (SiMe*Me*), 1.2 (Si*Me*$_3$), 14.5 (Me), 18.2 (*C*Me$_3$), 25.8 (C*Me*$_3$), 29.9 (*C*Me), 59.0 (OMe), 76.7 (*C*HOTBS), 79.3 (*C*HOMe), 95.5 (COH), 96.5 (alkyne), 99.9 (alkyne), 113.9 (nitrile), 114.0 (alkene) and 160.3 (alkene); *m/z* (ES$^+$) 397.2337 (M+NH_4^+, $C_{19}H_{37}Si_2N_2O_3$, requires 397.2337) and 362 (100 %).

(2*S*,3*S*,4*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-2-methyl-5-oxo-2-trimethylsilanylethynyl-cyclopentanecarbonitrile 409



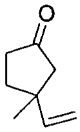
A stirred solution of TMSA (300 mg, 3.05 mmol) in dry Et_2O (6 mL) was cooled to 0 °C under argon, ^{n}BuLi (1.95 mL of a 1.6 M solution in hexane, 3.1 mmol) added dropwise and the mixture stirred for 30 min. A stirred solution of diethylaluminium chloride (3.0 mL of a 1.0 M solution in hexane, 3.0 mmol) under argon was diluted with dry Et_2O (3 mL), the solution of lithium acetylide added dropwise and the mixture stirred for 2.5 hr. A solution/suspension of Ni(acac)$_2$ (46 mg, 0.18 mmol) in dry Et_2O (4 mL) was cooled to 0 °C with vigorous stirring under argon, DIBAL-H (0.18 mL of a 1.0 M solution in hexane, 0.18 mmol) was added dropwise, stirred for 10 min, cooled to -10 °C and the previously prepared solution (13 mL, 2.8 mmol) added slowly. After stirring for 2 min a solution of cyclopentenone **395** (250 mg, 0.89 mmol) in dry Et_2O (4 mL) was added dropwise, stirred for 90 min, warmed to room temperature, stirred for 16 hr, diluted with Et_2O (15 mL) and quenched with water (10 mL). A solution of H_2SO_4 (2 mL) in water (5 mL) was added cautiously, the mixture stirred vigorously for 10 min, separated, extracted with Et_2O (20 mL) and the combined organic phase washed with sat. aq. $NaHCO_3$ (15 mL), water (15 mL) and brine (15 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a brown oil. Purification by silica gel chromatography (Et_2O: pet, ether, 1:4 then 1:1 then EtOAc: pet. ether, 1:4 as eluent) gave cyclopentenone **395** (100 mg) and the title compound (71 mg, 21 %), both brown oils. ν_{max} (film) /cm^{-1} 3181 (br), 3021, 2217, 2170, 1771, 1738, 1674, 1633, 1472, 1464, 1386 and 1252; δ_H (500 MHz, $CDCl_3$) 0.14 (3H, s, SiMe*Me*), 0.14 (3H, s, Si*Me*Me), 0.15 (9H, s, Si*Me*$_3$), 0.93 (SiC*Me*$_3$), 1.38 (3H, s, Me), 3.50 (1H, d, *J* 8.5, C*H*OMe), 3.58 (1H, s, C*H*CN), 3.61 (3H, s, OMe) and 4.15 (1H, d, *J* 8.5, C*H*OTBS); δ_C (126 MHz, $CDCl_3$) -4.7 (Si*Me*Me), -4.6 (SiMe*Me*), -0.1 (Si*Me*$_3$), 0.0 (Si*Me*$_2$), 18.2 (*C*(Me)(C_2H_3)), 18.6 (Si*C*Me$_3$), 21.5 (Me), 25.8 (SiC*Me*$_3$), 39.4 (*C*HCN), 60.1 (OMe), 79.4 (*C*HOTBS), 84.9 (*C*HOMe), 88.4 (alkyne), 106.5 (alkyne), 113.1 (CN) and 200.7 (C=O); HRMS (CI$^+$) 397.2338 (M+NH_4^+, $C_{19}H_{37}Si_2N_2O_3^+$, requires 397.2337, 100 %).

Vinyl lithium^{470}



^{n}BuLi (26.0 mL of a 1.6 M solution in hexane, 41.6 mmol) was added slowly to stirred tetravinyltin (2.43 g, 10.7 mmol) under argon. The resulting milky yellow solution was stirred at room temperature for 3 hr before being allowed to settle for 10 min. The supernatant liquid was removed using a syringe and the resulting solid washed with hexane (3 x 25 mL). Drying in vacuo gave vinyl lithium (0.947 g, 67 %) as a white solid which was dissolved in dry THF (27.9 mL) to give a 1.0 M solution.

3-Methyl-3-vinyl-cyclopentanone 410



Nickel catalysed alane addition

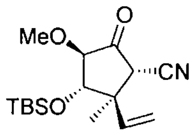
Dimethylaluminium chloride (5.0 mL of a 1.0 M solution in hexanes, 5.0 mmol) was diluted with Et_2O (5.0 mL) with stirring under argon, vinylmagnesium bromide (5.0 mL of a 1.0 M solution in THF, 5.0 mmol) added dropwise (white solid precipitates) and the mixture stirred for 2.5 hr before allowing to settle. To a stirred solution/suspension of Ni(II) acetylacetonate (100 mg, 0.40 mmol) in dry Et_2O (10 mL) at 0 °C under argon was added DIBAL-H (0.40 mL of a 1.0 M solution in hexane, 0.40 mmol) dropwise and the mixture stirred for 10 min before cooling to -10 °C to allow the slow addition of a solution of the previously prepared alane (12 mL, 4.0 mmol). After stirring for a further 5 min methylcyclopentenone **351** (0.196 mL, 2.0 mmol) was added dropwise, stirred for 2 hr, warmed to room temperature and quenched by the careful addition of ice cold 20

% aq. H_2SO_4 (10 mL). After stirring vigorously for 20 min the mixture was partitioned between Et_2O (40 mL) and water (20 mL), separated, re-extracted with Et_2O (20 mL) and the combined organic phase washed with sat. aq. $NaHCO_3$ (30 mL) and brine (30 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow/orange oil. Purification by silica gel chromatography (EtOAc: pet. ether, 1:9 as eluent) gave the title compound (48 mg, 19 %) as a pale yellow oil.

Cuprate addition

To a stirred suspension of copper(I) iodide (230 mg, 1.2 mmol) in dry THF (3 mL) under argon was added trioctylphosphine (0.60 mL, 1.3 mmol) dropwise (iodide dissolves) and the mixture cooled to -78 °C to allow the dropwise addition of vinylmagnesium bromide (2.4 mL of a 1.0 M solution in THF, 2.4 mmol). After stirring 5 min methylcyclopentenone **351** (0.10 mL, 1.0 mmol) was added dropwise, stirred for 2 hr, warmed to -50 °C, stirred for 1 hr and warmed to 10 °C gradually over 2 hr. The reaction was quenched by the addition of sat. aq. NH_4Cl (1 mL), passed through Celite with elution with Et_2O (60 mL) and washed with 5 % HCl (20 mL) and brine (20 mL). Drying ($MgSO_4$) and evaporation gave the crude as an orange oil. Purification by silica gel chromatography (EtOAc: pet. ether, 1:9 as eluent) gave the title compound (50 mg, 40 %) as a pale yellow oil. ν_{max} (film) / cm^{-1} 2959, 1743, 1601, 1454, 1405, 1377, 1252 and 1165; δ_H (500 MHz, $CDCl_3$) 1.19 (3H, s, Me), 1.79-1.82 (1H, m), 1.95-1.99 (1H, m), 2.06 (1H, d, J 18), 2.27 (2H, t, J 8), 2.31 (1H, d, J 18), 4.98 (1H, d, J 17.5), 5.00 (1H, d, J 11) and 5.87 (1H, dd, J 17.5, 11); δ_C (126 MHz, $CDCl_3$) 25.9 (Me), 35.3 (CH_2), 36.8 (CH_2), 42.4 (q), 51.0 (CH_2), 111.9 (CH_2), 145.4 (=CH) and 219.1 (C=O); HRMS (EI) 124.0882 (M^+, $C_8H_{12}O^+$, requires 124.0883), 96 and 67 (100 %).

(1*S*,2*R*,3*S*,4*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-2-methyl-5-oxo-2-vinyl-cyclopentanecarbonitrile 411



Nickel catalysed alane addition

Dimethylaluminium chloride (2.0 mL of a 1.0 M solution in hexanes, 2.0 mmol) was diluted with Et_2O (2.0 mL) with stirring under argon, vinyl lithium (2.0 mL of a .0 M solution in Et_2O, 2.0 mmol) added dropwise (white solid precipitates) and the mixture stirred for 2.5 hr before being allowed to settle. To a stirred solution/suspension of

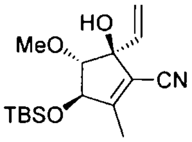
Ni(II) acetylacetonate (28 mg, 0.11 mmol) in dry Et_2O (2.0 mL) at 0 °C under argon was added DIBAL-H (0.11 mL of a 1.0 M solution in hexane, 0.11 mmol) dropwise and the mixture stirred for 10 min before cooling to -10 °C to allow the slow addition of a solution of the previously prepared alane (4.0 mL, 1.3 mmol). After stirring for a further 3 min a solution of cyclopentenone **395** (150 mg, 0.53 mmol) in dry Et_2O (2.0 mL) was added dropwise, stirred for 2 hr, warmed to room temperature, stirred for 30 min and quenched by the careful addition of 25 % aq. H_2SO_4 (4 mL). After stirring vigorously for 8 min the mixture was partitioned between Et_2O (20 mL) and water (10 mL), separated, re-extracted with Et_2O (10 mL) and the combined organic phase washed with sat. aq. $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow/orange oil. Purification by silica gel chromatography (EtOAc: pet. ether, 1:4 then 2:3 then 1:0 as eluent) gave the title compound (66 mg, 40 %) as a light yellow wax.

Cuprate addition

To a stirred suspension of copper(I) iodide (150 mg, 0.79 mmol) in dry THF (2 mL) under argon was added trioctylphosphine (0.45 mL, 1.0 mmol) dropwise (iodide dissolves) and the mixture cooled to -78 °C to allow the dropwise addition of vinylmagnesium bromide (1.8 mL of a 1.0 M solution in THF, 1.8 mmol). After stirring 5 min a solution of cyclopentenone **395** (180 mg, 0.64 mmol) in dry THF (1.5 mL) was added dropwise, stirred for 2 hr, warmed to -50 °C, stirred for 1 hr and warmed to 10 °C gradually over 2 hr. The reaction was quenched by the addition of sat. aq. NH_4Cl (2 mL), passed through Celite with elution with Et_2O (70 mL) and washed with 5 % HCl (20 mL) and brine (20 mL). Drying ($MgSO_4$) and evaporation gave the crude as a yellow oil. Purification by silica gel chromatography (EtOAc: pet. ether, 12:88 then 1:4 then 1:1 then 1:0 as eluent) gave the title compound (160 mg, 81 %, 10:1 mixture of diastereoisomers) as a pale yellow oil which crystallised on cooling. $[\alpha]_D^{23}$ = +33.8 (c = 1.3, DCM); ν_{max} (film) /cm^{-1} 3407, 2956, 2929, 2857, 2253, 1767, 1643, 1471, 1380, 1259 and 1097; δ_H (500 MHz, $CDCl_3$) 0.06 (3H, s, SiMe*Me*), 0.08 (3H, s, Si*Me*Me), 0.89 (9H, s, SiC*Me*$_3$), 1.24 (3H, s, Me), 3.36 (1H, s, CHCN), 3.60 (1H, d, *J* 8, C*H*OTBS), 3.86 (1H, d, *J* 8, C*H*OMe), 5.23 (1H, d, *J* 17.5, =CH*H*), 5.29 (1H, d, *J* 10.5, C*H*H) and 5.82 (1H, dd, *J* 17.5, 10.5, C*H*=CH_2); δ_C (126 MHz, $CDCl_3$) -5.0 (SiMe*Me*), -4.4 (Si*Me*Me), 15.7 (Me), 18.2 (SiCMe_3), 25.8 (SiC*Me*$_3$), 45.4 (*C*Me), 49.5 (*C*-CN), 59.9 (OMe), 79.3 (*C*HOTBS), 85.2 (*C*HOMe), 113.5 (CN), 116.3 (=*C*H_2), 140.3 (*C*H=CH_2) and 201.7 (C=O); HRMS (ES$^-$) 308.1690 (M-H$^-$, $C_{16}H_{26}SiNO_3^-$ requires

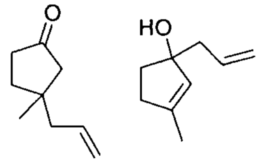
308.1688). The stereochemistry of this molecule was assigned based on interactions in its ^{1}H NOESY spectrum from the known stereochemistries of the CHOMe and CHOTBS centres. The stereochemistry of the CHCN centre was assigned from the cross-ring interaction between C*H*OTBS and C*H*CN and that of the CMe(CHCH$_2$) centre was assigned from the cross-ring interaction between C*Me*(CHCH$_2$) and C*H*OMe.

(3*R*,4*S*,5*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-hydroxy-4-methoxy-2-methyl-5-vinyl-cyclopent-1-enecarbonitrile 412



To a stirred solution of vinylmagnesium bromide (1.3 mL of a 0.23 M solution in THF, 0.3 mmol) at -78 °C was added cyclopentenone **395** (40 mg, 0.14 mmol) dropwise, the reaction stirred for 45 min, warmed to -42 °C and stirred for 1 hr. After warming to room temperature the reaction was quenched by the addition of sat. aq. NH_4Cl (0.3 mL), diluted with Et_2O (20 mL) and washed with brine (10 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a pale yellow solid. Purification by silica gel chromatography (EtOAc: pet. ether, 5:95 as eluent) gave the title compound (31 mg, 70%) as a white solid. Mpt = 82 – 83 °C; $[\alpha]^{23}_D$ = -150 (c = 0.47, DCM); ν_{max}/cm^{-1} 3464, 2930, 2300, 1345, 1258, 1121 and 1091; δ_H (700 MHz, $CDCl_3$) 0.10 (6H, s, Si*Me*$_2$), 0.91 (9H, s, C*Me*$_3$), 1.56 (1H, s, OH), 1.98 (3H, d, *J* 1.4, Me), 3.47 (3H, s, OMe), 3.67 (1H, d, *J* 6, C*H*OMe), 4.32 (1H, dd, *J* 6, 1.4, C*H*OTBS), 5.36 (1H, d, *J* 10.5, =C*H*H), 5.42 (1H, d, *J* 17.5, =CH*H*) and 5.88 (1H, dd, *J* 17.5, 10.5, C*H*=CH$_2$); δ_C (176 MHz, $CDCl_3$) -5.0 (Si*Me*Me), -4.4 (SiMe*Me*), 14.5 (Me), 18.2 (*C*Me$_3$), 25.8 (C*Me*$_3$), 59.1 (OMe), 79.1 (*C*HOTBS), 82.9 (*C*CH=CH$_2$), 97.2 (*C*HOMe), 114.2 (*C*-CN), 114.6 (CN), 116.5 (CH=*C*H$_2$), 135.4 (*C*H=CH$_2$) and 159.9 (Me*C*=); *m/z* (CI$^+$) 327 (M+NH$_4^+$), 292, 181 and 146 (100%); HRMS (ES$^+$) 327.2101 (M+NH$_4^+$, $C_{16}H_{31}SiN_2O_3^+$, requires 327.2098); Elemental anal. C 62.47, H 8.81, N 4.36, $C_{16}H_{27}SiNO_3$ requires C 62.14, H 8.74, N 4.53.

(±)-3-Allyl-3-methyl-cyclopentanone 415 and (±)-1-Allyl-3-methyl-cyclopent-2-enol 416.



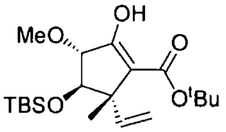
Method 1.

To a stirred suspension of copper(I) iodide (195 mg, 1.03 mmol) in dry THF (5 mL) under argon was added trioctylphosphine (0.50 mL, 1.0 mmol) dropwise and the mixtue stirred for 5 min before cooling to -42 °C to allow the dropwise addition of allylmagnesium bromide (2.2 mL of a 1.0 M solution in Et_2O, 2.2 mmol). After stirring for a further 5 min methylcyclopentenone **351** (0.10 mL, 1.0 mmol) was added dropwise, the reaction stirred for 45 min, warmed in air for 5 min and quenched by the addition of sat. aq. NH_4Cl (2 mL). The mixture was passed through Celite eluting with Et_2O (60 mL) and washed with water (20 mL) and brine (20 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow oil. Purification by silica gel chromatography (EtOAc: pet. ether, 1:9 then 1:4 as eluent) gave **415** (10 mg, 7 %) and **416** (117 mg, 85 %). **415**: ν_{max} /cm^{-1} (film) 2956, 1739, 1405 and 1169; δ_H ($CDCl_3$, 700 MHz) 1.07 (3H, s, Me), 1.70-1.78 (1H, m), 1.82-1.91 (1H, m), 1.96-2.01 (1H, m), 2.10-2.17 (3H, m), 2.26-2.34 (2H, m), 5.03-5.12 (2H, m) and 5.75-5.86 (CH_2-C*H*=CH_2); δ_C (176 MHz, $CDCl_3$) 25.7 (Me), 34.8 (CH_2), 37.0 (CH_2), 39.6 (q), 45.8 (CH_2), 51.7 (CH_2), 118.1 (CH_2), 134.6 and 219.9; *m/z* (EI) 138.1039 (M^+, $C_9H_{14}O^+$ requires 138.1039), 97 and 69 (100 %); **416**: ν_{max} /cm^{-1} (film) 3344 (br), 2920, 1664, 1642, 1437 and 1377; δ_H (700 MHz, $CDCl_3$) 1.68 (1H, brs, OH), 1.84 – 1.90 (1H, m), 2.04 – 2.10 (1H, m), 2.15 – 2.21 (1H, m), 2.38 (2H, d, *J* 7, C*H*$_2$-CH=CH_2), 2.38-2.46 (1H, m), 5.11 – 5.15 (2H, m), 5.33 (1H, s, =C*H*-COH) and 5.84-5.88 (1H, m); δ_C (176 MHz, $CDCl_3$) 16.9 (Me), 35.4 (CH_2), 38.4 (CH_2), 45.8 (CH_2), 85.5 (*C*HOH), 118.4 (CH_2), 130.3 (CH), 134.5 (CH) and 144.5 (q); *m/z* (EI) 138.1039 (M^+, $C_9H_{14}O^+$ requires 138.1039), 120 and 95 (100%).

Method 2.[435]

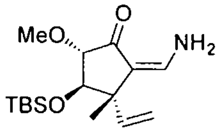
To a dry flask under a positive pressure of argon was added copper(I) bromide dimethyl sulphide complex (226 mg, 1.1 mmol), anhydrous lithium chloride (47 mg, 1.1 mmol) and anhydrous THF (2 mL) and the stirred mixture cooled to -78 °C to allow the dropwise addition of allylmagnesium bromide (1.0 mL of a 1.0 M solution in Et_2O). Chlorotrimethylsilane (0.13 mL, 1.0 mmol) and methylcyclopentenone **351** (0.10 mL, 1.0 mmol) were added dropwise, the reaction stirred for 1 hr, quenched by the addition of sat. aq. NH_4Cl (0.5 mL) and 5% HCl (0.5 mL), stirred for 3 min and passed through Celite eluting with Et_2O (60 mL). The mixture was washed with brine (20 mL), dried ($MgSO_4$) and evaporated to give the crude product as a yellow oil. Purification by silica gel chromatography (EtOAc: pet. ether, 5:95 then 1:9 then 1:1 as eluent) gave **415** (46 mg, 33 %) and starting material (34 mg, 35 %), both clear oils.

(3*S*,4*R*,5*S*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-2-hydroxy-3-methoxy-5-methyl-5-vinyl-cyclopent-1-enecarboxylic acid *tert*-butyl ester 417



To a stirred suspension of copper(I) iodide (29 mg, 0.15 mmol) in dry THF (1.5 mL) under argon was added trioctylphosphine (0.10 mL, 0.19 mmol), the mixture cooled to -78 °C to allow the dropwise addition of vinylmagnesium bromide (0.31 mL of a 1.0 M solution in THF 0.31 mmol), the mixture stirred for 30 min and a solution of cyclopentenone **324** (50 mg, 0.14 mmol) in dry THF (1.5 mL) added dropwise. The mixture was stirred for 1 hr, warmed to room temperature gradually over 90 min, quenched by the addition of sat. aq. NH_4Cl (0.5 mL), passed through Celite eluting with Et_2O (30 mL) and washed with 5% HCl (15 mL) and brine (15 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a clear oil. Purification by silica gel chromatography (Et_2O: pet. ether 5:95 as eluent) gave the title compound (29 mg, 54%) as a clear oil as an 11:9 mixture of diastereoisomers. ν_{max} /cm^{-1} (film) 2955, 2929, 2857, 1651, 1466, 1253, 1151, 1122 and 1062; δ_H (700 MHz, $CDCl_3$) *Major:* 0.07 (6H, s, Si*Me*$_2$), 0.90 (9H, s, SiC*Me*$_3$), 1.31 (3H, s, Me), 1.47 (9H, s, OC*Me*$_3$), 3.58 (3H, s, OMe), 3.72 (1H, d, *J* 7, C*H*OTBS), 3.98 (1H, d, *J* 7, C*H*OMe), 4.84 (1H, d, *J* = 17, =C*H*H), 5.00 (1H, d, *J* 11, =CH*H*), 5.81 (1H, dd, *J* 17, 11, =C*H*=CH_2) and 11.9 (1H, brs, OH, exchanges with D_2O); *Minor:* 0.02 (6H, s, Si*Me*$_2$), 0.89 (9H, s, SiC*Me*$_3$), 1.13 (3H, s, Me), 1.44 (9H, s, OC*Me*$_3$), 3.59 (3H, s, OMe), 3.80 (1H, d, *J* 7, C*H*OTBS), 4.05 (1H, d, *J* 7, C*H*OMe), 4.94 (1H, d, *J* 17, C*H*H), 4.97 (1H, d, *J* 11, CH*H*), 5.76 (1H, dd, *J* 17, 11, C*H*=CH_2) and 10.6 (1H, brs, OH, exchanges with D_2O); δ_C (176 MHz, $CDCl_3$) *Major*: -5.0 (SiMe*Me*), -4.5 (Si*Me*Me), 18.2 (Si*C*Me_3), 23.6 (Me), 26.0 (SiC*Me*$_3$), 28.2 (OC*Me*$_3$), 47.8 (*C*Me), 59.4 (OMe), 81.6 (O*C*Me_3), 84.2 (*C*HOTBS), 86.0 (*C*HOMe), 105.5 (=C-CO_2^{t}Bu), 112.3 (=*C*H_2), 141.5 (*C*H=CH_2), 169.9 (*C*O_2^{t}Bu) and 171.9 (=COH); *Minor:* -4.5 (SiMe*Me*), -4.3 (Si*Me*Me), 14.3 (Me), 18.0 (Si*C*Me_3), 26.0 (SiC*Me*$_3$), 28.2 (OC*Me*$_3$), 47.2 (*C*Me), 59.3 (OMe), 81.6 (O*C*Me_3), 82.2 (*C*HOTBS), 86.6 (*C*HOMe), 108.2 (=C-$CO_2{}^tBu$), 112.6 (=CH_2), 145.2 (*C*H=CH_2), 169.3 (*C*$O_2{}^tBu$) and 170.4 (=COH); HRMS (ES^+) 402.2670 ($C_{20}H_{40}SiNO_5{}^+$, $M+NH_4{}^+$ requires 402.2670). The stereochemistry of the major isomer was assigned based on interactions in its ^1H NOESY spectrum from the known stereochemistries of the CHOMe and CHOTBS centres. The stereochemistry of the single new CMe($CHCH_2$) centre was assigned from the cross-ring interaction between C*H*OMe and C*Me*($CHCH_2$).

(3*S*,4*R*,5*S*)-2-[1-Amino-meth-(*Z*)-ylidene]-4-(*tert*-butyl-dimethyl-silanyloxy)-5-methoxy-3-methyl-3-vinyl-cyclopentanone 418



*DIBAL-H reduction of cyclopentanone **411**.*

To a stirred solution of cyclopentenanone **411** (30 mg, 0.097 mmol) in dry THF (4 mL) at -42 °C under argon was added DIBAL-H (0.4 mL of a 1.0 M solution in hexane, 0.4 mmol) dropwise, the mixture stirred for 30 min, warmed to room temperature and quenched by the addition of MeOH (0.5 mL). Sat. aq. NH_4Cl (10 mL) then 5% HCl (10 mL) were added and the mixture extracted with Et_2O (50 mL). The organic phase was washed with brine (20 mL), dried ($MgSO_4$) and evaporated to give the crude product as a yellow oil. Purification by silica gel chromatography (Et_2O: pet ether, 1:4 then 2:3 then 1:0 as eluent) gave the title compound as a clear oil (17 mg, 56%). $[\alpha]_D{}^{23}$ = +88.3 (c = 1.6, DCM); ν_{max}/cm^{-1} (film) 3304 (br), 2956, 2929, 2857, 1664, 1633, 1522, 1472, 1379, 1249, 1111 and 1079; δ_H (700 MHz, $CDCl_3$) 0.01 (3H, s, Si*Me*Me), 0.07 (3H, s, SiMe*Me*), 0.88 (9H, s, C*Me*$_3$), 1.15 (3H, s, Me), 3.68 (3H, s, OMe), 3.79 (2H, ABq, C*H*OMe and C*H*OTBS), 5.08 (1H, d, *J* 17, =C*H*H), 5.11 (1H, d, *J* 11, =CH*H*), 5.15 (1H, brs, NH*H*, exchanges with D_2O), 5.66 (1H, dd, *J* 17, 11, C*H*=CH_2), 6.50 (1H, m, simplifies to t, *J* 6.5 on heating to 50 °C or dd, *J* 14, 7.5 on cooling to -50 °C, =C*H*-NH_2) and 8.55 (1H, brs, N*H*H, exchanges with D_2O); δ_C (176 MHz, $CDCl_3$) -4.5 (Si*Me*Me), -4.4 (SiMe*Me*), 18.3 (*C*Me_3), 20.4 (Me), 26.0 (C*Me*$_3$), 45.5 (*C*Me), 59.8 (OMe), 81.5 (*C*HOTBS), 87.38 (*C*=CNH_2), 87.44 (*C*HOMe), 114.1 (=*C*H_2), 145.5 (*C*=CH_2), 146.6 (=*C*HNH_2) and 200.0 (*C*=O); *m/z* (CI^+) 312 ($M+H^+$, 100%); HRMS (ES^+) 312.1988 ($C_{16}H_{30}SiNO_3{}^+$, $M+H^+$ requires 312.1989).

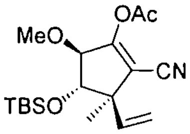
*Lithium aluminium hydride reduction of cyclopentanone **411**.*

To a stirred solution of cyclopentanone **411** (100 mg, 0.32 mmol) in dry THF (4 mL) at -10 °C under argon was added lithium aluminium hydride (50 mg, 1.3 mmol) portionwise over 5 min. The mixture was stirred for 1 hr, warmed to room temperature gradually over 30 min, stirred for a further 70 min, cooled to 0 °C and quenched by the cautious addition of 5% HCl (1 mL). The mixture was diluted with Et_2O (40 mL), water (20 mL) and 5% HCl (20 mL), separated, reextracted with Et_2O (20 mL) and the combined organic phase washed with water (20 mL) and brine (20 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a brown oil. Purification by silica gel chromatography (EtOAc: pet. ether, gradient elution, 1:4 to 1:1 as eluent) gave the title compound (25 mg, 25%) as a pale yellow wax.

*DIBAL-H reduction of enol acetate **419**.*

To a stirred solution of enol acetate **419** (45 mg, 0.13 mmol) in dry THF (2 mL) at -42 °C under argon was added DIBAL-H (0.26 mL of a 1.0 M solution in hexane, 0.26 mmol) dropwise, the mixture stirred for 45 min, warmed to room temperature and quenched by the addition of 5% HCl (0.5 mL). The mixture was stirred for 5 min, diluted with Et_2O (40 mL) and washed with water (10 mL) and brine (10 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a clear oil. Purification by silica gel chromatography (Et_2O: pet. ether, 1:4 then 2:3 then 1:0 as eluent) gave enol acetate **419** (10 mg, 22% recovery) and the title compound (10 mg, 25%), both clear oils.

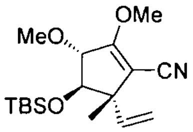
Acetic acid (3*R*,4*S*,5*R*)-4-(*tert*-butyl-dimethyl-silanyloxy)-2-cyano-5-methoxy-3-methyl-3-vinyl-cyclopent-1-enyl ester 419



To a stirred solution of cyclopentanone **411** (70 mg, 0.23 mmol) in dry THF (2 mL) at -10 °C under argon was added pyridine (0.03 mL, 0.37 mmol) and acetic anhydride (0.03 mL, 0.32 mmol) dropwise, the mixture stirred for 90 min, and warmed to room temperature. After stirring for a further 90 min the mixture was diluted with Et_2O (25 mL) and washed with 5% HCl (10 mL), sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a pale yellow oil. Purification by silica gel chromatography (Et_2O: pet. ether, 1:4 as eluent) gave the title compound (54 mg, 68%) as a clear oil. $[\alpha]_D^{23} = +72$ (c = 0.83, DCM); ν_{max} /cm^{-1} (film)

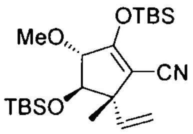
2930, 2857, 2220, 1780, 1653, 1472, 1369, 1252 and 1178; δ_H (700 MHz, $CDCl_3$) 0.04 (3H, s, Si*Me*Me), 0.09 (3H, s, SiMe*Me*), 0.90 (9H, s, C*Me*$_3$), 1.25 (3H, s, Me), 2.28 (3H, s, *Me*CO), 3.45 (3H, s, OMe), 3.96 (1H, d, *J* 6.3, C*H*OTBS), 4.46 (1H, d, *J* 6.3, C*H*OMe), 5.20 (1H, d, *J* 17.5, =C*H*H), 5.28 (1H, d, *J* 10.5, =CH*H*) and 5.77 (1H, dd, *J* 17.5, 10.5, C*H*=CH_2); δ_C (176 MHz, $CDCl_3$) -4.7 (Si*Me*Me), -4.5 (SiMe*Me*), 18.1 (Si*C*Me_3), 18.6 (Me), 20.7 (*Me*CO), 25.9 (SiC*Me*$_3$), 49.6 (*C*(Me)(CH=CH_2)), 59.6 (OMe), 84.0 (*C*HOTBS), 86.4 (*C*HOMe), 112.7 (CN), 116.9 (*C*H_2), 141.6 (*C*H=CH_2), 159.9 (=*C*-O) and 166.6 (*C*O_2); *m/z* (CI^+) 369 ($M+NH_4^+$, 100%); HRMS (ES^+) 369.2209 ($C_{18}H_{33}SiN_2O_4^+$, $M+NH_4^+$, requires 369.2204).

(3*S*,4*R*,5*S*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-2,3-dimethoxy-5-methyl-5-vinyl-cyclopent-1-enecarbonitrile 420



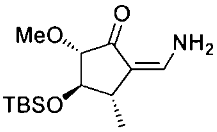
To a stirred solution of cyclopentanone **411** (70 mg, 0.23 mmol) in dry DMSO (2.5 mL) under argon was added K_2CO_3 (63 mg, 0.46 mmol), the mixture stirred for 5 min and dimethyl sulphate (0.04 mL, 0.4 mmol) added dropwise. The reaction was stirred for 4 hr, diluted with water (10 mL), extracted with Et_2O (2 ×15 mL) and the combined organic phase washed with brine (10 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a pale yellow oil. Purification by silica gel chromatography (Et_2O: pet. ether, 1:4 as eluent) gave the title compound (34 mg, 46%) as a clear oil. $[\alpha]_D^{23}$ = -19 (c = 0.53, DCM); ν_{max}/cm^{-1} (film) 2929, 2857, 2207, 1626, 1461, 1351, 1250 and 1141; δ_H (500 MHz, $CDCl_3$) 0.03 (3H, s, SiMe*Me*), 0.07 (3H, s, Si*Me*Me), 0.88 (9H, s, C*Me*$_3$), 1.19 (3H, s, Me), 3.52 (3H, s, OMe), 3.81 (1H, d, *J* 6.5, C*H*OMe), 3.98 (1H, d, *J* 6.5, C*H*OTBS), 4.14 (3H, s, =C-OMe), 5.16 (1H, d, *J* 17.5, =CH*H*), 5.22 (1H, d, *J* 10.5, =C*H*H) and 5.75 (1H, dd, *J* 105., 17.5, C*H*-CH_2); δ_C (126 MHz, $CDCl_3$) -4.6 (SiMe*Me*), -4.5 (Si*Me*Me), 18.2 (*C*Me_3), 18.6 (Me), 25.9 (C*Me*$_3$), 49.7 (*C*Me), 59.8 (OMe), 59.9 (OMe), 81.8 (*C*HOTBS), 87.3 (*C*HOMe), 88.2 (*C*CN), 115.9 (=*C*H_2), 116.3 (CN), 142.6 (*C*H=CH_2) and 167.5 (MeO-*C*=); *m/z* (CI^+) 341, 179 and 72 (100%); HRMS (ES^+) 341.2250 ($M+NH_4^+$, $C_{17}H_{33}SiN_2O_3$ requires 341.2255).

(3S,4R,5S)-2,4-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-methoxy-5-methyl-5-vinyl-cyclopent-1-enecarbonitrile 421



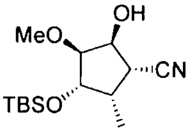
To a stirred solution of cyclopentanone **411** (130 mg, 0.42 mmol) in dry DCM (4 mL) at -10 °C under argon was added 2,6-lutidine (0.10 mL, 0.86 mmol) dropwise, the mixture stirred for 2 min and TBSCl (127 mg, 0.85 mmol) added in one portion. After stirring for 15 min the reaction was warmed to room temperature, stirred for a further 16 hr, diluted with Et_2O (40 mL) and washed with 0.5% HCl (10 mL) and brine (10 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a brown oil. Purification by silica gel chromatography (Et_2O: pet. ether, 5:95 as eluent) gave the title compound (118 mg, 66%) as a clear oil. $[\alpha]_D^{23}$ = -15 (c = 0.67, $CHCl_3$); ν_{max} /cm^{-1} (film) 2930, 2858, 2213, 1624, 1472, 1361, 1256, 1141 and 1101; δ_H (500 MHz, $CDCl_3$) 0.04 (3H, s, Si*Me*Me), 0.08 (3H, s, SiMe*Me*), 0.31 (3H, s, Si*Me*Me), 0.32 (3H, s, SiMe*Me*), 0.89 (9H, s, C*Me*$_3$), 0.98 (9H, s, C*Me*$_3$), 1.18 (3H, s, Me), 3.47 (3H, s, OMe), 3.85 (1H, d, *J* 6, C*H*OTBS), 3.96 (1H, d, *J* 6, C*H*OMe), 5.13 (1H, d, *J* 17, =C*H*H), 5.19 (1H, d, *J* 10.5, =CH*H*) and 5.75 (1H, dd, *J* 17, 10.5); δ_C (126 MHz, $CDCl_3$) -4.6 (SiMe*Me*), -4.1 (Si*Me*Me), -3.9 (SiMe*Me*), -3.7 (Si*Me*Me), 14.3 (Me), 25.5 (*C*Me$_3$), 25.9 (*C*Me$_3$), 29.4 (C*Me*$_3$), 29.5 (C*Me*$_3$), 48.9 (*C*Me), 58.9 (OMe), 82.0 (*C*HOTBS), 88.0 (*C*HOMe), 96.6 (=*C*-CN), 115.5 (CN), 115.6 (CH=*C*H$_2$), 142.9 (*C*H=CH$_2$) and 164.8 (TBSO-*C*=); *m/z* (CI$^+$) 441 (100%, M+NH$_4^+$); HRMS (CI$^+$) 441.2963 ($C_{22}H_{45}Si_2N_2O_3^+$, M+NH$_4^+$, requires 441.2963).

(3*S*,4*R*,5*S*)-2-[1-Amino-meth-(*Z*)-ylidene]-4-(*tert*-butyl-dimethyl-silanyloxy)-5-methoxy-3-methyl-cyclopentanone 424



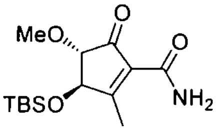
To a stirred solution of cyclopentenone **395** (20 mg, 0.071 mmol) in dry THF (2 mL) at -42 °C under argon was added DIBAL-H (0.21 mL of a 1.0 M solution in hexane, 0.21 mmol) dropwise, the mixture stirred for 40 min, warmed to room temperature and quenched by the addition of 5% HCl (0.5 mL). After stirring for 5 min the mixture was diluted with Et_2O (20 mL) and washed with brine (10 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a clear oil. Purification by silica gel chromatography (Et_2O: pet. ether, 3:7 as eluent) gave the title compound (11 mg, 54 %) as a pale yellow wax. $[\alpha]_D^{23}$ = -30 (c = 0.17, DCM); ν_{max}/cm^{-1} (film) 3396 (br), 3297 (br), 2956, 2929, 2856, 1668, 1621, 1524, 1462, 1377, 1249, 1146 and 1090; δ_H ($CDCl_3$, 500 MHz) 0.09 (3H, s, SiMe*Me*), 0.10 (3H, s, Si*Me*Me), 0.91 (9H, s, C*Me*$_3$), 1.11 (3H, d, J 6.5, Me), 2.48 (1H, m, CHMe), 3.52 (1H, t, J 8.5, CHOTBS), 3.66 (3H, s, OMe), 3.68 (1H, d, J 8.5, CHOMe), 5.0 (1H, brs, NHH) 6.58 (1H, dt, J 11, 1.5, converts to dd, J 14, 7.5 at -20 °C) and 8.5 (1H, brs, NHH); δ_C ($CDCl_3$, 126 MHz) -4.6 (SiMeMe), -4.2 (SiMeMe), 16.5 (Me), 18.3 (CMe_3), 26.0 (CMe_3), 37.4 (CMe), 59.5 (OMe), 82.0 (CHOTBS), 89.2 (CHOMe), 107.5 ($C{=}CNH_2$), 144.3 ($CHNH_2$) and 200.8 (C=O); m/z (CI^+) 286, 124 (100%) and 91; HRMS (ES^+) 286.1836 ($C_{14}H_{31}SiN_2O_3$, $M+H^+$ requires 286.1833).

(1*S*,2*S*,3*S*,4*S*,5*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-hydroxy-4-methoxy-2-methyl-cyclopentanecarbonitrile 425



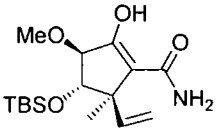
To a stirred solution of cyclopentenone **395** (50 mg, 0.18 mmol) in dry MeOH (0.5 mL) and dry DCM (0.5 mL) at -78 °C under argon was added sodium borohydride (9.0 mg, 0.24 mmol), the mixture stirred for 4 hr, warmed to room temperature and quenched by the addition of 5% HCl (0.25 mL). The mixture was extracted with Et_2O (20 mL) and washed with water (10 mL) and brine (10 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a clear oil. Purification by silica gel chromatography gave a single diastereoisomer (24 mg, 47 %) and a mixture of diastereoisomers (11 mg, 21 %), both clear oils. Combined diastereomeric ratio: 5:1. $[\alpha]_D^{23}$ = -45 (c = 0.4); ν_{max} /cm^{-1} (film) 3300 (br), 2929, 2857, 2244, 1472 and 1252; δ_H (500 MHz, $CDCl_3$) 0.08 (3H, s, Si*Me*Me), 0.09 (3H, s, SiMe*Me*), 0.89 (9H, s, SiC*Me*$_3$), 1.20 (3H, d, *J* 7, Me), 1.98-2.04 (1H, m, C*H*Me), 2.38 (1H, dd, *J* 10.5, 7.5, C*H*CN), 2.76 (1H, d, *J* 7.5, OH), 3.42 (1H, t, *J* 4.5, C*H*OMe), 3.45 (3H, s, OMe), 3.60 (1H, dd, *J* 6.5, 4.5, C*H*OTBS) and 4.35 (1H, q, *J* 7.5, C*H*OH); δ_C (126 MHz, $CDCl_3$) -4.6 (SiMe*Me*), -4.4 (Si*Me*Me), 17.6 (Me), 18.0 (*C*Me$_3$), 25.8 (C*Me*$_3$), 41.3 (*C*CN), 43.0 (*C*Me), 58.6 (OMe), 72.7 (*C*OH), 79.5 (*C*OTBS), 86.9 (*C*OMe) and 120.9 (CN); *m/z* (CI^+) 303 ($M+NH_4^+$, 100%); HRMS (ES^+) 303.2099 ($C_{14}H_{31}SiN_2O_3^+$, $M+NH_4^+$ requires 303.2098). The stereochemistry of this molecule was assigned based on interactions in its ^{1}H NOESY spectrum from the known stereochemistries of the CHOMe and CHOTBS centres. The stereochemistry of the CHOH centre was assigned from the interactions between C*H*OMe and C*H*OH which allowed the assignment of the CHMe centre from the cross-ring interaction between C*H*OH and CH*Me*. The stereochemistry of the CHCN centre was assigned from the cross-ring interaction between C*H*OTBS and C*H*CN.

(3*R*,4*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-2-methyl-5-oxo-cyclopent-1-enecarboxylic acid amide 427



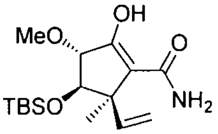
To a stirred solution of cyclopentenone **395** (70 mg, 0.25 mmol) in EtOH/H_2O (2:1, 3 mL) was added catalyst **426** (5 mg, 0.01 mmol) and the mixture heated to 80 °C. After 18 hr the mixture was cooled, diluted with Et_2O (30 mL) and washed with water (10 mL) and brine (10 mL). Drying ($MgSO_4$) and evaporation gave the crude product as an orange wax. Purification by silica gel chromatography (EtOAc:pet. ether, 3:7 as eluent) gave the title compound (68 mg, 91%). Mpt. 82-83 °C; $[\alpha]_D^{23} = +115$ (c = 1.0, DCM); ν_{max} /cm^{-1} (film) 3382 (br), 3160 (br), 2930, 2857, 1707, 1684, 1626, 1462, 1390, 1358, 1253, 1112 and 1074; δ_H (500 MHz, $CDCl_3$) 0.17 (3H, s, Si*Me*Me), 0.18 (3H, s, SiMe*Me*), 0.94 (9H, s, C*Me*$_3$), 2.55 (3H, s, Me), 3.69 (3H, s, OMe), 3.81 (1H, d, *J* 3, C*H*OTBS), 4.51 (1H, d, *J* 3, C*H*OMe), 5.55 (1H, brs, N*H*H) and 7.92 (1H, s, NH*H*); δ_C (126 MHz, $CDCl_3$) -5.0 (Si*Me*Me), -4.5 (SiMe*Me*), 15.8 (Me), 18.2 (*C*Me$_3$), 25.8 (C*Me*$_3$), 59.6 (OMe), 77.0 (*C*HOMe), 88.6 (*C*HOTBS), 128.6 (*C*-CONH$_2$), 163.4 (CONH$_2$), 183.4 (*C*=C-CONH$_2$) and 201.9 (*C*=O); *m/z* (CI$^+$) 317 ($M+NH_4^+$) and 300 ($M+H^+$, 100%); HRMS (ES$^+$) 300.1624 ($C_{14}H_{26}NO_4Si^+$, $M+H^+$, requires 300.1626). Anal. calc. for $C_{14}H_{25}SiNO_4$, C 56.19, H 8.36, N 4.68, found C 55.96, H 8.41, N 4.54.

(3*R*,4*S*,5*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-2-hydroxy-3-methoxy-5-methyl-5-vinyl-cyclopent-1-enecarboxylic acid amide 428



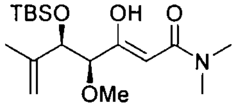
To a stirred solution of enol acetate **419** (50 mg, 0.14 mmol) in EtOH/H_2O (2:1, 3 mL) was added catalyst **426** (3 mg, 7 μmol) and the mixture heated to 80 °C. After 18 hr the mixture was cooled, diluted with Et_2O (30 mL), washed with water (10 mL) and brine (10 mL) and the combined aqueous phase extracted with Et_2O (15 mL). The combined organic phase was dried ($MgSO_4$) and evaporated to give the crude product as a yellow solid. Purification by silica gel chromatography (EtOAc: pet. ether, 1:4 then 3:7 as eluent) gave the title compound (34 mg, 74%) as a pale yellow solid. $[\alpha]_D^{23}$ = +30.0 (c = 0.33, DCM); ν_{max} /cm^{-1} (film) 3463, 3162 (br), 2928, 2856, 1666, 1590, 1442, 1384, 1312, 1258, 1132 and 1060; δ_H (700 MHz, $CDCl_3$) 0.01 (3H, s, Si*Me*Me), 0.07 (3H, s, SiMe*Me*), 0.89 (9H, s, C*Me*$_3$), 1.17 (3H, s, Me), 3.62 (3H, s, OMe), 3.83 (1H, d, *J* 7, C*H*OTBS), 4.10 (1H, d, *J* 7, C*H*OMe), 5.22 (1H, d, *J* 17.5, =C*H*H), 5.29 (1H, d, *J* 10.5, =CH*H*), 5.65 (2H, brs, NH_2), 5.88 (1H, dd, *J* 17.5, 10.5, C*H*=CH_2) and 12.4 (1H, brs, =C-OH); δ_C (176 MHz, $CDCl_3$) -4.5 ($SiMe_2$), 17.3 (Me), 18.2 (*C*Me$_3$), 25.9 (C*Me*$_3$), 47.1 (Me*C*), 59.5 (OMe), 82.6 (*C*HOTBS), 86.2 (*C*HOMe), 106.0 (*C*-$CONH_2$), 116.2 (=*C*H_2), 145.9 (*C*H=CH_2), 171.5 (*C*ONH_2) and 171.6 (=*C*-OH); *m/z* (CI^+) 328 ($M+H^+$, 100%); HRMS (ES^+) 328.1943 ($C_{16}H_{30}NO_4Si^+$, $M+H^+$, requires 328.1939).

(3*S*,4*R*,5*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-2-hydroxy-3-methoxy-5-methyl-5-vinyl-cyclopent-1-enecarboxylic acid amide 429



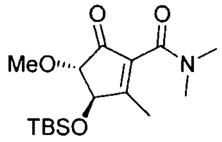
To a stirred suspension of copper(I) iodide (41 mg, 0.22 mmol) in dry THF (2 mL) under argon was added trioctylphosphine (0.12 mL, 0.27 mmol) dropwise, the mixture stirred for 5 min and cooled to -78 °C to allow the dropwise addition of vinylmagnesium bromide (0.65 mL of a 1.0 M solution in THF, 0.65 mmol). After stirring for a further 2 min, a solution of amide **427** (55 mg, 0.18 mmol) in dry THF (2 mL) was added dropwise, the mixture stirred for 2 hr, warmed to -42 °C, stirred for 45 min and warmed to room temperature. The reaction was quenched by the addition of sat. aq. NH_4Cl (0.5 mL), the mixture passed through Celite eluting with Et_2O (40 mL) and washed with 5% HCl (15 mL) and brine (15 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow solid. Purification by silica gel chromatography (EtOAc: pet. ether, 1:4 then 3:7 as eluent) gave the title compound (34 mg, 58%) as a pale yellow solid. Major diastereoisomer: δ_H ($CDCl_3$, 500 MHz) 0.07 (3H, s, Si*Me*Me), 0.09 (3H, s, SiMe*Me*), 0.89 (9H, s, C*Me*$_3$), 1.34 (3H, s, Me), 3.59 (3H, s, OMe), 3.77 (1H, d, *J* 5, C*H*OTBS), 4.01 (1H, d, *J* 5, C*H*OMe), 5.07 (1H, d, *J* 18, =C*H*H), 5.18 (1H, d, *J* 10.5, =CH*H*), 5.33 (2H, brs, NH_2), 5.93 (1H, dd, *J* 18, 10.5, C*H*=CH_2) and 12.3 (1H, brs, =C-OH); δ_C ($CDCl_3$, 126 MHz) -4.9 ($SiMe_2$), 18.3 (*C*Me$_3$), 23.5 (Me), 25.9 (C*Me*$_3$), 48.1 (Me*C*), 59.3 (OMe), 83.7 (*C*HOTBS), 87.1 (*C*HOMe), 105.4 (*C*-$CONH_2$), 114.2 (=CH$_2$), 142.4 (*C*H=CH$_2$), 171.8 (*C*ONH$_2$) and 171.9 (=*C*-OH); *m/z* (CI$^+$) 328 (M+H$^+$, 100%); HRMS (ES$^+$) 328.1943 ($C_{16}H_{30}NO_4Si^+$, M+H$^+$, requires 328.1939). The stereochemistry of the major isomer was assigned based on interactions in its ^{1}H NOESY spectrum from the known stereochemistries of the CHOMe and CHOTBS centres. The stereochemistry of the single new CMe(CHCH$_2$) centre was assigned from the interaction between C*H*OTBS and C*Me*(CHCH$_2$).

(Z)-(4*S*,5*R*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-3-hydroxy-4-methoxy-6-methyl-hepta-2,6-dienoic acid dimethylamide 430



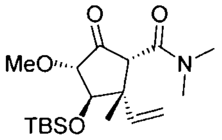
To a stirred solution of LiHMDS (2.0 mL of a 1.0 M solution in THF, 2.0 mmol) at -78 °C under argon was added DMA (0.20 mL, 2.2 mmol) dropwise , the reaction stirred for 30 min and phenyl ester **323** (350 mg, 1.0 mmol) added dropwise. The reaction was stirred 2.5 hr, warmed to room temperature, quenched by the addition of 5% HCl (1.5 mL), diluted with Et$_2$O (50 mL) and washed with 5% HCl (20 mL) and brine (20 mL). Drying (MgSO$_4$) and evaporation gave the crude product as a yellow oil. Purification by silica gel chromatography (Et$_2$O: pet. ether, 1:4 then 1:1 as eluent) gave the title compound (299 mg, 87%). $[\alpha]_D^{23}$ = -69.6 (c = 0.83, DCM); ν_{max} (film) /cm^{-1} 2930, 2856, 1726, 1632, 1603, 1503, 1463, 1363, 1252, 1187 and 1083; δ_H (700 MHz, CDCl$_3$) *Major enol tautomer:* 0.01 (3H, s, SiMe*Me*), 0.01 (3H, s, Si*Me*Me), 0.86 (9H, s, CMe$_3$), 1.77 (3H, s, Me), 3.00 (6H, s, NMe$_2$), 3.37 (3H, s, OMe), 3.58 (1H, d, *J* 4.9, C*H*OMe), 4.25 (1H, d, *J* 4.9, C*H*OTBS), 4.88 (1H, s, CH*H*), 4.99 (C*H*H), 5.44 (1H, s, HOC=C*H*) and 14.0 (1H, s, OH); *Minor keto tautomer:* 0.02 (3H, s, SiMe*Me*), 0.04 (3H, s, Si*Me*Me), 0.89 (9H, s, CMe$_3$), 1.75 (3H, s, Me), 2.96 (3H, s, NMe*Me*), 2.97 (3H, s, N*Me*Me), 3.41 (3H, s, OMe), 3.45 (1H, d, *J* 15, C*H*H), 3.82 (1H, d, *J* 4.2, C*H*OMe), 3.84 (1H, d, *J* 15, CH*H*), 4.32 (1H, d, *J* 4.2, C*H*OTBS), 4.91 (1H, s, =C*H*H) and 5.02 (1H, s, =CH*H*); δ_C (176 MHz, CDCl$_3$) *Major:* -5.0 (Si*Me*Me), -4.9 (SiMe*Me*), 18.4 (Me), 18.7 (*C*Me$_3$), 25.9 (C*Me*$_3$), 35.4 (NMe$_2$), 59.0 (OMe), 77.4 (*C*HOTBS), 87.3 (*C*HOMe), 89.9 (=*C*CONMe$_2$), 113.1 (=CH$_2$), 144.8 (*C*=CH$_2$), 172.1 (*C*-OH) and 173.8 (*C*ONMe$_2$); HRMS (ES$^+$) 344.2253 (M+H$^+$, $C_{17}H_{34}SiNO_4^+$ requires 344.2252).

(3*R*,4*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-2-methyl-5-oxo-cyclopent-1-enecarboxylic acid dimethylamide 431



Ozone was passed through a solution of *β*-keto amide **430** (50 mg, 0.15 mmol) in dry MeOH (2 mL) at -78 °C until blue colour appeared, oxygen passed through to remove the excess ozone and solid supported triphenylphosphine (75 mg of 3 mmol g^{-1}, 0.23 mmol) added. The reaction was warmed to room temperature, stirred for 30 min, filtered and cooled to 0 °C to allow the addition of potassium carbonate (42 mg, 0.30 mmol). The reaction was stirred for 45 min, warmed to room temperature, diluted with water (15 mL) and extracted with DCM (3 × 10 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a pale yellow oil. Purification by silica gel chromatography (Et_2O: pet. ether, 1:1 then 3:1 then 1:0 as eluent) gave the title compound (16 mg, 34%) as a white solid. Mpt. = 63-65 °C; $[\alpha]_D^{23}$ = -52.0 (c = 0.25, $CHCl_3$); ν_{max}/cm^{-1} (film) 2932, 2858, 1717, 1630, 1402, 1255, 1110 and 1067; δ_H (700 MHz, $CDCl_3$) 0.16 (6H, s, Si*Me*$_2$), 0.93 (9H, s, C*Me*$_3$), 2.10 (3H, d, *J* 0.7, Me), 2.89 (3H, s, NMe*Me*), 3.04 (3H, s, N*Me*Me), 3.67 (3H, s, OMe), 3.79 (1H, d, *J* 2.8, C*H*OMe) and 4.56 (1H, dd, *J* 2.8, 0.7, C*H*OTBS); δ_C (176 MHz, $CDCl_3$) -5.0 (Si*Me*Me), -4.5 (SiMe*Me*), 14.9 (Me), 18.2 (*C*Me$_3$), 25.8 (C*Me*$_3$), 34.8 (N*Me*Me), 38.0 (NMe*Me*), 59.3 (OMe), 76.9 (*C*HOTBS), 88.7 (*C*HOMe), 136.7 (*C*-CONMe$_2$), 164.0 (*C*ONMe$_2$), 171.6 (=*C*Me) and 198.1 (C=O); HRMS (ES^+) 328.1939 ($M+H^+$, $C_{16}H_{30}SiNO_4^+$ requires 328.1939).

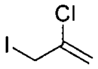
(1*R*,2*S*,3*R*,4*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-2-methyl-5-oxo-2-vinyl-cyclopentanecarboxylic acid dimethylamide 432



To a stirred suspension of copper(I) iodide in dry THF (2 mL) was added trioctylphosphine (0.080 mL, 0.17 mmol), the mixture stirred for 5 min, cooled to -78 °C, vinylmagnesium bromide (0.28 mL of a 1.0 M solution in THF, 0.28 mmol) added dropwise followed by a solution of cyclopentenone **431** (40 mg, 0.12 mmol) in dry THF (1.5 mL). The reaction was stirred for 1 hr, warmed to -50 °C, stirred for a further 2 hr and warmed to room temperature. The reaction was quenched by the addition of sat. aq. NH_4Cl (0.5 mL), passed through Celite eluting with Et_2O (30 mL) and washed with 5%

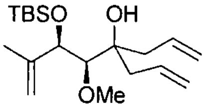
HCl (15 mL) and brine (15 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow oil. Purification by silica gel chromatography (Et_2O: pet. ether, 1:4 then 3:1 then 4:1 as eluent) gave the title compound (20 mg, 46%) as a clear oil. $[\alpha]_D^{23}$ = +36.0 (c = 0.33, DCM); ν_{max}/cm^{-1} (film) 2931, 2856, 1759, 1635, 1465, 1397, 1253, 1111 and 1093; δ_H (700 MHz, $CDCl_3$) 0.10 (3H, s, SiMe*Me*), 0.11 (3H, s, Si*Me*Me), 0.91 (9H, s, CMe_3), 1.22 (3H, s, Me), 2.95 (3H, s, NMe*Me*), 3.06 (3H, s, N*Me*Me), 3.56 (3H, s, OMe), 3.59 (1H, dd, *J* 9.1, 2.1, C*H*OMe), 3.80 (1H, d, *J* 2.1, C*H*$CONMe_2$), 4.47 (1H, d, *J* 9.1, C*H*OTBS), 5.04 (1H, d, *J* 17.5, CH=C*H*H), 5.17 (CH=CH*H*) and 6.20 (1H, dd, *J* 17.5, 11.2, C*H*=CH_2); δ_C (176 MHz, $CDCl_3$) -4.9 (Si*Me*Me), -4.2 (SiMe*Me*), 18.3 (*C*Me_3), 20.4 (Me), 25.9 (C*Me*$_3$), 35.6 (*C*Me), 38.6 (NMe*Me*), 45.3 (N*Me*Me), 56.5 (OMe), 58.7 (*C*H$CONMe_2$), 79.3 (*C*HOTBS), 86.9 (*C*HOMe), 113.3 (=*C*H_2), 141.8 (*C*H=CH_2), 168.9 (*C*$ONMe_2$) and 211.3 (C=O); HRMS (ES^+) 356.2260 ($M+H^+$, $C_{18}H_{34}SiNO_4^+$ requires 356.2252). The stereochemistry of this molecule was assigned based on interactions in its ^1H NOESY spectrum from the known stereochemistries of the CHOMe and CHOTBS centres. The stereochemistry of the CMe($CHCH_2$) centre was assigned from the cross-ring interaction between C*H*OMe and C*Me*($CHCH_2$) and that of the $CHCONMe_2$ centre was assigned from the interaction between C*Me*($CHCH_2$) and C*H*$CONMe_2$.

2-Chloro-3-iodo-propene 435b



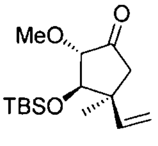
To a stirred solution of 2,3-dichloro-propene (4.1 mL, 45 mmol) in acetone (20 mL) was added a solution of sodium iodide (8.1 g, 54 mmol) in acetone (25 mL). The reaction was stirred for 4 hr, diluted with water (80 mL), extracted with DCM (2 × 60 mL) and the combined organic phase washed with 5% aq. sodium metabisulphite (15 mL) and brine (50 mL). Drying ($MgSO_4$) and evaporation afforded the title compound (5.6 g, 61%) as a pale red oil. All spectral and analytical properties were identical to those reported in the literature.[459]

(5*S*,6*R*)-4-Allyl-6-(*tert*-butyl-dimethyl-silanyloxy)-5-methoxy-7-methyl-octa-1,7-dien-4-ol 437



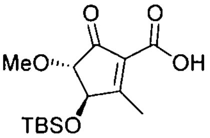
To a stirred solution of phenyl ester **323** (250 mg, 0.71 mmol) in dry THF (1 mL) at -78 °C under argon was added allylmagnesium bromide (1.8 mL of a 1.0 M solution in THF, 1.8 mmol) dropwise. The reaction was stirred for 1 hr, warmed to room temperature, quenched by the addition of sat. aq. NH_4Cl (2 mL), diluted with Et_2O (30 mL) and washed with 5% HCl (15 mL) and brine (15 mL). Drying ($MgSO_4$) and evaporation gave the drude product as a clear oil. Purification by silica gel chromatography (Et_2O: pet. ether, 5:95 as eluent) gave the title compound (188 mg, 78%) as a clear oil. $[\alpha]_D^{23}$ = -2.1 (c = 0.97, $CHCl_3$); ν_{max}/cm^{-1} (film) 3550 (br), 2954, 2929, 2856, 1639, 1253 and 1061; δ_H (700 MHz, $CDCl_3$) 0.05 (3H, s, SiMe*Me*), 0.11 (3H, s, Si*Me*Me), 0.91 (9H, s, C*Me*$_3$), 1.82 (3H, s, Me), 2.26 (1H, dd, *J* 14, 8, C*H*H-C=), 2.34 (1H, dd, *J* 14, 8, CH*H*-C=), 2.43 (1H, dd, *J* 14, 7, C*H*H-C=), 2.45 (1H, dd, *J* 14, 7, CH*H*-C=), 3.09 (1H, d, *J* 5, C*H*OMe), 3.19 (1H, s, OH), 3.48 (3H, s, OMe), 4.39 (1H, d, *J* 5, C*H*OTBS), 4.95 (1H, s, *H*HC=CMe), 5.05 (1H, s, H*H*C=CMe), 5.07-5.12 (4H, m, 2 × =CH_2) and 5.88-5.95 (2H, m, 2 × C*H*=CH_2); δ_C (176 MHz, $CDCl_3$) -4.6 (Si*Me*Me), -4.3 (SiMe*Me*), 18.3 (Me), 18.9 (*C*Me$_3$), 26.0 (C*Me*$_3$), 40.5 (CH_2), 41.3 (CH_2), 61.9 (OMe), 76.7 (*C*OH), 77.0 (*C*HOMe), 85.5 (*C*HOTBS), 113.9 (MeC=*C*H$_2$), 117.9 (*C*H$_2$), 118.0 (*C*H$_2$), 134.4 (*C*H=CH_2), 134.5 (CH=*C*H$_2$) and 146.7 (Me*C*=CH_2); HRMS (ES^+) 341.2507 ($C_{19}H_{37}SiO_3^+$, M+H$^+$, requires 341.2506).

(2*S*,3*R*,4*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methoxy-4-methyl-4-vinyl-cyclopentanone 438



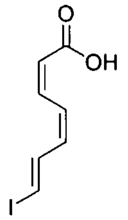
To a solution of cyclopentanone **417** (20 mg, 0.052 mmol) in $CDCl_3$ (0.6 mL) was added TFA (0.10 mL of a 2.5 M solution in $CDCl_3$, 0.25 mmol). After 20 hr the mixture was evaporated to give the crude product as a yellow solid. Purification by silica gel chromatography (Et_2O: pet ether, 5:95 then 1:4 then 1:0 as eluent) gave the title compound (5 mg, 34%) as a pale yellow oil. 1.8:1 mixture of diastereoisomers. ν_{max} /cm^{-1} (film) 2952, 2926, 2860, 1753, 1640, 1259, 1092 and 1009; δ_H (500 MHz, $CDCl_3$) *Major:* 0.10 (3H, s, Si*Me*Me), 0.11 (3H, s, SiMe*Me*), 0.93 (9H, s, C*Me*$_3$), 1.21 (3H, s, Me), 2.05 (1H, d, *J* 19, C*H*H), 2.68 (1H, dd, *J* 19, 2, CH*H*), 3.50 (1H, dd, *J* 8.5, 2), 3.58 (3H, s, OMe), 3.80 (1H, d, *J* 8.5), 5.00 (1H, d, *J* 18, =C*H*H), 5.12 (1H, d, *J* 11, =CH*H*) and 6.12 (1H, dd, *J* 18, 11, C*H*=CH_2); δ_C (176 MHz, $CDCl_3$) -5.0 (Si*Me*Me), -4.2 (SiMe*Me*), 18.3 (*C*Me$_3$), 19.2 (Me), 25.9 (C*Me*$_3$), 41.7 (*C*Me), 46.3 (*C*H_2CO), 59.8 (OMe), 81.4 (*C*HOTBS), 87.5 (*C*HOMe), 113.5 (=*C*H_2) and 141.2 (*C*H=CH_2) and 214.0 (C=O); *m/z* (CI^+) 302 ($M+NH_4^+$) and 170 (100%); HRMS (ES^+) 302.2141 ($M+NH_4^+$, $C_{15}H_{32}SiNO_3^+$ requires 302.2146). The stereochemistry of the major isomer was assigned based on interactions in its ^1H NOESY spectrum from the known stereochemistries of the CHOMe and CHOTBS centres. The two signals of the CH_2 group were assigned from their interactions with the C*H*OMe and C*H*OTBS protons. The stereochemistry of the C*Me*($CHCH_2$) centre was assigned from the interactions between C*Me*($CHCH_2$) and both C*H*OTBS and a single proton of the CH_2 group.

(3*R*,4*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-2-methyl-5-oxo-cyclopent-1-enecarboxylic acid 439



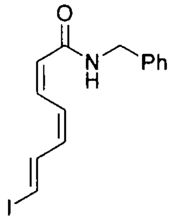
Ozone was bubbled through a solution of **321** (100 mg, 0.27 mmol) in dry MeOH at -78 °C until a blue colour was seen. Oxygen was passed though to remove the excess ozone, solid-supported triphenylphosphine (0.15 g of 3 mmol g^{-1}, 0.45 mmol) added, the reaction warmed to room temperature, stirred for 25 min, filtered and evaporated. Purification by silica gel chromatography (Et_2O: pet. ether, 1:9 as eluent) gave a clear oil (80 mg) which was dissolved in $CDCl_3$ (3 mL), TFA (0.4 mL of a 2.5 M solution in $CDCl_3$, 1.0 mmol) added, the mixture stirred for 3 days and evaporated to give the crude product as a light brown oil. Purification by silica gel chromatography (Et_2O: pet. ether, 1:4 then 3:7 then 2:3 as eluent) gave the title compound (60 mg, 74%) as a pale yellow oil. $[\alpha]_D^{23}$ = -50.0 (c = 0.3, $CHCl_3$); ν_{max}/cm^{-1} (film) 3200 (br), 2930, 2858, 1753, 1695, 1629, 1368, 1255, 1117 and 1072; δ_H (500 MHz, $CDCl_3$) 0.18 (3H, s, Si*Me*Me), 0.19 (3H, s, SiMe*Me*), 0.94 (9H, s, C*Me*$_3$), 2.57 (3H, s, Me), 3.71 (3H, s, OMe), 3.90 (1H, d, *J* 3, C*H*OMe) and 4.60 (1H, dd, *J* 3, 0.7, C*H*OTBS); δ_C (126 MHz, $CDCl_3$) -5.1 (Si*Me*Me), -4.6 (SiMe*Me*), 16.1 (Me), 18.2 (*C*Me$_3$), 25.7 (C*Me*$_3$), 59.8 (OMe), 77.7 (*C*HOTBS), 88.0 (*C*HOMe), 126.0 (*C*CO_2H), 161.4 (*C*O_2H), 188.0 (*C*Me) and 204.6 (ketone); *m/z* (CI^+) 318 ($M+NH4^+$) and 144 (100%); HRMS (ES^+) 301.1461 ($M+H^+$, $C_{14}H_{25}SiO_5^+$ requires 301.1466).

(2Z,4Z,6E)-7-Iodo-hepta-2,4,6-trienoic acid 440



To a stirred solution of iodide **254** (70 mg, 0.28 mmol) in THF (3 mL) at 0 °C was added a solution of lithium hydroxide monohydrate (41 mg, 0.98 mmol) in water (3 mL). The reaction was warmed to 4 °C, stirred for 22 hr, quenched by the dropwise addition of 5% HCl (1 mL) and extracted with Et_2O (2 × 20 mL). Drying ($MgSO_4$) and evaporation gave the title compound (70 mg, 100%) as a pale yellow solid. Cooling a solution in DCM produced crystals suitable for XRD. ν_{max} /cm^{-1} 2983, 1684, 1605 and 1293; δ_H (700 MHz, $CDCl_3$) 5.83 (1H, d, *J* 11.9, C*H*CO_2H), 6.27 (1H, t, *J* 11.6, alkene), 6.72 (1H, d, *J* 14.7, C*H*I), 7.12 (1H, t, *J* 11.6, alkene), 7.27 (1H, t, *J* 11.2, alkene) and 7.59 (1H, ddd, *J* 14.7, 11.2 and 1, C*H*=CHI); δ_C (176 MHz, $CDCl_3$) 86.5 (*C*HI), 118.5 (alkene), 124.2 (alkene), 136.7 (alkene), 139.8 (alkene), 139.9 (alkene) and 171.0 (CO_2H); *m/z* (EI) 250 (M^+), 127, 77 and 51 (100%); HRMS (CI^+) 267.9827 ($M+NH_4^+$, $C_7H_{11}INO_2^+$ requires 267.9829).

(2Z,4Z,6E)-7-Iodo-hepta-2,4,6-trienoic acid benzylamide 447



To a stirred solution of acid **440** (40 mg, 0.12 mmol) in dry DCM (4 mL) at 0 °C under argon was added CDI (25 mg, 0.16 mmol), the mixture stirred for 30 min and benzylamine (0.040 mL, 0.32 mmol) added. The reaction was warmed to 4 °C, stirred for 21 hr, diluted with Et_2O (40 mL) and washed with 5% HCl (15 mL), sat. aq. $NaHCO_3$ (8 mL) and brine (10 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a yellow solid. Purification by silica gel chromatography (gradient elution, EtOAc: pet. ether, 1:4 to 3:7, eluent cooled to 0 °C) gave the title compound (25 mg, 61%) as a white solid. Mpt. 127-128 °C (dec); ν_{max} /cm^{-1} 3269 (br), 2912, 1625, 1608, 1521, 1452, 1290, 1242 and 1173; δ_H (500 MHz, $CDCl_3$) 4.49 (2H, d, *J* 6, CH_2), 5.72 (1H, d, *J* 11.5, C*H*CONH), 5.85 (1H, brs, NH), 6.17 (1H, t, *J* 11.5, C*H*CHCHI), 6.60 (1H, d, *J* 14, CHI), 6.86 (1H, t, *J* 11.5, C*H*CHCONH), 7.28-7.36 (5H, m, Ar), 7.44 (1H, t, *J* 11.5, C*H*CHCHCONH) and 7.56 (1H, ddd, *J* 14, 11.5, 1); δ_C (126 MHz, $CDCl_3$) 43.7 (CH_2), 84.7 (CHI), 122.1, 124.9, 127.8, 128.1, 128.9, 134.6, 134.9, 138.2, 140.1 and 165.9; *m/z* (CI^+) 340 ($M+H^+$), 108 and 72 (100%); HRMS (CI^+) 340.0191 ($M+H^+$, $C_{14}H_{15}NOI^+$ requires 340.0193).

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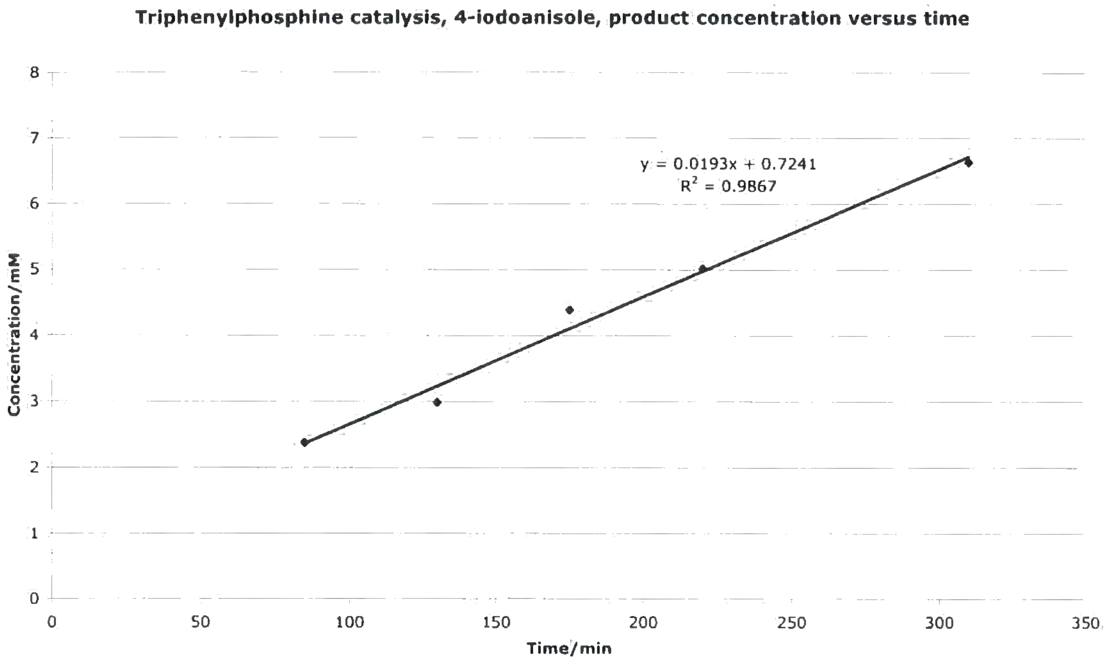
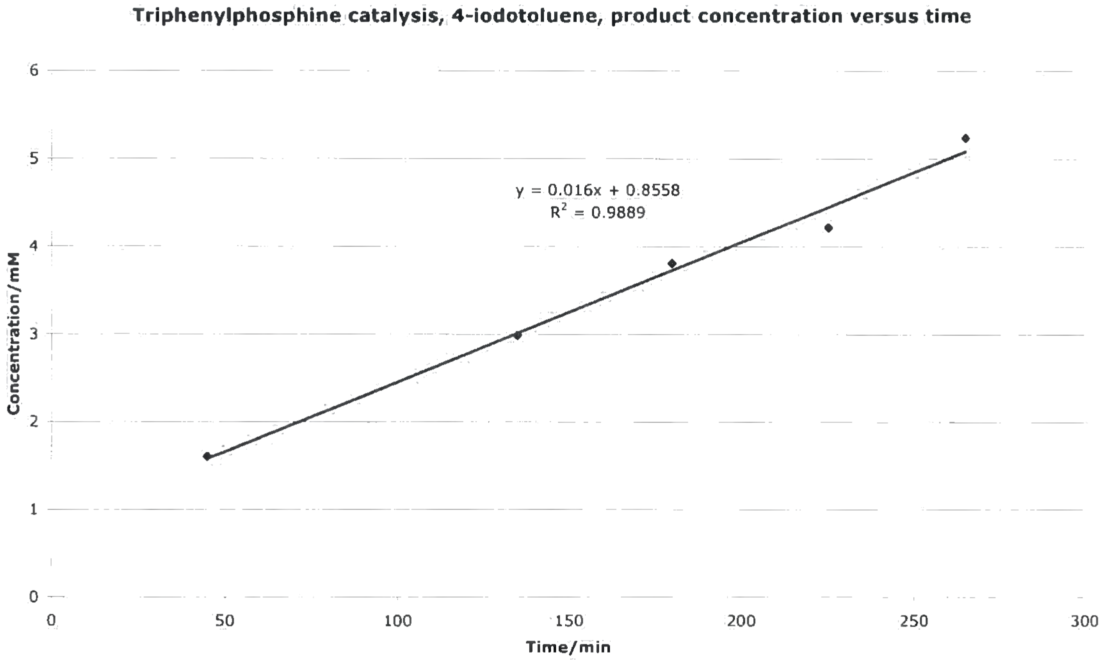
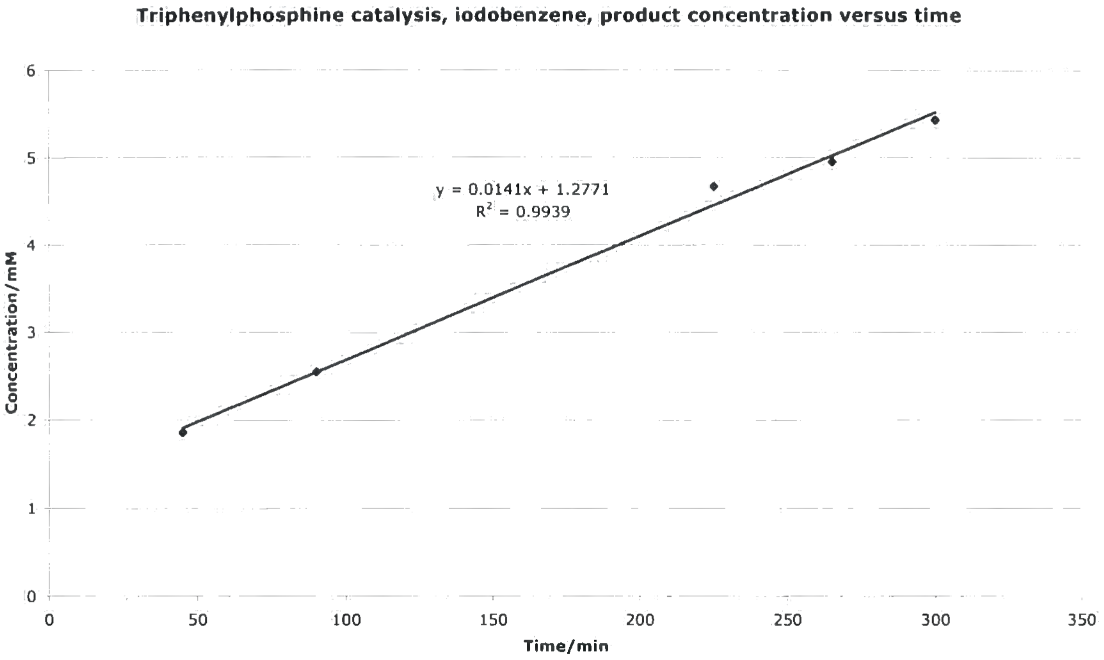
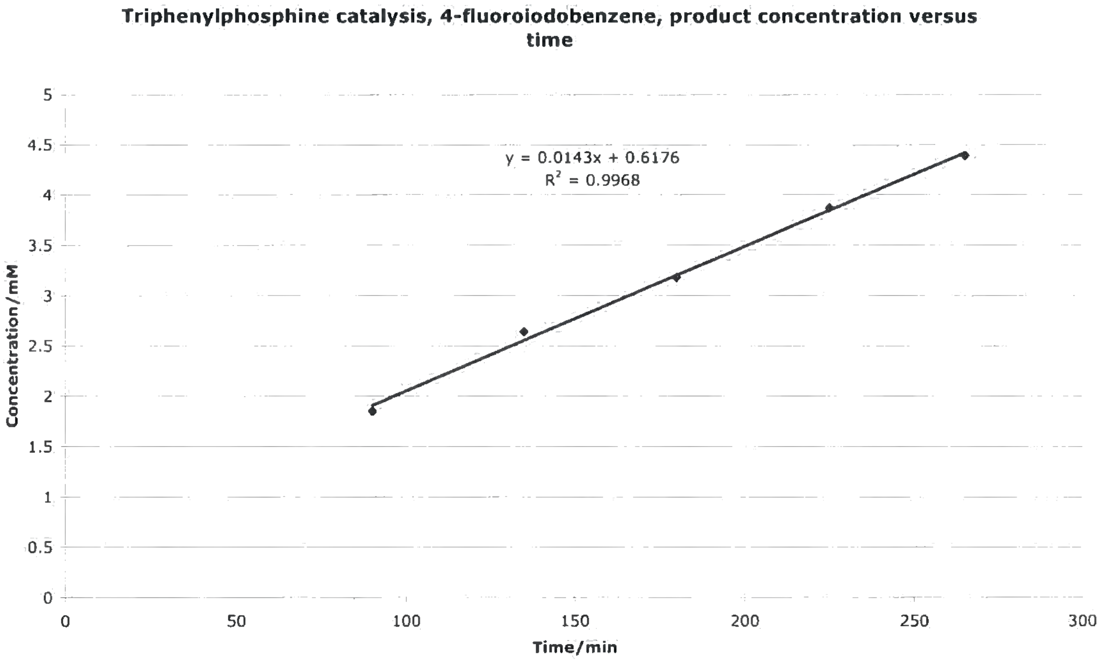
Appendix 1: kinetic data

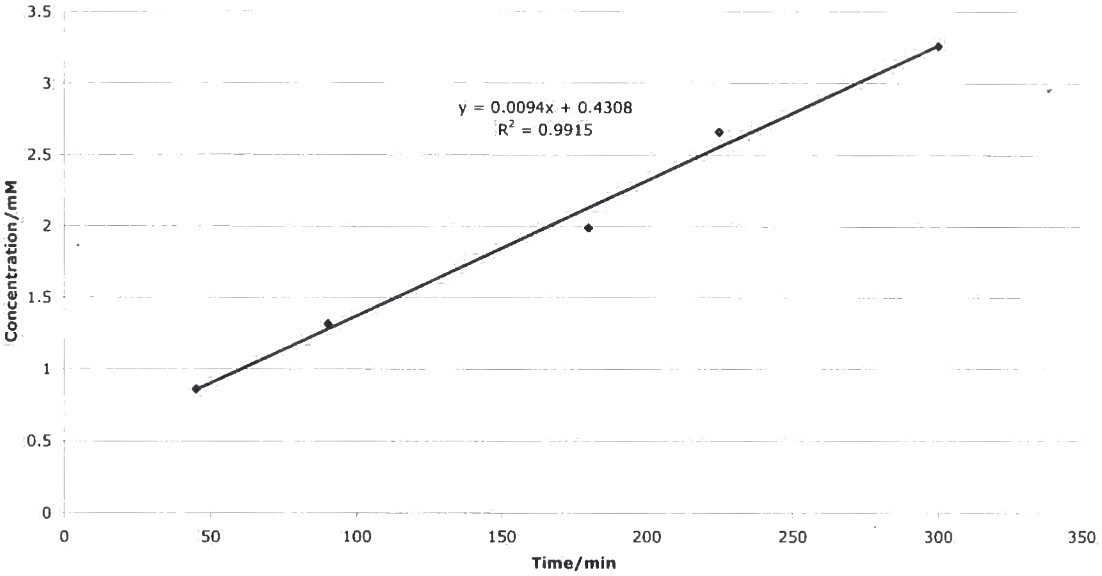




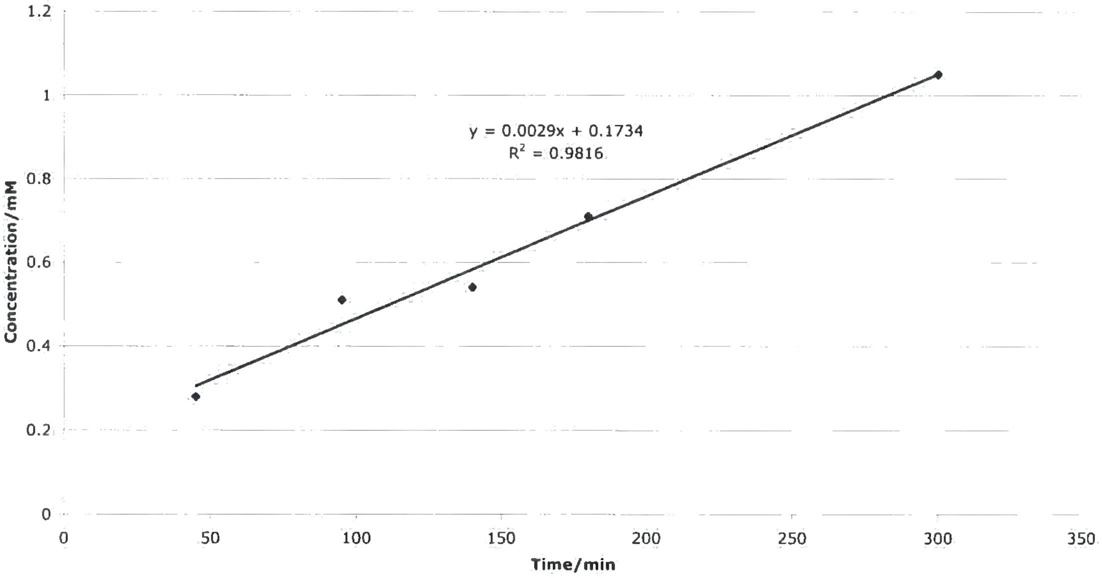

Triphenylphosphine catalysis, iodobenzene, product concentration versus time
y = 0.0141x + 1.2771
R² = 0.9939
Concentration/mM
6
5
4
3
2
1
0
0
50
100
150
200
250
300
350
Time/min


Triphenylphosphine catalysis, 4-fluoroiodobenzene, product concentration versus time
y = 0.0143x + 0.6176
R² = 0.9968
Concentration/mM
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0
50
100
150
200
250
300
Time/min

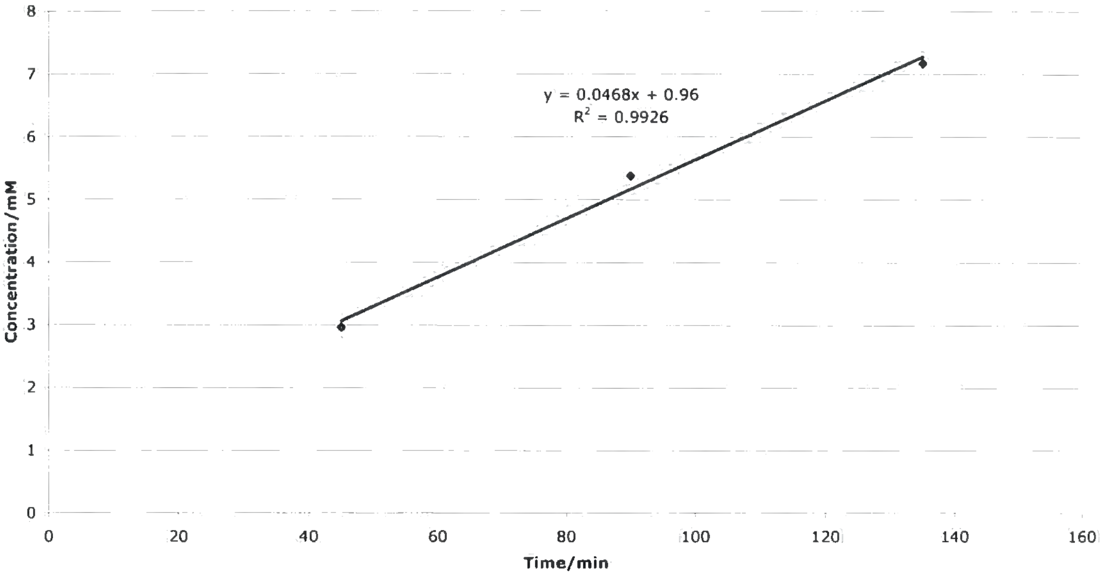
Triphenylphosphine catalysis, 4-chloroiodobenzene, product concentration versus time



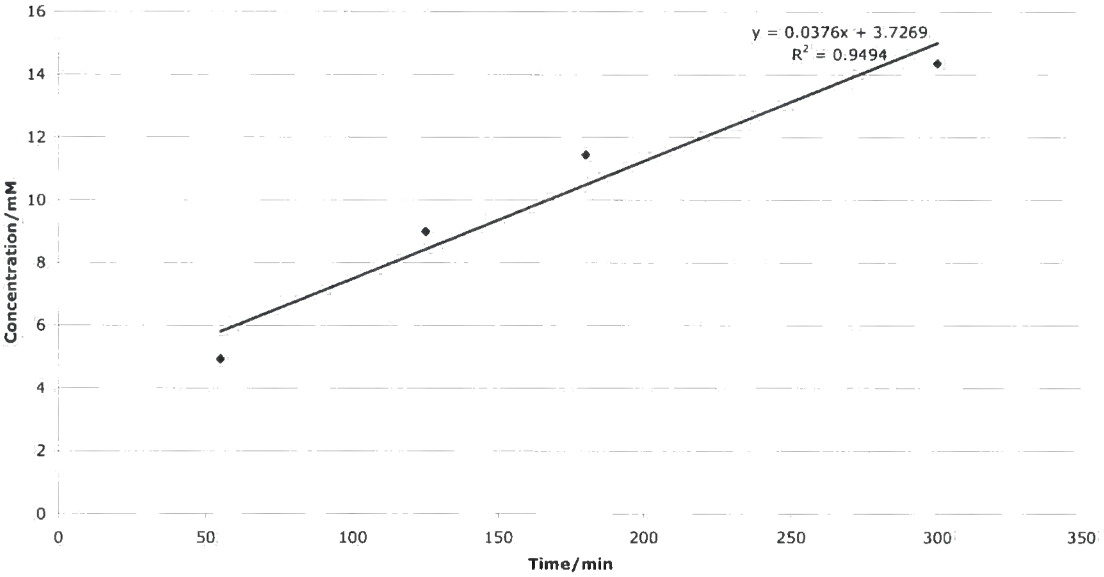
Triphenylphosphine catalysis, 4-nitroiodobenzene, product concentration versus time



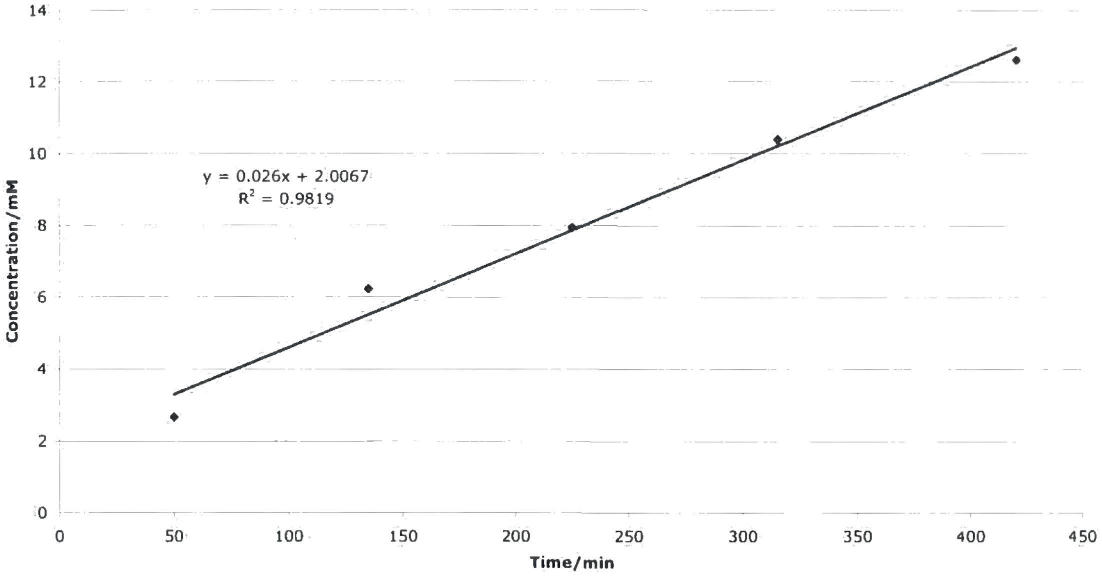
Tris(4-methoxyphenyl)phosphine catalysis, 4-iodoanisole, product concentration versus time



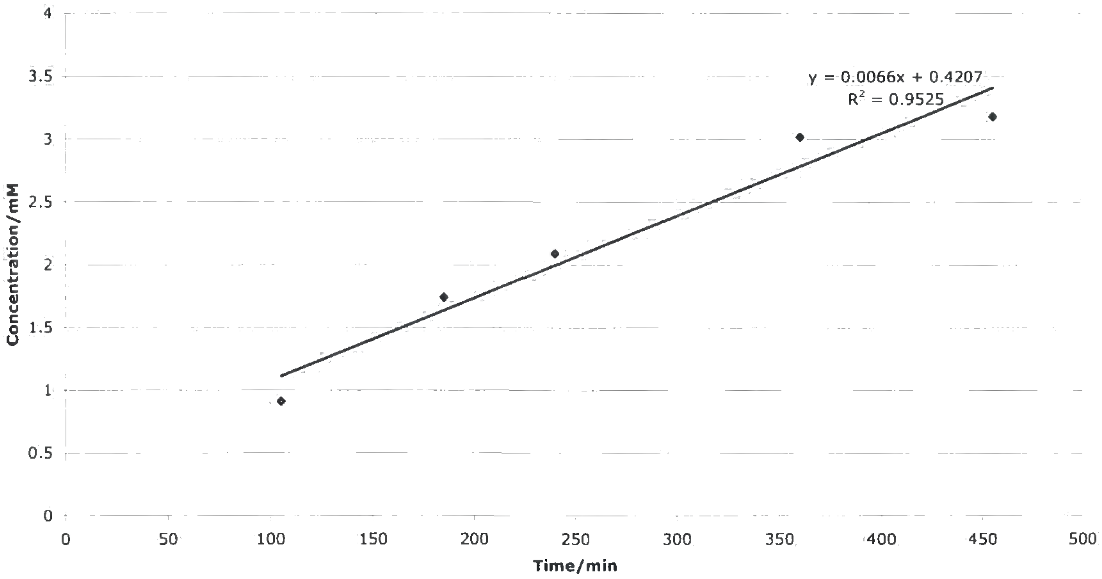
Tris(4-methoxyphenyl)phosphine catalysis, 4-iodotoluene, product concentration versus time



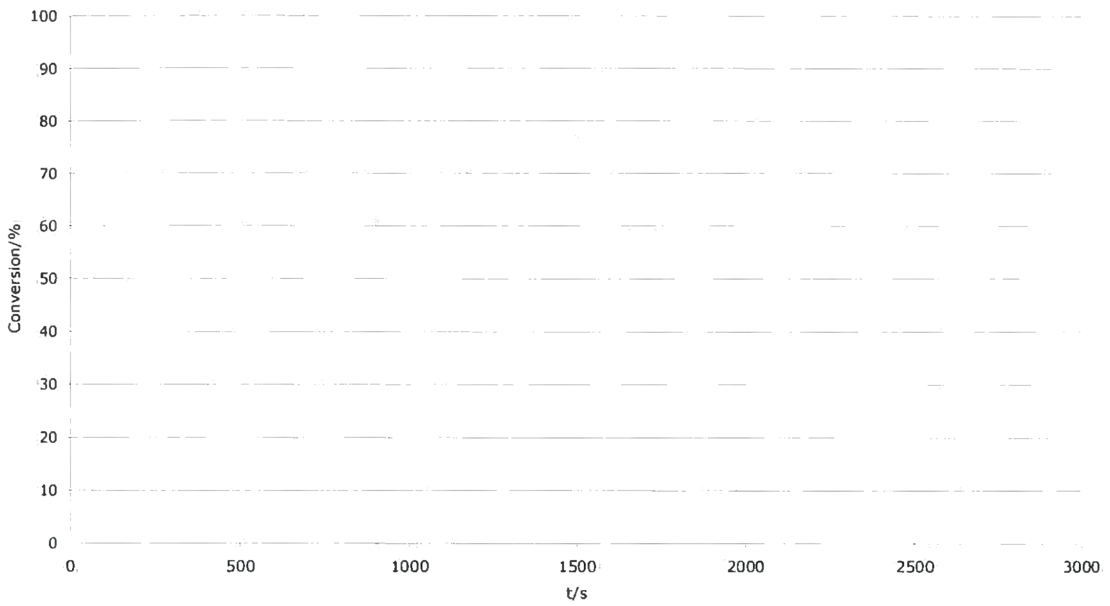
Tris(4-methoxyphenyl)phosphine catalysis, iodobenzene, product concentration versus time



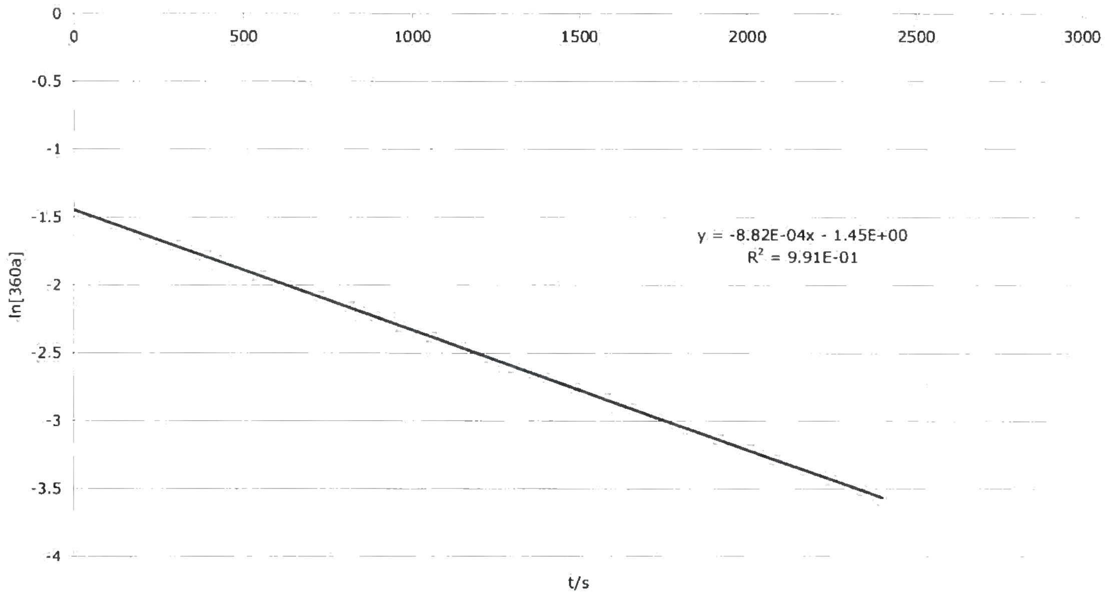
Tris(4-methoxyphenyl)phosphine catalysis, 4-iodonitrobenzene, product concentration versus time



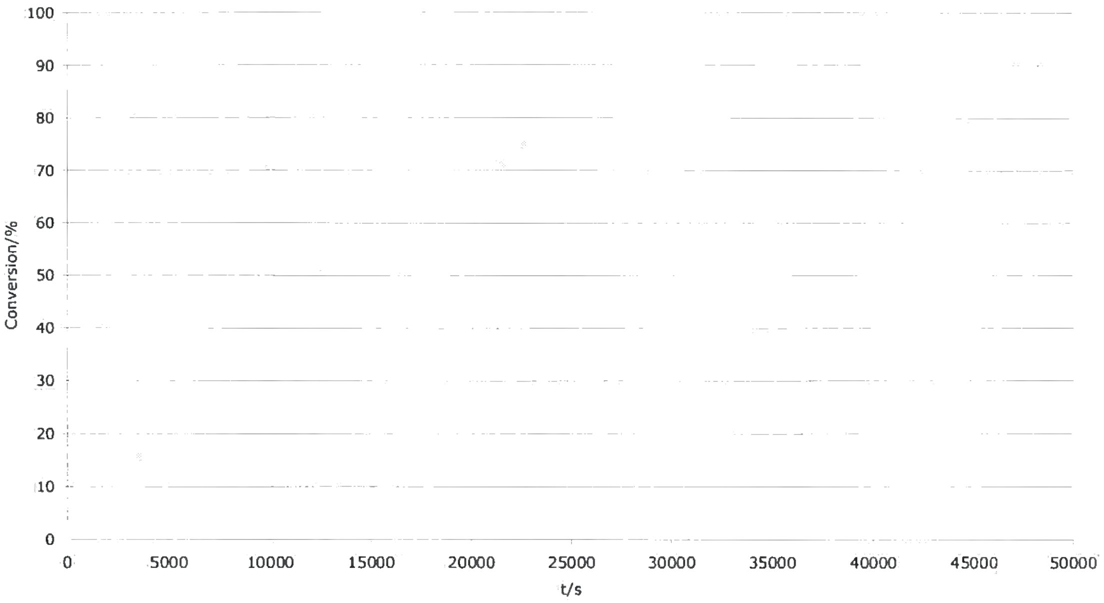
360a, 50% DCl, conversion versus time



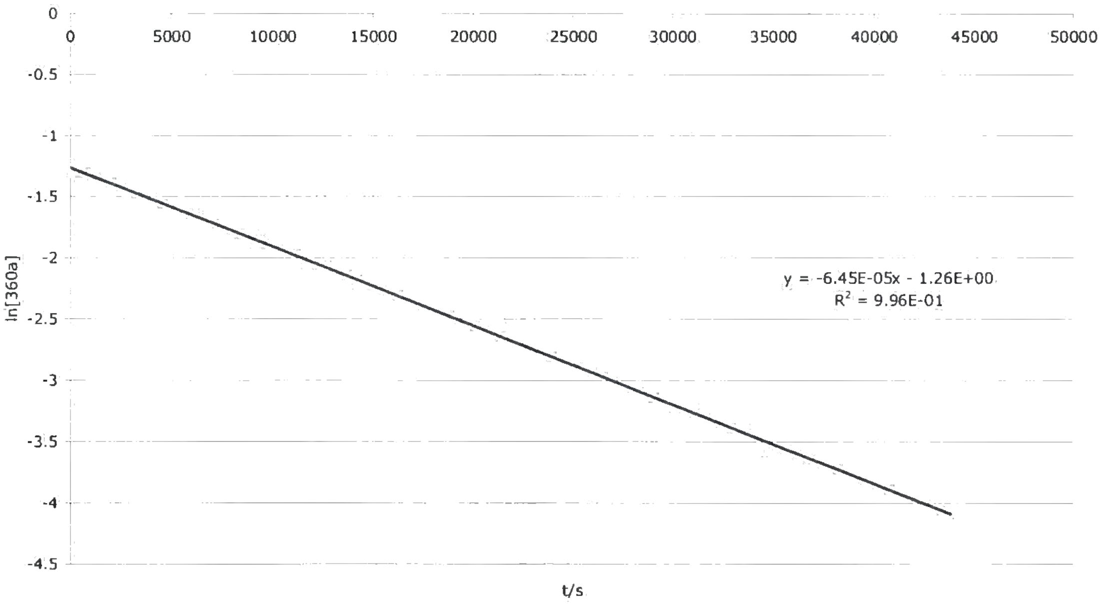
360a, 50% DCl, ln[**360a**] versus time

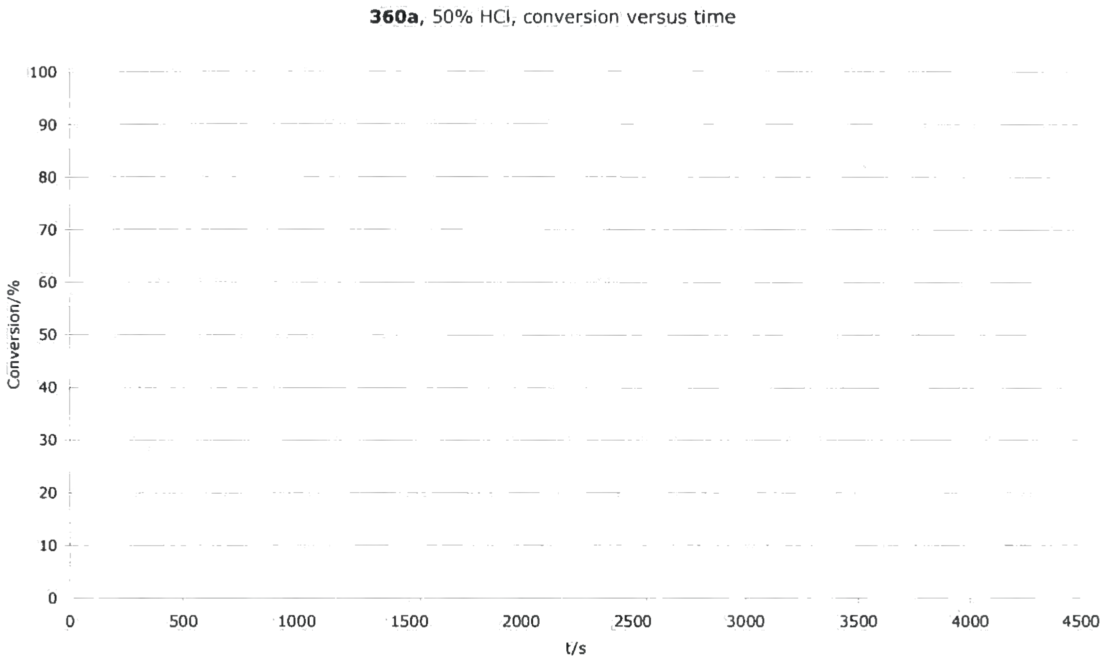


360a, 5% DCl, conversion versus time

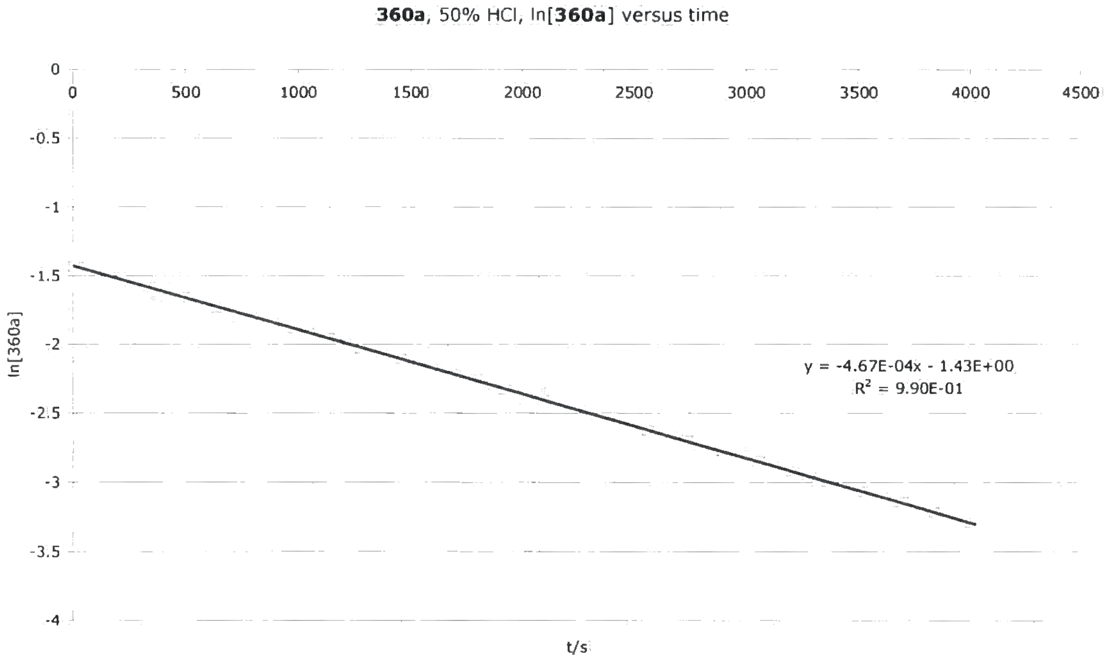


360a, 5% DCl, ln[**360a**] versus time



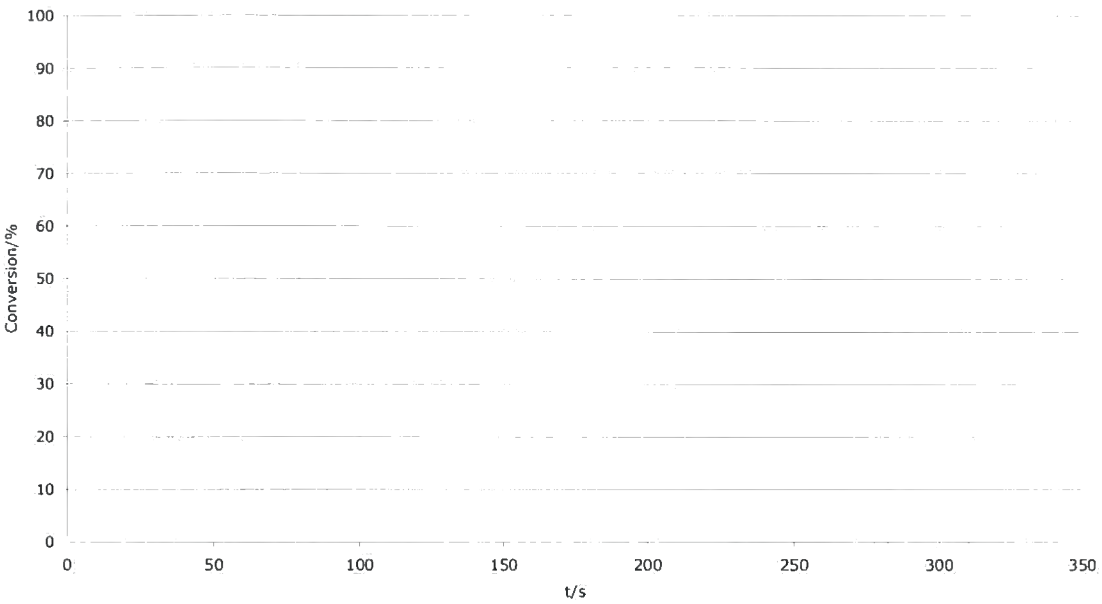


360a, 50% HCl, conversion versus time

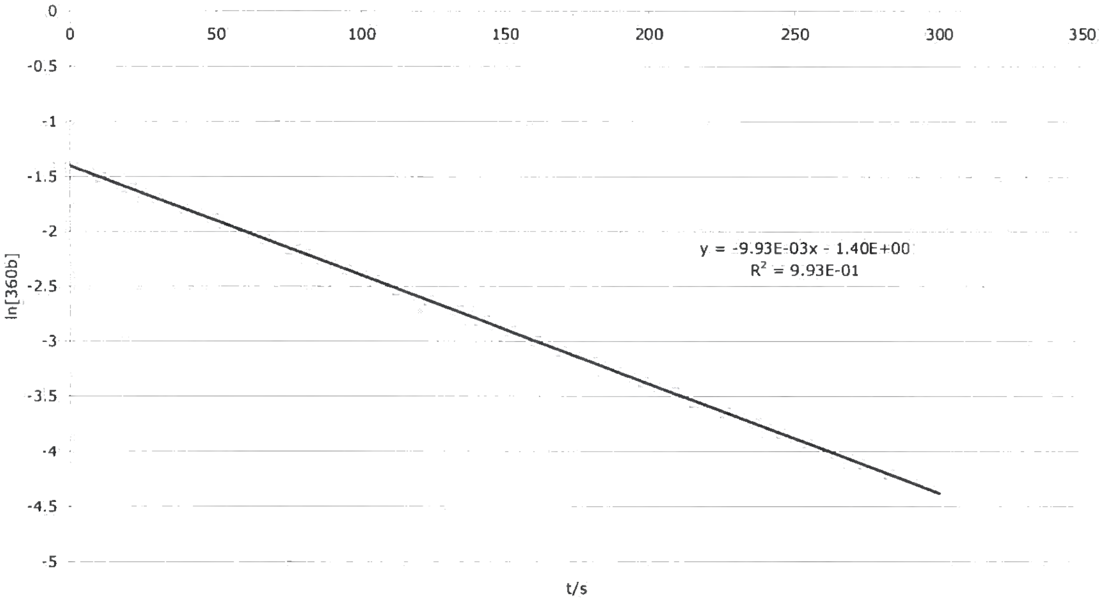


360a, 50% HCl, ln[**360a**] versus time

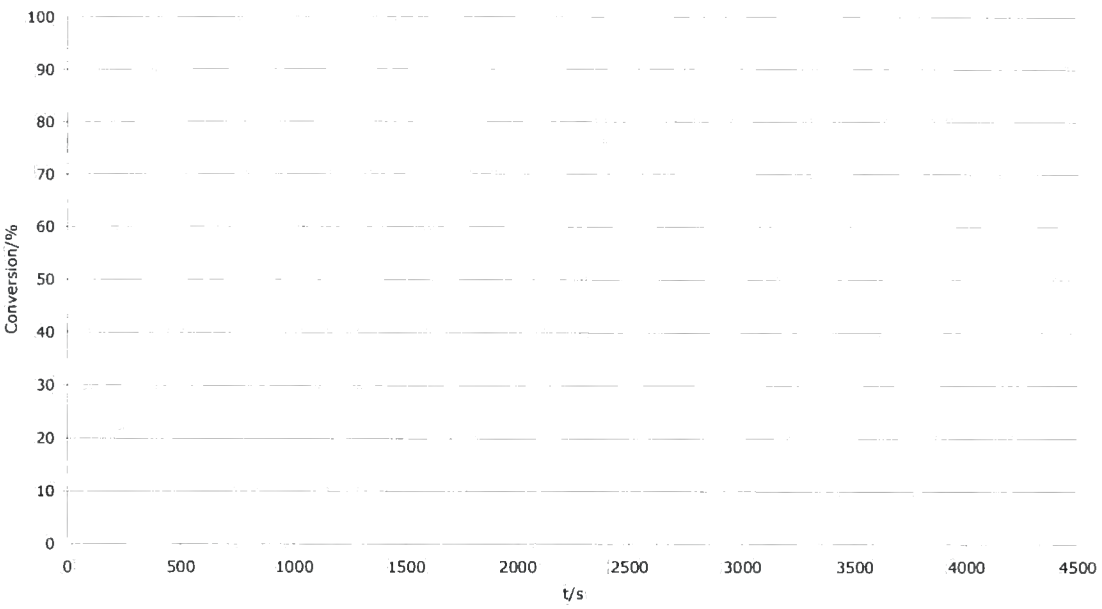
360b, 50% DCl, conversion versus time



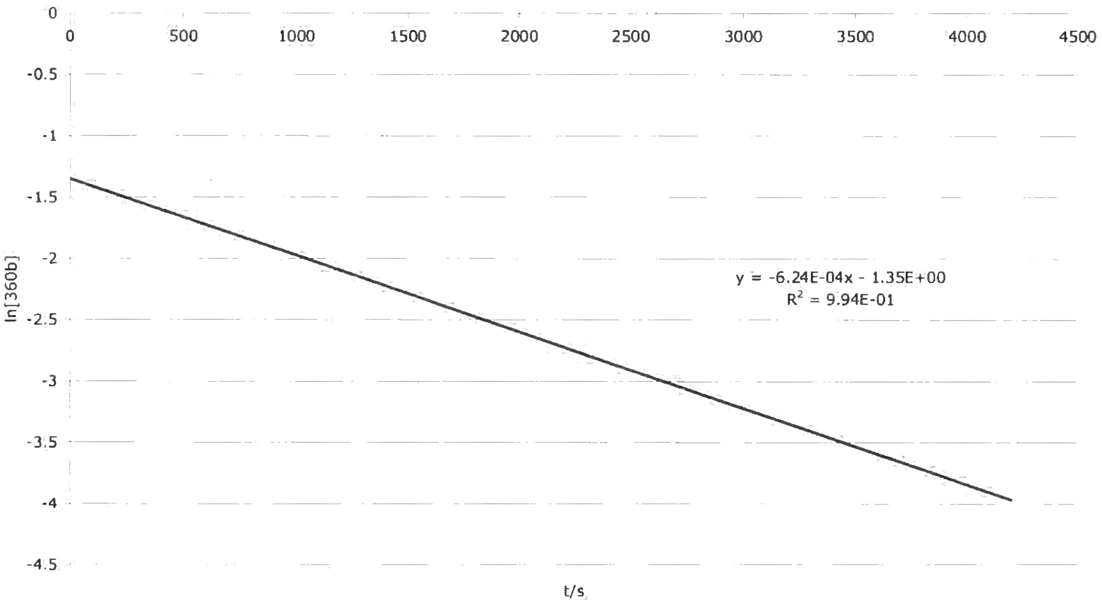
360b, 50% DCl, ln[**360b**] versus time

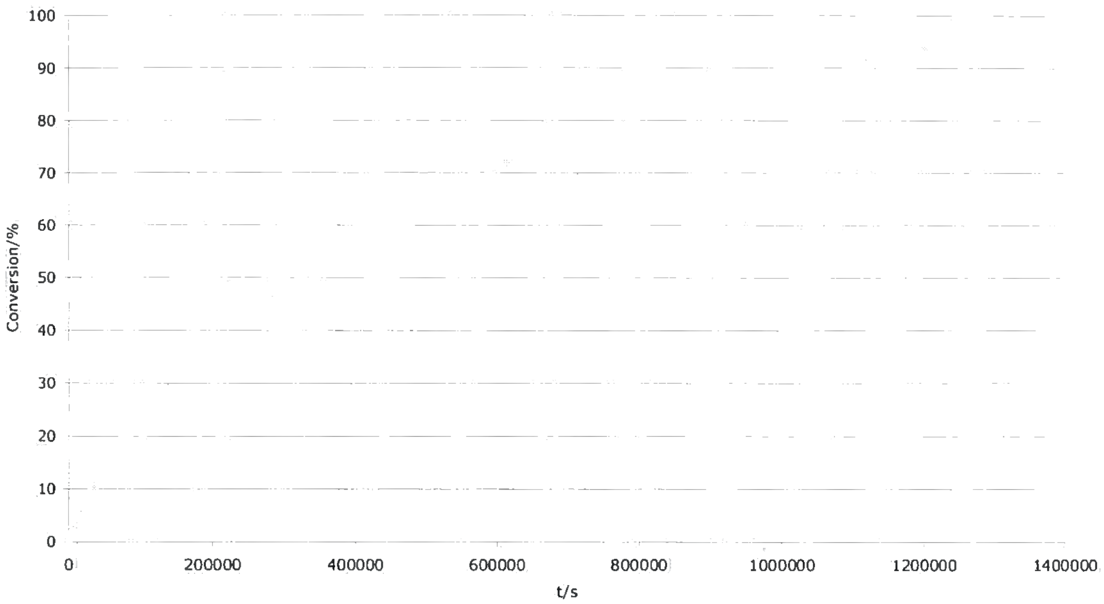


360b, 5% DCI, conversion versus time

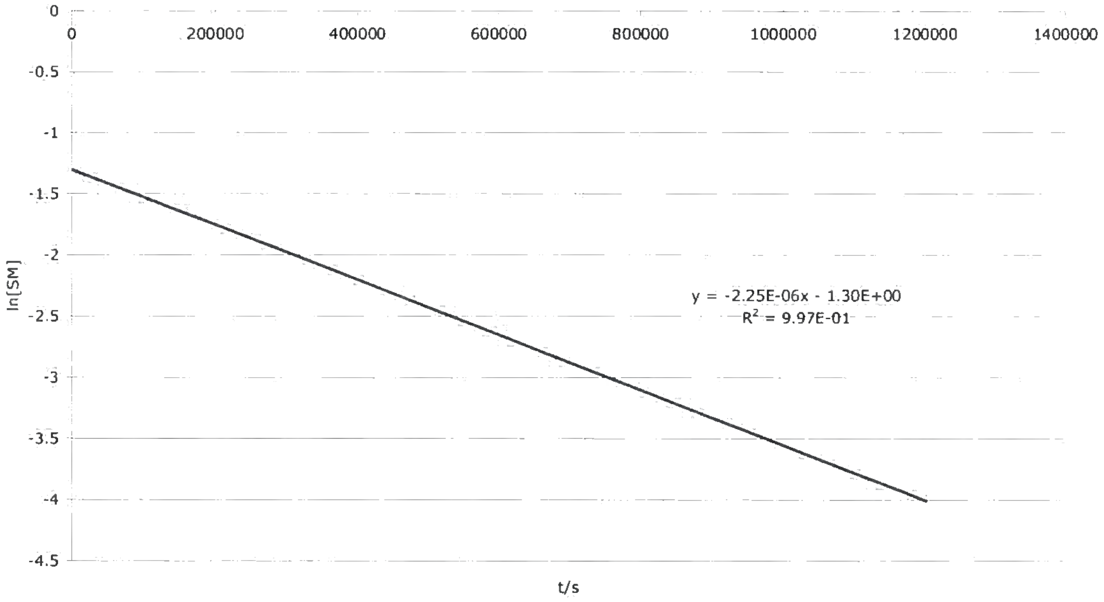


360b, 5% DCI, ln[**360b**] versus time

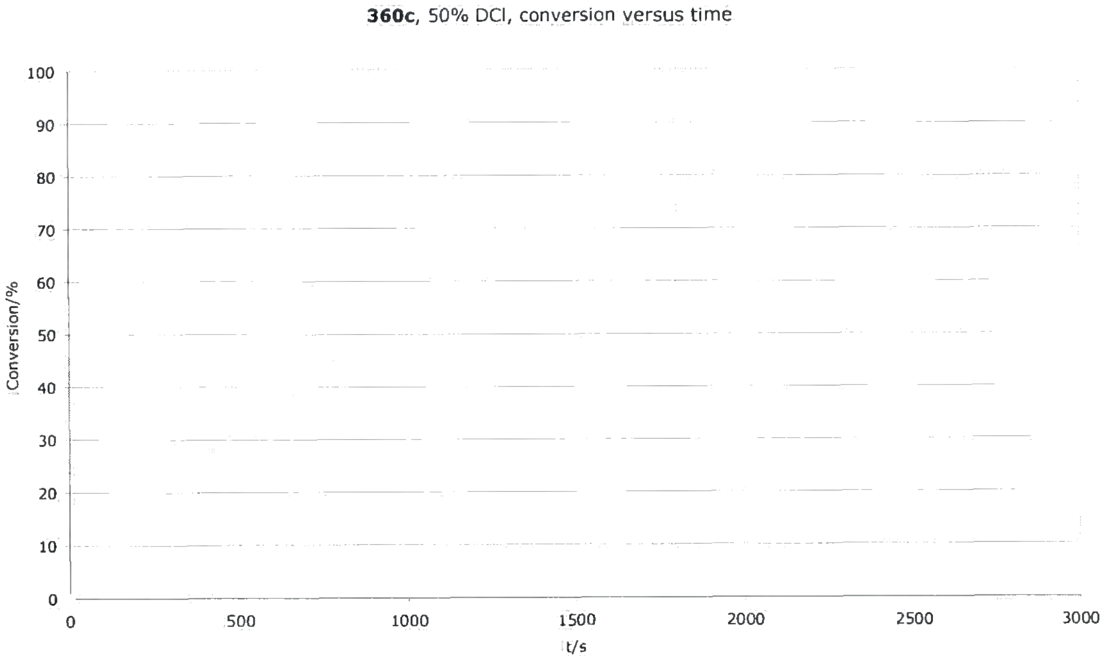


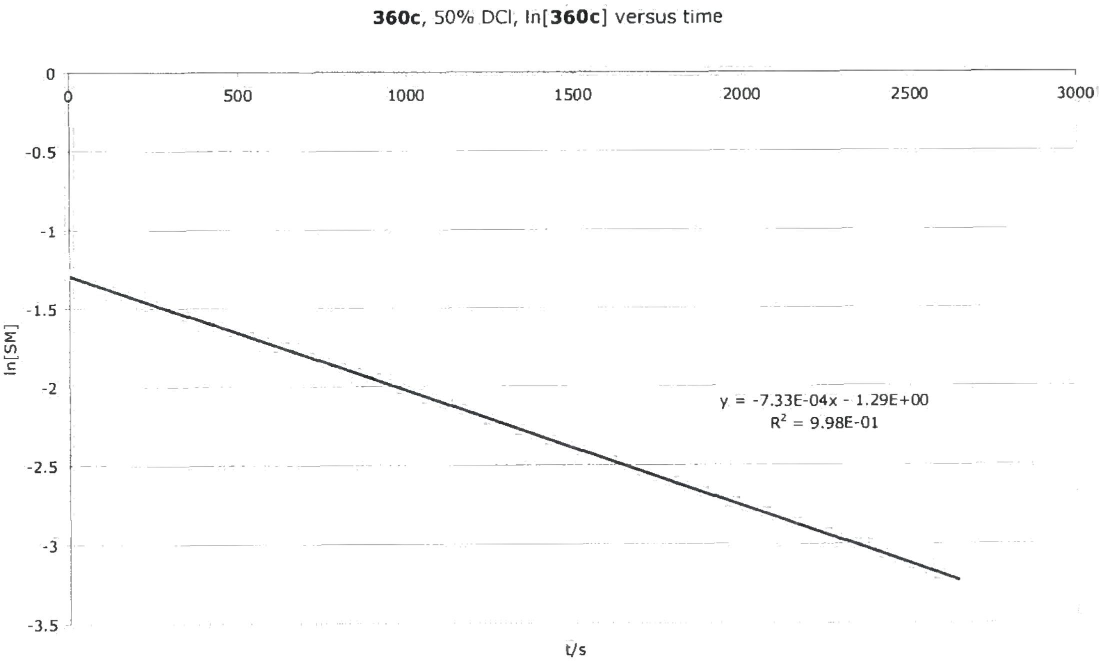


359b, 50% DCl, conversion versus time



359b, 50% DCl, ln[**359b**] versus time


360c, 50% DCl, conversion versus time
Conversion/%
100
90
80
70
60
50
40
30
20
10
0
0
500
1000
1500
2000
2500
3000
t/s


360c, 50% DCl, ln[**360c**] versus time
ln[SM]
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
0
500
1000
1500
2000
2500
3000
y = -7.33E-04x - 1.29E+00
R² = 9.98E-01
t/s

Appendix 2: selected crystallographic data (for full data see accompanying CD).

Diiodide **270**

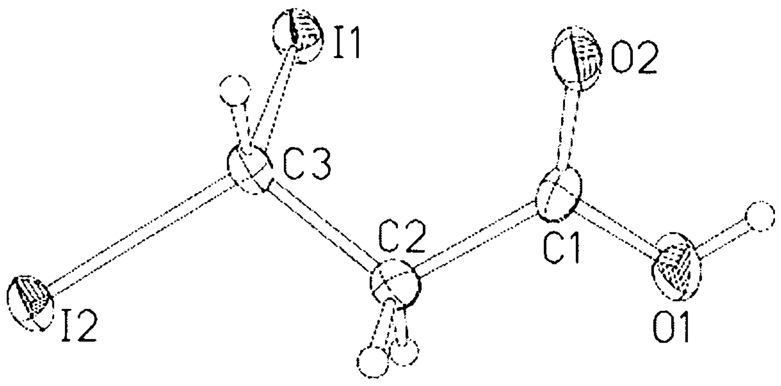


Table 12. Crystal data and structure refinement for **270**

Empirical formula	$C_3H_4I_2O_2$	
Formula weight	325.86	
Temperature	130(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$ (no 14)	
Unit cell dimensions	a = 12.7244(17) Å	α = 90°
	b = 6.5787(9) Å	β = 102.61(1)°
	c = 8.8078(12) Å	γ = 90°
Volume	719.52(17) Å^3	
Z	4	
Density (calculated)	3.008 g/cm^3	
Absorption coefficient	8.651 mm^{-1}	
F(000)	576	
Crystal size	0.20 × 0.07 × 0.06 mm^3	
θ range for data collection	1.6 to 29.0°.	
Index ranges	$-17 \leq h \leq 17, -8 \leq k \leq 8, -11 \leq l \leq 12$	
Reflections collected	8140	
Independent reflections	1898 [R(int) = 0.0264]	
Reflections with I>2σ(I)	1739	
Completeness to θ = 29°	99.8 %	
Absorption correction	Integration	

Max. and min. transmission	0.6394 and 0.3387
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1898 / 0 / 68
Largest final shift/e.s.d. ratio	0.002
Goodness-of-fit on F^2	1.104
Final R indices [I>2□(I)]	R1 = 0.0181, wR2 = 0.0442
R indices (all data)	R1 = 0.0207, wR2 = 0.0451
Largest diff. peak and hole	0.427 and -1.227 e.Å^{-3}

Table 13. Bond lengths [Å] and angles [°] for **270**.

I(1)-C(3)	2.156(3)	O(2)-C(1)	1.219(3)
I(2)-C(3)	2.145(2)	C(1)-C(2)	1.505(4)
O(1)-C(1)	1.309(3)	C(2)-C(3)	1.511(4)
O(2)-C(1)-O(1)	123.8(3)	C(2)-C(3)-I(2)	110.27(18)
O(2)-C(1)-C(2)	122.7(2)	C(2)-C(3)-I(1)	110.64(17)
O(1)-C(1)-C(2)	113.5(2)	I(2)-C(3)-I(1)	110.61(11)
C(1)-C(2)-C(3)	112.5(2)		

Table 14. Hydrogen bonds for 05srv333 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(0)...O(2)#1	0.80(5)	1.90(5)	2.695(3)	173(5)

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

Tetraene **291**

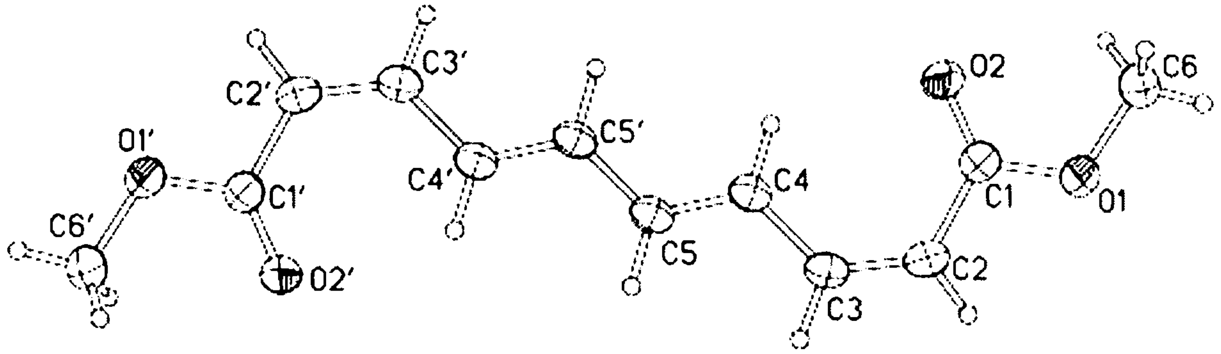


Table 15. Crystal data and structure refinement for **291**

Empirical formula	$C_{12}H_{14}O_4$	
Formula weight	222.23	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*P*2$_1$/*n* (no 14, non-standard setting)	
Unit cell dimensions	*a* = 8.1275(9) Å	□= 90°
	b = 7.4649(9) Å	□= 92.77(2)°
	c = 9.6239(11) Å	□ = 90°
Volume	583.21(12) Å^3	
Z	2	
Density (calculated)	1.265 g/cm^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	236	
Crystal size	0.44 × 0.18 × 0.03 mm^3	
□ range for data collection	3.2 to 29.0°.	
Index ranges	$-11 \leq h \leq 10, -9 \leq k \leq 10, -13 \leq l \leq 13$	
Reflections collected	6531	
Independent reflections	1541 [R(int) = 0.0290]	
Reflections with I>2□(I)	1196	
Completeness to □ = 29°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8619 and 0.7248	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	1541 / 0 / 101
Largest final shift/e.s.d. ratio	0.002
Goodness-of-fit on F^2	1.058
Final R indices [I>2σ(I)]	R1 = 0.0458, wR2 = 0.0969
R indices (all data)	R1 = 0.0643, wR2 = 0.1048
Largest diff. peak and hole	0.262 and -0.172 e.Å^{-3}

Table 16. Bond lengths [Å] and angles [°] for **291**.

O(1)-C(1)	1.3419(17)	C(4)-C(5)	1.348(2)
O(1)-C(6)	1.4428(19)	C(4)-H(4)	0.964(15)
O(2)-C(1)	1.2001(17)	C(5)-C(5)#1	1.439(3)
C(1)-C(2)	1.4730(19)	C(5)-H(5)	0.996(15)
C(2)-C(3)	1.344(2)	C(6)-H(61)	0.97(2)
C(2)-H(2)	0.929(17)	C(6)-H(62)	0.97(2)
C(3)-C(4)	1.440(2)	C(6)-H(63)	0.94(3)
C(3)-H(3)	0.988(16)		
C(1)-O(1)-C(6)	115.11(12)	C(5)-C(4)-H(4)	119.3(9)
O(2)-C(1)-O(1)	122.30(13)	C(3)-C(4)-H(4)	118.5(9)
O(2)-C(1)-C(2)	127.15(14)	C(4)-C(5)-C(5)#1	123.63(16)
O(1)-C(1)-C(2)	110.55(12)	C(4)-C(5)-H(5)	118.2(9)
C(3)-C(2)-C(1)	125.31(13)	C(5)#1-C(5)-H(5)	118.2(9)
C(3)-C(2)-H(2)	119.9(11)	O(1)-C(6)-H(61)	109.5(12)
C(1)-C(2)-H(2)	114.8(11)	O(1)-C(6)-H(62)	110.6(13)
C(2)-C(3)-C(4)	128.02(13)	H(61)-C(6)-H(62)	105.8(17)
C(2)-C(3)-H(3)	117.4(9)	O(1)-C(6)-H(63)	108.0(15)
C(4)-C(3)-H(3)	114.6(9)	H(61)-C(6)-H(63)	111.3(19)
C(5)-C(4)-C(3)	122.26(13)	H(62)-C(6)-H(63)	112(2)

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

Table 17. Torsion angles [°] for **291**.

C(6)-O(1)-C(1)-O(2)	2.0(2)	C(1)-C(2)-C(3)-C(4)	1.4(2)
C(6)-O(1)-C(1)-C(2)	-177.43(14)	C(2)-C(3)-C(4)-C(5)	-178.65(14)
O(2)-C(1)-C(2)-C(3)	-1.9(2)	C(3)-C(4)-C(5)-C(5)#1	179.33(16)
O(1)-C(1)-C(2)-C(3)	177.42(13)		

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

Amide **332**

Structure shown on page 125

Table 18. Crystal data and structure refinement for **332**

Empirical formula	$C_{19}H_{29}N_3O_7Si$	
Formula weight	439.54	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$ (no 4)	
Unit cell dimensions	a = 13.1833(12) Å	α = 90°
	b = 6.6134(6) Å	β = 109.32(1)°
	c = 13.7973(12) Å	γ = 90°
Volume	1135.2(2) Å^3	
Z	2	
Density (calculated)	1.286 g/cm^3	
Absorption coefficient	0.147 mm^{-1}	
F(000)	468	
Crystal size	0.64 × 0.10 × 0.09 mm^3	
θ range for data collection	1.56 to 30.0°.	
Index ranges	$-18 \leq h \leq 18$, $-9 \leq k \leq 9$, $-19 \leq l \leq 19$	
Reflections collected	15792	
Independent reflections	6620 [R(int) = 0.0290]	
Reflections with $I>2\sigma(I)$	5963	
Completeness to θ = 30°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.8159	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6620 / 1 / 387	
Largest final shift/e.s.d. ratio	0.000	
Goodness-of-fit on F^2	1.048	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0363, wR2 = 0.0920	
R indices (all data)	R1 = 0.0419, wR2 = 0.0954	
Absolute structure parameter	0.00(8)	
Largest diff. peak and hole	0.379 and -0.209 e.Å^{-3}	

Table 19. Bond lengths [Å] and angles [°] for **332**.

Si-O(1)	1.6573(11)	C(7)-H(72)	1.01(2)
Si-C(14)	1.8539(18)	C(7)-H(73)	1.03(3)
Si-C(15)	1.8604(18)	C(8)-C(9)	1.4088(19)
Si-C(16)	1.8872(16)	C(8)-C(13)	1.4125(19)
O(1)-C(4)	1.4225(18)	C(9)-C(10)	1.3918(19)
O(2)-C(5)	1.4139(17)	C(10)-C(11)	1.375(2)
O(2)-C(7)	1.4302(18)	C(10)-H(10)	0.94(2)
O(3)-C(6)	1.2157(17)	C(11)-C(12)	1.382(2)
O(4)-N(2)	1.2355(17)	C(12)-C(13)	1.3827(19)
O(5)-N(2)	1.2194(18)	C(12)-H(12)	1.01(2)
O(6)-N(3)	1.224(2)	C(13)-H(13)	0.908(19)
O(7)-N(3)	1.2260(18)	C(14)-H(141)	1.02(3)
N(1)-C(6)	1.3693(19)	C(14)-H(142)	0.99(2)
N(1)-C(8)	1.3823(17)	C(14)-H(143)	0.93(2)
N(1)-H(1N)	0.84(3)	C(15)-H(151)	0.93(3)
N(2)-C(9)	1.4656(18)	C(15)-H(152)	1.02(3)
N(3)-C(11)	1.4692(18)	C(15)-H(153)	0.99(3)
C(1)-C(2)	1.339(3)	C(16)-C(17)	1.536(3)
C(1)-C(3)	1.489(3)	C(16)-C(19)	1.538(2)
C(1)-C(4)	1.5177(18)	C(16)-C(18)	1.541(3)
C(2)-H(21)	0.93(3)	C(17)-H(171)	0.97(3)
C(2)-H(22)	0.95(3)	C(17)-H(172)	0.98(2)
C(3)-H(161)	0.83(4)	C(17)-H(173)	0.94(3)
C(3)-H(32)	0.94(3)	C(18)-H(181)	0.89(2)
C(3)-H(163)	0.95(3)	C(18)-H(182)	0.83(3)
C(4)-C(5)	1.5424(19)	C(18)-H(183)	0.99(3)
C(4)-H(4)	0.916(18)	C(19)-H(191)	0.97(3)
C(5)-C(6)	1.5392(18)	C(19)-H(192)	0.98(2)
C(5)-H(5)	0.987(19)	C(19)-H(193)	1.04(2)
C(7)-H(71)	0.93(3)		

O(1)-Si-C(14)	104.93(7)	O(1)-Si-C(16)	111.23(6)
O(1)-Si-C(15)	111.47(7)	C(14)-Si-C(16)	109.72(9)
C(14)-Si-C(15)	109.30(9)	C(15)-Si-C(16)	110.06(8)

C(4)-O(1)-Si	127.06(9)	O(3)-C(6)-C(5)	121.70(13)
C(5)-O(2)-C(7)	112.78(13)	N(1)-C(6)-C(5)	111.86(12)
C(6)-N(1)-C(8)	129.18(12)	O(2)-C(7)-H(71)	106.6(16)
C(6)-N(1)-H(1N)	112.1(17)	O(2)-C(7)-H(72)	110.4(12)
C(8)-N(1)-H(1N)	118.6(17)	H(71)-C(7)-H(72)	108.6(19)
O(5)-N(2)-O(4)	122.44(13)	O(2)-C(7)-H(73)	113.0(14)
O(5)-N(2)-C(9)	118.33(12)	H(71)-C(7)-H(73)	108(2)
O(4)-N(2)-C(9)	119.23(12)	H(72)-C(7)-H(73)	111(2)
O(6)-N(3)-O(7)	124.33(13)	N(1)-C(8)-C(9)	121.08(12)
O(6)-N(3)-C(11)	118.46(13)	N(1)-C(8)-C(13)	121.63(12)
O(7)-N(3)-C(11)	117.20(13)	C(9)-C(8)-C(13)	117.30(12)
C(2)-C(1)-C(3)	122.91(15)	C(10)-C(9)-C(8)	121.81(12)
C(2)-C(1)-C(4)	118.03(15)	C(10)-C(9)-N(2)	115.18(13)
C(3)-C(1)-C(4)	119.00(14)	C(8)-C(9)-N(2)	123.00(12)
C(1)-C(2)-H(21)	118.6(17)	C(11)-C(10)-C(9)	118.27(13)
C(1)-C(2)-H(22)	125.2(17)	C(11)-C(10)-H(10)	124.7(12)
H(21)-C(2)-H(22)	116(2)	C(9)-C(10)-H(10)	116.7(12)
C(1)-C(3)-H(161)	110(2)	C(10)-C(11)-C(12)	122.37(13)
C(1)-C(3)-H(32)	111.7(17)	C(10)-C(11)-N(3)	118.02(13)
H(161)-C(3)-H(32)	104(3)	C(12)-C(11)-N(3)	119.61(13)
C(1)-C(3)-H(163)	107.8(16)	C(11)-C(12)-C(13)	119.11(13)
H(161)-C(3)-H(163)	116(3)	C(11)-C(12)-H(12)	118.7(12)
H(32)-C(3)-H(163)	107(2)	C(13)-C(12)-H(12)	122.2(12)
O(1)-C(4)-C(1)	112.36(12)	C(12)-C(13)-C(8)	121.14(14)
O(1)-C(4)-C(5)	109.20(11)	C(12)-C(13)-H(13)	122.4(11)
C(1)-C(4)-C(5)	110.47(11)	C(8)-C(13)-H(13)	116.4(11)
O(1)-C(4)-H(4)	109.4(11)	Si-C(14)-H(141)	113.9(19)
C(1)-C(4)-H(4)	108.2(11)	Si-C(14)-H(142)	110.5(15)
C(5)-C(4)-H(4)	107.1(11)	H(141)-C(14)-H(142)	102(2)
O(2)-C(5)-C(6)	111.83(11)	Si-C(14)-H(143)	112.1(16)
O(2)-C(5)-C(4)	109.65(11)	H(141)-C(14)-H(143)	105(2)
C(6)-C(5)-C(4)	108.76(11)	H(142)-C(14)-H(143)	113(2)
O(2)-C(5)-H(5)	112.4(10)	Si-C(15)-H(151)	118.2(14)
C(6)-C(5)-H(5)	108.2(11)	Si-C(15)-H(152)	110.5(16)
C(4)-C(5)-H(5)	105.8(10)	H(151)-C(15)-H(152)	109(2)
O(3)-C(6)-N(1)	126.41(13)	Si-C(15)-H(153)	110.4(15)

H(151)-C(15)-H(153)	101(2)	H(172)-C(17)-H(173)	114(2)
H(152)-C(15)-H(153)	107(2)	C(16)-C(18)-H(181)	107.1(17)
C(17)-C(16)-C(19)	108.50(18)	C(16)-C(18)-H(182)	114(2)
C(17)-C(16)-C(18)	108.96(18)	H(181)-C(18)-H(182)	112(3)
C(19)-C(16)-C(18)	108.50(14)	C(16)-C(18)-H(183)	109.9(15)
C(17)-C(16)-Si	110.84(12)	H(181)-C(18)-H(183)	112(2)
C(19)-C(16)-Si	109.48(13)	H(182)-C(18)-H(183)	102(2)
C(18)-C(16)-Si	110.51(12)	C(16)-C(19)-H(191)	112.3(17)
C(16)-C(17)-H(171)	108.9(13)	C(16)-C(19)-H(192)	109.5(14)
C(16)-C(17)-H(172)	108.2(12)	H(191)-C(19)-H(192)	107(2)
H(171)-C(17)-H(172)	109.4(18)	C(16)-C(19)-H(193)	109.6(12)
C(16)-C(17)-H(173)	109(2)	H(191)-C(19)-H(193)	104(2)
H(171)-C(17)-H(173)	107(2)	H(192)-C(19)-H(193)	114.9(18)

Table 20. Torsion angles [°] for **332**.

C(14)-Si-O(1)-C(4)	161.21(11)	C(13)-C(8)-C(9)-C(10)	-0.8(2)
C(15)-Si-O(1)-C(4)	43.02(13)	N(1)-C(8)-C(9)-N(2)	-2.5(2)
C(16)-Si-O(1)-C(4)	-80.22(12)	C(13)-C(8)-C(9)-N(2)	177.74(13)
Si-O(1)-C(4)-C(1)	113.79(11)	O(5)-N(2)-C(9)-C(10)	9.8(2)
Si-O(1)-C(4)-C(5)	-123.28(10)	O(4)-N(2)-C(9)-C(10)	-170.02(13)
C(2)-C(1)-C(4)-O(1)	-146.00(14)	O(5)-N(2)-C(9)-C(8)	-168.83(14)
C(3)-C(1)-C(4)-O(1)	36.71(18)	O(4)-N(2)-C(9)-C(8)	11.4(2)
C(2)-C(1)-C(4)-C(5)	91.78(16)	C(9)-C(10)-C(11)-N(3)	-179.13(12)
C(3)-C(1)-C(4)-C(5)	-85.51(17)	O(6)-N(3)-C(11)-C(10)	-3.4(2)
C(7)-O(2)-C(5)-C(6)	83.08(15)	O(7)-N(3)-C(11)-C(10)	176.26(12)
C(7)-O(2)-C(5)-C(4)	-156.20(12)	O(6)-N(3)-C(11)-C(12)	176.76(14)
O(1)-C(4)-C(5)-O(2)	-62.12(13)	O(7)-N(3)-C(11)-C(12)	-3.6(2)
C(1)-C(4)-C(5)-O(2)	61.93(15)	C(10)-C(11)-C(12)-C(13)	-0.6(2)
O(1)-C(4)-C(5)-C(6)	60.45(14)	N(3)-C(11)-C(12)-C(13)	179.20(13)
C(1)-C(4)-C(5)-C(6)	-175.50(13)	N(1)-C(8)-C(13)-C(12)	-178.94(13)
C(8)-N(1)-C(6)-O(3)	3.4(2)	O(1)-Si-C(16)-C(17)	-50.11(17)
C(8)-N(1)-C(6)-C(5)	-178.57(13)	C(14)-Si-C(16)-C(17)	65.53(17)
O(2)-C(5)-C(6)-O(3)	-163.29(13)	C(15)-Si-C(16)-C(17)	-174.16(16)
C(4)-C(5)-C(6)-O(3)	75.46(17)	O(1)-Si-C(16)-C(19)	-169.76(12)
O(2)-C(5)-C(6)-N(1)	18.52(16)	C(14)-Si-C(16)-C(19)	-54.12(15)
C(4)-C(5)-C(6)-N(1)	-102.72(13)	C(15)-Si-C(16)-C(19)	66.19(15)
C(6)-N(1)-C(8)-C(9)	172.53(13)	O(1)-Si-C(16)-C(18)	70.79(13)
C(6)-N(1)-C(8)-C(13)	-7.7(2)	C(14)-Si-C(16)-C(18)	-173.57(13)
N(1)-C(8)-C(9)-C(10)	179.02(13)	C(15)-Si-C(16)-C(18)	-53.26(14)

Table 21. Hydrogen bonds for **332** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(2)	0.84(3)	2.10(2)	2.6084(16)	118(2)
N(1)-H(1N)...O(4)	0.84(3)	1.98(3)	2.6229(17)	132(2)

Ozonide **405**

Structure shown on p163

Table 22. Crystal data and structure refinement for **405**.

Empirical formula	$C_{14}H_{25}NO_5Si$	
Formula weight	315.44	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$ (no 4)	
Unit cell dimensions	a = 10.726(1) Å	α= 90°
	b = 8.1169(5) Å	β= 115.27(1)°
	c = 11.027(1) Å	γ = 90°
Volume	868.16(12) $Å^3$	
Z	2	
Density (calculated)	1.207 g/cm^3	
Absorption coefficient	0.154 mm^{-1}	
F(000)	340	
Crystal size	0.58 × 0.20 × 0.18 mm^3	
θ range for data collection	2.0 to 30.0°.	
Index ranges	$-15 \leq h \leq 14, -11 \leq k \leq 11, -15 \leq l \leq 15$	
Reflections collected	11173	
Independent reflections	4818 [R(int) = 0.0333]	
Reflections with $I>2\sigma(I)$	4706	
Completeness to θ = 29.00°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4818 / 1 / 205	
Largest final shift/e.s.d. ratio	0.000	
Goodness-of-fit on F^2	1.070	
Final R indices $[I>2\sigma(I)]$	R1 = 0.0271, wR2 = 0.0728	
R indices (all data)	R1 = 0.0281, wR2 = 0.0738	
Absolute structure parameter	0.016(63)	
Largest diff. peak and hole	0.302 and -0.220 $e.Å^{-3}$	

Table 23. Bond lengths [Å] and angles [°] for **405**.

Si-O(5)	1.6628(8)	C(7)-H(7B)	0.9800
Si-C(8)	1.8633(12)	C(7)-H(7C)	0.9800
Si-C(9)	1.8650(11)	C(8)-H(8A)	0.9800
Si-C(10)	1.8820(11)	C(8)-H(8B)	0.9800
O(2)-C(1)	1.4347(13)	C(8)-H(8C)	0.9800
O(2)-O(3)	1.4860(12)	C(9)-H(9A)	0.9800
O(3)-C(4)	1.4437(13)	C(9)-H(9B)	0.9800
O(5)-C(5)	1.4152(11)	C(9)-H(9C)	0.9800
O(6)-C(6)	1.4058(12)	C(10)-C(11)	1.5310(15)
O(6)-C(14)	1.4211(14)	C(10)-C(13)	1.5385(15)
O(7)-C(1)	1.4126(13)	C(10)-C(12)	1.5392(17)
O(7)-C(4)	1.4290(12)	C(11)-H(11A)	0.9800
N-C(3)	1.134(2)	C(11)-H(11B)	0.9800
C(1)-C(2)	1.5132(15)	C(11)-H(11C)	0.9800
C(1)-C(6)	1.5447(14)	C(12)-H(12A)	0.9800
C(2)-C(3)	1.464(2)	C(12)-H(12B)	0.9800
C(2)-H(2A)	0.9900	C(12)-H(12C)	0.9800
C(2)-H(2B)	0.9900	C(13)-H(13A)	0.9800
C(4)-C(7)	1.4938(15)	C(13)-H(13B)	0.9800
C(4)-C(5)	1.5359(13)	C(13)-H(13C)	0.9800
C(5)-C(6)	1.5428(13)	C(14)-H(14A)	0.9800
C(5)-H(5)	1.0000	C(14)-H(14B)	0.9800
C(6)-H(6)	1.0000	C(14)-H(14C)	0.9800
C(7)-H(7A)	0.9800		

O(5)-Si-C(8)	108.33(5)	C(1)-O(7)-C(4)	95.39(7)
O(5)-Si-C(9)	109.21(5)	O(7)-C(1)-O(2)	104.04(8)
C(8)-Si-C(9)	110.83(6)	O(7)-C(1)-C(2)	112.53(9)
O(5)-Si-C(10)	103.78(4)	O(2)-C(1)-C(2)	107.31(9)
C(8)-Si-C(10)	112.59(6)	O(7)-C(1)-C(6)	102.63(8)
C(9)-Si-C(10)	111.78(5)	O(2)-C(1)-C(6)	108.50(8)
C(1)-O(2)-O(3)	101.79(7)	C(2)-C(1)-C(6)	120.61(9)
C(4)-O(3)-O(2)	102.90(7)	C(3)-C(2)-C(1)	110.88(10)
C(5)-O(5)-Si	122.63(6)	C(3)-C(2)-H(2A)	109.4
C(6)-O(6)-C(14)	113.71(9)	C(1)-C(2)-H(2A)	109.5

C(3)-C(2)-H(2B)	109.5
C(1)-C(2)-H(2B)	109.5
H(2A)-C(2)-H(2B)	108.1
N-C(3)-C(2)	178.02(15)
O(7)-C(4)-O(3)	102.28(8)
O(7)-C(4)-C(7)	113.84(9)
O(3)-C(4)-C(7)	109.42(9)
O(7)-C(4)-C(5)	103.68(8)
O(3)-C(4)-C(5)	106.87(8)
C(7)-C(4)-C(5)	119.22(9)
O(5)-C(5)-C(4)	109.99(8)
O(5)-C(5)-C(6)	111.26(8)
C(4)-C(5)-C(6)	100.59(7)
O(5)-C(5)-H(5)	111.5
C(4)-C(5)-H(5)	111.5
C(6)-C(5)-H(5)	111.5
O(6)-C(6)-C(5)	111.51(8)
O(6)-C(6)-C(1)	114.73(8)
C(5)-C(6)-C(1)	100.26(7)
O(6)-C(6)-H(6)	110.0
C(5)-C(6)-H(6)	110.0
C(1)-C(6)-H(6)	110.0
C(4)-C(7)-H(7A)	109.5
C(4)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
C(4)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
Si-C(8)-H(8A)	109.5
Si-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
Si-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
Si-C(9)-H(9A)	109.5
Si-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
Si-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(11)-C(10)-C(13)	109.43(10)
C(11)-C(10)-C(12)	109.20(10)
C(13)-C(10)-C(12)	108.74(10)
C(11)-C(10)-Si	109.75(8)
C(13)-C(10)-Si	109.99(8)
C(12)-C(10)-Si	109.70(8)
C(10)-C(11)-H(11A)	109.5
C(10)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(10)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(10)-C(12)-H(12A)	109.5
C(10)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(10)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(10)-C(13)-H(13A)	109.5
C(10)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(10)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
O(6)-C(14)-H(14A)	109.5
O(6)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
O(6)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5

Enolamide **428**.

Table 24. Crystal data and structure refinement for **428**.

Empirical formula	$C_{16}H_{29}NO_4Si$	
Formula weight	327.49	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*I*2 (no)	
Unit cell dimensions	*a* = 16.5699(9) Å	□= 90°
	b = 7.2490(4) Å	□= 111.330(2)°
	c = 17.0668(9) Å	□ = 90°
Volume	1909.56(18) $Å^3$	
Z	4	
Density (calculated)	1.139 g/cm^3	
Absorption coefficient	0.139 mm^{-1}	
F(000)	712	
Crystal size	0.4 × 0.3 × 0.1 mm^3	
□ range for data collection	1.47 to 30.03°.	
Index ranges	$-23 \leq h \leq 23, -10 \leq k \leq 10, -20 \leq l \leq 24$	
Reflections collected	8761	
Independent reflections	5140 [R(int) = 0.0257]	
Reflections with I>2□(I)	4498	
Completeness to □ = 30.03°	99.4 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5140 / 1 / 230	
Largest final shift/e.s.d. ratio	0.000	
Goodness-of-fit on F^2	1.062	
Final R indices [I>2□(I)]	R1 = 0.0409, wR2 = 0.1062	
R indices (all data)	R1 = 0.0483, wR2 = 0.1118	
Absolute structure parameter	0.03(11)	
Largest diff. peak and hole	0.384 and -0.348 e.$Å^{-3}$	

Disorder: The methyl and vinyl substituents at C(5) are disordered in a 6:1 ratio, i.e. C(10) with attached hydrogens is distributed between positions A and B with occupancies 0.840(6) and 0.160(6), while H(82A) and H(83A) have occupancies of 0.84, H(92B) and H(93B) of 0.16.

Table 25. Bond lengths [Å] and angles [°] for **428**.

Si-O(3)	1.6494(12)	C(8)-H(82A)	0.9801
Si-C(12)	1.857(2)	C(8)-H(83A)	0.9800
Si-C(11)	1.862(2)	C(9)-C(10A)	1.314(3)
Si-C(13)	1.8801(18)	C(9)-H(91)	0.9499
O(1)-C(6)	1.2563(17)	C(9)-H(92B)	0.9600
O(3)-C(4)	1.4170(18)	C(9)-H(93B)	0.9600
O(4)-C(2)	1.3350(18)	C(10A)-H(101)	0.9500
O(4)-H(0)	0.88(3)	C(10A)-H(102)	0.9501
O(5)-C(7)	1.416(2)	C(10B)-H(103)	0.9600
O(5)-C(3)	1.4240(19)	C(10B)-H(104)	0.9600
N-C(6)	1.3366(18)	C(11)-H(111)	0.9802
N-H(1N)	0.85(2)	C(11)-H(112)	0.9802
N-H(2N)	0.85(2)	C(11)-H(113)	0.9801
C(1)-C(2)	1.3493(19)	C(12)-H(121)	0.9802
C(1)-C(6)	1.464(2)	C(12)-H(122)	0.9801
C(1)-C(5)	1.519(2)	C(12)-H(123)	0.9801
C(2)-C(3)	1.500(2)	C(13)-C(14)	1.529(3)
C(3)-C(4)	1.531(2)	C(13)-C(16)	1.537(3)
C(3)-H(3)	1.0000	C(13)-C(15)	1.537(3)
C(4)-C(5)	1.566(2)	C(14)-H(141)	0.9801
C(4)-H(4)	1.0000	C(14)-H(142)	0.9801
C(5)-C(9)	1.511(2)	C(14)-H(143)	0.9799
C(5)-C(8)	1.532(2)	C(15)-H(151)	0.9801
C(7)-H(71)	0.9801	C(15)-H(152)	0.9801
C(7)-H(72)	0.9802	C(15)-H(153)	0.9800
C(7)-H(73)	0.9801	C(16)-H(161)	0.9802
C(8)-C(10B)	1.292(13)	C(16)-H(162)	0.9800
C(8)-H(81)	0.9799	C(16)-H(163)	0.9799
O(3)-Si-C(12)	110.88(8)	C(11)-Si-C(13)	111.50(9)
O(3)-Si-C(11)	110.14(9)	C(4)-O(3)-Si	125.17(11)
C(12)-Si-C(11)	108.95(12)	C(2)-O(4)-H(0)	102.5(16)
O(3)-Si-C(13)	103.09(7)	C(7)-O(5)-C(3)	114.35(14)
C(12)-Si-C(13)	112.19(10)	C(6)-N-H(1N)	118.4(16)

C(6)-N-H(2N)	119.4(14)	C(10B)-C(8)-H(81)	121.0
H(1N)-N-H(2N)	122(2)	C(5)-C(8)-H(81)	109.2
C(2)-C(1)-C(6)	119.77(13)	C(5)-C(8)-H(82A)	109.5
C(2)-C(1)-C(5)	111.67(13)	H(81)-C(8)-H(82A)	109.5
C(6)-C(1)-C(5)	128.27(12)	C(5)-C(8)-H(83A)	109.8
O(4)-C(2)-C(1)	127.05(14)	H(81)-C(8)-H(83A)	109.5
O(4)-C(2)-C(3)	120.19(12)	H(82A)-C(8)-H(83A)	109.5
C(1)-C(2)-C(3)	112.74(13)	C(10A)-C(9)-C(5)	126.6(2)
O(5)-C(3)-C(2)	113.73(13)	C(10A)-C(9)-H(91)	116.6
O(5)-C(3)-C(4)	108.67(13)	C(5)-C(9)-H(91)	116.7
C(2)-C(3)-C(4)	101.66(12)	C(5)-C(9)-H(92B)	108.2
O(5)-C(3)-H(3)	110.8	H(91)-C(9)-H(92B)	108.1
C(2)-C(3)-H(3)	110.7	C(5)-C(9)-H(93B)	108.1
C(4)-C(3)-H(3)	110.8	H(91)-C(9)-H(93B)	108.1
O(3)-C(4)-C(3)	112.14(13)	H(92B)-C(9)-H(93B)	107.3
O(3)-C(4)-C(5)	112.29(12)	C(9)-C(10A)-H(101)	119.7
C(3)-C(4)-C(5)	107.07(12)	C(9)-C(10A)-H(102)	120.3
O(3)-C(4)-H(4)	108.4	H(101)-C(10A)-H(102)	120.0
C(3)-C(4)-H(4)	108.4	C(8)-C(10B)-H(82A)	49.2
C(5)-C(4)-H(4)	108.4	C(8)-C(10B)-H(83A)	45.2
C(9)-C(5)-C(1)	112.53(13)	H(82A)-C(10B)-H(83A)	94.3
C(9)-C(5)-C(8)	113.75(14)	C(8)-C(10B)-H(103)	120.0
C(1)-C(5)-C(8)	110.50(14)	C(8)-C(10B)-H(104)	120.0
C(9)-C(5)-C(4)	108.14(14)	H(103)-C(10B)-H(104)	120.0
C(1)-C(5)-C(4)	100.30(11)	Si-C(11)-H(111)	109.6
C(8)-C(5)-C(4)	110.78(13)	Si-C(11)-H(112)	109.4
O(1)-C(6)-N	120.94(13)	H(111)-C(11)-H(112)	109.5
O(1)-C(6)-C(1)	119.89(12)	Si-C(11)-H(113)	109.4
N-C(6)-C(1)	119.16(13)	H(111)-C(11)-H(113)	109.5
O(5)-C(7)-H(71)	109.3	H(112)-C(11)-H(113)	109.4
O(5)-C(7)-H(72)	109.5	Si-C(12)-H(121)	109.5
H(71)-C(7)-H(72)	109.5	Si-C(12)-H(122)	109.4
O(5)-C(7)-H(73)	109.6	H(121)-C(12)-H(122)	109.5
H(71)-C(7)-H(73)	109.5	Si-C(12)-H(123)	109.5
H(72)-C(7)-H(73)	109.5	H(121)-C(12)-H(123)	109.5
C(10B)-C(8)-C(5)	128.4(7)	H(122)-C(12)-H(123)	109.5

C(14)-C(13)-C(16)	109.21(17)	C(13)-C(15)-H(151)	109.7
C(14)-C(13)-C(15)	109.37(16)	C(13)-C(15)-H(152)	109.5
C(16)-C(13)-C(15)	109.20(16)	H(151)-C(15)-H(152)	109.5
C(14)-C(13)-Si	110.22(13)	C(13)-C(15)-H(153)	109.2
C(16)-C(13)-Si	109.50(12)	H(151)-C(15)-H(153)	109.5
C(15)-C(13)-Si	109.34(13)	H(152)-C(15)-H(153)	109.5
C(13)-C(14)-H(141)	109.3	C(13)-C(16)-H(161)	109.8
C(13)-C(14)-H(142)	109.4	C(13)-C(16)-H(162)	109.3
H(141)-C(14)-H(142)	109.4	H(161)-C(16)-H(162)	109.4
C(13)-C(14)-H(143)	109.7	C(13)-C(16)-H(163)	109.3
H(141)-C(14)-H(143)	109.5	H(161)-C(16)-H(163)	109.5
H(142)-C(14)-H(143)	109.5	H(162)-C(16)-H(163)	109.5

Table 26. Hydrogen bonds for **428** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(4)-H(0)...O(1)	0.88(3)	1.79(3)	2.5941(15)	151(2)
N-H(2N)...O(1)#1	0.85(2)	2.04(2)	2.8838(17)	179(2)

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

Appendix 3: assignment of olefin geometry.

General notes.

In most cases the identification of the terminal two protons of each olefin was not difficult because the signals for both tend to be doublets. However, it is less easy to know which doublet belongs to which end without first assuming a geometry. In this case, the nature of the structures made allowed the two doublets to be assigned because the coupling constant across such bonds varies depending on the substitution as well as the geometry. This work as well as other work done within the group has shown that a *trans*-double bond substituted by a boronate group at one end will invariably show a 17-18 Hz coupling constant. In contrast, carboxylate terminated *trans*-double bonds have been found to show couplings of 14.5-16 Hz whilst iodine terminated *trans*-double bonds show slightly lower coupling constants of 14 Hz. In the case of cis-double bonds, although no such species have been prepared in this study, it would be expected that boronate-terminated bonds would show a 12 Hz coupling constant (based on vinylboronate **222**), carboxylate-terminated bonds show 10.5-12 Hz constants and iodine-terminated bonds show a much lower constant of ~8 Hz.

Using this method to assign the two terminal protons allowed ^{1}H COSY studies to be used to assign the remaining signals and thus the geometry of the molecule. In the three cases where this did not prove possible (*vide infra*), in two cases there was enough data from the NMR studies to be certain of their geometry and in the other case the structure was determined by X-ray diffraction.

Two substrates (**238** and **289**) have been reported elsewhere and NMR data obtained was consistent with that reported. These cases are not dealt with here although it was checked that their data was consistent with the proposed structure.

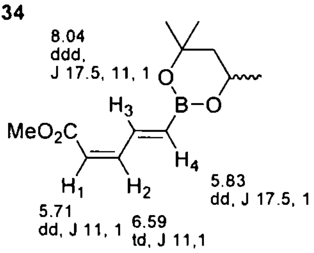
Alkenes.

A large number of alkenes have been prepared in this study, the geometry of which were all determined by coupling constant for the two olefinic protons with the assumption that

$J_{cis} \leq 12$ and $J_{trans} \geq 14$. In the unusual case of **273**, clearly no coupling constant could be calculated and the geometry has been taken to be as reported.[287]

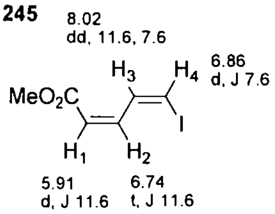
Polyenes.

234



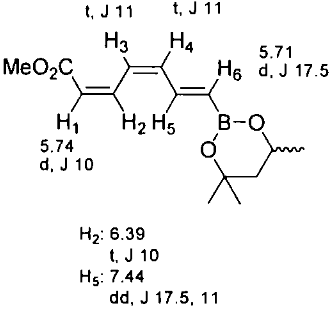
H_4 assigned as being doublet 5.83 based on magnitude of J, allowed H_1 to be assigned as doublet 5.71 thus H_1-H_2 *cis*, H_3-H_4 *trans*. H_2 and H_3 were assigned from their coupling to H_1 and H_4 respectively.

245



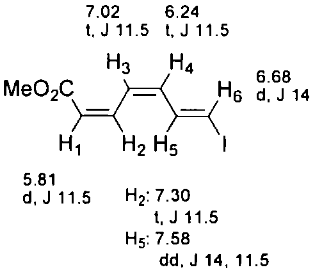
H_4 assigned as being doublet 6.86 based on very small J value allowing assignment of H_1 as doublet 5.91 thus both double bonds *cis*. H_2 and H_3 were assigned from their coupling to H_1 and H_4 respectively.

253



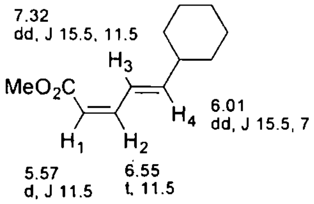
H_6 was assigned as being doublet 5.71 based on magnitude of J, allowed H_1 to be assigned as doublet 5.74. H_2, H_3 H_4 and H_5 were assigned from the ^{1}H COSY NMR study using H_1 and H_6 as starting points. Geometry of H_3-H_4 asssigned from the coupling constant between these two atoms.

254



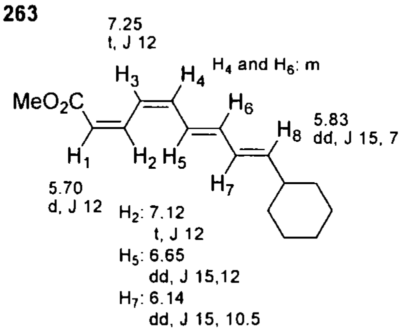
H_6 was assigned as being doublet 6.68 based on the small *trans J*, allowed H_1 to be assigned as doublet 5.81. H_2, H_3 H_4 and H_5 were assigned from the ^{1}H COSY NMR study using H_1 and H_6 as starting points. Geometry of H_3-H_4 assigned from the coupling constant between these two atoms.

264



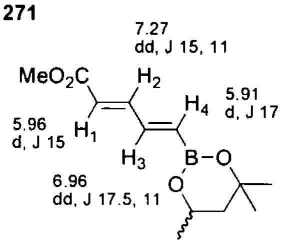
H_4 was assigned as being doublet of doublets 6.01 based on the small coupling with alkyl H of the cyclopentane ring, this allowed H_1 to be assigned as doublet 5.57. H_2 and H_3 were assigned from their coupling to H_1 and H_4 respectively and the *J* values H_1-H_2 and H_3-H_4 gave the geometry of the diene.

263



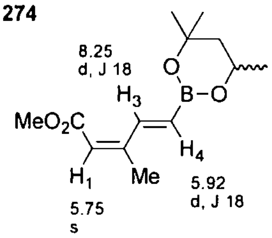
H_8 was assigned as being doublet of doublets 5.83 based on the small coupling with alkyl H of cyclopentane ring, this allowed H_1 to be assigned as doublet 5.70. H_2, H_3 and H_7 were assigned from the ^1H NMR COSY study using these two starting points. The signals for H_4 and H_6 overlap and could not be assigned, however, H_5 was assigned as it showed COSY correlations to H_4/H_6 multiplet only. Thus the geometry of double bonds H_3-H_4 and H_5-H_6 were determined from the *J* values of H_3 and H_5 respectively whilst the remaining two double bonds could be assigned from the *J* values of both H atoms.

271



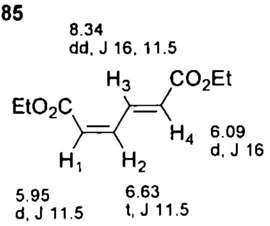
H_4 was assigned as being doublet 5.91 based on the magnitude of *J*, this allowed H_1 to be assigned as doublet 5.96. H_2 and H_3 were assigned based on their coupling to H_1 and H_4 respectively and the *J* values H_1-H_2 and H_3-H_4 allowed the determination of both double bond geometries.

274



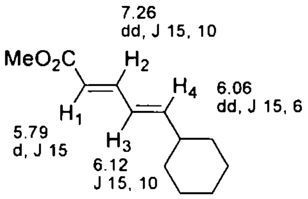
The geometry of the less-substituted double bond H_3-H_4 has been assigned based on the large *J* value. Clearly, the geometry of the other double bond could not be determined from a *J* value and it has been assumed that the geometry is unaltered from the starting material as seen in previous HM reactions.

285



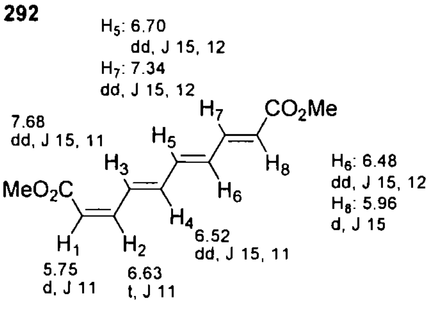
The ^{1}H NMR spectrum indicated an asymmetric species with four olefin hydrogen environments which is only consistent with the structure drawn given the formula (*Z,Z* and *E,E* being symmetric with two olefin hydrogen environments). H_1 and H_4 were assigned based on their *cis* and *trans* coupling constants and H_2 and H_3 were assigned based on their coupling to H_1 and H_4 respectively.

299



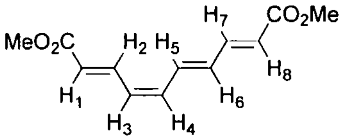
H_4 was assigned as doublet of doublets 6.06 based on the small *J* with alkyl H of cyclopentane, this allowed H_1 to be assigned as doublet 5.79. H_2 and H_3 were assigned from their coupling to H_1 and H_4 respectively and the geometries of the double bonds were assigned from the *J* values H_1-H_2 and H_3-H_4.

292



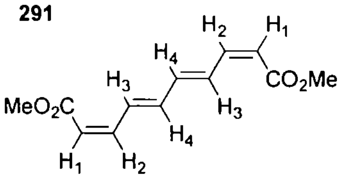
Initial analysis of the NMR data indicated that this molecule was an asymmetric tetraene (eight olefinic hydrogen environments) and that it possessed a single *cis* double bond (two small *J*). Given that one doublet had *J* 11, this allowed the assignment of H_1 as doublet 5.75 and thus H_8 as doublet 5.96. This also proved the geometry of the molecule. H_2-H_7 have been assigned based on the ^{1}H COSY NMR study.

290



The hydrogen environments for this molecule have not been unambiguously assigned, however, it is clear from the data that three double bonds are *trans* and thus only one is *cis*. In addition, the fact that the two *cis*-coupled protons (6.39, t, J 12 and 6.26, t, J 12) are triplets shows them not to be terminal and the only arrangement with a single internal *cis* double bond is that shown.

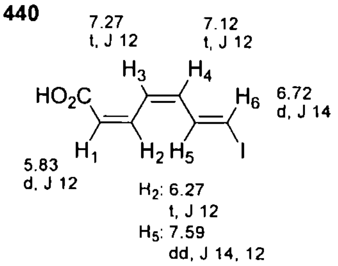
291



H_1: 5.74, 2H, d, J 11
H_2: 6.69, 2H, t, J 11
H_3: 7.68, 2H, m
H_4: 6.64, 2H, m

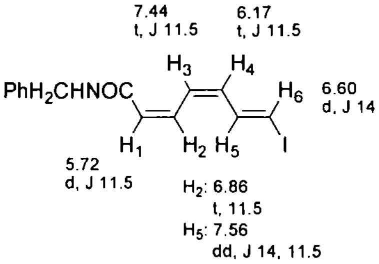
The ^1H NMR spectrum of this molecule was impossible to fully assign given that the system represented an AA'BB' system in which the coupling is not a first order problem. Only the *E,Z,Z,E* and *Z,E,E,Z*-isomers could show such behaviour given that there were clearly at least two *cis* double bonds present. The geometry of the internal double bonds was proven by X-ray diffraction (see Appendix 2).

440



H_6 was assigned as doublet 6.72 based on the small *trans* J value which allowed H_1 to be assigned as doublet 5.83. H_2, H_3, H_4 and H_5 were assigned from the ^1H COSY study using H_1 and H_6 as starting points. The geometries of the three double bonds were determined from the J values of H_1-H_2, H_3-H_4 and H_5-H_6.

447



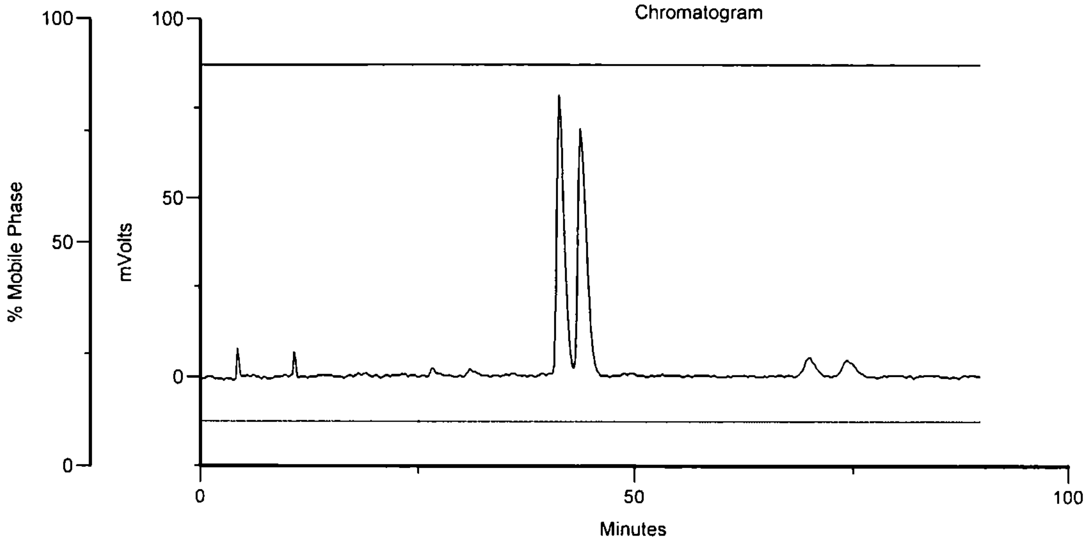
H_6 was assigned as doublet 6.60 based on the small *trans* *J* value which allowed H_1 to be assigned as doublet 5.72. H_2, H_3, H_4 and H_5 were assigned from the ^1H COSY study using H_1 and H_6 as starting points. The geometries of the three double bonds were determined from the *J* values of H_1-H_2, H_3-H_4 and H_5-H_6.

Appendix 4: HPLC methods

All HPLCs were run on a Gilson 321 using 30 cm columns and a 10 μL injection.

Method for phenyl ester **329**

Racemic standard:

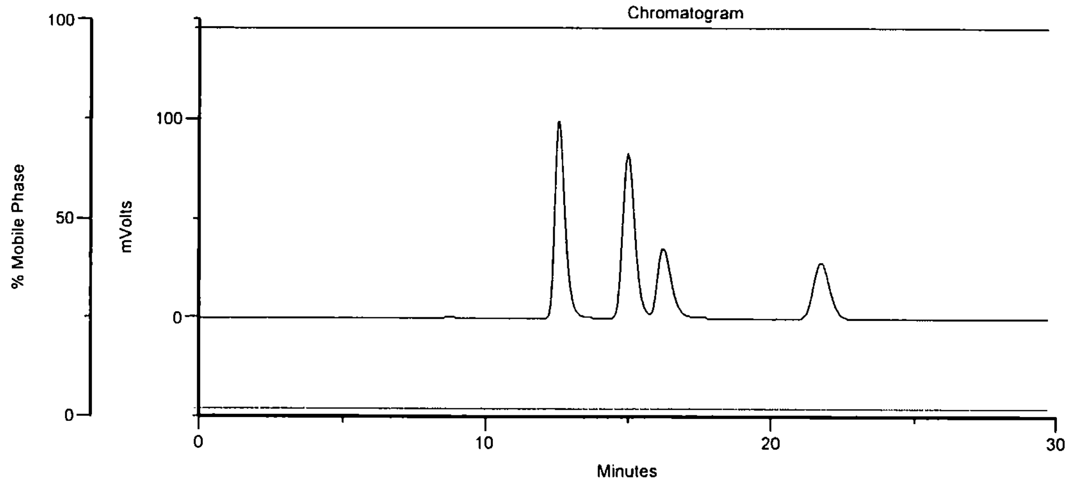


Chiracel OJ-H, hexane: IPA, 1;9, 1 mL min^{-1}, λ = 210 nm.

Method	t_1	t_2	t_3	t_4
Rac-**338**	7666041	7875090	751203	873198
D-**315**	19860316	890570	1550077	3366512
L-**337**	4864867	128537280	-	-
L-**338**	1112447	23850016	-	-
L-**339**	24812	5109603	437455	5358
Cat. L-**339**	245749	2669571	108303	8184

t_1 = 40.7 min (*S*,*R*), t_2 = 44.4 min (*R*,*S*), t_3 = 70.2 min (*anti*) and 73.8 (*anti*).

Method for diazoketone **331**.
Racemic standard:



Chiracel OJ-H, hexane: IPA, 49:1, 1 mL min^{-1}, λ = 254 nm.

Method	t_1	t_2	t_3	t_4
Racemic	4196223	4142056	2097168	1909839
Via **323**	8039435	515346	452582	768929
Via **302b**	1496231	639562	1606122	2414852

t_1 = 13.2 min (*S*,*R*), t_2 = 15.6 min (*R*,*S*), t_3 = 16.9 min (*anti*) and t_4 = 22.2 min (*anti*).