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NOVEL TANDEM REACTIONS OF ALLENIC SUBSTRATES

A thesis presented by

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DECLARATION

I Philip James Gray, confirm that the work presented in this thesis is my own. Where work has been derived from other sources, I confirm that this has been indicated in the thesis.

Contents

For Dinah Wilkinson and Bryan Reynolds

Always loved, never forgotten

Abstract

This thesis describes the development of novel tandem reactions of allenic substrates, designed for the synthesis of structurally complex heterocyclic and carbocyclic systems together with the development of methodology for stereocontrolled preparation of functionalised olefins. Consequently, the thesis is divided into three sections. The first of these introduces the allenic functionality highlighting the special properties associated with allenic compounds and the recent advances in allene chemistry with particular emphasis on the application of allenic substrates to heterocyclisation, carbocyclisation and carbometallation.

The second section describes the results obtained during the course of this study and is divided into three sub-sections. The first of these summarises the development of novel aza-annulation methodology for the preparation of biologically relevant nitrogen containing molecular architectures using electron deficient allenes as substrates for regioselective vinylogous urethane and amide formation. The application of this methodology towards the synthesis of the cytotoxic alkaloid N-oxo-rhazinilam is also discussed. This is followed by a discussion of a tandem enamine formation cyclisation sequence using allenic substrates for the preparation of substituted cyclopentanones. The final section describes a preliminary study of a novel carbometallation reaction of allenic substrates for stereocontrolled preparation of functionalised alkenes.

Chapter three provides a summary of these three areas of research as well as highlighting potential avenues for further exploration. Chapter four details all of the relevant experimental procedures and compound characterisations.

Acknowledgements

I would like to begin, first and foremost, by thanking my supervisor, Professor William Motherwell, for providing me with the opportunity to spend three years doing the thing I enjoy most, chemistry. The inspiration, guidance and education he has provided to me over these years is priceless and I am eternally grateful for this. I would also like to thank Dr^2 Robyn Motherwell (the real boss) for her help dealing with laboratory ethics, office politics, proofreading of this and many other manuscripts, but most of all for her sense of humour and fun. I would also like to thank Andrew Whitehead for his guidance and GSK for the financial support provided to me to complete my studies.

I have been extremely lucky to work with two excellent postdoctoral research workers in Dr Tom Sheppard and Dr Steve Hilton. I would like to thank both of them for all the support and advice they have provided and for the memorable good cop bad cop routine they acted out so naturally.

The Motherwell lab has been an incredible place to work, sleep and dine over these years and I am grateful to all the colourful characters I have encountered in this, my home from home. I would like to say a special thanks to Thierry de Merode my drinking partner and friend, Alex Cayley for his comedy beard and rapping, Sunhill Moosa Chi and all other group members past and present.

Bert, you deserve to be in the family paragraph, so thanks for these memorable years of true friendship, at work and more importantly in the cold reality of the outside world, I am lucky to have you as a friend. Thanks to my family, especially my beautiful loving wife Olga, it is impossible to fail when I am armed with your love.

Abbreviations

Acc – Acceptor group
AcCl – Acetyl chloride
AcOH – Acetic acid
Bn - Benzyl
BOC –*tert*-butyloxycarbonyl
BuLi - Butyllithium
CSA – Camphorsulfonic acid
DCM – Dichloromethane
DIOP – 4,5-bis-[(diphenylphosphanyl)methyl]-2,2-dimethyl-[1,3]dioxolane
DME – 1,2-dimethoxyethane
DMF – Dimethylformamide
DMSO - Dimethylsulfoxide
dppb – 1,2-bis(diphenylphosphino)butane
dr – Diastereomeric ratio
E - Electrophile
FGI – Functional group interconversion
HATU – O-(7-azabenzotriazol-1-yl)-N,N,N,N-tetramethyluronium hexaflourophosphate
HPLC – High pressure liquid chromatography
HRMS – High resolution mass spectrometry
hrs - Hours
IR - Infra Red
LDA – Lithium diisopropylamide
LRMS – Low resolution mass spectrometry
LUMO – Lowest Unoccupied Molecular Orbital
MCPBA – *meta*-chloroperoxybenzoic acid
mg - milligrams
MHz – megahertz
mmole - millimoles
MOM – methoxymethyl
Mp – Melting point
NBS – N-bromosuccinimide
NMR – Nuclear magnetic resonance
NOE – Nuclear Overhauser Effect
Nu – Nucleophile
[O] - Oxidation
PhMe - Toluene
p-TsOH – *para*-Toluenesulfonic acid
RT – Room temperature
TBAC – tetrabutylammonium chloride
TBDMS – Tertiarybutyldimethylsilyl
TBDMSCl – Tertiarybutyldimethylsilyl chloride
TBS – Tributylsilyl
Tf- Trifluoromethanesulfonate
TFP – tris(2-furyl)phosphine
THF – Tetrahydrofuran
TLC – Thin layer chromatography
TMS - Trimethylsilyl
TMSCl – Trimethylsilyl chloride
Ts – Tosyl

CHAPTER 1

INTRODUCTION

1.0 Thesis Background

The present thesis is concerned with the discovery and development of new reactions utilising the versatile allene functional group. In particular, the use of functionalised allenic substrate, in the three key areas of heterocyclisation, carbocyclisation and carbometallation have provided the framework for the studies described herein. In consequence, the following introduction provides a series of brief overviews which highlight the exciting developments in these selected areas and emphasise the value of this unique unit.

1.1 Introduction to the Allene Functional Group

The allenic moiety is defined as a three carbon functional group consisting of two cumulated double bonds separated by a single sp hybridised carbon atom. Even although the first allenic compound was prepared in 1887 by Burton and Pechmann,[1] its structure was not confirmed until 1954.[2] The initial development of allene chemistry was seriously hampered by the common misconception that such a system of cumulated double bonds would be inherently unstable and this situation was further exacerbated by a lack of reliable synthetic methods for the preparation of this unit.

In 1924, pyrethrolone, a natural product containing the allenic functionality was isolated by Staudinger and Ruzicka [3] (Figure 1) and, as is often the case, this was followed by the isolation of a number of other allenic natural products from higher organisms such as brown algae.[4]

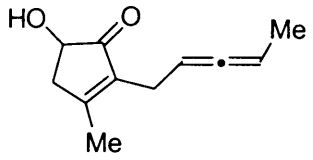


Figure 1

Isolation of these allenes from natural sources led to an increase in interest in allenic compounds, and in consequence, to a variety of synthetic methods for their preparation as readily evidenced by a two volume set in the Wiley-VCH series.[5] The surge of activity into allene chemistry is nothing less than phenomenal and in recent years this remarkable functional group has been used to devise a wide variety of novel synthetic methods and to combat a range of synthetic challenges.

1.2 Allenes: Structure, Spectroscopy and Reactivity

The unique structure of the allene moiety has a significant impact upon the physical properties of allenic compounds. The 1,2-diene unit, the characteristic signature mark of allenes, comprises an sp-hybridised carbon atom separating two sp^2-hybridised carbons. The two orthogonal p-orbitals of the central carbon form π-bonds with the outer carbon atoms by overlapping with the appropriate p-orbitals on the two sp^2 hybridised carbon atoms. For maximum orbital overlap to occur the resulting π-bonds must be orthogonal to each other, and in consequence no conjugation between the two double bonds exists (Figure 2).

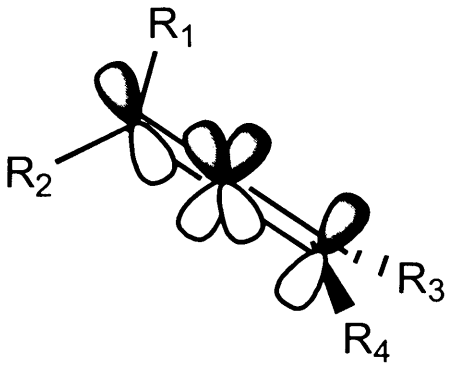


Figure 2

This characteristic orthogonal bonding arrangement leads to what is probably the most fundamental and distinguishing property of allenic compounds, namely, their axial chirality. The intrinsic chirality of allenes was first recognised by van't Hoff in 1875,[6] and has since been confirmed by the classical resolution of allenic acids with a variety of alkaloids.[7]

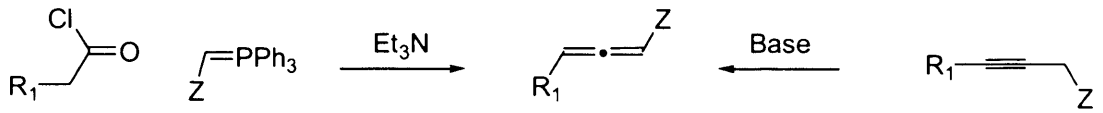
The spectroscopic properties of allenes are also unique, making their identification extremely facile. For instance, the characteristic IR shift, arising due to asymmetric stretching of the allene, appears around 1950 cm^{-1}, a region largely unoccupied by other functional groups. Moreover, ^{13}C NMR spectroscopy provides an excellent

method for the structural analysis of allenes. In general, the peak corresponding to the central sp- hybridised carbon atom appears at extremely low field, between 200-220 ppm, depending upon the nature of the substituents surrounding the allenic nucleus. By way of contrast the sp hybridised carbon atoms of an acetylene are generally found in the region between 80-100 ppm, and, once again the actual value depends upon the nature of the substituents surrounding the centre of unsaturation.

1.3 Synthesis of Allenic Compounds

A comprehensive account on the synthesis of allenes is simply too vast a topic to be placed on these pages. Furthermore, a number of excellent reviews on this topic have been published in recent years.[8] Nevertheless, it is appropriate to provide a very brief summary of the major routes used to prepare these fascinating compounds.

Electron deficient allenes, viz, those containing a 1,2-diene unit directly attached to an electron withdrawing group such as allenic ketones and esters, have been extensively studied during the course of this research and can be prepared in a variety of ways (Scheme 1). Thus, as summarised in Scheme (1), the classic approach to the synthesis of allenic esters and ketones (3) involve either the Wittig reaction of ketenes, [9] derived from acid chlorides (1) with ylides (2), or the base induced isomerisation of acetylenes (4).[10]



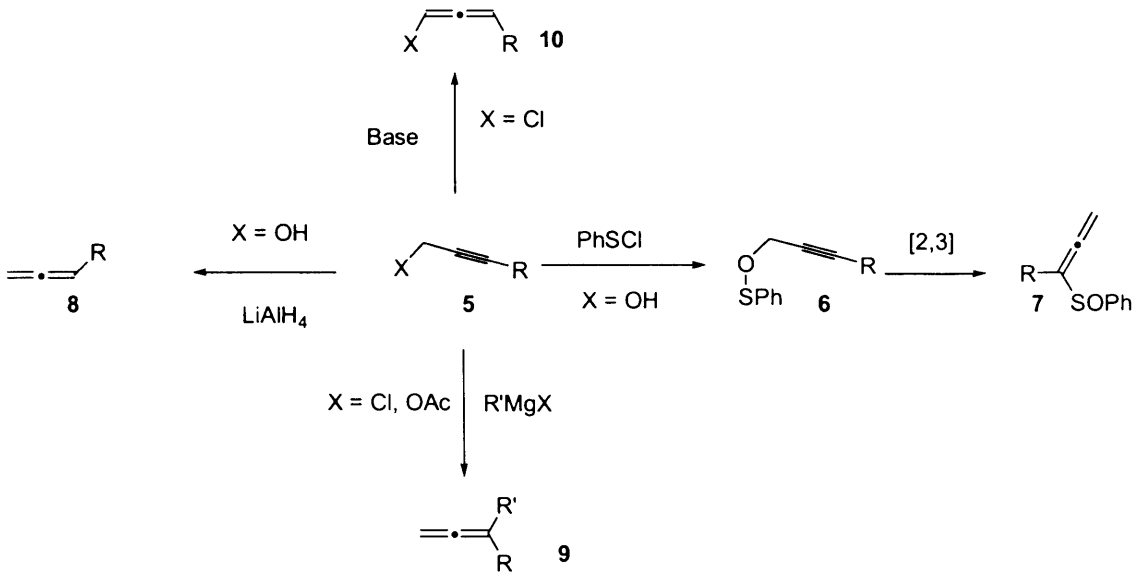
1 **2** **3** **4**

Z = COR, CO_2R
R/R_1 = Alkyl/Aryl

Scheme 1

Propargylic substrates (5) are commonly used for the preparation of allenic compounds. As shown in Scheme (2), sigmatropic rearrangements,[11] nucleophilic

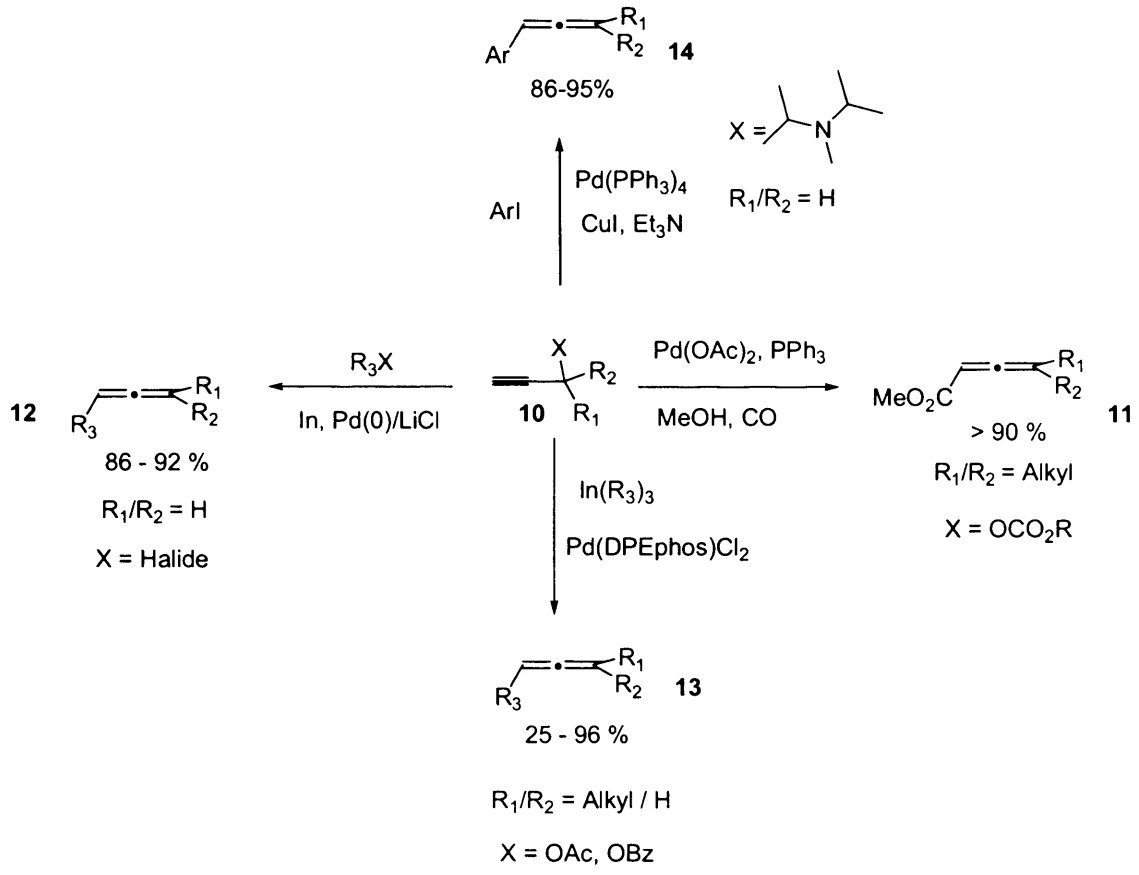
additions [12] and isomerisation reactions [13] have all been reported to provide access to allenes (7-10).



Scheme 2

For example, as depicted above, the treatment of propargylic alcohols with sulfenyl chlorides leads to the synthetically versatile allenic sulfoxides (7) *via* the rapid [2,3] sigmatropic rearrangement of intermediates (6). Propargylic halides can be efficiently converted into allenyl halides (10) upon treatment with base, whereas addition of a range of organometallic reagents to propargylic electrophiles such as chlorides and acetates leads to a variety of substituted allenic hydrocarbons (9). Propargylic alcohols can also be converted directly into allenes (8) upon reaction with a range of aluminium hydrides.

In recent years transition metal catalysed synthesis of allenes, in particular catalysis by palladium complexes, has become an extremely useful method for the preparation of a vast array of structurally complex allenic compounds.[13] Some of the most often encountered protocols are summarised in Scheme (3).



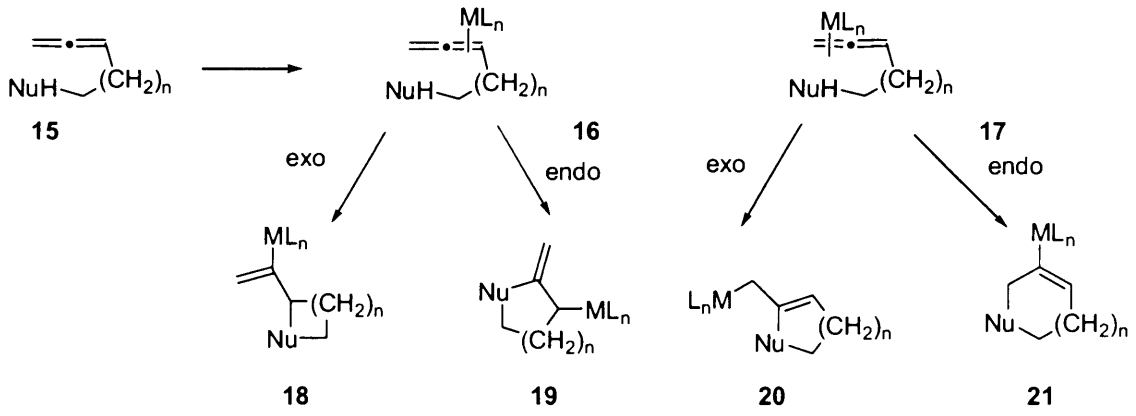
Scheme 3

The successful development of efficient methodology for the synthesis of functionalised allenes has enabled a detailed exploration of the chemistry of these unique compounds and the remainder of this introduction aims to highlight the areas of this fascinating field related to the current study, namely, heterocyclisation, carbocyclisation and carbometallation of functionalised allenes.

1.40 Modern Synthetic Applications of Functionalised Allenic Substrates

1.41 Heterocyclisation *via* Metal Catalysed Cycloisomerisation of Functionalised Allenic Substrates

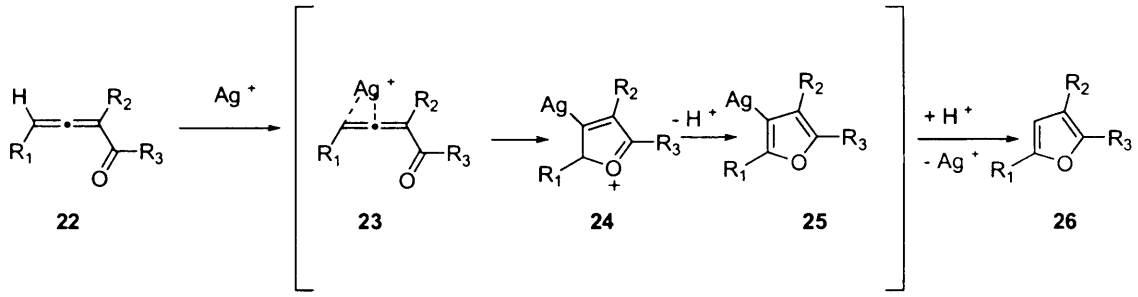
Perhaps the most successful application of allenes in organic synthesis has been the development of novel methodology for the regioselective synthesis of a vast array of substituted heterocycles. Cycloisomerisation reactions, involving activation of one of the allenic double bonds with an electrophilic metal centre, followed by nucleophilic attack by a tethered heteroatom and subsequent proto-demetallation, forms the basis of the vast majority of heterocyclisation reactions of allenic substrates (15) (Scheme 4).[14]



Scheme 4

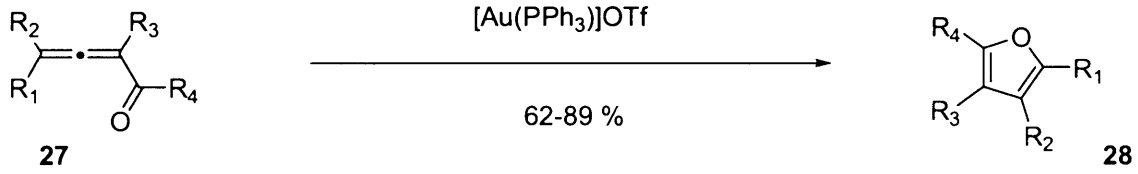
Steric and electronic factors determine whether activation of the allenic proximal (16) or distal bond (17) occurs. In principle, for each activated allene, *exo* or *endo* cyclisation can occur, and in consequence, provided that some degree of predictive control can be achieved in terms of the four possible pathways, a huge variety of heterocyclic systems (18-21) can be prepared using this chemistry.

Marshall and co-workers were the first to report the synthesis of substituted furans (26) *via* Ag (I) catalysed cycloisomerisation reactions of allenic ketones (22) (Scheme 5).[15]



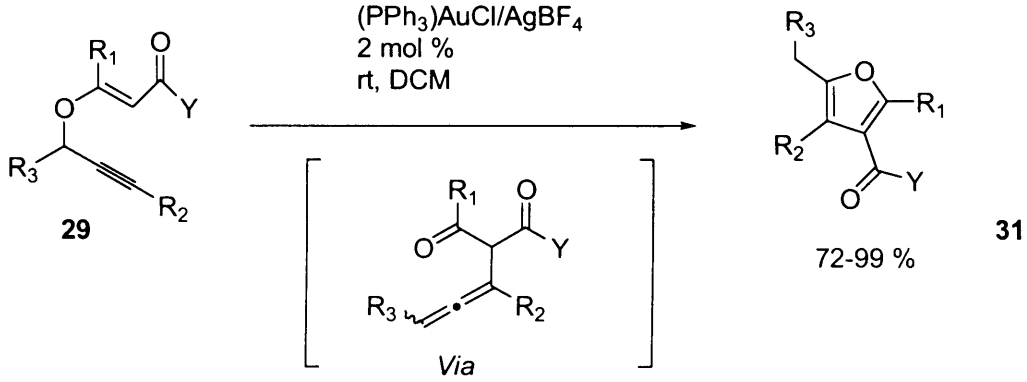
Scheme 5

The authors proposed that the silver catalyst plays a pivotal role in the reactions, activating the distal allenic double bond towards attack by the ketonic oxygen leading to cationic intermediates (24), which upon aromatisation and proto-demetallation give substituted furans (26). The use of cationic Au (I) complexes for the preparation of substituted furans from allenic ketones has also been described. [16] Gevorgyan and co-workers demonstrated that λ-alkyl-disubstituted allenic ketones (27), undergo cycloisomerisation to give fully substituted furans (28), with the authors describing a novel [1,2] alkyl shift as the key step in the formation of such fully carbon-substituted furans (28) (Scheme 6). [17]



Scheme 6

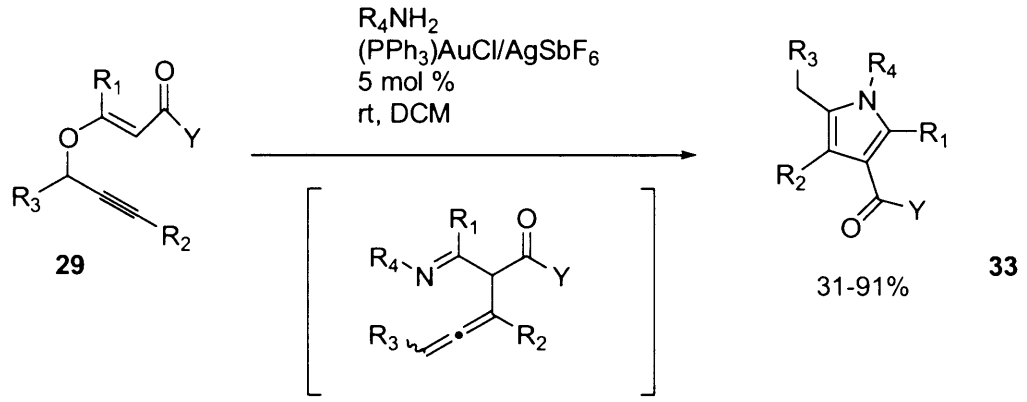
Kirsch and co-workers have reported an elegant tandem reaction sequence involving a formal [3,3]-sigmatropic rearrangement and subsequent heterocyclisation. The group used a Au (I) catalysed rearrangement of readily prepared propargyl-vinyl ethers (29) to provide reactive allenic intermediates (30), which were shown to undergo *in situ* heterocyclisation, giving both tri- and tetra-substituted furans (31) (Scheme 7). [18]



29 30 31

Scheme 7

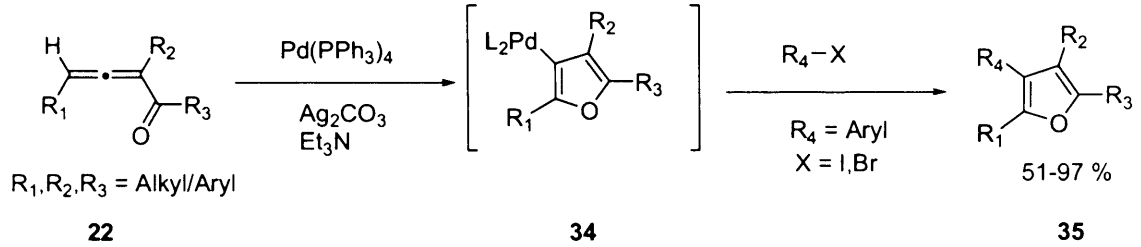
Furthermore, addition of primary amines in these reaction mixtures was investigated and reported to enable the preparation of the corresponding tetra-substituted pyrroles (33) *via* intermediate imines (32) (Scheme 8). [19]



29 32 33

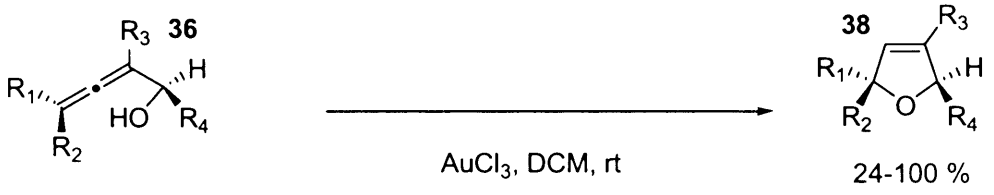
Scheme 8

A tandem cycloisomerisation-cross coupling reaction of allenic ketones catalysed by Pd (0) complexes has been reported by Ma *et al.* (Scheme 9).[20] Thus, cyclisation of ketones (22) to vinyl palladium intermediates (34) is followed by cross coupling with aryl halides to give fully substituted furans (35).



Scheme 9

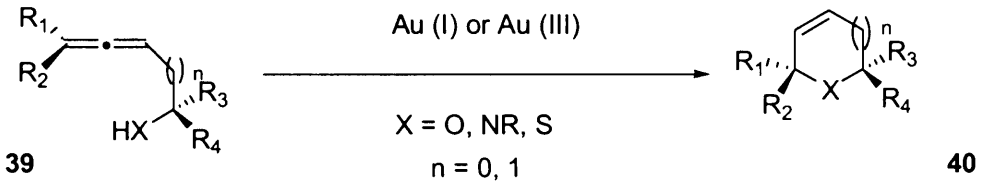
Chiral dihydrofurans and tetrahydrofurans are common structural motifs found in a wide variety of natural products and pharmacologically active molecules.[21] Metal catalysed cyclisation of α-hydroxy allenes of defined absolute and / or relative stereochemistry, offer an extremely powerful method for the stereoselective construction of these important structural motifs. Krause and co-workers [22] have used gold catalysis to effect stereoselective dihydrofuran (38) formation from allenols (36). The group demonstrated that the gold catalysed cycloisomerisation takes place with efficient transfer of chirality from the allenic axis to the newly formed stereogenic centre (Scheme 10).



Scheme 10

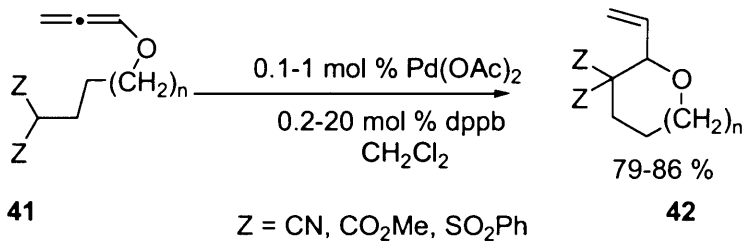
This stereoselective cycloisomerisation reaction is not only restricted to α-hydroxy allenes, as the corresponding β-hydroxy allenes, α- and β- aminoallenes and α-thioallenes (39) also undergo cyclisation, thus providing an extremely versatile and

powerful method for the construction of the corresponding O, N and S five and six membered heterocycles (40) (Scheme 11).[23]



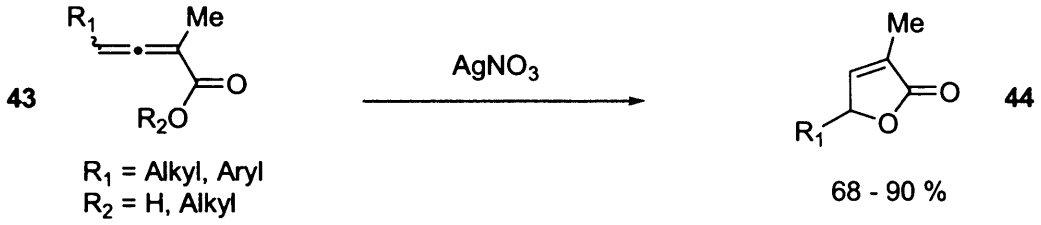
Scheme 11

Activated carbon atoms have also been shown to add to the π system of allenes. For example, allenyl ethers (41) undergo Pd (II) catalysed cyclisation providing cyclic ethers (42) in excellent yield (Scheme 12).[24] A related highly efficient method for the preparation of 5, 10, 15 and 17-membered lactones and lactams has been reported by Trost and co-workers.[25]



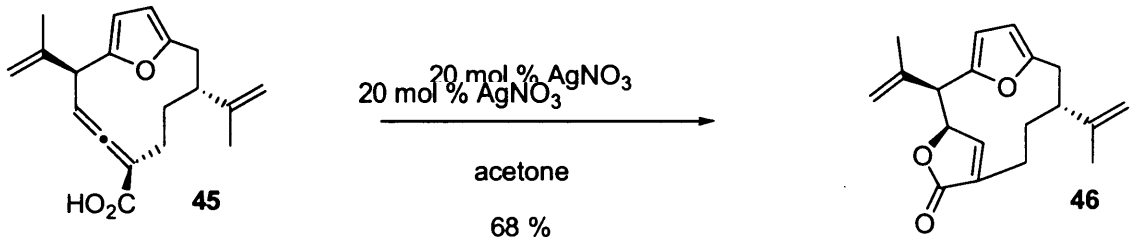
Scheme 12

Polysubstituted butenolides are a class of compounds of immense interest due to their broad range of biological activities and occurrence in natural products.[26] In recent years, cycloisomerisation reactions of allenic esters and acids have provided a convenient route to these compounds. Marshall and co-workers were the first to report the $AgNO_3$ mediated cyclisation of allenic acids and esters (43) into substituted butenolides (44) (Scheme 13).[27]



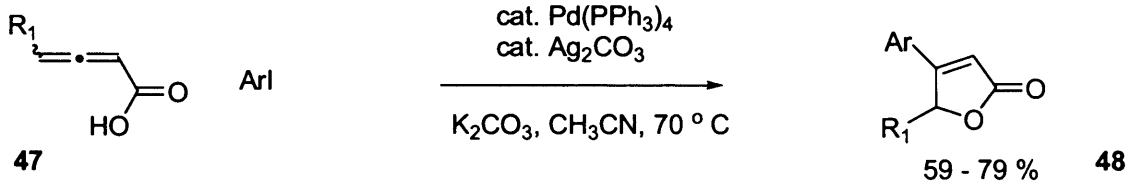
Scheme 13

The group followed up these initial studies by developing a related route to enantioenriched butenolides (44) from nonracemic allenic acids and then provided an elegant demonstration of the methodology during the course of a total synthesis of (-)-kallolide (46).[28] Thus, exposure of allenic acid (45) to $AgNO_3$ in acetone resulted in the stereospecific formation of the butenolide fragment present within the natural product (46) (Scheme 14). The synthesis of (-)-deoxypukalide and rubifolide have also been reported to use a Ag (I) catalysed cycloisomerisation of allenic acids into butenolides in the key steps .[29]



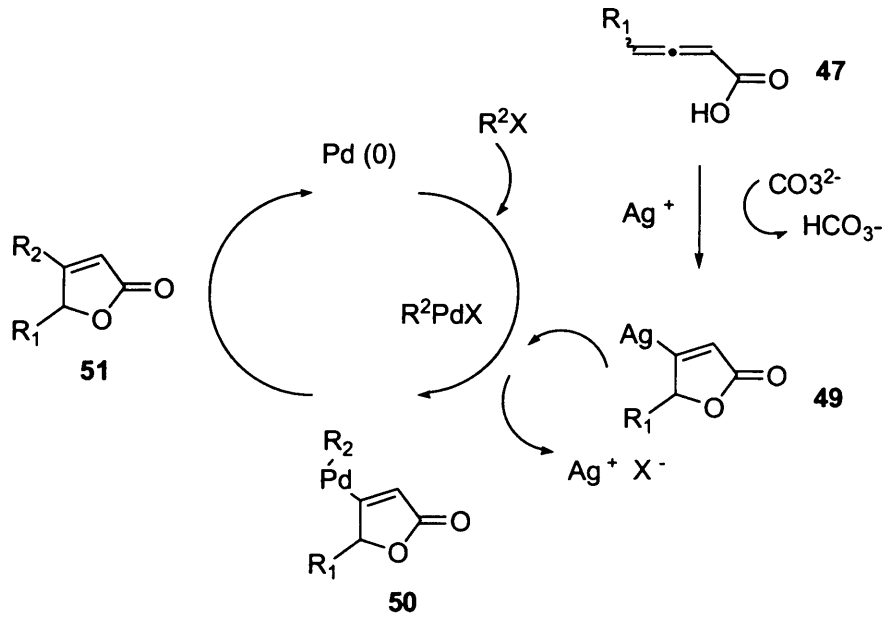
Scheme 14

Cycloisomerisation reactions of allenic carboxylic acids have also been intensively studied by Ma and co-workers. In their initial studies, the group demonstrated that the reaction of allenic acids (47) with aryl iodides, catalysed by $Pd(PPh_3)_4$ led to the formation of substituted butenolides (48) (Scheme 15).[30] It was shown that the highest yields of butenolides (48) were obtained when a substoichiometric amount of Ag_2CO_3 was used as base.



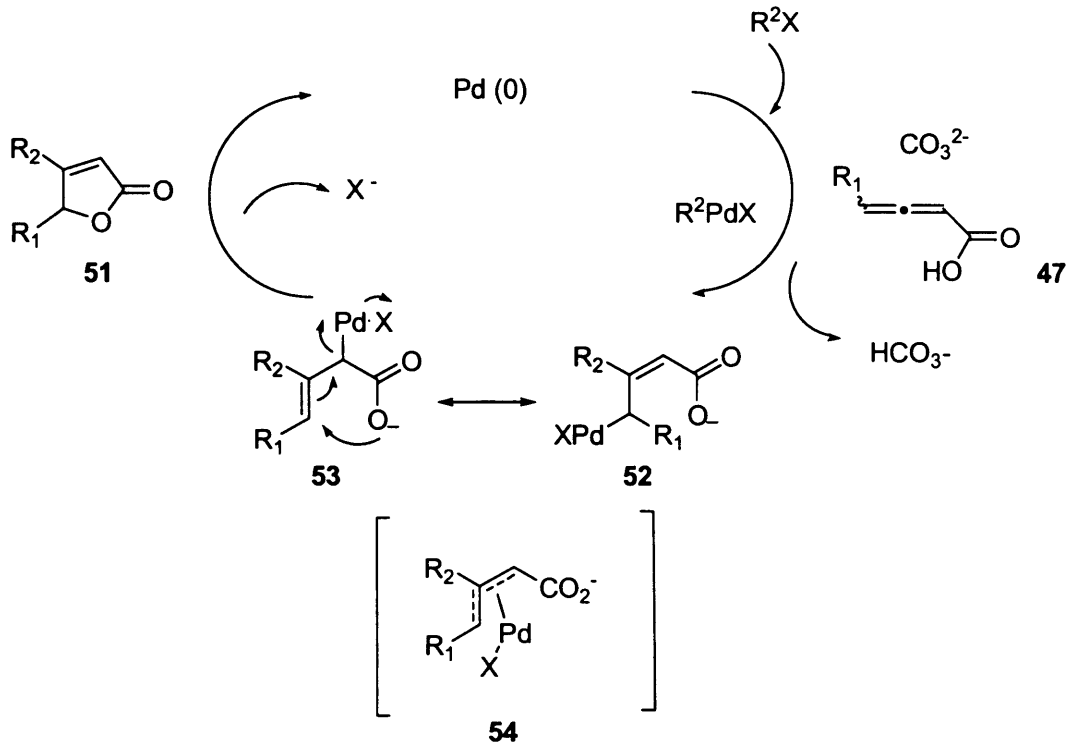
Scheme 15

The authors proposed that the Ag (I) ions acts as a Lewis acid mediating the formation of 3-silver-2-butenolide intermediates (49), which undergo transmetallation with aryl palladium halides to give vinyl palladium intermediates (50) followed by reductive elimination to give the described butenolides (51) and regenerating the Pd (0) catalyst (Scheme 16).



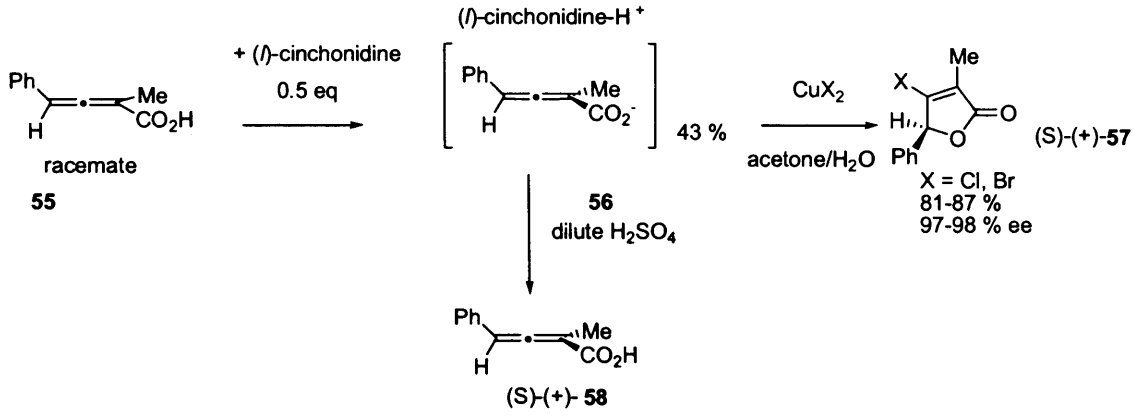
Scheme 16

The reaction was also shown to proceed in the absence of Ag_2CO_3 leading to an alternative reaction mechanism being observed. Thus, oxidative addition of the aryl halide to the Pd (0) catalyst followed by carbopalladation to give π-allyl palladium complexes (52) and (53) followed by intramolecular allylic substitution could also lead to butenolides (51) (Scheme 17).



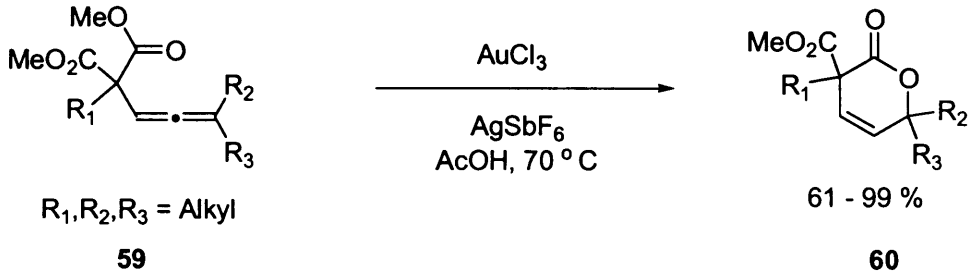
Scheme 17

The successful development of several methodologies for the synthesis of β-halobutenolides from 2,3 allenoic acids [31] led Ma and co-workers to investigate the potential of transferring axial chirality from allenes to central chirality in butenolides. Thus, as shown in Scheme (18), resolution of racemic allenic acid (55) with 0.5 equivalents of the cheap and readily available (l)-cinchonidine, afforded the optically active salt (56) in 43 % yield. The free acid could be released upon exposure of (56) to dilute sulfuric acid providing (S)-(+)-(58). However, direct halolactonisation of the optically active salt (56) with $CuCl_2$ and $CuBr_2$ in acetone gave the corresponding chloro- and bromo-butenolides (57) in excellent yield and with almost complete translation of axial chirality (Scheme 18).[32]



Scheme 18

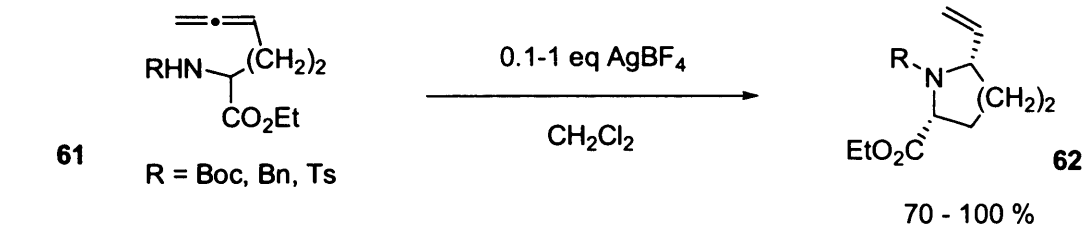
The same group have also reported Pd (0) catalysed synthesis of polysubstituted butenolides using polymer supported aryl iodides [33] and Pd (0) catalysed asymmetric coupling reactions of racemic carboxylic acids with aryl iodides.[34] Recently, a Au (III) catalysed cyclisation of homoallenic esters to β,γ- unsaturated δ-lactones has also been reported.[35] Thus, as depicted in Scheme (19), exposure of homoallenic esters (59) to a solution of $AuCl_3$ in acetic acid led to the formation of lactones (60). It was shown that the presence of Ag(I) salts was crucial to the reactions, with significantly lower yields of lactones (60) obtained in their absence.



Scheme 19

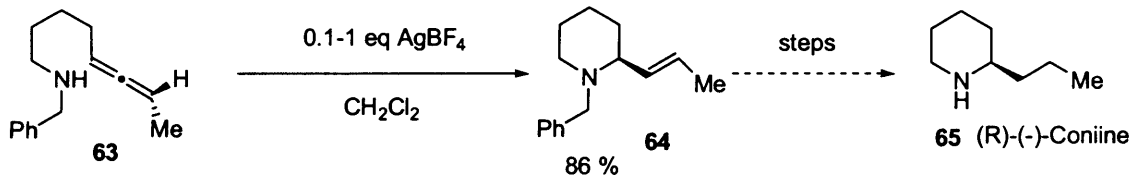
The formation of pyrrolidine and piperidine derivatives *via* cycloisomerisation of allenic substrates has also received considerable attention.[36] Gallagher and co-workers studied the cyclisation of allenes (61) in the presence of $AgBF_4$, demonstrating that these reactions offer a convenient regio- and stereoselective route to biologically important substituted pyrrolidines (62). Activation of the proximal allenic double

bond followed by *endo* cyclisation led to the selective formation of the cis-diastereoisomers (62) (Scheme 20).[37]



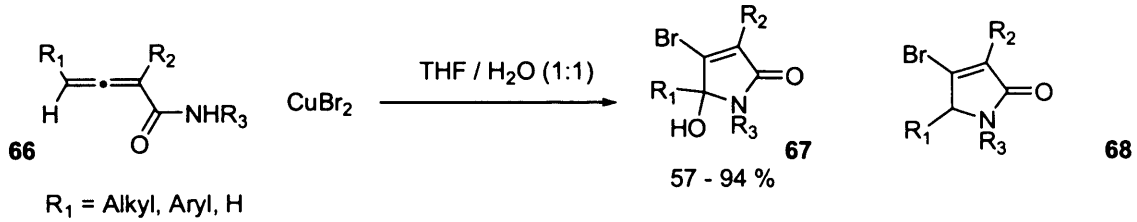
Scheme 20

The utility of this approach for piperidine synthesis was also demonstrated during the course of a total synthesis of (R)-(-)-Coniine (65) (Scheme 21). Thus, efficient transfer of axial to central chirality was observed upon cycloisomerisation of the enantiomerically pure allene (63) to piperidine (64).[38]



Scheme 21

Ma and co-workers [39] have reported a tandem halolactamisation-hydroxylation reaction of 2,3-allenamides for the synthesis of the biologically significant pyrrole-2-(*5H*)-ones . As shown in Scheme (22) reaction of allenamides (66) with $CuBr_2$ did not lead to the expected bromolactamisation products (68), but to the oxidised hydroxyl substituted pyrrol-2-(*5H*)-ones (67).



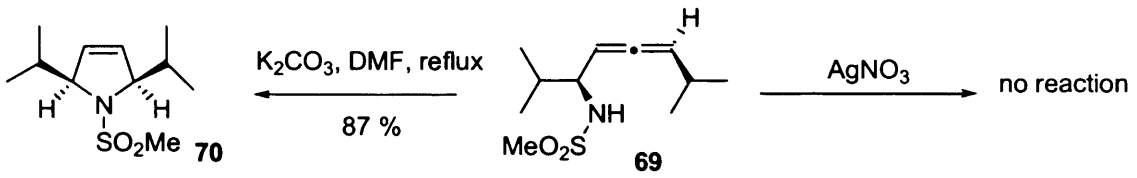
R_1 = Alkyl, Aryl, H
R_2 = Alkyl, H

Scheme 22

The authors proposed that further *in situ* oxidation of the expected lactams (68) by Cu (II) is responsible for the formation of the hydroxyl substituted pyrrole-2-(5H)-ones (67).

Brummond *et al.* have shown that allenic amino acids derivatives also undergo efficient Ag (I) catalysed cycloisomerisation to provide a range of functionalised pyrrolines and oxazines in good yields, [40] whereas Dieter *et al.* have reported a regioselective synthesis of substituted pyrrolines and pyrroles *via* a Pd (0) catalysed cycloisomerisation reaction of homo-allenylamines. [41]

Interestingly, Tanaka studied the cycloisomerisation of sulfonyl-substituted allenyl amines in the absence of a transition metal catalyst and demonstrated that cyclisation to the corresponding pyrrolines could be achieved thermally under mild basic conditions, providing the described heterocycles in good yields.[42] The group showed that cyclisation of allene (69) to pyrroline (70) occurred smoothly under basic conditions. However, cyclisation failed to occur in the presence of a silver catalyst (Scheme 23). The authors proposed that steric constraints around the allenic nucleus inhibit the essential co-ordination of Ag (I) ions, thus preventing cyclisation.

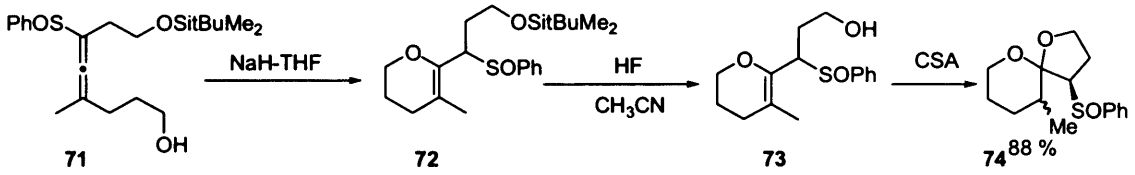


Scheme 23

1.42 Heterocyclisation *via* Nucleophilic Addition to Activated Allenes

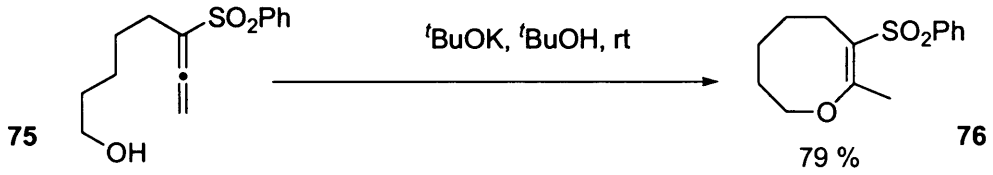
In recent years, the addition of nucleophilic heteroatoms and stabilised carbanions to activated allenes, such as electron deficient allenic sulfones, sulfoxides and ketones has been explored. Consequently, novel methodology for the regioselective synthesis of a variety of biologically significant heterocyclic systems has been developed.

Parsons and co-workers [43] were first to report the intramolecular base catalysed cyclisation of allenic sulfoxides, as a key step for the construction of spiroketals. Thus, treatment of the alcohol (71) with NaH followed by addition of the resulting alkoxide anion to the central allenic carbon, led to pyran (72) (Scheme 24).



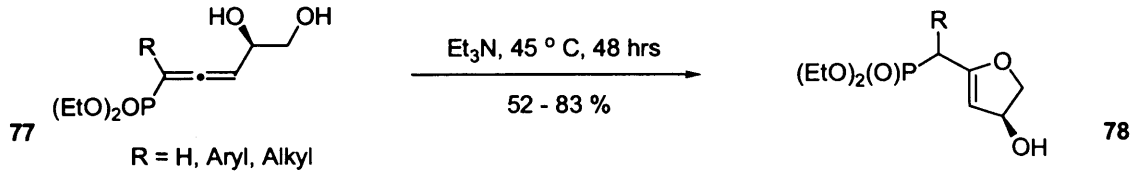
Scheme 24

The spiroketal (74) was then obtained by the removal of the silyl protecting group followed by reaction of the resulting alcohol (73) with a substoichiometric amount of camphorsulfonic acid (CSA). Mukai and co-workers have shown that allenic sulfones possessing a hydroxyl appendage also undergo base mediated endo cyclisation providing a variety of five to eight-membered oxygen heterocycles in high yields .[44] For example, cyclisation of allenic sulfone (75) in the presence of ^{t}BuOK provided an eight membered ring (76) in 79 % isolated yield (Scheme 25). The reaction was also successful with the corresponding allenyl sulfoxides and phosphonates, providing a range of heterocyclic structures under very mild reaction conditions.[45]



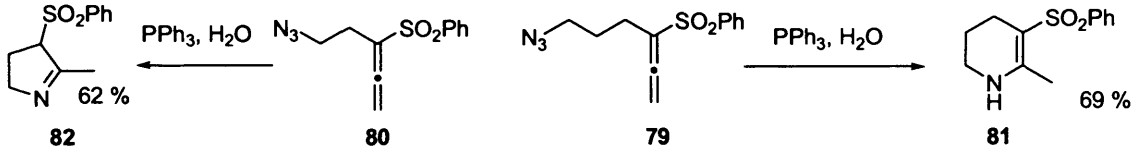
Scheme 25

The synthesis of phosphorylated dihydrofurans *via* cyclisation of the corresponding phosphorylated allenic carbinols (77) was reported by Brel *et al.*[46] The reactions were shown to occur *via* addition of the primary alcohol to the central allenic carbon providing dihydrofurans (78) in good yields (Scheme 26).



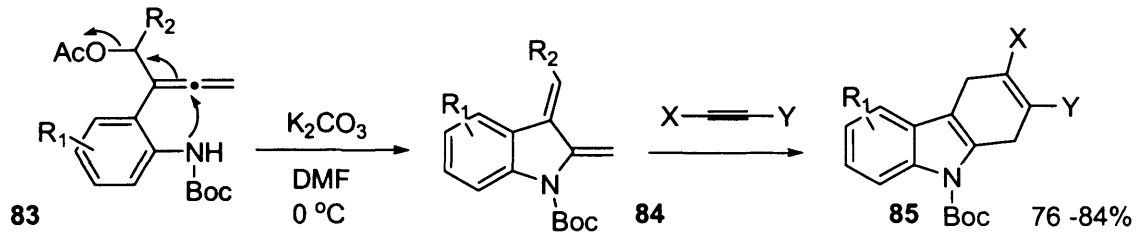
Scheme 26

The preparation of piperidines and pyrrolidines *via* addition of amino groups to the central carbon of activated allenes has also been reported (Scheme 27). In this instance, reduction of azides (79) and (80) followed by cyclisation provided the corresponding heterocycles (81) and (82) in moderate yields. [47]



Scheme 27

Heteroatom addition to activated allenes has also enabled the development of an elegant tandem reaction sequence for the preparation of highly functionalised indoles.[48] Mukai and co-workers demonstrated that the highly reactive indole-2,3-quinodimethane intermediates (84), can be readily obtained from allenylanilines (83), *via* nucleophilic addition of the aryl amine to the central allenic carbon. These intermediates were shown to undergo cycloaddition with a range of dienophiles providing substituted dihydrocarbazoles (85) (Scheme 28).

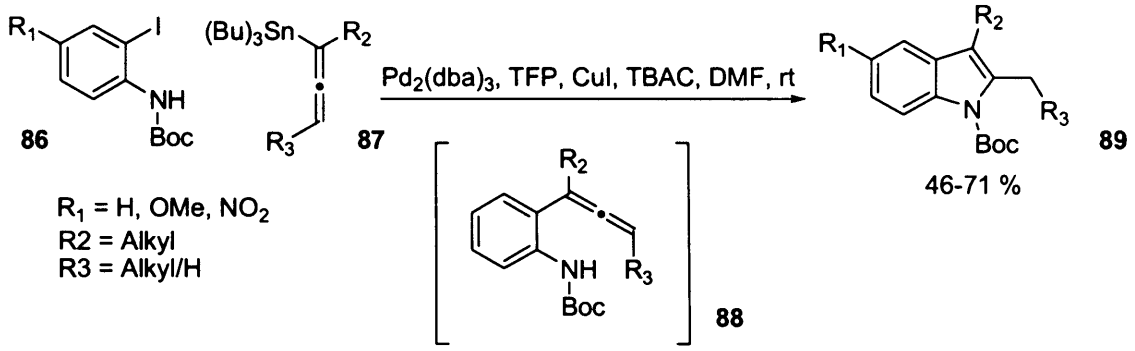


R^1 = H, OMe, OCH_2O, Cl, CO_2Et R^2 = H, Me

X,Y = CO_2R

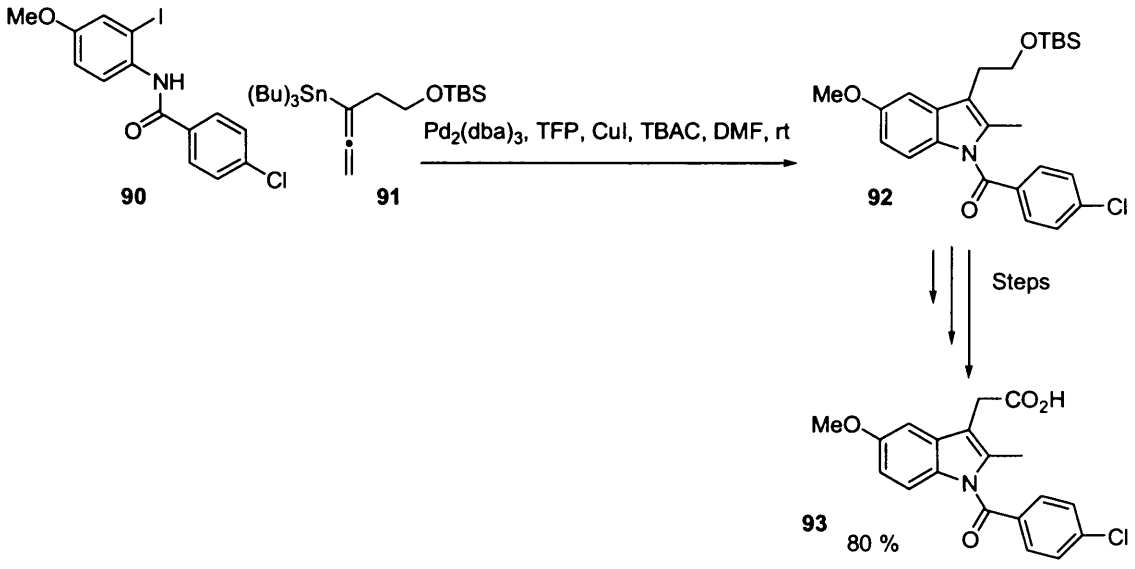
Scheme 28

The same group have also reported an efficient Pd (0) catalysed coupling reaction of *N*-acyl-2-iodoanilines (86) with allenylstannanes (87), providing the corresponding 2-allenylanilines (88), which, upon cyclisation of the nucleophilic nitrogen atom onto the allenic sp hybridised carbon atom, evolve to indoles (89) (Scheme 29).[49]



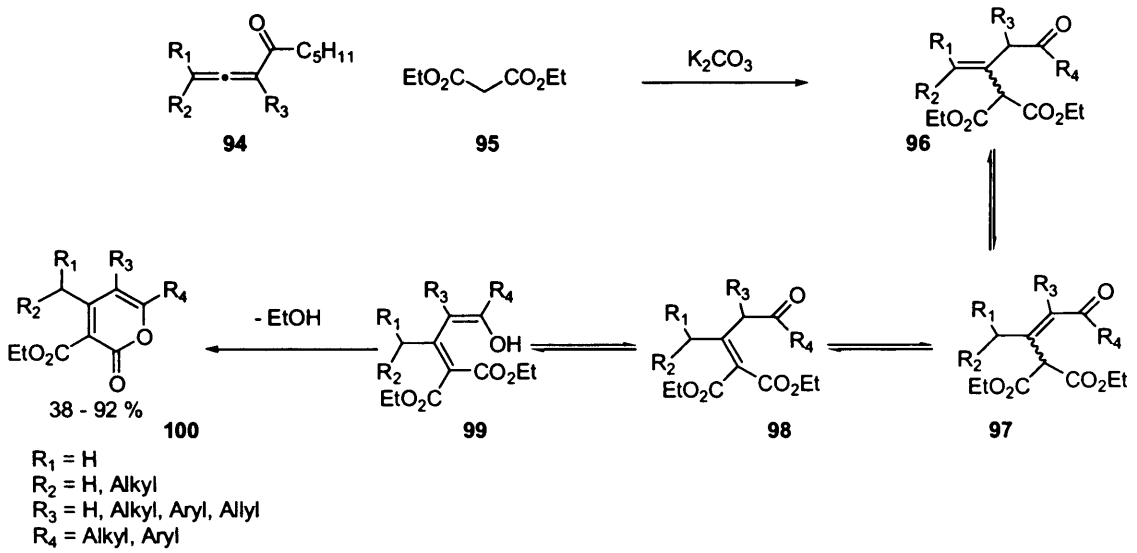
Scheme 29

The group demonstrated the scope of this novel transformation during the synthesis of indomethacin, [49] an anti-inflammatory non-steroidal agent containing an indole nucleus. Thus, Pd (0) catalysed coupling of aniline (90) with allenyl stannane (91) provided indole (92), which was then converted to indomethacin (93) in three steps in 80 % overall yield (Scheme 30).



Scheme 30

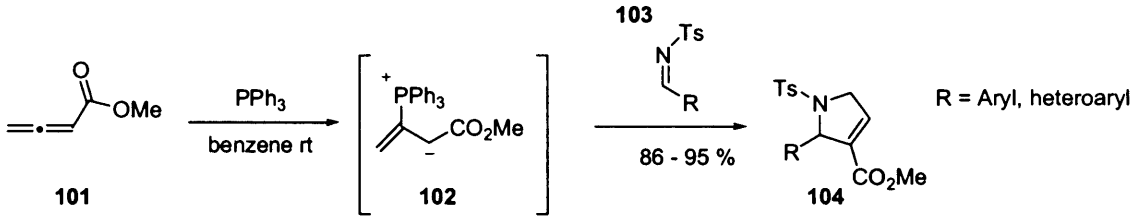
Ma and co-workers have demonstrated that in the presence of base, compounds containing an activated methylene group such as (95) take part in a tandem reaction with allenic ketones (94) leading to α-pyrone derivatives (100) (Scheme 31).[50]



Scheme 31

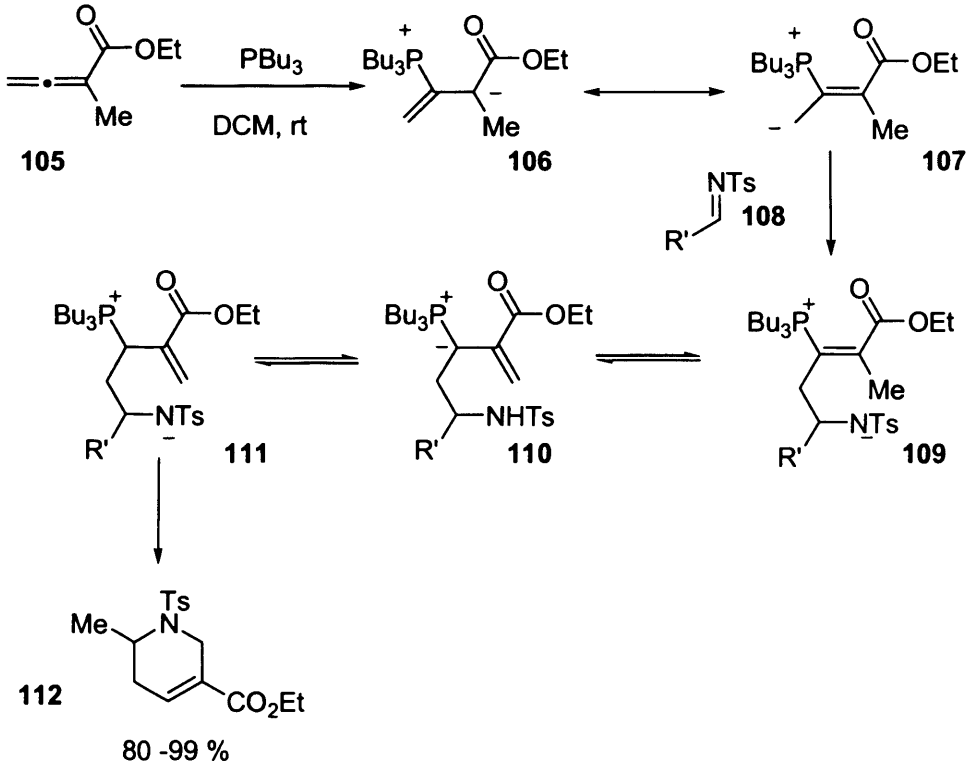
Thus, nucleophilic addition of diethyl malonate (95) to allenic ketones (94) leads to the initial adducts (96), which upon double bond isomerisation afford (97) and (98). Cyclisation via (99) and elimination of ethanol provides α-pyrone derivatives (100).

A novel approach to nitrogen based heterocycles was reported by Lu and co-workers, who demonstrated that nucleophilic addition of phosphines to allenic ester (101) generates reactive [1,3] dipoles (102), which undergo [3+2] cycloaddition reactions with N-tosylimines (103) leading to pyrrolidines (104) (Scheme 32). [51]



Scheme 32

Following on from this pioneering discovery, Kwon and co-workers demonstrated that a similar reaction with α-substituted allenic esters (105) led to the diastereoselective synthesis of tetrahydropyridines (112).[52] The authors proposed that the presence of the α-substituent on the allene favours attack on the imines (108) through the γ-carbon of zwitterionic species (107) instead of attack through the sterically congested α-carbon in betaine (106) (Scheme 33). [52]



Scheme 33

Thus, as depicted above, addition of the zwitterionic species (107), formed by addition of PPh_3 to allenic ester (105), to imines (108) to give intermediates (109) is followed by two consecutive proton transfer steps *via* (110) leading to the αβ-unsaturated esters (111), which, upon 6-*endo* cyclisation and elimination of triphenyl phosphine yield tetrahydropyridines (112).

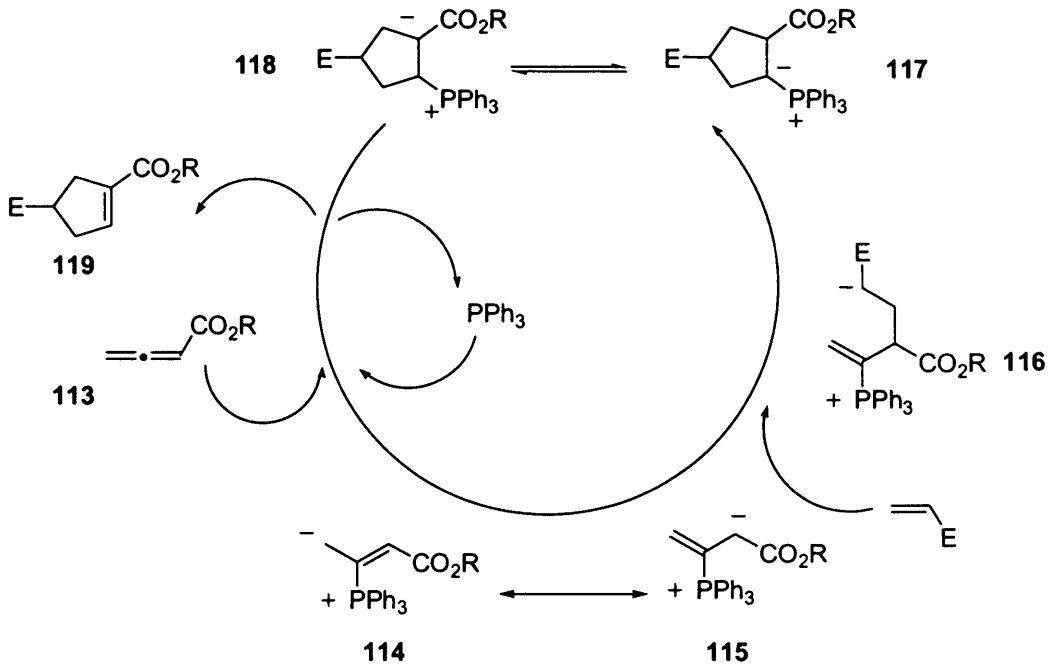
Subsequent studies demonstrated that replacement of tributylphosphine with chiral alkyl and aryl phosphines enabled the development of asymmetric variants of the

reaction giving the corresponding tetrahydropyridines in excellent enantiomeric excess.[53]

1.43 Carbocyclisation *via* Cycloaddition Reactions of Functionalised Allenic Substrates

The versatile allenic nucleus has also played a key role in the development of efficient regio- and stereo-controlled synthetic approaches to complex carbocyclic systems *via* cycloaddition chemistry ([2+2], [3+2] & [4+2]). Some of the more important synthetic routes are covered in some detail upon the following pages.

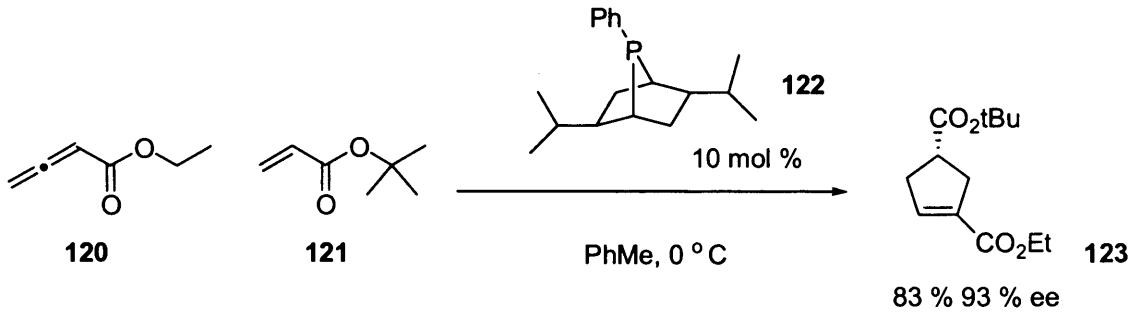
In recent years, phosphine catalysis has emerged as a powerful tool in asymmetric synthesis.[54] Lu and co-workers were the first to report the phosphine catalysed cycloaddition reaction of allenic carboxylates with electron deficient olefins as an efficient route to a variety of substituted cyclopentenes.[55] As depicted in Scheme (34) these reactions are thought to proceed *via* addition of phosphines to allenic carboxylates (113) generating 1,3-dipoles (114) and (115). Conjugate addition of dipoles (115) to activated olefins give intermediates (116) which, upon ring closure gives cyclic systems (117). Anionic rearrangement to (118) and elimination liberating the catalyst provides the described cyclopentenes (119).



Scheme 34

The regioselectivity of these reactions is thought to result from nucleophilic attack on the electron deficient olefin through the more stable (α-position) of the 1,3-dipole. However, subsequent studies have demonstrated that the substitution pattern of the allenic carboxylates has a tremendous impact upon regioselectivity. Thus, as we have seen in the heterocyclic series (Scheme 33), addition of a phosphine to certain α-substituted allenic esters has led to reaction through the γ-position. Likewise, reaction of allenic carboxylates with β-substituted enones can also show γ-selectivity. [56] Since Lu's pioneering discovery, dipole additions to a range of double bonds have been reported, including those of fullerenes.[57]

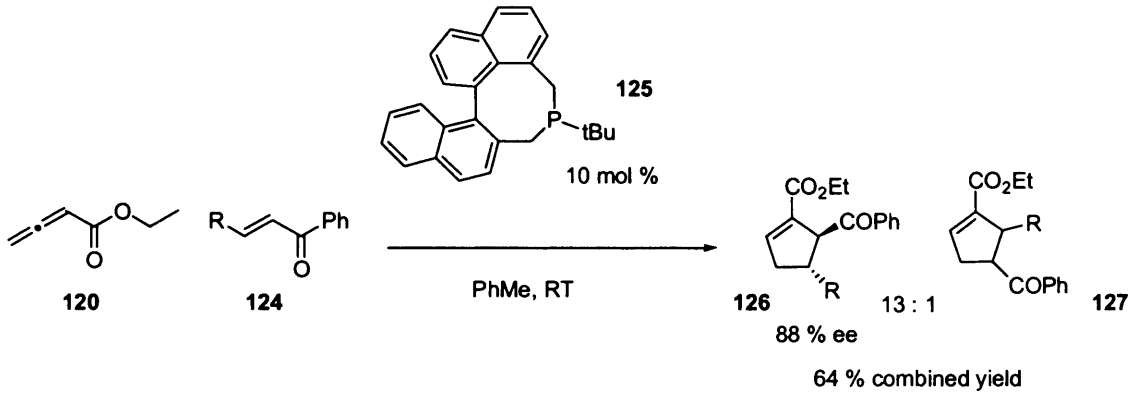
As depicted in Scheme (35), Zhang and co-workers have used a chiral monophosphine (122) for the regio- and stereoselective synthesis of substituted cyclopentenes (123) from the simple allenic ester (120) and acrylate (121).[58]



Scheme 35

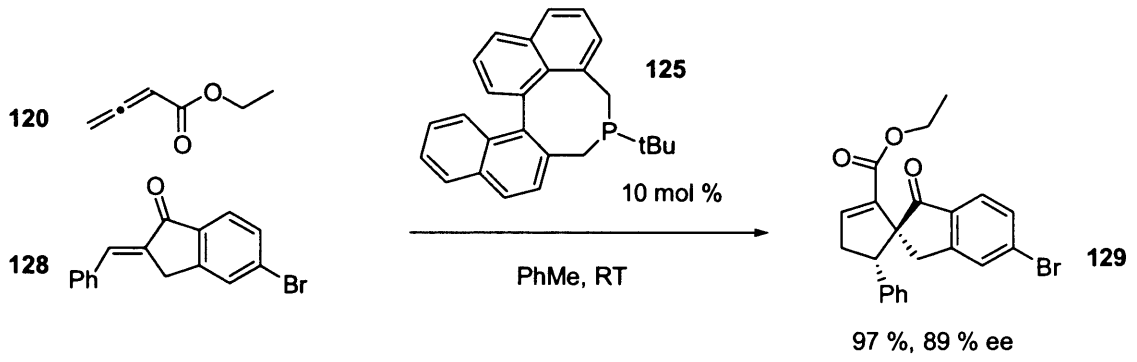
In a related study, Fu and co-workers [59] reported that the chiral phosphepine (125) is a superior catalyst for enantioselective [3+2] cycloadditions than other well known chiral phosphines. As depicted in Scheme (36), the group demonstrated that substituted cyclopentenes (126) are obtained in good yield and in high enantiopurity upon reaction of allenic ester (120) and chalcone derivatives (124). In all cases, small

quantities of the cyclopentenes (127) were also obtained, resulting from attack on the chalcone derivatives (124) through the α-carbon of the zwitterion formed by addition of the phosphine to the allenic ester (120).



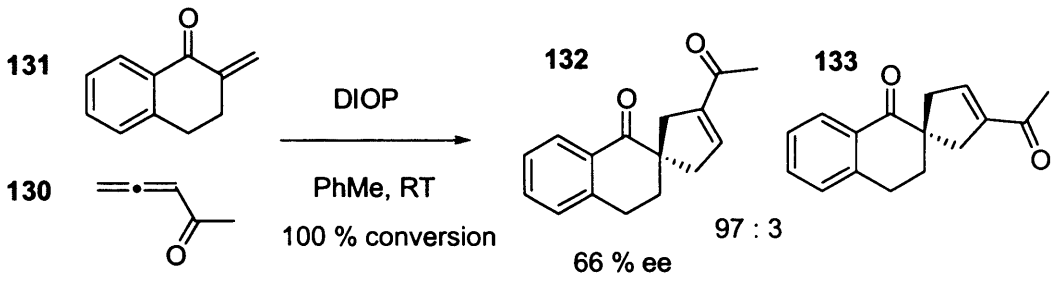
Scheme 36

The same group have also reported the synthesis of spirocycles (129) using the chiral phosphepine (125) as a catalyst for [3+2] cycloaddition reactions of allenic ester (120) and exocyclic enones (128). In this instance the stereoselective formation of the tertiary and quaternary carbon centres present within these compounds is particularly noteworthy (Scheme 37).[59]



Scheme 37

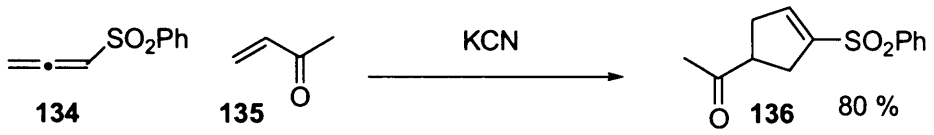
In similar fashion, Wallace *et al.* [60] reported that the addition of DIOP as the chiral phosphine to allenyl methyl ketone (130) in the presence of exocyclic enone (131) led to spirocyclic systems (132) and (133) (Scheme 38).



Scheme 38

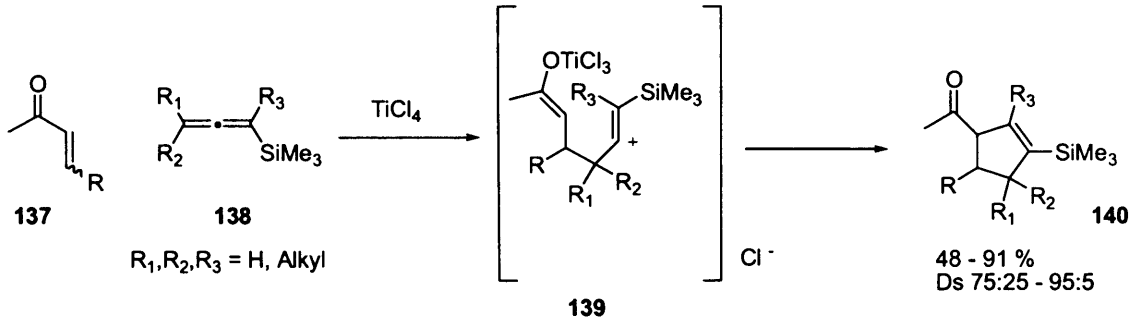
The group demonstrated that the reaction was applicable to a range of enones giving rise to a variety of structurally diverse spirocyclic cyclopentenes. Although the reaction was shown to be catalysed by a variety of commercially available chiral and achiral phosphines, the highest regio- and enantioselectivites were obtained with DIOP.

The [3+ 2] cycloaddition reaction of allenic sulfones with α,β-unsaturated ketones catalysed by KCN was reported by Padwa and co-workers.[61] The group described how treatment of allenic sulfone (134) and methyl vinyl ketone (135) with KCN led to the formation of cyclopentene (136) as the sole product (Scheme 39). The group also demonstrated that α,β-unsaturated esters and nitriles were also suitable substrates for this [3 + 2] cycloaddition reaction.



Scheme 39

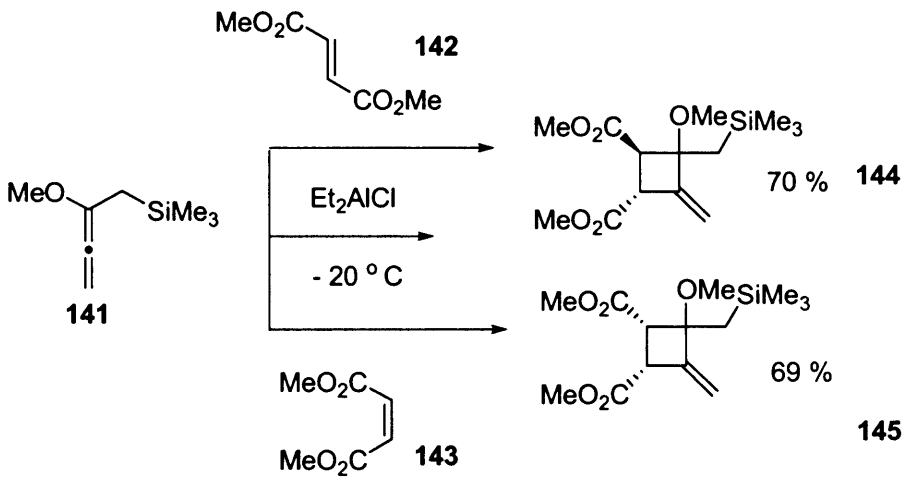
Along with electron deficient allenes such as allenic esters, sulfones & ketones, allenyl silanes have proven to be useful partners in [3 + 2] cycloaddition reactions with activated olefins, enabling the highly regioselective preparation of silyl-substituted cyclopentenes. These annulation reactions first introduced by Danheiser and co-workers, combine trialkylsilylallenes (138) with α,β-unsaturated ketones (137) in the presence of a Lewis acid (Scheme 40). [62]



Scheme 40

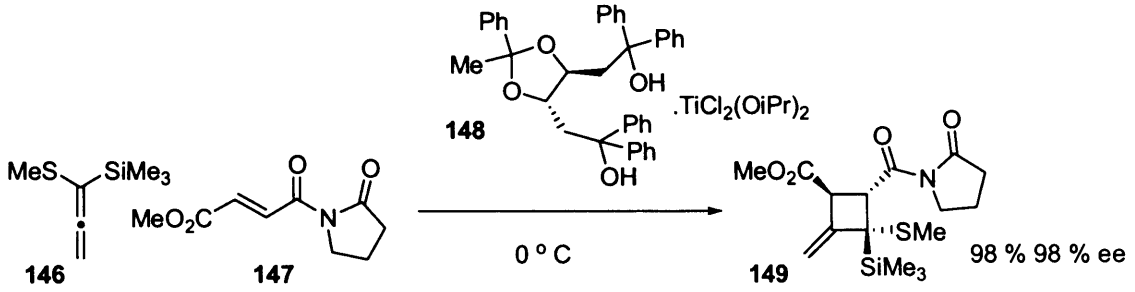
The reaction is thought to proceed *via* conjugate addition of allenyl silanes (138) to α,β-unsaturated ketones (137) providing silyl-stabilised vinyl carbocations (139), which undergo silyl group migration and cyclisation through the titanium enolate yielding carbocycles (140).

Efficient [2+2] cycloadditions of allenes with electron deficient allene partners have been reported to yield a variety of methylene cyclobutanes. Electron rich allenes, such as allenyl ethers, amines and sulfides take part with greater ease and efficiency than simple allenic hydrocarbons, providing a range of highly substituted cyclobutanes in good yields and with excellent stereo-control. Thus, as depicted in Scheme (41), allenyl ether (141) undergoes [2+2] cycloaddition with dimethyl maleate (143) and dimethyl fumarate (142), catalysed by Et_2AlCl, giving the corresponding cycloadducts (144) and (145) respectively.[63]



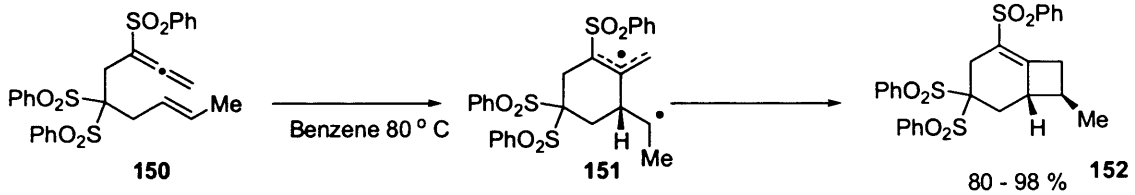
Scheme 41

The use of a chiral titanium catalyst (148) in an enantioselective [2+2] cycloaddition reaction of allenyl sulfide (146) with olefin (147) was shown to provide the cycloadduct (149) in high optical purity (Scheme 42).[64]



Scheme 42

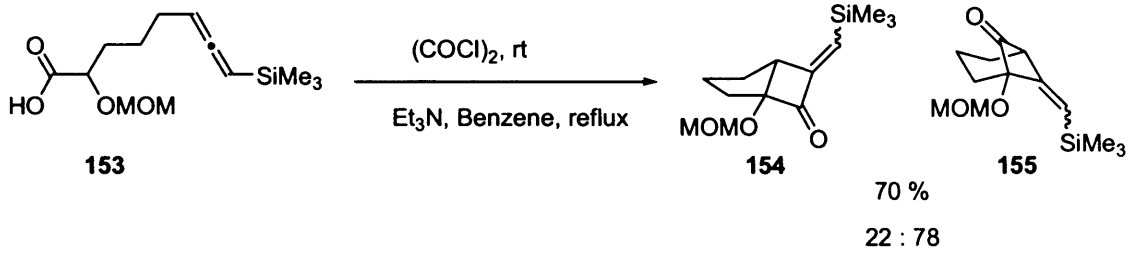
[2+2] Cycloaddition reactions of electron deficient allenes have also been studied, with allenic esters [65] and sulfones [66] used in combination with Lewis acids and high pressure giving cycloadducts in good yields. An example of a stereoselective intramolecular [2+2] cycloaddition reaction of allenic sulfones (150) reported by Padwa and co-workers is depicted in Scheme (43).[67] The authors proposed that initial carbon-carbon bond formation occurred between the central allenic carbon and the proximal olefinic carbon to give the diradical intermediate (151) which, upon rapid ring closure, led to stereoselective formation of the cycloadduct (152).



Scheme 43

Other [2 + 2] cycloaddition reactions of allenes include those with alkynes yielding highly strained methylene cyclobutenes, [68] with ketenes leading to a variety of methylene cyclobutanones [69] and a nickel catalysed [2 + 2] dimerisation reaction of electron deficient allenes leading to cyclobutanes.[70] A particularly interesting

intramolecular allene-ketene cycloaddition reaction was reported by Halcomb and co-workers. [71] A reactive ketene was generated *in situ* from the parent acid (153) and shown to undergo a thermal [2 + 2] cycloaddition reaction with the tethered allene moiety providing the two regioisomeric adducts (154) and (155) (Scheme 44).



Scheme 44

The introduction of an electron-withdrawing substituent on the allenic nucleus lowers the LUMO energy level and locates the largest LUMO coefficient upon the central allenic carbon (2) and the second largest on the carbon atom (1) substituted with the electron acceptor group (Figure 4).

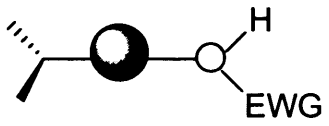
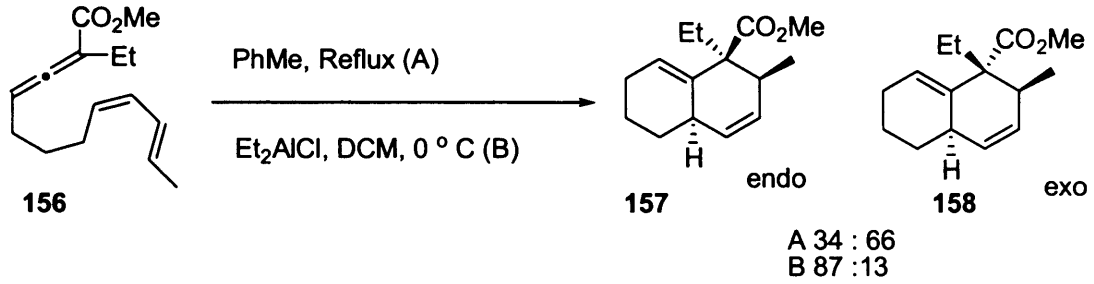


Figure 4

These effects ensure that [4 + 2] cycloaddition reactions of electron deficient allenes occur with relative ease in good yield and with excellent regioselectivity. Allenic esters, [72] ketones, [73] lactones, [74] cycloalkanones, [75] sulfones, [76] sulfoxides [77] & phosphonates [78] have all been used in [4 + 2] cycloaddition reactions with electron rich dienes providing a stereoselective route to a large variety of substituted carbocycles.

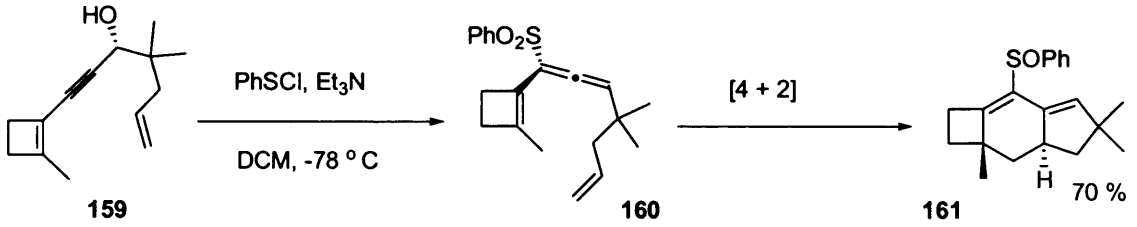
Intramolecular [4 + 2] cycloaddition reactions of allenes enable the rapid construction of complex polycyclic ring systems. Sutherland and co-workers [79] were the first to

report the intramolecular Diels-Alder reaction of allenic esters (156) providing the bicyclic compounds (157) and (158) under thermal and Lewis acid catalysed conditions (Scheme 45). Interestingly the choice of conditions had a tremendous impact upon the *exo/endo* selectivity.



Scheme 45

A tandem [2,3]-sigmatropic rearrangement-[4+2]-intramolecular cycloaddition reaction was developed during the course of the total synthesis of (+)-sterpurene. Okamura and co-workers [80] treated the enantiomerically enriched propargylic alcohol (159) with phenylsulfonylchloride generating the intermediate allenic sulfoxide (160) which cyclised in a highly enantio- and diastereoselective fashion affording the tricyclic sulfoxide (161) in 70 % yield (Scheme 46).



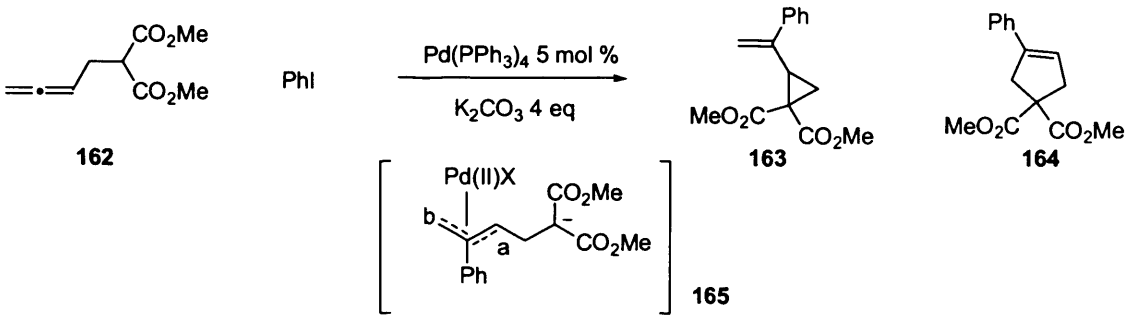
Scheme (46)

1.44 Palladium Catalysed Carbocyclisation of Functionalised Allenic Substrates

In recent years palladium catalysed cyclisation reactions of allenic substrates have become a rapidly growing and exciting field of modern allene chemistry, and in consequence, have been the subject of several reviews.[81] Carbocyclisation of allenic substrates catalysed by palladium complexes has enabled the synthesis of a variety of

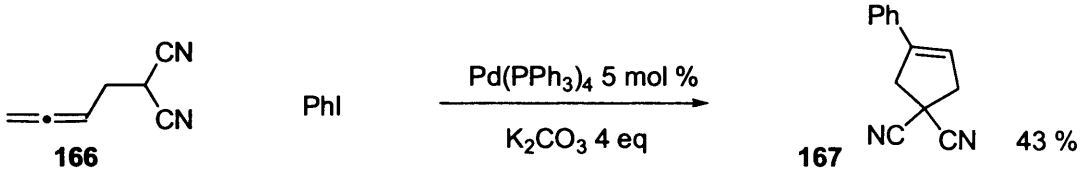
heavily substituted carbocyclic systems, which are difficult to access *via* alternative approaches.

The syntheses of vinylic cyclopropanes (163) and cyclopentenes (164) by Pd (0) catalysed tandem coupling-cyclisation reactions of allenic substrates have been reported (Scheme 47). Thus, oxidative addition of an aryl iodide to Pd (0) is followed by carbopalladation of the allene (162) to give an intermediate π-allyl complex (165), which upon nucleophilic addition of the activated carbon atom led to the described carbocyclic systems (163) and (164).[82] The regioselectivity of this tandem reaction sequence is dependent upon whether nucleophilic attack occurs at carbon atom (a) or (b) and this in turn was shown to rely heavily upon the nature of the solvent and the presence of additives. Thus the authors described how in all cases, formation of cyclopropanes (163) is favoured over formation of the cyclopentenes (165). However, the reactions carried out in toluene in the presence of tetrabutylammonium iodide showed the highest level of selectivity, with the cyclopropanes (163) being formed exclusively.



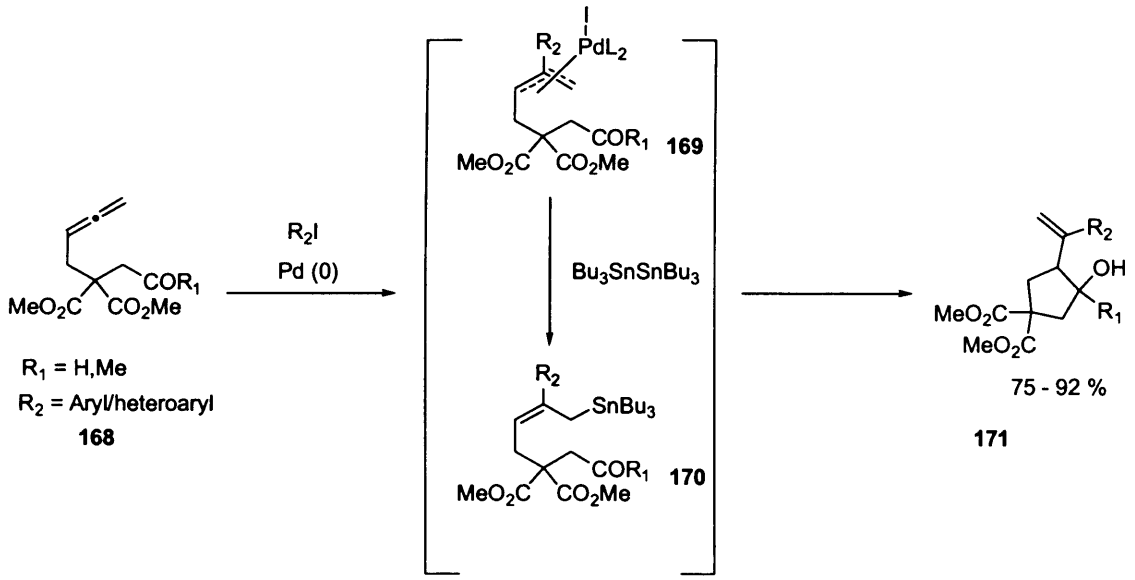
Scheme 47

Interestingly, this high regioselectivity is limited to malonate derivatives (162), as the corresponding malononitriles (166), under identical reaction conditions, gave the corresponding cyclopentenes (167) as the sole products (Scheme 48).



Scheme 48

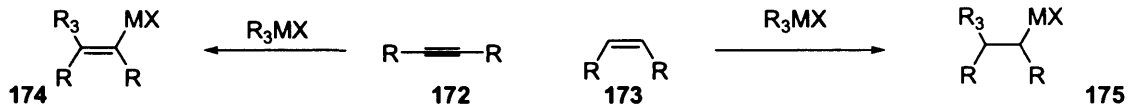
A related tandem palladium catalysed cyclisation of allenyl aldehydes and ketones has been reported by Kang *et al.*[83] As depicted in Scheme (49) carbopalladation of allenes (168) followed by transmetallation of the resulting allyl palladium intermediates (169) with $Bu_3SnSnBu_3$ led to allyl stannanes (170) which were show to undergo carbonyl allylation *in situ* to give cyclopentanols (171).



Scheme 49

1.45 Carbometallation of Allenic Substrates

Carbometallation is defined as the addition of an organometallic reagent across a double or triple bond (Scheme 50).[84]



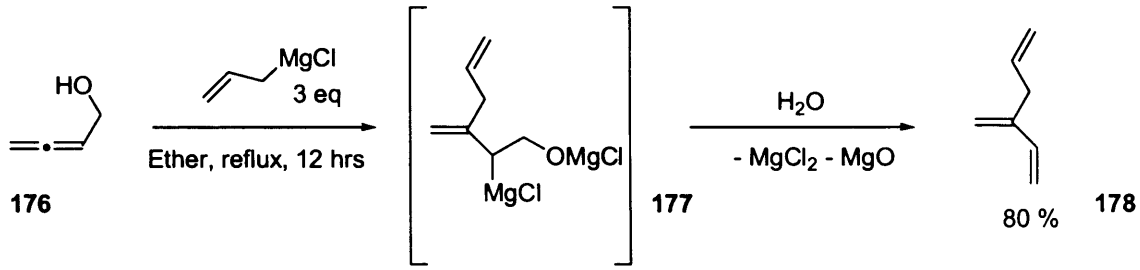
Scheme 50

Intermolecular and uncatalysed additions of organometallic reagents to non-functionalised alkenes (173) or alkynes (172) proceed only under very severe conditions, providing low yields of the corresponding intermediates (174) and (175). As a result, these reactions are of limited synthetic importance. In contrast, heteroatom assisted carbometallation of alkenes and alkynes proceeds under milder reaction conditions, providing useful yields of the corresponding addition adducts.[85] For example, heteroatom assisted carbometallation of propargylic alcohols provides a convenient and stereoselective route to substituted allylic alcohols. The reaction was first pioneered by Normant and co-workers,[86] and since its discovery, it has evolved into an extremely useful synthetic procedure for stereoselective double bond formation. [87]

The high reactivity of the allenic nucleus and the ready availability of allenols has encouraged research into the application of these compounds to carbometallation, as outlined below.

Heteroatom Assisted Carbometallation of Allenic Substrates

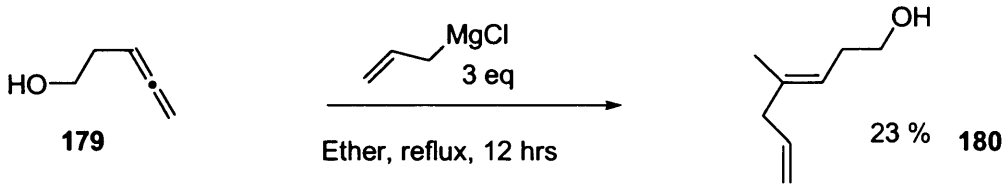
As depicted in Scheme (51), Richey and co-workers demonstrated that the reaction of allylmagnesium chloride with allenol (176), occurred *via* addition of the organometallic reagent to the central allenic carbon.[88]



176 177 178

Scheme 51

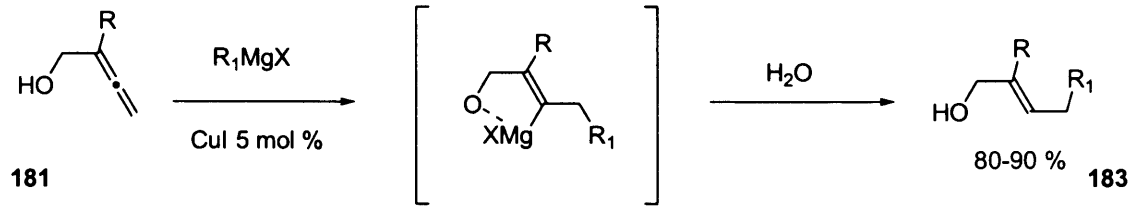
The authors proposed that diene (178) is formed by the loss of $MgCl_2$ and MgO from the intermediate (177). Furthermore, the reaction with homoallenol (179) also proceeded with C-C bond formation occurring at the central allenic carbon. In this instance the homoallylic alcohol (180) was isolated in 23 % yield (Scheme 52).



179 180

Scheme 52

The addition of Grignard reagents to substituted and unsubstituted α-allenic alcohols, in the presence of Cu (I) salts has also been examined. As depicted in Scheme (53), Duboudin and co-workers reported that under these conditions the organometallic reagent was shown to add to the γ-position of the allenol (181), providing the stereochemically pure allylic alcohols (183) in high yields after hydrolysis of the proposed intermediates (182) .[89]



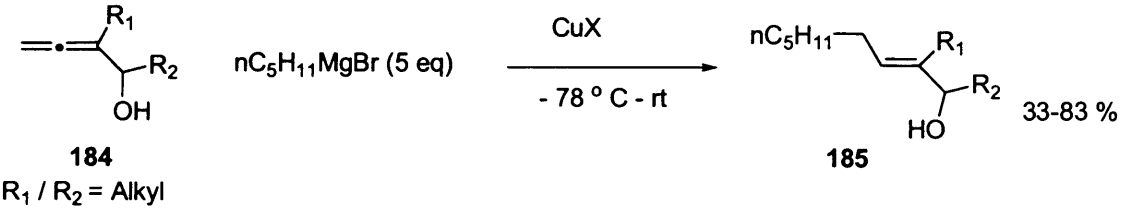
181 182 183

R = H, Me, n-Bu
R_1 = Et, i-Pr, n-Bu

Scheme 53

Evidence supporting the involvement of chelated vinyl-magnesium intermediates (182), was obtained upon quenching the reaction mixtures with a variety of electrophiles. For example, the addition of molecular iodine led to the formation of the corresponding vinyl-iodides, whereas addition of allyl bromide led to successful alkylation at the vinylic position.[89]

Following on from their studies upon the Cu (I) catalysed carbometallation of propargylic alcohols,[90] Ma and co-workers went on to examine the reactivity of α-substituted allenic alcohols (184) under the same reaction conditions.[91] As depicted in Scheme (54), the group showed that the reactions proceeded with high regio- and stereoselectivity, under very mild reaction conditions, providing a range of substituted allylic alcohols (185) in moderate yields.

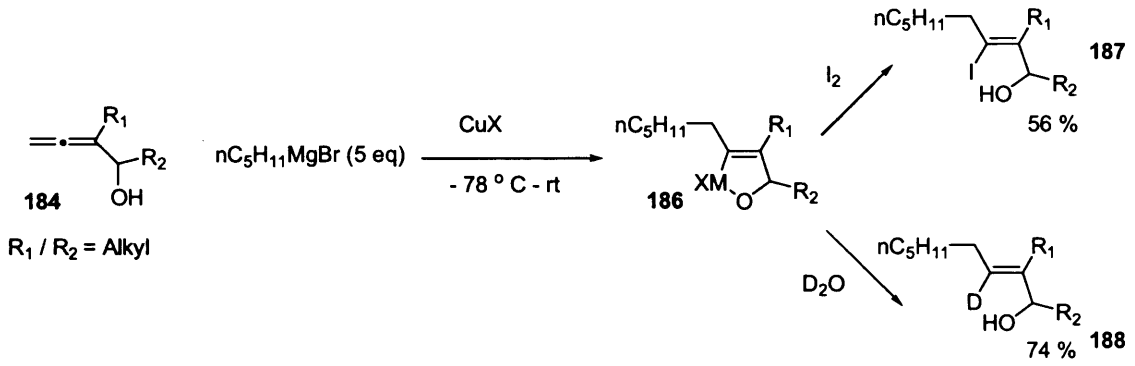


184
R_1 / R_2 = Alkyl

185

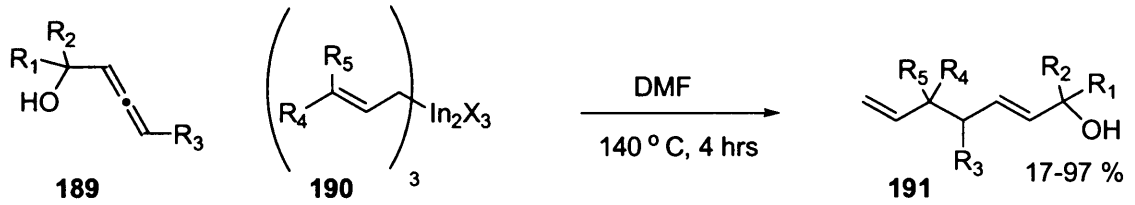
Scheme 54

Once again, evidence for the involvement of a hydroxyl chelated 6-membered intermediate (186), was obtained upon changing the identity of the quenching electrophile. As depicted in Scheme (55), quenching with iodine and D_2O led to the formation of the corresponding vinyl-iodides (187) and deuterated alkenes (188) respectively.



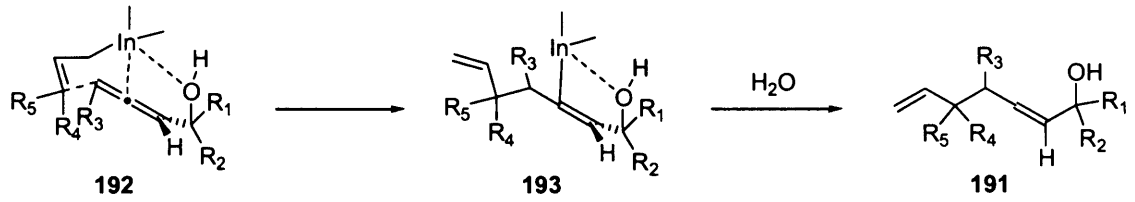
Scheme 55

The allylindation of allenols has been reported by Araki and co-workers.[92] In this study it was demonstrated that allenols (189) undergo smooth addition of allylindium reagents (190) in DMF at elevated reaction temperatures (Scheme 56). In this instance, the reactions proceeded with excellent regio- and stereoselectivity, providing the *E*-alkenes (191) in moderate to high yields, *via* addition of the organometallic reagent to the γ-allenic carbon.



Scheme 56

The reaction was shown to be successful with a variety of substituted allenols (189) and allyl indium reagents (190). However, secondary allenols showed diminished reactivity whilst tertiary allenols were inert to allylindation.



Scheme 57

As depicted in scheme (57), it is postulated that the hydroxyl group of allenol (189) co-ordinates to the indium atom forming a chelated five-membered ring (192). In consequence, the allylic terminus of the indium reagent approaches the γ- carbon of the allenic nucleus to give intermediates (193) leading to the high stereo- and regioselectivity observed in this reaction.

In contrast to the smooth reactions observed with allenols (189), the corresponding homoallenols were shown to be inert to the reaction conditions. It was proposed that a possible explanation for this fact, is that formation of the required six-membered hydroxyl chelated transition state could be less energetically favourable than formation of the corresponding five-membered transition state.

1.46 Summary and Objectives of Current Study

The foregoing introduction to this thesis has hopefully outlined the special properties associated with allenic substrates and their application in the three key areas of, heterocyclisation, carbocyclisation and carbometallation reactions. The following chapter describes our own contributions in this exciting area of research.

CHAPTER 2

RESULTS AND DISCUSSION

Section 2.1

Tandem Reactions (I) – Development of A Novel One-Pot Aza-annulation Methodology

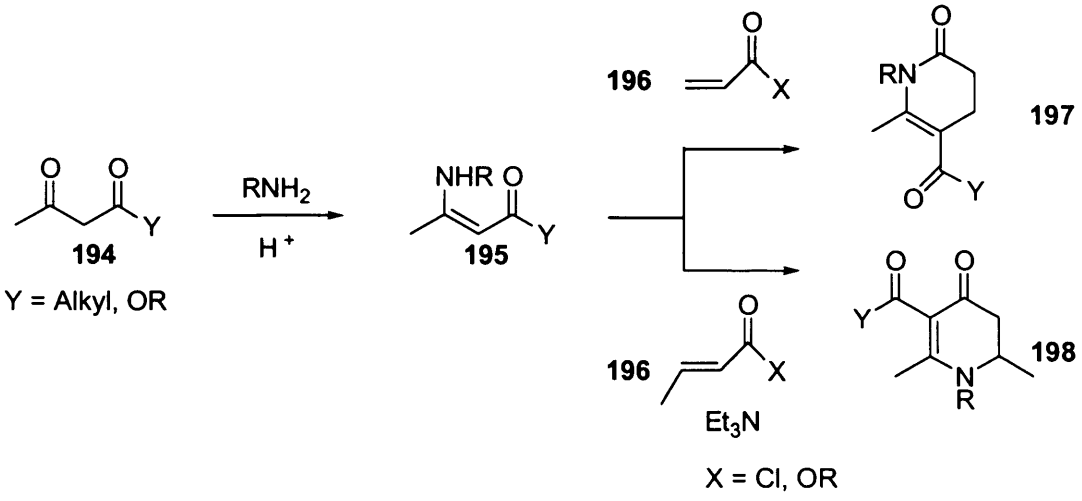
2.0 Results and Discussion

2.1 Tandem Reactions (I)

Development of a Novel One-Pot Aza-annulation Methodology – Studies Directed Towards the Total Synthesis of (+/-) N-oxo-rhazinilam

2.11 Introduction

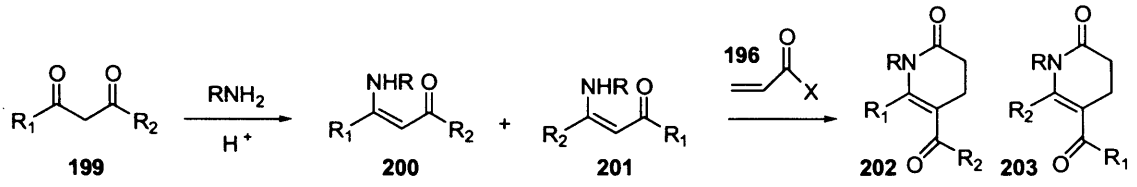
A vast array of naturally occurring biologically active alkaloids posses the basic piperidine unit within their molecular architectures, [93] and in consequence, the corresponding piperidine-2-ones are particularly attractive synthetic precursors for further elaboration of the versatile lactam moiety towards more complex systems.[94] Pioneering studies by Hickmott and co-workers led to the introduction of a highly effective [3+3] annulation sequence enabling the rapid construction of piperidinones from readily available starting materials.[95] As depicted in Scheme (58), this well established synthetic protocol involved the condensation of a primary amine with a 1,3-dicarbonyl compound (194) to give the corresponding vinylogous urethane or amide derivative (195), which, upon annulation with α,β-unsaturated carbonyl derivatives (196), yielded piperidinones (197).



Scheme 58

The utility of vinylogous urethanes and amides for the synthesis of important piperidines *via* 2-piperidinones has been demonstrated by several groups including

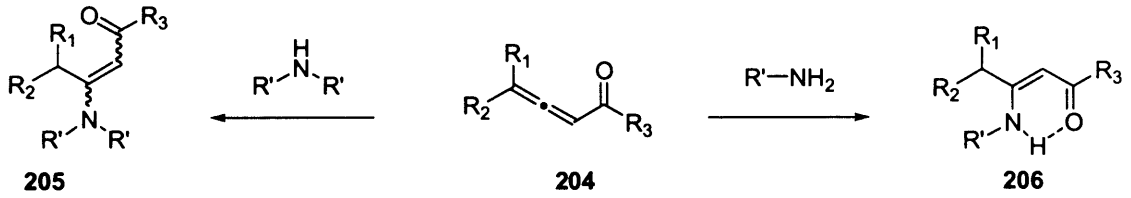
those of Stille [96] and Agami.[97] Moreover, as recognized by Stevenson [98] in an elegant mechanistic study capitalising upon the ambidient nucleophilic character of enaminones, a further attractive feature of this annulation sequence was that the overall regioselectivity could be reversed to provide 4-piperidinones (198) by adding triethylamine as a mediator (Scheme 58). Nevertheless, from a simple preparative standpoint, close scrutiny of this sequence revealed that the required vinylogous amides and urethanes were generally prepared in a separate step by the azeotropic removal of water from a 1,3-dicarbonyl compound. Of potentially greater concern however, in terms of widespread use was the fact that the selection of an unsymmetrical 1,3-diketone raised issues of regioselectivity in terms of enaminone formation. Thus, as depicted in Scheme (59), selection of an unsymmetrical 1,3-dicarbonyl compound (199) could, in principle, lead to the formation of two regioisomeric vinylogous amides (200) and (201) and subsequent annulation of these enaminones would then lead to a mixture of the two regioisomeric piperidinones (202) and (203).



Scheme 59

We were however aware that the facile and regioselective nucleophilic addition of primary and secondary amines to allenic ketones to yield the corresponding vinylogous amides had been studied previously.[99] The addition of secondary amines to allenic ketones (204) is shown to provide a mixture of *E*- and *Z*-enaminones (205), whilst addition of primary amines offers a stereoselective route to the corresponding *Z*-enaminones (206) (Scheme 60). A likely explanation for the stereoselectivity

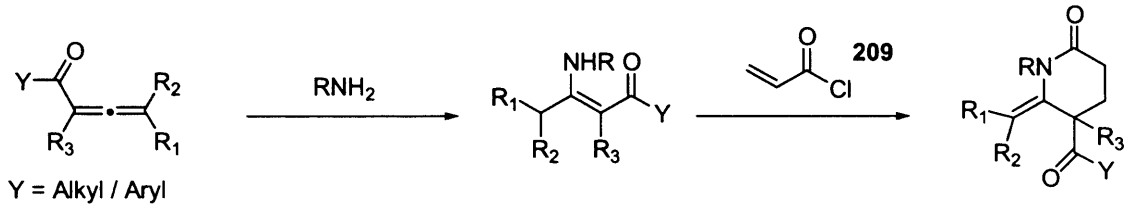
observed in the latter case, is the establishment of a thermodynamically favourable hydrogen bonding interaction between the amino and carbonyl groups in this geometry.



205 204 206

Scheme 60

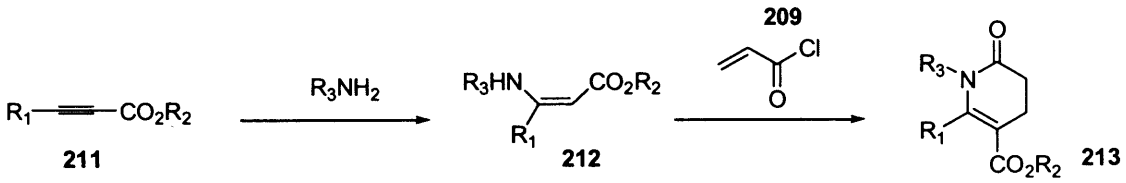
Consequently, it was envisaged that selection of readily prepared allenic ketones as substrates for regioselective enaminone formation could enable the development of a simple and preparatively useful one-pot sequence for the preparation of a variety of structurally diverse piperidinones. Furthermore, addition of primary amines to α-substituted allenic ketones (207) would lead to the corresponding α-substituted enaminones (208), which upon annulation with acryloyl chloride (209) could evolve to the exocyclic enamides (210) (Scheme 61).



207 208 210

Scheme 61

The advantage of using allenic ketones and esters over their corresponding acetylenic congeners lies within the extra substitution level that is possible with the former. In Scheme (62), the application of acetylenic ketones/carboxylates (211) in the described annulation sequence is shown to yield endocyclic dihydropiperidinones (213). [100]

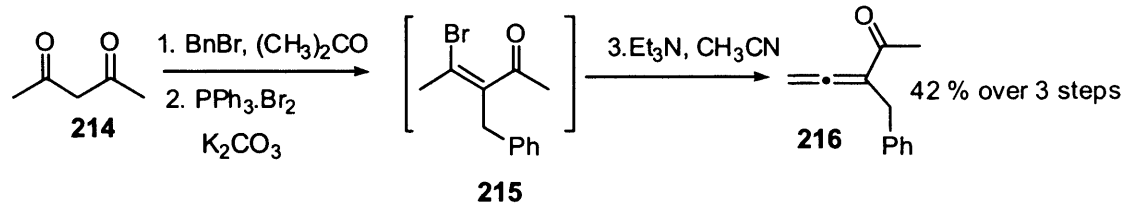


Scheme 62

Moreover, it was anticipated that the synthetic versatility of such exocyclic enamides (210), would enable further synthetic manipulations to provide access to more structurally complex heterocyclic systems.

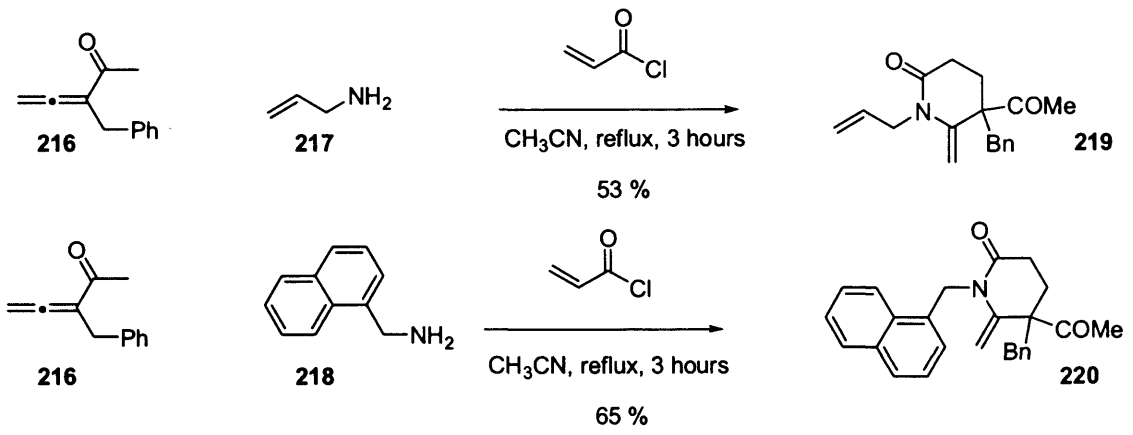
2.12 Preliminary Annulation Studies.

In light of the foregoing analysis, the synthesis and reactivity of some simple α-substituted allenic ketones was examined. Benzyl-substituted allenic ketone (216) was prepared using a standard synthetic procedure from commercially available pentane-2,4-dione (214) (Scheme 63). Alkylation of (214) with benzyl bromide was followed by bromination with a freshly prepared solution of $PPh_3.Br_2$,[101] providing the desired vinyl-bromide (215). Base induced elimination of hydrogen bromide gave the described allenic ketone (216) in 42 % yield, after purification of the crude reaction mixture by flash column chromatography. [50]



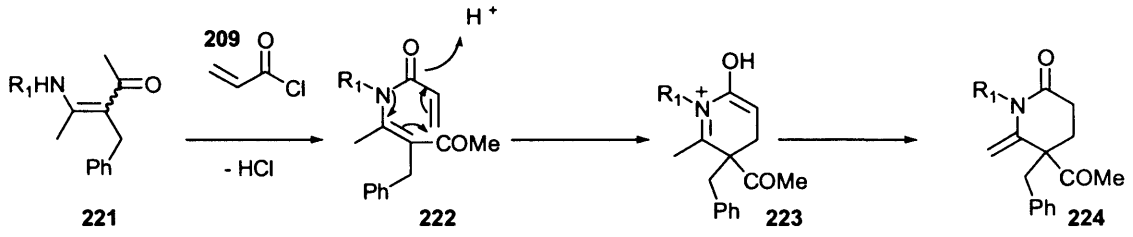
Scheme 63

In order to test the hypothesis outlined in Scheme (61), the allenic ketone (216) was reacted with commercially available primary amines (217) & (218) and acryloyl chloride. Pleasingly, the one-pot annulation sequence was successful providing the expected exo-cyclic enamides (219) & (220) in moderate yields (Scheme 64).



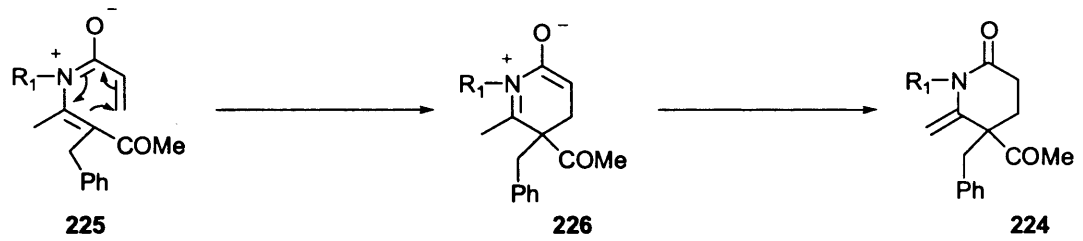
Scheme 64

A plausible mechanistic pathway accounting for the formation of enamides (219) and (220) would involve initial vinylogous urethane formation *via* addition of the amine to the central sp hybridised carbon atom of the allenic ketone, followed by N-acylation of the conjugated enamine (221) with acryloyl chloride (209) and finally, intramolecular Michael addition of the vinlyogous urethane (222) onto the α,β-unsaturated amide. Loss of a proton from the intermediate N-acyl iminium ion (223) would then provide the observed exocyclic enamides (224) (Scheme 65).



Scheme 65

It is also interesting to speculate that cyclisation can be viewed as a disrotatory electro cyclic 6π electron ring closure of a possible zwitterionic intermediate (225) to give (226), which upon proton exchange would provide enamides (224) (Scheme 66).



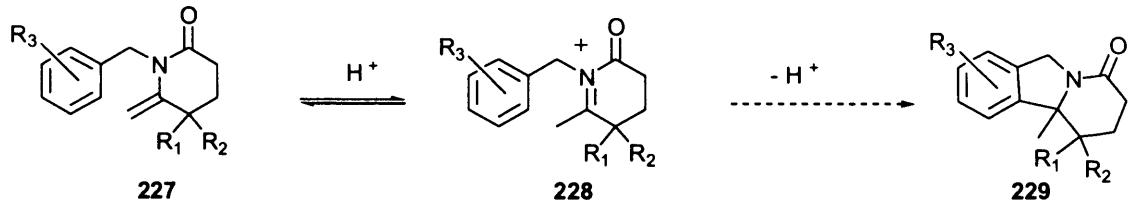
Scheme 66

2.13 Studies Directed Towards the Development of Tandem Aza-Annulation Reactions

The protonation of enamides provides a simple route to highly electrophilic and synthetically important N-acyl iminium cations.[102] As depicted in Scheme (65), such a reactive intermediate was proposed in the reaction pathway for conversion of the allenic ketone (216) into the exocyclic enamides (219) and (220).

In a preliminary attempt to develop a tandem sequence, intramolecular trapping of an *in situ* generated N-acyl iminium cation by an aromatic ring was considered.

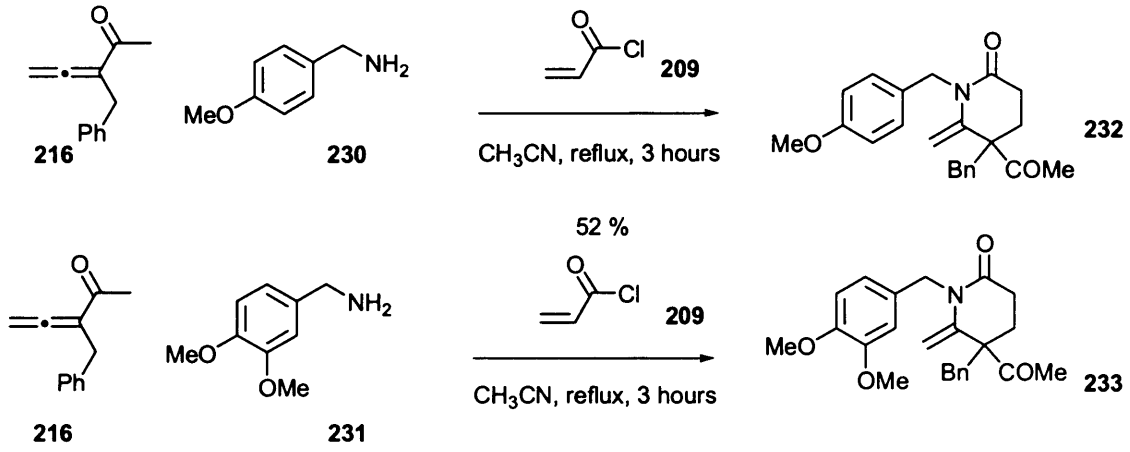
Thus, as shown in Scheme (67), it was envisaged that the reaction of an electron-rich aromatic amine, an allenic ketone and acryloyl chloride would lead to the corresponding aryl substituted enamide (227). Under the acidic conditions of the reaction medium it was anticipated that trapping of the intermediate N-acyl-iminium ion (228) could then occur, *via* electrophilic attack on the electron rich aromatic ring, delivering tricyclic systems (229).



Scheme 67

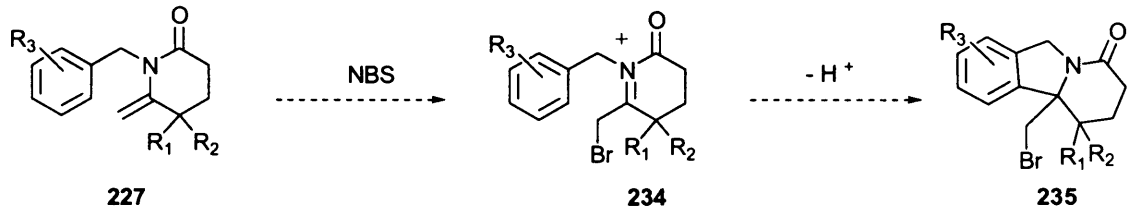
Disappointingly however, the reactions of aromatic amines (230 & 231), allenic ketone (216) and acryloyl chloride (209) failed to provide the desired tricyclic

systems (229), and instead, the exo-cyclic enamides (232) & (233) were the only products to be isolated from the crude reaction mixtures (Scheme 68).



Scheme 68

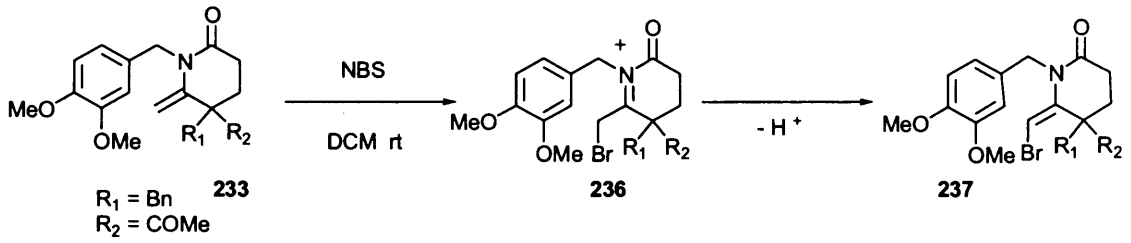
Undeterred by the initial failure of the desired tandem reaction, the conversion of enamides (227) to tricyclic systems *via* a slightly different approach was examined. It was envisaged that reactive N-acyl iminium ions could also be formed by addition of an alternative electrophilic species to the enamide (227). Thus, in the first instance, the reactivity of aryl-substituted exo-cyclic enamides (227) towards N-bromosuccinimide (NBS) was examined. It was hoped that successful bromination would be followed by the trapping of the resulting intermediate iminium ions (234) by the electron rich aromatic nucleus, leading to the substituted tricyclic systems (235) as shown in Scheme (69).



Scheme 69

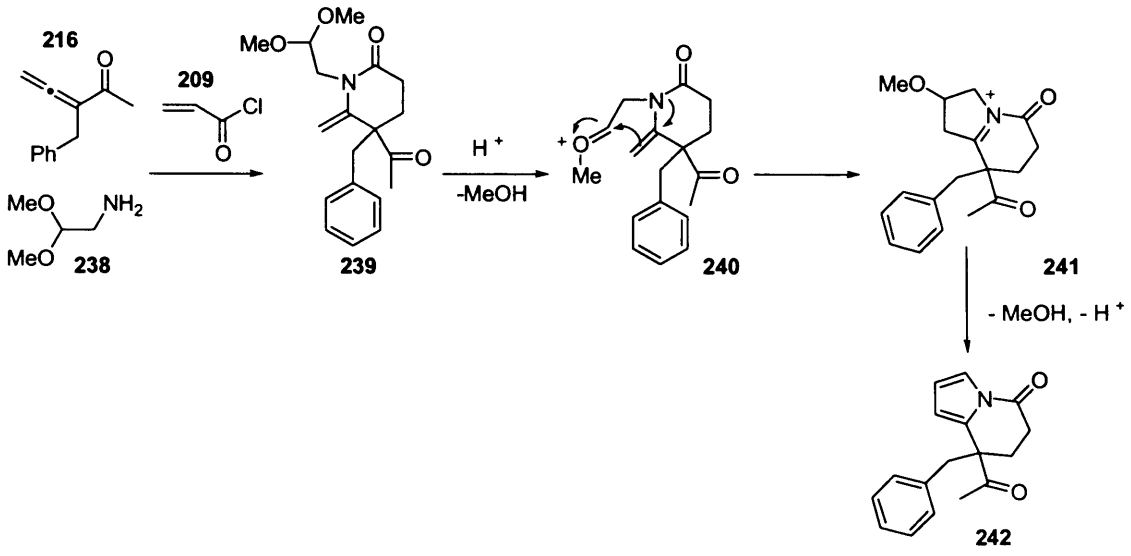
In the event, treatment of enamide (233) with NBS did not lead to the desired tricyclic system (235), and an intractable mixture of compounds was obtained. Attempts to

isolate the components of this mixture by column chromatography proved difficult. However, one partially purified fraction provided significant spectroscopic evidence for the presence of the vinylbromide (237). Bromination of enamide (233) followed by the loss of a proton instead of the desired ring closure, provides a simple explanation for the formation of (237) (Scheme 70).



Scheme 70

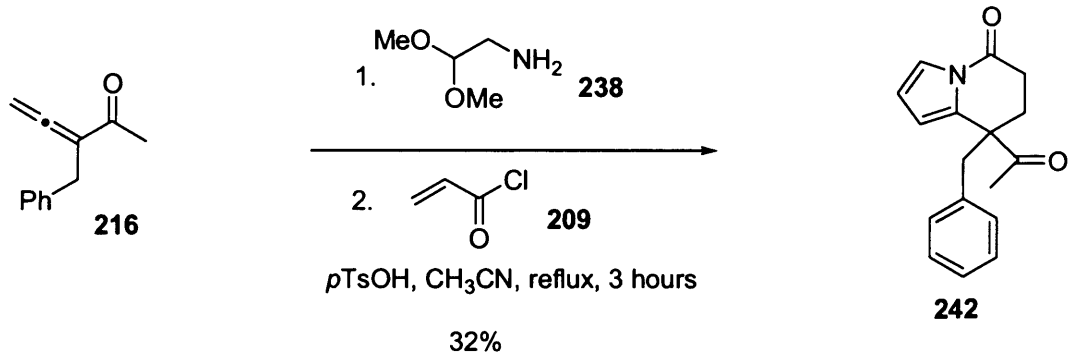
In light of these failed preliminary attempts at developing a tandem reaction sequence by capitalising upon the high electrophilic reactivity of the N-acyl iminium cation intermediates, it was anticipated that the same goal could be achieved by making use of the inherent nucleophilicity of their enamide precursors. Thus, a one-pot synthesis of [4.3.0] azabicyclo systems, known to be useful precursors to the biologically important indolizine alkaloids,[103] was attempted.



Scheme 71

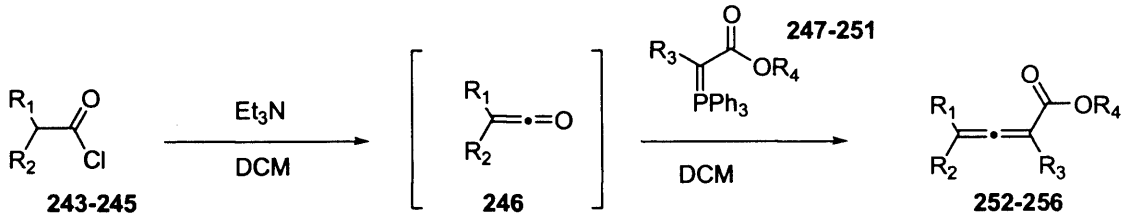
Thus, as shown in Scheme (71), it was envisaged that selection of the commercially available 2,2-dimethoxyethanamine (238) as the primary amine component would furnish enamide (239) upon annulation with allenic ketone (216) and acryloyl chloride (209). However, under the acidic conditions of the reaction medium, this product (239) could then evolve *via* nucleophilic ring closure of the enamide onto the oxocarbenium ion (240) derived from the acetal. Aromatisation of the intermediate (241) *via* the loss of methanol would then furnish the fused pyrrole (242).

Gratifyingly, in a preliminary experiment carried out using a catalytic amount of *para*-toluenesulfonic acid, this tandem cyclisation sequence featuring successive formation of two carbon-nitrogen bonds followed by two carbon-carbon bonds, gave the expected fused pyrrole (242) (Scheme 72).[104]



Scheme 72

Studies by Tidwell and co-workers have demonstrated that polymer supported allenic carboxylates could serve as useful precursors to the corresponding polymer bound vinylogous urethanes, which have been shown to undergo efficient annulation reactions with α,β-unsaturated carbonyl derivatives.[105] In light of this, the application of readily prepared allenic esters to this novel tandem reaction sequence was examined.



Scheme 73

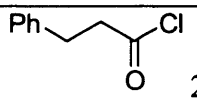
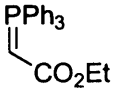
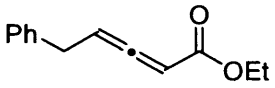
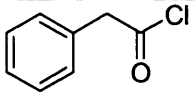
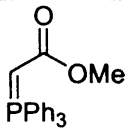
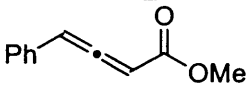
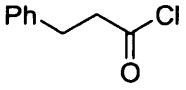
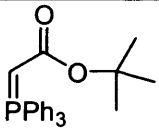
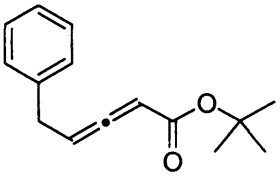
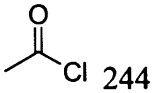
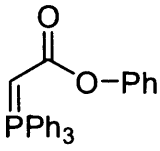
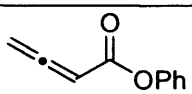
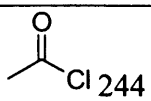
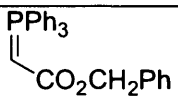
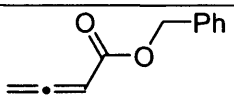
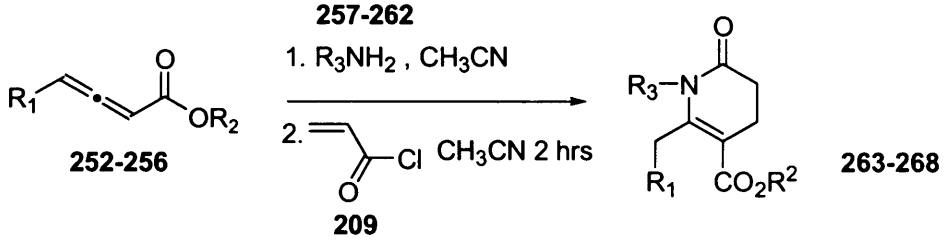
Acid Chloride	Phosphonium ylide	Allenic Ester	Yield (%)
 243	 247	252 	58
 244	 248	 253	72
 243	 249	 254	49
 244	 250	 255	48
 244	 251	 256	51

Table 1

The required allenic esters (252-256), were prepared by the Wittig reaction of acid chlorides (243-245) with phosphonium ylides (246-251) (Scheme 73, Table 1).[106] The acid chlorides were all commercially available and the phosphorous ylides (246-251) were either purchased or made *in situ* from the parent phosphonium salts, themselves readily prepared *via* the reaction of triphenylphosphine with the corresponding bromides.

In the first instance, to ensure that allenic carboxylates could be successfully applied to the previously developed one-pot solution chemistry, esters (252-256) were reacted with amines (257-262) and acryloyl chloride (209). As expected, the internally unsaturated dihydropiperidinones (263-268) were shown to be the major products, isolated in moderate yields after purification by flash column chromatography (Scheme 74 & Table 2).



Scheme 74

As shown in Table (2) endocyclic dihydropiperidinones (263-268) were formed exclusively, and no exocyclic enamides were detected in the crude reaction mixtures. The thermodynamic preference for internal unsaturation is due to a combination of the extra stability associated with conjugation of the nitrogen atom lone pair with the ester carbonyl, along with the natural preference for internal over external unsaturation with regards to six membered rings.

In similar fashion to the previous examples, the reaction of α-unsubstituted allenic esters (252-255) with aminoactealdehyde dimethyl acetal (238) and acryloyl chloride, should lead to the corresponding internally unsaturated dihydropiperidinones (269).

For ring closure of any derived oxonium ions to be successful, isomerisation of dihydropiperidinones (269) to the reactive exocyclic enamides (270) is, of course, required (Scheme 75)

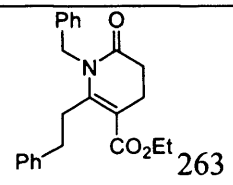
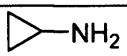
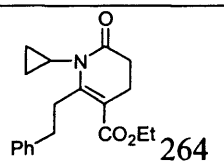
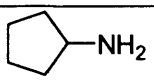
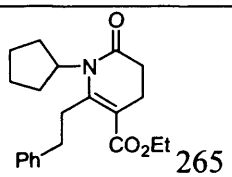
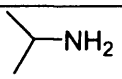
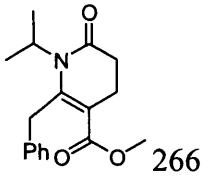
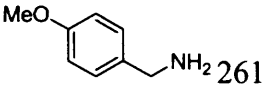
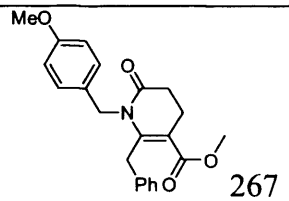
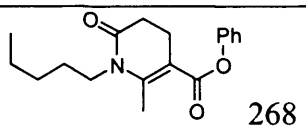
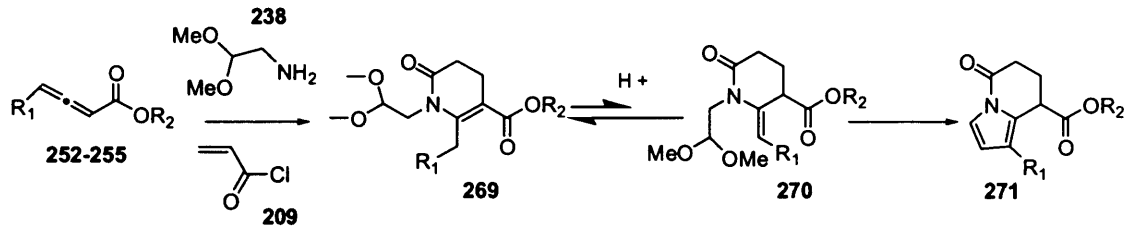
Entry (xx)	Allenic ester	Amine	Dihydropiperidinone	Isolated Yield (%)
1	252	$BnNH_2$ 257	 263	66
2	252	 258	 264	48
3	252	 259	 265	48
4	253	 260	 266	54
5	253	 261	 267	62
6	255	$nC_5H_{11}-NH_2$ 262	 268	65

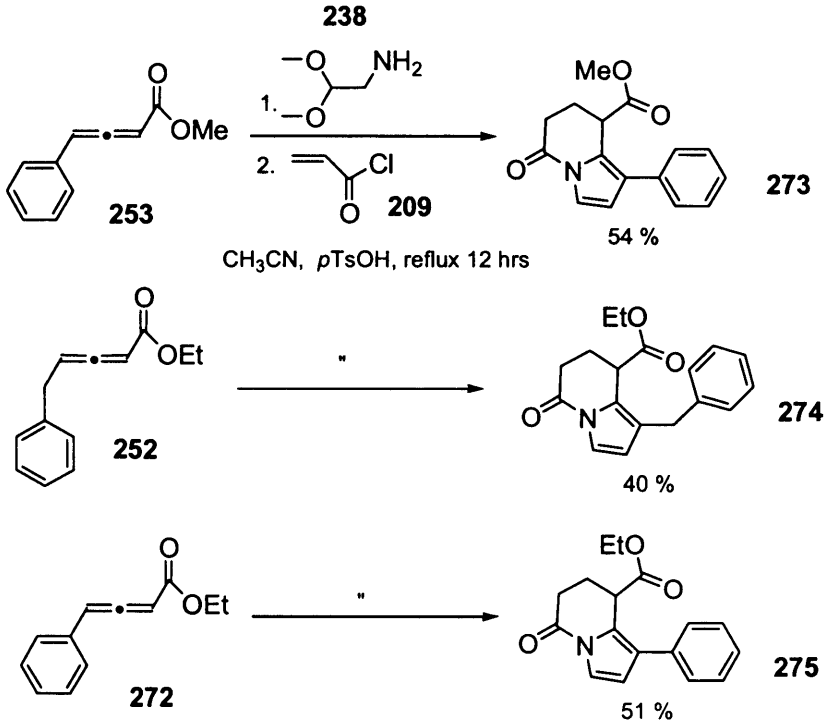
Table 2

It was anticipated however that the acidic conditions of the reaction medium could promote this isomerisation and thus cyclisation to occur, allowing the preparation of fused pyrroles (271) from allenic esters (252-255) to proceed.



Scheme 75

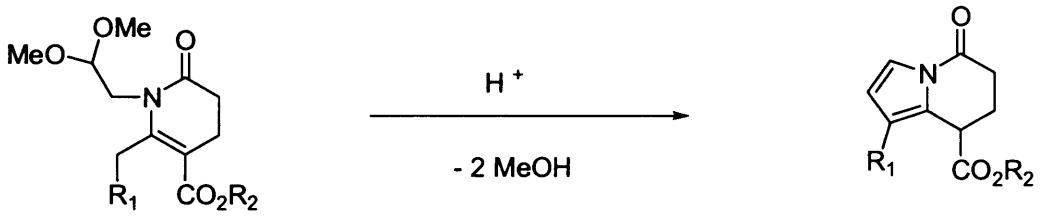
Pleasingly, subjection of allenic esters (252), (253) and (272) to the described annulation reaction gave the corresponding fused pyrroles (273-275), which were isolated in moderate yields after purification of the crude products by flash column chromatography (Scheme 76).



Scheme 76

2.14 Mechanistic Studies

In light of the successful conversion of α-unsubstituted allenic esters (252), (253) and (272) into the corresponding fused pyrroles (273-275), a brief study of the reaction mechanism responsible for this conversion was undertaken. The mechanism shown in Scheme (75) for the conversion of allenic esters (252-255) into pyrroles (271), proposes that dihydropiperidinones (269) act as key intermediates along the reaction pathway (Scheme 77).

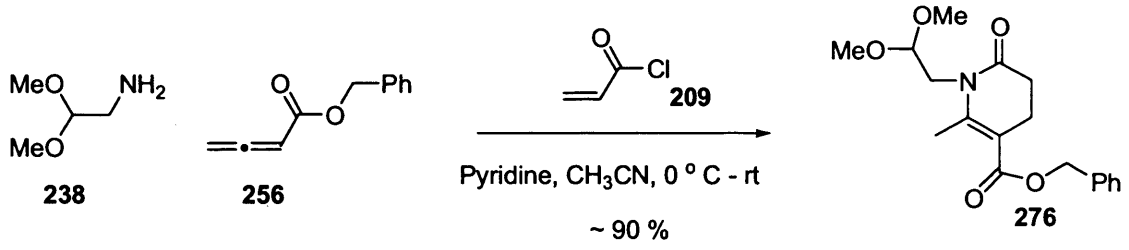


269 **271**

Scheme 77

It was hoped that the successful isolation and identification of piperidinones (269) from the crude reaction mixtures and subsequent conversion of these proposed intermediates into the corresponding bicyclic pyrroles (271), under acidic conditions, would provide strong evidence for the mechanistic pathway shown in Scheme (75).

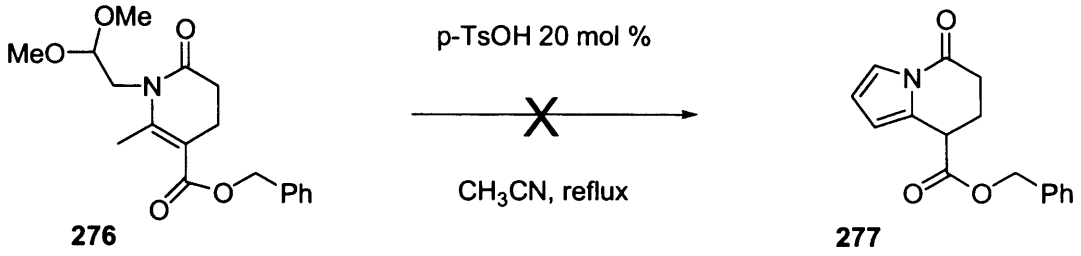
Close monitoring of the annulation reactions by HPLC analysis was anticipated to aid such mechanistic studies. Thus, allenic ester (256) was chosen as the test substrate due to its high activity towards HPLC analysis (Scheme 78). In the first instance, allenic ester (256) was reacted with amine (238) and acryloyl chloride (209) in the presence of one molar equivalent of pyridine, added to trap the HCl liberated upon N-acylation and hence prevent premature activation of the acetal (Scheme 78).



Scheme 78

Upon completion of the reaction (as determined by HPLC analysis), dihydropiperidinone (276) was isolated in 90 % yield, essentially free from impurities, after aqueous work up of the crude reaction mixture. Attempts to purify (276) by flash column chromatography failed, presumably due to the sensitivity of acetals to silica gel, however complete characterisation of (276) was possible from the crude compound.

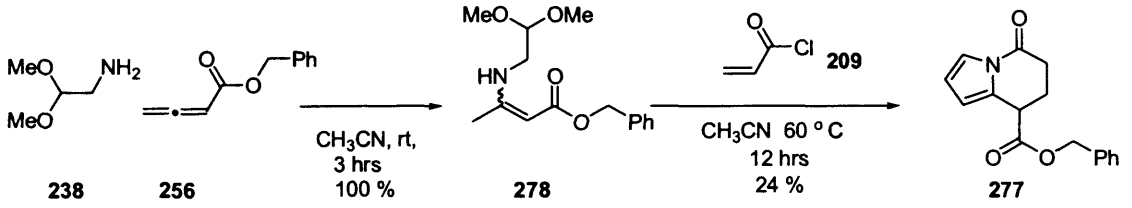
The conversion of dihydropiperidinone (276) into the corresponding bicyclic pyrrole (277) under acidic conditions was then examined. Initially, a solution of piperidinone (276) in acetonitrile, was reacted with a substoichiometric amount of *para*-toluenesulfonic acid (20 mol %). Analysis of the reaction mixture by HPLC showed that no reaction took place at room temperature and that piperidinone (276) remained unchanged (Scheme 79).



Scheme 79

Heating the mixture at reflux led to the total consumption of dihydropiperidinone (276). Disappointingly, after aqueous work up, crude ^{1}H NMR analysis indicated that a highly complicated mixture of compounds had formed, with little or no evidence for

the presence of the expected bicyclic pyrrole (Scheme 79). This result led to the assumption that the hydrochloric acid liberated upon N-acylation of the vinylogous urethane with acryloyl chloride plays a vital role in the conversion of the intermediate piperidinone (276) into the pyrrole (277). In order to test this hypothesis, the direct conversion of allenic ester (256) into the bicyclic pyrrole (277) in the absence of pyridine, was examined (Scheme 80).



Scheme 80

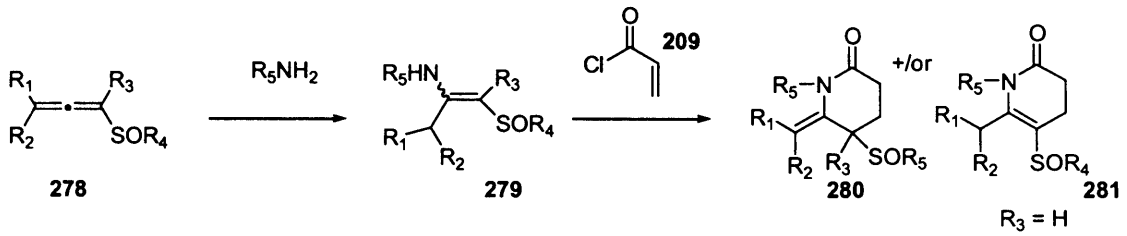
Formation of the key vinylogous urethane (278) upon reaction of allenic ester (256) and amine (238) took place quantitatively at room temperature within 3 hrs, as indicated by HPLC analysis. Addition of acryloyl chloride followed by gentle warming of the reaction mixture, led to the formation of the previously characterised piperidinone (276) as established by HPLC analysis. Heating the solution to 60 ° C led to the disappearance of the majority of piperidinone (276) after a 12 hour period, work up of the reaction mixture followed by chromatography then gave the bicyclic pyrrole (277) as the major product, albeit in only 24 % yield.

In summary, it has been demonstrated that the one-pot conversion of α-substituted allenic ketone (216) into bicyclic pyrrole (242) upon annulation with the commercially available aminoacetaldehyde-dimethylacetal (238) and acryloyl chloride (209), is also applicable to α-unsubstituted allenic esters (252-256). It was proposed that the conversion of allenic esters (252-256) into the corresponding bicyclic systems (273-275), required isomerisation of the initially formed internally unsaturated dihydropiperidinones (263-268) into the reactive exocyclic enamides and

monitoring the conversion of allenic ester (256) into the bicyclic pyrrole (277) by HPLC analysis has provided tentative evidence for this mechanism. Thus, the presence of the intermediate dihydropiperidinone (276) was clearly established with its full characterisation. The conversion of piperidinone (276) into the bicyclic pyrrole (277) in the presence of HCl was also observed by HPLC analysis, providing further evidence to support the proposed reaction mechanism.

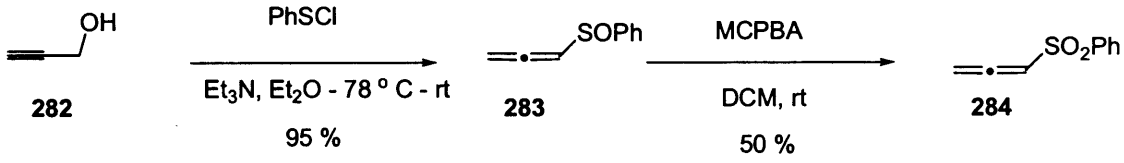
2.15 Studies With Allenic Sulfoxides and Sulfones

In an effort to expand upon the one-pot annulation chemistry, the use of alternative allenic substrates was also examined. The addition of amines to allenic sulfoxides (278) and their derived sulfones has been shown to provide the corresponding conjugated enamines (279), akin to those reported with allenic esters and ketones (Scheme 81).[107] It was anticipated that annulation of enamines (279) with acryloyl chloride would proceed to furnish either the exocyclic enamides (280) or the dihydropiperidinones (281) depending upon the nature of the substituent (R_3) (Scheme 81).



Scheme 81

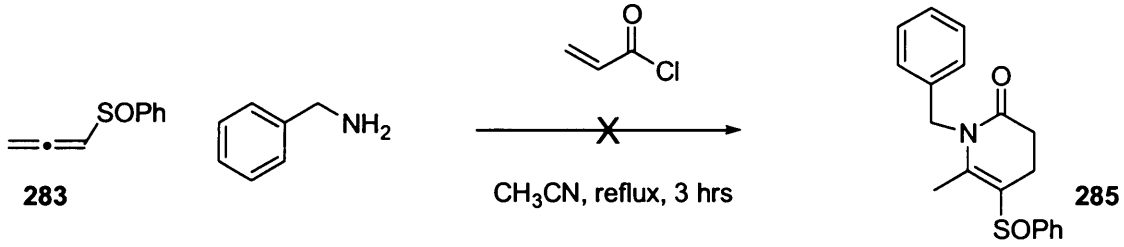
In order to examine the potential of developing a one pot annulation reaction of allenic sulfoxides and sulfones, allene (283) was prepared by the low temperature reaction of freshly prepared phenylsulfenyl chloride with propargyl alcohol (282). Oxidation of allenic sulfoxide (283) with MCPBA provided the corresponding sulfone (284) (Scheme 82).



282 **283** **284**

Scheme 82

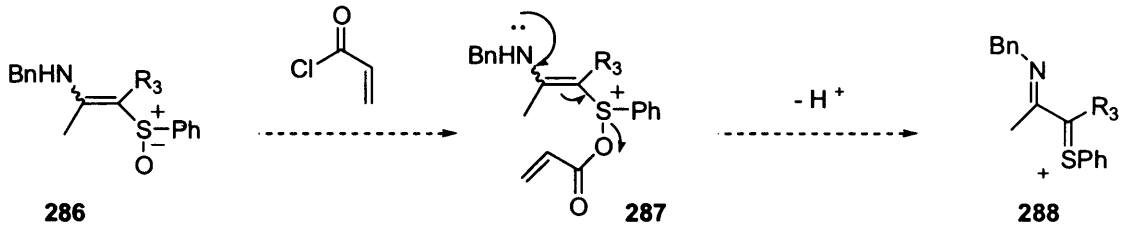
In a preliminary experiment, benzylamine, sulfoxide (283) and acryloyl chloride (209) were reacted under identical conditions to those employed with respect to the annulation reactions of allenic ketone (216) and esters (252-256) (Scheme 83). Disappointingly, analysis of the crude reaction mixture revealed that none of the expected dihydropiperidinone (285) was formed, and instead an intractable mixture of compounds was observed within the crude mixture. Attempts to isolate and identify any of these components proved fruitless.



283 **285**

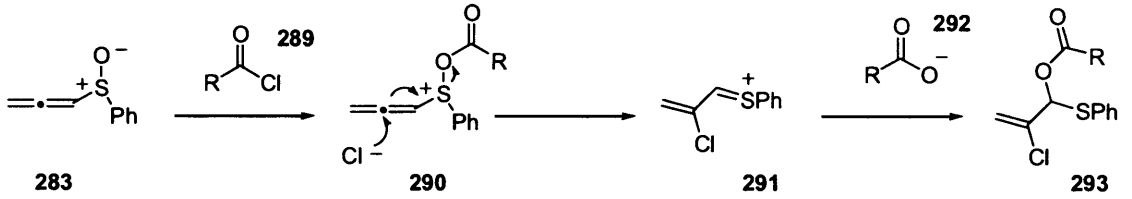
Scheme 83

As expected, the reaction of benzylamine and allenic sulfoxide (283) occurred quantitatively, leading to the conjugated enamine (286) as a mixture of stereoisomers, as shown by ^{1}H NMR analysis of the crude product (Scheme 84). From this observation, it became apparent that the failure of the attempted one-pot annulation reaction could be due to competitive O-acylation of the sulfoxide taking precedence over the desired N-acylation (Scheme 84).



Scheme 84

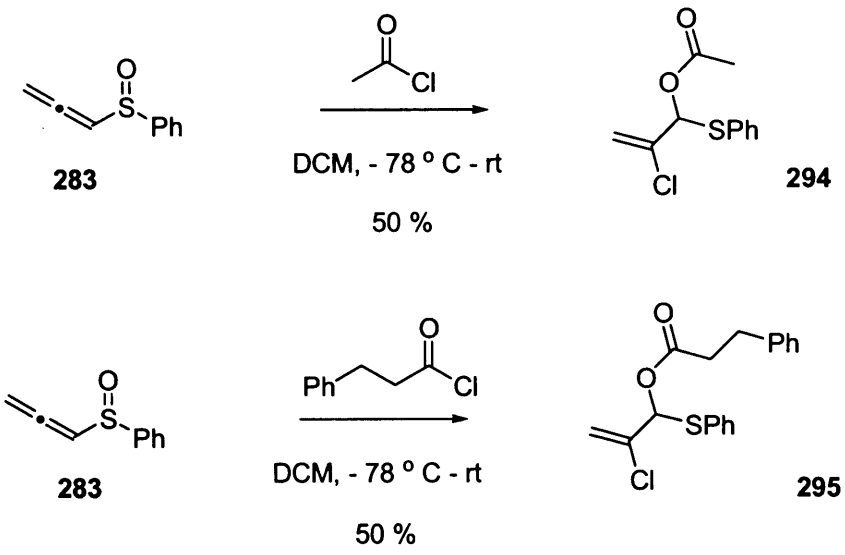
As depicted in Scheme (84), intermediate sulfoxonium cations (287) could evolve to sufonium ions (288) *via* a conjugative Pummerer rearrangement.[108] The presence of such highly reactive cationic intermediates (287 & 288) within the reaction medium could then well explain the plethora of products obtained upon attempted aza-annulation of allenic sulfoxide (283).



Scheme 85

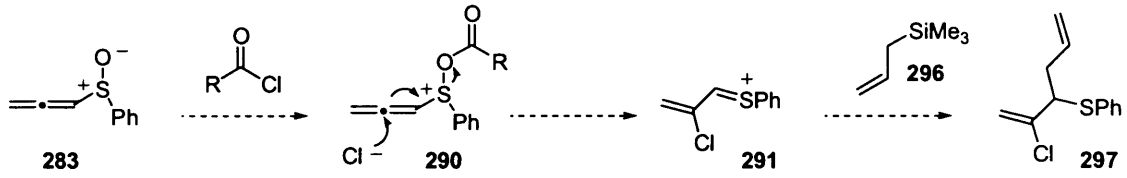
Although both vinyl and propargylic sulfoxides have been used as substrates for Pummerer rearrangements, the behaviour of the corresponding allenic sulfoxide (283), under similar reaction conditions, has not been studied.[109]

Since the allenic sulfoxide could also react with an acid chloride if conjugate addition of the amine component was incomplete, it was also of interest to examine the reaction of allenic sulfoxide (283) with acid chlorides (289) in anticipation of the Pummerer type rearrangement shown in Scheme (85). In the event the expected allylic sulfide (294) was obtained in a 50 % yield, after flash column chromatography. The reaction was also successful with 3-phenylpropionyl chloride, giving the corresponding sulfide (295) (Scheme 86).



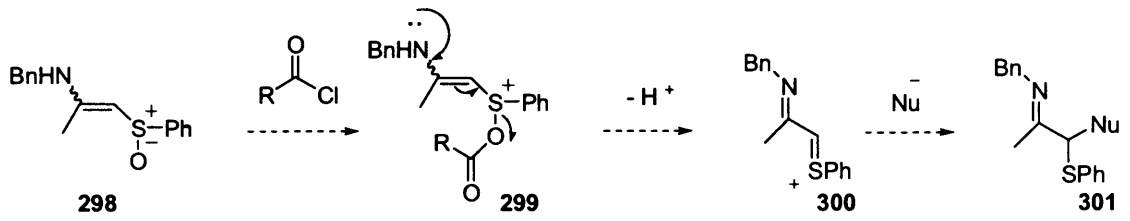
Scheme 86

It was anticipated that the diversion of the reaction pathway in (Scheme 85) to give more synthetically useful products could be achieved on the addition of a range of nucleophiles. For example, the reactivity of allyl silanes towards thionium ions, could be examined, which, if successful, could enable the formation of skipped dienes (297) *via* this novel Pummerer chemistry (Scheme 87).



Scheme 87

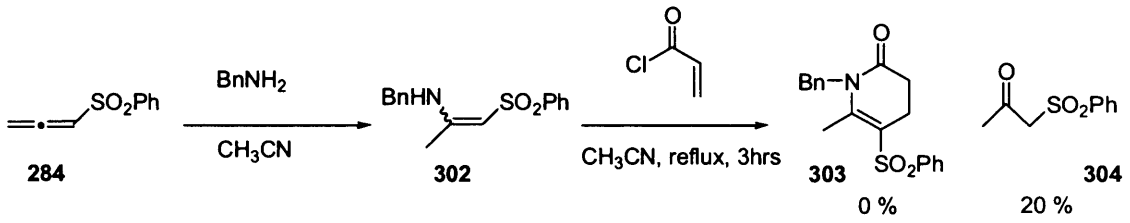
Examination of the reactivity of conjugated enamines (298) under similar reaction conditions also offered the potential for further development of this novel Pummerer chemistry (Scheme 88).



Scheme 88

However, in light of time constraints, it was decided that the development and application of the one-pot aza-annulation methodology should take precedent over any further examination of the described Pummerer chemistry.

In consequence, the next line of investigation was to examine the behaviour of allenic sulfone (284) towards aza-annulation. Thus, allenic sulfone (284) was reacted with benzylamine and acryloyl chloride (Scheme 89). Disappointingly, none of the expected dihydropiperidinone (303) was obtained, and only the β-keto-sulfone (304) was isolated.



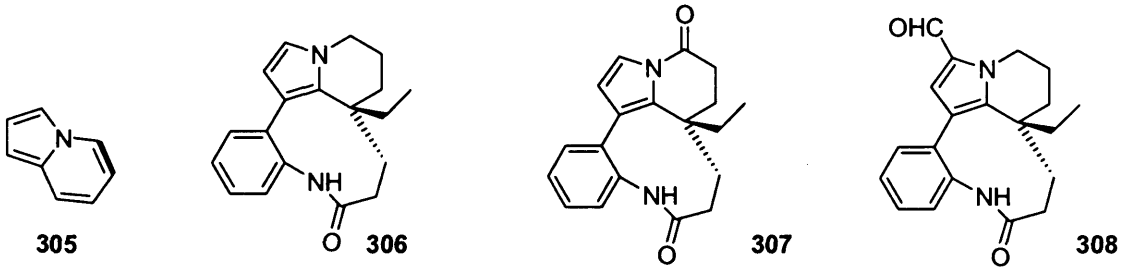
Scheme 89

Hydrolysis of the conjugated enamine (302), or its N-acylated derivative, would in both instances provide the β-keto-sulfone (304). Failure to form any sulfone substituted dihydropiperidinone (303), upon attempted aza-annulation of allenic sulfone (284), could be due to a variety of reasons. The identification of β-keto-sulfone (304) from the crude reaction mixture, in combination with previous studies upon the reactivity of allenic sulfones towards primary amines, provided strong evidence that the formation of the required conjugated enamine (302) occurred as

expected and the failure of the reaction would be due to complications at either the N-acylation stage (as observed with allenic sulfoxides) or the Michael cyclisation stage of the annulation process. In light of the difficulties faced upon the attempted application of allenic sulfoxides and sulfones to the one-pot aza-annulation reaction, it was then decided to capitalise on the more successful annulation sequences by applying them towards natural product synthesis.

2.16 Application to Total Synthesis: Cytotoxic Aspidosperma Alkaloids

The indolizine nucleus (305) and its tetrahydro-derivatives, form the structural backbone of a variety of biologically active alkaloids. The natural products rhazinilam (306),[110] its N-oxo derivative (307)[110] and rhazinal (308)[112] are members of the *Aspidosperma* family of alkaloids, isolated from a number of plant sources (Figure 4).[113]



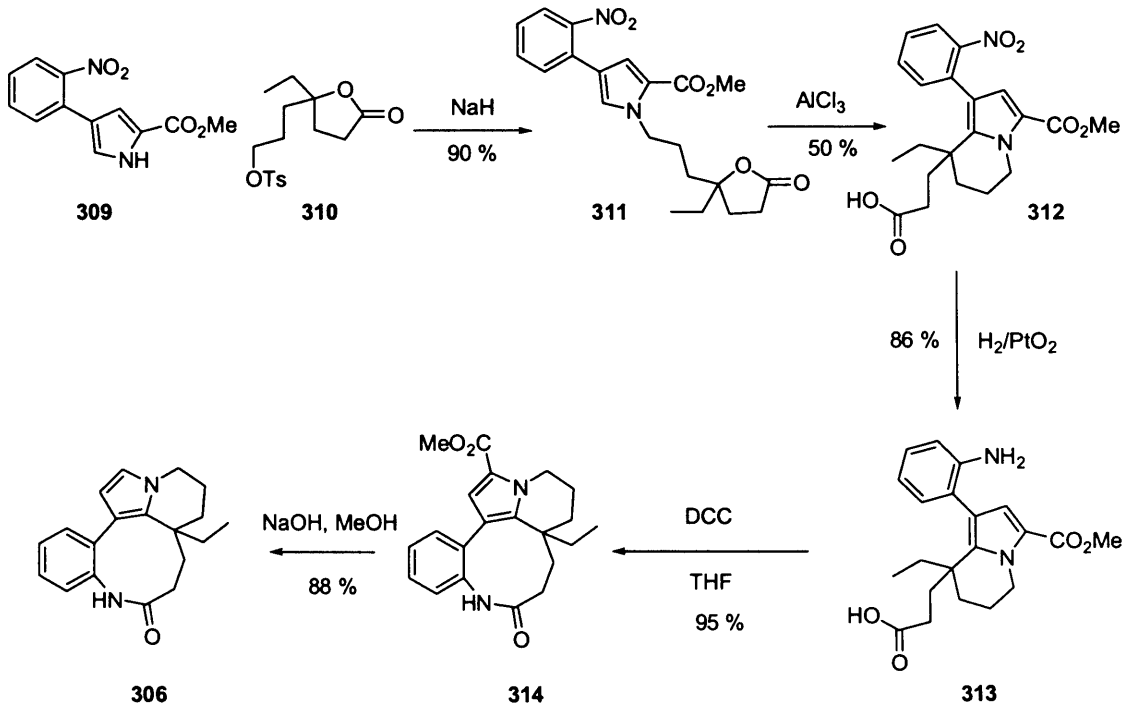
305 306 307 308

Figure 4

The *Aspidosperma* alkaloids have attracted significant attention from the scientific community due to their interesting modes of biological activity. The natural product rhazinilam (306) and its congeners, were found to be similar to both taxol and vincristine by interfering with tubulin polymerisation dynamics and promoting the formation of asters in mitotic cell lines.[114] Moreover, the synthetic community's interest in rhazinilam (306) and its derivatives, has been driven by these biological activities, coupled with the interesting synthetic challenges posed by their assembly.

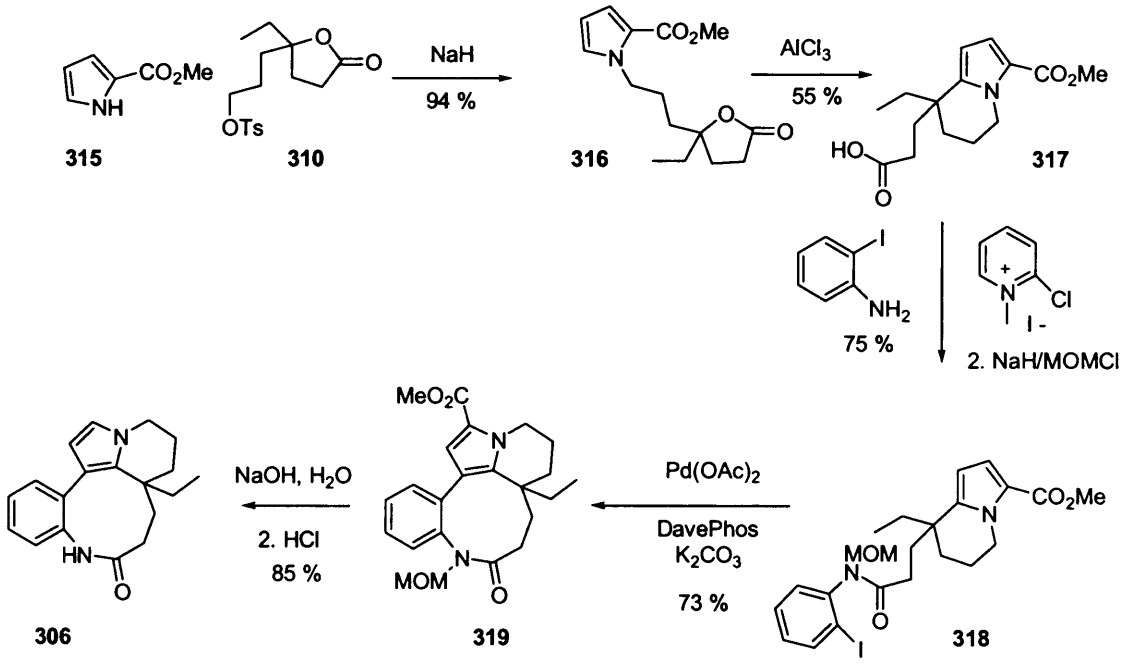
Such challenges include the formation of the strained 9-membered lactam skeleton and the stereogenic quaternary carbon centre.

Due to these properties, rhazinilam (306) and rhazinal (308) have both succumbed to total synthesis. rhazinilam (306) has been prepared by a number of groups and the 'classical' synthesis by Smith, [115] conducted more than 30 years ago has been followed up by no less than six elegant racemic and asymmetric syntheses. The synthesis conducted by Smith is depicted in Scheme (90) and commenced from the substituted pyrrole (309), which upon N-alkylation with tosylate (310) gave lactone (311). Cyclisation of (311) promoted by anhydrous aluminium chloride and directed by the ester group on the pyrrole ring gave the carboxylic acid (312), which, upon reduction of the nitro group to give amine (313) lactamised readily in the presence of dicyclohexylcarbodiimide to give (314). The synthesis was then completed by ester saponification and decarboxylation.



Scheme 90

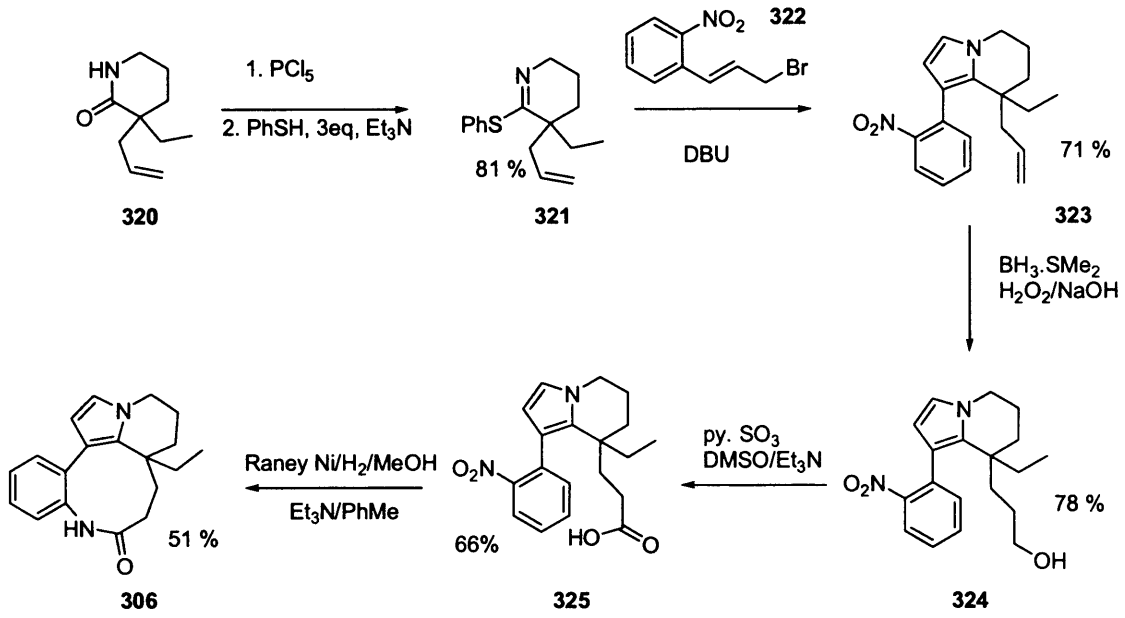
Trauner and *co-workers* have reported a similar approach to rhazinilam (306).[116] Thus, as shown in Scheme (91), cyclisation of lactone (316), derived from pyrrole (315) and lactone (310) in the presence of aluminium chloride provided the carboxylic acid (317), which, upon coupling with 2-iodoaniline gave amide (318) after protection of the amine with MOM chloride which then allowed the strained 9 membered lactam to be constructed by a palladium catalysed direct intramolecular coupling reaction between the aryl iodide and the pyrrole ring providing (319). The synthesis was, once again, completed by a deprotection and decarboxylation sequence.



Scheme 91

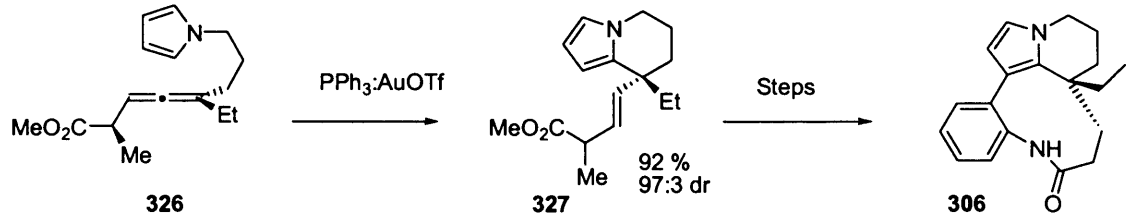
Magnus and co-workers utilised the conversion of a lactam to a pyrrole *via* a thiophenyl imine as the key step.[117] Thus, as shown in Scheme (92), the reaction of thiophenyl imine (321), itself synthesised from the readily prepared substituted lactam (320), with allylic bromide (322), in the presence of DBU gave the key bicyclic pyrrole intermediate (323) in 71 % yield. The synthesis was then completed in three simple chemical steps involving hydroboration of alkene (323) followed by oxidation

of the resulting alcohol (324) to the carboxylic acid (325), which, upon exposure to Raney nickel and hydrogen gas cyclised to give the natural product (306).



Scheme 92

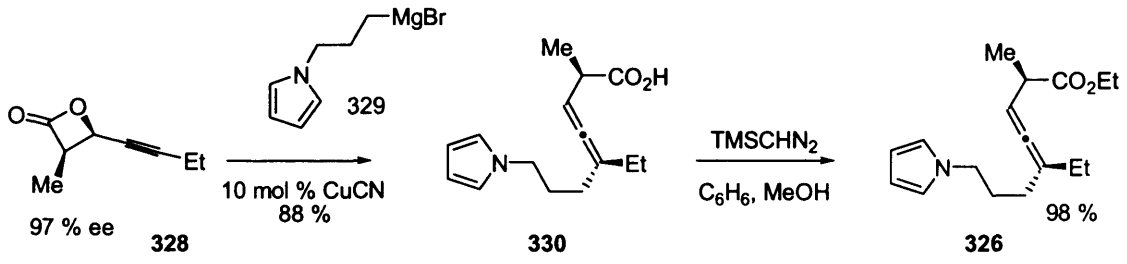
A particularly elegant and interesting asymmetric approach to (-)-rhazinilam, deserving of more attention, was reported by Nelson and co-workers, and made use of a Au(I)-catalysed annulation of an enantioenriched allene in the key step.[118] In scheme (93), the Au(I) catalysed annulation of pyrrole substituted allene (326) provided the key tetrahydroindolizine (327), with almost complete translation of axial to central chirality.



Scheme 93

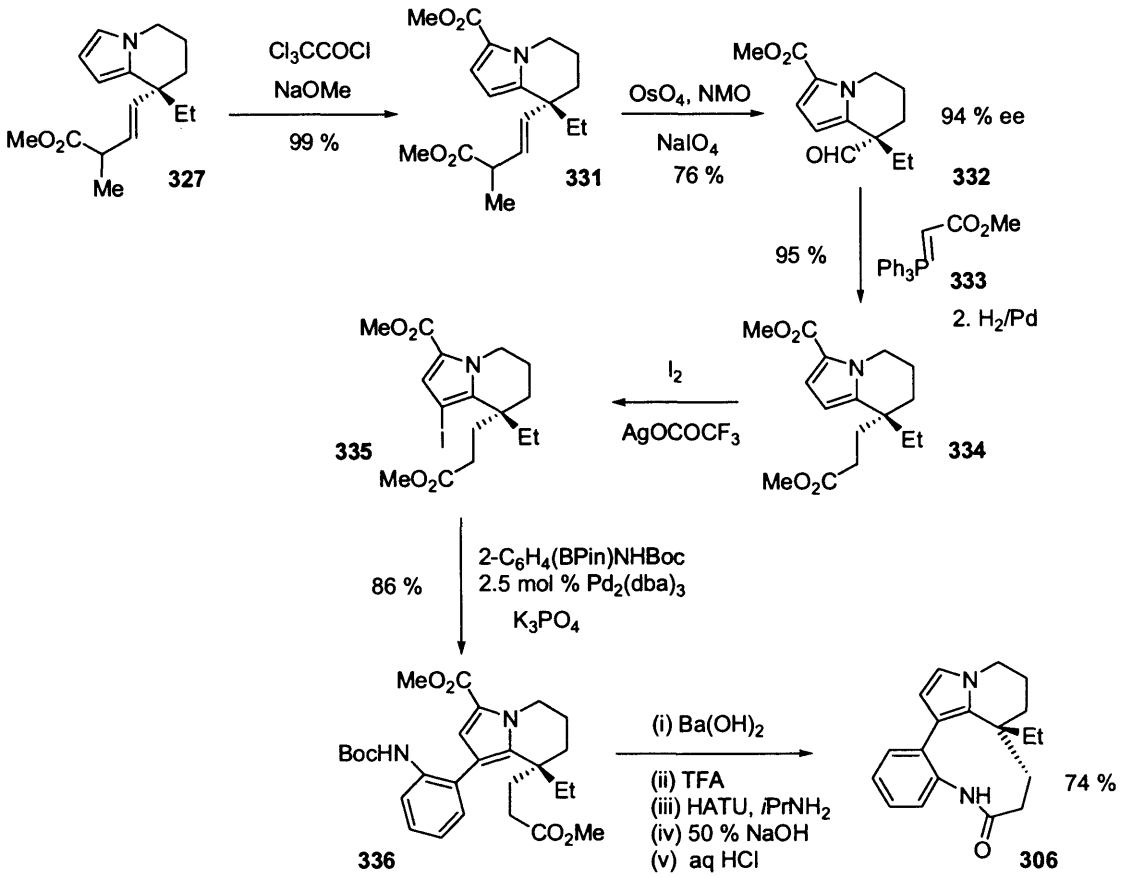
The enantioenriched pyrrole substituted allene (326) was prepared by a S_N2' ring opening reaction of optically active β-lactone (328) with Grignard reagent (329).

Thus, as shown in Scheme (94), in the presence of Cu (I), β-lactone (328) underwent a ring opening reaction with the pyrrole substituted Grignard reagent (329), providing the enantioenriched allene (330) in 88 % yield, and this, in turn was converted to the key allenic substrate (326) upon esterification.



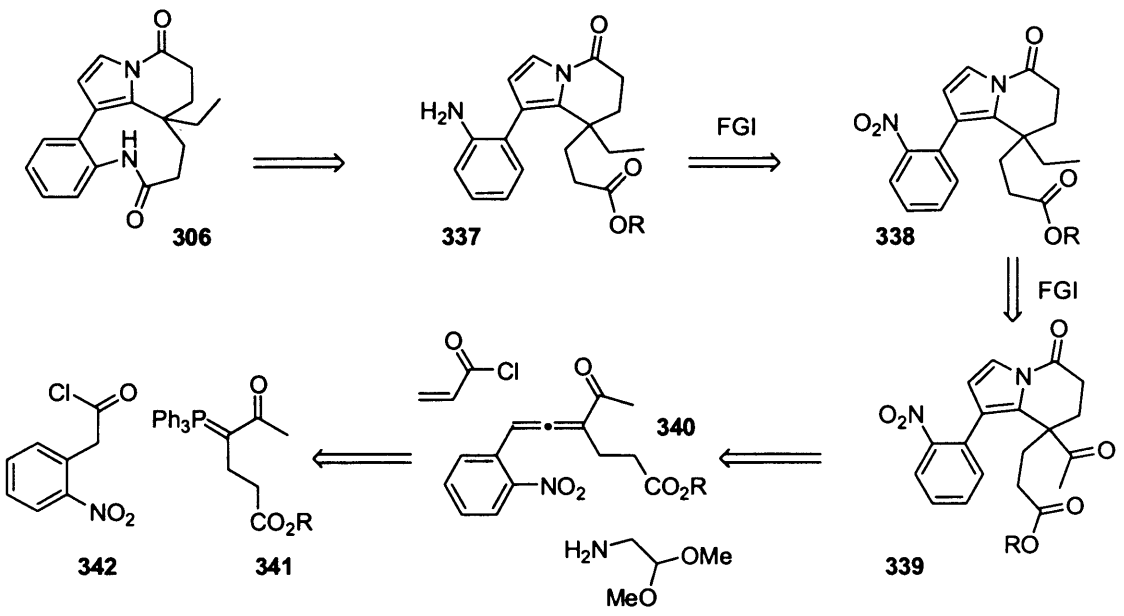
Scheme 94

Conversion of tetrahydroindolizine (327) into the natural product (306) was achieved in six synthetic steps and the sequence is depicted in Scheme (95). Thus, in order to circumvent the problems associated with heterocycle oxidation, pyrrole (327) was carboxylated to give (331) in order to attenuate pyrrole basicity. Oxidative cleavage of the double bond to give aldehyde (332) was followed by Horner–Wittig homologation with ylide (333) and catalysed dehydrogenation affording ester (334). Iodination of the pyrrole ring gave iodide (335), which was then converted into the 3-aryl-pyrrole (336) *via* a Suzuki –Miyaura cross coupling reaction. The synthesis was then completed by Boc deprotection, followed by base mediated lactamisation and acid promoted decarboxylation.



Scheme 95

Because of the structural resemblance of the fused pyrroles obtained from the developed one-pot aza-annulation chemistry, to the core structure of rhazinilam (306) and its derivatives, it was anticipated that this methodology could be applied to the total synthesis of these natural products as revealed by the retrosynthetic analysis of N-oxo rhazinilam shown in Scheme (96).



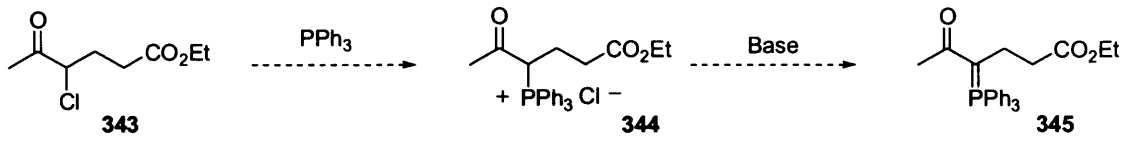
Scheme 96

Thus, after initial disconnection of the amide bond and masking of the resulting amino group as its nitro derivative and the acid moiety as an ester, as in (338), functionalisation of the ethyl group to the corresponding methyl ketone shown in (339) then enabled multiple disconnection, based upon the aza-annulation methodology, to allenic ketone (340), the commercially available aminoacetaldehyde dimethyl acetal and acryloyl chloride (Scheme 96). Although disconnection of the allenic ketone (340) could be achieved in a number of ways, it was initially anticipated that the simplest method of preparing this key allenic intermediate would involve the Wittig olefination of acid chloride (342) with phosphorane (341).

Studies Towards The Synthesis Of Allenic Ketone (340)

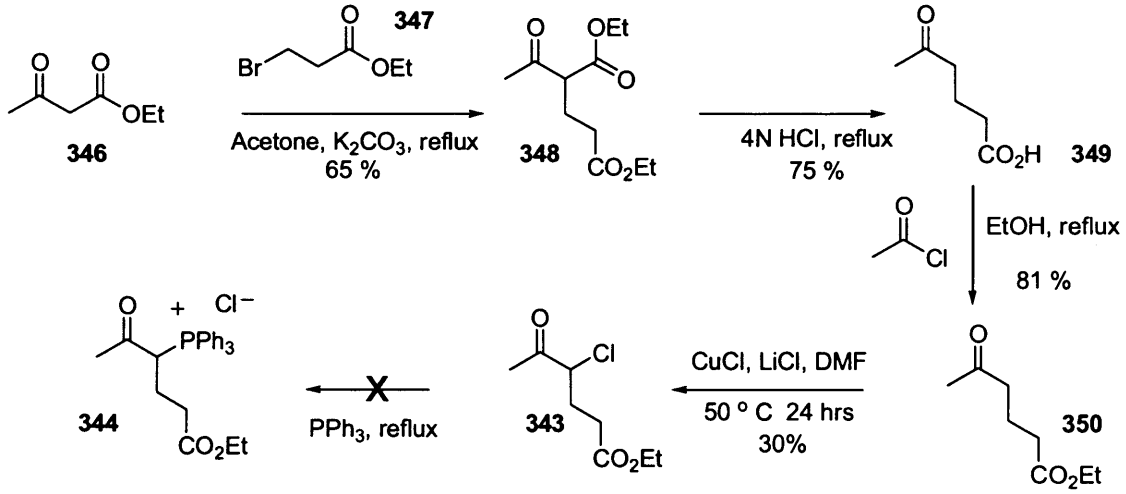
As outlined in the preliminary retrosynthetic analysis shown in Scheme (96), the preparation of the key intermediate allenic ketone (340) *via* the Wittig reaction of the ketene derived from acid chloride (342) and ylide (341), was selected as the most convenient route. Consequently, a simple synthesis of the required phosphorane (341) was envisaged from the known chloride (343). It was anticipated that the reaction of chloride (343) with triphenylphopshine would provide the corresponding

phosphonium salt (344), which could be converted into the phosphorane (345) upon reaction with base (Scheme 97).



Scheme 97

Chloride (343) was prepared in four simple synthetic steps starting from the commercially available ethyl acetoacetate (346) (Scheme 98).

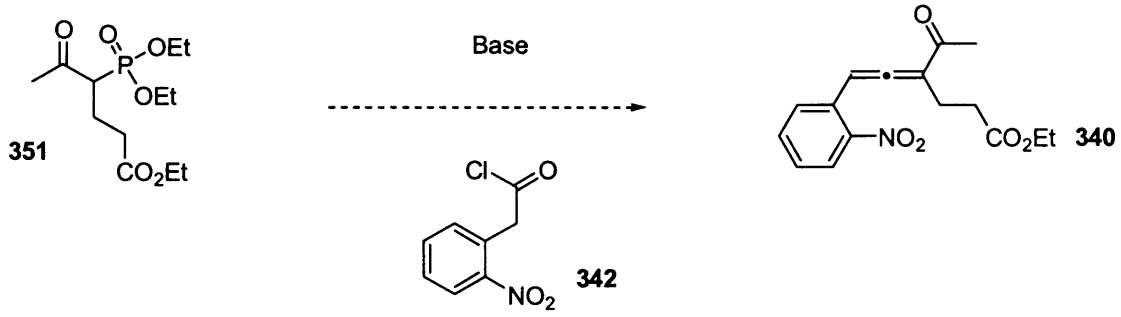


Scheme 98

Alkylation of ethyl acetoacetate (346) with bromide (347) in the presence of K_2CO_3 gave the substituted β-ketoester (348) in 65 % yield after 48 hrs at reflux in acetone. Decarboxylation of (348) in aqueous HCl provided carboxylic acid (349), which was isolated by a simple acid-base extraction. Esterification of acid (349) with ethanol and dry HCl provided the required 1,5-dicarbonyl compound (350), which on chlorination with CuCl/LiCl in DMF provided the chloride (343), albeit in low isolated yield. Disappointingly, however, all attempts to convert chloride (343) to phosphonium salt (344) proved problematic. The reaction of chloride (343) with triphenylphosphine in a range of solvents at different temperatures failed to provide the required phosphonium salt (344). Performing the reaction in molten triphenylphosphine led to complete

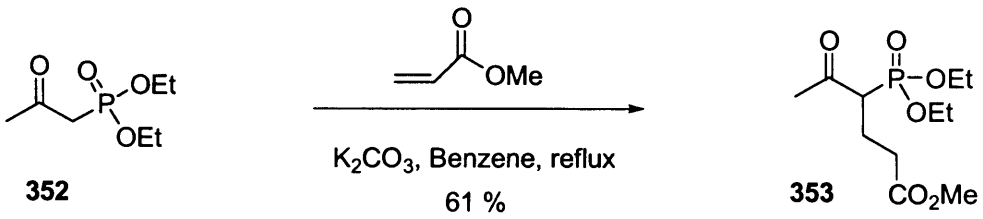
decomposition of the starting material. Attempts to convert chloride (343) to the more reactive iodide *in situ*, led to de-halogenation and the identification of the previously prepared 1,5-dicarbonyl compound (350) within the crude reaction mixture.

Due to these problems, the preparation of the allenic ketone (340) *via* the related Horner-Wadsworth-Emmons olefination of phopshonate (351) and acid chloride (342) was investigated (Scheme 99).



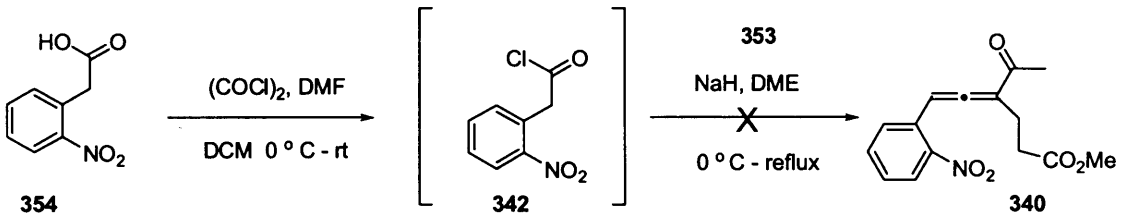
Scheme 99

Within this framework, phosphonate (353) was readily prepared *via* the base mediated conjugate addition of commercially available phosphonate (352) to freshly distilled methyl acrylate (Scheme 100).



Scheme 100

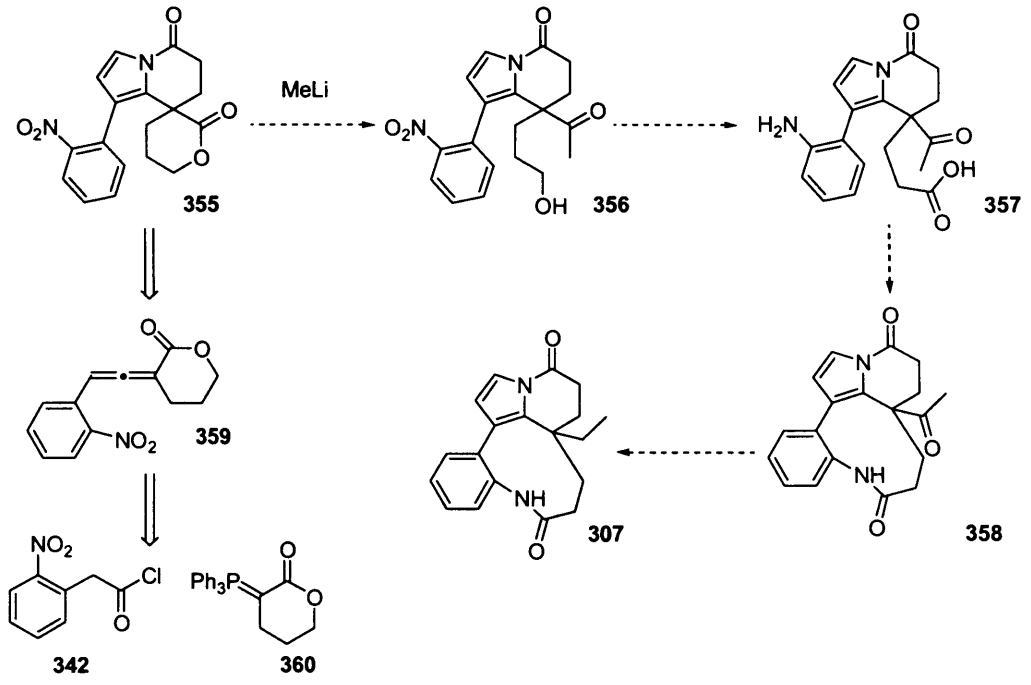
Acid chloride (342) was prepared by the action of oxalyl chloride on the commercially available carboxylic acid (354) in the presence of catalytic DMF and the crude acid chloride (342) was reacted immediately with the phosphonate ester (353) (Scheme 101).



Scheme 101

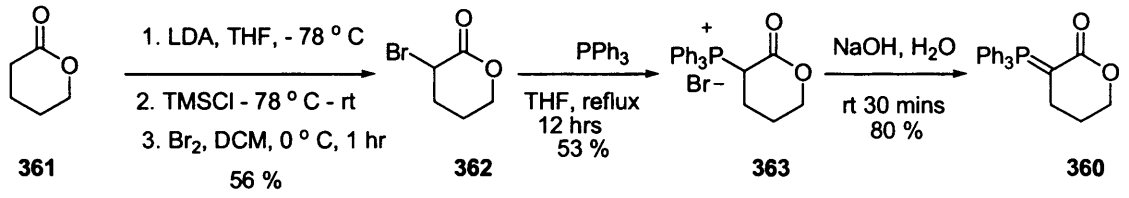
Disappointingly, the reaction failed to provide any of the required allene (340) under a variety of conditions and in all cases, an intractable mixture of compounds and polymeric material was obtained, thus an alternative pathway was sought.

It was then reasoned that the required substituted fused pyrrole could be obtained from the spirocyclic lactone (355) (Scheme 102). Addition of methyllithium to lactone (355) to yield alcohol (356), which would be followed by oxidation to acid (357). Reduction of the nitro moiety would then set up an intramolecular amide coupling to give (358). Lactone (355) could be disconnected to the allene (359) which, in turn, could be obtained from the Wittig reaction of phosphorane (360) with the previously described acid chloride (342).



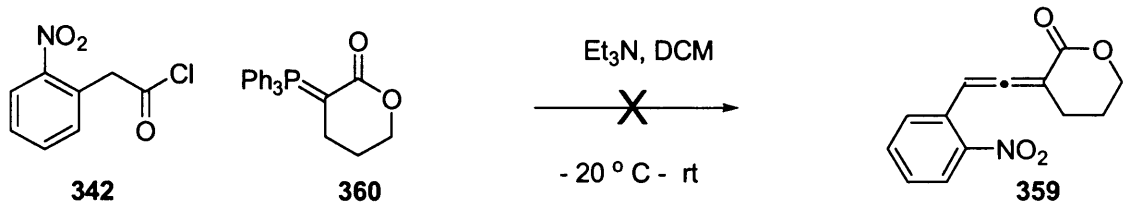
Scheme 102

In order to test the viability of this new pathway to N-oxo-rhazinilam, phosphorane (360) was prepared in three synthetic steps commencing from the commercially available δ-valerolactone (361). Conversion of lactone (361) to its derived silyl ketene acetal followed by reaction with molecular bromine, provided bromide (362) and reaction of this crude bromide (362) with triphenylphosphine in THF, gave the desired phosphonium salt (363). Treatment of the phosphonium salt (363) with aqueous NaOH in the presence of phenolphthalein indicator, provided phosphorane (360) as a cream coloured precipitate (Scheme 103).



Scheme 103

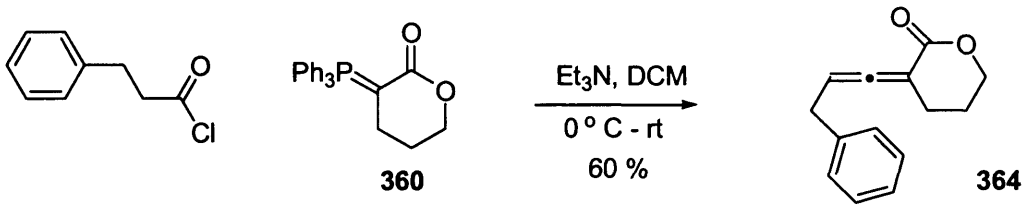
Frustratingly, attempts to access the required allene (359) by the Wittig reaction of phosphorane (360) and acid chloride (342) failed. Once again a range of reaction conditions were examined with variations in temperature and solvent. However, in all cases, only complex mixtures of unidentified compounds and polymeric material were obtained (Scheme 104).



Scheme 104

In order to clarify whether or not the novel phosphorane (360) would be suitable to effect the formation of allenic carboxylates from acid chlorides, it was reacted with the ketene derived from commercially available 3-phenylpropionyl chloride. This acid

chloride has been previously utilised for the synthesis of a number of substituted allenic esters, *via* a Wittig reaction with phosphoranes.[119] In the event, the reaction of phosphorane (360) with 3-phenylpropionyl chloride in the presence of Et_3N, proceeded as expected, to provide the allenic lactone (364), which was isolated in a healthy 60 % yield after purification by flash column chromatography (Scheme 105).

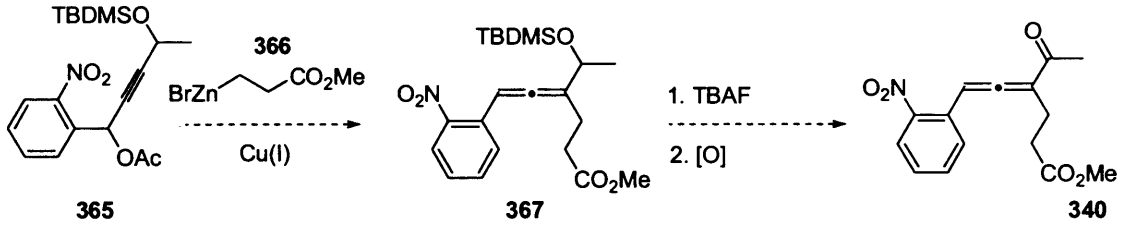


360 364

Scheme 105

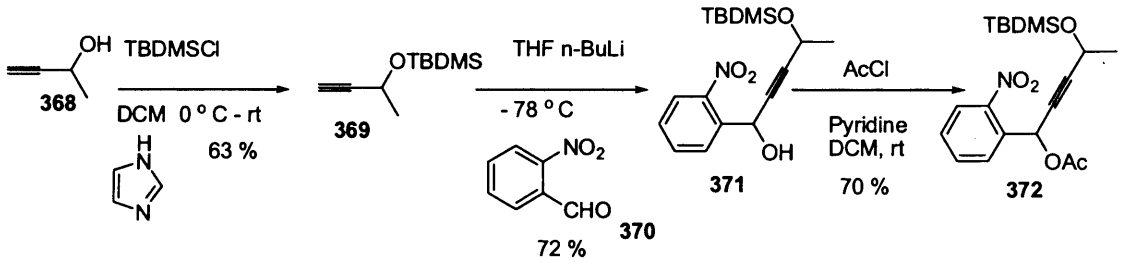
The successful preparation of allenic lactone (364) from phosphorane (360) indicated that the failure to prepare the allenic lactone (359) could be due to the fact that the acid chloride (342) was unsuitable for tandem ketene formation/olefination. It was anticipated that the stability of the ketene derived from its parent acid chloride (342) could be compromised by the presence of the nitro moiety and that this may be responsible for the complex mixtures of products observed upon attempted reaction with phosphorane (360).Thus, alternative routes to the key allenic intermediate were examined.

As described in Section (1), the addition of organometallic reagents to propargylic electrophiles can provide a facile route to a number of functionalised allenic compounds. Consequently, it was envisaged that addition of the known organo-zinc reagent (366) [120] to propargylic acetate (365) in the presence of Cu(I), could enable the preparation of allene (367). Removal of the TBDMS group followed by oxidation of the resulting secondary alcohol would then provide the key intermediate allenic ketone (340) (Scheme 106).



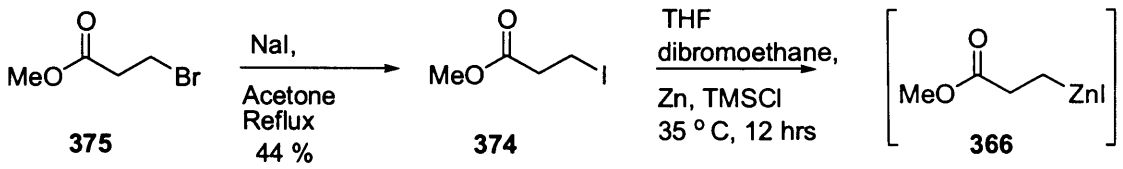
Scheme 106

Propargylic acetate (365) was prepared as shown in Scheme (107). Conversion of the commercially available alcohol (368) to its silyl ether (369) *via* reaction with TBDMSCl and imidazole, was followed by lithiation and reaction of the resulting acetylide with ortho-nitrobenzaldehyde (370). Alcohol (371) was subsequently converted to the required secondary acetate (372) on reaction with acetyl chloride in the presence of pyridine.



Scheme 107

The organometallic reagent (366), required to effect the conversion of acetate (372) into allene (373) was prepared from iodide (374) which was itself prepared by the reaction of the commercially available bromide (375) with NaI in acetone (Scheme 108).

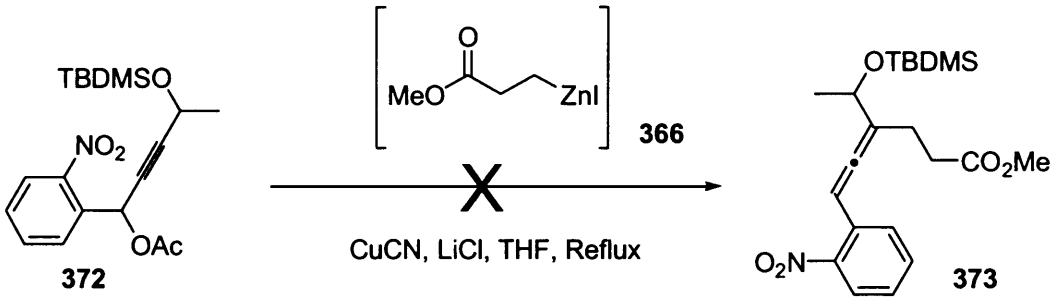


Scheme 108

Disappointingly, addition of propargylic acetate (372) to a solution of the freshly prepared organo-zinc reagent (366) in the presence of CuCN and LiCl, failed to give

the desired allene (373), after a 12 hour period at room temperature. Analysis of the reaction mixture by TLC showed that the starting material remained unchanged. The temperature was increased to 50 ° C and the reaction was allowed to stir a further 12 hrs. Once again TLC analysis of the crude reaction mixture indicated that the starting propargylic acetate (372) was left unchanged (Scheme 109).

In a second attempt, the required organometallic reagent (366) was prepared by the addition of iodide (364) to a freshly prepared Zn/Cu couple.[120] Unfortunately, addition of acetate (372) to a solution of this freshly prepared organometallic reagent failed to provide any of the desired allene (373), even after a 12 hour period at reflux. Once again, only starting material was observed by TLC analysis (Scheme 109).

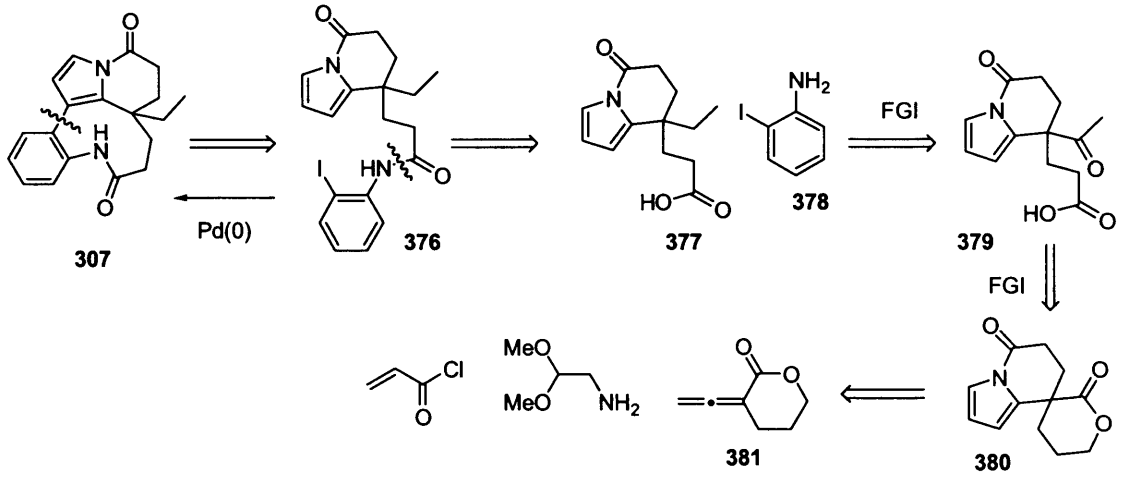


Scheme 109

With both the Wittig reaction of acid chloride (342) and the addition of organozinc reagent (366) to propargylic acetate (372), failing to provide the key allenic intermediates, a completely different approach to N-oxo-rhazinilam (307) was sought. As previously discussed, the problems associated with the Wittig approach were attributed to the presence of the ortho nitro group of the aryl moiety. It is highly likely that this functionality could also play a role in the failure to convert the propargylic acetate (372) into allene (373), *via* the addition of organozinc reagent (366), in light of its reactivity towards related organometallic reagents.[121]

Therefore, it was decided to remove the nitro moiety from the key allenic intermediate and the retro synthesis of N-oxo-rhazinilam was readdressed with the previously encountered problems in mind (Scheme 110).

It was envisaged that an intramolecular Pd(0) catalysed coupling reaction of the aryl iodide (376) with the pyrrole moiety could be used for the construction of the key 9-membered ring (Scheme 110). As we have seen, recent studies by Trauner and co-workers have demonstrated the utility of this methodology for the synthesis of the core structure of rhazinilam.[116]

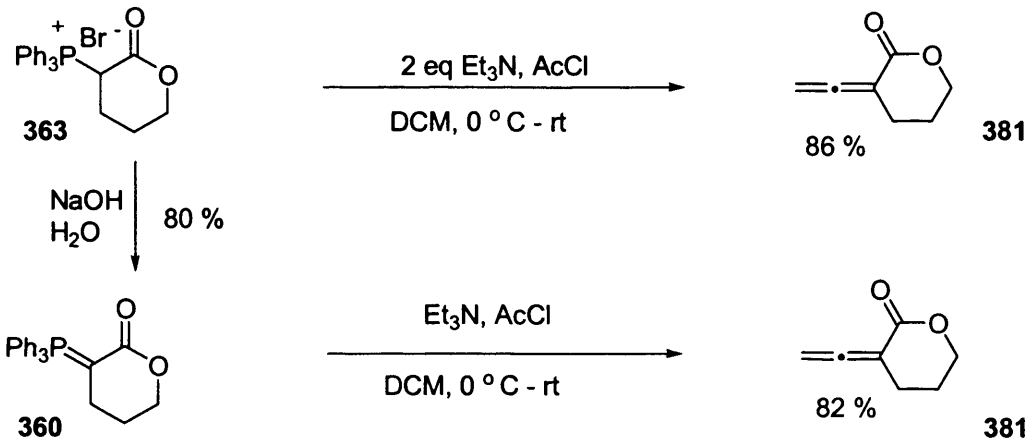


Scheme 110

Disconnection of the amide bond, followed by functionalisation of the ethyl group would lead to the 1,5-keto-acid (379), with functional group interconversion to lactone (380) enabling a three way disconnection based upon the developed aza-annulation methodology, leading to the allenic lactone (381), aminoacetaldehyde dimethyl acetal and acryloyl chloride.

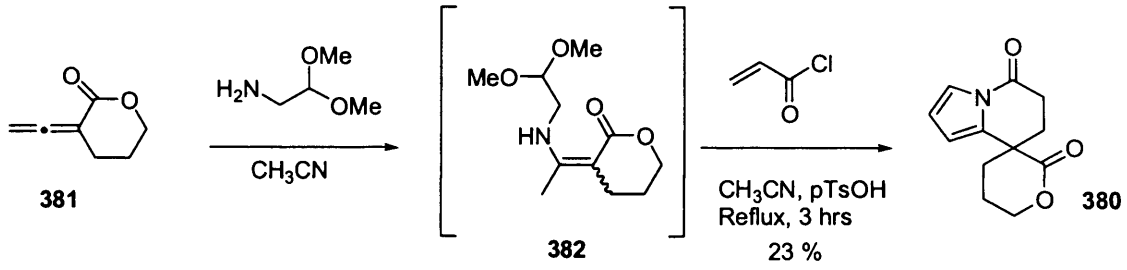
The allenic lactone (381) was prepared from the previously obtained ylide (360). Reaction of ylide (360) with acetyl chloride in the presence of triethylamine, gave the desired allenic lactone (381), in 82 % yield after purification by chromatography. Formation of the required ylide *in situ* from phosphonium salt (363), by using two

equivalents of triethylamine, also provided the desired allenic lactone (381), in a slightly higher isolated yield, of 86 % (Scheme 111).



Scheme 111

With the required allenic lactone (381) in hand, the one-pot aza-annulation reaction was attempted. The addition of aminoacetylaldehyde dimethyl acetal to allene (381) led to complete conversion to the vinylogous urethane (382) within 3 hrs at room temperature and annulation of this vinylogous urethane (382) with acryloyl chloride proceeded as desired, to provide the fused pyrrole (380) (Scheme 112) in combination with a range of unidentified side products.

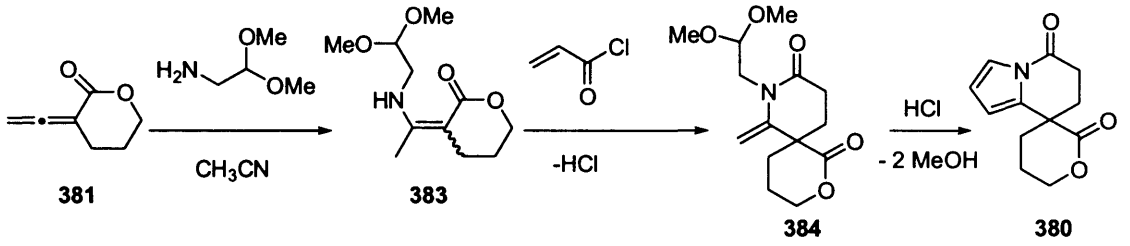


Scheme 112

2.17 Optimisation Studies

Although successful conversion of the allenic lactone (381) to the key intermediate tricyclic compound (380), had been achieved, it was anticipated that in order for the total synthesis of N-oxo-rhazinilam to be successful, the yield for this key step would have to be improved. Initially, it was decided that the separation of the one-pot

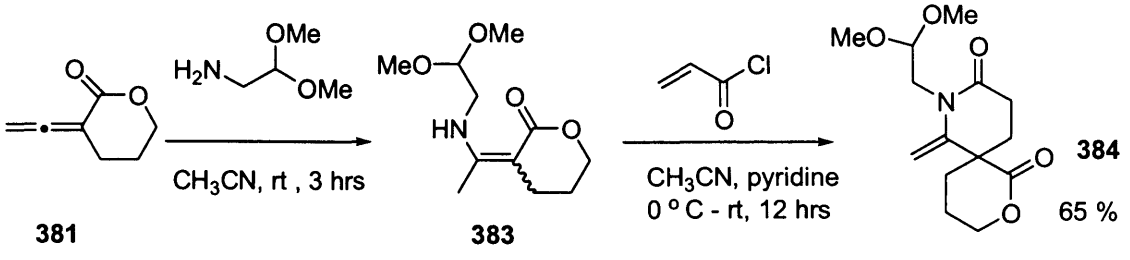
process into its individual components would enable a better understanding of where material was being lost, and therefore aid efforts towards the optimisation of the reaction conditions.



Scheme 113

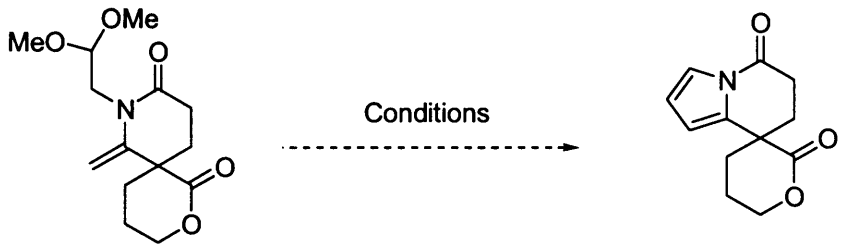
The reaction of aminoacetylaldehyde dimethylacetal with allenic lactone (381) was shown to proceed quantitatively, providing enaminone (383) as a mixture of geometric isomers essentially free from impurities, as demonstrated by ^{1}H NMR and HPLC analysis of the crude reaction mixture (Scheme 113). Therefore, it was anticipated that the loss of material on passing from allenic lactone (381) to bicyclic pyrrole (380), occurred after the addition of acryloyl chloride.

As discussed earlier (Scheme 75), the annulation reaction of allenic ester (256) in the presence of pyridine enabled the clear identification of the intermediate dihydro-piperidinone (276). In this instance, the addition of pyridine to a mixture of the crude enaminone (383) prior to the addition of acryloyl chloride was examined (Scheme 114). Aqueous work up of the crude reaction mixture and subsequent ^{1}H NMR analysis clearly showed the expected exocyclic enamide (384), essentially free from impurities.



Scheme 114

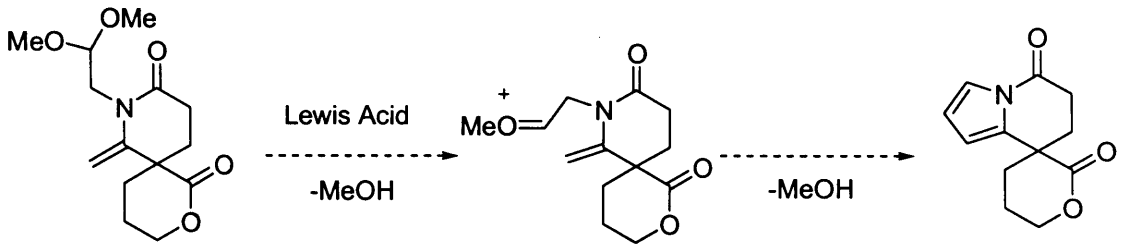
Secure in the knowledge that the first two stages of the one pot procedure took place with high efficiency, it became apparent that the final stage, involving formation of the pyrrole ring, was causing the problems. Consequently, alternative methods of converting the exocyclic enamide (384) to the tricyclic pyrrole (380) were investigated (Scheme 115).



384 **380**

Scheme 115

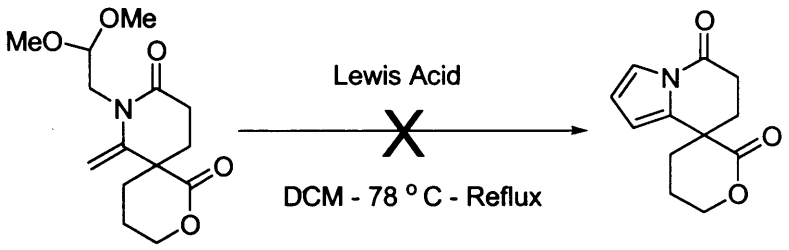
As shown in scheme (116), it was envisaged that activation of the acetal functionality with an oxophilic Lewis acid, would promote cyclisation of the enamide onto the derived oxonium ion (385). Elimination of methanol would then provide the tricyclic pyrrole (380).



384 **385** **380**

Scheme 116

To test this hypothesis, enamide (384) was reacted with a range of Lewis acids under a variety of reaction conditions (Scheme 117 & Table 4).



384 **380**

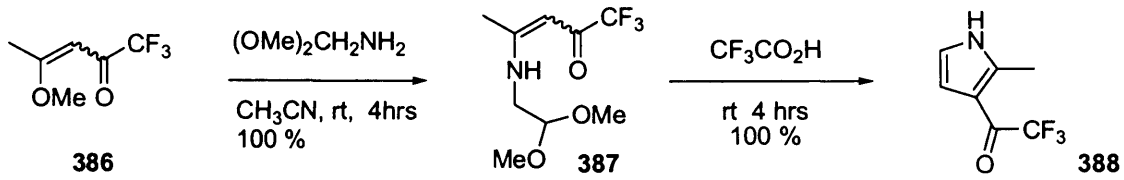
Scheme 117

From Table (4), it can be seen that the vast majority of the Lewis acids investigated had, at best, no effect upon the enamide (384). When starting material was consumed, analysis of the crude reaction mixtures by TLC, HPLC & ^{1}H NMR showed no signs of the desired tricyclic pyrrole (380) being formed, and only starting material, aldehyde formed by deprotection of the acetal group and a range of unidentified impurities and oligomeric material were observed.

Lewis Acid	Quantity	Reaction Solvent	Reaction Temperature (°C)	Result
$In(OTf)_3$	1 eq	DCM	- 78	No reaction
$In(OTf)_3$	1 eq	DCM	25	Decomposition
TMSCl	1 eq	DCM	25	No reaction
TMSCl	1 eq	DCM	40	No reaction
TMSOTf	1 eq	DCM	- 78	No reaction
TMSOTf	1 eq	DCM	- 78	Partial acetal deprotection
$BF_3.Et_2O$	1 eq	DCM	- 78	No reaction
$BF_3.Et_2O$	1 eq	DCM	25	Decomposition

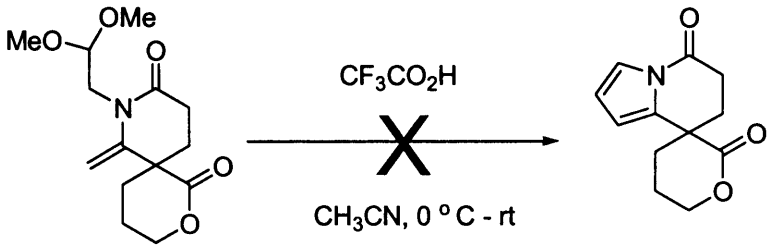
Table 4

Due to these unpromising results obtained by the preliminary Lewis acid screen, the effects of protic acids upon enamide (384) were examined. Hojo *et al.* have demonstrated that N-β-trifluoroacetylvinyl amino acid esters (387), derived from vinyl ethers (386) undergo essentially quantitative conversion to the corresponding substituted pyrroles (388), upon stirring in trifluoroacetic acid at room temperature (Scheme 118).[122]



Scheme 118

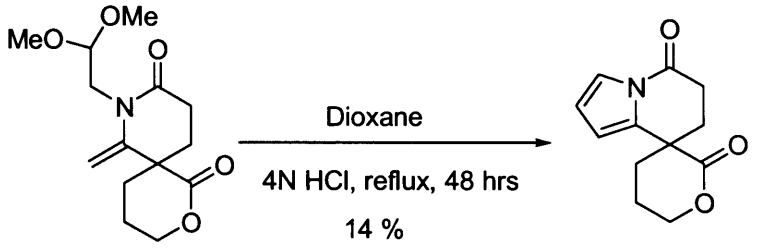
Thus, it was hoped that similar conditions could be employed to induce pyrrole formation from the exocyclic enamide (384). Disappointingly, the reaction of enamide (384) with cold trifluoroacetic acid led to the complete decomposition of starting material, with little or no evidence for the formation of the pyrrole (380) (Scheme 119).



384 **380**

Scheme 119

Clearly, the stability of the strained spirocyclic lactone under such harsh acidic conditions is questionable. The nucleophilic ring opening of lactones in the presence of an acid catalyst is plausible and it was anticipated that in order to prevent such competitive lactone ring opening, the use of a milder acid catalyst would be required.

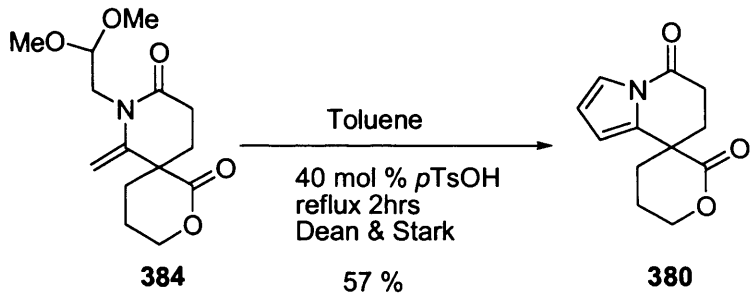


384 **380**

Scheme 120

Therefore, the enamide (384) in dry dioxane, was treated with a small quantity of HCl (4N in dry dioxane). No reaction was observed at room temperature. However, heating the solution at reflux for 48 hrs led to the formation of the previously prepared

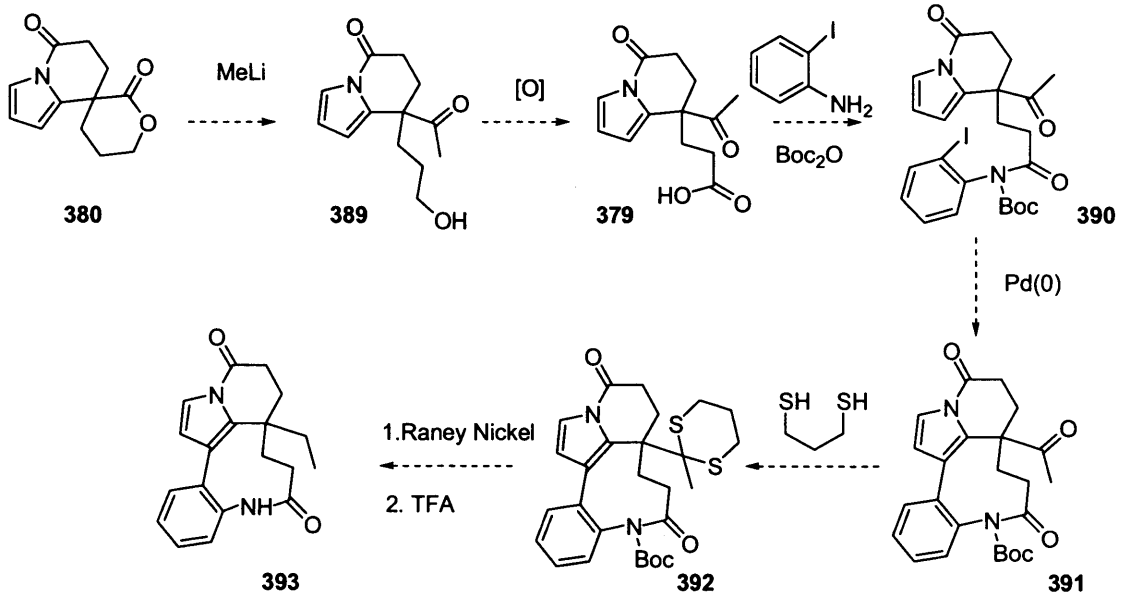
bicyclic pyrrole (380), along with a number of unidentified compounds. Flash chromatography of the crude oil enabled the isolation of pyrrole (380), in 14 % yield. The successful conversion of enamide (384) into the tricyclic pyrrole (380), under protic conditions, provided direct evidence for the proposed mechanistic pathway for this transformation. Encouraged by this, further optimisation studies were conducted and the effects of carrying out the described annulation reaction under dehydrating conditions was investigated. It was anticipated that the use of a Dean and Stark apparatus, could aid the conversion of enamide (384) into pyrrole (380), as the continuous removal of methanol from the reaction system would be beneficial in two ways. Primarily, the absence of nucleophilic methanol from the reaction medium would help to keep the strained spirocyclic lactone moiety intact and also the constant removal of methanol would also push the cyclisation reaction towards completion, by aiding the elimination step. Gratifyingly, heating the enamide (384) in dry toluene at reflux, in the presence of a small quantity of *para*-toluenesulfonic acid, led to the complete consumption of the starting material within 2 hrs (Scheme 121). Purification of the crude oil by flash column chromatography furnished the desired pyrrole (380) in 57 % yield.



Scheme 121

With an efficient route to the key tricyclic pyrrole (380) in hand it is hoped that the synthesis of N-oxo rhazinilam should proceed with relative ease. Thus, as shown in

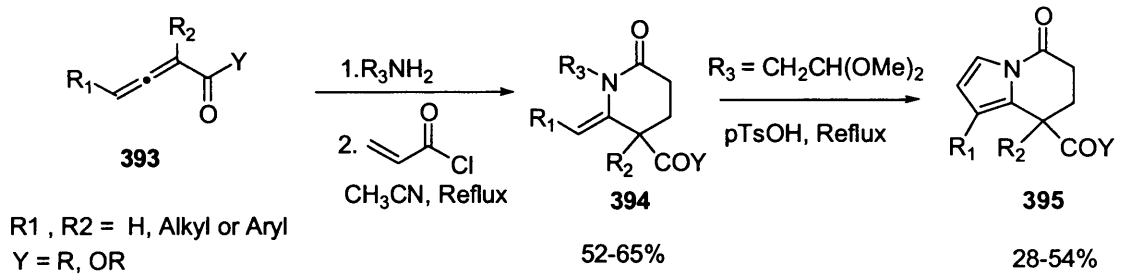
Scheme (122), ring opening of the strained spirocyclic lactone with MeLi followed by oxidation of the resulting alcohol (389) to the previously described carboxylic acid (379) would be followed by amide coupling yielding amide (390). Intramolecular coupling to provide the key 9 membered lactam (391) and formation of dithiane (392) could then be followed by desulfurisation. The synthesis would then be completed by removal of the nitrogen protecting group.



Scheme 122

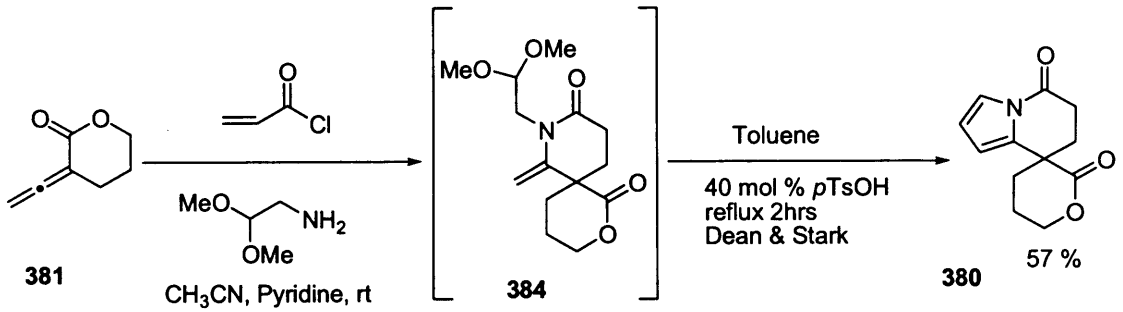
Section 2.18 Conclusions and Perspectives

Within this area of study, it has been shown that the selection of readily prepared allenic esters and ketones for regioselective vinylogous urethane and amide formation, has enabled the development of simple and experimentally convenient one pot protocols for the preparation of substituted dihydropiperidinones and exocyclic enamides (394). Furthermore, the further utility of these sequences was demonstrated upon selection of the commercially available aminoactealdehyde dimethyl acetal as the primary amine component (Scheme 123).



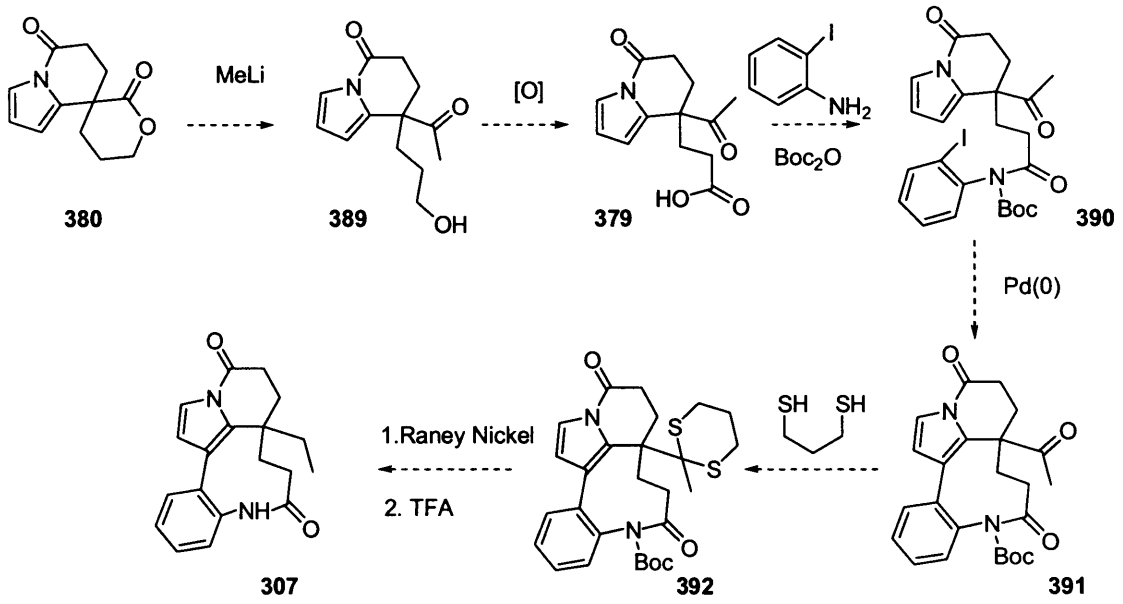
Scheme 123

The development of such a tandem reaction sequence for the construction of heavily substituted bicyclic pyrroles (395), from readily available starting materials is potentially useful since this structural motif is a common molecular scaffold found within a large variety of naturally occurring, biologically active natural products. Towards this end a simple route to the spirocyclic lactone (380), a key intermediate along a proposed pathway to the cytotoxic alkaloid N-oxo-rhazinilam (307), has been developed (Scheme 124). Unfortunately, time constraints precluded further evolution of this intermediate.



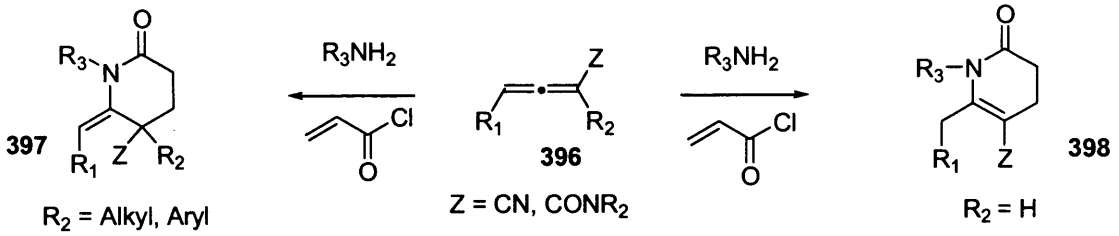
Scheme 124

Nevertheless, as already outlined in Scheme (122) it is hoped that the synthesis of N-oxo-rhazinilam from lactone (380) should proceed with relative ease.



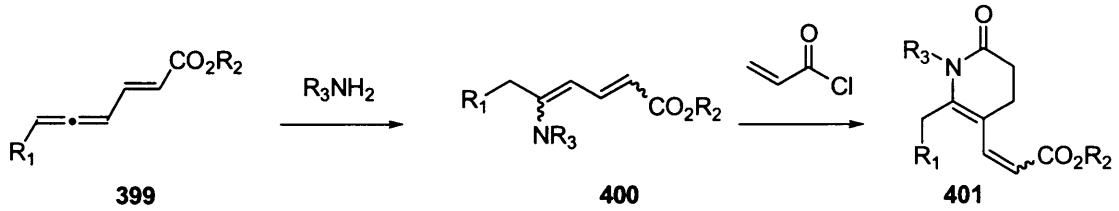
Scheme 122

By way of contrast, the application of allenic sulfoxides and sulfones to this one-pot aza-annulation chemistry proved unsuccessful due to a variety of competing side reactions taking precedence. However, it is envisaged that the selection of alternative electron deficient allenes (396), such as allenamides and allenic nitriles, in combination with a variety of substituted α,β-unsaturated carbonyl derivatives could extend this methodology and thus enable the synthesis of further functionalised heterocyclic systems such as (397) and (398) (Scheme 125).



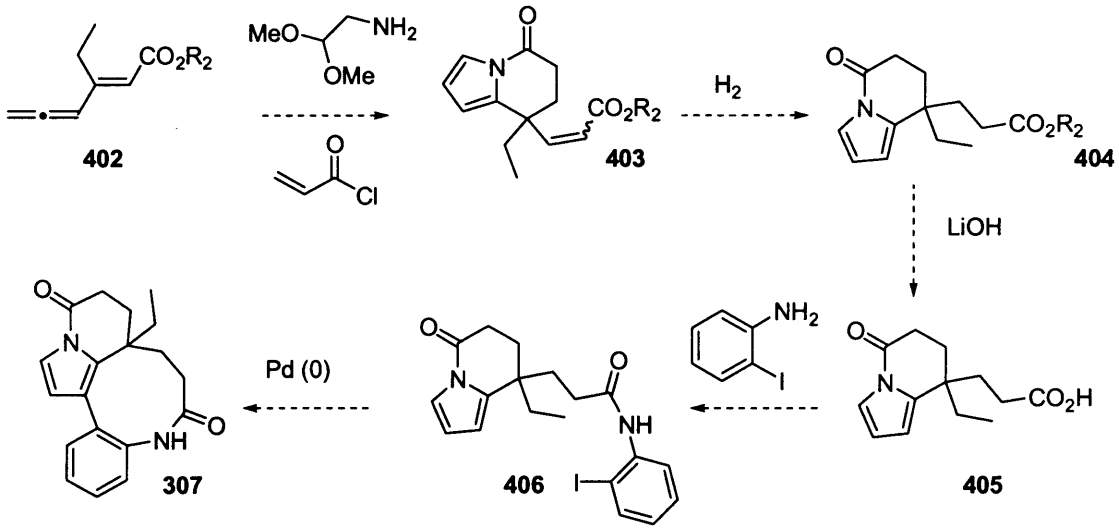
Scheme 125

Furthermore, it is anticipated that examination of the reactivity of ene-allenes (399) could also enable the expansion of this annulation methodology. Thus, as depicted in Scheme (126), addition of primary amines to the central allenic carbon of allenes (399) would lead to enamines (400), which, upon annulation with α,β- unsaturated carbonyl derivatives, could evolve to the corresponding dihydropiperidinones (401).



Scheme 126

The successful application of ene-allenes (400) to this one-pot aza-annulation chemistry would have an impact upon the total synthesis of N-oxo-rhazinilam (307). Thus, as shown in Scheme (127), the preparation of ene-allene (402) followed by a successful annulation with aminoacetaldehyde dimethyl acetal and acryloyl chloride, could provide bicyclic pyrrole (403). Reduction and then conversion of the ester to the required amide (406) *via* the acid (405), followed by Pd catalysed cyclisation could then provide the natural product (307) directly.



Scheme 127

In conclusion, this area of research has established that electron deficient allenes act as extremely useful substrates for tandem reaction sequences, enabling the regioselective synthesis of a variety of synthetically versatile and biologically relevant nitrogen containing heterocycles.

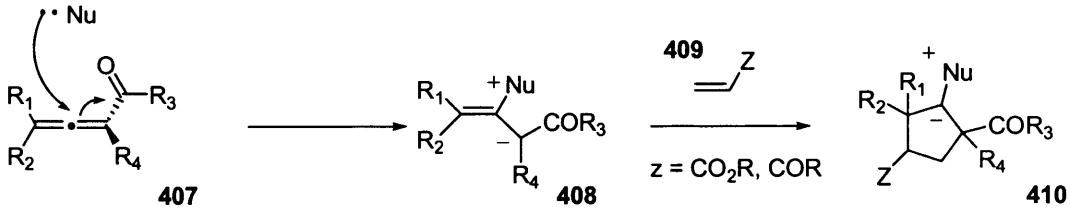
Section 2.2

Tandem Reactions (II) – Carbocyclisation of Allenic Substrates

2.2 Tandem Reactions (II)-Carbocyclisation Of Allenic Substrates

2.21 Introduction

The use of the allenic unit to enable rapid construction of highly substituted carbocyclic systems was discussed, in chapter (1), with particular reference to phosphine and amine catalysed [3+2] cycloaddition reactions of electron deficient allenes with α,β-unsaturated carbonyl compounds and other related Michael acceptors (Scheme 128).

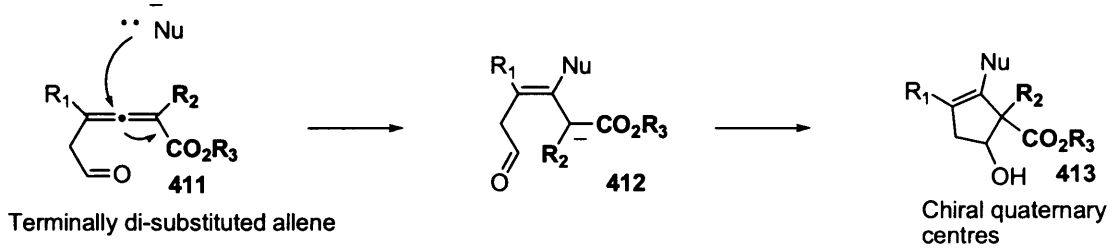


Scheme 128

The vast majority of these carbocyclisation reactions involve activation of the electron deficient allene (407) *via* addition of a nucleophile to the central allenic carbon (Scheme 128). The resulting zwitterionic species (408) undergo regioselective cycloaddition with a number of dipolarophiles (409), providing a range of substituted cyclopentanes (410). The nature of the substituents surrounding the allenic nucleus, in combination with the identity of the added nucleophile, have a profound impact upon the eventual outcome of the reactions (Chapter 1) and in consequence, this chemistry provides an efficient route for the construction of a variety of useful molecular architectures.

To our surprise however, in spite of the considerable body of research within this area of allene chemistry, it is very difficult to find related intramolecular variants. A likely explanation for the existence of this caveat is the difficulty associated with assembly of the necessary allenic precursors. Consequently, it was envisaged that the synthesis

and study of allenic esters containing an internal electrophilic site could enable the development of novel methodology for the construction of substituted carbocyclic systems. Thus, as shown in Scheme (129) the addition of nucleophiles to allenic esters (411) leading to stabilised carbanions (412) could be followed by cyclisation, providing cyclopentanols (413).

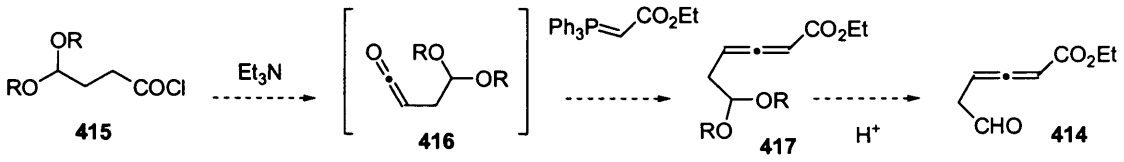


Scheme 129

Furthermore, it was envisaged that the use of highly substituted allenic esters (411) would enable the formation of cyclopentanols (413) containing chiral quaternary carbon centres.

2.22 Studies Directed Towards the Synthesis of Functionalised Allenes (411).

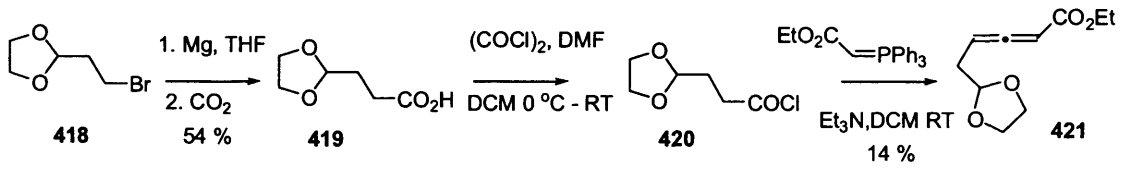
In the first instance, the synthesis and reactivity of the simple α-unsubstituted allenic ester (414) was examined. It was outlined in Chapter (1) that a plethora of methods exist for the construction of allenic esters. However the synthesis of functionalised allenes such as (414) has received minimal attention. A simple synthesis of allenic ester (414), involving the Wittig olefination of acid chloride (415) followed by acid mediated deprotection of the acetal was proposed (Scheme 130).



Scheme 130

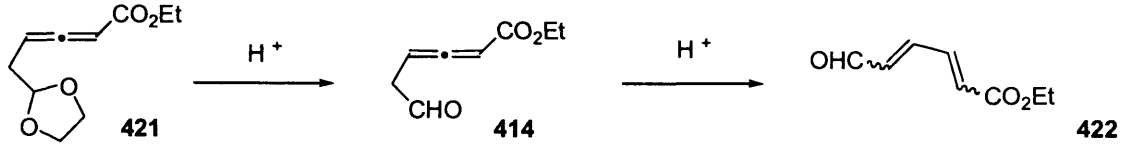
Acid chloride (420) was prepared according to the synthetic sequence shown in

Scheme (131), where in reaction of the Grignard reagent derived from the commercially available bromide (418) with CO_2 provided carboxylic acid (419) in 54 % yield. Conversion of carboxylic acid (419) to acid chloride (420) was achieved upon reaction with oxalyl chloride in the presence of a substoichiometric amount of DMF. Direct reaction of the crude acid chloride (420), with commercially available ethyl triphenylphosphoranylideneacetate, in the presence of triethylamine, provided the required allene (421), in a 14 % yield after purification of the crude compound by flash column chromatography.



Scheme 131

Disappointingly, attempts to remove the acetal-protecting group from the allene (421) failed to provide the corresponding aldehyde (414), and instead, the conjugated diene (422), derived by further isomerisation was the only component of the crude reaction mixture to be identified (Scheme 132).

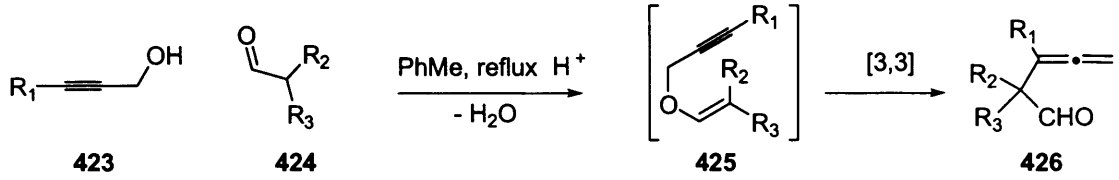


Scheme 132

Liberation of the carbonyl group in (414), would provide a strong driving force for isomerisation to the fully conjugated diene (422) and isomerisations of related allenic aldehydes, esters, ketones and amides to the corresponding conjugated dienes under acidic and basic conditions are well documented.[123] Consequently, attempts to prepare the simple δ-unsubstituted allenic ester (414) were abandoned, and alternatively the

synthesis of allenic substrates in which the troublesome double bond transposition would be precluded were investigated.

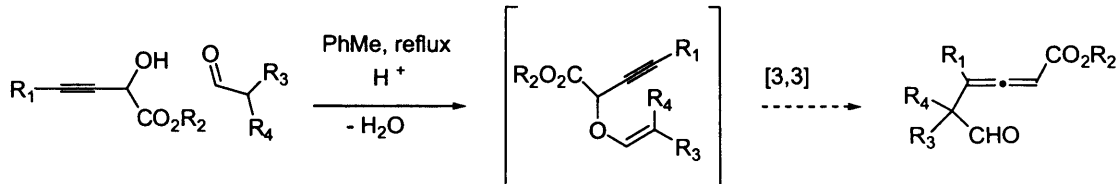
Marbet and Saucy have demonstrated that allenic aldehydes (426) can be obtained by the Claisen rearrangement of propargyl vinyl ethers (425), themselves prepared *in situ* by the acid catalysed condensation of readily prepared propargylic alcohols (423) and aldehydes (424) (Scheme 133).[124]



423 **424** **425** **426**

Scheme 133

Within this framework, it was envisaged that selection of suitably substituted propargylic alcohols (427) in combination with aldehydes (424), would enable the preparation of propargyl vinyl ethers (428), which upon [3,3] sigmatropic rearrangement would furnish the required δ-substituted allenic esters (429) (Scheme 134).



427 **424** **428** **429**

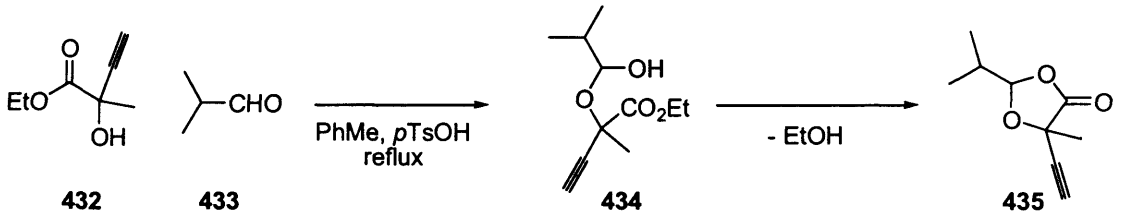
Scheme 134

This proposed route to δ-substituted allenic esters (429) (Scheme 134) appeared attractive due to its convergent nature and it was anticipated that the versatility of this approach would be exemplified upon simple variation of both the alcohol and aldehyde components. The ready availability of substituted propargylic alcohols (427) and α-substituted aldehydes (424) also added to the appeal of this route.

In an initial experiment, propargylic alcohol (432) was prepared by the addition of a solution of ethynyl magnesium bromide (430) in THF,[125] to commercially available ethyl pyruvate (431) (Scheme 135).

Scheme 135

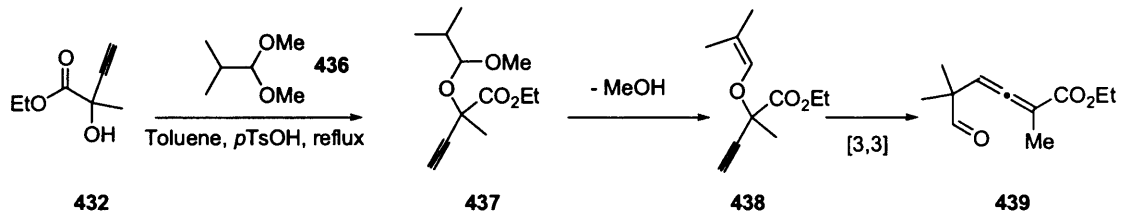
A sample of the freshly prepared alcohol (432) was reacted with isobutryaldehyde (433) and TLC analysis indicated that the starting material had been consumed within 24 hrs. Disappointingly, concentration of the reaction mixture, followed by ^{1}H NMR analysis of the resulting crude oil, showed only a trace quantity of the desired allenic ester and the major component of the reaction mixture was later identified as the "lactone" (435) (Scheme 136).



Scheme 136

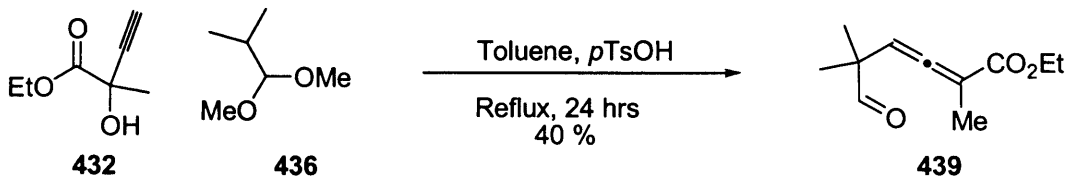
A plausible mechanistic rationale accounting for the formation of lactone (435) is shown in Scheme (136), whereby addition of alcohol (432) to aldehyde (433) to give hemiacetal (434) could be followed by intramolecular transesterification. Two methods of combating this competitive lactonisation process were considered. The first involved replacement of the ethyl ester moiety in alcohol (432) with a more sterically demanding group, such as the t-butyl or isopropyl congener, on anticipation that the increased size of such esters would reduce the rate of this competitive ring closure,[126] and hence, dehydration of hemiacetal (434) to the required propargyl vinyl

ethers (438) could proceed (Scheme 137). Alternatively, replacement of the aldehyde with its derived dimethyl acetal (436) would allow the reaction to proceed *via* a slightly different pathway, wherein acid catalysed condensation of alcohol (432) with acetal (436) would, in this instance, provide the mixed acetal (437) instead of the problematic hemiacetal (434) (Scheme 137).



Scheme 137

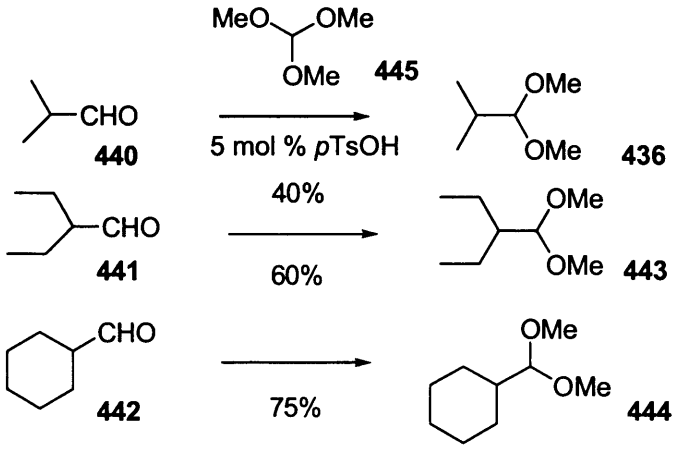
Loss of methanol from the ether (437) would then provide propargylic vinyl ether (438) for [3,3] sigmatropic rearrangement to give the desired allenic ester (439). Due to the ease with which acetals are obtained from their parent aldehydes, the reaction of propargylic alcohol (432) with the dimethyl acetal of isobutryaldehyde was examined. Propargylic alcohol (432) and acetal (435) were heated at reflux in dry toluene in the presence of a substoichiometric amount of *para*-toluenesulfonic acid and pleasingly, after concentration of the reaction mixture, crude ^{1}H NMR and ^{13}C NMR analysis indicated that a significant quantity of the allene (439) was present. Purification of this crude oil by flash column chromatography provided the pure allenic ester (439), in 40 % yield (Scheme 138).



Scheme 138

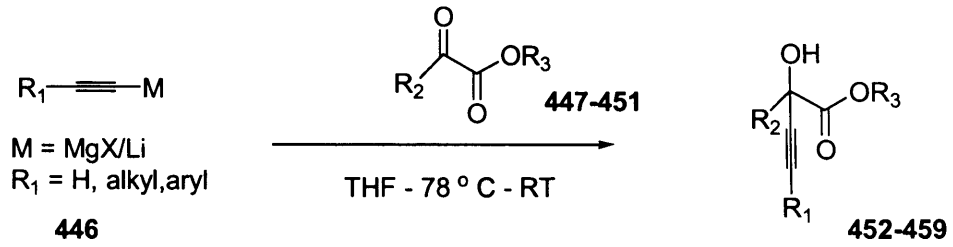
In order to examine the potential of applying this methodology to the synthesis of a variety of substituted allenic esters, a number of propargylic alcohols (452-459) and

acetals were prepared. The acetals (443) and (444) were obtained, in similar fashion to the previously described acetal (436) by the simple solvent free *para*-toluenesulfonic acid catalysed reaction of the corresponding aldehydes (440-442) with trimethyl orthoformate (445) (Scheme 139).



Scheme 139

Terminally un-substituted propargylic alcohols (452-457) were prepared by the reaction of ethynylmagnesium bromide with a range of commercially available pyruvic acid esters (447-451), while terminally substituted alcohols (458-459) were prepared by lithiation of the commercially available acetylenes followed by low temperature reaction of the resulting acetylides (446) with methyl and pyruvates (447-451) (Scheme 140, Table 5).



Scheme 140

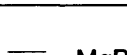
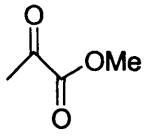
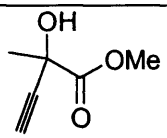
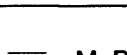
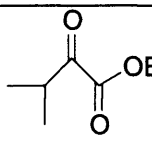
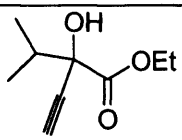
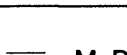
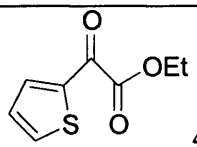
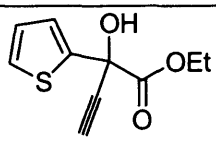
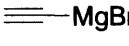
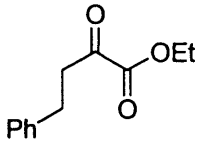
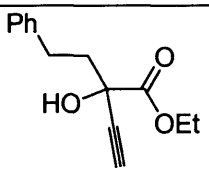
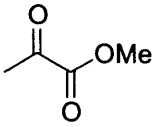
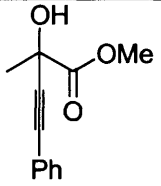
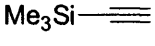
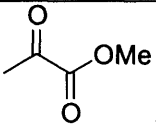
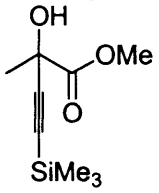
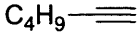
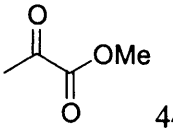
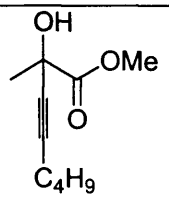
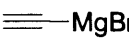
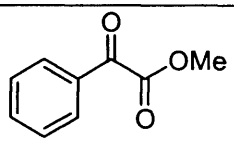
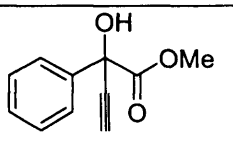
Acetylene	Pyruvate (447-451)	Alcohol (452-459)	Isolated Yield (%)
	 447	 452	43
	 448	 453	78
	 449	 454	48
	 450	 455	63
	 447	 456	88
	 447	 457	62
	 447	 458	67
	 451	 459	70

Table 5

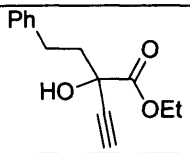
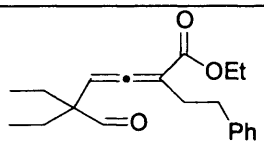
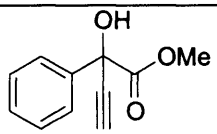
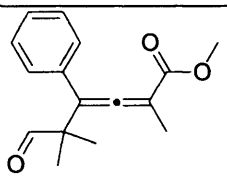
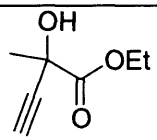
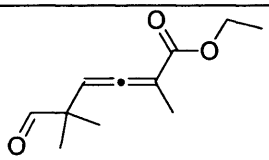
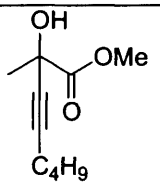
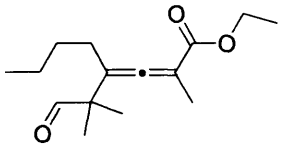
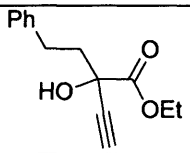
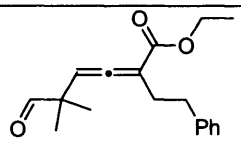
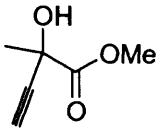
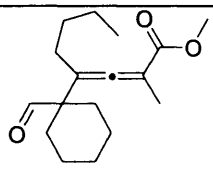
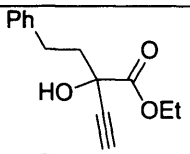
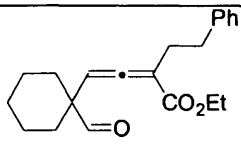
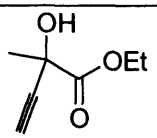
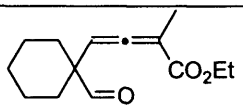
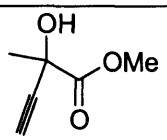
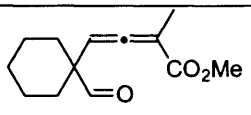
Entry	Acetal	Alcohol	Allene (460-468)	Isolated yield (%)
1	443		 460	35
2	436		 461	32
3	436		 462	40
4	436		 463	27
5	444		 464	25
6	444		 465	24
7	444		 466	32
8	444		 467	26
9	444		 468	41

Table 6

Gratifyingly, the reactions of propargylic alcohols (452-459) and acetals provided a variety of the expected allenic esters (460-468) (Table 6), which were isolated in high purity by flash column chromatography and showed a reasonable level of stability towards handling and storage.

As seen in Table (6), the described methodology was successful with both terminally substituted (458-459) and terminally un-substituted propargylic alcohols (452-457), enabling the synthesis of both tetra and tri-substituted allenes respectively.

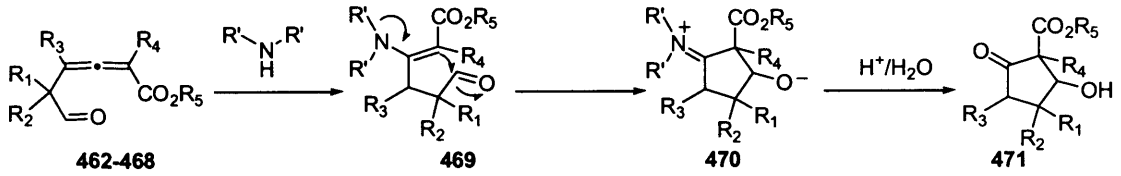
The preparation of more elaborate allenic structures proved less successful. Thus, reaction of TMS-substituted propargylic alcohol (457) with acetal (436) gave only trace quantities of the desired silyl substituted allene (from ^{1}H NMR analysis of the crude product), and attempts to purify this allenic ester failed, with only small quantities of impure material being recovered in all cases. Aryl substituted propargylic alcohols (459) and (454) also failed to provide any of the corresponding aryl substituted allenes.

2.23 Tandem Enamine Formation Cyclisation

With a successful preparation of allenic esters (460-468) in hand, studies towards the development of novel carbocyclisation methodology commenced.

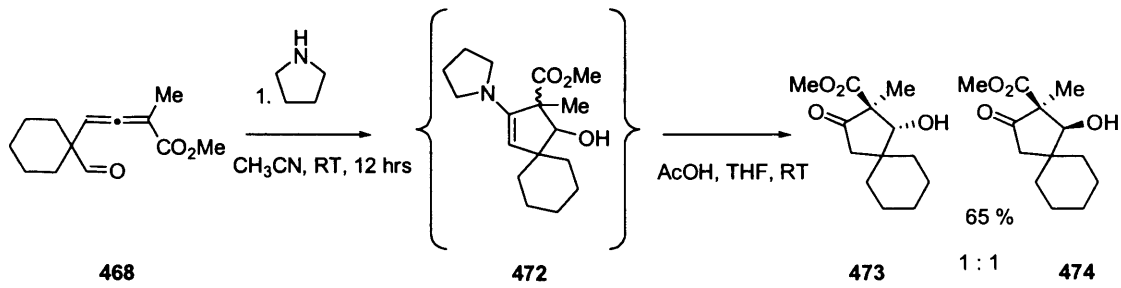
In Section (2.1), the facile regioselective formation of vinylogous amides and urethanes *via* the addition of primary amines to electron deficient allenes was described. In an attempt to build upon the principles learnt from these initial studies, the reaction of allenic esters (460-468) with amines was investigated. It was envisaged that in this instance, addition of amines to the central sp hybridised carbon atom of allenes (460-468) would yield the corresponding vinylogous urethanes (469),

which could undergo cyclisation leading to iminium ions (470) which upon hydrolysis would then yield the substituted β-hydroxy cyclopentanones (471) (Scheme 141).



Scheme 141

In order to test this hypothesis a solution of freshly prepared allenic ester (468) was reacted with one equivalent of pyrrolidine at room temperature (Scheme 142). After stirring for 12 hrs, TLC analysis indicated that the starting material had been consumed and replaced with a polar compound. Analysis of the crude mixture by ^{1}H NMR spectroscopy provided evidence for the presence of enamine (472). This 'crude enamine' was taken up in THF and treated with aqueous acetic acid (10 %). Pleasingly, subsequent work up and purification of the resulting crude oil by flash column chromatography provided two diastereomeric cyclopentanones (473 and 474) in a combined yield of 65 % . The diastereomeric ratio was later determined to be approximately 1:1 based upon integral measurements in the crude ^{1}H NMR spectrum.



Scheme 142

In light of this positive result, the reactivity of tri-substituted allenic esters (463) & (464) towards pyrrolidine was examined (Table 7). As depicted in Table (7), allenes (463) & (464) both underwent carbocyclisation upon reaction with pyrrolidine,

providing the corresponding cyclopentanones (475) & (476) and, once again, the compounds were isolated as mixtures of diastereoisomers with little or no selectivity observed.

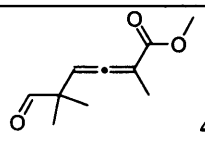
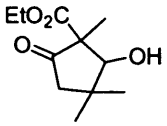
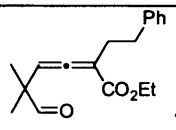
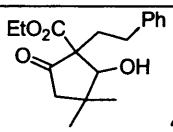
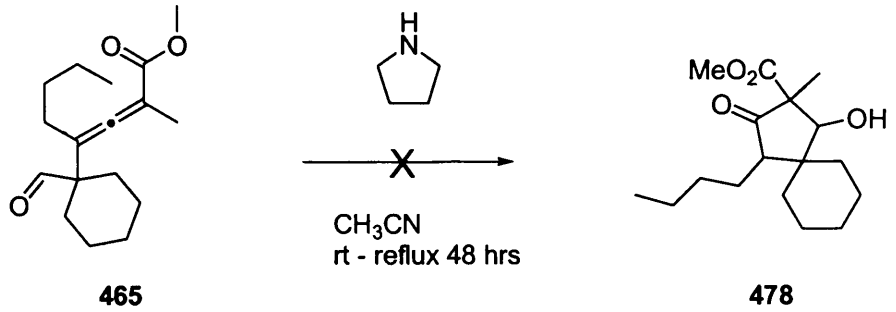
Allene	Carbocycle	Isolated Yield %
 463	 475 dr ~ 1:1	45
 464	 476 dr ~ 1:1	40

Table 7

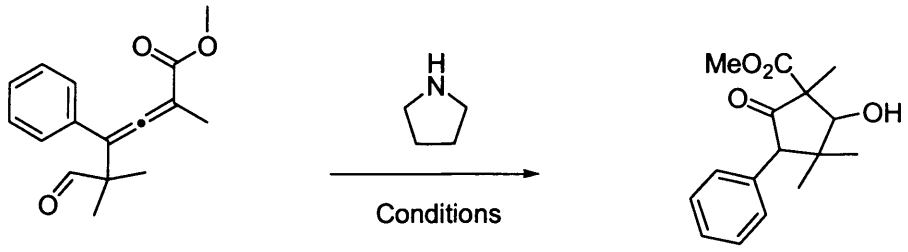
Attempts to apply tetra-substituted allenic esters (461) and (465) to the described carbocyclisation protocol proved less successful. Addition of pyrrolidine to a solution of allenic ester (465) failed to provide any of the desired cyclopentanone (478) after 24 hrs stirring at room temperature. Analysis of the reaction mixture by TLC indicated that the starting material remained unchanged and attempts to induce carbocyclisation by increasing the reaction temperature also failed. Heating a solution of allene (465) and pyrrolidine in acetonitrile at reflux for 48 hrs, followed by aqueous work up and crude ^{1}H NMR analysis showed that no carbocyclisation had occurred and the starting material (465) remained largely unchanged (Scheme 143).



465 **478**

Scheme 143

In similar vein, attempts to convert the phenyl substituted allenic ester (461) into the corresponding cyclopentanone (479) also failed. Yet again, only starting material and products of decomposition were observed within the crude mixtures after extended reaction times and elevated reaction temperatures. Addition of a Lewis acid and changes in the reaction solvent also failed to promote carbocyclisation (Scheme 144 and Table 8).



461 **479**

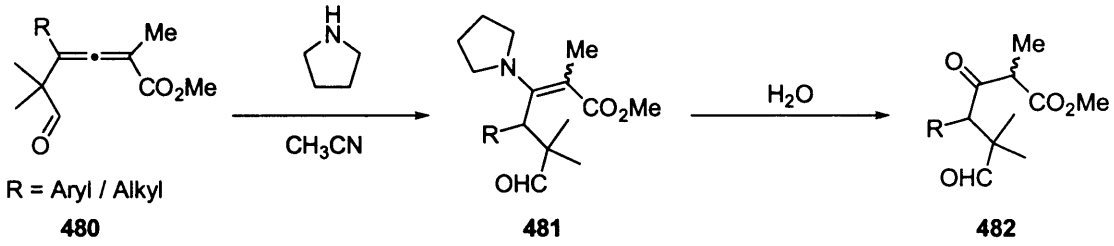
Scheme 144

Solvent	Temperature	Additive	Observations
CH_3CN	Reflux	None	SM recovered
CH_3CN	RT	$ZnBr_2$	SM recovered
CH_3CN	Reflux	$ZnBr_2$	SM + Complex mixture
DCM	RT	None	SM recovered
DCM	Reflux	None	SM recovered
DMSO	RT	None	SM recovered
DMSO	$80\ ^0C$	None	SM + Complex mixture

Table 8

If addition of pyrrolidine to allenic esters (480) led to the formation of vinylogous urethanes (481), hydrolysis of the crude reaction mixtures would lead to the formation

of the β-ketoesters (482) (Scheme 145). However, only starting material was identified within these crude reaction mixtures with no evidence for the presence of β-ketoesters (482) or products of their subsequent aldol reactions ever being observed.



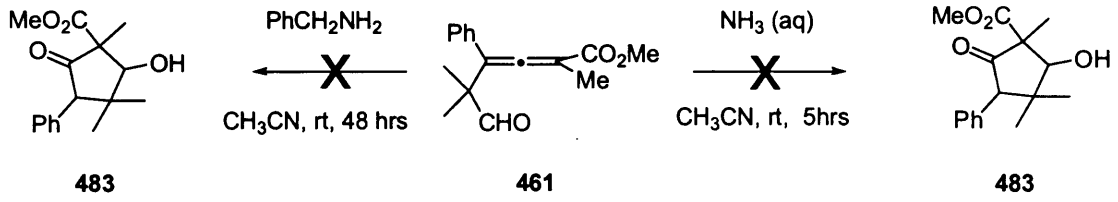
Scheme 145

Upon construction of a molecular model of tetra-substituted allene (461), it becomes apparent that a large level of steric crowding exists both above and below the plane of the central allenic carbon and in such a congested environment, and the approach of pyrrolidine to the central carbon atom may well be impeded thus preventing vinylogous urethane formation.

It was then proposed that selection of sterically less demanding amines would enable vinylogous urethane formation to proceed, permitting the preparation of substituted cyclopentanone (483) from tetra-substituted allene (461) (Scheme 146). Therefore, a solution of allenic ester (461) was treated with an aqueous solution of ammonia and stirred at room temperature whilst the reaction progress was monitored by TLC analysis, although after 6 hrs no starting material was observed, analysis of the crude reaction mixture by ^{1}H NMR spectroscopy indicated that none of the desired cyclopentanone (483) was present, and instead a highly complicated mixture of numerous components was observed (Scheme 146).

Replacement of ammonia with benzylamine led to the very slow consumption of allenic ester (461). After a prolonged reaction time the reaction mixture was worked up and analysed by ^{1}H NMR spectroscopy, and disappointingly, once again none of

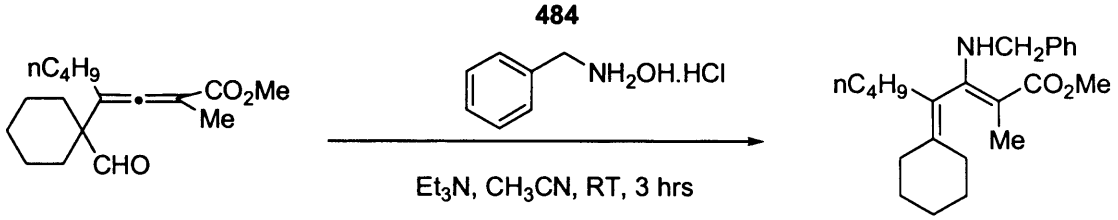
the desired cyclopentanone (483) was observed within the crude mixture. Instead, a complicated mixture of components was observed and all attempts to isolate and identify any of these proved fruitless.



483 **461** **483**

Scheme 146

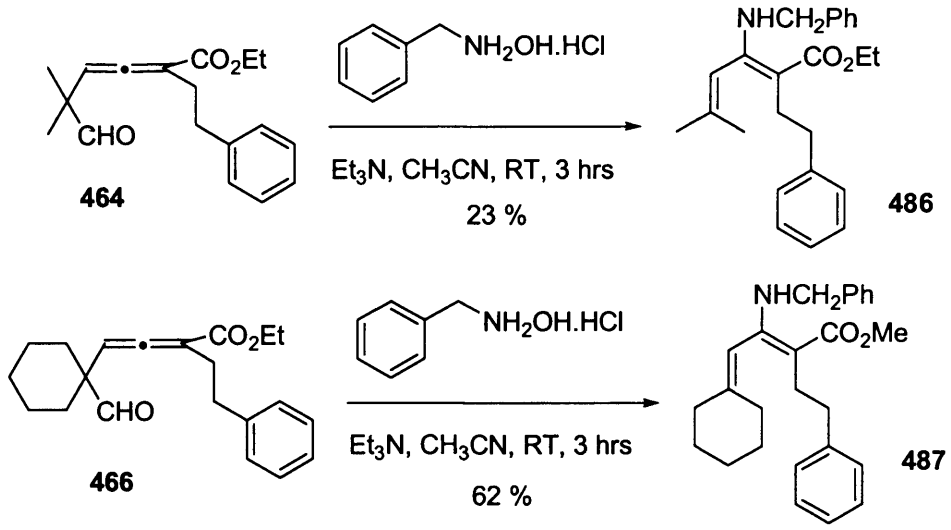
Interestingly, selection of N-benzylhydroxylamine (484) led to allenic ester (465) being consumed within 3 hrs at room temperature. Aqueous work up of the reaction mixture followed by flash column chromatography of the resulting crude oil led to the isolation of a new compound, identified as the aza-substituted diene (485), with its stereochemistry established by NMR NOE studies (Scheme 147).



465 59 % **485**

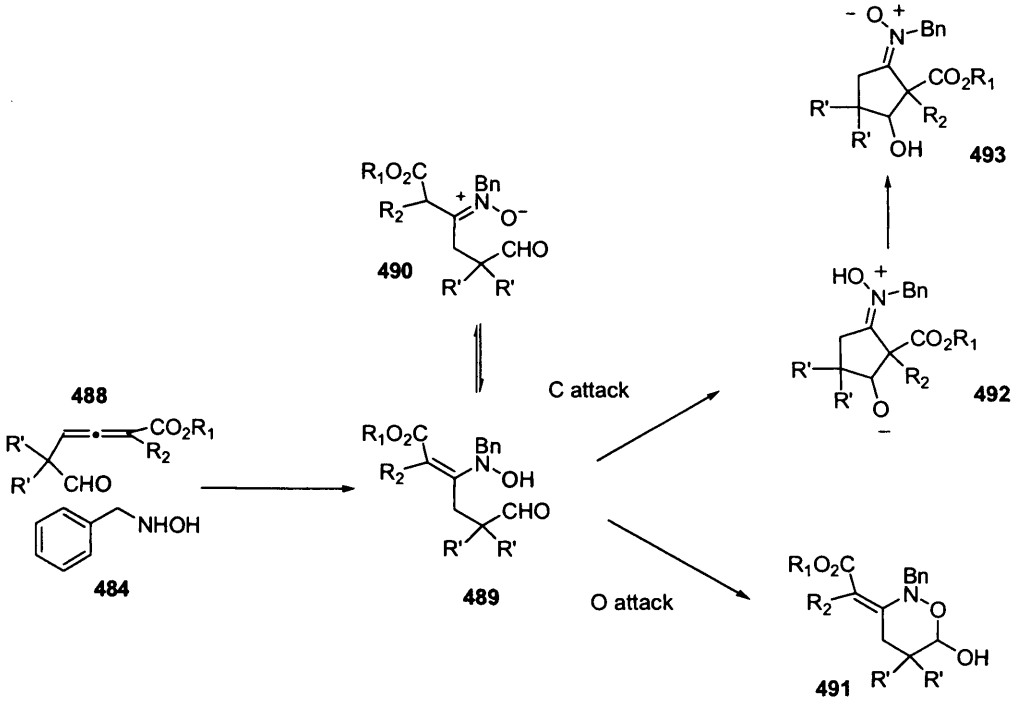
Scheme 147

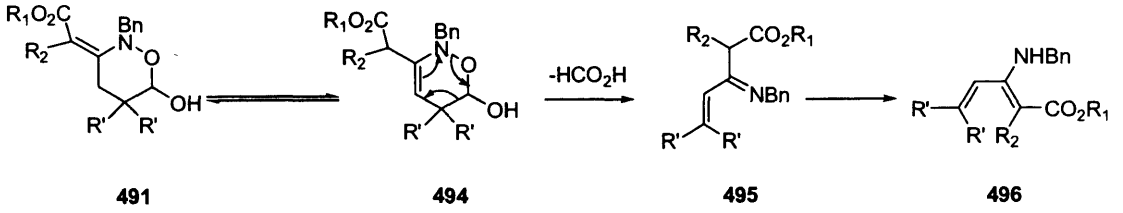
Reaction of tri-substituted allenes (464) and (466) with N-benzylhydroxylamine hydrochloride (484) in the presence of Et_3N also provided the corresponding aza-substituted dienes (486) and (487) (Scheme 148).



Scheme 148

A possible mechanistic rationale for the unexpected formation of dienes (485-487) is outlined in Scheme (149). Thus, after the nucleophilic addition of N-benzyl hydroxylamine (484) to allenes (488) to give (489), the reaction can proceed *via* two distinct mechanistic pathways. Cyclisation through the oxygen atom of the nucleophilic hydroxylamine would provide cyclic "lactol" like intermediates (491) whereas attack through the nucleophilic carbon atom would presumably lead to cyclic nitrones (493) *via* (492) (Scheme 149).





491 494 495 496

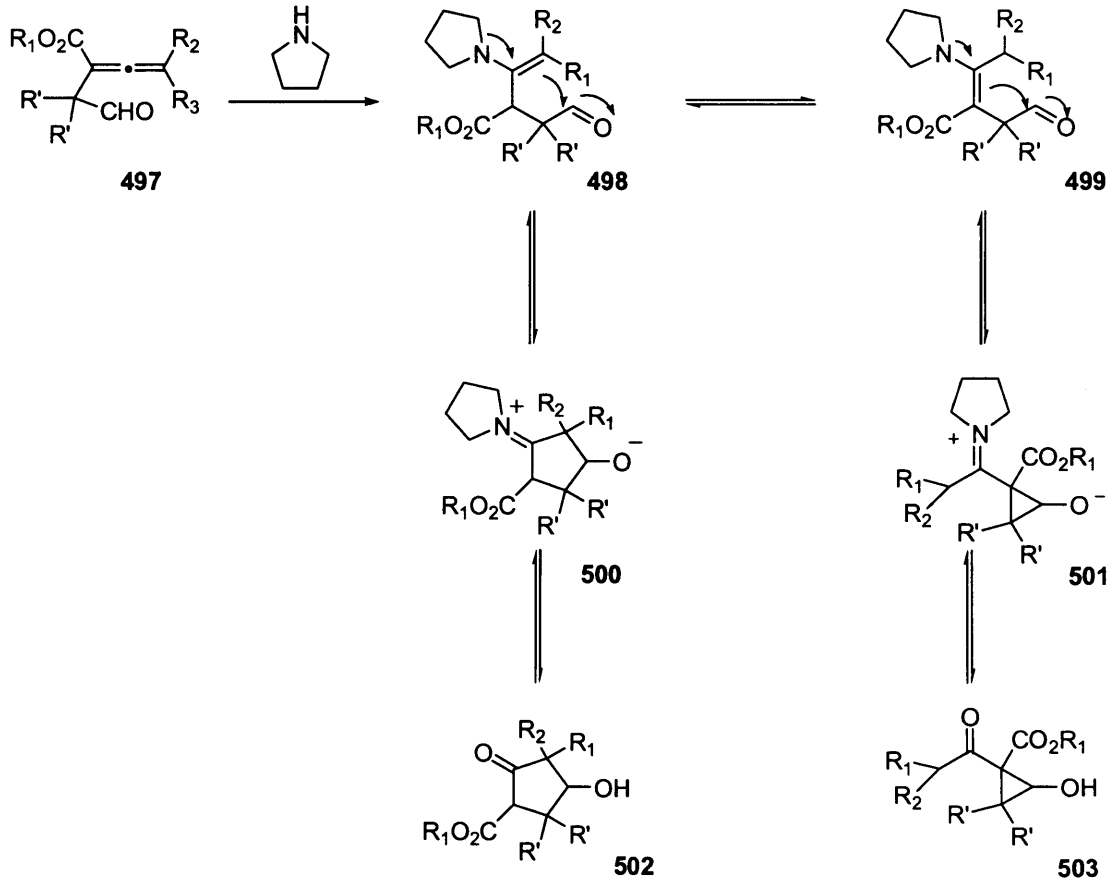
Scheme 149

Double bond isomerisation in (491) leading to (494) followed by retrocycloaddition with liberation of formic acid would provide conjugated imines (495), which upon tautomerisation would give the observed dienes (496).

It is interesting to note that in this instance cyclisation onto the aldehyde through oxygen to give the six membered cyclic intermediates (491) would occur in preference either to tautomerisation to acyclic nitrone (490) or cyclisation through the nucleophilic carbon atom of the vinlyogous urethane to give the corresponding five membered cyclic systems (492). The high nucleophilicity of the oxygen lone pair as a consequence of the α effect, coupled with the irreversible nature of the final step (elimination of formic acid) would be the most probable explanations for the formation of the conjugated dienes (496). The observed stereochemical outcome of these reactions can be explained by the proposition that the isomer in which carbonyl and amino groups are orientated cis to each other is favoured on thermodynamic grounds due to the formation of an intramolecular hydrogen bonding interaction in this geometry. [127]

Despite the potential for capitalising upon this serendipitous discovery by developing novel tandem reaction sequences using the functionalised dienes (496) as key intermediates, it was decided that the development of the novel carbocyclisation strategy should take precedent. Consequently, it was reasoned that nucleophilic

addition of amines to allenes of type (497) would lead to vinylogous urethanes (499) *via* isomerisation of the initially formed enamines (498) and if isomerisation of enamines (498) to vinylogous urethanes (499) was slower than cyclisation of these more reactive species onto the pendant aldehydes, carbocyclic systems (502) could be obtained as shown in Scheme (150).

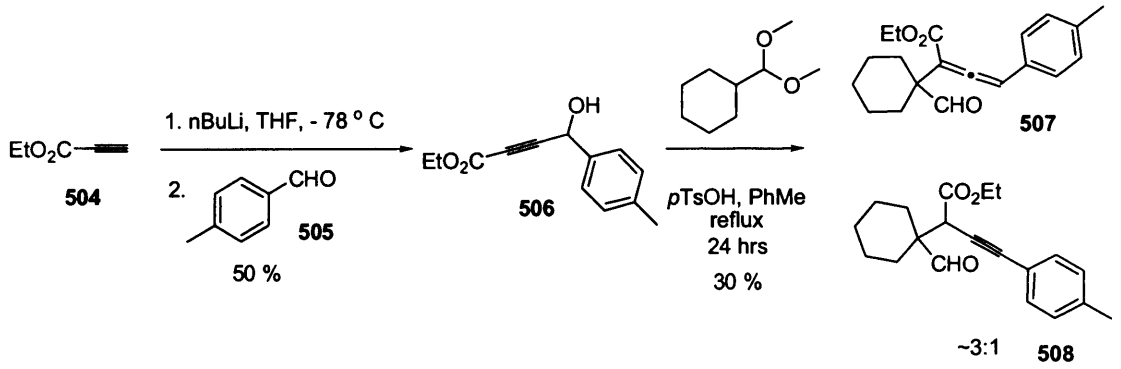


Scheme 150

Alternatively, if the enamine (498) and vinylogous urethane (499) were to exist in equilibrium, cyclisation *via* the enamine (498) (5-*exo*-*trig*) might still be favoured as the reaction through (499) (3-*exo*-*trig*) is potentially reversible and would lead to the strained cyclopropanol (503).

In order to test this hypothesis, the synthesis of allenic ester (507), *via* the reaction of propargylic alcohol (506) and acetal (444), was attempted. Alcohol (506) was

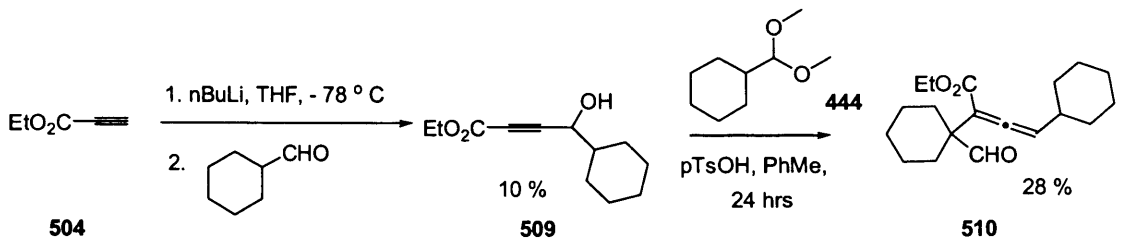
obtained *via* the low temperature reaction of lithiated ethyl propiolate (504) with *para*-tolualdehyde (505) (Scheme 151).



Scheme 151

Interestingly, concentration of the crude reaction mixture and purification of the resulting oil by flash column chromatography provided an inseparable mixture of the desired allene (507) and undesired alkyne (508) in a combined yield of 30 % and ratio of approximately 3 : 1 as determined by ^{1}H NMR. Alkyne (508) could be formed by transposition of one allenic double bond out of conjugation with the ester group and into conjugation with the aryl moiety under the high temperature and acidic conditions of the reaction medium.

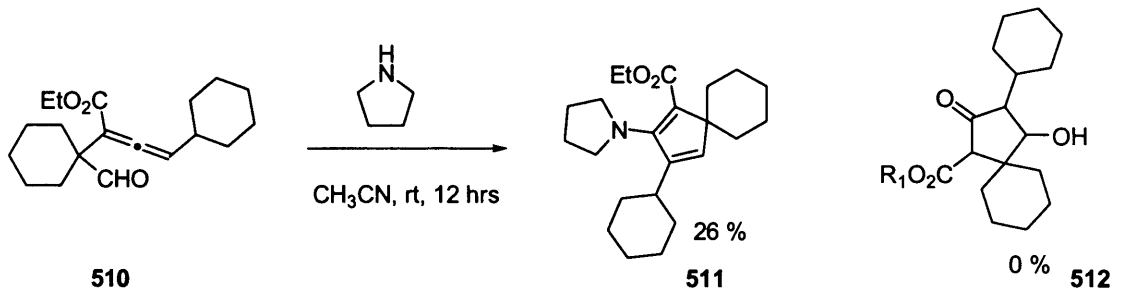
In light of this result, the synthesis of the allenic ester (510) was attempted. It was envisaged that replacement of the aryl moiety with the simple aliphatic cyclohexyl group would prevent double bond migration due to the lack of conjugation obtained in the resulting alkyne (Scheme 152).



Scheme 152

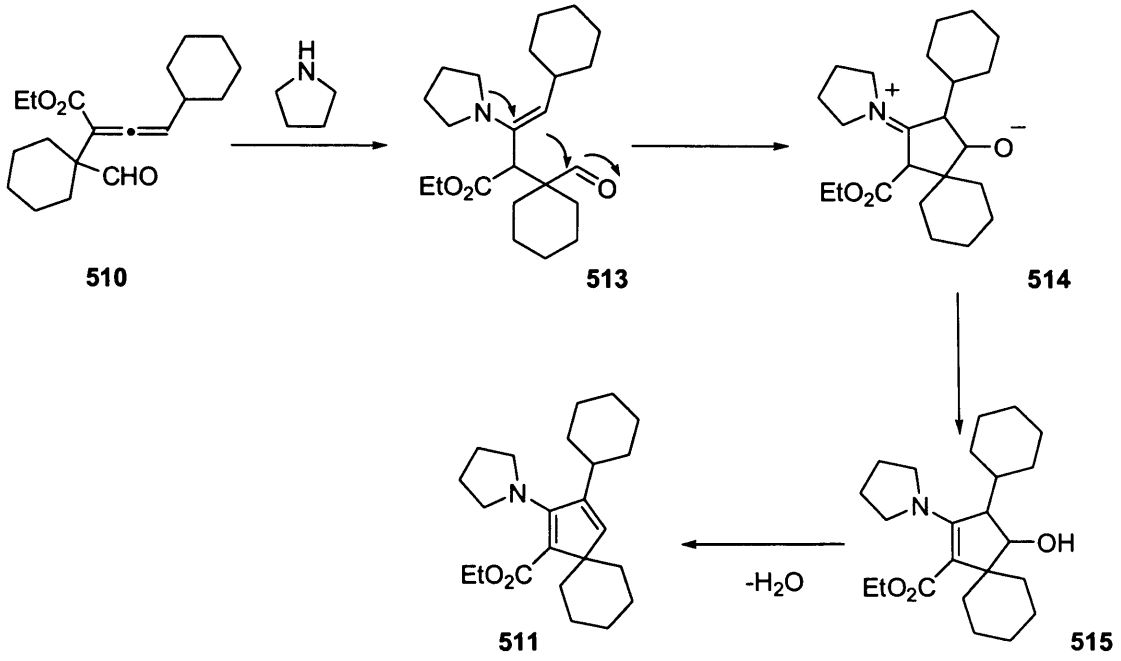
Reaction of the propargylic alcohol (509), prepared from propiolate (504) and cyclohexanecarboxyaldehyde, and acetal (444) provided the required allenic ester (510), isolated in 28 % yield, with none of the corresponding alkyne observed.

With a pure sample of allene (510) in hand, amine-induced carbocyclisation was attempted. In the event, treatment of a solution of allene (510) with one molar equivalent of pyrrolidine at room temperature did not give any of the expected cyclopentanone (512). However, cyclopentadiene (511) was isolated in 26 % yield after purification of the crude oil by flash column chromatography (Scheme 153).



Scheme 153

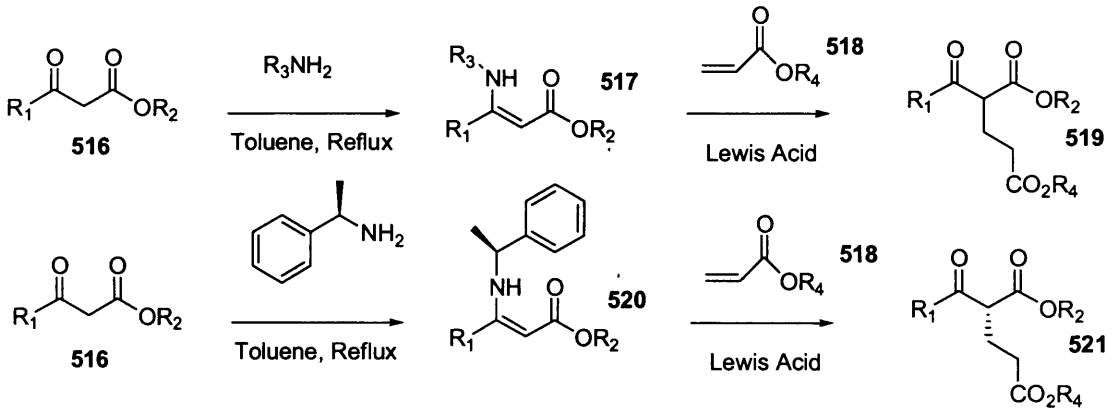
The mechanism proposed for the formation of diene (511) is in scheme (154), where nucleophilic addition of pyrrolidine to allene (510) leading to the initial enamine (513) is followed by cyclisation providing alcohol (515), which upon elimination of water would evolve to the conjugated diene (511).



Scheme 154

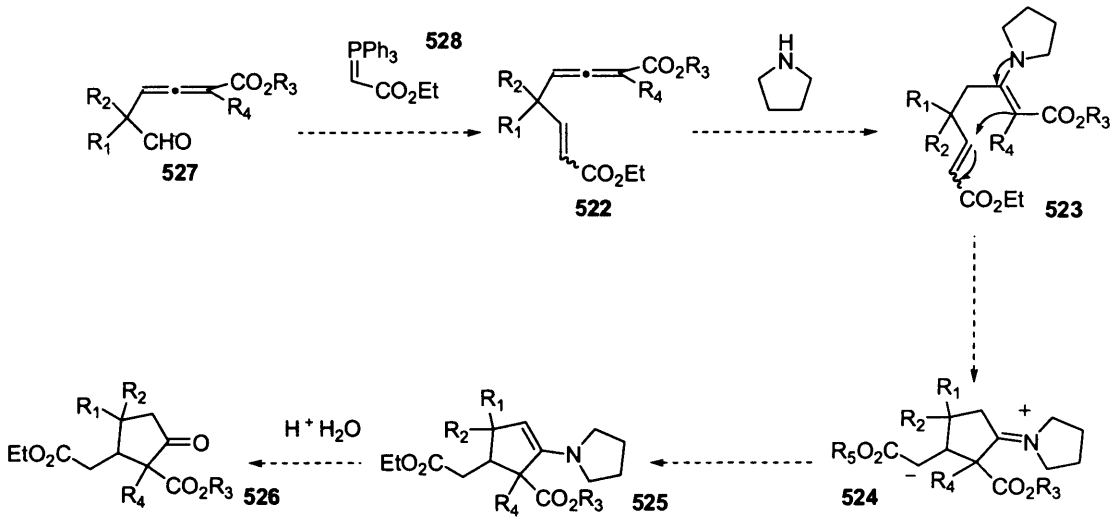
2.24 Tandem Enamine Formation Michael Cyclisation

Vinylogous urethanes (517), derived from dicarbonyl compounds (516), have been shown to undergo Michael addition to α,β-unsaturated esters (518) providing β-ketoesters (519) under either high pressure or Lewis acid catalysis. Asymmetric variants making use of readily available chiral amines yielding the same β-ketoesters (521) in excellent enantiomeric excesses have also been reported (Scheme 155). [128]



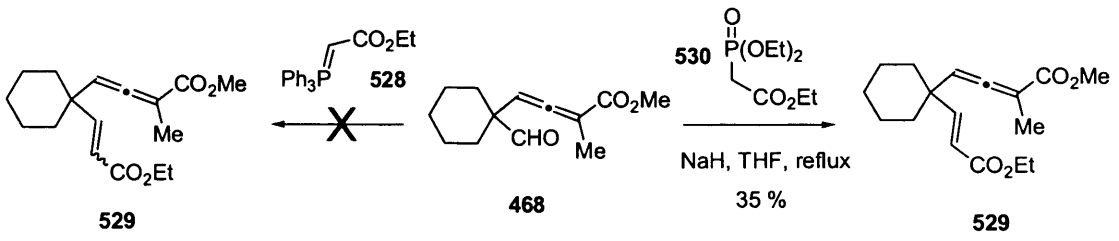
Scheme 155

In similar fashion, the preparation of suitably tethered allenic esters (522) could enable the development of a novel one pot tandem reaction sequence involving addition of an amine to allenes (522) generating vinylogous urethanes (523) followed by intramolecular Michael cyclisation affording carbocyclic systems (526) *via* enamines (525) (Scheme 156). Moreover, it was assumed that the allenic esters (522) required to embark upon this study could be readily obtained from the previously prepared allenic aldehydes (527) *via* simple Wittig olefination with commercially available phosphoranes (528) (Scheme 156).



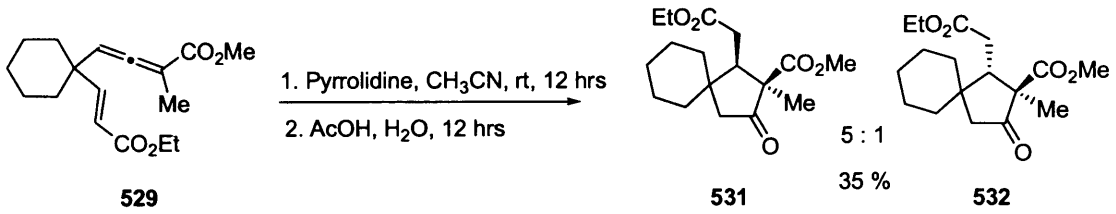
Scheme 156

However, attempts to prepare allene (529) from allenic aldehyde (468) *via* a Wittig reaction with the commercially available phosphorane (528) failed to provide any of the desired product under a range of reaction conditions varying from room temperature in DCM to refluxing in toluene (Scheme 157). Gratifyingly, replacement of phosphorane (528) with the more reactive anion derived from phosphonate (530) provided the desired α,β-unsaturated ester (529), isolated as the trans isomer in a 35 % yield after purification of the crude compound by flash column chromatography (Scheme 157) .



Scheme 157

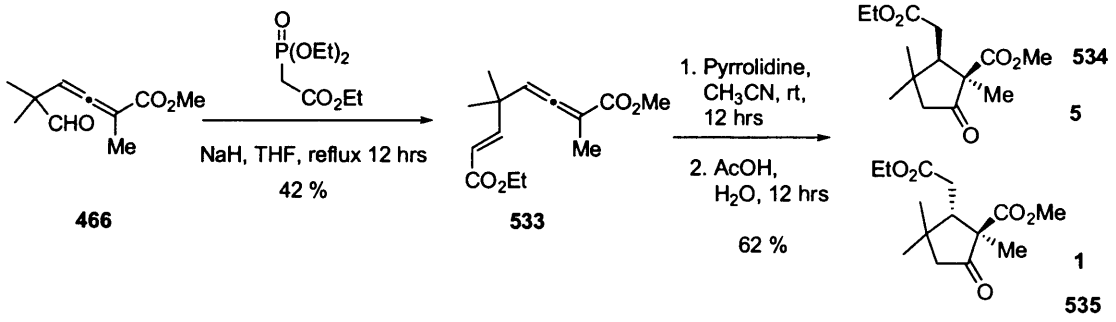
Pleasingly, reaction of allene (529) with pyrrolidine at room temperature followed by mild acidic work up, provided the desired cyclopentanones (531) and (532) as a diastereomeric mixture (Scheme 158).



529 531 532

Scheme 158

Analysis of a pure sample of the diastereomeric cyclopentanones (531) and (532) by NOE studies enabled identification of the major diastereoisomer. Subsequent integration of signals in the proton resonance spectrum of the crude mixture established the diastereomeric ratio to be approximately (5:1) in favour of (531). This tandem enamine formation-Michael cyclisation sequence was also successful with allenic ester (533), prepared in an analogous fashion to ester (529) (Scheme 159).



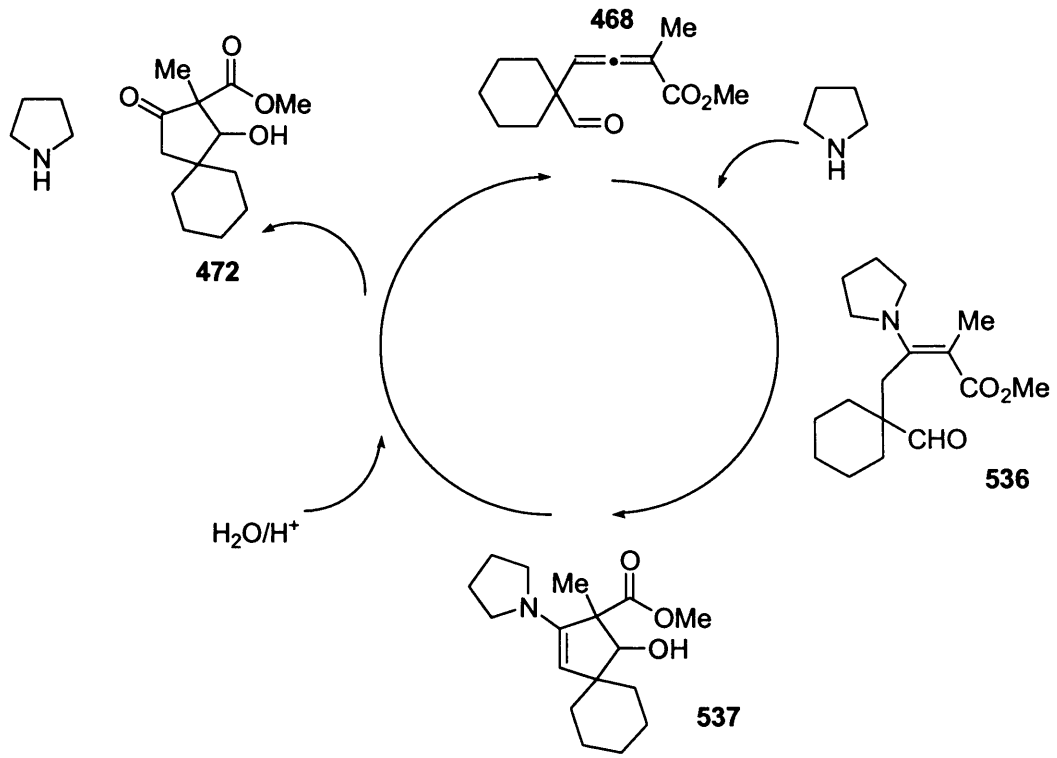
Scheme 159

Once again, a mixture of two inseparable diastereomeric cyclopentanones (534 and 535) was obtained in a combined yield of 62 % and the diastereomeric ratio was shown to be (5:1) in favour of (534), from ^{1}H NMR NOE experiments.

2.25 Organocatalysed Carbocyclisation Of Allenic Substrates

In recent years, the application of small organic molecules as catalysts for a variety of chemical transformations has developed into a rapidly growing field. In particular, the application of the amino acid *l*-proline for aldol and michael-aldol reactions has enabled the stereoselective synthesis of a variety of complex cyclic and acyclic systems in high yield using inexpensive reagents under environmentally benign

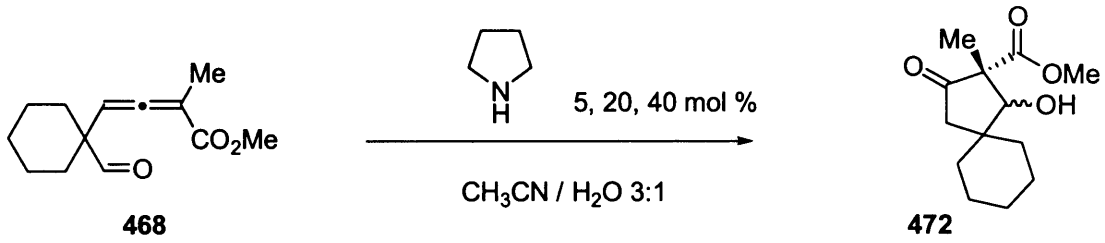
reaction conditions.[129] Moreover, the design and development of related catalysts has had a huge impact upon modern synthetic organic chemistry, with catalytic asymmetric Diels-Alder, Friedel-Crafts and a number of other fundamentally important reactions appearing in the literature in recent years.[130] It was anticipated that the development of catalytic variants of the previously described carbocyclisation reactions would add further value to this chemistry. In order to achieve this goal the presence of water within the reaction medium would clearly be essential (Scheme 160). Addition of a substoichiometric amount of pyrrolidine to allenic ester (468) would lead to the formation of the intermediate enamine (537) and, the presence of water would enable the hydrolysis of enamine (537) to cyclopentanone (472) to occur *in situ*, releasing pyrrolidine to complete another catalytic cycle.



Scheme 160

In order to test this hypothesis three experiments were conducted. Solutions of allenic ester (468) in acetonitrile/water mixtures (approximately 3:1) were treated with 0.05, 0.20 and 0.40 equivalents of pyrrolidine respectively. The reactions using 0.2 and 0.4

equivalents of pyrrolidine were complete within 12 hrs at room temperature, with no starting material detected by TLC. However, the reaction employing 0.05 equivalents proceeded at a lower rate, with the starting material consumed after a 24 hour period at room temperature (Scheme 161 and Table 9).



Scheme 161

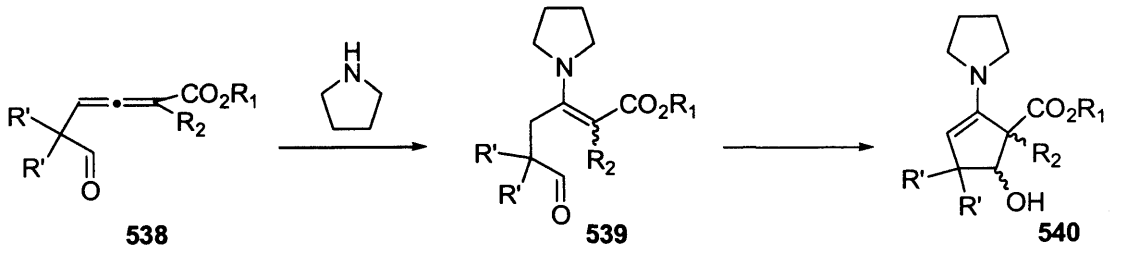
Catalyst Loading (mol %)	Reaction Time (Hrs)	Isolated Yield (%)	Diastereomeric Ratio
5	24	38	6 : 1
20	12	42	5.6 : 1
40	12	50	1.6 : 1

Table 9

Pleasingly, the carbocyclisation reaction was successful using, 5, 20 and 40 mol % of pyrrolidine, providing the expected cyclopentanone (472) in 38, 42 and 50 % isolated yield respectively. More importantly, and of particular interest, was the observed increase in diastereoselectivity upon decreasing the quantity of catalyst. The overall increase in the diastereoselectivity observed could be attributed to the presence of water, but, this does not explain the steep increase in selectivity upon decreasing the quantity of catalyst.

The diastereoselectivity of the carbocyclisation reaction would be largely controlled by two independent steps. Primarily, the stereochemistry of the vinylogous urethane (539), formed by the addition of the amine to the allenic ester (538) would control one

stereocentre, whilst steric constraints in the five membered transition state are likely to control the stereochemistry at the other stereocentre in cyclopentanol (540) (Scheme 162).

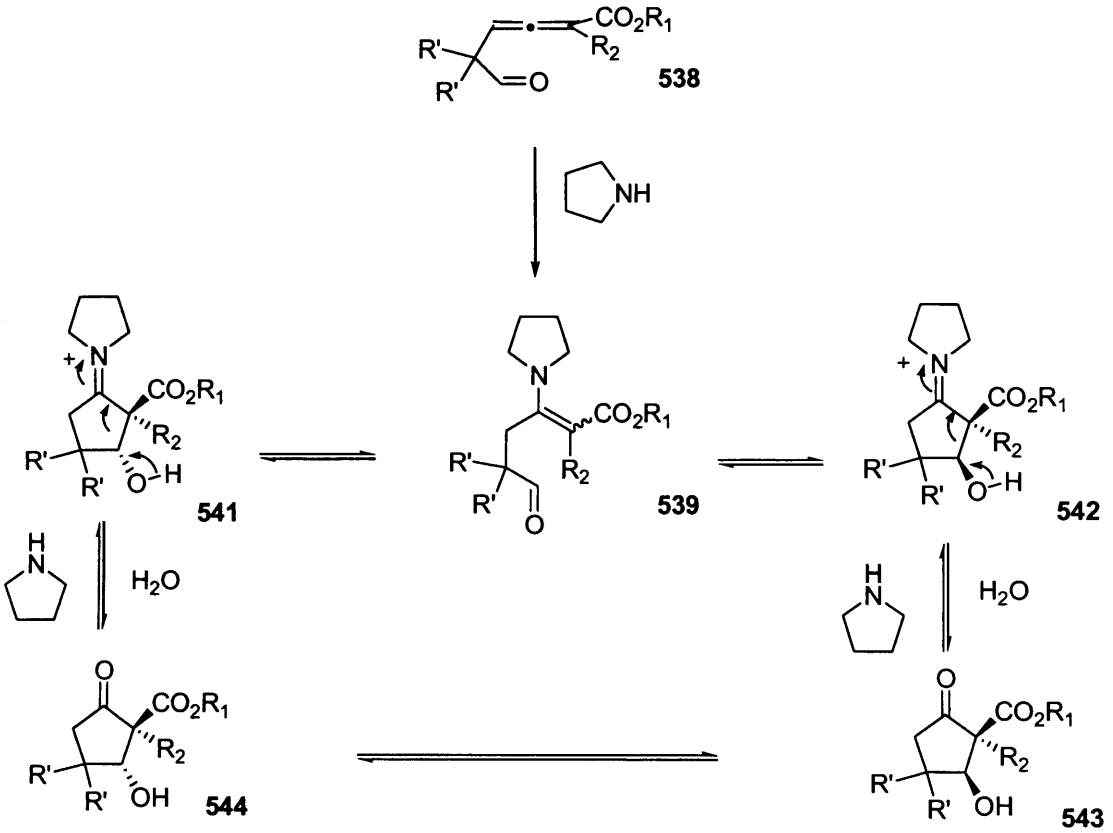


Scheme 162

A plausible explanation for this interesting change in diastereoselectivity is depicted in Scheme 163. Thus, the presence of higher quantities of pyrrolidine could lead to a retro-aldol reaction, *via* an iminium species (541) to give the enamine (539), which could then cyclise to give the alternative diastereoisomer (542). Thus, a lower quantity of amine catalyst allows the reaction to proceed under kinetic control, leading to an increase in the observed diastereoselectivity. However, on increasing the quantity of catalyst, the reaction becomes reversible, i.e., under thermodynamic control and the diastereoselectivity decreases.

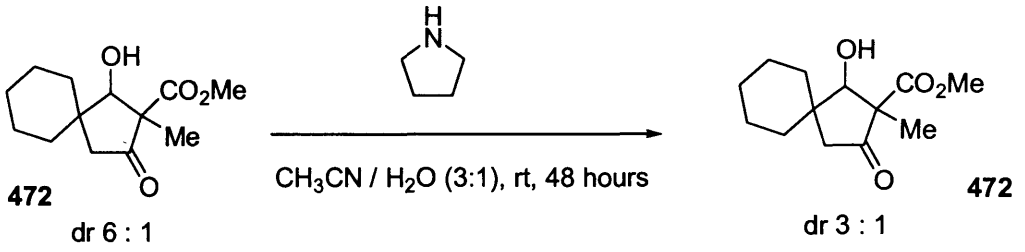
As depicted in Scheme (163), addition of pyrrolidine to allenic esters (538) would give the corresponding enaminone (539), likely to exist as a mixture of stereoisomers, which upon cyclisation could yield two diastereoisomeric iminium ions (541) & (542). Hydrolysis of iminum species (541) & (542) would then proceed to give the described diastereomeric cyclopentanones (543) & (544). In the presence of lower amounts pyrrolidine, such as 0.05 molar equivalents, the kinetic product predominates and in consequence, a higher diastereoselectivity is observed.

However, in the presence of larger quantities of pyrrolidine, the reaction comes under thermodynamic control as retro-aldol reactions of iminium ions (541) & (542) effectively enable equilibration of the two diastereomeric cyclopentanones (543) & (544), and consequently, the observed diastereoselectivity decreases.



Scheme 163

In order to clarify whether the presence of excess amine is responsible for the decrease in diastereoselectivity a simple experiment was conducted (Scheme 164). Thus, the 6:1 diastereomeric mixture obtained when allenic ester (468) was converted into cyclopentanone (472) with 0.05 equivalents of pyrrolidine was dissolved in an CH_3CN / H_2O mixture (3:1), and one molar equivalent of pyrrolidine was added. Pleasingly, after stirring for 48 hrs at room temperature, aqueous work up followed by ^1H NMR analysis of the crude mixture showed that the diastereomeric ratio had decreased to 3:1.

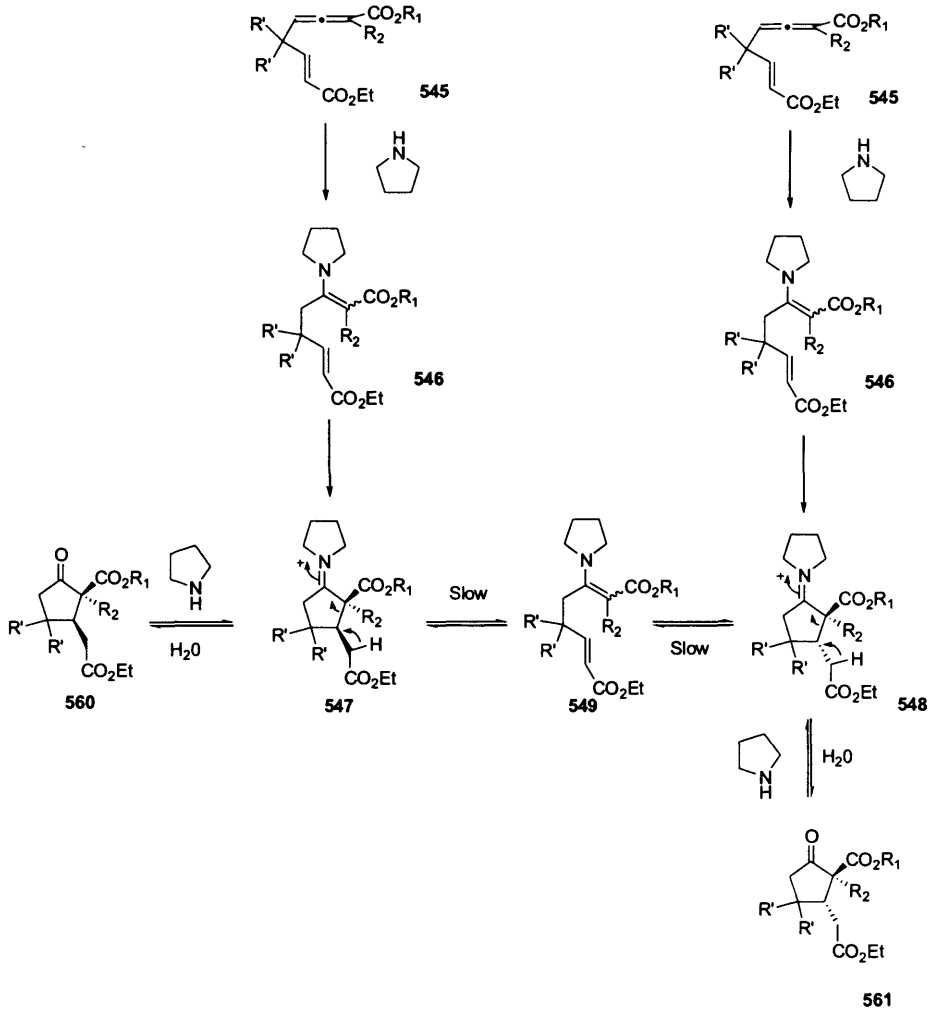


Scheme 164

The change in diastereoselectivity observed under these reaction conditions provides evidence for the proposed reversible nature of the carbocyclisation reaction depicted in Scheme (163), and the fact that, when 0.05 molar equivalents of pyrrolidine are employed, the reaction is proceeding under kinetic control.

Further evidence for the proposition that kinetic control in the presence of lower quantities of pyrrolidine is responsible for the increase in diastereoselectivity is obtained on examination of the stereoselectivity observed with respect to the cyclisation of allenic substrates (529) & (533). Thus, as depicted in Scheme (159), in the case of allenic esters (529) & (533), cyclisation induced by a molar equivalent of pyrrolidine took place to provide the corresponding diastereomeric cyclopentanones (534) & (535) in a ratios of 5:1.

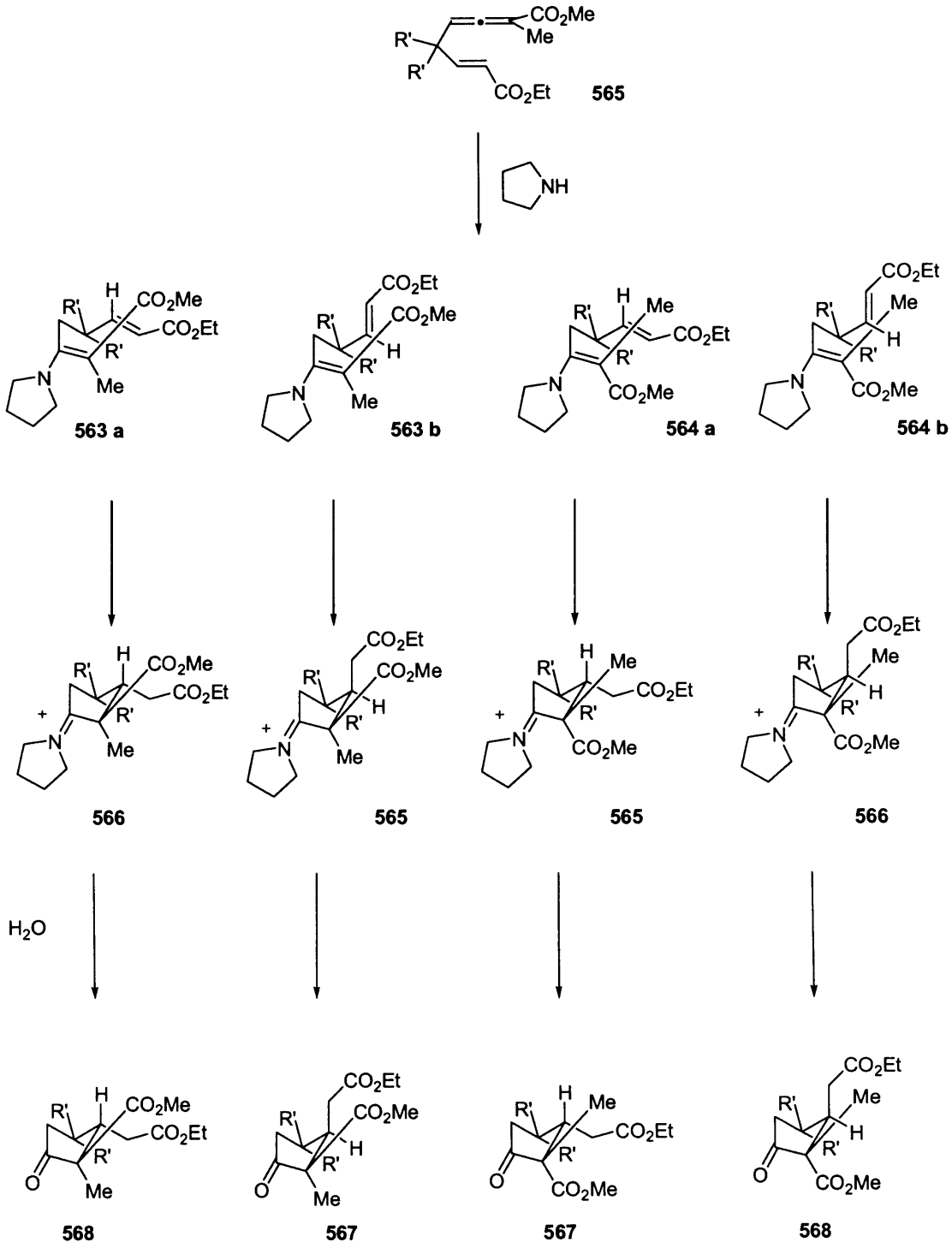
In this instance, addition of pyrrolidine to allenic esters (545) would also proceed to give enaminones (546), likely to exist as a mixture of two possible stereoisomers, which upon cyclisation would yield two possible diastereomeric cyclopentanones (560) & (561). However, the retro-Michael reaction of iminium ions (547) & (548), is likely to be significantly slower than the previously discussed retro-aldol reaction, and in consequence, equilibration between the two diastereoisomers is less likely and a higher diastereoselectivity is observed with stoichiometric amine (Scheme 165).



Scheme 165

The major stereoisomer obtained from the carbocyclisation reactions of allenic esters (565) was shown to be (560), in which the two ester groups lie upon the same face of the five membered ring, by NOE studies. In order to rationalise this result examination of the possible transition states for cyclisation is required. As shown in Scheme (166), addition of pyrrolidine to the allenic esters (565) could give the enaminones (563) or (564), or alternatively, a mixture of both. For each of these stereoisomers two distinct transition states for cyclisation are possible, and in consequence, either stereoisomer can give rise to the two diastereomeric iminium ions

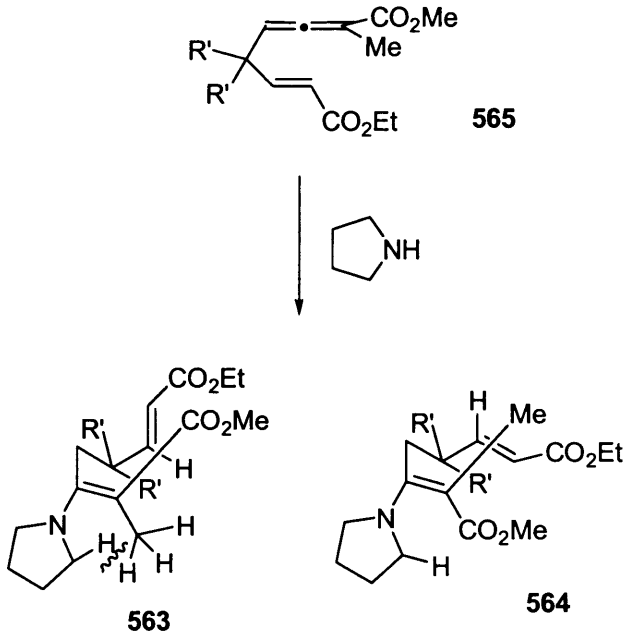
(565) & (566), which upon hydrolysis give the two diastereomeric cyclopentanones (567) & (568).



Scheme 166

Thus, the major diastereoisomer (567) formed upon addition of pyrrolidine to allenic ester (565) could be formed from either of the stereoisomers (563) and (564) of the enaminone, *via* the cyclisation transition states (563 b) & (564 a).

Previous studies upon the addition of secondary amines to allenic esters suggest that the stereoselectivity of enaminone formation is determined by the difference in steric congestion between the two possible stereoisomers. In the case of allenic esters (565), addition of pyrrolidine leads to both enaminone (563), in which the pyrrolidine ring suffers steric interactions with the hydrogen atoms of the methyl group or alternatively, enaminone (564) in which the major steric interaction is that between the pyrrolidine ring and the ester moiety (Scheme 167).



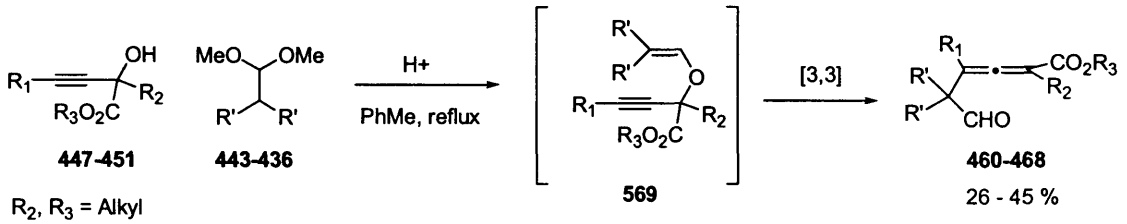
Scheme 167

It is clear from Scheme (167) that the steric clash between the C-H bonds of the pyrrolidine ring and the methyl group in the E-enaminone (563) exists, and therefore it would be fair to assume that the Z-enaminone (564) would be favoured upon thermodynamic grounds. If this were to be true, the major diastereoisomer would be

formed *via* the transition state (564 a) depicted in Scheme (166) and that drawn in Scheme (167).

2.26 Conclusions and Future Perspectives

It was discussed during the course of section 2.2 that functionalised allenic esters (460-468) can be obtained by the reaction of readily prepared propargylic alcohols (447-451) with acetals (443-446), under acidic conditions, *via* Claisen rearrangement of the intermediate propargyl-vinyl ethers (569) (Scheme 168).



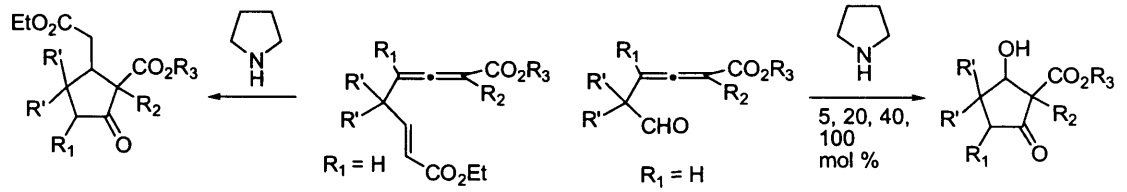
447-451 **443-436** **569** **460-468**

R_2, R_3 = Alkyl
R_1 = Alkyl / Aryl
R' = Alkyl

26 - 45 %

Scheme 168

Allenic esters (460-468) and their derivatives (468) & (533) were shown to undergo tandem enamine formation-cyclisation reactions, under mild reaction conditions, providing a range of highly substituted cyclopentanones (570) & (571) (Scheme 169).



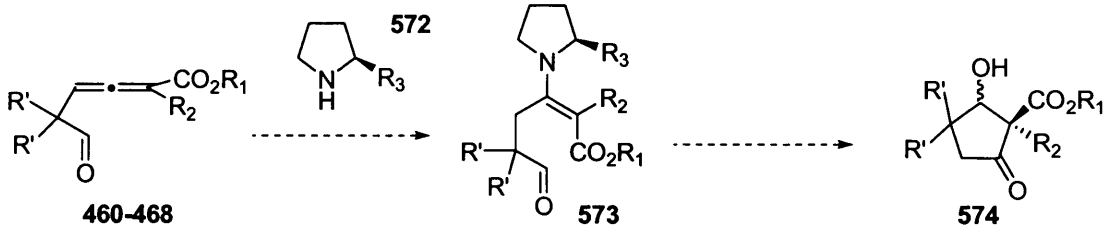
571 35 -62 % dr 5:1 **468 & 533** **460-468** **570** 40 - 65 % dr 1:1 - 6:1

Scheme 169

The potential of rendering the described methodology catalytic with respect to the amine was also examined and on carrying out the carbocyclisation reactions in an acetonitrile/water solvent mixture, catalyst concentrations as low as 5 mol % could be

employed, although higher yields of the cyclopentanones were obtained using higher catalyst concentrations.

An obvious extension to this methodology would be the development of stereoselective variants. As we have seen, an exciting increase in diastereoselectivity was observed when lower catalyst concentrations were employed and this was attributed to a retro-aldol reaction being promoted in the presence of higher catalyst concentrations, with a control experiment supporting this hypothesis. In light of these results, it is anticipated that the application of chiral secondary amines as catalysts could enable the development of both a stereoselective and an enantioselective variants (Scheme 170).



Scheme 170

Thus, addition of an enantiomerically pure chiral amine (572) to esters (460-468) should lead to the corresponding vinylogous urethanes (573) in which the stereochemistry of the enamine could be controlled by steric clashes between the substituents on the amine and the allene. If a sterically cumbersome ester was reacted, selective formation of vinylogous urethane (573) would be expected due to the minimisation of the steric clash between substituents R_3 & R_4. Such selectivity could be translated into selective formation of one stereocentre in the product cyclopentanones (574), with the other likely to be controlled by steric parameters in the cyclisation transition state. It is anticipated that good control could be obtained by inhibiting the retro-aldol process and preliminary experiments have demonstrated that catalyst loading, reaction time and temperature are all important parameters for

further investigation. Furthermore, the reaction of racemic allenic esters (460-468) with enantiomerically pure amines (572) could lead to kinetic resolution. Such a process would have important stereochemical consequences whilst also increasing the overall complexity of the proposed experiments.

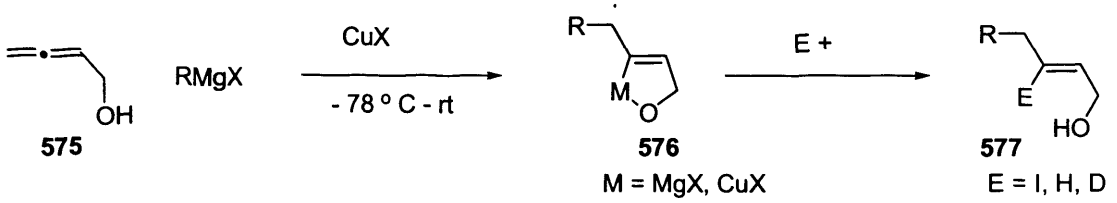
Section 2.30

Tandem Reactions (III) – Carbometallation of Allenic Substrates

2.30 Tandem Reactions (III) – Carbometallation of Allenic Substrates

2.31 Introduction

As outlined in Chapter (1) carbometallation reactions provide a regio- and stereoselective route to substituted allylic alcohols. Moreover, detailed study of the reaction mechanisms involved has enabled the development of novel pathways to vinyl-iodides, deuterated alkenes and a vast array of highly substituted stereo-chemically pure olefins. Furthermore, carbomagnesiation of allenols (575) has been shown to lead to chelated metallocycles (576), which upon reaction with electrophiles evolve to substituted allylic alcohols (577) (Scheme 171).[89]



575 576 577

M = MgX, CuX

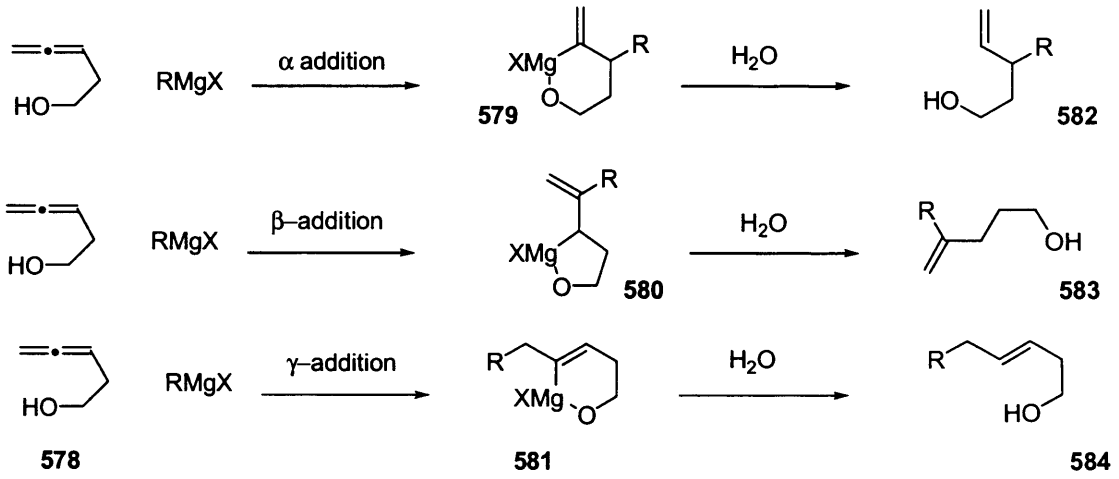
E = I, H, D

Scheme 171

Within this framework, it was envisaged that research into carbometallation reactions of related allenic substrates would provide an opportunity to develop novel methodology for the stereoselective synthesis of substituted alkenes. Moreover, it was anticipated that with the correct design of allenic substrates, tandem reaction sequences could be realised, making use of the synthetically versatile intermediate metallocycles analogous to (576).

2.32 Carbometallation of Homoallenols

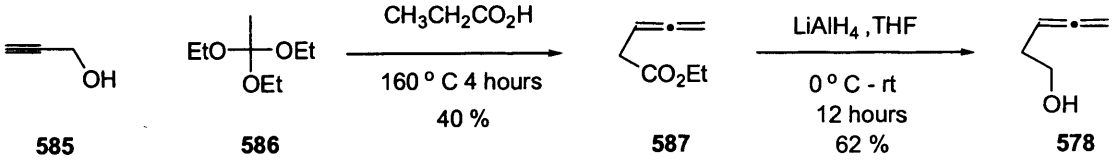
In contrast to the extensive work on the carbometallation of allenols for the stereo-selective preparation of substituted allylic alcohols, the study of homoallenols has received little attention *vide infra.*[131] Initially, it was decided that a brief study into the carbometallation of these allenic substrates would be conducted and it was of particular interest to examine the regioselectivity observed upon reaction of homoallenol (578) with organometallic reagents. As shown in Scheme (172), addition of an organometallic reagent to (578) could, in principle, occur at three positions leading to three different regioisomeric alcohol products (582-584), *via* metallocycles (579-581), on protic work up as shown in Scheme (172).



Scheme 172

In the first instance, the reactivity of the simple unsubstituted homoallenol (578) towards organometallic reagents was examined.

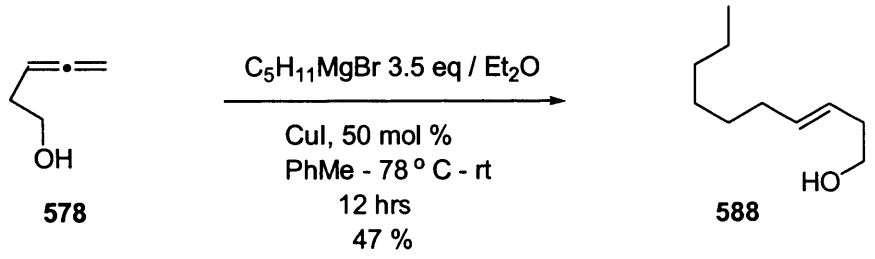
Alcohol (578) was prepared in two steps from the commercially available propargyl alcohol (585) by reaction with triethylorthoacetate (586) in the presence of propionic acid, to afford homoallenic ester (587), and subsequent reduction with lithium aluminium hydride (Scheme 173).



585 586 587 578

Scheme 173

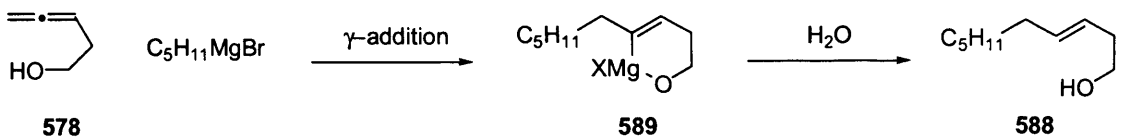
Carbomagnesiation of this allene (578) was then investigated. Thus, a solution of allene (578) in dry toluene was treated with 3.5 equivalents of pentyl magnesium bromide, in the presence of CuI (50 mol %). The Grignard reagent was prepared as a solution in Et_2O, titrated and used immediately (Scheme 174).



578 588

Scheme 174

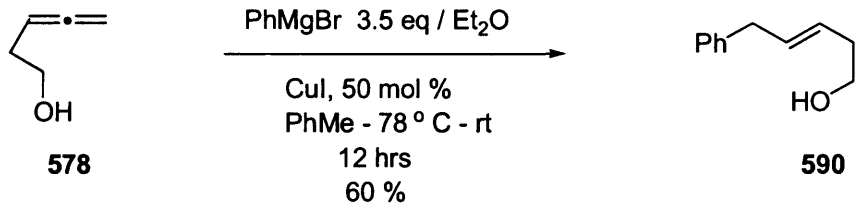
Pleasingly, TLC analysis of the crude reaction mixture indicated that the starting allenic alcohol (578) had been consumed after stirring for 12 hrs at room temperature. Interestingly, the only compound isolated from the crude reaction mixture *via* flash column chromatography was shown to be the homoallylic alcohol (588), by ^1H NMR analysis. Isolation of the trans-substituted alkene (588) indicated that the addition of the Grignard reagent to the homoallenol (578) occured at the γ-position of the allene, leading to the corresponding 6-membered intermediate chelated metallocycle (589) (Scheme 175).



578 589 588

Scheme 175

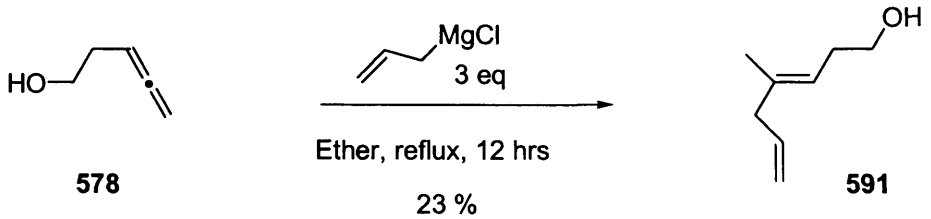
Secondly, the reactivity of allenol (578) towards phenyl magnesium bromide was examined and once again, the organometallic was shown to add to the γ-carbon of the allene, providing the corresponding trans-alkene (590), in 60 % yield, after purification of the crude reaction mixture by flash column chromatography (Scheme 176).



578 590

Scheme 176

In these examples the addition of the organometallic reagent at the γ-position of the allene was favoured over addition at the α-position. A possible explanation for this result is that formation of the internally unsaturated intermediate metallocycle (581) is favoured over the corresponding exocyclic unsaturated species (579) formed when addition takes place at the α-position (Scheme 172). However, studies by Richey and co-workers on the carbomagnesiation of homoallenol (578) with allyl magnesium chloride (see Chapter 1), in the absence of Cu (I) salts, showed that addition occurred at the central allenic carbon providing homoallylic alcohol (591) (Scheme 177).[131]

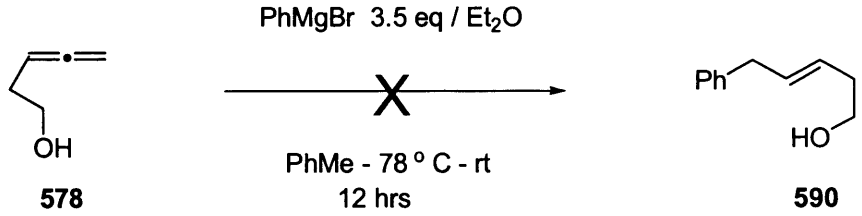


578 591

Scheme 177

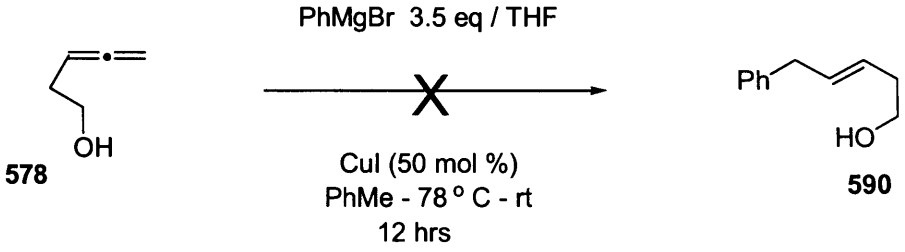
Because of this difference in regioselectivity, the role of the Cu (I) additive in the carbomagnesiation reactions was examined. Thus, allenic alcohol (578) was reacted

with phenyl magnesium bromide in the absence of CuI (Scheme 178). In the event, allenol (578) was left unchanged within the reaction mixture, even after an extended reaction time of 24 hrs. Addition of an alternative metal salt was also examined and the same reaction in the presence of $ZnBr_2$ was attempted. However, only starting material was observed by TLC analysis even after extended reaction periods.



Scheme 178

After it was shown that the Cu (I) salt was an essential component of the carbomagnesiation reactions, the role of the reaction solvent was investigated and the reaction of allenic alcohol (578) with phenylmagnesium bromide, prepared in THF, was attempted (Scheme 179).



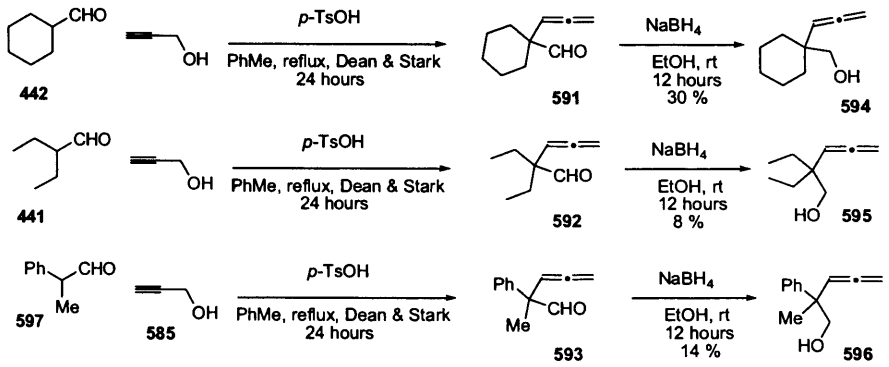
Scheme 179

Surprisingly, the reaction failed to provide any of the homoallylic alcohol (578), even after refluxing for extended periods. A possible explanation for this result is that the increased coordinating ability of THF could reduce the reactivity of the Grignard

reagent and also the co-ordinating ability of the allenic hydroxyl group, which is an integral part of the carbometallation reaction mechanism (Scheme 172).

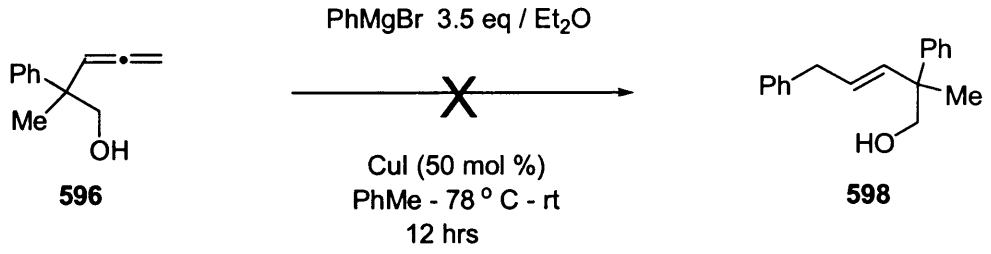
The difference in the regioselectivity observed between the present studies and those conducted by Richey and co-workers may also lie in the difference in nucleophilicity between Grignard reagents and organo-cuprates. Therefore, the active species could be the organo-cuprate formed *in situ* by the transmetallation of the Grignard reagent with the added copper. The soft nucleophilic nature of the organo-cuprate compared to the harder nature of the corresponding Grignard reagent could therefore be responsible for the change in regioselectivity. However, the difference could also be due to the difference in reactivity between allyl magnesium bromide, used in the Richey group, and the aryl and alkyl Grignard reagents used here.

The effect of substitution around the allenic nucleus was then investigated and as shown in Scheme (180), substituted allenols (594-596) were prepared by the reaction of the aldehydes (441, 442 and 597), with propargyl alcohol (585). The initially formed allenic aldehydes (591-593) were reduced to the required alcohols with $NaBH_4$.



Scheme 180

The reaction of allenol (596) with phenyl-magnesium bromide, in the presence of CuI, failed to give the expected homoallylic alcohol (598), and instead only the starting material was observed within the crude reaction mixture (Scheme 181).

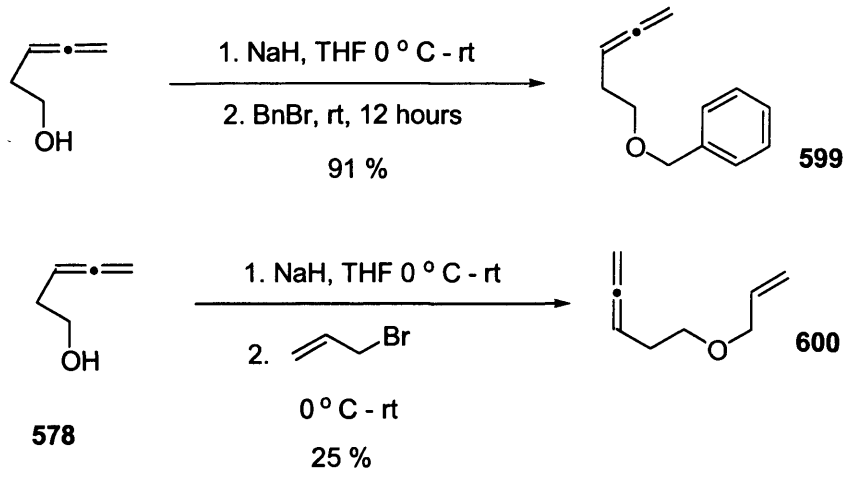


Scheme 181

Likewise, substituted allenols (594) and (595) also failed to undergo carbometallation with phenyl-magnesium bromide. Similarly, studies by Araki and co-workers showed that secondary and tertiary allenols failed to undergo carbometallation with allylic indium reagents whereas unsubstituted primary allenols reacted smoothly. The authors proposed that steric crowding around the hydroxyl group was responsible for this lack of reactivity interfering with the coordination of indium.[132]

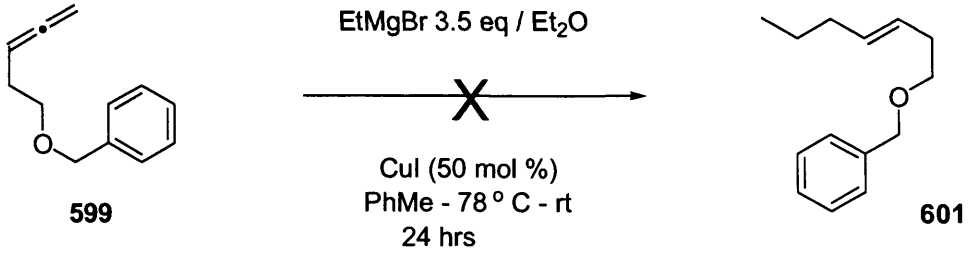
2.33 Carbomagnesiation of Related Allenic Substrates

In light of the successful development of a mild carbomagnesiation reaction of homoallenic alcohol (578), the behaviour of related substrates under these reaction conditions was investigated. In the first instance, the carbomagnesiation of homoallenyl ethers was examined and homoallenol (578) was converted into the corresponding ethers (599) and (600) (Scheme 182).



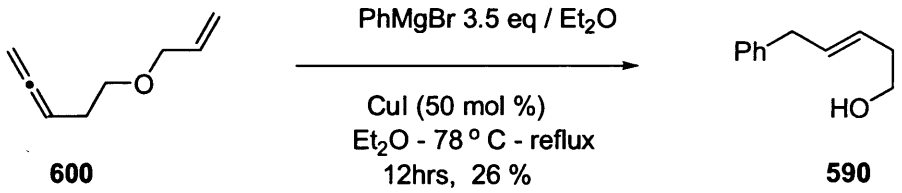
Scheme 182

Ether (599) was reacted with a freshly prepared solution of ethyl magnesium bromide in Et_2O and analysis of the reaction mixture by TLC showed that the starting material remained unchanged after 24 hrs at room temperature. Analysis by ^1H NMR spectroscopy, of the crude mixture after aqueous work up, showed no evidence for carbomagnesiation occurring to give (601), with the starting material left largely unchanged (Scheme 183).



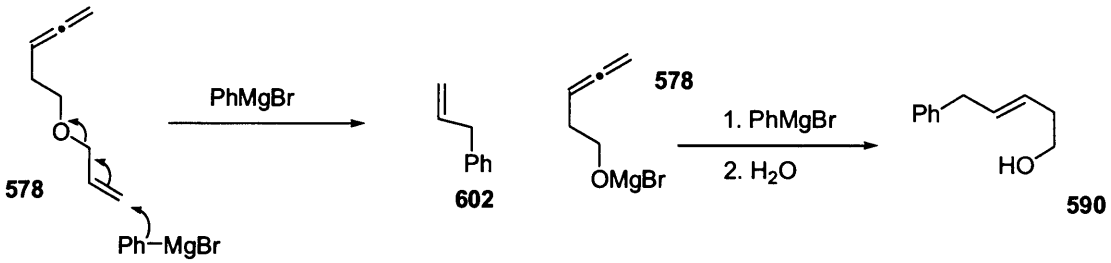
Scheme 183

By way of contrast, the reaction of allenyl ether (600) with phenyl magnesium bromide led to the total consumption of starting material after a 12 hour period at reflux in Et_2O. Aqueous work up of the crude reaction mixture followed by purification by flash column chromatography, led to the isolation of the previously prepared homoallylic alcohol (590) (Scheme 184).



Scheme 184

The cleavage of allyl ethers with Grignard reagents has been previously reported [133] and a plausible mechanistic rationale for the formation of homoallylic alcohol (590) is shown in Scheme (185). Thus, it is anticipated that cleavage of the allyl ether (600) with PhMgBr leads to the formation of allyl benzene (602) and the magnesium alkoxide of homoallenol (578). Subsequent carbometallation of the magnesium alkoxide (578) would then proceed as previously described, to give homoallylic alcohol (590).



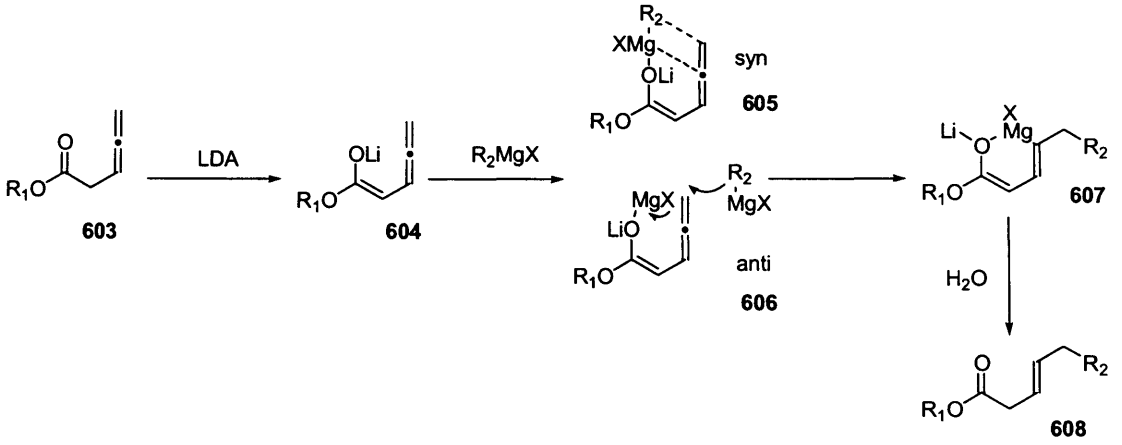
Scheme 185

The lack of reactivity shown by allenyl ethers (599) and (600), towards carbomagnesiation could be due to the inferior coordinating ability of the ethereal oxygen atom in comparison with that of the alkoxide moiety formed during carbometallation of the parent alcohols as such coordination is thought to be essential to the carbomagnesiation reaction mechanism. Therefore, poor coordination of the ethereal oxygen atom could inhibit the initial reaction of the Grignard reagent with the allenic nucleus and also lower the stability of the intermediate metallocycle.

2.34 Enolate Anion Assisted Carbometallation of Allenic Substrates

During the course of our investigation into the carbomagnesiation reactions of homoallenol (578), and by studies on related substrates, it was shown that the hydroxyl group assists the addition of the organometallic across the allenic moiety, by coordinating to a magnesium atom in the transition state of the reaction and in the initially formed intermediate metallocycles.

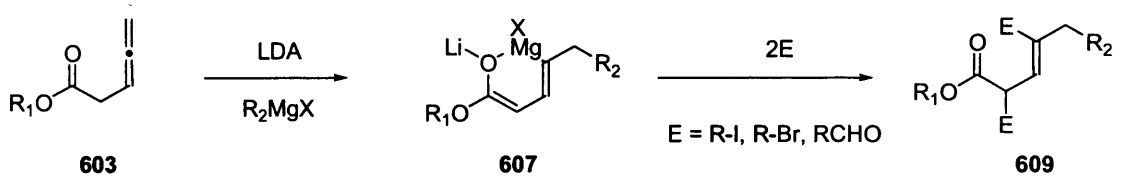
Within this framework, it was envisaged that the lithium enolate of a ketone or ester moiety could also assist carbometallation of the allenic nucleus (Scheme 186). Thus, it was anticipated that the formation of the enolate (604), *via* the stoichiometric deprotonation of homoallenic ester (603), could be followed by either *syn* or *anti* carbomagnesiation of the allenic moiety *vide infra*.



Scheme 186

It was considered that addition of the organometallic reagent would then occur at the γ-position of the allene *via* transition states (606) or (606), similar to that observed during investigations into the carbometallation reaction of homoallenol (578). Thus, C-C bond formation at the allenic terminus would give the intermediate metallocycles (607), which on protonation, would provide the trans- substituted alkenes (608). Moreover, the ambidient nucleophilic nature of the intermediate metallocycles (607),

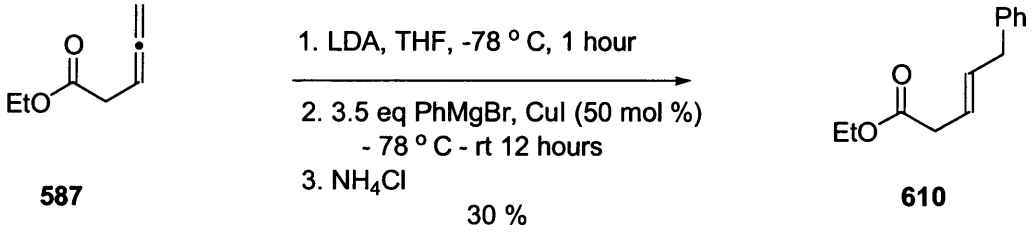
could be used to enable further synthetic manipulations, enabling the stereoselective synthesis of a variety of complex olefins (Scheme 187).



603 607 609

Scheme 187

In order to test this hypothesis the previously prepared allenic ester (587) was treated with a solution of LDA and the resulting enolate was then reacted with a freshly prepared solution of phenylmagnesium bromide in Et_2O, in the presence of CuI (Scheme 188).



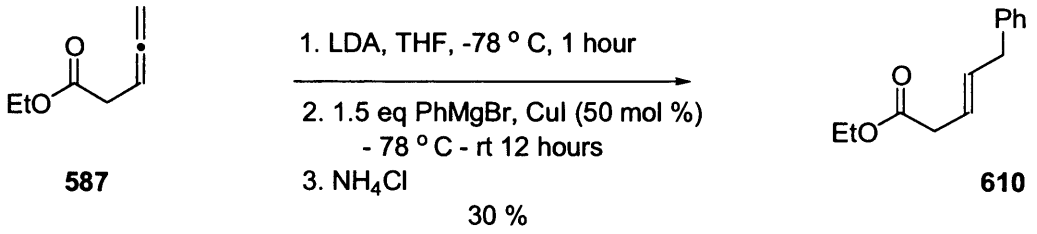
587 610

Scheme 188

Pleasingly, TLC analysis of the reaction mixture showed that the starting allenic ester (587) had been completely consumed after stirring for 12 hrs at room temperature. Aqueous work up and flash column chromatography of the resulting crude oil led to the isolation of the desired alkene (610).

During the course of studies on the carbometallation reactions of homoallenol (578), 3-4 equivalents of the organometallic reagent were employed and reactions of related alcohols also used a large excess of the organometallic reagent. In these reactions one equivalent of the organometallic reagent was consumed immediately upon addition, due to the presence of the acidic hydroxyl group and it was anticipated that the carbomagnesiation reaction of the enolate derived from homoallenic ester (587),

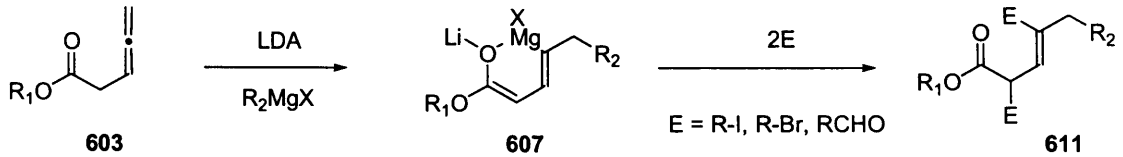
would not require such an excess of the organometallic reagent due to the absence of any such acidic sites. Consequently, the carbomagnesiation reaction of homoallenic ester (587) was then attempted with 1.5 equivalents of organometallic reagent. The reaction was shown to be successful and provided the expected homoallylic ester (610) in identical yield, whilst increasing the overall atom economy of the reaction (Scheme 189).



587 610

Scheme 189

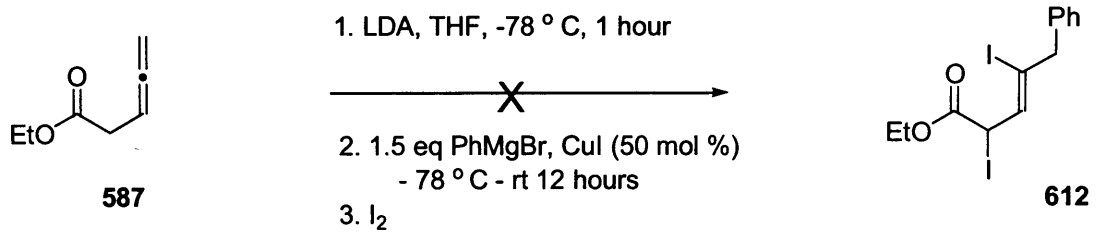
The next line of investigation was to establish whether or not the metallocycles (607) were true intermediates in this novel carbomagnesiation reaction. Thus, in the first instance, quenching of the reactions by the addition of a variety of electrophiles leading to the successful incorporation at the α- and γ-positions of alkenes (611) was attempted as it was anticipated that this would provide direct evidence for the involvement of metallocyclic intermediates (607) (Scheme 190).



603 607 611

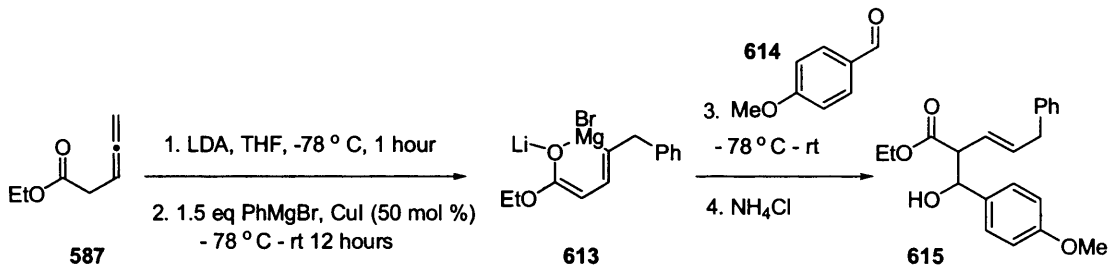
Scheme 190

Disappointingly, carbomagnesiation of homoallenic ester (587) followed by addition of iodine, did not lead to the desired vinyl iodide (612), and an intractable mixture of compounds was obtained (Scheme 191).



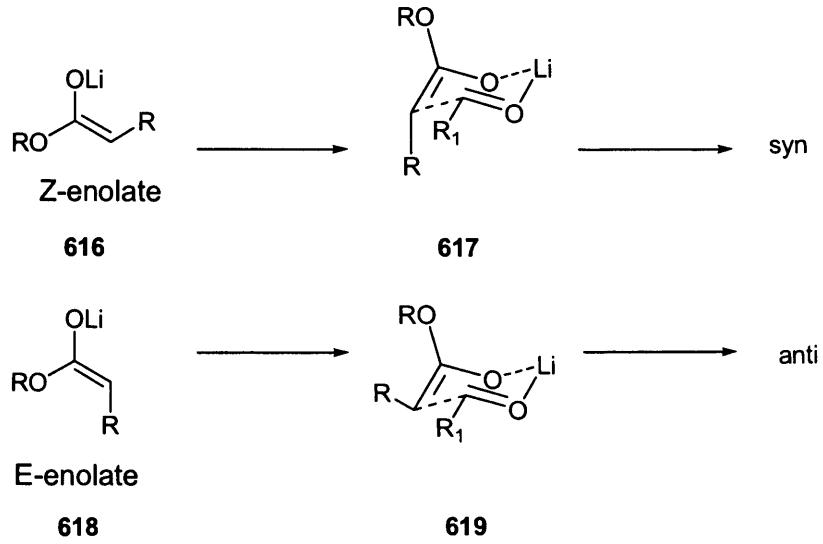
Scheme 191

In contrast, quenching the reaction mixture by the addition of aldehyde (614), led to the formation of a polar compound, identified as the aldol adduct (615) (Scheme 192) as a single diastereoisomer.



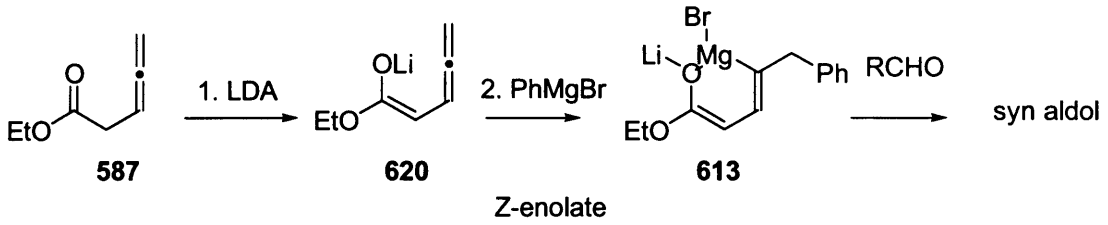
Scheme 192

Elucidation of the relative stereochemistry of the aldol adduct (615) would provide crucial information on the geometry of the initially formed ester enolate. Thus, an analysis of this stereochemical outcome by application of the widely accepted Zimmermann-Traxler model is shown in Scheme (193).



Scheme 193

Thus, the favourable transition states for aldol reaction between both Z (616) and E enolates (618) with aldehydes are (617) and (619), as shown in Scheme (193). If the major aldol adduct formed was indeed identified as the *syn* isomer this would provide evidence for the formation of the corresponding Z-enolate (620) from homoallenic ester (587) upon treatment with LDA (Scheme 194).

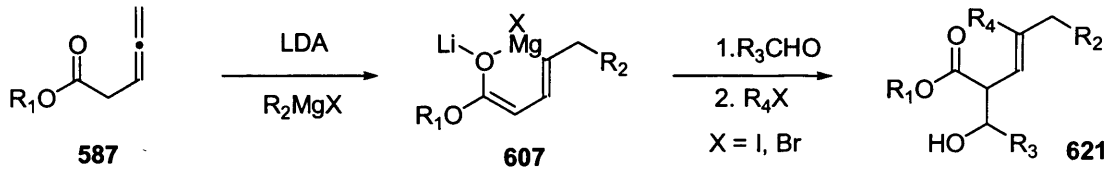


Scheme 194

However, the simple notion that the Z-enolate (620) would lead to the selective formation of the *syn* aldol isomer may not be applicable here. In this instance, the presence of the vinylic magnesium atom in the tightly bound chelated metallocycle (613) may have a profound effect upon the aldol transition state, and in consequence, further experiments are required to establish which ester enolate geometry is favoured upon treatment of homoallenic ester (587) with LDA *vide infra*.

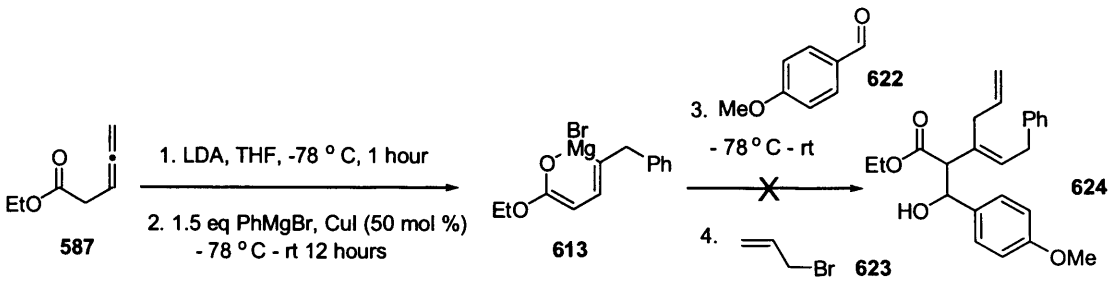
The formation of aldol adduct (615) provided direct evidence for the presence of the ester enolate moiety after carbometallation occurred. However, in order to prove the existence of a chelated metallocycle (607), a reaction with an electrophile at the vinylic position was also required.

Due to the regioselectivity observed upon reaction with aldehyde (614), it was anticipated that a tandem reaction could be realised in which carbometallation of homoallenic ester (587) would be followed by an aldol reaction with an added aldehyde and subsequent reaction with an electrophile at the vinylic position of the proposed intermediate (607) (Scheme 195).



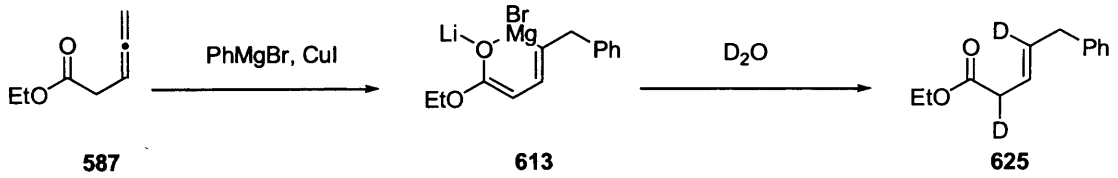
Scheme 195

Successful development of such a tandem reaction sequence could be of great significance, as primarily, the one-pot stereoselective formation of such highly substituted alkenes (621) would be noteworthy. Moreover, a successful reaction with two added electrophiles would provide direct evidence for the existence of the proposed metallocyclic intermediates (607). Therefore, carbomagnesiation of homoallenic ester (587) was followed by the addition of *para*-tolualdehyde (622) and allyl bromide (623) respectively. Disappointingly, a highly complicated mixture of compounds was obtained with all attempts to isolate any of the expected tri-substituted alkene (624) failing (Scheme 196).



Scheme 196

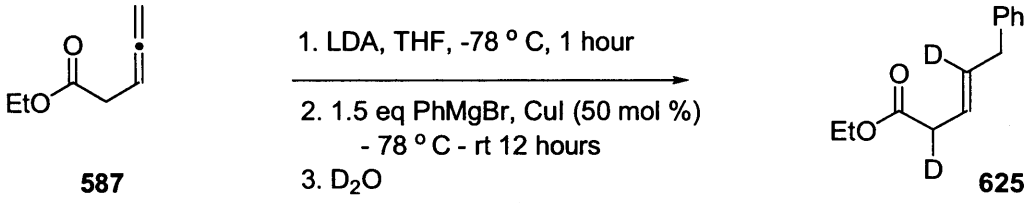
In order to simplify matters, the carbomagnesiation reaction was quenched by the addition of deuterated water. Thus, it was anticipated that deuterium incorporation at both the α- and γ-positions of the product homoallylic esters, would provide direct evidence for the involvement of metallocycle (613) in the reaction mechanism (Scheme 197).



587 613 625

Scheme 197

Pleasingly, carbomagnesiation of homoallenic ester (587) with PhMgBr, followed by quenching with deuterated water, led to the formation of the doubly-deuterated homoallylic ester (625), isolated in a 26 % yield, after purification of the crude reaction mixture by flash column chromatography (Scheme 198).



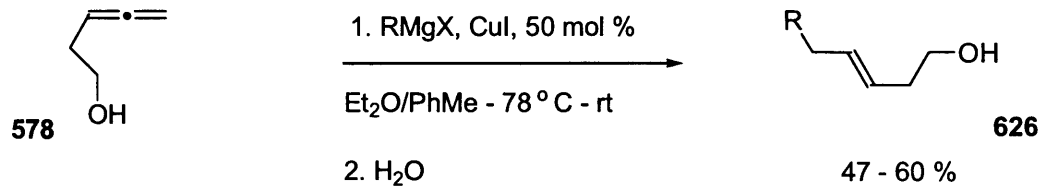
587 625

Scheme 198

^1H NMR and ^{13}C NMR spectroscopy of the homoallylic ester (625) showed clearly that deuterium incorporation at the α- and γ-positions had occurred. Overlapping the proton spectrum of the ester formed upon quenching with water and that formed by quenching with deuterated water showed that in the positions where deuterium incorporation was expected, the magnitude of the integrals for the corresponding proton resonances decreased accordingly. Measurements upon these integrals indicated that 100 % deuterium incorporation at the α-position and 66 % incorporation at the γ-position had occurred. The presence of two triplets in the ^{13}C spectrum provides, with one present in the olefinic region, provided direct evidence for the formation of two C-D bonds upon quenching and therefore, the involvement of the metallocycle (613) in the described carbometallation reaction.

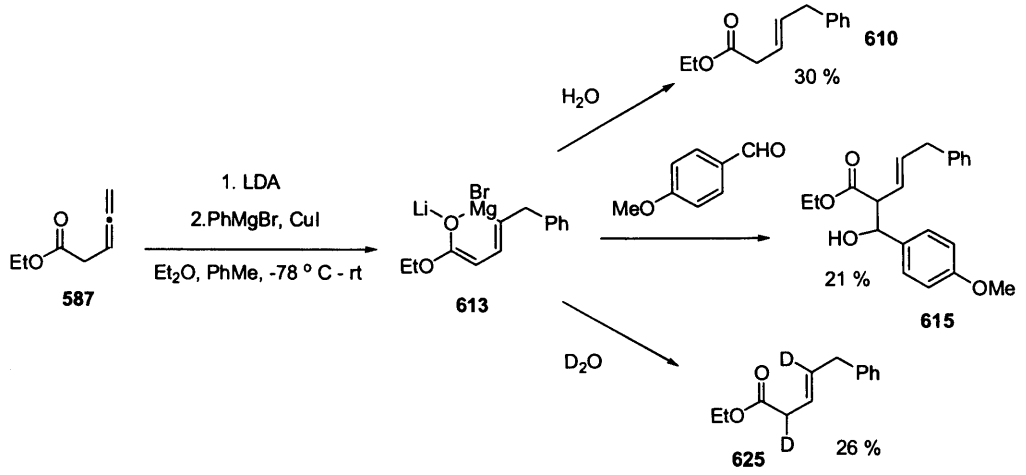
2.35 Conclusions and Future Perspectives

The foregoing section has shown that allenic compounds can be used as substrates for a variety of tandem reaction sequences designed to enable the rapid, stereoselective synthesis of functionalised alkenes, using carbometallation as the initial step in the reaction sequence. Initial studies upon the Cu(I) catalysed carbometallation of homoallenol (578), showed that addition of the organometallic occurs, in a regioselective manner, with C-C bond formation shown to occur at the γ-position of the allene, providing the trans-substituted homoallylic alcohols (626) in moderate yields (Scheme 199).



Scheme 199

The successful development of this carbometallation reaction aided the design and implementation of a novel enolate assisted carbometallation reaction of the parent homoallenic ester (587) (Scheme 200).



Scheme 200

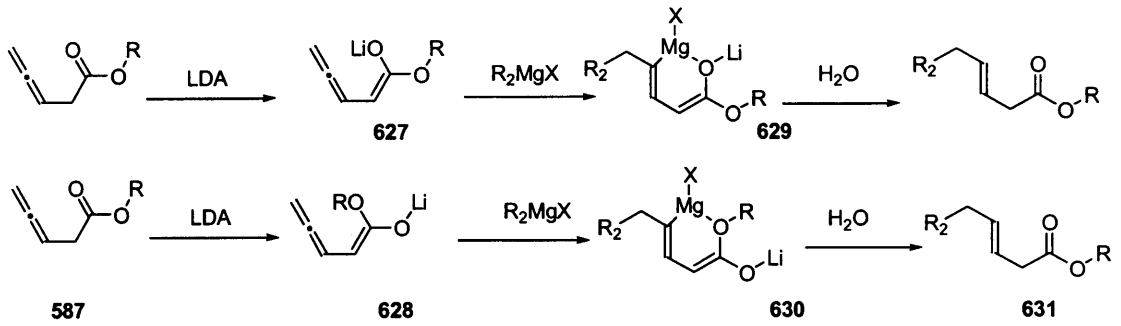
The enolate derived from homoallenic ester (587) was shown to undergo carbometallation with phenyl-magnesium bromide providing a range of products depending upon the method used to quench the proposed intermediate metallocycle (613). Thus addition of water gave the simple alkene (610), whereas addition of an aldehyde was shown to provide the aldol product (615). Evidence for the involvement of the metallocycle (613) along this reaction pathway was obtained upon quenching the reaction with D_2O, as the doubly deuterated alkene (625) was isolated in 26 % yield.

It is anticipated that future work in this area aimed at the optimisation of the reaction conditions employed to effect the transformations depicted in Scheme (200) will enable both higher yields of products to be obtained along with a larger variety of substituted alkenes to be formed.

The low yield of homoallylic ester (610) obtained upon the carbometallation of the enolate derived from homoallenic ester (587) could be attributed to a number of factors. Primarily the sensitive nature of the proposed intermediates, namely the conjugated enolate and intermediate metallocycle (613) (Scheme 200) is one potential explanation. Thus, investigations into the reaction conditions employed to enable the formation of these species and their subsequent reactions is required. It is anticipated that both reaction temperature and time will have profound effects upon the stability and reactivity of these intermediates, therefore the overall yield of the reactions depicted in Scheme (200).

Another possible explanation for the low yield is obtained upon considering enolate stereochemistry. Thus, deprotonation of allenic ester (587), could provide a mixture of the two isomeric enolates (627 and 628). However, one of these enolates will direct

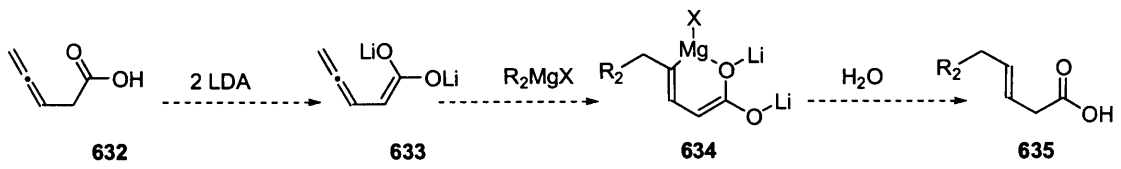
carbometallation *via* the lithium alkoxide (629), whilst the other will direct carbometallation through the ethereal oxygen (630) (Scheme 201).



Scheme 201

Carbometallation may only be occurring effectively through one of these isomers due to the differing coordinating abilities of the respective oxygen's. In light of results obtained during the studies with homoallenyl ethers, where the ethereal oxygen atom failed to promote carbometallation of the allenic nucleus, it is fair to assume that carbometallation is more likely to occur through the alkoxide oxygen, therefore, *via* enolate (629).

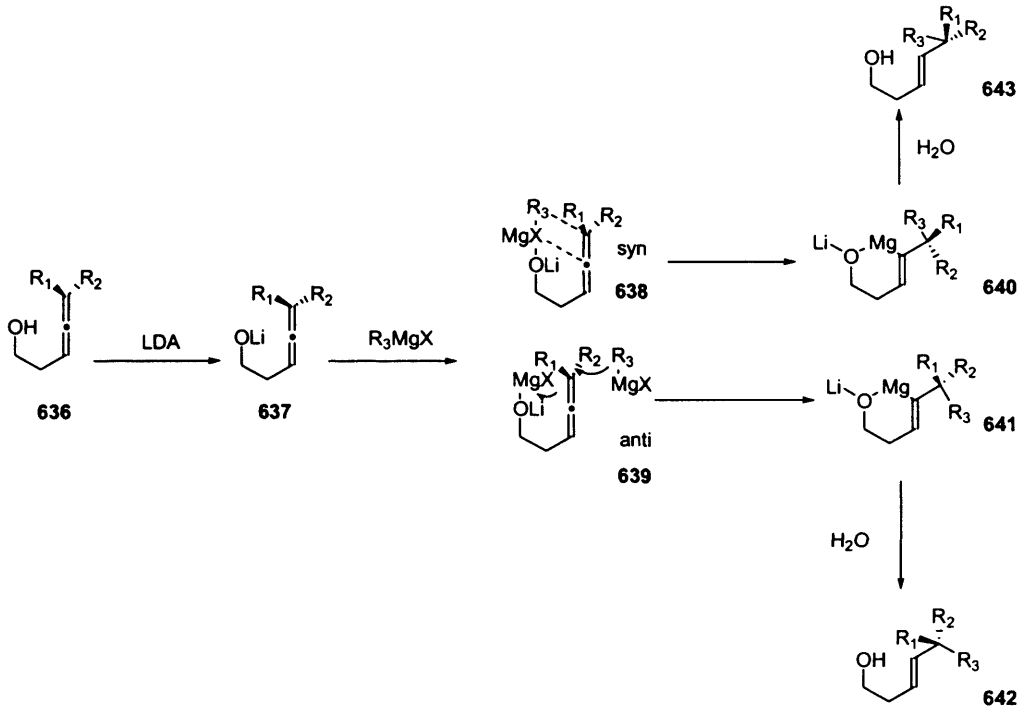
Studies with the homoallenic acid (632) would provide an opportunity to assess if enolate geometry is important to this novel carbometallation reaction (Scheme 202). Thus, the double deprotonation of acid (632) would provide the corresponding enolate (633), in which geometry is no longer an issue. If the carbometallation reaction was to proceed leading to (634) in higher yield than in the case of homoallenic ester (587), enolate geometry could be assigned as a critical feature of the reaction sequences discussed.



Scheme 202

In the case of such a result, the stereoselective generation of enolates from a range of allenic and propargylic substrates and the subsequent carbometallation of these anionic species would be examined.

It was discussed earlier how the carbometallation of the allene moiety could be occurring *via* either a *syn* or *anti* mechanism. In order to examine this mechanistic pathway in more detail a series of advanced experiments would be required. As depicted in Scheme (203) it is anticipated that the synthesis of an enantiomerically enriched homoallenol (636) and a study of the stereochemistry observed upon carbomagnesiation would be one such experiment suitable to determine the exact mechanistic pathway involved during the course of carbometallation (Scheme 203).



Scheme 203

Thus, deprotonation of homoallenol (636) to give the corresponding alkoxide (637) could be followed by carbomagnesiation, *via* either the *syn* (638) or *anti* (639) transition states. The absolute stereochemistry of the newly formed homoallylic alcohols would be dependent upon which mechanism is involved, thus, *syn* carbomagnesiation would be expected to lead to alcohol (643) whereas *anti* carbomagnesiation would lead to alcohol (642). Preparation of a stereochemically pure sample of either homoallylic alcohol (643) or (642) would then enable the determination of the absolute stereochemistry of the products formed *via* carbometallation of homoallenol (636), and in consequence, provide further information on the mechanism of this transformation.

CHAPTER 3

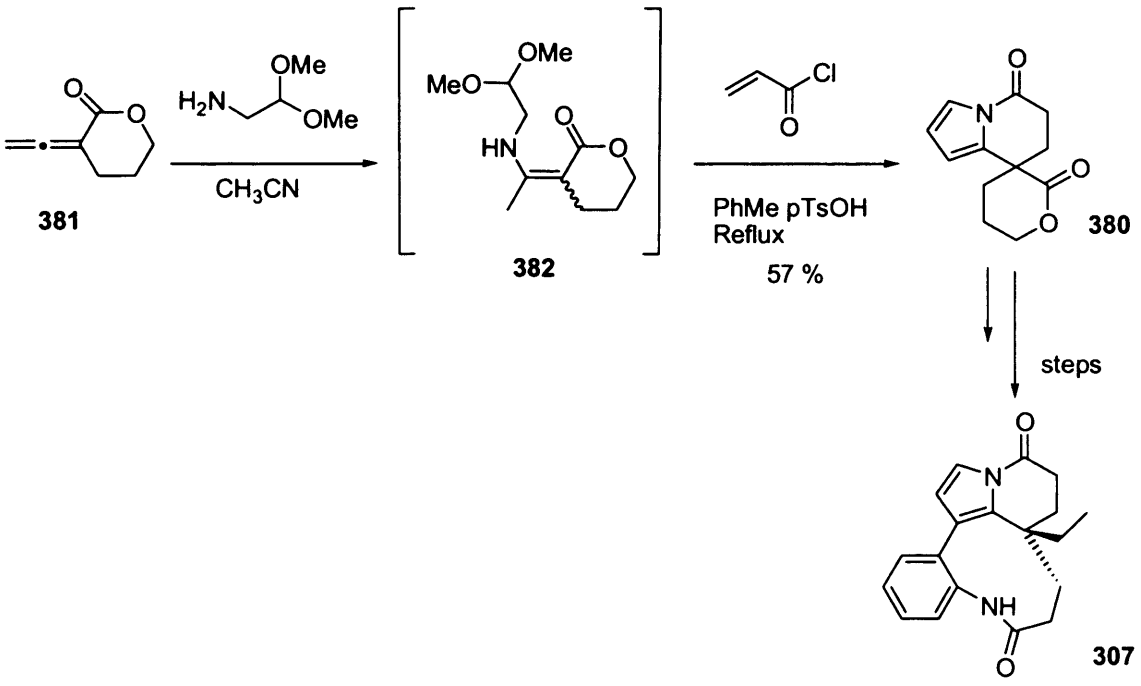
CONCLUDING REMARKS

3.0 Concluding Remarks

The foregoing chapter has demonstrated that allenic compounds offer the potential for the development of novel tandem reaction sequences enabling the preparation of a vast array of complex heterocyclic, carbocyclic and acyclic systems.

In section 2.1, the regioselective preparation of vinylogous urethanes and amides from allenic esters and ketones respectively, enabled the development of novel one pot aza-annulation methodology for the preparation of dihydropiperidinones, exocyclic enamides and bicyclic pyrroles.

It was described how this methodology was applied towards the synthesis of the cytotoxic alkaloid N-Oxo-rhazinilam (307), in which an efficient route to the proposed key intermediate tricyclic pyrrole (380) was developed (Scheme 204).

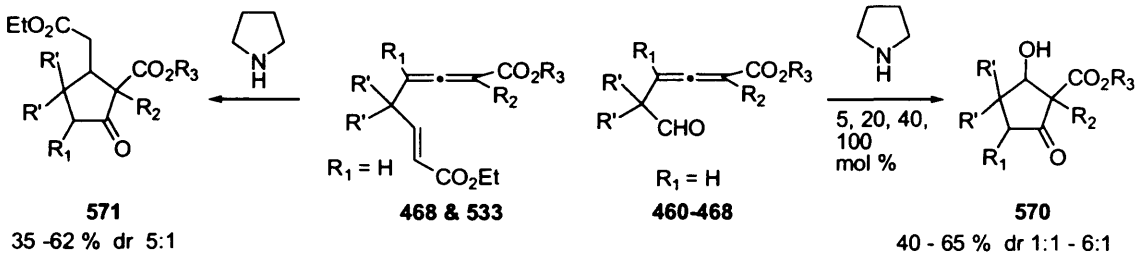


Scheme 204

Unfortunately, due to time constraints, the synthesis of the natural product could not be completed. However, it is hoped that the conversion of the tricyclic pyrrole (380)

into N-Oxo-rhazinilam should proceed with relative ease, following the synthetic sequence depicted in Scheme (122).

In section (2.2) the development of novel carbocyclisation methodology making use of readily prepared functionalised allenic esters was described. Thus, as depicted in Scheme (205), it was demonstrated that allenic esters (460-468) and their derivatives (468 & 533) undergo facile amine induced carbocyclisation to afford a range of substituted cyclopentanones (570) and (571). Preliminary experiments have shown that the development of catalytic and stereoselective variants of these novel transformations should be possible.



571
35 -62 % dr 5:1

468 & 533

460-468

570
40 - 65 % dr 1:1 - 6:1

Scheme 205

The final section of the foregoing chapter described our preliminary studies directed towards the development of novel carbomagnesiation reactions of allenic substrates. It must be stated that this area of study is still at an extremely premature stage and that a huge amount of work is still required in this area for a thorough understanding of the results presented, in terms of yields and selectivity's, to be achieved.

CHAPTER 4

EXPERIMENTAL PROCEDURES

4) EXPERIMENTAL

4.1 General Experimental Procedures.

Unless otherwise stated, all reactions were performed under an atmosphere of nitrogen using oven dried glassware, which was cooled under a flow of nitrogen prior to use. Benzene and DMSO were distilled from calcium hydride; THF, CH_2Cl_2, Et_2O, MeCN, toluene and *n*-hexane, were prepared as anhydrous, degassed solvents from anhydrous engineering® zeolite drying apparatus. Methanol was distilled from magnesium methoxide. Hexanes refers to light petroleum ether bp 40-60°C.

3.1.2 Data Collection.

Melting points were performed on a Reichert Thermovar hot stage apparatus and are uncorrected. Boiling points were measured during distillation.

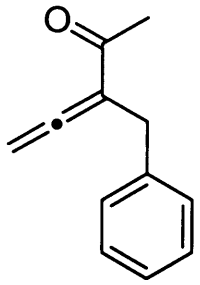
Proton magnetic resonance (^{1}H NMR) spectra were recorded at 300 MHz on a Bruker AMX300 spectrometer at 300K unless otherwise stated, and are reported as follows: chemical shift δ (ppm) (multiplicity, number of protons, assignment, coupling constant J (Hz)). The coupling constants are quoted to the nearest 0.1 Hz (s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, sp=septet m=multiplet, b=broad) and are reported as measured splittings on each individual resonance. The residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm, s) DMSO (δ_H = 2.50 ppm, qn) or MeOH (δ_H = 3.30 ppm, q) was used as an internal reference. ^{13}C spectra were recorded at 75 MHz on a Bruker AMX300 spectrometer (^{13}C NMR). The central reference of $CDCl_3$ (δ_C = 77.0 ppm, t), DMSO (δ_C = 39.4 ppm, septuplet) or MeOH (δ_C = 49.0 ppm, septuplet) was used as an internal reference. Chemical shifts are reported to the nearest 0.1 ppm or 0.01 ppm in cases where adjacent peaks are less than 0.1 ppm apart.

Infrared spectra were carried out on a Shimadzu FTIR –8700 and are recorded as a neat oil or a nujol® mull in between NaCl disks. Only selected absorbencies (ν_{max}) >1400 cm^{-1} are reported with the exception of strong structurally important fingerprint region peaks (1400-600 cm^{-1}).

Mass spectra and accurate mass measurements were recorded using a Micromass 70-SE magnetic sector spectrometer at the University College London Chemistry Department.

4.2 Tandem Reactions (I) – Development Of Aza-annulation Methodology

3-Benzylpenta-3,4-dien-2-one (216) [50]



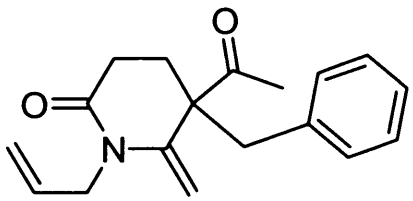
$C_{12}H_{12}O$ 172.22308 g mol^{-1}

To a solution of pentane-2,3-dione (10.00 g, 0.10 mol) , KI (8.30 g, 0.05 mol) and K_2CO_3 (15.20 g, 0.11 mol) in acetone (50 ml), was added benzyl bromide (18.80 g, 0.11 mol) dropwise. The solution was heated at reflux for 48 hrs and then cooled to room temperature. The mixture was filtered and the filtrate was concentrated at reduced pressure. The crude oil was added dropwise to a freshly prepared solution of $PPh_3.Br_2$ [137] (0.10 mol) in dry DCM (100 ml) at – 10 ° C. The mixture was allowed to warm to room temperature and stirred for 24 hrs. The solution was diluted with Et_2O (200 ml) and the resulting precipitate was filtered off. The filtrate was concentrated at reduced pressure and dissolved in dry acetonitrile (100 ml). The mixture was treated

with Et_3N (7.50 g, 75.00 mol) and heated at reflux for 23 hrs. To the resulting dark brown solution was added Et_2O (100 ml) and the precipitate was filtered off through a thick plug of SiO_2 (*ca.* 25 g). The filtrate was concentrated at reduced pressure to give a crude oil, which was purified by flash column chromatography eluting with petroleum ether / ethyl acetate (20:1) to give the title allenic ketone (216) (7.20 g, 42 %) as a pale yellow oil, with spectral data identical to that described in the literature.[50]

General Procedure (I) – Synthesis of Exocyclic Enamides

5-acetyl-1-allyl-5-benzyl-6-methylenepiperidin-2-one (219)

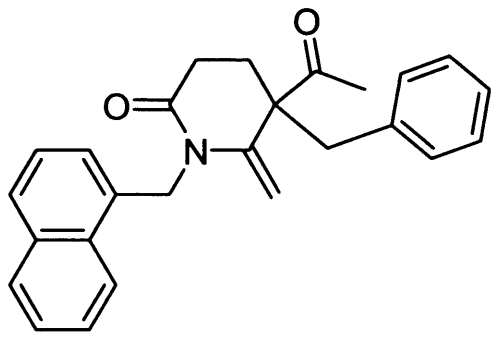


$C_{18}H_{21}NO_2$ 283.15723 g mol $^{-1}$

To a solution of allenic ketone (216) (0.23 g, 1.33 mmol), in dry acetonitrile (15 ml), was added allyl amine (0.08 g, 1.47 mmol) dropwise at room temperature. The solution was heated at reflux for 1 hr. The mixture was cooled, and acryloyl chloride (0.13 g, 1.47 mmol) was added dropwise. The solution was heated at reflux for 2 hrs, cooled to room temperature and then concentrated at reduced pressure. The crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (2:1) to give the title compound (219) (0.20 g, 53%) as a yellow oil. **HRMS**: **$C_{18}H_{21}NO_2$** (M+) Requires = 283.15722 (M+) Found = 283.15782 **IR** (neat) υ max (cm^{-1}): 3000 (CH), 1725, 1620 (C=O). **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.61 (m, 1H, **CH_2CH_2CO**), 2.13 (m, 1H, **CH_2CH_2CO**), 2.20 (s, 3H, Me), 2.35-2.49 (m, 2H,

CH_2CO), 2.96 (d, 1H, CH_2Ph, J = 13.7), 3.26 (d, 1H, CH_2Ph, J = 13.7), 4.18 (m, 1H, CH_2N), 4.62 (m, 1H, CH_2N), 4.61 (d, 1H, =CH, J = 2.5), 4.83 (d, 1H, =CH, J = 2.5), 5.1 (m, 2H, $=CH_2$), 5.8 (m, 1H, =CH), 7.02-7.05 (m, 2H, ArH), 7.19-7.54 (m, 3H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 206.5, 168.7, 147.2, 135.7, 132.4, 130.3, 128.5, 127.1, 116.8, 96.2, 56.2, 47.5, 41.6, 28.0, 25.8, 25.3.

5-Acetyl-5-benzyl-6-methylene-1-(naphthalen-1-ylmethyl)piperidin-2-one (220)

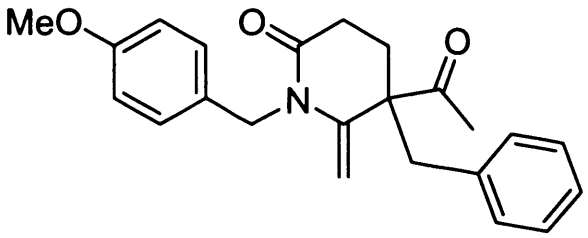


$C_{26}H_{25}NO_2$ 383.18853 g mol $^{-1}$

The title compound was prepared according to the general procedure (I) by reacting allenic ketone (216) (0.10 g, 0.58 mmol), naphthalen-1-ylmethanamine (0.09 g, 0.58 mmol) and acryloyl chloride (0.06 g, 0.65 mmol). The crude compound was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (2:1) to give the title compound (220) (0.15 g, 65%) as a clear oil. **HRMS**: **$C_{26}H_{25}NO_2$** (M+H) Requires = 384.19634 (M+) Found = 386.19484 **IR** (neat) υ max (cm^{-1}): 3060, 3010 (CH), 1708 (C=O), 1670 (C=O amide), 1624 (C=C), 1355. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.74 (td, 1H, **CH_2**CH_2CO, J = 2.4, 7.0), 2.05 (s, 1H, Me), 2.2 (m, 1H, **CH_2**CH_2CO), 2.53-2.68 (m, 2H, CH_2CO), 2.96 (d, 1H, CH_2Ph, J = 13.8), 3.32 (d, 1H, CH_2Ph, J = 13.8), 4.60 (d, 1H, =CH, J = 2.6), 4.65 (d, 1H, =CH, J = 2.6), 5.27 (d, 1H, CH_2N, J = 16.3), 5.60 (d, 1H, CH_2N, J = 16.3), 7.05-7.42 (m, 9H, ArH), 7.79 (d, 1H, ArH, J = 8.2), 7.88 (m, 1H, ArH), 8.00 (d, 1H, ArH, J = 8.0). **^{13}CNMR:**

$CDCl_3$ (75 MHz) δ ppm: 206.6, 169.4, 147.0, 135.7, 133.8, 130.8, 130.7, 130.3, 129.7, 128.9, 128.6, 128.3, 127.7, 127.2, 126.4, 125.8, 125.3, 123.4, 122.6, 97.5, 56.3, 46.5, 41.8, 29.1, 25.7, 25.5.

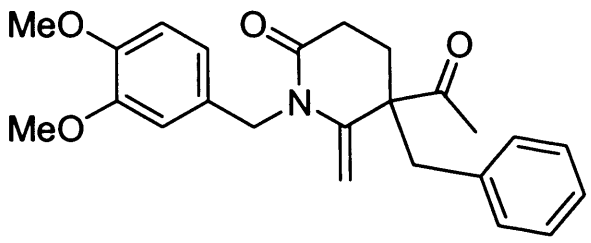
1-(4-Methoxybenzyl)-5-acetyl-5-benzyl-6-methylenepiperidin-2-one (232)



$C_{23}H_{25}NO_3$ 363.18344 g mol $^{-1}$

The title compound was prepared according to the general procedure (I), by reacting allenic ketone (216) (0.20 g, 1.16 mmol), *para*-methoxybenzylamine (0.16 g, 1.16 mmol) and acryloyl chloride (0.12 g, 1.12 mmol). The crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (3:1) to give the title heterocycle (232) (0.23 g, 54 %) as a clear oil. **HRMS**: **$C_{23}H_{25}NO_3$** (M+H) Requires = 364.19126 (M+H) Found = 364.19026 **IR** (neat) υ max (cm^{-1}): 3028, 3003, 2933 (CH), 1708 (C=O), 1670 (C=O amide), 1616 (C=C), 1514, 1496. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.64 (td, 1H, **CH_2**CH_2CO, J = 2.0, 6.8), 2.01 (s, 3H, Me), 2.12 (m, 1H, **CH_2**CH_2CO), 2.39-2.59 (m, 2H, CH_2CO), 2.91 (d, 1H, CH_2Ph, J = 13.7), 3.28 (d, 1H, CH_2Ph, J = 13.7), 3.77 (s, 3H, OMe), 4.61 (d, 1H, =CH, J = 2.4), 4.87 (d, 1H, =CH, J = 2.4), 5.0 (s, 2H, CH_2N), 6.85 (d, 2H, ArH, J = 8.5), 7.00 (m, 2H, ArH), 7.13 (d, 2H, ArH, J = 8.5) 7.22 (m, 3H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 206.7, 169.3, 158.7, 146.7, 135.7, 130.3, 128.9, 128.4, 128.2, 127.6, 127.1, 113.9, 96.9, 56.2, 55.3, 47.0, 41.7, 29.0, 25.7, 25.2.

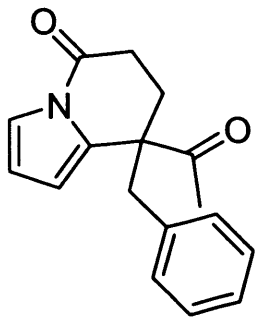
1-(3,4-Dimethoxybenzyl)-5-acetyl-5-benzyl-6-methylenepiperidin-2-one (233)



$C_{24}H_{27}NO_4$ 393.19401 g mol $^{-1}$

According to the general procedure (I) the title compound was prepared by the reaction of allenic ketone (216) (0.20 g, 1.16 mmol), 3,4-dimethoxybenzylamine (0.19 g, 1.16 mmol) and acryloyl chloride (0.12 g, 1.30 mmol). The crude product was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (1:1) to give the title compound (233) (0.22 g, 52 %) as a clear oil. **HRMS**: **$C_{24}H_{27}NO_4$** (M+H) Requires = 394.20182 (M+H) Found = 394.20222 **IR** (neat) υ max (cm^{-1}): 3012, 2935, 2835 (CH), 1708 (C=O), 1670 (C=O amide). **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.65 (m, 1H, **CH_2**CH_2CO), 2.01 (s, 3H, Me), 2.14 (m, 1H, **CH_2**CH_2CO), 2.44 (m, 1H, CH_2CO), 2.56 (m, 1H, CH_2CO), 2.90 (d, 1H, CH_2Ph, J = 13.8), 3.23 (d, 1H, CH_2Ph, J = 13.8), 3.77 (s, 3H, OMe), 3.81 (s, 3H, OMe), 4.62 (d, 1H, =CH, J = 2.4), 4.82 (d, 1H, =CH, J = 2.4), 4.96 (s, 2H, CH_2N), 6.70-6.87 (m, 3H, ArH), 7.00 (m, 2H, ArH), 7.19-7.46 (m, 3H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 206.7, 169.3, 149.2, 148.2, 146.7, 135.7, 130.2, 129.5, 128.3, 127.1, 119.5, 111.0, 110.5, 96.9, 56.1, 55.9, 47.4, 41.7, 29.0, 25.7, 25.2, 21.0.

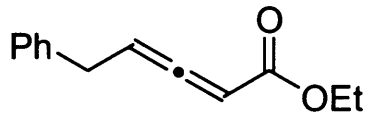
8-Acetyl-8-benzyl-7,8-dihydroindolizin-5(6H)-one (242)



$C_{17}H_{17}NO_2$ 267.12593 g mol^{-1}

To a solution of the allenic ketone (216) (0.20 g, 1.16 mmol) in dry acetonitrile (10 ml), was added aminoactealdehyde dimethyl-acetal (0.12 g, 1.16 mmol), dropwise at room temperature. The mixture was heated at reflux for 40 min and cooled to room temperature. Acryloyl chloride (0.11 g, 1.28 mmol) was added dropwise and the reaction mixture was heated at reflux for 1.5 hrs, cooled to room temperature and concentrated at reduced pressure. Purification of the crude compound by flash column chromatography, eluting with petroleum ether / ethyl acetate (3:1) gave the title compound (242) (0.10 g, 32%) as a white solid. **mp** 72-74 ° C. **HRMS: $C_{17}H_{17}NO_2$** (M+H) Requires = 268.13375. (M+H) Found = 268.13321. **IR** (nujol) υ max (cm^{-1}): 3020, 2923, 2852 (CH), 1720, 1712 (C=O), 1456, 1400. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.79 (m, 1H, **CH_2**CH_2CO), 2.19 (s, 3H, Me), 2.36 (m, 1H, **CH_2**CH_2CO), 2.57-2.69 (m, 2H, C**H_2**CO), 3.14 (d, 1H, CH_2Ph, J = 13.8), 3.41 (d, 1H, CH_2Ph, J = 13.8), 6.34 (t, 1H, ArH, J = 3.3), 6.39 (m, 1H, ArH), 7.05 (m, 2H, ArH), 7.23-7.28 (m, 3H, ArH), 7.41 (m, 1H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 207.3, 167.7, 135.3, 134.0, 130.0, 128.4, 127.2, 117.6, 112.8, 111.9, 52.9, 43.3, 30.4, 28.2, 26.7.

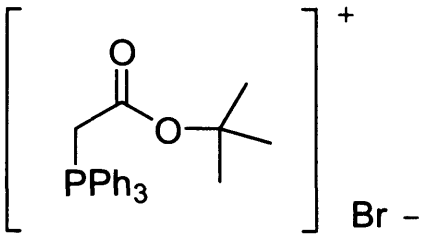
Ethyl 5-phenylpenta-2,3-dienoate (252) [134]



$C_{13}H_{14}O_2$ 202.09938 gmol^{-1}

The title allenic ester was prepared *via* a modified literature procedure.[134] To a solution of the commercially available ethoxycarbonylmethyl triphenylphosphonium bromide (247) (9.30 g, 21.70 mmol) in dry DCM (75 ml), at room temperature, was added a solution of Et_3N (4.40 g, 43.40 mmol) in dry DCM (25 ml) over a 10 minute period. The reaction mixture was stirred at room temperature for 40 minutes. At this point, a solution of 3-phenylpropionyl chloride (3.65 g, 21.70 mmol) in dry DCM (25 ml) was added slowly over 15 minutes. The reaction mixture was stirred at room temperature for 40 minutes and then concentrated at reduced pressure. The solid residue was taken up into Et_2O (150 ml) and filtered through a thick plug of silica gel (*ca.* 30 g). The filtrate was concentrated at reduced pressure to give a crude oil, purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (8:1) to give the title allene (252) (2.56 g, 58 %) as a pale yellow oil. **HRMS:** **$C_{13}H_{14}O_2$** (M+) requires 202.09938 (M+) Found = 202.09953 **IR** (neat) υ max (cm^{-1}): 2090 (C=C=C), 1750 (C=O). **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.30 (t, 3H, CH_3, *J* = 7.12), 3.49 (m, 2H, CH_2Ph), 4.18 (m, 2H, CH_2), 5.62 (m, 1H, =CH), 5.77 (m, 1H, =CH) 7.20-7.46 (m, 5H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 212.8, 165.9, 138.7, 128.5, 128.4, 126.6, 94.7, 88.6, 60.9, 34.2, 14.3.

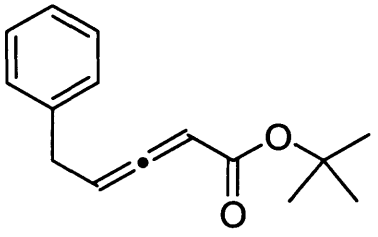
Phosphonium salt (249) [135]



$C_{24}H_{26}BrO_2P$ 456.08538 g mol $^{-1}$

To a solution of triphenylphosphine (29.60 g, 112.80 mmol), in benzene (300 ml) and hexane (300 ml), was added the commercially available tert-butyl 2-bromoacetate (20.00 g, 102.53 mmol), dropwise at room temperature. The mixture was stirred for 24 hrs and the precipitate was collected by suction filtration. The white solid was washed with benzene (30 ml) and Et_2O (30 ml). Drying under suction gave the pure phosphonium salt (249) (29.00 g, 62 %) with spectroscopic properties identical to those reported previously. [135]

tert-Butyl 5-phenylpenta-2,3-dienoate (254)

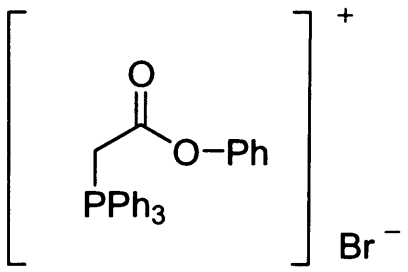


$C_{15}H_{18}O_2$ 230.13068 g mol $^{-1}$

To a solution of phosphonium salt (249) (5.25 g, 11.00 mmol) in dry DCM (50 ml) at room temperature was added a solution of Et_3N (2.32 g, 22.00 mmol) in dry DCM (10 ml), dropwise over 5 minutes. The solution was allowed to stir for 1.5 hrs and a solution of 2-phenylacetyl chloride (1.85 g, 11.00 mmol) in dry DCM (15 ml), was added dropwise over a 15 minute interval. The reaction mixture was allowed to stir at

room temperature for 2 hrs and then concentrated at reduced pressure. The residual oil was treated with Et_2O (50 ml) and the precipitate filtered off through a thick plug of silica gel (*ca.* 30 g). The filtrate was concentrated at reduced pressure and the crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (10:1) to give the title allenic ester (254) (1.24 g, 49%) as a clear oil. **HRMS:** **$C_{15}H_{18}O_2$** (M+Na) requires = 253.12044 (M+Na) Found = 253.11990. **IR** (neat) υ max (cm^{-1}): 3062, 3028, 2979 (CH), 1961 (C=C=C), 1705 (C=O), 1305. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.49 (s, 9H, Me), 3.46 (m, 2H, CH_2Ph), 5.53 (m, 1H, =CH), 5.72 (m, 1H, =CH), 7.19-7.49 (m, 5H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 212.3, 165.2, 138.9, 128.6, 128.5, 126.6, 94.4, 90.2, 80.9, 34.2, 28.1.

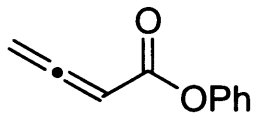
Phosphonium Salt (250) [136]



$C_{26}H_{22}BrO_2P$ 476.05408 g mol^{-1}

To a solution of triphenylphosphine (14.60 g, 56.00 mmol), in toluene (70 ml) was added a solution of the commercially available phenyl 2-bromoacetate (10.00 g, 46.55 mmol) in toluene (70 ml), dropwise over 10 minutes. The mixture was stirred for 24 hrs and the precipitate was collected by suction filtration. The white solid was washed with benzene (50 ml). Drying under suction gave the pure phosphonium salt (250) (12.50 g, 56 %) with spectroscopic properties identical to those reported previously.[136]

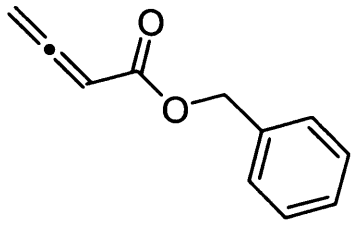
Phenyl buta-2,3-dienoate (255)



$C_{10}H_8O_2$ 160.05243 g mol $^{-1}$

To a solution of phosphonium salt (250) (5.00 g, 12.65 mmol) in dry DCM (40 ml) at room temperature, was added a solution of Et_3N (2.60 g, 25.30 mmol) in dry DCM (20 ml) over a 5 minute interval. The mixture was allowed to stir at room temperature for 40 minutes, at which point, a solution of acetyl chloride (0.99 g, 12.70 mmol) in dry DCM (20 ml) was added dropwise over 10 minutes. The reaction mixture was allowed to stir at room temperature for 1.5 hrs and then concentrated at reduced pressure. The resulting oil was treated with Et_2O (40 ml) and the solution was filtered through a thick plug of silica gel (*ca.* 30 g). The filtrate was concentrated at reduced pressure to give a crude oil. Purification by flash column chromatography, eluting with petroleum ether / ethyl acetate (4:1) gave the title allenic ester (255) (0.95 g, 48%) as a clear oil. **HRMS: $C_{10}H_8O_2$** (M+) requires 160.05243 (M+) Found = 160.05206. **IR** (neat) υ max (cm^{-1}): 3050 (CH), 1967 (C=C=C), 1735 (C=O), 1596, 1488. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 5.35 (d, 2H, $=CH_2$, J = 3.8), 5.85 (t, 1H, =CH, J = 3.8), 7.11 (d, 2H, *o*ArH, J = 5.4), 7.22-7.65 (m, 3H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 216.0, 164.2, 150.8, 129.4, 125.9, 121.5, 87.2, 79.8.

Benzyl buta-2,3-dienoate (256)

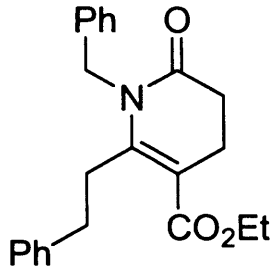


$C_{11}H_{10}O_2$ 174.06808 g mol $^{-1}$

To a solution of the commercially available benzyl-(triphenylphosphoranylidene acetate (251) (15.00 g, 36.50 mmol), in dry DCM (100 ml) at room temperature, was added Et_3N (3.70 g, 36.50 mmol) dropwise. The solution was allowed to stir at room temperature for 1 hour and then the solution was cooled in an ice bath as acetyl chloride (3.15 g, 40.15 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 hrs. The solution was concentrated at reduced pressure and Et_2O (100 ml) was added to the crude oil. The precipitate was removed by filtration through a thick plug of SiO_2 gel (*ca.* 30 g). The filtrate was concentrated at reduced pressure and the crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (10:1), to give the title compound (256) (3.25 g, 51 %) as a clear oil. **HRMS: $C_{11}H_{10}O_2$** (M+H) requires = 175.07590 (M+H) Found = 175.07553. **IR** (neat) υ max (cm^{-1}): 3066, 3033, 2991, 2954 (CH), 1969 (C=C=C), 1718 (C=O) **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 5.20 (s, 2H, CH_2Ph), 5.23 (d, 2H, $=CH_2$, J = 6.4), 5.69 (t, 1H, =CH, J = 6.4), 7.33-7.39 (m, 5H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 216.0, 165.6, 135.9, 128.6, 128.2, 128.1, 87.9, 79.4, 66.7.

General Procedure (II) – Synthesis Of Dihydropiperidinones (263-268)

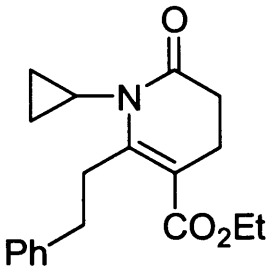
Ethyl 1-benzyl-6-oxo-2-phenethyl-1,4,5,6-tetrahydropyridine-3-carboxylate (263)



$C_{23}H_{25}NO_3$ 363.18344 $gmol^{-1}$

To a solution of allenic ester (252) (0.20 g, 1.00 mmol) in dry acetonitrile (10 ml) was added benzylamine (0.11 g, 1.00 mmol) dropwise at room temperature followed by *para*-toluenesulfonic acid (25 mg). The reaction mixture was heated at reflux for 0.5 hrs and then cooled to room temperature. Freshly distilled acryloyl chloride (0.10 g, 1.10 mmol) was added dropwise to the solution. The mixture was heated at reflux for 2 hrs, cooled to room temperature and concentrated at reduced pressure. The crude compound was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (4:1) to give the title heterocycle (263) (0.24 g, 66%) as a yellow oil. **HRMS: $C_{23}H_{25}NO_3$** (M+H) requires = 364.19072 (M+H) found = 364.19112. **IR** (neat) υ max (cm^{-1}): 3062, 3026, 2902 (CH), 1670, 1616 (C=O). **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.25 (t, 3H, CH_3, J=7.2), 2.60 (m, 2H, **CH_2**CH_2CO), 2.65 (m, 2H, **CH_2**CO), 2.75 (t, 2H, CH_2CN, J = 7.4), 3.06 (t, 2H, CH_2Ph, J = 7.4), 4.22 (q, 2H, CH_2, J = 7.2), 5.27 (s, 2H, CH_2N), 7.13-7.54 (m, 10H, ArH) . **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 171.7, 166.9, 151.7, 140.6, 137.7, 128.9, 128.5, 128.3, 127.3, 126.3, 126.2, 110.5, 60.4, 44.7, 35.4, 31.5, 31.0, 21.2, 14.3.

Ethyl 1-cyclopropyl-6-oxo-2-phenethyl-1,4,5,6-tetrahydropyridine-3-carboxylate (264)

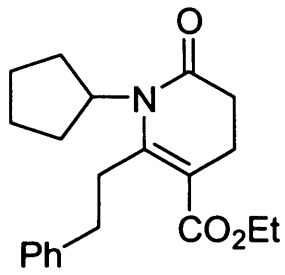


$C_{19}H_{23}NO_3$ 313.16779 g mol $^{-1}$

According to the general procedure (II), the title heterocycle was prepared by the reaction of cyclopropylamine (0.06 g, 1.00 mmol), allenic ester (252) (0.20 g, 1.00 mmol) and acryloyl chloride (0.10 g, 1.10 mmol). The crude compound was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (4:1) to give the title compound (264) (0.15 g, 48%) as a white solid. **Mp (°C)** = 50-52 **HRMS:** $C_{19}H_{23}NO_3$ (M+H) requires = 314.17562 (M+H) found = 314.17544 **IR** (nujol) υ max (cm^{-1}): 3014, 2981 (CH), 1689 (C=O), 1620 (C=O), 1454, 1276. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 0.55 (m, 2H, ^{cy}Pr CH_2), 1.00 (m, 2H, ^{cy}Pr CH_2), 1.30 (t, 3H, CH_3, J = 7.2), 2.33 (2d, 2H, **CH_2**CH_2CO, J = 6.1, 5.1), 2.40 (2d, 2H, CH_2CO, J = 6.1, 5.1), 2.46 (m, 1H, CHN), 2.83 (t, 2H, C**H_2**CH_2Ph, J = 7.3), 3.37 (t, 2H, CH_2Ph, J = 7.3), 4.17 (q, 2H, CH_2, J = 7.2), 7.15-7.30 (m, 5H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 173.5, 166.8, 153.4, 140.7, 128.43, 128.42, 126.3, 111.7, 60.3, 35.7, 32.6, 31.0, 25.2, 20.7, 14.4, 9.9.

Ethyl 1-cyclopentyl-6-oxo-2-phenethyl-1,4,5,6-tetrahydropyridine-3-carboxylate

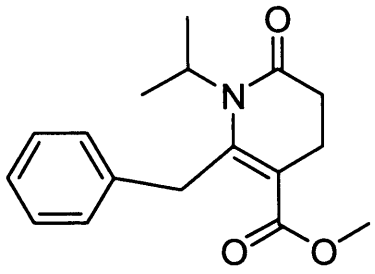
(265)



$C_{21}H_{27}NO_3$ 341.19909 gmol^{-1}

According to the general procedure (II) the title heterocycle (265) was prepared by the reaction of cyclopentylamine (0.09 g, 1.00 mmol), allenic ester (252) (0.20 g, 1.00 mmol) and acryloyl chloride (0.10 g, 1.00 mmol). The crude product was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (4:1) to give the title compound (265) (0.17 g, 48%) as a pale yellow solid. **Mp** (° C) 41-42. **HRMS:** $C_{21}H_{27}NO_3$ (M+H) requires 342.20691 (M+H) found = 342.20704. **IR** (neat) υ max (cm^{-1}): 2954 (CH), 1681 (C=O), 1604 (C=O), 1365, 1272. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.30 (t, 3H, CH_3, J = 7.2), 1.54-2.13 (m, 8H, $4CH_2$), 2.35 (m, 2H, $\mathbf{CH_2}CH_2CO$), 2.50 (m, 2H, CH_2CO), 2.83 (m, 2H, $\mathbf{CH_2}CH_2Ph$), 3.18 (m, 2H, CH_2Ph), 4.20 (q, 2H, CH_2, J = 7.2), 4.25 (m, 1H, CHN), 7.10-7.40 (m, 5H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 171.8, 167.1, 153.1, 140.7, 128.5, 128.4, 126.3, 111.3, 60.3, 57.2, 35.4, 33.2, 31.7, 29.9, 25.8, 21.0, 14.4.

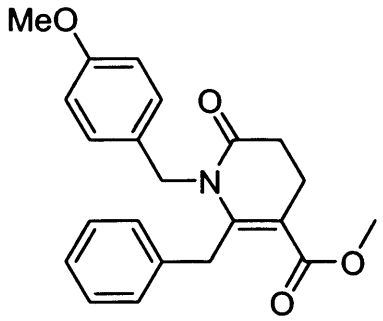
Methyl 2-benzyl-1-isopropyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (266)



$C_{17}H_{21}NO_3$ 287.15214 g mol $^{-1}$

The title dihydro-piperidinone (266) was prepared according to the general procedure (II) by reacting allenic ester (253) (0.20 g, 1.15 mmol), isopropylamine (0.07 g, 1.15 mmol) and acryloyl chloride (0.12 g, 1.30 mmol). The crude product was purified by flash column chromatography eluting with petroleum ether / ethyl acetate (2:1) to give the title compound (266) (0.18 g, 54%) as a clear oil. **HRMS: $C_{17}H_{21}NO_3$** (M+H) Requires = 288.15996 (M+H) Found = 288.16003. **IR** (neat) υ max (cm^{-1}): 3050 (CH), 1701 (C=O), 1612 (C=O), 1407. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.21 (d, 6H, Me_2, *J* = 7.0), 2.45 (m, 2H, **CH_2CH_2CO**), 2.64 (m, 2H, CH_2CO), 3.66 (s, 3H, OMe), 3.91 (sp, 1H, CHN, *J* = 7.0), 4.33 (s, 2H, CH_2Ph), 7.10-7.30 (m, 5H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 171.8, 167.7, 150.4, 132.5, 128.7, 127.8, 126.4, 111.9, 51.6, 49.3, 35.1, 33.0, 21.4, 20.2

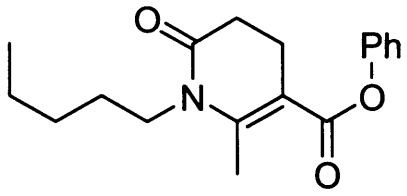
Methyl-1-(4-methoxybenzyl)-2-benzyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (267)



$C_{22}H_{23}NO_4$ 365.16271 g mol $^{-1}$

The title compound was prepared according to the general procedure (II) by reacting allenic ester (253) (0.20g, 1.15 mmol), *para*-methoxybenzylamine (0.16 g, 1.15 mmol) and acryloyl chloride (0.12 g, 1.26 mmol). The crude product was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (2:1) to give the title compound (267) (0.26 g, 62 %) as a clear viscous oil. **HRMS:** **$C_{22}H_{23}NO_4$** (M+H) Requires = 366.17052. (M+H) Found = 366.16967. **IR** (neat) υ max (cm^{-1}): 3014, 2950 (CH), 1681, 1616 (C=O), 1514, 1434. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 2.65 (m, 2H, **CH_2CH_2CO**), 2.75 (m, 2H, CH_2CO), 3.70 (s, 3H, CO_2Me), 3.75 (s, 3H, OMe), 4.20 (s, 2H, CH_2Ph), 4.8 (s, 2H, CH_2N), 6.85 (d, 2H, ArH, *J* = 8.8), 7.05 (d, 2H, ArH, *J* = 8.8), 7.25-7.4 (m, 5H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 171.4, 167.6, 158.8, 149.5, 137.0, 129.7, 128.9, 126.7, 127.6, 127.3, 114.3, 111.7, 55.3, 51.7, 43.8, 34.3, 31.4, 21.6

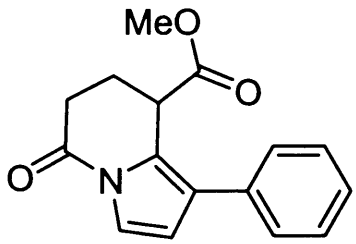
Phenyl 2-methyl-6-oxo-1-pentyl-1,4,5,6-tetrahydropyridine-3-carboxylate (268)



$C_{18}H_{23}NO_3$ 301.16779 g mol $^{-1}$

The title compound was prepared according to the general procedure (II) reacting allenic ester (255) (0.22 g, 1.40 mmol), pentylamine (0.12 g, 1.40 mmol) and acryloyl chloride (0.14 g, 1.54 mmol). The crude product was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (3:1) to give the title heterocycle (268) (0.28 g, 65%) as a clear oil. **HRMS: $C_{18}H_{23}NO_3$** (M+H) Requires = 302.17561. (M+H) Found = 302.17535. **IR** (neat) υ max (cm^{-1}): 2958, 2929, 2869, 2858 (CH), 1720, 1662 (C=O), 1492, 1365. **^{1}H NMR:** $CDCl_3$ (300 Mz) δ ppm: 0.91 (t, 3H, CH_3, *J* = 7.0), 1.25-1.40 (m, 6H, $3CH_2$), 2.50 (s, 3H, Me), 2.50 (t, 2H, **CH_2**CH_2CO, *J* = 7.9), 2.73 (t, 2H, CH_2CO, *J* = 7.9), 3.84 (t, 2H, CH_2N, *J* = 6.6) 6.57-7.41 (m, 5H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 171.1, 166.1, 156.5, 151.1, 129.4, 121.8, 115.4, 107.9, 42.2, 31.3, 29.0, 28.9, 22.3, 21.1, 16.5, 14.0.

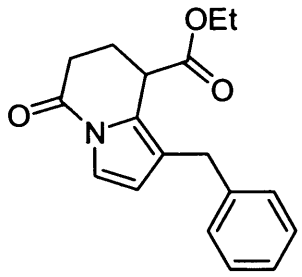
Methyl 5-oxo-1-phenyl-5,6,7,8-tetrahydroindolizine-8-carboxylate (273)



$C_{16}H_{15}NO_3$ 269.10569 g mol $^{-1}$

To a solution of the allenic ester (253) (0.20 g, 1.15 mmol) in dry acetonitrile (10 ml) was added *para*-toluenesulfonic acid (30 mg) followed by aminoactealdehyde-dimethyl acetal (0.12 g, 1.15 mmol).The reaction mixture was heated at reflux for 1.5 hrs. After cooling to room temperature, acryloyl chloride (0.10 g, 1.30 mmol) was added dropwise and the reaction mixture was heated at reflux for a further 1.5 hrs. The solution was cooled to room temperature and concentrated at reduced pressure. The crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (2:1) to give the title compound (273) (0.17 g, 54%) as a clear oil. **HRMS: $C_{16}H_{15}NO_3$** (M+H) Requires = 270.11301 (M+H) Found = 270.11309 **IR** (neat) υ max (cm^{-1}): 3055 (CH), 1738 (C=O, ester), 1654 (C=O, amide) 1436 **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 2.28-2.44 (m, 2H, **CH_2**CH_2CO), 2.69-2.87 (m, 2H, CH_2CO), 3.66 (s, 3H, OMe), 4.11 (m, 1H, $CHCO_2Me$), 6.46 (d, 1H, ArH, J = 3.4), 7.28-7.50 (m, 5H, ArH), 7.5 (d, 1H, ArH, J = 3.4). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 172.4, 167.5, 134.4, 128.6, 127.7, 126.9, 126.4, 124.8, 117.4, 113.6, 52.6, 38.5, 30.2, 25.4, 14.2.

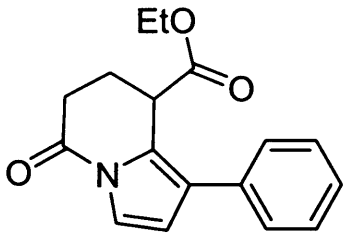
Ethyl 1-benzyl-5-oxo-5,6,7,8-tetrahydroindolizine-8-carboxylate (274)



$C_{18}H_{19}NO_3$ 297.13649 g mol $^{-1}$

To a solution of allenic ester (252) (0.22 g, 1.08 mmol) in dry acetonitrile (10 ml) was added aminoactealdehyde-dimethyl acetal (0.11 g, 1.08 mmol) and *para*-toluenesulfonic acid (40 mg). The reaction mixture was heated at reflux for 40 minutes. The solution was cooled to room temperature and acryloyl chloride (0.11 g, 1.18 mmol) was added. The mixture was heated at reflux for 8 hrs, cooled and concentrated at reduced pressure. The crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (3:1), to give the title heterocycle 274) (0.13 g, 40 %) as a yellow solid. **Mp (^{o} C)** = 55-57. **HRMS:** **$C_{18}H_{19}NO_3$** (M+H) Requires = 298.14431 (M+H) Found = 298.14378 **IR** (nujol) υ max (cm^{-1}): 2952, 2852 (CH), 1725 (C=O), 1700 (C=O), 1460, 1375. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.14 (t, 3H, CH_3, *J* = 7.2), 2.21 (m, 1H, **CH_2**$CHCO_2Et$), 2.41 (m, 1H, **CH_2**$CHCO_2Et$), 2.67 (m, 1H, CH_2CO) 2.98 (m, 1H, CH_2CO), 3.80 (s, 2H, CH_2Ph), 3.93 (dd, 1H, $CHCO_2Et$, *J* = 2.94, 5.62), 4.06 (m, 2H, CH_2), 6.09 (d, 1H, ArH, *J* = 3.5), 7.15-7.30 (m, 5H, ArH), 7.38 (d, 1H, ArH, *J* = 3.5) $CDCl_3$ (75 MHz) δ ppm:171.5, 167.5, 140.2, 128.5, 128.4, 126.1, 125.1, 124.2, 116.7, 114.6, 61.4, 36.8, 31.9, 29.9, 24.5, 14.0

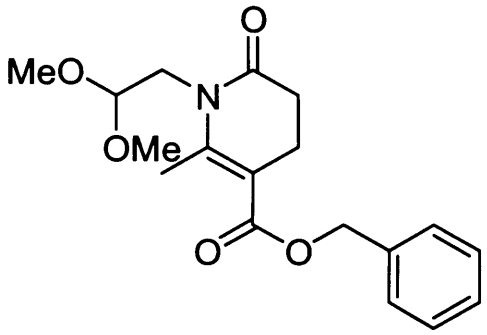
Ethyl-5-oxo-1-phenyl-5,6,7,8-tetrahydroindolizine-8-carboxylate (275)



$C_{17}H_{17}NO_3$ 283.12084 g mol $^{-1}$

To a solution of allenic ester (272) (0.55 g, 2.93 mmol), in dry acetonitrile (20 ml) was added aminoactealdehyde-dimethyl acetal (0.31 g, 2.93 mmol), and *para*-toluenesulfonic acid (30 mg). The reaction mixture was heated at reflux for 1 hour, cooled to room temperature and acryloyl chloride (0.29 g, 3.20 mmol), was added dropwise. The mixture was heated at reflux for 24 hrs, cooled and concentrated at reduced pressure. The crude compound was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (3:1), to give the title heterocycle (275) (0.43 g, 51%) as a brown oil. **HRMS: $C_{17}H_{17}NO_3$** (M+) Requires = 283.12084 (M+) Found = 283.12009 **IR** (neat) υ max (cm^{-1}): 3050 (CH) 1725 (C=O) ester, 1650 (C=O) amide. **^{1}H NMR:** $CDCl_3$ (300MHz) δ ppm: 1.18 (t, 3H, CH_3, J = 7.2), 2.22-2.46 (m, 2H, CH_2CH_2CO), 2.72 (dt, 1H CH_2CO, J = 9.1, 4.3), 2.90 (m, 1H, CH_2CO), 4.09 (m, 1H, $CHCO_2Et$), 4.12 (m, 2H, CH_2CH_3), 6.47 (d, 1H, =CH, J = 3.5), 7.30-7.42 (m, 5H, ArH), 7.50 (d, 1H, =CHN, J = 3.5) **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 171.8, 167.6, 134.5, 128.6, 127.7, 126.3, 124.9, 117.7, 113.6, 61.5, 38.5, 30.2, 27.2, 25.3, 14.0.

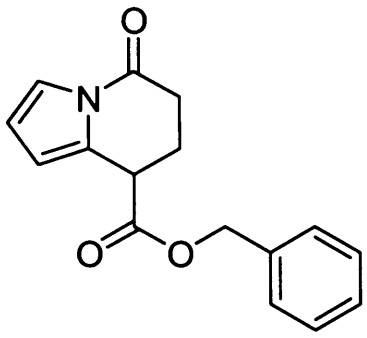
Benzyl 1-(2,2-dimethoxyethyl)-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (276)



$C_{18}H_{23}NO_5$ 333.15762 g mol $^{-1}$

To a solution of allenic ester (256) (0.35 g, 2.01 mmol), in dry acetonitrile (20 ml), was added aminoacetaldehyde-dimethylacetal (0.21 g, 2.01 mmol), dropwise at room temperature. The reaction mixture was stirred for 1 hour and then cooled in an ice bath as pyridine (0.19 g, 2.41 mmol) followed by acryloyl chloride (0.23 g, 2.61 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature overnight. The solution was diluted with ethyl acetate (30 ml) and washed with saturated aqueous $CuSO_4$ solution (2 x 10 ml), dried ($MgSO_4$) and then concentrated at reduced pressure to give the title compound (276) (0.60 g, 90%) essentially free from impurities. **HRMS: $C_{18}H_{23}NO_5$** (M+Na) Requires = 356.14739 (M+) Found = 356.14612 **IR** (neat) υ max (cm^{-1}): 3057, 2939, 2910 (CH), 1683, 1620 (C=O). **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 2.46 (s, 3H, Me), 3.37 (s, 6H, $(OMe)_2$), 3.64 (d, 2H, CH_2N, J = 5.4), 4.43 (t, 1H, $CH(OMe)_2$, J = 5.4), 5.15 (s, 2H, CH_2Ph), 7.31-7.37 (m, 5H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 171.2, 167.2, 149.6, 136.2, 128.4, 128.1, 108.6, 103.2, 66.2, 66.1, 55.5, 44.5, 31.2, 21.1, 16.8

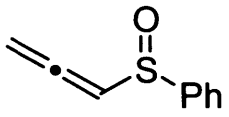
Benzyl 5-oxo-5,6,7,8-tetrahydroindolizine-8-carboxylate (277)



$C_{16}H_{15}NO_3$ 269.10519 g mol $^{-1}$

To a solution of allenic ester (256) (0.35 g, 2.01 mmol), in dry acetonitrile (20 ml), was added aminoactealdehyde dimethyl-acetal (0.21 g, 2.10 mmol). The reaction mixture was stirred at room temperature for 3 hrs. At this point acryloyl chloride (0.24 g, 2.61 mmol) was added and the reaction mixture was heated at reflux for 12 hrs. The reaction mixture was cooled and concentrated at reduced pressure and the crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (2 : 1) to give the title compound (277) (0.13 g, 24 %) as a pale yellow oil. **HRMS:** $C_{16}H_{15}NO_3$ (M+) Requires = 269.10464 (M+) Found = 269.10422 **IR** (neat) υ max (cm^{-1}): 3033, 2958, 2893 (CH), 1728 (C=O, ester), 1654 (C=O, amide) **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 2.30 (m, 2H, CH_2CH_2CO), 2.65 (m, 1H, CH_2CO), 2.85 (m, 1H, CH_2CO), 3.95 (t, 1H, $CHCO_2Ph$, J = 5.60), 5.22 (s, 2H, CH_2Ph), 6.15 (d, 1H, ArH, J = 2.8), 6.23 (t, 1H, ArH, J = 3.6), 7.25-7.45 (m, 6H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 171.1, 167.3, 135.4, 128.7, 128.5, 128.4, 128.2, 117.0, 112.6, 111.3, 67.1, 39.1, 30.8, 24.5.

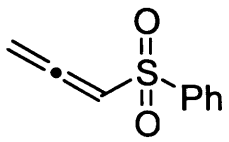
1-(Propa-1,2-dienylsulfinyl)benzene (283) [136]



C_9H_8OS 164.02959 g mol $^{-1}$

SO_2Cl_2 (8.09 g, 0.06 mol) was cooled to 0 ° C and thiophenol (6.60 g, 0.06 mol) was added dropwise with vigorous stirring. Upon completion of the addition a small vacuum was applied to the reaction flask and the mixture was left to stand for 5 minutes. To this concentrated solution was added dry Et_2O (35 ml). This deep red solution was transferred *via* cannular, to a mixture of propargyl alcohol (3.40 g, 0.06 mol) and Et_3N (6.07 g, 0.06 mol) at – 80 ° C, in dry Et_2O (100 ml). The solution was stirred at – 80 ° C for 1 hour and then warmed to room temperature. The solution was diluted with 30 ml of aqueous HCl (1 %). The phases were separated and extracted with Et_2O (3 x 50 ml). The combined organic fractions were washed with brine (30 ml), dried ($MgSO_4$) and then concentrated at reduced pressure. The crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (1:1), to give the title allene (9.20 g, 95 %) as a pale yellow oil, with spectroscopic properties identical to those reported previously.[136]

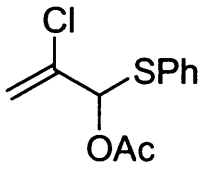
1-(Propa-1,2-dienylsulfonyl)benzene (284) [137]



$C_9H_8O_2S$ 180.02450 g mol $^{-1}$

Allenic sulfoxide (283) (4.00 g, 24.40 mmol) was dissolved in DCM (40 ml) and cooled in an ice bath. To this chilled solution was added *meta*-chloroperoxybenzoic acid (6.40 g, 24.40 mmol), in small portions, over a 10 minute period. The solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was washed with saturated $NaHCO_3$ solution (3 x 10 ml) and then the organic phase was concentrated at reduced pressure. The residual oil was allowed to stand overnight in the freezer. The resulting white solid was recrystallised from a hexane / Et_2O mixture (5 : 1), to give the title allene (284) (2.00 g, 50 %) as a white crystalline solid, with spectroscopic and physical properties identical to those reported previously. **Mp (° C)** Literature = 44-45 **Mp (° C)** Found = 45-47.

2-Chloro-1-(phenylthio)allyl acetate (294)

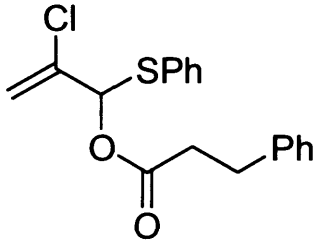


$C_{11}H_{11}ClO_2$ 242.01683 g mol $^{-1}$

To a solution of the allenic sulfoxide (283) (0.14 g, 0.85 mmol), in dry DCM (10 ml), cooled to – 78 ° C, was added acetyl chloride (0.07 g, 0.93 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 12 hrs. The mixture was concentrated at reduced pressure and the crude compound was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (12:1), to give the title compound (0.09 g, 50%) as a pale yellow oil. **HRMS**: **$C_{11}H_{11}ClO_2$** (M+)

Requires = 242.01683 (M+) Found = 242.01633. **IR** (neat) υ max (cm^{-1}): 3060 (CH), 1755 (C=O), 1629 (C=C) 1209 (C-O).**^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 2.12 (s, 3H, Me), 5.28 (d, 1H, =CH, *J* = 1.6), 5.32 (d, 1H, =CH, *J* = 1.6), 6.42 (s, 1H, CH), 7.30-7.35(m, 3H, ArH), 7.50-7.55 (m, 2H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 168.6, 135.9, 134.8, 130.3, 129.1, 128.9, 115.0, 81.1, 20.9.

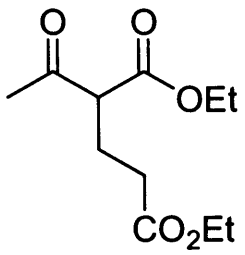
2-Chloro-1-(phenylthio)allyl 3-phenylpropanoate (295)



$C_{18}H_{17}ClO_2S$ 332.06378 g mol $^{-1}$

To a solution of the allenic sulfoxide (283) (0.14 g, 0.85 mmol), in dry DCM (10 ml), cooled to – 78 ° C, was added 3-phenyl-propionyl chloride (0.16 g, 0.93 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 12 hrs. The solution was concentrated at reduced pressure and the crude compound was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (10:1), to give the title compound (0.09 g, 50%) as a yellow oil. **HRMS**: **$C_{18}H_{17}ClO_2S$** (M+) Requires = 332.06377 (M+) Found = 332.063848. **IR** (neat) υ max (cm^{-1}): 3060 (CH), 1751 (C=O), 1629 (C=C), 1218 (C-O).**^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 2.71 (t, 2H, CH_2Ph, *J* = 7.5), 2.96 (t, 2H, CH_2CO, *J* = 7.5), 5.22 (d, 1H, =CH, *J* = 1.6), 5.24 (d, 1H, =CH, *J* = 1.6) 6.44 (s, 1H, CH), 7.17-7.54 (m, 10H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 170.6, 139.9, 135.9, 134.8, 130.2 129.0, 128.9, 128.6, 128.2, 126.4, 115.0, 81.1, 35.7, 30.6

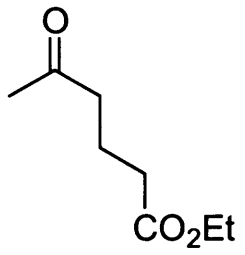
Diethyl 2-acetylpentanedioate (348) [138]



$C_{11}H_{15}O_5$ 230.11542 g mol^{-1}

To solution of ethylacetoacetate (10.80 g, 83.00 mmol) in acetone (50 ml) was added KI (7.60 g, 46.00 mmol), K_2CO_3 (12.70 g, 92.00 mmol) followed by the dropwise addition of ethyl 3-bromopropanoate (16.80 g, 92.00 mmol). The solution was heated at reflux for 68 hrs, cooled to room temperature, filtered and then concentrated at reduced pressure to give the title compound (348) (12.45 g, 65 %) which was used without further purification, and with spectral properties identical to those reported previously. [138]

Ethyl 5-oxohexanoate (349)[139]

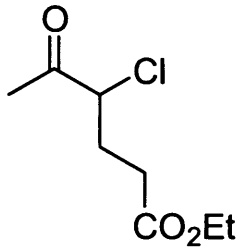


$C_8H_{14}O_3$ 158.09429g mol^{-1}

A solution of β-ketoester (348) (10.00 g, 43.50 mmol) in 4N HCl (35 ml) was heated at reflux for 5 hrs. The reaction mixture was cooled to room temperature and extracted with DCM (3 x 30 ml). The combined extracts were washed with brine (30 ml) and concentrated to give a misty oil. This oil was dissolved in absolute ethanol

(75 ml) and acetyl chloride (5 ml) was added. The solution was heated at reflux for 2 hrs and then concentrated at reduced pressure. The crude compound was purified by flash column chromatography eluting with petroleum ether / ethyl acetate (7:1) to give the title compound as a pale yellow liquid (4.10 g, 60 % over 2 steps) with spectral properties identical to those previously reported.[139]

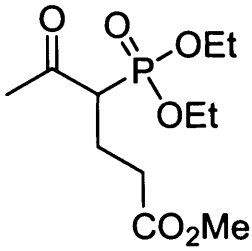
Ethyl 4-chloro-5-oxohexanoate (343) [140]



$C_8H_{13}ClO_3$ 192.05532 g mol $^{-1}$

A solution of (350) (2.60 g, 16.45 mmol) in DMF (25 ml) was treated with LiCl (0.87 g, 20.56 mmol) and $CuCl_2.2H_2O$ (7.00 g, 41.12 mmol). The solution was heated to 50 ^{o} C and stirred for 48 hrs. The cooled solution was diluted with water (100 ml) and extracted with Et_2O (4 x 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated at reduced pressure. The crude oil was purified by flash column chromatography eluting with petroleum ether / ethyl acetate (10:1) to give the title chloride (343) (1.00 g, 30 %) as a clear oil with identical spectral properties to those previously reported.[140]

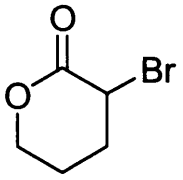
Methyl 4-(diethoxyphosphoryl)-5-oxohexanoate (351) [141]



$C_{11}H_{21}O_6P$ 280.10757 g mol $^{-1}$

To a solution of the commercially available dimethyl 2-oxopropylphosphonate (1.00 g, 6.02 mmol) in benzene (40 ml) at room temperature, was added K_2CO_3 (1.25 g, 9.03 mmol), followed by the dropwise addition of freshly distilled methyl acrylate (0.91 g, 6.60 mmol). The solution was heated at reflux for 12 hrs, filtered and concentrated at reduced pressure. The crude oil was purified by flash column chromatography, eluting with ethyl acetate (100 %) to give the title compound (0.92g, 61 %), as an oil with spectroscopic properties identical to those reported previously.[141]

3-Bromo-tetrahydropyran-2-one (362) [142]

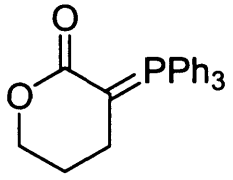


$C_5H_7BrO_2$ 177.96294 g mol^{-1}

A solution of the commercially available δ-valerolactone (5.00 g, 50.00 mmol) in dry THF (15 ml) was added dropwise to a freshly prepared solution of LDA (50.00 mmol) in THF (120 ml) at – 78 ° C. The reaction mixture was stirred at – 78 ° C for one hour, at which point TMSCl (9.23 g, 85.00 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for one hour. The THF was removed

at reduced pressure and replaced with dry DCM (60 ml). The solution was cooled to – 78 ° C and dry Et_3N (5.82 g, 57.50 mmol) was added, followed by the dropwise addition of a solution of bromine (7.99 g, 50.00 mmol) in dry DCM (30 ml). The reaction mixture was allowed to warm to room temperature and poured directly into a separating funnel. The solution was washed with saturated aqueous ammonium chloride (2 x 20 ml) followed by brine (20 ml). The organic phase was dried (Na_2SO_4), filtered and concentrated at reduced pressure. The crude oil was treated with dry diethyl-ether (10 ml) and the resulting precipitate filtered off. The filtrate was concentrated at reduced pressure to afford the bromide (362) (5.03 g, 56 %) as a dark oil used directly without further purification. **HRMS: $C_5H_7BrO_2$** (M+) requires 178.97076 (M+H) Found (M+H) = 178.97150 **IR** (neat) υ max (cm^{-1}): 2960 (CH), 1739 (C=O), 1259 , 1178 **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.80-1.87 (m, 1H, CH), 2.18-2.45 (m, 3H, CH), 4.36-4.39 (m, 1H, CHBr), 4.50-4.76 (m, 2H, CH_2O) **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 166.9, 70.0, 41.1, 30.3, 19.9

3-Triphenylphosporanylidene tetrahydropyran-2-one- (360)

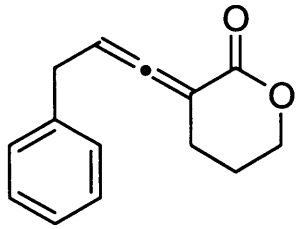


$C_{23}H_{21}O_2P$ 360.12792 g mol $^{-1}$

To a solution of 3-bromo-tetrahydropyran-2-one (362) (2.00 g, 11.20 mmol) in dry THF (15 ml) at room temperature, was added triphenylphosphine (2.93 g, 11.20 mmol) in one portion. The reaction mixture was heated at reflux for 22 hrs and then cooled to room temperature. The resulting solid was collected by suction filtration. The precipitate was washed with Et_2O (4 x 10 ml) and allowed to dry to give the

corresponding phosphonium bromide (363) (2.62 g, 53%) as an off white solid. To a solution of this phosphonium bromide (2.10 g, 4.77 mmol) in water (20 ml) containing a few crystals of phenolphthalein, at room temperature, was added 10 % aqueous NaOH solution, dropwise until the pink end-point was reached. The aqueous phase was extracted with DCM (4 x 20 ml). The combined organic extracts were washed with brine (20 ml) dried (Na_2SO_4), filtered and concentrated at reduced pressure to give the title ylide (360) (1.38 g, 80%) as a light brown solid. **Mp (° C)** = 139 - 142 **HRMS: $C_{23}H_{21}O_2P$** (M+H) requires 361.13573 (M+H) Found = 361.13620 **IR** (nujol) υ max (cm^{-1}): 1585 (C=O), 1438, 1265. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.80 – 1.90 (m, 4H, $2CH_2$), 4.23 (t, 2H, CH_2O, *J* = 5.4), 7.40 - 7.55 (m, 8H, ArH), 7.59 – 7.68 (m, 7H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 24.3 (d, *C-P*, *J* = 10.0), 24.6 (d, *C-P*, *J* = 10.2), 35.0 (d, *C-P*, *J* = 123. 3) 67.4, 126.5 (d, *C-P*, *J* = 90.8), 128.7 (d, *C-P*, *J* = 12.1), 131.9, 133.6 (d, *C-P*, *J* = 9.7), 170.1 (d, *C-P*, *J* = 14.0).

3-(3-Phenylprop-1-enylidene)tetrahydropyran-2-one (364)

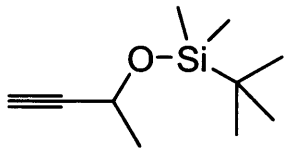


$C_{14}H_{14}O_2$ 214.09938 g mol $^{-1}$

To a solution of phosphorane (360) (0.50 g, 1.40 mmol) in dry DCM (20 ml) at room temperature, was added a solution of Et_3N (0.15 g, 1.40 mmol) in DCM (10 ml), dropwise over a 10 minute period. The solution was stirred at room temperature for 5 minutes, at which point a solution of 3-phenylpropionyl chloride (0.24 g, 1.40 mmol) in dry DCM (20 ml) was added over a ten minute period. The solution was stirred at

room temperature for 2 hrs and then concentrated at reduced pressure. The crude residue was treated with Et_2O (20 ml) and left to stand in the freezer overnight. The precipitate was filtered off and the filtrate concentrated at reduced pressure. The crude oil was purified by flash column chromatography eluting with petroleum ether / ethyl acetate (2:1) to give the title allene (364) (0.18 g, 60 %) as a pale yellow oil. **HRMS:** **$C_{14}H_{14}O_2$** (M+H) requires 215.10720 (M+H) Found = 215.10738 IR (neat) υ max (cm^{-1}): 3060, 3022, 2902 (CH), 1925 (C=C=C), 1720 (C=O). **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.84 (m, 2H, **CH_2CH_2O**), 2.52 (m, 2H, CH_2C=), 3.46 (d, 2H, CH_2Ph, *J* = 6.9), 4.27 (m, 2H, CH_2O), 5.79 (m, 1H, =CH), 7.16-7.34 (m, 5H, ArH) **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 211.5, 164.9, 138.6, 128.5, 128.4, 126.3, 95.9, 95.3, 70.2, 35.0, 24.6, 22.6.

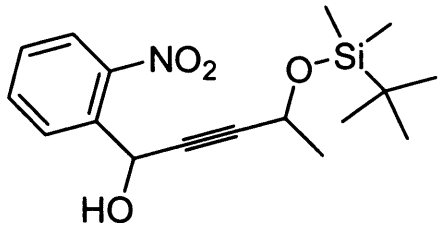
(But-3-yn-2-yloxy)(tert-butyl)dimethylsilane (369) [143]



$C_{10}H_{20}OSi$ 184.12834 g mol^{-1}

To a solution of but-3-yn-2-ol (3.00 g, 42.80 mmol) in dry DCM (40 ml) was added imidazole (3.20 g, 47.00 mmol) and a crystal of DMAP. The mixture was cooled in an ice bath as a solution of TBDMSiCl (7.10 g, 47.00 mmol) in dry DCM (10 ml) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 24 hrs. The mixture was diluted with Et_2O and filtered. The filtrate was extracted with Et_2O (40 ml) and the organic phase was washed successively, with water (40 ml) and brine (20 ml) and then dried ($MgSO_4$), filtered and concentrated at reduced pressure to give the title compound (5.02 g, 63 %) as a clear liquid with spectral properties consistent with those reported previously.[143]

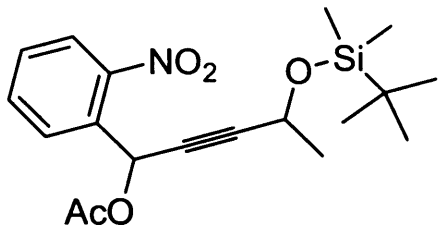
4-(tert-Butyldimethylsilyloxy)-1-(2-nitrophenyl)pent-2-yn-1-ol (371)



$C_{17}H_{25}NO_4Si$ 355.15528 g mol $^{-1}$

To a solution of alkyne (369) (4.17 g, 22.70 mmol) in dry THF (80 ml) at – 78 ° C was added nBuLi (22.70 mmol, 9.10 ml of a 2.50 M solution in hexanes) dropwise. The solution was stirred at – 78 ° C for 1 hour, at which point *ortho* nitrobenzaldehyde (3.43 g, 22.70 mmol) was added in one portion. The reaction mixture was stirred at – 78 ° C for 1 hour. Saturated aqueous ammonium chloride (20 ml) was added and the mixture was allowed to warm to room temperature. The aqueous phase was separated and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated at reduced pressure. The crude oil was purified by flash column chromatography, eluting petroleum / ether ethyl acetate (10:1) to give the title compound (5.53 g, 72 %) as an orange oil. **HRMS: $C_{17}H_{25}NO_4Si$** (M+Na) requires 358.14505 (M+Na) Found = 358.15274 **IR** (neat) υ max (cm^{-1}): 3332 bs (OH), 2954, 2929, 2856 (CH), 1530, 1350 (NO_2) **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 0.03 (s, 6H, Me_2), 0.81 (s, 9H, $(CH_3)_3$), 1.36 (d, 3H, CH_3, J = 6.4), 3.58 (bs, 1H, OH), 4.52 (q, 1H, CH(OSi), J = 6.4), 6.00 (s 1H, CH(OH)), 7.42 (t, 1H, ArH, J = 8.0), 7.60 (t, 1H, ArH, J = 7.5), 7.88 (dd, 2H, ArH, J = 8.0, 2.1) **^{13}C NMR:** $CDCl_3$ (300 MHz) δ ppm: 147.8, 136.6, 133.8, 129.1, 124.8, 89.2, 81.1, 60.8, 58.9, 25.7, 25.1, 18.1, -4.73, -4.78.

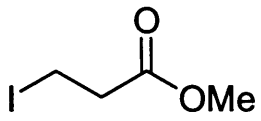
4-(tert-Butyldimethylsilyloxy)-1-(2-nitrophenyl)pent-2-ynyl acetate (372)



$C_{19}H_{27}NO_5Si$ 377.16585 g mol $^{-1}$

To a solution of alcohol (371) (2.91 g, 8.20 mmol) in dry DCM (60 ml), cooled in an ice bath, was added pyridine (2.63 g, 33.30 mmol) followed by acetyl chloride (2.60 g, 33.30 mmol) dropwise. The solution was allowed to warm to room temperature and stirred for 24 hrs and then poured into 20 ml of saturated aqueous $CuSO_4$ solution. The separated aqueous phase was extracted with DCM (3 x 30 ml) and the combined extracts were washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated at reduced pressure. The crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (10:1) to give the title compound (2.87 g, 92 %) as an orange oil. **HRMS: $C_{19}H_{27}NO_5Si$** (M+Na) requires = 400.15562 (M+Na) Found = 400.15375 **IR** (neat) υ max (cm^{-1}): 3055, 2956, 2858 (CH), 1745 (C=O), 1531, 1352 (NO_2). **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 0.05 (s, 6H, Me_2), 0.87 (s, 9H, $(CH_3)_3$), 1.41 (d, 3H, Me, J = 6.5,) 2.08 (s, 3H, CO_2Me), 4.56 (m, 1H, CH(OSi*t*BuMe$_2$)), 6.84 (s, 1H, CH(OAc)), 7.51 (t, 1H, ArH, J = 8.0), 7.65 (t, 1H, ArH, J = 7.6), 7.89 (m, 1H, ArH), 7.98 (d, 1H, ArH, J = 8.0) **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 168.9, 147.7, 133.3, 132.1, 129.5, 129.4, 124.8, 90.7, 61.8, 58.9, 25.7, 24.5, 20.6, 18.0, -4.8, -5.0.

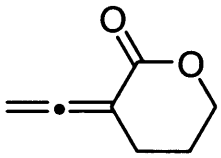
Methyl 3-iodopropanoate (374) [144]



$C_4H_7IO_2$ 213.94907 g mol $^{-1}$

To a solution of NaI (6.54 g, 43.60 mmol) in acetone (30 ml) was added methyl 3-bromopropanoate (5.80 g, 34.90 mmol) dropwise at room temperature. The solution was heated at reflux for 30 minutes, cooled to room temperature and filtered. The filtrate was concentrated at reduced pressure to give the pure iodide (374) (3.30 g, 44 %) as an orange oil with spectroscopic properties identical to those previously reported.[144]

3-Vinylidene-tetrahydropyran-2-one (381)

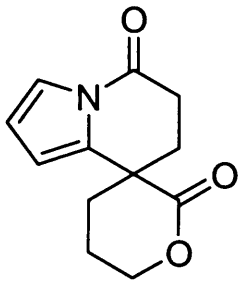


$C_7H_8O_2$ 124.05243 g mol $^{-1}$

To a solution of phosphonium salt (363) (4.53 g, 10.30 mmol) in dry DCM, cooled in an ice bath, was added Et_3N (2.07 g, 20.50 mmol) dropwise over a 5 minute period. The solution was allowed to warm to room temperature and stirred for 1 hour. The solution was cooled in an ice bath and acetyl chloride (0.88 g, 11.33 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for 2 hrs. The reaction mixture was concentrated at reduced pressure and Et_2O (100 ml) was added. The precipitate was filtered through a plug of SiO_2 gel (*ca.* 30 g) and the cake was washed with Et_2O (50 ml). The combined filtrate and washings were concentrated to give a crude oil which was purified by flash column chromatography,

eluting with petroleum ether / ethyl acetate (3:2) to give the title allene (381) (1.10 g, 86 %) as a clear oil. HRMS: $C_7H_8O_2$ (M+) requires = 124.05188 (M+) Found = 124.05214 IR (thin film) υ max (cm^{-1}):3050 (CH), 1967 (C=C=C), 1735 (C=O), 1596, 1488 **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.95 (m, 2H, CH_2CH_2O), 2.66 (m, 2H, CH_2C=), 4.37 (t, 2H, CH_2O, J = 6.0), 5.23 (t, 2H, =CH_2, J = 4.0). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 215.0, 164.8, 94.5, 79.4, 69.6, 25.2, 22

Indolozinone (380)



$C_{12}H_{13}NO_3$ 219.08954 g mol^{-1}

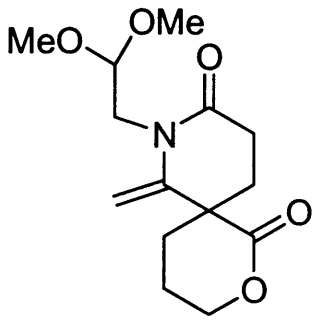
Method 1

To a solution of allenic lactone (381) (0.10 g, 0.81 mmol) in dry acetonitrile (5 ml) was added aminoactealdehyde dimethyl acetal (0.08 g, 0.81 mmol) dropwise at room temperature. The solution was stirred for 3 hrs and then acryloyl chloride (0.09 g, 0.97 mmol) was added followed by *para*-toluenesulfonic acid (30 mg). The solution was heated under reflux for 3 hrs, cooled to room temperature and concentrated at reduced pressure. The crude oil was purified by flash column chromatography eluting with petroleum ether / ethyl acetate (1:1) to give the title compound (0.04 g, 23 %) as a white solid.

Method 2

A solution of enamide (384) (0.10 g, 0.35 mmol) and *para*-toluenesulfonic acid (30 mg) in dry toluene (20 ml), was heated under reflux in a flask fitted with a Dean and Stark apparatus for 1 hour. The solution was cooled to room temperature and Et_3N (0.02 g, 0.16 mmol) was added. The solution was stirred at room temperature overnight. The mixture was concentrated at reduced pressure and the crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (1:1) to give the title compound (380) (0.04 g, 57 %) as a white crystalline solid. **Mp (° C)** = 133-136 **HRMS:** $\mathbf{C_{12}H_{13}NO_3}$ (M+H) requires = 220.09737 (M+H) Found = 220.09790 **IR** (thin film) υ max (cm^{-1}): 2950 (CH), 1720 (C=O ester), 1676 (C=O amide) **^{1}H NMR:** 2.04 (m, 4H, $\mathbf{CH_2CH_2}CH_2O$), 2.43 (m, 1H, $\mathbf{CH_2}CH_2CO$), 2.66 (m, 1H, $\mathbf{CH_2}CH_2CO$) 2.70 (m, 1H, $\mathbf{CH_2}CO$), 2.89 (m, 1H, $\mathbf{CH_2}CO$), 4.48 (bt, 2H, CH_2O, J = 5.9), 6.12 (dd, 1H, ArH, J = 1.6, 3.5), 6.23 (t, 1H, ArH, J = 3.5), 7.40 (dd, 1H, ArH, J = 1.6, 3.5). $CDCl_3$ (300 MHz) δ ppm: **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 171.2, 167.0, 134.0, 117.6, 112.3, 110.0, 70.7, 42.4, 32.7, 32.2, 29.4, 19.9.

Enamide (384)



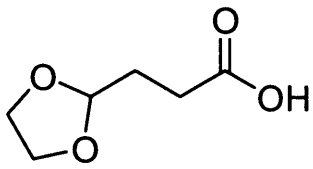
$C_{14}H_{21}NO_5$ 283.14197 g mol $^{-1}$

To a solution of allene (381) (0.10 g, 0.81 mmol) in dry acetonitrile (10 ml) was added aminoactealdehyde dimethyl acetal (0.09 g, 0.81 mmol) and the mixture was

stirred at room temperature for 3 hrs. The solution was cooled in an ice bath and pyridine (0.08 g, 0.97 mmol) was added followed by acryloyl chloride (0.10 g, 1.10 mmol) dropwise. The solution was allowed to warm to room temperature and stirred for 12 hrs. The mixture was diluted with ethyl acetate (20 ml) and washed with saturated aqueous $CuSO_4$ solution (10 ml) and brine (10 ml). The organic phase was collected and dried ($MgSO_4$), filtered and concentrated at reduced pressure to give the title compound (0.14 g, 65 %) as a yellow oil, used without further purification. **HRMS:** $C_{14}H_{21}NO_5$ (M+H) requires = 284.14979 (M+H) Found = 284.14895 **IR** (neat) υ max (cm^{-1}): 2943, 2837 (CH), 1708 (C=O lactone), 1654 (C=O, amide), 1544. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.63-1.86 (m, 4H, $\mathbf{CH_2CH_2}CH_2O$), 1.98-2.21 (m, 2H, $\mathbf{CH_2}CH_2CO$), 2.52-2.71 (m, 2H, CH_2CO), 3.32 (s, 3H, OMe), 3.33 (s, 3H, OMe), 3.99 (dd, 1H, CH_2N, J = 5.6, 14.4), 3.98 (dd, 1H, CH_2N J = 5.62, 14.4), 4.30 (m, 1H, CH_2O),4.39 (d, 1H, =CH, J = 3.2) 4.47 (m, 1H, CH_2O), 4.57 (t, 1H, $CH(OMe)_2$, J = 5.3), 4.84 (d, 1H, =CH, J = 3.2) **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 172.1, 168.6, 146.2, 101.2, 97.7, 69.9, 54.2, 54.0, 48.0, 46.0, 29.7, 29.1, 28.3, 19.5.

4.3 Tandem Reactions (II)-Carbocyclisation Of Allenic Substrates

3-(1,3-Dioxolan-2-yl)propanoic acid (419) [145]

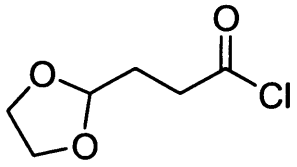


$C_6H_{10}O_4$ 146.05791 g mol^{-1}

To oven dried magnesium turnings (5.00 g, 0.21 mol) in dry THF (100 ml) was added a solution of 2-(2-Bromo-ethyl)-[1,3]-Dioxolan (10.00 g, 0.06 mol) in dry THF (30 ml) at such a rate to ensure that the internal temperature did not rise above 30 ° C. On completion of the addition, the reaction mixture was stirred at room temperature for 1

hour and then cooled below – 40 ° C. To this mixture was added a large excess of crushed dry ice, followed by saturated aqueous ammonium chloride solution (30 ml) and water (30 ml). The resulting slurry was filtered through glass wool and the filtrate was concentrated at reduced pressure. The aqueous solution was basified with saturated $NaHCO_3$ solution and washed with Et_2O (100 ml). The aqueous phase was acidified with concentrated HCl and extracted with Et_2O (6 x 100 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated at reduced pressure to give the title acid (419) (4.40 g, 54 %) as a clear liquid. **IR** (neat) υ max (cm^{-1}): 1725 (C=O), 1425, 1500. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.95 (m, 2H, CH_2), 2.41 (t, 2H, CH_2CO_2H, J = 7.23), 3.8 (m, 4H, $2CH_2O$), 4.96 (t, 1H, CH, J = 4.3), 11.5 (bs, 1H, OH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 178.6, 102.9, 65.1, 28.5, 27.9.

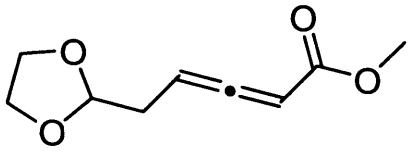
3-(1,3-Dioxolan-2-yl) propanoyl chloride (420)



$C_6H_9ClO_3$ 164.02402 g mol $^{-1}$

3-(1,3-Dioxolan-2-yl)propanoic acid (419) (1.00 g, 6.85 mmol), in dry DCM (20 ml) was cooled in an ice bath and oxalyl chloride (1.04 g, 8.22 mmol) was added dropwise followed by a single drop of dry DMF. The reaction mixture was stirred in the ice bath for 30 minutes, warmed to room temperature and stirred a further 15 minutes. The crude acid chloride was used without purification or characterisation.

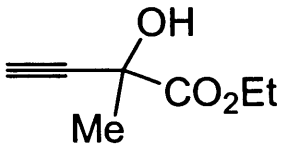
Methyl 5-(1,3-dioxolan-2-yl)penta-2,3-dienoate (421)



$C_9H_{12}O_4$ 184.07356 g mol $^{-1}$

Commercially available methyl(triphenylphosphoranylidene)acetate (2.50 g, 7.50 mmol) was dissolved in dry DCM (25 ml) and cooled in an ice bath. To this mixture was added dropwise over a 5 minute period a solution of Et_3N (1.45 g, 14.40 mmol) in dry DCM (10 ml). The reaction mixture was stirred at room temperature for 10 minutes, cooled in an ice bath and a solution of the crude acid chloride (420) (6.85 mmol) in dry DCM (20 ml) was added dropwise over 10 minutes, the reaction mixture was warmed to room temperature and stirred for 40 minutes. The solution was concentrated at reduced pressure and the residual oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (5:1) to give the title allene (421) (0.17 g, 14 %) as a clear oil. **HRMS: $C_9H_{12}O_4$** (M+) requires = 184.07356 (M+) found = 184.07305. **IR** (neat) υ max (cm^{-1}): 1960 (C=C=C), 1725 (C=O). **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 2.46 (m, 2H, CH_2), 3.68 (s, 3H, OMe), 3.80-3.97 (m, 4H, $2CH_2O$), 5.56-5.61 (m, 2H, =CH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 212.9, 166.3, 102.8, 89.5, 87.9, 65.2, 65.1, 51.9, 32.6.

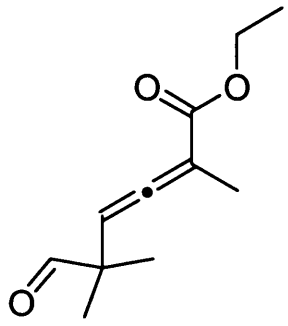
Ethyl 2-hydroxy-2-methylbut-3-ynoate (432) [146]



$C_7H_{10}O_3$ 142.06299 g mol $^{-1}$

A solution of ethyl pyruvate (4.00 g, 34.00 mmol) in THF (35 ml) was cooled in an ice bath and ethynyl magnesium bromide (34.00 mmol, 69.00 ml, 0.5 M in THF) was added dropwise over 5 minutes. The mixture was stirred in the ice bath for 30 minutes, warmed to room temperature and stirred 2 hrs. The mixture was poured into a saturated solution of aqueous ammonium chloride (15 ml). The aqueous phase was separated and extracted with Et_2O (3 x 20 ml) and the organic extracts were combined, dried ($MgSO_4$) filtered and concentrated at reduced pressure to give the title alcohol (432) (3.00 g, 62 %), essentially free from impurities and with spectroscopic properties identical to those reported previously. [146]

Ethyl 5-formyl-2,5-dimethylhexa-2,3-dienoate (439)



General Procedure (III)

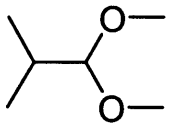
$C_{11}H_{16}O_3$ 196.10994 g mol $^{-1}$

To a solution of propargylic alcohol (432) (1.00 g, 7.00 mmol) and *para*-toluenesulfonic acid (30 mg), in dry toluene (15 ml), was added isobutryaldehyde-dimethyl acetal (436) (1.00 g, 8.40 mmol) in one portion. The solution was heated at

reflux, in a flask fitted with a Dean and Stark apparatus for 24 hrs. The cooled mixture was concentrated at reduced pressure, and the crude product was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (7:1) to give the title allene (439) (0.54 g, 40 %) as a pale yellow oil. **HRMS:** $C_{16}H_{18}O_3$ (M+H) requires 196.10094 (M+H) found = 196.10954. **IR** (neat) υ max (cm^{-1}): 2933 (CH), 2860 (CH), 1975 (C=C=C), 1716 (C=O), 1448, 1436 **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.19 (s, 6H, Me_2), 1.23 (t, 3H, CH_3, J = 6.7), 1.87 (m, 3H, Me), 4.15 (m, 2H, CH_2), 5.43 (m, 1H, =CH), 9.39 (s, 1H, CHO). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 209.7, 201.4, 167.2, 98.6, 97.1, 60.6, 47.2, 21.9, 21.6, 14.9, 14.1.

General Procedure (IV)

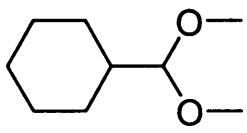
1,1-Dimethoxy-2-methylpropane (436) [147]



$C_6H_{14}O_2$ 118.09938 g mol $^{-1}$

To an ice-cold mixture of isobutyraldehyde (5.00 g, 69.40 mmol) and trimethylorthoformate (8.10 g, 76.30 mmol), was added *para*-toluenesulfonic acid (0.70 g, 3.50 mmol), in small portions over 10 minutes. The solution was stirred at room temperature for 12 hrs and then poured directly into saturated aqueous $NaHCO_3$ solution (20 ml). The aqueous mixture was extracted with Et_2O (4 x 10 ml), and the combined extracts were dried ($MgSO_4$), filtered and concentrated at reduced pressure. The title acetal was obtained as a clear liquid (3.23 g, 40 %), with spectral properties identical to those reported previously.[147]

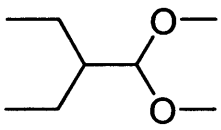
(Dimethoxymethyl)cyclohexane (444) [148]



$C_9H_{18}O_2$ 158.13068 g mol $^{-1}$

The title acetal was prepared according to the general procedure (IV), reacting cyclohexanecarboxyaldehyde with trimethylorthoformate. The acetal (444) was isolated in a 75 % yield as a colourless liquid with spectral properties identical to those reported previously. [148]

3-(Dimethoxymethyl)pentane (443) [149]

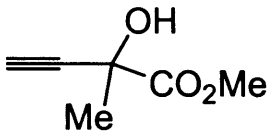


$C_8H_{18}O_2$ 146.13068 g mol $^{-1}$

The title acetal was prepared according to the general procedure (IV), reacting the commercially available 2-ethylbutanal with trimethylorthoformate. The acetal (443) was isolated as a clear liquid, in a 60 % yield with spectral properties identical to those reported previously. [149]

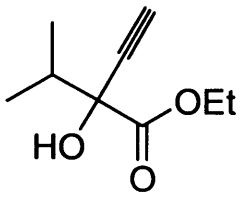
Methyl 2-hydroxy-2-methylbut-3-ynoate (452)

$C_6H_8O_3$ 128.04734 g mol $^{-1}$



A solution of methyl pyruvate (2.00 g, 20.00 mmol) in THF (20 ml) was cooled in an ice bath and ethynyl magnesium bromide (20.00 mmol, 40.00 ml, 0.5 M in THF) was added dropwise over 5 minutes. The mixture was stirred in the ice bath for 30 minutes, warmed to room temperature and stirred 2 hrs. The mixture was poured into a saturated solution of aqueous ammonium chloride (15 ml). The aqueous phase was separated and extracted with Et_2O (3 x 20 ml) and the organic extracts were combined, dried ($MgSO_4$) filtered and concentrated at reduced pressure to give the title alcohol (452) (1.20 g, 46 %) as an oil. **HRMS: $C_6H_8O_3$** (M+) requires = 128.04734 (M+) found = 128.04789 **IR** (neat) υ max (cm^{-1}): 3286 bs (OH) 2997, 2943 (CH), 1729 (C=O). **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.65 (s, 3H, Me), 2.39 (s, 1H, CH), 3.10 (bs, 1H, OH), 3.80, (s, 3H, OMe) **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 172.8, 83.0, 72.4, 67.2, 53.7, 27.2.

Ethyl 2-hydroxy-2-isopropylbut-3-ynoate (453)

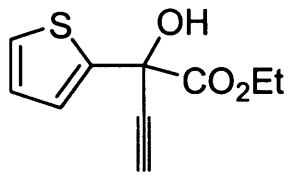


$C_9H_{14}O_3$ 170.09429 g mol $^{-1}$

To a solution of the commercially available ethyl-3-methyl-2-oxobutanoate (2.00 g, 13.90 mmol), in dry THF (25 ml), cooled in an ice bath was added ethynyl

magnesium bromide (13.90 mmol, 28.00 ml, 0.50 M solution in THF), dropwise over five minutes. The reaction mixture was stirred in the ice bath for 30 minutes, warmed to room temperature and stirred for a further 2 hrs, before being poured directly into a solution of saturated aqueous NH_4Cl / Et_2O (1:1, 40 ml). The separated aqueous phase was extracted with Et_2O (3 x 15 ml) and the combined organic extracts were washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated at reduced pressure to give the title compound (1.86 g, 78%) as a pale yellow oil, used directly without further purification. **HRMS: $C_{12}H_{12}O_3$** (M+Na) requires 193.08406 (M+Na) found = 193.08493. **IR** (neat) υ max (cm^{-1}): 3417 bs (OH), 2974, 2937, 2877 (CH), 1732 (C=O) **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 0.88 (d, 3H, CH_3, J = 6.7), 1.11 (d, 3H, CH_3, J = 6.7), 1.32 (m, 3H, CH_3), 2.19 (qn, 1H, CH, J = 6.8), 2.48 (s, 1H, CH), 3.45 (s, 1H, OH), 4.30 (m, 2H, CH_2). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 172.4, 82.2, 74.2, 73.0, 63.0, 36.8, 16.6, 16.1, 14.0.

Ethyl 2-hydroxy-2-(thiophen-2-yl)but-3-ynoate (454)

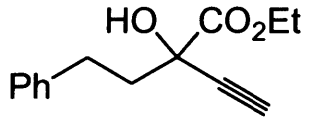


$C_{10}H_{10}O_3S$ 210.035 $gmol^{-1}$

To a solution of the commercially available ethyl-2-oxo-2-(thiophen-2-yl)acetate (449) (2.00 g, 11.00 mmol) in dry Et_2O (20 ml), cooled to 0 ° C, was added a solution of ethynyl magnesium bromide (11.00 mmol, 22 ml, 0.5 M solution in THF) over a five minute period. The reaction mixture was stirred at 0 ° C for 1 hour, warmed to room temperature and stirred a further two hrs. The mixture was then poured into saturated aqueous ammonium chloride solution (20 ml) and the aqueous phase was

separated and extracted with Et_2O (3 x 15 ml). The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ solution (20 ml), brine (20 ml), dried ($MgSO_4$) filtered and concentrated to give a crude oil. The oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (4:1), to give the title propargylic alcohol (454) (1.10 g, 48%) as a pale yellow oil. **HRMS:** **$C_{10}H_{10}O_3S$** (M+) requires 210.03506 (M+) Found = 210.03444. **IR** (neat) υ max (cm^{-1}): 3475 bs (OH), 1743 (C=O), 1255. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.23 (t, 3H, CH_3, J = 8.3), 2.68 (s, 1H, CH), 4.29 (m, 2H, CH_2), 4.51 (s, 1H, OH), 6.97 (t, 1H, ArH, J = 4.4), 7.26 (m, 2H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 170.4, 143.0, 128.7, 126.9, 126.4, 81.5, 74.0, 70.0, 64.0, 13.8.

Ethyl 2-hydroxy-2-phenethylbut-3-ynoate (455)

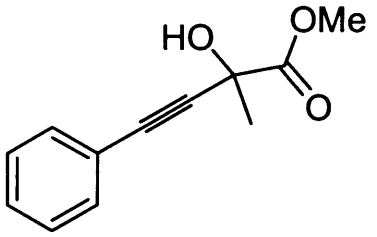


$C_{14}H_{16}O_3$ 232.10994 g mol $^{-1}$

To a solution of the commercially available ethyl-2-oxo-4-phenylbutanoate (1.00 g, 4.80 mmol), in dry THF (10 ml), cooled in an ice bath, was added a 0.5M solution of ethynyl magnesium bromide in THF (10.00 ml, 4.80 mmol), dropwise over 5 minutes. The reaction mixture was stirred in the ice bath for 30 minutes, warmed to room temperature and stirred a further 4 hrs. The mixture was then poured directly into saturated aqueous ammonium chloride solution (20 ml) and the aqueous phase was separated and extracted with Et_2O (4 x 20 ml). The combined organic extracts were washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated at reduced pressure to give propargylic alcohol (455) (0.70 g, 63 %) as a pale yellow oil, which was used without further purification. **HRMS:** **$C_{14}H_{16}O_3$** (M+Na) requires 255.09971

(M+Na) Found = 255.09990. **IR** (neat) υ max (cm^{-1}): 3496 bs (OH), 3284 s (≡CH) 2981 (CH), 1735 (C=O), 1496, 1454, 1247. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm:1.32 (t, 3H, CH_3, J = 7.0), 2.25 (m, 2H, **CH_2CH_2Ph**), 2.55 (s, 1H, CH), 2.70 (m, 1H, CH_2Ph), 2.90 (m, 1H, CH_2Ph), 3.67 (s, 1H, OH), 4.30 (q, 2H, CH_2, J = 7.0), 7.15-7.34 (m, 5H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm:172.1, 140.9, 128.6, 128.5, 126.1, 82.5, 73.0, 70.4, 63.2, 40.9, 28.9, 14.0.

Methyl 2-hydroxy-2-methyl-4-phenylbut-3-ynoate (456)

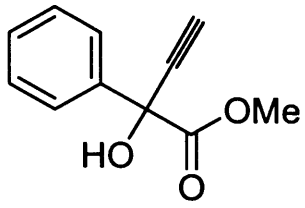


$C_{12}H_{12}O_3$ 204.07864 g mol $^{-1}$

A solution of phenylacetylene (5.00 g, 49.00 mmol), in dry THF (75 ml), cooled to – 78 ° C was treated with n-BuLi (19.00 ml, 2.50 M solution in hexanes, 49.00 mmol), dropwise over 10 minutes. The yellow solution was stirred at – 78 ° C for 40 minutes and then a solution of methyl pyruvate (5.00 g, 49.00 mmol), in dry THF (75 ml) was added dropwise over 10 minutes. The mixture was stirred at – 78 ° C for 2 hrs and then poured into iced water (150 ml). The aqueous phase was separated and extracted with Et_2O (5 x 30 ml), and the combined organic extracts were washed successively with water (40 ml) and brine (40 ml), dried ($MgSO_4$) and filtered. Removal of the solvent at reduced pressure gave a crude oil, which was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (5:1). The title alcohol (8.90 g, 88 %) was isolated as a pale yellow oil. **HRMS: $C_{12}H_{12}O_3$** (M+) requires = 204.07864 (M+) Found = 204.07828. **IR** (neat) υ max (cm^{-1}): 3500 bs (OH), 2222

(C≡C), 1750 (C=O). **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.78 (s, 3H, CH_3), 3.80 (bs, 1H, OH), 3.98 (s, 3H, OMe), 7.20-7.60 (m, 5H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 173.3, 131.9, 128.8, 128.3, 121.9, 88.2, 84.0, 68.3, 53.8, 27.2

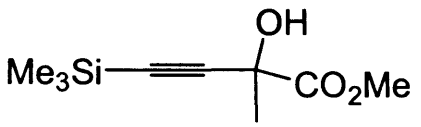
Methyl 2 hydroxy-2-phenylbut-3-ynoate (459) [150]



$C_{11}H_{10}O_3$ 190.06299 g mol^{-1}

To a solution of the commercially available oxophenylacetic acid methyl ester (1.00 g, 6.00 mmol) in dry THF (15 ml), cooled to - 78 °C, was added a 0.5M solution of ethynyl magnesium bromide in THF, (12.00 ml, 6.00 mmol) over 5 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 12 hrs. The mixture was poured into saturated aqueous ammonium chloride solution (20 ml) and the separated aqueous phase was extracted with Et_2O (4 x 20 ml). The combined organic extracts were washed with brine (20 ml), dried ($MgSO_4$) filtered and concentrated at reduced pressure. The crude product was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (5:2), to give the title propargylic alcohol (459) (0.80 g, 70 %) as a pale yellow oil, with spectroscopic data identical to that reported previously.[150]

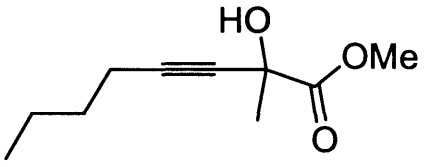
2-Hydroxy-2-methyl-4-trimethylsilanyl-but-3-ynoic acid (457)



$C_9H_{16}O_3Si$ 200.086 $gmol^{-1}$

Trimethylsilylacetylene (2.00g, 0.02 mol) in dry THF (40 ml), cooled to - 78 °C, was treated with n-BuLi (0.03 mol, 13.80 ml, 1.8M solution in hexanes), dropwise over ten minutes. The reaction mixture was stirred at – 78 °C for 0.5 hrs, at which point the commercially available methyl pyruvate (2.04g, 0.02 mol) was added dropwise. After stirring at – 78 °C for 40 minutes the reaction mixture was poured directly into iced water (100 ml). The separated aqueous phase was extracted with ethyl acetate (3 x 50 ml) and the combined organic extracts were washed with brine, (50 ml) dried ($MgSO_4$), filtered and concentrated at reduced pressure. The crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (5:1), to afford the title compound (457) (2.50 g, 62 %) as a clear oil, with spectroscopic properties identical to those reported previously.[150]

Methyl 2-hydroxy-2-methyloct-3-ynoate (458)

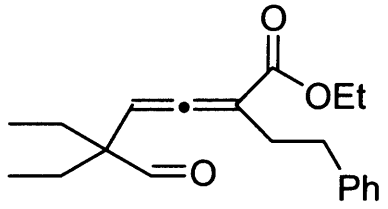


$C_{10}H_{16}O_3$ 184.10994 g mol^{-1}

To a solution of hex-1-yne (5.00 g, 60.90 mmol) in dry THF (60 ml), cooled to – 78 °C, was added n-BuLi (2.5 M solution in hexanes, 24.30 ml, 60.90 mmol), dropwise over 10 minutes. The solution was stirred at – 78 °C for 1.5 hrs, at which point methyl pyruvate (6.20 g, 60.90 mmol) was added. The reaction mixture was allowed to warm to room temperature overnight and then poured directly into saturated aqueous

ammonium chloride solution (20 ml). The separated aqueous phase was extracted with Et_2O (4 x 20 ml) and the combined organic extracts were washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated. The crude oil was purified by flash column chromatography, eluting petroleum ether / ethyl acetate (5:1) to give the title propargylic alcohol (3.00 g, 67 %), as a clear oil. **HRMS: $C_{10}H_{16}O_3$** (M+H) requires 185.11776 (M+H) Found = 185.11743. **IR** (neat) υ max (cm^{-1}):3447 bs (OH), 2935 (CH), 2248 s (C≡C), 1738 (C=O) **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 0.90 (m, 3H, CH_3), 1.40 (m, 4H, CH_2CH_2), 1.65 (s, 3H, Me), 2.2 (m, 2H, $CH_2C{\equiv}C$), 3.45 (bs, 1H, OH), 3.85 (s, 3H, OMe).**^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm:173.6, 85.0, 80.0, 67.9, 53.5,30.3, 27.4, 21.8, 18.3, 13.5.

Ethyl 5-ethyl-5-formyl-2-phenethylhepta-2,3-dienoate (460)

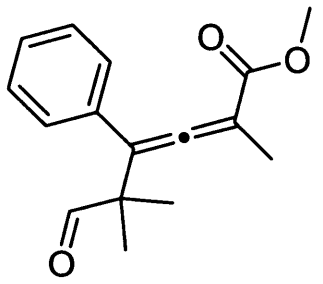


$C_{20}H_{26}O_3$ 314.18819 g mol $^{-1}$

The title allene was prepared according to the general procedure (III), by reacting propargylic alcohol (455) (0.92 g, 4.00 mmol) and acetal (441) (0.57 g, 4.00 mmol) in dry toluene (20 ml) in the presence of *para*-toluenesulfonic acid (40 mg). The crude compound was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (20:1) to give the title allene (0.44 g, 35%) as a pale yellow oil. **HRMS: $C_{20}H_{26}O_3$** (M+H) requires 315.19601 (M+H) found = 315.19634. **IR** (neat) υ max (cm^{-1}): 3085, 3028, 2981, 2858 (CH), 1953 (C=C=C), 1712 (C=O) **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 0.80 (t, 6H, $(CH_3)_2$ J = 7.3), 1.23 (t, 3H, CH_3, J = 7.1), 1.63 (q, 4H, $(CH_2)_2$, J = 7.4), 2.45 (m, 2H, CH_2), 2.78 (t, 2H, CH_2Ph, J = 7.9), 4.2 (m, 2H,

CH_2), 5.44 (m, 1H, =CH), 7.0-7.40 (m, 5H, ArH), 9.31 (s, 1H, CHO). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 210.1, 202.5, 167.0, 141.2, 128.5, 128.3, 126.0, 102.2, 95.5, 61.0, 55.3, 34.4, 30.5, 26.1, 26.0, 14.2, 8.4, 8.3.

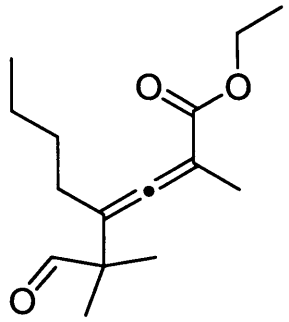
Methyl-5-formyl-2,5-dimethyl-4-phenylhexa-2,3-dienoate (461)



$C_{16}H_{18}O_3$ 258.12259 g mol $^{-1}$

According to the general procedure (III), allene (461) was prepared by reacting propargylic alcohol (0.5 g, 2.45 mmol) (456) and acetal (436) (0.34 g, 2.94 mmol). The crude product was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (7:1) to give the title compound (0.20 g, 32 %) as a pale yellow oil. **HRMS: $C_{16}H_{18}O_3$** (M+) requires 258.12259 (M+) found = 258.12579. **IR** (thin film) υ max (cm^{-1}): 1710 (C=O). **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm 1.27 (s, 3H, Me_2), 1.28 (s, 3H, Me_2), 1.98 (s, 3H, Me), 3.80 (s, 3H, OMe), 7.1-7.35 (m, 5H, ArH), 9.70 (s, 1H, CHO). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 211.0, 202.2, 167.7, 134.0, 128.6, 128.2, 127.9, 111.7, 98.2, 52.4, 50.0, 21.5, 15.3.

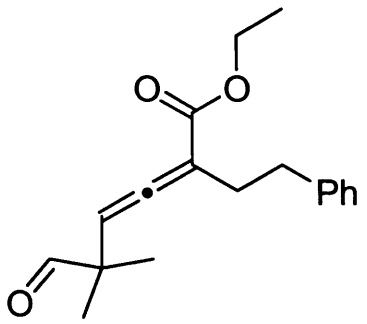
Ethyl 2-methyl-4-(2-methyl-1-oxopropan-2-yl)octa-2,3-dienoate (463)



$C_{15}H_{24}O_3$ 253.17254 g mol $^{-1}$

The title allene was prepared according to the general procedure (III), by reacting propargylic alcohol (458) (0.60 g, 3.26 mmol) and acetal (436) (0.38 g 3.91 mmol). The crude product was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (10:1) to give the title compound as a pale yellow (0.22 g, 27 %) **HRMS: $C_{15}H_{24}O_3$** (M+H) requires 253.18036 (M+) found = 253.18044. **IR** (neat) υ max (cm^{-1}): 2935, 2860 (CH), 1955 (C=C=C), 1716 (C=O) **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 0.95 (t, 3H, CH_3, J = 6.7), 1.16 (s, 6H, Me_2), 1.23 (t, 3H, CH_3, J = 7.2), 1.0-1.35 (m, 6H, CH_2), 1.86 (s, 3H, Me), 4.15 (m, 2H, CH_2O), 9.32 (s, 1H, CHO). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 209.5, 201.8, 167.8, 109.3, 98.8, 60.7, 49.0, 29.7, 22.2, 20.8, 20.3, 15.1, 14.2, 13.8

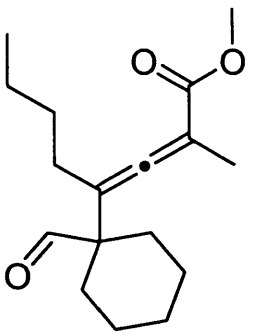
Ethyl 5-formyl-5-methyl-2-phenethylhexa-2,3-dienoate (464)



$C_{18}H_{22}O_3$ 286.15689 g mol $^{-1}$

Allene (464) was prepared according to the general procedure (IV), by reacting propargylic alcohol (455) (1.02 g, 4.40 mmol) and acetal (436) (0.63 g, 5.30 mmol). The title allene was obtained as a pale yellow oil (0.32 g, 1.11 mmol, 25 %), after purification of the crude compound by flash column chromatography, eluting with petroleum ether / ethyl acetate (10:1). **HRMS:** $C_{18}H_{22}O_3$ (M+H) required = 287.16417 (M+H) found = 287.16421 **IR** (neat) υ max (cm^{-1}): 3028 (=CH), 2871 (CH), 1957 (C=C=C), 1732 (C=O), 1496, 1456.^{1}**H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.13 (s, 3H, Me), 1.14 (s, 3H, Me), 1.26 (t, 3H, **CH_3CH_2**, J = 7.50), 2.66 (m, 2H, **CH_2CH_2**Ph), 2.96 (t, 1H, CH_2Ph, J = 7.2), 3.18 (t, 1H, CH_2Ph, J = 7.2), 4.21 (m, 2H, CH_2CH_3), 5.46 (t, 1H, =CH, J = 2.9), 7.12-7.31 (m, 5H, ArH), 9.34 (s, 1H, CHO). ^{13}**C NMR:** $CDCl_3$ (75 MHz) δ ppm: 209.0, 201.5, 141.1, 128.5, 128.4, 126.0, 102.9, 98.5, 61.0, 47.1, 34.2, 30.1, 21.8, 21.6, 14.2.

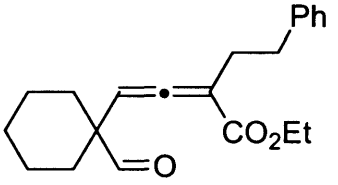
Methyl 4-(1-formylcyclohexyl)-2-methylocta-2,3-dienoate (465)



$C_{17}H_{26}O_3$ 278.18819 g mol $^{-1}$

The title compound was prepared according to the general procedure (IV), by reacting propargylic alcohol (455) (0.60 g, 3.26 mmol) and acetal (444) (0.62 g, 3.91 mmol). The title allene (465) was isolated as a pale yellow oil (0.21 g, 24 %) after purification of the crude compound by flash column chromatography, eluting with petroleum ether / ethyl acetate (10:1). **HRMS:** $C_{15}H_{24}O_3$ (M+Na) requires 301.17795 (M+Na) found = 301.17800. **IR:** (neat) υ max (cm^{-1}): 2933 (CH), 2860 (CH), 1975 (C=C=C), 1716 (C=O), 1448, 1436. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 0.75 (t, 3H, CH_3, J = 7.1), 1.21-1.80 (m, 16H, CH_2), 1.90 (s, 3H, Me), 3.70 (s, 3H, OMe), 9.21 (s, 1H, CHO). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 209.8, 201.5, 168.4, 107.0, 98.6, 53.9, 52.1, 29.8, 29.5, 29.2, 27.0, 25.6, 22.5, 22.4, 22.3, 15.3, 13.9.

Ethyl 4-(1-formylcyclohexyl)-2-phenethylbuta-2,3-dienoate (466)

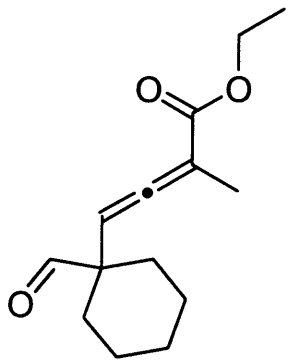


$C_{21}H_{26}O_3$ 326.18819 g mol^{-1}

The title compound was prepared according to the general procedure (IV) by reacting propargylic alcohol (455) (0.80 g, 3.50 mmol) and acetal (444) (0.60 g, 3.80 mmol). The crude compound was purified by flash column chromatography, eluting with

petroleum ether / ethyl acetate (10:1), to give the title allene (0.36 g, 32 %) as a pale yellow oil. **HRMS:** $C_{21}H_{26}O_3$ (M+H) requires 327.19601 (M+H) Found = 327.19676 **IR** (neat) υ max (cm^{-1}): 2933 (CH), 1953 (C=C=C), 1716 (C=O), 1452, 1244. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.28 (t, 3H, CH_3, J = 3.5), 1.25-1.85 (m, 10H, $(CH_2)_5$), 2.56 (m, 2H, CH_2C=), 2.77(t, 2H, CH_2Ph, J = 7.1), 4.15 (m, 2H, $\mathbf{CH_2CH_3}$), 5.26 (t, 1H, CH, J = 2.7), 7.18-7.21 (m, 3H, ArH), 7.21-.7.29 (m, 2H, ArH), 9.27 (s, 1H, CHO) . **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 210.6, 201.5, 166.8, 141.1, 128.5, 128.4, 126.0, 102.6, 96.9, 61.0, 51.5, 34.3, 31.0, 25.5, 22.1, 22.0, 14.2

Ethyl 4-(1-formylcyclohexyl)-2-methylbuta-2,3-dienoate (467)

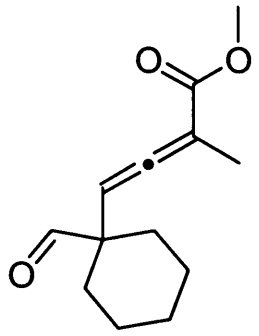


$C_{14}H_{20}O_3$ 236.14124 g mol $^{-1}$

The title allene was prepared according to the general procedure (IV), by reacting propargylic alcohol (432) (0.50 g, 3.52 mmol) and acetal (444) (0.67 g, 4.22 mmol). The crude product was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (10:1) to give the title allene (0.22 g, 26 %) as a pale yellow oil. **HRMS:** $C_{14}H_{20}O_3$ (M+) Requires = 236.14124 (M+) Found = 236.14182 **IR** (neat) υ max (cm^{-1}): 2933, 2856 (CH), 1957 (C=C=C), 1712 (C=O), 1448. **^{1}H**

NMR: $CDCl_3$ (300 MHz) δ ppm: 1.27 (m, 3H, $\mathbf{CH_3}CH_2$), 1.4-1.61 (m, 10H, CH_2), 1.89 (d, 3H, CH_3, J = 3.7), 4.17 (m, 2H, CH_2), 5.27 (m, 1H, CH), 9.61 (s, 1H, CHO). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 210.8, 201.5, 98.4, 95.5, 61.1, 51.6, 30.8, 30.4, 25.6, 22.0, 21.9, 14.9, 14.2.

Methyl 4-(1-formylcyclohexyl)-2-methylbuta-2,3-dienoate (468)

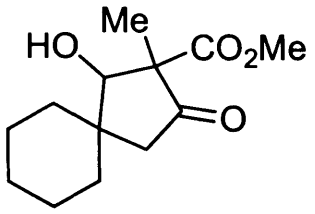


$C_{13}H_{18}O_3$ 222.12559 g mol $^{-1}$

According to the general procedure (IV) allene (468) was prepared by the reaction of propargylic alcohol (452) (0.45 g, 3.51 mmol) and acetal (0.66 g, 4.21 mmol). The crude product was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (20:1), to give the title allene (0.32 g, 41 %) as a pale yellow oil. **HRMS:** $\mathbf{C_{16}H_{18}O_3}$ (M+H) requires = 223.13341 (M+H) found = 223.13276. **IR** (neat) υ max (cm^{-1}): 2933 (CH), 2804 (CH), 1957 (s) (C=C=C), 1716 (C=O), 1450. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.50-1.80 (m, 10H, CH_2), 1.87 (d, 3H, Me, J = 2.9), 3.72 (s, 3H, OMe), 5.27 (q, 1H, CH, J = 2.9), 9.32 (s, 1H, CHO). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 210.7, 201.4, 167.7, 98.2, 95.7, 52.3, 51.5, 30.7, 30.6, 25.5, 22.0, 22.0, 15.0.

General Procedure (V)

Methyl 2-hydroxy-1-methyl,3-cyclohexyl-5-oxocyclopentanecarboxylate (473)

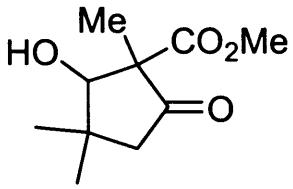


$C_{13}H_{20}O_4$ 240.13616 g mol $^{-1}$

To a solution of allenic ester (468) (0.10 g, 0.45 mmol) in acetonitrile (8 ml) at room temperature, was added pyrrolidine (0.03 g, 0.45 mmol). The solution was stirred at room temperature for 12 hrs and then concentrated at reduced pressure. The crude oil was dissolved in THF (10 ml) and acetic acid (10 %, 10 ml) was added. The acidic solution was stirred at room temperature for 12 hrs then the mixture was poured into saturated aqueous $NaHCO_3$ solution (10 ml). The aqueous phase was separated and extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated at reduced pressure. The crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (5:1) to give the title cyclopentanone (473) (0.07 g, 65%) as a pale yellow solid, as a mixture of diastereoisomers in a ratio of approximately 1:1. **Mp (° C)** = 34-36 **HRMS: $C_{13}H_{20}O_4$** (M+H) required = 241.14398 (M+H) found = 241.14411 **IR** (nujol) υ max (cm^{-1}): 3496 bs (OH), 2929, 2856 (CH), 1747 (C=O, ketone), 1728 (C=O, ester), 1452. **Diastereoisomer 1 ^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.30-1.74 (m, 10H, $(CH_2)_5$), 1.47 (s, 3H, Me), 2.27 (d, 1H, CH_2CO, J = 18.4), 2.53 (bs, 1H, OH), 2.82 (d, 1H, CH_2CO, J = 18.4), 3.11 (s, 1H, CH(OH)), 3.70 (s, 1H, OMe).**^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 213.7, 173.6, 77.9, 62.3, 54.2, 49.6, 42.5, 39.0, 29.4, 25.7, 24.3, 22.8, 22.3, 16.4. **Diastereoisomer 2 ^{1}H NMR:** $CDCl_3$ (75

MHz) δ ppm: 1.20-1.75 (m, 10H, $(CH_2)_5$), 1.33 (s, 3H, Me), 2.18 (d, 1H, OH, J = 5.6), 2.22 (d, 1H, CH_2CO, J = 17.4), 2.59 (d, 1H, CH_2CO, J = 17.4), 3.69 (s, 3H, OMe), 4.39 (d, 1H, CH(OH) J = 5.4). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 212.3, 172.9, 85.9, 60.0, 52.8, 47.3, 42.2, 36.7, 29.0, 25.6, 23.3, 22.1, 15.6.

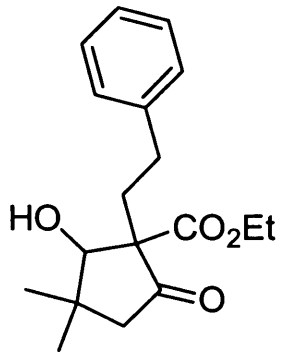
Methyl 2-hydroxy-1,3,3-trimethyl-5-oxocyclopentanecarboxylate (475)



$C_{10}H_{16}O_4$ 200.10486 g mol $^{-1}$

The title compound was prepared according to the general procedure (V) using allenic ester (463). The title cyclopentanone was isolated as a colourless oil in a 45 % yield after purification of the crude compound by flash column chromatography, eluting with petroleum ether / ethyl acetate (3:1), as a mixture of two inseparable diastereoisomers, in a ratio of approximately 1:1. **HRMS: $C_{10}H_{16}O_4$** (M+H) required = 201.11214 (M+H) found = 201.11169. **IR** (neat) υ max (cm^{-1}): 3496 bs (OH), 2958, 2873 (CH), 1751 (C=O, ketone), 1732 (C=O ester), 1452, 1436, 1375. **Diastereoisomer 1 ^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.04 (s, 3H, Me_2), 1.15 (s, 3H, Me_2), 1.45 (s, 3H, Me), 1.70 (bs, 1H, OH), 2.14 (d, 1H, CH_2CO, J = 18.4), 2.28 (d, 1H, CH_2CO, J = 18.4), 3.71 (s, 3H, OMe), 3.73 (bs, 1H, CH(OH)). **Diastereoisomer 2 ^{1}H NMR:** $CDCl_3$ (75 MHz) δ ppm: 0.97 (s, 3H, Me_2), 1.22 (s, 3H, Me_2), 1.67 (s, 3H, Me), 2.34 (d, 1H, CH_2CO, J = 17.6), 2.40 (d, 1H, CH_2CO, J = 17.6), 2.46 (bd, 1H, OH, J = 4.8) 3.68 (s, 3H, OMe), 4.44 (bd, 1H, CH(OH), J = 4.8).**^{13}C NMR: Diastereomeric Mixture** $CDCl_3$ (75 MHz) δ ppm: 211.9, 211.4, 172.9, 85.7, 81.3, 60.1, 58.6, 52.8, 52.4, 51.3, 38.7, 38.4, 28.1, 27.6, 22.8, 21.5, 15.1.

Ethyl 2-hydroxy-3,3-dimethyl-5-oxo-1-phenethylcyclopentanecarboxylate (476)

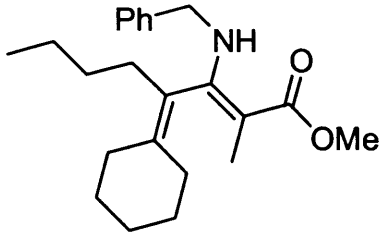


$C_{18}H_{24}O_4$ 304.16746 g mol $^{-1}$

Cyclopentanone (476) was prepared according to the general procedure (V) using allenic ester (464) (0.12 g, 0.42 mmol). The title cyclopentanone (476) (0.05 g, 40 %) was isolated as a pale yellow oil, after purification of the crude compound by flash column chromatography, eluting with petroleum ether / ethyl acetate (4:1) as a 1:1 mixture of two separable diastereoisomers. **HRMS:** $C_{18}H_{24}O_4$ (M+Na) required = 327.15722 (M+Na) found = 327.15643 **IR** (neat) υ max (cm^{-1}): 3467 bs (OH), 2964, 2935, 2871 (CH), 1724 (C=O), 1635, 1496, 1454, 1369. **Diastereoisomer 1 ^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.08 (s, 3H, Me_2), 1.13 (s, 3H, Me_2), 1.30 (t, 3H, **CH_3CH_2**, J = 7.0), 1.98 (bs, 1H, OH), 2.15 (m, 2H, **CH_2CH_2Ph**), 2.25 (d, 1H, CH_2CO, J = 17.6), 2.35 (d, 1H, CH_2CO, J = 17.6), 2.65 (m, 1H, CH_2Ph), 2.85 (m, 1H, CH_2Ph), 4.20 (m, 2H, **CH_2CH_3**), 4.45 (bs, 1H, CH(OH)), 7.15-7.29 (m, 5H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 211.7, 170.9, 142.0, 131.5, 128.4, 126.0, 81.4, 64.1, 61.7, 51.0, 38.4, 33.5, 31.3, 27.8, 22.7, 14.1. **Diastereoisomer 2 ^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.00 (s, 3H, Me_2), 1.22 (s, 3H, Me_2), 1.30 (t, 3H, **CH_3CH_2**, J = 7.2), 1.95 (m, 1H, **CH_2CH_2Ph**), 2.15 (d, 1H, CH_2CO, J = 18.2), 2.30 (m, 1H, **CH_2CH_2Ph**), 2.42 (d, 1H, CH_2CO, J = 18.2), 2.75 (m, 2H, CH_2Ph), 3.94 (d, 1H, OH, J = 9.3), 4.20

(q, 2H, $\mathbf{CH_2CH_3}$, J = 7.2), 4.41 (d, 1H, CH(OH), J = 9.3) 7.15-7.30 (m, 5H , ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 209.6, 171.0, 140.9, 128.5, 128.4, 126.2, 84.3, 62.1, 61.0, 51.6, 38.9, 38.7, 30.9, 27.8, 21.4, 14.0.

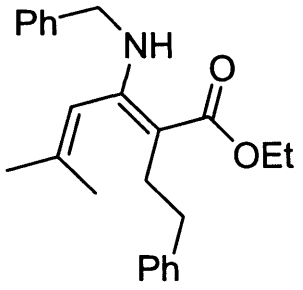
(Z)-Methyl 3-(benzylamino)-4-cyclohexylidene-2-methyloct-2-enoate (485)



$C_{23}H_{33}NO_2$ 355.25113 g mol $^{-1}$

To a solution of allenic ester (465) (0.10 g, 0.36 mmol), in dry acetonitrile (15 ml) at room temperature, was added Et_3N (0.04 g, 0.43 mmol) followed by N-benzyl-hydroxylamine-hydrochloride (0.06 g, 0.36 mmol). The solution was stirred at room temperature for 3 hrs and then concentrated at reduced pressure. The crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (20:1), to give the title vinylogous urethane (485) (0.08 g, 59 %) as a pale yellow oil. **HRMS: $C_{23}H_{33}NO_2$** (M+H) requires = 356.25894 (M+H) Found = 356.25983. **IR** (neat) υ max (cm^{-1}): 3253 bs (NH), 2929, 2856 (CH), 1728 (C=O), 1616 (C=O). **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 0.88 (t, 3H, CH_3, J = 6.9) 1.27-1.55 (m, 10H, $(CH_2)_5$) 1.67 (s, 3H, Me), 2.21-2.31 (m, 6H, $(CH_2)_3$), 3.61 (s, 3H, OMe), 4.28 (d, 2H, CH_2Ph, J = 5.9), 7.19-7.49 (m, 5H, ArH), 9.28 (t, 1H, NH, J = 5.9) **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 171.9, 163.8, 139.6, 138.9, 128.5, 127.0, 124.8, 87.2, 50.4, 48.1, 32.0, 31.8, 30.6, 29.5, 27.8, 27.2, 26.6, 23.2, 13.98, 13.93.

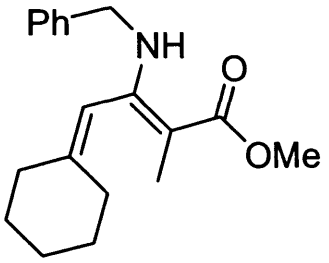
(Z)-Ethyl 3-(benzylamino)-5-methyl-2-phenethylhexa-2,4-dienoate (486)



$C_{24}H_{29}N0_2$ 363.21983 g mol $^{-1}$

To a solution of allenic ester (464) (0.10 g, 0.35 mmol) in dry acetonitrile (15 ml) at room temperature, was added Et_3N (0.04 g, 0.42 mmol), followed by N-benzylhydroxylamine hydrochloride (0.06 g, 0.35 mmol). The solution was stirred at room temperature for 48 hrs and then concentrated at reduced pressure. The crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (10:1), to give the title compound (0.03 g, 23 %) as a clear oil. **HRMS:** **$C_{24}H_{29}NO_2$** (M+H) requires 364.22765 (M+H) Found = 364.22829. **IR** (neat) υ max (cm^{-1}): 3320 (NH) 3026, 2976, 2931 (CH), 1733 (C=O), 1643 (C=C) **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.33 (t, 3H, $CH_2\mathbf{CH_3}$, J = 7.2), 1.56 (s, 3H, Me_2), 1.79 (s, 3H, Me_2) 2.3-2.6 (m, 4H, CH_2CH_2Ph), 4.17 (q, 2H, $\mathbf{CH_2}CH_3$, J = 7.2), 4.29 (d, 2H, NCH_2Ph, J = 5.3), 5.35 (s, 1H, CH), 7.11-7.35 (m, 10H, ArH), 9.37 (t, 1H, NH, J = 5.3) **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 171.2, 159.8, 143.2, 139.9, 139.2, 128.6, 128.5, 128.1, 127.0, 126.9, 125.4, 118.4, 92.9, 58.7, 47.7, 37.1, 30.7, 24.8, 19.7, 14.7.

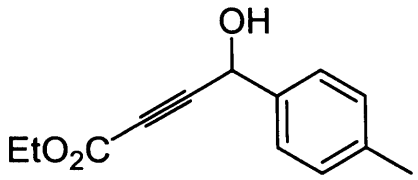
(Z)-Methyl 3-(benzylamino)-4-cyclohexylidene-2-methylbut-2-enoate (487)



$C_{19}H_{25}NO_2$ 299.18853 g mol $^{-1}$

To a solution of allenic ester (466) (0.10 g, 0.45 mmol), in dry acetonitrile (15 ml) at room temperature, was added Et_3N (0.06 g, 0.54 mmol), followed by N-benzylhydroxylamine hydrochloride (0.07 g, 0.45 mmol). The solution was stirred at room temperature for 12 hrs and then concentrated at reduced pressure. The crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (7:1), to give the title vinylogous urethane (487) (0.08 g, 62 %) as a clear oil. **HRMS: $C_{19}H_{25}NO_2$** (M+) requires = 299.18852 (M+) Found = 299.18872. **IR** (neat) υ max (cm^{-1}): 2931, 2856 (CH), 1743 (C=O) 1645 (C=C) **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.48-1.64 (m, 6H, $(CH_2)_3$), 1.73 (s, 3H, Me), 2.03 (t, 2H, $=CCH_2$, J = 6.1), 2.20 (t, 2H, $=CCH_2$, J = 6.1), 3.73 (s, 3H, OMe), 4.38 (d, 2H, CH_2Ph, J = 6.4), 5.55 (s, 1H, CH), 7.21-7.4 (m, 5H, ArH), 9.28 (bt, 1H, NH, J = 6.4) **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 171.2, 158.9, 147.2, 140.2, 128.5, 126.9, 115.0, 88.5, 50.4, 47.8, 36.2, 30.2, 28.3, 26.8, 26.3, 13.6.

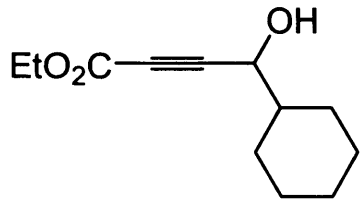
Ethyl 4-hydroxy-4-p-tolylbut-2-ynoate (506)



$C_{13}H_{14}O_3$ 218.09429 g mol $^{-1}$

To a solution of ethyl propiolate (2.00 g, 20.40 mmol), in dry THF (40 ml), cooled to – 78 ° C, was added a 2.5 M solution of n-BuLi in hexanes (20.40 mmol, 8.20 ml), dropwise over 5 minutes. The mixture was stirred at – 78 ° C for 10 minutes, at which point *para*-tolualdehyde (2.42 g, 20.14 mmol) was added dropwise. The solution was stirred at – 78 ° C for 20 minutes, warmed to approximately – 20 ° C and saturated aqueous ammonium chloride solution (15 ml) was added. The mixture was diluted with Et_2O (50 ml) and the organic phase was separated. The solution was washed with brine (30 ml), dried ($MgSO_4$), filtered and concentrated at reduced pressure. The crude compound was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (4:1) to give the title alcohol (506) (2.15 g, 50 %) as a yellow oil. **HRMS: $C_{13}H_{14}O_3$** (M+H) requires = 219.10157 (M+H) Found = 219.10232 **IR** (neat) υ max (cm^{-1}): 3423 bs (OH), 2900 (CH), 1716 (C=O) **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.30 (t, 3H, **CH_3CH_2**, J = 7.5), 2.35 (s, 3H, Me), 3.30 (bs, 1H, OH), 4.25 (q, 2H, **CH_2CH_3**, J = 7.5), 5.48 (d, 1H, CH(OH), J = 6.1), 7.16, (d, 2H, ArH, J = 8.3), 7.37 (d, 2H, ArH, J = 8.3). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 153.5, 138.7, 135.8, 129.4, 126.7, 86.7, 64.0, 62.3, 60.5, 21.1, 14.0.

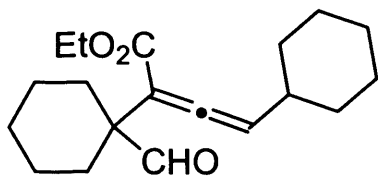
Ethyl 4-cyclohexyl-4-hydroxybut-2-ynoate (509)



$C_{12}H_{18}O_3$ 210.12599 g mol $^{-1}$

According to the procedure outlined for the preparation of alcohol (506), the title compound was prepared from ethylpropiolate (3.40 g, 34.30 mmol) and cyclohexane-carboxyaldehyde (3.80 g, 34.30 mmol). The crude compound was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (5:1) to give (509) as a pale yellow oil (0.72 g, 10 %). **HRMS: $C_{12}H_{18}O_3$** (M+Na) requires = 233.11536 (M+Na) Found = 233.11561 **IR** (neat) υ max (cm^{-1}): 3411 bs (OH), 2981, 2931, 2854 (CH), 1697 (C=O), 1452, 1249 **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.02-1.86 (m, 11H, $(CH2)_5CH$)), 1.25 (t, 3H, CH_3, J = 7.0), 3.11 (bs, 1H, OH), 4.05 (d, 1H, CH(OH), J = 6.9), 4.17 (q, 2H, **CH_2CH_3**, J = 7.0). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 153.6, 87.5, 70.0, 66.7, 43.6, 28.4, 28.1, 25.9, 25.7, 13.9.

Ethyl 4-cyclohexyl-2-(1-formylcyclohexyl)buta-2,3-dienoate (510)

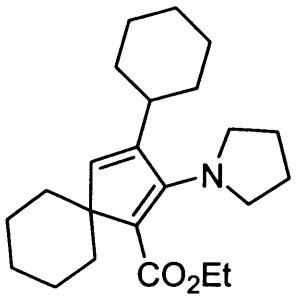


$C_{19}H_{28}O_3$ 304.20384 g mol $^{-1}$

To a solution of alcohol (509) (0.35 g, 1.66 mmol) and acetal (444) (0.28 g, 1.82 mmol) in dry toluene (15 ml), was added *para*-toluenesulfonic acid (30 mg). The solution was heated at reflux for 24 hrs in a flask fitted with Dean & Stark apparatus. The solution was cooled and concentrated at reduced pressure to give a crude oil,

which was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (20:1) to give the title allene (0.13 g, 28 %) as a pale yellow oil. **LRMS: FAB (M^+)** 194, 174, 221, 299, 300. **IR** (neat) υ max (cm^{-1}): 2929, 2854 (CH), 1949 (C=C=C), 1720, 1705 (C=O), 1448, 1259: **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.05-1.99 (m, 20H, $(CH_2)_{10}$), 1.20 (t, 3H, CH_3, J = 7.5), 2.13 (m, 1H, CH), 4.10 (q, 2H, CH_2, J = 7.5), 5.63 (d, 1H, =CH, J = 6.7), 9.61 (s, 1H, CHO). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 209.7, 203.8, 166.9, 105.4, 102.8, 60.9, 50.6, 37.1, 32.8, 32.6, 30.8, 30.6, 25.9, 25.88, 25.83, 25.7, 25.6, 22.3, 14.0.

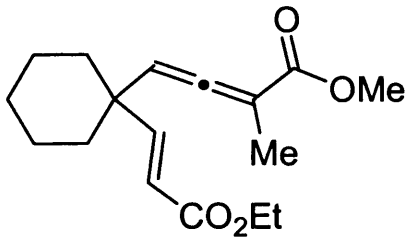
ethyl 3-cyclohexyl-2-(pyrrolidin-1-yl)spiro[4.5]deca-1,3-dienecarboxylate (511)



$C_{23}H_{35}NO_2$ 357.26678 g mol $^{-1}$

To a solution of allene (510) (0.09 g, 0.30 mmol), in dry acetonitrile (10 ml) at room temperature, was added pyrrolidine (0.01 g, 0.30 mmol). The solution was stirred at room temperature for 12 hrs and then concentrated at reduced pressure. The crude oil was purified by flash column chromatography, eluting with ethyl acetate (100 %) to give the title compound (0.02 g, 19 %) as a clear oil. **HRMS: $C_{23}H_{35}NO_2$** (M+Na) requires = 380.25600 (M+Na) Found = 380.25372 **IR** (neat) υ max (cm^{-1}): 3020 (=CH), 1602 (C=O), 1494, 1456. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.20-1.35 (m, 8H, $(CH_2)_4$), 1.27 (t, 3H, $\mathbf{CH_3}CH_2$, J = 7.0), 1.45-1.81 (m, 12H, $(CH_2)_6$), 1.87 (t, 4H, $(\mathbf{CH_2}CH_2)_2N$, J = 6.4) , 2.18 (m, 1H, CH), 3.46 (t, 4H, $(CH_2)_2N$, J = 6.4), 4.15 (m, 2H, $\mathbf{CH_2}CH_3$), 6.66 (s, 1H, =CH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 165.3, 146.1, 142.1, 112.9, 60.4, 58.6, 51.7, 51.3, 38.1, 34.3, 32.8, 26.9, 26.3, 25.9, 25.2, 14.7, 14.2.

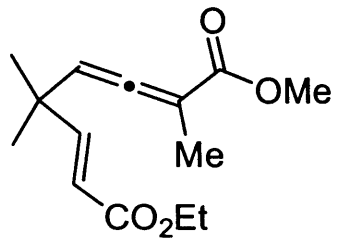
(E)-Methyl-4-(1-(3-ethoxy-3-oxoprop-1-enyl)cyclohexyl)-2-methylbuta-2,3-dienoate (529)



$C_{17}H_{24}O_4$ 292.17646 g mol $^{-1}$

To a slurry of NaH (60 % dispersion in mineral oil, 0.07 g, 1.78 mmol) in dry THF (20 ml), cooled in an ice bath, was added triethylphosphonoacetate (0.48 g, 2.14 mmol) dropwise. The slurry was stirred in the ice bath for 10 minutes, warmed to room temperature and stirred another 20 minutes. The mixture was cooled to 0 ° C and a solution of allenic ester (468) (0.39 g, 1.78 mmol) in dry THF (10 ml), was added dropwise. The mixture was allowed to warm to room temperature and then heated at a gentle reflux for 12 hrs. After cooling and quenching by the addition of water (20 ml), the aqueous phase was separated and extracted with ethyl acetate (4 x 20 ml). The combined organic fractions were washed with brine (20 ml), dried ($MgSO_4$) filtered and concentrated at reduced pressure. The crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (8:1) to give the title compound (529) (0.24 g, 46 %) as a clear oil. **HRMS: $C_{17}H_{24}O_4$** (M+H) requires = 293.17528 (M+H) Found = 293.17394 **IR** (neat) υ max (cm^{-1})**:** 2983, 2931, 2856 (CH), 1959 (C=C=C), 1712 (C=O), 1448, 1390. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.28 (t, 3H, **CH_3CH_2**, J = 7.5), 1.45-1.65 (m, 10H, $(CH_2)_5$), 1.88 (s, 3H, Me), 3.74 (s, 3H, OMe), 4.18 (m, 2H, **CH_2CH_3**), 5.28 (m, 1H, =CH allene), 5.92 (d, 1H, =CH, J = 15.8), 6.88 (d, 1H, =CH, J = 15.8).**^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 210.2, 168.1, 167.0, 155.4, 119.5, 99.7, 97.6, 60.3, 52.1, 42.5, 35.8, 35.6, 25.8, 22.2, 22.0, 14.8, 14.3.

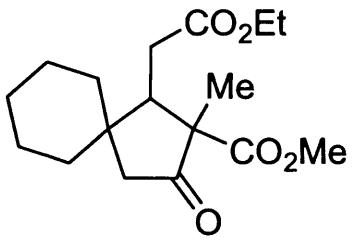
(E)-8-Ethyl 1-methyl 2,5,5-trimethylocta-2,3,6-trienedioate (533)



$C_{14}H_{20}O_4$ 252.13616 g mol^{-1}

To a slurry of NaH (60 % dispersion in mineral oil, 0.07 g, 1.78 mmol) in dry THF (20 ml) cooled in an ice bath, was added triethylphosphonoacetate (0.48 g, 2.14 mmol) dropwise. The slurry was stirred in the ice bath for 10 minutes, warmed to room temperature and stirred another 20 minutes. The mixture was cooled to 0 ° C and a solution of allenic ester (466) (0.27 g, 1.48 mmol) in dry THF (10 ml), was added dropwise. The mixture was allowed to warm to room temperature and then heated at a gentle reflux for 12 hrs. After cooling and quenching by the addition of water (20 ml), the aqueous phase was separated and extracted with ethyl acetate (4 x 20 ml) and the combined organic extracts were washed with brine (20 ml), dried ($MgSO_4$) filtered and concentrated at reduced pressure. The crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (8:1) to give the title compound (533) (0.16 g, 42 %) as a clear oil. **HRMS: $C_{14}H_{20}O_4$** (M+H) requires = 253.14398 (M+H) Found = 253.14365 **IR** (neat) υ max (cm^{-1})**:** 2981 (CH), 1950 (C=C=C), 1724 (C=O), 1647 (C=C) 1436, 1369. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.21 (s, 6H, Me_2), 1.27 (t, 3H, **CH_3CH_2**, J = 7.2), 1.86 (d, 3H, Me, J = 2.9), 3.72 (s, 3H, OMe), 4.2 (q, 2H, **CH_2CH_3**, J = 7.2), 5.4 (q, 1H, =CH, allene, J = 2.9), 5.84 (d, 1H, =CH, J = 15.8), 6.92 (d, 1H, =CH, J = 15.8). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 208.9, 168.0, 166.9, 155.4, 118.7, 101.6, 97.9, 60.3, 52.2, 38.4, 27.2, 27.1, 15.1, 14.2.

Methyl 2-(2-ethoxy-2-oxoethyl)-1,methyl-2-cyclohexyl-5-oxocyclopentanecarboxylate (531)

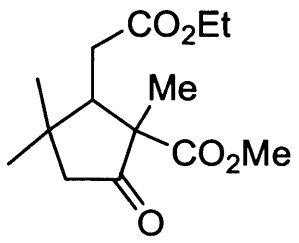


$C_{17}H_{26}O_5$ 310.17802 g mol $^{-1}$

To a solution of allene (529) (0.16 g, 0.55 mmol) in dry acetonitrile (10 ml) at room temperature, was added pyrrolidine (0.04 g, 0.60 mmol) and the solution was stirred at room temperature for 24 hrs. The reaction mixture was concentrated at reduced pressure and THF (15 ml) was added followed by acetic acid (10 % aqueous solution, 8 ml). The mixture was stirred at room temperature for 12 hrs and then poured into ethyl acetate (25 ml). The organic phase was separated and was washed successively with saturated aqueous $NaHCO_3$ solution (2 x 20 ml) and brine (20 ml) then dried ($MgSO_4$) filtered and concentrated at reduced pressure to give a crude oil, purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (5:1) to provide the title compound (531) (0.06 g, 35 %) as a clear oil and as a mixture of two diastereoisomers in a ratio of approximately (5:1). **HRMS: $C_{17}H_{26}O_5$** (M+H) requires = 311.18585 (M+H) Found = 311.18491 **IR** (thin film) υ max (cm^{-1}): 2983, 2933, 2856 (CH), 1743, 1724 (C=O), 1452, 1407. **Major Diastereoisomer ^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.19 (s, 3H, Me), 1.22 (t, 3H, **CH_3CH_2**, *J* = 7.2), 1.4-1.76 (m, 10H, $(CH_2)_5$), 2.40 (d, 1H, CH_2CO, *J* = 17.8), 2.70 (d, 1H, CH_2CO, *J* = 17.8), 2.34-2.52 (m, 2H, **CH_2CO_2Et**), 3.01 (dd, 1H, **$CHCH_2CO_2Et$**, *J* = 7.5, 3.7), 3.66 (s, 3H, OMe), 4.10 (m, 2H, **CH_2CH_3**). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 214.2, 172.7, 172.4, 60.7, 58.1, 52.1, 50.7, 48.8, 40.9, 37.5, 30.4, 30.2, 25.7, 23.9, 22.1, 16.4, 14.1.**Minor Diastereoisomer ^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.24 (t, 3H,

CH_3CH_2, J = 7.2), 1.35 (s, 3H, Me), 1.4-1.76 (m, 10H, $(CH_2)_5$), 2.42 (d, 1H, CH_2CO, J = 18.2), 2.34-2.52 (m, 2H, **CH_2CO_2Et**, m, 1H, **$CHCH_2CO_2Et$**), 2.71 (d, 1H, CH_2CO, J = 18.2), 3.64 (s, 3H, OMe), 4.10 (m, 2H, **CH_2CH_3**) **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 214.3, 172.7, 171.9, 60.7, 58.9, 54.6, 52.1, 47.5, 41.0, 38.6, 31.5, 29.8, 25.7, 23.9, 22.9, 16.4, 14.1.

Methyl 2-(2-ethoxy-2-oxoethyl)-1,3,3-trimethyl-5-oxocyclopentanecarboxylate (534)



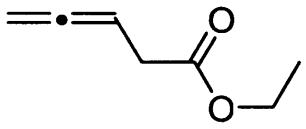
$C_{14}H_{22}O_5$ 270.14672 g mol $^{-1}$

To a solution of allene (533) (0.14 g, 0.54 mmol) in dry acetonitrile (10 ml), was added pyrrolidine (0.05 g, 0.64 mmol) at room temperature and the solution was stirred for 24 hrs. The reaction mixture was concentrated at reduced pressure and THF (15 ml) was added followed by acetic acid (10 % aqueous solution, 8 ml). The mixture was stirred at room temperature for 12 hrs and then poured into ethyl acetate (25 ml). The organic phase was separated and washed successively with saturated $NaHCO_3$ solution (2 x 20 ml) and brine (20 ml) then dried ($MgSO_4$), filtered and concentrated at reduced pressure. The resultant crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (5:1), to give the title compound (534) (0.09 g, 62 %) as a clear oil and as a mixture of two diastereoisomers in a ratio of approximately (5:1). **HRMS: $C_{14}H_{22}O_5$** (M+Na) requires = 293.13649 (M+Na) Found = 293.13673 **IR** (neat) υ max (cm^{-1}): 2958, 2873 (CH), 1732, 1699 (C=O). **Major Diastereoisomer ^1H NMR:** $CDCl_3$ (300 MHz) δ ppm: 0.86 (s, 3H, Me), 1.20 (s, 3H, Me_2), 1.21 (t, 3H, **CH_3CH_2**, J = 7.2), 1.23 (s, 3H, Me_2), 2.22 (d, 1H,

CH_2CO, J = 17.1), 2.30-2.45 (m, 2H, **CH_2CO_2Et**), 2.58 (d, 1H, CH_2CO, J = 17.1), 3.08 (dd, 1H, **$CHCH_2CO_2Et$**, J = 7.2, 4.1), 3.67 (s, 3H, OMe), 4.09 (m, 2H, **CH_2CH_3**).**^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 213.8, 172.6, 172.2, 60.8, 58.5, 54.4, 52.7, 49.7, 36.7, 30.6, 28.1, 23.2, 15.9, 14.1. **Minor Diastereoisomer ^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 0.98 (s, 3H, Me), 1.11 (s, 3H, Me_2), 1.21 (t, 3H, **CH_3CH_2**, J = 7.2), 1.36 (s, 3H, Me_2), 2.30 (d, 1H, CH_2CO, J = 11.5), 2.32-2.48 (m, 3H, **CH_2CO_2Et**, **$CHCH_2CO_2Et$**), 3.64 (s, 3H, OMe), 4.10 (m, 2H, **CH_2CH_3**). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 213.8, 172.5, 171.8, 60.7, 59.4, 53.7, 52.9, 52.1, 37.1, 31.7, 29.4, 22.9, 15.9, 14.1.

4.4 Tandem Reactions (III) – Carbometallation of Allenic Substrates

Ethyl penta-3,4-dienoate (587) [151]

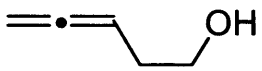


$C_7H_{10}O_2$ 126.06808 g mol^{-1}

The title allene was prepared *via* a modified literature procedure.[151] A mixture of propargyl alcohol (9.0 ml, 0.16 mol) and triethylorthoacetate (60 ml, 0.33 mol) was heated to 100 ° C in a two neck round bottom flask fitted with a still head, under nitrogen. Propionic acid (0.2 ml, 2.7 mmol) was added and the reaction mixture was raised to 160 ° C, allowing the steady distillation of ethanol out of the reaction flask. When the distillation of ethanol ceased (ca 1.5 hrs) propargyl alcohol (9.0 ml, 0.16 mol) was added slowly over 15 minutes. The reaction mixture was heated at 160 ° C for a subsequent hour and then treated with propionic acid in 0.2 ml portions until no more ethanol was distilled (ca 0.6 ml added). The solution was cooled to room temperature and diluted with 2N HCl (20 ml). The aqueous phase was separated and extracted with Et_2O (3 x 20 ml), washed with saturated aqueous $NaHCO_3$ solution and

dried with $MgSO_4$. After filtration the solvent was removed by distillation at atmospheric pressure and the residual liquid was distilled at 20 mmHg to give a clear liquid at 161-163 ° C as the title allene (15.53 g, 123 mmol, 40%). Bp Literature [151] (165 ° C, 20 mmHg). **IR** (thin film) υ max (cm^{-1}): 2983, 2939, 2908 (CH), 1959 (C=C=C), 1735 (C=O) **^{1}HNMR:** $CDCl_3$ (300Mz) δ ppm: 1.23 (t, 3H, CH_3 J = 7.1), 3.01 (m, 2H, CH_2CO_2Et), 4.11 (q, 2H, CH_2CH_3, J = 7.1) 4.67 (m, 2H, $=CH_2$), 5.23 (m, 1H, =CH) **^{13}CNMR:** $CDCl_3$ (300Mz) δ ppm: 209.3, 171.3, 83.5, 75.7, 60.8, 34.2, 14.2.

Penta-3,4-dien-1-ol [152] (578)

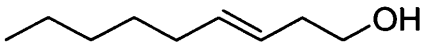


C_5H_8O 84.05751 g mol $^{-1}$

Allenol (578) was prepared following a literature procedure.[152] To a suspension of $LiAlH_4$ (5.06 g, 0.13 mol) in dry THF (40 ml), cooled in an ice bath was slowly added a solution of the allenic ester (587) (22.60 g, 0.18 mol) in dry THF (20 ml) over 10 minutes. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was cooled to 0 ° C and quenched at by the addition of a THF/H_2O mixture (3:1) (20 ml). The solid was filtered off and washed with ether (30 ml). The filtrate and combined washings were dried ($MgSO_4$), filtered and the solvent was removed by distillation at atmospheric pressure. The residual liquid was distilled at reduced pressure to give the title compound (7.00 g, 62%) as a clear liquid (80-84 ° C, 55 mmHg). Literature bp (80 ° C, 58 mmHg). **IR** (thin film) υ max (cm^{-1}): 3500 (OH), 1925 (C=C=C). **^{1}HNMR:** $CDCl_3$ (300Mz) δ ppm: 1.90 (bs, 1H, OH), 2.25 (m, 2H, CH_2), 3.69 (t, 2H, CH_2O, J = 6.35), 4.67 (m, 2H, CH_2), 5.05 (m, 1H, CH). **^{13}C NMR:** $CDCl_3$ (300Mz) δ ppm: 209.0, 86.4, 75.2, 61.2, 31.6.

General Procedure (VI)

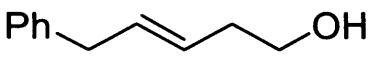
(*E*)-non-3-en-1-ol (588)



$C_9H_{18}O$ 142.13577 g mol $^{-1}$

To a solution of homoallenol (578) (0.50 g, 5.95 mmol), in dry toluene (8 ml), was added CuI (0.54 g, 2.97 mmol). The reaction mixture was cooled to – 78 ° C and a solution of freshly prepared pentyl-magnesium bromide (20.82 mmol, 28.50 ml, 0.73 M solution in Et_2O) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 12 hrs. Saturated aqueous ammonium chloride solution (30 ml) was added, followed by water (30 ml) and the aqueous phase was separated and extracted with Et_2O (4 x 30 ml). The combined organic fractions were washed with brine (20 ml), dried ($MgSO_4$) filtered and concentrated at reduced pressure. The crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (6:1), to give the title compound (0.40 g, 47 %) as a clear oil. **IR** (neat) υ max (cm^{-1}): 3330 bs (OH), 2956, 2925, 2856 (CH), 1460, 1379. **HRMS: $C_9H_{18}O$** (M+H) requires = 157.15923 (M+H) Found = 157.15884. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 0.87 (t, 3H, CH_3, J = 6.4), 1.19-1.36 (m, 6H, $3CH_2$), 1.61 (bs, 1H, OH), 1.99 (t, 2H, CH_2C=, J = 7.0), 2.26 (t, 2H, CH_2C=, J = 7.0), 3.60 (t, 2H, CH_2OH, J = 7.0), 5.44 (m, 2H, =CH). **^{13}C NMR:** $CDCl_3$ (300 MHz) δ ppm: 134.4, 125.7, 62.0, 36.0, 32.7, 31.7, 29.4, 28.9, 22.6, 14.0.

(*E*)-5-phenylpent-3-en-1-ol (590)

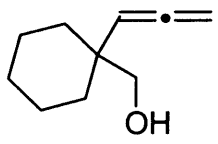


$C_{11}H_{14}O$ 162.10447 g mol $^{-1}$

According to the general procedure (VI), homoallylic alcohol (590) was prepared by the reaction of homoallenol (578) (0.50 g, 5.95 mmol) with freshly prepared PhMgBr in Et_2O (3.5 eq).[ref] The title compound (0.57 g, 60 %) was isolated after purification of the crude oil by flash column chromatography, eluting with petroleum ether / ethyl acetate (6:1) as a pale yellow oil. **HRMS: $C_{11}H_{14}O$** (M+) requires = 162.10446 (M+) Found = 162.10483 **IR** (neat) υ max (cm^{-1}): 3342 bs (OH), 2929, 2883 (CH), 1494, 1452. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 2.31 (m, 2H, CH_2), 3.38 (d, 2H, CH_2Ph, *J* = 7.0), 3.66 (t, 2H, CH_2OH, *J* = 6.4), 5.61 (m, 2H, =CH), 7.15-7.44 (m, 5H, ArH). **^{13}C NMR:** $CDCl_3$ (300 MHz) δ ppm: 138.2, 129.5, 128.3, 128.1, 126.6, 125.2, 62.4, 38.4, 35.3.

General Procedure (VII)

(1-(Propa-1,2-dienyl)cyclohexyl)methanol (594)

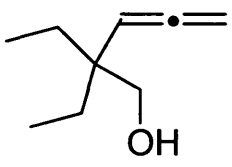


$C_{10}H_{16}O$ 152.12012 g mol $^{-1}$

To a solution of cyclohexancarboxyaldehyde (4.00 g, 36.00 mmol) and propargyl alcohol (2.01 g, 36.00 mmol) in toluene (60 ml), was added *para*-toluenesulfonic acid

(60 mg). The solution was heated at reflux in a flask fitted with a Dean and Stark separator. After 24 hrs, the reaction mixture was cooled and concentrated at reduced pressure. The crude oil was dissolved in EtOH (70 ml) and cooled in an ice bath as sodium borohydride (1.36 g, 36.00 mmol) was added in portions over ten minutes. The mixture was allowed to warm to room temperature and stirred for 12 hrs. The mixture was diluted with water (120 ml), cooled in an ice bath and acetone (30 ml) was added. The EtOH was removed at reduced pressure and the aqueous phase was separated and extracted with ethyl acetate (4 x 20 ml). The combined organic fractions were washed with brine (50 ml), dried ($MgSO_4$) filtered and concentrated at reduced pressure. The crude oil was purified by flash column chromatography, eluting with petroleum ether / ethyl acetate (4:1), to give the title compound (1.61 g, 30 %) as a clear oil. **HRMS: $C_{10}H_{16}O$** (M+H) requires = 153.12793 (M+H) Found = 153.12756 **IR** (neat) υ max (cm^{-1}): 3354 bs (OH), 2925, 2852 (CH), 1953 (C=C=C), 1448. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.18-1.57 (m, 10H, 5(CH_2)), 1.82 (bs, 1H, OH), 3.33 (s, 2H, CH_2OH), 4.74 (d, 2H, =CH_2, J = 7.0), 4.94 (t, 1H, =CH, J = 7.0).**^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 208.2, 95.6, 76.4, 68.7, 40.6, 32.8, 26.3, 22.0

2,2-Diethylpenta-3,4-dien-1-ol (595)

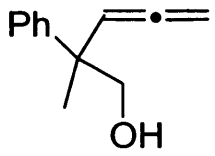


$C_9H_{16}O$ 140.12012 g mol $^{-1}$

According to the general procedure (VII), the title compound was prepared by the reaction of 2-ethylbutanal (7.20 g, 72.00 mmol) and propargyl alcohol (4.04 g, 72.00 mmol). Allenol (595) (0.80 g, 8 %) was isolated as a clear oil after purification of the

crude oil by flash column chromatography, eluting with petroleum ether / ethyl acetate (8:1). **HRMS: $C_9H_{16}O$** (M+H) requires = 141.12793 (M+H) Found = 141.12764 **IR** (neat) υ max (cm^{-1}): 3361 bs (OH), 1953 (C=C=C), 1460.**^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 0.83 (t, 6H, $2CH_3$, J = 7.4), 1.32 (q, 4H, $2CH_2$, J = 7.4), 3.43 (s, 2H, CH_2OH), 4.70 (d, 2H, $=CH_2$, J = 6.7), 4.94 (t, 1H =CH, J = 6.7) **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 207.9, 95.5, 76.4, 66.9, 42.9, 26.4, 7.9.

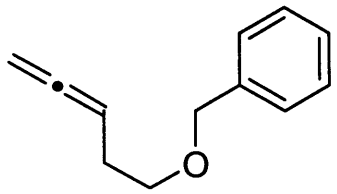
2-methyl-2-phenylpenta-3,4-dien-1-ol (596)



$C_{12}H_{14}O$ 174.10447 g mol $^{-1}$

The title compound was prepared according to the general procedure (VII) by reacting 2-phenyl-propanal (19.20 g, 0.14 mol) and propargyl alcohol (8.00 g, 0.14 mol). The title allenol (3.50 g, 14 %) was isolated as a pale yellow oil after purification of the crude oil by flash column chromatography, eluting with petroleum ether / ethyl acetate (5:1). **IR** (neat) υ max (cm^{-1}): 3384 bs (OH), 1953 (C=C=C), 1600, 1494 **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.45 (s, 3H, Me), 1.62 (s, 1H, OH), 3.71 (d, 1H, CH_2OH, J = 11.2), 3.78 (d, 1H, CH_2OH, J = 11.2), 5.62 (dd, 2H, $=CH_2$, J = 2.14, 6.4), 5.44 (t, 1H, =CH, J = 6.4), 7.23-7.44 (m, 5H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 207.3, 144.8, 128.5, 126.8, 126.6, 96.9, 77.1 71.0, 44.6, 23.5.

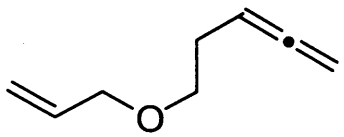
1-((Penta-3,4-dienyloxy)methyl)benzene (599)



$C_{12}H_{14}O$ 174.10447 g mol $^{-1}$

To a suspension of NaH (0.40 g, 10.05 mmol, 60 % dispersion in mineral oil) in dry THF (20 ml) cooled in an ice bath was added a solution of the allenol (578) (0.65 g, 7.7 mmol) in dry THF (10 ml) slowly over a ten minute period. The solution was raised to room temperature and stirred for 10 minutes. Benzyl bromide (1.45 g, 8.5 mmol) was added dropwise and the reaction mixture stirred at room temperature for 12 hrs. Water (10 ml) was slowly added at room temperature and the aqueous phase was extracted with ethyl acetate (3 x 20 ml), dried ($MgSO_4$) filtered and concentrated at reduced pressure. The crude compound was purified by flash column chromatography, eluting with petroleum ether/ethyl acetate (50:1) to give the title ether (599) (1.23 g, 91 %) as a clear oil. **HRMS: $C_{12}H_{14}O$** (M+) requires = 174.10447 (M+) Found = 174.10423 **IR** (thin film) υ max (cm^{-1}): 2925, 2864 (CH), 1957 (C=C=C), 1716, 1602, 1585. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 2.37 (m, 2H, CH_2), 3.57 (t, 2H, CH2O, J = 6.7), 4.58 (s, 2H, CH_2Ph), 4.72 (m, 2H, $=CH_2$), 5.13 (m, 1H, =CH), 7.31-7.63 (m, 5H, ArH). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 208.9, 137.8, 128.8, 128.4, 127.6, 86.8, 75.0, 72.9, 69.6, 28.9.

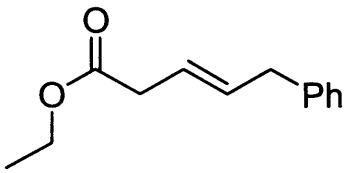
5-(Allyloxy)penta-1,2-diene (600)



$C_8H_{12}O$ 124.08882 g mol $^{-1}$

To a slurry of NaH (1.30 g, 60 % dispersion in mineral oil, 33.00 mmol), in dry THF (30 ml), cooled in an ice bath, was added a solution of allenol (578) (2.50 g, 30.00 mmol), in dry THF (20 ml) dropwise over ten minutes. The mixture was stirred in the ice bath for 1 hour and then allyl bromide (3.60 g, 30.00 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. Saturated ammonium chloride solution (10 ml) was added, followed by water (10 ml). The aqueous phase was extracted with Et_2O (50 ml) and the combined organic fractions were washed with brine (30 ml). The solvent was removed by distillation at atmospheric pressure, to give a crude oil. Distillation at reduced pressure (30 mmHg), gave a clean liquid distilling at 50-52 $^{\circ}$C (0.95 g, 25 %). **LRMS FAB pos CH_4:** 90, 95, 109, 123. **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 2.28 (m, 2H, **CH_2**CH=C=CH_2), 3.50 (t, 2H, CH_2O, J = 5.6), 3.97 (dt, 2H, **CH_2**CH=CH_2, J = 5.6, 1.34), 4.66 (m, 2H, C=C=**CH_2**), 5.12 (m, 1H, CH_2=C=**CH**), 5.16 (dd, 1H, =CH_2, J = 9.37, 1.61), 5.25 (dd, 1H, =CH_2, J = 17.40, 1.61), 5.90 (m, 1H, **CH**=CH_2). **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 208.9, 134.8, 116.8, 86.5, 74.8, 71.8, 69.5, 28.8.

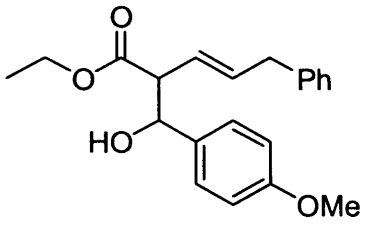
(E)-ethyl 5-phenylpent-3-enoate (610)



$C_{13}H_{16}O_2$ 204.15503 g mol $^{-1}$

To a solution of LDA at – 78 ° C , prepared by the addition of n-BuLi (4.5 mmol, 1.80 ml, 2.5 M solution in hexanes) to di-isopropylamine (0.65 ml, 4.60 mmol) at - 78 ° C in Et_2O (10 ml), was added homoallenic ester (587) (0.50 g, 3.96 mmol) dropwise. The solution was stirred at – 78 ° C for 40 minutes and then added dropwise to a solution of CuI (0.38 g, 1.98 mmol) and phenyl-magnesium bromide (13.80 mmol, 13.80 ml, 1 M solution in Et_2O) in toluene (10 ml) at – 78 ° C. The mixture was allowed to warm to room temperature and stirred for 12 hrs. The solution was poured into saturated aqueous ammonium chloride solution (20 ml). The aqueous phase was separated and extracted with ethyl acetate (3 x 20 ml). The combined organic fractions were washed with brine (20 ml), dried ($MgSO_4$) filtered and concentrated at reduced pressure. The crude oil was purified by flash column chromatography eluting with petroleum ether / ethyl acetate (10:1), to give the title compound (0.25 g, 30 %) as a pale yellow liquid. **HRMS: $C_{13}H_{16}O_2$** (M+) requires = 204.10952 (M+) Found = 204.10996 **IR** (thin film) υ max (cm^{-1}): 2960, 2873 (CH), 1728 (C=O), 1600, 1494. **^{1}H NMR** $CDCl_3$ (300 MHz) δ ppm: 1.30 (t, 3H, CH_3, J = 7.2), 3.09 (d, 2H, CH_2Ph, J = 5.89), 3.41 (d, 2H, CH_2CO_2Et, J = 5.62) 4.17 (q, 2H, CH_2, J = 7.2), 5.72 (m, 2H, =CH), 7.19-7.46 (m, 5H, ArH) **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 171.9, 140.2, 133.1, 128.7, 126.1, 123.3, 68.1, 60.6, 38.7, 38.0, 14.1.

(E)-ethyl 2-(hydroxy(4-methoxyphenyl)methyl)-5-phenylpent-3-enoate (615)

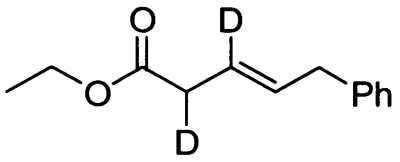


$C_{21}H_{24}O_4$ 340.16746 g mol $^{-1}$

To a solution of LDA at – 78 ° C , prepared by the addition of n-BuLi (4.5 mmol, 1.80 ml, 2.5 M solution in hexanes) to di-isopropylamine (0.65 ml, 4.60 mmol) at - 78 ° C in Et_2O (10 ml), was added homoallenic ester (587) (0.50 g, 3.96 mmol) dropwise. The solution was stirred at – 78 ° C for 40 minutes and then added dropwise to a solution of CuI (0.38 g, 1.98 mmol) and phenyl-magnesium bromide (5.94 mmol, 7.2 ml, 0.83 M solution in Et_2O) in toluene (10 ml) at – 78 ° C. The mixture was allowed to warm to room temperature and stirred for 12 hrs. The mixture was cooled to – 78 °C and anisaldehyde (0.54 g, 4.75 mmol) was added dropwise. The solution was warmed to room temperature and then poured into a saturated solution of ammonium chloride (20 ml). The aqueous phase was extracted with ethyl acetate (3 x 20 ml). The combined organic fractions were washed with brine (20 ml), dried ($MgSO_4$) filtered and concentrated at reduced pressure. The crude oil was purified by flash column chromatography eluting with petroleum ether / ethyl acetate (3:1), to give the title compound (0.29 g, 21 %) as pale yellow liquid. **HRMS: $C_{21}H_{24}O_4$** (M+) requires = 340.16691 (M+) Found = 340.16609 **IR** (thin film) υ max (cm^{-1}): 3483 bs (OH), 3060, 2979, 2835 (CH), 1728 (C=O). **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.14 (t, 3H, CH_3, J = 7.2), 2.98 (bs, 1H, OH), 3.29 (m, 1H, $CHCO_2Et$), 3.38 (m, 2H, CH_2Ph), 3.79 (s, 3H, OMe), 4.06 (q, 2H, CH_2, J = 7.2), 4.97 (d, 1H, CH(OH), J = 5.6), 5.70

(m, 2H, =CH), 6.84 (d, 2H, ArH, J = 8.0), 7.08 (d, 2H, ArH, J = 8.0), 7.18-7.38 (m, 5H, ArH) **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 172.9, 159.2, 139.8, 135.4, 133.0, 128.5, 128.4, 127.9, 126.1, 124.9, 113.9, 73.7, 60.8, 57.4, 55.3, 39.0, 14.1.

Deuterated-(E)-ethyl 5-phenylpent-3-enoate (625)



$C_{13}H_{14}D_2O_2$ 206.12758 g mol^{-1}

To a solution of LDA at – 78 ° C , prepared by the addition of n-BuLi (2.70 mmol, 1.70 ml, 1.60 M solution in hexanes) to di-isopropylamine (0.34 ml, 2.62 mmol) at -78 ° C in Et_2O (10 ml), was added homoallenic ester (587) (0.30 g, 2.38 mmol) dropwise. The solution was stirred at – 78 ° C for 40 minutes and then added dropwise to a solution of CuI (0.23 g, 1.20 mmol), phenyl-magnesium bromide (8.30 mmol, 2.80 ml, 3 M solution in Et_2O) in toluene (10 ml) at – 78 ° C. The mixture was allowed to warm to room temperature and stirr for 12 hrs. The solution was poured into D_2O (10 ml) and stirred for 20 minutes. The aqueous phase was extracted with ethyl acetate (3 x 20 ml). The combined organic fractions were washed with brine (20 ml), dried ($MgSO_4$) and concentrated at reduced pressure. The crude oil was purified by flash column chromatography eluting with petroleum ether / ethyl acetate (10:1), to give the title compound (0.12 g, 26 %) as a pale yellow liquid. **HRMS: $C_{13}H_{16}O_2$** (M+) requires = 206.12682 (M+) Found = 206.12635 **^{1}H NMR:** $CDCl_3$ (300 MHz) δ ppm: 1.28 (t, 3H, CH_3, J = 7.2), 3.07 (m, 1H, CDH), 3.41 (m, 2H, CH_2Ph), 4.16 (q, 2H, CH_2, J = 4.2) 5.74 (m, 1.5H =CH), 7.19-7.40 (m, 5H, ArH) **^{13}C NMR:** $CDCl_3$ (75 MHz) δ ppm: 171.9, 140.2, 132.8 (t, C-D, J = 23.5), 128.5, 126.1, 123.2, 68.1, 60.6, 38.9, 37.7 (t, C-D, J = 20.5), 14.1.

CHAPTER 5

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5.0 References

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