DOCTOR OF PHILOSOPHY

Approaches to the synthesis of Nitensidine D and E

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Approaches to the Synthesis of Nitensidine D and E

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Contents

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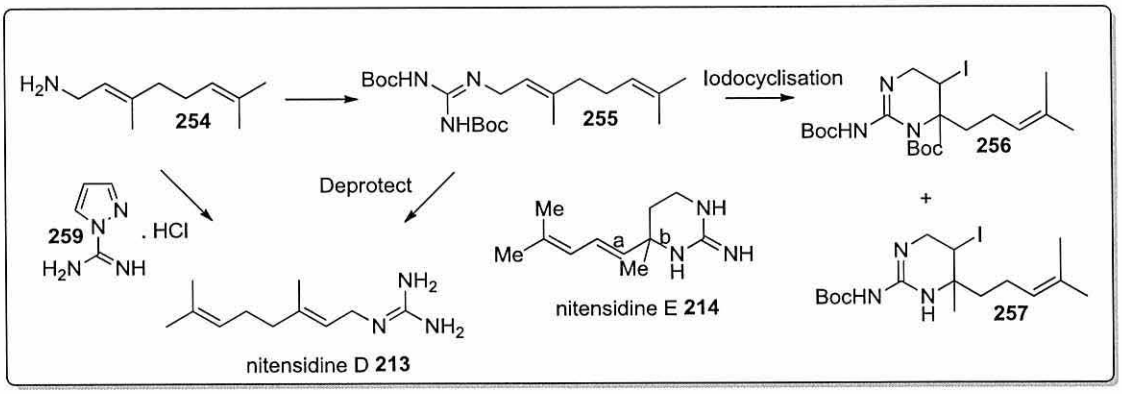
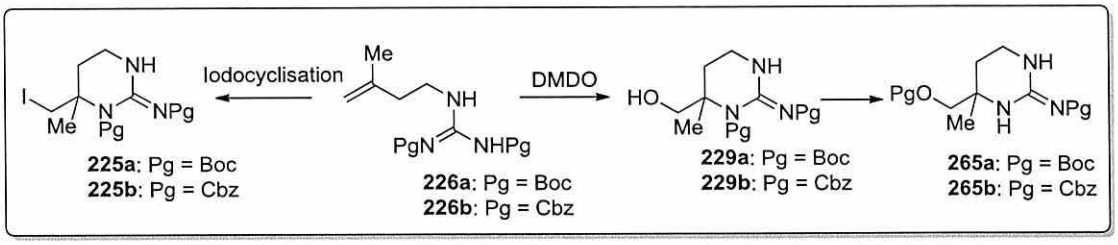
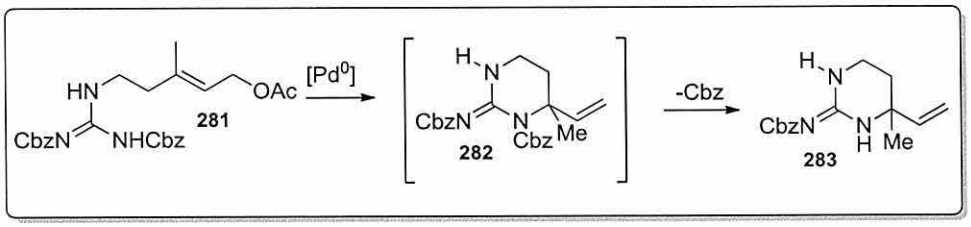
Abstract

This thesis describes synthetic approaches directed towards the synthesis of the alkaloid natural products nitensidine D **213** and nitensidine E **214**. The structurally less complex metabolite nitensidine D was prepared by the guanylation of commercially available geranylamine **254** whilst four synthetic approaches were attempted to prepare nitensidine E. Initially the 6-membered guanidines **225a-b**, **256** and **257** were prepared *via* an iodocyclisation of the corresponding allylic **226a-b** and homoallylic guanidines **255**, whilst the guanidines **265a-b** were prepared *via* a DMDO mediated epoxidation and acid catalysed cyclisation/ rearrangement reaction. Attempts to convert these to the desired metabolite were unsuccessful. Finally, the cyclic guanidine **283** was prepared from the allylic acetate **281** *via* a palladium π-allyl cyclisation.







Abbreviations

General

Å	Ångström
AIDS	Acquired immunodeficiency syndrome
°C	Degree Celsius
ee	Enantiomeric excess
GI_{50}	Concentration required for 50% growth inhibition of cancer cells
HIV	Human immunodeficiency virus
h	Hour(s)
HRMS	High resolution mass spectrometry
HRFABMS	High resolution fast atom bombardment
HWE	Horner-Wadsworth-Emmons
IC_{50}	Half maximal inhibitory concentration
Mpt	Melting point
MS	Molecular sieves
NMR	Nuclear Magnetic Resonance
pKa	Acid dissociation constant
rt	Room temperature
TLC	Thin Layer Chromatography

Reagents

Ac_2O	Acetic anhydride
Boc_2O	Di-*tert*-butyl dicarbonate
CbzCl	Benzyl chloroformate
Cbz-NCS	Benzyloxycarbonyl-isothiocyanate
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate

DIBAL	Diisobutylaluminium hydride
DIPA	Diisopropylamine
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMDO	Dimethyldioxirane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	Dimethyl sulfoxide
Dppe	1,2-Bis(diphenylphosphino)ethane
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	Ethyl acetate
IBBO	(+)-2,2-isopropylidenebis[(4*R*)-4-benzyl-2-oxazoline)]
IMS	Industrial Methylated Spirit
LDA	Lithium diisopropylamide
MsOH	Methanesulfonic acid
NBS	*N*-bromosuccinimide
NMM	*N*-methylmorpholine
PIDA	Phenyliodonium diacetate
TBAF	Tetra-*n*-butylammonium fluoride
TBSCl	*t*-Butyldimethylsilyl chloride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMSCl	Trimethylsilyl chloride
TMSI	Trimethylsilyl iodide
TosCl	4-Toluenesulfonyl chloride

Functional Groups

Ac	Acetyl
Bn	Benzyl
Boc	*t*-Butoxycarbonyl
Cbz	Carbobenzyloxy
Et	Ethyl
i-Bu	*i*-Butyl

i-Pr	*i*-Propyl
Me	Methyl
MOM	Methoxymethyl
OBO	4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl - alias
Ph	Phenyl
Tf	Triflyl
Tr	Trityl
Ts	*p*-toluenesulfonyl

Introduction

Structural and basic properties of guanidine

The guanidine moiety is one of the most basic neutral nitrogen containing organic compounds known, having a pKa of 13.6[1] in water, which is close to that of the hydroxide ion. The reason for this basicity is that once protonated, the guanidinium cation is able to distribute the positive charge generated throughout the π-system *via* delocalisation and thus making guanidine a particularly basic functional group (Figure 1).[2]

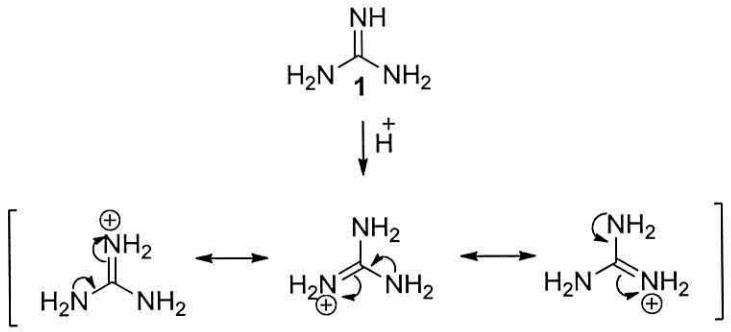


Figure 1: The three resonance structures of the guanidinium cation.

The guanidinium cation is characterised by three amino groups bonded to a central carbon atom leading to a cross-conjugated or Y-delocalized system containing six π-electrons.[3] Guanidine and its derivatives have been studied by X-ray crystallography and this has shown that the three C-N bonds in the guanidine average a value of 1.33 Å. This is much closer to the estimated value[4] for a C=N bond 1.29 Å, and shorter than a typical C-N bond length of 1.41 Å.[5] As well as this, the guanidine group has the ability to interact through hydrogen bonding and charge pairing interactions by forming a pair of zwitterionic N-H···O hydrogen bonds with anionic species such as carboxylates, phosphates, sulfates and nitrates.[6] Thus, the guanidine group is protonated under physiological conditions and is able to bind strongly to a substrate, ligand, or receptor *via* these electrostatic interactions. In addition, it readily reacts with carbon dioxide and water from air leading to the corresponding guanidinium hydrogen carbonate salts.[7]

It has long been known that nature offers a vast potential source of compounds which have a very important role in medicine and much of synthetic and medicinal chemistry deal with the isolation and exploitation of these materials.[8]

The guanidine group **1** (Figure 1) is of considerable interest as it is found in many natural products which have a wide range of activity.[9] It is also found in the amino acid L- arginine **2** (Figure 2) which is ubiquitous in protein structures. Arginine as one of the core group of 20 amino acids and is an essential substrate for living organisms for example, it is a precursor in the biosynthesis of creatine, which holds a major role in energy metabolism in muscle and nerve tissues.[10]

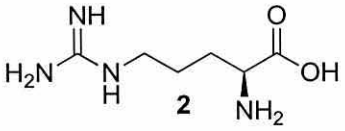


Figure 2: Structure of amino acid L- arginine **2**.

Guanidine containing natural products

Our research group has a long term interest in guanidine containing natural products[11-15] and their analogues.[16] Of particular interest with our group are those guanidines isolated from marine organisms which typically have cyclic structures and posses wide ranging biologically activity.

The guanidine motif is also found in many heterocyclic natural products many of which have powerful biological activities.[17] The cyclic guanidines tetrodotoxin **3** and saxitoxin **4** (Figure 3) for example, are neurotoxins whose activity arises from their ability to block Na^+ ion channels. Tetrodotoxin is associated with the edible pufferfish however, it is also found in several other animal species, including parrotfish, porcupine fish, ocean sunfish, and species of newts and salamanders.[18]

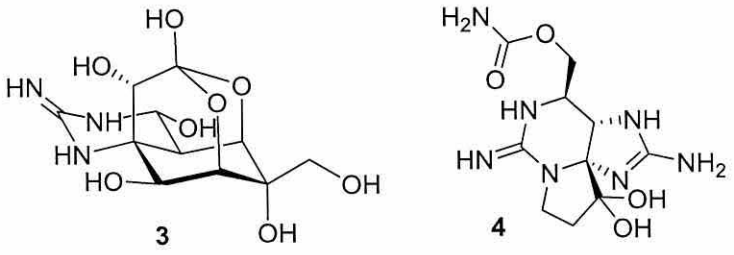


Figure 3: Structures of tetrodotoxin **3** and saxitoxin **4**.

Other guanidine natural products were isolated from the Caribbean sponge *Batzella sp.* for example, batzelladine A **5** which has been shown to disrupt the AIDS infective process (Figure 4).[19] This disruption occurs *via* inhibition of the binding of the HIV glycoprotein gp120 to the human CD4 receptor.

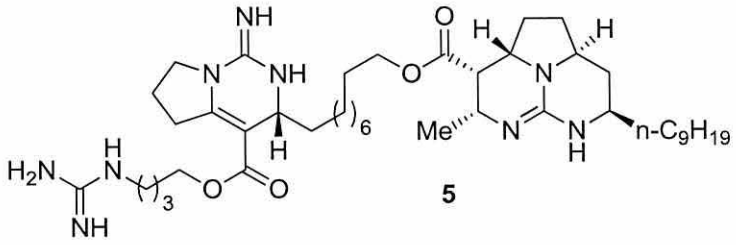


Figure 4: Structure of batzelladine A **5**.

Some confusion has arisen in the literature, as this sponge was found to be identical to the sponge *Ptilocaulis spiculifer*[20] from which **5** and a large number of other related guanidines have been isolated, e.g. the tricyclic guanidine ptilomycalin A **6** (Figure 5). This metabolite was also isolated from the Red Sea sponge *Hemimycale sp* and later from the starfishes *Fromia monilis* and *Celerina heffernani*.[21] Ptilomycalin A has been shown to have wide ranging cytotoxic, antifungal, antimicrobial, and antiviral activities.

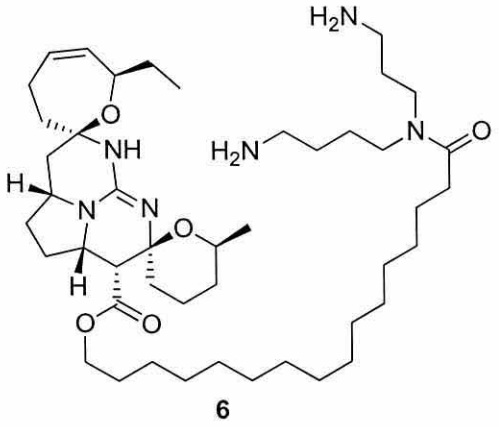


Figure 5: Structure of ptilomycalin A **6**.

Marine ascidians are a good source of biologically active secondary metabolites for example, the novel β-carboline guanidine alkaloid tiruchanduramine **7** (Figure 6) was isolated from an ascidian *Synoicum macroglossum*, which was obtained from

tiruchandur in India[22a] and displayed promising α-glucosidase (not specified in the reference) inhibitory activity (IC_{50} 78.2 μg/mL) when compared to acarbose and might have potential application in the treatment of diabetes mellitus type 2.[22b]

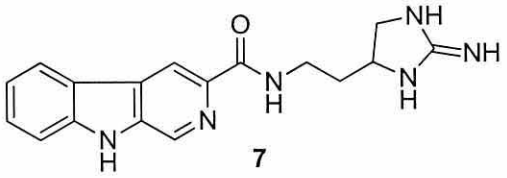


Figure 6 Structure of tiruchanduramine **7**.

Further work led to the isolation of novel compounds netamines A-G (**8-14**) (Figure 7). Seven new tricyclic guanidine alkaloids were extracted from the poecilosclerida sponge *Biemna laboutei* and were found to be cytotoxic. The sponge was collected near the Sainte-Marie Island on the east coast of Madagascar.[23] These metabolites were tested for their cytotoxicity against three human tumor cell lines: NSCL (A-549), colon (HT-29) and breast (MDA-MB-231). Netamines C and D demonstrated promising activity against A549 (GI_{50} = 4.3 and 6.6 μM) HT29 (GI_{50} = 2.4 and 5.3 μM) and MDA-MB-231 (GI_{50} = 2.6 and 6.3 μM), while other compounds were establish to be less toxic.

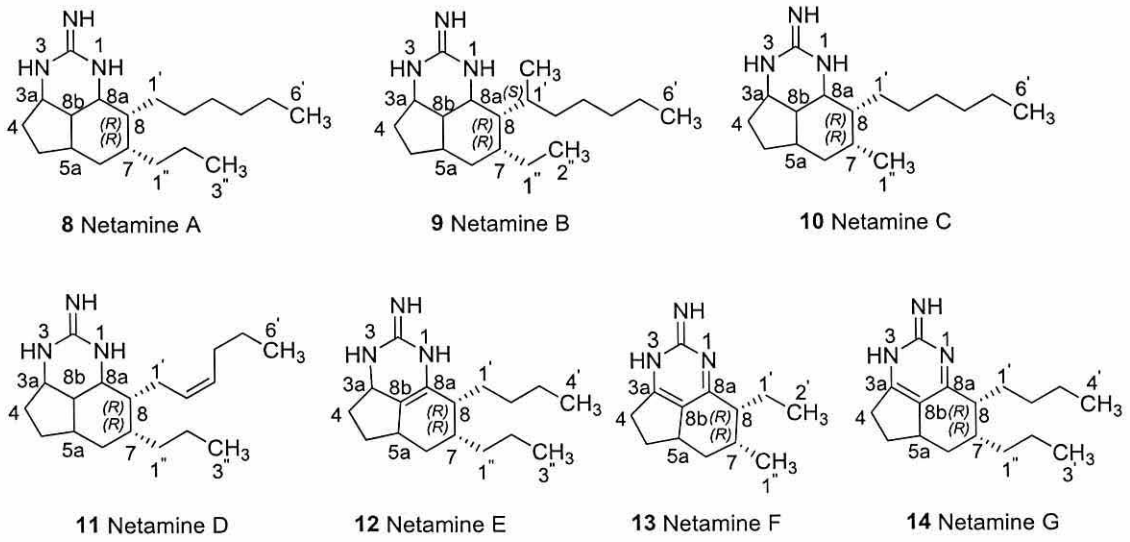


Figure 7: Structures of netamines A-G (**8-14**).

Ageladine A **15**, a pyrrole imidazole alkaloid, was first described and isolated by Fujita *et al.*[24] using bioassay guided fractionation of extracts of the marine sponge *Agelas nakamurai* (Figure 8). Ageladine A displayed biological effects such as anti-angiogenic effects and metallo-protease inhibition.

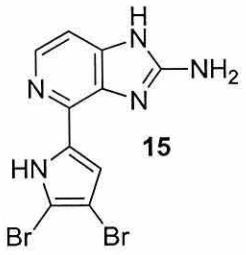
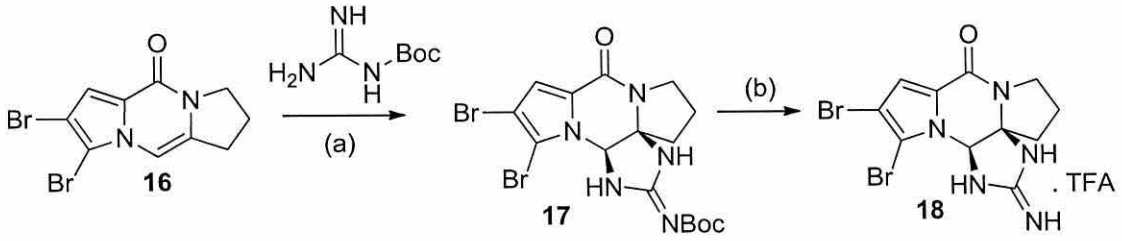


Figure 8: Structure of ageladine A **15**.

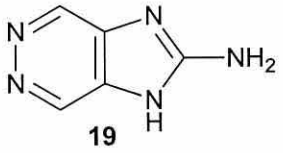
Recently, considerable attention was given towards dibromophakellin **18**.[25] The total synthesis of which has been achieved racemically in eight linear steps from pyrrole in 4.9% overall yield. The key reaction was the guanylation of an alkene intermediate **16** by treatment with NBS in the presence of Boc-protected guanidine to give the Boc-proctected natural product **17** in 29% yield. Boc-group deprotection of guanidine **17** was achieved by treatment with TFA in DCM producing dibromophakellin **18** in an 89% yield as its TFA salt (Scheme 1).



Scheme 1: (a) NBS, DMF/DCM, 14 h, rt, 29%; (b) TFA, DCM, 7 h, rt, 89%.

Amongst the nitrogen-containing compounds, those which possess a guanidine unit are frequently unique to marine organisms, as reported by Baker and Murphy.[26] A new 4,5-guanidino-pyridazine compound zarzissine **19** (Figure 9) was isolated from the Mediterranean sponge *A. paupertas*.[27] The structure of zarzissine was characterised using spectroscopic methods, as well as the application of a number of 2D NMR

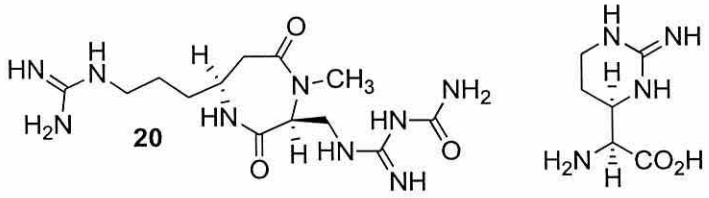
techniques. The cytotoxic activity of zarzissine articulated by IC_{50} values were examined against three tumor cell lines, with IC_{50} values of 12 μg/mL for murine leukemia cells (P-388), 5 μg/mL for human nasopharyngeal carcinomacells (KB), and 10 μg/mL for human lung carcinoma cells (NSCLC-N6), respectively.



19

Figure 9: Structure of zarzissine **19**.

The previously discussed natural products are found in marine organisms, however guanidine containing metabolites are found in many other species. For example, TAN-1057 D **20** is a bis-guanidine isolated from the *Flexibacter sp.* PK-74 bacterium and has powerful antibiotic activity.[28] Additionally, the unusual amino acid capreomycidine **21** has been identified as a biosynthetic precursor to the potent cyclic peptide antibiotic capreomycin (Figure 10).[29]



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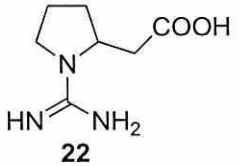
21

Figure 10: Structures of TAN-1057 D **20**, capreomycidine **21**.

Another interesting cyclic guanidine alkaloid cimipronidine **22** was isolated from *Cimicifuga racemosa* roots and displayed 5-HT_7 acceptor inhibiting activity.[30] The structurally simple guanidine galegine **23** (Figure 11), which was first isolated from *Verbena encelioides*, was later identified as the toxic component in *Galega officinalis* L. (Goat's Rue).[30]



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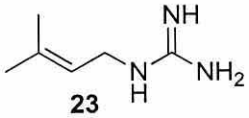

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Figure 11: Structures of cimipronidine **22** and galegine **23**.

Plantago-guanidinic acid **24** is a new guanidine derivative that was isolated from the seeds of *Plantago asiatica* (Figure 12).[31] These seeds were used as a crude drug for diuretic, antitussive, expectorant, and antiphlogistic purposes.

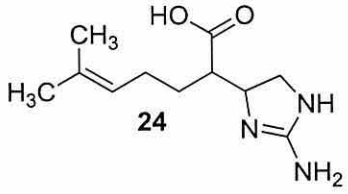


Figure 12: Structure of plantagoguanidinic acid **24**.

Guanidine containing pharmaceuticals

The guanidine moiety is also found in a many commercial pharmaceuticals compounds, for example zanamivir **25** (Figure 13) which acts as a neuraminidase inhibitor used in the treatment of both flu (influenza) A and B viruses.[32] As well as this, zanamivir should be chosen for stockpiling against the next H5N1 influenza[33] epidemic.

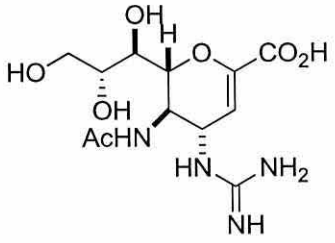


Figure 13: Structure of zanamivir **25**.

Blasticidin S **26** was first isolated as a nucleoside antibiotic from *Streptomyces griseochromogenes* by Takeuchi *et al.*[34] in 1958 and was found to contain a cytosine moiety and an unsual β-amino acid which was named *L*-blastidic acid (Figure 14). It was found to be a potent inhibitor of protein biosynthesis in both eukaryotic and prokaryotic cells, which acts rapidly by inhibiting peptide bond generation by the ribosome.

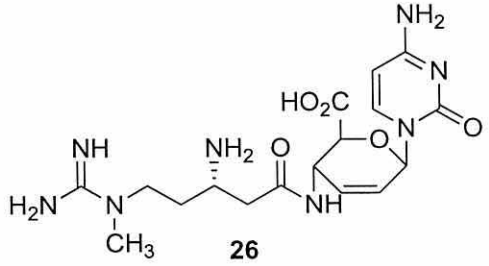
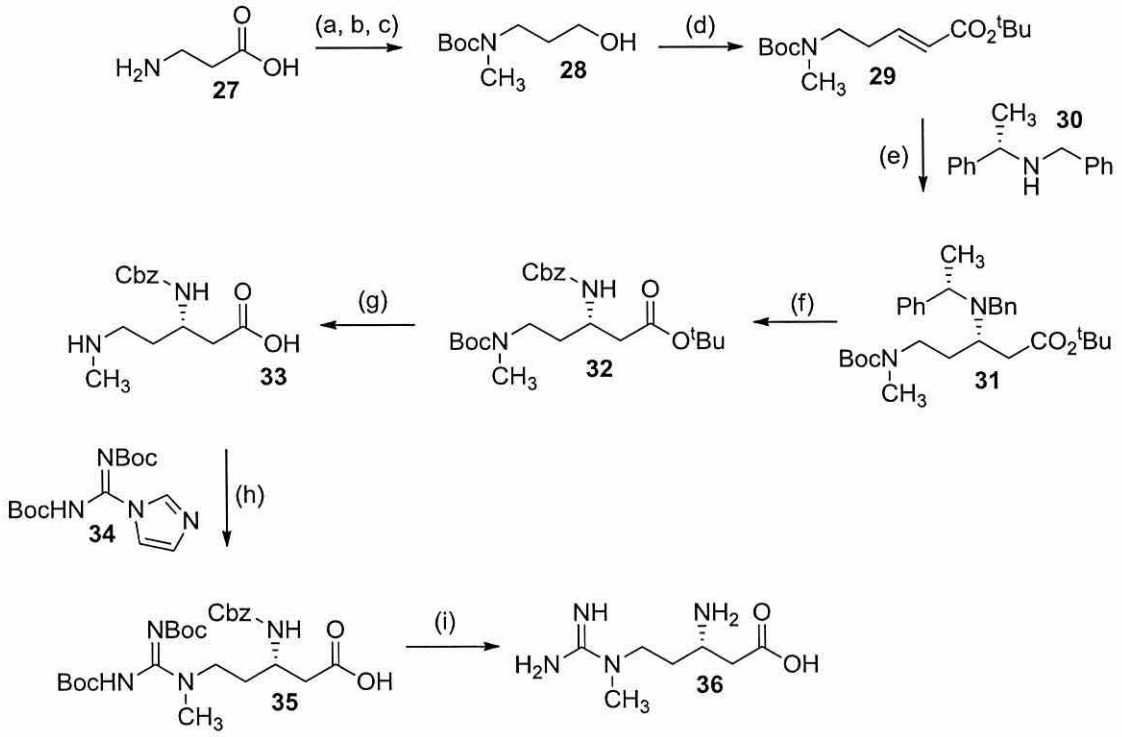


Figure 14: Structure of blasticidin S **26**.

(+)-Blastidic acid **36** has been prepared using β-alanine **27** as the starting material and an asymmetric conjugate addition reaction to effect the key step.

The first step of the synthesis involved the preparation of β-ornithine derivative **31** from β-alanine **27** by methylation, followed by reduction to give the desired alcohol **28**. Alcohol **28** was then converted directly into *E*-allylic ester **29** using a Swern oxidation/Wittig olefination reaction. Asymmetric conjugate addition with chiral amine **30** using the Davies protocol completed the synthesis of **31** in 85% yield. The β-amino group of **31** was deprotected using transfer hydrogenation conditions and subsequently reprotected with CbzCl to give β-ornithine derivative **32** in 74% yield over two steps (Scheme 2).

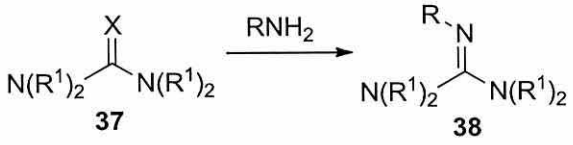


Scheme 2: (a) i) TMSCl, MeOH, (ii) NEt_3, Boc_2O, 99% over two steps; (b) MeI, NaH, THF, 93%; (c) DIBAL (2.2 equiv.), Et_2O, -78 °C to rt, 79%; (d) i) $(COCl)_2$, DMSO, NEt_3, 78 °C to rt, (ii) $Ph_3P{=}CHCO_2{}^tBu$, 97% over two steps; (e) **30**, *n*BuLi, THF, -78 °C, 85%; (f) i) 5% Pd/C, ammonium formate, ^{t}BuOH, Δ, (ii) CbzCl, $NaHCO_3$, acetone, H_2O, 74% over two steps; (g) TFA, DCM; (h) DIPEA, **34**, MeOH, 82% over two steps; (i) TMSI, $CHCl_3$, HCl, MeOH, 82%.

Deprotection of both the Boc-group and the *tert*-butyl ester of **32** using TFA in DCM gave **33**, which on reaction with DIPEA and *N,N'*-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine **34** gave orthogonally protected **35** in 82% yield for the two steps. Conversion of **35** to blastidic acid **36** was achieved by reaction with TMSI and acidic methanol in 82% yield.[35]

Synthetic methods for the preparation of guanidines

Several groups have reported various synthetic approaches for the synthesis of guanidines. One of the most common methods used to prepare substituted guanidines involve the use of thioureas, isoureas or activated amidine derivatives **37** (Scheme 3). The general reaction is then dependent on the displacement of a thiol, alcohol or amine leaving group by a simple amine to give the guanidine **38**.[36]

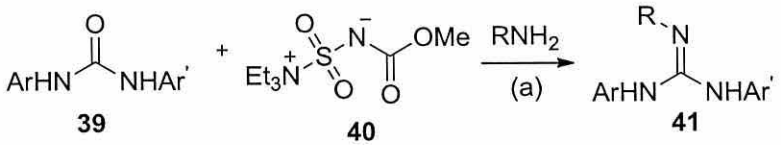


37 **38**

Scheme 3: Generalised reaction for the formation of a guanidine;
R, R^1 = alkyl, aryl, heteroaryl, X = O, S, NH, NR, OR^+, SR^+, $N(R_2)^+$

Synthesis from urea and thiourea derivatives

An example of the synthesis of a guanidine using a simple urea is the conversion of the *N,N'*-bis-aryl substituted urea **39** which on sequential treatment with Burgess' Reagent **40** and then amines leads to the guanidines **41**.[37] This reaction is thought to proceed through a carbodiimide intermediate (Scheme 4).

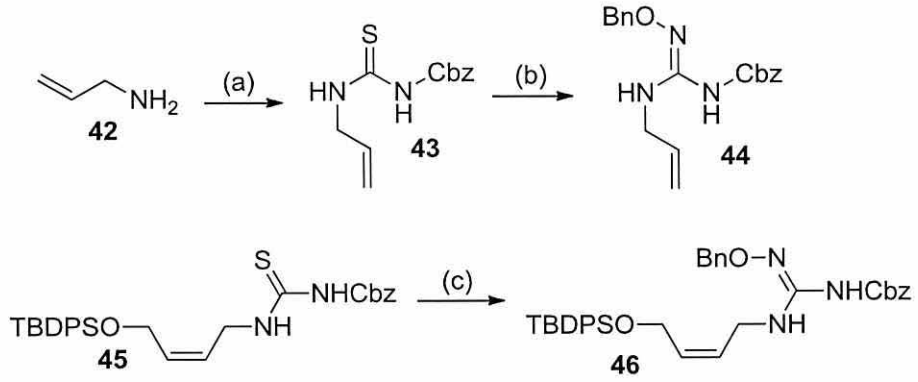


39 **40** **41**

Scheme 4: (a) DCM, 0 °C; Ar' = Tr, Ar = Ph.

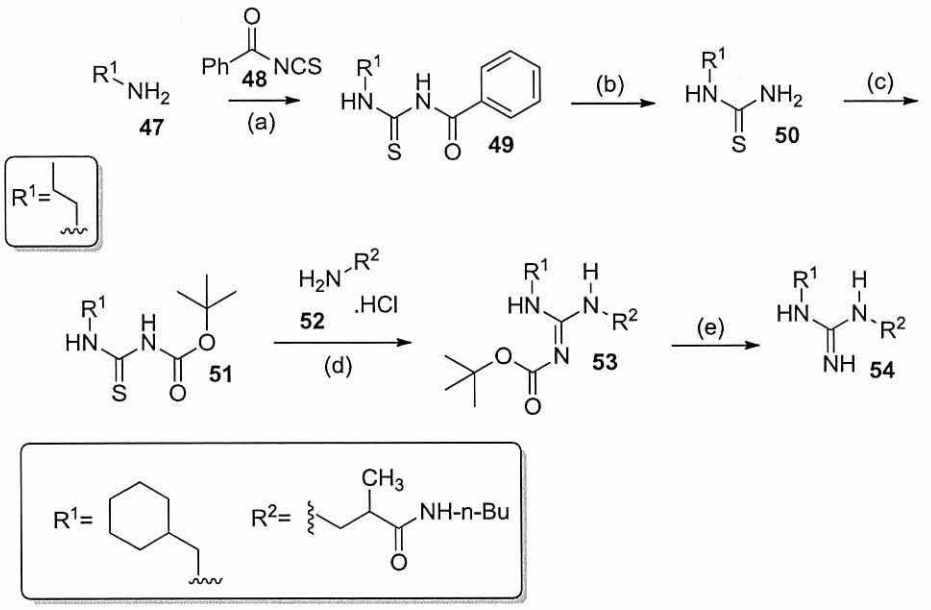
Similar chemistry is known for thioureas, for example the allylic guanidine **44** was prepared from the reaction of allylamine **42** with CbzNCS to form the thiourea **43**

in 99% yield, which was then treated with $H_2NOBn.HCl$ in the presence of EDCI and DIPEA to give allylic guanidine **44** in a yield of 76%. Similarly, thiourea **45** was coupled with $H_2NOBn.HCl$ in the presence of DIPEA and EDCI to give guanidine **46** in 71% yield (Scheme 5).[38]



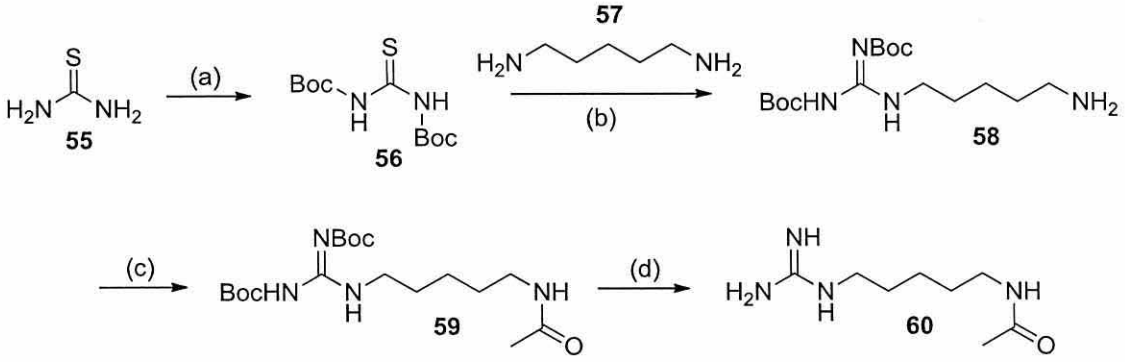
Scheme 5: (a) CbzNCS, CH_2Cl_2, 99%; (b) $H_2NOBn.HCl$, DIPEA, EDCI, CH_2Cl_2, 0 °C-rt, 76%; (c) $H_2NOBn.HCl$, DIPEA, EDCI, CH_2Cl_2, 0 °C-rt, 71%

The use of *N*-(*tert*-butoxycarbonyl) thioureas also offers a flexible method for the preparation of guanidines. For example, reaction of amines **47** with benzoyl isothiocyanate **48** gave the benzoyl thioureas **49**, which on deprotection followed by reaction with Boc_2O yielded *N*-(*tert*-butoxycarbonyl) thiourea **51**. Reaction of **51** with amine hydrochloride **52** in the presence of the water soluble carbodiimide, 1-(3-dimethylamino propyl)-3-ethylcarbodiimide hydrochloride afforded the *N*-(*tert*-butoxycarbonyl) guanidine **53** in good yield. Subsequent cleavage of the *tert*-butoxycarbonyl group by treatment of **53** with HCl provided the guanidines **54** as their hydrochloride salts (Scheme 6).[39]



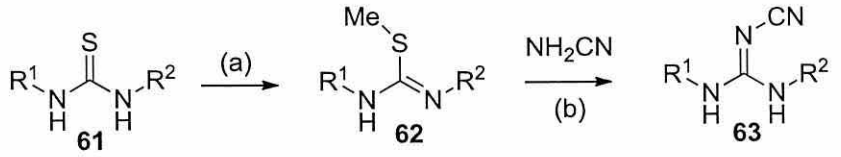
Scheme 6: (a) $CHCl_3$; (b) K_2CO_3, CH_3OH, H_2O, 82%; (c) Boc_2O, NaH, THF, 95%; (d) DMF, Et_3N, rt, 80%; (e) HCl, 90%.

Thiourea derivatives can be directly guanylated by amines, for example in the first total synthesis of acetylhomoagmatine **60** a natural product isolated from the methanolic extracts from the sponge *Cliona celata*, the protected *N,N'*-di-*tert*-butoxycarbonyl thiourea **56** was obtained by treatment of thiourea **55** with NaH and Boc_2O. Reaction of cadaverine **57** with reagent **56** gave **58** directly in 92% yield.[40] Compound **58** was then acetylated with Ac_2O in pyridine to give the product **59** in 81% yield, which was then deprotection by treatment with TFA in CH_2Cl_2 producing **60** in 98% yield (Scheme 7).[41]



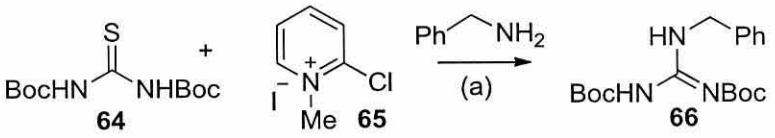
Scheme 7: (a) Boc_2O, NaH, THF, 98% yield; (b) DMF, **57**, 92% yield; (c) Ac_2O, pyridine, THF, 81% yield; (d) TFA, CH_2Cl_2, 98% yield.

Cyanoguanidines **63** can be prepared in high yields by the reaction of cyanamide[42] with substituted isothiourea **62** in the presence of DABCO (Scheme 8).



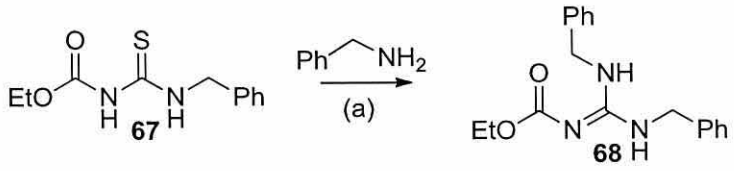
Scheme 8: (a) CH_3I, acetone; (b) DABCO, BuOH, reflux, 77%:
R^1= Ph, R^2= Allyl.

Activation, using Mukaiyama's reagent **65** is also a useful process and has been used in the formation of guanidine **66** from *N,N'*-bis-Boc-thiourea **64** and benzylamine (Scheme 9).[43]



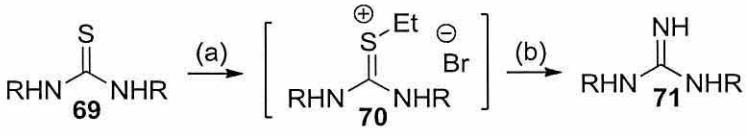
Scheme 9: (a) DMF, 91%.

Similarly, guanidine **68** was prepared from reaction of ethoxycarbonyl substituted thiourea **67** with benzylamine using EDCI as a coupling reagent in the presence of Et_3N (Scheme 10).[44]



Scheme 10: (a) EDCI, Et_3N, CH_2Cl_2, 80%.

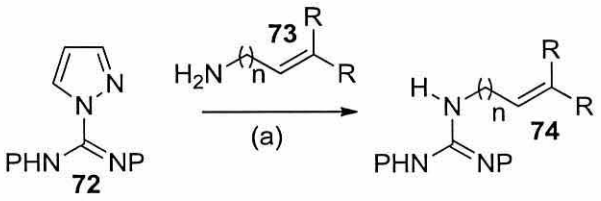
Thiourea derivatives can also be converted to reactive intermediates, which are then reacted with amines to yield guanidines. For example, reaction of the thiourea **69** with ethyl bromide led to the formation of the *S*-alkylated intermediate **70**, which on treatment with ethanolic ammonia gave the guanidine **71** (Scheme 11).[45]



Scheme 11: (a) EtBr, EtOH; (b) RNH_2, $EtOH/H_2O$
R = H, CH_2CO_2H.

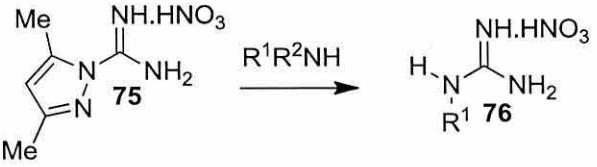
Synthesis by displacement of nitrogen heterocycles

A convenient method for the preparation of guanidines is the displacement of nitrogen heterocycles from amidine precursors. For example the *N,N'*-bis-Cbz or bis-Boc-1*H*-pyrazole carboxamidines **72** undergoes reactions with allyl- and homoallyl amines **73** to give the corresponding *N*-allyl and *N*-homoallylguanidines **74** in high yields (Scheme 12).[46]



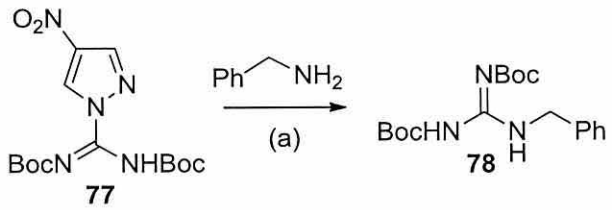
Scheme 12: (a) CH_3CN, 16-24 h; P = Cbz, Boc, R = H, Me, n = 1,2.

These pyrazole guanylating reagents are frequently used for the synthesis of guanidines, for example the reaction of 3,5-dimethyl-l-guanylpyrazole nitrate **75** with amines gave the desired guanidines **76** in good yields (Scheme 13).[47]



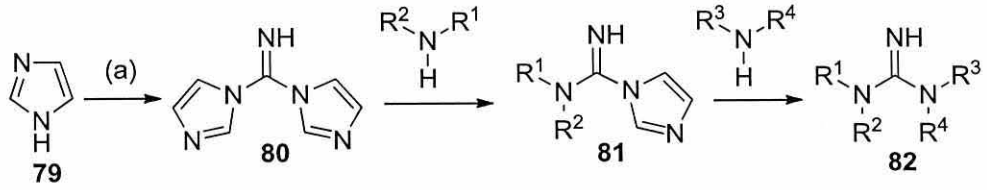
Scheme 13: Method A: Neat, reflux, 2 h, $R^1 = C_4H_8N$, $R^2 = H$, 92%,
Method B: H_2O, reflux, 24 h, $R^1 = PhCH_2CH_2NH$, $R^2 = H$, 75%.

A recently developed method for preparing guanidines utilised the bis-Boc-4-nitropyrazole-1-carboxamidine **77**. It was found that the nitro substituent accelerated the rate of reaction and gave typically higher yields than the unsubstituted analogues, for example the guanidine **78** was formed in 94% yield (Scheme 14).[48]



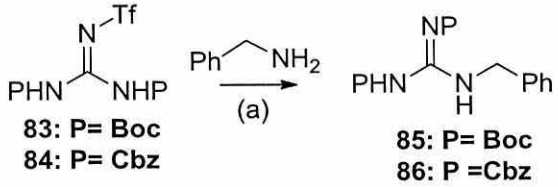
Scheme 14: (a) DMF, 25 °C, 94%.

Another interesting guanidine precursor is di(imidazole-1-yl)methanimine **80** which is easily prepared by the reaction of cyanogen bromide with imidazole **79**. This intermediate can then undergo sequential reaction with primary and secondary alkyl or arylamines to give a wide range of di-, tri- and tetrasubstituted guanidines **81** and **82** by displacement of the two imidazole groups (Scheme 15).[49]



Scheme 15: (a) BrCN, R^1-R^4 = alkyl, aryl, cycloalkyl.

Whilst not a heterocyclic displacement, the preparation of guanidines has also been reported using *N,N'*-di-Boc-*N''*-triflylguanidine **83** and *N,N'*-di-Cbz-*N''*-triflylguanidine **84**, which on reaction with benzylamine afforded the guanidines **85** and **86** in excellent yields (Scheme 16).[50]

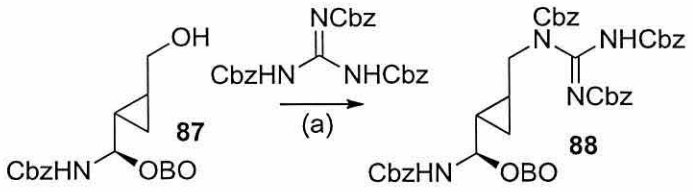


Scheme 16: (a) i) CH_2Cl_2, 0.5 h, rt, **85**: 100%, (ii) CH_2Cl_2, 1.0 h, rt, **86**: 94%.

Synthesis by Mitsunobu reactions

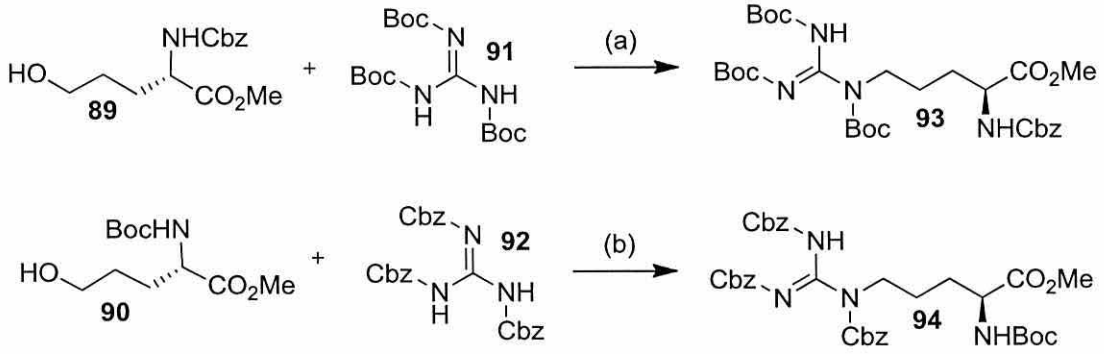
A recently developed effective method for preparing mono-alkylated guanidines utilises the Mitsunobu reaction, for example a key step in the preparation of *trans*-

cyclopropyl arginine derivatives was the Mitsunobu substitution of the alcohol **87** (Scheme 17) to give the fully protected guanidine **88**.[51]



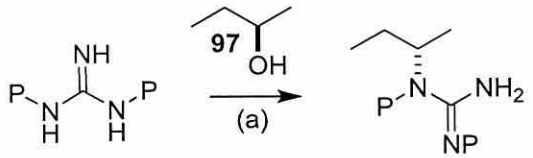
Scheme 17: (a) PPh_3, DEAD, THF, 16 h, 74% yield.

In addition to this work, Goodman and co-workers reported the synthesis of protected alkylated guanidines **93** and **94** by condensation of a primary or secondary alcohol **89** and **90** with the guanylating reagents *N,N′,N′′*-tri-Boc-guanidine or *N,N′,N′′*-tri-Cbz-guanidine **91** and **92** (Scheme 18).[52]



Scheme 18: (a) PPh_3, DEAD, THF, reflux, 72% yield;
(b) PPh_3, DEAD, THF, rt, 100% yield.

An efficient method for the synthesis of protected alkylated guanidines **98** and **99** was carried out by the reaction of alcohol **97** with *N,N'*-bis-(*tert*-butyloxy carbonyl) guanidine **95** or *N,N'*-bis-(benzyloxycarbonyl) guanidine **96** under standard Mitsonobu conditions (Scheme 19).[53] In this case, the protected guanidines act as the nucleophiles. Addition of azodicarboxylate and PPh_3 and either a primary or secondary alcohol results in the synthesis of corresponding guanidines in >95% yields.



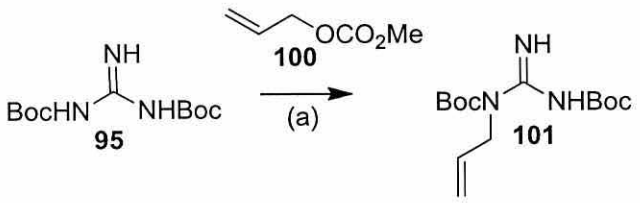
95: P= Boc
96: P= Cbz

98: P= Boc
99: P =Cbz

Scheme 19: (a) PPh_3, DIAD, toluene, rt, 5 h, >95% yield.

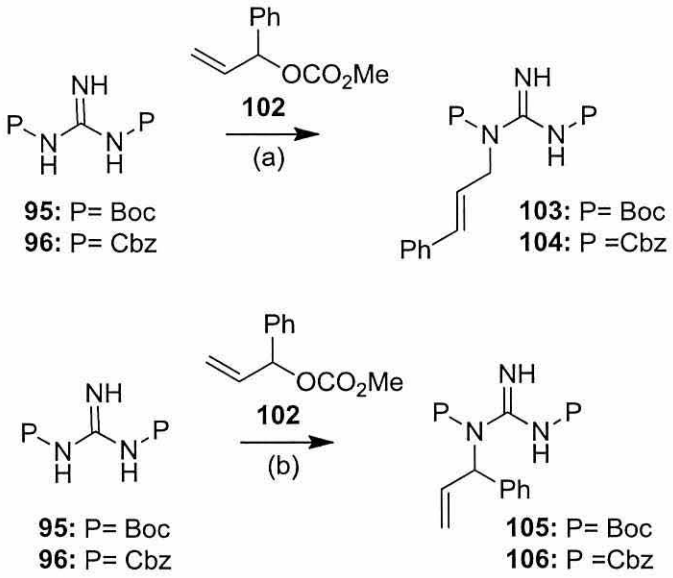
Palladium catalysed synthesis of guanidines

A reaction of considerable interest to the present study is the palladium catalysed allylic substitution of guanidines reported by Miyabe and co-workers.[54] They demonstrated that reaction of guanidines possessing strongly electron withdrawing substituents, for example the reaction of bis-protected guanidine **95** with allylic carbonate **100** in the presence of $Pd(PPh_3)_4$ gave the corresponding guanidines **101** in 82% yield (Scheme 20).



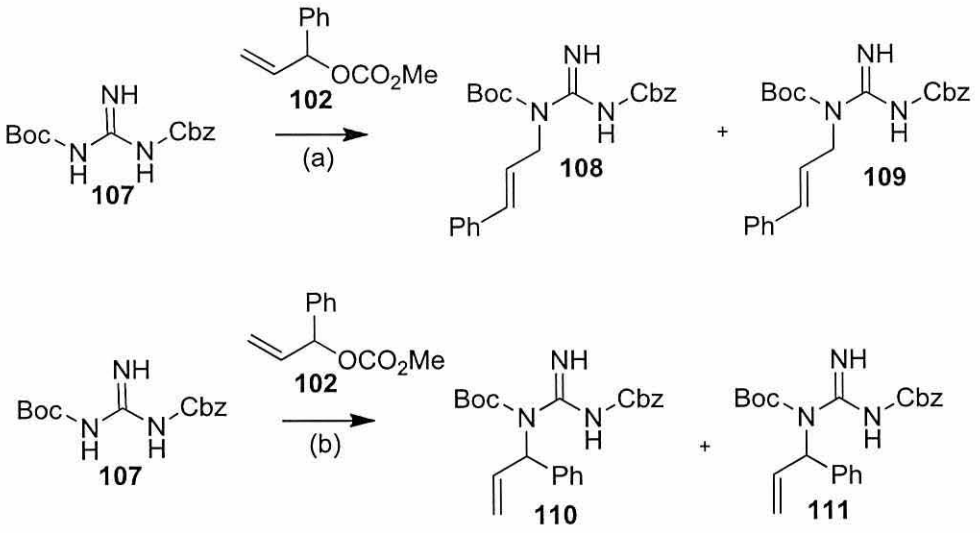
Scheme 20: (a) $Pd(PPh_3)_4$, CH_2Cl_2, 20 °C, 2 h, 82%.

They also reported that the reaction of bis-protected guanidines **95** and **96** with allylic carbonate **102** in the presence of $Pd(PPh_3)_4$ gave the corresponding guanidines **103** (P = Boc) in 86% yield and **104** (P = Cbz) in 88% yield (Scheme 21).[54] In a related reaction, the iridium-catalysed reaction of the same substrates using $[IrCl(cod)]_2$ (4 mol%) gave the corresponding isomeric guanidines **105** (P = Boc) and **106** (P = Cbz) in excellent yields (Scheme 21).[54]



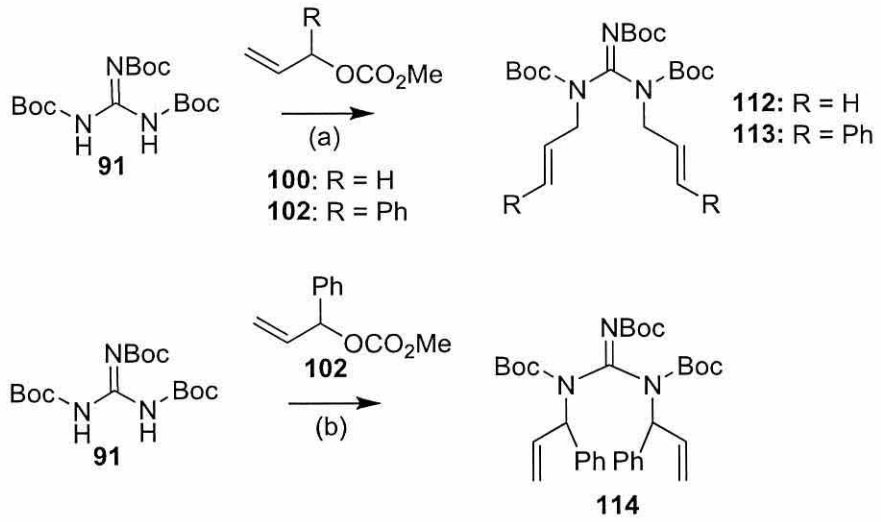
Scheme 21: (a) $Pd(PPh_3)_4$ (8 mol%), CH_2Cl_2, 20 °C, 2 h, **103**: 86%; **104**: 88%; (b) $[IrCl(cod)]_2$ (4 mol%), CH_3CN, 20 °C, 2 h, **105**: 88%; **106**: 87%.

The same workers also investigated the allylation of the unsymmetrically substituted guanidine **107**. Under these conditions and found that reaction with carbonate **102** in the presence of $Pd(PPh_3)_4$ in CH_2Cl_2 at 20 °C for 2 h gave a 3:1 mixture of the allylated guanidine products **108** and **109** in 88% combined yield. Similarly reaction of guanidine **107** with carbonate **102** using $[IrCl(cod)]_2$ in MeCN at 20 °C for 2 h gave the corresponding isomeric guanidine products **110** and **111** in a 2:1 ratio and an overall yield of 93%. Both these reaction show a preference for the Boc protected nitrogen which might suggest that an electronic rather than a steric effect is in operation (Scheme 22).[54]



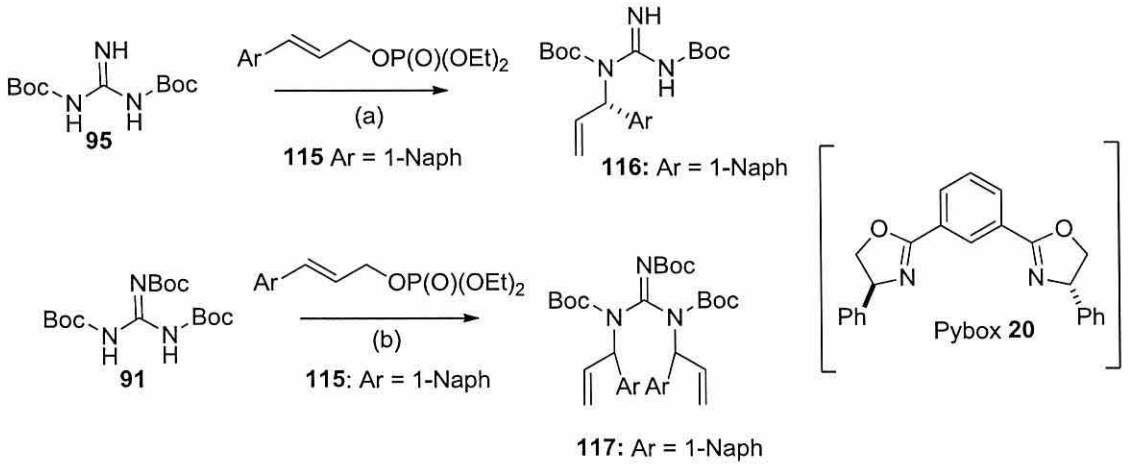
Scheme 22: (a) $Pd(PPh_3)_4$, CH_2Cl_2, 20 °C, 2 h, 88% (**108**:**109** = 3:1); (b) $[IrCl(cod)]_2$, CH_3CN, 20 °C, 2 h, **110**: 62%; **111**: 31%.

They also reported that a double allylic substitution was possible by treating the tri-Boc-guanidine **91** with allylic carbonate **100** (4 equiv.) in the presence of Pd $(PPh_3)_4$ in CH_2Cl_2 at 20 °C for 1 h to give diallylated product **112** in 99% yield. Similarly, reaction of **91** with carbonate **102** gave the diallylated product **113** in 94% yield. They also reported iridium-catalyzed reaction of the same substrates using $[IrCl(cod)]_2$ in MeCN at 20 °C for 1 h giving the isomeric diallylated **114** in 85% yield (Scheme 23).[54]



Scheme 23: (a) $Pd(PPh_3)_4$, CH_2Cl_2, 20 °C, 1 h, **112**: 99%; **113**: 94%; (b) $[IrCl(cod)]_2$, CH_3CN, 20 °C, 1 h, 85%.

An asymmetric version of the $[IrCl(cod)]_2$ catalysed reaction was also developed in which the catalyst was used in combination with the chiral ligand pybox **20** and an allylic phosphonate **115** which gave the corresponding guanidine **116** in 69% yield and 96% ee (Scheme 24). Similarly the use of this combination of reagents was reported for the double allylic substitution of tri-Boc-guanidine **91** with phosphate **115** which was carried out in the presence of $[IrCl(cod)]_2$ (8 mol%) and pybox **20** (16 mol%) in CH_2Cl_2 at -20 °C for 20 h to give the corresponding guanidine **117** in 81% yield and >99% ee.[54]



Scheme 24: (a) $[IrCl(cod)]_2$ (8 mol%), pybox **20** (16 mol%), $CsOH.H_2O$, CH_2Cl_2, -20 °C, 8 h, 69% (96% ee); (b) $[IrCl(cod)]_2$ (8 mol%), pybox **20** (16 mol%), $CsOH.H_2O$, CH_2Cl_2, -20 °C, 20 h, 81% (>99% ee).

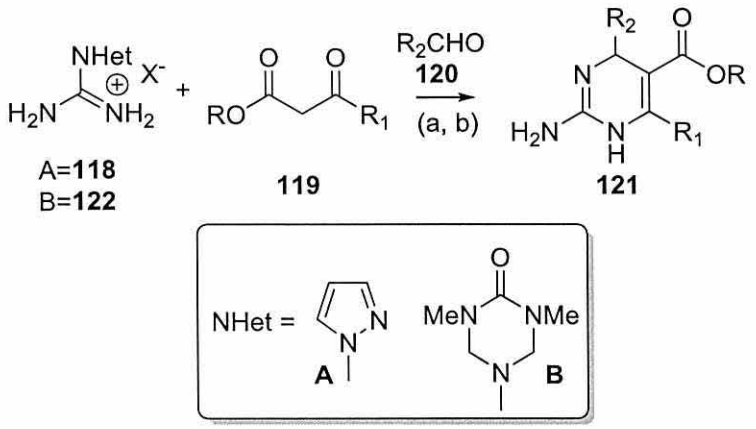
Synthesis of cyclic guanidines

The nature of the current work is the synthesis of cyclic guanidines and in particular saturated guanidine heterocycles. Many reports on the synthesis of guanidine heterocycles are known and this section will focus on those most commonly employed.

Biginelli and Michael additions

A classic method for the preparation of guanidine and related amidine heterocycles is the Biginelli cyclisation which uses an amidine in conjunction with a 1,3-dicarbonyl compound and an aldehyde and leads to the synthesis of a pyrimidine. This reaction was originally reported in 1893 by Pietro Biginelli[55] and has seen a recent increase in activity due to its use in the preparation of complex guanidine containing marine natural products.

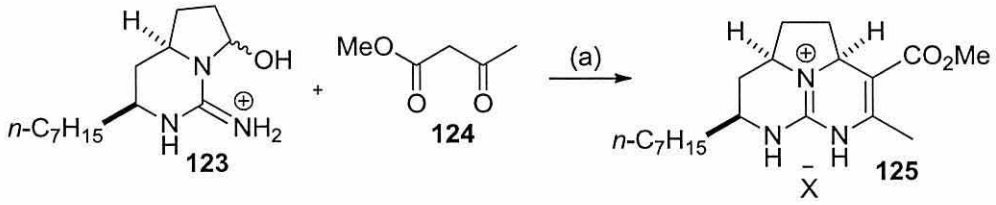
A recent application of the Biginelli reaction was reported by Overman *et al.*[56] who described the reaction of the pyrazole carboxamidine **118** with dicarbonyl compound **119**, and aldehyde **120** leading to the formation of the 2-imino-5-carboxy-3,4-dihydropyrimidines **121** after aminolysis (Scheme 25). A similar method uses the triazone-protected guanidine **122**, which after acidic deprotection of the triazone also led to the formation of the 2-imino-5-carboxy-3,4-dihydropyrimidines **121** in two steps (Scheme 25).



Scheme 25: (a) $NaHCO_3$, DMF, 70 °C; (b) for A: NH_3; for B: HCl (6N), 70 °C, 6 h. R= Et, Bn; R^1= Me, Ph; R^2= Ph, *i*-Pr, cyclohexyl, *m*-NO_2-C_6H_4, 60-74%.

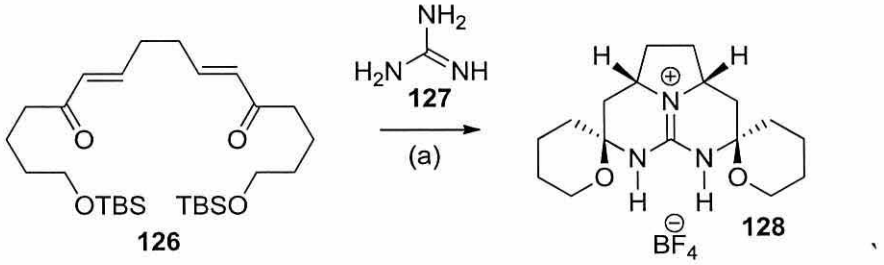
As a multi-component reaction, the Biginelli reaction is a very powerful tool for the synthesis of natural products and Overman later used a similar tethered Biginelli strategy to construct the tricyclic core of the batzelladine alkaloids. He reported that

reaction of the guanidine **123**, which contains the aldehyde function masked within it, with the ß-ketoester **124** gave the tricyclic guanidine **125** in 94% yield (Scheme 26).[57]



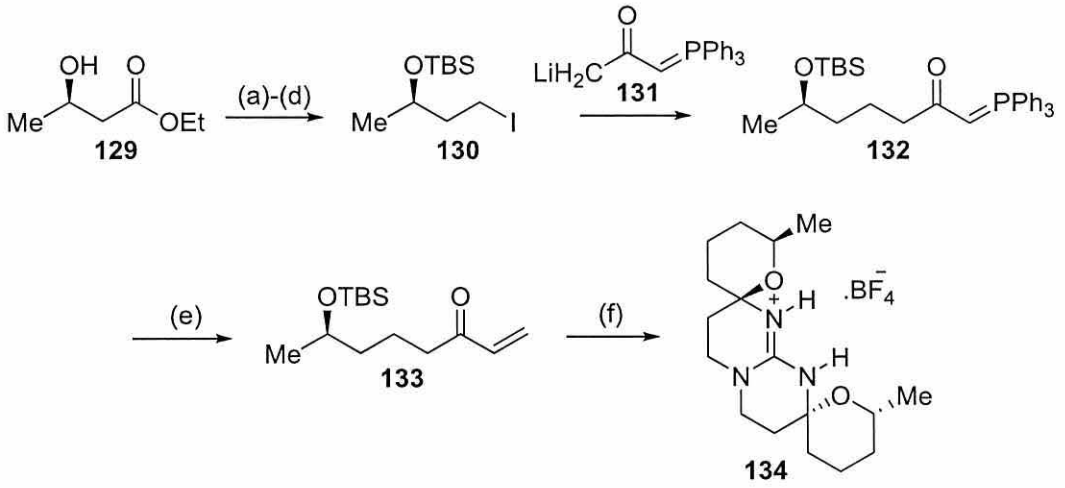
Scheme 26: (a) morpholine, AcOH, Na_2SO_4, Δ, ROH.

Within our own research group the synthesis of guanidines using a tandem conjugate (Michael) addition approach has been extensively studied. For example the addition of guanidine **127** to the bis-α,β-unsaturated ketone **126** followed by deprotection of the spirocyclisation gave the symmetrical pentacyclic guandine **128** (Scheme 27) in good overall yield.[58]



Scheme 27: (a) i) DMF, 3 h, (ii) MeOH, HCl, 0 °C-rt, 24 h, (iii) $NaBF_4$ (sat. aq.), 25% overall.

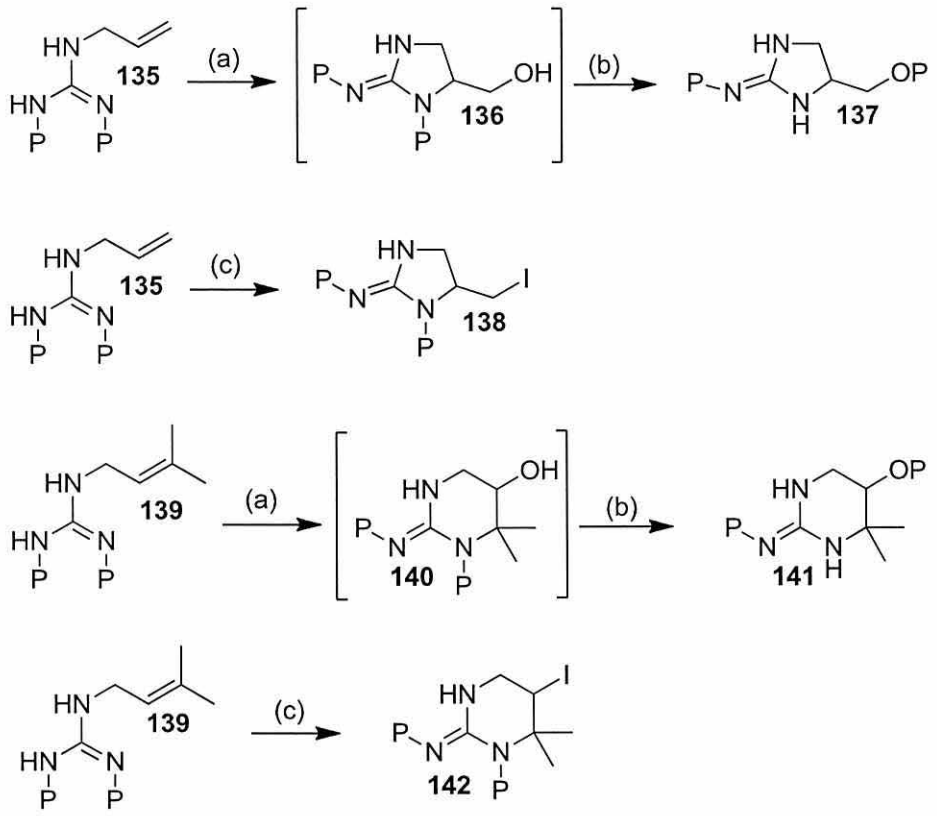
An intermolecular version of this reaction was also reported for the synthesis of tetracyclic *C*2-symmetric guanidine **134**. The enantiopure ketone **133** was prepared in six steps from commercially available ethyl (*R*)-3-hydroxybutyrate **129** and reaction of this substrate with guanidine gave after desilylation and cyclisation, the required guanidine **134** as a single enantiomer in 44% yield (Scheme 28).[59]



Scheme 28: (a) TBDMSCl/Imidazole, DMF, 99%; (b) DIBAL-H, -78 °C, 95%; (c) TosCl/Pyridine, 85%; (d) NaI/acetone, 89%; (e) i) $CH_3COCHPPh_3$/*n*-BuLi, (ii) aq. CH_2O 79%; (f) i) guanidine/DMF/0 °C, 16 h, (ii) HCl/MeOH, 3 h, (iii) $NaBF_4$ (aq.), 44%.

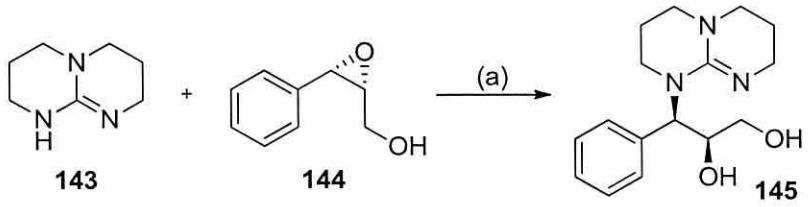
Synthesis of guanidines by heterocyclisation

In a related study, the heterocyclisation of protected guanidines has also been investigated within our group. It was found that the protected guanidines **135** underwent cyclisation on treatment with DMDO under neutral conditions to give the 5-membered guanidines **136** in good yields. An interesting observation was that the Boc- and Cbz-protecting groups undergo migration during the reaction to give the O-protected compounds **137**. A similar reaction of **135** with iodine in the presence of potassium carbonate leads to the cyclic guanidine **138** in very good yields (Scheme 29). The next investigation by the group was on the epoxidation of the protected guanidines **139**, which on treatment with DMDO initially gave an epoxide, which slowly underwent ring opening to give 6-membered guanidines **140** in good yields. It was observed that the Boc- and Cbz-protecting groups undergo migration during the reaction to give the O-protected compounds **141**. A similar reaction of protected guanidine **139** with iodine in the presence of potassium carbonate gave the cyclic guanidine **142** again in very good yields (Scheme 29).[60]



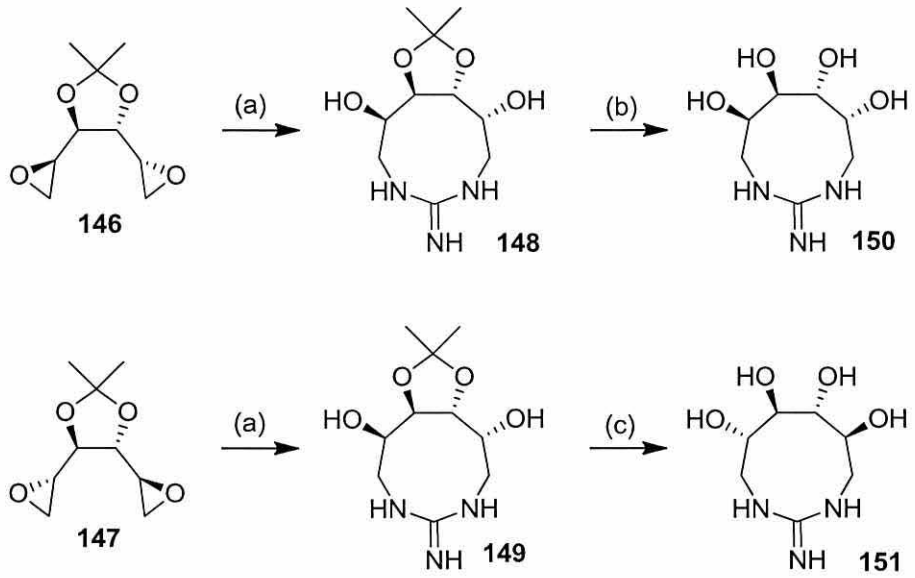
Scheme 29: (a) DMDO, acetone -20 °C - rt, 7 days; (b) silica gel, CH_2Cl_2, 16–24 h; (c) I_2, CH_3CN, K_2CO_3, -20 °C - rt, 16-24h, P = Boc, Cbz.

Very few other examples of epoxide ring openings using guanidines have been reported in the literature, however a report by Taylor and co-workers demonstrated that cyclic guanidine **143** readily reacts with epoxides to give ring-opened products. For example, the reaction of **143** with (2*S*,3*R*)-phenylglycidol epoxide **144** and two equivalents of titanium *iso*-propoxide in CH_2Cl_2 gave the guanidine **145** in 81% yield (Scheme 30).[61]



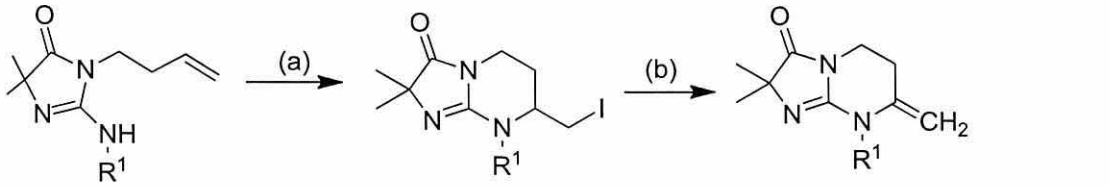
Scheme 30: (a) Ti(O ^{i}Pr)$_4$, CH_2Cl_2, 81%.

Similarly Le Merrer *et al.*[62] reported the reaction of carbohydrate derived epoxides **146** and **147** with guanidine in refluxing EtOH leading to the 9-membered cyclic guanidines **148** and **149** in high yields. The acetonide group was removed using hydrogen chloride in MeOH or aqueous TFA to give the glycomimetics **150** and **151** (Scheme 31).



Scheme 31: (a) Guanidine, EtOH, Δ, **148**: 97%; **149**: 97%;
(b) HCl (g), MeOH, 70%; (c) TFA, H_2O, 70%.

Iodocyclisations have proven to be of use in synthesis, and Watanabe *et al.*[63] reported the reaction of 3-(but-3-enyl)-1-imidazolin-4-ones **152a-c** leading to the imidazo[1,2-*a*]pyrimidines **153a-c** in high yields *via* a 6-exo cyclisation. The structures of imidazopyrimidines **153a-c** were determined by their conversion to the 7-*exo* methylene compounds **154a-c** by the removal of hydrogen iodide (Scheme 32).



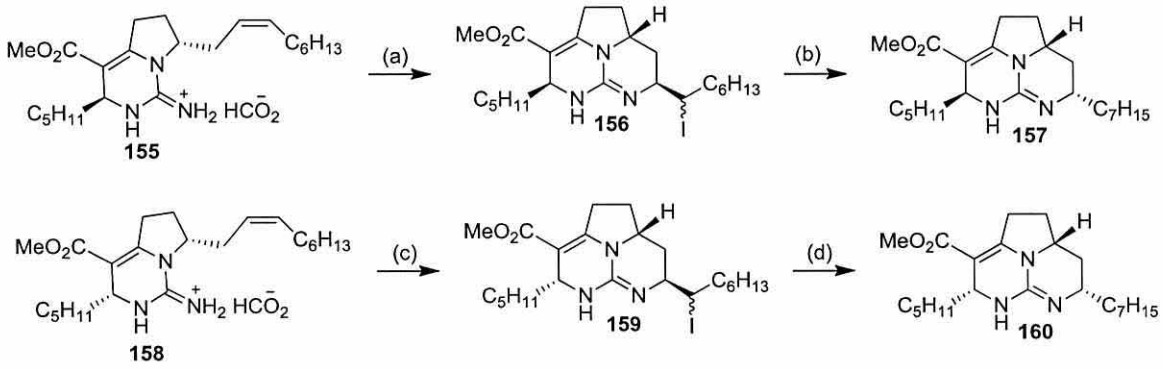
152a: R_1=Ph
152b: R_1=Ts
152c: R_1=1-Naphthyl

153a (Y. 98% with K_2CO_3)
153b (Y. 96%)
153c (Y. 89% with K_2CO_3)

154a: R_1=Ph (Y. 88%)
154b: R_1=Ts (Y. 96%)
154c: R_1=1-Naphthyl (Y. 88%)

Scheme 32: (a) I_2, K_2CO_3, DME, rt, 1 d; (b) DBU, toluene, reflux, 1 h.

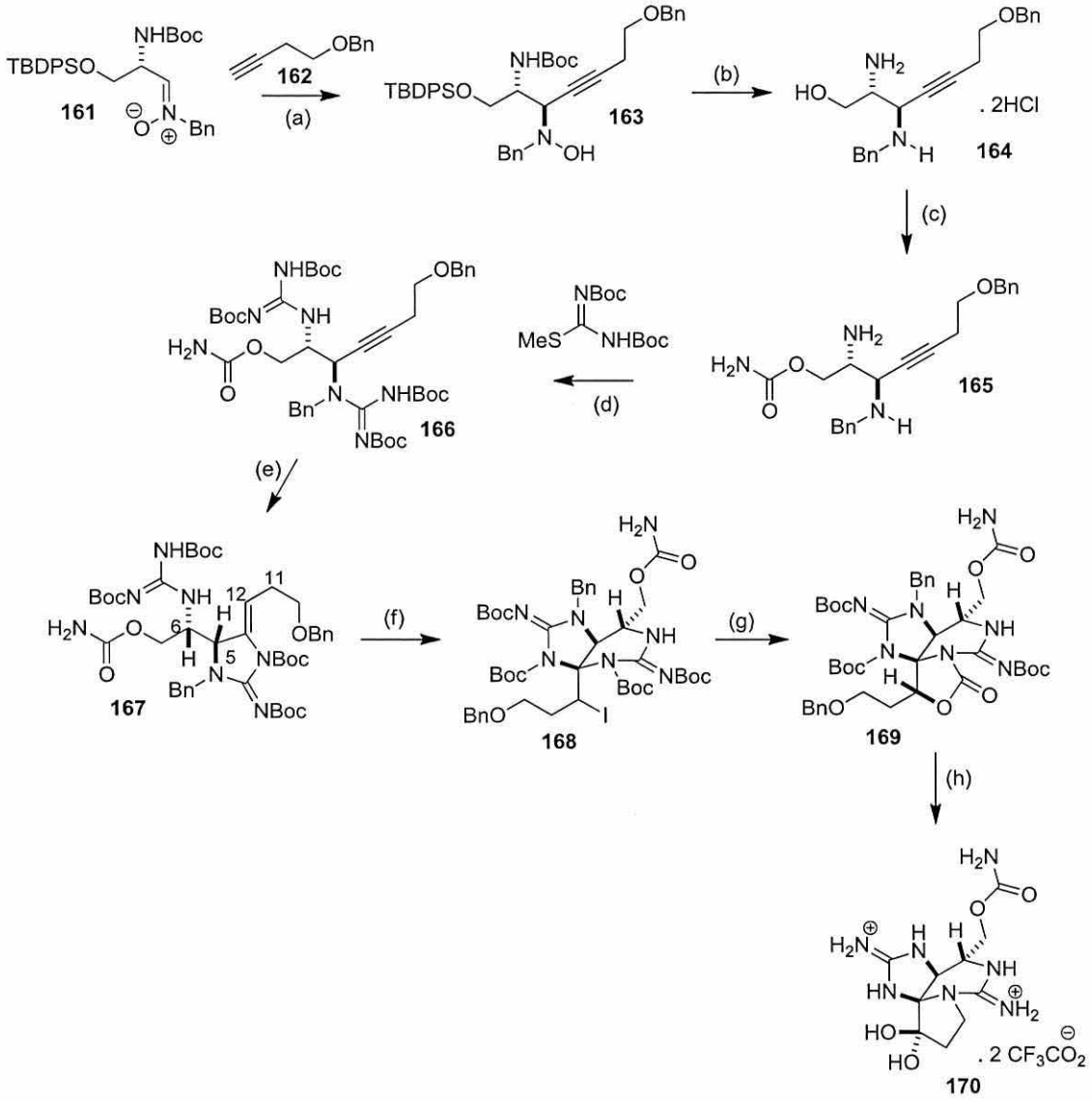
A further interesting reaction involving an iodocyclisation was reported in the synthesis of the batzelladine alkaloids in which the synthetic intermediate **156** was formed by iodocyclisation of guanidine **155** using iodine/potassium carbonate in MeCN, which after hydrogenolysis provided compound **157** (Scheme 33). Iodocyclisation of diastereoisomer **158** was more difficult, but was ultimately achieved using iodine monochloride/potassium carbonate in CH_2Cl_2 to give the intermediate compound **159** (Scheme 33). Hydrogenolysis of compound **159** then gave compound **160**. The reason for the more demanding iodocyclisation of compound **158** is unclear.[64]



Scheme 33: (a) I_2, K_2CO_3, MeCN, 25 °C, 3 h; (b) H_2, Pd/C, Et_3N, EtOAc, 25 °C, 16 h, 55% (2 steps); (c) ICl, K_2CO_3, CH_2Cl_2, 0 °C to 25 °C, 3 h, 81%, (d) H_2, Pd/C, Et_3N, EtOAc, 25 °C, 16 h, 55%.

In a landmark synthesis of guanidine alkaloid (+)-saxitoxin **170**, Bhonde and Looper utilised a silver mediated intramolecular cyclisation of guanidine **166** with an alkyne, which was followed by a subsequent iodocyclisation on the alkene thus formed. The synthesis began with addition of the metallated homopropargyl benzyl ether **162** to L-serine aldonitrone **161** giving *N*-hydroxydiamine **163** in good yield. Reductive cleavage of the N-O bond and acidic removal of both the silyl and carbamate protecting groups gave the diamine **164** as its bis-hydrochloride salt. This was treated with potassium cyanate in concentrated MsOH to give **165** as its free base. Mercuric oxide-assisted guanylation with di-Boc-pseudothiourea generated the desired alkynyl bisguanidine **166**. Compound **166** was then treated with Ag (I) which led to a single regio- and stereoisomer of a cyclic ene-guanidine product **167** in 98% yield. Treatment of **167** with iodine in the presence of Ag (I) gave the bicyclic aminal **168** in

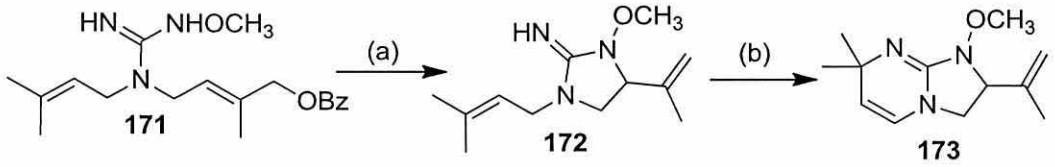
82% yield as a single diastereomer. This secondary alkyl iodide was then treated with Ag (I) and AcOH providing **169** in 77% yield, which was converted to (+)-saxitoxin **170** in 81% yield (Scheme 34).[65]



Scheme 34: (a) *i*PrMgCl, THF, -78 °C-55 °C, 9:1 d.r. (86%); (b) i) $Cu(OAc)_2$, Zn, AcOH, H_2O, 92%, (ii) 1M HCl in MeOH, 40 °C, 89%; (c) KOCN, MsOH, CH_2Cl_2, 78%; (d) HgO, Et_3N, CH_2Cl_2, 83%; (e) AgOAc (10 mol%), CH_2Cl_2, 98%; (f) I_2, AgOAc, Et_2O, 82%; (g) AgOAc, AcOH, MeCN, 55 °C, 77%; (h) five further steps: 81% from **169**.

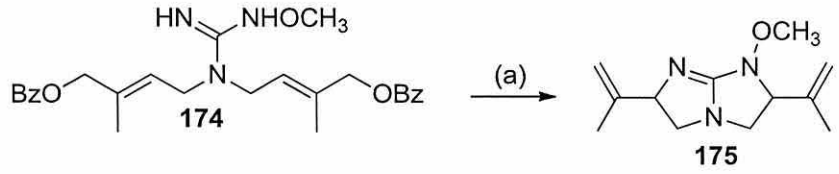
Palladium catalysed cyclisations

One approach we were intending to investigate was the intramolecular cyclisation of guanidines with allylic acetates under palladium catalysis. This reaction is a common strategy for amines,[66,67] and other amidines,[68,69] however at the outset of this work, examples using simple guanidines were largely unknown. A related cyclisation had been reported by Büchi *et al.*[70] in their 1989 approach to the synthesis of (±)-alchorneine **173** and (±)-isoalchorneine **175**. They found that treatment of the *N*-methoxyguanidine **171** with $Pd(PPh_3)_4$ in CH_3CN at 50 °C for 3 h in the presence of NEt_3 gave the 5-membered guanidine **172** in 81% yield. This was probably formed either *via* an intermediate π-allyl Pd(II) complex or *via* a *cis*-amidopalladation. Further reaction of **172** under oxidative conditions using two equivalents of $PdCl_2(CH_3CN)_2$ in CH_2Cl_2 at 40 °C for 48 h gave (±)-alchorneine **173** in 46% yield (Scheme 35).



Scheme 35: (a) $Pd(PPh_3)_4$, Et_3N, CH_3CN, 81% yield;
(b) $PdCl_2(CH_3CN)_2$, CH_2Cl_2, 40 °C, 46% yield.

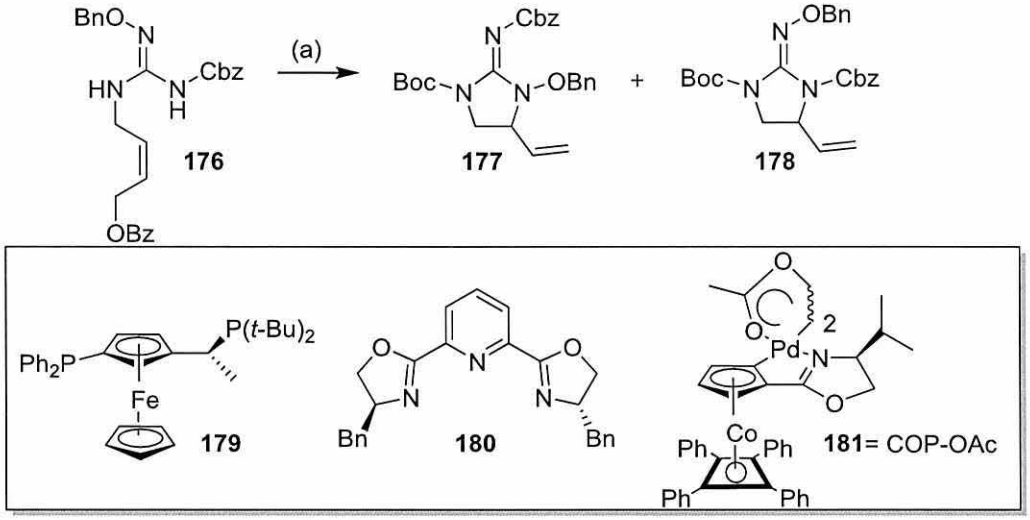
Similarly, cyclisation of the *N*-methoxyguanidine **174** with $Pd(PPh_3)_4$ (0.2 equiv.) in CH_3CN at 50 °C for 24 h in the presence of NEt_3 gave a 1:1 mixture of (±)-isoalchorneine **175** (Scheme 36).[70]



Scheme 36: (a) $Pd(PPh_3)_4$, Et_3N, CH_3CN, 50 °C.

Following on from this work, Buck and Wipf reported[38] the cyclisation of allylic guanidine **176** under Pd(II) catalyzed conditions (Scheme 37, Table 1). They reported that using $Pd_2(dba)_2$ (0.5 equiv.) as the catalyst gave a highly regioselective synthesis of **177**, however in a poor 14% yield (Entry 1). The use of $Pd(OAc)_2$ in THF (0.05 M) gave a higher yield of 57% but a complete loss of regioselectivity (Entry 2). However, changing the catalyst to $PdCl_2(CH_3CN)_2$ in THF afforded **177** in 84% yield with

complete regioselectivity (Entry 3). Attempts to use chiral catalysis in this reaction were disappointing. The use of the ligands **179**, **180**, sparteine or Overman's chiral palladium (II) catalyst COP-OAc[71] **181** gave mixed results (Entries 4-7), with only the last catalyst being effective giving a 50:50 mixture of **177** and **178** in a 70% combined yield with a 48% ee for **177** being obtained.

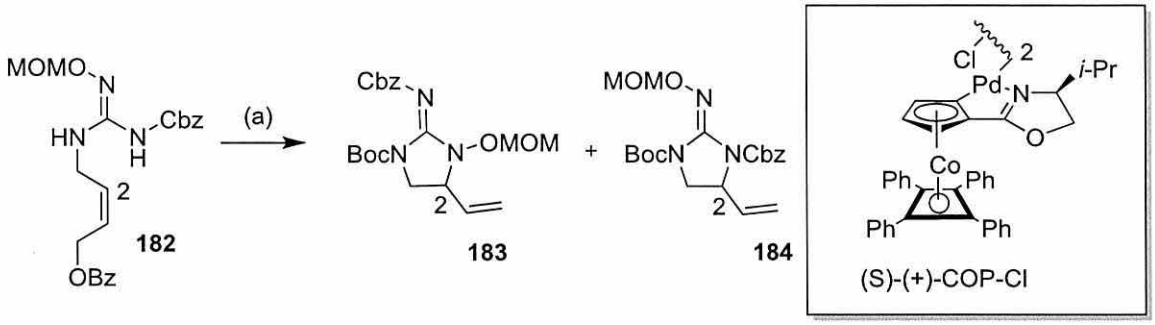


Scheme 37: (a) i) Conditions, (ii) Boc_2O, DMAP, Et_3N, THF.

Entry	Conditions	Ligand	Ratio 177:178	Result[a]
1	$Pd_2(dba)_2$ (0.5 equiv.), Et_3N (1.1 equiv.), CH_2Cl_2 (0.05 M)	-	100:0	14%
2	$Pd(OAc)_2$ (0.2 equiv.), THF (0.05 M)	-	50:50	57%
3	$PdCl_2(CH_3CN)_2$ (0.2 equiv.), THF (0.2 M)	-	100:0	84%
4	(R)-(-)-COP-OAc **181** (0.1 equiv.), CH_2Cl_2 (0.6 M)	-	50:50	70% (**177**: 48% ee)[c]
5	$PdCl_2(CH_3CN)_2$ (0.2 equiv.), DCE (0.5 M), 85°C	**179** (0.4 equiv.)	-	NR
6	$PdCl_2(CH_3CN)_2$ (0.2 equiv.), THF (0.5 M)	(-)-sparteine	100:0	55% (< 1% ee)[c]
7	$PdCl_2(CH_3CN)_2$ (0.2 equiv.), DCE (0.5 M), 85 °C	**180** (0.4 equiv.)	100:0	67% (< 2% ee)[c]

Table 1: Showing conditions for key amidoalkylation of guanidine **176**.[38]

The related guanidine derivative **182** was subjected to the Pd(II)-mediated cyclisation using $PdCl_2(CH_3CN)_2$ in THF (0.2 M) to give exclusively **183** in 95% yield (Entry 1). The use of (*S*)-(+)-COP-Cl as a chiral catalyst gave the same selectivity for theformation of **183** which was obtained in 76% yield with a 3:1 e.r (50% ee) (Entry 2). The use of the opposite enantiomer (*R*)-(-)-COP-Cl gave a similar yield but with the enantioselectivity reversed (Entry 3) (Scheme 38, Table 2).[38]

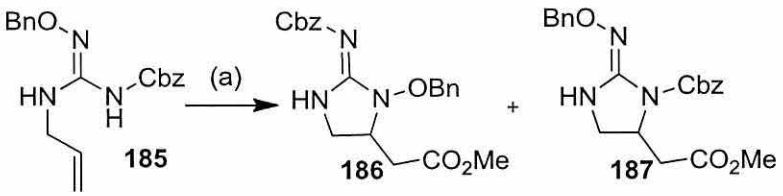


Scheme 38: (a) i) Conditions, (ii) Boc_2O, DMAP, Et_3N, THF.

Entry	Conditions	Ratio (183:184)	Yield (e.r.)[a]
1	$PdCl_2(CH_3CN)_2$ (0.2 equiv.), THF (0.2 M)	100:0	95%
2	(*S*)-(+)-COP-Cl (0.025 equiv.), CH_2Cl_2 (0.6 M)	100:0	76% (3:1)[b]
3	(*R*)-(-)-COP-Cl (0.025 equiv.), CH_2Cl_2 (0.6 M)	100:0	74% (1:3)[b]

Table 2: Pd(II)-mediated cyclization of MOM-derivative **182**.

Buck and Wipf also studied[38] the Pd(II) catalysed amidocarbonylation of the substrate **185** (Scheme 39, Table 3). They reported that treatment of **185** with 10 mol% of $Pd(OAc)_2$ and $CuCl_2$ (3 equiv.) in CH_3OH under 1 atm of CO gave a 68.7:31.3 mixture of methyl esters **186** and **187** in 76% yield. Attempts at improving the selectivity for the product **186** by the use of additives were unsuccessful with all cases favouring the formation of the isomeric **187** (Entries 2-8).



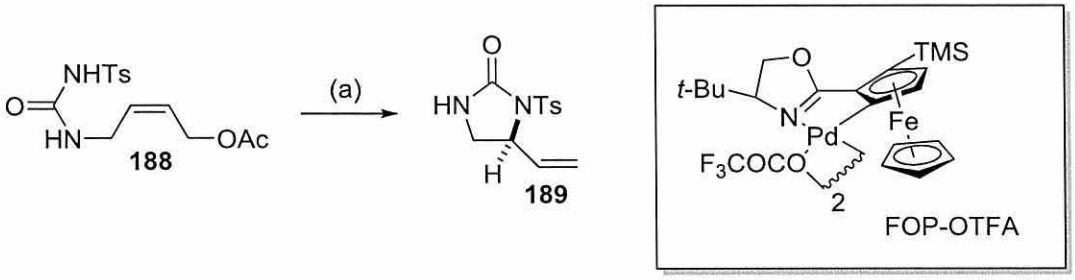
Scheme 39: (a) $Pd(OAc)_2$ (0.1 equiv.), $CuCl_2$ (3 equiv.), additive (0.4 equiv.), CO, CH_3OH, 0 °C-rt, 76% yield.

Entry	Additive	Ratio (186:187)[a]	Yield (%)
1	None	68.7:31.3	76[b]
2	(-)-sparteine	0:100	55[c,d]
3	NMM	0:100	64[c]
4	*N*, *N*-dimethylaniline	16.7:83.3	70[b]
5	hydroquinine	7.7:92.3	75[b,d]
6	IBBO	40:60	91[b,d]
7	*i*-Pr_2NEt	0:100	ND
8	AcOH	33.3:66.7	ND

[a]Determined by ^{1}H-NMR.[b] Isolated yield. [c]Yield of crude mixture.
[d]Observed ee% was less than 5% as determined by chiral SFC.

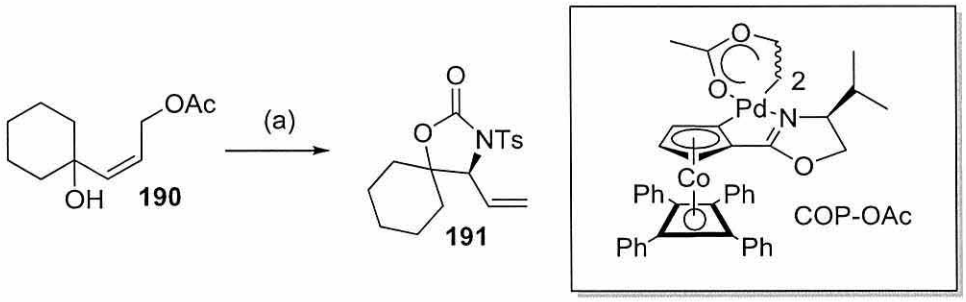
Table 3: Amidocarbonylation conditions of guanidine **185**.

On inspection of the literature for similar transformation of urea derivatives it was found that Overman *et al.*[72] had reported in 2002 a set of chiral Pd(II) catalysts for the asymmetric annulation of allylic ureas to give oxazolines. For example, treatment of allylic urea **188** with 5 mol% of the catalyst FOP-OTFA in 1:1 CH_2Cl_2/CH_3NO_2 gave urea **189** in 96% yield and 90% ee (Scheme 40). FOP-OTFA is formed *in situ* by reacting the corresponding Pd-I complex with AgOTFA. Although a range of silver salts was investigated, the best result was achieved with silver trifluoroacetate.



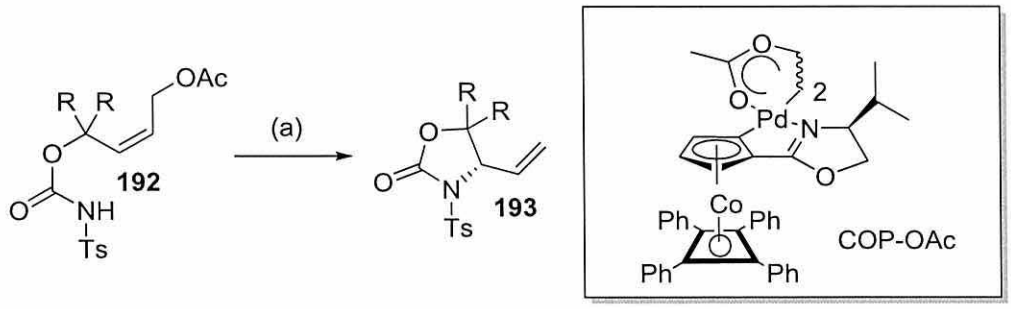
Scheme 40: (a) FOP-OTFA (5 mol%), 1:1 CH_2Cl_2/CH_3NO_2, 96% (90% ee).

In 2005, a second generation catalyst was developed by Overman *et al.*[71] which replaced the ferrocene ligand with a cobalt oxazoline palladacycle (COP). Reaction of an allylic alcohol **190** with TsNCO in THF produced the *N*-tosyl urea, which on cyclisation using COP-OAc in CH_2Cl_2/AcOH (4:1) formed the spirocycle **191** in 82% yield and 97% ee (Scheme 41).



Scheme 41: (a) i) TsNCO, THF, (ii) COP-OAc (1% mol), 38 °C, CH_2Cl_2/AcOH (4:1), 82% (97% ee).

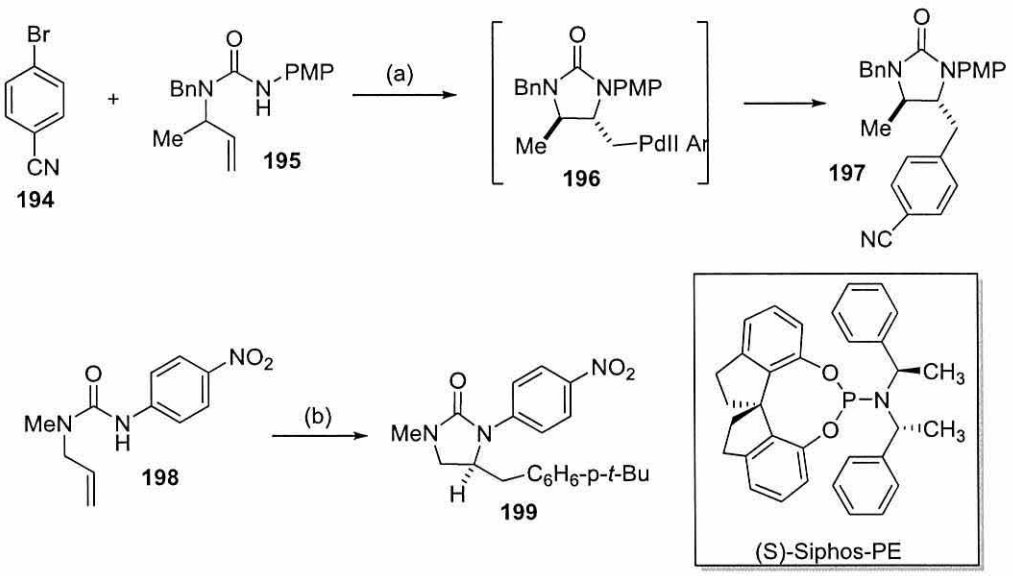
A subsequent publication by Overman detailing the palladium catalysed enantioselective cyclisation of carbamates **192**. This is of considerable interest as it describes the access to a range of 4-vinyloxazolidin-2-ones **193** (Scheme 42).[71]



Scheme 42: (a) COP-OAc (1% mol), CH_2Cl_2/AcOH (4:1), 81-94% (91-98% ee).

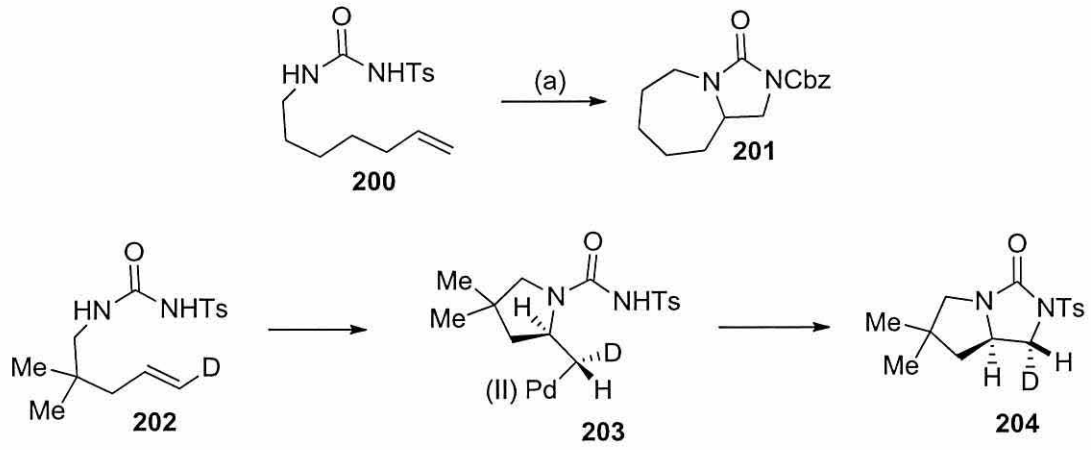
Wolfe and co-workers[73] reported the synthesis of urea derivatives using the $Pd_2(dba)_3$/Xantphos catalyst system. Treatment of aryl bromide **194** with $Pd_2(dba)_3$/Xantphos resulted in oxidative addition to the aryl bromide bond to give an intermediate palladium complex, which initiated amidopalladation of allylic urea **195**, and generated the alkyl-palladium complex **196**. This complex then underwent a reductive elimination to give cyclic urea **197** in 88% yield and a 12:1 dr. The use of

base in the reaction is essential to encourage amidopalladation. The Wolfe group followed this work with a report in 2012 on an enantioselective alternative of this methodology using the phosphoramidite ligand, (*S*)-Siphos-PE to generate **199** in 81% yield (92% ee) (Scheme 43).[74]



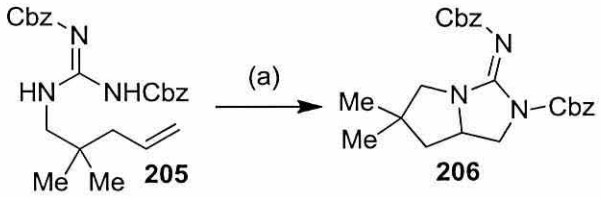
Scheme 43: (a) $Pd_2(dba)_3$/Xantphos, NaO*t*-Bu, toluene, 100 °C, 12:1 dr, 88%; (b) P-*t*-Bu-C_6H_4Br, [$Pd_2(dba)_3$] (2 mol%), (*S*)-Siphos-PE (6 mol%), NaO*t*-Bu, toluene, 90 °C, 81% (92% ee).

In 2005, the Muñiz group[75] reported an interesting diamination of terminal olefins that was catalyzed by Pd(II). They reported that treatment of urea **200** with $Pd(OAc)_2$ and PIDA in CH_2Cl_2 gave the bicyclic urea **201** in 89% yield (Scheme 44). To explore the reaction mechanism, deuterated olefin **202** was activated by Pd(II) and subsequent nucleophilic addition generated the alkyl Pd(II)-species **203**. Due to the observed *trans* H-H relationship in the product, they proposed that PIDA oxidizes Pd(II) to Pd(IV), and subsequent nucleophilic substitution by the remaining secondary nitrogen with concomitant loss of Pd(II) gave the diamination product **204** as a single diastereomer.



Scheme 44: (a) $Pd(OAc)_2$, PIDA, CH_2Cl_2, 89%.

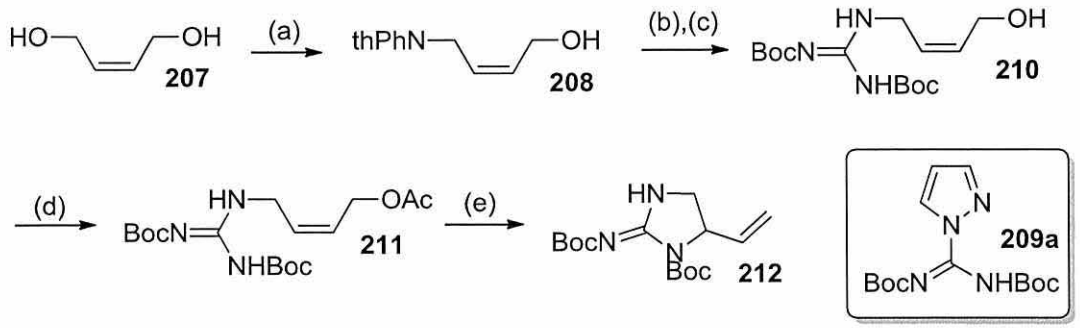
A similar cyclisation was reported by Hövelmann *et al.*[76] who prepared the bicyclic guanidines **206** by treatment of the substituted guanidine **205** with $Pd(OAc)_2/CuBr_2$ in DMF to give the bicyclic guanidine **206** in 99% yield (Scheme 45).



Scheme 45: (a) $Pd(OAc)_2$ (10 mol%), $CuBr_2$ (3 equiv.), K_2CO_3 (1 equiv.), DMF, rt, 99% yield.

An unpublished palladium catalysed cyclisation was known within the Murphy research group. The substrate (**213**) for this cyclisation was easily prepared from commercially available 2-*cis*-butene-1,4-diol **207**, which on reaction with phthalimide in the presence of PPh_3 and DEAD gave the protected amine **208** in 82% yield. Reaction of **208** with hydrazine hydrate effected deprotection of the amine, which on treatment with Et_3N and the commercially available guanylating agent **209a** gave the guanidine **210** in 56% yield.

Acetylation of **210** was achieved by treatment with Ac_2O in pyridine leading to the required substrate **211** in 72% yield. Cyclisation of **211** was easily achieved by treatment with $Pd(PPh_3)_4$ in THF to give the 5-membered guanidine **212** in 90% yield after chromatography (Scheme 46).[77,78]



Scheme 46: (a) PPh_3, phthalimide, THF, DIAD, 82%; (b) i) $NH_2NH_2.H_2O$, EtOH, reflux, (ii) Et_3N, **209a**, rt, 24 h, 56%; (c) Ac_2O, pyridine, DMAP, DCM, 0 °C, 30 mins,72 %; (e) $Pd(OAc)_2/PPh_3$, THF, reflux, 3 h, 90%.

Conclusion

It is obvious that the guanidine motif plays a significant role in biological systems as it is found in numerous marine and terrestrial natural products and is ubiquitous in proteins and peptides. Amongst the many roles played by the guanidium group, it has the ability to function as a very strong base and once protonated has a strong affinity for binding anionic substrates and has considerable applications in catalysis. Several palladium mediated cyclisations of guanidines have been reported, however the range of applications is limited and applications in natural product synthesis are few.

Aims

The primary aim of the project was to investigate the synthesis of the guanidines nitensidine D **213** and nitensidine E **214** recently isolated from *Pterogyne nitens*, a native tree common in South America.[79] These alkaloids are active against several human cancer cell lines, for example nitensidine E **214** exhibited cytotoxicity for HL-60 (human myeloblastic leukemia) and SF-245 (human glioblastoma) cells. Previous studies on phytochemicals found within the leaves and fruits of *P. nitens* have shown that they contain several interesting guanidine alkaloids, including galegine **215**, pterogynidine **216** and pterogynine **217**. These three alkaloids exhibited cytotoxic activity toward the DNA-repair deficient strains of yeast and other cancer cells.[79] The related metabolites nitensidine A **218**, nitensidine B **219** and nitensidine C **220** were also isolated from *Pterogyne nitens*. They were shown to have moderate antimicrobial activity against *Candida albicans*, *C. krusei*, *C. parapsilosis* and *Cryptococcus neoformans*.[80] Nitensidine A **218** and pterogynine **217** also exhibited anti-osteoclastic effects which have potential application in the treatment of myeloma related bone disease.[81]

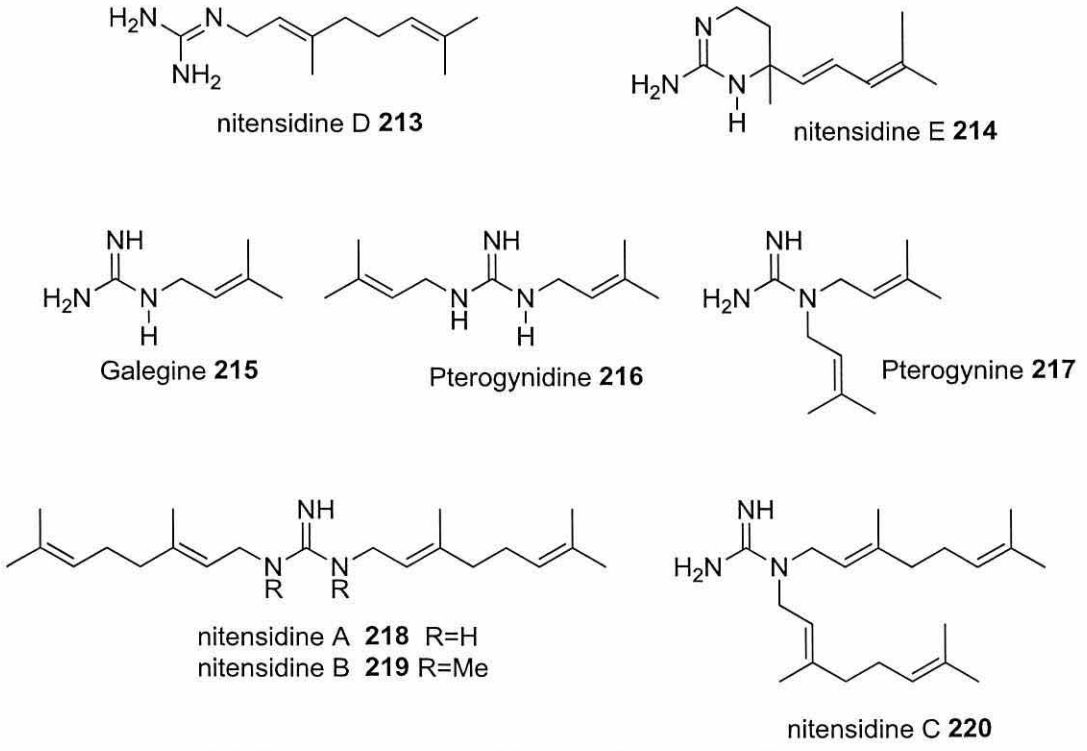
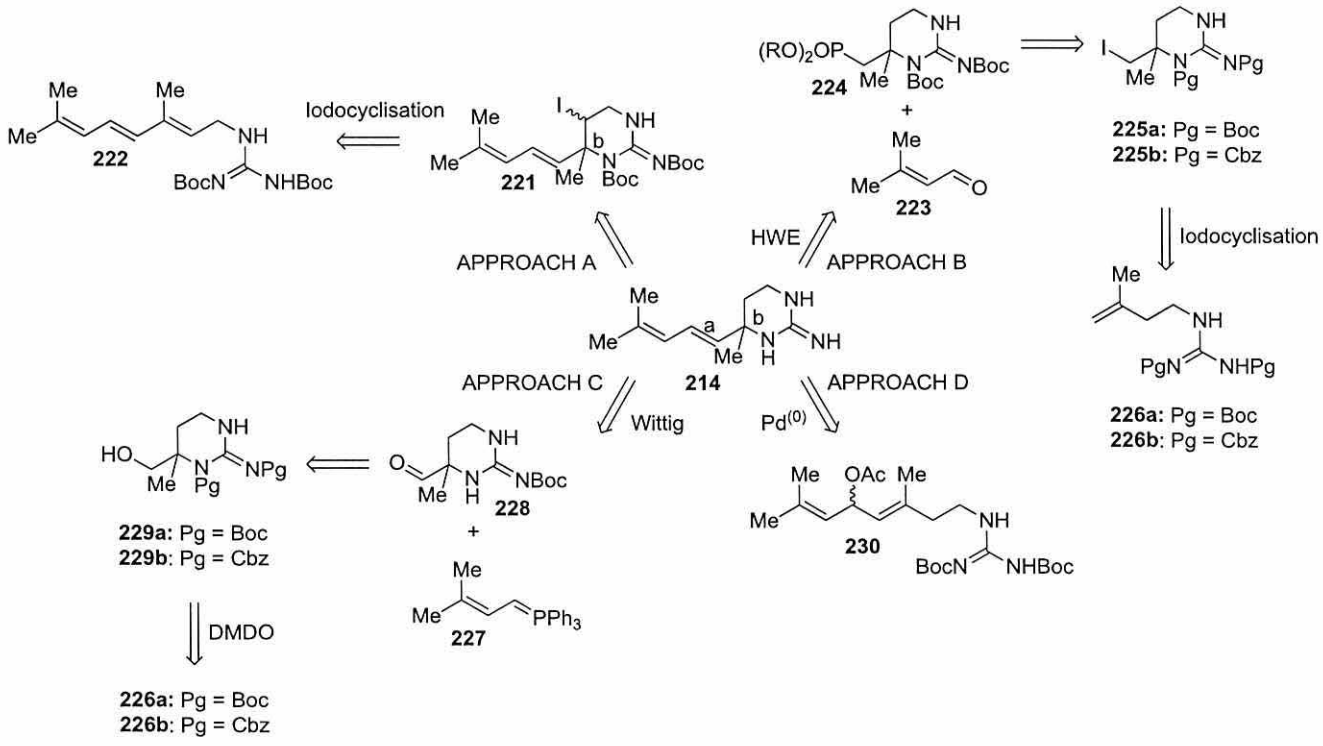


Figure 15: Structures of guanidines isolated from *Pterogyne nitens*.

We propose four possible synthetic approaches for the formation of nitensidine E **214**, the most structurally complex of these metabolites (Scheme 47). All four retrosynthetic analyses focus on a disconnection at the ring junction with the method of construction of, or the elongation of the side chain, being the key modifications. Retrosynthetic approach **A** relies upon the 6-endo-trig cyclisation of the triene **222**, which will introduce all the structural features required for the synthesis in one step but will require a deiodination step. Approach **B** relies upon the HWE reaction of phosphonate **223** with aldehyde **224**. The required phophonate precursor **225a** could be accessed from the iodocyclisation of guanidine **226a**. Approach **C** reverses this alkene-forming step by employing a Wittig reaction of aldehyde **228** with phosphonate **227**. The aldehyde **228** could be obtained *via* the DMDO cyclisation of guanidine **226a** proposed in pathway **B**. Approach **D** is the most ambitious route to this metabolite **214** and relies upon a π-allyl type palladium catalysed cyclisation reaction of homo-allyl substituted guanidine **230**.

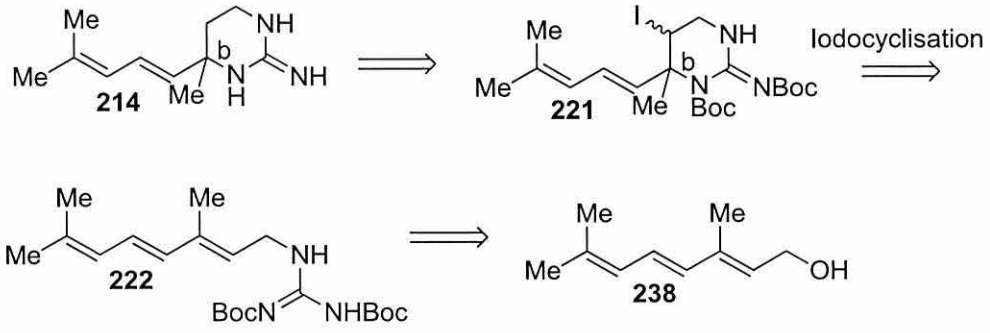


Scheme 47: Retrosynthetic analysis of nitensidine E **214**.

Results and Discussion

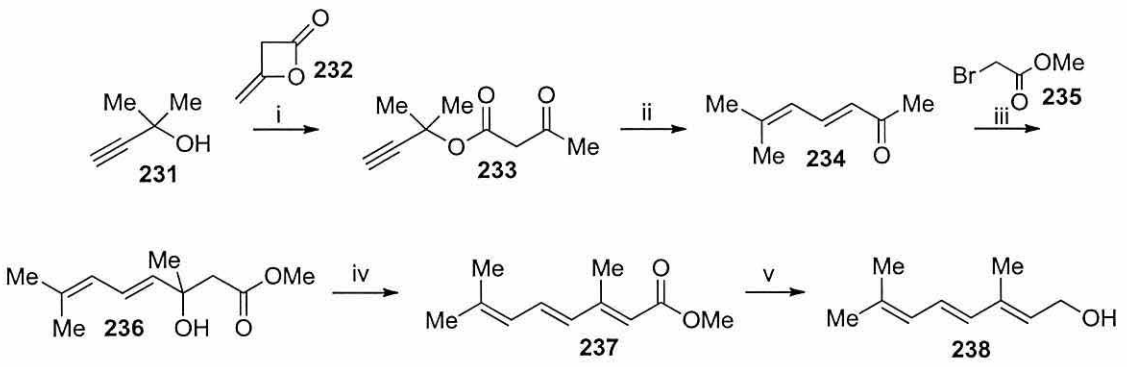
Approach A1: Iodocyclisation and deiodination

Initially we envisaged the synthesis of the most structurally complex of these compounds. Nitensidine E **214** could be achieved *via* a heterocyclisation of the type previously investigated in these laboratories, followed by a reductive deiodination. This retrosynthetic analysis (disconnecting at b) leads back to the allyl substituted guanidine **222** which in turn should be accessible from the alcohol **238** (Scheme 48).



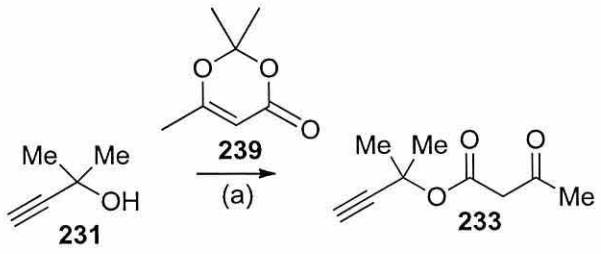
Scheme 48: Retrosynthesis of target compound **214**.

The alcohol **238** is known in the literature[82] and Richard *et al.*[83] reported that it could be prepared from alcohol **231** in 5 steps. Thus, reaction of **231** with Et_3N and diketene leads to the β-keto ester **233** in 98% yield,[84] which on heating with *p*-toluene sulfonic acid gave the ketone **234** in 54% yield. Reformatsky reaction of **234** with bromoester **235** gave the alcohol **236** in 90% yield, which in turn was dehydrated to give ester **237** in 86% yield. Reduction of ester **237** had been reported by Cardillo *et al.*[82] using $LiAlH_4$ to give the desired alcohol **238** in 90% yield (Scheme 49).



Scheme 49: (i) Et_3N (0.2%), then **232**, 70 °C, 98%; (ii) pTSA, Δ, 170-180 °C, 3 h, CH_3COONa, 54%; (iii) PhH, **234**, Zn, Et_2O, Δ, 3 h, 90% ; (iv) pTSA, PhH, Δ, 1 h, 86%; (v) $LiAlH_4$, E_2O, -10 °C, 0.5 h, 90%.

On embarking on this synthetic route, it was found that preparation of the keto ester **233** from diketene was not possible, as this reagent has been discontinued from major suppliers owing to its high toxicity and instability leading to polymerisation during transport and storage.[85] We thus prepared **233** *via* an alternate method reported by Carroll,[86] which involved the use of 2,2,6-trimethyl-1,3-dioxen-4-one **239** and is a masked 1,3-dicarbonyl equivalent and is acting as diketene surrogate. Thus the alcohol **231** was first stirred with NaH to form an alkoxide salt which was then treated with **239** and stirred overnight at rt.[87] Following work up and purification, the β-keto ester **233** was formed in 61-64% yield over 4 attempts (Scheme 50).

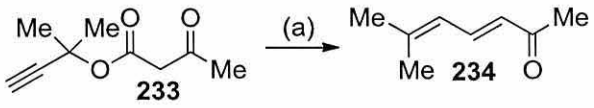


Scheme 50: (a) NaH, then **239**, rt, 16 h, 61-64%.

Keto ester **233** gave diagnostic ^1H NMR spectrum signals at δ 1.67 (6H, s) and 2.25 (3H, s) ppm for the methyl protons together with signals at δ 2.55 (1H, s) ppm for the alkyne proton and δ 3.38 (2H, s) ppm for the methylene protons. The ^{13}C NMR spectrum also showed methyl carbon signals at δ 28.6 and 29.9 ppm, a methylene carbon at δ 50.7 ppm. The alkyne CH signal was present at δ 83.9 ppm, whilst

diagonistic quaternary signals at 165.3 and 200.4 ppm were observed for the ester and ketone quaternaries. This data was in close agreement with the literature. [86]

With the ester **233** in hand, we next investigated its pyrolysis in the presence of a catalytic amount of *p*-toluenesulfonic acid employing the reaction conditions reported in the literature[84] (Entry 1, Table 4). Upon cooling to rt the reaction was distilled under reduced pressure with anhydrous sodium acetate to give the ketone 6-methylhepta-3,5-dien-2-one **234** as a mixture of isomers (Scheme 51) in only 6% yield after chromatography. This was somewhat disappointing as the compound appeared to be a mixture of geometric isomers and was very low yielding. On repeating the reaction, consistently poor yields (6-35%) were obtained, even with variations in reaction time and equivalents of *p*-toluenesulfonic acid (Entries 2-6, Table 4). The best yield for this reaction was 35% after distillation, which was much lower than that reported by Richard *et al.*[83] The estimated purity of this material from NMR was at best 50%.



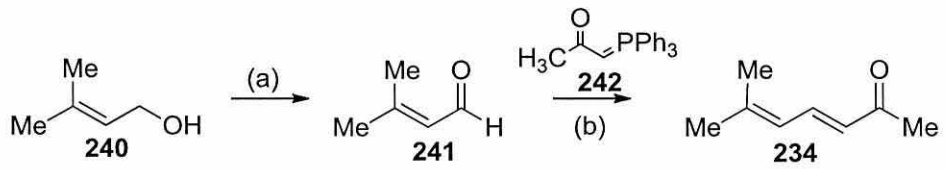
Scheme 51: (a) See Table 4.

Entry	Reaction time (h)	H^+ (equiv.)	Temp.	Estimated Conversion (NMR)	Isolated yield
1	2.5	0.05	170-190 °C	80%	6% (chromatography)
2	3.5	0.02	170-190 °C	80%	14% (chromatography)
3	3	0.02	170-190 oC	80%	13% (distillation)
4	2.5	0.01	170-190 °C	76%	31% (distillation)
5	4	0.01	170-190 °C	80%	35% (distillation)
6	3	0.03	170-190 °C	80%	11% (distillation)
7	3	0.04	170-190 °C	76%	10% (distillation)

Table 4: Reaction conditions employed to optimise the preparation of ketone **234**.

This synthetic route to this ketone was not as straightforward as Richard *et al.*[83] reported, as he achieved an overall yield of 54%, whilst our best was 35% with very low purity as indicated by NMR. It was also apparent that the ketone **234** once formed was not stable over long periods as considerable decomposition occurred on storage. The reason for this instability has not been investigated fully but dienes are known to be prone to acid catalysed polymerisation.[88]

These difficulties led us to consider another approach using Wittig chemistry. We proposed that Swern oxidation[89] of the commercially available alcohol **240**, followed by Wittig reaction of the aldehyde **241** with phosphorane **242** should lead to the desired alkene **234** (Scheme 52).



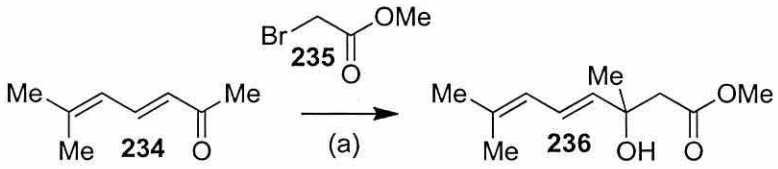
Scheme 52: (a) DCM, DMSO, CO_2Cl_2, -78 °C, 1.5 h, Et_3N, 30 min, rt, 24 h, 17-44%.

The Swern oxidation of alcohol **240** was accomplished by addition of a solution of the alcohol **240** in DCM to a cooled (-78 °C) solution of CO_2Cl_2 and DMSO, followed by the addition of Et_3N to give after work up a quantitative yield of the aldehyde **241** as determined by NMR. Aldehyde **241** was the treated with phosphorane **242** to give after work up and chromatography, the required ketone **234** in high purity but in mediocre yields ranging between 17 and 44% over four attempts.

Inspection of the ^1H NMR spectrum showed the presence of the signals at δ 1.90 (3H, s), 1.92 (3H, s) and 2.28 (3H, s) ppm for the three methyl groups. The alkene signals were found at δ 5.96 (1H, d, J = 11.3 Hz), 6.07 (1H, d, J = 15.1Hz) and 7.42 (1H, dd, J = 11.3, 15.1 Hz) ppm confirming the presence of the diene. The ^{13}C NMR spectrum also gave diagnostic signals at δ 24.6, 27.4 and 30.9 ppm for the methyl groups together with alkene CH signals at δ 124.1, 128.1 and 139.7 ppm and the quaternary signal 197.7 ppm for the carbonyl group.

Having successfully prepared ketone **234**, albeit in low yield, the synthesis of alcohol **236** was undertaken using the Reformatsky reaction[83] of **234** with bromoester **235** (Scheme 53). Thus, a solution of the ketone **234** and methyl bromoacetate **235** in

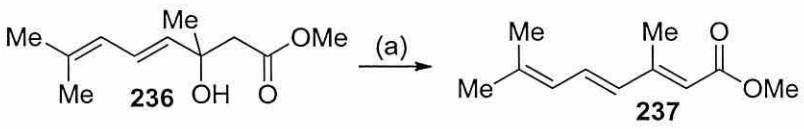
benzene was added dropwise to a stirred refluxing suspension of zinc in dry Et_2O. The reaction was heated to reflux for 3 h and after cooling to rt, the mixture was subjected to an aqueous workup and the crude material purified by column chromatography on silica gel. This gave the desired alcohol **236** in yields ranging between 17 and 53% over four attempts.



Scheme 53: (a) PhH, **235**, Zn, Et_2O, Δ, 3 h, 17-53%

Identification of the resultant alcohol **236** was confirmed by the presence of a diagnostic broad OH stretch in the IR spectra at 3479 cm^{-1}. Further confirmation was achieved by the observation in the ^1H NMR spectrum which showed a signal at δ 3.60 (3H, s) ppm for the methyl ester group together with a signal at δ 2.49 (2H, s) ppm for the methylene group. The alkene protons signals were found at δ 5.61 (1H, d, J = 15.4 Hz), 5.80 (1H, d, J = 11.0 Hz) and 6.49 (1H, dd, J= 11.0, 15.4 Hz) ppm confirming the presence of the diene. The ^{13}C NMR spectrum gave signal at δ 51.8 ppm for the methyl ester together with signal at δ 44.5 ppm for the methylene group. Alkene CH signals were observed at δ 123.2, 123.5 and 134.9 ppm and the quaternary signals at 71.0 and 173.0 ppm were from the carbon attached to the alcohol and the carbonyl carbon respectively.

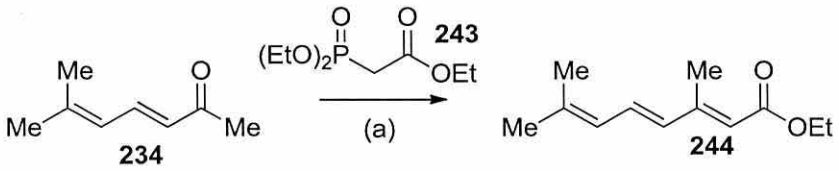
The next step in the synthetic sequence involved the dehydration of alcohol **236** in the presence of *p*-toluene sulfonic acid in benzene to give ester **237**. A mixture of **236** and pTSA in benzene was heated to reflux until TLC analysis (ca 1.5 h) indicated no starting material was present. After work up and purification the desired ester **237** was obtained, however only in mediocre yields ranging between 21 and 41% over four attempts (Scheme 54).[83]



Scheme 54: (a) pTSA, PhH, Δ, 1.5 h, 21-41%.

The structure of triene **237** was identified using ^{1}H NMR which gave the alkene proton signals at δ 5.75 (1H, s) and 5.96 (1H, d, J = 11.3 Hz), 6.16 (1H, d, J= 15.4 Hz) and 6.83 (1H, dd, J = 11.3, 15.4 Hz) ppm, confirming the presence of the triene unit. The ^{13}C NMR spectrum gave signals at δ 117.2, 125.0, 125.7 and 132.7 ppm for the alkene CH groups and a quaternary signal at δ 166.6 ppm for the ester carbonyl group.

In an effort to improve this process to an acceptable yield, a HWE reaction[90] between ketone **234** and triethyl phosphonoacetate **243** was then investigated. Thus, a THF suspension of NaH was cooled (0 °C) and treated with commercially available triethyl phosphonoacetate **243**. After stirring for 10 min at 0 °C, a solution of ketone **234** in THF (1 mL) was then added. The reaction was stirred at rt over 16-24 h, and subjected to an aqueous workup followed by purification of the resultant material by column chromatography on silica gel to give the desired ester **244** in yields ranging between 20 and 47% over ten attempts (Scheme 55).

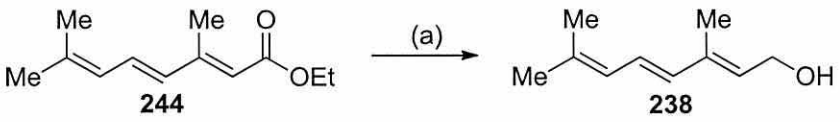


Scheme 55: (a) NaH, THF, 0 °C-rt, 16-24 h, 20-47%.

Inspection of the ^{1}H NMR spectrum of **244** showed the presence of signals at δ 1.29 (3H, t, J = 7.1 Hz) and 4.17 (2H, m) ppm for the ethyl group of ester. This together with alkene signals at δ 5.74 (1H, s), 5.96 (1H, d, J =11.1 Hz), 6.16 (1H, d, J =15.2 Hz) and 6.83 (1H, dd, J = 11.1, 15.2 Hz) ppm confirmed the presence of the triene unit. The ^{13}C NMR spectrum also gave diagnostic signals at δ 14.3 (CH_3) and 59.5 (CH_2) ppm for the ethyl ester as well as signals at δ 116.1, 125.3, 126.1 and 133.1 ppm for the alkene CH carbons with the quaternary signal at δ 167.3 ppm representing the ester carbonyl group.

Despite the problems encountered in the synthesis of the triene ester **244** sufficient amounts were available to investigate the reduction and thus ester **244** was reduced to the alcohol **238** by treatment with DIBAL in toluene at -78 °C. After 3 h, TLC analysis indicated the complete consumption of ester **244** and the reaction mixture was quenched by the slow addition of methanol, Rochelle's salt was then

added slowly, and after dilution with Et_2O the mixture was stirred at rt until the solution cleared. Extraction and purification by column chromatography gave the desired alcohol **238** in yields ranging between 10 and 34% over six attempts (Scheme 56).

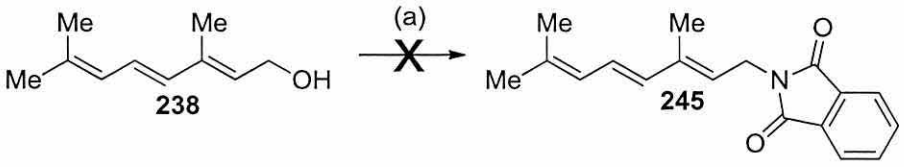


Scheme 56: (a) DIBAL, toluene,-78 °C-0 °C, 3 h, 10-34%.

The ^1H NMR spectrum of the alcohol **238** indicated that the ethyl ester proton signals were no longer present and a new signal was at δ 4.30 (2H, d, J = 6.7 Hz) ppm corresponding to the methylene group. This together with the alkene proton signals at δ 5.65 (t, 1H, J = 6.7 Hz, CH), 5.90 (d, 1H, J = 10.9 Hz, CH), 6.16 (d, 1H, J =15.3 Hz, CH), 6.46 (dd, 1H, J = 10.9, 15.3 Hz, CH) ppm confirmed the presence of the triene unit. The ^{13}C NMR spectrum also showed a signal at δ 59.5 ppm for the methylene group and signals at δ 125.3, 125.4, 128.9 and 134.0 ppm for the alkene CH carbons. IR spectroscopy gave a band at 3337 cm^{-1} corresponding to the hydroxyl group. Additionally, inspection of the ESI mass spectrum of the alcohol **238** gave an observed mass of 151.1114 Daltons corresponding to the formula $C_{10}H_{15}O$ $[M-H]^+$ requiring 151.1117 Daltons.

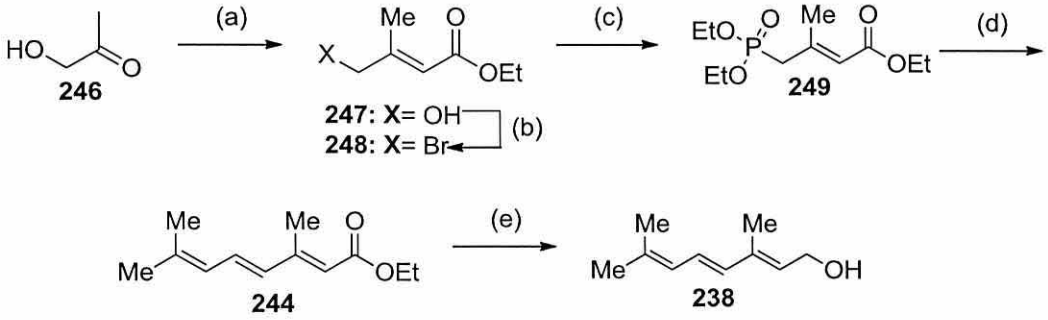
The overall route to the alcohol **238** was not as efficient as the literature[82,83] route suggested which reported an overall yield of 37% over five steps. In our hands, the repeat of the literature route gave an overall yield of 0.15-1.7%, whilst our Wittig/HWE gave a slightly improved overall yield of 0.34-7.0 %. Both these methods were deemed irreproducible and some doubt must be put on the literature methods.

Despite this and with alcohol **238** in hand it was treated with PPh_3 and phthalimide in anhydrous THF at 0 °C in the presence of DEAD for 3 h[91,92] at which point TLC analysis indicated the complete consumption of alcohol **238**. After aqueous workup and column chromatography on silica gel there was no direct NMR evidence for the formation of the desired phthalimide **245** (Scheme 57).



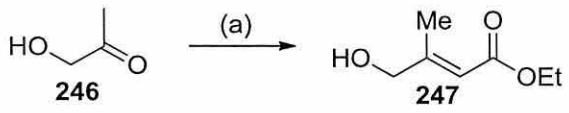
Scheme 57: (a) PPh_3, phthalimide, THF, 0 °C, DEAD, stir 3 h.

This reaction was surprising as we have previously been successful in achieving this transformation on simpler alcohols and were at a loss to explain this result. With the numerous problems encountered in the synthesis of alcohol **238** and the failure of the amination reaction, we wished to modify our synthetic route to one that would lead to a more efficient convergent methodology. Since we had been unsuccessful at preparing the amine for the above synthesis, we decided to test the different methodology reported in the literature[93] in which the desired alcohol **238** was prepared from ketone **246** in five steps (Scheme 58).



Scheme 58: (a) $Ph_3P{=}CHCO_2Et$, MeCN, 12 h, 82 °C, 74%; (b) CBr_4, PPh_3, MeCN, rt, 24 h, 80%; (c) $(EtO)_3P$, 2.5 h, 120 °C, 47%; (d) DMPU, *n*-BuLi, THF, 0 °C, stir, 40 mins, -78 °C, **250**, stir, 2 h, rt, 24 h, 60%; (e) DCM, -78 °C, 2 h, DIBAL, 40%.

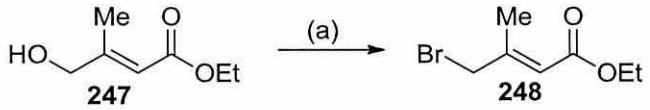
The starting point of the above synthesis is the commercially available hydroxyacetone **246**, which on reaction with the stabilized phosphorane $Ph_3P{=}CHCO_2Et$ in MeCN gave the allylic alcohol **247** in 74% yield after chromatography (Scheme 59).[93]



Scheme 59: (a) $Ph_3P{=}CHCO_2Et$, MeCN, Δ, 12 h, 74%.

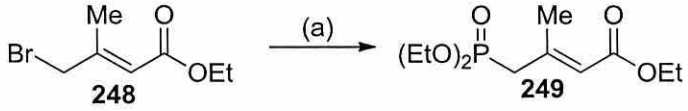
The ^{1}H NMR of ester **247** spectrum showed signals at δ 1.24 (3H, t, J = 7.1 Hz), 2.03 (3H, s) and 4.11 (4H, m) ppm representing the methyl and methylene groups. The alkene proton signal was found at δ 5.93 (1H, m) ppm. The ^{13}C NMR spectrum gave signals at δ 14.2 and 15.5 ppm for the methyl groups together with signals at δ 59.7 and 66.8 ppm for the methylene groups. Signals at δ 113.5 and 157.6 ppm correspond to the alkene C and CH carbon whilst the quaternary carbon atom signal at δ 167.1 ppm corresponds to the ester carbonyl group. This data was in agreement with the literature. [93]

Reaction of alcohol **247** with PPh_3 and CBr_4 in dry MeCN at 0 °C for 24 h gave the bromide **248** in 80% yield (Scheme 60).[93]



Scheme 60: (a) PPh_3, MeCN, CBr_4, 0 °C- rt, 24 h, 80%.

The structure of bromide **248** was identified using the ^{1}H NMR spectrum, which gave a new signal at δ 3.92 (2H, s), and in the ^{13}C NMR spectrum a new signal at δ 38.2 ppm for the CH_2Br group. Following this, reaction of bromide **248** with neat triethyl phosphite under reflux for 2.5 h led to the formation of the desired *E*-phosphonate ester **249** in 47% yield (Scheme 61).[93]

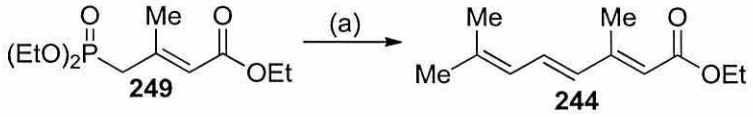


Scheme 61: (a) $(EtO)_3P$, Δ, 2.5 h, 47%.

The ^{1}H NMR spectrum displayed signals at δ 1.28 (3H, t, J = 7.1 Hz), 1.33 (6H, t, J = 7.1 Hz) and 2.31 (3H, dd, J_{PH} = 3.4 and J_{HH} = 1.0 Hz) ppm representing the methyl protons together with signals at δ 2.69 (2H, d, J_{PH} = 23.4 Hz) and 4.16 (6H, m) ppm for the methylene protons. The alkene proton signal was found at δ 5.79 (1H, broad d, J_{PH} = 5.2 Hz) ppm. The ^{13}C NMR spectrum showed signals at δ 14.2, 16.3 (2C, d, $^{3}J_{PC}$ = 6.0 Hz) and 18.1 (d, $^{3}J_{PC}$ = 2.6 Hz) ppm for the methyl groups as well as signals at δ 39.2, 61.4 (d, $^{1}J_{PC}$ = 134.6 Hz) and 62.2 (2C, d, $^{2}J_{PC}$ = 6.7 Hz) ppm for the methylene groups. The alkene signals were found at δ 120.1 (d, $^{3}J_{PC}$ = 11.8 Hz) ppm

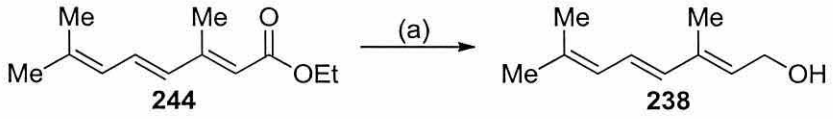
and δ 149.5 (C, d, $^{2}J_{PC}$ = 10.9 Hz) ppm. The quaternary carbon atom signal at δ 166.0 (d, $^{4}J_{PC}$ = 3.6 Hz) ppm corresponded to the ester carbonyl group. This data was in agreement with the literature.[93]

Having successfully prepared *E*-phosphonate ester **249**, the preparation of ester **244** was undertaken using a HWE reaction. Thus, a solution of **249** in dry THF was cooled to 0 °C and treated with DMPU and *n*-BuLi, the reaction mixture was stirred at 0 °C and allowed to stir for 40 min. The reaction mixture was then cooled to -78 °C, followed by the dropwise addition of 3-methyl-2-butenal **250**. After stirring at -78 °C for 2 h, the reaction was warmed to 0 °C and after 24 h, TLC analysis indicated the complete consumption of ester **249**. The excess *n*-BuLi was destroyed by the careful addition of a 5% aqueous solution of NH_4Cl to pH 7-8 and the mixture was extracted with EtOAc. Purification was achieved by column chromatography on silica gel to give the desired ester **244** in 60% yield (Scheme 62).[93] Inspection of the NMR spectra obtained indicated complete agreement with the previously reported data.



Scheme 62: (a) DMPU, *n*-BuLi, THF, 0 °C, stir, 40 min, -78 °C, **250**, stir, 2 h, rt, 24 h, 60%.

Having accomplished the preparation of ester **244**, reduction of the ester functionality directly to the corresponding alcohol **238** was undertaken. Thus a solution of ester **244** in dry DCM was cooled to -78 °C and treated with DIBAL (Scheme 63).[93]



Scheme 63: (a) DIBAL, DCM, -78 °C, 2 h, 40%.

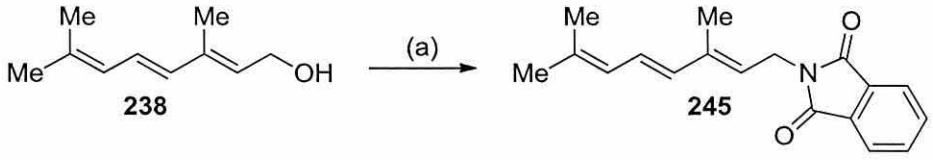
The addition of DIBAL to the cooled reaction mixture was achieved in a dropwise manner and the progress of the reduction followed carefully by TLC. After 2 h, ester **244** was no longer detectable by TLC, and the reaction was quenched by the

dropwise addition of MeOH and then EtOAc followed by dilution with Et_2O. At this point, a saturated solution of Rochelle's salt was added to sequester any unwanted aluminium salts, and the reaction mixture stirred at rt until the solution cleared. After separation and column chromatography on silica gel the desired alcohol **238** in a 40% yield. Inspection of the NMR spectra obtained indicated complete agreement with the previously reported data.

Unfortunately, it was found that the desired alcohol **238** was not stable over a long period, and considerable decomposition occurred on storage. The nature of this instability was not readily apparent but trienes are prone to acid catalysed polymerisation[88] and aerial oxidation[94] as well as the potential for dimerisations (Diels-Alder) and other sigmatropic processes.[95]

Despite these problems, the alcohol **238** was obtained in five steps from ketone **246** in an overall yield of 7%.

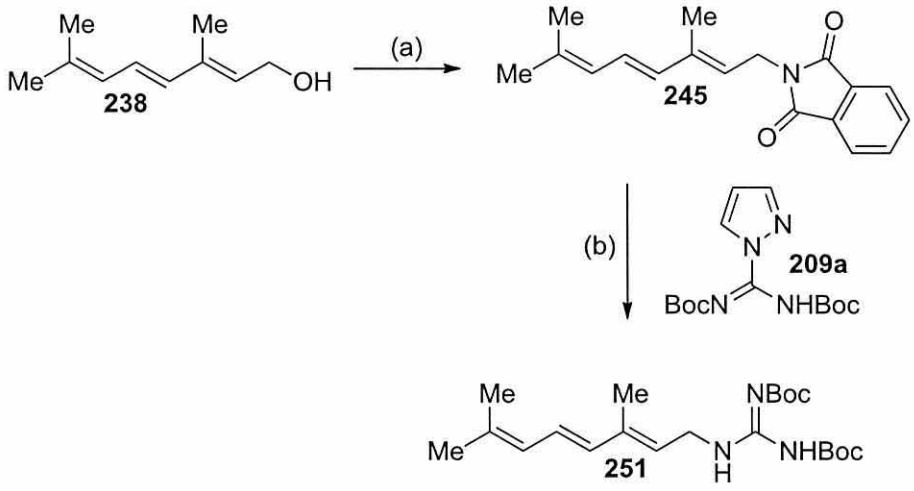
We next attempted to prepare the phthalimide derivative **245** directly from alcohol **238** under Mitsunobu conditions. Thus, reaction of alcohol **238** with phthalimide in the presence of PPh_3 and DIAD in THF gave the phthalimide **245** (Scheme 64). It became apparent on purification that the crude phthalimide **245** thus obtained could not be purified by column chromatography, as it appeared to undergo decomposition on silica gel. Again, we have not studied the decomposition but the reactivity of the triene portion of the molecule might be to blame for this instability. We proceeded to the next step of the synthesis using crude **245**.



Scheme 64: (a) PPh_3, phthalimide, THF, DIAD, 0 °C, stir 2 h.

The crude phthalimide **245** was treated with ethylenediamine in pure EtOH and the mixture was then heated under reflux for 3 h.[96] The reaction progress was followed by TLC. Upon consumption of the phthalimide **245** the reaction mixture was cooled to rt. Filtration to remove the solid by-product gave a solution of amine, which was treated with Et_3N and the commercially available guanylating agent **209a**. After stirring for 24 h, the reaction mixture was concentrated and the residue purified by

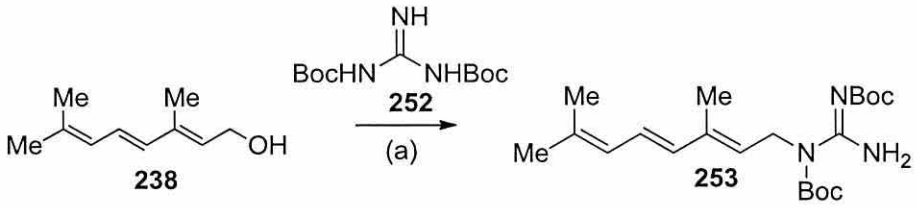
column chromatography. This gave the desired bis-Boc protected guanidine **251** in a 12% yield over three steps (Scheme 65).



Scheme 65: (a) PPh_3, phthalimide, THF, DIAD; (b) i) ethylenediamine, EtOH, reflux, 3 h, (ii) Et_3N, **209a**, rt, 16-24 h, 12%.

Inspection of the ^1H NMR spectrum showed the presence of signals associated with the Boc protecting groups of guanidine **251** which appeared as two singlets at δ 1.50 (s, 9H) and 1.52 (s, 9H) ppm together with signals at δ 1.80 (3H, s), 1.82 (3H, s) and 1.84 (3H, s) ppm for three methyl protons. The signal for the methylene protons appeared as an apparent triplet at δ 4.17 (apparent t, 2H, J = 7.1 Hz) ppm which is indicative of coupling to the adjacent vinylic and NH protons. The alkene proton signals were observed at δ 5.48 (t, 1H, J = 7.1 Hz), 5.88 (d, 1H, J = 11.0 Hz), 6.14 (d, 1H, J = 15.3 Hz) and 6.44 (dd, 1H, J = 11.0, 15.3 Hz) ppm which confirmed the presence of the triene. The ^{13}C NMR spectrum showed signals at δ 27.0 and 27.2 ppm representing the *t*-butyl methyl groups and 78.3 and 82.0 ppm corresponding to the *t*-butyl quaternary carbon atoms, as well as a signal at δ 38.2 ppm for the methylene group together with signals at δ 123.7, 124.1, 124.3 and 132.6 ppm for the alkene CH. The three most downfield signals of the spectrum appeared at δ 152.2, 154.8 and 162.5 ppm representing the indicative guanidine quaternary carbon atom and two Boc-carbonyl atoms respectively.

As this was a poor yield, we took the alternate approach of reacting alcohol **238** with 1,3-bis(tert-butoxycarbonyl) guanidine **252** under Mitsunubu conditions.[97] Thus reaction of alcohol **238** with PPh_3 and DIAD in THF gave the isomeric guanidine **253** in 35% yield (Scheme 66).



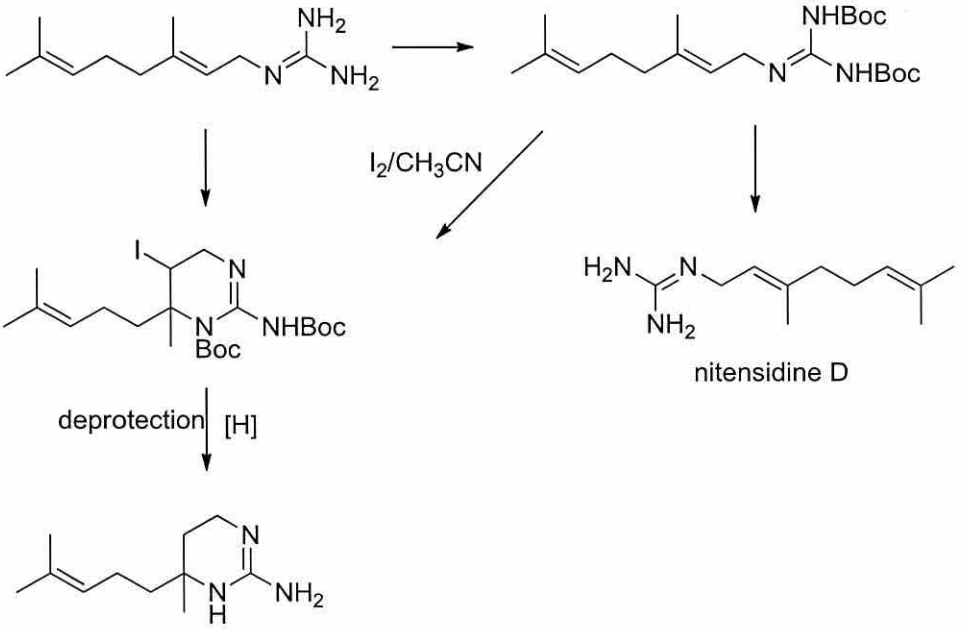
Scheme 66: (a) PPh_3, **252**, THF, 0 °C, DIAD, rt, 16-24 h, 35%.

Inspection of the ^1H NMR spectrum showed the presence of signals associated with the Boc protecting groups of guanidine **253** which appeared as two singlets at δ 1.49 (s, 9H) and 1.49 (s, 9H) ppm together with signals at δ 1.80 (3H, s), 1.83 (3H, s) and 1.86 (3H, s) ppm for three methyl protons. The signal for the methylene protons in this compound appeared at lower field, δ 4.71 (d, 2H, J = 6.6 Hz) ppm and appeared as a doublet indicating that the adjacent nitrogen bore a Boc-protecting group. The alkene proton signals were observed at δ 5.39 (t, 1H, J = 6.6 Hz), 5.88 (d, 1H, J = 10.8 Hz), 6.13 (d, 1H, J = 15.2 Hz) and 6.40 (dd, 1H, J = 10.8, 15.2 Hz) ppm which confirmed the presence of the triene. In the ^{13}C NMR spectrum signals were evident at δ 27.0 and 27.2 ppm 77.7 and 82.7 ppm corresponding to the *t*-butyl quaternary carbon atoms, as well as a signal at 42.2 ppm for the methylene group together with signals at δ 123.2, 124.5, 126.1 and 133.2 ppm for the alkene CH. The three most downfield signals of the spectrum appeared at δ 154.0, 159.4 and 162.7 ppm representing the indicative guanidine quaternary carbon atom and two Boc-carbonyl atoms respectively.

The overall outcome of this reaction sequence was quite disappointing, and as with the alcohol **238**, it was apparent that on standing in the NMR solvent or on prolonged storage in the freezer at -20 °C considerable decomposition was occuring. Our overall conclusions from this chemistry are that the triene substituted guanidines, phthalimides and alcohols are in general unstable to prolonged storage. The exact nature of this instability is not known, and the spectral of the decompositions products are complex in nature, however acid catalysed polymerisation or electrocyclic type dimerisations or rearrangements might be occurring.

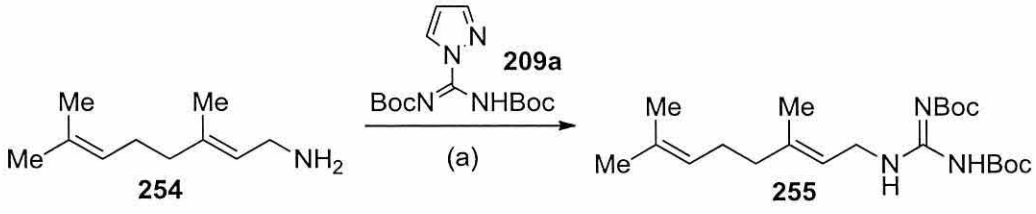
Approach A2: Cyclisation of a nitensidine E analogue

Whilst the synthesis of the triene **251** was in progress we investigated the preparation of the related natural product nitensidine D as it was felt that the cyclisation and deprotection of this would give an insight into the chemistry required to cyclise **251** (Scheme 67).



Scheme 67: Preparation of the related natural product nitensidine D and the iodocyclisation approach.

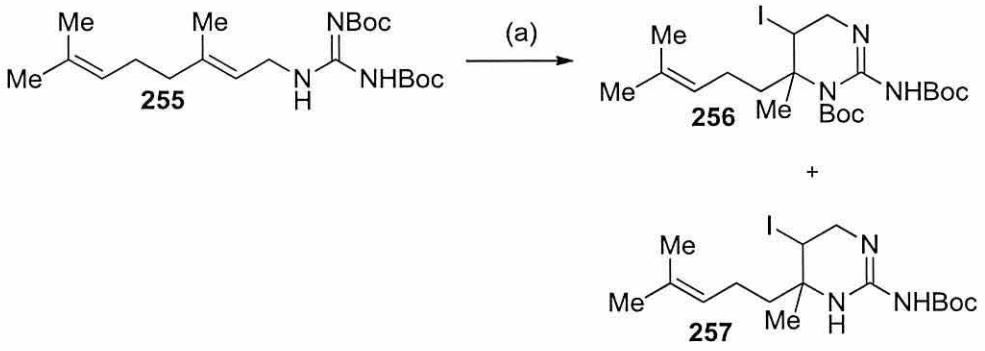
Geranylamine **254** is commercially available and was reacted with *N,N'*-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine **209a**[98] in MeCN. After purification by column chromatography the required protected guanidine **255** was obtained in 64% yield as a white solid (Scheme 68).



Scheme 68: (a) CH_3CN, stir, rt, 24 h, 64%.

Inspection of the ^{1}H NMR spectrum showed diagnostic signals at δ 1.42 (9H, s) and 1.44 (9H, s) ppm for the Boc-protecting groups of guanidine **255** together with signals at δ 1.53 (3H, s), 1.59 (3H, s) and 1.61 (3H, s) ppm for the methyl protons. In addition, there were signals at δ 1.98 (4H, m) and 3.96 (2H, t, J = 6.1 Hz) ppm for the methylene protons, with signals at δ 5.00 (1H, t, J = 6.4 Hz) and 5.16 (1H, t, J = 6.1) ppm for the alkene protons. The ^{13}C NMR spectrum showed signals at δ 28.0, 28.2, 79.2 and 82.9 ppm for the methyls and quaternary carbons of the Boc-protecting groups, with signals at δ 26.3, 39.1 and 39.5 ppm for the methylene groups. Signals at δ 119.1 and 123.8 ppm corresponded to the alkene CH, and the quaternary carbon atom signals at δ 153.2, 155.8 and 163.6 ppm represented the guanidine and two Boc carbonyl groups respectively. Accurate mass spectrometry confirmed the structure as mass of 396.2858 Daltons was obtained, which corresponds well with the expected value of 396.2857 Daltons.

Having introduced the required bis-Boc-guanidine functionality, the iodocyclisation reaction[99] was undertaken. Thus a solution of the guanidine **255** in dry MeCN was treated with iodine and the mixture was stirred at rt over 16-24 h, then sodium thiosulphate solution (aq., sat.) was added until decolourisation occurred. The reaction mixture was then diluted with water, extracted with EtOAc and the combined organic phases dried ($MgSO_4$), filtered and evaporated *in vacuo* to give crude **256**, which was dissolved in Et_2O and diluted with petroleum ether to the cloud point. After cooling (-20 °C) for a week the mono-protected cyclic guanidine **257** precipitated and was obtained as a yellow gum in 6% yield after decanting the mother liquor. Further dilution of the decanted mother liquor with petrol and standing overnight in the freezer gave a precipitate of the bis-protected cyclic guanidine **256** as yellow gum in 65% yield. Attempted purification of these compounds by silica gel chromatography was unsuccessful as the compounds decomposed, which was thought to be due to the loss or rearrangement of the Boc protecting groups, as has been observed in previous work within the group (Scheme 69).



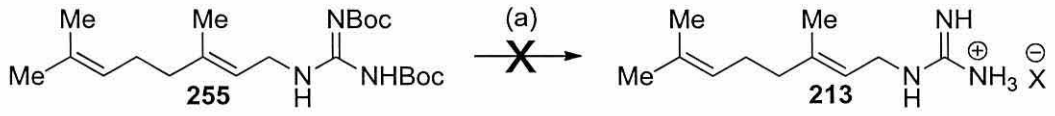
Scheme 69: (a) I_2, CH_3CN, -15°C - rt, 16-24 h, **256**: 65%; **257**: 6%.

Inspection of the ^1H NMR spectrum of guanidine **256** gave diagnostic singlets for the Boc-protecting groups at δ 1.49 (9H, s) and 1.51 (9H, s) ppm together with signals at δ 1.60 (3H, s), 1.66 (3H, s), 1.68 (3H, s) and 2.08 (4H, m) ppm for the methyl and methylene protons respectively. Signals were observed at δ 3.85 (1H, dd, J = 13.9, 9.0 Hz) and 3.97 (1H, dd, J = 13.9, 4.8 Hz) for the methylene protons of the heterocycle together with a signal at δ 4.25 (1H, dd, J = 9.0, 4.8 Hz) ppm for the expected ring CHI proton. The alkene proton signal was observed at δ 5.23 (1H, t, J = 6.9 Hz) ppm. The ^{13}C NMR also gave signals at δ 28.0 and 28.2 ppm for the Boc protecting groups together with a signal at δ 45.5 ppm for the methylene group of the heterocycle and at δ 44.5 ppm for the ring CHI group. A signal at δ 123.7 ppm corresponded to the alkene CH whilst the quaternary carbon signals of Boc appeared at δ 79.1 and 82.8 ppm with the Boc carbonyls were present at δ 155.7 and 163.5 ppm. The guanidine quaternary carbon was present at δ 153.1 ppm.

Additionally, analysis of the ^1H NMR spectrum of cyclic guanidine **257** indicated the presence of only one Boc-protecting group evidenced by the signal at δ 1.51 (9H, s) ppm. Other characteristic signals were observed at δ 1.52 (3H, s), 1.64 (3H, s), 1.69 (3H, s) and 1.95 (4H, m) ppm for the methyl and methylene protons respectively. Signals at δ 3.85 (1H, dd, J = 13.8, 8.8 Hz) and 4.04 (1H, dd, J = 13.8, 4.5 Hz) were indicative of the methylene protons on the heterocycle, together with the signal at δ 4.29 (1H, dd, J = 8.8, 4.5 Hz) ppm for the ring CHI proton. The alkene proton signal was observed at δ 5.10 (1H, t, J = 7.2 Hz) ppm. The ^{13}C NMR spectrum also showed signal at 27.8 ppm for the Boc-group together with signal at δ 45.8 ppm for the methylene group of the heterocycle and signal at δ 41.3 ppm for the ring CHI group. The signal at δ 121.6 ppm corresponded to the alkene CH whilst the quaternary carbon signal for the Boc group appeared at δ 85.7 ppm with the carbonyl appearing at

δ 152.6 ppm. The guanidine quaternary carbon signal was present at δ 151.0 ppm. Analysis of the mass spectrum of **256** gave a peak at 522.1818 Daltons which was in excellent agreement with the calculated value of 522.1817 Daltons. Similarly, **257** gave a mass of 422.1300 Daltons, which was in excellent agreement with the calculated mass of 422.1299 Daltons. This result proved in that, in principle, the iodocyclisation was a feasible reaction and that the strategic approach was valid.

Further to this cyclisation, we studied the deprotection of the guanidine **255** and were keen to do this, as it would allow access to the natural product nitensidine D **213** as its salt. Initially, we employed the reaction conditions reported in the literature[100-103] (Entries 1-4, Table 5). Thus, treatment of guanidine **255** with a solution of TFA in DCM (Scheme 70) was expected to give easy access the natural product after deprotection. However, analysis by ^{1}H NMR the product of this reaction indicated cosiderable decomposition and a complete loss of the alkene signals (Entry 1 Table 5). Similarly, when guanidine **255** was treated with a solution of HCl (3M) in MeOH, nitensidine D **213** was also not obtained and only products of decomposition were observed (Entry 2 Table 5). An attempt was made to remove the Boc protecting groups by treatment of guanidine **255** with $SnCl_4$[102] in EtOAc, however this reaction failed to give any evidence of the expected nitensidine D **213** and again mostly decomposed unidentifiable by-products were observed (Entry 3 Table 5).

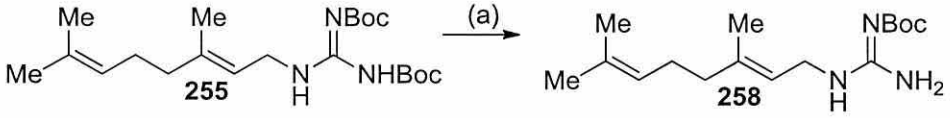


Scheme 70: (a) See Table 5.

Entiry	Reaction conditions[100-103]	Yield
1	TFA/ DCM/ rt/ 24 h	-
2	HCl (3M)/ MeOH/ rt/ 16-48 h	-
3	$SnCl_4$ (4 equiv.)/AcOEt/ rt/ 3 h/ MeOH	-
4	KO*t*Bu (10 equiv.)/ H_2O (2 equiv.)/ THF/ Δ/ 12 h	40%

Table 5: Optimisation of the reaction conditions for the formation of nitensidine D **213**.

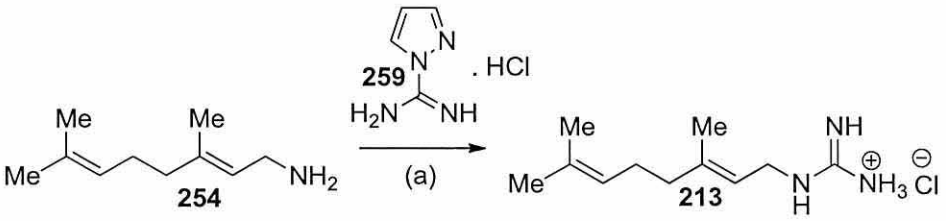
As the acid catalysed methods employed so far were unsuccessful, we attempted the deprotection under basic conditions.[103] Thus, guanidine **255** was treated with excess potassium *t*-butoxide in THF and 2 equivalents of water (Entry 4 Table 5). The reaction was heated to reflux for 12 hours, cooled to rt and subjected to an aqueous workup to give the mono-protected guanidine **258** in 40% yield (Scheme 71).



Scheme 71: (a) See Table 5.

Analysis of **258** by ^{1}H NMR showed that the signal corresponding to the one Boc protecting group was present at δ 1.48 ppm together with signals at δ 1.61 (3H, s), 1.68 (3H, s) and 1.71 (3H, s) ppm for the methyl protons. Signals at δ 2.10 (4H, m) and 3.83 (2H, d, J = 6.4 Hz) ppm for the methylene protons, the alkene proton signals were found at δ 5.10 (1H, t, J = 6.5 Hz) and 5.27 (1H, t, J = 6.4 Hz) ppm. The ^{13}C NMR spectrum also showed signal at δ 27.1 ppm representing the *t*-butyl methyl group and 68.9 ppm corresponding to the *t*-butyl quaternary carbon atom. As well as signals at δ 15.0, 16.4 and 24.5 ppm for methyl groups, there were signals at δ 25.9, 38.7 and 39.1 ppm for the methylene groups. The alkene proton signals were found at δ 107.5 and 123.5 ppm; however, the four quaternary carbon atom signals were not detected due to the small amount of sample used.

Having accomplished only partial deprotection of guanidine **255** under basic conditions, we were proceded to synthesise the required natural product *via* a protecting group free synthesis. Thus, geranylamine **254** was treated with 1*H*-pyrazole-1-carboxamidine hydrochloride **259** and DIPEA in DMF.[104] The reaction mixture was stirred at rt for 48 h while being monitored by TLC. After completion the reaction mixture was then diluted with dry Et_2O to precipitate the product, which was triturated with further dry Et_2O and dried under vacuum to give the natural product nitensidine D **213** in 53% yield as a yellow gum (Scheme 72).



Scheme 72: (a) DIPEA, DMF, stir, rt, 48 h, 53%.

Nitensidine D **213** (NMR **DMSO-d_6, ppm** data)			
Reported[79]		Synthetic	
δ_H J in Hz	δ_C	δ_H J in Hz	δ_C
1.55, s	16.0, CH_3	1.57, s	16.1, CH_3
1.61, s	17.5, CH_3	1.57, s	17.5, CH_3
1.63, s	25.4, CH_3	1.65, s	25.4, CH_3
1.97, m 2.03, s	25.9, CH_2	2.04, m, 4H	25.8, CH_2
3.63, d (6.0)	38.5, CH_2	3.72, t (6.0)	38.6, CH_2
5.07, t (7.0)	38.9, CH_2	5.08, t (6.5)	38.8, CH_2
5.17, t (6.0)	119.6, CH	5.19, t (6.0)	118.7, CH
8.85, brs 7.68, brs	123.8, CH	7.21, brs	123.7, CH
8.85, brs 7.98, brs	130.9, $_qC$	7.71, brs	131.0, $_qC$
	138.3, $_qC$		139.4, $_qC$
	157.6, $_qC$		156.8 $_qC$

Table 6: ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) for Nitensidine D **213** in DMSO-d_6.

Inspection of the ^{1}H NMR spectrum of nitensidine D **213** showed signals at δ 1.57 (6H, s) and 1.65 (3H, s) ppm corresponding to the three methyl protons together with signals at δ 2.04 (4H, m) and 3.72 (2H, apparent t, J = 6.0 Hz) ppm for the methylene protons. The alkene proton signals were found at δ 5.08 (1H, t, J = 6.5 Hz) and 5.19 (1H, t, J = 6.0 Hz) ppm. The ^{13}C NMR spectrum also showed signals at δ 16.1, 17.5 and 25.4 ppm for the methyl groups together with signals at δ 25.8, 38.6 and 38.8 ppm for the methylene groups. The signals at δ 118.7 and 123.7 ppm for alkene

CH and the two quaternary alkene signals were found at δ 131.0 and 139.4 ppm. As well as the quaternary signal at δ 156.8 ppm for guanidine carbon atom. The synthetic data were in close accordance with the reported data (Table 6).[79] The 2-D NMR experiments (DEPT 135, HMQC, COSY and HMBC) shows correlation between the signal at 3.72 (2H, t, J = 6.0 Hz) ppm with the guanidine quaternary signal.

Conclusions on approach A

This approach suffers from several shortfalls, firstly and most importantly, the triene alcohol **238** and guanidine **251** are particularly unstable and prone to considerable decomposition on standing. Added to this, problems associated with deprotection of the Boc protecting groups and the associated decomposition were observed, and it was felt that introduction of the side-chain could be done post formation of the heterocycle. The next approach tested this eventuality and centered on the iodocyclisation and DMDO cyclisation of the guanidine substrates **226a-b**.

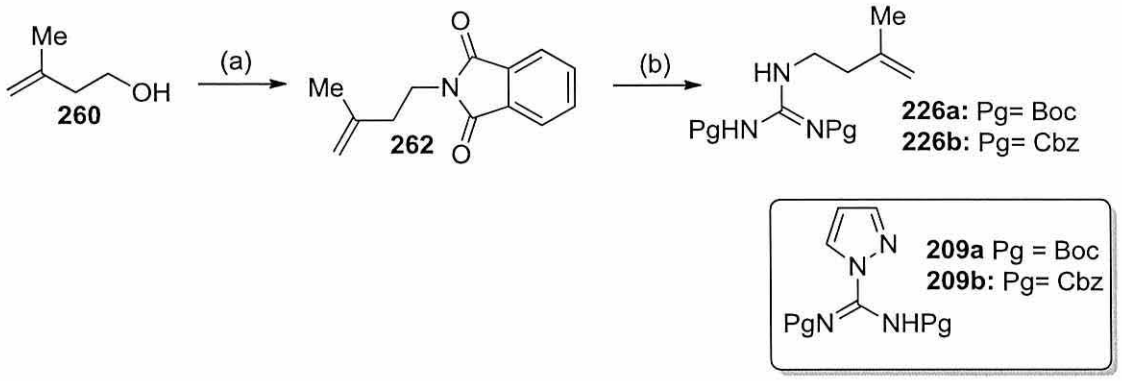
Approach B Iodocyclisation and HWE approach

At the outset to this approach, it was decided to prepare the substrates **226a-b** as both the Boc and Cbz-protected analogues. These guanidines **226a-b** were prepared from the corresponding primary alcohols **260** and phthalimide **261** under Mitsunubu coniditons.[91,92] Thus **260** and **261** were treated with PPh_3 and DEAD in dry THF at 0°C and after work-up gave the phthalimide **262** in 42% yield. This was then treated with hydrazine hydrate in refluxing pure EtOH to remove the phthalimide protecting group. Treatment of the amine thus obtained with Et_3N and the commercially available guanylating agent **209a**, gave the guanidine **226a** in 55% yield after purification by column chromatography (Scheme 73).

Inspection of the ^1H NMR showed the presence of signals associated with the Boc protecting groups of guanidine **226a** which appeared as two singlets at 1.48 and 1.50 ppm. The ^{13}C NMR spectrum gave signals at 28.0 and 28.2 ppm representing the *t*-butyl methyl groups and 79.3 and 82.9 ppm corresponding to the *t*-butyl quaternary carbon atoms. The three most downfield signals of the spectrum appeared at 153.1, 156.0 and 163.8 ppm representing the indicative guanidine quaternary carbon atom and two Boc-carbonyl atoms respectively. The presence of guanidine **226a** was further confirmed by accurate mass spectrometry giving a mass of 328.2234 Daltons, which is in good agreement with the required mass of 328.2231 Daltons.

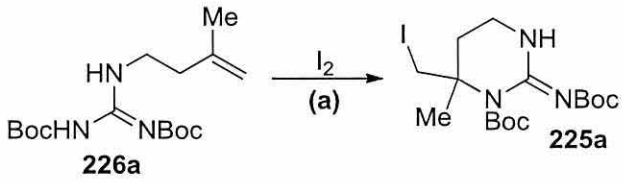
A similar result was observed by treatment of the protected amine **262** with hydrazine hydrate in refluxing pure EtOH to remove the phthalimide protecting group followed by treatment with Et_3N and the commercially available guanylating agent **209b**, with stirring overnight. Purification by column chromatography gave the corresponding guanidine **226b** in 84% yield (Scheme 73).

The ^1H NMR spectrum of the guanidine **226b** showed diagnostic signals at δ 5.17 (2H, s) and 5.19 (2H, s) ppm for the two CH_2 environments of the Z-groups together with signals at 7.30-7.44 ppm corresponding to the phenyl environments of the Z-groups. The ^{13}C NMR spectrum gave signals at δ 67.2 and 68.1 ppm for the CH_2 groups of the two Z-groups as well as signals at δ126.9-128.8 ppm for the 10 carbons of the phenyl groups. There were diagnostic quaternary signals at δ 153.8, 155.9 and 163.7 ppm for the guanidine and Z-carbonyl groups. Accurate mass spectrometry gave a mass of 396.1917 Daltons, which is in close agreement with the required mass of 396.1918 Daltons.



Scheme 73: (a) PPh_3, phthalimide **261**, DEAD, THF, 3 h, 42%; (b) i) $NH_2NH_2.H_2O$, EtOH, reflux, (ii) Et_3N, **209a** or **209b**, rt, 16-24 h, **226a**: 55%; **226b**: 84%.

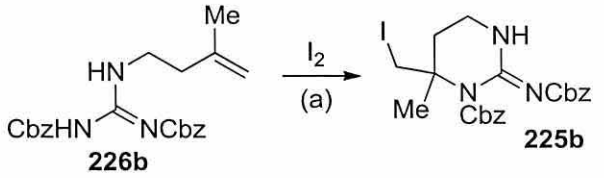
We first attempted the iodocyclisation of the bis-Boc protected guanidine **226a** which was treated with iodine and potassium carbonate in dry MeCN to give the corresponding 6-membered guanidine **225a** as a yellow gum (Scheme 74). Attempted purification of **225a** *via* column chromatography resulted in decomposition and the compound was sufficiently pure to be used in the next step without further purification.



Scheme 74: (a) K_2CO_3, CH_3CN, -15 °C-rt, 16-24 h.

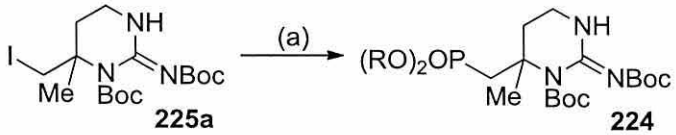
Inspection of the ^1H NMR spectrum showed signals at δ 1.44 and 1.54 (18H, s) ppm for the two *t*-butyl methyl groups of the Boc protecting groups, together with signals at δ 1.90 (1H, ddd, J = 6.0, 10.0, 15.0 Hz), 2.33 (1H, dt, J = 4.7, 15.0 Hz), and 3.31 (2H, m) ppm for the methylene protons of the heterocycle. Signals at δ 3.46 (1H, d, J = 10.7 Hz) and 3.75 (1H, d, J = 10.7 Hz) ppm corresponded to the CH_2I protons. The ^{13}C NMR spectrum gave a signal at δ 12.7 ppm for the CH_2I together with signals representing the *t*-butyl methyl groups, and quaternary carbon atom at δ 27.5, 28.2, 77.9 and 84.0 ppm, respectively. Signals at δ 33.2 and 35.6 ppm for the methylene groups of the heterocycle and gave diagnostic quaternary signals at δ 152.6, 157.1 and 163.6 ppm for guanidine carbon atom and two Boc-carbonyl atoms respectively. The 2-D NMR COSY.b spectra for heterocycle **225a** shows correlations between the proton signals at δ 1.90 and 2.33 ppm, and the two proton signal at δ 3.31 ppm which support the structure of the product. In addition, analysis by accurate mass spectrometry confirmed that the measured mass of 454.1195 corresponded very well to the expected mass of 454.1197 Daltons required for the $[M+H^+]$ ion.

A similar reaction of the bis-Cbz protected guanidine **226b** with iodine in the presence of potassium carbonate led to the cyclic guanidine **225b** in 68% yield. This product could be purified by dissolving the crude in dichloromethane and precipitating **225b** by the addition of petrol. This process gave pure **225b** as a yellow gum (Scheme 75).



Scheme 75: (a) K_2CO_3, CH_3CN, -15 °C - rt, 16-24 h, 68%.

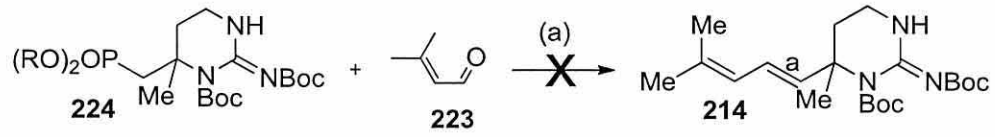
The ^{1}H NMR spectrum of guanidine **225b** had many similarities to the previously prepared Boc protected analogue **225a**, with signals at δ 1.90 (1H, ddd, J = 6.0, 9.0, 13.8 Hz), 2.37 (1H, dt, J = 4.9, 13.8 Hz), 3.33 (2H, m) ppm for the methylene protons of the heterocycle. This together with signals at δ 3.53 (1H, d, J = 10.6 Hz) and 3.73 (1H, d, J = 10.6 Hz) ppm corresponded to the CH_2I protons. Signals at δ 5.07 (1H, d, J = 12.5 Hz), 5.13 (1H, d, J = 12.5 Hz), 5.23 (1H, d, J = 12.1 Hz), 5.32 (1H, d, J = 12.1 Hz) for the two CH_2 environments of the Cbz-groups together with signals at 7.28-7.48 (10H, m) ppm correspond to the phenyl environments of the Cbz-groups. The ^{13}C NMR spectrum gave a signal at δ 10.5 ppm for the CH_2I together with signals at δ 31.2 and 33.8 ppm for the methylene groups of the heterocycle. Signals appeared at δ 65.0 and 68.2 ppm for the methylene groups of the Cbz protecting groups and signals at δ125.8-127.8 ppm for the 10 carbons of the phenyl groups. Resonances at δ 152.2, 155.7 and 161.8 ppm were for the quaternary guanidine and Cbz-carbonyl groups. Accurate mass spectrometry gave an observed mass of 493.0498, which corresponds well with the predicted mass of 493.0499 Daltons for the $[M+H^{+}]$ ion.With compound **225a** in hand preparation of phosphonate **224** could now be undertaken. This was achieved using the Michaelis-Arbuzov procedure[105]which involved the reaction of iodocycle guanidine **225a** with triethyl phosphite in anhydrous toluene. The reaction was heated to 50-70 °C for 3 h, with the reaction progress being monitored by TLC, which indicated the complete consumption of **225a**. The reaction mixture was then cooled to rt followed by evaporation to remove excess triethyl phosphite. The crude material was then crystallised from dichloromethane/petrol to give the phosphonate **224** in 28% yield as a white solid which was used directly for the next step without further purification (Scheme 76).



Scheme 76: (a) $P(OEt)_3$, $C_6H_5CH_3$, Δ, 50-70 °C, 3 h, rt, 24 h.

Initially we envisaged the synthesis of the nitensidine E **214** (disconnecting at a) using a HWE reaction between phosphonate **224** and prenal **223** in the presence of LDA in anhydrous THF.[106] The reaction mixture was cooled to -78 °C and after 2 h, it was allowed to warm to rt and stir for 24 h. After aqueous workup, the crude residue

was purified by column chromatography and the analysis by ^{1}H NMR spectrum was indicative of a complex mixture and devoid of signals diagnostic of the nitensidine E **214** or any diene side chain that might be associated with structure **214** (Scheme 77).



Scheme 77: (a) THF, excess LDA, -78 °C - rt, 2-24 h.

Conclusions on approach B

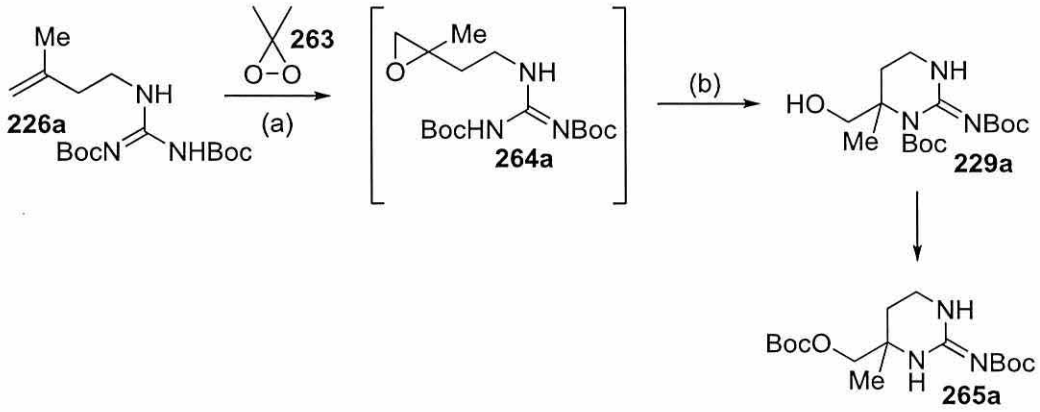
In this approach we attempted the iodocyclisation of the corresponding allylic guanidines **226a-b** were successfully prepared from the corresponding primary alcohols **262** and phthalimide **263** under Mitsunubu coniditons. The reaction attempts to form the phosphonate **224** were inconclusive, as were subsequent reactions of **224** with LDA and prenal, which gave only a complex mixture of products. This reaction was not attempted in the corresponding Cbz series and perhaps this might be an avenue for further investigation.

Approach C: DMDO cyclisation and Wittig approach

In this approach, the formation of the cyclic alcohols **229a** and **229b** is to be attempted. Following this, their oxidation to the corresponding aldehydes and the subsequent HWE reactions of these aldehydes will be investigated.

Thus reaction of the Boc-protected guanidine **226a** with an excess of DMDO[107] **263** was carried out in acetone at -20 °C. On monitoring the reaction by ^{1}H NMR it was apparent that after 16-24 h stirring at rt the substrate had been converted slowly into the intermediate epoxide **264a** (Entry 1, Table 7), as evidenced by signals at δ 2.62 (1H) and 2.71 (1H). On continued stirring, guanidine **265a** was formed presumably *via* the intermediate guanidine **229a**. After stirring for 5 weeks the consumption of the epoxide intermediate was completed and on work up and chromatography the 6-membered guanidine **265a** was obtained in 18% overall yield (Entry 2, Table 7) (Scheme 78).[108]

In order to accelerate this rearrangement process after 16 hours the reaction was evaporated, dried, dissolved in methanol and a catalytic amount of water added. After stirring at rt for 4 days this gave after work up and purification, a 72% yield (Entry 3, Table 7) of the 6-membered guanidine **265a**. Similarly, the complete conversion of **229a** into **265a** could be achieved by evaporating the reaction to dryness and dissolving the crude reaction mixture in methanol and adding a catalytic amount of TFA. After stirring for 24 h, work up and purification gave **265a** in 61% yield (Entry 4, Table 7) (Scheme 78).



Scheme 78: (a) and (b) See Table 7.

Entry	Reaction conditions[107,108]	265a Yield
1	Acetone, -20 °C - rt, 24 h.	-
2	Acetone, rt, 5 wks.	18%
3	MeOH, H_2O, rt, 4 d.	72%
4	MeOH, TFA, rt, 24 h.	61%

Table 7:- Reaction conditions investigated for the preparation of guanidine **265a**.

Analysis of **265a** by ^{1}H NMR showed signals at δ 1.49 (9H, s) and 1.51 (9H, s) ppm for the Boc protecting groups together with signals at δ 1.80 (1H, m), 2.10 (1H, m) and 3.52 (2H, m) ppm for methylene protons of the heterocycle. Signals at δ 4.03 (1H, d, J = 11.3 Hz) and 4.14 (1H, d, J = 11.3 Hz) ppm for the CH_2O group. The ^{13}C NMR spectrum had corresponding signals at δ 27.3 and 27.5 ppm for the *t*-butyl methyl groups and 81.9 and 82.9 ppm corresponding to the *t*-butyl quaternary carbon atoms, together with signals at δ 29.6 and 35.4 ppm for the methylene groups in the

heterocycle. The CH_2O methylene was observed at δ 70.7 ppm whilst the three most downfield signals at δ 153.1, 155.2 and 171.1 ppm corresponded to the guanidine quaternary carbon atom, the carbamate C=O and the carbonate C=O respectively. Accurate mass spectrometry gave a mass of 344.2184 Daltons, which is in close agreement with the required mass of 344.2180 Daltons for $[M+H^+]$. Final structural proof was obtained by X-ray crystallographic analysis (Fig 16).

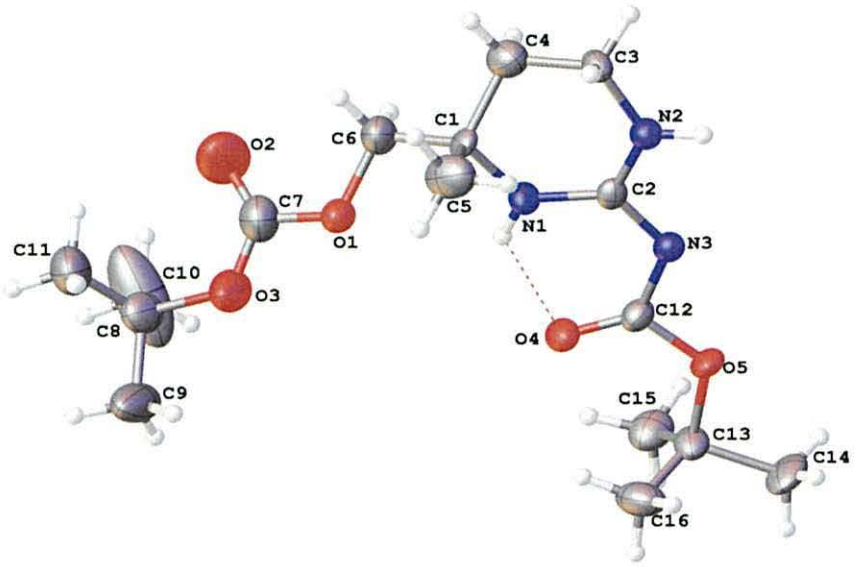
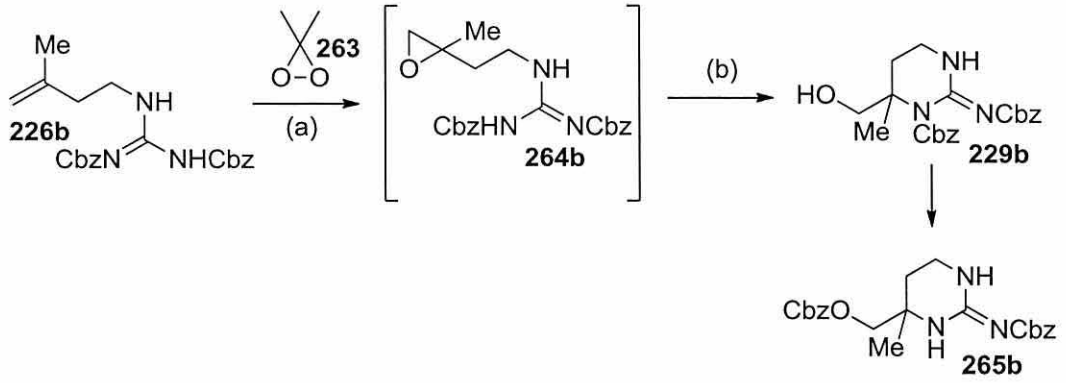


Figure 16: X-Ray structure of heterocycle **265a**.

In a similar manner the epoxidation of the Cbz- protected guanidine **226b** was carried out using an excess of DMDO[107] **263** in acetone at –20 °C and the reaction was again monitored by ^1H NMR. It was apparent that after 24 h stirring at rt the substrate had been converted into the intermediate epoxide **264b** (Entry 1, Table 8), as evidenced by signals at δ 2.62 (1H) and 2.71 (1H). After evaporation and drying, the crude epoxide was dissolved in a MeOH/H_2O mix and stirred at rt for 7 days. After work up and chromatography the 6-membered guanidine **265b** was obtained in 79% yield (Entry 2, Table 8). A similar acceleration of the rearrangement could be achieved if the crude reaction mixture was treated with TFA in MeOH and stirred at rt for 24 h leding to **265b** in 95% yield after chromatography (Entry 3, Table 8) (Scheme 79).[108]



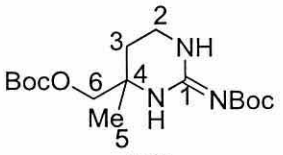
Scheme 79: (a) and (b) See Table 8.

Entry	Reaction conditions[107,108]	265b Yield
1	Acetone, -20 °C - rt, 24 h.	-
2	MeOH, H_2O, rt, 7 d.	79%
3	MeOH, TFA, rt, 24 h.	95%

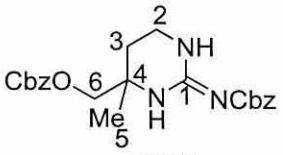
Table 8:- Reaction conditions investigated for the preparation of guanidine **265b**.

Analysis of the product **265b** by ^{1}H NMR showed signals at δ 1.78 (1H, m), 2.02 (1H, m), 3.50 (2H, m) ppm for the methylene protons of the heterocycle together with signals at δ 4.10 (1H, d, J = 11.2 Hz) and 4.21 (1H, d, J = 11.2 Hz) ppm for the methylene-oxygen group. In addition, there are two CH_2 environments of the Z-groups, appearing at δ 5.18 (2H, s) and 5.26 (2H, s) ppm. Following this is a cluster of signals at δ 7.34-7.43 ppm, which correspond to the phenyl environments of the Z-groups. The ^{13}C NMR spectrum also showed signals at δ 27.7 and 35.5 ppm for the methylene groups in the heterocyclic ring. The methylene-oxygen environment was found at δ 70.3 ppm as well as signals were at δ 68.4 and 71.4 ppm for the methylene groups of the two Z-groups together with signals at δ 128.1-128.8 ppm which for the 10 carbons of the phenyl groups. Quaternary signals at δ 152.1, 154.5 and 171.1 ppm were from the guanidine and carbonyls of the Z-groups quaternaries. Accurate mass spectrometry gave a mass of 412.1867 Daltons, which was in exact agreement with the required mass of 412.1867 Daltons. The structure of heterocycle **265b** was confirmed by 2-D NMR(HMBC), which indicated that no cross peak between the guanidine carbon and the CH_2 in the Z-group was present, but a long range correlation between the CH_2 protons of the Z-group and the carbonyl carbon was observed. We were

unable to grow suitable crystals for X-ray crystallographic analysis. However, direct comparison of the chemical shift data for analogues **265a** and **265b** showed a near exact correlation in chemical shifts and coupling constants for the ring and side chain proton and carbon signals (Table 9).



265 a



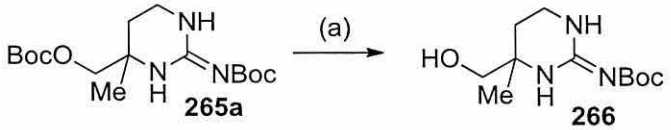
265 b

	Cyclic guanidine 265a		Cyclic guanidine 265b	
Position	**^{1}H (*J* in Hz)**	**^{13}C**	**^{1}H (*J* in Hz)**	**^{13}C**
1	----	153.1	----	152.1
2	3.52, m, 2H	35.4	3.50, m, 2H	35.5
3	1.80, m, 1H	29.6	1.78, m, 1H	27.7
	2.10, m, 1H		2.02, m, 1H	
4	----	51.5	----	52.0
5	1.42, s	24.7	1.42, s	24.7
6	4.03, d (11.3)	70.7	4.10, d (11.2)	70.3
	4.14, d (11.3)		4.21, d (11.2)	

Table 9:- ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data for guanidines **265a** and **265b** in $CDCl_3$.

Synthesis of alcohol 266 and attempted deprotection of the carbonate

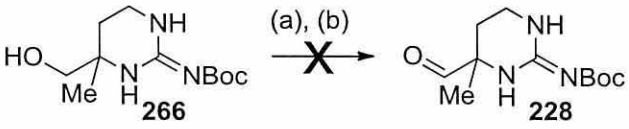
We were able to prepare alcohol **266** by deprotection of the cyclic product **265a** with potassium carbonate in dry MeOH. The reaction mixture was stirred at rt overnight and after removing the solvent the resulting mixture was then diluted with a mixture of MeOH/EtOAc (1:10, 22 mL). The filtrate was then evaporated, and the residue purified by column chromatography to give the 6-membered guanidine **266** in a 31% yield (Scheme 80).



Scheme 80: (a) 1.2 equiv K_2CO_3, MeOH, rt, 16-24 h, 31%.

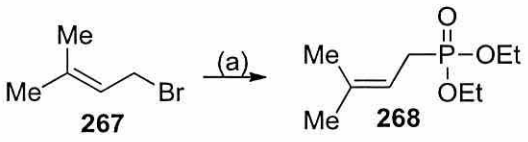
Analysis of the product **266** by ^{1}H NMR showed a singlet at δ 1.44 (9H) ppm for the Boc protecting group together with signals at δ 1.67 (1H, m), 1.81 (1H, m) and 3.30 (2H, m) ppm for the methylene protons of the heterocyclic ring. Signals were also observed at δ 3.39 (1H, d, J = 11.1 Hz) and 3.51 (1H, d, J = 11.1Hz) ppm for the CH_2OH group. The ^{13}C NMR showed signals at δ 27.5 ppm for the *t*-butyl methyl group and 80.6 ppm corresponding to the *t*-butyl quaternary carbon atom, together with signals at δ 29.5 and 37.6 ppm for the methylene groups in the heterocyclic ring. The CH_2OH signal appeared at δ 70.2 ppm with the ring quaternary observed at δ 53.4 ppm. The two most downfield signals of the spectrum appeared at δ 155.4 and 158.7 ppm representing the guanidine quaternary carbon atom and Boc carbonyl respectively. Accurate mass spectrometry gave a mass of 244.1656 Daltons which was in exact agreement well with the calculated mass of 244.1656 Daltons.

Having introduced the required cyclic guanidine alcohol **266**, preparation of the corresponding aldehyde was attempted using Dess-Martin periodinane oxidation. Thus, alcohol **266** was dissolved in CH_3CN at 0 °C and exposed to an excess of the Dess-Martin reagent (Scheme 81).[109] Reaction progress was monitored by TLC and after 3 h no more starting material was shown to be present. The reaction mixture was then diluted with EtOAc and filtered through a short plug of silica gel (ca. 1 cm), eluting with further EtOAc. After evaporation, the crude residue was analysed (NMR) and showed no indication of the required aldehyde **228**. On repeating, the reaction was carried out using dry THF followed by the addition of H_2O at 0 °C and allowing the mixture to stir and warm to rt for 24 h. The reaction mixture was then diluted with THF, and was then filtered through a short plug of Celite (ca. 1 cm) which was eluted with further THF. This reaction was attempted four times and the crude ^{1}H NMR spectra in all cases indicated that no cyclic guanidine aldehyde **228** was present. At this point, it was suspected that aldehyde **228** might have formed under the reaction conditions but that it may be unstable (Scheme 81).



Scheme 81: (a) DMP, CH_3CN, 0°C, 3 h; (b) DMP, THF, H_2O, 0 °C- rt, 24 h. 0 %.

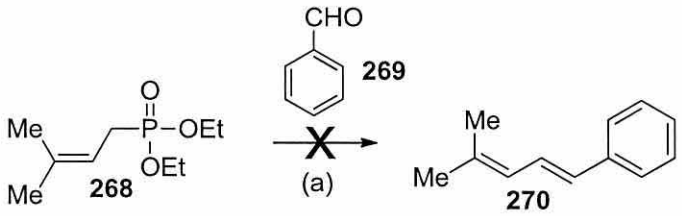
As we had been unsuccessful at preparing the aldehyde for the previous synthesis, we decided to turn to the investigation of an alternative method utilising phosphonate **268** generated from the Michaelis-Arbuzov procedure.[105] Therefore, a mixture of 4-bromo-2-methyl-2-butene **267** and triethyl phosphite was heated to reflux at 130 °C for 3 h and the reaction progress was monitored by TLC. The reaction mixture was then cooled to rt and concentrated *in vacuo* until excess triethylphosphite was removed. Purification of the crude material was achieved by column chromatography on silica gel to give the desired product **268** in 67% yield as an oil (Scheme 82).



Scheme 82: (a) $P(OEt)_3$, Δ, 130 °C, 3 h, 67%.

Inspection of the ^{1}H NMR spectrum showed the presence of signals at δ 1.16 (6H, t, J = 7.2 Hz), 1.51 (3H, d, J = 4.1 Hz) and 1.60 (3H, d, J = 5.3 Hz) for the methyl groups together with signals at δ 2.39 (2H, dd, J = 7.5, 22.0 Hz) and 3.94 (4H, m) ppm corresponding to the methylene protons. In addition, a signal at δ 5.02 (1H, m) ppm was observed for the alkene proton. The ^{13}C NMR spectrum gave signals at δ 16.5, 16.6, 18.0 (d, $^3J_{PC}$ = 2.5 Hz) and 25.6 ppm for the methyl groups, as well as signals at δ 25.7 (d, $^1J_{PC}$ = 138.2 Hz) and 61.8 ppm for the methylene groups. The alkene signals were found at δ 112.6 (d, $^2J_{PC}$ = 11.3 Hz) and 136.6 (d, $^3J_{PC}$ = 14.5 Hz) ppm.

It was then decided to perform a test of the HWE reaction using benzaldehyde **269** and phosphonate **268** in the presence of LDA in anhydrous THF.[106] The reaction mixture was initiated at -23 °C and after 2 h, the mixture was allowed to stir and warm to rt. After 24 h, TLC analysis indicated the complete consumption of the starting material. The reaction was then subjected to an aqueous workup, dried over $MgSO_4$ and evaporated. Unfortunately analysis of the ^{1}H NMR spectrum of the crude material indicated the presence of a complex mixture and the absence of signals expected for the product **270** (Scheme 83).



Scheme 83: (a) THF, LDA, -23 °C-rt, 2-24 h.

Conclusions on approach C

Approach C aimed to reverses the alkene forming step by utilising a HWE reaction of aldehyde **228** with phosphonate **227**. The alcohol **266** was prepared by the DMDO oxidation and cyclisation of guanidine **226a**, followed by the selective hydrolysis of the carbonate protecting group. Attempts at oxidising this alcohol to the corresponding aldehyde **228** proved unsuccessful and thus this proved to be dead end for the synthesis of nitensidine E. The required phosphonate **270** was prepared and a test reaction with benzaldehyde was attempted, however this was also unsuccessful. The reasons for the failure of this reaction are unclear.

Approach D: π-allyl palladium cyclisation approach

The final synthetic approach we considered was the cyclisation of acetoxy guanidine **230** under palladium-catalysed conditions as put forward in the retrosynthetic approach D (Scheme 47). As has been previously noted, the existing literature in this area of chemistry is sparse, with only reports by Buchi[70] and Buck[38] along with our own investigations on the cyclisation of 5-membered systems being known. The key step in this synthesis is envisaged to be the cyclisation of substrate **230** to give the 6-membered heterocycle **214** (Figure 17).

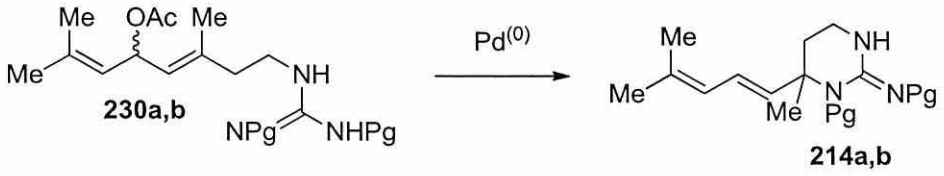
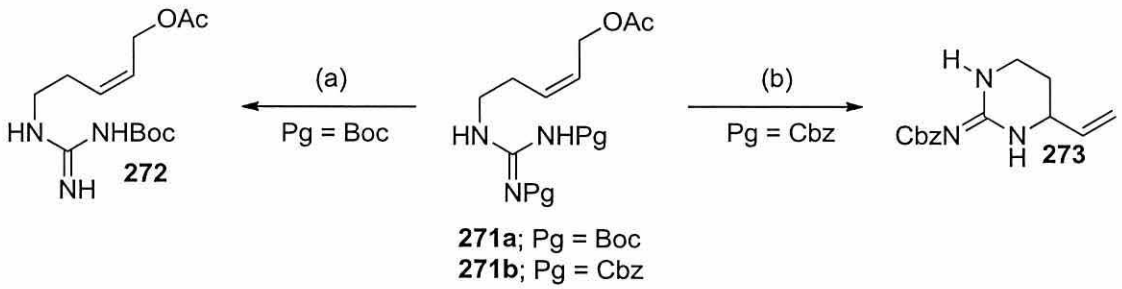


Figure 17: Proposed synthetic approach D; Pg = Boc, Cbz.

This is an ambitious approach as it constructs the completed carbon framework in one transformation but unfortunately still leaves the problems associated with deprotection.

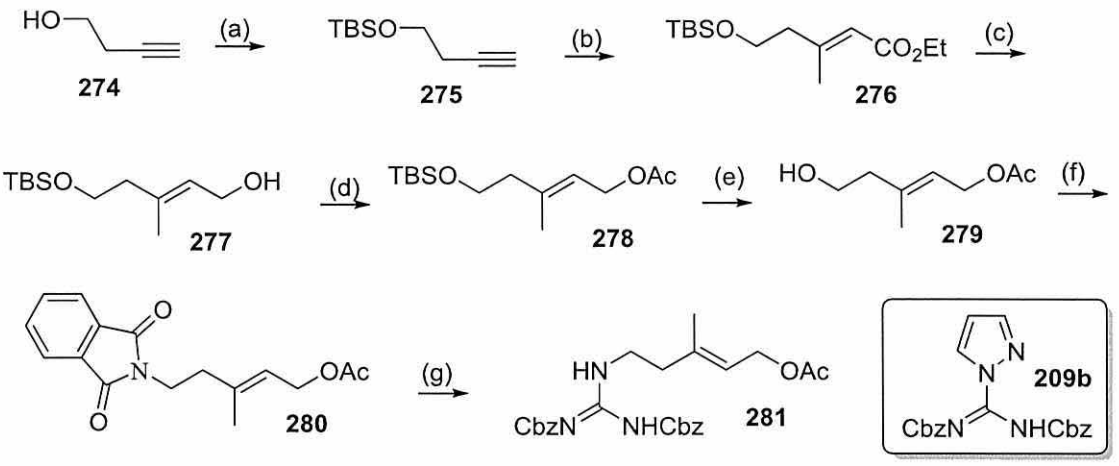


271a; Pg = Boc
271b; Pg = Cbz

Scheme 84: (a) $Pd(OAc)_2/PPh_3$, THF, Et_3N, Δ, 57%; (b) i) $Pd(OAc)_2$/ LiBr, Δ, THF, Et_3N, 39% or (ii) $Pd(dppe)_2$, THF, Et_3N, Δ, 84%.

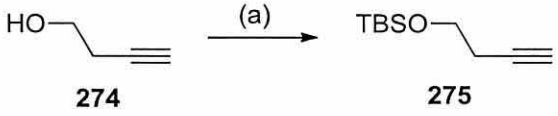
A member of our group[110] has previously investigated the $Pd^{(0)}$ mediated cyclisation of the related substrates **271a** and **271b**, which both lack the methyl group at the ring junction that is required for nitensidine E. This process was proven to be unsuccessful for **271a** leading to the deprotected guanidine **272** only. However, repeating this work with the Cbz-protected guandine **271b** led to the formation of the mono-protected cyclic guanidine **273** in 84% yield. The loss of the protecting group in **273** is thought to have occurred after the cyclisation reaction and was possibly due to steric crowding at the ring junction. In addition, the mono-Boc-protected guanidine **272** was inert to cyclisation under the conditions employed to give **273**, which similarly suggests that deprotection occurred after cyclisation (Scheme 84).

The substrate (**281**) required for our study is similar to the one previously employed in Scheme 84 but differs by the addition of a methyl substituent on the alkene. This should be accessed from alcohol **274** in seven steps (Scheme 85).



Scheme 85: (a) DMF, TBSCl, imidazole; (b) i) Cp_2ZrCl_2, DCM, -23°C, Me_3Al, H_2O, (ii) $ClCO_2Et$, (c) DCM, -78 °C, DIBAL; (d) Ac_2O, pyridine, DMAP, DCM; (e) THF, TBAF, 0 °C - rt 4 h; (f) PPh_3, phthalimide, THF, DIAD; (g) i) $NH_2NH_2.H_2O$, EtOH, reflux, (ii) Et_3N, **209b**, rt.

The first reaction in the synthesis was the silylation of 3-butyn-1-ol **274** using a literature procedure.[111] The conversion was achieved using TBSCl and imidazole in DMF at 0°C with stirring to rt overnight. After work up, the required product **275** was obtained in 92% yield as an oil, which was used without further purification in the next step (Scheme 86).

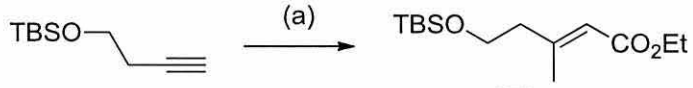


Scheme 86: (a) DMF, TBSCl, imidazole, 0 °C - rt, 16-24 h, 92%.

Inspection of the ^1H NMR spectrum showed signals at δ 0.07 (6H, s) and 0.90 (9H, s) ppm for the two methyl groups and the *tert*-butyl group of the silyl protecting group. This, together with a signal at δ 1.95 (1H, t, J = 2.6 Hz) ppm for the alkyne proton, and the methylene signals at δ 2.39 (2H, dt, J = 2.6, 7.1 Hz) and 3.74 (2H, t, J = 7.1 Hz) ppm confirmed the structure of **277**. The ^{13}C NMR spectrum was also in

agreement with this structure, with key signals at δ -5.3 and 25.8 ppm representing the silicon bound carbon atoms and the *tert*-butyl methyl groups, with the quaternary carbon atom of the newly introduced protecting group resonating at δ 18.3 ppm.

The next objective was the incorporation of the methyl group onto the alkene. This was achieved using zirconium mediated methylation which ultimately leads to the ester **276**. Thus, a solution of [Cp_2ZrCl_2] in CH_2Cl_2 at -23 °C was treated with Me_3Al and after stirring at -5 °C over 1 h, the reaction cooled (-23 °C) and 1.5 equivalents of water as added slowly over 10 min with vigorous stirring. At this point, a solution of the alkyne **275** dissolved in CH_2Cl_2 was added and the reaction mixture was stirred at -5 °C for 5 h. Following this, an excess of ethyl chloroformate ($ClCO_2Et$) was added and the mixture stirred at rt overnight. After work up and purification the ester **276** was formed in 22-42% yields over seven attempts (Scheme 87).[112]



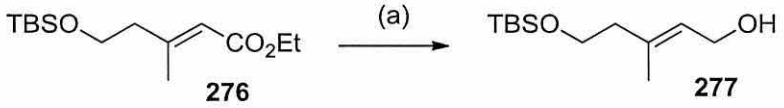
275 **276**

Scheme 87: (a) i) Cp_2ZrCl_2, DCM, Me_3Al, H_2O, -23 °C, (ii) $ClCO_2Et$, stir, rt, 24 h, 22-42%.

Inspection of the ^1H NMR spectrum showed signals at δ 1.27 (3H, t, J = 7.1 Hz) and 4.15 (2H, q, J = 7.1 Hz) ppm for the ethyl ester protons, together with a signal at δ 2.18 (3H, d, J = 1.1 Hz) ppm for the methyl protons on the alkene. As well, the alkene proton signal was found at δ 5.68 (1H, q, J = 1.1 Hz) ppm, with signals at δ 2.35 (2H, t, J = 6.7 Hz) and 3.75 (2H, t, J = 6.7 Hz) ppm corresponding to methylene protons. The ^{13}C NMR also gave diagnostic signals at δ 14.3 and 61.3 ppm for the ethyl ester group together with a signal at δ 19.1 ppm for the methyl group on the alkene and signals at δ 44.0 and 59.5 ppm representing the methylene carbons. Signals at δ 117.2 and 156.8 ppm were observed for the alkene CH and C and a quaternary at δ 166.6 ppm represents ester carbonyl group.

Having successfully prepared ester **276**, reduction was achieved by dissolving it in DCM, cooling to -78 °C and treatment with a solution of DIBAL(1M in hexane).[113] The reaction mixture was stirred for 3-4 h at -78 °C, and monitored by TLC which indicated the full consumption of the ester **276**. The reaction was quenched by the slow

addition of EtOAc, followed by dilution with MeOH at -78 °C. To aid in the removal of the resulting aluminium salts from the reaction mixture, it was then diluted with Et_2O and Rochelle's salt was added, followed by stirring to rt until the solution cleared to give after work up and purification alcohol **277** in 59-73% yields over seven attempts (Scheme 88).

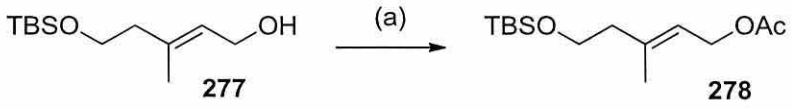


276 **277**

Scheme 88: (a) DIBAL, DCM, -78 °C, 59-73%.

Inspection of the ^1H NMR spectrum indicated that the ethyl ester proton signals were no longer present and a new signal had appeared at δ 4.10 (2H, d, J = 7.0 Hz) ppm for the CH_2OH. The signal at 1.65 (3H, d, J = 1.1 Hz) represented the methyl protons on the alkene and the alkene CH signal was observed at δ 5.39 (1H, qt, J = 1.1, 7.0 Hz) ppm. Analogous changes were observed in the ^{13}C NMR spectrum, with the methyl, methylene and methine groups being found at δ 16.6, 62.1 and 125.3 ppm respectively. IR spectroscopy gave a band at 3339 cm^{-1} corresponding to the hydroxyl group.

With alcohol **277** in hand, the acetylation of the hydroxyl group was achieved using pyridine and Ac_2O in DCM at at 0°C in the presence of a catalytic amount of DMAP.[114] The reaction was stirred at rt for 3 h at which point TLC indicated complete comsumption of the starting material. After work up and chromatography, the ester **278** was obtained in 80-92% yield over six attempts (Scheme 89).



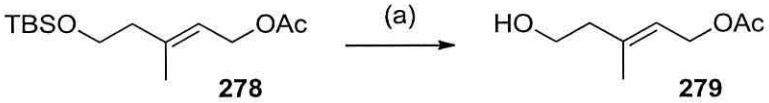
277 **278**

Scheme 89: (a) Ac_2O, pyridine, DMAP, DCM, 0 °C -rt, 3 h, 80-92%.

The ^1H NMR spectrum of **278** indicated the presence of a signal at δ 1.72 (3H, broad s) ppm for the methyl group and a signal at 2.05 (3H, s) ppm for the methyl of acetate group. This together with signals at δ 2.25 (2H, t, J = 6.8 Hz), 3.70 (2H, t, J = 6.8 Hz) and 4.58 (2H, d, J = 7.1 Hz) ppm for the methylene protons and the presence of the alkene proton at δ 5.37 (1H, t, J = 7.1 Hz) ppm confirmed the structure of **280**.

Similarly, the ^{13}C NMR spectrum gave a signal at δ 16.7 ppm for the methyl group, together with signals at δ 42.7, 61.2 and 61.7 ppm for the three methylene carbons. Other signals at δ 21.0 and δ 171.1 ppm, were assigned as the methyl and the quaternary carbon of the acetate group. Inspection of the IR spectrum showed the expected C=O absorption of the acetate group at 1742 cm^{-1}.

The next step in the synthesis involved the removal of the TBS protecting group. This was achieved using TBAF in THF, which was cooled to 0 °C and the reaction mixture allowed stirring at rt over after 24 h. At this point, TLC analysis indicated the complete consumption of silyl ether **278** and after aqueous work up and column chromatography, the alcohol **279** was isolated in yields of between 85 and 96% over six attempts (Scheme 90).[115]

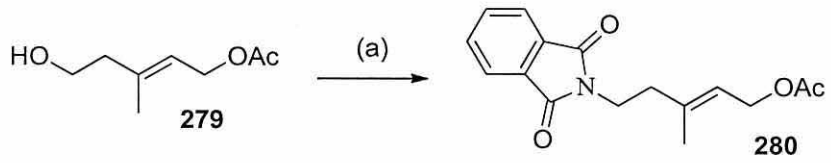


278 **279**

Scheme 90: (a) TBAF, THF, 0 °C -rt, 24 h, 85-96%.

Identification of the alcohol **279** was confirmed by the presence of a diagnostic broad OH stretch in the IR spectra at 3438 cm^{-1}. Further confirmation was achieved by the observation of changes in the ^{1}H NMR spectrum that no longer contained signals representative of a TBS ether functional group. Signals appeared at δ 1.74 (3H, broad s) ppm for the methyl protons on the alkene and 2.05 (3H, s) ppm for the methyl of the acetate group, together with signals at δ 2.31 (2H, t, J =6.4 Hz), 3.72 (2H, t, J = 6.4 Hz) and 4.60 (2H, d, J = 7.0 Hz) ppm for the methylene protons. A signal was also observed at δ 5.42 (1H, qt, J = 1.0, 7.0 Hz) ppm for the alkene proton. The ^{13}C NMR spectrum similarly showed that the signals representing to the *t*-butyl methyl groups, quaternary carbon atom and silicon bound methyl groups of TBS ether were absent.

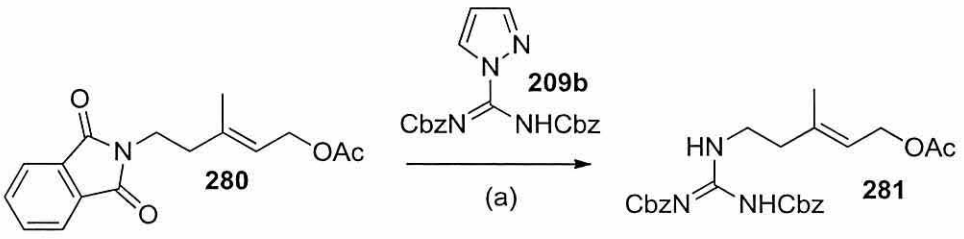
With **279** in hand, its reaction with phthalimide was carried out in the presence of PPh_3 and DIAD in THF, cooled to 0 °C (Scheme 91).[91,92] The reaction progress was followed by TLC, and upon consumption of the alcohol the reaction was subjected to an aqueous workup. The crude product was purified by column chromatography to give phthalimide **280** in yields ranging between 71 and 84% over five attempts.



Scheme 91: (a) PPh_3, phthalimide, THF, DIAD, 0 °C- rt, 71-84%.

Inspection of the ^1H NMR spectrum indicated the presence of signals at δ 1.81 (3H, s) ppm for the methyl protons on the alkene together with signals at δ 2.42 (2H, t, J = 7.0 Hz), 3.82 (2H, t, J = 7.0 Hz) and 4.49 (2H, d, J = 7.0 Hz) ppm for the methylene protons. The alkene proton signal was found at δ 5.31 (1H, t, J = 7.0 Hz) ppm. In addition, signals were between 7.70-7.89 (4H, m) ppm for the aromatic ring protons. The ^{13}C NMR spectrum corroborated the evidence observed in the ^1H NMR spectrum, there was a signal at δ 16.1 ppm for the methyl group on the alkene together with signals at δ 36.2, 38.1 and 60.8 ppm for the methylene groups. The alkene carbon signal was found at δ 121.2 ppm, as well as signals at δ 123.2, 123.5, 133.8 and 134.3 ppm representing the aromatic CH. Diagnostic quaternary carbon atom signals were also observed at δ 168.2 and 170.8 ppm for the phthalimide protecting group and acetate quaternaries.

Phthalimide **280** was then treated with hydrazine hydrate in refluxing pure EtOH to remove the phthalimide protecting group.[96] After filtration to remove the by-product a solution of amine was obtained which was treated with Et_3N and the commercially available guanylating agent **209b** to give the guanidine **281** in yields ranging between 31 and 47% over six attempts (Scheme 92).

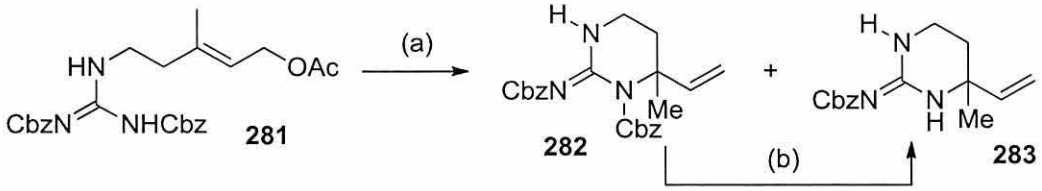


Scheme 92: (a) i) $NH_2NH_2.H_2O$, EtOH, reflux,
(ii) Et_3N, **209b**, rt, 16-24 h, 31-47%.

The guanidine **281** gave diagnostic ^1H NMR spectrum signals at δ 1.74 (3H, s) ppm for the alkene methyl protons, together with signals at δ 2.31 (2H, t, J = 6.7 Hz),

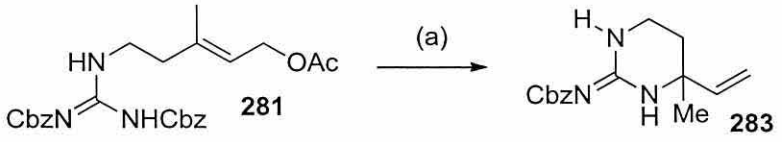
3.57 (2H, apparent q, J = 6.7 Hz) and 4.60 (2H, d, J = 7.0 Hz) ppm corresponding to the methylene protons. The signal at δ 5.45 (1H, t, J = 7.0 Hz) ppm corresponds to the alkene proton, whilst the two CH_2 environments of the Cbz-groups signals were at δ 5.14 (2H, s) and 5.18 (2H, s) ppm, together with signals at δ 7.29-7.41 ppm for the phenyl CH environments of the Z-groups. The two NH protons of the guanidine were found at δ 8.31 (1H, broad s) and 11.72 (1H, broad s) ppm. The ^{13}C NMR spectrum gave a signal at δ 15.7 ppm for the methyl group on the alkene, together with signals at δ 37.9, 38.7 and 60.4 ppm for the methylene groups. Signals at δ 121.2 and 137.7 ppm correspond to the alkene CH and C, whilst those at δ 66.8 and 67.8 ppm correspond to the CH_2 carbons of the two Z-groups, together with signals at δ 127.5-128.4 ppm indicating the 10 carbons of the phenyl groups. Diagnostic quaternary signals were present at δ 153.3, 155.3, 168.1 and 170.8 ppm representing the guanidine carbon atom, two Z-carbonyl atoms and the acetate carbonyl atom respectively. The product gave an accurate mass ion at 468.2126 Daltons, which corresponds very well to the expected mass of 468.2129 Daltons.

With the successful preparation of the required bis-Cbz guanidine **281** *via* a zirconium mediated methylation, we next investigated its use as a potential substrate for π-allyl palladium cyclisation to allow access to the natural product nitensidine E. Under the previously investigated conditions, a THF solution of guanidine **281** was treated with Et_3N and $Pd(dppe)_2$ catalyst.[117] The reaction mixture was heated to reflux and monitored by TLC and after 48 h, it was apparent that all of the starting material **281** had been consumed. After work up and analysis of the crude ^1H NMR spectrum, it was apparent that there were at least two cyclised products present as the vinylic CH proton gave a complex pattern due to partial cleavage of one of the Cbz-groups. Treatment of the product from this reaction with TFA in MeOH and stirring for 48 h led to the formation of a single product which displayed the simple double doublet which was expected for the vinylic CH. Purification *via* column chromatography gave the desired mono-protected cyclic guanidine **283** in a 43% isolated yield (Scheme 93).



Scheme 93: (a) THF, $Pd(dppe)_2$, Et_3N, Δ, 48 h, (b) TFA, MeOH, rt, 48 h, 43%.

The spectral data obtained were in agreement with those expected for heterocycle **283**. The ^1H NMR spectrum displayed a signal at δ 1.48 (3H, s) ppm for the methyl protons, and the signals for the methylene groups contained within the 6-membered ring appeared at δ 1.81 (1H, m), 1.92 (1H, m), 3.30 (1H, m) and 3.46 (1H, m) ppm. Signals at δ 5.14 (1H, d, J = 17.0 Hz), 5.28 (2H, s) and 5.30 (1H, d, J = 10.5 Hz) ppm corresponded to the vinylic and benzylic protons, whilst the signal at δ 5.76 (1H, dd, J = 10.5, 17.0 Hz) ppm corresponded to the vinylic CH. The ^{13}C NMR spectrum showed signals at δ 31.0 and 35.9 ppm for the methylene groups contained within the 6-membered ring and a resonance at δ 54.5 ppm for the quaternary allylic carbon. Signals at δ 68.4 and 116.0 ppm corresponded to the benzyl and vinylic methylene groups, as well as a signal at δ 140.2 ppm for the vinylic CH. The quaternary signals at δ 151.6 and 155.0 ppm representing the guanidine carbon and the Z-carbonyl quaternary respectively. The product gave a mass ion of 274.1547 Daltons by accurate mass spectrometry, which corresponds very well to the expected mass of 274.1550 Daltons. We attempted to improve this reaction to give an acceptable yield for the cyclisation of guanidine **281** and a modification of the reaction conditions was attempted. Thus a 1,4-dioxane solution of guanidine **281** was treated with Et_3N and $Pd(dppe)_2$ catalyst[116] and the reaction mixture was heated at 90 °C. Monitoring of the reaction by TLC demonstrated that after 24 h, all of the starting material **281** had been consumed and on cooling to rt the solvent was evaporated followed by purification *via* column chromatography. This gave the desired cyclic guanidine **283** in a 15% isolated yield (Scheme 94). Inspection of the NMR spectra obtained indicated agreement with the previous data.



Scheme 94: (a) 1,4-dioxane, $Pd(dppe)_2$, Et_3N, Δ, 90 °C, 24 h, 15%.

This attempt at improving the yield was not successful and indeed the yield of the reaction was significantly decrease to 15% when 1,4-dioxane was employed. Further investigation on the modification of the reaction conditions was not investigated further due to time constraints; however, the synthesis of the model compound **283** represented a significant step forward in the goal of the total synthesis of nitensidine E.

Spurred on by this achievement, we next attempted to prepare the substrate **230b** which if accessible would allow cyclisation to give the cyclic guanidine **214b** or a mono-deprotected analogue. This product contains the complete carbon skeleton found in the natural material (Figure 18).

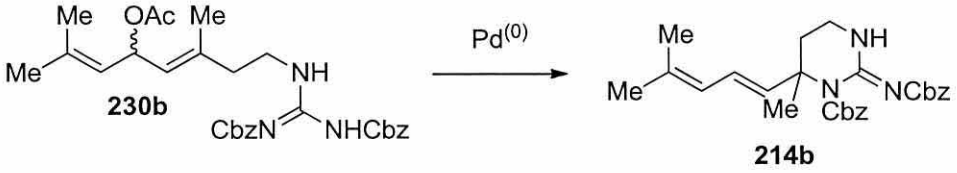
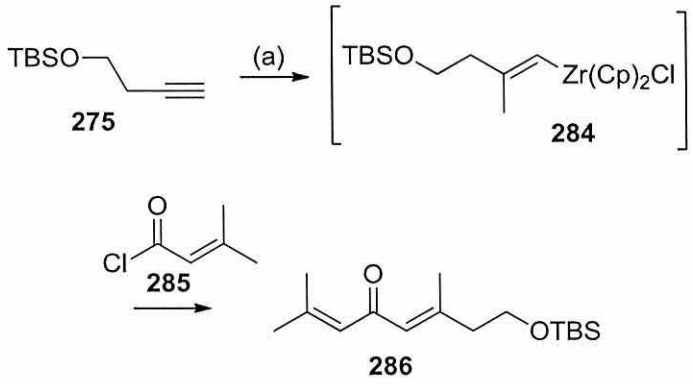


Figure 18: Proposed synthetic approach D.

In order to achieve this we attempted to modify the zirconium mediated acylation process to introduce the dimethylalkenyl group required for the substrate **230b**. The zirconium intermediate **284** was prepared from the alkyne **275** as previously and was treated with 3,3-dimethylacryloyl chloride **285** at -23 °C and stirred to rt overnight. After work up and purification the ketone **286** was obtained in 34% yield as an oil (Scheme 95).[112]

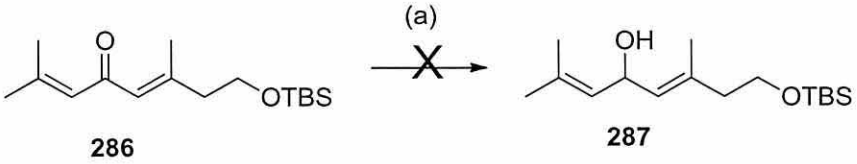


Scheme 95: (a) Cp_2ZrCl_2, DCM, -23 °C, Me_3Al, H_2O, **285**, rt, 24 h, 34%.

Inspection of the ^{1}H NMR spectrum showed the incorporation of the desired silyl ether group, evident by the presence of two singlets at δ 0.06 (6H, s) and 0.90 (9H, s) ppm representing the two silicon bound methyl groups and the three *tert*-butyl methyl groups respectively. Signals at δ 1.89 (3H, s), 2.17 (3H, s) and 2.18 (3H, s) ppm were observed for the methyl protons, as well as resonances at δ 2.33 (2H, t, J = 6.6 Hz) and 3.75 (2H, t, J = 6.6 Hz) ppm for the methylene protons. The two alkene proton signals were found at δ 6.07 (1H, s) and 6.10 (1H, s) ppm. The ^{13}C NMR spectrum was also in agreement with signals at δ -5.37 ppm and 25.8 ppm for the silicon bound methyls and *tert*-butyl methyl groups, with the quaternary carbon atom of the protecting group resonating at δ 31.6 ppm. Signals for the methylene groups were observed at δ 44.4 and 61.4 ppm, whilst signals at δ 126.2 and 127.2 ppm were representative of the two methine groups with the diagnostic quaternary signal for the carbonyl was seen at δ 191.5 ppm.

Having successfully prepared the ketone **286**, reduction of the ketone functionality directly to the corresponding alcohol **287** was undertaken. Thus, a solution of ketone **286** in MeOH was cooled to 0 °C and treated with sodium borohydride (Scheme 96).[118] The mixture was stirred to rt for 24 h and after aqueous work up, the ^{1}H NMR spectrum and TLC analysis of the crude material indicated the presence of a complex mixture of products. Attempted modification of this reaction by varying the reaction time, temperature and the number of equivalents of reducing agent failed to effect clean reduction and on no occasion was the starting material recovered. It was decided to repeat this work using $LiAlH_4$ by addition of a solution of the ketone **286** in Et_2O to a cooled (0 °C) suspension of $LiAlH_4$ in ether (Scheme 96).[119] The gray/white mixture was refluxed for 3 h and after the reaction was complete as monitored by TLC. The reaction was quenched by the dropwise addition of saturated aqueous Na_2SO_4, a white precipitate was formed which was extracted with EtOAc and dried over $MgSO_4$. As with the sodium borohydride reduction, only a complex mixture of products was isolated, as confirmed by both ^{1}H and ^{13}C NMR. The reduction of ketone **286** was next attempted using DIBAL, which was added to the substrate **286** dissolved in DCM at -78 °C (Scheme 96).[120,121] The progress of the reduction was monitered by TLC, and after 3 h the reaction was quenched at -78 °C by the dropwise addition of MeOH. After dilution with EtOAc, a saturated solution of Rochelle's Salt was added to remove aluminium salts and an aqueous workup the crude material was purified by column chromatography on silica gel. As with the other methods

attempted, this reaction also supplied only a complex mixture of products with no evidence of the formation of the desired alcohol **287**.



286 **287**

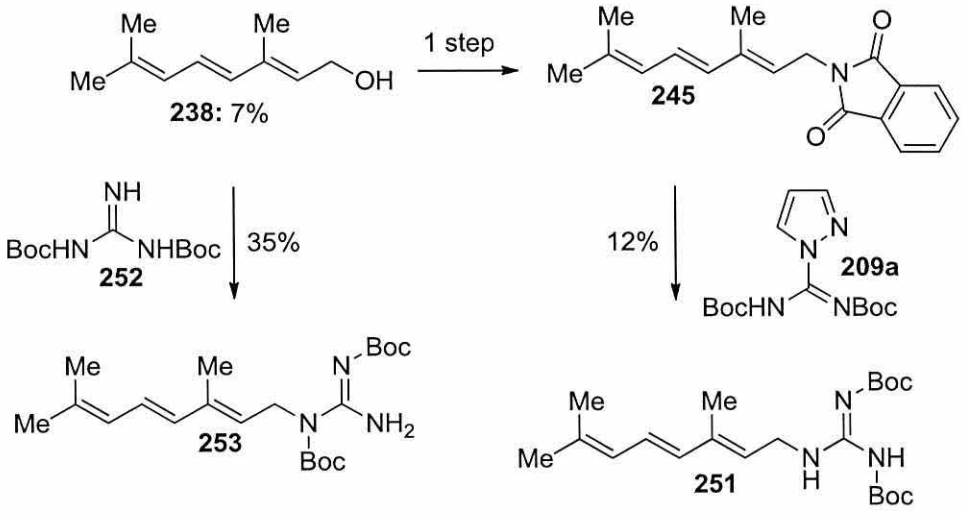
Scheme 96: (a) i) $NaBH_4$, MeOH, 0 °C-rt, 24 h, (ii) $LiAlH_4$, Et_2O, 0 °C, reflux, 1 h, (iii) DIBAL, DCM, -78 °C, 2 h.

This failure to obtain the alcohol **287** was surprising, as the reduction of ketones is normally an easy FGI to achieve. The only possible explanation is the over-reduction of the system leading to conjugate addition of hydride to the enone before reduction of the ketonic function.

Conclusions and Future Work

The goal of this project was to investigate the synthesis of the recently isolated guanidines nitensidine D **213** and nitensidine E **214** from *Pterogyne nitens*, a native tree common in South America.[79]

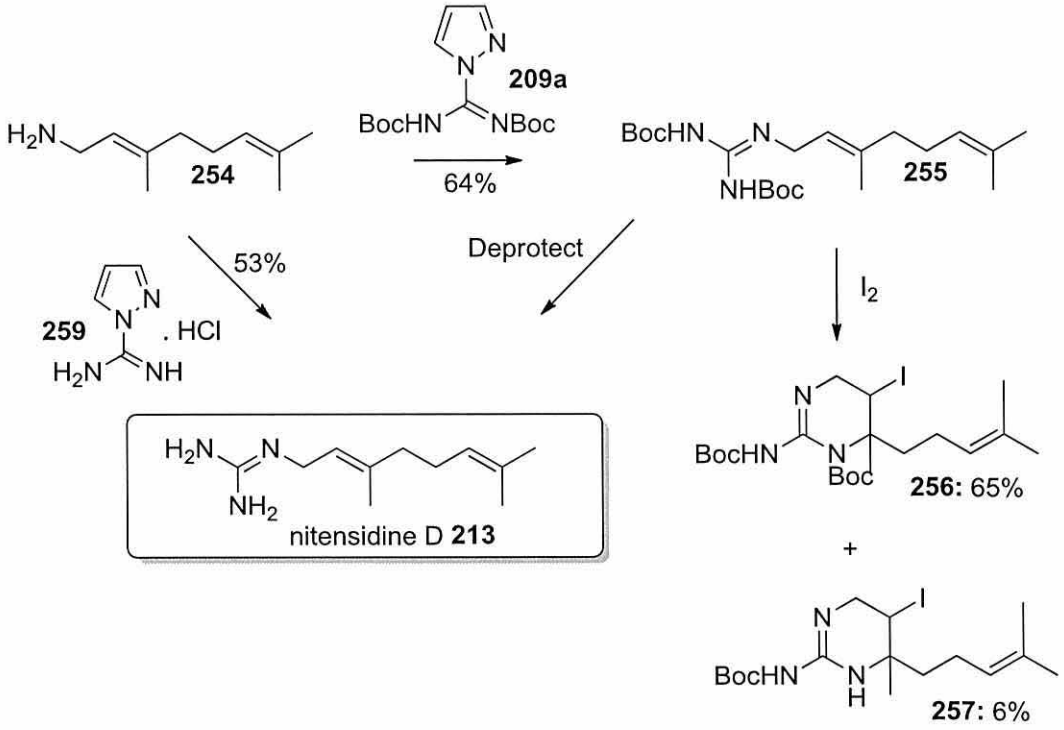
In the initial effort towards the synthesis of nitensidine E **214** it was hoped that the synthesis could be achieved *via* a heterocyclisation of the type previously investigated in these laboratories. Therefore, allyl substituted guanidines **251** and **253** were prepared from alcohol **238** using two different methods in 12% and 35% yields respectively (Scheme 97).



Scheme 97: Synthesis of the intermediate guanidines **251** and **253**.

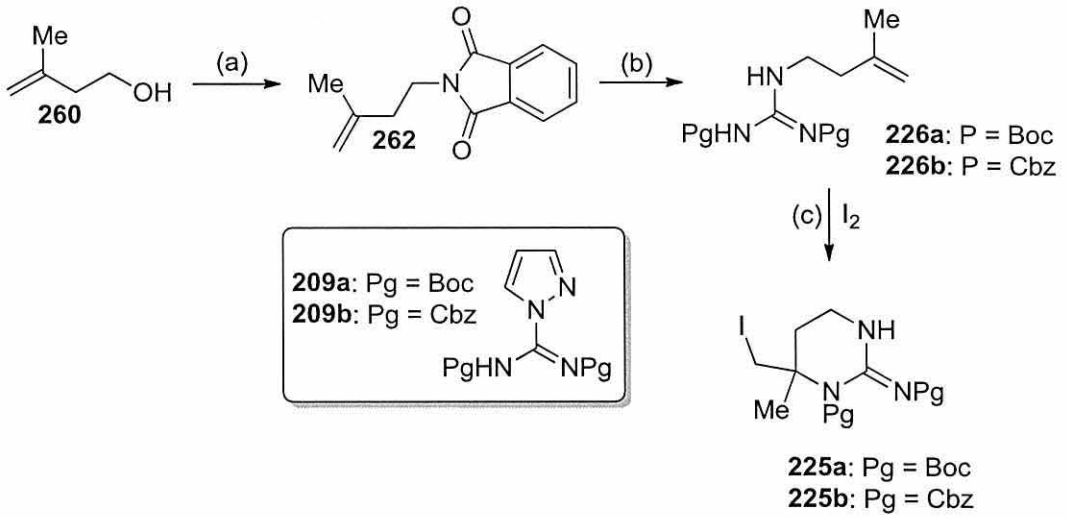
However, the desired alcohol **238** and the guanidine **251** were found to be unstable and considerable decomposition occurs on even short term storage or during purification. An alternative methodology using commercially available geranylamine **254** was next attempted and was envisaged as a model study for the synthesis of nitensidine D **213**. The bis-Boc-protected guanidine **255** was prepared by the reaction of geranylamine **254** with *N,N'*-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carbox amidine **209a** to give the required protected guanidine **255** in 64% yield (Scheme 98). This underwent iodocyclisation to give the bis-protected **256** and mono- **257** cyclic guandines in 65% and 6% yields respectively (Scheme 98). In addition to the model

study, we have also demonstrated the preparation of the related natural product nitensidine D as it was felt that the cyclisation and deprotection of this would give an insight into the chemistry required to cyclise the designed guanidine **251** (scheme 98).



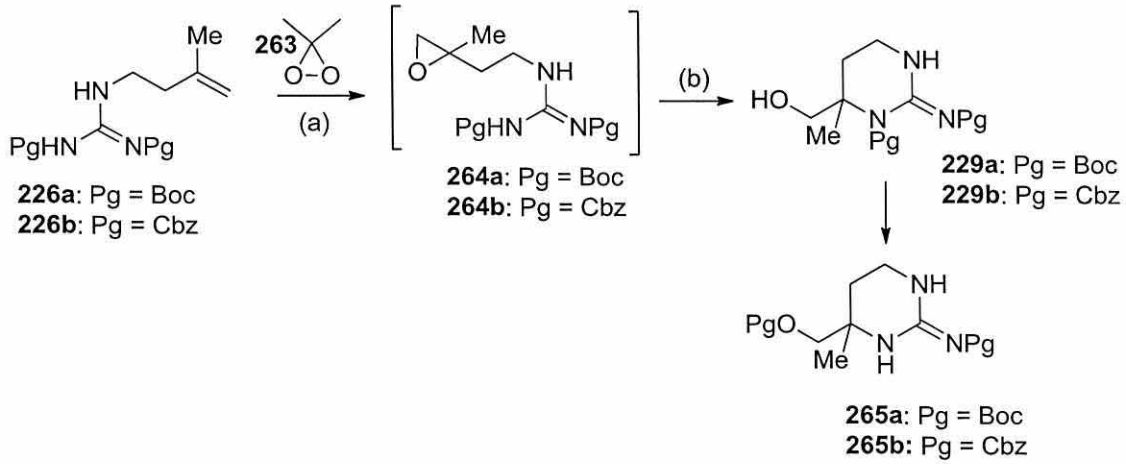
Scheme 98: Preparation of the natural product nitensidine D and iodocyclisation of guanidine **255**.

Another approach involved the preparation of the Boc- and Cbz-protected guanidines **226a** and **226b** from alcohol **260** in 55% and 84% yields. The iodocyclisations of guanidines **226a** and **226b** were successful and gave the cyclic guanidines **225a** and **225b** in 71% and 68% yields. Attempted modification of these intermediates to obtain nintesidine E was unsuccessful (Scheme 99).



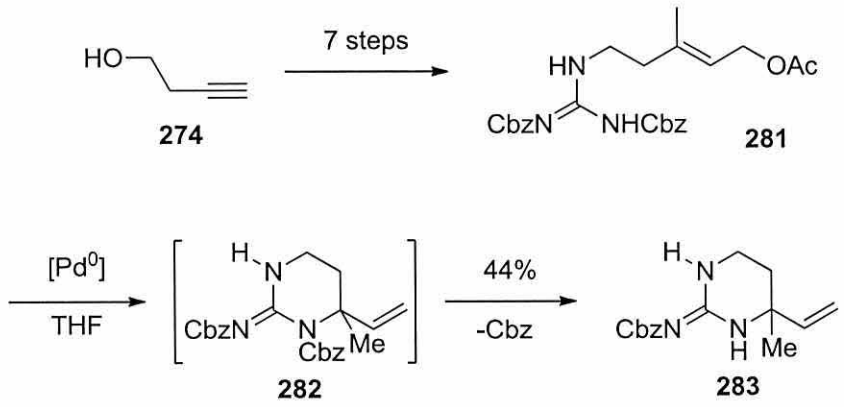
Scheme 99: (a) PPh_3, phthalimide **261**, DEAD, THF, 3h; (b) i) $NH_2NH_2.H_2O$, EtOH, reflux, (ii) Et_3N, **209a** or **209b**, rt, 16-24 h; (c) K_2CO_3, CH_3CN, -15 °C - rt, 16-24 h.

We also demonstrated that the Boc- and Cbz-protected guanidines **226a** and **226b** undergo cyclisation on oxidation with DMDO **263** to give the cyclic guanidines **265a** and **265b** in 18-72% and 79-95% yields. It was found that one of the protecting groups (Boc or Cbz) in each substrate undergoes migration to the hydroxyl group in a predictable manner. Again, attempted modification of these intermediates to obtain nintesidine E was unsuccessful (Scheme 100).



Scheme 100: (a) acetone, -20 °C - rt, 16-24 h; (b) i) acetone, rt, 5 wks, (ii) MeOH, H_2O, rt, 4 d, (iii) MeOH, TFA, rt, 16-24 h.

In the final approach, the allylic acetate guanidine **281** was prepared from the alcohol **274** in seven steps (Scheme 85). Cyclisation of **281** using palladium-catalysed conditions gave the mono-protected 6-membered guanidine **283** in 44% yield (Scheme 101).

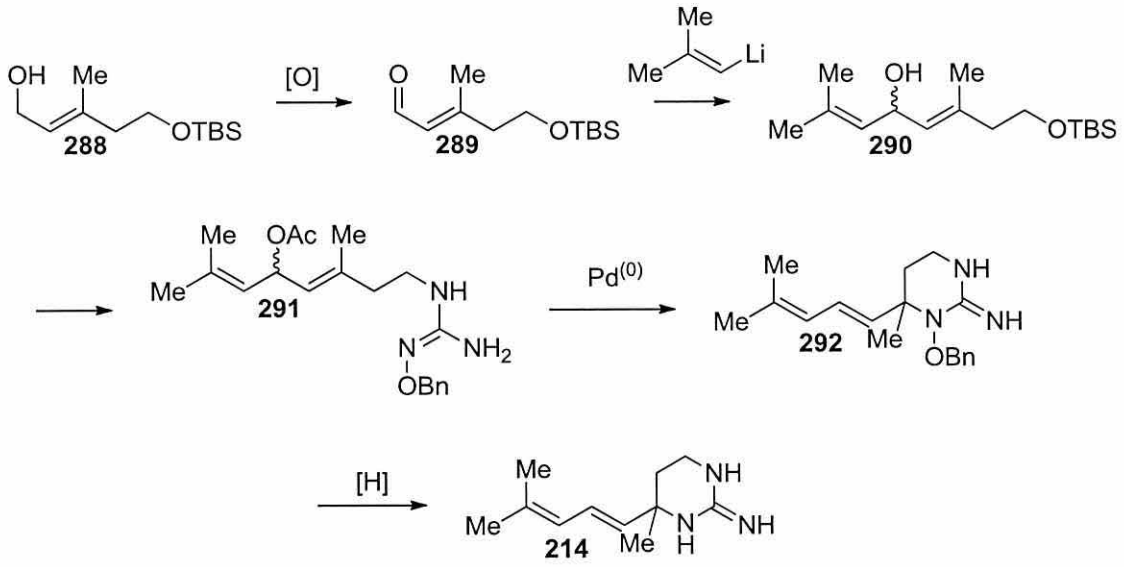


Scheme 101: Synthetic of the cyclic guanidine **283.**

This method was successful in that it generated the unsubstituted guanidine ring and introduced a vinylic group to the side chain. The possible future of this route it that potentially the remainder of the side chain could be introduced *via* olefin metathesis, however the drawback of removing the Cbz-protecting group still remains.

It is apparent that of the methodologies adopted, the one that has shown the greatest success is the palladium-catalysed methodology detailed in Scheme 101. However, some problems still exist in that the deprotection of these cyclic guanidines can not be achieved under acid catalysis due to problems associated with the sensitivity of the side chains. Another problem appears to be the preparation of a suitable substrate for the cyclisation, which will introduce the correct diene containing side chain. One possible route to overcome the first problem would to be to reinvestigate the reduction of the ketone **286** and to see if a selective reduction is possibly. An alternative would be to introduce the dimethylvinyl group *via* an organometallic addition to the corresponding aldehyde **289** (Figure 19) and to then modify this to the guanidine **291**. This methoxy-substituted guanidine should undergo cyclisation more readily than the Boc- and Cbz-protected substrates in a similar manner to that reported by Wifp and Buck.[38] The deprotection step is then dependent

on a selective reduction of the N-OBn function and might be achieved by a dissolving metal type reduction.



(Figure 19): Retrosynthetic approach E.

Experimental

General Procedures

Unless otherwise noted, reactions were stirred and monitored by TLC. Compounds were visualised using either iodine, phosphomolybdic acid, dragendorff, 2,4-dinitrophenylhydrazine or under UV light. All anhydrous reactions were conducted under a static argon atmosphere using oven dried glassware that had previously been cooled under a constant stream of nitrogen.

Materials

Reagents and starting materials were purchased from commercial suppliers and used without further purification unless otherwise noted. Rochelle salt[122] was prepared by dissolving KOH (10.66 g, 0.27 mol) and NaOH (14.92 g, 0.27 mol) in water (100 mL) before tartaric acid (40.00 g, 0.27 mol) was added. All anhydrous solvents used in reactions were distilled over either sodium wire and benzophenone (THF/Et_2O) or calcium hydride (DCM/DMPU/DIPA), and used either immediately or stored over molecular sieves prior to use.[123] Anhydrous DMF was prepared by sequential drying of reagent grade DMF with 3 Å molecular sieves.[124] NaH was purchased as a 60% dispersion in mineral oil and given three successive washes with hexane prior to use. The concentration of *n*-BuLi was determined by titration against DPAA.[125] Flash column chromatography was performed on Davisil® silica gel (35-70 microns) with the eluent specified in each case, TLC was conducted on precoated E.Merck silica gel 60 F_{254} glass plates.

Instrumentation

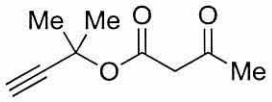
Melting points were determined using a Gallenkamp MF370 instrument and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 or 500 spectrometer with an internal deuterium lock at ambient temperature at 400 500 MHz and 100 or 125 MHz with internal references of δ_H 7.27 and δ_C 77.0 ppm for $CDCl_3$ and δ_H 3.31 and δ_C 49.00 ppm for CD_3OD. All mass spectra were performed at the EPSRC National Mass Spectrometry Service Centre based in Swansea. Low resolution Chemical Ionisation (CI) and Electrospray Ionisation (ESI) mass spectra were recorded on a Micromass Quattro II spectrometer and high resolution mass spectra were

recorded on either a Finnigan MAT 900 XLT or a Finnigan MAT 95 XP. Infrared samples were prepared as thin films, solutions or as KBr discs using sodium chloride plates and the spectra recorded on a Bruker Tensor 37 FT-IR.

Spectra

Spectrometric data (NMR, X-Ray and Mass Spec) for all characterised compounds is available for viewing on the attached electronic supplementary data CD.

1,1-Dimethyl-2-propynyl-3-oxobutanoate (233)[86,87]

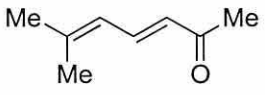


Chemical Formula: $C_9H_{12}O_3$
Exact Mass: 168.0786
Molecular Weight: 168.1898

2-Methylbut-3-yn-2-ol **231** (4.21 g, 4.87 mL, 50.0 mmol) was added to a stirred suspension of NaH (2.0 g, 50.0 mmol) in anhydrous THF (70 mL). After 30 min 2,2,6-trimethyl-1,3-dioxen-4-one **239** (7.11 g, 6.49 mL, 50.0 mmol) was added dropwise and the reaction mixture stirred at rt overnight. The reaction mixture was then diluted with Et_2O (200 mL) and washed with NH_4Cl (aq. sat., 150 mL), and brine (200 mL) and the organic layer dried over ($MgSO_4$). Purification by flash column chromatography on silica gel (0-20% diethyl ether/petroleum ether) gave ester **233** (5.4 g, 32.2 mmol) in 64% yield as an oil.

Rf = 0.20 (20% diethyl ether in petrol); ν_{max} (cm^{-1}) 2992, 2942 (CH), 2119 (alkyne), 1748 (C=O), 1719 (C=O) δ_H (500 MHz; $CDCl_3$) 1.67 (s, 6H, CH_3), 2.25 (s, 3H, CH_3), 2.55 (s, 1H, CH), 3.38 (s, 2H, CH_2) δ_C (125 MHz; $CDCl_3$) 28.6 (CH_3), 29.9 (CH_3), 50.7 (CH_2), 72.8 (C), 83.9 (CH), 90.1 (C), 165.3 (C), 200.4 (C); HRMS (ES) found 169.0857, $C_9H_{13}O_3$ ($[M+H]^+$) requires 169.0859

6-Methylhepta-3-5-dien-2-one (234)[84,89]



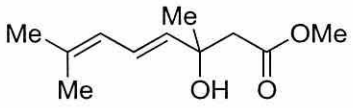
Chemical Formula: $C_8H_{12}O$
Exact Mass: 124.0888
Molecular Weight: 124.1803

Method A: A stirred mixture of 1,1-dimethyl-2-propynyl-3-oxobutanoate **233** (15.0 g, 89.28 mmol) and toluene-p-sulfonic acid (10 mg) was heated at 180-190 °C under an argon atmosphere for 4 h. Upon cooling to rt anhydrous sodium acetate (0.10 g) was added and the mixture was distillated giving ketone **234** (3.90 g, 31.45 mmol, 35%) as yellow oil.

Method B: A solution of oxalyl chloride (11.7 g, 92.8 mmol) in anhydrous DCM (200 mL) was cooled (-78 °C) under an argon atmosphere and anhydrous DMSO (13.2 g, 168.3 mmol) was added dropwise. After 20 min a solution of 3-methyl-2-buten-1-ol **240** (5.0 g, 58.1 mmol) in dry DCM (50 mL) was added to the reaction mixture. After a further 20 min NEt_3 (48.5 mL, 35.2 g, 348.3 mmol) was added dropwise. After 3 h TLC analysis indicated the complete consumption of starting material and the reaction mixture was diluted with water (2 x 300 mL), washed with brine (300 mL), extracted with DCM (3 x 300 mL) and the organic layer dried ($MgSO_4$) to give a quantitative yield of the aldehyde **241**. Aldehyde **241** was then treated with phosphorane **242** (40.8 g, 128.2 mmol) and the reaction mixture was stirred at rt for 14 days. The crude product was then dissolved in diethyl ether (ca. 50 mL), diluted with petroleum ether (ca. 50 mL), filtered and evaporated. Purification was carried out by column chromatography on silica gel (0-20% diethyl ether /petroleum ether) to give ketone **234** (3.18 g, 25.64 mmol, 44%) as yellow oil.

R*f* = 0.20 (20% diethyl ether in petrol); ν_{max} (cm^{-1}) 2975, 2930 (CH), 1682 (C=O), 1665, 1633 (C=C); δ_H (500 MHz; $CDCl_3$)1.90 (s, 3H, CH_3), 1.92 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 5.96 (d, 1H, *J* = 11.3 Hz, CH), 6.07 (d, 1H, *J* =15.1 Hz, CH), 7.42 (dd, 1H, *J* = 11.3, 15.1 Hz, CH); δ_C (125 MHz; $CDCl_3$) 24.6 (CH_3), 27.4 (CH_3), 30.9 (CH_3), 124.1(CH), 128.1 (CH), 139.7 (CH), 147.7 (C), 197.7 (C).

Methyl-3-hydroxy-3,7-dimethylocta-4,6-dienoate (236)[83]

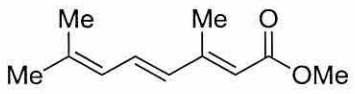


Chemical Formula: $C_{11}H_{18}O_3$
Exact Mass: 198.1256
Molecular Weight: 198.2588

A solution of 6-methylhepta-3-5-dien-2-one **234** (2.45 g, 19.75 mmol) and methyl bromoacetate **235** (3.62 g, 2.18 mL, 23.70 mmol, 1.2 equiv.) dissolved in dry benzene (25 mL) was added dropwise over 15 min to a stirred refluxing suspension of zinc (1.54 g, 23.70 mmol, 1.2 equiv.) in dry Et_2O (25 mL) under an argon atmosphere. The reaction mixture was then heated under reflux for 3 h. After cooling to room temperature, the reaction mixture was treated with a solution of acetic acid (6.0 mL) in water (150 mL) at (0 °C). The organic fraction was washed with water (2 x 250 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by column chromatography on silica gel (eluent: 20% diethyl ether/petroleum ether) to give the hydroxy ester **236** in 53% yield (2.06 g, 10.39 mmol).

R*f* = 0.15 (20% diethyl ether in petrol); ν_{max} (cm^{-1}) 3479 (OH), 2975, 2944 (CH), 1732 (C=O), 1634 (C=C); δ_H (500 MHz; $CDCl_3$)1.35 (s, 3H, CH_3), 1.77 (s, 6H, CH_3), 2.6 (s, 2H, CH_2), 3.7 (s, 3H, CH_3), 5.61 (d, 1H, *J* = 15.4 Hz, CH), 5.80 (d, 1H, *J* = 11.0 Hz, CH), 6.49 (dd, 1H, *J*= 11.0, 15.4 Hz, CH); δ_C (125 MHz; $CDCl_3$) 17.3 (CH_3), 25.0 (CH_3), 27.5 (CH_3), 44.5 (CH_2), 51.8 (CH_3), 71.0 (C), 123.2 (CH), 123.5 (CH), 134.9 (CH), 142.2 (C), 173.0 (C).

Methyl-3,7-dimethylocta-2-trans-4-trans-6-trienoate (237)[83]

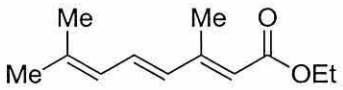


Chemical Formula: $C_{11}H_{16}O_2$
Exact Mass: 180.1150
Molecular Weight: 180.2435

Hydroxy ester **236** (610 mg, 3.08 mmol) and p-toluenesulfonic acid (17 mg) were dissolved in anhydrous benzene (10 mL) and the mixture heated under reflux for 1.5 h. After completion (TLC) the reaction mixture was cooled to rt and treated with a solution of sodium bicarbonate (aq., sat., 100 mL) and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), evaporated and purified by flash column chromatography on silica gel (0-5% diethyl ether/petroleum ether) to give **237** (230 mg, 1.27 mmol, 41%) as a clear oil.

R*f* = 0.29 (5% diethyl ether in petrol); ν_{max} (cm^{-1}) 2994, 2952 (CH), 1715 (C=O), 1687, 1634, 1605 (C=C); δ_H (500 MHz; $CDCl_3$) 1.85 (s, 6H, CH_3), 2.33 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 5.75 (s, 1H, CH), 5.96 (d, 1H, *J* = 11.3 Hz, CH), 6.16 (d, 1H, *J*= 15.4 Hz, CH), 6.83 (dd, 1H, *J* = 11.3, 15.4 Hz, CH); δ_C (125 MHz; $CDCl_3$) 14.2 (CH_3), 20.7 (CH_3), 26.1 (CH_3), 50.6 (CH_3), 117.2 (CH), 125.0 (CH), 125.7 (CH), 132.7 (CH), 140.4 (C), 151.4 (C), 166.6 (C).

(2*E*,4*E*)-ethyl 3,7-dimethylocta-2,4,6-trienoate (244) [90]

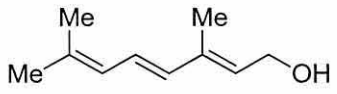


Chemical Formula: $C_{12}H_{18}O_2$
Exact Mass: 194.1307
Molecular Weight: 194.2701

A stirred solution of NaH (0.86 g, 21.62 mmol) in anhydrous THF (10 mL) was cooled (0 °C) and triethyl phosphonoacetate **243** (4.84 g, 21.62 mmol) was added dropwise over a period of 5 min. After stirring for 10 mins at 0 °C a solution of 6-methylhepta-3-5-dien-2-one **234** (0.89 g, 7.20 mmol) in anhydrous THF (1 mL) was added to the reaction mixture. After 1 h at 0 °C, the reaction was stirred at rt over 16-24 h. The reaction mixture was then washed with brine (2 x 50 mL), extracted with Et_2O, and the combined organic layer was dried ($MgSO_4$). Purification was achieved by column chromatography on silica gel (0-5% diethyl ether/petroleum ether) to give ester **244** (0.66 g, 3.40 mmol, 47%) as an oil.

R*f* = 0.15 (5% diethyl ether in petrol); ν_{max} (cm^{-1}) 3045, 2979, 2928, 2911, 2873 (C-H), 1709 (C=O), 1639 (C=C), 1605 (C=C), 1446; δ_H (500 MHz; $CDCl_3$) 1.29 (t, 3H, *J* = 7.1 Hz, CH_3), 1.85 (s, 6H, CH_3), 2.33 (s, 3H, CH_3), 4.17 (m, 2H, CH_2), 5.74 (s, 1H, CH), 5.96 (d, 1H, *J* =11.1 Hz, CH), 6.16 (d,1H, *J* =15.2 Hz, CH), 6.83 (dd, 1H, *J* = 11.1, 15.2 Hz, CH); δ_C (125 MHz; $CDCl_3$) 14.3 (CH_3), 18.8 (CH_3), 20.9 (CH_3), 26.4 (CH_3), 59.5 (CH_2), 116.1 (CH), 125.3(CH), 126.1 (CH), 133.1 (CH), 140.2 (C), 153.0 (C), 167.3 (C); HRMS (ES) found 195.1379, $C_{12}H_{19}O_2$ ([M+H^+]) requires 195.1380.

(2*E*,4*E*)-3,7-dimethylocta-2,4,6-trien-1-ol (238)[82]

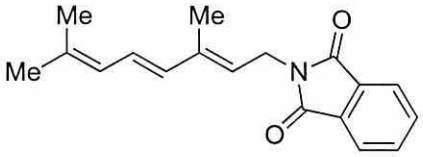


Chemical Formula: $C_{10}H_{16}O$
Exact Mass: 152.1201
Molecular Weight: 152.2334

A stirred solution of ester **244** (0.59 g, 3.06 mmol) in anhydrous toluene (10 mL) was cooled (-78 °C), whereupon a solution of DIBAL (1.0 M solution in hexane, 9.18 mL, 9.18 mmol) was added dropwise. After 3 h at -78 °C TLC analysis indicated the complete consumption of ester **244** and the reaction was quenched at -78 °C by the dropwise addition of MeOH (2 mL). Upon warming (0 °C) a solution of Rochelle's salt (sat, 10 mL) was added dropwise and then diluted with the same volume of Et_2O (10 mL) and the mixture stirred at rt until the solution cleared. The reaction was separated and the aqueous layer extracted with Et_2O (3 x 20 mL) and the combined organic layers dried ($MgSO_4$). After evaporation, purification was achieved by flash column chromatography on silica gel (0-20% diethyl ether/petroleum ether) to give the desired alcohol **238** as oil (0.16 g, 1.05 mmol, 34%).

R*f* = 0.10 (20% diethyl ether in petrol); ν_{max} (cm^{-1}) 3337 (OH), 2975, 2921 (CH), 1673, 1632 (C=C); δ_H (500 MHz; $CDCl_3$) 1.81 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 4.30 (t, 2H, *J* = 6.7 Hz, CH_2), 5.65 (t, 1H, *J* = 6.7 Hz, CH), 5.90 (d, 1H, *J* = 10.9 Hz, CH), 6.16 (d, 1H, *J* =15.3 Hz, CH), 6.46 (dd, 1H, *J* = 10.9, 15.3 Hz, CH); δ_C (125 MHz; $CDCl_3$) 12.6 (CH_3), 18.5 (CH_3), 26.2 (CH_3), 59.5 (CH_2), 125.3 (CH), 125.4 (CH) 128.9 (CH), 134.0 (CH), 136.1 (C), 137.0 (C).

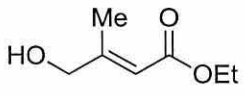
Attempted preparation of 2-((2*E*,4*E*)-3,7-dimethylocta-2,4,6-trien-1-yl)isoindoline -1,3-dione (245)



Chemical Formula: $C_{18}H_{19}NO_2$
Exact Mass: 281.1416
Molecular Weight: 281.3490

A stirred solution of alcohol **238** (150 mg, 1.026 mmol, 1 equiv.) in anhydrous THF (10 mL) was treated with PPh_3 (400 mg, 1.53 mmol, 1.5 equiv.) and phthalimide (190 mg, 1.33 mmol, 1.3 equiv.). The reaction was cooled (0 °C) and DEAD (210 mg, 0.19 mL, 1.23 mmol, 1.2 equiv.) in anhydrous THF (2 mL) was then added dropwise over a period of 15 min to the reaction mixture and the reaction stirred for a further 3 h at rt. After evaporation onto silica gel (1.5 g), column chromatography (20-60% diethyl ether/petroleum ether) gave several fractions, which on analysis by NMR possessed no signals indicative of the formation of the desired phthalimide **245**.

(*E*)-ethyl 4-hydroxy-3-methylbut-2-enoate (247)[93]

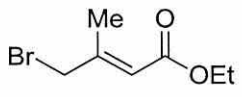


Chemical Formula: $C_7H_{12}O_3$
Exact Mass: 144.0786
Molecular Weight: 144.1684

A suspension of hydroxyacetone **246**(4.11 mL, 60.0 mmol) and (carbethoxymethylene) triphenylphosphorane (25.13 g, 72.0 mmol) in anhydrous MeCN (120 mL) was heated to reflux for 12 h. The reaction mixture was evaporated to dryness, triturated with Et_2O (ca. 100 mL) and cooled (-20 °C) overnight. The precipitated of triphenylphosphine oxide and excess phosphorane were filtered off and discarded. The filtrate was evaporated and the crude product was purified by column chromatography on silica gel (0-50 % ethyl acetate/petroleum ether) to give the allylic alcohol **247** as yellow oil (6.39 g, 44.3 mmol, 74%).

R*f* = 0.34 (40% ethyl acetate in petrol); ν_{max} (cm^{-1}) 3438 (br OH), 2983, 2926 (CH), 1716 (C=O), 1697 (C=C); δ_H (400 MHz; $CDCl_3$) 1.24 (t, 3H, J = 7.1 Hz, CH_3), 2.03 (s, 3H, CH_3), 2.93 (1H, s br, OH), 4.11 (m, 4H, 2 x CH_2), 5.93 (m, 1H, CH); δ_C (100 MHz; $CDCl_3$) 14.2 (CH_3), 15.5 (CH_3), 59.7 (CH_2), 66.8 (CH_2), 113.5 (CH), 157.6 (C), 167.1 (C); HRMS (ES) found 145.0856, $C_7H_{13}O_3$ ([M+H^+]) requires 145.0859.

(*E*)-ethyl 4-bromo-3-methylbut-2-enoate (248)[93]

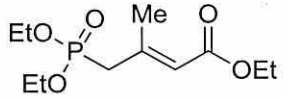


Chemical Formula: $C_7H_{11}BrO_2$
Exact Mass: 205.9942
Molecular Weight: 207.0650

A mixture of alcohol **247** (5.80 g, 40.23 mmol) and PPh_3 (11.0 g, 40.23 mmol) in anhydrous MeCN (50 mL) was cooled (0 °C) and tetrabromomethane (13.34 g, 40.23 mmol) was then added carefully and the reaction was stirred at ambient temperature overnight. The reaction mixture was evaporated to dryness and the crude product was purified by column chromatography on silica gel (0-5% ethyl acetate/petroleum ether) to give the bromide **248** as colourless oil (6.64 g, 32.06 mmol, 80%).

R*f* = 0.20 (5% ethyl acetate in petrol); ν_{max} (cm^{-1}) 2982, 2936 (CH), 1717 (C=O), 1648 (C=C); δ_H (400 MHz; $CDCl_3$) 1.26 (t, 3H, *J* = 7.2 Hz, CH_3), 2.25 (s, 3H, CH_3), 3.92 (s, 2H, CH_2), 4.14 (q, 2H, *J* = 7.2 Hz, CH_2), 5.93 (m, 1H, CH); δ_C (100 MHz; $CDCl_3$) 14.2 (CH_3), 17.1 (CH_3), 38.2 (CH_2), 60.1 (CH_2), 119.5 (CH), 152.3 (C), 165.8 (C); HRMS (ES) found 207.0019, $C_7H_{12}O_2Br$ ([M+H^+]) requires 207.0015.

(*E*)-ethyl 4-(diethoxyphosphoryl)-3-methylbut-2-enoate (249)[93]

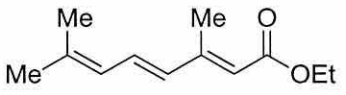


Chemical Formula: $C_{11}H_{21}O_5P$
Exact Mass: 264.1127
Molecular Weight: 264.2552

Bromide **248** (4.97 g, 24.00 mmol) was added dropwise to neat triethyl phosphite (10.30 mL, 60.01 mmol) and the mixture heated to reflux for 2.5 h. After cooling the crude product was then concentrated *in vacuo* to remove excess triethyl phosphite and the residue purified by silica gel chromatography (0-50% ethyl acetate/petroleum ether) to give the desired *E*-phosphonate ester **249** as a colourless oil (2.98 g, 11.27 mmol, 47%).

R*f* = 0.10 (30% ethyl acetate in petrol); ν_{max} (cm^{-1}) 2984, 2936 (CH), 1716 (C=O), 1648 (C=C); δ_H (400 MHz; $CDCl_3$) 1.28 (t, 3H, J = 7.1 Hz, CH_3), 1.33 (t, 6H, J = 7.1 Hz, 2 x CH_3), 2.31 (dd, 3H, J_{PH} = 3.4 and J_{HH} = 1.0 Hz, CH_3), 2.69 (d, 2H, J_{PH} = 23.4 Hz, CH_2), 4.16 (m, 6H, 3 x CH_2), 5.79 (broad d, 1H, J_{PH} = 5.2 Hz, CH); δ_C (100 MHz; $CDCl_3$) 14.2 (CH_3), 16.3 (d, 2C, $^3J_{PC}$ = 6.0 Hz, CH_3), 18.1 (d, $^3J_{PC}$ = 2.6 Hz, CH_3), 39.2, 61.4 (d, $^1J_{PC}$ = 134.6 Hz, CH_2), 62.2 (d, 2C, $^2J_{PC}$ = 6.7 Hz ,CH_2), 120.1 (d, $^3J_{PC}$ = 11.8 Hz, CH), 149.5 (d, $^2J_{PC}$ = 10.9 Hz, C), 166.0 (d, $^4J_{PC}$ = 3.6 Hz, C); HRMS (ES) found 265.1202, $C_{11}H_{22}O_5P$ ([M+H^+]) requires 265.1199.

(2*E*,4*E*)-ethyl 3,7-dimethylocta-2,4,6-trienoate (244)[93]



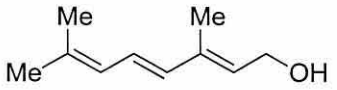
Chemical Formula: $C_{12}H_{18}O_2$
Exact Mass: 194.1307
Molecular Weight: 194.2701

A solution of phosphonate **249** (9.69 g, 36.68 mmol) in anhydrous THF (61 mL) was cooled (0 °C) before sequential treatment with DMPU (9.40 g, 8.87 mL, 73.36 mmol) and *n*-BuLi (2.5M in hexane, 16.13 mL, 40.34 mmol, 1.1 equiv.). The resulting mixture was stirred at 0 °C for 40 mins and then cooled (-78 °C) and 3-methyl-2-butenal **250** (4.21 mL, 44.01 mmol) was added dropwise over 10 min. The reaction mixture was stirred (-78 °C) for 2 h and then warmed (0 °C) to complete the reaction (monitored by TLC). Excess *n*-BuLi was destroyed by the careful addition of a 5% aqueous solution of NH_4Cl (ca. 50 mL) to pH 7-8, and the reaction mixture was extracted with EtOAc (twice). The combined organic layers were washed with water brine, dried ($MgSO_4$) and evaporated to dryness. Purification of the crude product using silica gel chromatography (gradient elution: 0-2% ethyl acetate/petroleum ether), gave the desired ester **244** (4.25 g, 21.87 mmol, 60%) as oil.

R*f* = 0.10 (2% ethyl acetate in petrol); ν_{max} (cm^{-1}) 2979, 2928 (CH), 1709 (C=O), 1639, 1605 (C=C); δ_H (400 MHz; $CDCl_3$) 1.29 (t, 3H, *J* = 7.1 Hz, CH_3), 1.85 (s, 6H, CH_3), 2.33 (s, 3H, CH_3), 4.17 (m, 2H, CH_2), 5.74 (s, 1H, CH), 5.96 (d, 1H, *J* =11.1 Hz, CH), 6.16 (d,1H, *J* =15.2 Hz, CH), 6.83 (dd, 1H, *J* = 11.1, 15.2 Hz, CH); δ_C (100 MHz; $CDCl_3$) 14.3 (CH_3), 18.7 (CH_3), 20.9 (CH_3), 26.4 (CH_3), 59.5 (CH_2), 116.1 (CH), 125.3(CH), 126.1 (CH), 133.1 (CH), 140.2 (C), 153.0 (C), 167.3 (C); HRMS (ES) found 195.1379, $C_{12}H_{19}O_2$ ([M+H^+]) requires 195.1380.

.

(2*E*, 4*E*)-3,7-dimethylocta-2,4,6-trien-1-ol (238)[93]

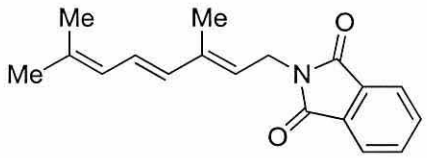


Chemical Formula: $C_{10}H_{16}O$
Exact Mass: 152.1201
Molecular Weight: 152.2334

A solution of ester **244** (0.51 g, 2.62 mmol) was dissolved in anhydrous DCM (10 mL) and cooled (-78 °C). DIBAL (1 M solution in hexane, 6.56 mL, 6.56 mmol, 2.5 equiv.) was added dropwise over 5 min and after stirring for 2 h the solution was diluted with EtOAc (2 mL) and stirred for 10 min then MeOH (2 mL) was added. The solution was then diluted with Et_2O (20 mL) and a solution of Rochelle's salt (20 mL) was added dropwise over 10 min and the mixture stirred at rt until the solution cleared. The reaction mixture was then separated and the aqueous layer further extracted with Et_2O (2 x 50 mL) and the combined organic extracts were then washed with H_2O (50 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (0-10% ethyl acetate/petroleum ether) gave the desired alcohol **238** (0.16 g, 1.05 mmol, 40% yield) as a colorless oil.

R*f* = 0.20 (10% ethyl acetate in petrol); ν_{max} (cm^{-1}) 3337 (br O-H), 3041, 2975, 2921, 2875 (C-H), 1673 (C=C), 1632 (C=C), 1595 (C=C); δ_H (400 MHz; $CDCl_3$) 1.81 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 4.30 (d, 2H, *J* = 6.7 Hz, CH_2), 5.65 (t, 1H, *J* = 6.7 Hz, CH), 5.90 (d, 1H, *J* = 10.9 Hz, CH), 6.16 (d, 1H, *J* =15.3 Hz, CH), 6.46 (dd, 1H, *J* = 10.9, 15.3 Hz, CH); δ_C (100 MHz; $CDCl_3$) 12.6 (CH_3), 18.5 (CH_3), 26.2 (CH_3), 59.5 (CH_2), 125.3 (CH), 125.4 (CH) 128.9 (CH), 134.0 (CH), 136.1 (C), 137.0 (C); HRMS (ES) found 151.1114, $C_{10}H_{15}O$ ([M-H^+]) requires 151.1117.

2-((2*E*,4*E*)-3,7-dimethylocta-2,4,6-trien-1-yl)isoindoline-1,3-dione (245)

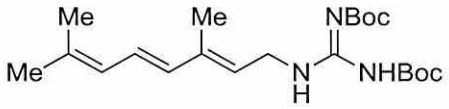


Chemical Formula: $C_{18}H_{19}NO_2$
Exact Mass: 281.1416
Molecular Weight: 281.3490

Method A: Alcohol **238** (217 mg, 1.43 mmol), PPh_3 (520 mg, 1.99 mmol, 1.4 equiv.) and phthalimide (250 mg, 1.72 mmol, 1.2 equiv.) were dissolved in anhydrous THF (20 mL) under argon. After cooling (0 °C) and stirring for 30 min, DIAD (0.37 mL, 380 mg,1.86 mmol, 1.3 equiv.) in anhydrous THF (3 mL) was added dropwise and the reaction mixture stirred for a further 2 h. Attempted purification by silica gel chromatography led to a white solid which on analysis (NMR) gave a complex spectrum.

Method B: Alcohol **238** (72 mg, 0.47 mmol), PPh_3 (170 mg, 0.66 mmol, 1.4 equiv.) and phthalimide (82 mg, 0.56 mmol, 1.2 equiv.) were dissolved in anhydrous THF (20 mL) under argon. After cooling (0 °C) and stirring for 30 min, DIAD (0.12 mL, 120 mg, 0.61 mmol, 1.3 equiv.) in anhydrous THF (1 mL) was added dropwise and the reaction stirred for a further 2 h gave crude **245** (132 mg). The, phthalimide **245** obtained could not be purified by column chromatography as it appeard to undergo decomposition on silica gel and was thus used crude in the following stage of the synthesis.

2,3-bis-*tert*-Butyl(*tert*-butoxycarbonyl)1-((2*E*,4*E*)-3,7-dimethylocta-2,4,6-trien-1-yl) guanidine (251)

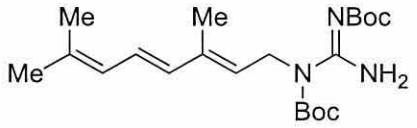


Chemical Formula: $C_{21}H_{35}N_3O_4$
Exact Mass: 393.2628
Molecular Weight: 393.5203

Phthalimide **245** (132 mg, 0.47 mmol) was dissolved in pure EtOH (20 mL), ethylenediamine (0.062 mL, 56 mg, 0.94 mmol, 2 equiv.) was added and the solution heated to reflux. After completion of the reaction (TLC, ca. 3-4 h) the solution was cooled, filtered and the filter pad washed with further EtOH (ca. 20-30 mL) and **209a** (580 mg, 1.88 mmol, 4 equiv.) and NEt_3 (0.7 mL, 480 mg, 4.70 mmol, 10 equiv.) were added to the filtrate. After stirring for 16-24 h the reaction mixture was evaporated onto silica gel (ca. 3 g) and purified by column chromatography (0-20% ethyl acetate/petroleum ether to give **251** (22 mg, 0.055 mmol) as a white solid in 12% yield.

Mpt 50-52 °C; R*f* = 0.20 (10% ethyl acetate in petrol); ν_{max} (cm^{-1}) 3387 (br N-H), 2978, 2931 (C-H), 1714 (C=O), 1647 (C=N), 1611 (C=C), 1509; δ_H (400 MHz; $CDCl_3$) 1.50 (s, 9H, 3 x CH_3), 1.52 (s, 9H, 3 x CH_3), 1.80 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 4.71 (apparent t, 2H, *J* = 7.1 Hz, CH_2), 5.48 (t, 1H, *J* = 7.1 Hz, CH), 5.88 (d, 1H, *J* = 11.0 Hz, CH), 6.14 (d, 1H, *J* = 15.3 Hz, CH), 6.44 (dd, 1H, *J* = 11.0, 15.3 Hz, CH), 8.25 (1H, br s, NH), 11.49 (1H, s, NH); δ_C (100 MHz; $CDCl_3$) 11.7 (CH_3), 17.4 (CH_3), 25.1 (CH_3), 27.0 (3 x CH_3), 27.2 (3 x CH_3), 38.2 (CH_2), 78.3 (C), 82.0 (C), 123.7 (CH), 124.1 (CH), 124.3 (CH), 132.6 (CH), 135.1 (C), 136.9 (C), 152.2 (C), 154.8 (C), 162.5 (C).

1,2-bis-*tert*-Butyl(*tert*-butoxycarbonyl)1-((2*E*,4*E*)-3,7-dimethylocta-2,4,6-trien-1-yl) guanidine (253)

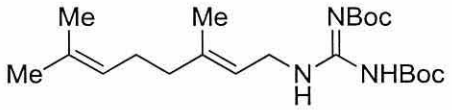


Chemical Formula: $C_{21}H_{35}N_3O_4$
Exact Mass: 393.2628
Molecular Weight: 393.5203

Alcohol **238** (0.320 g, 2.12 mmol), 1,3-bis(*tert*-butoxycarbonyl) guanidine **252** (1.14 g, 4.41 mmol, 2 equiv.) and PPh_3 (0.85 g, 3.25 mmol, 1.55 equiv.) were dissolved in anhydrous THF (10 mL) and cooled (0 °C). DIAD (0.64 mL, 0.65 g, 3.23 mmol, 1.54 equiv.) in anhydrous THF (1 mL) was then added dropwise. The reaction was stirred for 16-24 h and water (1 mL) was then added, and the reaction stirred for a further 30 min, whereupon the reaction solvent was removed *in vacuo* and the crude product dissolved in DCM (ca. 25 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. Attempted purification by column chromatography (0-20% ethyl acetate/petroleum ether) gave **253** (0.290 g, 0.737 mmol, 35% yield) as a white solid.

Mpt 50-52 °C; R*f* = 0.20 (10% ethyl acetate in petrol); ν_{max} (cm^{-1}) 3387 (br N-H), 2978, 2931 (C-H), 1714 (C=O), 1647 (C=N), 1611 (C=C), 1509; δ_H (400 MHz; $CDCl_3$) 1.49 (s, 9H, 3 x CH_3), 1.49 (s, 9H, 3 x CH_3), 1.80 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 1.86 (s, 3H, CH_3), 4.71 (d, 2H, *J* = 6.6 Hz, CH_2), 5.39 (t, 1H, *J* = 6.6 Hz, CH), 5.88 (d, 1H, *J* = 10.8 Hz, CH), 6.13 (d, 1H, *J* = 15.2 Hz, CH), 6.40 (dd, 1H, *J* = 10.8, 15.2 Hz, CH), 9.23 (1H, br s, NH), 11.49 (1H, s, NH); δ_C (100 MHz; $CDCl_3$) 11.7 (CH_3), 17.4 (CH_3), 25.1 (CH_3), 27.0 (3 x CH_3), 27.2 (3 x CH_3), 42.2 (CH_3), 77.7 (C), 82.7 (C), 123.2 (CH), 124.5 (CH), 126.1 (CH), 133.2 (CH), 134.4 (C), 134.6 (C), 154.0 (C), 159.4 (C), 162.7 (C).

***O-tert*-Butyl(*tert*-butyl)((*E*)-3,7-dimethylocta-2,6-dienylamino) methylene carbamate (255)**

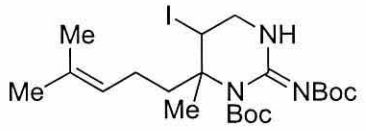


Chemical Formula: $C_{21}H_{37}N_3O_4$
Exact Mass: 395.2784
Molecular Weight: 395.5362

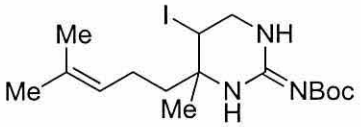
To a stirred solution of geranylamine **254** (0.66 g, 0.8 mL, 4.33 mmol, 1 equiv.) in anhydrous CH_3CN (20 mL) was added *N,N'*-bis-(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine **209a** (1.61 g, 5.19 mmol, 1.2 equiv.) and the reaction mixture was stirred over 16-24 h at rt. After evaporation, purification by flash column chromatography on silica gel (25% dichloromethane/petroleum ether) gave the protected guanidine **255** (1.10 g, 2.79 mmol, 64% yield) as a white solid.

Mpt 58-60°C; R*f* = 0.12 (25% dichloromethane in petrol); ν_{max} (cm^{-1}) 3339 (N-H), 3108 (N-H), 3003, 2979, 2929, 2860 (CH), 1739 (C=O), 1651 (C=N), 1626 (C=O), 1562 (C=C), 1475; δ_H (500 MHz; $CDCl_3$) 1.42 (s, 9H, 3 x CH_3), 1.44 (s, 9H, 3 x CH_3), 1.53 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.98 (m, 4H, 2 x CH_2), 3.96 (t, 2H, *J* = 6.1 Hz, CH_2), 5.00 (t, 1H, *J* = 6.4 Hz, CH), 5.16 (t, 1H, *J* = 6.1 Hz, CH), 8.12 (1H, br s, NH), 11.42 (1H, s, NH); δ_C (125 MHz; $CDCl_3$) 16.4 (CH_3), 17.7 (CH_3), 25.7 (CH_3), 26.3 (CH_2), 28.0 (3 x CH_2), 28.2 (3 x CH_2), 39.1 (CH_2), 39.5 (CH_2), 79.2 (C), 82.9 (C), 119.1 (CH), 123.8 (CH), 131.8 (C), 140.5 (C), 153.2 (C), 155.8 (C), 163.6 (C); HRMS (ES) found 396.2858, $C_{21}H_{38}N_3O_4$ ($[M+H]^+$) requires 396.2857.

tert-Butyl-2-((_tert_-butoxycarbonyl)imino)-5-iodo-6-methyl-6-(4-methylpent-3-en-1-yl)tetrahydropyrimidine-1(2*H*)-carboxylate (256) and _tert_-butyl (5-iodo-4-methyl-4-(4-methylpent-3-en-1-yl)tetrahydropyrimidin-2(1*H*)-ylidene)carbamate (257)



Chemical Formula: $C_{21}H_{36}IN_3O_4$
Exact Mass: 521.1750
Molecular Weight: 521.4327



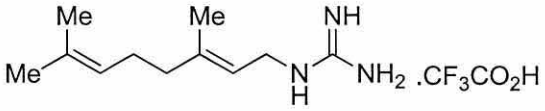
Chemical Formula: $C_{16}H_{28}IN_3O_2$
Exact Mass: 421.1226
Molecular Weight: 421.3169

To a stirred solution of guanidine **255** (0.50 g, 1.26 mmol, 1 equiv.) in anhydrous MeCN (20 mL) cooled (-15 °C) using an ice/ salt bath was added iodine (0.35 g, 1.39 mmol, 1.1 equiv.). The reaction stirred to rt over 16-24 h, then sodium thiosulphate solution (aq., sat.) was added until decolourisation occurred. The reaction mixture was then diluted with water (50 mL) and extracted with EtOAc (3 x 20 mL) and the combined organic phases dried ($MgSO_4$), filtered and evaporated *in vacuo* to give crude **256** (0.52 g) which was dissolved in Et_2O (ca. 5 mL) and diluted with petroleum ether to the cloud point. After cooling (-20 °C) for a week to give **257** (37 mg, 6% yield) as a yellow gum initially precipitated which was removed by decanting the mother liquor. Further dilution of the decanted mother liquor with petrol (ca. 1-2 mL) and standing overnight in the freezer gave a gum yellow precipitate of **256** (0.43 g, 0.82 mmol, 65% yield).

256 ν_{max} (chloroform)/cm^{-1} 3338 (N-H), 3114 (N-H), 2979, 2929 (CH), 1739 (C=O), 1651 (C=N), 1633 (C=O), 1563, 1531; δ_H (500 MHz; $CDCl_3$) 1.49 (s, 9H, 3 x CH_3), 1.51 (s, 9H, 3 x CH_3), 1.60 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 2.08 (m, 4H, 2 x CH_2), 3.85 (dd, 1H, J = 13.9, 9.0 Hz, CH), 3.97 (dd, 1H, J = 13.9, 4.8 Hz, CH), 4.25 (dd, 1H, J = 9.0, 4.8 Hz, CH), 5.23 (t, 1H, J = 6.9 Hz, CH), 8.38 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 17.6 (CH_3), 21.7 (CH_2), 22.5 (CH_3), 25.5 (CH_3), 28.0 (3 x CH_3), 28.2 (3 x CH_3), 39.3 (CH_2), 44.5 (CH), 45.5 (CH_2), 56.2 (C), 79.1 (C), 82.8 (C), 123.7 (CH), 131.7 (C), 153.1 (C), 155.7 (C), 163.5 (C); HRMS(ES) found 522.1818, $C_{21}H_{37}IN_3O_4$ ([M+H^+]) requires 522.1817.

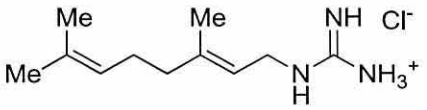
257 ν_{max} (chloroform)/cm^{-1} 3338 (N-H), 3114 (N-H), 2979, 2929 (CH), 1739 (C=O), 1651 (C=N), 1563, 1531; δ_H (500 MHz; $CDCl_3$) 1.51 (s, 9H, 3 x CH_3), 1.52 (s, 3H, CH_3),1.64 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.95 (m, 4H, 2 x CH_2), 3.85 (dd, 1H, J = 13.8, 8.8 Hz, CH), 4.04 (dd, 1H, J = 13.8, 4.5 Hz, CH), 4.29 (dd, 1H, J = 8.8, 4.5 Hz, CH)), 5.10 (t, 1H, J = 7.2 Hz, CH), 9.29 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 17.8 (CH_3), 21.8 (CH_2), 23.0 (CH_3), 25.6 (CH_3), 27.8 (3 x CH_3), 39.7 (CH_2), 41.3 (CH), 45.8 (CH_2), 56.3 (C), 85.7 (C), 121.6 (CH), 133.7 (C), 151.0 (C), 152.6 (C),; HRMS(ES) found 422.1300, $C_{16}H_{29}IN_3O_2$ ([M+H^+]) requires 422.1299.

Attempted synthesis of (*E*)-1-(3,7-dimethylocta-2,6-dien-1-yl)guanidine-2,2,2-trifluoroacetate (213) and chloride (215) salts (Nitensidine D)



Chemical Formula: $C_{13}H_{22}F_3N_3O_2$
Exact Mass: 309.1664
Molecular Weight: 309.3279

Method A: To a stirred solution of guanidine **255** (50 mg, 0.126 mmol, 1 equiv.) in anhydrous DCM (2 mL) at 0 °C was added TFA (1 mL) and the mixture stirred at rt for 24 h. After evaporation under reduced pressure and drying under high vacuum, the resultant guanidinium salt was purified by flash column chromatography on silica gel (0-30% methanol/chloroform). On evaporation, none of the fractions gave NMR data indicative of the the formation of **213**.

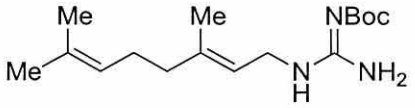


Chemical Formula: $C_{11}H_{22}ClN_3$
Exact Mass: 231.1502
Molecular Weight: 231.7655

Method B: To a stirred solution of guanidine **255** (100 mg, 0.252 mmol, 1 equiv.) in anhydrous MeOH (2 mL) was added HCl (3 M, 2 mL) and the mixture stirred at rt for 48 h (2 Attempts). After evaporation under reduced pressure and drying under high vacuum, the resultant guanidinium salt was purified by flash column chromatography on silica gel (0-30% methanol/chloroform). On evaporation, none of the fractions gave NMR data indicative of the the formation of **213**.

Method C: To a stirred solution of guanidine **255** (100 mg, 0.252 mmol, 1 equiv.) in EtOAc (2 mL) was added stannic chloride (260 mg, 1.0112 mmol, 4 equiv.) and the mixture stirred at rt for 3 h and progress monitored by TLC. The solvent and the excess of $SnCl_4$ were evaporated *in vacuo*, and the remaining solid diluted with MeOH (ca. 10 mL) and Et_2O was added until the formation of a white precipitate of the crude product occurred. After evaporation under reduced pressure and drying under high vacuum, the resultant guanidinium salt was purified by flash column chromatography on silica gel (0-30% methanol/chloroform). On evaporation, none of the fractions gave NMR data indicative of the the formation of **213**.

(*tert*-Butoxycarbonylamino)1-((2*E*,4*E*)-3,7-dimethylocta-2,4,6-trien-1yl)guanidine (258)

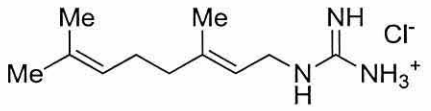


Chemical Formula: $C_{16}H_{29}N_3O_2$
Exact Mass: 295.23
Molecular Weight: 295.42

To a stirred solution of guanidine **255** (50 mg, 0.126 mmol, 1 equiv.) in THF (10 mL) was added potassium *t*-butoxide (140 mg, 0.17 mL, 1.264 mmol, 10 equiv.). Water (4.53 mg, 0.252 mmol. 2 equiv.) was then added and the mixture heated at reflux for 48 h (2 Attempts) and progress monitored by TLC. The reaction was cooled to rt and quenched with 10% citric acid solution (10 mL). The resulting mixture stirred at rt for 60 mins and then the pH was adjusted to 10–12 with 6N NaOH solution. The layers separated and aqueous layer was further extracted with EtOAc (10 mL). The combined organic layers dried ($MgSO_4$) and concentrated to afford the mono-protected guanidine **258** (15 mg, 0.050 mmol) was obtained in 40% yield as a yellow gum.

R*f* = 0.08 (20% methanol in chloroform); ν_{max} (chloroform)/cm^{-1} 3335 (NH), 3161 (NH), 2967, 2926, 2858 (CH), 1666 (C=N), 1663 (C=C), 1652 (C=C); δ_H (400 MHz; MeOD-d_4) 1.48 (s, 9H, 3 x CH_3), 1.61 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.10 (m, 4H, CH_2), 3.83 (d, 2H, J = 6.4 Hz, CH_2), 5.10 (t, 1H, J = 6.5 Hz, CH), 5.27 (t, 1H, J = 6.4 Hz, CH), 7.21(1H, br s, NH), 7.71 (1H, br s, NH); δ_C (100 MHz; MeOD-d_4) 15.0 (CH_3), 16.4 (CH_3), 24.5 (CH_3), 25.9 (CH_2), 27.1 (3 x CH_3, Boc), 38.7 (CH_2), 39.1 (CH_2), 68.9 (C, Boc), 107.5 (CH), 123.5 (CH), 131.3 (C), four quaternary carbon signals were not detected.

(*E*)-1-(3,7-Dimethylocta-2,6-dien-1-yl) guanidine(215) (Nitensidine D)

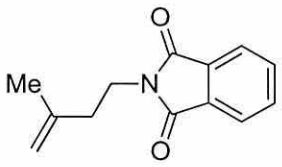


Chemical Formula: $C_{11}H_{22}ClN_3$
Exact Mass: 231.1502
Molecular Weight: 231.7655

To a stirred solution of geranylamine **254** (0.20 g, 1.30 mmol) in anhydrous DMF (2 mL) was added 1*H*-pyrazole-1-carboxamidine hydrochloride **259** (0.20 g, 1.30 mmol) and DIPEA (0.16 g, 0.22 mL, 1.30 mmol) and the reaction mixture stirred at rt for 48 h while being monitored by TLC. The reaction mixture was diluted with dry Et_2O (ca. 10-15 mL) which precipitated the crude product as a gum. The supernatant liquid was decanted and the residual gum was triturated with further dry Et_2O (ca. 15 mL). On drying under high vacuum the product **213** (0.16 g, 0.69 mmol) was obtained in 53% yield as a yellow gum.

R*f* = 0.06 (20% methanol in chloroform); ν_{max} (chloroform)/cm^{-1} 3334 (NH), 3160 (NH), 2969, 2927, 2859 (CH), 1667 (C=N), 1661 (C=C), 1651 (C=C); δ_H (400 MHz; DMSO-d_6) 1.57 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 2.04 (m, 4H, CH_2), 3.72 (apparent t, 2H, J = 6.0 Hz, CH_2), 5.08 (t, 1H, J = 6.5 Hz, CH), 5.19 (t, 1H, J = 6.0 Hz, CH), 7.21(1H, br s, NH), 7.71 (1H, br s, NH); δ_C (100 MHz; DMSO-d_6) 16.1 (CH_3), 17.5 (CH_3), 25.4 (CH_3), 25.8 (CH_2), 38.6 (CH_2), 38.8 (CH_2), 118.7 (CH), 123.7 (CH), 131.0 (C), 139.4 (C), 156.8 (C); HRMS (ES) found 196.1813, $C_{11}H_{22}N_3$ ([M+H^+]) requires 196.1808. Data were in agreement with the literature[79]

2-(3-Methylbut-3-enyl) isoindoline-1,3-dione (262)

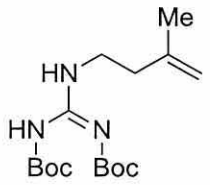


Chemical Formula: $C_{13}H_{13}NO_2$
Exact Mass: 215.0946
Molecular Weight: 215.2478

A stirred solution of 3-methyl-3-butene-1-ol **260** (5.0 g, 5.8 mL, 58.1 mmol, 1 equiv.) in anhydrous THF (200 mL) was treated with PPh_3 (21.3 g, 81.27 mmol, 1.4 equiv.) and phthalimide **261** (10.24 g, 69.66 mmol, 1.2 equiv.). The reaction was cooled (0 °C) and DEAD (13.14 g, 11.8 mL, 75.46 mmol, 1.3 equiv.) in anhydrous THF (5 mL) was then added dropwise over a period of 15 min to the reaction mixture. After 2 h at rt, the reaction was evaporated onto silica gel (60 g) and purified by column chromatography (0-30% ethyl acetate/petroleum ether) to give the phthalimide **262** (5.26 g, 24.44 mmol, 42%) as a white solid. A further quantity (4.83 g, 22.46 mmol, 39%) of lower purity material (ca. 90%) was also obtained which could be used without further purification in the next step.

MP 33-35 °C; R*f* = 0.25 (30% ethyl acetate in petrol); ν_{max} (cm^{-1}) 3059, 3029, 2980, 2952, 2917, 2853 (C-H), 1773 (C=O), 1705 (C=O), 1650, 1612 (C=C); δ_H (500 MHz; $CDCl_3$) 1.74 (s, 3H, CH_3), 2.33 (t, 2H, *J* = 7.1 Hz, CH_2), 3.75 (t, 2H, *J* = 7.1 Hz, CH_2), 4.60 (s, 1H, CH), 4.66 (s, 1H, CH), 7.70-7.74 (m, 4H, CH); δ_C (125 MHz; $CDCl_3$) 21.7 (CH_3), 36.2 (CH_2), 36.2 (CH_2), 112.4 (CH_2), 122.9 (CH), 131.8 (C), 133.5 (CH), 141.8 (C), 168.0 (C); HRMS (ES) found 216.1014, $C_{13}H_{14}NO_2$ ($[M+H]^+$) requires 216.1019.

***tert*-Butyl-(*tert*-butoxycarbonylamino)-(3-methylbut-3-enylamino)methylene carbamate (226a)**

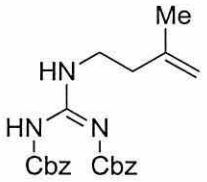


Chemical Formula: $C_{16}H_{29}N_3O_4$
Exact Mass: 327.2158
Molecular Weight: 327.4192

Hydrazine hydrate (1.57 g, 1.5 mL, 31.44 mmol, 1.3 equiv.) was added to a solution of 2-(3-methylbut-3-enyl) isoindoline-1, 3-dione **262** (5.26 g, 24.44 mmol, 1 equiv.) in IMS (100 mL) and the mixture was heated under reflux for 2.5 h. The reaction was then cooled to rt, filtered and the filter pad washed with further IMS (ca 10-20 mL). *N, N'*-bis-(*tert*-butoxycarbonyl)-*1H*-pyrazole-1-carboxamidine **209a** (5.0 g, 16.2 mmol, 0.67 equiv.) was then added to the filtrate. After stirring for 16-24 h at rt, the reaction was evaporated onto silica gel (ca. 10 g) and purified by column chromatography (0-10% ethyl acetate/ petroleum ether) to give the guanidine **226a** (2.89 g, 8.84 mmol, 55% yield) as a white solid.

Mpt 70-72 °C; R*f* = 0.20 (10% ethyl acetate in petrol); ν_{max} (cm^{-1}) 3326 (N-H), 3129 (N-H), 3077, 3002, 2976, 2954, 2933 (CH), 1742 (C=O), 1716 (C=N), 1654 (C=O), 1628 (C=C), 1568; δ_H (500 MHz; $CDCl_3$) 1.48 (s, 9H, CH_3), 1.50 (s, 9H, CH_3), 1.74 (s, 3H, CH_3), 2.27 (t, 2H, *J* = 6.9 Hz, CH_2), 3.55 (q, 2H, *J* = 6.9 Hz, CH_2), 4.78 (s, 1H, CH), 4.84 (s, 1H, CH), 8.30 (1H, br s, NH), 11.46 (1H, s, NH); δ_C (125 MHz; $CDCl_3$) 22.1 (CH_3), 28.0 (3 x CH_3), 28.2 (3 x CH_3), 36.8 (CH_2), 38.9 (CH_2), 79.3 (C), 82.9 (C), 112.6 (CH_2), 142.0 (C), 153.1 (C), 156.0 (C), 163.8 (C); HRMS (ES) found 328.2234, $C_{16}H_{30}N_3O_4$ ($[M+H]^+$) requires 328.2231.

N,N'bis-Cbz-N''-1-(3-methylbut-3-en-1-yl)guanidine (226b)

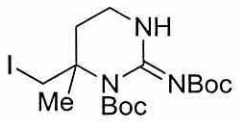


Chemical Formula: $C_{22}H_{25}N_3O_4$
Exact Mass: 395.1845
Molecular Weight: 395.4516

To a stirred solution of 2-(3-methylbut-3-enyl) isoindoline-1, 3-dione **262** (5.0 g, 23.25 mmol, 1 equiv.) in IMS (100 mL) was added hydrazine hydrate (1.51 g, 1.47 mL, 30.23 mmol, 1.3 equiv.) and the reaction was heated under reflux for 2.5 h. After completion of the reaction (TLC) the reaction was cooled to rt, filtered and the filter pad washed with further IMS (ca 10-20 mL). *N,N'*-bis-(benzyloxycarbonyl)-1*H*-pyrazole-1-carboxamidine **209b** (5.8 g, 15.58 mmol, 0.67 equiv.) was then added to the filtrate. After stirring for 16-24 h at rt the reaction was evaporated onto silica gel (25 g) and purified by column chromatography (0-15% ethyl acetate/petroleum ether) to give the guanidine **226b** (5.18 g, 13.09 mmol, 84% yield) as a waxy solid.

R*f* = 0.20 (15% ethyl acetate in petrol); ν_{max} (cm^{-1}) 3283 (N-H), 3168 (N-H), 3067, 3036, 2955, 2925, 2854 (C-H), 1723 (C=O) 1632 (C=N), 1607 (C=O), 1580 (C=C); δ_H (500 MHz; $CDCl_3$) 1.77 (s, 3H, CH_3), 2.31 (t, 2H, J = 6.7 Hz, CH_2), 3.60 (q, 2H, J = 6.7 Hz, CH_2), 4.83 (s, 1H, CH), 4.91 (s, 1H, CH), 5.17 (s, 2H, CH_2), 5.19 (s, 2H, CH_2), 7.30-7.44 (10H, m, 2 x Ph), 8.34 (1H, br s, NH), 11.78 (1H, s, NH); δ_C (125 MHz; $CDCl_3$) 22.0 (CH_3), 36.7 (CH_2), 39.0 (CH_2), 67.2 (CH_2), 68.1 (CH_2), 112.9 (CH_2), 126.9 (CH), 127.9 (CH), 128.1 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 128.8 (CH), 134.7 (CH), 136.8 (C), 141.9 (C), 153.8 (C), 155.9 (C), 163.7 (C); HRMS (ES) found 396.1917, $C_{22}H_{26}N_3O_4$ ($[M+H]^+$) requires 396.1918.

***tert*-Butyl-2-((tert-butoxycarbonyl)imino)-6-(iodomethyl)-6-methyltetrahydro pyrimidine-1(2H)-carboxylate (225a)**

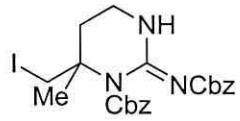


Chemical Formula: $C_{16}H_{28}IN_3O_4$
Exact Mass: 453.1124
Molecular Weight: 453.3157

To a stirred solution of guanidine **226a** (0.50 g, 1.53 mmol, 1 equiv.) in anhydrous MeCN (20 mL) cooled (-15 °C) using an ice/ salt bath was added potassium carbonate (1.26 g, 9.16 mmol, 6 equiv.) and iodine (1.55 g, 6.11 mmol, 4 equiv.). The reaction stirred to rt over 16-24 h, then sodium thiosulfate solution (aq., sat.) was added until decolourisation occurred. The resulting mixture was then diluted with water (50 mL) and extracted with EtOAc (3 x 20 mL) and the combined organic phases dried ($MgSO_4$), filtered and evaporated *in vacuo* gave crude **225a** (0.71 g) as a yellow gum.

ν_{max} (chloroform)/cm^{-1} 3263 (N-H), 3173 (N-H), 2977, 2932 (C-H), 1738 (C=O), 1645 (C=N), 1614 (C=O), 1505; δ_H (500 MHz; $CDCl_3$) 1.44 (s, 9H, CH_3), 1.54 (s, 9H, CH_3), 1.56 (s, 3H, CH_3), 1.90 (ddd, 1H, J = 6.0, 10.0, 15.0 Hz, CH), 2.33 (dt, 1H, J = 4.7, 15.0 Hz, CH), 3.31 (m, 2H, CH_2), 3.46 (d, 1H, J = 10.7 Hz, CH), 3.75 (d, 1H, J = 10.7 Hz, CH), 9.54 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 12.7 (CH_2), 24.0 (CH_3), 27.5 (3 x CH_3), 28.2 (3 x CH_3), 33.2 (CH_2), 35.6 (CH_2), 55.6 (C), 77.9 (C), 84.0 (C), 152.6 (C), 157.1 (C), 163.6 (C); HRMS(ES) found 454.1195, $C_{16}H_{29}IN_3O_4$ ([M+H^+]) requires 454.1197.

Benzyl-2-(((benzyloxy)carbonyl)imino)-6-(iodomethyl)-6-methyltetrahydro pyrimidine-1(2*H*)-carboxylate (225b)

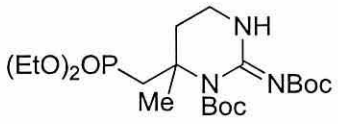


Chemical Formula: $C_{22}H_{24}IN_3O_4$
Exact Mass: 521.0811
Molecular Weight: 521.3481

To a stirred solution of guanidine **226b** (0.50 g, 1.26 mmol, 1 equiv.) in anhydrous MeCN (20 mL) cooled (-15 °C) using an ice/ salt bath was added potassium carbonate (1.05 g, 7.58 mmol, 6 equiv.) and iodine (1.27 g, 5.04 mmol, 4 equiv.). The reaction stirred to rt over 16-24 h, then sodium thiosulphate solution (aq., sat.) was added until decolourisation occurred. The resulting mixture was then extracted with DCM (3 x 20 mL) and the combined organic phases dried ($MgSO_4$), filtered and evaporated gave crude **225b** (0.69 g) which was dissolved in DCM (ca. 5 mL) and diluted with petrol to the cloud point. After cooling (-20 °C) overnight a small amount of dark oil precipitated and the supernatant was decanted, warmed to rt and diluted with petrol (50 mL). After cooling (-20 °C) overnight a gum precipitated which, after decanting the supernatant liquid, was washed with a small portion of petrol (ca. 10 mL). After decanting the petrol, drying of the residue under high vacuum gave **225b** (0.45 g, 0.86 mmol, 68% yield) as a yellow gum.

ν_{max} (chloroform)/cm^{-1} 3263, 3173 (N-H), 3063, 3032, 2943, 2886 (CH), 1743 (C=O), 1700 (C=N), 1610 (C=O), 1497, 1455; δ_H (500 MHz; $CDCl_3$) 1.52 (s, 3H, CH_3), 1.90 (ddd, 1H, J = 6.0, 9.0, 13.8 Hz, CH), 2.37 (dt, 1H, J = 4.9, 13.8 Hz, CH), 3.33 (m, 2H, CH_2), 3.53 (d, 1H, J= 10.6 Hz, CH), 3.73 (d, 1H, J = 10.6 Hz, CH), 5.07 (d, 1H, J = 12.5 Hz, CH), 5.13 (d, 1H, J = 12.5 Hz, CH), 5.23 (d, 1H, J = 12.1 Hz, CH), 5.32 (d, 1H, J = 12.1 Hz, CH), 7.28-7.48 (m, 10H, 2 x ph), 9.81 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 10.5 (CH_2), 22.2 (CH_3), 31.2 (CH_2), 33.8 (CH_2), 54.6 (C), 65.0 (CH_2), 68.2 (CH_2), 125.8 (CH), 126.1 (CH), 126.5 (CH), 126.6 (CH), 126.8 (CH), 127.1 (CH), 127.8 (CH), 132.6 (C), 135.3 (C), 152.2 (C), 155.7 (C), 161.8 (C); HRMS (EI) found 522.0878 $C_{22}H_{25}IN_3O_4$ ([M+H^+]) requires 522.0884.

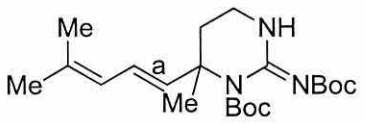
***tert*-Butyl-2-((*tert*-butoxycarbonyl)imino)-6-((diethoxyphosphoryl)methyl)-6-methyltetrahydropyrimidine-1(2*H*)-carboxylate (224)**



Chemical Formula: $C_{20}H_{38}N_3O_7P$
Exact Mass: 463.2447
Molecular Weight: 463.5054

To a stirred solution of iodocyclic guanidine **225a** (389 mg, 0.858 mmol, 1.0 equiv.) in anhydrous toluene was added triethyl phosphite (0.16 mL, 156.8 mg, 0.944 mmol, 1.1 equiv.). The reaction mixture was heated at 50-60 °C for 3 h and the reaction progress was monitored by TLC. The crude product was then cooled to rt and concentrated *in vacuo* until the excess triethyl phosphite was removed which was dissolved in DCM (ca. 5 mL) and diluted with petrol to the cloud point. After cooling (-20 °C) overnight, warmed to rt and diluted with petrol (50 mL). After cooling (-20 °C) overnight a white precipitated which, after decanting the supernatant liquid, was washed with a small portion of petrol (ca. 10 mL). After decanting the petrol, drying of the residue under high vacuum gave **224** (110 mg, 0.237 mmol, 28% yield) as a white solid which was used directly in the next step.

tert-Butyl-2-((_tert_-butoxycarbonyl)imino)-6-methyl-6-((_E_)-4-methylpenta-1,3-dien-1-yl)tetrahydropyrimidine-1(2_H_)-carboxylate (214)



Chemical Formula: $C_{21}H_{35}N_3O_4$
Exact Mass: 393.2628
Molecular Weight: 393.5203

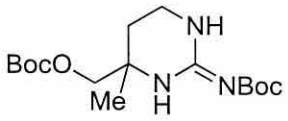
A stirred solution of diisopropylamine (0.85 mL, 600 mg, 6.0 mmol) in anhydrous THF (10 mL) was cooled (0 °C), to which *n*-BuLi (2.0 mL, 5.0 mmol) was added and the reaction stirred for 15 mins. The resulting solution of LDA was then cooled (-78 °C), phosphonate **224** (110 mg, 0.237 mmol) in anhydrous THF (2 mL) was added and the reaction was stirred for a further 1 h. Aldehyde **223** (0.5 mL, 42 mg, 5.0 mmol) in anhydrous THF (1 mL) was then added. The reaction was stirred further 1 h and allowed to warm slowly to rt over 24 h. The reaction was quenched by the addition of water (50 mL), extracted with EtOAc (3 x 50 mL) and the combined organic extracts washed with brine (3 x 50 mL) and dried ($MgSO_4$). The crude residue was analysed (NMR) and showed a complex spectrum, the resultant mixture was then dissolved in anhydrous MeOH (5 mL) and TFA (0.30 mL, 447 mg, 3.926 mmol, 5.0 equiv.) was then added. The reaction mixture stirred at rt overnight, after evaporation, purification was achieved by flash column chromatography on silica gel (0-10% ethyl acetate/petroleum ether followed by ethyl acetate (100%) and 5% methanol/ethyl acetate. NMR analysis of the combined fractions gave no indication of the formation of **214** or any other deprotected or rearranged analogues.

3,3-Dimethyldioxirane (263)[107]

Chemical Formula: $C_3H_6O_2$
Exact Mass: 74.0368
Molecular Weight: 74.0785

In a distillation apparatus equipped with a liquid nitrogen cooled collection flask, a mixture of sodium hydrogen carbonate (58.0 g, 700 mmol, 79.4 equiv.) in 3:4 acetone: water (95 mL: 127 mL) was cooled in an ice bath before the portion wise addition of oxone^R (6 x 12 g portions, 54.6 mmol) at 15 min intervals. At this point the collection of oxone was commenced by the application of a high vaccum and the reaction solution was distilled (At -78 °C) under high vacuum under liquid N_2 cooling of the collection flask until no further foaming was evident in the reaction vessel. After 90 mins further oxone^R (4 x 12 g, 18.2 mmol) was added to the solution and distillation continued for a further 90 min. The yellow distillate (ca. 100 mL) solution was dried with solid potassium carbonate, filtered through a cotton wool plug and used immediately.

***tert*-Butyl-(4-(((*tert*-butoxycarbonyl)oxy)methyl)-4-methyltetrahydropyrimidin-2(1*H*)-ylidene)carbamate (265a)**



Chemical Formula: $C_{16}H_{29}N_3O_5$
Exact Mass: 343.2107
Molecular Weight: 343.4186

Method A: A solid sample of guanidine **226a** (0.33 g, 1.01 mmol) in a RBF (250 mL) was cooled (-20 °C) and a solution of dry DMDO in acetone (excess) was added and the mixture stirred to rt over 16-24 h under an argon atmosphere. The reaction progress was monitored by ^{1}H NMR spectroscopy and was deemed complete after 5 weeks. After evaporation of the acetone the crude product was dissolved in DCM, dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification was achieved by flash column chromatography on silica gel (20-100% ethyl acetate/petroleum ether) gave **265a** (0.063 g, 0.183 mmol, 18% yield) as a white solid.

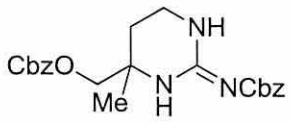
Method B: A solid sample of guanidine **226a** (0.33 g, 1.01 mmol) in a RBF (250 mL) was cooled (-20 °C) and a solution of dry DMDO in acetone (excess) was added and the mixture stirred to rt over 16-24 h under an argon atmosphere. After evaporation of the acetone the crude product was dissolved in DCM, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The resulting product was dissolved in MeOH (5 mL) and water (0.1 mL) was added, the reaction progress was monitored by ^{1}H NMR spectroscopy and was deemed complete after 4 days. After evaporation of MeOH the crude product was dissolved in DCM and evaporated *in vacuo*. Purification was achieved by column chromatography on silica gel (20-100% ethyl acetate/petroleum ether) gave **265a** (0.25 g, 0.73 mmol, 72% yield) as a white solid, which was recrystallised from dichloromethane/hexane to give crystals suitable for X-ray analysis (See appendices).

Method C: A solid sample of guanidine **226a** (0.33 g, 1.01 mmol) in a RBF (250 mL) was cooled (-20 °C) and a solution of dry DMDO in acetone (excess) was added and the mixture stirred to rt over 16-24 h under an argon atmosphere. After evaporation of the acetone the crude product was dissolved in DCM, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The resulting product was dissolved in MeOH (5 mL), cooled (0 °C) and TFA (0.36 mL, 5 equiv.) was added dropwise. After slow warming to rt stirring was continues for 24 h. After evaporation under reduced pressure, the crude

residue was dissolved in DCM (ca. 5 mL) and was then diluted with petrol to the cloud point. After cooling (-20 °C) overnight, gave **265a** (0.21 g, 0.61 mmol, 61%) as a white solid.

Mpt 143-145°C; ν_{max} (cm^{-1}) 3261 (N-H), 2978, 2931 (CH), 1745 (C=O), 1714 (C=O), 1644 (C=N); δ_H (500 MHz; $CDCl_3$) 1.49 (s, 9H, 3 x CH_3), 1.51 (s, 9H, 3 x CH_3), 1.42 (s, 3 H, CH_3), 1.80 (m, 1H, CH), 2.10 (m, 1H, CH), 3.52 (m, 2H, CH_2), 4.03 (d, 1H, J = 11.3 Hz, CH), 4.14 (d, 1H, J = 11.3 Hz, CH), 9.59 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 24.7 (CH_3), 27.3 (3 x CH_3), 27.5 (3 x CH_3), 29.6 (CH_2), 35.4 (CH_2), 51.5 (C), 70.7 (CH_2), 81.9 (C), 82.9 (C), 153.1 (C), 155.2 (C), 171.1 (C); HRMS(ES) found 344.2184, $C_{16}H_{30}N_3O_5$ ([M+H^+]) requires 344.2180.

Benzyl-(4-((((benzyloxy)carbonyl)oxy)methyl)-4-methyltetrahydropyrimidin-2(1*H*)-ylidene)carbamate (265b)



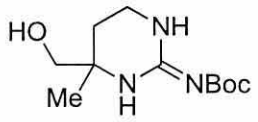
Chemical Formula: $C_{22}H_{25}N_3O_5$
Exact Mass: 411.1794
Molecular Weight: 411.4510

Method A: A solid sample of guanidine **226b** (0.50 g, 1.26 mmol) in a RBF (250 mL) was cooled (-20 °C) and a solution of dry DMDO in acetone (excess) was added and the mixture stirred to rt over 16-24 h. under an argon atmosphere. After evaporation of the acetone the crude product was dissolved in DCM, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The resulting product was dissolved in MeOH (5 mL) and water (0.1 mL) was added, the reaction progress was monitored by ^1H NMR spectroscopy and was deemed complete after 7 days. After evaporation of methanol, the crude product was dissolved in DCM and the reaction was then evaporated onto silica gel (ca. 0.6 g). Purification was achieved by column chromatography (50-70% ethyl acetate/petroleum ether), followed by 100% ethyl acetate and (2-4% methanol/ethyl acetate) gave **265b** (0.41 g, 0.99 mmol) in 79% yield as colorless gum, which was recrystallised from dichloro methane/ hexane to give the product **265b**.

Method B: A solid sample of guanidine **226b** (0.50 g, 1.26 mmol) in a RBF (250 mL) was cooled (-20 °C) and a solution of dry DMDO in acetone (excess) was added and the mixture stirred to rt over 16-24 h under an argon atmosphere. After evaporation of the acetone the crude product was dissolved in DCM, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The resulting product was dissolved in MeOH (5 mL), cooled (0 °C) and TFA (0.52 mL, 5 equiv.) was added dropwise. After slow warming to rt stirring was continues for 24 h. After evaporation of methanol the crude product was dissolved in DCM and evaporated *in vacuo*. Purification was achieved by flash column chromatography (50-70% ethyl acetate/petroleum ether), followed by 100% ethyl acetate and (2-4% methanol/ethyl acetate) gave **265b** (0.49 g, 1.19 mmol, 95%) as colorless gum, which was recrystallised from dichloromethane/hexane to give the product **265b** and the resultant product was also characterised by the 2-D NMR HSQC and HMBC correlation.

R*f* = 0.16 (60% ethyl acetate in petrol); ν_{max} (chloroform)/cm^{-1} 3243, 3154 (N-H), 3064, 3032, 2955, 2928, 2896 (C-H), 1748 (C=O), 1644 (C=N), 1634 (C=O), 1562, 1554; δ_H (500 MHz; $CDCl_3$) 1.42 (s, 3H, CH_3), 1.78 (m, 1H, CH), 2.02 (m, 1 H, CH), 3.50 (m, 2H, CH_2), 4.10 (d, 1 H, *J* = 11.2 Hz, CH), 4.21 (d, 1H, *J* = 11.2 Hz, CH), 5.18 (s, 2H, CH_2), 5.26 (s, 2H, CH_2), 7.34-7.43 (m, 10H, 2 x ph), 9.84 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 24.7 (CH_3), 27.7 (CH_2), 35.5 (CH_2), 52.0 (C), 68.4 (CH_2), 70.3 (CH_2), 71.4 (CH_2), 128.1 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 128.8 (CH), 134.6 (C), 134.8 (C), 152.1 (C), 154.5 (C), 171.1 (C); HRMS(ES) found 412.1867, $C_{22}H_{26}N_3O_5$ ([M+H^+]) requires 412.1867.

(*E*)-*tert*-Butyl-(4-(hydroxymethyl)-4-methyltetrahydropyrimidin-2(1*H*)-ylidene) carbamate (266)

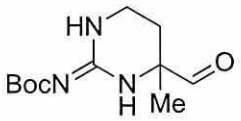


Chemical Formula: $C_{11}H_{21}N_3O_3$
Exact Mass: 243.1583
Molecular Weight: 243.3027

To a stirred solution of cyclic guanidine **265a** (180 mg, 0.53 mmol, 1.0 equiv.) in anhydrous MeOH (5 mL) was added potassium carbonate (80 mg, 0.64 mmol,1.2 equiv.) and the reaction stirred at rt under an argon atmosphere overnight. The solvent was removed *in vacuo* and the resulting mixture was then diluted with a mixture of MeOH/EtOAc (1:10, 22 mL), filtered and evaporated *in vacuo*. Purification by flash column chromatography on silica gel (50-75% ethyl acetate/petroleum ether) followed by (2-10% methanol in ethyl acetate) to afford the guanidine **266** (40 mg, 0.16 mmol, 31% yield).

R*f* = 0.10 (10% methanol in ethyl acetate); ν_{max} (cm^{-1}) 3447 (O-H), 2918, 2850 (CH), 1685 (C=O), 1647 (C=N); δ_H (500 MHz; MeOD-d_4) 1.44 (s, 9H, 3 x CH_3), 1.26 (s, 3H, CH_3), 1.67 (m, 1H, CH), 1.81 (m, 1H, CH), 3.30 (m, 2H, CH_2), 3.39 (d, 1H, J = 11.1 Hz, CH), 3.51 (d, 1H, J= 11.1 Hz, CH); δ_C (125 MHz; MeOD-d_4) 25.3 (CH_3), 27.5 (3 x CH_3), 29.5 (CH_2), 37.6 (CH_2), 53.4 (C), 70.2 (CH_2), 80.6 (C), 155.4 (C), 158.7 (C); HRMS (ES) found 244.1656, $C_{11}H_{22}N_3O_3$ ([M+H^+]) requires 244.1656.

Attempted preparation of *tert*-butyl (4-acetyl-4-methyltetrahydropyrimidin-2(1*H*) -ylidene)carbamate (228)

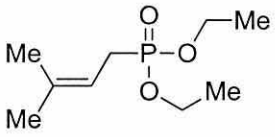


Chemical Formula: $C_{11}H_{19}N_3O_3$
Exact Mass: 241.1426
Molecular Weight: 241.2869

Method A: To a stirred solution of alcohol **266** (25 mg, 0.1028 mmol, 1.0 equiv.) in anhydrous CH_3CN (3 mL) at 0 °C was added Dess-Martin periodinane (65 mg, 0.1542 mmol, 1.5 equiv.) and the mixture stirred and warmed to rt over 2 h. The reaction was then diluted with EtOAc (20 mL), filtered through silica gel (ca. 1cm) and the filter pad washed with further EtOAc (ca. 10-20 mL). After evaporation, the crude residue was analysed (NMR) and showed no indication of the target molecule **228** and no recovered starting material was obtained.

Method B: To a stirred solution of alcohol **266** (38 mg, 0.156 mmol, 1.0 equiv.) in anhydrous THF (3 mL) at 0 °C was added Dess-Martin periodinane (99 mg, 0.234 mmol, 1.5 equiv.). The solution was stirred vigorously and H_2O (2.8 mg, 0.156 mmol, 1.0 equiv.) in THF (0.28 mL) was added slowly and the mixture was allowed to warm to rt and stirred for 24 h. The reaction was then filtered through Celite (ca. 1cm) and the filter pad washed with further THF (ca. 10-20 mL). After evaporation, the crude residue was analysed (NMR) and showed no indication of the target molecule **228** or any unreacted starting material.

Diethyl 3-methylbut-2-enylphosphonate (268)[105]



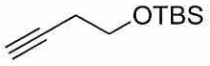
Chemical Formula: $C_9H_{19}O_3P$
Exact Mass: 206.1072
Molecular Weight: 206.2191

A solution of triethyl phosphite (1.11 g, 6.71 mmol, 1.0 equiv.) and 4-bromo-2-methyl-2-butene **267** (1.0 g, 6.7 mmol, 1.0 equiv.) was stirred under an argon atmosphere and the reaction heated under reflux for 3 h. The crude product was then cooled to rt and concentrated *in vacuo* until the excess triethyl phosphite was removed and purified by silica gel chromatography (100% diethyl ether) to give **268** (0.93 g, 4.50 mmol, 67% yield) as oil.

R*f* = 0.20 (diethyl ether); ν_{max} (cm^{-1}) 2982, 2931, 2913 (CH), 1646 (C=C); δ_H (500 MHz; $CDCl_3$) 1.16 (t, 6H, J = 7.2 Hz, 2 x CH_3), 1.51 (d, 3H, J = 4.1 Hz, CH_3), 1.60 (d, 3H, J = 5.3 Hz, CH_3), 2.39 (dd, 2H, J = 7.5, 22.0 Hz, CH_2), 3.94 (m, 4H, CH_2), 5.02 (m, 1H, CH); δ_C (125 MHz; $CDCl_3$) 16.5 (CH_3), 16.6 (CH_3), 18.0 (d, $^3J_{PC}$ = 2.5 Hz, CH_3), 25.6 (CH_3), 25.7 (d, $^1J_{PC}$ = 138.2 Hz, CH_2), 61.8 (2 x CH_2), 112.6 (d, $^2J_{PC}$ = 11.3 Hz, CH), 136.6 (d, $^3J_{PC}$ = 14.5 Hz, C).

.

(But-3-ynyloxy)(tert-butyl)dimethylsilane (275)

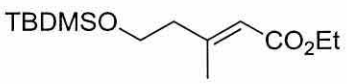


Chemical Formula: $C_{10}H_{20}OSi$
Exact Mass: 184.1283
Molecular Weight: 184.3507

A solution of 3-butyn-1-ol **274** (10.0 g, 142.7 mmol), was dissolved in anhydrous DMF (30 mL), cooled (0 °C) and imidazole (30.11 g, 442.3 mmol) was added in one portion. TBSCl (30.10 g, 199.74 mmol) was then added in portions over 15 mins and the reaction was stirred to rt overnight. The reaction was diluted with water (200 mL) and extracted with hexane (2 x 100 mL), the combined organic fractions where dried ($MgSO_4$) and concentrated *in vacuo* to give the required product **275** (24.14 g, 130.9 mmol, 92% yield) as oil which was used without further purification in the next step.

ν_{max} (cm^{-1}) 2955, 2930, 2885, 2858 (CH), 2123 (C≡C), 3315 (≡C-H); δ_H (400 MHz; $CDCl_3$) 0.07 (s, 6H, 2 x CH_3), 0.90 (s, 9H, 3 x CH_3), 1.95 (t, 1H, J = 2.6 Hz, CH), 2.39 (dt, 2H, J = 2.6, 7.1 Hz, CH_2), 3.74 (t, 2H, J = 7.1 Hz, CH_2); δ_C (100 MHz; $CDCl_3$) -5.3 (2 x CH_3), 18.3 (C), 25.8 (3 x CH_3), 26.3 (CH_2), 61.7 (CH_2), 69.3 (CH), 81.4 (C).

(*E*)-ethyl 5-(*tert*-butyldimethylsilyloxy)-3-methylpent-2-enoate (276)

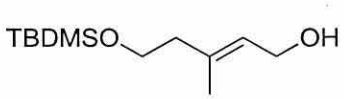


Chemical Formula: $C_{14}H_{28}O_3Si$
Exact Mass: 272.1808
Molecular Weight: 272.4558

A suspension of Cp_2ZrCl_2 (5.0 g, 17.11 mmol) in anhydrous DCM (60 mL) was cooled (-23 °C) and Me_3Al (25.6 mL, 51.2 mmol, 2 M solution in hexane) was added dropwise. The reaction mixture was stirred at -5 °C for 1 h before being cooled again (-23 °C). Water (461.3 μL) was then slowly added with vigorous stirring and after 10 mins a solution of **275** (3.20 g, 17.11 mmol) in anhydrous DCM (5 mL) was added to the reaction mixture. After 5 h $ClCO_2Et$ (3.7 g, 3.2 mL, 34.2 mmol, 2 equiv.) was added and the reaction was stirred at rt overnight. The reaction mixture was then cooled (0 °C) and diluted with Et_2O (50 mL) before a solution of Rochelle's salt (50 mL) was added dropwise over 20 mins, the mixture was then stirred at r.t for 2 h or until the solution cleared. The reaction mixture was separated and the aqueous layer extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed with H_2O (150 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification of the crude product by silica gel chromatography (0-2% ethyl acetate/ petroleum ether) gave **276** (1.96 g, 7.21 mmol, 42% yield) as a colorless oil.

Rf = 0.10 (2% ethyl acetate in petrol); ν_{max} (cm^{-1}) 2955, 2930, 2900, 2858 (CH), 1718 (C=O), 1651 (C=C); δ_H (400 MHz; $CDCl_3$) 0.05 (s, 6H, 2 x CH_3), 0.89 (s, 9H, 3 x CH_3), 1.27 (t, 3H J = 7.1 Hz CH_3), 2.18 (d, 3H, J = 1.1 Hz, CH_3), 2.35 (t, 2H, J = 6.7 Hz, CH_2), 3.75 (t, 2H, J = 6.7 Hz, CH_2), 4.15 (q, 2H, J = 7.1 Hz, CH_2), 5.68 (q, 1H, J = 1.1 Hz, CH); δ_C (100 MHz; $CDCl_3$) -5.4 (2 x CH_3), 14.3 (CH_3), 18.3 (C), 19.1 (CH_3), 25.8 (3 x CH_3), 44.0 (CH_2), 59.5 (CH_2), 61.3 (CH_2), 117.2 (CH), 156.8 (C), 166.6 (C); HRMS (ES) found 273.1885, $C_{14}H_{29}O_3Si$ ([M+H^+]) requires 273.1880.

(*E*)-5-(*tert*-butyldimethylsilyloxy)-3-methylpent-2-en-1-ol (277)

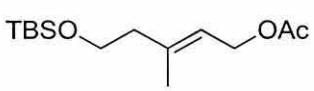


Chemical Formula: $C_{12}H_{26}O_2Si$
Exact Mass: 230.1702
Molecular Weight: 230.4191

To a stirred solution of ester **276** (0.97 g, 3.57 mmol) in anhydrous DCM (10 mL) cooled (-78 °C) was added dropwise over 5 mins DIBAL-H (1M in hexane, 8.5 mL, 8.5 mmol). After stirring for 4 h at -78 °C, the mixture was then diluted with EtOAc (1 mL), stirred for 10 mins at -78 °C, then MeOH (1 mL) was then added. The reaction was then diluted with Et_2O (50 mL) before a solution of Rochelle's salt (50 mL) was added dropwise over 5 mins, the mixture was then stirred at rt until the solution cleared (ca. 30 min-2 h). The mixture was then separated and the aqueous layer extracted with further Et_2O (2 x 100 mL), the combined organic extracts were then washed with H_2O (150 mL), then dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (0-10% ethyl acetate/petroleum ether) gave the alcohol **277** (0.60 g, 2.62 mmol, 73% yield) as a colorless oil.

R*f* = 0.20 (10% ethyl acetate in petrol); ν_{max} (cm^{-1}) 3339 (br, OH), 2955, 2929, 2886, 2858 (CH), 1670 (C=C); δ_H (400 MHz; $CDCl_3$) 0.06 (s, 6H, 2 x CH_3), 0.90 (s, 9H, 3 x CH_3), 1.65 (d, 3H, J = 1.1 Hz, CH_3), 2.19 (t, 2H, J = 7.0 Hz, CH_2), 3.65 (t, 2H, J = 7.0 Hz, CH_2), 4.10 (d, 2H, J = 7.0 Hz, CH_2), 5.39 (qt, 1H, J = 1.1, 7.0 Hz, CH); δ_C (100 MHz; $CDCl_3$) -5.3 (2 x CH_3), 16.6 (CH_3), 18.3 (C), 25.9 (3 x CH_3), 42.7 (CH_2), 59.3 (CH_2), 62.1 (CH_2), 125.3 (CH), 136.7 (C); HRMS (ES) found 248.2043, $C_{12}H_{26}O_2SiNH_4$ ([M+NH_4^+]) requires 248.2040.

(*E*)-5-(*tert*-butyldimethylsilyloxy)-3-methylpent-2-enyl acetate (278)

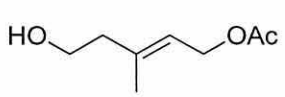


Chemical Formula: $C_{14}H_{28}O_3Si$
Exact Mass: 272.1808
Molecular Weight: 272.4558

Alcohol **277** (0.77 g, 3.35 mmol), dry pyridine (1.62 g, 1.66 mL, 20.58 mmol, 5 equiv.) and DMAP (25 mg) were dissolved in anhydrous DCM (5 mL) and cooled (0 ^{o}C). Ac_2O (1.26 g, 1.2 mL, 12.35 mmol, 3 equiv.) was then added dropwise and after stirring to rt for 3 h an aqueous solution of HCl (100 mL, 0.2 M) was added and the reaction extracted with DCM (3 x 70 mL). The organic layer was washed with aq. sat. NH_4Cl (50 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (0-5% diethyl ether/petroleum ether), afforded the desired compound **278**, as oil (0.84 g, 3.08 mmol, 92%).

R*f* = 0.20 (5% diethyl ether in petrol); ν_{max} (cm^{-1}) 2954, 2930, 2896, 2858 (CH), 1742 (C=O), 1671 (C=C); δ_H (400 MHz; $CDCl_3$) 0.04 (s, 6H, 2 x CH_3), 0.88 (s, 9H, 3 x CH_3), 1.72 (broad s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.25 (t, 2H, J = 6.8 Hz, CH_2), 3.70 (t, 2H, J = 6.8 Hz, CH_2), 4.58 (d, 2H, J = 7.1 Hz, CH_2), 5.37 (t, 1H, J = 7.1 Hz, CH); δ_C (100 MHz; $CDCl_3$) -5.3 (2 x CH_3), 16.7 (CH_3), 18.2 (C), 21.0 (CH_3), 25.8 (3 x CH_3), 42.7 (CH_2), 61.2 (CH_2), 61.7 (CH_2), 120.1 (CH), 139.4 (C), 171.1 (C); HRMS (ES) found 273.1885, $C_{14}H_{29}O_3Si$ ([M+H^+]) requires 273.1880.

(*E*)-5-hydroxy-3-methylpent-2-enyl acetate (279)

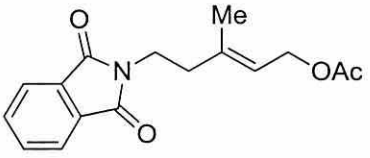


Chemical Formula: $C_8H_{14}O_3$
Exact Mass: 158.0943
Molecular Weight: 158.1950

To a cooled (0 °C) solution of silyl ether **278** (0.89 g, 3.29 mmol) in anhydrous THF (10 mL), was added a solution of TBAF (15 mL, 1M in THF, 3.62 mmol, 1.1 equiv.). After stirring to rt overnight the reaction was diluted with water (50 mL) and DCM (100 mL), the organic phase separated and the aqueous layer extracted with further DCM (2 x 25 mL). The combined organic layers were washed with water (3 x 50 mL), dried ($MgSO_4$) and evaporated. Purfiication by column chromatography (0-40% diethyl ether/petroleum ether), gave the alcohol **279**, as an oil (0.53 g, 3.16 mmol, 96%).

R*f* = 0.10 (40% diethyl ether in petrol); ν_{max} (cm^{-1}) 3438 (br, O-H), 2940, 2887 (CH), 1736 (C=O), 1671 (C=C); δ_H (400 MHz; $CDCl_3$) 1.74 (broad s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.31 (t, 2H, J = 6.4 Hz, CH_2), 3.72 (t, 2H, J = 6.4 Hz, CH_2), 4.60 (d, 2H, J = 7.0 Hz, CH_2), 5.42 (qt, 1H, J = 1.0, 7.0 Hz, CH); δ_C (100 MHz; $CDCl_3$) 16.2 (CH_3), 20.9 (CH_3), 42.3 (CH_2), 60.1 (CH_2), 61.1 (CH_2), 121.0 (CH), 138.4 (C), 171.1 (C); HRMS (ES) found 181.0833, $C_8H_{14}O_3Na$ ([M+Na^+]) requires 181.0835.

(*E*)-5-(1,3-dioxoisoindolin-2-yl)-3-methylpent-2-enyl acetate (280)

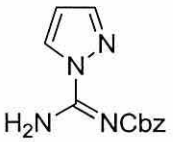


Chemical Formula: $C_{16}H_{17}NO_4$
Exact Mass: 287.1158
Molecular Weight: 287.3105

Alcohol **279** (0.50 g, 3.16 mmol), PPh_3 (1.25 g, 4.76 mmol, 1.4 equiv.) and phthalimide (0.60 g, 4.08 mmol, 1.2 equiv.) were dissolved in anhydrous THF (50 mL). After cooling (0 °C) and stirring for 30 mins, DIAD (0.87 mL, 0.89 g, 4.43 mmol, 1.3 equiv.) in anhydrous THF (5 mL) was added dropwise and the reaction stirred for a further 3 h. After evaporation onto silica gel (5.0 g), column chromatography (0-20% ethyl acetate/petroleum ether) gave the phthalimide **280** (0.76 g, 2.64 mmol, 84%) as a white solid.

Mpt 52-54; R*f* = 0.18 (20% ethyl acetate in petrol); ν_{max} (cm^{-1}) 3205, 2953, 2924, 2854 (C-H), 1769 (C=O), 1734 (C=O), 1711 (C=O), 1606 (C=C); δ_H (400 MHz; $CDCl_3$) 1.81 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 2.42 (t, 2H, J = 7.0 Hz, CH_2), 3.82 (t, 2H, J = 7.0 Hz, CH_2), 4.49 (d, 2H, J = 7.0 Hz, CH_2), 5.31 (t, 1H, J = 7.0 Hz, CH), 7.70-7.89 (m, 4H); δ_C (100 MHz; $CDCl_3$) 16.1 (CH_3), 20.8 (CH_3), 36.2 (CH_2), 38.1 (CH_2), 60.8 (CH_2), 121.2 (CH), 123.2 (CH), 123.5 (CH), 132.0 (C), 133.8 (CH), 134.3 (CH), 138.5 (C), 168.2 (C), 170.8 (C); HRMS (ES) found 310.1050, $C_{16}H_{17}NO_4Na$ ([M+Na^+]) requires 310.1050.

(*Z*)-benzyl (amino (1*H*-pyrazol-1-yl) methylene) carbamate (209c)[116]

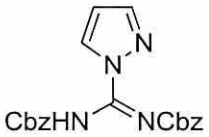


Chemical Formula: $C_{12}H_{12}N_4O_2$
Exact Mass: 244.0960
Molecular Weight: 244.2493

1*H*-pyrazole-1-carboxamidine hydrochloride **259** (10 g, 68 mmol, 1 equiv.) and benzyl chloroformate (14.5 mL, 102 mmol, 1.5 equiv.) were dissolved in anhydrous THF (40 mL) then stirred for 5 min. To the stirring solution, *N*-diisopropylethylamine (24 mL, 136 mmol, 2 equiv.) was added dropwise over 15 mins and the resultant solution left to stir overnight under argon. The reaction was diluted with water (200 mL), extracted with DCM (3 x 200 mL) and the organic phases combined and dried ($MgSO_4$). Evaporation gave the crude product which was dried under vacuum overnight then dissolved in minimum amount of hot DCM which on slow cooling to RT followed by storage in the freezer overnight gave rectangular transparent crystals of **209c** (7.82 g, 32.02 mmol, 47%). Futher crops could be obtained by evaporation of the mother liquor and recrystallization of combined mother liquors.

Mpt 104-107 °C, Lit.[13] 108-109 °C; R*f* = 0.36; ν_{max} (cm^{-1}) 3457 (N-H), 3275 (N-H), 3018 (C-H), 1669 (C=O), 1628 (C=N); δ_H (400 MHz; $CDCl_3$) 5.22 (br s, 2H, CH_2), 6.42 (br s, 1H, CH), 7.34-7.44 (m, 5H, Ph), 7.69 (br, 1H, CH), 8.47 (br s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 67.6 (CH2), 109.3 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 128.9 (CH), 136.3 (C), 143.7 (CH), 155.5 (C), 163.9 (C).

Benzyl ((((benzyloxy)carbonyl)amino)(1H-pyrazol-1-yl)methylene)carbamate (209b)[116]

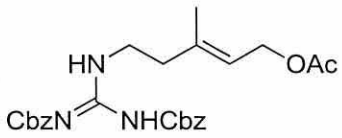


Chemical Formula: $C_{20}H_{18}N_4O_4$
Exact Mass: 378.1328
Molecular Weight: 378.3813

Mono-protected amidine **209c** (9.7 g, 39.9 mmols) was dissolved in anhydrous THF (50 mL) and cooled (0 °C). Solid NaH (5.78 g, of 60% dispersion in oil, 144 mmols) was added in portions over 30 mins and the reaction stirred for an additional 10 mins. CbzOSu (19.9 g, 80 mmol) was then added in portions over 30 mins. After stirring to rt 18 h the reaction solidified and further THF (50 mL) was added and the reaction cooled (0 °C). Water (100 mL) was added **VERY** cautiously to destroy excess NaH and after warming slowly to rt, the mixture washed into a separation funnel with chloroform (ca 100 mL). After separation, the aqueous layer was extracted with further chloroform (3 x 100 mL) and the combined organic extracts washed with water (100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to yield a dark brown oil which was purified by column chromatography (10-40% ethyl acetate/petroleum ether) to give the title product **209b** (7.84 g, 20.7 mmol) as a crystalline solid in 52% yield.

Mpt 81-38 °C, Lit.[26] 85-85 °C R*f* = 0.22 (30% ethyl acetate in petrol); ν_{max} (cm^{-1}) 3346 (N-H), 3153 (N-H), 3090, 3061 (C-H), 1782 (C=O), 1712 (C=O), 1692 (C=N); δ_H (400 MHz; $CDCl_3$) 5.24 (br s, 4H, 2 x CH_2), 6.45 (br s, 1H, CH), 7.346-7.43 (m, 10H, 2 x Ph), 7.64 (br s, 2H, CH), 8.30 (s, 1H, CH), 9.35 (br s, 1H, NH); δ_C (100 MHz; $CDCl_3$) 68.4 (CH_2), 68.7 (CH_2), 109.9 (CH), 110.3 (CH), 128.2 (CH), 128.4 (CH), 128.6 (CH), 128.7 (CH), 128.7 (CH), 128.8 (CH), 128.9 (CH), 128.9 (CH), 134.5 (C), 135.7 (C), 145.4 (C), 150.7 (C), 158.1 (C).

(2*E*)-5-(2,3-bis((benzyloxy)carbonyl)guanidino)-3-methylpent-2-en-1-yl acetate (281)

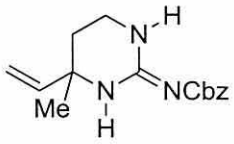


Chemical Formula: $C_{25}H_{29}N_3O_6$
Exact Mass: 467.2056
Molecular Weight: 467.5143

Phthalimide **280** (0.70 g, 2.43 mmol) was dissolved in pure EtOH (10 mL) and a solution of hydrazine hydrate in pure EtOH (7.29 mL, 158.7 mg, 3.17 mmol, 1.3 equiv.) was then added and the reaction was heated to reflux. After completion of the reaction (TLC, ca. 3-4 h) the mixture was cooled to rt, filtered and the filter pad washed with further EtOH (ca. 10-20 mL). At this point 1*H*-pyrazole-1-(*N,N'*-bis-(benzyloxy carbonyl)) carboxamidine **209b** (1.37 g, 3.64 mmol, 1.5 equiv.) was added to the filtrate along with NEt_3 (1.22 g, 1.69 mL, 12.15 mmol, 5 equiv.). After stirring for 16 h the reaction was evaporated onto silica gel (5.0 g) and purified by column chromatography (0-40% diethyl ether/petroleum ether) to give the guanidine **281** (0.53 g, 1.13 mmol, 47% yield) as a waxy solid.

R*f* = 0.16 (40% diethyl ether in petrol); ν_{max} (chloroform)/cm^{-1} 3334 (NH), 3144 (N-H), 3065, 3034, 2952, 2895 (C-H), 1738 (C=O), 1732 (C=O), 1651 (C=O), 1644 (C=N), 1634 (C=C), 1574, 1497; δ_H (400 MHz; $CDCl_3$) 1.74 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.31 (t, 2H, J = 6.7 Hz, CH_2), 3.57 (apparent q, 2H, J = 6.7 Hz, CH_2), 4.60 (d, 2H, J = 7.0 Hz, CH_2), 5.14 (s, 2H, CH_2), 5.18 (s, 2H, CH_2), 5.45 (t, 1H, J = 7.0 Hz, CH), 7.29-7.41 (m, 10H, 2 x Ph), 8.31 (1H, s, NH), 11.72 (1H, s, NH); δ_C (100 MHz; $CDCl_3$) 15.7 (CH_3), 20.5 (CH_3), 37.9 (CH_2), 38.7 (CH_2), 60.4 (CH_2), 66.8 (CH_2), 67.8 (CH_2), 121.2 (CH), 127.5 (CH), 127.7 (CH), 128.0 (CH), 128.04 (CH), 128.2 (CH), 128.4 (CH), 134.1 (C), 137.7 (C), 153.3 (C), 155.3 (C), 168.1 (C), 170.8 (C); HRMS (ES) found 468.2126, $C_{25}H_{30}N_3O_6$ ([M+H^+]) requires 468.2129.

Benzyl (4-methyl-4-vinyltetrahydropyrimidin-2(1*H*)-ylidene)carbamate (283)

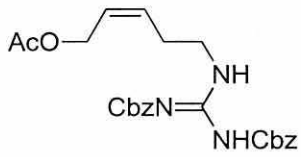


Chemical Formula: $C_{15}H_{19}N_3O_2$
Exact Mass: 273.1477
Molecular Weight: 273.3303

To a stirred solution of guanidine **281** (120 mg, 0.257 mmol) in dry THF (10 mL) was added NEt_3 (0.05 g, 0.07 mL, 0.51 mmol, 2 equiv.) and $Pd(dppe)_2$ (0.05 g, 0.05 mmol, 0.2 equiv.). The reaction mixture was then heated to reflux and monitored by TLC, after 48 h all of the guanidine **281** had been consumed. After cooling to rt the solvent was evaporated and the residue dissolved in MeOH (5 mL), TFA (0.33 mL) was added and the mixture stirred for 48 h. Purification by flash column chromatography on silica gel (dichloromethane 100%) followed by ethyl acetate in hexane (50-100%) gave **283** (30 mg, 0.1098 mmol) as a gum in 43% yield.

R*f* = 0.08 (70% ethyl acetate in hexane); ν_{max} (chloroform)/cm^{-1} 3291 (N-H), 3139 (N-H), 3041, 2958, 2925, 2854 (C-H), 1731 (C=O), 1682 (C=N), 1640 (C=C), 1564; δ_H (400 MHz; $CDCl_3$) 1.48 (s, 3H, CH_3), 1.81 (m,1H, C<u>H</u>H), 1.92 (m,1H, CH<u>H</u>), 3.30 (m,1H, C<u>H</u>H), 3.46 (m,1H, CH<u>H</u>), 5.14 (d,1H, *J* = 17.0 Hz, CH), 5.28 (s, 2H, CH_2), 5.30 (d, 1H, *J* = 10.5 Hz, CH), 5.76 (dd,1H, *J* = 10.5, 17.0 Hz, CH), 7.35-7.41 (m, 5H, Ph), 13.73 (s, 1H, NH); δ_C (100 MHz; $CDCl_3$) 27.4 (CH_3), 31.0 (CH_2), 35.9 (CH_2), 54.5 (C), 68.4 (CH_2), 116.0 (CH_2), 127.0 (CH), 128.1 (CH), 128.5 (CH), 128.6 (CH), 134.7 (C), 140.2 (CH), 151.6 (C), 155.0 (C) MS *m/z* 274 ($[M+H]^+$,100%) $C_{15}H_{20}N_3O_2$ ($[M+H]^+$), found 274.1547, expected 274.1550.

(2Z)-5-(2,3-bis((benzyloxy)carbonyl)guanidino)pent-2-en-1-yl acetate (271b)[110]

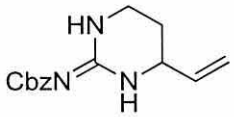


Chemical Formula: $C_{24}H_{27}N_3O_6$
Exact Mass: 453.1900
Molecular Weight: 453.4877

Phthalimide sample (1000 mg, 3.66 mmol) was dissolved in pure EtOH (20 mL), hydrazine hydrate (0.23 mL, 238.19 mg, 4.76 mmol) was added and the solution heated to reflux. After completion of the reaction (TLC, ca. 3-4 h) the solution was cooled, filtered and the filter pad washed with further EtOH (ca. 20-30 mL) and **209b** (2077 mg, 5.49 mmol, 1.5 eqv) and NEt_3 (2.6 mL, 1.84 mg, 18.3 mmol, 5 equiv.) were added to the filtrate. After stirring for 16 h the reaction was evaporated onto silica gel (ca. 3 g) and purified by column chromatography (0-30% ethyl acetate/petroleum ether to give **271b** (669 mg, 1.47 mmol) as a waxy solid in 40% yield.

R*f* = 0.27 (30% ethyl acetate in petroleum ether); ν_{max} 3332 (N-H), 3064, 3032, 2982, 2936, 2876 (C-H), 1732 (C=O), 1638 (C=N), 1627, 1578, 1533; δ_H (400 MHz; $CDCl_3$) 2.05, (s, 3H, CH_3), 2.43 (dt, 2H, *J* = 6.8, 7.0 Hz, CH_2), 3.52 (dt, 2H, *J* = 5.2, 7.0 Hz, CH_2), 4.62 (d, 2H, *J* = 7.0 Hz, CH_2), 5.14 (s, 2H, CH_2), 5.18 (s, 2H, CH_2), 5.77-5.56 (m, 2H, 2 x CH), 7.40-7.28 (m,10H, 2 x Ph), 8.36 (s, 1H, NH), 11.74 (s, 1H, NH); δ_C (100 MHz; $CDCl_3$) 20.9 (CH_3), 27.1 (CH_2), 40.5 (CH_2), 60.0 (CH_2), 67.2 (CH_2), 68.2 (CH_2), 126.6 (CH), 127.9 (CH), 128.1 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 128.8 (CH), 130.7 (CH), 134.6 (C), 136.7 (C), 153.8 (C), 156.0 (C), 163.5 (C), 170.8 (C). MS *m/z* 454 ($[M+H]^+$,100%) $C_{24}H_{28}N_3O_3$ ($[M+H]^+$), found 454.1971, expected 454.1973.

Benzyl (4-vinyltetrahydropyrimidin-2(1*H*)-ylidene) carbamate (273)



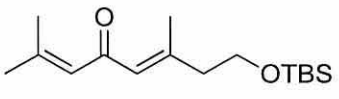
Chemical Formula: $C_{14}H_{17}N_3O_2$
Exact Mass: 259.1321
Molecular Weight: 259.3037

Using Pd(OAc)$_2$: $Pd(OAc)_2$ (220 mg, 0.966 mmol, 0.2 equiv.), LiBr (280 mg, 3.22 mmol, 1.0 equiv.) and NEt_3 (480 mg, 4.83 mmol, 1.5 equiv.) were added sequentially to a stirred solution of guanidine **271b** (1.46 g, 3.22 mmol) in dry degassed THF (20 mL). The reaction mixture was then heated to reflux for 2 days when TLC (diethyl ether) indicated the complete consumption of starting material. The reaction mixture was evaporated onto silica gel (ca. 1-2 g) and purified by column chromatography eluting with ethyl acetate in hexane (20-100%) to give **273** (330 mg, 1.27 mmol) as a gum in 39% yield.

Using Pd(dppe)$_2$: $Pd(dppe)_2$ (90 mg, 0.11 mmol, 0.2 equiv.) and NEt_3 (80 mg, 0.83 mmol, 1.5 equiv.) were added sequentially to a stirred solution of guanidine **271b** (250 mg, 0.55 mmol) in dry degassed THF (10 mL). The mixture was then heated at reflux for 24 h when TLC (diethyl ether) indicated the complete consumption of the starting material. The reaction was then evaporated onto silica gel and purified by column chromatography using ethyl acetate in hexane (20-100%) to give **273** (120 mg, 0.46 mmol) as a gum in 84% yield.

R*f* = 0.06 (70% ethyl acetate in hexane); ν_{max} 3342 (NH), 3156 (NH), 2980, 2933 (C-H), 1770 (C=O), 1712 (C=N), 1678 (C=C), 1639, 1502; δ_H (400 MHz; $CDCl_3$) 1.61, (m, 1H, C<u>H</u>H), 1.87 (m, 1H, CH<u>H</u>), 3.15 (t, 2H, *J* = 5.8 Hz, CH_2), 3.96 (m, 1H, CH), 5.04 (s, 2H, CH_2), 5.19 (d, 1H, *J* = 10.3 Hz, CH) 5.21 (d, 1H, *J* = 17.2 Hz, CH), 5.70 (ddd, 1H, *J* = 5.4, 10.3, 17.2 Hz, CH), 7.37-7.29 (m, 5H, Ph), 8.81 (s, 1H, NH), 9.27 (s, 1H, NH); δ_C (100 MHz; $CDCl_3$) 25.7 (CH_2), 36.1 (CH_2), 51.0 (C), 66.1 (CH_2), 116.7 (CH_2), 127.7 (CH), 128.0 (CH), 128.3 (CH), 132.1 (C), 137.6 (CH), 158.3 (C), 162.7 (C). MS *m/z* 260 ($[M+H]^+$, 100%) $C_{14}H_{18}N_3O_2$ ($[M+H]^+$), found 260.1394, expected found 260.1394.

(*E*)-8-((tert-butyldimethylsilyl)oxy)-2,6-dimethylocta-2,5-dien-4-one (286)

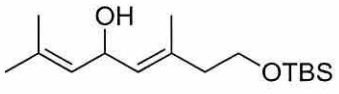


Chemical Formula: $C_{16}H_{30}O_2Si$
Exact Mass: 282.2015
Molecular Weight: 282.4937

A suspension of Cp_2ZrCl_2 (5.0 g, 17.11 mmol) in anhydrous DCM (60 mL) was cooled (-23 °C) and Me_3Al (25.6 mL, 51.2 mmol, 2M in hexane) was added dropwise and the mixture stirred to -5 °C for 1 h before being cooled again to -23 °C. Water (461.3 μL) was then slowly added with vigorous stirring for 10 min, whereupon a solution of **275** (3.20 g, 17.11 mmol) in anhydrous DCM (5 mL) was added and the reaction stirred to -5 °C for 4 h. A solution of 3,3-dimethylacryloyl chloride **285** (4.05 g, 3.8 mL, 34.20 mmol, 2 equiv.) was then added and the reaction was stirred to rt overnight. The reaction was then cooled (0 °C) and diluted with Et_2O (50 mL) before a solution of Rochelle's salt (50 mL) was added dropwise over 20 min. Stirring was continued until the solution cleared, whereupon the mixture was separated and the aqueous layer extracted with further Et_2O (2 x 100 mL). The combined organic extracts were then washed with H_2O (150 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification of the crude product by silica gel chromatography (0-2% ethyl acetate/petroleum ether) gave **286** as colorless oil (1.64 g, 5.78 mmol, 34% yield).

R*f* = 0.10 (2% ethyl acetate in petrol); ν_{max} (cm^{-1}) 2954, 2929, 2858 (CH), 1628 (C=O), 1555, 1541 (C=C); δ_H (400 MHz; $CDCl_3$) 0.06 (s, 6H, 2 x CH_3), 0.90 (s, 9H, 3 x CH_3), 1.89 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.33 (t, 2H, J = 6.6 Hz, CH_2), 3.75 (t, 2H, J = 6.6 Hz, CH_2), 6.07 (s, 1H, CH), 6.10 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) -5.37 (2 x CH_3), 19.5 (CH_3), 20.5 (CH_3), 25.8 (3 x CH_3), 27.7 (CH_3), 31.6 (C), 44.4 (CH_2), 61.4 (CH_2), 126.2 (CH), 127.2 (CH), 154.4 (C), 154.5 (C), 191.5 (C); HRMS (ES) found 283.2093, $C_{16}H_{31}O_2Si$ ([M+H^+]) requires 283.2088.

Attempted preparation of (*E*)-8-((tert-butyldimethylsilyl)oxy)-2,6-dimethylocta-2,5-dien-4-ol (287)



Chemical Formula: $C_{16}H_{32}O_2Si$
Exact Mass: 284.2172
Molecular Weight: 284.5096

Method A: Ketone **286** (160 mg, 0.59 mmol, 1 equiv.) in MeOH (10 ml) was cooled (0 °C) whereupon sodium borohydride (110 mg, 2.97 mmol, 5 equiv.) was added in portions over 5 min and the reaction was stirred to rt overnight. After completion of the reaction (TLC), water (10 mL) was then added and extracted with DCM (3 x 20 mL). The conbined extracts were dried ($MgSO_4$), evaporated and purified by column chromatography (eluting with 0-4% ethyl acetate/petroleum ether). A yellow oil was obtained, which gave no signals indicative of the desired product when analysed by NMR. No other major produucts were isolated.

Method B: Ketone **286** (100 mg, 0.35 mmol, 1 equiv.) in anhydrous Et_2O (10 ml) was added dropwise to a cooled (0 °C) suspension of $LiAlH_4$ (20 mg, 0.525 mmol, 1.5 equiv.) in Et_2O (1 mL). The reaction mixture was heated to reflux for 1 h and on completion of the reaction (TLC), the mixture was cooled (0 °C) and quenched by the dropwise addition of Na_2SO_4 (aq. sat. ca. 20 mL) and a white precipitate was formed. The reaction solvent was filtered, extracted with EtOAc (2 x 20 mL) and the combined extracts washed with brine (20 mL) and dried ($MgSO_4$). Analysis of the crude product by NMR indicated the presence of a complex mixture of product with no signals indicative of the desired product.

Method C: A solution of ketone **286** (240 mg, 0.849 mmol, 1 equiv.) was dissolved in anhydrous DCM (10 mL) and cooled (-78 °C). DIBAL (1M solution in hexane, 2.04 mL, 2.04 mmol, 2.4 equiv.) was added dropwise over 5 min and after stirring for 2 h the solution was diluted with EtOAc (2 mL), stirred for 10 min whereupon MeOH (2 mL) was added. The solution was then diluted with Et_2O (20 mL) and a solution of Rochelle's salt (20 mL) was added dropwise over 10 min and the mixture stirred at rt until the solution cleared. The organic layer was separated, the aqueous layer further extracted with diethyl ether (2 x 50 mL) and the combined organic extracts washed with H_2O (50 mL) then dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (0-4% ethyl acetate/petroleum ether), a yellow oil was

obtained, which possessed no signals indicative of the desired product when analysed by NMR. No other major produucts were isolated.

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Appendices

UK National Crystallography Service

Table 1. Crystal data and structure refinement details.

Identification code	**2012ncs0440dlsa**	
Empirical formula	$C_{16}H_{29}N_3O_5$	
Formula weight	343.42	
Temperature	100(2) K	
Wavelength	0.68890 Å	
Crystal system	Monoclinic	
Space group	*P*21/*c*	
Unit cell dimensions	a = **15.710(19) Å**	α = **90°**
	b = 10.**318(12) Å**	β = **99.243(15)°**
	c = **11.932(15) Å**	γ = **90°**
Volume	1909(4) Å^3	
Z	4	
Density (calculated)	1.195 Mg / m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	744	
Crystal	Plate; Colorless	
Crystal size	0.03 × 0.03 × 0.01 mm^3	
θ range for data collection	2.96 – 24.21°	
Index ranges	$-18 \le h \le 16$, $-11 \le k \le 12$, $-14 \le l \le 14$	
Reflections collected	11629	
Independent reflections	3303 [R_{int} = 0.1536]	
Completeness to θ = 24.21°	98.0 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9991 and 0.9973	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3303 / 204 / 224	
Goodness-of-fit on F^2	1.401	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.1650, *wR2* = 0.4002	
R indices (all data)	*R1* = 0.2433, *wR2* = 0.4501	
Largest diff. peak and hole	1.809 and –0.445 e Å^{-3}	

Diffractometer: Beamline I19 situated on an undulator insertion device with a combination of double crystal monochromator, vertical and horizontal focussing mirrors and a series of beam slits (primary white beam and either side of the focussing mirrors). The experimental hutch (EH1) is equipped with a Crystal Logic 4-circle kappa geometry goniometer with a Rigaku Saturn 724 CCD detector and an Oxford Cryosystems Cryostream plus cryostat (80-500K). For conventional service crystallography the beamline operates at a typical energy of 18 keV (Zr K absorption edge) and a Rigaku ACTOR robotic sample changing system is available. **Cell determination and data collection**: *CrystalClear-SM Expert 2.0 r5* (Rigaku, 2010). **Data reduction, cell refinement and absorption correction**: *CrystalClear-SM Expert 2.0 r5* (Rigaku, 2010). **Structure solution**: *SUPERFLIP* (Palatinus, L. & Chapuis, G. (2007). J. Appl. Cryst. 40, 786-790). **Structure refinement**: *SHELXL97* (Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122). **Graphics:** *OLEX2* (Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K. & Puschmann, H. (2009). J. Appl. Cryst. 42, 339-341).

Special details:
Large positive residual density likely results from a data collection from poor quality crystal at synchrotron source.

The data quality is poor but confirms connectivity. If it is intended to publish this data in the literature, I would recommend recrystallization and recollection.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	999(4)	2564(5)	3019(6)	28(2)	1
C2	784(4)	4199(5)	1489(5)	26(1)	1
C3	–297(5)	2488(6)	1509(6)	35(2)	1
C4	427(5)	1701(7)	2168(7)	52(2)	1
C5	445(6)	3130(9)	3894(7)	62(2)	1
C6	1734(6)	1794(8)	3586(8)	58(2)	1
C7	2960(6)	2068(10)	5001(9)	66(2)	1
C8	4187(6)	2514(7)	6459(9)	58(2)	1
C9	4379(8)	3771(9)	7129(13)	112(5)	1
C10	4855(9)	2090(20)	5837(12)	162(8)	1
C11	3966(7)	1546(10)	7303(10)	83(3)	1
C12	1734(4)	5912(6)	1372(7)	34(2)	1
C13	2500(5)	7927(7)	1048(7)	41(2)	1
C14	2264(5)	8975(8)	144(8)	63(3)	1
C15	3324(5)	7305(7)	888(8)	53(2)	1
C16	2496(6)	8487(8)	2219(7)	60(2)	1
N1	1289(3)	3651(5)	2380(5)	29(1)	1
N2	27(3)	3684(5)	1109(5)	31(1)	1
N3	1004(3)	5252(5)	943(5)	29(1)	1
O1	2297(4)	2624(4)	4372(5)	48(2)	1
O2	3132(5)	918(7)	4889(7)	102(3)	1
O3	3393(5)	2872(6)	5648(7)	93(3)	1
O4	2273(3)	5651(4)	2181(5)	44(1)	1
O5	1771(3)	7001(4)	739(4)	38(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–N1	1.469(7)
C1–C6	1.473(10)
C1–C4	1.529(10)
C1–C5	1.575(11)
C2–N2	1.315(8)
C2–N3	1.340(8)
C2–N1	1.345(8)
C3–N2	1.445(8)
C3–C4	1.511(11)
C3–H3A	0.9900
C3–H3B	0.9900
C4–H4A	0.9900
C4–H4B	0.9900
C5–H5A	0.9800
C5–H5B	0.9800
C5–H5C	0.9800
C6–O1	1.460(10)
C6–H6A	0.9900
C6–H6B	0.9900
C7–O2	1.229(12)
C7–O3	1.256(12)
C7–O1	1.314(11)
C8–C10	1.449(16)
C8–O3	1.496(11)
C8–C11	1.498(14)
C8–C9	1.527(14)
C9–H9A	0.9800
C9–H9B	0.9800
C9–H9C	0.9800
C10–H10A	0.9800
C10–H10B	0.9800
C10–H10C	0.9800
C11–H11A	0.9800
C11–H11B	0.9800
C11–H11C	0.9800
C12–O4	1.208(8)
C12–N3	1.361(9)
C12–O5	1.361(8)
C13–C15	1.484(11)
C13–O5	1.492(8)
C13–C16	1.514(12)
C13–C14	1.530(10)
C14–H14A	0.9800
C14–H14B	0.9800
C14–H14C	0.9800
C15–H15A	0.9800
C15–H15B	0.9800
C15–H15C	0.9800
C16–H16A	0.9800
C16–H16B	0.9800
C16–H16C	0.9800
N1–H1	0.8800
N2–H2	0.8800
N1–C1–C6	111.4(6)
N1–C1–C4	107.3(5)
C6–C1–C4	109.0(6)
N1–C1–C5	108.1(5)
C6–C1–C5	111.8(7)
C4–C1–C5	109.2(6)
N2–C2–N3	116.7(6)
N2–C2–N1	119.3(5)
N3–C2–N1	124.0(6)
N2–C3–C4	110.8(6)
N2–C3–H3A	109.5
C4–C3–H3A	109.5
N2–C3–H3B	109.5
C4–C3–H3B	109.5
H3A–C3–H3B	108.1
C3–C4–C1	110.3(6)
C3–C4–H4A	109.6
C1–C4–H4A	109.6
C3–C4–H4B	109.6
C1–C4–H4B	109.6
H4A–C4–H4B	108.1
C1–C5–H5A	109.5
C1–C5–H5B	109.5
H5A–C5–H5B	109.5
C1–C5–H5C	109.5
H5A–C5–H5C	109.5
H5B–C5–H5C	109.5
O1–C6–C1	109.2(6)
O1–C6–H6A	109.8
C1–C6–H6A	109.8
O1–C6–H6B	109.8
C1–C6–H6B	109.8
H6A–C6–H6B	108.3
O2–C7–O3	126.7(10)
O2–C7–O1	121.8(9)
O3–C7–O1	111.3(9)
C10–C8–O3	109.9(10)
C10–C8–C11	113.9(11)
O3–C8–C11	109.9(8)
C10–C8–C9	115.4(12)
O3–C8–C9	101.7(7)
C11–C8–C9	105.2(10)
C8–C9–H9A	109.5
C8–C9–H9B	109.5
H9A–C9–H9B	109.5
C8–C9–H9C	109.5
H9A–C9–H9C	109.5
H9B–C9–H9C	109.5
C8–C10–H10A	109.5
C8–C10–H10B	109.5
H10A–C10–H10B	109.5
C8–C10–H10C	109.5
H10A–C10–H10C	109.5
H10B–C10–H10C	109.5
C8–C11–H11A	109.5
C8–C11–H11B	109.5
H11A–C11–H11B	109.5
C8–C11–H11C	109.5
H11A–C11–H11C	109.5
H11B–C11–H11C	109.5
O4–C12–N3	129.0(6)
O4–C12–O5	122.7(6)
N3–C12–O5	108.3(6)
C15–C13–O5	110.0(6)
C15–C13–C16	114.7(7)
O5–C13–C16	110.8(6)

C15–C13–C14	109.5(7)
O5–C13–C14	100.8(6)
C16–C13–C14	110.1(7)
C13–C14–H14A	109.5
C13–C14–H14B	109.5
H14A–C14–H14B	109.5
C13–C14–H14C	109.5
H14A–C14–H14C	109.5
H14B–C14–H14C	109.5
C13–C15–H15A	109.5
C13–C15–H15B	109.5
H15A–C15–H15B	109.5
C13–C15–H15C	109.5
H15A–C15–H15C	109.5
H15B–C15–H15C	109.5
C13–C16–H16A	109.5
C13–C16–H16B	109.5
H16A–C16–H16B	109.5
C13–C16–H16C	109.5
H16A–C16–H16C	109.5
H16B–C16–H16C	109.5
C2–N1–C1	122.6(5)
C2–N1–H1	118.7
C1–N1–H1	118.7
C2–N2–C3	125.3(6)
C2–N2–H2	117.3
C3–N2–H2	117.3
C2–N3–C12	119.3(6)
C7–O1–C6	117.0(7)
C7–O3–C8	123.2(8)
C12–O5–C13	119.4(5)

Symmetry transformations used to generate equivalent atoms:

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	35(4)	23(3)	24(3)	9(2)	4(3)	−4(2)
C2	29(3)	25(3)	24(3)	−1(2)	6(3)	7(2)
C3	39(4)	38(4)	26(4)	6(3)	−3(3)	−12(3)
C4	66(5)	44(4)	44(5)	2(3)	3(4)	−8(3)
C5	86(7)	60(5)	45(5)	−1(4)	21(5)	−10(4)
C6	70(5)	42(4)	53(5)	6(4)	−18(4)	0(3)
C7	74(6)	62(5)	56(6)	11(4)	−11(4)	1(4)
C8	45(5)	51(4)	72(6)	2(4)	−13(4)	3(3)
C9	104(9)	50(5)	151(12)	11(6)	−75(8)	−13(5)
C10	85(9)	330(20)	72(9)	1(11)	10(7)	49(11)
C11	96(8)	72(6)	67(7)	14(5)	−27(6)	−5(5)
C12	35(4)	28(3)	37(4)	7(3)	4(3)	−1(2)
C13	36(4)	40(4)	43(4)	12(3)	−3(4)	−16(3)
C14	65(6)	42(4)	77(6)	31(4)	−4(5)	−22(3)
C15	40(4)	49(4)	70(6)	13(4)	7(4)	−10(3)
C16	77(6)	51(5)	50(5)	−7(4)	6(5)	−24(4)
N1	22(3)	33(3)	32(3)	6(2)	1(2)	−4(2)
N2	32(3)	30(3)	30(3)	3(2)	2(3)	−3(2)
N3	32(3)	26(2)	27(3)	2(2)	3(2)	−1(2)
O1	56(3)	33(2)	48(3)	7(2)	−14(3)	−4(2)
O2	123(6)	64(4)	104(6)	−14(4)	−25(5)	35(4)
O3	95(5)	53(3)	107(6)	19(4)	−55(5)	−11(3)
O4	54(3)	36(2)	38(3)	10(2)	−6(3)	−13(2)
O5	44(3)	24(2)	42(3)	10(2)	−3(2)	−10(2)

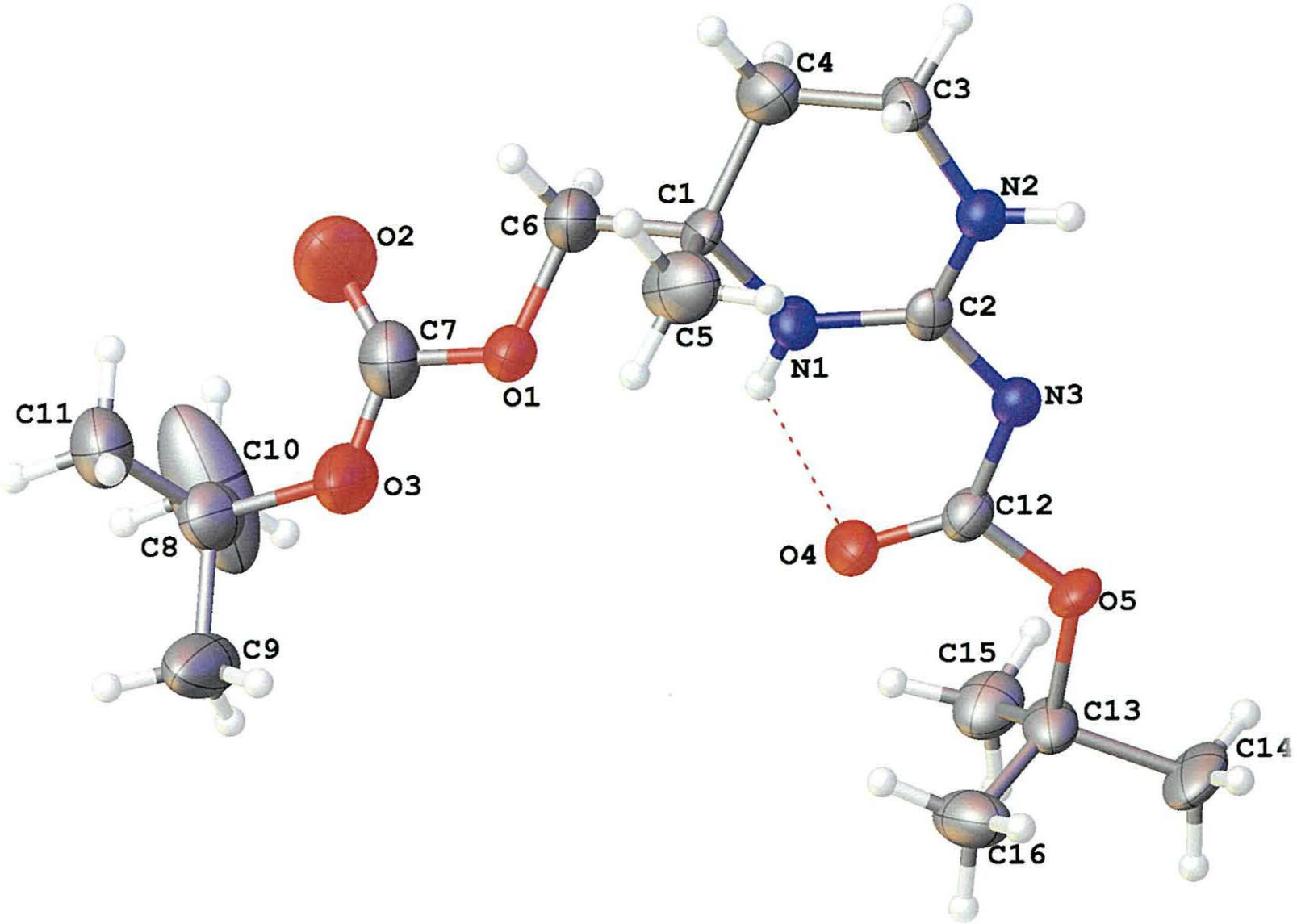
Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H3A	−583	1976	852	42	1
H3B	−731	2684	2001	42	1
H4A	777	1310	1636	62	1
H4B	184	992	2576	62	1
H5A	815	3649	4464	94	1
H5B	191	2416	4270	94	1
H5C	−15	3677	3493	94	1
H6A	1522	1065	4005	70	1
H6B	2058	1430	3013	70	1
H9A	4605	3566	7923	168	1
H9B	3848	4278	7091	168	1
H9C	4808	4275	6802	168	1
H10A	4676	1274	5440	244	1
H10B	5391	1942	6368	244	1
H10C	4950	2749	5283	244	1
H11A	3765	742	6909	124	1
H11B	3509	1896	7686	124	1
H11C	4479	1366	7866	124	1
H14A	2258	8599	−611	95	1
H14B	2690	9675	266	95	1
H14C	1691	9322	199	95	1
H15A	3509	6703	1515	80	1
H15B	3766	7972	873	80	1
H15C	3240	6828	168	80	1
H16A	1935	8886	2251	90	1
H16B	2950	9144	2380	90	1
H16C	2602	7794	2786	90	1
H1	1814	3956	2589	35	1
H2	−310	4103	568	38	1

Table 6. Torsion angles [°].

N2–C3–C4–C1	46.7(8)
N1–C1–C4–C3	−55.1(8)
C6–C1–C4–C3	−175.8(7)
C5–C1–C4–C3	61.9(8)
N1–C1–C6–O1	59.9(8)
C4–C1–C6–O1	178.1(6)
C5–C1–C6–O1	−61.2(8)
N2–C2–N1–C1	−5.7(9)
N3–C2–N1–C1	174.7(5)
C6–C1–N1–C2	155.3(6)
C4–C1–N1–C2	36.1(8)
C5–C1–N1–C2	−81.5(7)
N3–C2–N2–C3	174.0(6)
N1–C2–N2–C3	−5.6(9)
C4–C3–N2–C2	−16.4(9)
N2–C2–N3–C12	172.7(6)
N1–C2–N3–C12	−7.7(9)
O4–C12–N3–C2	4.6(10)
O5–C12–N3–C2	−174.0(5)
O2–C7–O1–C6	4.3(14)
O3–C7–O1–C6	−179.5(8)
C1–C6–O1–C7	176.0(7)
O2–C7–O3–C8	−3.8(18)
O1–C7–O3–C8	−179.9(8)
C10–C8–O3–C7	64.6(15)
C11–C8–O3–C7	−61.6(13)
C9–C8–O3–C7	−172.7(11)
O4–C12–O5–C13	−0.4(10)
N3–C12–O5–C13	178.3(5)
C15–C13–O5–C12	65.6(8)
C16–C13–O5–C12	−62.2(8)
C14–C13–O5–C12	−178.9(6)

Symmetry transformations used to generate equivalent atoms:


C4
C3
N2
C1
C6
O2
C2
C7
C5
O1
N1
N3
C11
C10
O3
C12
O4
C8
O5
C9
C15
C13
C14
C16

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Intramolecular palladium mediated π-allyl cyclisation of bis-Cbz- and bis-Boc-protected guanidines

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ABSTRACT

The Pd-mediated π-allyl cyclisation of bis-Cbz- and bis-Boc-protected guanidines **4** and **14b** led to the formation of five- and six-membered heterocycles **5** and **17** in high yields.

We have previously reported on the synthesis of cyclic guanidines via the epoxide ring opening,[1] iodocyclisation[2] and Mitsunubu[3] condensations and have shown these methods to be effective and predictable for the preparation of five- and six-membered guanidine heterocycles. We were interested in extending this methodology to include palladium catalysed π-allyl cyclisations, and prompted by the report of Miyabe[4] on intermolecular palladium- and iridium-catalysed allylation of substituted guanidines, we now report our initial findings on intramolecular allylation of bis-protected guanidines. It is worthy of note that at the outset of this work the only known cyclisation of this type had been reported by Büchi et al., in 1989, who cyclised an N-methoxyguainidine in their synthesis of alchorneine and isoalchorneine.[5,6]

Our initially required substrate **4** was easily prepared from commercially available 2-*cis*-butene-1,4-diol (**1**), which on reaction with phthalimide in the presence of PPh_3 and DEAD gave the protected amine **2** in 82% yield. Reaction of **2** with hydrazine hydrate affected deprotection of the amine, which on treatment with triethylamine and the commercially available guanylating agent **6a**, gave the guanidine **3** in 56% yield. Acetylation of **3** was achieved by treatment with acetic anhydride in pyridine leading to the required substrate **4** in 72% yield. Cyclisation of **4** was achieved by treatment with $Pd(OAc)_2$ and PPh_3 in THF to give the five-membered guanidine **5** in 90% yield after chromatography (Scheme 1).

Following this success, we investigated the formation of a six-membered system and set about the preparation of substrate **14a**. The commercially available alcohol **7** was silyl protected using tBDMSCl/imidazole to give **8** in quantitative yield, which in turn was metallated with *n*-BuLi and treated with paraformaldehyde to give on work-up the alcohol **9** in 64% yield. Selective reduction of **9** was achieved using $Ni(OAc)_2/NaBH_4$ leading to alcohol **10** (88% yield), which was acetylated using pyridine and acetic anhydride affording **11** in 95% yield. The silyl ether was deprotected using TBAF to give alcohol **12** in 84% yield. Reaction of **12** with phthalimide in the presence of PPh_3 and DIAD gave the protected amine **13**, which was treated with hydrazine hydrate to remove the phthalimide protecting group, and then guanylated with **6a** to give the bis-Boc-protected substrate **14a** in 90% yield over 2 steps. Similar treatment of **13** with hydrazine hydrate followed by guanylation with **6b** gave the bis-Cbz-protected substrate **14b** in 47% yield over 2 steps.

Attempted cyclisation of **14a** using the previously employed conditions of $Pd(OAc)_2$ and PPh_3 in THF or CH_3CN failed to give any evidence of cyclisation, and on prolonged reaction the only product isolated was the mono-protected guanidine **15**, which also did not undergo cyclisation under these conditions. Attempts were made to modify the conditions including pre-forming the palladium catalyst in situ using $Pd(OAc)_2$ or $PdCl_2(CH_3CN)$ in acetonitrile or THF, using $Pd(dppe)_2$ in THF or 1,4-dioxane, but in all cases no cyclisation products were observed and either **14a** was recovered or complete decomposition occurred. We suspected

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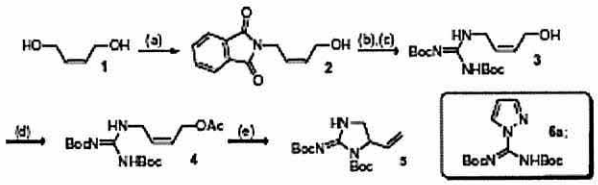

Scheme 1. Reagents and conditions: (a) PPh_3, phthalimide, THF, DEAD, 82%; (b) $NH_2NH_2.H_2O$, EtOH, reflux, (c) Et_3N, 6a rt, 24 h, 56%; (d) Ac_2O, py, DMAP, CH_2Cl_2, 0 °C, 30 min, 72% (e) $Pd(OAc)_2/PPh_3$, THF, reflux 3 h, 90%.

the lack of cyclisation might be based on the presence of the bulky Boc-protecting groups and we thus turned our attention to the Z-protected analogue **14b** (Scheme 2).

Reaction of **14b** with $Pd(PPh)_4$ in acetonitrile at reflux led to a rapid consumption of the starting material as evidenced by TLC, and the appearance of a new product at a similar *Rf* to the previously prepared **5**. A small sample was removed from the reaction mixture and ^1H NMR spectroscopy demonstrated the presence of the bis-protected guanidine **16** as evidenced by an ABX signal at δ_H 5.85 (1H, ddd, J = 4.4, 10.4, 17.4 Hz) for the vinylic CH and a complex multiplet at δ_H 5.22–5.00 (6H, m) for the benzyl and vinylic methylene protons. Attempted purification of the reaction product after work-up failed to yield any material at this *Rf* and instead a lower running fraction was obtained which was identified as the mono-Cbz-protected guanidine **17**, and which unfortunately co-eluted with Ph_3PO formed as a by-product in the reaction. In order to circumvent this problem we reacted **14b** with $Pd(OAc)_2$ and LiBr in THF in the presence of Et_3N under phosphine-free conditions and obtained **17** in 39% yield after chromatography. In an attempt to improve this yield we reacted **14b** with a catalytic amount of $Pd(dppe)_2$ in THF in the presence of Et_3N under reflux for 24 h which gave **17** in 84% yield. (Scheme 2) Diagnostic signals in the ^1H NMR spectrum were at δ_H 5.70 (1H, ddd, J = 5.4, 10.3, 17.2 Hz) for the vinylic methine proton and at δ_H 5.19 (1H, d, J = 10.3 Hz, CH) and 5.21 (1H, d, J = 17.2 Hz, CH) for the vinylic methylene protons. Long range HMBC correlations between the guanidine carbon at δ_C 158.2 and the signals at δ_H 3.15 (2H, t, J = 5.8 Hz, CH_2N) and 3.94–3.98 (1H, m, CHN) were also observed.

In conclusion we have demonstrated that the Pd-mediated π-allyl cyclisation of bis-Cbz- and bis-Boc-protected guanidines is a feasible and high yielding process, particularly in the case of five-membered ring systems. However, problems exist in the labile nature of the protecting groups and this might be a limiting factor in their use. Despite this, the reaction has potential applications in synthesis[6] and similar reactions of carbamates and ureas[7–10] have been reported with considerable success. We are currently applying our findings to the synthesis of the novel guanidine-containing natural product, nitensidine E,[11] and will report our findings in due course.

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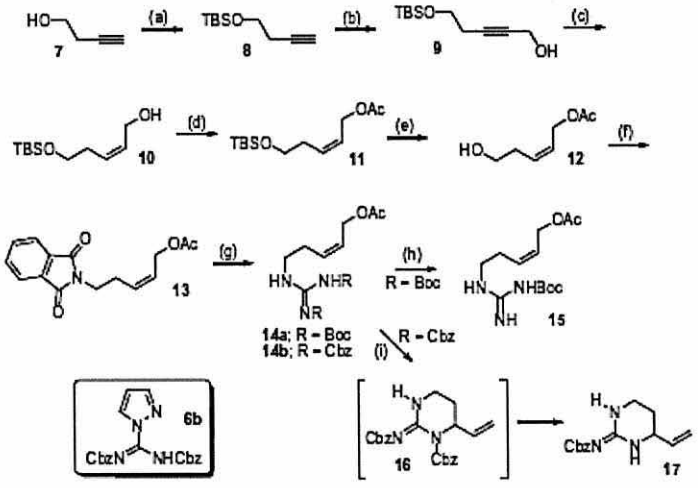
A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.093. These data include MOL files and InChiKeys of the most important compounds described in this article.



Scheme 2. Reagents and conditions: (a) DMF, IBDMSCl/imid., 0 °C to rt, 16–24 h, 100%; (b) THF, *n*-BuLi, paraformaldehyde, −78 °C to rt, 1 h, 64%; (c) $Ni(OAc)_2.4H_2O$, EtOH, H_2, $NaBH_4$, ethylenediamine, 88%; (d) Ac_2O, py, DMAP, CH_2Cl_2, 0 °C, 30 min, 95%; (e) THF, TBAF, 0 °C to rt 4 h, 84%; (f) PPh_3, phthalimide, THF, DIAD; (g) (i) $NH_2NH_2.H_2O$, EtOH, reflux, (ii) Et_3N, 6a or 6b, rt, 16–24 h, 14a: 90% (from 12); 14b: 47% (from 12); (h) $Pd(OAc)_2/PPh_3$, THF, reflux; (i) see text.

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