Novel Synthesis of *N*-Heterocycles

A thesis submitted to Cardiff University

by

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With all my love
To my big sister Carla

Abbreviations:

Abbreviations used in this text:

Ac	Acetyl
Ad	Adamantane
Alloc	Allyloxycarbonyl
APCI	Atmospheric Pressure Chemical Ionisation (mass spectrometry)
Ar	Aromatic
atm	Atmosphere (unit of pressure)
Ax	Axial
Aq.	Aqueous
Binap	2,2'-bis(diphenylphospino)-1,1'-binaphthyl
Bu	Butyl
$_i$Bu	*iso*-Butyl
$_t$Bu	*tert*-Butyl
Boc	*tert*-Butyloxycarbonyl
bp	Boiling point
Bu_4NOH	Tetrabutylammonium hydroxide
n-BuLi	Butyl lithium
t-BuOH	*tert*-butanol
°C	Degrees Centigrade (Celcius)
Cat	Catalytic
CCDC No	Cambridge Crystallographic Data Centre number
*m*CPBA	*meta*-chloroperoxybenzoic acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
dap	*N,N*-Dimethylaminomethylpyrrolyl
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
dig	Digonal
DMA	Dimethylacetamide
DMF	Dimethylformamide

DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*) pyrimidinone
DMSO	Dimethyl sulfoxide
dppm	1,1-Bis(diphenylphosphino)methane
EDA	Ethylenediamine
EI	Electron impact (mass spectrometry)
Eq	Equitorial
Equiv/eq	Equivalents
ES	Electrospray ionisation (mass spectrometry)
Et_2O/ether	Diethyl ether
g	Grams
G2	Gaussian-2
h	Hours
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
IBX	*o*-iodoxybenzoic acid
ICPMS	Inductively coupled plasma mass spectrometry
IR	Infrared
J	Coupling constant (in Hertz)
LDA	Lithium diisopropylamide
Ln	Ligand
LUMO	Lowest unoccupied molecular orbital
m	Meta
M	Molar (moles L^{-1})
Me	Methyl
MeCN	Acetonitrile
MEM	β-Methoxyethoxymethyl ether
Min	Minutes
Moc	Methoxycarbonyl
M.p.	Melting Point
ms	Mass Spectrometry
MW	Microwave
NaHMDS	Sodium bis(trimethylsilyl)amide
NMP	*N*-methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
Nosyl or Ns	*para*-Nitrobenzenesulfonyl

NsCl	*para*-Nitrobenzenesulfonyl chloride
o	Ortho
p	Para
PDC	Pyridinium dichromate
Ph	Phenyl
Phen	Phenanthroline
pKa	Acid dissociation constant
Ppm	Parts per million
^{i}Pr	*iso*-Propyl
Pyr	Pyridine
RT	Room Temperature
$(Sia)_2BH$	Disiamylborane
SiO_2	Silica gel
t or *tert*	Tertiary
TBAF	Tetrabutylammonium fluoride
TBDMS or TBS	*tert*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
Tf_2O	Trifluoromethansulfonic anhydride
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Tosyl or Ts	*para*-Toluenesufhonyl
TsCl	*para*-Toluenesulfonyl chloride

Abstract

The Knight group has been working on the synthesis of substituted heterocycles *via* 5-*endo*-dig cyclisation for some time. In particular, the use of metals $[M]^{n+}$ such as silver(I) and copper(I) have been employed to catalyse these cyclisations to give heterocyclic products in near quantitative yields and cleanly without any need for purification. In a continuation of these studies into metal-catalysed 5-*endo*-dig cyclisations, we investigated their application to the synthesis of a range of *N*-heterocycles: indoles, pyrazoles and pyrroles.

The second chapter describes an investigation of the application of silver(I) cyclisation methodology to the synthesis of 1,2-disubstituted indoles. Our methodology was applicable to a range of functional groups in both positions, allowing for terpenes, alkenes, aromatic, alkyl, and alcohol substituents in position two. Additionally, a range of nitrogen protecting groups were tolerated, including sulfonamides, carbamates, amides, and even methyl groups. A few substrates would not cyclise; the current hypothesis is this is due to pKa differences, however, this is insufficient to explain the differing reactivities. This is supported by computational work carried out by a collaborator. Also reported is a successful synthesis of an indole in a flow system; this was achieved using silver nitrate on silica as the stationary phase.

Chapter three focuses on the synthesis of pyrazoles from hydrazines prepared using the Mitsunobu alkylation. A regioselective Mitsunobu alkylation has been defined using non-symmetrical disubstituted hydrazines to give a single regioisomer. Exposure of these hydrazines to silver(I) met with limited success with steric hindrance explaining why some for the hydrazines would not cyclise

Chapter four reports the synthesis of pyrroles using silver(I) and copper(II). The first part focuses on the improvement of Sharland's copper(I)-catalysed pyrrole synthesis which, upon improvement, gave pyrroles cleanly in high yields. Also reported are the successful silver(I)-catalysed synthesis of fused pyrroles such as annulated pyrroles and *N*-fused pyrrolizines and indolizines by use of silver(I). Finally the silver(I) cyclisation methodology was applied to the successful synthesis of a natural product, pyrrolostatin.

Chapter One

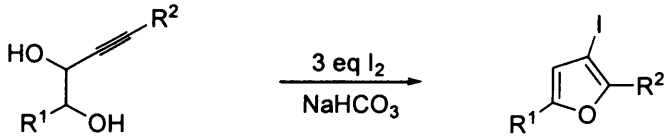
Introduction

1.1 Introduction to metal-catalysed heterocyclic synthesis.

Heterocycles form the core of a large number of potent drugs and natural products. Their prevalence and potency have led to a growing need to develop methods that access these important structures and descriptions of many of these methods can be found in the latest edition of Comprehensive Heterocyclic Chemistry, 2008.[1a] Many of the methods entail the nucleophilic attack of a heteroatom onto an electron deficient carbon atom.

1.2 Previous work in the Knight group.

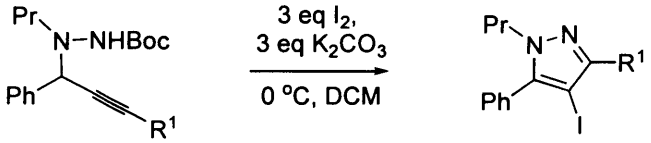
Initial work carried out by the Knight group on heterocyclic synthesis involved the use of molecular iodine as a stoichiometric reagent for the 5-*endo*-dig cyclisation of 3-alkyne-1,2-diols **1**. The reaction involved using three equivalents of iodine with sodium hydrogen carbonate to give β-iodofurans **2** in good yields (Scheme **1**).[1b]



1 **2**

Scheme 1: *Iodocyclisation of alkyne-1,2-diols 1.*

This method was later used to synthesise a range of other heterocycles including Song's iodocyclisation of hydrazines **3** to yield 4-iodo pyrazoles **4**.[1c] The reaction again required three equivalents of iodine and three equivalents of potassium carbonate in dichloromethane at 0 °C for 16 h (Scheme **2**). The reaction involved a two-step process of iodocyclisation and decarbonoylation with yields of 97% (where R^1 = Ph) and only 29% (where R^1 = Bu).



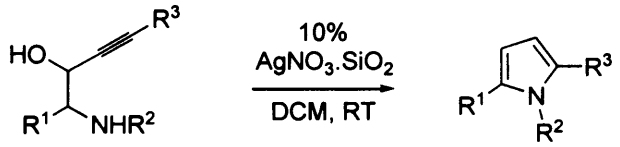
3 **4**

Scheme 2: *Song's synthesis of 4-iodo pyrazoles 4.*

The added benefit of this method was that with the introduction of an iodine in the 4-position, further chemistry such as palladium-catalysed couplings could be carried out. However, there

was an obvious drawback to the chemistry, this being the use of three equivalents of iodine, making large scale reactions impractical.

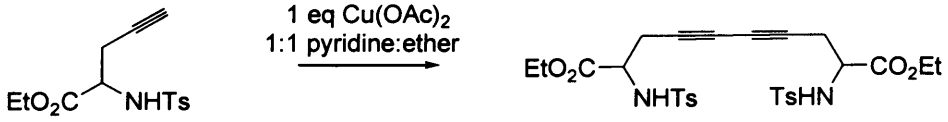
With this in mind the need for a method that was practical and scalable became apparent. This led to an investigation into catalytic methods to synthesise heterocycles in this way. Many catalysts have been used to synthesise heterocycles,[1a] many of which involve using metals [M^{n+}] such as palladium, mercury, etc (see reviews in Chapters 2, 3 and 4). It was during this investigation that Sharland came across Marshall's report (See section **2.4**) on the use of silver(I) as a catalyst for furan synthesis. Sharland found that upon exposure of pyrrole precursors **5** to 10 % silver(I) nitrate on silica (Scheme **3**), pyrroles **6** were formed in near quantitative yields which were clean by ^{1}H-NMR analysis with no need for purification, aside from a simple filtration through silica to remove the silver(I) catalyst.[2]



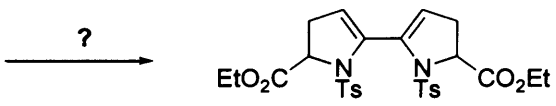
5 **6**

Scheme 3: *Sharland's silver(I)-catalysed synthesis of pyrroles.*

During Sharland's investigation into the synthesis of pyrroles, he attempted to synthesise dihydropyrrole dimers in the hopes of building porphyrin analogues. His synthesis involved the Eglington coupling of acetylenes **7** to give the diynes **8** which would then be followed by cyclisation using to give the dihydropyrrole dimer **9** (Scheme **4**).[2]



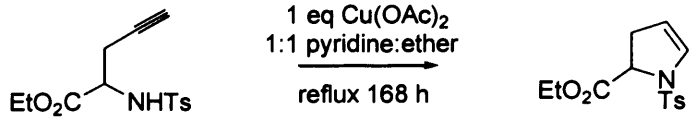
7 **8**



9

Scheme 4: *Sharland's proposed synthesis of dihydropyrrole dimer **9**.*

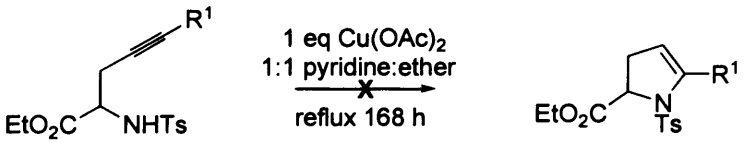
However, upon attempted Eglington coupling of acetylene **7** the diyne **8** was not isolated. Suprisingly, the attempted coupling resulted in the formation of the dihydropyrrole **10** (Scheme **5**). In other words, Sharland had accidently discovered a new copper-catalysed pyrrole synthesis.[2]



7 **10**

Scheme 5: *Sharland's successful copper-mediated cyclisation.*

He then set out to achieve the same result with a small range of analogues of acetylene **7**. Unfortunately no pyrrole **12** was observed with substrates **11** (Scheme **6**) and this led Sharland to the assumption that a propargylic alcohol group (See Scheme **3**) was required to facilitate cyclisation, and that the example **7** was an exception.

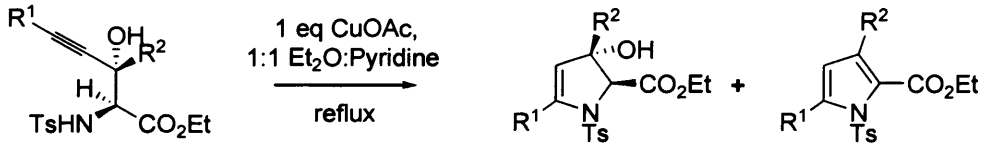


11 **12**

where R^1 = thiophene
where R^1 = Ph
where R^1 = C_5H_{11}

Scheme 6: *Sharland's failed attempted cyclisations using copper method.*

It was then that Sharland synthesised a range of β-hydroxy amino esters **13** using Kazmier's method (See section **4.2.1.2**) and by exposure to one equivalent of copper(I) acetate in a 1:1 mixture of ether and pyridine in a sealed tube (Scheme 7), achieved successful cyclisations to give predominantely hydroxydihydropyrrole **14a** with little elimination to pyrrole **14b**.[2]



13 **14a** **14b**

Scheme 7: *Examples of copper(I) acetate cyclisation of a β-hydroxy amino ester.*

Hayes[3], Proctor[4] and Song[1c] further expanded the silver(I)-catalysed methodology and applied it to a range of heterocycles, including pyrazoles, isoxazoles and furans and equally found the

method to yield these heterocycles cleanly and without the need for column chromatography. Hayes developed this method further by investigating Marshall's use of silver(I) in a flow system and by developing a new and highly successful silver(I) flow system for the cyclisation of pyrrole and furan precursors which proved highly successful (See section **2.7**). With previous work in mind, we set out to expand this current methodology to other types of heterocycles, in particular, nitrogen-based examples and also to optimise some of the foregoing methodology.

1.3 Current work.

The main aims of this project were to improve and to expand the metal-catalysed 5-*endo*-dig cyclisations. The current silver(I)-catalysed cyclisation methodology using commercially available 10% silver nitrate on silica gel is applied to the synthesis of indoles, pyrroles and pyrazoles.

1.3.1 Indoles

The synthesis of indoles from 2-alkynyl anilines using 10% silver nitrate on silica is reported in Chapter 2. Also included are investigations into a possible synthesis of indoles in flow using Hayes' silver(I) flow system.

1.3.2 Pyrazoles

Song's pyrazole synthesis by the sequential Mitsunobu coupling of trisubstituted hydrazines with propargylic alcohols is expanded upon in Chapter 3. Also reported are the regioselective Mitsunobu alkylations using unsymmetrical hydrazines with propargylic alcohols, which provide a new and useful approach to unsymmetrically substituted pyrazoles.

1.3.3 Pyrroles

Sharland's copper(I)-catalysed synthesis of hydroxydihydropyrroles is improved upon resulting in a safer and much more scalable method. The result of this change in method is that it has become a method for synthesising pyrroles, as in most cases no hydroxydihydropyrrole was observed. Also reported are the syntheses of both *N*-fused pyrroles and annulated pyrroles using silver(I). This methodology is then applied to the synthesis of the natural product pyrrolostatin. All this is reported in Chapter 4.

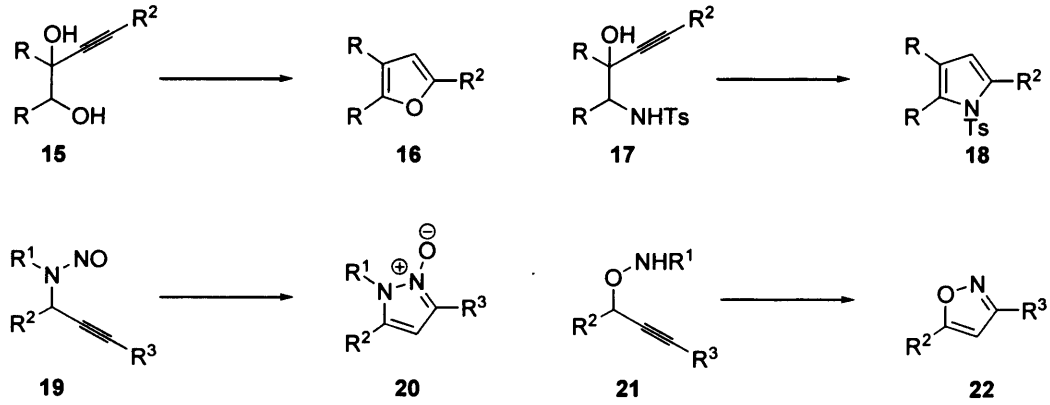
Chapter Two

Indoles

2.1 Aims

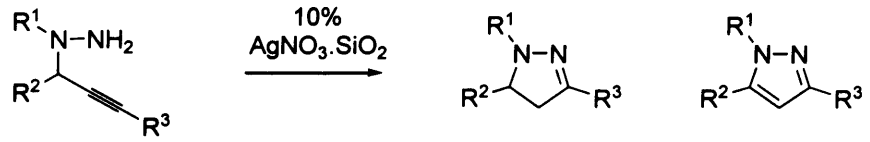
The importance of indoles and their application to the treatment of a wide range of diseases is widely noted. Therefore of equal importance is the development of new methods that allow a broad and efficient synthesis of substituted indoles. Upon searching the literature a large number of methods exist (*c.f.* Section **2.2**), some requiring harsh conditions and in many cases having limitations. The aim of this project was to develop a widely applicable method to synthesise 2-substituted indoles under a common set of conditions in high yields and ultimately achieve this synthesis using a flow system.

Previous work by Hayes[3], Sharland[2] and Procter[4] had shown that a varied number of heterocyclic precursors could be cyclised using a catalytic amount of 10% $AgNO_3.SiO_2$ and in high yields; these include 3-alkyne-1,2-diols **15**, 3-alkyne-2-hydroxy-1-sulfonamides **17**, *N*-nitroso-propargylamines **19** and propargylhydroxylamines **21** to give furans **16**, pyrroles **18**, pyrazole *N*-oxides **20** and isoxazoles **22** respectively (Scheme **8**).



Scheme 8: *Compounds synthesised by $AgNO_3.SiO_2$ mediated cyclisation.*

The common feature of the majority of these precursors is the presence of a propargylic oxygen atom that can coordinate with the silver and bring it in close proximity to the acetylene. However, it was felt that even without the presence of a propargylic alcohol group the cyclisation would still be successful. Evidence of this was found in work done by Song involving the successful cyclisation of propargylic hydrazines **23** using 0.1 equivalents of 10% $AgNO_3.SiO_2$ to give dihydropyrazoles **24** and pyrazoles **25** respectively (Scheme **9**) in near quantitative yields and reasonably short reaction times (5-19 h).[1c]



23 24 25

Scheme 9: *Synthesis of pyrazoles from propargylic hydrazines.*

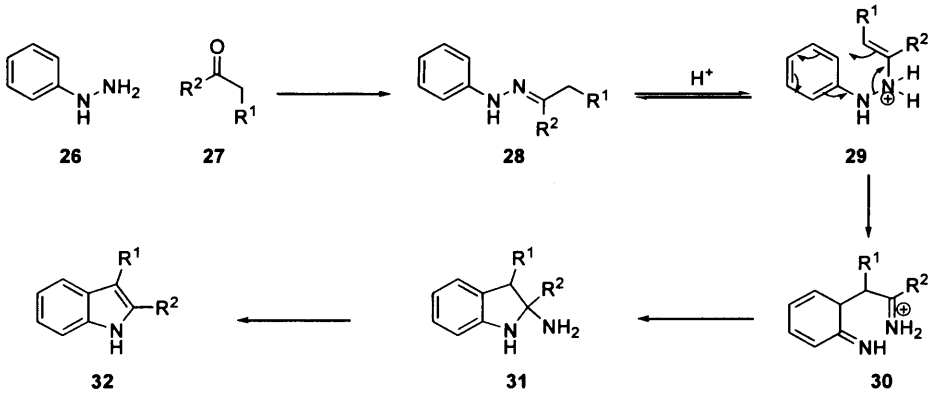
With this in mind it was felt that 2-alkynyl anilines could undergo successful cyclisation using a silver salt and that this could be extended to a successful cyclisation of these substrates in a flow system.

2.2 Literature review

A search through the literature shows numerous methods, both specific and general, for the synthesis of indoles. This is hardly surprising considering the importance of indoles to the pharmaceutical industry, their prevalence in nature and the high biological activities often associated with the ubiquitous indole core.

2.2.1 Fischer Indole synthesis[5-7]

The Fischer indole synthesis is one of the most common and widely used methods for the synthesis of indoles, which provides a simple and economical method to access indoles. The reaction involves heating a ketone or aldehyde **27** with an aryl hydrazine **26** and is often catalysed by an acid or metals that have Lewis-acid character (Scheme **10**).



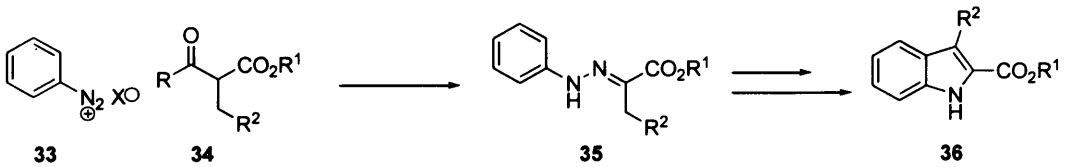
26 27 28 29 30 31 32

Scheme 10: *Mechanism for Fischer Indole synthesis.*

The reaction involves condensation of an aldehyde or ketone **27** with a hydrazine **26** to form a hydrazone **28** which under acidic conditions converts to the protonated ene-hydrazine **29**. It is

worth noting that tautomerisation can result in a mixture of ene-hydrazines, and hence a mixture of indoles if the ketone is unsymmetrical The hydrazine **29** then undergoes a [3,3]-sigmatropic rearrangement to give a *bis*-iminobenzyl ketone **30** which then undergoes cyclisation to give a 2-3 dihydroindole **31**. Aromatisation by loss of ammonia gives the final indole product **32**.

The Fischer indole synthesis has proven to be quite adaptable and highly useful since its discovery in the late nineteenth century. Many modifications exist including the Japp-Klingemann reaction[8-9] (Scheme **11**); this involves an alternative route to the aryl hydrazone by the use of diazonium salts **33** which are reacted with β-ketoesters or β-ketoacids **34** to form the hydrazone **35**. These then undergo deacylation (if a β-ketoester is used) or decarboxylation (if a β-ketoacid is used) and finally lead to the indole **36** by a similar mechanism.

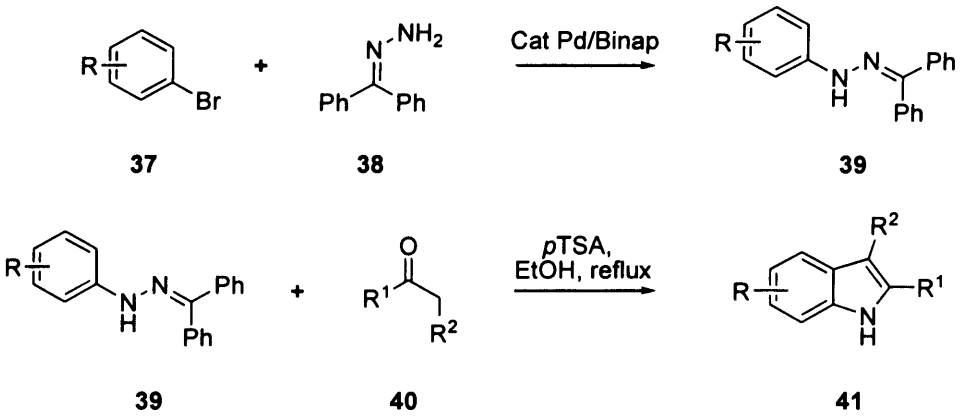


33 **34** **35** **36**

Scheme 11: *Japp-Klingemann modification using a β-ketoester.*

The limitations of the Fischer indole synthesis are the availability of starting hydrazines and hydrazones which as mentioned were synthesised by condensation of aryl hydrazines with carbonyls or using the Japp-Klingemann reaction. However, in recent years metal-mediated syntheses of hydrazones have been reported giving rise to a greater range of hydrazines and hydrazones for the Fischer indole synthesis.

Buchwald reported a synthesis of indoles (Scheme **12**) by the formation of hydrazones **39** from commercially available benzophenone hydrazone **38** and aryl bromides **37** catalysed by palladium.[10] The hydrazones were then reacted with ketones **40** and then underwent Fischer cyclisation to form indoles **41** in yields ranging 5-95%. When unsymmetrical N,N-diarylhydrazones were employed the Fischer cyclisation occurred largely on the more electron rich arene.[11] Similarly hydrazines were prepared from the palladium coupling of *tert*-butyl carbazate and aryl halides.[12]

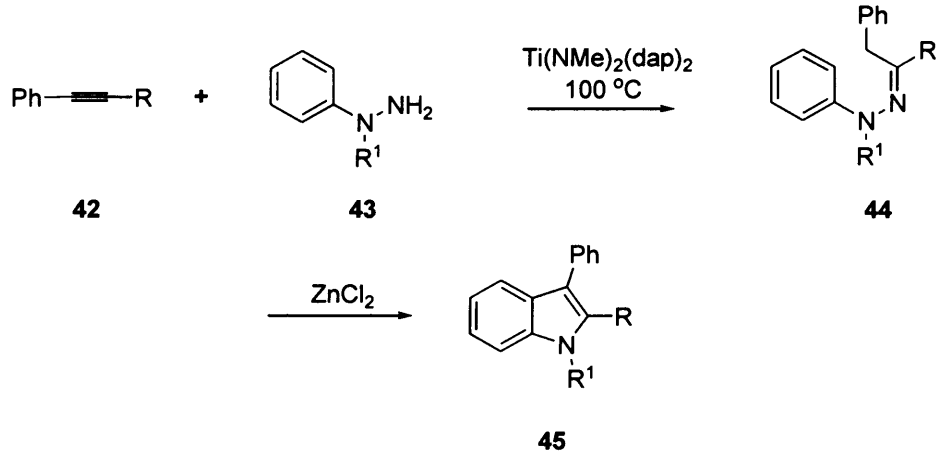


37 38 39

39 40 41

Scheme 12: *Synthesis of hydrazones from beznophenone hydrazone and aryl bromides.*

Some of the more recent modifications have allowed for the synthesis of indoles from the metal-catalysed hydroamination of alkynes as reported by Odom[13] (Scheme **13**). The hydroamination involves the reaction of alkynes **42** with aryl hydrazines **43** using titanium catalysts to give hydrazones **44**, followed by subsequent Fischer cyclisation by the addition of Lewis acids such as zinc(II) chloride while maintaining the temperature to give indoles **45** in good to excellent yields (69-95 %).



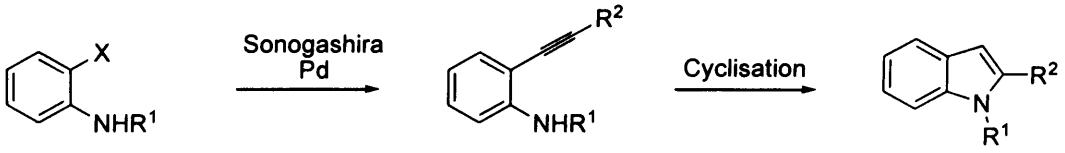
42 43 44

45

Scheme 13: *Odom's Lewis acid catalysed Fischer cyclisation.*

2.2.2 From 2-alkynyl anilines.

There are many methods for the synthesis of indoles **48** via intramolecular cyclisation of 2-alkynyl anilines **47** which are typically synthesised *via* the palladium catalysed coupling of 2-halo anilines **46** with alkynes (Scheme **14**).[14-15]

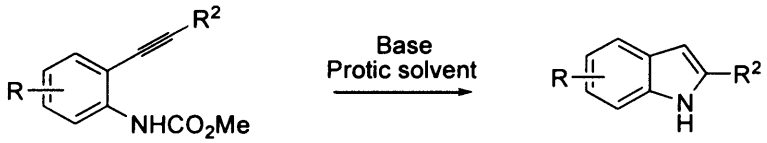


46 **47** **48**

Scheme 14: *General example of synthesis of indoles from 2-alkynyl anilines.*

2.2.2.1 Alkoxide mediated cyclisation[16-18]

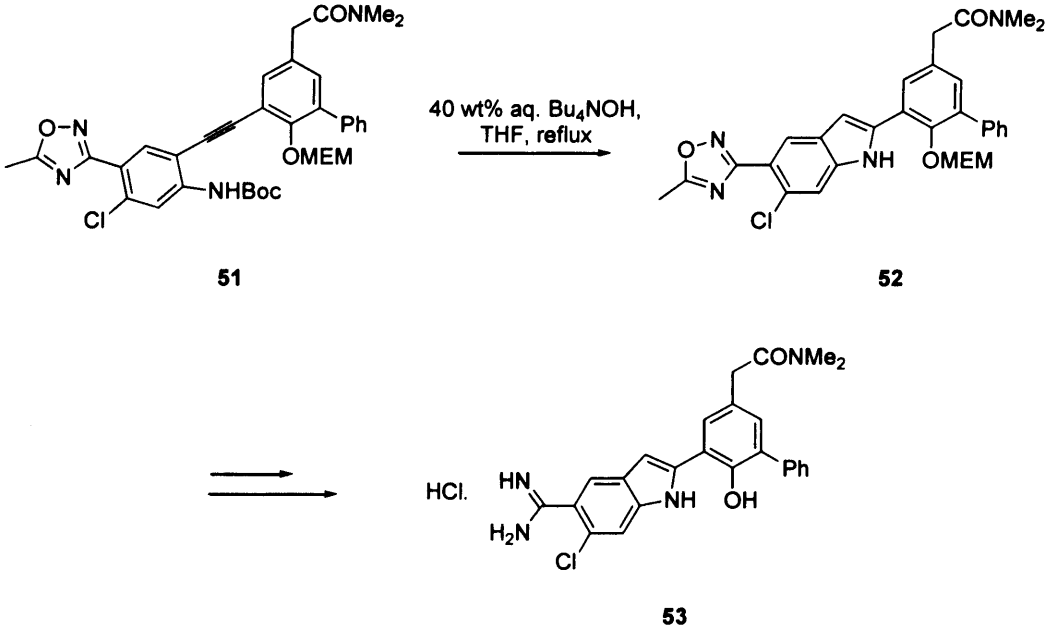
This cyclisation involves the use of bases such as sodium ethoxide or potassium *tert* butoxide for the conversion of 2-alkynyl anilines to indoles (Scheme **15**). The reaction is typically carried out in a protic solvent at variable temperatures. The reaction allows for the cyclisation of either carbamates **49** or free amines, however, upon cyclisation the carbamate is cleaved under the basic conditions to give the free indole **50**. The method allows for the inclusion of many groups around the benzene ring including halides, amines and oxygen bearing substituents making the chemistry highly practical for the development of synthetically useful targets.



49 **50**

Scheme 15: *Example of indole synthesis using a base.*

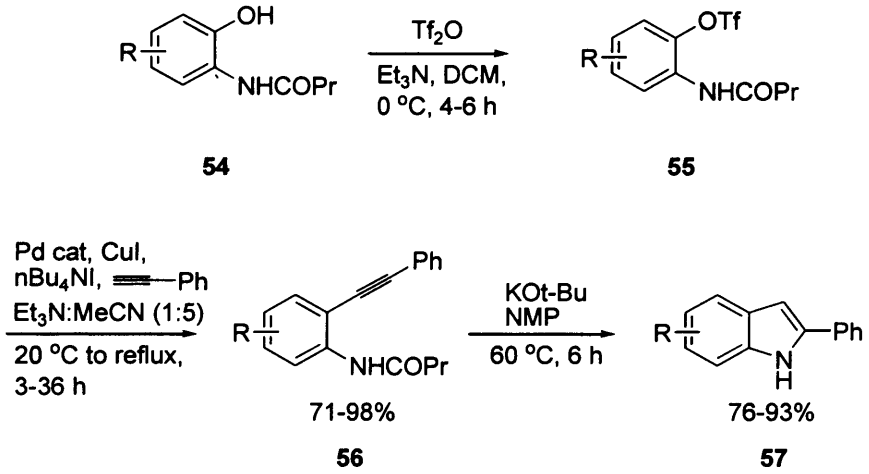
Wang and coworkers used this methodology to develop a precursor to a rebeccamycin analogue[19] and Sendzik and Hui reported the tetrabutylammonium hydroxide mediated cyclisation of 2-alkynyl aniline **51** (Scheme **16**) in aqueous media for the synthesis of indole **52** in 89 % yield, a precursor to a uPA/urokinase inhibitor **53**.[20]



51 52 53

Scheme 16: Sendzik and Hui's indole precursor to a uPA inhibitor

Dai has also extended the method by the conversion of 2-amino phenols **54** into 2-alkynyl anilines **56** *via* triflates **55** (Scheme **17**).[21] Conversion of the triflate **55** to the alkynyl aniline **56** proceeded with excellent yields as did the cyclisation using base to give indoles **57** with yields in the range of 76-93%.



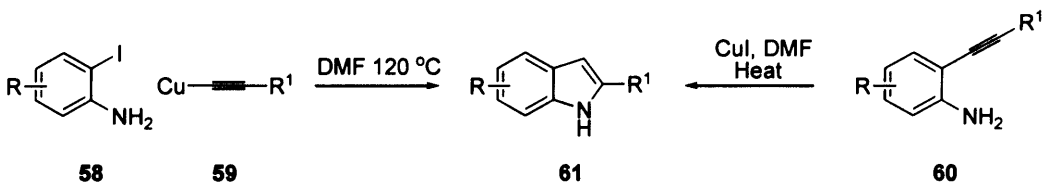
54 55 56 57

Scheme 17: Dai and coworkers synthesis of indoles from 2-amino phenols.

2.2.2.2 Copper-mediated synthesis[22-23]

One important method known as the Castro-indole synthesis (Scheme **18**) involves the conversion of 2-alkynyl anilines **60** to indoles **61** using an excess of copper(I) salts such as

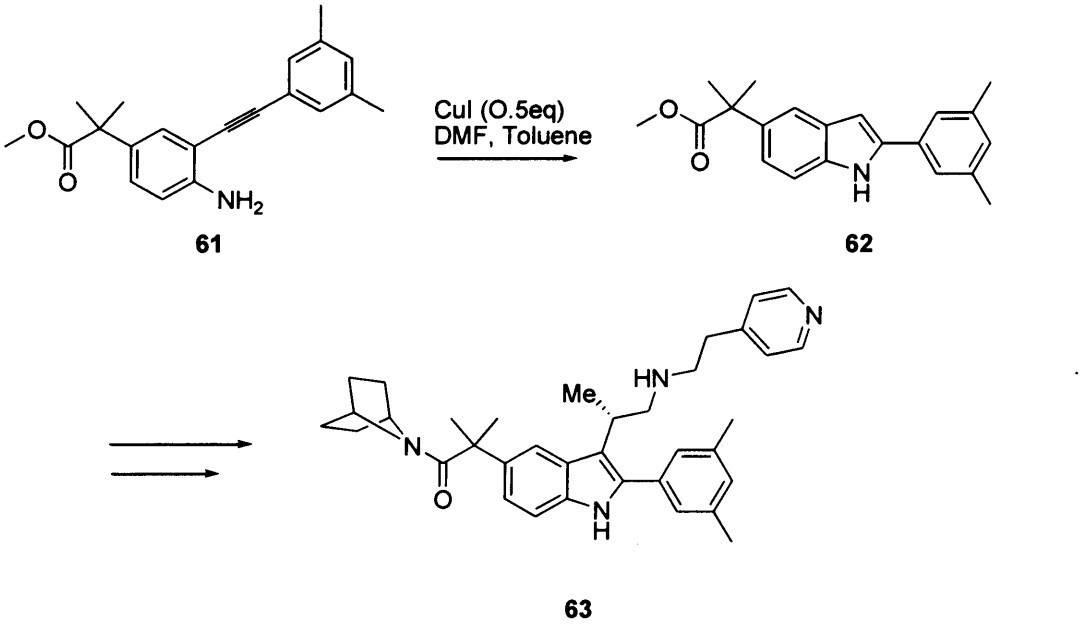
copper(I) iodide in DMF. The reaction can also be carried out in one-pot starting from 2-iodoanilines **58** using cuprous acetylides **59**.[23]



58 **59** **61** **60**

Scheme 18: *Castro indole synthesis.*

There have been a few recent developments in this area allowing for the use of catalytic copper allowing for some scalability. Farr reported the kilogram-scale preparation of an important intermediate **62** from 2-alkynyl aniline **61** (Scheme **19**) to a ganantropin releasing hormone antagonist **63**.[24] Purification of indole **62** by crystallisation allowed for the reaction to become scalable resulting in 88% yield.



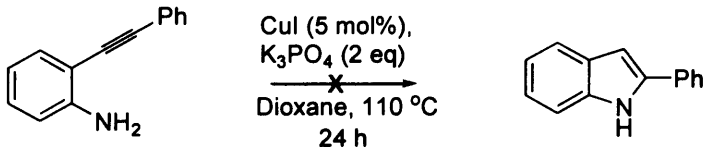
61 **62**

63

Scheme 19: *Farr and coworkers synthesis of drug intermediate.*

The Castro indole synthesis has also been employed by Cook and co-workers for the synthesis of L-isotryptophan.[25] It was found that upon using DMF as solvent, the stereocentre was epimerised; however, it was found that if ethylene glycol was used then no epimerisation was seen.

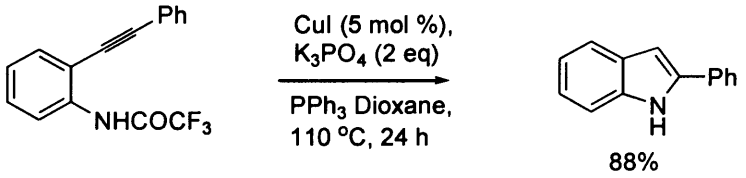
In a similar manner, Cacchi and co-workers attempted cyclisation of 2-phenylethynyl aniline **64** using catalytic copper iodide (5 mol%) and potassium phosphate (Scheme **20**) but found only trace amounts of indole **65** were formed after 24 h.[26]



64 **65**

Scheme 20: *Cacchi attempted cyclisation of 2-phenylethynyl aniline.*

Upon the addition of chelating ligand 1,2-*trans*-cyclohexanediamine (CHDA), the yield of indole **65** increased to 50%. This was a major improvement, however it was felt that the yield could be further improved by increasing the acidity of the 'NH' by means of a protecting group. The group they chose to protect the nitrogen with was a trifluoroacetamido group. Treatment of the *N*-protected aniline **66** with the current conditions did not improve the yield, however, upon replacement of CHDA with triphenylphosphine the yield increased to 88% possibly owing to the formation of a more active copper phosphine species (Scheme **21**).

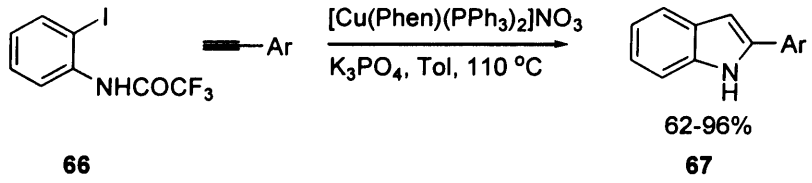


66 **65**

Scheme 21: *Cacchi's improved method for cyclisation of 2-phenylethynyl aniline.*

Using this improved method a range of 2-substituted indoles with both alkyl and aryl alkynes were synthesised in moderate to good yields (49-88 %). In all cases exposure of the *N*-acyl protected anilines to these conditions resulted in cleavage of the protecting group.[26]

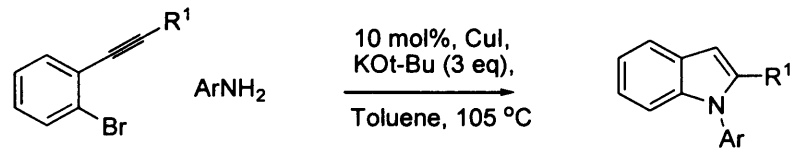
They also reported a one-pot synthesis of indoles **67** from 2-iodo anilines (Scheme **22**) initially by protection with a trifluoroacetamido group to give *N*-protected *2*-iodoanilines **66** followed by coupling of an acetylene, cyclisation and deprotection of the acetamide group to give indoles **67** in good to excellent yields (62-96%). The chemistry, however, appears to be limited to acetylenes with aromatic substituents as aliphatic alkynes such as hexyne gave low yields (11%).



66 **67**

Scheme 22: *Cacchi's synthesis 2-aryl indoles via a one-pot method.*

Ackermann reported the one-pot synthesis of 1,2-substituted indoles **70** from *o*-alkynyl bromo arenes **68** (Scheme **23**) and aromatic amines **69**.[27] The reaction involves copper(I) iodide but is different in that it is alkoxide-mediated and proceeds *via* an Ullmann-Goldberg/Castro type reaction. The reaction successfully furnished 2-substituted *N*-aryl indoles **70** in good to excellent yields (69-84%).



68 **69** **70**

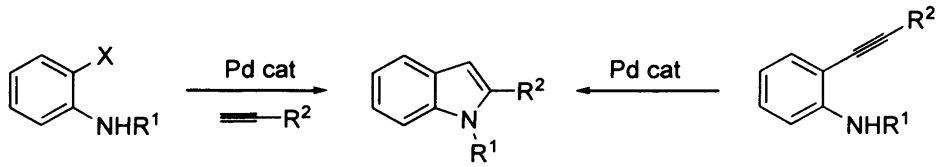
Scheme 23: *Ackermann synthesis of indoles from alkynyl halo-arenes.*

Recently Hiroya reported the synthesis of *N*-substituted and unsubstituted indoles from 2-alkynyl anilines using copper(II) salts.[28] They found the best catalyst for *N*-substituted anilines was copper(II) acetate and for *N*-unsubstituted reactants the ideal catalyst was found to be copper(II) trifluoroacetate. Unlike the other methods reported above, which largely involve temperatures above 100 °C, the method involves refluxing in 1,2-dichloroethane (~84 °C). The reactions were also found to work in other solvents such as toluene and were insensitive to moisture. Reaction times were found to vary between 2-48 h but gave excellent yields ranging from 84-100%. Other Lewis acids such as zinc(II) chloride and tin(IV) chloride were also screened but found to give much poorer results.

2.2.2.3 Palladium-mediated synthesis.

As with the copper-mediated indole syntheses, there are a number of examples of palladium-catalysed processes allowing for a range of substituents to be tolerated. The disadvantages of using palladium over copper include the high cost of the necessary palladium complexes and although required in catalytic quantities, this does limit the scalability of the reactions. Also the high temperatures needed can limit the reaction to substrates that are temperature tolerant.

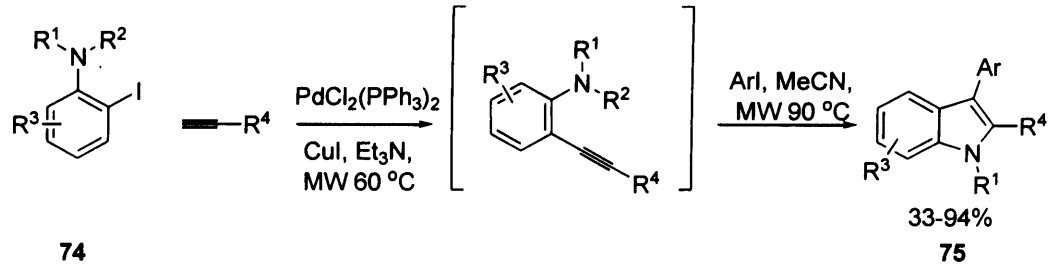
Typically, the one-pot synthesis of indoles using palladium involves extended Sonogashira reaction times (Scheme **24**). It is thought that the first step involves Sonogashira coupling of a halo-arene **71** to an acetylene to give the 2-alkynyl aniline **73** followed by coordination of the palladium species to the acetylene. This coordination activates the acetylene towards nucleophilic attack by the amine by making the acetylene more electron poor. This is then followed by cyclisation to give the indole **72**.



71 **72** **73**

Scheme 24: *Typical one/two step synthesis of indoles using palladium catalyst.*

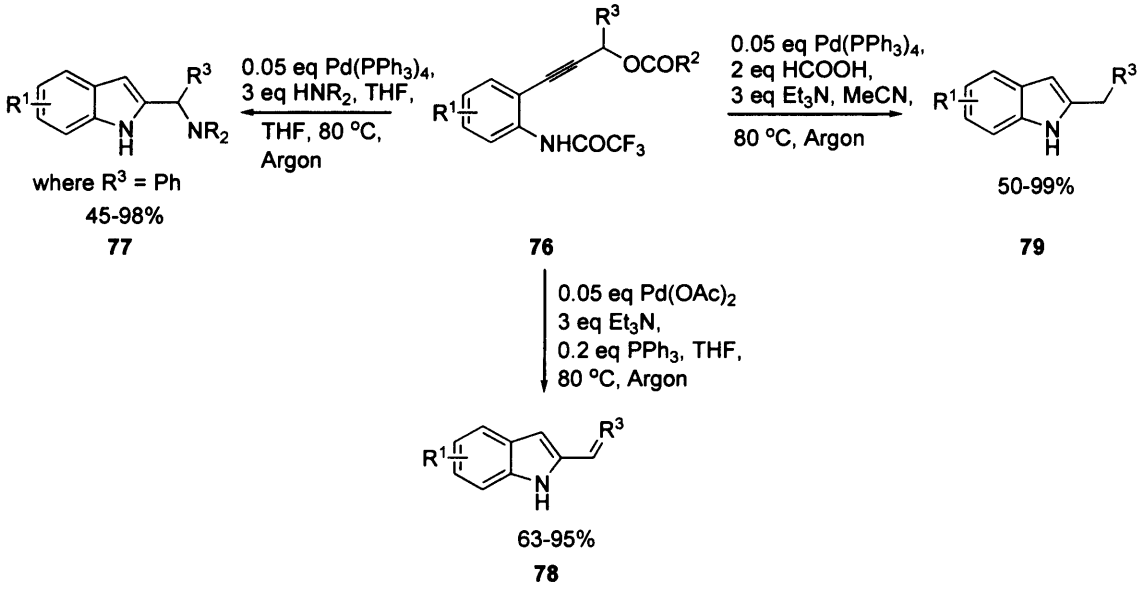
Larock and co-workers reported the microwave assisted synthesis of 2-substituted and 2,3-substituted indoles from iodoanilines **74** by a one-pot method *via* a typical Sonogashira reaction (Scheme **25**).[29a] Introduction of an aryl iodide into the mixture gave the 2,3-disubstituted indoles **75**. The reaction gave indoles **75** in good to moderate yields (33-94%) and could accommodate both electron-withdrawing and donating groups on both the arene and the acetylene. Microwave reactions are generally limited by scalability and reactions are usually limited to a few hundred milligram quantities, however, recent publications have circumvented the issue associated with scalability by development of a flow reactor attached to a microwave, which have been used by Bagley and co-workers for the synthesis of pyridines by the intramolecular condensation of aminodienones.[29b]



74 75

Scheme 25: *Larock's microwave synthesis of indoles.*

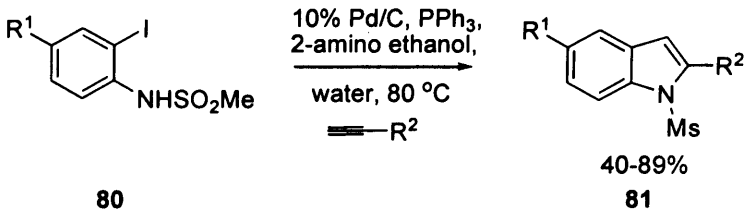
Recently Cacchi and co-workers showed the selective synthesis of indoles from 3-(*o*-trifluoroacetamidoaryl)-1-propargyl esters **76**.[30] It was shown that by changing the conditions and reagents 2-aminomethylindoles **77**, 2-vinylic indoles **78** and 2-alkylindoles **79** could be isolated (Scheme **26**).



77 76 79 78

Scheme 26: *Cacchi's selective synthesis of indoles starting from alkynyl anilines.*

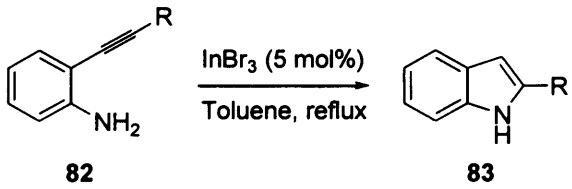
Although a number of the methods involve expensive palladium catalysts such as $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$, Pal and co-workers reported the one-pot synthesis of indoles **81** from *N*-(2-iodophenyl) methanesulfonamides **80** using the less expensive 10% palladium on carbon (3 mol%) in water (Scheme **27**).[31] Though this catalyst is more commonly used in the hydrogenation of alkenes,[32] it provides an inexpensive alternative, resulting in formation of indoles in moderate to good yields (40-89%). The reaction provides a simple and inexpensive alternative that lends itself well to possible large-scale indole synthesis.



Scheme 27: *Pal's one-pot synthesis of indoles.*

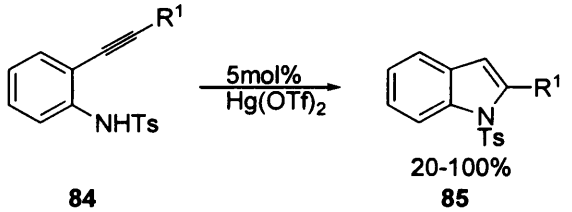
2.2.2.4 Methods using other metals.

Sakai and co-workers demonstrated the cyclisation of 2-alkynyl anilines **82** using stoichiometric indium tribromide in refluxing toluene (Scheme **28**), with quantitative yields achieved after only 10 minutes.[33] By using catalytic indium(III) bromide (5 mol%), quantitative yields were still achieved but required extending the reaction to 1 h. They also found that prolonged heating (24 h) resulted in a dramatic decrease in the yield of indoles **83**.



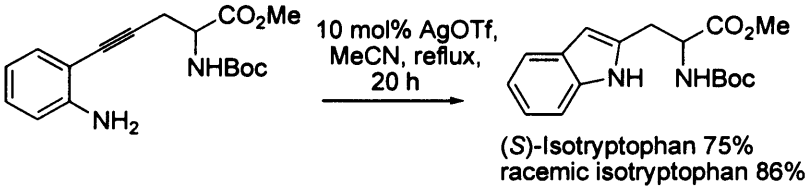
Scheme 28: *Indium(III) bromide synthesis of indoles.*

Another more recent method by Kurisaki involves the synthesis of 2-substituted *N*-tosyl indoles **85** from 2-alkynyl sulfonamides **84** using catalytic mercury(II) triflate (Scheme **29**).[34] The cyclisations were carried out under mild conditions (in DCM at room temperature) and resulted in highly variable yields (20-100%) with the catalyst being reusable over 100 times. The reaction, however, was limited to *N*-sulfonamides with the corresponding carbamates and acyl derivatives resulting in little or no indole formation. A comparison of *p*-tolueunesulfonamide with *o*-nitro and *p*-nitro-benzenesulfonamide was also carried out with *p*-toluenesulfonamide giving the best results. Another problem with this chemistry is that although the mercury is catalytic (5 mol%), it is still extremely toxic and attempts to scale the reaction would inevitably lead to issues of containment and disposal.



Scheme 29: *Kurisaki and coworkers synthesis of 2-substituted N-tosyl indoles.*

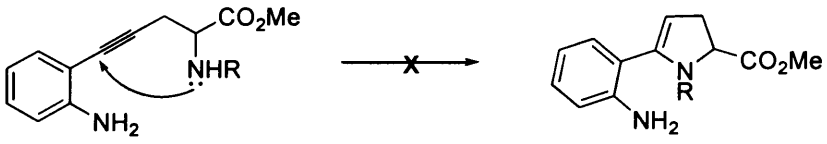
Rutjes and co-workers reported the synthesis of isotryptophan **87** in 75% yield from the *N*-Boc protected amino acid derivative **86** using silver(I) triflate (Scheme **30**).[35] They also successfully cyclised the racemic *N*-tosyl derivative of aniline **86** resulting in racemic isotryptophan in 86% yield.



86 **87**

Scheme 30: Rutjes et al's synthesis of indoles using silver(I) triflate.

An interesting point about this reaction is that there was no competing cyclisation and no pyrrole **88** derivative observed (Scheme **31**) with only the tryptophan derivatives being formed.

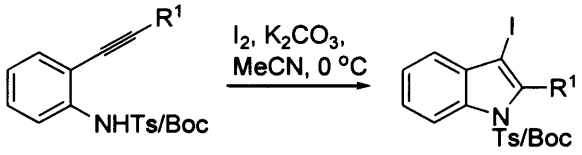


86 **88**

Scheme 31: *Competing 5-endo-dig cyclisation (not observed).*

2.2.2.5 Iodocyclisations.

Knight and co-workers reported the iodocyclisation of 2-alkynyl anilines **89** using 3 equivelants of molecular iodine and potassium carbonate at 0 °C (Scheme **32**) to give 3-iodo-indoles **90**.[36] The reaction was shown to work for both Boc-carbamates and sulfonamides with good to excellent yields. A range of alkynes were screened and both aliphatic and aromatic groups proved successful as did bulky groups such as trimethylsilyl.



75-96%

89 **90**

Scheme 32: *Knight's synthesis of indoles using iodine.*

Yue and Larock similarly reported the synthesis of *N*-methyl-3-iodoindoles **92** by iodocyclisation of *N,N*-dimethyl-2-alkynylanilines **91** using molecular iodine in dichloromethane at room temperature (Scheme **33**).[37] The reaction proceeded with demethylation. They found that the reaction gave *N*-methyl-3-iodoindoles **92** in good to excellent yields (73-100%) with a range of alkyl and aryl alkynes, although the reaction was limited to dimethyl protected anilines.

73-100%

91 **92**

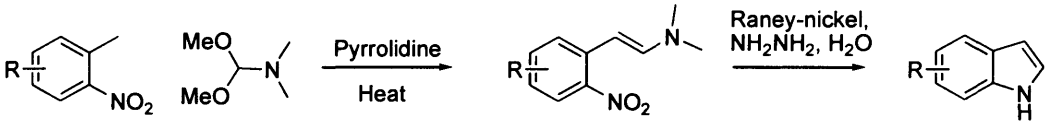
Scheme 33: *Yue and Larock's iodocyclisation of 2-alkynyl anilines.*

2.2.3 By reductive cyclisation.

Despite the availability of other methods, reductive cyclisation is still a commonly used method to scale-up the synthesis of indoles. The reaction involves the reduction of a nitro group followed by cyclisation. The reduction is carried out by catalytic hydrogenation using Pd/C, Raney-nickel and hydrazine, or zinc in acetic acid, *etc* (See examples below).

2.2.3.1 Leimgruber-Batcho indole synthesis[38-39]

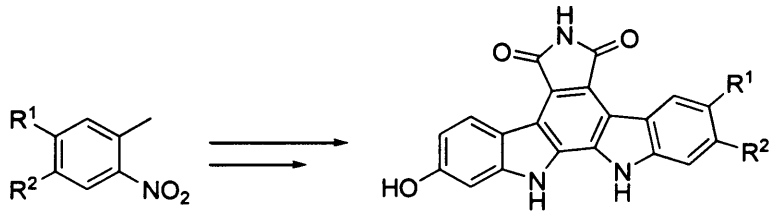
The Leimgruber-Batcho indole synthesis involves the condensation of *o*-nitrotoluenes **93** with dimethyl formamide dimethyl acetal (DMF DMA) **94** to give enamines **95**. The reaction is usually carried out in DMF (heated to 140 °C) or toluene (reflux). The resulting enamines **95** then undergo reductive cyclisation to give indoles **96**. The reaction usually involves using Raney-nickel as catalyst (Scheme **34**).



93 **94** **95** **96**

Scheme 34: *Leimgruber-Batcho indole synthesis.*

The benefits of the Leimgruber-Batcho indole synthesis are that the *o*-nitrotoluenes are readily available and the enamines that result are usually quite stable due to the presence of electron-withdrawing and electron-donating groups on either end of the olefin creating a push-pull effect. This method has proven useful for the synthesis of a great number of biologically active indoles including Simig and co-workers synthesis of the antimigrane drug naratriptan[40] and Ohkubo and co-workers synthesis of indolopyrrolocarbazole alkaloids known as acryriaflavins **98** from nitro-toluenes **97** (Scheme **35**).[41]



97 **98**

Acryriaflavin C R^1 = H, R^2 = OH
Overall yield = 68%
Acryriaflavin D R^1 = OH, R^2 = H
overall yield = 75%

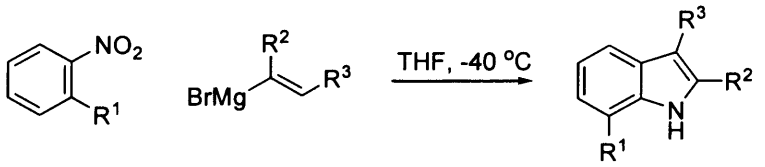
Scheme 35: *Ohkubo's synthesis of indole alkaloids using Leimgruber-Batcho.*

Other reductive methods are similar and vary in substrates that are condensed with the *o*-nitrotoluenes, including the Reissert indole synthesis[42] which involves the reductive cyclisation of *o*-nitrobenzylcarbonyl compounds to give indole-2-carboxylic acids which decarboxylate upon heating.

2.2.4 Other methods.

2.2.4.1 Bartoli indole synthesis[43-44]

The reaction provides a short and flexible route to 7-substituted indoles **101** from *o*-substituted nitroarenes **99** and vinyl Grignard reagents **100** (Scheme **36**). A particular drawback of this chemistry is the poor atom economy due to the requirement of three equivalents of Grignard reagent.

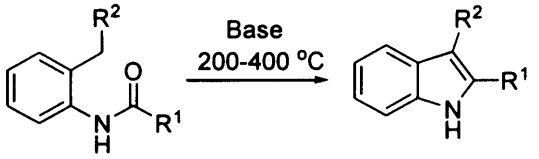


99 **100** **101**

Scheme 36: *Bartoli's indole synthesis.*

2.2.4.2 Madelung indole synthesis[45]

The reaction involves the synthesis of indoles **103** by the intramolecular cyclisation of *N*-amide anilines **102** using bases such as sodium ethoxide at high temperatures (Scheme **37**). The drawbacks of this chemistry are the high temperatures used and the use of base limiting its use to alkyl substituted indoles.



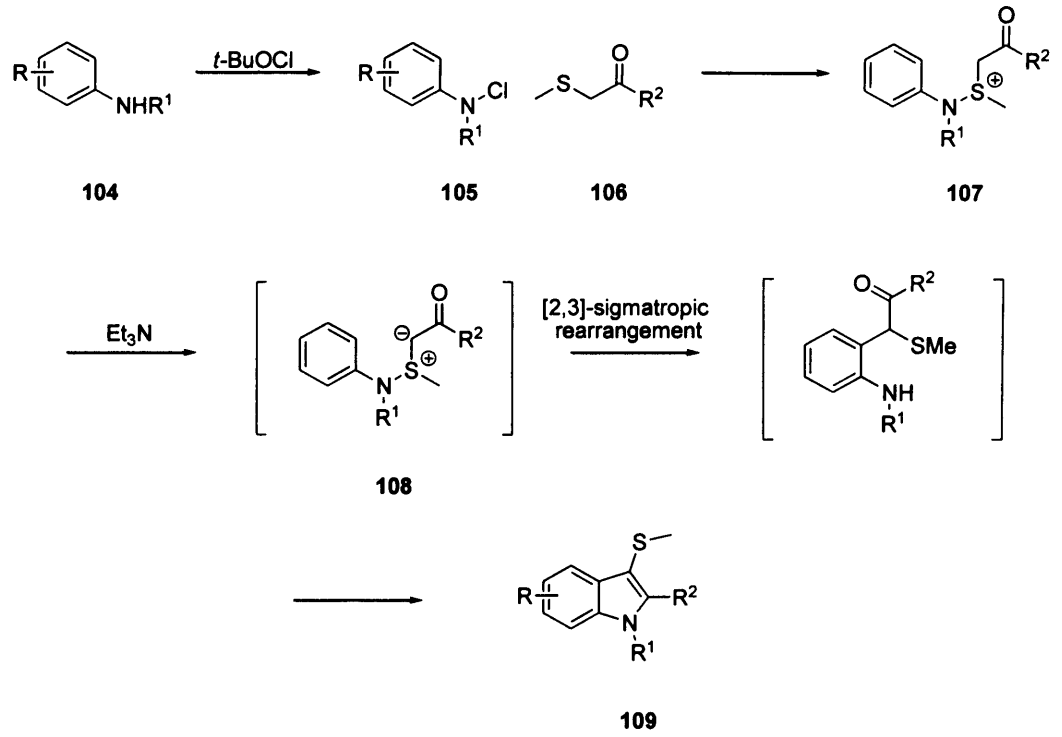
102 **103**

Scheme 37: *Madelung's indole synthesis*

The high temperatures were circumvented by Houlihan who reported the cyclisation of *N*-acylated *o*-alkylanilines at low temperatures by using *n*BuLi as base at temperatures between 15-20 °C.[46]

2.2.4.3 Gassmann indole synthesis[47-48]

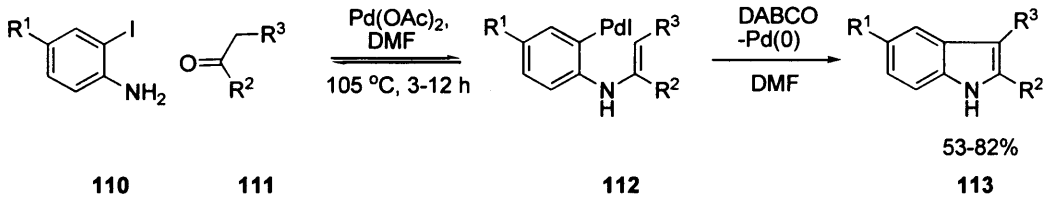
This method involves the one-pot synthesis of indoles via the initial oxidation of the aniline **104** using *tert*-butyl hypochlorite to give the chloramine **105** followed by addition of the methyl thio-ketone **106** to give the sulfonium ion **107**. Addition of a base such as triethylamine deprotonates the sulfonium ion to give the sulfonium ylide **108** and is followed by [2,3]-sigmatropic rearrangement and loss of water to give the 3-thiomethylindole **109**. The thiomethyl group could then be cleaved using Raney-nickel to give the 3-unsubstituted indole (Scheme **38**). One of the drawbacks of this method is that electron rich anilines usually do not participate.



Scheme 38: *Gassmann indole synthesis.*

2.2.4.4 Intramolecular Heck cyclisations.

An example of an intramolecular Heck cyclisation is reported by Chen, involving the palladium-catalysed coupling of 2-iodoanilines **110** with ketones **111** to give enamines **112** that then undergo intramolecular Heck cyclisation to give indoles **113** (Scheme **39**).[49] It was found that the choice of base and solvent was important with non-oxidisable bases such as DABCO often being the most suitable.



Scheme 39: *Intramolecular Heck cyclisation.*

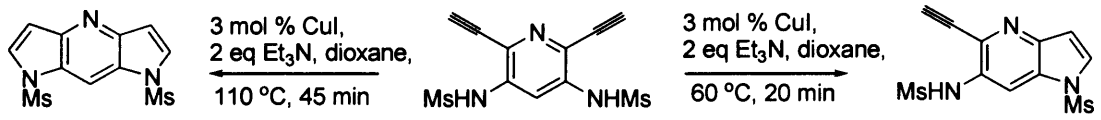
2.2.5 Azaindole synthesis.

There are fewer examples of azaindole synthesis and this is attributed to the difficulty in their synthesis due to the electron-deficient nature of the aza-benzene ring and the strong metal

binding affinity of the aromatic nitrogen. Methods towards the azaindoles are often limited to cyclisations of 2-alkynyl anilines,[50] Heck cyclisations[51] and examples based on Suzuki couplings.[52] A few of the more important examples of azaindole synthesis will be highlighted.

2.2.5.1 Copper-catalysed synthesis of azaindoles

There are a few examples of this method; recently copper(I) iodide was used by Ohno and coworkers for the synthesis of indoles and was shown to be effective for the synthesis of aza-indoles (Scheme **40**).[53] They found that they were able to control which products were formed by the changing of conditions and additives, to give mono-cyclisation **115** or *bis*-cyclisation **116** of symmetrical 2-alkynyl anilines **114**.

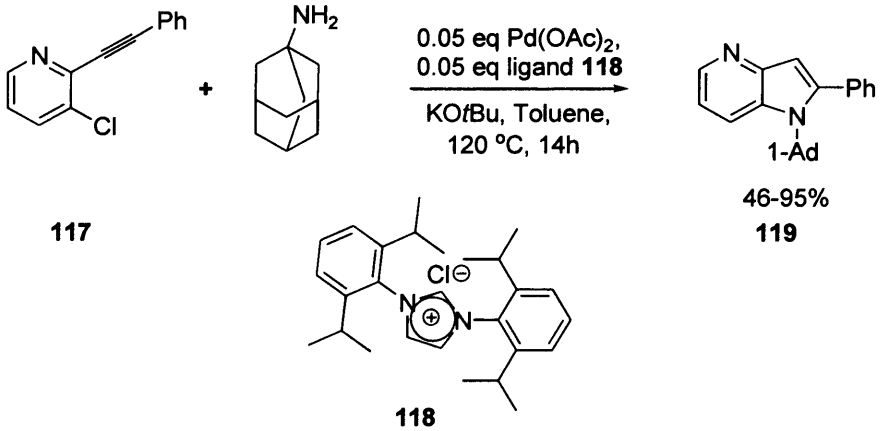


100% **116** | **114** | 81% **115**

Scheme 40: *Ohno's synthesis of (aza)-indoles.*

2.2.5.2 Palladium-catalysed synthesis of azaindoles

Ackermann and co-workers reported the cyclisation of 2-alkynyl halo-arenes **117** with hindered amines such as 1-aminoadamantane (example shown) or *tert*-butyl amine in the presence of palladium(II) acetate to give aza-indoles **119** (Scheme **41**) in moderate to excellent yields (46-95%).[54] The reaction often involves high temperatures and extended reaction times providing 1,2-substituted aza-indoles.

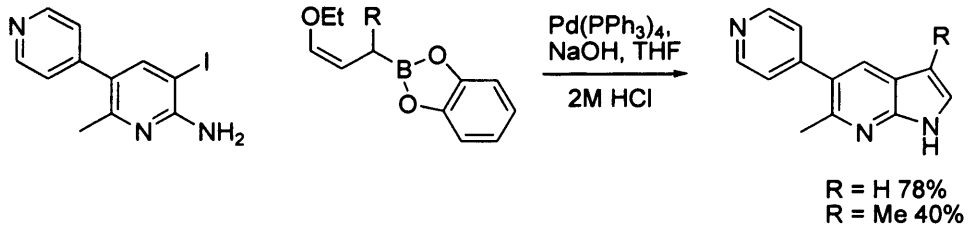


117 | 46-95% **119**

118

Scheme 41: *Ackermann's synthesis of azaindoles using hindered amines.*

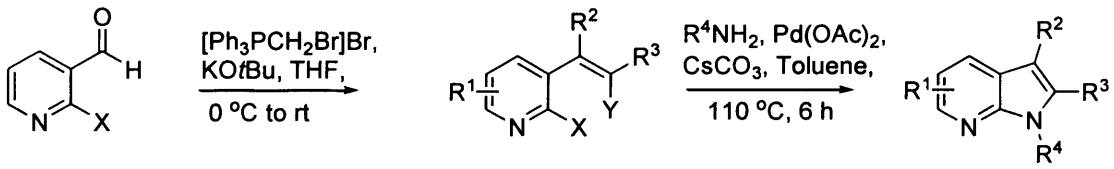
Other methods involving palladium include Kumar's report on the one-pot synthesis of aza-indoles synthesis using a Suzuki cross-coupling[55] (Scheme **42**) of 2-iodo aminopyridines **120** and boranes **121** (where R = H or methyl) to give vinyl ethers that upon stirring with 2M hydrochloric acid for 48 h cyclised to give azaindoles **122** in 78% yield (for R = H) and 40% yield (for R = methyl).



120 **121** **122**

Scheme 42: *Kumar's synthesis of azaindoles using Suzuki coupling.*

Another interesting synthesis highlights a palladium-catalysed cascade reaction involving an intermolecular and intramolecular amination to give 7-azaindoles as reported by Willis and co-workers (Scheme **43**).[56] Starting from commercially available 2-halonicotinaldehyde **123**, a Wittig reaction was carried out to give the (2-haloalkenyl)-pyridylhalide **124** that would then undergo the tandem reaction to give azaindoles **125** in poor to excellent yields. The issues with the chemistry include the difficulty in synthesising 4- 5- and 6-azaindoles due to the instability of many of the (2-haloalkenyl)-pyridylhalides **124**. The catalyst used is also not general in that a single catalyst could not be found to work in all examples.

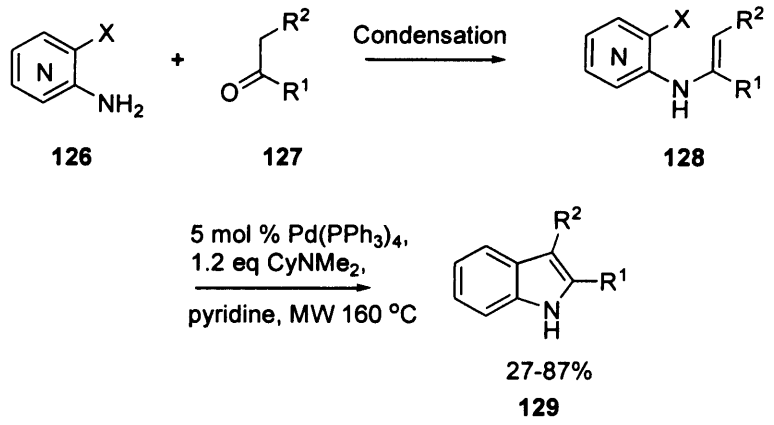


70-80% 18-96%

123 **124** **125**

Scheme 43: *Willis and co-workers synthesis of 7-azaindoles.*

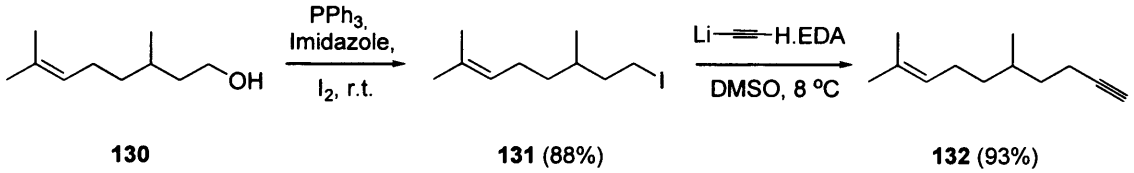
Similar to the Heck chemistry for indole synthesis reported by Chen and co-workers (*cf.* Scheme **39**, pg. 23), Lachance reported a one-pot microwave synthesis of aza-indoles[57] (Scheme **44**) involving an initial condensation of a 2-halo azaaniline **126** with a ketone **127**, followed by tautomerisation to the enamine **128** and intramolecular Heck cyclisation using a palladium catalyst to form the aza-indoles **129**.



Scheme 44: *Lachance's synthesis of aza-indoles using Heck chemistry.*

2.3 Indoles: Results and Discussion

The proposed strategy for indole synthesis was to develop a range of indole precursors that displayed a range of functionality and to test the scope and limitations of the silver(I) cyclisation for indole synthesis. Commercially available 2-iodoaniline was protected with various protecting groups followed by a Sonogashira reaction with various alkynes (See following Schemes). This would then be followed by cyclisation using 10% silver nitrate on silica. All but one of the alkynes were commercially available. Terpenoid **132** (Scheme **45**), was synthesised from citronellyl iodide **131** using a lithium acetylide-ethylene diamine complex. The iodide **131** was formed from citronellol **130**.

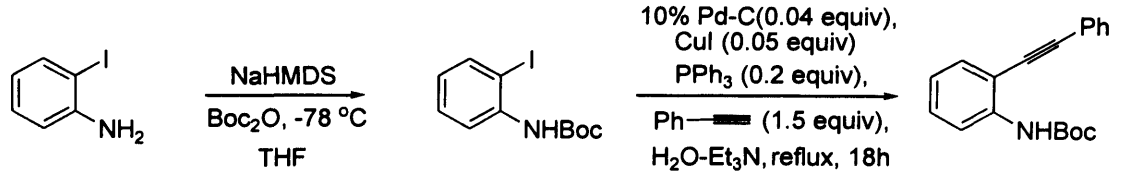


130 **131** (88%) **132** (93%)

Scheme 45: *Synthesis of citronellyl acetylene 132.*

2.3.1 Synthesis of 2-alkynyl anilines and aza-anilines

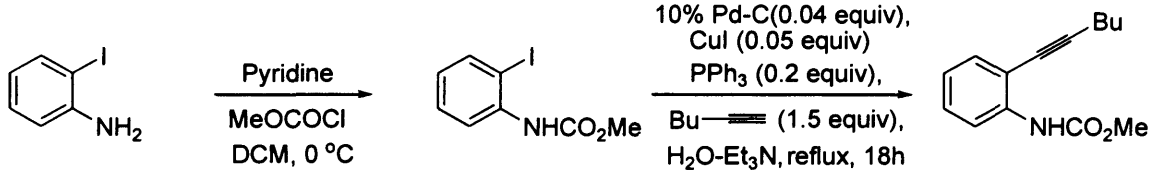
The 2-alkynyl aniline **135** was prepared by initial Boc protection of 2-iodoaniline **133** to give the Boc-protected aniline **134** in 92% yield followed by a Sonogashira reaction with phenylacetylene to give the 2-phenyl ethynyl aniline **135** in 98% yield (Scheme **46**).



133 **134** (92%) **135** (98%)

Scheme 46: *Synthesis of N-tert-butyloxycarbonyl 2-alkynyl aniline **135**.*

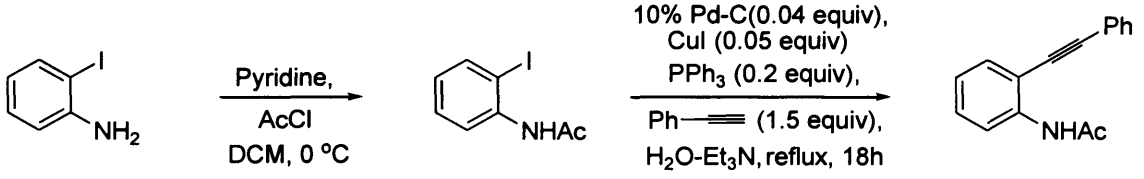
The carbamate protected 2-alkynyl aniline **137** was prepared by protection of 2-iodoaniline **133** with methyl choroformate to give the carbamate **136** in 87% yield followed by a Sonogashira reaction with1-hexyne to give the 2-alkynyl aniline **137** in 98% yield (Scheme **47**).



133 **136** (87%) **137** (98%)

Scheme 47: *Synthesis of N-methoxycarbonyl 2-alkynyl aniline **137**.*

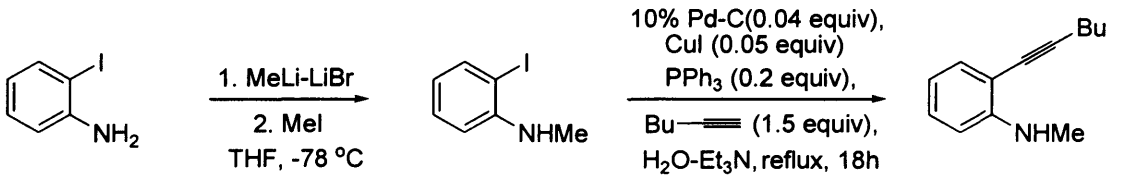
Acylation of 2-iodoaniline **133** using acetyl chloride to give *N*-acyl 2-iodoaniline **138** in 85% yield which underwent a Sonogashira reaction with phenylacetylene gave the 2-alkynyl aniline **139** in 67% yield (Scheme **48**).



133 **138** (85%) **139** (67%)

Scheme 48: *Synthesis of N-acyl 2-alkynyl aniline **139**.*

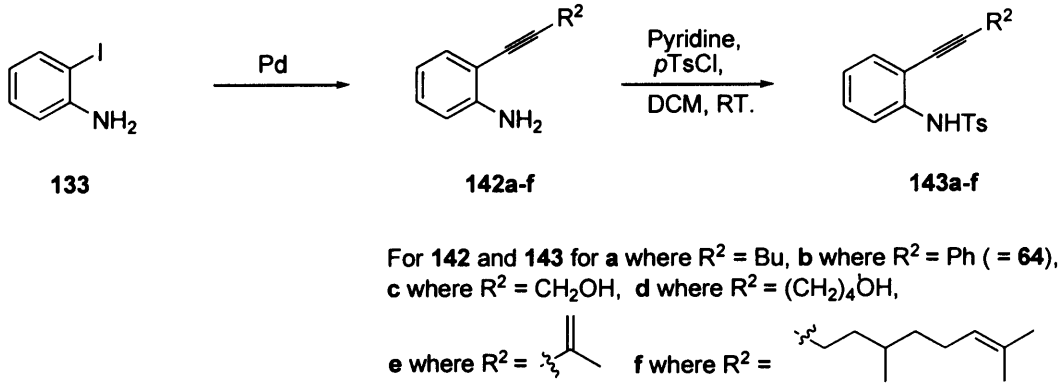
Aniline **141** was prepared by methyl protection of 2-iodoaniline **133** to give the methyl protected aniline **140** in a good yield of 68%, followed by a Sonogashira reaction with 1-hexyne to give the 2-alkynyl *N*-methyl aniline **141** in 76% yield (Scheme **49**).



133 **140** (68%) **141** (76%)

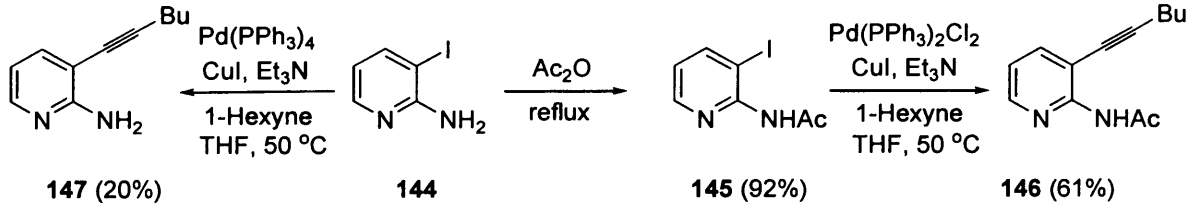
Scheme 49: *Synthesis of N-methyl 2-alkynyl aniline **141**.*

The *N*-tosyl derivatives were prepared by initial Sonogashira to give the 2-alkynyl anilines **142a-f** which was followed by *N*-tosylation to give the sulfonamides **143a-f** (Scheme **50**) in variable yields (40-98%). The reason for the reversal in steps was due to the lower yields associated with Sonogashira coupling of the *N*-tosylated aniline with acetylenes. In some cases where an *N*-tosylated aniline was used, the Sonogashira coupling with the acetylene and cyclisation occurred in one-pot; this was particularly the case with substrates **143c** and **143d**.



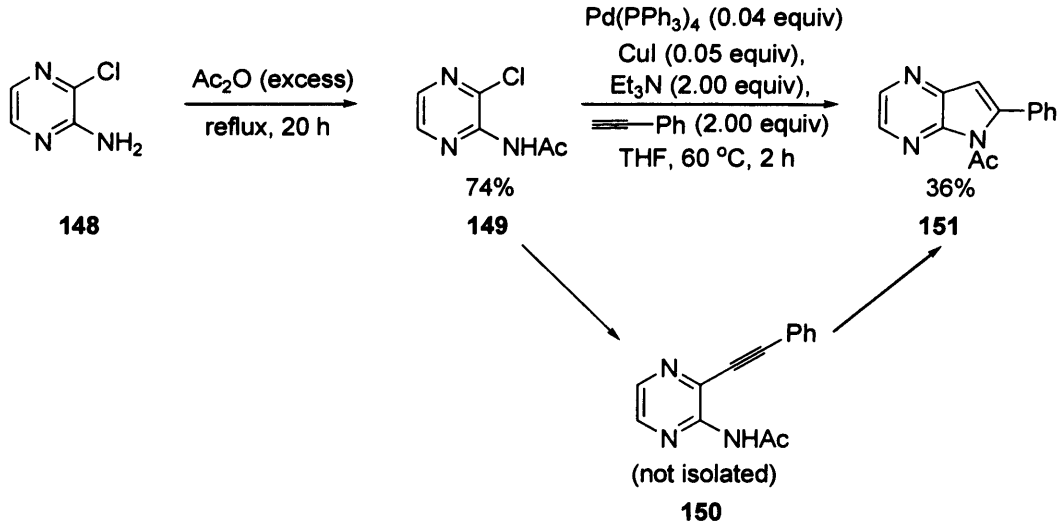
Scheme 50: *Synthesis of N-tosyl 2-alkynyl anilines (yield and Sonogashira conditions varied).*

The 2-alkynyl-amino-pyridine derivative **146** was prepared by initial acetyl protection of the pyridine **144** to give the *N*-acyl derivative **145** in 92% yield, followed by a Sonogashira reaction with 1-hexyne to give the 2-alkynyl pyridine **146** in 61% yield. The free amino-pyridine **147** was prepared in a very low yield of 20% by the Sonogashira coupling of pyridine **144** with 1-hexyne (Scheme **51**).



Scheme 51: *Synthesis of 2-alkynyl amino-pyridines.*

Preparation of 2-alkynyl pyrazine **150** was attempted by initial acylation of pyrazine **148** to give the *N*-acyl pyrazine **149**, followed by a Sonogashira coupling with phenylacetylene (Scheme **52**).



Scheme 52: *One-pot Sonogashira and cyclisation with palladium.*

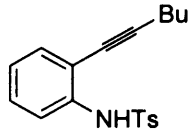
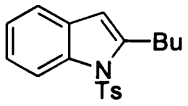
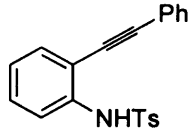
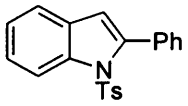
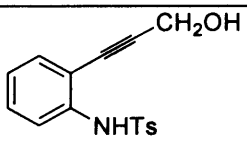
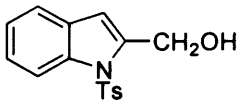
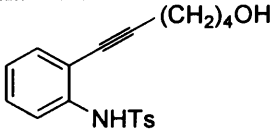
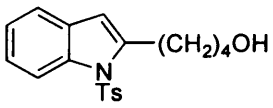
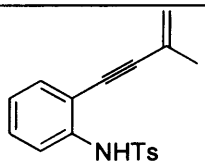
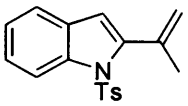
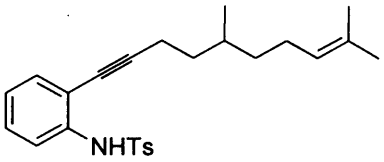
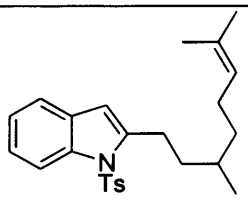
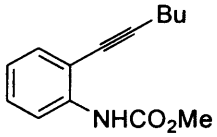
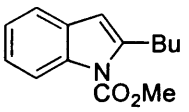
Unfortunately attempted Sonogashira coupling resulted in no detectable 2-alkynyl pyrazine **150**. In fact only aza-indole **151** was isolated in 36% yield due to the 2-step one-pot coupling and cyclisation catalysed by palladium.

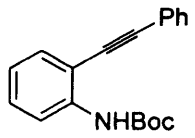
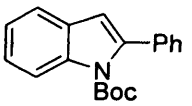
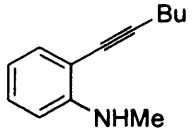
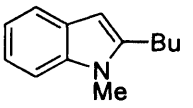
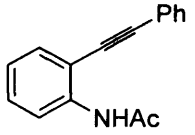
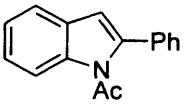
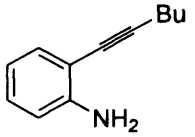
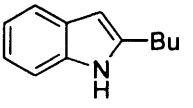
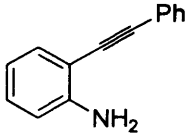
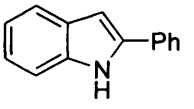
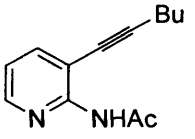
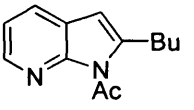
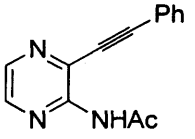
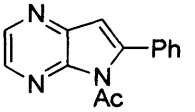
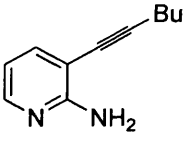
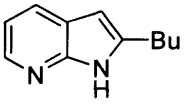
The result of this methodology was that a wide variety of 2-alkynyl anilines were synthesised that displayed a wide range of functionality. Therefore, by varying both the nitrogen protecting group and the alkyne, the robustness and limitations of the silver(I)-catalysed cyclisations could then be properly assessed.

2.3.2 Cyclisation of indole and aza-indole precursors

Upon exposure to 0.1-0.2 equivalents of 10% $AgNO_3.SiO_2$ in dichloromethane in a foil-wrapped flask, a large variety of indoles were synthesised in near quantitative yields from the corresponding 2-alkynyl anilines (Table **1**). The indoles were shown to be clean by ^{1}H-NMR analysis with no need for further purification. The silver cyclisation was even shown to work in the presence of impurities showing the method was robust. Reaction times varied with most requiring overnight stirring; thus, such cyclisations were significantly slower than was the case with the related furan and pyrrole syntheses.[2, 3]

Table 1: Silver(I)-catalysed synthesis of indoles and aza-indoles.

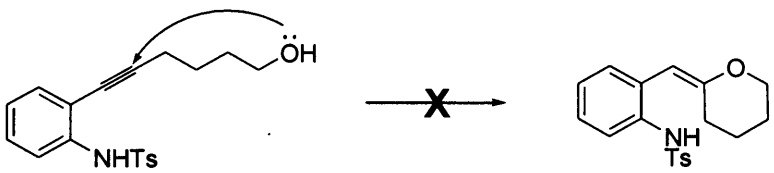
2-alkynyl aniline	Time (h)	Indole	Isolated yield (%)
 **143a**	18	 **152a**	99
 **143b**	18	 **152b**	99
 **143c**	3	 **152c**	99
 **143d**	18	 **152d**	99
 **143e**	18	 **152e**	99
 **143f**	18	 **152f**	99
 **137**	18	 **153**	99

 **135**	24	 **154**	99
 **141**	48	 **155**	99
 **139**	24	 **156**	99
 **142a**	24	 **157a**	0
 **142b (=64)**	24	 **157b**	0
 **146**	5	 **158**	99
 **150**[1]	-	 **151**	-
 **147**	24	 **159**	50[2]

[1]Product cyclised during Sonogashira. [2] Product not isolated; crude yield from ^{1}H-NMR integration.

As can be seen from Table **1**, a wide variety of indoles have been successfully synthesised with the key cyclisation step producing indoles in mostly quantitative yields. The method has displayed great flexibility with a wide range of protecting groups being tolerated, including carbamates, amides, alkylamines and sulfonamides, as well as a wide variety of acetylenes

A result of particular interest was the successful cyclisation of 2-alkynyl aniline **143d** (Scheme **53**). It was felt that as the cyclisation of the 2-alkynyl anilines was slow, there would be an increased chance of a competing 6-*exo*-dig cyclisation taking place as it is favoured by Baldwin's rules. However, upon exposure of **143d** to 0.1 equivalents of 10% silver nitrate on silica gel over 18 hours, only clean indole **152d** was observed. Even upon using stoichiometric silver(I) there were no observable side products and no pyrane **160** was observed. As can be seen from comparison of the ^{1}H-NMR of aniline **143d** and indole **152d** (Figure **1**) the CH_2 next to the OH does not shift a great deal going from 3.73 ppm in the starting aniline **143d** to 3.63 ppm in the indole product **152d**. The CH_2 next to the acetylene in the aniline **143d** is at 2.46 ppm and in the indole **152d** is at 2.94 ppm. More importantly what can clearly be seen is the appearance of the 3-H indole proton at 6.32 ppm in the product **152d**. The indole **152d** was isolated without any purification aside from a quick filtration through Celite, clearly showing the benefit of the silver(I) methodology.



143d **160**

Scheme 53: Competing 6-*exo*-dig cyclisation.

Another highlight included the successful cyclisation of aniline **141** to give the *N*-methyl indole **155**. As *N*-methyl is very different to *N*-carbamates and sulfonamides it is a result that highlights the methods robustness and indicates that the synthesis of other *N*-alkyl indoles could be possible using this methodology.

Other highlights include the successful cyclisation of *N*-Acyl-2-alkynyl amino-pyridine **146** to give aza-indole **158** in a nearly quantitative yield. As can be seen from the ^{1}H-NMR analysis (Figure **2**) the silver(I) cyclisation methodology can be applied successfully to the synthesis of

aza-indoles as well as indoles. Analysis of the ^{1}H-NMR shows only minor impurities with almost complete conversion to azaindole. This can be clearly seen by the appearance of the 3-H indole proton at 6.23 ppm and the shifting of the Acyl CH_3 from 2.42 ppm for the amino-pyridine **146** to 2.99 ppm for the azaindole **158**.

What was also intriguing was the difference in reaction times between aniline **139** and amino-pyridine **146** with **139** taking more than 24 hours for complete conversion to products, yet amino-pyridine **146** reached complete conversion after only four hours. This is perhaps due to the electron deficient nature of the pyridine ring resulting in a lowering of the pKa of the NH of *N*-acyl amino-pyridine **146** when compared to the *N*-acyl aniline **139**. By comparison of these two examples one could assume that pKa plays an important role in these cyclisations. Another interesting result came from the successful cyclisation of the free amino-pyridine **147** which gave 50% conversion into aza-indole **159** after exposure to 0.1 equivelants of silver(I) over 24 h. Increasing the amounts of catalyst and reaction time did not improve the yield greatly, resulting in only an increase to a 60% conversion to aza-indole **159**.

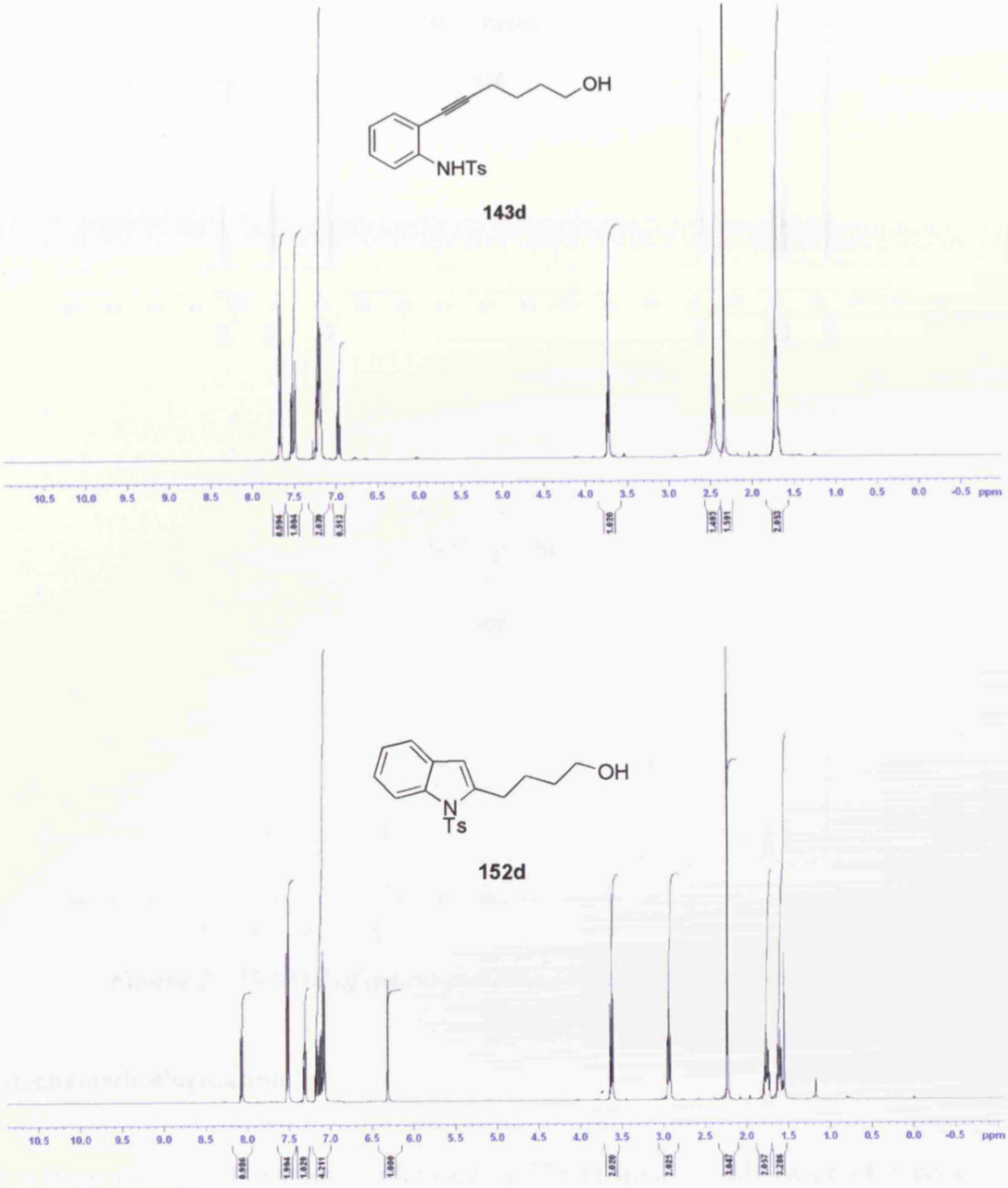


Figure 1: *^{1}H-NMR of starting aniline* ***143d*** *and crude indole* ***152d****.*

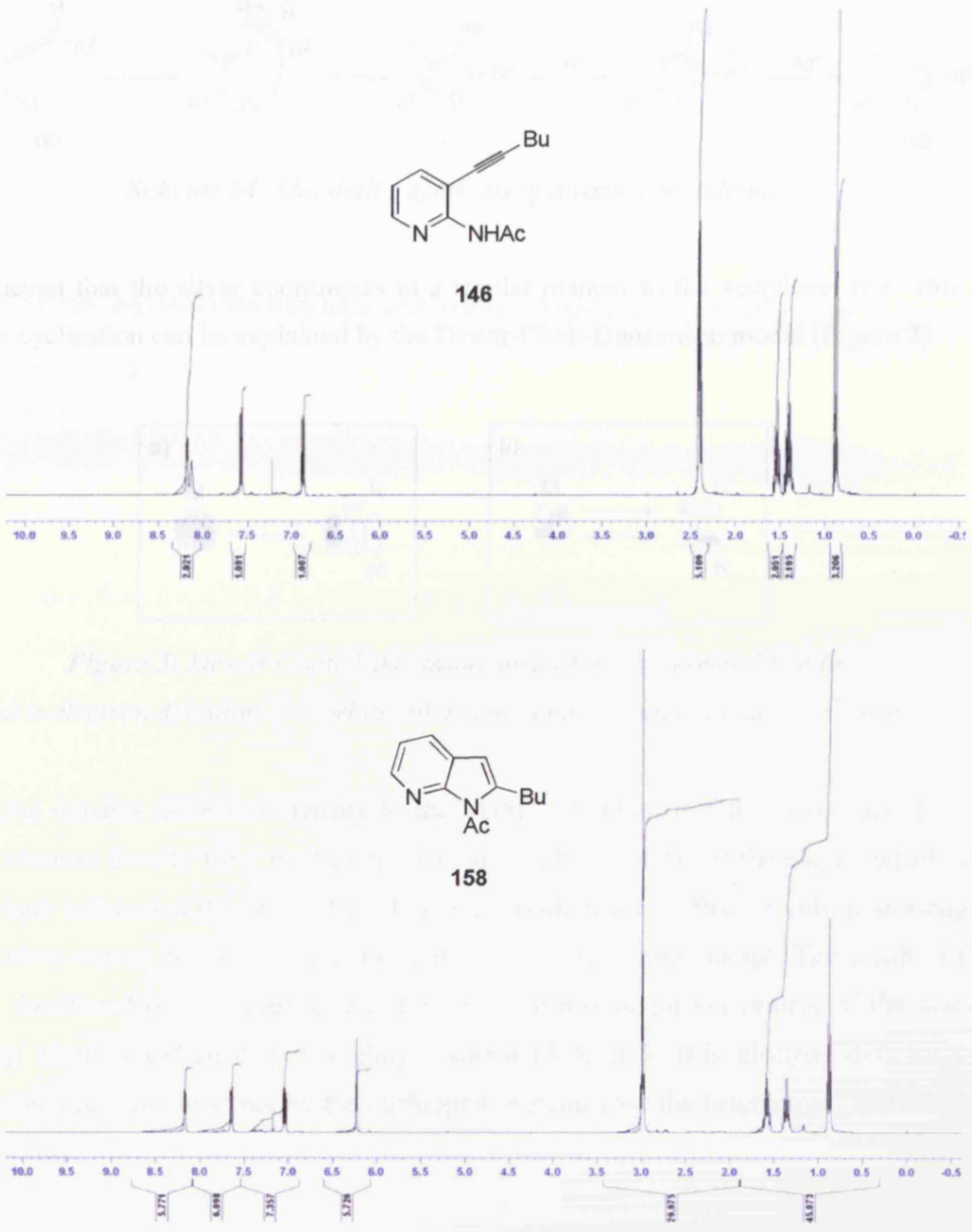
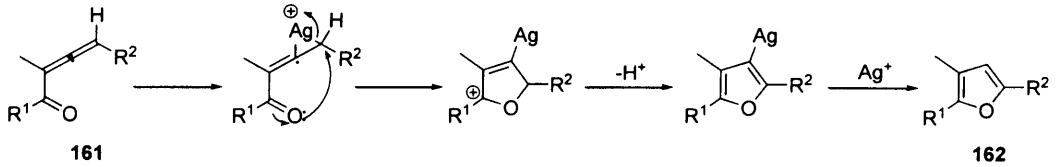


Figure 2: *^{1}H-NMR of amino-pyridine* ***146*** *and crude aza-indole* ***158****.*

2.4 Mechanistic elucidation.

With a large number of indoles synthesised (Table **1**) from a wide range of acetylenes and containing a wide range of nitrogen protecting groups it was of interest to try to ascertain a possible mechanism. Marshall[58] had previously shown the successful cyclisation of allenones **161** using 10% w/w silver nitrate on silica gel to give furans **162** and it was during this synthesis that he began assessing the mode of action of the silver salt. He performed deuterium labelling studies and was able to show that the silver coordinated with the allene allowing ring closure by donation from the lone-pair of the carbonyl (Scheme **54**).



Scheme 54: *Marshall's synthesis of furans from allenones.*

It is believed that the silver coordinates in a similar manner to the acetylene. How this helps facilitate cyclisation can be explained by the Dewar-Chatt-Duncanson model (Figure **2**).

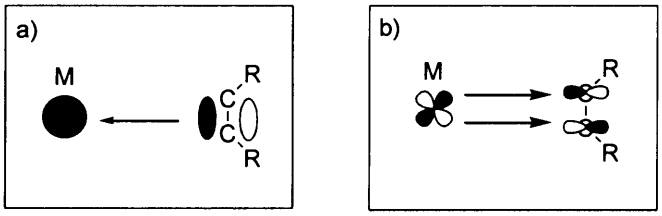
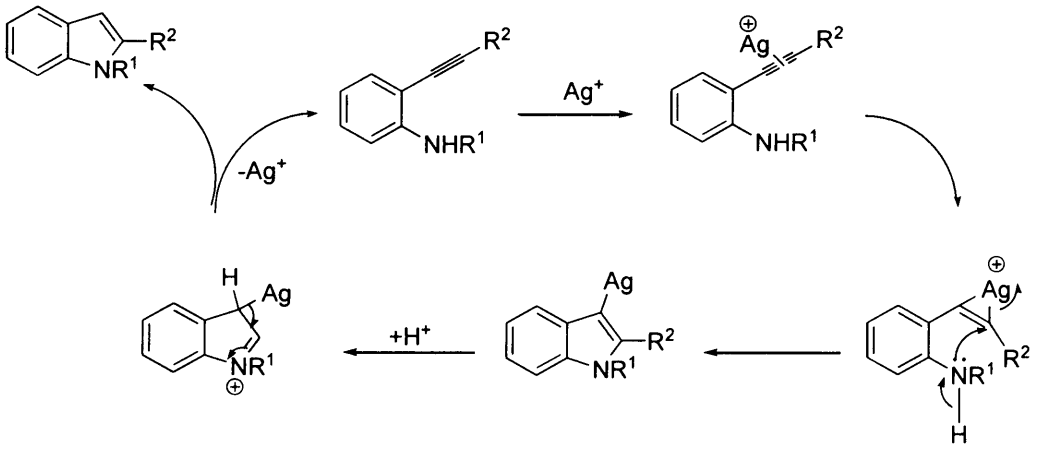


Figure 3: *Dewar-Chatt-Duncanson model for alkyne-metal bonding.*
a) π-electron donation to σ-orbital b) d orbital backbonding to alkyne π-orbital.*

The alkyne donates π-electron density to the LUMO (σ-orbital) of the silver, also the silver donates electron density from its d-orbital into an empty π^*-orbital of the alkyne which results in a stronger interaction (known as back-bonding). Both of these effects result in an elongation of the carbon-carbon bond and a rehybridisation of the sp centres to sp^2. The result of the π-electron donation from the acetylene to the metal results in carbon centres of the acetylene becoming electron deficient and slightly positive (δ+). It is this electron deficiency that activates the acetylene to attack by the nucleophile (in this case the heteroatom) and this results in ring closure.



Scheme 55: *Proposed catalytic cycle (loss of amine H probably not concerted).*

As can be seen from the proposed mechanism (Scheme **55**), the initial ring closure appears to be driven by the activation of the acetylene by the silver resulting in an electron deficient carbon centre. Additionally the nucleophile is activated by the initial loss of a proton. This is of course a pKa argument in that in order for the nitrogen to lose a proton the NH would have to be acidic enough. With the proposed mechanism in mind the results for the silver(I) cyclisation (Table **1**) suggest that an NH_2 is not acidic enough for cyclisation to take place. An NH tosyl on the other hand successfully cyclised and when considering pKa values, this was hardly suprising; a comparison between the acidity of aniline with a pKa of 30.6 and *N*-methylsulfonyl aniline with a pKa of 12.9 clearly shows a p*K*a difference of 17.7 units.

In order to quantify the pKa values for various *N*-protecting groups, as well as for that of the aza derivatives computational studies were carried out in order to ascertain pKa values in relation to the pKa of aniline which has a value of 30.6 in dimethylsulfoxide. The following computational studies were carried out by L. Goldman, a member of the Carpenter group at Cardiff University, for which we are very grateful.[59]

2.5 Computational Studies.

Acidity calculations were carried out by Goldman using the Gaussian03[60] suite of programs. All calculations were carried out at two levels of theory, the first was O3LYP/6-31+G(d) which is a commonly used density functional theory (DFT) method. The second level of theory was G2 which is a composite method defined in Gaussian. The G2 method is meant to be one of the most accurate methods available, however, it is also very expensive computationally (very labour intensive).

The first stage in the acidity calculations was to benchmark these two methods against literature pKa values for anilines.[61] The benchmark values can be found in Table **2**.

Table 2: Comparative computational results for known compounds.

Literature compound	Lit pKa (DMSO)	pKa before fit	PKa after fit	pKa before fit	pKa after fit
		DFT	DFT	G2	G2
Aniline	30.6	30.6	30.2	30.6	30.5
3-Methyl aniline	31.0	31.1	30.6	30.8	30.7
2-Chloro aniline	27.6	28.1	28.4	28.3	28.5
2-Fluoro aniline	28.7	28.5	28.7	28.7	28.8
3-Cyano aniline	27.5	27.0	27.5	27.2	27.5
4-Cyano aniline	25.3	24.2	25.4	24.7	25.2
***N*-acetyl aniline**	21.5	18.8	21.4	20.7	21.6
2-amino pyridine	27.7	26.9	27.4	26.7	27.0
RMS error		1.2	0.35	0.63	0.45

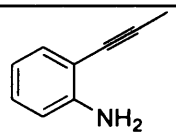
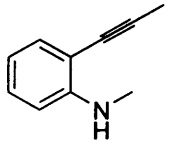
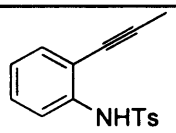
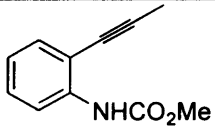
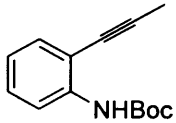
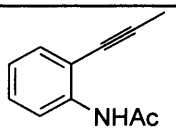
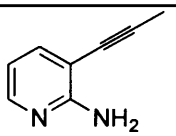
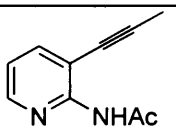
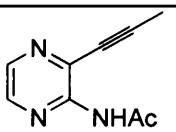
All pKa results are calculated in DMSO. RMS = root mean square.

The column labelled "before fit DFT" gives the raw results of the DFT calculation and shows an average error of 1.2 pKa units. While this error is not very large, it can be improved by fitting the data to the line: new pKa = A x old pKa + B. The variable A (0.75) is a scaling factor that corrects for the fact that the computational results become less accurate as the structures get further away from aniline. The variable B (7.3) is a correction term which references the pKa to aniline. From Table **2**, it can be clearly seen that the fitting method improves the accuracy of the pKa values. The results for the high level calculations (G2) show an initial error of 0.63 pKa units and in comparison to that of low level theory, these are an improvement. However, after the linear fit, the DFT and G2 methods have nearly identical accuracies. It is also important to note that the fitting for the G2 method has different variable values with A having a value of 0.9 and variable B having a value of 3.

Now that the benchmarks have shown that the calculations were accurate for the test compounds, calculations were performed on analogues based around the anilines used in the synthesis of indoles (Table **1**) and were referenced to aniline. The compounds were calculated for pKa values in both dimethyl sulfoxide and dichloromethane (Tables **3** and **4**). DMSO was the solvent that the test compounds were calculated for, and was the only solvent that the linear fit would be correct for. In contrast, the cyclisations were experimentally carried out in DCM,

so it was of greater interest to calculate the pKa values for anilines in DCM. Due to there being no literature pKa values in DCM, the numbers given are relative to aniline rather than absolute pKa values. Additionally they could not be scaled to a linear fit.

Table 3: Calculated pKa differences (Relative to aniline) for compounds of interest using DFT level.

Compound	Compound No	DMSO pKa difference before fit	DMSO pKa difference after fit	DCM pka difference
	**163a**	-1.3	-1.3	-1.1
	**163b**	-0.5	-0.7	-0.4
	**163c**	-20.4	-15.7	-18.8
	**163d**	-12.2	-9.5	-11.5
	**163e**	-10.3	-8.1	-8.5
	**163f**	-9.9	-7.8	-10.6
	**163g**	-5.7	-4.6	-4.6
	**163h**	-13.7	-10.7	-14.0
	**163i**	-15.9	-12.3	-16.0

According to the DFT calculations, the difference between the p*K*a of aniline and that of 2-propynyl aniline **163a** in DMSO was 1.1 p*K*a units, meaning that the acidity of 2-propynyl aniline **163a** was only about one order of magnitude more acidic than that of aniline. The fitting resulted in no increase in the difference of p*K*a. This small difference between the acidity of aniline and 2-propynyl aniline **163a** was not significant and this was hardly suprising. Equally the p*K*a difference between 2-propynyl aniline **163a** and *N*-methyl 2-propynyl aniline **163b** was also very small. The calculated p*K*a difference between aniline and *N*-Boc 2-propynyl aniline **163e**, *N*-Moc 2-propynyl aniline **163d** and *N*-acetyl 2-propynyl aniline **163f** were 10.3 (8.1), 12.2 (9.5) and 9.9 (7.8) respectively. All of them showed similiar p*K*a values to each other, and were all significantly more acidic than aniline. The *N*-tosyl 2-propynyl aniline **163c** was much more acidic than all the other anilines that were calculated, and this was to be expected. The tosyl group is very electron-withdrawing and therefore has a significant effect on the p*K*a of the amine group. Other results of interest include the p*K*a values of the 2-propynyl aza-anilines, in particular the p*K*a value for 3-propynyl pyridine-2-amine **163g**, which according to the calculations, has an acidity 4.4 p*K*a units more acidic than its comparable 2-propynyl aniline **163a** (3.3 units more acidic with fit). The *N*-acyl aza-anilines **163h** and **163i** were shown to be more acidic than their aniline counterparts and displayed values in a range between that of the carbamates and the sulfonamide. Another interesting result was that the substitution of a second nitrogen into the benzene ring increased the acidity by ~ 2 p*K*a units.

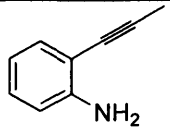
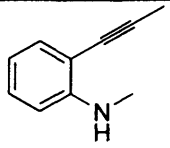
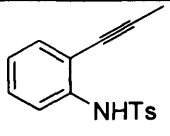
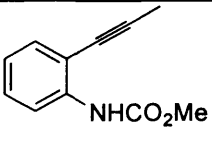
The differences in p*K*a found using both dimethyl sulfoxide and dichloromethane were very similar and appeared to follow the same trends, these being that *N*-tosyl 2-propynyl aniline **163c** was more acidic than the other anilines tested and that both the carbamate (**163d** and **163e**) and *N*-acyl derivatives (**163f**, **163h** and **163i**) were between 11.5-8.5 p*K*a units more acidic than aniline. Equally, the difference in p*K*a between that of aniline and 2-propynyl aniline **163a** or *N*-methyl 2-propynyl aniline **163b** were around 1 p*K*a units of difference. The aza derivatives equally followed a similar pattern with the free aniline having indentical p*K*a values in dichloromethane and in dimethyl sulfoxide with fit (both 4.6 units more acidic than aniline). The *N*-acyl aza-anilines (**163h** and **163i**) were shown to have an even greater p*K*a difference in dichloromethane relative to its aniline counterpart, with acidities even closer to the sulfonamide. The pyridine derivative had a p*K*a 14 units more acidic than aniline and the pyrazine was shown to have a p*K*a 16 units more acidic than aniline.

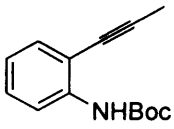
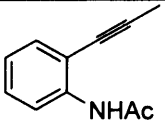
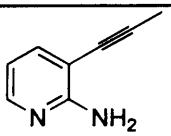
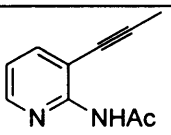
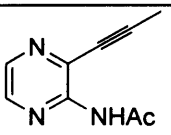
The reason for carrying out these calculations was to try to explain the overall trends of the cyclisation. An interesting discovery was that no cyclisation of **142a** and **142b** was observed even upon increasing the silver to stoichiometric amounts and prolonged reaction times of 48

hours. Only starting material was observed. However, the attempted cyclisation of *N*-methyl aniline **141** over 48 hours proved successful resulting in complete conversion into indole **155** after 48 hours using 0.2 equivalents of 10% silver nitrate on silica. This was suprising considering the p*K*a values of *N*-methyl aniline **141** and free aniline **142** were essentially the same. According to our p*K*a arguments, either both of those anilines should have cyclised, or neither should have cyclised. Instead, N-methyl aniline **141** cyclised while free anilines **142a** and **142b** did not.

This would suggest that the p*K*a arguments do not provide a complete picture and this suggests that the mechanism (See Scheme **55**) cannot be completely correct and that maybe there is more than one mechanism taking place. Another interesting result was the successful cyclisation of the free amino-pyridine **147** upon exposure to 10% $AgNO_3.SiO_2$ resulting in 50% conversion to aza-indole **159** in 24 hours. However, attempts to achieve complete conversion with exposure to one equivalent over a further 24 hours resulting in only 60% conversion; this was a slight oddity. A hypothesis for this could be that pyridines have been known to be good chelators to metals and hence it could be that the silver was being made inactive towards cyclisation by coordination with the nitrogen of the pyridine.

Table 4: Calculated p*K*a differences for compunds of interest using G2 level.

Compound	Compound No	DMSO pKa difference before fit	DMSO pKa difference after fit	DCM pKa difference
	**163a**	-1.0	-1.0	-0.9
	**163b**	-0.7	-0.7	-0.5
	**163c**	Too large		Too large
	**163d**	Too large		Too large

	**163e**	Too large		Too large
	**163f**	Too large		Too large
	**163g**	-4.9	-4.5	-4.6
	**163h**	Too large		Too large
	**163i**	Too large		Too large

High level theory (G2) was shown to be unable to determine the p*K*a values for all but three compounds (Table **4**). This was due to the compounds being too large for the G2 method. The results that worked were shown to follow the trends seen in the DFT calculations. This suggested that DFT was a sufficient level of theory to carry out the calculations.

The computational results show that the pKa of the methyl aniline and the free aniline are essentially the same. This highlights that the mechanism suggested (Scheme **55**) is either incorrect or incomplete. It is possible that the difference in reactivity between the N-methyl aniline **141** and the free aniline **142** could have been explained had we investigated the indolinium salts. In other words, cyclisation may have occurred prior to proton loss. Possible future work would be to carry out computational experiments using on the indolinium salts.

2.6 Significance of a propargylic alcohol.

Hayes had previously studied the mechanistic pathway of the silver catalysed cyclisation.[3] He found that in the case of furans, a propargylic alcohol was indeed required to achieve successful cyclisation; it was also believed that aromatisation may have been a driving force for the reaction by providing a 'thermodynamic sink'. The cyclisation of 2-alkynyl anilines, when compared to the silver cyclisation of pyrroles, furans, *etc* are in general much slower. It is possible that this may be due to the lack of a propargylic OH which according to previous work

was believed to accelerate the reaction. In order to ascertain the importance of a propargylic alcohol, a comparison study of butyl **143a** against alcohol **143c** was undertaken. A 1.5:1 mixture of 2-alkynyl anilines **143a** and **143c** respectively (45 mg) in 1 ml of deuterated chloroform was exposed to 0.1 equivelants of 10% silver nitrate on silica (~24 mg) over 45 minutes and the cyclisation followed by ^{1}H-NMR analysis (Figure **4**).

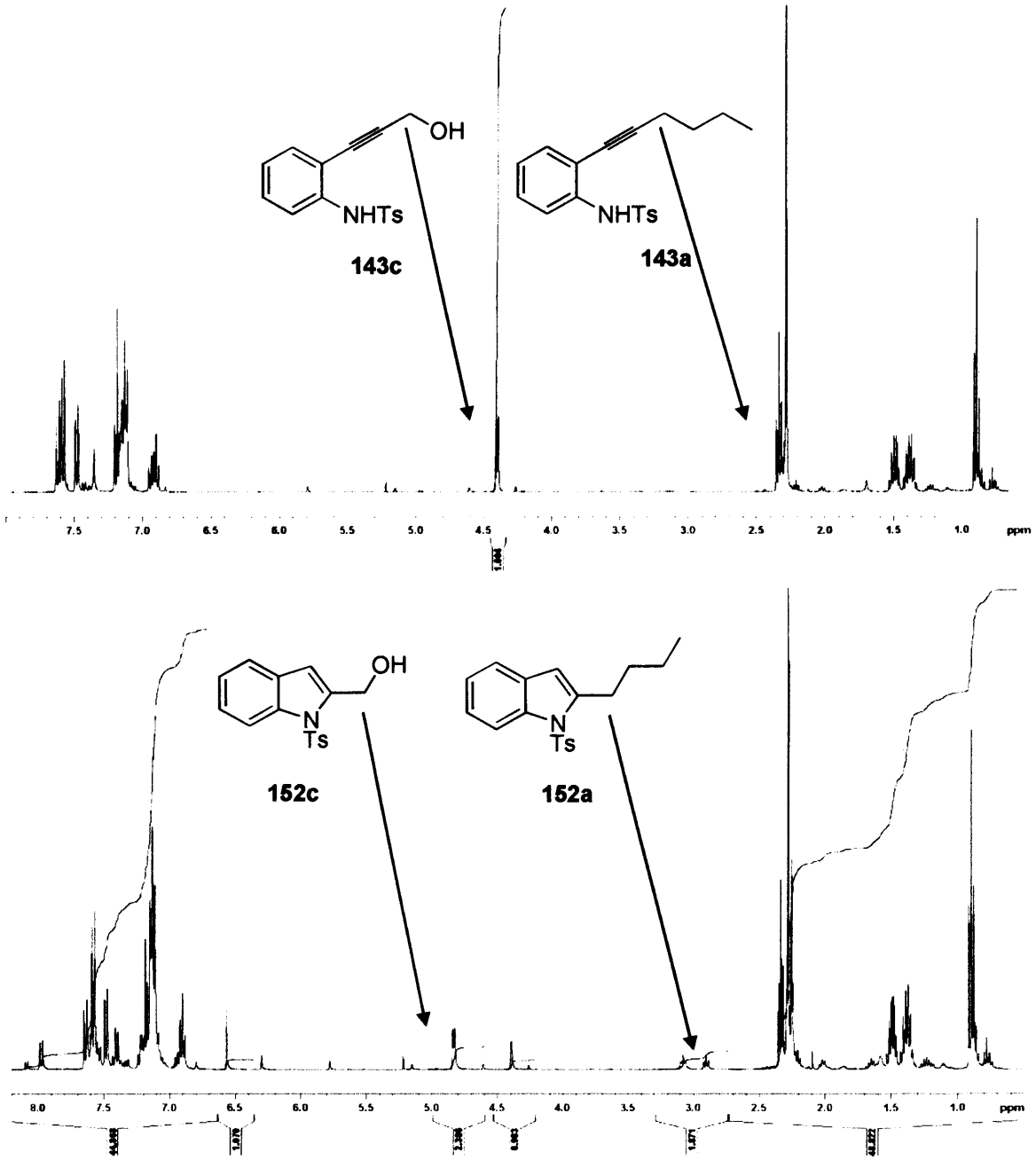


Figure 4: *^{1}H-NMR of starting aniline **143a** and **143c** and product mixture after 45 mins.*

As can be seen from the ^{1}H-NMR (Figure **4**), the cyclisation of **143a** gave ~10% conversion to indole **152a** as could be seen from the integration of the C≡C-CH_2 of the starting aniline at 2.32

ppm and that of the product at 2.91 ppm. This can also be seen by the appearance of the 3-H at 6.30 ppm. In stark contrast the cyclisation of alcohol **143c** was drastically accelerated with 75% conversion to indole **152c**. This can be seen by the ^{1}H-NMR integration of the starting material $\mathbf{CH_2}$OH at 4.39 ppm and that of the product at 4.84 ppm. The product can also be clearly seen by the 3-H peak at 6.57 ppm. This result gives a clear indication that a propargylic alcohol group does increase the rate of cyclisation as previously suggested by Pale and Dalla.[62-63] It is believed it accelerates the reaction by coordination of the silver(I) by the propargylic oxygen bringing it within close proximity to the acetylene.

2.7 Flow chemistry.

An additional goal for this methodology was the development of a flow system to give a highly efficient scale-up of the indole synthesis. Flow chemistry has become of growing importance to the pharmaceutical industry and its use has also been increasing outside the industry. Traditionally, manufacturing plants have used a method known as batch processing in a range of different syntheses. The process involves an almost conveyor belt-type system whereby a component would reach a workstation and undergo a process and then move on to another workstation. The process was continued until a product was reached. This process is common and applicable to a number of businesses including the pharmaceutical industry for the process of both small and large scale drug development. This process was at times inefficient, and as a result there is a growing need for continuous processes that are both more efficient and safe. This led to the development of fixed bed reactors, the most common of which is a trickle bed reactor,[64-65] which is essentially a tube containing a catalyst. A substrate is then passed through the tube and the catalyst performs the transformation on the substrate which comes out the other end of the tube as product.

With the idea of a trickle bed reactor in mind, Hayes set out to develop a suitable flow system for the silver cyclisation of heterocyclic precursors, thereby allowing for the continuous processing of heterocyclic compounds and potentially efficient large scale syntheses. Initial studies into the cyclisation of furan precursors in flow carried out by Hayes involved using Marshall's suggestion of 10% silver nitrate on silica in a column. Although this proved successful, there was an issue of silver(I) leaching into the product, as was clearly seen by the product collected turning black (Ag(0) deposition). In an attempt to avoid this issue, a number of counter ions and supports were assessed for their suitability and cost effectiveness. It was decided that the cheapest out of those tested, Amberlite 200c sodium form (a sulfonic acid resin), would be chosen as the resin as both the support and as the counter-ion (mimic for the

triflate counter-ion). It was felt that as the resin was strongly acidic, it would load the most efficiently and not undergo leaching. A stainless steel column (8 x 0.5 inches) packed with Amberlite 200c sodium form with a bed volume of 50 cm^3 was successfully exchanged with Ag^+ ions using a 10% aqueous silver nitrate solution (Figure **5**). The silver nitrate solution was passed through the column five times to ensure complete exchange, and was followed by washing with water, methanol, diethyl ether and then dichloromethane to prepare the column for use.

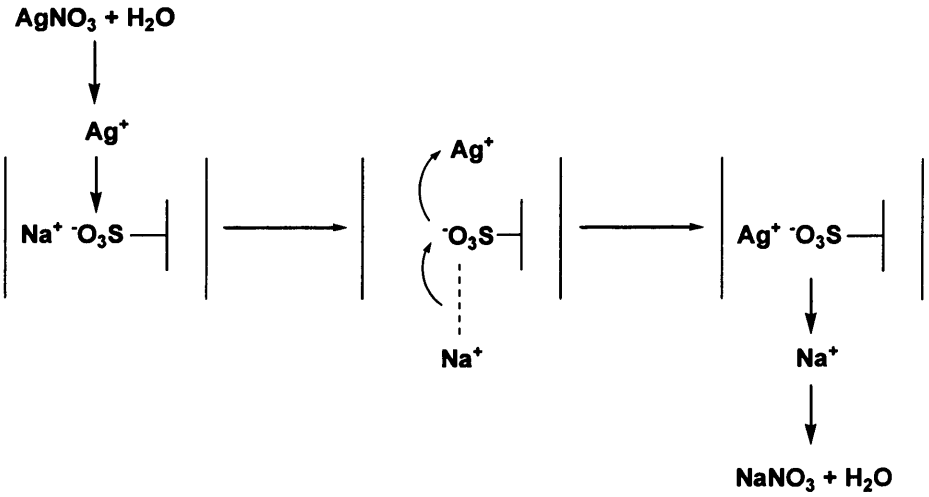
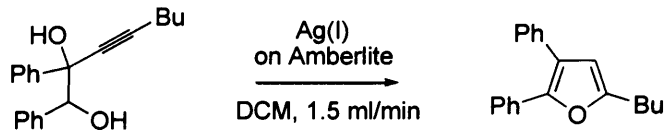


Figure 5: *Silver exchange on an ion exchange resin.*

Hayes then tested the column by passing furan and pyrrole precursors through the flow system. The flow system was found to be very successful in the synthesis of furans and pyrroles. What was also found was that the issue of silver(I) leaching was solved with very little silver(I) detected (<1 ppm by ICPMS). With this success in mind, it was hoped that this methodology could be extended to the cyclisation of 2-alkynyl anilines to give indoles cleanly, quantitatively and quickly. Such a method could be a significant alternative to the methods described in the beginning of this chapter.

Anilines **143a**, **143b** and **135** were passed through the Hayes amberlite flow system in an attempt to achieve cyclisation in flow. Unfortunately this proved fruitless resulting in 100% recovery of starting materials at flow rates of 0.2-2.5 ml/min in dichloromethane, ether and acetonitrile for all the substrates tested. These results were somewhat surprising and disappointing considering that slow conversion was seen when aniline **143a** was stirred with silver-exchanged amberlite in a flask. The flow system was checked several times using furan precursor **164** (known to cyclise on the silver(I) Amberlite column) to determine whether the silver(I) had sufficiently deposited on the Amberlite resin. Upon passing the substrate **164**

through the silver(I) on Amberlite column at 0.5, 1 and 1.5 ml/min, successful cyclisations were observed with complete conversion into furan **165** (Scheme **56**) even at 1.5 ml/min. Because of the above results, a successful silver-catalysed cyclisation of anilines to indoles in flow looked unlikely.

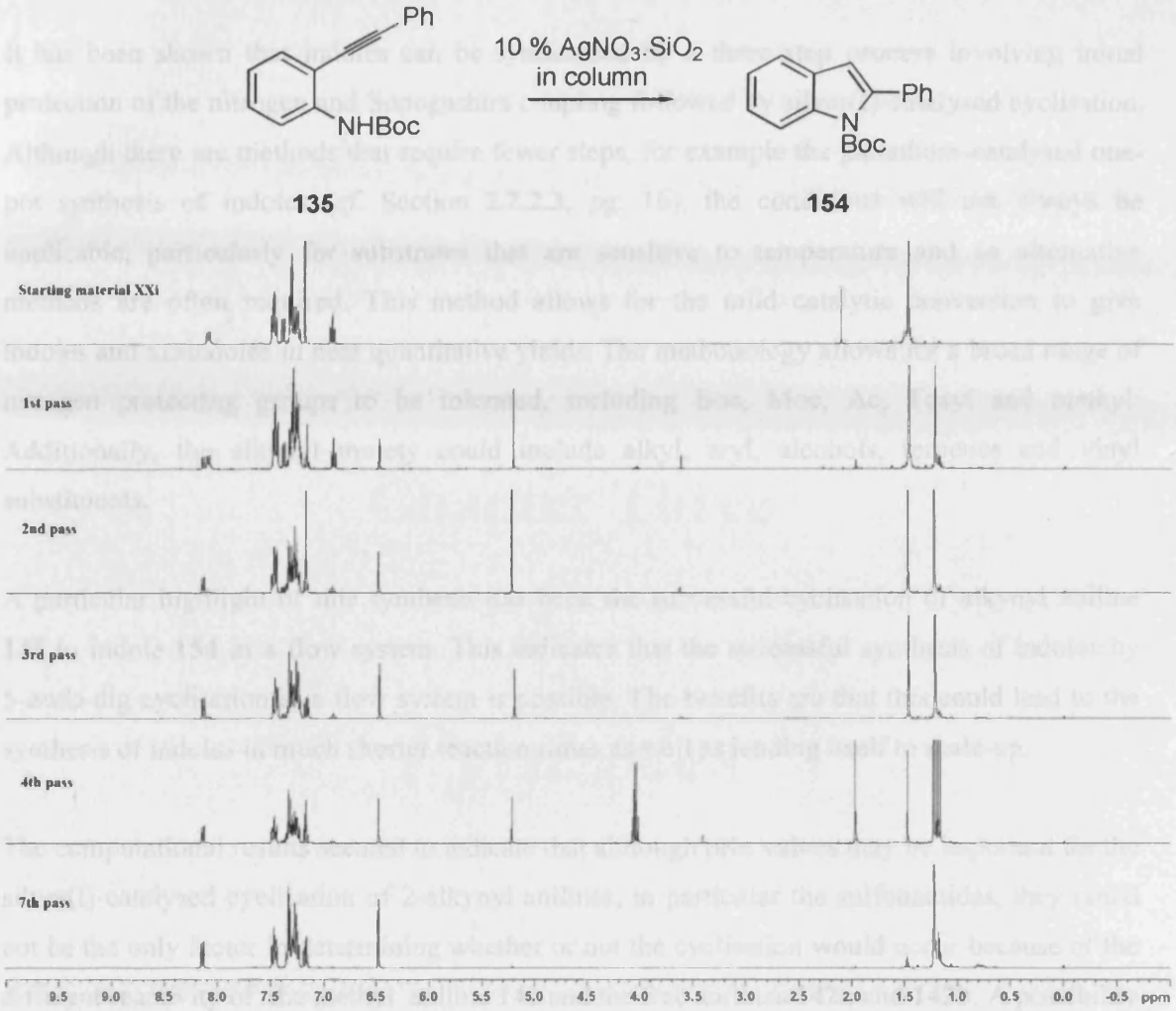


164 **165**

***Scheme 56:** Furan **165** synthesis in flow.*

We then decided that, despite the issue of leaching, the readily prepared 10% $AgNO_3.SiO_2$ could provide potential for indole synthesis in flow as suggested by Marshall.[58] We used a very simple set-up of a glass column (20 x 2.5 cm^3) primed with 10% silver nitrate on silica (60 g) covered in foil to protect the silver(I) from photoreduction and nitrogen as the source of pressure to push the compound through the column. Priming the column with substrate **135** (0.10 g) in dichloromethane (1.00 ml) followed by a flow of dichloromethane at a rate of 1.5 ml/min resulted in 66% conversion into indole **154** and no side-product formation after two passes through the column. Further passes through the column resulted in complete conversion into the indole **154** after seven passes (Figure **6**). This can be clearly seen from the ^{1}H-NMR analysis (Figure 6) by the shifting of the Boc peak from 1.47 ppm in the starting aniline **135** to 1.23 ppm in the indole product **154**, as well as the appearance of the 3-H indole proton at 6.48 ppm in the product **154**. What can also be seen from the ^{1}H-NMR analysis is that no side-products were formed despite exposure to a large amount of silver(I) catalyst. This was a fantastic result, showing that 2-alkynyl anilines *could* be converted into indoles successfully in flow rather quickly without any need for purification Another interesting point was that although the product collected from the flow system was not properly analysed for silver leaching, the product collected remained yellow and darkening of the oil due to silver(I) deposition was not observed. Overall this result shows that synthesis of indoles in a flow system is possible. The method allows for a much quicker conversion of 2-alkynyl anilines to indoles with complete conversion for aniline **135** to indole **154** after seven passes at 1.5 ml/min compared to 24 h exposure to 0.1 equivalents of silver(I) nitrate on silica. Although the use of silver(I) nitrate on silica in flow involves using a great excess of silver(I), the catalyst is re-usable many times.

Figure 6: *^{1}H-NMR of conversion of **135** to **154** using 10% $AgNO_3.SiO_2$ column.*



A comparison of the successful cyclisation in flow using 10% $AgNO_3.SiO_2$ with that of the unsuccessful attempt at cyclisation in the flow method using silver(I) on Amberlite lead to the question of why would there be such a vast difference in the conversion of aniline **135** to indole **154** in these two flow systems. A possible reasons could be that the silver(I) on silica has a greater surface area for interaction between substrate and catalyst. However, silver(I) on Amberlite had a lower surface area, one would expect that at a flow rate of 0.2 ml/min, *some* conversion would be expected to occur especially since the flow rate with silver(I) on silica was 1.5 ml/min. Another possible explanation could be the difference in the stationary phases that the silver is embedded on. The silver on Amberlite is essentially neutral yet the silver on silica is slightly acidic. Perhaps the cyclisation works best with an acidic surface. Future work would focus on optimisation of the flow system and better understanding of the flow process.

2.8 Conclusions.

It has been shown that indoles can be synthesised by a three step process involving initial protection of the nitrogen and Sonogashira coupling followed by silver(I)-catalysed cyclisation. Although there are methods that require fewer steps, for example the palladium-catalysed one-pot synthesis of indoles (*cf.* Section **2.2.2.3**, pg. 16), the conditions will not always be applicable, particularly for substrates that are sensitive to temperature and so alternative methods are often required. This method allows for the mild catalytic conversion to give indoles and azaindoles in near quantitative yields. The methodology allows for a broad range of nitrogen protecting groups to be tolerated, including Boc, Moc, Ac, Tosyl and methyl. Additionally, the alkynyl moiety could include alkyl, aryl, alcohols, terpenes and vinyl substituents.

A particular highlight of this synthesis has been the successful cyclisation of alkynyl aniline **135** to indole **154** in a flow system. This indicates that the successful synthesis of indoles by 5-*endo*-dig cyclisation in a flow system is possible. The benefits are that this could lead to the synthesis of indoles in much shorter reaction times as well as lending itself to scale-up.

The computational results seemed to indicate that although pKa values may be important for the silver(I)-catalysed cyclisation of 2-alkynyl anilines, in particular the sulfonamides, they could not be the only factor in determining whether or not the cyclisation would occur because of the different reactivity of the methyl aniline **141** and the free anilines **142a** and **142b**. A possibility is that the mechanism considered (Scheme **55**) is either incorrect or incomplete. Despite this uncertainty the silver(I) catalysed cyclisation of anilines appeared to be a good alternative for indole synthesis.

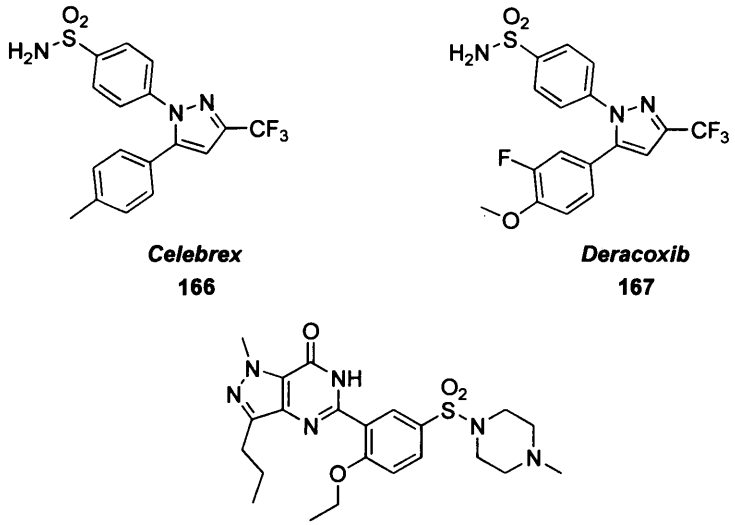
Chapter Three

Pyrazoles

3.1 Introduction.

Another important class of heterocycles are the pyrazoles: characterised as alkaloids, they consist of a 5-membered ring with two neighbouring nitrogen atoms, having one pyrrole type nitrogen that gives the ring its aromaticity and a nitrogen that has an exposed lone pair giving it a basicity on a par with pyridine. Nature appears to be unable to form many compounds with N-N bonds, with only a few examples found, including withasomnine which was isolated from the root of the Indian medicinal plant *Withania somnifera*.[66,67] Despite their absence in Nature, many synthetic pyrazoles form the core of drugs that are used for their analgesic, antibacterial, anti-inflammatory and many other medicinal properties; this is unsuprising in view of their varied ability to form hydrogen bonds.

Examples of some important drugs that contain a pyrazole core include celecoxib which is marketed by Pfizer under the brand name Celebrex **166**[68] which selectively inhibits the enzyme cyclooxygenase-2 (COX-2) that is responsible for pain and inflammation and is used as a treatment for arthritis. Similarly Deracoxib **167**[69] has been shown to display moderate COX-2 inhibition and is a treatment for inflammation and pain in dogs. Another important drug that contains the pyrazole core is Sildenafil **168**[70] a very well known vasodilator, better known as Viagra. It acts by inhibiting Cgmp-specific phosphodiesterase type 5, an enzyme found in various tissues (Figure 7).



Celebrex
166

Deracoxib
167

Sildenafil
168

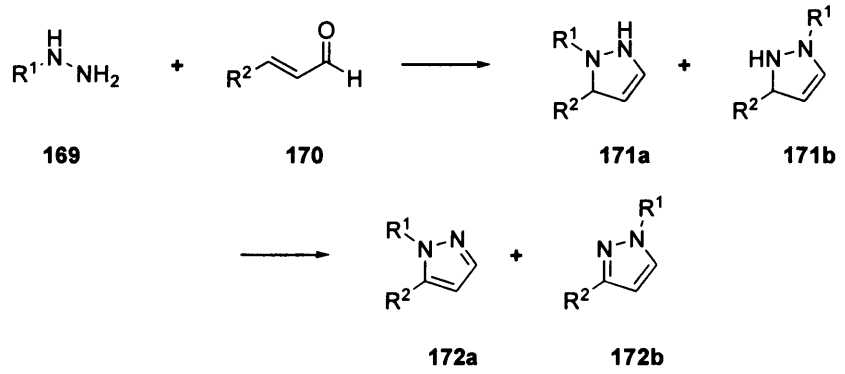
Figure 7: *Important pyrazoles Celebrex* ***166****, Deracoxib* ***167*** *and Sildenafil* ***168****.*

There are a number of established methods used to synthesise pyrazoles, many of which involve the use of commercially available hydrazines. The disadvantage with a number of these methods is a lack of regioselectivity.

3.2 Literature methods to make pyrazoles

3.2.1 Synthesis of pyrazoles from hydrazines.

One of the more common methods to make pyrazoles is by Michael addition of hydrazines **169** to α,β-unsaturated carbonyls **170**,[71-72] followed by attack of the second nitrogen onto the carbonyl forming the ring which tautomerizes. This is followed by oxidation of the dihydropyrazoles **171a** and **171b** to yield the pyrazoles **172a** and **172b** (Scheme 57).



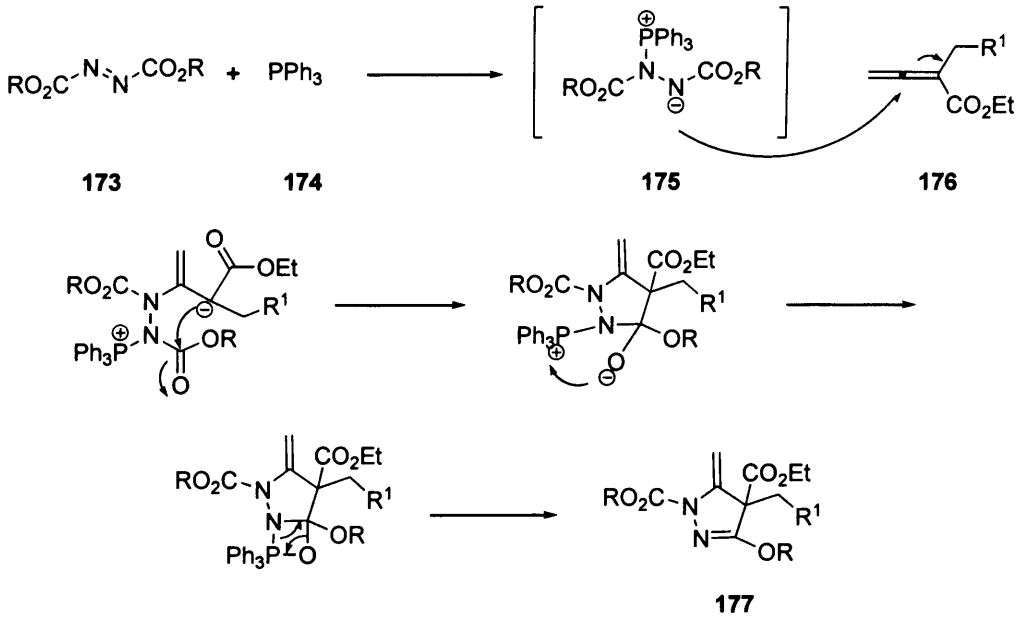
Scheme 57: *Synthesis of pyrazoles from α, β-unsaturated carbonyls and hydrazines.*

There is usually a lack of regioselectivity with unsymmetrical hydrazines resulting in a mixture of regioisomers which can be difficult to separate. This chemistry is therefore often limited to symmetrical reagents.

3.2.2 By reaction between Huisgen zwitterions and electron-deficient alkenes.

Nair and co-workers showed that pyrazoles could be synthesised from Huisgen zwitterions **175** and allenic esters **176** (Scheme **58**). The reaction involved the initial formation of a Huisgen zwitterion **175** from azodicarboxylates **173** and triphenylphosphine **174**. It was shown that pyrazolines **177** could be obtained from the addition of the zwitterion **175** to the electron-deficient double bond of the terminal allenic ester **176** to give a tetrahedral intermediate that then eliminates triphenylphosphine oxide *via* a mechanism reminiscent of that which occurs in

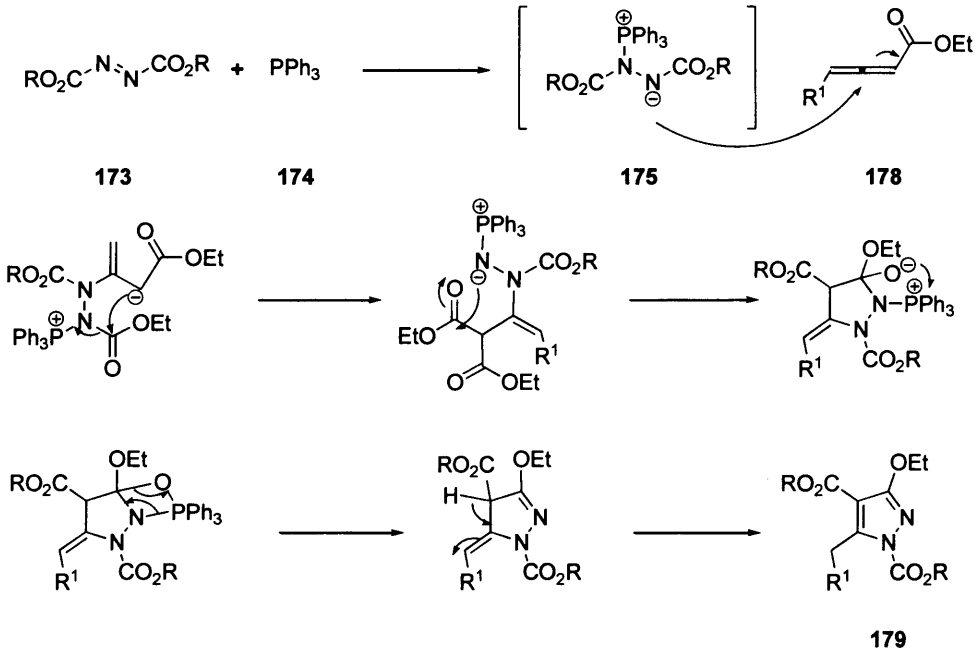
the last step in a Wittig olefination to give the pyrazolines **177** in moderate to good yields (33-74%).[73]



173 **174** **175** **176** **177**

Scheme 58: *Nair and co-workers synthesis of pyrazolines 177 from terminal allenes.*

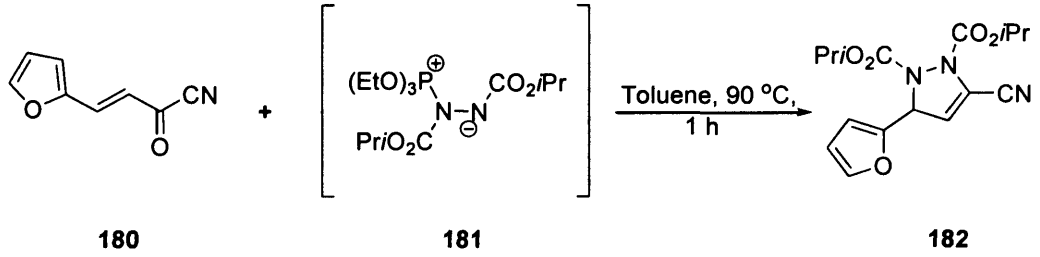
Exchanging the terminal allenic ester **176** for a terminally substituted allenic ester **178** results in formation of a pyrazole **179** in moderate to good yields (35-72%). It is believed that the pyrazole is formed by a slightly different mechanism (Scheme **59**).



173 **174** **175** **178** **179**

Scheme 59: *Nair's synthesis of pyrazoles 179 from disubstituted allenes.*

Similarly Lui and co-workers showed that a reaction between an α,β-unsaturated acyl cyanide **180** and Huisgen zwitterions **181** could give 2,5-dihydropyrazoles (Scheme **60**), however there was only one example of a 2,5-dihydropyrazole **182** with a moderate yield of 50%.[74]

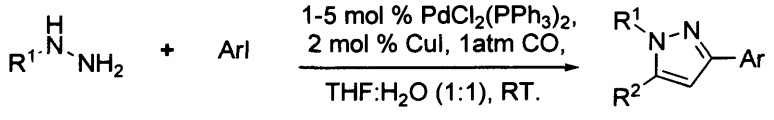


180 **181** **182**

Scheme 60: *Lui and coworkers synthesis of a 2,5-dihydropyrazole **182**.*

3.2.3 Palladium-catalysed synthesis

Mori and co-workers reported a regioselective pyrazole synthesis by the four component coupling of mono-substituted hydrazines **169**, terminal alkynes, aryl iodides **183** and carbon monoxide (Scheme **61**). The reaction is catalysed by 1-5 mol% palladium as $[(PdCl_2(PPh_3)_2]$ in the presence of copper iodide (2 mol%). The reaction proceeds by the palladium-catalysed coupling of the alkyne, aryl iodide **183** and carbon monoxide to form the propargylic ketone. The ketone then reacts with the hydrazine **169** and cyclises to form the pyrazole **184**. The yields for the reaction are moderate to excellent (59-93%).[75] This route is limited because the reaction only seems to work with aryl iodides.



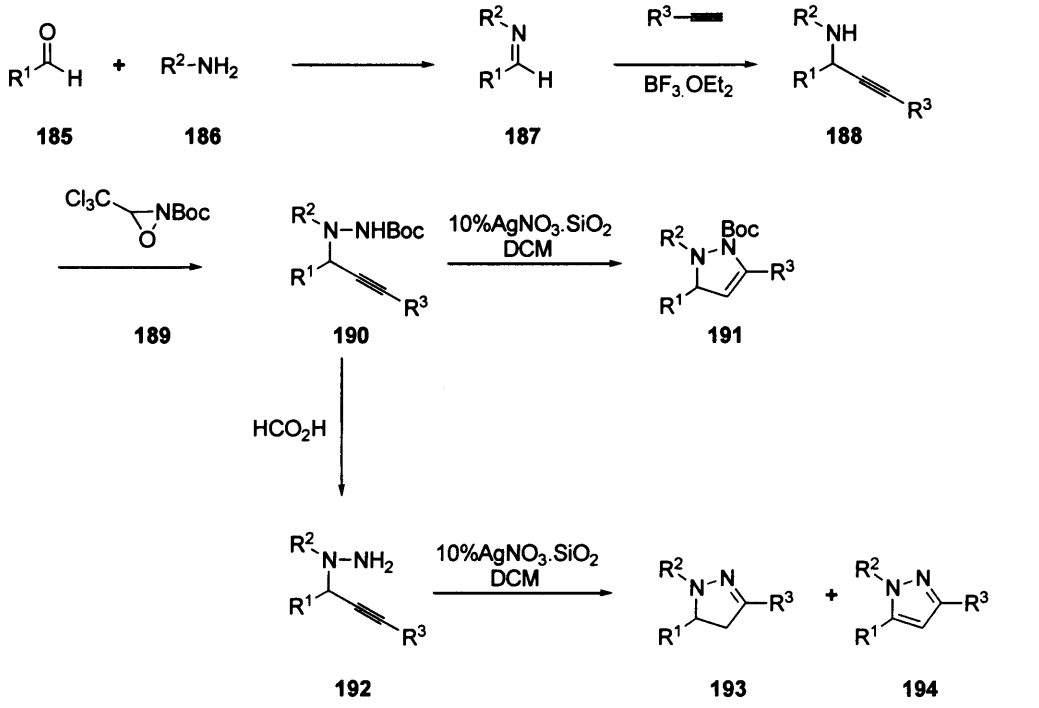
169 **183** R^2 **184**

Scheme 61: *Mori and co-workers four component coupling for pyrazole synthesis.*

3.2.4 Silver(I)-catalysed pyrazole synthesis.

With the successful cyclisations of pyrroles using catalytic (0.1 equiv) 10% $AgNO_3.SiO_2$, Knight and Song assessed its potential application to pyrazole synthesis, starting from the condensation between commercially available aldehydes **185** and amines **186** to give imines **187** in excellent yields (Scheme **62**).[1c] The next step involved the addition of lithio-acetylides to the imines in the presence of the Lewis acid $BF_3.OEt_2$ to form propargyl amines **188** with yields in the range 65-75%. This was then followed by *N*-amination using oxaziridine **189** to give the

propargyl hydrazine **190**. The Boc-group of the propargyl hydrazine was then removed using formic acid to give the free hydrazine **192**. The free hydrazines **192** were not isolated due to their relative instability but were instead carried through to cyclisation using 10% $AgNO_3.SiO_2$. The cyclisation resulted in variable mixtures of 4,5-dihydropyrazole **193** and pyrazole **194** in reasonable yields over the two steps.[1c] The pyrazoles **194** appeared to be formed by an, as yet, obscure oxidation process.

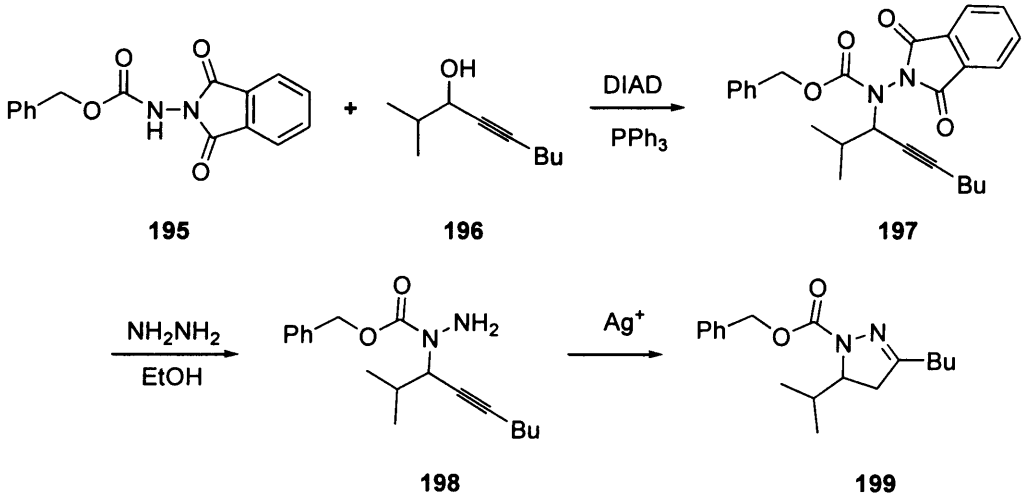


where R^1 = Ph, R^2 = Pr, R^3 = Bu: 48% **193** and 9% **194**
where R^1 = Ph, R^2 = Pr, R^3 = Ph: 0% **193** and 10

3.3 Pyrazoles: Results and Discussion

3.3.1 Origins of the current work.

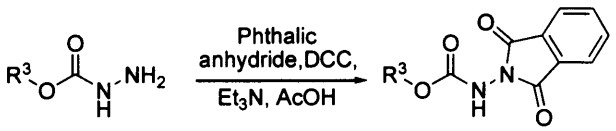
Knight and Song also found that 4,5-dihydropyrazoles **199** could be accessed by use of the Mitsunobu reaction.[1c] They found that *N*-alkyloxycarbonylaminophthalimides made good substrates for alkylation using primary and secondary alcohols as previously shown by Jamart-Grégoire and co-workers.[76] For example, Song showed that coupling of benzyloxycarbonylaminophthalimide **195** with propargylic alcohol **196** provided propargylic phthalimide **197** in a good yield (73%). This was followed by deprotection to give the free hydrazine **198** (68%) and successful cyclisation using 0.1 equivalents of 10% $AgNO_3.SiO_2$ to give the 4,5-dihydropyrazole **199** cleanly in a moderate yield (57%) after 1 h (Scheme **63**).[1c]



***Scheme 63**: Song's synthesis of a 4,5-dihydropyrazole **199**.*

As Song did only this one example we decided to expand this methodology towards a number of examples and to determine whether there were any limitations with the chemistry.

3.3.2 Synthesis of 4,5-dihydropyrazoles *via* Mitsunobu coupling of phthalimides and alcohols.



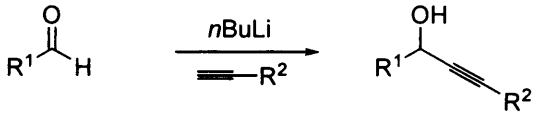
200a-c **201a-c**

a where R^3 = Benzyl,
b where R^3 = Me,
c where R^3 = *t*Bu

a (=195) where R^3 = Benzyl (85%)
b where R^3 = Me (90%)
c where R^3 = *t*Bu (99%)

***Scheme 64**: Synthesis of phthalimides.*

The first step involved the phthalimide protection of a carbazate **200** using phthalic anhydride to give a trisubstituted hydrazine **201**. This resulted in isolation of clean phthalimides after recrystalisation with yields ranging between 85-97% (Scheme **64**). The next step was the synthesis of propargylic alcohols **202** from the addition of lithioacetylides to aldehydes **185** to give the propargylic alcohols **202** cleanly (Scheme **65**) and in high yields (>90%).



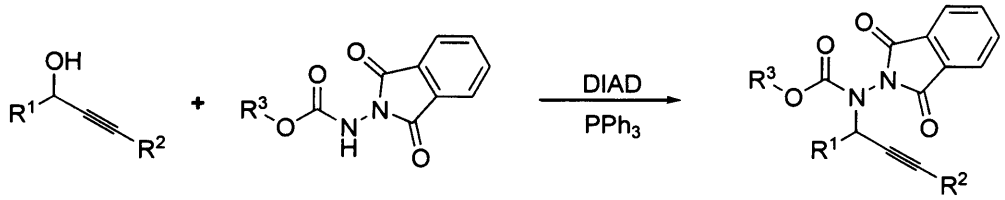
185a-b **202a-c**

a where R^1 = *i*Bu
b where R^1 = *i*Pr

a where R^1 = *i*Bu, R^2 = Bu (93%)
b (= 196) where R^1 = *i*Pr, R^2 = Bu (93%)
c where R^1 = *i*Pr, R^2 = Ph (96%)

***Scheme 65:** Synthesis of propargylic alcohols.*

This was followed by the key Mitsunobu coupling of a propargylic alcohol **202** and a phthalimide **201** to introduce the hydrazine functionality to give propargylic hydrazines **203** after chromatography with good yields ranging between 69-78% (Scheme **66**).

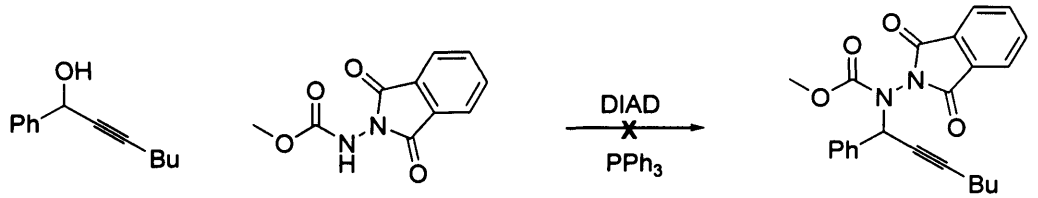


202 **201** **203a-c**

a where R^1 = *i*Bu, R^2 = Bu, R^3 = Me (69%)
b where R^1 = *i*Pr, R^2 = Bu, R^3 = *t*Butyl (78%)
c where R^1 = *i*Pr, R^2 = Ph, R^3 = Benzyl (76%)

***Scheme 66:** Mitsunobu Synthesis of propargylic hydrazines **203**.*

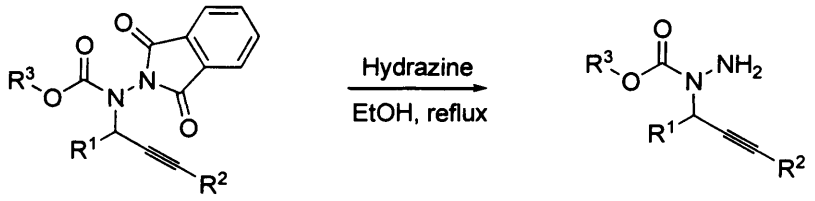
One significant limitation with this step were that attempted Mitsunobu coupling of the phthalimides **201b** with propargylic alcohol **204** with aromatic substituents in the β-position resulted in no product **205** being isolated and in complete recovery of starting material **201b** (Scheme **67**).



204 **201b** **205**

Scheme 67: *Failed Mitsunobu reaction*

The next step was the phthalimide deprotection by refluxing the hydrazines **203** with hydrazine hydrate in ethanol to give the free hydrazines **206** in around 1.5 h (Scheme **68**). Yields for this step ranged between 72-94%. The free hydrazines **206** were not purified but were used crude in the next step as they still contained small amounts of phthalimide residues and chromatography resulted in decomposition.



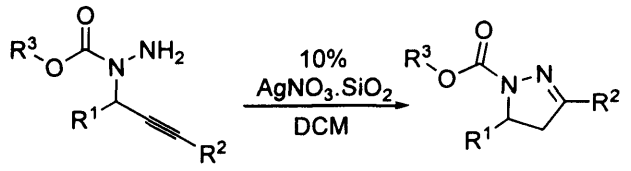
203a-c **206**

a where R^1 = *i*Bu, R^2 = Bu, R^3 = Me (86%)
b where R^1 = *i*Pr, R^2 = Bu, R^3 = *t*Butyl (72%)
c where R^1 = *i*Pr, R^2 = Ph, R^3 = Benzyl (94%)

Scheme 68: *Phthalimide deprotection using hydrazine hydrate.*

The key final step in the reaction involved the 5-*endo*-dig cyclisation of the free hydrazines **206** using catalytic (0.1 equivalents) 10% $AgNO_3.SiO_2$ which gave the 4,5-dihydropyrazoles **207** in high yields (83-96%).

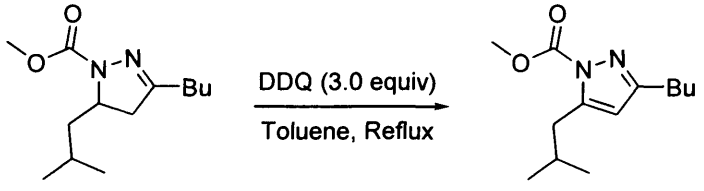
***Table 5:** Silver(I)-catalysed synthesis of 4,5-dihydropyrazoles.*



206 207

Hydrazine 206	R^1	R^2	R^3	4,5-Dihydropyrazole 207	Yield (%)
206a	*i*Bu	Bu	Me	**207a**	96
206b	*i*Pr	Bu	*t*Butyl	**207b**	83
206c	*i*Pr	Ph	Benzyl	**207c**	94

As can be seen, a small variety of 4,5-dihydropyrazoles **207a-c** were synthesised successfully and regioselectively allowing for the inclusion of alkyl groups in both positions three and five and for aromatic groups in position three. For all three examples above there was no oxidation to the pyrazole observed with only 4,5-dihydropyrazoles isolated. This is in stark contrast to Song's synthesis of pyrazoles from imines in which he obtained a mixture of pyrazole and dihydropyrazole (*cf.* Section **3.2.4**, Pg 51). The method has also allowed for benzyl, methyl and *tert*-butyl carbamates to be incorporated into the ring. Exposure of **207a** to three equivalents of DDQ in toluene[77] at reflux for 18 h resulted in oxidation of the 4,5-dihydropyrazole to pyrazole **208** in 71% yield (Scheme **69**). This indicated that the 4,5-dihydropyrazoles could be easily oxidised to the pyrazoles.



207a **208**

***Scheme 69:** Oxidation of **207a** using DDQ.*

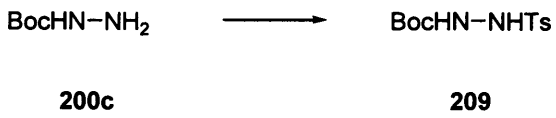
3.3.3 Limitations.

One particular issue associated with this chemistry was that aryl groups could not be introduced in the 5-position. Under the current conditions this resulted in complete recovery of starting phthalimide **201b** during the Mitsunobu step. Another issue with this methodology is that of

atom economy: The introduction of a large group such as phthalimide that has to be removed is very atom uneconomical, as is the use of excess reagents such as triphenylphosphine and DIAD during the Mitsunobu alkylation.

3.3.4 A change in hydrazine: hopes for a regioselective Mitsunobu.

Due to the issue associated with using phthalimide as a protecting group, it was decided that during my industrial placement at Glaxo-Smith-Kline in Stevenage, the phthalimide group would be abandoned and that a group that would not require removal such as tosyl would be incorporated. The new route would involve tosylation of *tert*-butyl carbazate **200c**. It was found that mono-tosylation could be achieved at -78 °C with 1.01 equivalents of pyridine and only one equivalent of *p*-toluenesulfonyl chloride to give clean tosylate **209** after recrystalisation typically in 75% yield (Scheme **70**).

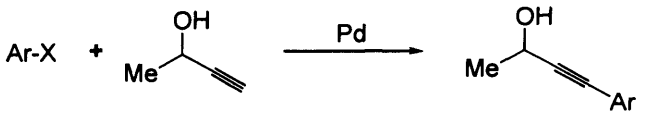


200c **209**

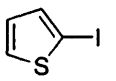
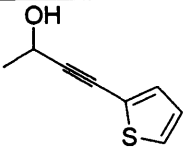
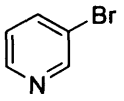
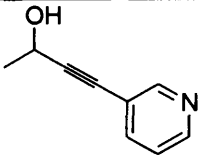
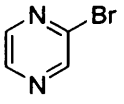
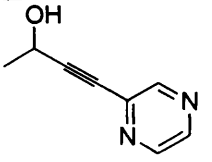
Scheme 70: *Tosylation of tert-butyl carbazate.*

A range of propargylic alcohols were then prepared with propargylic alcohol **210** (where R^1 = *i*Bu, R^2 = Ph) prepared by the lithioacetylide addition of phenylacetylene to isovaleraldehyde (*cf.* Table **8**, pg. 58 for structure). The remaining propargylic alcohols **213a**, **213b**, and **213c** were prepared by Sonogashira coupling of 3-butyn-2-ol **212** with aryl halides **211** (Table **6**).

Table 6: Synthesis of propargylic alcohols 213 by Sonogashira.



211 212 213

Ar-X	Alcohol 213	Yield (%)
 **211a**	 **213a**	70
 **211b**	 **213b**	66
 **211c**	 **213c**	78

This was then followed by Mitsunobu alkylation using the tosylate **209** and the propargylic alcohols. It was believed that the p*K*a difference between the NHTs and NHBoc groups of the hydrazine **209** would be different enough that the Mitsunobu reaction would proceed regioselectively at the more acidic *N*-tosyl nitrogen, to give a single product selectively. Although exact comparisons of NHTs and NHBoc for hydrazine **209** could not be made, a look at the Bordwell p*K*a table[61] allows for an interesting comparison between sulfonyl hydrazines and acyl hydrazines (Table 7).

Table 7: Bordwell pKa values of some common hydrazines.

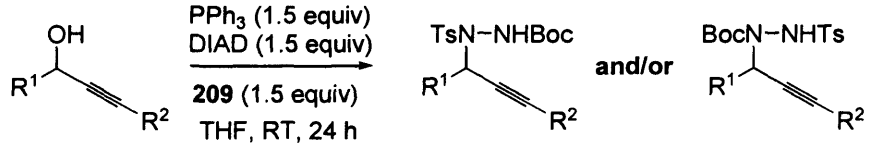
No	Substrate	pKa in DMSO
214	$PhSO_2N\mathbf{H}NH_2$	17.1
215	$EtO_2CN\mathbf{H}NH_2$	22.2
216	$AcN\mathbf{H}NH_2$	21.8
217	AcN**H**NHAc	16.7
218	$PhSO_2N\mathbf{H}_2$	16.1

The pKa values quoted are of the hydrogens in bold.

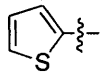
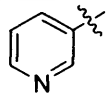
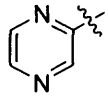
A direct comparison of the values for hydrazines **214**, **215** and **216** highlights that sulfonamide groups as predicted are more acidic than those of *N*-acetyl and *N*-CO_2Et. The sulfonamide **214** is 4.7 p*K*a units more acidic than *N*-acetyl **216** and 5.1 p*K*a units more acidic than ethylcarbazate **215**. Another interesting result is that the *bis*-acetyl hydrazine **217** has a p*K*a comparable to that of the sulfonamide. Having another electron withdrawing group such as that found in substrate **217** increases the overall acidity as expected. However, it was believed that the relative acidities when comparing a sulfonamide to an acyl or a carbamate group should not change. Another interesting point is that upon comparing the sulfonamide of a hydrazine **214** with that of an amine **218** it seems that the differences between the p*K*a of the mono-substituted hydrazines and mono-substituted carbamates is small.

These results are of course for solutions in dimethylsulfoxide and although results may change in tetrahydrofuran, they should remain qualitatively the same. With these results in mind it is believed that the Mitsunobu alkylation should occur preferentially on the more acidic NHTs as opposed to the NHBoc of the hydrazine **209**.

***Table 8**: Mitsunobu alkylation of hydrazine **209** with propargylic alcohols.*



202, 210, 213 **219**

Alcohol	R^1	R^2	Hydrazine 219	Yield (%)
202a	*i*Bu	Bu	**219a**	91
210	*i*Bu	Ph	**219b**	59
213a	Me		**219c**	44
213b	Me		**219d**	44
213c	Me		**219e**	12

Although the yields of some of the Mitsunobu alkylations (Table **8**) were low only a single product was isolated with the remaining material recovered being starting materials. The question was which nitrogen was alkylated: the *N*-tosyl or the *N*-Boc group? It was believed as previously mentioned that alkylation should occur at the more acidic nitrogen, this being the *N*-tosyl nitrogen. Unfortunately this could not be determined by 1D or 2D NMR, but could be determined by X-ray crystallography. Fortuitously, both products **219a** and **219b** were recrystallised to give ideal crystals for X-ray analysis. It was found that alkylation for hydrazine **219a** occurred on the *N*-tosyl only as predicted as can be seen in the X-ray crystal structure in Figure **8** and has an R-value of 0.0467 (*cf.* Appendix for X-ray crystal data, data can also be found in the Cambridge structure database[78] CCDC No:783430).

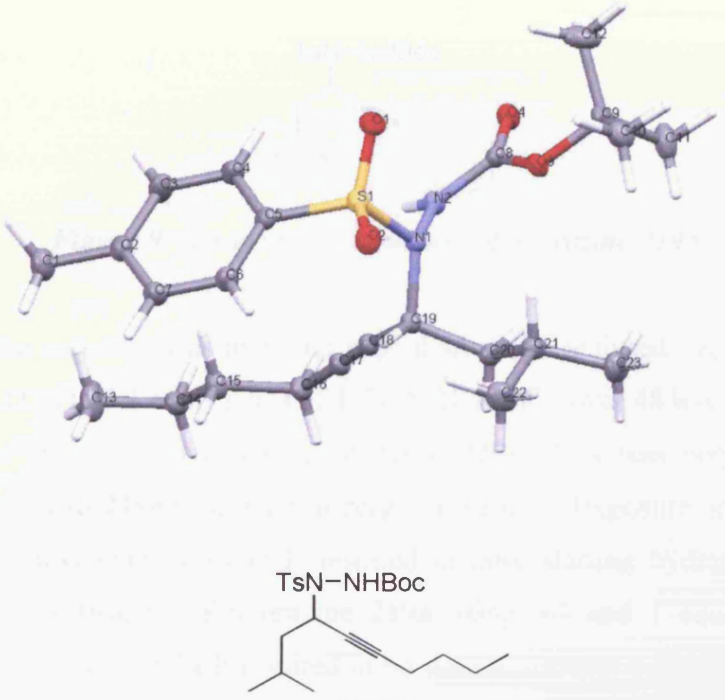


Figure 8: *X-ray crystal structure of hydrazine* ***219a****.*

Equally the X-ray crystal structure of hydrazine **219b** in Figure **9** (*cf.* Appendix for X-ray crystal data, CCDC No[78]: 783431, R-value = 0.0537) showed that Mitsunobu alkylation also occurred on *only* the *N*-tosyl group as predicted, thus confirming the regioselectivity of the alkylation.

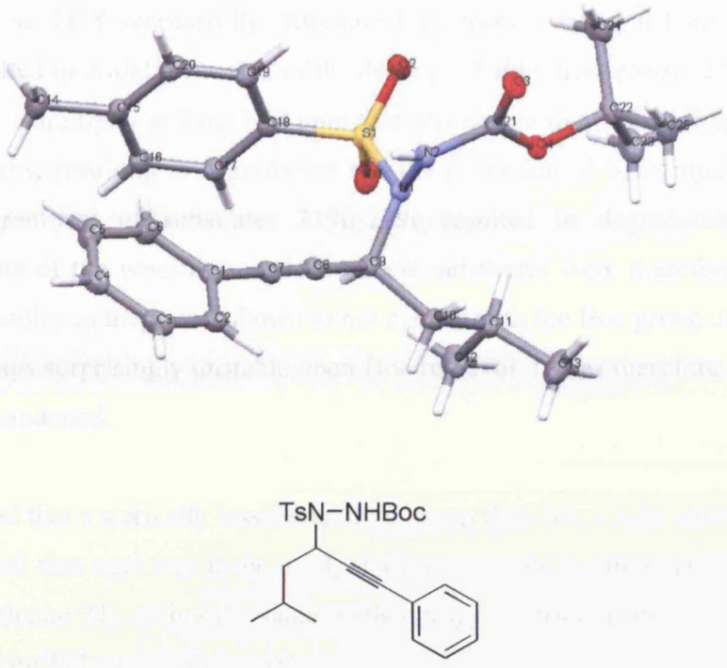
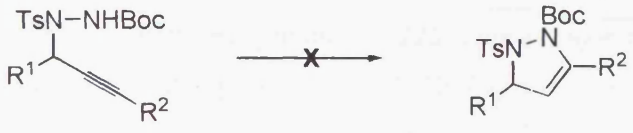


Figure 9: *X-ray crystal structure of hydrazine* ***219b****.*

The next step in the sequence was to be the central silver(I)-catalysed cyclisation of substrates **219**. Exposure of **219a** to 0.1 equivalents of 10% $AgNO_3.SiO_2$ over 48 h resulted in no pyrazole being formed and only recovered starting material **219a**. This was very disappointing and similarly substrates **219b-219e** would not undergo cyclisation. Exposure of substrate **219a** with 1, 2 and even 3 equivalents of silver(I) resulted in only starting hydrazine **219a** recovery. Equally, attempted cyclisation of hydrazine **219a** using 0.1 and 1 equivalents of silver(I) trifluoromethanesulfonate over 24 h resulted in no desired product being detectable but mainly hydrazine **219a** (Scheme **71**) together with a small amount of indistinguishable products. Attempted iodocyclisation of hydrazine **219a** resulted in only starting material being isolated.



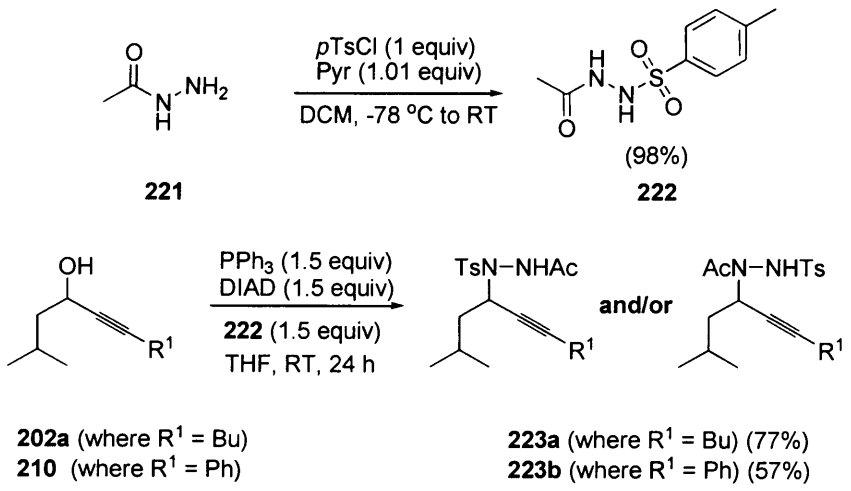
219 **220**

Scheme 71: *Unsuccessful cyclisation of hydrazines* ***219****.*

These results were disappointing but a possible explaination for this was that the hydrazines **219** were too sterically hindered for the silver(I) to access the acetylene moiety. It was also possible that the cyclised product would be thermodynamically unfavourable due to steric

impact. A possible solution to the problem of sterics was the removal of the Boc-group; this was achieved using 20% trifluoroacetic acid in dichloromethane. Boc removal of substrate **219a** gave free hydrazine **219f** successfully. Attempted cyclisation using 0.1 equivalents of 10% $AgNO_3.SiO_2$ resulted in initial formation of the desired 4,5-dihydropyrazole **220** as indicated by the appearance of a multiplet at 3.62-3.58 ppm that was due to the C-5 hydrogen, however, the product was unstable resulting in degradation and the formation of indistinguishable products. Attempted Boc removal of substrates **219b-219e** resulted in degradation with possible detosylation as one of the possible reactions. These substrates were therefore not suitable as precursors to pyrazoles as they were shown to not cyclise with the Boc group attached and were shown to be perhaps surprisingly unstable upon Boc removal. It was therefore decided that this route was to be abandoned.

It was then decided that a sterically less demanding group than Boc could allow for cyclisation. It was then decided that acyl was to be used, starting from the commercially available acetyl hydrazide **221** (Scheme **72**). Using the same methodology mono-tosylation of acetic hydrazide **221** gave the tosylate **222** successfully (98% yield).



***Scheme 72**: Mitsunobu alkylation using tosylate 222.*

Similarly to the Mitsunobu alkylation using hydrazine **222**, only a single product was isolated when R^1 = butyl (77%) **223a** and R^1 = phenyl (57%) **223b**. Crystallisation followed by X-ray analysis of **223a** (*cf.* Appendix for X-ray crystal data, CCDC No[78]: 783434, R-value = 0.0586) showed the single product was that of Mitsunobu alkylation on the *N*-tosyl nitrogen (Figure **10**), indicating that these alkylations showed identical regioselectivity to the previous examples **219a** and **219b**.

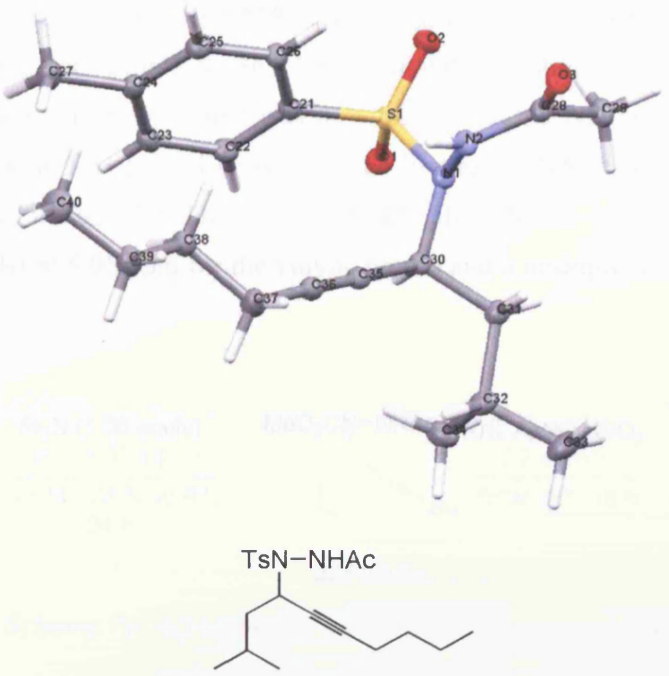
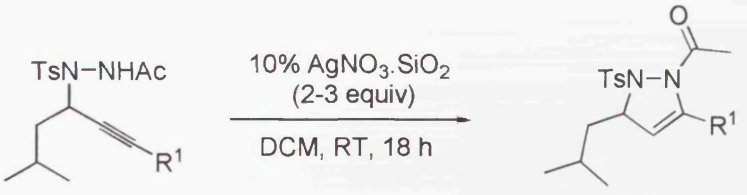


Figure 10: *X-ray crystal structure of hydrazine* ***223a****.*

Exposure of substrate **223a** to 3 equivalents of 10% $AgNO_3.SiO_2$ over 18 h and exposure of substrate **223b** to 2 equivalents of silver(I) over 18 h gave 2,5-dihydropyrazoles **224a** (R^1 = Bu, 50% yield) and **224b** (R^1 = Ph, 40% yield) cleanly after column chromatography with the remaining material recovered being starting material (Scheme **73**). This was in stark contrast to substrates **219a-219f** which would not undergo 5-*endo*-dig cyclisation upon exposure to silver(I).



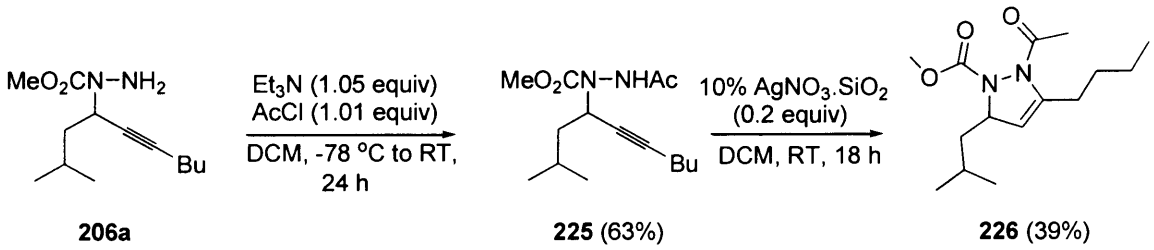
223a (R^1=Bu)
223b (R^1=Ph)

224a (R^1=Bu) (50%)
224b (R^1=Ph) (40%)

Scheme 73: *Cyclisation of substrates* ***223a*** *and* ***223b****.*

As a comparison with hydrazines **223a** and **223b**, hydrazine **206a** was acylated using acetyl chloride and triethylamine at -78 °C to give the acylated hydrazine **225** in a good yield (63%) after column chromatography (Scheme **74**). As with all the carbamate protected propargylic hydrazines, the hydrazine **225** was rotomeric with three separate rotomers out of the four rotomers separating out. This could be seen by the three NH peaks at 7.11 ppm (2 rotomers by integration), 7.00 ppm (one rotomer) and 6.89 ppm (one rotomer), aswell as three methoxy

peaks at 3.82 ppm (one rotomer), 3.79 ppm (one rotomer) and 3.76 (two rotomers by integration) being detectable by ^{1}H-NMR analysis (Figure **11**) at 300 kelvin in deuterated chloroform. Heating the sample to 367 Kelvin in DMSO showed that the rotomers had converged and only a single compound was detectable, with the NH peak at 9.43 ppm and a broad methoxy peak at 3.63 ppm. Exposure of the hydrazine **225** to 0.2 equivalents of 10% $AgNO_3.SiO_2$ resulted in clean 2,5-dihydropyrazole **226** after 18 h as detected by the appearance of an apparent singlet at 5.05 ppm for the vinylic proton and a multiplet around 4.64-4.58 ppm for the 5-H proton.

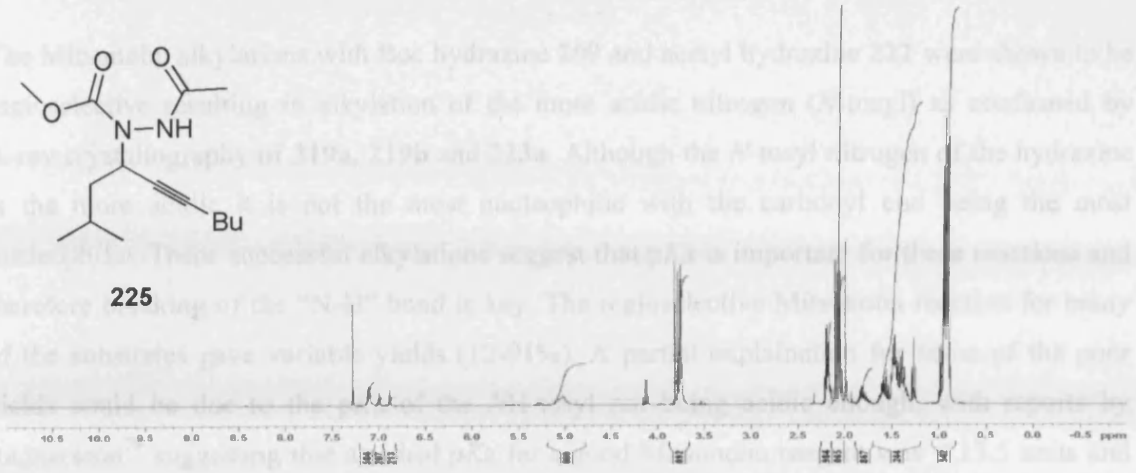


206a **225** (63%) **226** (39%)

Scheme 74: *Acylation and catalytic cyclisation of* ***206a****.*

Column chromatography resulted in isolation of the dihydropyrazole **226** in 39% yield with the remainder being recovered starting material **225**.

Hydrazine **225** at 300 K (in chloroform):



Hydrazine **225** at 367 K (in DMSO):

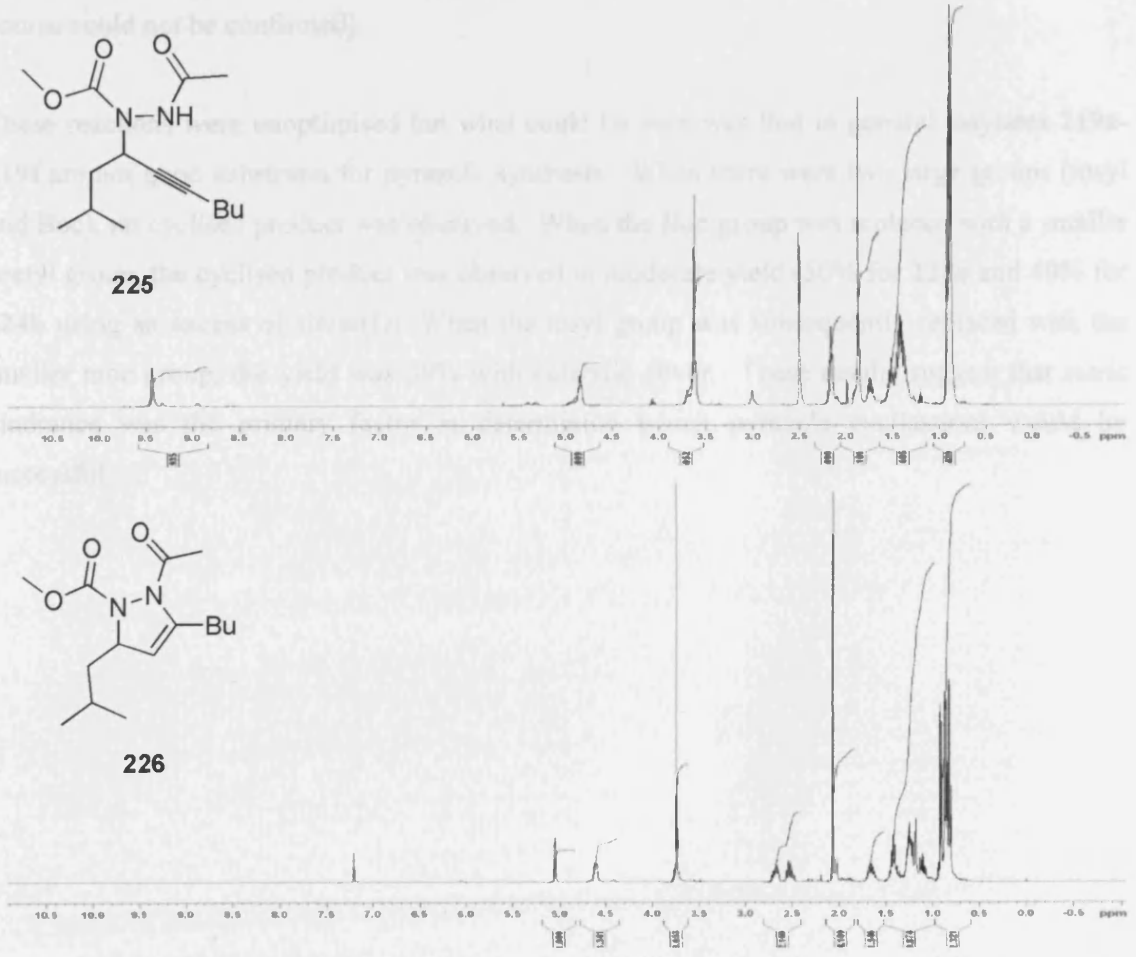


Figure 11: *^{1}H-NMR comparison of starting hydrazine **225** at 300 k and 367 k and of dihydropyrazole **226** at 300 k.*

3.4 Conclusions.

The Mitsunobu alkylations with Boc hydrazine **209** and acetyl hydrazine **222** were shown to be regioselective resulting in alkylation of the more acidic nitrogen (*N*-tosyl) as confirmed by X-ray crystallography of **219a**, **219b** and **223a**. Although the *N*-tosyl nitrogen of the hydrazine is the more acidic it is not the most nucleophilic with the carbonyl end being the most nucleophilic. These successful alkylations suggest that p*K*a is important for these reactions and therefore breaking of the "N-H" bond is key. The regioselective Mitsunobu reaction for many of the substrates gave variable yields (12-91%). A partial explaination for some of the poor yields could be due to the p*K*a of the *N*H-tosyl not being acidic enough, with reports by Ragnarsson[79] suggesting that an ideal p*K*a for a good Mitsunobu reagent was < 13.5 units and perhaps the p*K*a of the hydrazines **209** and **222** were somewhat above this (although this of course could not be confirmed).

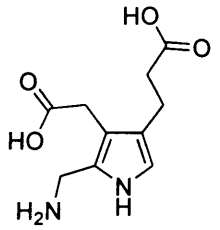
These reactions were unoptimised but what could be seen was that in general tosylates **219a-219f** are not good substrates for pyrazole synthesis. When there were two large groups (tosyl and Boc), no cyclised product was observed. When the Boc group was replaced with a smaller acetyl group, the cyclised product was observed in moderate yield (50% for **224a** and 40% for **224b** using an excess of silver(I)). When the tosyl group was subsequently replaced with the smaller moc group, the yield was 39% with catalytic silver. These results suggest that steric hindrance was the primary factor in determining which pyrazole cyclisations would be successful.

Chapter Four

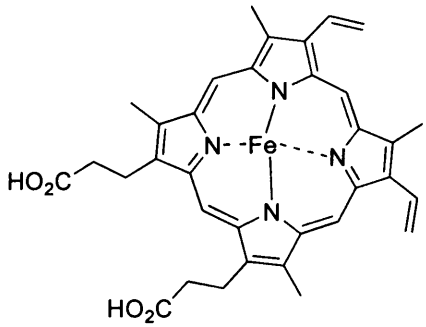
Pyrroles

4.1 Introduction

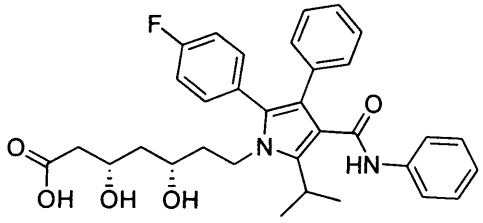
Pyrroles are an important class of compounds in the context of this thesis and in Nature, forming the components of large macrocycles known as porphyrins such as those found in chlorophyll which is made in plants from succinyl-CoA and glycine.[80a] This light harvesting porphyrin provides the basis for the majority of life on Earth and gives the Earth its luscious green colour. Another important porphyrin is heme which is made from the trisubstituted pyrrole Porphobilinogen **227** (Figure **12**) by a series of enzymatic processes, and is responsible for all mammalian life on earth by its efficient transfer of oxygen to tissue for the conversion of sugars such as glucose to energy by total oxidation.[80b] Due to the highly conjugated nature of porphyrins they have intense absorptions in the visible region and hence are intensly coloured, Examples include heme B **228** which is deep red in colour. Due to their importance and prevalence in nature porphyrins are also important to the synthetic chemist. Pyrrole also forms the core of many important biologically active pharmacophores.



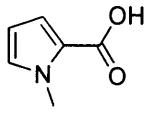
227 Porphobilinogen



228 Heme B



229 Atorvastatin

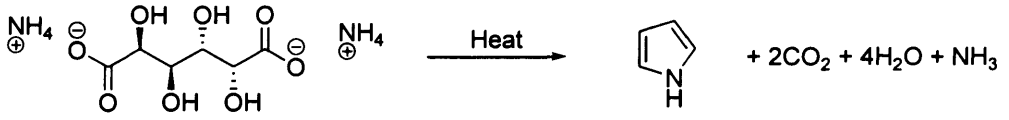


230 *N*-Methyl-pyrrole 2-carboxylic acid

Figure 12: *Some important pyrroles.*

A number of important pyrroles include the current number one selling drug Atorvastatin commercially known as Lipitor **229**,[80c] a statin used to lower cholesterol by acting as a competitive inhibitor of the enzyme HMG-CoA in man. Another important pyrrole is *N*-methyl pyrrole carboxylic acid **230** which is an important building block in the pharmaceutical industry along with many others.

Pyrrole itself is a clear colourless oil with any colour being attributed to impurities such as polypyrroles, and is produced industrially by the reaction of furan with ammonia in the presence of solid phase acid catalysts.[80d] Another synthetic route to pyrrole involves the thermal decarboxylation of ammonium mucate **231** (Scheme **75**) to give pyrrole **232**.



Scheme 75: *Synthesis of pyrrole from the decarboxylation of ammonium mucate **231**.*

When considering the synthesis of pyrroles it can be seen that there are various possibilities to build the skeleton, although there are mainly four types that are commonly used (Figure **13**).

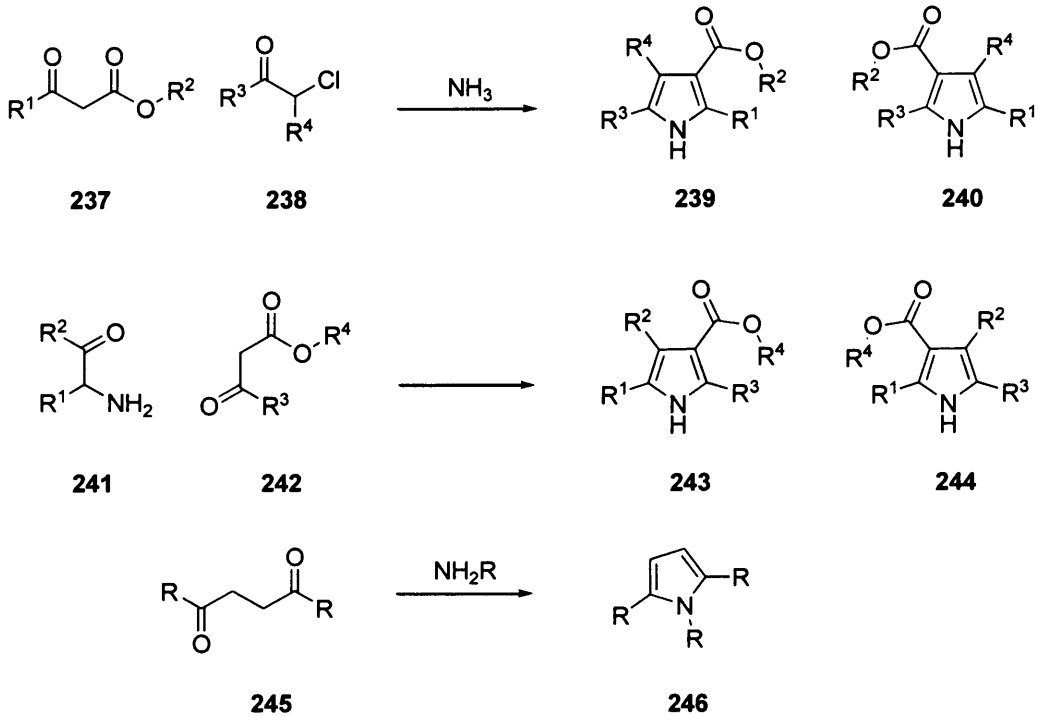
Figure 13: *Possible double disconnections for the synthesis of pyrroles.*

4.2 Literature methods

4.2.1 Some classical methods

A few classical methods for the synthesis of pyrroles are available: these include the Hantzsch,[81] Knorr[82] and the Paal-Knorr[83] pyrrole syntheses (Scheme **76**). All of these reactions involve the condensation of an amine with a ketone to form an imine that then tautomerises to the corresponding enamine. This is usually then followed by cyclisation and finally dehydration to the pyrrole. In the case of the Hantzsch synthesis, the disconnection **235** (Figure **13**) involves β-keto esters **237**, ammonia or amines and α-halo ketones **238** as reactants to give pyrroles **239** and **240**. The Knorr pyrrole synthesis uses the same disconnection but involves the reaction between an α-amino ketone **241** and a ketone **242** to give pyrroles **243** and **244**. The Paal-Knorr method uses a different disconnection approach **233** and involves the condensation of a 1,4-dicarbonyl **245** with ammonia or a primary amine to give pyrroles **246**. All these methods have their limitations. One common issue with these "textbook" methods is a requirement for an ester or similar electron-withdrawing group around the ring. In the case of the Knorr pyrrole synthesis, this helps reduce the self condensation of α-amino ketones. Another issue is the

difficulty in preparation of the starting materials and this can often be a limitation to the chemistry.



237 238 239 240

241 242 243 244

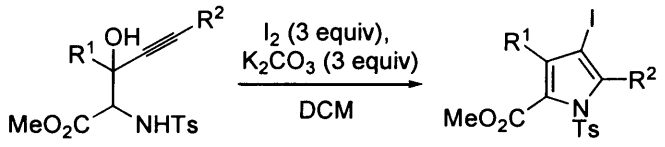
245 246

Scheme 76: Hantzsch, Knorr and Paal-Knorr pyrrole synthesis.

Due to the limitations of these methods, additional routes to pyrroles are of great importance There are a number of less well known methods to synthesise pyrroles that provide a broader applicability and which have been used to synthesise a number of important synthetic targets that in many cases would be inaccessible by these classical methods.

4.2.2 Iodocyclisation

Knight's successful iodocyclisation of furan precursors[84] led to an interest in the possible cyclisation of 2-alkynyl-2-hydroxy-1-sulfonamides **247** to give pyrroles (Scheme 77). The reactions proceeded successfully to give 3-iodopyrroles **248** regioselectively and in high yields (65-85%).[85] The downside of this chemistry was the requirement for a large amounts of iodine (3 equivalents), making the reaction atom inefficient.



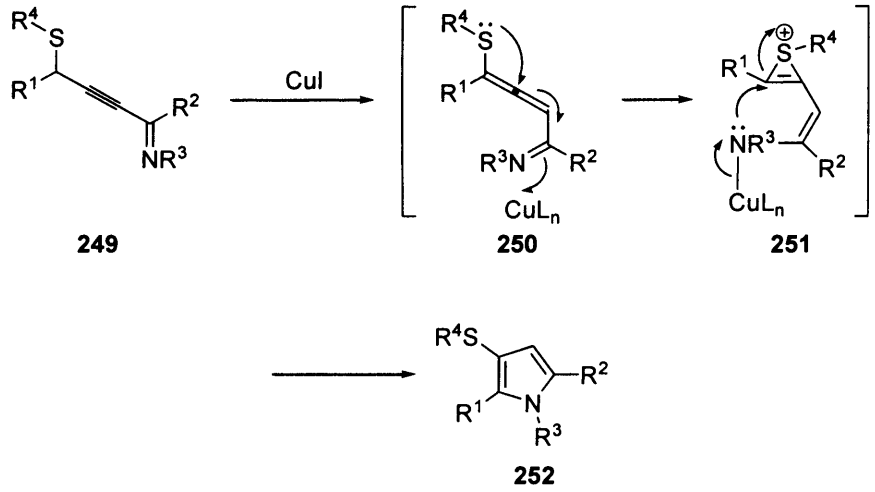
247 **248**

Scheme 77: Iodocyclisation of 3-alkyne-2-hydroxy-1-sulfonamides.

The benefit of this chemistry is that iodine is cheap and a range of chemistry can be carried out at iodine, for example, palladium-catalysed cross coupling reactions could be carried out between the 3-iodopyrrole and a vinyl or aryl group to give fully substituted pyrrole derivatives.

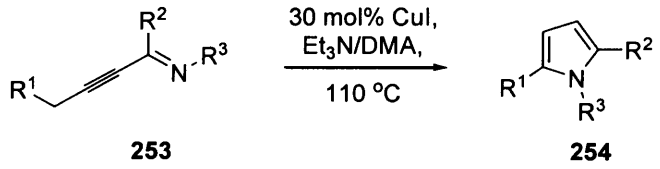
4.2.3 Metal-catalysed pyrrole synthesis

Gevorgyan and coworkers[86] reported the synthesis of pyrroles **252** by heating a mixture of propargyl imine **249** and catalytic copper(I) iodide in *N,N*-dimethylacetamide (Scheme **78**). The key step in the reaction is believed to be the 1,2-migration of SR^4 from the sp^2 centre in the allenyl intermediate **250** to give the intermediate **251**. The nucleophilic nitrogen then attacks the episulfenium ion **251** and subsequently forms the pyrrole **252**.



Scheme 78: *Gevorgyan's copper(I) iodide catalysed synthesis of pyrroles from alkynyl imines.*

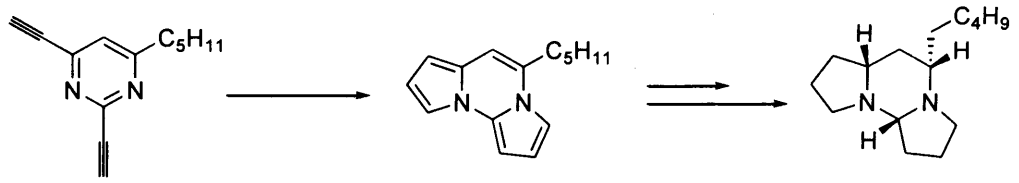
Similarly, Gevorgyan and co-workers[87] showed the successful cyclisation of acetylenic imines **253** using 30 mol% copper iodide in a mixture of triethylamine and dimethylacetamide at 110 °C to give pyrroles **254** with yields ranging between 50-93% (Scheme **79**).



Scheme 79: *Synthesis of pyrroles **254** from propargylic imines **253**.*

It was revealed by mechanistic studies that the reaction proceeded *via* isomerisation of the propargyl imine to give the corresponding allenyl imine. This was followed by nucleophilic

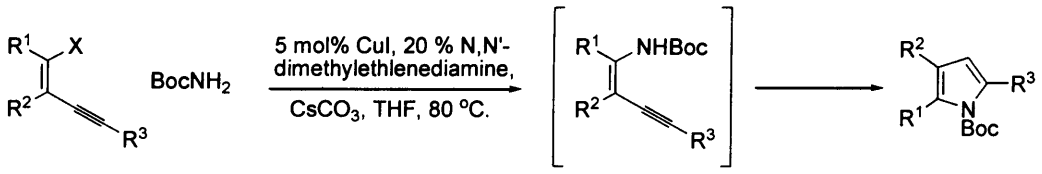
attack of the imine nitrogen onto the electron deficient carbon of the allene, isomerisation and protonation or possible [1,5]-hydride shift along with regeneration of the copper catalyst. This method has been used in the highly diastereoselective synthesis of (+/-)-tetraponerine T6 **256** from diyne **255**[88] using copper(I) bromide instead of copper(I) iodide as catalyst (Scheme **80**).



255 **256**

Scheme 80: *Application of Gevorgyan's pyrrole synthesis towards (+/-)-tetraponerine T6.*

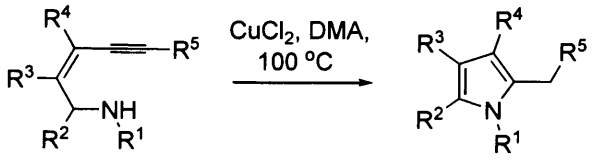
Buchwald and coworkers[89] reported the synthesis of 2,4,5-trisubstituted pyrroles **259** from the reaction between halo-enynes **257** and *t*-butyl carbamate **258** by substitution in the presence of 5 mol% copper(I) iodide, N,N'-dimethylethylenediamine and cesium carbonate (Scheme **81**). The reaction gave pyrroles with yields in the range 52-92%. A limitation of the reaction is that terminal alkynes would not react to give α-unsubstituted pyrroles.



257 **258** **259**

Scheme 81: *Buchwald's synthesis of substituted pyrroles using copper(I) iodide.*

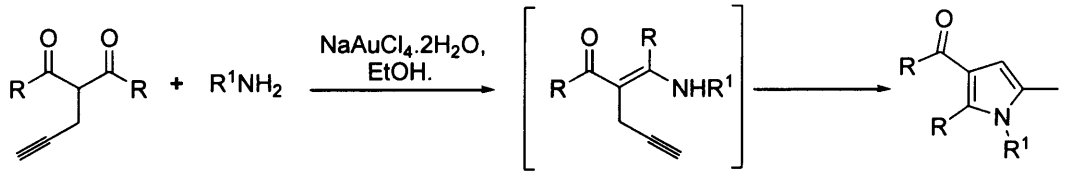
Gabriele and co-workers[90] reported the cyclisation of (*Z*)-(2-en-4-ynyl)amines **260** using copper(II) chloride and dimethylacetamide to give, in particular, C-3 substituted pyrroles **261** (Scheme **82**) in good to excellent yields (63-91%). Another interesting observation was that for C-3 unsubstituted pyrroles, copper(II) chloride was not the best choice, but replacement with palladium(II) chloride and in the presence of potassium iodide gave C-3 unsubstituted pyrroles in good yields.



260 **261**

Scheme 82: *Gabriele and coworkers synthesis of C-3 substituted pyrroles.*

Gold has also proven to be a good catalyst for the synthesis of pyrroles. An example of this can be seen in the successful cyclisation of 2-propynyl-1,3-dicarbonyl **262** compounds with primary amines **263** using a gold(III) catalyst (Scheme **83**).[91] The reaction involves the initial formation of an imine followed by tautomerisation to give the enamine **264**. This was then followed by a gold(III)-catalysed 5-*exo*-dig cyclisation to give 3-carbonylpyrroles **265**. The yields of the reaction were moderate to excellent (49-100%).

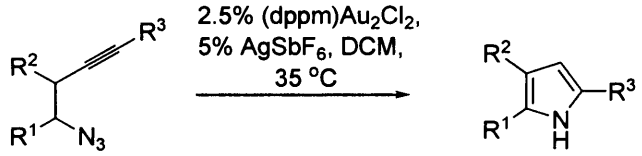


262 **263** **264** **265**

Scheme 83: *Synthesis of pyrroles from amines and 2-propynyl-1,3-dicarbonyls.*

The limitation of this chemistry is the issue of regioselectivity with the reaction often requiring symmetrical 1,3-dicarbonyls. The reaction was also only carried out with terminal alkynes resulting in a methyl in the 5 position of the pyrrole product **265**.

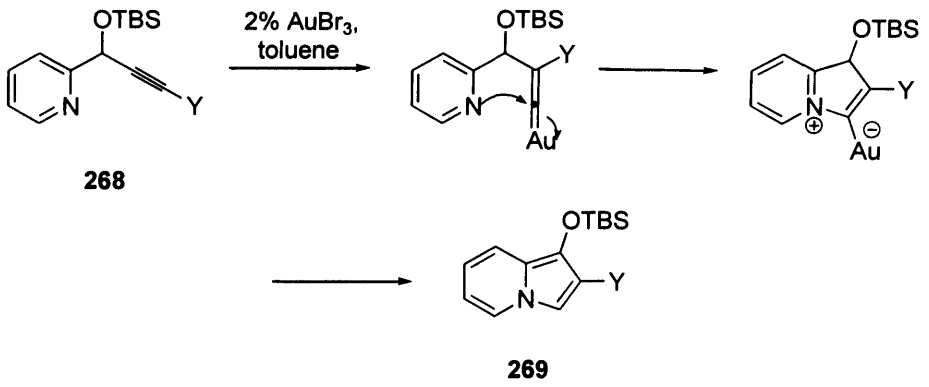
Similarly Toste and co-workers[92] used both gold(I) and silver(I) to catalyse the intramolecular acetylenic Schmidt-type reaction (Scheme **84**) of homopropargyl azides **266** under mild conditions to give pyrroles **267** in moderate to excellent yields (41-93%).



266 **267**

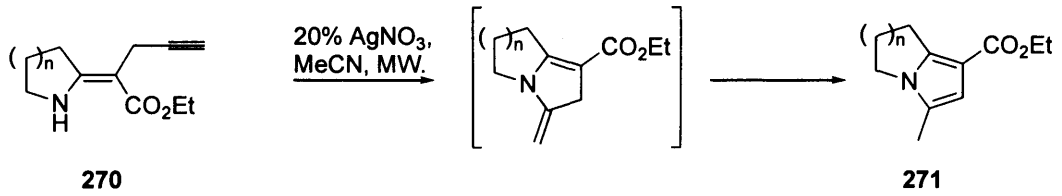
Scheme 84: *Synthesis of pyrroles from homopropargyl azides.*

Gold(III) has also been used to synthesise *N*-fused pyrrole derivatives **269** from pyridine-2-propargylic silyl-ethers **268** (Scheme **85**).[93] The reaction involves the cascade isomerisation of the propargylic derivative resulting in a vinyl carbene complex, with 1,2-migration of the "Y" group followed by nucleophilic attack of the pyridine nitrogen onto the allene and subsequent 1,2-hydride shifts to give the C-2 substituted fused pyrroles **269** in good to excellent yields (63-92%). The poorest result was found when Y = trimethylsilyl and the best result was seen when Y = $GeMe_3$.



Scheme 85: *Gold(II)-catalysed synthesis of N-bridgehead pyrroles.*

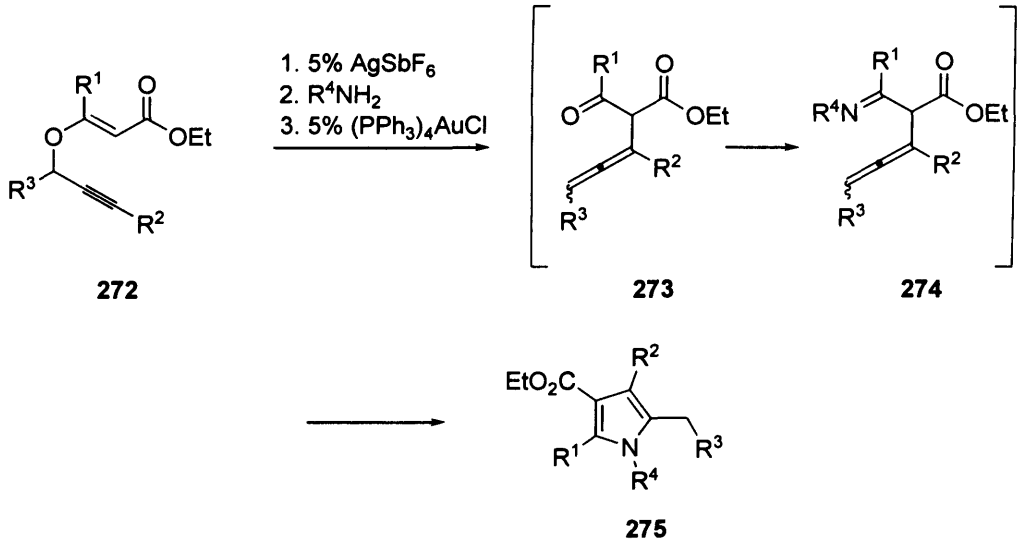
Similarly, Dovey and coworkers[94] reported the synthesis of *N*-bridgehead pyrroles **271** of the type shown (Scheme **86**) via the silver(I)-catalysed intramolecular hydroamination of amino alkynes **270** using microwave irradiation.



Scheme 86: *Synthesis of pyrrolizines by Dovey and coworkers.*

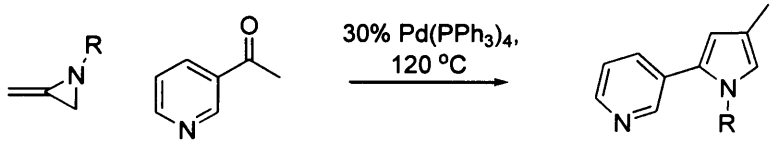
The reaction involves a 5-*exo*-dig cyclisation and proceeds *via* an intermediate that undergoes tautomerisation to give the pyrrolizine. Yields for the reaction are good resulting in pyrrolizines with yields in the range of 71-75%. There are a few other methods to synthesise *N*-bridgehead pyrroles, these include: using a mixture of gold(III) chloride and silver trifluoromethansulfonate to facilitate cyclisation of β-alkynyl ketones and amines[95] and [1,3]-dipolar cycloadditions between an azomethine ylide and a dipolarophile.[96]

Kirsch and coworkers[97] have carried out the one-pot synthesis of pyrroles from propargyl vinyl ethers **272** and aromatic amines using a mixture of silver(I) and gold(I). The reaction is effectively a silver(I)-catalysed Claisen rearrangement **273** followed by amine condensation **274** and finally gold(I)-catalysed 5-*exo*-dig heterocyclisation to give the pyrrole-3-carboxylate **275** (Scheme **87**).



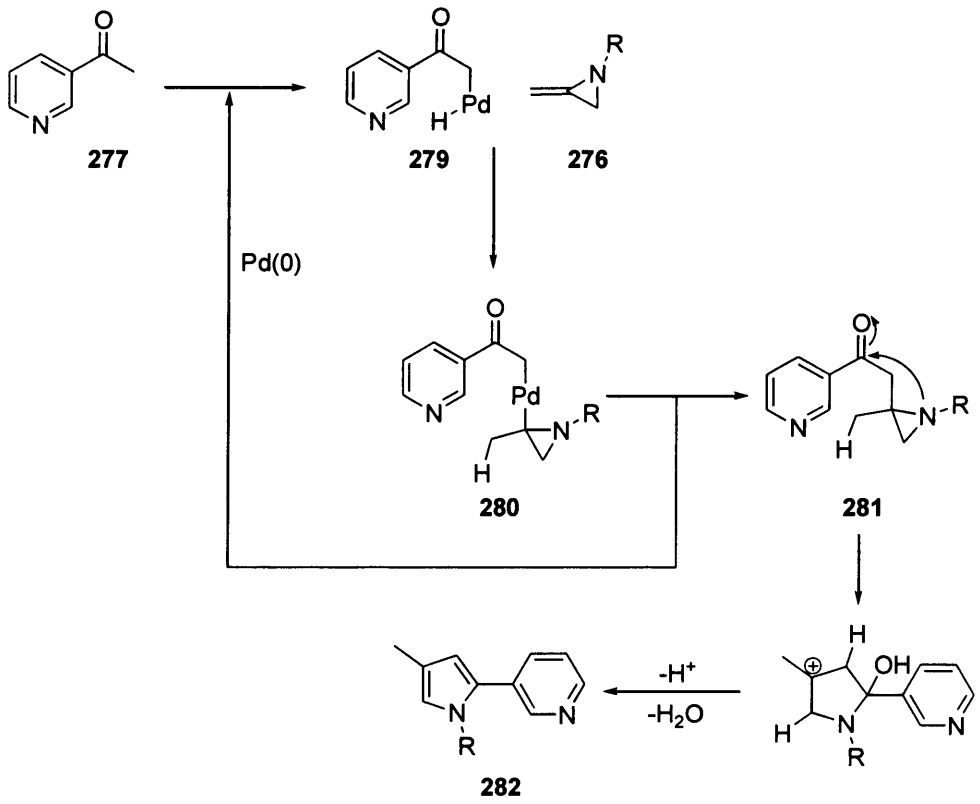
Scheme 87: *Kirsch and co-workers synthesis of pyrroles from propargyl vinyl ethers.*

Palladium has also found uses for the catalytic synthesis of pyrroles **278**. An example is the reaction between methyleneaziridines **276** and *o*, *p* or *m*-acetylpyridines **277** (Scheme **88**).[98]



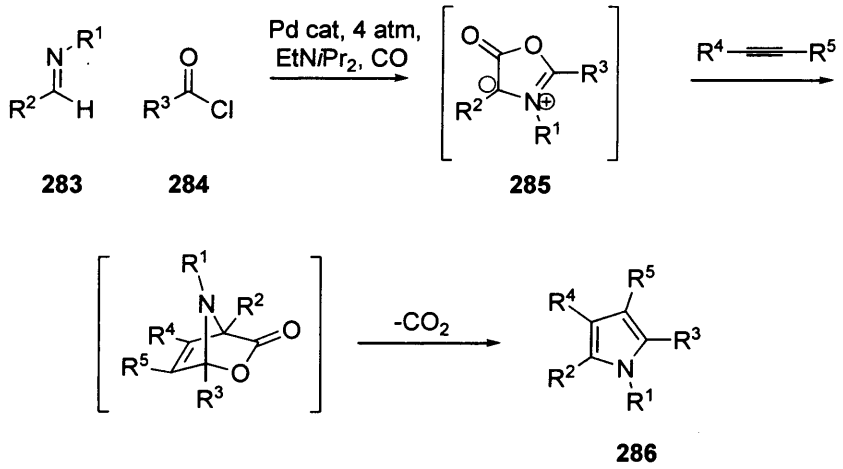
Scheme 88: *Palladium catalysed synthesis of 4-methyl pyrrole-2-pyridines.*

The mechanism (Scheme **89**) is believed to begin with oxidative insertion of palladium(0) into the α-CH bond of the acetyl pyridine **277** to give the hydridopalladium **279**. This is then followed by hydropalladation **280** between the hydridopalladium **279** species and the methyleneaziridine **276**. This is then followed by reductive elimination of the palladium species to give palladium(0) and an intermediate **281** which undergoes cyclisation and dehydration to give the pyrrole **282**.



Scheme 89: *Palladium-catalysed cycle for the synthesis of pyrrole-2-pyridines.*

Another example of a palladium-catalysed multi-component reaction involves the coupling of alkynes, imines and acyl chlorides (Scheme **90**).[99] The reaction involves the initial formation of a 1,3-oxazolium-5-oxide **285** which is formed from the coupling of the imine **283**, acyl chloride **284** and carbon monoxide catalysed by palladium. The 1,3-oxazolium-5-oxide **285** then undergoes cycloaddition with an alkyne to form the pyrrole **286** after loss of carbon dioxide.

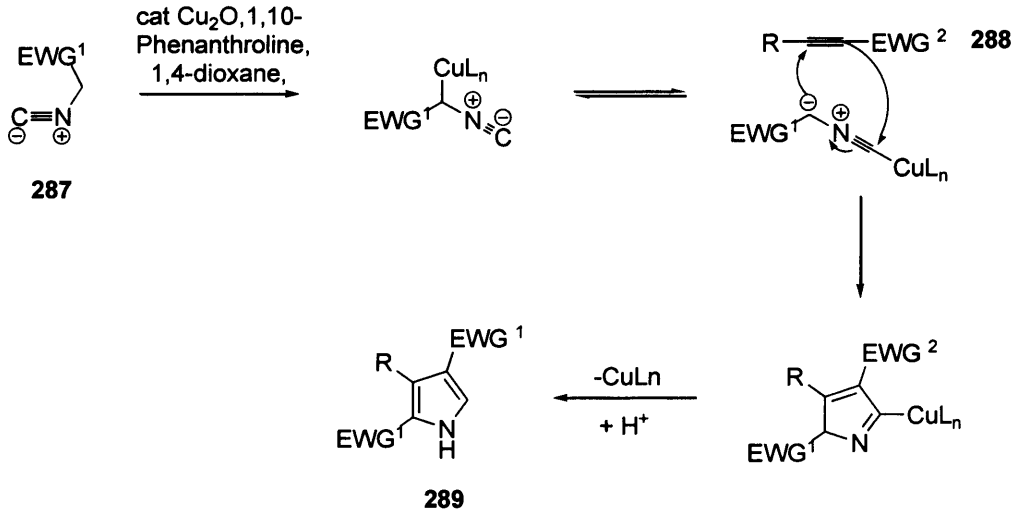


Scheme 90: *Palladium catalysed multi-component coupling involving a cycloaddition.*

Other methods include the titanium-catalysed intermolecular hydroamination of 1,4-diynes and 1,5-diynes with primary amines,[100] followed by 5-*endo*-dig and 5-*exo*-dig cyclisations respectively to give 1,2,5-substituted pyrroles in good to excellent yields.

4.2.4 Synthesis from isocyanides.

Examples of syntheses of pyrroles from isocyanides also often involve the use of metals. One example uses copper(I) oxide[101] in the reaction between an isocyanide **287** with an electron withdrawing substituent such as a carboxylate group β to the isocyano group and an alkyne **288**, also with an electron withdrawing substituent (Scheme **91**). A mixture of copper(I) oxide and 1,10-phenanthroline gave the best results.

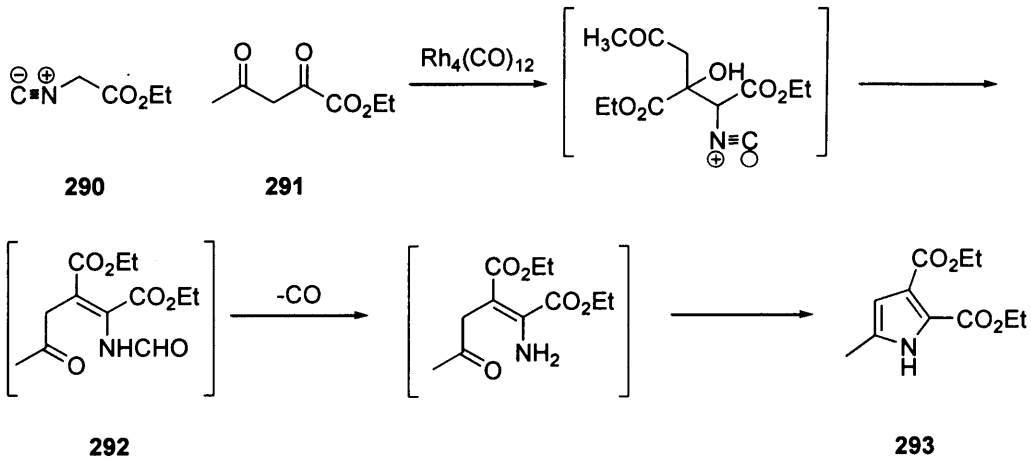


***Scheme 91**: Copper(I)-catalysed synthesis of pyrroles from isocyanides and alkynes.*

The reaction involves the 1,4-addition of a nucleophilic intermediate to the alkyne **288**. The copper enolate that is formed then intramolecularly attacks the isonitrile carbon to generate the cyclised intermediate. This is then followed by isomerisation and protonation along with regeneration of the copper catalyst to give the pyrrole **289** in good to excellent yields (79-100%).

Another synthesis of pyrroles from isocyanides was reported by Murahashi and coworkers (Scheme **92**).[102] The reaction involves a rhodium-catalysed pyrrole formation from isonitriles **290** and 1,3-dicarbonyl compounds **291**. This involves activation of the α-H bond of the isonitrile followed by addition to the 1,3-dicarbonyl to give the α,β-unsaturated formamides **292**. The rhodium then catalyses the decarbonylation of the formamide followed by

cyclocondensation to give the pyrrole **293**. Much like the Knorr pyrrole synthesis this method is also limited by the availability of starting materials.



290 **291** **292** **293**

Scheme 92: *Murahashi's Rhodium-catalysed synthesis of pyrroles from isocyanides.*

4.3 Pyrroles: Results and Discussion

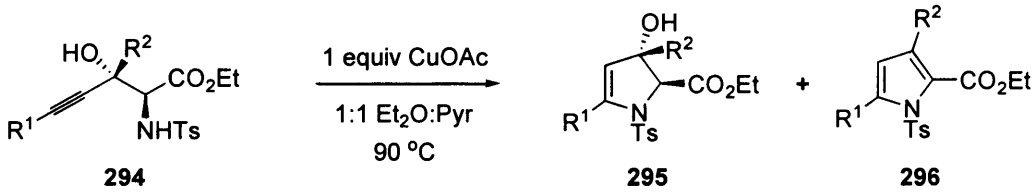
4.3.1 Aims

Due to the successful synthesis of substituted pyrrole-2-carboxylates and the hydroxydihydropyrrole analogues reported by Sharland[2] requiring extreme and somewhat impractical reaction conditions (*cf.* following Section **4.3.2.1**), it was deemed wise to improve the methodology to provide a more practical means to synthesise such pyrroles. This would then provide an opportunity to extend the chemistry to a wider range of substrates including ones without carboxylate groups in the 2 position. It was also prudent to determine whether other *N*-protecting groups can be incorporated as only *N*-tosyl was tested during the original studies. Other aims include the extension of the 5-*endo*-dig cyclisation using transition metal salts to fused ring systems such as annulated pyrroles including tetrahydroindoles and to *N*-junction fused systems such as pyrrolizines. Attempts were also made to extend the cyclisation methodology to a synthesis of the natural product pyrrolostatin.

4.3.2 Copper(II)-catalysed 5-*endo*-dig cyclisation

4.3.2.1 Sharlands original method

The main focus of this project was to improve on Sharland's procedure for the copper(I)-catalysed synthesis of pyrroles. Sharland's method involved the heating of a solution of β-hydroxyamino ester **294** and copper(I) acetate in a mixture of diethyl ether:pyridine (1:1) at 90 °C in a sealed tube (Scheme **93**). This resulted in predominantly hydroxydihydropyrrole **295** with pyrrole **296** as a minor product in the mixture. The combined yields for this reaction were typically in the range of 56-88%.

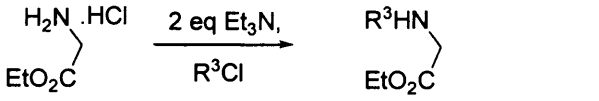


294 **295** **296**

Scheme 93: *Sharlands copper(I)-catalysed hydroxydihydropyrrole synthesis.*

4.3.2.2 Synthesis of β-hydroxy amino esters

Following on from the approach work carried out by Sharland towards the synthesis of β-hydroxy amino esters **294**, we set out to synthesise a range of substrates as a means to assess and improve upon Sharland's recipe. The first step involved protection of the nitrogen of commercially available glycine ethyl ester hydrochloride **297** (Scheme **94**) using either *p*-nitro benzenesulfonyl chloride or *p*-toluenesulfonyl chloride in the presence of two equivalents of triethylamine to yield the protected amine **298** (>95%).

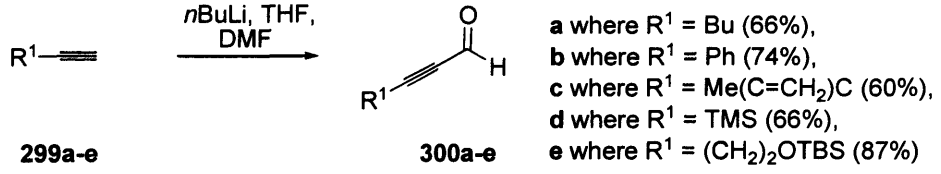


297 **298**

a where R^3 = Ts (96%)
b where R^3 = Ns (98%)

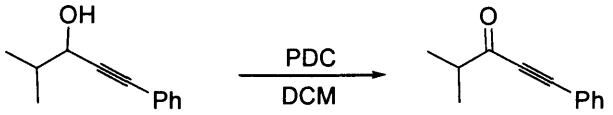
Scheme 94: *Protection of glycine ethyl ester hydrochloride.*

The next step involved the synthesis of acetylenic carbonyls, which were prepared by deprotonation of a terminal acetylene **299** with *n*BuLi followed by reaction with dimethylformamide to yield alkynyl aldehydes **300** (Scheme **95**). The procedure involved a reverse quench using 10 % aqueous potassium dihydrogen phosphate as a means to prevent the formation of undesirable side-products.[103]



Scheme 95: *Synthesis of acetylenic aldehydes.*

The alkynyl ketone **301** was prepared by the oxidation of propargylic alcohol **202c** with pyridinium dichromate (Scheme **96**).



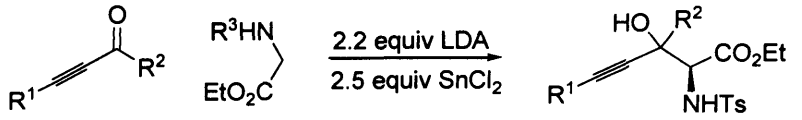
202c **301** (88%)

Scheme 96: *Synthesis of acetylenic ketone **301**.*

Oxidation of the propargylic alcohol **202c** gave the propargylic ketone **301** cleanly with no need for purification. Synthesis of the acetylenic aldehydes **300** gave predominantly the desired product but contained some minor inpurities. Purification was not required as these side-products were minor and would presumably not affect the next step in the reaction.

The following step involved Sharland's coupling of the alkynyl carbonyls with an *N*-protected glycine ethyl ester **298**.[104] This method was first employed by Kazmier, who reported the coupling of aldehydes with amino esters such as glycine and valine. The reaction involves the formation of a tin(II) enolate by the initial deprotonation of the glycine **298** using lithium diisopropylamide followed by the addition of 2.5 equivalents of tin(II) chloride to give the tin(II) enolate, which is then coupled with the acetylenic aldehydes **300** or ketone **301** to yield the β-hydroxy amino ester **294**. Following this procedure we synthesised a range of β-hydroxy amino esters (Table **9**).

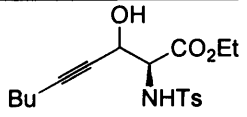
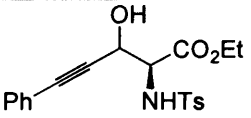
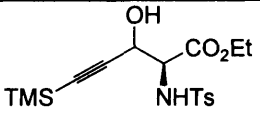
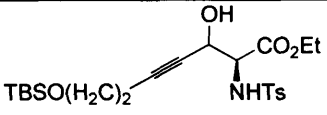
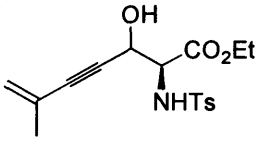
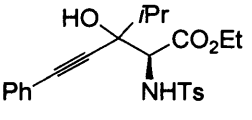
Table 9: *Tin(II) chloride-mediated coupling of acetylenic carbonyls with glycine.*

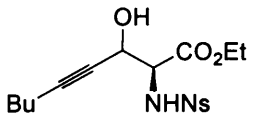
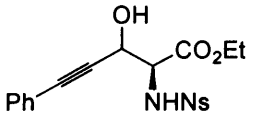


300a-e (R^2 = H) or **301** where R^1 = Ph, R^2 = *i*Pr

298

294

amino esters 294	R^1	R^2	R^3	Ratio[a] Anti	Ratio[a] Syn	Yield (%) Anti[b]
 **294a**	Bu	H	Ts	86	14	79
 **294b**	Ph	H	Ts	91	9	82
 **294c**	TMS	H	Ts	85	15	83[c]
 **294d**	$(CH_2)_2OTBS$	H	Ts	86	14	83[c]
 **294e**		H	Ts	93	7	71
 **294f**	Ph	*i*Pr	Ts	84	16	82

 **294g**	Bu	H	Ns	NA	NA	0
 **294h**	Ph	H	Ns	NA	NA	0

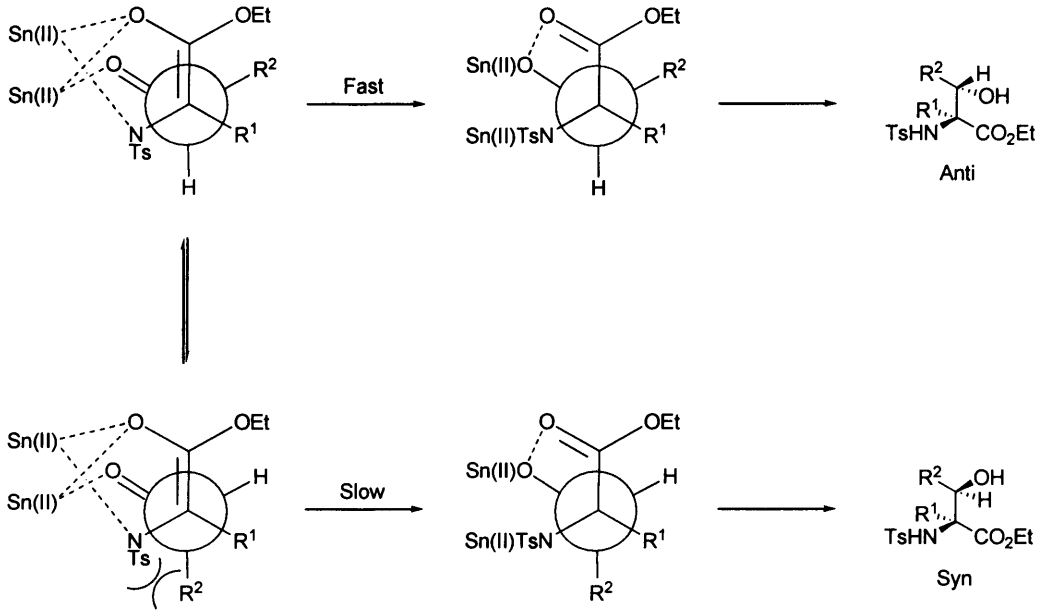
Substrates synthesised following Sharland's protocol. [a] By ^{1}H-NMR analysis of crude. [b] After recrystalisation. [c] these were oils so yield is of syn + anti for these examples.

As can be seen from Table **9** by using Sharland's method for the coupling of acetylenic carbonyls to amino esters a range of β-hydroxy amino esters were synthesised with a high degree of stereoselectivity. The minor isomer was detected by ^{1}H-NMR analysis of the crude and could be seen by the integrations of the **CH**OH, **CH**NH, OH and NH (where minor peaks were visible). A large number of the β-hydroxy amino esters had been previously synthesised by Sharland and were confirmed to show the correct stereochemistry by comparison using ^{1}H-NMR analysis. The chemistry was further expanded upon with the successful coupling of silyl protected acetylenic carbonyls **300c** and **300d** with *N*-tosyl glycine ethyl ester **298a**. These examples were not crystalline solids like those previously synthesised but were viscous oils so purification was carried out using column chromatography and therefore the isolated yields were diastereomeric mixtures.

We also attempted to expand the chemistry further by attempting to incorporate a stronger electron withdrawing sulfonamide such as an *N*-nosyl group. This unfortunately was not possible under these conditions as coupling of acetylenic carbonyls **300a** and **300b** with *N*-nosyl glycine ethyl ester **298b** were unsuccessful as LDA deprotonation of *N*-nosyl glycine ethyl ester resulted in a black solution. Upon ^{1}H-NMR analysis of the black solution an indeterminate mixture of products were observed. This is unsurprising in light of things as this is a common problem with nitro groups and alkyl lithiums and is most probably due to cleavage of the nosyl group.[105] Attempts were also made to optimise the conditions by reducing the amount of tin(II) chloride to one or one and a half equivalents. This proved unsuccessful as reducing the tin(II) chloride for the synthesis of both **294a** and **294b** resulted in very little product being isolated and a large amount of *N*-tosyl glycine ethyl ester being present in the mixture.

4.3.2.4 Stereochemistry

As previously mentioned, the approach work of coupling aldehydes with amino esters is not new; Kazmaier and co-workers had previously reported on the synthesis of β-hydroxy amino esters from the tin(II) chloride-mediated coupling of the enolate of amino esters such as glycine and valine with aldehydes and found a high degree of diastereoselectivity.[106] He proposed that the high *anti* diastereoselectivity was due to the fixed enolate geometry and chelation control (Scheme **97**).



Scheme 97: *Stereoselectivity of Kazmaier's synthesis using chelation control.*

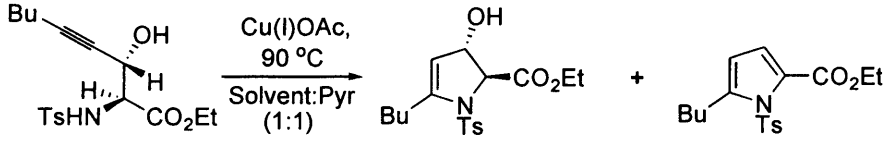
As can be seen in Scheme **97** the high anti-diastereoselectivity can be explained by the unfavourable steric clash between the *N*-tosyl group and R^2 in the resulting tin(II) complex for the syn geometry. The methodology of Kazmaier and co-workers was also used by Sharland for the synthesis of the β-hydroxy amino esters **294**, and a similar degree of stereoselectivity was observed. Upon synthesis of **294a**, Sharland showed that by examination of the ^{1}H-NMR analysis of the crude product, a high degree of stereoselectivity was observed. It was seen that by ^{1}H-NMR integration the ratio was 1 to 7.5 respectively, seen from the aromatic protons of the N-tosyl moiety. To add further proof that the *anti* diastereoismoner was the major product, recrystallisation of compound **294a** was confirmed to have the anti-geometry and comparison with ^{1}H-NMR of the crude confirmed it to be the major. Sharland's recrystalisation of the major isomer of **294b** and X-ray crystallography also confirmed the major product to be *anti* as did the recrystalisation of **294f**, providing further evidence that the reaction proceeds to give *anti* as the major product.

4.3.2.4 Assessing and improving Sharland's copper-mediated cyclisations.

The method set out by Sharland for the synthesis of hydroxydihydropyrroles and pyrroles proved both impractical and unsafe due to the use of one equivalent of copper(I) acetate, the use of high temperatures in a sealed system and the use of toxic pyridine as a cosolvent. Due to the impractical nature of this method we felt it prudent to investigate alternative reaction conditions that alleviate these issues and allow for potential large scale synthesis.

One of the first issues to be dealt with was the need for a sealed tube. In order to overcome this we felt that as the reaction required a temperature of approximately 90 °C as determined by Sharland, a range of suitable solvents would have to be screened. Several solvents were screened as a 1:1 mixture with pyridine (Table **10**); these included THF, acetonitrile, toluene and even water was assessed. All reactions were carried out using 1 equivelant of copper(I) acetate in a flask attached to a condenser at a temperature of 90 °C or reflux. In the case of tetrahydrofuran and acetonitrile which have lower boiling points than 90 °C (66 °C and 81 °C respectively) we decided to assess these solvents in order to confirm whether a solvent with a boiling point of 90 °C or above was indeed required

Table 10: *Solvent screening for the copper(I) acetate mediated cyclisation of* ***294a.***



294a **295a** **296a**

Solvent	294a	295a	296a
THF	100	0	Negligible
Acetonitrile	100	0	0
Water	100	0	0
Toluene	0	89	11

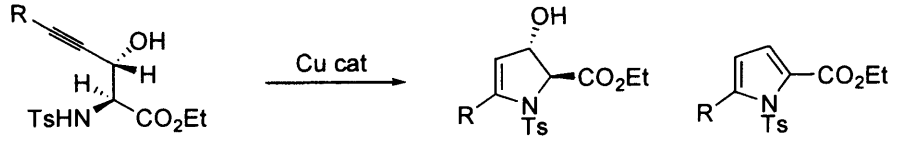
In all the above cases the reaction was carried out overnight (18 h)

The results of the solvent screening test revealed that both water and acetonitrile gave the worst results. In the case of water this was largely due to the insolubility of the substrate **294a** which tended to clump together and stick to the sides of the reaction flask despite the presence of pyridine. The solubility of the copper(I) acetate was not an issue due to the presence of pyridine. Acetonitrile gave poor results with no products observed and recovery of starting

material. Tetrahydrofuran did not give that much of an improved yield as still only a very small amount of pyrrole was observed as determined by ^{1}H-NMR analysis. Tetrahydrofuran was only heated to its boiling point (66 °C) and this poor result may have been due to the lower temperature. It would seem that from the select solvent screening that was carried out, a solvent suitable that could be heated to temperatures in excess of 90 °C was required for successful cyclisation.

The solvent of choice was therefore toluene as it gave much better results for conversion of the β-hydroxyamino ester **294a** to the cyclised products, but in a ratio of 9:1 for hydroxydihydropyrrole **295a** to pyrrole **296a**. The other variables that needed to be tested were the copper species being used and the amount of copper to be used, the importance of base as a co-solvent to the reaction as well as the reaction temperature (Table **11**).

Table 11: *Assessing conditions for pyrrole synthesis.*



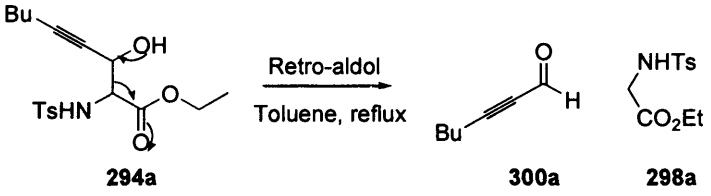
294 **295** **296**

a where R = Bu
b where R = Ph

294	Copper (eq)	Solvent	Amount pyr	Time (h)	Temp °C	295	296
294a[1]	CuOAc (1eq)	Et_2O	1:1 co-solvent	6	90	86	14
294b[1]	CuOAc (1eq)	Et_2O	1:1 co-solvent	1	90	95	5
294a	CuOAc (1eq)	toluene	1:1 co-solvent	4	90	89	11
294b	CuOAc (1eq)	toluene	1:1 co-solvent	4	90	67	33
294a	CuOAc (1eq)	toluene	2 equiv	4	Reflux	17	83
294a	$Cu(OAc)_2$ (1eq)	toluene	1:1 co-solvent	4	90	20	80
294a	CuI (1eq)	toluene	1:1 co-solvent	18	90	0	0
294a	CuI (1eq)	toluene	1:1 co-solvent	18	Reflux	0	0
294a	$Cu(OAc)_2$ (1eq)	toluene	None	8	90	0	100
294a	$Cu(OAc)_2$ (1eq)	toluene	None	1	Reflux	0	100
294a	$Cu(OAc)_2$ (0.1eq)	toluene	None	1	Reflux	0	100
294a	$Cu(OAc)_2$ (0.1eq)	toluene	None	18	70	0	80

[1] Original recipe by Sharland. In cases where total yield < 100% the remaining was starting material as determined by ^{1}H-NMR analysis. Ratios determined by ^{1}H-NMR integration of crude material.

Although not mentioned in the results quoted (Table **11**), very small amounts of glycine ethyl ester were present in the product mixture (<5 %) when the reaction was carried out at reflux and it was felt that this was due to a retro-aldol reaction taking place (Scheme **98**). It was therefore important to determine whether the copper species or the pyridine played a role in formation of this glycine ethyl ester **298a**. In the absence of pyridine and copper(I/II) acetate but with heating substrate **294a** at reflux for 4 hours in toluene a small amount of retro-aldol was still taking place, and it was therefore determined that the heating was causing the retro-aldol reaction, confirming that this was a purely thermal phenomenon. No *N*-tosyl glycine ethyl ester was detected by ^{1}H-NMR analysis when the reactions were carried out at 90 °C. The importance of the copper catalyst was also confirmed by no products being detected in the absence of copper (I)/(II) acetate at both 90 °C and reflux.



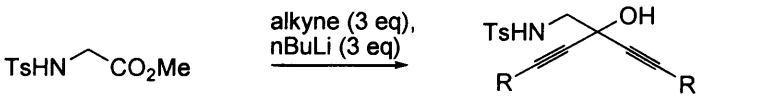
***Scheme 98:** Retro-aldol of substrate **294a**.*

Changing the copper species from copper(I) acetate to copper(II) acetate in the presence of pyridine showed a reversal in the ratio of products, with copper(II) resulting in predominantly the formation of pyrrole **296** as opposed to hydroxydihydropyrrole **295**, which is the major product when copper(I) is used. This may have been a result of the ability of the copper(II) acetate to encourage the elimination of water from the hydroxydihydropyrrole **295** to give pyrrole **296**. It is also important to note that in the absence of pyridine, both copper(I) and copper(II) acetate displayed the same activity in cyclisation of **294a** resulting in isolation of only pyrrole **296a** within the same time period. The presence of oxygen was also unimportant as reactions carried out under nitrogen or open to the air gave pyrrole **296** exclusively in much the same yields. The elimination of water appears to be thermally induced, again confirming that high temperatures favoured the entropic products. Although the copper(II) acetate was purified, the presence of copper(I) in copper(II) acetate and vice versa is possible and therefore the reactive copper species cannot be determined with any great certainty. At present we do not fully understand the differing behaviours of copper(I) and copper(II) salts in the reaction. Another possible facet is that in the presence of pyridine we are not dealing with simple copper(I) and copper(II) acetate salts but possible complexes that form with the pyridine.

By simply exchanging the ether for toluene as solvent, the requirement for a sealed tube was happily removed, making the reaction safer and more easily scalable. Finding that the pyridine was unnecessary has both decreased the health hazards of the reaction and has simplified the workup procedure drastically requiring only a straightforward filtration. The cost has been reduced by the use of 0.1 equivelants of copper(II) acetate as opposed to one equivalent of the more expensive copper(I) acetate.

4.3.2.5 Synthesis of other pyrrole precursors

In order to fully assess this method and to determine if pyrrole precursors other than β-hydroxy amino esters are applicable to this methodology a range of other substrates were synthesised in preparation for the copper(II)-catalysed cyclisation. Substrates **303a** and **303b** were synthesised by the reaction of three equivalents of lithio-acetylides with *N*-tosyl glycine methyl ester **302** (Scheme **99**) by a double addition reaction onto the ester group. The third equivalent was required to deprotonate the amine. Athough this may be viewed as wasteful, when compared to the alternative of using a second protecting group for the amine which would involve a further two steps it can be regarded as much more atom efficient.

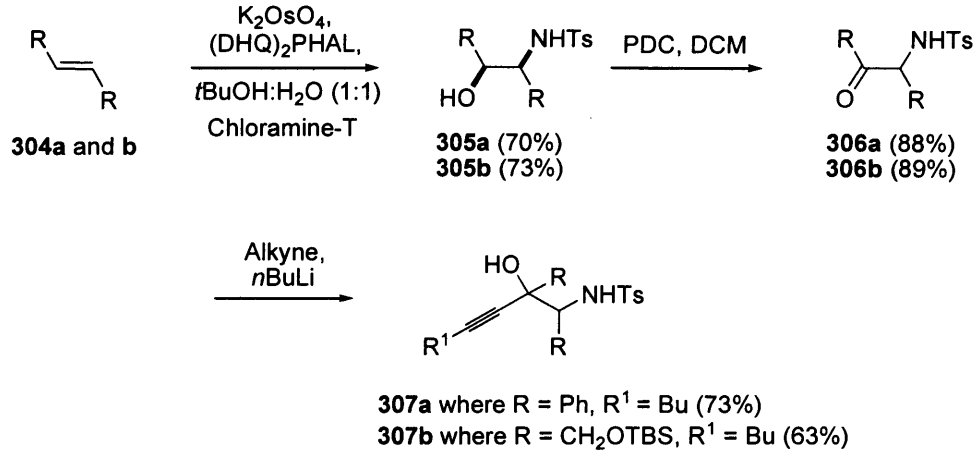


302

303a where R = Bu (98%)
303b where R = Ph (77%)

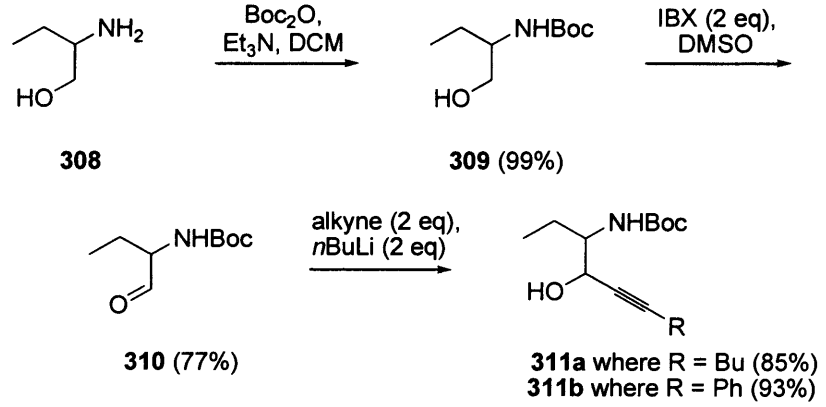
Scheme 99: *Synthesis of substrates **303a** and **303b**.*

Substrates **307a** and **307b** (Scheme **100**) were synthesised by the amino hydroxylation of the corresponding symmetrical alkenes **304** followed by oxidation to give the β-keto sulphonamide **306** and then attack by a lithio-acetylide to give the β-alkynyl sulfonamide **307**.



Scheme 100: *Synthesis of substrates **307a** and **307b**. **a** is where R = Ph, **b** is where R = CH_2OTBS.*

Substrates **314** and **315** (Table **12**) were synthesised in a similar manner to the synthesis of **307a** and **307b** (*cf.* Section **4.3.3.1**, Pg 91). Substrates **311a** and **311b** were synthesised from (+/-)-2-amino-1-butanol **308** (Scheme **101**) which underwent carbamate protection (**309**) and then oxidation to the aldehyde **310**, which was then followed by attack onto the aldehyde **310** by a lithium acetylide to give the products **311a** and **311b**.

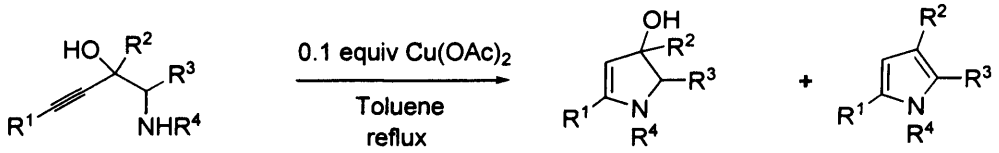


Scheme 101: *Synthesis of substrates **311a** and **311b** from 2-amino-1-butanol **308**.*

4.3.2.6 Assessing the optimised copper(II)-catalysed methodology

With a range of substrates synthesised the next step in the synthesis was the key step to test our optimised copper(II)-catalysed methodology. This was important in order to determine whether there were any limitations with the chemistry. The results of this new optimised method can be seen in Table **12**.

Table 12: Synthesis of pyrroles by optimised copper-catalysed cyclisations.



SM **312** **313**

SM	R^1	R^2	R^3	R^4	Time	entry	312 | 313 Ratio		Yield (%)
294a	Bu[a]	H	CO_2Et	Ts	0.7 h	**a**	0	100	91
294b	Ph[a]	H	CO_2Et	Ts	1.2 h	**b**	0	100	97
294c	TMS	H	CO_2Et	Ts	18 h	**c**	0	0	0[b]
294i	H	H	CO_2Et	Ts	12 h	**d**	0	100	85[c]
294i	H[d]	H	CO_2Et	Ts	18 h		0	100	79[c]
294e		H	CO_2Et	Ts	3.5 h	**e**	25	75	84
294d	$(CH_2)_2OTBS$	H	CO_2Et	Ts	0.8 h	**f**	0	100	95
294j	$(CH_2)_2OH$	H	CO_2Et	Ts	1h	**g**	0	100	98
294f	Ph	*i*Pr	CO_2Et	Ts	24h	**h**	0	0	0[b]
303a	Bu	BuC≡C	H	Ts	0.7 h	**i**	0	100	87
303b	Ph	PhC≡C	H	Ts	0.8 h	**j**	0	100	98
307a	Bu	Ph	Ph	Ts	24h	**k**	0	0	0[b]
307b	Bu	CH_2OTBS	CH_2OTBS	Ts	24h	**l**	0	0	0[b]
314	Bu	$-(CH_2)_4-$		Ts	4h	**m**	0	100	50[e]
315	$(CH_2)_2OTBS$	$-(CH_2)_4-$		Ts	18h	**n**	0	0	0[e]
311a	Bu	H	Et	Boc	24h	**o**	0	0	0[b]
311a	Bu[f]	H	Et	Boc	24h		0	0	0[b]
311b	Ph	H	Et	Boc	24	**p**	0	0	0[b]

[a] Contained very small amounts of retro-aldol product. [b] Starting material recovered. [c] Remaining yield was retro-aldol product. [d] Reaction involves using one equivalent of copper(II) acetate and carried out at 90°C. [e] Decomposition products observed. [f] Reaction using one equivalent of copper(II) acetate.

As can be seen from Table **12**, a large selection of β-hydroxysulfonamides were successfully cyclised to give pyrroles. In particular, both the silyl-protected alkynol **294f** and the free alkynol **294g** were successfully cyclised to give pyrroles **313f** and **313g** in 95% and 98% yield respectively. Another result of great interest was the successful cyclisation of cyclohexyl derivative **314** to give a tetrahydroindole **313m** in 50% yield. This reduced yield was due to

decomposition with the only other detectable product in the mixture that was distinguishable from ^{1}H-NMR analysis was *bis*-coupled 1-hexyne believed to be from the loss of hexyne from the substrate **314** followed by coupling by the copper(II) acetate. What can also be seen from Table **12** is that in all but one example (**294e**) only pyrrole **313** was isolated, which was in stark contrast to Sharland's results whereby the major product was the corresponding hydroxydihydropyrrole **312**. Attempts were made to isolate the hydroxydihydropyrroles **312** by reducing the temperature to 90 °C, however, only pyrrole **313** and β-hydroxyamino ester **294** was observable by ^{1}H-NMR analysis. In the case of β-hydroxyamino ester **294e** there was no increase in hydroxydihydropyrrole formation at 80 °C or at 90 °C with only slower conversion observed.

4.3.2.7 Scope and Limitations

This method has allowed for the synthesis of a wide range of pyrroles, although some limitations have come to light, as is often the case. The attempted coupling of *N*-nosyl glycine ethyl ester (as opposed to *N*-tosyl glycine ethyl ester) with acetylenic aldehydes was unsuccessful as attempted deprotonation of the glycine moiety using LDA or NaHMDS resulted in black sludge. The coupling also proved sensitive to the amount of tin(II) chloride used, as attempts to reduce the tin(II) chloride resulted in lower yields or no reaction. Another important caveat about the cyclisation reaction was the method only seemed to work for *N*-sulfonamides and did not give any products from carbamates **311a** and **311b**. When using other solvents such as tetrahydrofuran or acetonitrile, no products were observed and only starting material was recovered. The reaction would also not allow the inclusion of bulky groups such as those found with substrates **294c**, **294h**, **307a** and **307b** (Figure **14**); this was perhaps due to steric hindrance preventing copper complexation with the acetylene. The yield from cyclisation of substrate **314** was also low with possible degradation to starting materials indicated by the presence of diyne which was identified in the ^{1}H-NMR spectrum.

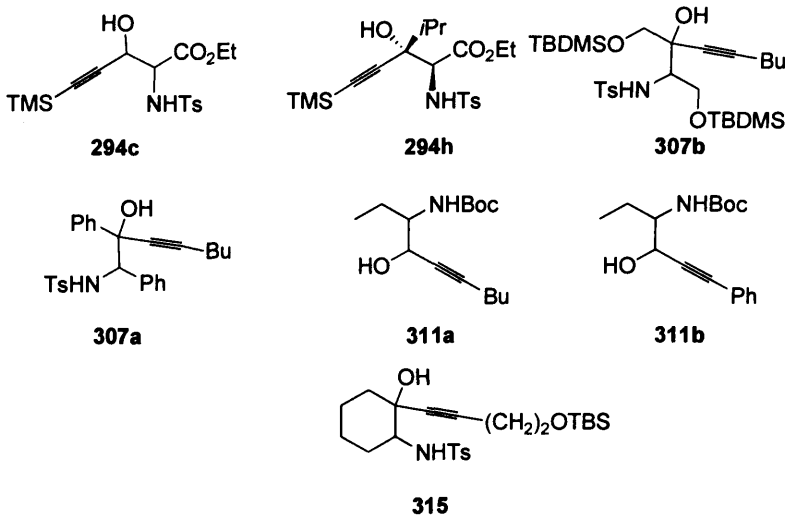
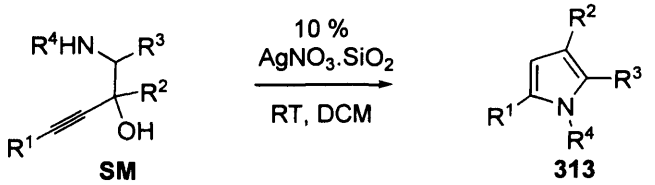


Figure 14: *Limitations of the Copper(II) acetate mediated cyclisations.*

4.3.2.8 Silver(I)-catalysed cyclisation and comparisons with Copper(II).

It was felt that due to the successful cyclisation of indoles (See Chapter 2) and other pyrroles[2,3] using 10% silver nitrate on silica that the substrates that would not undergo cyclisation using copper(II) acetate (Figure **14**) might successfully undergo 5-*endo*-dig cyclisation using silver(I). Upon exposure to 10% silver nitrate on silica gel we found that the substrates successfully cyclised to give pyrroles in high yields (Table **13**). The results showed that the silver-catalysed cyclisation was useful where copper(II) failed although reaction times were generally longer for silver-catalysed cyclisations. For example, a comparison study of both the silver(I) and copper(II) methods for the cyclisation of β-hydroxy sulfonamide **294a** gave clean pyrrole **294a** in 18 hours with 10% silver(I) nitrate on silica and only 0.75 hours using copper(II) acetate. The yield for the pyrrole **313a** using the silver(I)-catalysed method appeared to be quantitative whereas the copper(II)-catalysed method gave pyrrole **313a** in 90% yield. Another important factor is the cost of using 0.1 equivalents of copper(II) acetate which is much cheaper than using 0.1 equivalents of 10% $AgNO_3.SiO_2$. The important point to make is that in the cases where the copper(II) acetate reaction proved unsuccessful, 10% silver(I) nitrate on silica was an excellent alternative and had its own advantages. These include the silver catalyst is heterogenous making recovery of it much easier. Another advantage is that the silver(I)-catalysed reaction is carried out at room temperature, whereas the copper(II)-catalysed method is carried out at reflux in toluene. This could be seen from the attempted cyclisation of amino alcohols **314** and **315** which under the reflux conditions with copper led to decomposition, but with silver(I) at ambient temperature led only to pyrrole **313**.

Table 13: Silver(I)-catalysed cyclisation on substrates that failed with $Cu(OAc)_2$.



SM 313

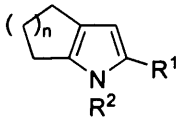
SM	R^1	R^2	R^3	R^4	Equiv $AgNO_3.SiO_2$	Time (h)	Pyrrole 313	Yield (%)
294a	Bu	H	CO_2Et	Ts	0.2	18	**313a**	98
294f[a]	Ph	*i*Pr	CO_2Et	Ts	0.1	8	**313h**	95
303a	Bu	Bu-C≡C	H	Ts	0.1	24	**313i**	98
307a	Bu	Ph	Ph	Ts	0.2	30	**313k**	94
307b	Bu	CH_2OTBS	CH_2OTBS	Ts	0.2	24	**313l**	98
314	Bu	$-(CH_2)_4-$		Ts	0.5	27	**313m**	85
315	CH_2OTBS	$-(CH_2)_4-$		Ts	1.0	48	**313n**	74
311a	Bu	H	Et	Boc	0.2	4	**313o**	96
311b	Ph	H	Et	Boc	0.2	4	**313p**	98

The reactions were carried out in dichloromethane in the dark and at ambient temperature. [a] Result was reported by Sharland.

As can be seen from Table **13**, the silver(I)-catalysed cyclisations proved successful in the cases that were unsuccessful using the copper(II) acetate reaction. These included examples having bulky groups (substrates **294h**, **307a** and **307b**) which gave pyrroles in nearly quantitative yields. Equally, carbamates **311a** and **311b** also successfully underwent 5-*endo*-dig cyclisation using 10% silver nitrate on silica in 4 hours. The cyclisations of both substrates **314** and **315** also proved successful to give anulated pyrroles cleanly. The successful synthesis of annulated pyrroles led us to wonder what other fused ring pyrroles could be made using this very effective method.

4.3.3 Extension of silver-cyclisation methodology: Synthesis of annulated pyrroles.

The synthesis of substituted pyrroles is of great interest to the synthetic chemist. Methods that give access to a range of substitution patterns around the pyrrole ring are also very important. In particular, the sponsors at GlaxoSmithKline showed a great deal of interest in pyrroles that have aliphatic groups around the ring especially those that are fused to carbocyclic rings **316** (Figure **15**).



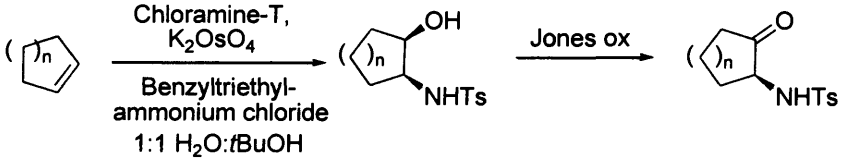
316

Figure 15: *General structure of annulated pyrroles.*

With the successful cyclisation of **314** and **315** using 10% silver nitrate on silica the methodology used to access these intriguing and uncommon ring systems was extended to a wider range of substrates.

4.3.3.1 General method towards annulated pyrroles.

The first step involved the amino-hydroxylation of symmetrical cyclo-alkenes **317** using Osmium(VIII) tetroxide to give β-hydroxyamines **318** in moderate yields (36-59 %). This was then followed by oxidation using Jones reagent to give the β-keto amines **319** (Scheme **102**) in good to excellent yields (70-99 %).



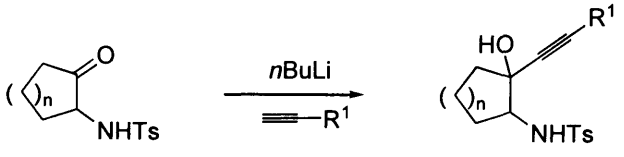
317a-d

318a (36%)
318b (44%)
318c (59%)
318d (50%)

319a (73%)
319b (99%)
319c (70%)
319d (73%)

Scheme 102: *Synthesis of β-keto amines (a is where n =1, b where n = 2, c where n = 4 and d where n = 8).*

The subsequent step involved addition of lithio-acetylides to the β-keto sulfonamides resulting in the 2-alkynyl-2-hydroxy amines **314**, **315** and **320a-g** with a high degree of diastereoselectivity observed in most cases (Scheme **103**).



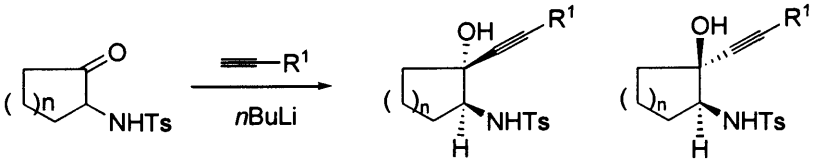
319 **314, 315, 320a-g**

Scheme 103: *Lithio-acetylide addition to β-ketosulfonamides.*

4.3.3.2 Stereochemistry

The addition of the lithium acetylides to the keto-amines **319** gave the 2-alkynyl-2-hydroxy amines **314**, **315** and **319a-g** in moderate to excellent yields, with a high degree of diastereoselectivity observed for examples where the ring size was 5 and 6 carbons. The selectivity was reduced where the ring size was larger (8 and 12 carbons). The ratio of diastereoisomers was determined by ^{1}H-NMR from the integration of the NH peaks and the **CH**NH peaks and these were therefore relatively rough estimates (Table **14**).

Table 14: Product ratios for the addition of lithium acetylides to ketones.



319a-d **314, 315 and 320**

Product	(n)	R^1	Major: Minor Ratio	Yield (%)
320a	1	Bu	91:9	70
320b	1	Ph	84:16	85
320c	1	$(CH_2)_2OTBS$	98:2	53
314	2	Bu	86:14	83
320d	2	Ph	86:14	73
315	2	$(CH_2)_2OTBS$	94:6	43
320e	4	Bu	50:50	77
320f	4	Ph	73:27	52
320g	8	Bu	70:30	92

The major isomers of 2-alkynyl-2-hydroxyamines **320b** and **320d** were isolated by recrystalisation and were confirmed to be the major diastereomer by ^{1}H-NMR analysis. In the case of the cyclohexane **320d**, the ^{1}H-NMR spectrum for the major isomer shows a **CH**NH with coupling constants of 4 Hz and 12 Hz. This is consistent with the unsurprising conclusion that the hydrogen is in an axial position which implies that the sulfonamide is in the equatorial position as the 12 Hz value is consistent with that of an axial-axial coupling. The major isomer was confirmed to be that of the *anti*-diastereoisomer by X-ray crystallography which has an R-value of 0.0674 (Figure **16**), showing indeed that the **CH**NH is in the axial position and the sulfonamide is in the equatorial position. What could also be determined from the X-ray crystal

data for 2-alkynyl-2-hydroxyamine **320d** was the bond length between the O-**H**-**N** was 1.8 Å indicating possible hydrogen bonding. The distance between the N-**H**-**O** was 2.6 Å and was too large to indicate any possibility for hydrogen bonding. The major isomer for the cyclopentyl derivative **320b** was also confirmed to be that of the *anti*-diastereoisomer by X-ray crystallography and has an R-value of 0.0735 (Figure **17**). In this case the distance between the O-**H**-**N** and the N-**H**-**O** was around 3.2 Å and was too large to indicate any possibility for hydrogen bonding (*cf.* Appendix for X-ray crystal data, data can also be found at the Cambridge structure database[78]).

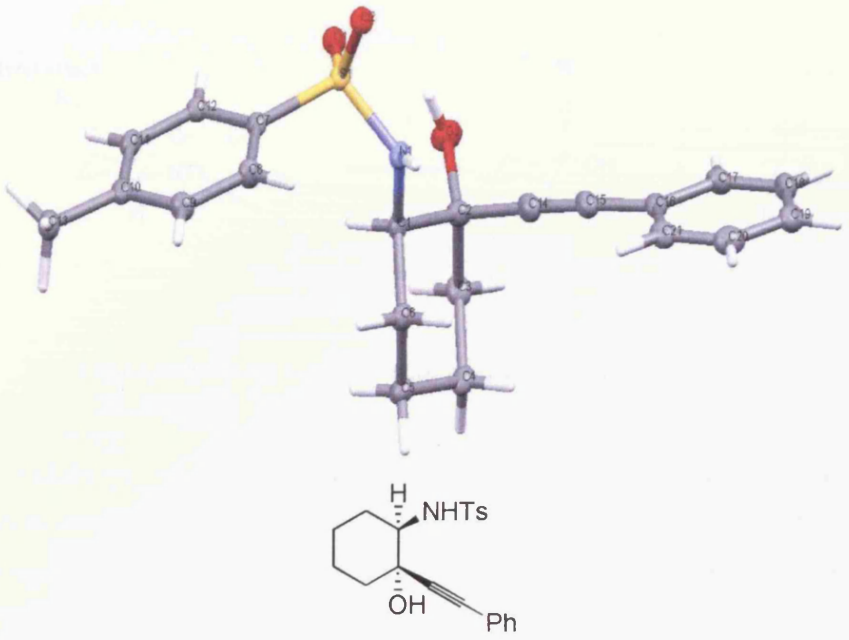


Figure 16: *X-ray crystal structure of* ***320d*** *(CCDC No[78]:783432).*

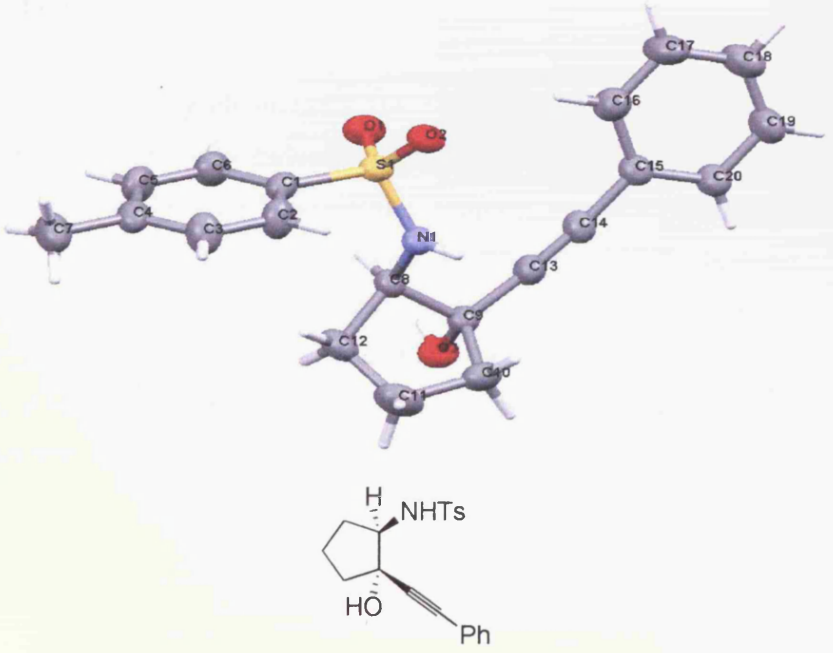


Figure 17: *X-ray crystal structure of* ***320b*** *(CCDC No[78]: 783433).*

Previously the addition of lithium acetylides to β-hydroxy ketones[107] displayed a high degree of stereoselectivity resulting in predominantly chelation control product by Lewis acid lithium (Li^+). Similarly these reactions should also involve a variation of chelation control where the lithium coordinates the amine in the equatorial position to bring it in close proximity to the carbonyl. This would then be followed by axial attack of the acetylide onto the carbonyl at an angle of 107 ° (Bürgi-Dunitz angle) to give the major product with the hydroxide and sulfonamide in equatorial positions, i.e the *anti* diastereoisomer (Figure **18**). This explaination is consistent with the X-ray crystal data which shows the major isomer to be that of the *anti* diastereoisomer.

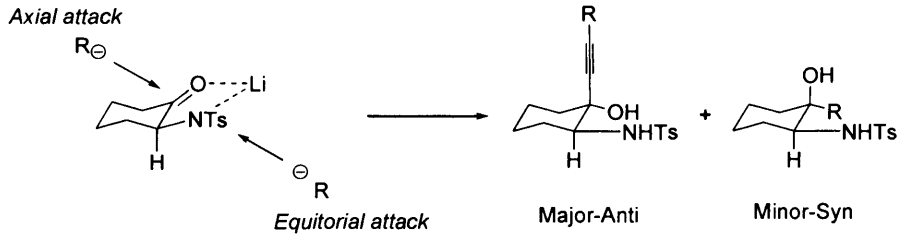


Figure 18: *Axial vs equatorial attack on cyclohexyl ketone.*

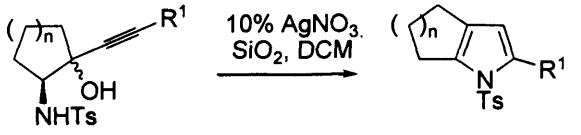
As with cyclohexyl the cyclopentyl derivatives displayed a similar degree of diastereoselectivity with the major isomer having the hydroxy group and the amine anti to each other. This cannot be explained using the above model as axial and equatorial cannot be applied to the cyclopentyl ring due to fast ring flipping.

4.3.3.3 Cyclisation.

The cyclisations of β-hydroxysulfonamides **314**, **315**, and **320a-g** were very successful resulting in annulated pyrroles with fused carbocyclic rings of various sizes. The reaction times were slow and in the order of 48 hours when using 0.1 equivalents of silver(I) in the form of 10% silver nitrate on silica gel. The cyclisations could be accelerated by using quantitative silver(I) catalyst but still often required overnight stirring. The successful cyclisations shows just how versatile this methodology can be (Table **15**). The cyclisations were carried using the diastereomeric mixture (both *syn* and *anti*) and so the rate of cyclisation of the *syn* vs the *anti* diastereoisomer was not determined. It is expected that the *syn* diastereoisomer would cyclise

faster than that of the *anti* as work carried out previously by Hayes[3] on the cyclisations on both *syn* and *anti* diastereoisomers of furan precursors determined that *syn* cyclised faster than *anti*.

Table 15: *Results for the silver-mediated synthesis of annulated pyrroles.*



314, 315, 320 **313, 321**

Amino-alcohol	N	R^1	Equiv Silver(I)	Time (h)	Pyrrole	Product yield (%)
320a	1	Bu	1	18	**321a**	92
320b	1	Ph	1	3.5	**321b**	96
320c	1	$(CH_2)_2OTBS$	1	18	**321c**	99
314	2	Bu	0.5	27	**313m**	85
320d	2	Ph	1	3	**321d**	99
315	2	$(CH_2)_2OTBS$	1	48	**313n**	74
320e	4	Bu	1	18	**321e**	91
320f	4	Ph	1	23	**321f**	83
320g	8	Bu	3	3	**321g**	84

As can be seen from the results in Table **15**, a wide range of annulated pyrroles have been synthesised in high yields ranging between 74-99%. This method has allowed for the incorporation of 5, 6, 8 and even 12 carbon carbocycles fused to a pyrrole. This suggests that this methodology represents a rather general strategy for the synthesis of annulated pyrroles as well as a range of substituted pyrroles. There is a high degree of interest in compounds of this kind to the pharmaceutical industry and the success of this methodology could be further explored to allow for a range of ring sizes and alkynes.

4.3.4 Extension towards the synthesis of *N*-bridgehead pyrroles.

This also led to the question that if *C*-fused pyrroles could be synthesised using 10% silver nitrate on silica then what about *N*-fused heterocycles? A look at the literature[108-114] highlights the importance of *N*-junction heterocycles in nature and to the pharmaceutical industry; this idea was strongly encouraged by the project sponsors at Stevenage. The specific heterocycles

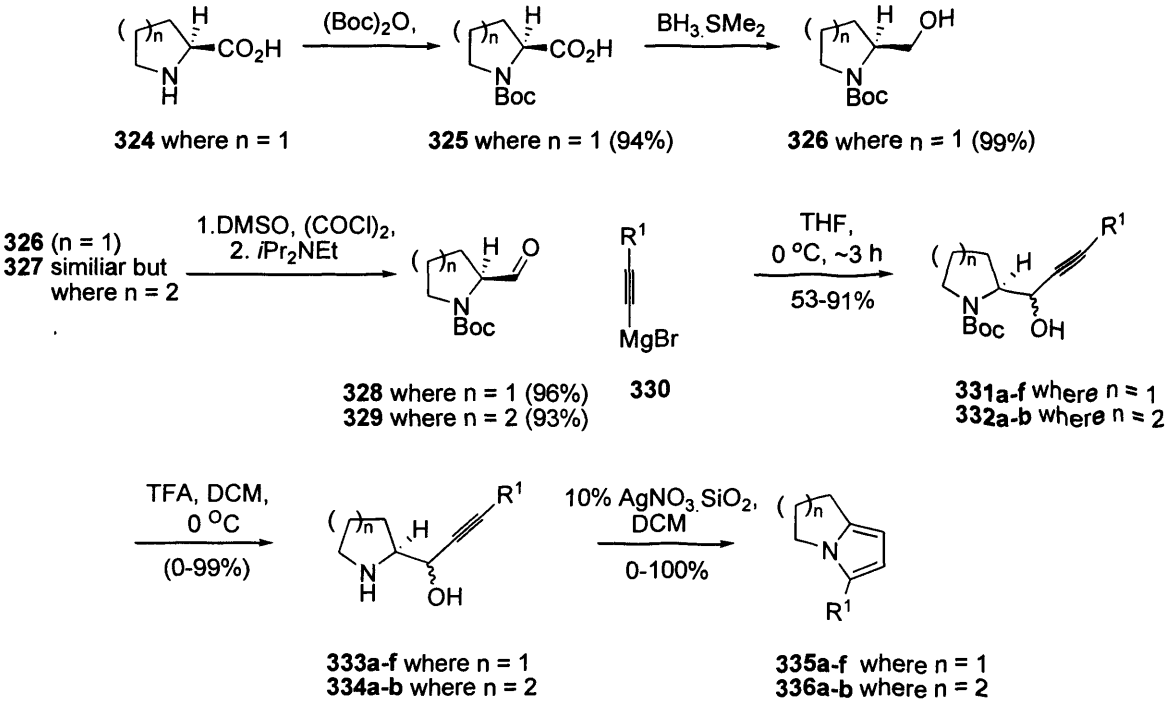
that we chose to target due to their potential ease of access were pyrrolizines and indolizines (Figure **19**)

322 **323**

Figure 19: *A parent pyrrolizine 322 and indolizine 323.*

4.3.4.1 General method towards *N*-bridgehead pyrroles

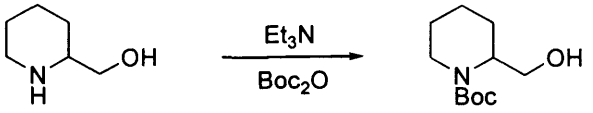
With the success of the silver cyclisation method in synthesising the indoles, pyrroles and in particular annulated pyrroles, it was felt that this methodology could be extended to the synthesis of pyrrolizines and indolizines. Using an approach outlined by Reed and coworkers,[108] a range of β-hydroxycarbamates were synthesised in preparation for the putative silver-mediated cyclisation (Scheme **104**).



Scheme 104: *Synthetic route to pyrrolizines and indolizines.*

The method involved the initial protection of the amine of (*S*)-proline **324** with Boc anhydride to give *N*-Boc (*S*)-proline **325**, which was then reduced to *N*-Boc (*S*)-prolinol **326** using borane-dimethyl sulphide, as this provided the easiest method of reduction and gave the prolinol **326** in

high yields (~98%). The (*S*)-prolinol **326** was then oxidised using the Swern method to give (*S*)-prolinal **328**. Oxidation by other methods such as those using PDC or IBX gave lower yields. The next step involved the coupling of acetylides to the aldehyde **328** to give the propargylic prolinol **331**. This was achieved by the addition of Grignard reagents **330** obtained from the deprotonation of acetylenes using ethyl magnesium bromide as base. The usual reagent used for deprotonation of acetylides in preparation for coupling is butyl lithium. This method was less suited as the lithium acetylides gave a significant reduction in yields, possibly due to enolisation, as a large amount of the starting aldehyde was detected by ^{1}H-NMR analysis of the crude product mixtures in these cases. The same route (See Scheme **104**) was carried out using piperidine-2-methanol **337** to gain access to the 6,5-fused systems (Scheme **105**).

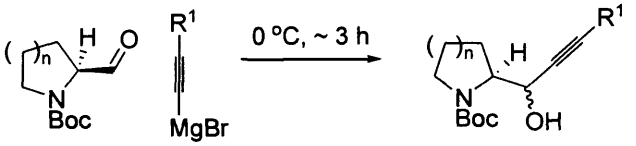


337 **327** (89%)

Scheme 105: *Boc-protection of piperidine-2-methanol 337.*

The key addition of Grignard reagents to the aldehydes resulted in a mixture of diastereoisomers with good to excellent overall yields (Table **16**).

Table 16: *Substrates synthesised using Reed's method.*



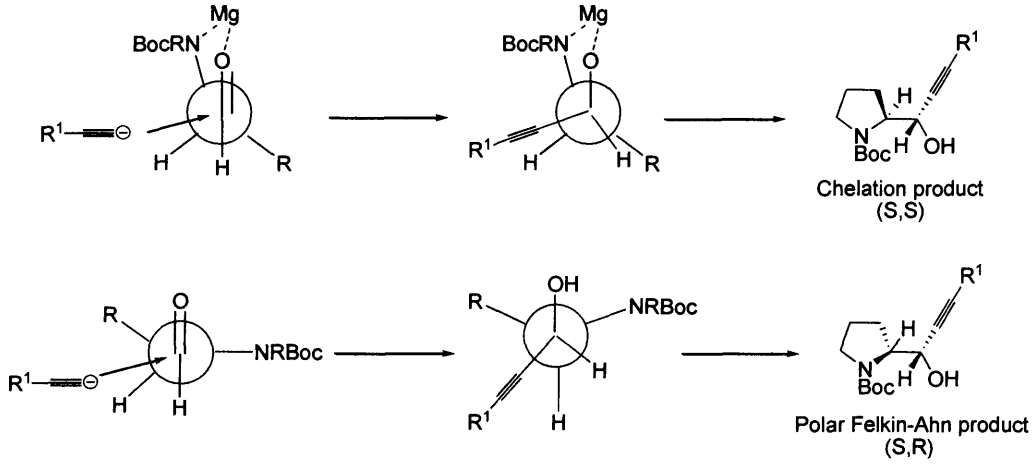
328, 329 **330** **331, 332**

Product	(n)	R^1	Major diastereoisomer	Minor Diastereoisomer	Overall Yield (%)
331a	1	Me	63	37	83
331b	1	Bu	56	44	91
331c	1	Ph	63	37	75
331d	1	TMS	67	33	66
331e	1	CH_2OTBS	60	40	68
331f	1	CO_2Et	73	27	51
332a	2	Bu	85	15	72
332b	2	Ph	76	24	68

The major and minor product ratios were determined by ^{1}H-NMR analysis from integration of the OH group resonances of the major and minor diastereoisomers and as a result are rough estimates. The presence of rotamers made this determination difficult and uncertain when using other resonances.

4.3.4.2 Stereochemistry.

As reported by Reed and co-workers,[108] the alkynylation of (*S*)-prolinal **328** using the Grignard of trimethylsilylacetylene resulted in a major and a minor diastereomer. It was found that this was a 2:1 ratio for **331d** in favour of the *anti*-Felkin-Ahn product, or the (*S,S*) diastereoisomer. This was also believed to be the case for all the alkynylations of (*S*)-prolinal resulting in predominantly the (*S,S*) diastereomer as predicted by a chelation control model (Scheme **106**).



Scheme 106: *Chelation control vs Felkin-Ahn for the addition of Grignard reagents to (S)-prolinal.*

X-ray analysis of the major isomer of product **332b** showed this to be that of the chelation control product (Figure **20**). In the example of piperidine-2-methanol (purchased as a racemate) chelation control gave the major diastereoisomer as two enantiomers (*1S,2S*) and (*1R,2R*), both of which were detected in the X-ray. The X-ray crystal structure shown is that of the 1S,2S enantiomer and has an R-value of 0.0586 (*cf.* Appendix for X-ray crystal data, CCDC No[78]: 783435).

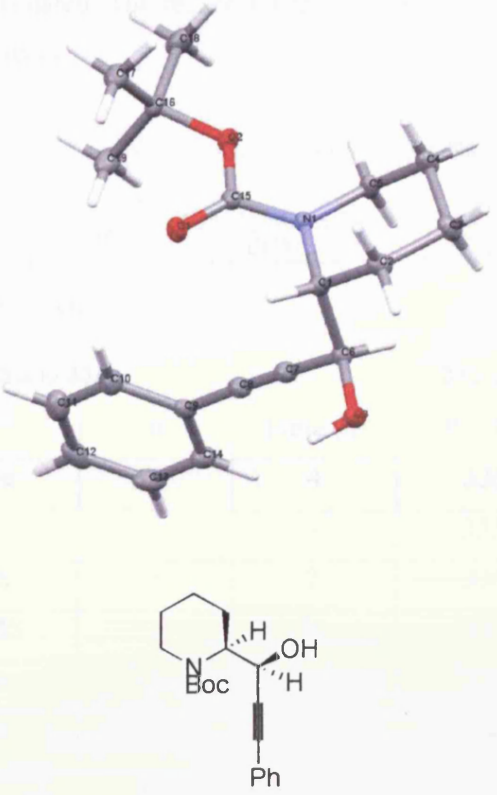


Figure 20: *X-ray crystal structure of* ***332b*** *showing the (S,S) diastereoisomer, the other major product was the mirror image: the (R,R) diastereoisomer.*

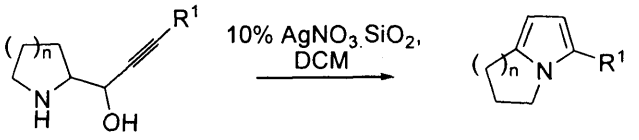
The next step involved the Boc deprotection of 2-propargyl prolinols **331** and 2-propargyl piperidinols **332** using 20% trifluoroacetic acid in dichloromethane. The prolinols **331a-d** underwent Boc deprotection successfully and after column chromatography the free prolinols **333a-d** were isolated in excellent yields (87-99%). Attempted Boc deprotection of 2-propargyl prolinols **331e** and **331f** was unsuccessful resulting in great loss and an indistinguishable mixture in the ^{1}H-NMR spectrum. The piperidinols **332a** and **332b** underwent Boc deprotection to give the free piperidinols **334a** and **334b**, attempted column chromatography on the piperidinols **334a** and **334b** resulted in great loss and so they were used crude in the next step. The next step being the key silver(I)-catalysed cyclisation.

4.3.4.3 Silver cyclisation of 2-propargylic pyrrolidines and piperidines

Exposure of these free prolines/pyrrolidines **333** and **334** to 0.1 equivalents of 10% $AgNO_3.SiO_2$ in dichloromethane resulted in successful cyclisation to give 2-substituted pyrrolizines and indolizines in near quantitative yields in under 4 hours (Table **17**). There was of course one example that would not cyclise, this being the TMS-protected propargylic prolinol **333d**. Attempts to prolong reactions times to 30 h resulted in no conversion to product

and only starting material isolated. The reason for this was unclear but may have been due to either steric or electronic effects.

Table 17: *Cyclisation of substrates using 0.1 eq 10% $AgNO_3.SiO_2$.*



333 and **334** **335** and **336**

Starting	R^1	n	Time (h)	Product	Yield (%)
333a	Me	1	4	**335a**	80
333b	Bu	1	3	**335b**	>98
333c	Ph	1	2	**335c**	>98
333d	TMS	1	30	**335d**	0
334a	Bu	2	4	**336a**	86[1]
334b	Ph	2	4	**336b**	71[1]

[1]Yield over 2 steps.

As can be seen from Table **17**, the cyclisation of pyrrolidines **333a-333d** and piperidines **334a** and **334b** was highly successful resulting in clean pyrrolizines and indolizines respectively in good to excellent yields and in relatively short reaction times. The versatility of this method can be clearly seen in the ^{1}H-NMR spectrum of 2-propargyl prolinol **333c** which upon cyclisation gave pyrrolizine **335c** cleanly and in 98% yield without any purification (Figure **21**). Upon analysis of the 1H-NMR spectrum of both starting pyrrolidine **333c** and product **335c**, the disappearance of the **CH**OH peak at 4.57 ppm (minor diastereoisomer) and 4.27 ppm (major diastereoisomer) as well as the disappearance of the 2-H peak at 3.36-3.29 (Major and minor) in the product **335c** ^{1}H-NMR spectrum can be clearly seen. What can also be seen is the appearance of the pyrrole peaks at 6.33 ppm and 5.81 ppm in the pyrrolizine **335c** 1H-NMR spectra. What can also be seen from the ^{1}H-NMR spectrum of the crude pyrrolizine **335c** is that there are no impurities in the product. This is a common feature with many of the silver cyclisations of a range of heterocyclic precursors and highlights the elegance of the reaction towards these heterocycles.

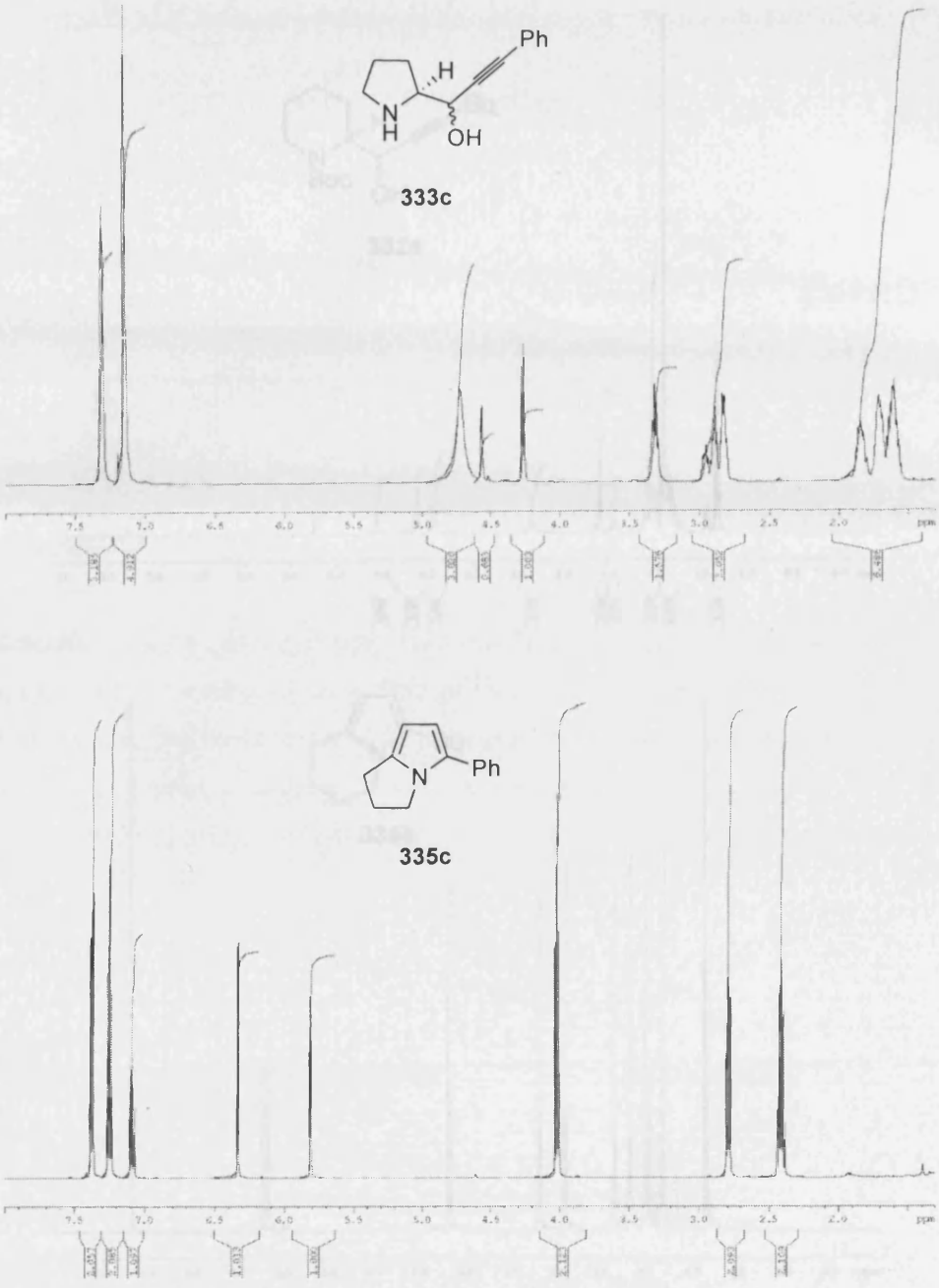


Figure 21: *[1]H-NMR of starting pyrrolidine **333c** and pyrrolizine **335c**.*

Equally the Boc-protected piperidine **332a** was successfully deprotected and cyclised crude to give the indolizine **336a** in 86% yield over two steps, highlighting the flexibility of this method towards the cyclisation of impure precursors with no detriment to yield (Figure **22**).

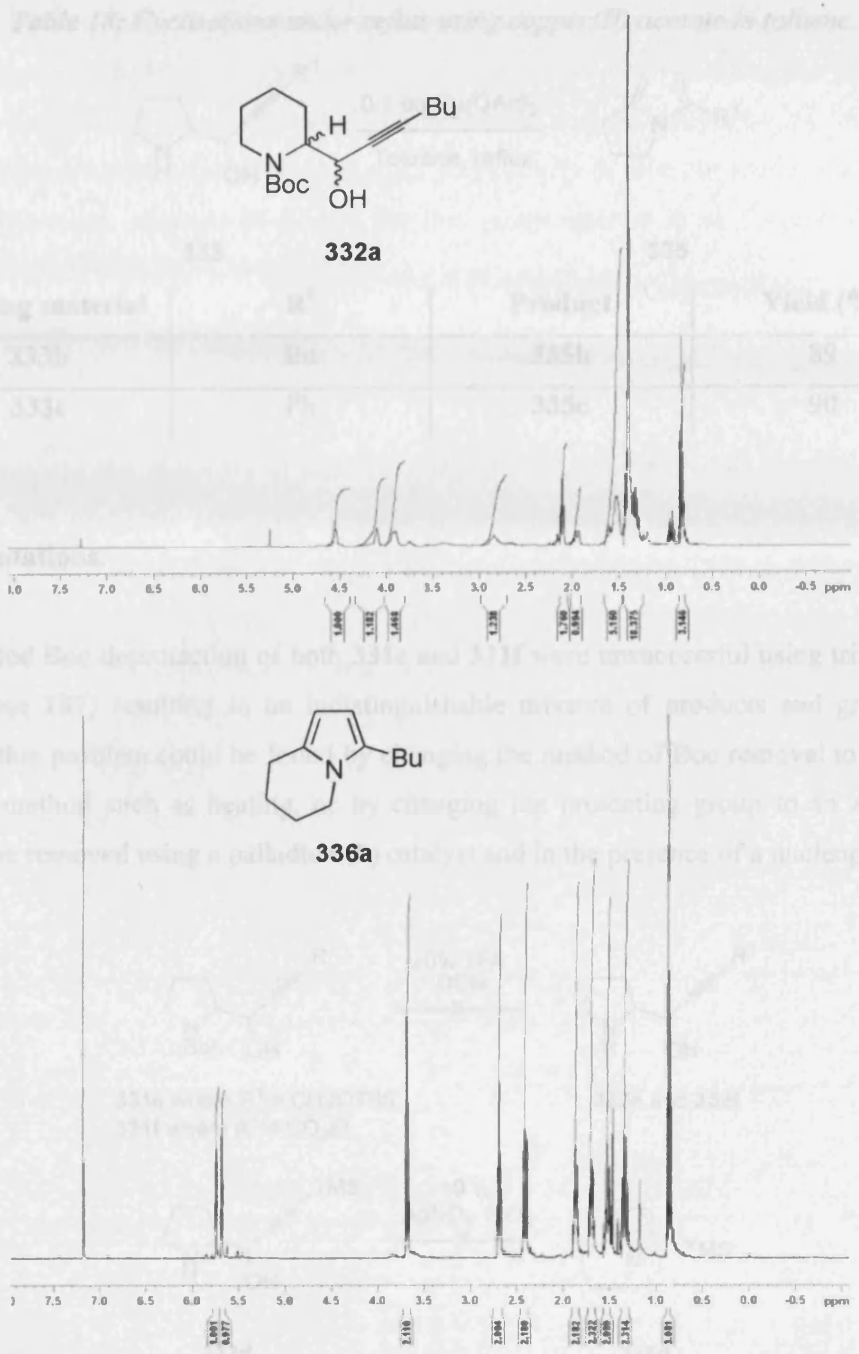
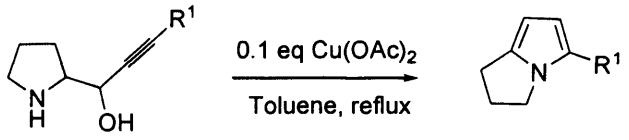


Figure 22: *[1]H-NMR of starting Boc-piperidine* ***333a*** *and final product* ***335a*** *(Indolizine).*

Another interesting and yet suprising observation came from the successful cyclisation of both substrates **333b** and **333c** using copper(II) acetate in toluene at reflux. The cyclisations were achieved in 4 hours and gave only the pyrrolizines in high yields of 89% and 90% repectively for **335b** and **335c** (Table **18**).

Table 18: Cyclisations under reflux using copper(II) acetate in toluene.

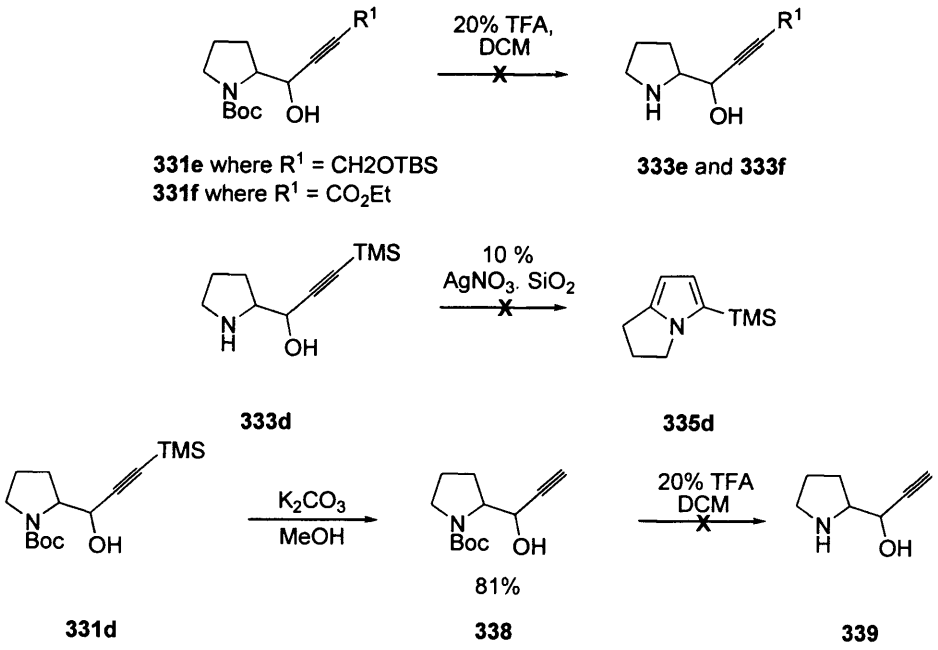


333 **335**

Starting material	R^1	Product	Yield (%)
333b	Bu	**335b**	89
333c	Ph	**335c**	90

4.3.4.4 Limitations.

The attempted Boc deprotection of both **331e** and **331f** were unsuccessful using trifluoroacetic acid (Scheme **107**) resulting in an indistinguishable mixture of products and great loss. A solution to this problem could be found by changing the method of Boc removal to a milder or non acidic method such as heating, or by changing the protecting group to an Alloc group which can be removed using a palladium(0) catalyst and in the presence of a nucleophilic trap.

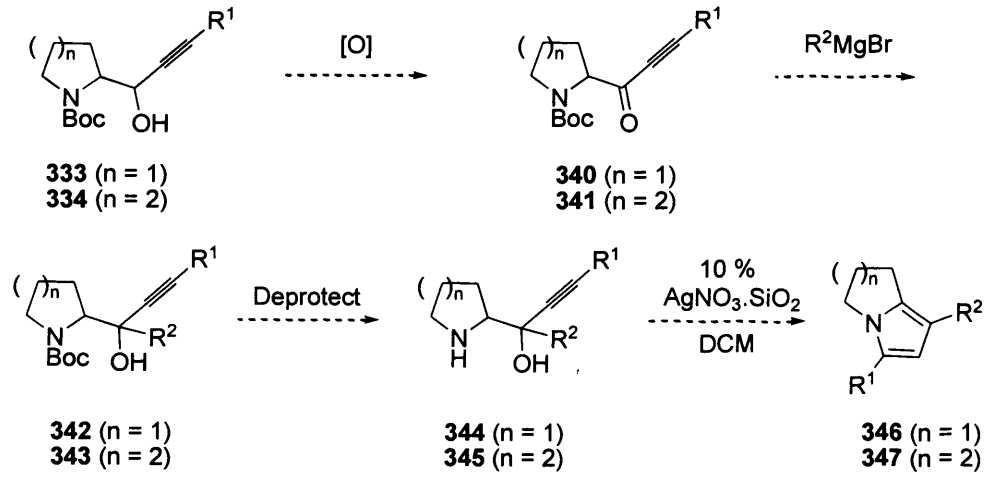


Scheme 107: Some unsuccessful results.

Another limitation is that exposure of pyrrolidine **333d** to 0.1 equivalents of 10% $AgNO_3.SiO_2$ gave no pyrrolizine **335d**, even after prolonged exposure (30 h). Increasing the silver(I) to 0.5 equivalents and even to one equivalent no product **335d** was observable by ^{1}H-NMR analysis. Removal of the trimethylsilyl group proceeded successfully to give the terminal alkyne **338** in 81% yield, however, attempts to remove the Boc group resulted in an ill-defined mixture of products and great loss.

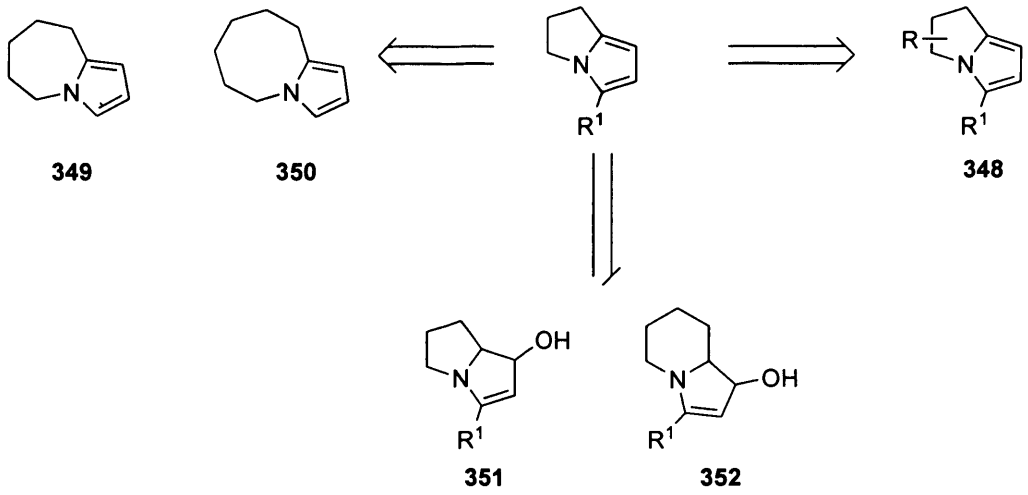
4.3.4.5 Future work.

Future avenues for the chemistry include the synthesis of 3,5-disubstituted pyrrolizines **346** and indolizines **347** (Scheme **108**), This would involve oxidising the 2-hydroxy-2-propargylic pyrrolidines **334** or piperidines **334** to give the propargylic ketones **340** or **341**, followed by addition of a Grignard reagent such as methyl magnesium bromide to give the tertiary propargylic alcohol **342/343**. This would then be followed by removal of the Boc group to give the free amines **344/345** which could be an issue with a sensitive tertiary propargylic alcohol. If this were to be an issue then maybe changing the protecting group would be a good strategy such as replacing the Boc group with an Alloc group.



Scheme 108: *Proposed synthesis of 3,5-substituted pyrrolizines **346** and indolizines **347**.*

Other possibilities (Figure **23**) include allowing for functionality around the saturated ring **348** to be incorporated, as well as a possible extention of the chemistry into smaller or larger ring systems such as pyrrolo-azepines **349** (7,5-fused rings) and pyrrolo-azocines **350** (8,5-fused rings) which would be of great interest.



349 **350** **348** **351** **352**

Figure 23: *Future avenues for the pyrrolizine and indolizine chemistry.*

Another interesting facet was the successful cyclisations of pyrrolidines **333b** and **333c** using copper(II) acetate in toluene (Table **18**) to give pyrrolizines **335b** and **335c**. Due to the success of these reactions, further examples would need to be assessed. This success also suggests that isolation of hydroxydihydropyrrolizines **351** and hydroxydihydroindolizines **352** (Figure **23**) by use of Sharland's chemistry[2] may be possible. All this of course opens up a wide area of chemistry waiting to be explored giving possible access to new structures, natural targets and potential drugs.

4.3.4.6 Possible applications to natural products.

The chemistry that leads to the core structure of the pyrrolizines and indolizines can give access to a wide range of polycyclic compounds many of which can be found in nature. Many of these compounds possess potent biological activity and have found uses for the treatment of many diseases.

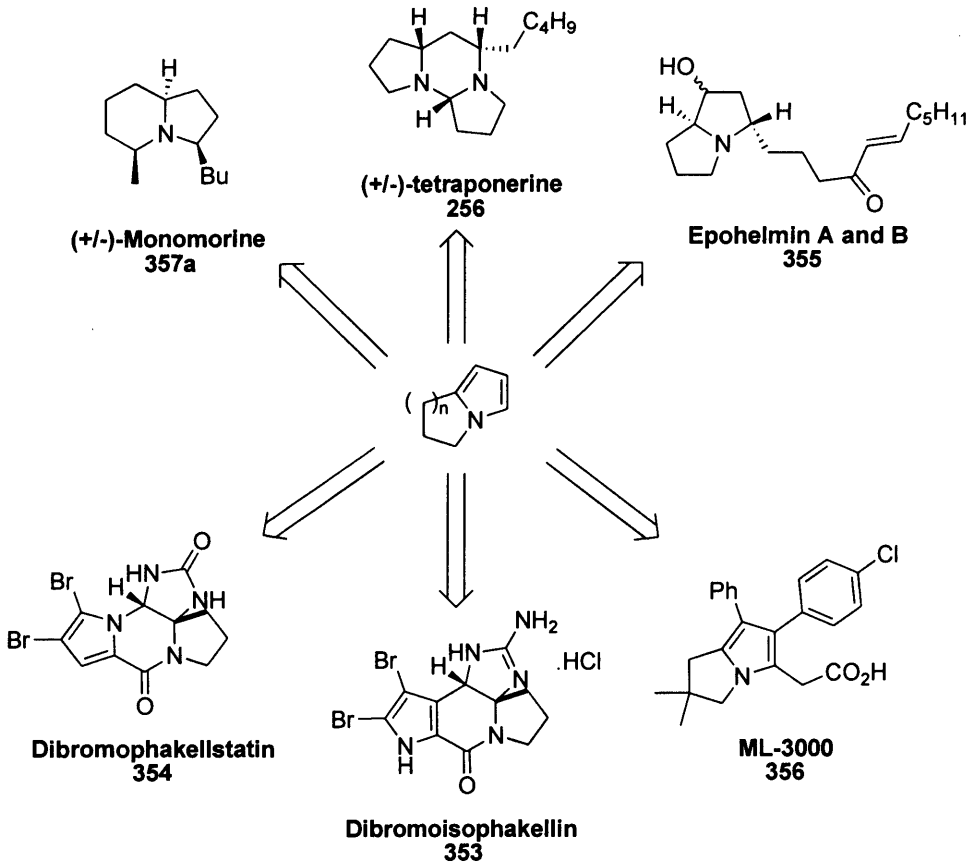
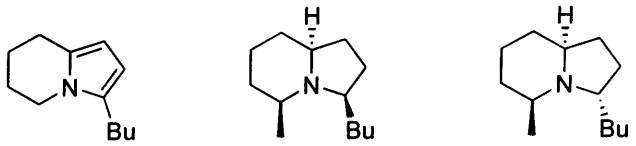


Figure 24: *Some important biologically active natural and synthetic fused-pyrroles.*

Examples include the phakellin family of compounds including dibromoisophakellin **353**[109] isolated from the sponge *Acanthella carteri* and dibromophakellstatin **354**[110] which was isolated from *Phakellia mauritiana*, which showed potent anti-tumor activity in a large range of human cells. Others include Epohelmin A and B **355**[111-112] that display lanosterol synthase inhibition, as well as ML-3000 **356**[113] that is a cyclooxygenase and 5-lipoxygenase inhibitor and Monomorine **357a**[114] (Figure **24**).

As can be seen upon inspection of the structures of the pyrroles (Figure **24**), the core of these compounds contains a pyrrole or pyrrolidine ring that is fused at the nitrogen and at C-1 to a saturated cyclohexane or cyclopentane ring that has some functionality attached. By elaboration of the chemistry used to synthesise the pyrrolizines and indolizines reported in this thesis, access to these highly biologically active compounds could be achieved. In particular a similarity between Monomorine **357a** and **357b** and substrate **336a** can be clearly seen so extension of this chemistry should lead to this natural product (Figure **25**).

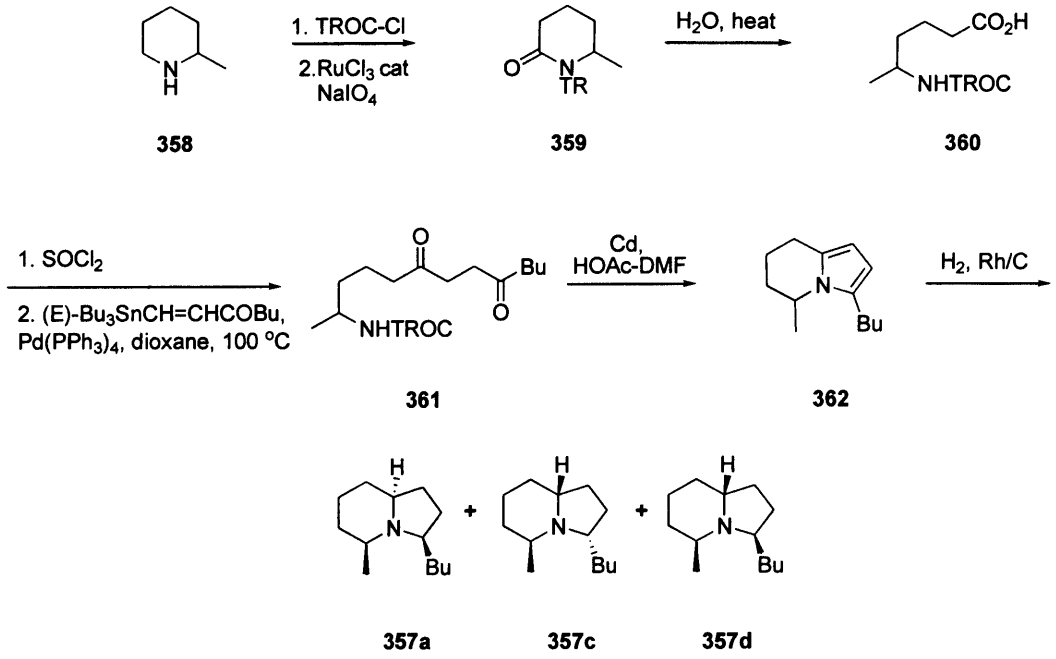


336a **357a** **357b**

Figure 25: *Comparison of Monomorine **349a/349b** and indolizine **335a.***

The alkaloid Monomorine is an important indolizine alkaloid, two isomers in particular: Monomorine I **357a** as above was isolated from the ant *Monomorium phataonis* and its epimer **357b** was isolated from the skin of the poisonous frog *Dentrobates histrionicus* (Figure **25**). A seven step synthesis of (+/-)-Monomorine I was carried out by Echavarren and co-workers.[115] Starting from 2-methylpiperidine **358**, the synthesis (Scheme **109**) involves TROC (2,2,2-trichloroethoxycarbonyl) protection with the chloroformate (TROC-Cl), followed by oxidation using ruthenium(III) chloride to give the lactam **359**.

This is then followed by ring opening hydrolysis by heating in water to give the acid **360**, followed by formation of acid chloride using thionyl choride and then palladium-catalysed reductive coupling with a β-stannyl enone to give the dione **361**. The reductive-coupling was believed to be catalysed by the palladium species and promoted by tributyltin(I) chloride (a by product of the coupling reaction). The reduction does, however, appear to be in part thermally induced as reduction of the temperature to 40 °C for the coupling resulted in isolation of the α,β-unsaturated diketone (an intermediate in the reaction step). The reductive cleavage of the TROC protecting group was then carried out using cadmium in a 1:1 mixture of acetic acid and dimethyl formamide to give the indolizine **362**. Finally, hydrogenation using ruthenium on carbon resulting in a 2:2:1 mixture of Monomorine I **357a** and two of its diastereomers **357c** and **357d** respectively with an overall yield of 20% for the mixture.



Scheme 109: *Echavarren and coworkers synthesis of Monomorine I and two of its diastereomers.*

Similarly Mori and coworkers[116] reported a three step synthesis of (+/-)-Monomorine I using nitrogen fixation as a key step to give Monomorine I **357a** in 6% overall yield as a mixture with other diastereoisomers to give a total overall yield of 10%.

Using the disconnection approach (Figure **26**) it would seem that the route used for the synthesis of pyrrolizines and indolizines developed herein could be applied to the synthesis of the natural product Monomorine. A look at the commercial compounds found a suitable starting material, this being 6-methyl piperidine-2-carboxylic acid **363** which is available as a diastereomeric mixture. This would of course result in a racemic mixture of monomorine and its isomers.

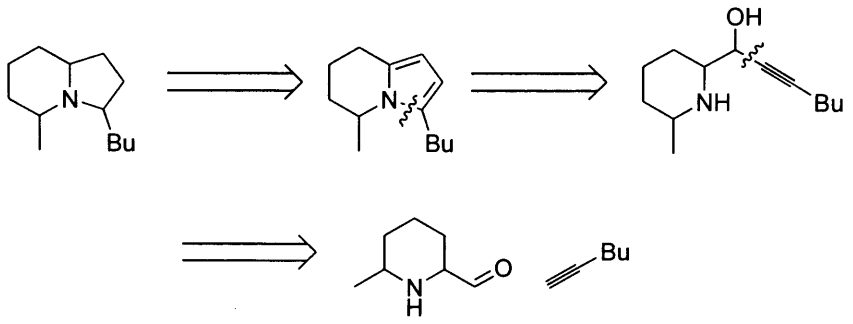
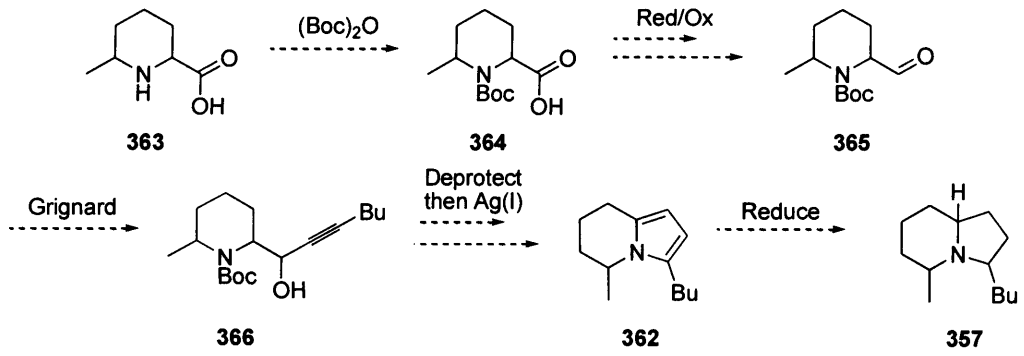


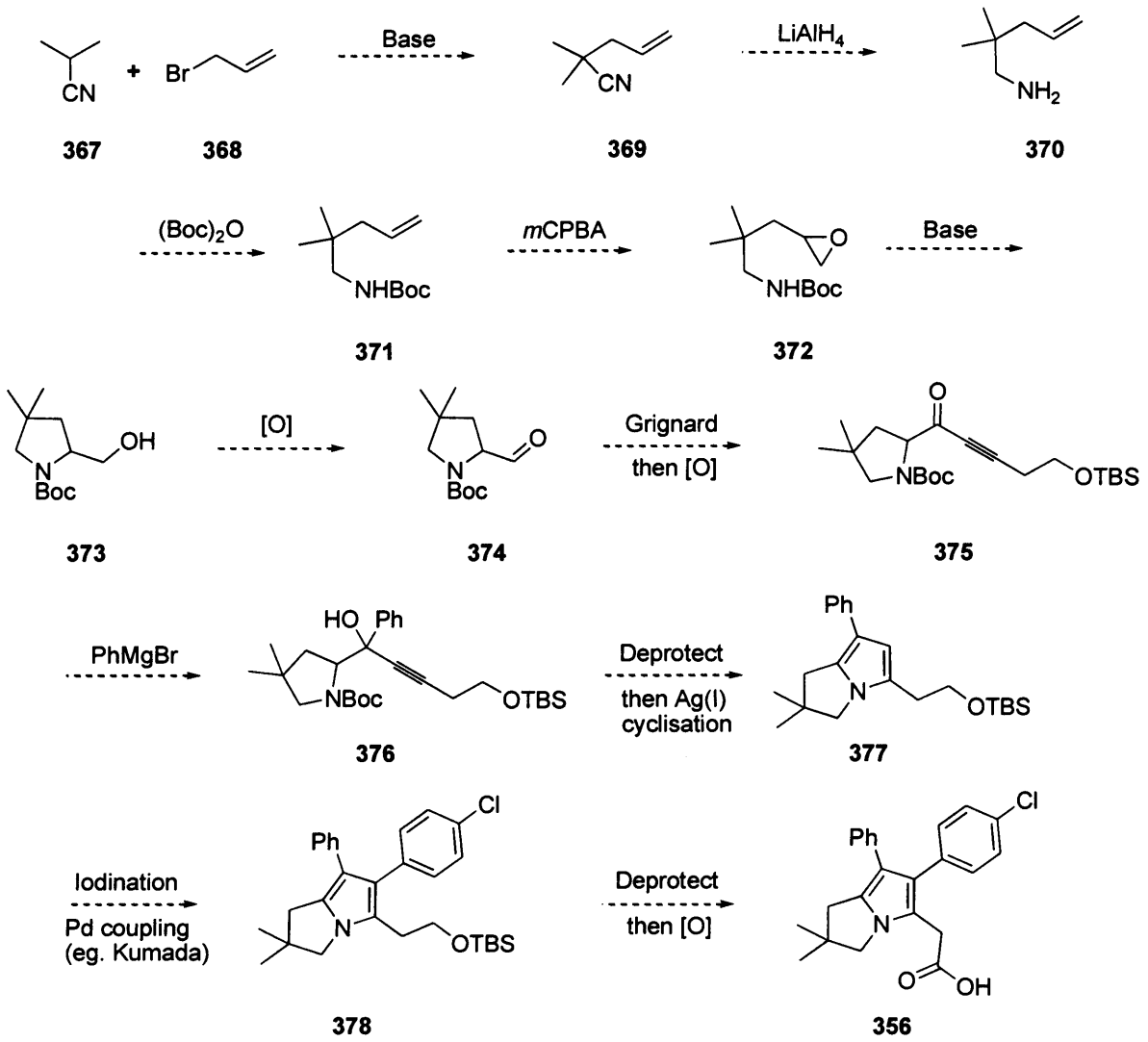
Figure 26: *Retrosynthesis of monomorine.*

Starting from commercially available 6-methylpiperidine 2-carboxylic acid **363** (Scheme **110**), Boc protection to give the carbamate **364** would be followed by conversion into the aldehyde **365**. Care to prevent epimerisation would not need to be taken as cyclisation would result in all but one of the stereocentres being removed. Addition of the Grignard reagent derived from 1-hexyne would give *N*-Boc protected 1-(6-methylpiperidin-2-yl)hept-2-yn-1-ol **366** which would then undergo deprotection to give 1-(6-methylpiperidin-2-yl)hept-2-yn-1-ol. Cyclisation would then be carried out using 10% silver nitrate on silica gel to give the indolizine **362** as previously reported. Subsequent reduction using a catalyst such as ruthenium on carbon would produce the natural product monomorine I and its diastereomers **357**. The advantages of this suggested route are that the preparation of the indolizines has proven to be very successful and high yielding with the synthesis of the indolizine **336a** having an overall yield of 41% in 5 steps starting from piperidine 2-methanol **337**. The subsequent and final step would be the hydrogenation using the ruthenium catalyst which in the example shown by Echavarren gave monomorine I and its isomers in a yield of 60% (for the one step). Another possibility would be to start from 6-methyl-pyridine-2-methanol and apply the same methodology, however attempts to cyclise onto aromatic systems using this method has yet to be carried out and is a possibility for future work.



Scheme 110: *Proposed route to monomorine I and its diastereomers.*

Another possible application of the chemistry could be towards the synthesis of the drug ML-3000. A non-steroidal dual inhibitor of both cyclooxygenase and 5-lipoxygenase it has shown great potential for the treatment of arthritis. Previous methods for the synthesis have proven low yielding with an original method resulting in 5% yield of ML-3000 **356**.[117] Cossy and coworkers[118] improved upon the synthesis by using an 8 step process to give ML-3000 **356** in 19% overall yield, with the key step being the acid-promoted bicyclisation of a ω-acetylenic amino-ester.



367 **368** **369** **370** **371** **372** **373** **374** **375** **376** **377** **378** **356**

Scheme 111: *A proposed synthesis of ML-3000* ***356****.*

The new proposed synthesis (Scheme **111**) would involve starting from cheap commercially available isopropyl cyanide **367** (£17.40 per 100 ml). Deprotonation using a base such as LDA followed by addition with allyl bromide **368** would give the 2,2-dimethylpent-4-enenitrile **369**. This would then be followed by reduction using lithium aluminium hydride to give the amine **370** which would then be protected using Boc anhydride to give the carbamate **371**. This would be followed by epoxidation using *m*CPBA to give the epoxide **372**. Then deprotonation of the carbamate **372** with a hindered base such as LDA would then result in attack on the epoxide to give the alcohol **373**, which would then be oxidised to the aldehyde **374**. The aldehyde would then be reacted with an acetylenic Grignard reagent followed by oxidation to give the propargylic ketone **375**. Addition of phenylmagnesium bromide to the ketone would give the tertiary alcohol **376**. The tertiary alcohol would then undergo deprotection, followed by

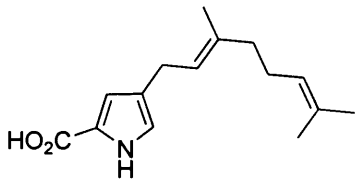
cyclisation using catalytic (0.1 eq) 10 % $AgNO_3.SiO_2$ to give the disubstituted pyrrolizine **377**. Iodination in the C-4 position of pyrrolizine **377** followed by palladium catalysed coupling with the Grignard of 1,4-dichlorobenzene to give the trisubstituted pyrrolizine **378**. The alcohol moiety of the pyrrolizine **378** could then undergo deprotection and oxidation to give the final product ML-3000 **356**.

4.3.5 Application of the silver-mediated cyclisation towards a natural product.

4.3.5.1 Introduction to pyrrolostatin

A wide range of heterocycles have been synthesised by silver-based 5-*endo*-dig cyclisation. Its wide ranging application has allowed for the synthesis of pyrroles, pyrrolizines, tetrahydroindolizines, indoles and pyrazoles in generally high yields (>95%).

Due to the success of the cyclisation of a wide range of model substrates, this raised the question of whether this could be applied to the synthesis of a specific target such as a natural product. There has been a hive of activity of late in the area of lipid peroxidation[119] and an ever growing interest in its inhibition by antioxidants. This growing interest has been fuelled by an increase in the number of sufferers of heart disease due to a combination of a bad diet and a sedentary lifestyle. This has therefore become big business for the pharmaceutical industry. One drug in particular which is known to treat this condition is Atorvastatin,[80] the highest selling drug of 2006 grossing Pfizer $12.9 billion. One particular compound which we will be focusing on was isolated from *Streptomyces chrestomyceticus*[120] was shown to display lipid peroxidation inhibition activity on a par with Vitamin E (α-Tocopherol). This novel compound known as pyrrolostatin **379** (Figure **27**) is a 2,4-disubstituted pyrrole with a carboxylic acid in position 2 and a geranyl residue in position 4.



379

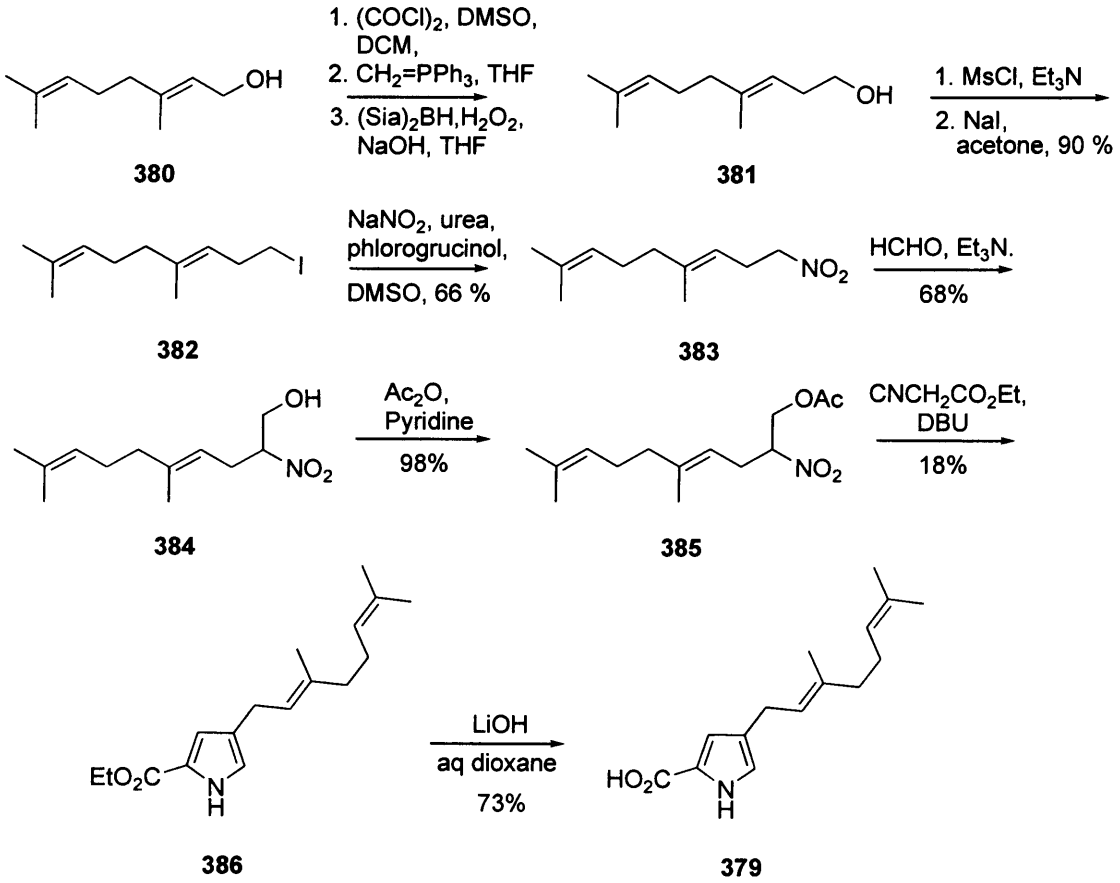
Figure 27: *Natural lipid peroxidation inhibitor pyrrolostatin **379**.*

Syntheses of 2,4-disubstituted pyrroles are few and far between and only a handful of methods have been established.[121-122] The silver(I) and copper(II)-mediated cyclisation methodologies

have been shown to be suitable for the synthesis of 2,4-disubstituted pyrroles as the synthesis of **313i** and **313j** has shown (*cf.* Section **4.3.2.6**, pg. 87-88 and Section **4.3.2.8**, pg 89-90).

4.3.5.2 Previous synthesis of pyrrolostatin

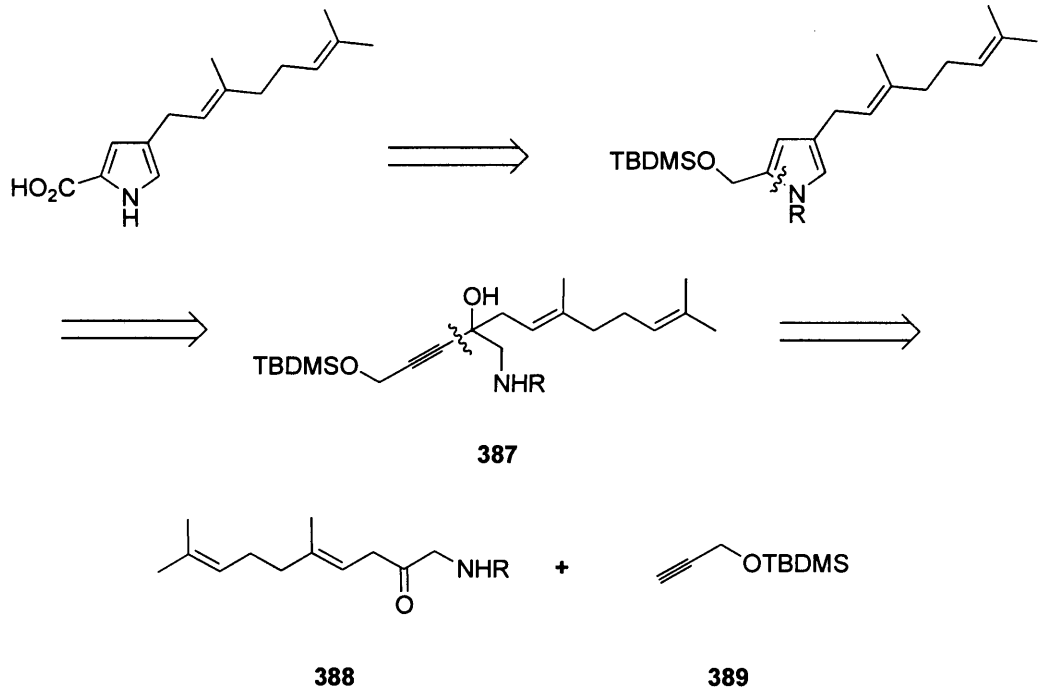
Ono and coworkers[123] reported the only previous synthesis of pyrrolostatin **379** by a seven step sequence starting from geraniol **380** (Scheme **112**). The sequence involved conversion of geraniol **380** into homo-geraniol **381** followed by substitution to give the iodide **382** in 90% yield. This was then converted to the nitroalkane **383** in 66% yield, which underwent coupling with formaldehyde to give the β-nitro-alcohol **384** in 68% yield. This was then treated with acetic anhydride to give the β-nitro-acetate **385** in 98% yield. The next step was a Barton-Zard reaction[122] to give the pyrrole-2-carboxylate **386** in a very low yield of 18%. Finally, hydrolysis using lithium hydroxide gave the pyrrolostatin **379** in 73% yield as a yellow crystallisable solid resulting in an overall yield of 5%.



Scheme 112: *Ono and co-workers synthesis of pyrrolostatin 379.*

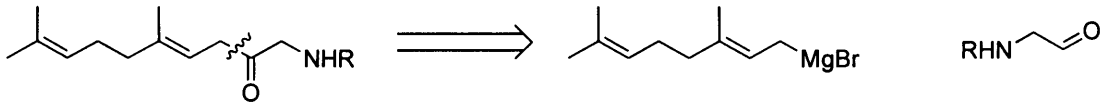
4.3.5.3 Proposed syntheses of pyrrolostatin

Using the silver-mediated approach to pyrrole synthesis, it was necessary that a key step for our projected pyrrolostatin synthesis be the nucleophilic attack of an amine onto the sp centre (an alkyne). A look at the disconnection of pyrrolostatin (Scheme **113**) shows that in order get the 2,4-disubstituted pattern the required structure of the pyrrole precursor would have to be that of the mono-protected diol **387**. It was then important to consider the nature of the acetylide. The acetylide would of course have to be introduced as the nucleophile and the electrophile would therefore be the ketone **388**. But in what form would the acetylide be introduced? If the acetylide was introduced as the acid then it probably would not cyclise due to it being too electron deficient. A means of overcoming this issue would be to have the acetylene introduced as the protected alcohol **389** as it was believed that this group would have no issues in regards to cyclisation with silver(I). The acetylide would be deprotonated by means of a nucleophilic base such as ethylmagnesium bromide or *n*butyl lithium, which would then be added to the ketone. With the acetylene **389** and ketone **388** decided upon it was then necessary to ascertain how the geranyl group would be introduced and two possible pathways were determined. The geranyl group would either need to be introduced as an electrophile or as a nucleophile.



Scheme 113: *Retrosynthesis of pyrrolostatin: ketone **388** as electrophile and alkyne **389** as nucleophile*

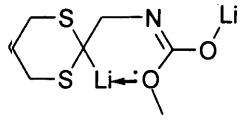
An obvious choice would be by disconnection to introduce the geranyl as a nucleophile. This route could start from a masked glycinate derivative, which would undergo protection and oxidation to give the *N*-protected amino aldehyde **390**. Introduction of the geranyl group as a nucleophile would require either the lithium or Grignard reagent **391** (Figure **28**). This at first glance looks like an ideal method to access pyrrolostatin; however, upon closer inspection problems with introducing this part as a nucleophile can be clearly seen. The geranyl moiety is an allylic nucleophile, in other words a negative charge next to an alkene. This could present problems as the negative charge could be displaced across the allylic system and upon nucleophilic attack onto the amino aldehyde (masked glycinate) would result in a mixture of regioisomers which are likely to be inseparable. Due to sterics it is likely that the desired Grignard would be the major product from the transmettalation. However, we felt that due to the possible issue of regioselectivity this was perhaps not the best route.



388 **391** **390**

Figure 28: *Geranyl bromide as a nucleophile-possible route to pyrrolostatin.*

In order to eliminate the issue of regioselectivity the other possible route would be to have the geranyl moiety as the electrophile and hence the amino alcohol component would be the nucleophile. Examination of the literature revealed a possible solution in the form of a masked glycinate. Work carried out by Seebach and co-workers[124] showed the use of the desired amino aldehyde masked as a dithiane which by lithiation of the dithiane, resulted in generation of the required nucleophile (an example of an Umpolung reagent). The nucleophile (intermediate) probably exists as a tight monomeric complex **392** (Figure **29**) or possibly a dimeric species.



392

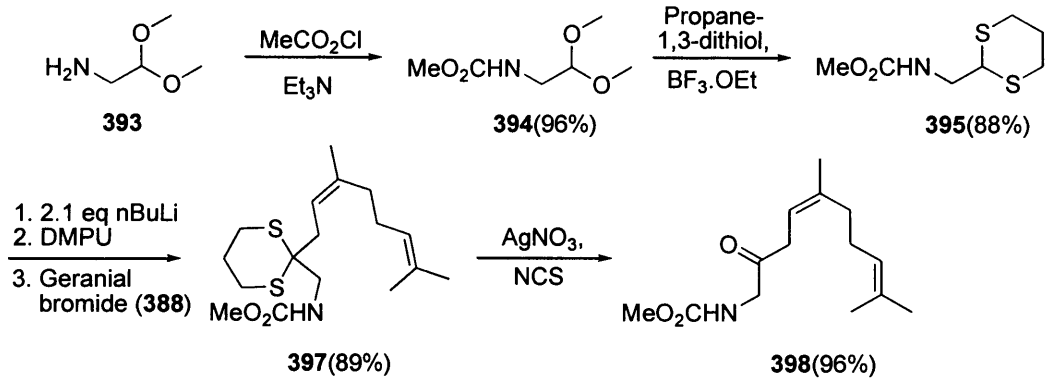
Figure 29: *Monomeric complex of nucleophile 392.*

This was followed by the addition of DMPU (a safe alternative to HMPA) which complexes strongly with lithium breaking up the intermediate complex **392** rendering it much more nucleophilic. This was then reacted with an appropriate electrophile with a good leaving group to give a product. A range of electrophiles have been used with this chemistry including

triflates, sulfonates, epoxides alkyl, aryl and allyl halides.[125] In other words having the geranyl bromide as the electrophile seems much more attractive and we therefore set out to incorporate this methodology into our synthesis of pyrrolostatin.

4.3.5.4 Our synthesis of pyrrolostatin

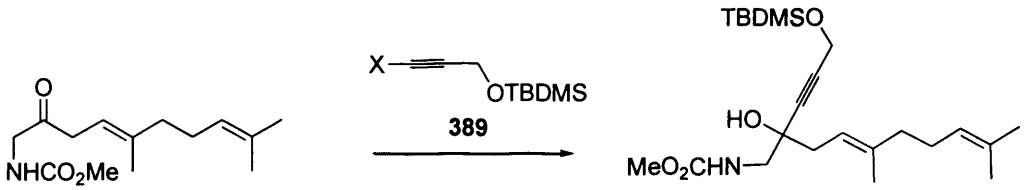
Our proposed synthesis of pyrrolostatin involved the initial protection of commercially available aminoacetaldehyde dimethyl acetal (effectively a masked glycinate) **393** (Scheme **114**) with methyl chloroformate which gave methyl 2,2-dimethoxyethylcarbamate **394** as a pure orange oil in 93% yield. This was then followed by exchange of the acetal group with a dithiane using propane-1,3-dithiol and the Lewis acid boron trifluoride-diethyl etherate to give the dithiane **395** as a colourless solid (93%). This was then followed by the chemistry outlined by Seebach, which involved coupling of the dithiane **395** and an electrophile with a good leaving group which in this case was geranyl bromide **396**. This successfully gave the desired product **397** in 88% yield as an orange oil. It is important to note that not using the DMPU resulted in no product being formed and a large amount of starting dithiane being recovered with a mixture of unidentified by-products. The benefits of the method were that with the dithiane in place, a simple cleavage using a mixture of silver nitrate and *N*-chlorosuccinimide with a reaction time of only three minutes resulted in the free ketone **398** in 90-98% yield that was neatly set up ready for the acetylide addition. However, this turned out not to be a "simple cleavage": extension of the reaction time resulted in a very significant reduction in yield and by-products formation apparently from the addition of chlorine to the alkene groups. It is also worth noting that purification of the ketone **398** was not required and any attempt to purify it resulted in a roughly 50% drop in yield. It was only after some experimentation that these very specific conditions were discovered. The upside of this is that the resulting ketone samples **398** were remarkably clean and suitable for direct coupling with an acetylide.



Scheme 114: *Proposed synthesis of pyrrolostatin- the first four steps.*

The next step was then the addition of the silyl-protected propargyl alcohol **389** to the ketone **398** and this step also proved to have its own issues. Initial attempts to react the lithium acetylide of the propargylic alcohol **389** with the ketone **398** resulted in complete recovery of starting material and no detectable product being formed at -78 °C. Although the reaction was not fully optimised, by investigation of various set of conditions, the best result for the addition of the acetylide **389** to the ketone **389** was found to be addition of the Grignard reagent at -15 °C which after 4 hours gave 45% conversion to products according to ^{1}H-NMR analysis (Table **19**).

Table 19: *Conditions attempted for the addition of acetylide **389** to ketone **398**.*



398 **399**

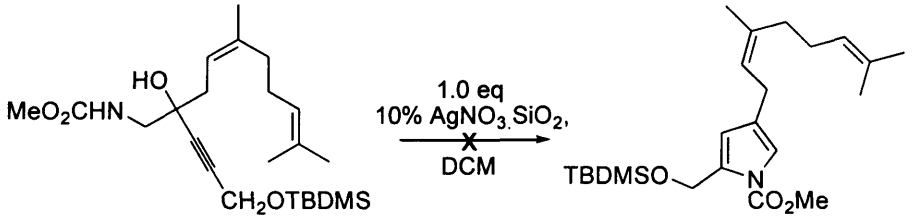
X	Temperature (°C)	% conversion to product
Li to $CeCl_3$	-78	0
Li	-78	0
MgBr	-78	0
MgBr to $ZnCl_2$	0	0
MgBr	0	Indistinguishable Mixture
MgBr[a,]	-40	25
MgBr[a,]	-15	45

Remaining yield was recovered starting material. % conversion is a crude estimate based on ^{1}H-NMR analysis and are not isolated yields. Results are taken after 4 h.

With this in mind, the best conditions for the acetylide **389** addition to the ketone **389** was chosen to be -15 °C as it gave the best result for acetylide coupling and no by-products. Under these conditions by extension of the reaction time to 18 hours an increase in yield to 51% was achieved as indicated by ^{1}H-NMR analysis of the crude mixture. Upon passing the crude mixture through a plug of silica using hexane to pure ethyl acetate as eluent the silyl protected diol **399** was isolated, still as a crude mixture with a ratio of 67% diol **399** and 33% ketone **398**. Further attempts were not made to purify the silyl protected diol **399** due to its sensitivity. This gave the mono-protected propargylic diol **399** in a crude yield of 49%. If the starting material could be recovered then the yield would increase to 83% (based on recovered starting material),

although this is based on there being no loss of the diol **399** upon column chromatography, which is unlikely.

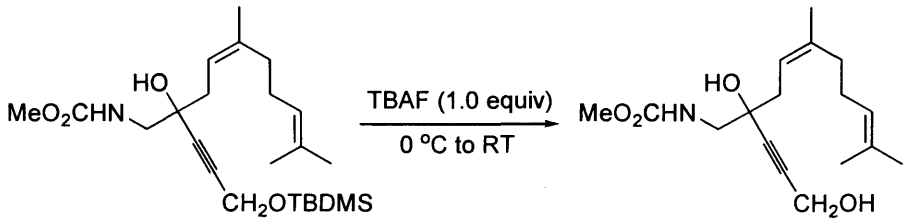
The next step was initially planned to be the silver-mediated cyclisation of the silyl-protected diol **399**. However, exposure of this mono-protected diol **399** to 0.1 equivalents of 10% $AgNO_3.SiO_2$ gave negligible amounts of pyrrole **400**. Worryingly, even exposure to one equivalent of the silver reagent gave very poor results (Scheme **115**).



399 **400**

Scheme 115: *Unsuccessful silver(I) cyclisation of protected diol **399**.*

It was hoped that upon deprotection of the silyl group using tetrabutylammonium fluoride, the resulting diol should cyclise successfully. The deprotection strategy proved successfully resulting in cleavage of the silyl group to give the deprotected diol **401**, albeit with a large amount of TBAF in the mixture (Scheme **116**).



399 **401** (54%)

Scheme 116: *Deprotection of silyl protected diol **399**.*

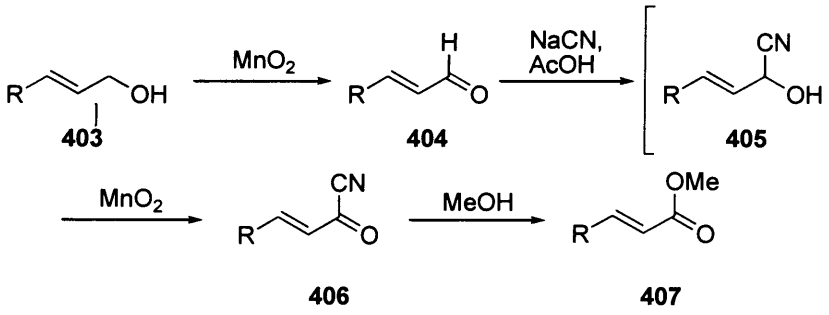
Due to the sensitive nature of tertiary propargylic alcohols, it was felt that column chromatography could result in great loss so cyclisation was attempted on this crude mixture. Unfortunately the crude mixture would not cyclise even upon exposure to an equivalent of silver(I). It was therefore decided that the TBAF residue must be interfering with the cyclisation, and this may have been due to the TBAF reacting with the 10% silver nitrate on silica to give silver(I) fluoride which it appears is unreactive towards the diol. It was therefore

decided that, despite the worry of loss, purification became necessary. Upon column chromatography, pure diol **401** was isolated in 54% yield. The isolated diol **401** was then immediately treated with 0.1 equivalents of 10% silver nitrate on silica gel, which we were delighted to find that after three hours the pyrrole **402** was isolated cleanly in >98% yield after passing through a plug of celite (Scheme **117**). This was a clear case of "rubbish in-rubbish out."

401 **402** (100%)

Scheme 117: *Cyclisation of diol **401**.*

With the core pyrrole now synthesised, it was then necessary to oxidise the pyrrole 2-methanol **402** to give the corresponding pyrrole-2-carboxylate. A look through the literature led us to one particular method as reported by both Corey[126] and later expanded upon by Taylor,[127] displaying the successful and experimentally direct oxidation of alcohols to esters by a tandem oxidation using manganese(IV) dioxide. The reaction involves the initial oxidation of a conjugated alcohol **403** with manganese dioxide to give a conjugated aldehyde **404**. The aldehyde was then exposed to a mixture of manganese dioxide and sodium cyanide in methanol in the presence of acetic acid to give the ester **407** (Scheme **118**).

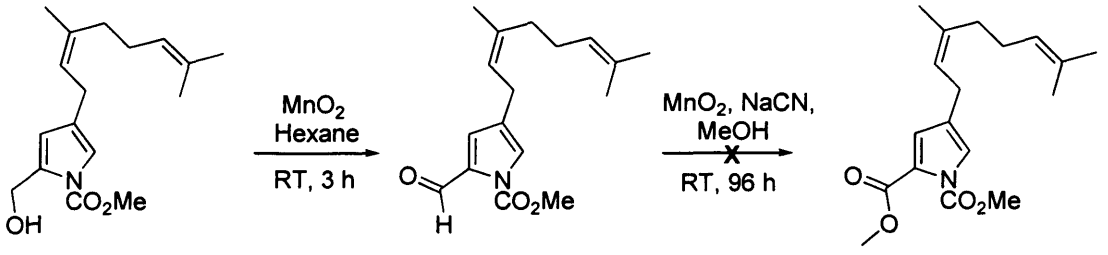


Scheme 118: *Corey's oxidation of alcohols to conjugated esters.*

The reaction involves nucleophilic attack of cyanide anion at the carbonyl centre of the aldehyde to form a cyanohydrin **405** thereby effectively regenerating an allylic alcohol. The manganese dioxide would then futher oxidise the cyanohydrin **405** to the acyl cyanide **406**. The acyl cyanide **406** then undergoes acid-catalysed methanolysis to give the conjugated methyl

ester **407**. In the absence of acetic acid yields were found to be lower and reaction times extended due to slower methanolysis.

Oxidation of pyrrole-2-methanol **402** with activated manganese(IV) dioxide in hexane gave the pyrrole-2-aldehyde **408** very cleanly in three hours at ambient temperature in near quantitative yields. The following oxidation using manganese dioxide and sodium cyanide in the presence of acetic acid was unexpectedly unsuccessful. Extention of the reaction time to 96 hours resulted in no product **409** being formed and only aldehyde **408** being recovered (Scheme **119**).



402 **408** (100%) **409** (0%)

Scheme 119: *Attempted oxidation using Corey's method.*

This was disappointing and it was somewhat suprising that no reaction took place; this may have been in part due to resonance reducing its reactivity towards the nucleophile which as a result shifts the equilibrium towards the starting materials. In effect by the principle of vinylogy, the aldehyde **408** more resembles a formamide (Figure **30**).

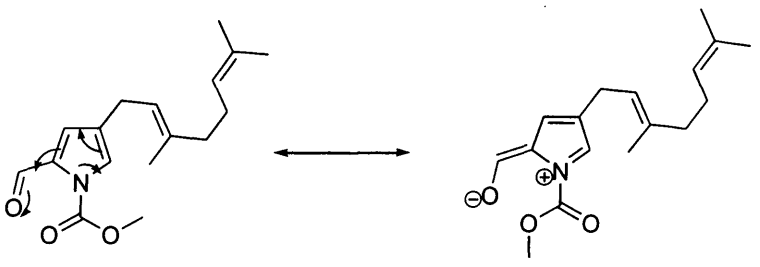
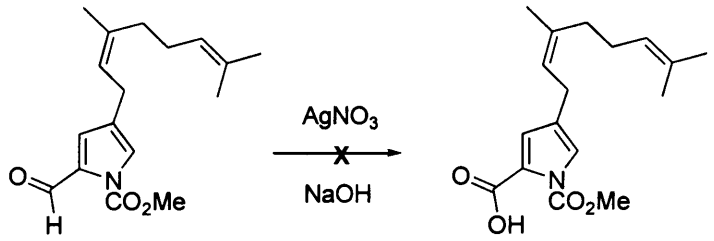


Figure 30: *Resonance of pyrrole-2-aldehyde **408**.*

As we had the aldehyde **408** in hand which proved to be quite stable (stable to air, weak acid and nucleophilic attack by cyanide), we decided to continue and attempt to oxidise the aldehyde to the acid. By examination of the literature, a possible method was the oxidation of the pyrrole-2-aldehyde to the acid by the use of silver(I) oxide (a harsh oxidant). The procedure proved to be applicable to pyrrole-2-aldehydes as an example in the literature proved.[128] The *in situ* generation of silver(I) oxide by reaction of silver nitrate with sodium hydroxide gave the

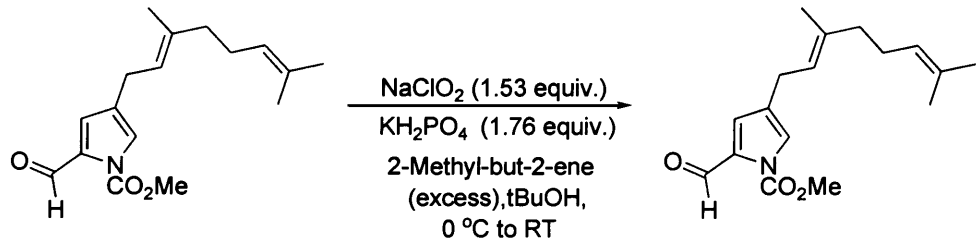
silver(I) oxide as a brown solid. Addition of the pyrrole-2-aldehyde **408** to the mixture and stirring proved to be unsuccessful resulting in an unfortunate indistinguishable mixture of products after just three hours. The desired pyrrole 2-carboxylic acid **410** was not detected by ^{1}H-NMR analysis but only a very small amount of starting aldehyde **408** was detected (Scheme **120**).



408 **410**

Scheme 120: *Unsuccessful oxidation of pyrrole-2-aldehyde **408** with silver(I) oxide.*

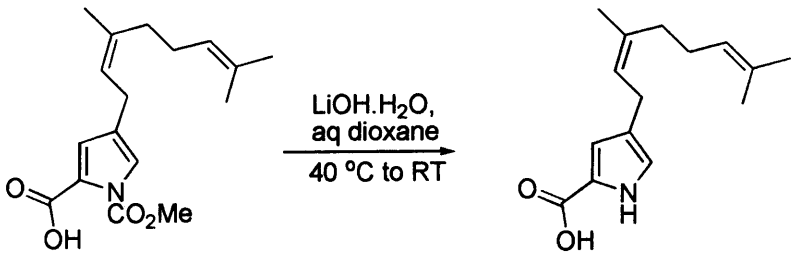
It was a case of back to the drawing board to find a more suitable method for oxidising the pyrrole 2-aldehyde **408** to the acid **410**. A look in the literature found a method that was much milder than silver(I) oxide. The reaction known as the Pinnick oxidation[129] involved using sodium chlorite as the oxidant and potassium dihydrogen phosphate as buffer and in the presence of 2-methyl-2-butene as a chlorine scavenger. Under these very popular conditions, we were delighted to find the oxidation to be very successful to give almost clean pyrrole 2-carboxylic acid **410** in 80% yield contaminated with negligible amounts of chlorinated 2-methyl 2-butene as a result of trapping the hypochlorite by-products (Scheme **121**).



408 **410** (80%)

Scheme 121: *Pinnick oxidation of aldehyde **408**.*

The final step in the synthesis was the removal of the carbamate group to give pyrrolostatin **379**. Following on from Ono's synthesis, we felt that as the use of lithium hydroxide dihydrate was successful in the cleavage of the pyrrole 2-carboxylate **386**, it should successfully cleave the carbamate of the pyrrole 2-carboxylic acid **410** (Scheme **122**). Using this methodology we were delighted to find that lithium hydroxide successfully cleaved the carbamate at 40 °C to give clean pyrrolostatin **379** (Figure **31**) after work up in 18 hours and in excellent yield (70%).



410 **379** (70%)

Scheme 122: *Final step in the synthesis of pyrrolostatin **379**.*

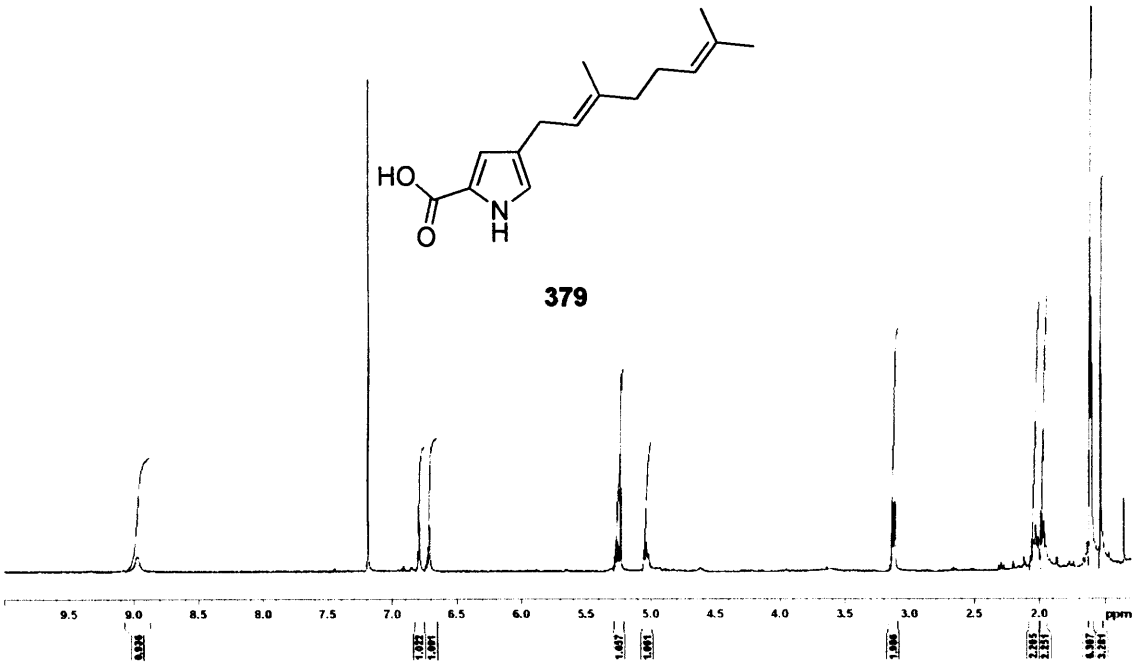


Figure 31: *^{1}H-NMR of the natural product pyrrolostatin **379**.*

Analysis of the ^{1}H-NMR of the synthesised pyrrolostatin **379** agreed with literature values as quoted by Ono and co-workers.[123] The melting point of the pyrrolostatin that we synthesised was 110-112 °C which was similar to that reported by Ono (Lit. m.p. 117-119 °C). The overall yield of the reaction was 15% over ten steps, and when compared with Ono's result of 5% overall yield over seven steps this proves to be a fantastic result and a major improvement in yield over Ono's synthesis.

4.4 Conclusions.

In conclusion, Sharland's method for the synthesis of hydroxydihydropyrroles **312** and pyrroles **313**[2] has been improved by removal of pyridine as co-solvent and by using the cheaper copper(II) catalyst as opposed to copper(I). This made the reaction both much less hazardous and also more scalable. The new reaction conditions, although unsuitable for the synthesis of hydroxydihydropyrroles **312**, gave pyrroles **313** cleanly in relatively short reaction times and in high yields (50-98%). The reaction did have some limitations in that so far it only seemed applicable to sulfonamides and the pyrolizines **335**. The reaction also seemed to be incompatible with large bulky groups which can hinder the cyclisation.

In the cases where the copper(II) reaction gave no reaction or very little product 10% $AgNO_3.SiO_2$ was used giving pyrroles in high yields at ambient temperature. The silver(I)-catalysed cyclisation was also shown to be applicable to the synthesis of fused pyrroles including anulated pyrroles and the *N*-junction pyrrolizines **335** and indolizines **336** resulting in clean products in high yields with only work-up of a simple filtration. Equally, the 10% $AgNO_3.SiO_2$ protocol was applicable to the synthesis of the natural product pyrrolostatin **379** with the key cyclisation step resulting in clean pyrrole in near quantitative yields.

Of course, there are issues that need to be addressed including finding a more suitable method for Boc removal of the pyrrolidines **331**, in particular those that decomposed. Further extension of the *N*-junction ring systems to include a wider variety of ring sizes and substitution patterns would also be of interest for future work. It seems that this method could, using the right starting materials, be used to access biologically active compounds such as Monomorine I **357**, as well as new potentially biologically active compounds.

Chapter Five

Experimental

Experimetal

5.1 General experimental:

Solvents and reaction conditions:

All non-aqueous reactions were, unless otherwise stated, conducted using oven or flame-dried glassware with dry solvents and under an atmosphere of dry nitrogen. Dry dichloromethane was obtained by fresh distillation from calcium hydride. Dry tetrahydrofuran was obtained by fresh distillation from sodium wire and benzophenone as indicator. All other dry solvents were obtained commercially from Fisher Scientific Ltd.

Reactions conducted at -78 °C were cooled using an acetone-solid carbon dioxide bath. Reactions carried out at 0 °C were cooled using an ice-water bath. Heated reactions were conducted in a stirred oil bath or heating mantle heated on a hotplate. Unless otherwise stated, reactions were stirred magnetically. Evaporated refers to solvent removal using a Buchi rotary evaporator with water pump vacuum and water bath at 25 °C. Overnight refers to stirring for 18-24 hours.

Purifications and TLC:

Silica gel chromatography and filtration was performed using Matrex Silica (35-70 μm). All reactions were monitored by tlc, using Merck silica gel 60 F254 pre-coated aluminium-backed plates and were visualised using ultraviolet light, potassium permanganate or ammonium molybdate.

M.p. data:

All melting points (m.p. °C) were determined on a Kofler hot-stage apparatus and are uncorrected.

IR data:

Infrared spectra were obtained using a Perkin Elmer 1600 series FourierTransform Infrared Spectrometer as a solution in dichloromethane (DCM), chloroform ($CHCl_3$) or neat.

NMR data:

δ_H refers to proton (^{1}H)-NMR and δ_C refers to carbon (^{13}C)-NMR and unless otherwise stated, NMR spectra were recorded on a Bruker DPX 400 instrument with ^{1}H-NMR recorded at 400 MHz and ^{13}C-NMR recorded at 100 MHz. NMR spectra recorded at 500 MHz were recorded using a Bruker DRX 500 instrument with ^{1}H-NMR recorded at 500 MHz and ^{13}C-NMR recorded at 125 MHz. Unless otherwise stated spectra were obtained from dilute solutions in deuteriochloroform and at 300 K. The abbreviations used for multiplicity are: singlet (s), doublet (d), triplet (t), quartet (q), pentet (pent.), septet (sept.), hextet (hex.), unresolved multiplet (m) or combinations. Apparent (app.) refers to overlapping peaks appearing to display a given multiplicity. Coupling constants (*J* values) are expressed in Hertz. Chemical shifts are reported relative to residual, undeuterated solvent (*e.g.*residual chloroform, 7.27 ppm in proton NMR).

Mass spectrometry

Mass spectra were recorded on a Waters GCT premier instrument using electron ionisation [EI], and recorded on a Waters LCT premier XE instrument using atmospheric pressure chemical ionisation [APCI] and electrospray techniques [ES]. Accurate high resolution mass spectrometric data were determined using the HRMS Service at Cardiff University, with the molecular formula corresponding to the observed signal using the most abundant isotopes of each element. The molecular formulae is quoted as either molecule (M), molecule + hydrogen $(M+H)^+$, molecule + potassium $(M+K)^+$, molecule + sodium $(M+Na)^+$ or molecule - water $(M-H_2O)$.

X-ray crystallography

X-ray crystal data were obtained from Dr Benson Kariuki at Cardiff University. Data was recorded on a Nonius Kappa CCDD diffractometer equipped with an Oxford Cryosystem cryostat. In general structures were solved by direct methods with additional light atoms found by Fourier methods. Hydrogen atoms were added at calculated positions and refined using a riding model. Anisotropic displacement parameters were used for all atoms other than hydrogen; hydrogen atoms were given isotropic displacement parameters equal to 1.2 or 1.5 times the equivalent isotropic displacement of the atom to which the hydrogen atom is attached.

Literature compounds

Compounds with references associated within the title compound are known compounds and any data recorded in this thesis matches well with those reported in the associated references.

5.2 Experimental for the synthesis of indoles

General procedure A for Sonogashira coupling [130]

Palladium on carbon (0.04 equiv), copper iodide (0.05 equiv), triphenylphosphine (0.2 equiv) and an aromatic halide (1.00 equiv) were suspended in a mixture of triethylamine (~1-1.5 ml per mmol of halide) and water (2-3 ml per mmol of halide) and stirred for 20 min. This was followed by the addition of a 1-alkyne (1.50 equiv) and the solution was then refluxed overnight. Upon cooling to ambient temperature, the resulting mixture was passed through a plug of silica to remove the metal and the silica was washed with ethyl acetate. The combined filtrates were washed with 2M hydrochloric acid (2 x volume of mixture), water (2 x volume of mixture) and brine (1 x volume of mixture) then dried over sodium sulphate, filtered and evaporated to yield the 2-alkynyl aniline which was usually sufficiently pure for use in the next step.

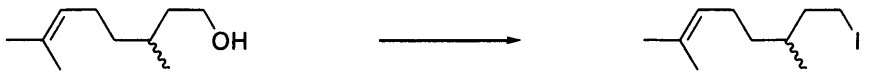
General procedure B for *N*-tosylation of 2-alkynyl anilines[131]

A solution of a 2-alkynyl aniline (1.00 equiv) in dichloromethane (~5-6 ml per mmol of aniline) was stirred for ten minutes before the addition of pyridine (2.00 equiv). The reaction was stirred for 15 minutes followed by the addition of *p*-TsCl (1.10 equiv). The reaction mixture was allowed to stir for a further 18h at room temperature, then was diluted with ethyl acetate (2 x volume of mixture) and washed with concentrated aqueous copper(II) sulphate (2 x volume of mixture). The aqueous layer was then back-extracted with ethyl acetate (3 x volume of mixture). The combined organic solutions were then washed with brine (1 x volume of mixture) then dried over sodium sulphate, filtered and evaporated. The crude mixture was then purified by column chromatography to yield the pure *N*-tosyl protected 2-alkynyl aniline.

General procedure C for Cyclisation using 10% $AgNO_3.SiO_2$

In a flask wrapped with metal foil, 10% w/w silver nitrate on silica gel (0.10 equiv) was added to a stirred solution of an *N*-protected 2-alkynyl aniline (1.00 equiv) in dry dichloromethane (20 mL g^{-1}). The resulting suspension was stirred for 18-48 h then filtered through celite and the solvent evaporated to yield the indole.

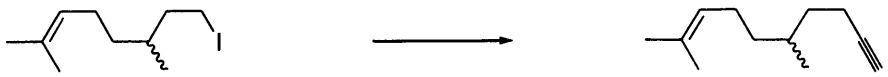
1-Iodo-3,7-dimethyloct-6-ene 131[1]



130 **131**

A solution of triphenylphosphine (7.40 g, 28.1 mmol) and imidazole (3.92 g, 57.6 mmol) in dry dichloromethane (40 ml) was stirred at ambient temperature until the solids dissolved. Iodine (6.82 g, 26.9 mmol) was added and the mixture was stirred for 15 min and was followed by the addition of citronellol **130** (2.00 g, 12.8 mmol). The mixture was then allowed to stir for 3 h, then quenched by the addition of water (10 ml) and extracted with diethyl ether (3 x 20 ml). The combined organic solutions were then washed with saturated aqueous sodium thiosulphate (2 x 10 ml) the mixture stirred and then dried, filtered and evaporated to give a white solid. Hexane (2 x 40 ml) was added and the solution was decanted from the solid and then evaporated to leave a clear oil of *citronellyl iodide* **131** (3.01 g, 88%); δ_H 5.11 (1H, app t, *J* 7.1, 6-H), 3.27 (1H, td, *J* 5.8, 4.4, 1-H_A), 3.22-3.16 (1H, m, 1-H_B), 2.07-1.86 (2H, m, 5-CH_2), 1.71 (3H, s, 7-Me), 1.70-1.64 (1H, m, 3-H), 1.63 (3H, s, 7-Me), 1.41-1.28 (2H, m, 2-CH_2), 1.28-1.15 (2H, m, 4-CH_2), 0.91 (3H, d, *J* 6.5, 3-Me).

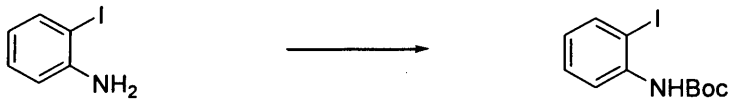
5,9-Dimethyldec-8-en-1-yne 132[1]



131 **132**

According to the established procedure,[132] lithium acetylide-diethylamine (0.90 g, 9.70 mmol) and dry dimethyl sulfoxide (10 ml) was stirred for 10 min to make a slurry. This was then cooled to 8 °C and citronell iodide **131** (2.00 g, 7.51 mmol) was added then the reaction was allowed to warm to room temperature and stirred for a further 1 h. Water (20 ml) was then added carefully and the product was extracted with hexane (3 x 20 ml) The combined extracts were dried, filtered and evaporated to give the *1-alkyne* **132** as a clear oil (1.15 g, 93%); δ_H 5.05-5.00 (1H, app. t, *J* 7.1, 8-H), 2.21-2.05 (2H, m, 3-CH_2), 1.98-1.87 (2H, m, 7-CH_2), 1.86 (1H, t, *J* 2.6, 1-H), 1.61 (3H, s, 9-Me), 1.54 (3H, s, 9-Me), 1.53-1.44 (2H, m, 4-CH_2), 1.32-1.19 (2H, m, 6-CH_2), 1.13-1.03 (1H, m, 5-H), 0.82 (3H, d, *J* 6.6, 5-Me).

***tert*-Butyl 2-iodophenylcarbamate 134**[133]

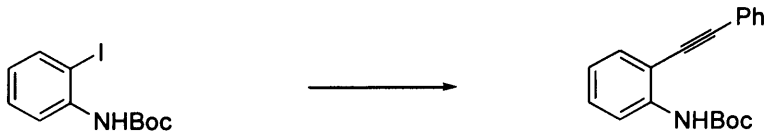


133 **134**

According to the established procedure[134] a solution of 2-iodoaniline **133** (3.00 g, 13.7 mmol) in tetrahydrofuran (80 ml) was cooled to -78 °C and a 2M solution of NaHMDS in tetrahydrofuran (13.70 ml, 27.39 mmol) was added dropwise. The mixture was allowed to stir for 0.5 h at -78 °C before warming to room temperature for 0.5 h. The solution was then re-cooled before the dropwise addition of Boc_2O (3.02 g, 13.8 mmol) in tetrahydrofuran (20ml). The mixture was stirred at -78 °C for 0.25 h before being quenched with saturated aqueous ammonium chloride. The solution was then allowed to warm to room temperature, followed by extraction with ethyl acetate (3 x 20 ml). The organics were washed with brine (2 x 20 ml), dried with sodium sulphate, filtered and evaporated to give crude orange oil. Column chromatography using 10% ethyl acetate in hexane afforded the *Boc-protected aniline* **134** as a yellow oil (4.00 g, 92%); υ_{max}/cm^{-1} (DCM): 3395, 3054, 2984, 2303, 1734, 1588, 1516, 1432,

1369, 1265, 1156, 1062; δ_H 7.89 (1H, d, *J* 8.1, CH (Ar)), 7.58 (1H, d, *J* 8.0, CH (Ar)), 7.15 (1H, t, *J* 8.0, CH (Ar)), 6.66 (1H, s, NH), 6.61 (1H, t, *J* 7.9, CH (Ar)), 1.38 (9H, s, 3 x CH_3C).

tert-Butyloxycarbonyl 2-(2-phenylethynyl)aniline 135[135]



134 **135**

According to the general procedure A, phenylacetylene (0.50 ml, 4.70 mmol) was added to a solution of *t*butyl 2-iodophenylcarbamate **134** (1.00 g, 3.13 mmol), triphenylphosphine (0.17 g, 0.63 mmol), copper iodide (0.03 g, 0.18 mmol), and 10% palladium on carbon (0.13 g, 0.12 mmol) in a 1:2 mixture of water and triethylamine (15 ml) to give the *2-alkynyl aniline* **135** as a yellow solid (0.90 g, 98%); m.p. 58-59 °C (lit. m.p.[134] 62-65 °C) υ_{max}/cm^{-1} (neat) 3406 (NH), 2978, 1734 (C=O), 1579, 1516, 1449, 1367, 1305, 1241, 1220, 1155, 1049, 753; δ_H 8.09 (1H, d, *J* 8.4, CH (Ar)), 7.49-7.44 (2H, m, 2 x CH (Ar)), 7.33-7.23 (5H, m, 5 x CH (Ar)), 6.92 (1H, t, *J* 8.0, CH (Ar)), 1.47 (9H, s, 3 x CH_3C); δ_C 152.7 (C=O), 139.5 (C), 132.5 (CH (Ar)), 131.6 (CH (Ar)), 129.7 (2 x CH (Ar)), 128.8 (CH (Ar)), 128.5 (2 x CH (Ar)), 122.2 (CH (Ar)), 121.8 (C), 117.6 (CH (Ar)), 96.1 (C≡C), 84.6 (C), 80.9 (C), 28.4 (3 x CH_3C).

Methyl 2-iodophenylcarbamate 136

133 **136**

A solution of 2-iodoaniline **133** (2.00 g, 9.13 mmol) and pyridine (2.20 ml, 27.4 mmol) in dichloromethane (50 ml) was cooled to 0 °C before the addition of methyl chloroformate (0.70 ml, 9.13 mmol). The reaction mixture was allowed to warm to ambient temperature and stirred overnight. The mixture was then diluted with dichloromethane (100 ml) washed with 0.2M hydrochloric acid (2 x 20 ml), water (3 x 20 ml) and brine (20 ml), dried with sodium sulphate, filtered and evaporated to give the *carbamate* **136** as an orange oil (2.20 g, 87%); υ_{max}/cm^{-1} (DCM): 3396, 3054, 2980, 2303, 1740, 1587, 1522, 1439, 1265, 1217, 1078; δ_H 8.07 (1H, d, *J*

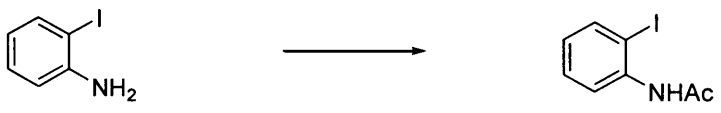
8.2, CH (Ar)), 7.78 (1H, dd, *J* 8.0, 1.5, CH (Ar)), 7.36 (1H, td, *J* 7.9, 1.5, CH (Ar)), 6.98 (1H, s, NH), 6.82 (1H, td, *J* 7.9, 1.6, CH (Ar)), 3.83 (3H, s, Me); δ_C 153.9 (C=O), 138.9 (CH (Ar)), 138.4 (C), 129.3 (CH (Ar)), 125.2 (CH (Ar)), 120.4 (CH (Ar)), 88.9 (C), 52.6 (CH_3); *m/z* (EI) 277 (M^+, 100%), 245 (100%), 217 (90%) [Found: $[M]^+$, 276.9602. $C_8H_8NO_2I$ required: *M*, 276.9600].

_N_-Methyloxycarbonyl 2-(hex-1-yn-1-yl)aniline 137

136 **137**

According to the general procedure A, 1-hexyne (0.60 ml, 5.41 mmol) was added to a solution of methyl 2-iodophenylcarbamate **136** (1.00 g, 3.61 mmol), triphenylphosphine (0.19 g, 0.72 mmol), copper iodide (0.03 g, 0.18 mmol), and 10% palladium on carbon (0.15 g, 0.14 mmol) in a 1:2 mixture of water and triethylamine (15 ml) followed by work-up to give the *2-alkynyl aniline* **137** as a yellow oil (0.82 g, 98%); υ_{max}/cm^{-1} (neat) 3396, 2957, 2872, 1744, 1581, 1522, 1452, 1308, 1233, 1065, 754; δ_H 8.04 (1H, d, *J* 8.2, CH (Ar)), 7.37 (1H, s, NH), 7.27-7.18 (2H, m, 2 x CHAr), 6.88 (1H, t, *J* 7.6, CH (Ar)), 3.71 (3H, s, MeO_2C), 2.41 (2H, t, *J* 7.0, 1'-CH_2), 1.55 (2H, *quintet*, *J* 7.1, 2'-CH_2), 1.43 (2H, *sextet*, *J* 7.2, 3'-CH_2), 0.89 (3H, t, *J* 7.2, 4'-CH_3); δ_C 153.8 (C=O), 139.0 (C), 131.7 (CH (Ar)), 128.7 (CH (Ar)), 122.4 (CH (Ar)), 117.3 (CH (Ar)), 112.2 (C), 97.8 (C≡C), 75.8 (C≡C), 52.4 (MeO_2C), 30.8 (1'-CH_2), 22.1 (CH_2), 19.3 (CH_2), 13.6 (4'-CH_3); *m/z* (ES) 232 ($M+H^+$, 100%); [Found: $[M+H]^+$, 232.1340. $C_{14}H_{18}NO_2$ requires: *M+H*, 232.1338].

_N_-(2-Iodophenyl)acetamide 138[136]

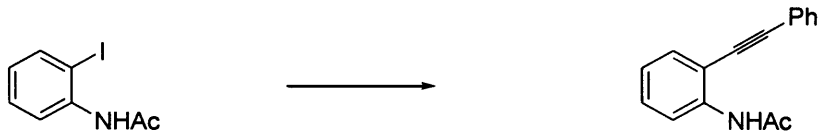


133 **138**

A solution of 2-iodoaniline **133** (1.00 g, 4.56 mmol) and pyridine (0.80 ml, 9.13 mmol) in dichloromethane (25 ml) was cooled to 0 °C before the addition of acetyl chloride (0.35 ml,

4.56 mmol). The reaction mixture was allowed to warm to ambient temperature and stirred overnight. This was followed by the addition of aqueous sodium carbonate (5 ml), followed by washing with water (2 x 20 ml) and brine (20 ml). The solution was then dried over sodium sulphate, filtered and evaporated to give the *amide* **138** as a white solid (1.01 g, 85%); m.p. 104-106 °C (lit. m.p.[137] 109-110 °C); δ_H 8.24 (1H, d, *J* 8.2, CH (Ar)), 7.80 (1H, d, *J* 8.1, CH (Ar)), 7.43 (1H, s, NH), 7.37 (1H, t, *J* 7.9, CH (Ar)), 6.87 (1H, t, *J* 7.9, CH (Ar)), 2.27 (3H, s, CH_3Ac).

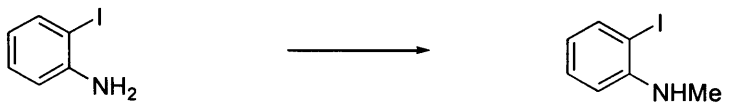
N-Acyl 2-(2-phenylethynyl)aniline 139[138]



138 **139**

According to the general procedure A, phenylacetylene (0.60 ml, 5.70 mmol) was added to a solution of *N*-(2-iodophenyl)acetamide **138** (1.00 g, 3.80 mmol), triphenylphosphine (0.20 g, 0.76 mmol), copper iodide (0.04 g, 0.19 mmol), and 10% palladium on carbon (0.16 g, 0.15 mmol) in a 1:2 mixture of water and triethylamine (15 ml) to give the *2-alkynyl aniline* **139** as a white solid (0.60 g, 67%); m.p. 119 °C (lit. m.p.[131] 119-120 °C); δ_H 8.33 (1H, d, *J* 8.4, CH (Ar)), 7.91 (1H, s, NH), 7.48-7.45 (2H, m, 2 x CH (Ar)), 7.43-7.40 (1H, m, CH (Ar)), 7.34-7.31 (3H, m, 3 x CH (Ar)), 7.30-7.25 (1H, m, CH (Ar)), 7.00 (1H, t, *J* 7.6, CH (Ar)), 2.17 (3H, s, CH_3Ac); *m/z* (EI) 235 (M^+, 40%), 193 (100%); [Found: $[M]^+$, 235.0999. $C_{16}H_{13}NO$ requires: *M*, 235.0997].

2-Iodo-N-methylbenzenamine 140[139]

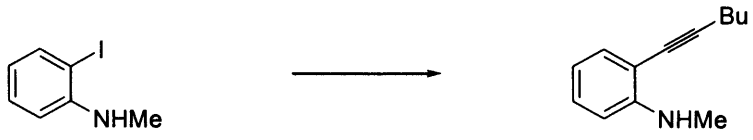


133 **140**

According to the established procedure[140] a solution of 2-iodoaniline **133** (2.00 g, 9.10 mmol) in tetrahydrofuran (40 ml) was cooled to -78°C before the addition of MeLi-LiBr (1.5 M in tetrahydrofuran, 6.07 ml, 9.10 mmol). The mixture was stirred for a further 1.5 h maintaining

the temperature at -78°C. Methyl iodide (0.60 ml, 9.10 mmol) was then added slowly and the reaction was warmed to room temperature over 2 h. Water (10 ml) was then added, followed by neutralisation with 2M HCl. The solution was then extracted with diethyl ether (2 x 30 ml), then dried, filtered and evaporated to give a crude orange oil. The product was purified by column chromatography (90:10 hexane-ethyl acetate) to give the *N-methyl aniline* **140** as an orange oil (1.45 g, 68%); υ_{max}/cm^{-1} (DCM): 3365, 2931, 2871, 1582, 1471, 1367, 1338, 1117, 919; δ_H 7.57 (1H, d, *J* 7.8, CH (Ar)), 7.16 (1H, t, *J* 7.7, CH (Ar)), 6.48 (1H, d, *J* 7.8, CH (Ar)), 6.37 (1H, t, *J* 7.7, CH (Ar)), 4.12 (1H, app s, NH), 2.80 (3H, d, *J* 5.1, Me); δ_C 148.2 (C), 138.9 (CH (Ar)), 129.6 (CH (Ar)), 118.5 (CH (Ar)), 110.0 (CH (Ar)), 85.2 (C), 31.0 (CH_3).

2-(Hex-1-yn-1-yl) *N*-Methyl aniline 141



140 **141**

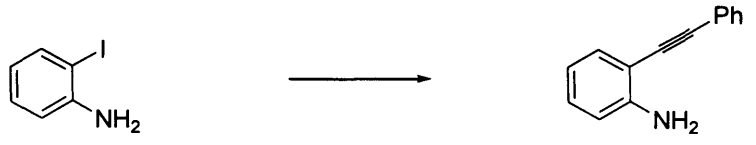
According to the general procedure A, 1-hexyne (1.00 ml, 9.01 mmol) was added to a solution of 2-iodo-*N*-methylbenzenamine **140** (1.40 g, 6.00 mmol), triphenylphosphine (0.32 g, 1.20 mmol), copper iodide (0.06 g, 0.30 mmol), and 10% palladium on carbon (0.26 g, 0.24 mmol) in a 1:2 mixture of water and triethylamine (24 ml) to give the *2-alkynyl aniline* **141** as a yellow oil (0.85 g, 76%); υ_{max}/cm^{-1} (neat): 2930, 2870, 1637, 1589, 1511, 1461, 1425, 1320, 1287, 1168, 1067; δ_H 7.19-7.14 (2H, m, 2 x CH (Ar)), 7.10 (1H, app dd, *J* 7.6, 1.5, CH (Ar)), 7.02 (1H, app dt, *J* 7.8, 1.6, CH (Ar)), 2.74 (3H, s, 1-Me), 2.32 (2H, t, *J* 7.1, 3'-CH_2), 1.46 (2H, *quintet*, *J* 7.1, 4'-CH_2), 1.33 (2H, *sextet*, *J* 7.0, 5'-CH_2), 0.80 (3H, t, *J* 7.2, 6'-CH_3); δ_C 146.3 (C), 133.9 (CH (Ar)), 128.5 (CH (Ar)), 113.8 (CH (Ar)), 117.2 (C), 116.4 (CH (Ar)), 96.2 (C≡C), 79.6 (C≡C), 31.1 (1'-CH_2), 30.7 (NMe), 22.1 (CH_2), 19.4 (CH_2), 13.6 (4'-CH_3); *m/z* (APCI) [Found: $[M+H]^+$, 188.1434. $C_{13}H_{18}N$ requires: *M+H*, 188.1439].

2-(Hex-1-yn-1-yl)aniline 142a[141]

133 **142a**

According to the general procedure A, 1-hexyne (0.80 ml, 6.85 mmol) was added to a solution of 2-iodoaniline **133** (1.00 g, 4.56 mmol), triphenylphosphine (0.24 g, 0.91 mmol), copper iodide (0.04 g, 0.23 mmol), and 10% palladium on carbon (0.19 g, 0.18 mmol) in a 1:2 mixture of water and trethylamine (15 ml) to give the *2-alkynyl aniline* **142a** as a yellow oil (0.78 g, 99%); υ_{max}/cm^{-1} (neat) 3382, 3054, 2959, 2932, 2873, 2306, 1699, 1615, 1493, 1456, 1306, 1266, 1159, 1092; δ_H 7.29-7.20 (2H, m, 2 x CH (Ar)), 7.17 (1H, app. d, *J* 7.6 CH (Ar)), 7.00 (1H, app. t, *J* 7.7, CH (Ar)), 4.09 (2H, s, NH_2), 2.40 (2H, t, *J* 7.2, 3'-CH_2), 1.54 (2H, *quintet*, *J* 7.5, 4'-CH_2), 1.42 (2H, *sextet*, *J* 7.4, 5'-CH_2), 0.88 (3H, t, *J* 7.4, 6'-CH_3).

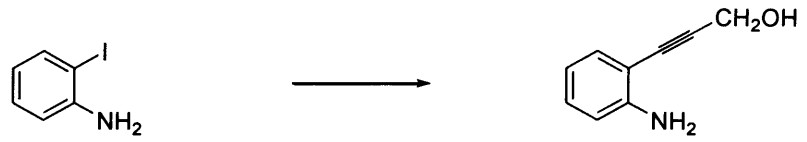
2-Phenylethynyl aniline 142b[138]



133 **142b**

According to the general procedure A, phenylacetylene (0.80 ml, 6.85 mmol) was added to a solution of 2-iodoaniline **133** (1.00 g, 4.56 mmol), triphenylphosphine (0.24 g, 0.91 mmol), copper iodide (0.04 g, 0.23 mmol), and 10% palladium on carbon (0.19 g, 0.18 mmol) in a 1:2 mixture of water and trethylamine (15 ml) to give the *2-alkynyl aniline* **142b** as a yellow solid (0.83 g, 94%); m.p. 90-92 °C (lit m.p.[138] 91-92 °C); δ_H 7.48-7.41 (2H, m, 2 x CH (Ar)), 7.31-7.24 (4H, m, 4 x CH (Ar)), 7.14-7.10 (1H, m, CH (Ar)), 6.65-6.57 (2H, m, 2 x CH (Ar)), 4.21 (2H, s, NH_2).

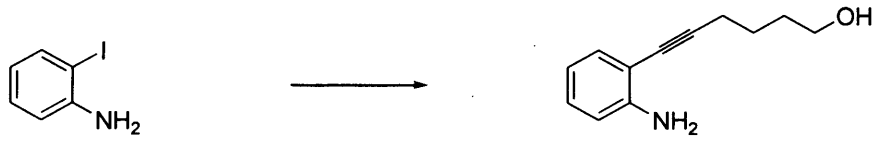
3-(2-Aminophenyl)prop-2-yn-1-ol 142c[142]



133 **142c**

According to the general procedure A, propargyl alcohol (0.60 ml, 9.13 mmol) was added to a solution of 2-iodoaniline **133** (1.00 g, 4.56 mmol), triphenylphosphine (0.24 g, 0.91 mmol), copper iodide (0.04 g, 0.23 mmol), and 10% palladium on carbon (0.19 g, 0.18 mmol) in a 1:2 mixture of water and triethylamine (15 ml) to give the *2-alkynyl aniline* **142c** as a yellow oil (0.60 g, 90%); υ_{max}/cm^{-1} (neat) 3455, 3054, 2987, 2305, 1615, 1422, 1265, 1159; δ_H 7.20 (1H, d, *J* 8.4, CH (Ar)), 7.06 (1H, t, *J* 8.4, CH (Ar)), 6.62 (1H, d, *J* 8.4, CH (Ar)), 6.61 (1H, t, *J* 8.4, CH (Ar)), 4.47 (2H, s, 1-CH_2), 4.15 (3H, br s, OH, NH_2).

3-(2-Aminophenyl)hex-5-yn-1-ol 142d[143]

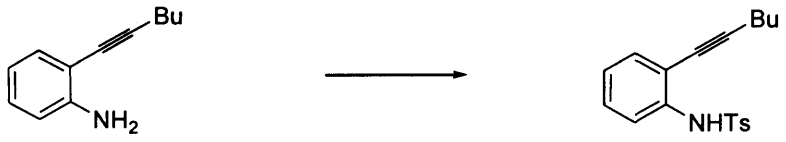


133 **142d**

According to the established procedure,[138] a solution of 2-iodoaniline **133** (4.00 g, 18.3 mmol), palladium *bis*(triphenylphosphine) dichloride (0.64 g, 0.91 mmol) and copper iodide (0.17 g, 0.91 mmol) in triethylamine (45 ml) was stirred at ambient temperature for 0.5 h. After which hex-5-yn-1-ol (2.00 ml, 18.4 mmol) was added and the solution was heated to 50 °C for 5 h. The solution was cooled and the solvent was evaporated. The residue was then partitioned between water (30 ml) and ether (50 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic solutions were washed with water (3 x 20 ml) and brine (2 x 20 ml), then dried, filtered and evaporated to give the *alcohol* **142d** as an orange oil (3.00 g, 87%); υ_{max}/cm^{-1} (neat) 3465, 3383, 3053, 2942, 2866, 2305, 1614, 1493, 1456, 1266, 1158, 1058; δ_H 7.26 (1H, d, *J* 7.7, CH (Ar)), 7.09 (1H, t, *J* 7.7, CH (Ar)), 6.71-6.66 (2H, m, 2 x CH (Ar)), 3.68 (2H, t, *J* 6.3, 1-CH_2), 3.52 (3H, br s, NH_2 and OH), 2.51 (2H, t, *J* 6.3, 4-CH_2), 1.76-1.68 (4H,

m, 2 and 3-CH_2); δ_C 147.6 (C=O), 132.0 (CH (Ar)), 128.9 (CH (Ar)), 118.0 (CH (Ar)), 114.4 (CH (Ar)), 108.9 (C), 95.4 (C≡C), 77.4 (C≡C), 62.2 (1-CH_2), 31.9 (CH_2), 25.2 (CH_2), 19.5 (CH_2).

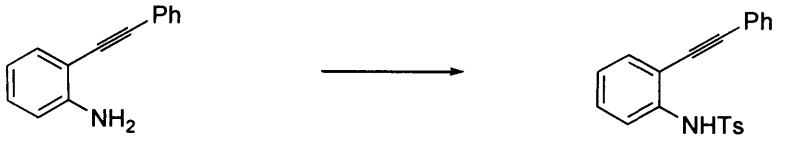
2-(Hex-1-yn-1-yl) *N*-tosyl aniline 143a[138]



142a **143a**

According to the general procedure B, a solution aniline **142a** (1.00 g, 5.77 mmol) was stirred with *p*-TsCl (1.16 g, 6.07 mmol) and pyridine (0.93 ml, 11.5 mmol) in dry dichloromethane (30 ml) followed by column chromatography (90:10 hexane-ethyl acetate) gave the *2-alkynyl N-tosyl aniline* **143a** as a light yellow oil (1.70 g, 89%); υ_{max}/cm^{-1} (neat) 3312, 2958, 2932, 2872, 2225, 1599, 1575, 1491, 1454, 1400, 1340, 1168, 1092; δ_H 7.68 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.58 (1H, d, *J* 8.2, CH (Ar)), 7.28-7.24 (2H, m, 2 x CH (Ar)), 7.24-7.21 (3H, m, 2 x CHAr, NH), 7.02-6.98 (1H, m, CH (Ar)), 2.32 (2H, t, *J* 7.0, 3'-CH_2), 2.39 (3H, s, CH_3Ar), 1.59 (2H, *quintet*, *J* 7.2, 4'-CH_2), 1.48 (2H, *sextet*, *J* 7.4, 5'-CH_2), 0.99 (3H, t, *J* 7.4, 6'-CH_3); δ_C 143.9 (C), 137.5 (C), 136.1 (C), 131.9 (CH (Ar)), 129.6 (2 x CH (Ar)), 128.8 (CH (Ar)), 127.2 (2 x CH (Ar)), 124.2 (CH (Ar)), 119.3 (CH (Ar)), 114.9 (C), 97.9 (C≡C), 75.3 (C≡C), 30.7 (CH_2), 22.1 (CH_2), 21.6 (CH_3Ar), 19.2 (CH_2), 13.7 (CH_3).

2-(Phenylethynyl) *N*-tosyl aniline 143b[138]

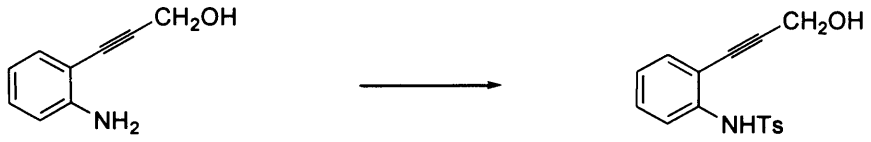


142b **143b**

According to the general procedure B, a solution of aniline **142b** (1.30 g, 6.73 mmol) was stirred with *p*-TsCl (1.35 g, 7.07 mmol) and pyridine (1.08 ml, 13.5 mmol) in dry dichloromethane (40 ml) followed by column chromatography (90:10 hexane-ethyl acetate) gave the *2-alkynyl N-tosyl aniline* **143b** as a yellow solid (2.10 g, 90%); m.p. 110-112 °C (lit m.p.[138] 112-113 °C); δ_H 7.69 (2H, d, *J* 8.3, 2 x CH (Ar)), 7.65 (1H, d, *J* 8.2, CH (Ar)), 7.51-7.48

(2H, m, 2 x CH (Ar)), 7.43-7.38 (4H, m, 4 x CH (Ar)), 7.34-7.30 (1H, m, CH (Ar)), 7.23 (1H, s, NH), 7.19 (2H, d, J 8.2, 2 x CH (Ar)), 7.11-7.07 (1H, m, CH (Ar)), 2.36 (3H, s, CH_3Ar); δ_C 144.1 (C), 137.5 (C), 136.0 (C), 132.0 (CH (Ar)), 131.6 (2 x CH (Ar)), 129.6 (3 x CH (Ar)), 129.1 (CH (Ar)), 128.6 (2 x CH (Ar)), 127.3 (2 x CH (Ar)), 124.6 (CH (Ar)), 122.0 (C), 120.3 (CH (Ar)), 114.6 (C), 96.1 (C≡C), 83.7 (C≡C), 21.6 (CH_3Ar).

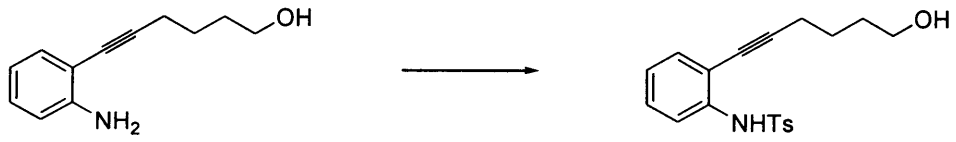
3-(2-Tosylaminophenyl)prop-2-yn-1-ol 143c[138]



142c **143c**

According to the general procedure B, a solution of aniline **142c** (0.60 g, 4.08 mmol) was stirred with *p*-TsCl (0.86 g, 4.49 mmol) and pyridine (0.66 ml, 8.16 mmol) in dry dichloromethane (20 ml) followed by work-up and recrystalisation using ethyl acetate:hexane to give *2-alkynyl N-tosyl aniline* **143c** as a white solid (1.20 g, 98%); m.p. 161-162 °C (lit m.p.[138] 159-160 °C); υ_{max}/cm^{-1} (DCM) 3419, 3054, 2987, 2305, 1492, 1422, 1267, 1167, 1091; δ_H 7.62 (2H, d, *J* 8.4, 2 x CH (Ar)), 7.49 (1H, d, *J* 8.2, CH (Ar)), 7.24-7.18 (2H, m, 2 x CHAr), 7.15 (2H, d, *J* 8.3, 2 x CH (Ar)), 6.95 (1H, t, *J* 7.8, CH (Ar)), 4.41 (2H, br. s, 1-CH_2), 2.30 (3H, s, CH_3Ar), 1.99 (2H, br. s, OH, NH); δ_C 144.2 (C), 137.8 (C), 136.0 (C), 132.3 (CH (Ar)), 129.8 (CH (Ar)), 129.7 (2 x CH (Ar)), 127.4 (2 x CH (Ar)), 124.5 (CH (Ar)), 120.2 (CH (Ar)), 113.9 (C), 94.3 (C≡C), 80.3 (C≡C), 51.5 (1-CH_2), 21.6 (CH_3Ar); *m/z* (EI) 301 (M^+, 60%), 145 (60%), 91 (100%); [Found: $[M]^+$, 301.0775. $C_{16}H_{15}NO_3S$ requires: *M*, 301.0773].

3-(2-*N*-Tosylaminophenyl)hex-5-yn-1-ol 143d[34]

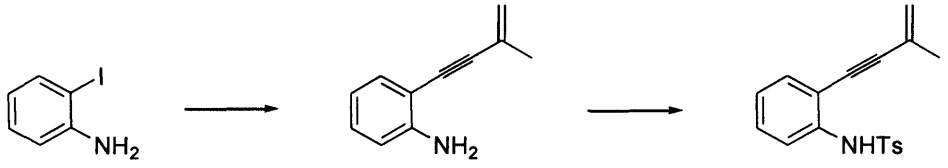


142d **143d**

According to the general procedure B, a solution of the alcohol **142d** (1.50 g, 7.93 mmol) was stirred with *p*-TsCl (1.66 g, 8.72 mmol) and pyridine (1.30 ml, 15.9 mmol) in dichloromethane (50 ml) overnight, followed by work-up and column chromatography using 30% ethyl acetate

in hexane to give the *2-alkynyl N-tosyl aniline* **143d** as an orange oil (1.10 g, 40%); υ_{max}/cm^{-1} (neat) 3544, 3319, 3056, 2939, 2867, 2305, 2226, 1599, 1575, 1398, 1337, 1166, 1091; δ_H 7.68 (2H, d, *J* 8.3, CH (Ar)), 7.53 (1H, d, *J* 8.2, CH (Ar)), 7.50 (1H, s, NH), 7.25-7.17 (4H, m, 4 x CH (Ar)), 6.97 (1H, t, *J* 8.2, CH (Ar)), 3.73 (2H, t, *J* 6.2, 1-CH_2), 2.46 (2H, t, *J* 6.2, 4-CH_2), 2.32 (3H, s, CH_3Ar), 1.77-1.66 (4H, m, 3 and 2-CH_2); δ_C 144.1 (C), 137.6 (C), 136.0 (C), 131.9 (CH (Ar)), 129.6 (2 x CH (Ar)), 128.8 (CH (Ar)), 127.2 (2 x CH (Ar)), 124.3 (CH (Ar)), 119.5 (CH (Ar)), 115.0 (C), 97.6 (C≡C), 75.7 (C≡C), 62.1 (1-CH_2), 31.8 (CH_2), 24.9 (CH_2), 21.6 (CH_3Ar), 19.3 (CH_2); *m/z* (EI) 343 (M^+, 40%), 225 (60%), 188 (100%); [Found: $[M]^+$, 343.1235. $C_{19}H_{21}NO_3S$ requires: *M*, 343.1242].

2-(3-Methylbut-3-en-1-yn-1-yl) *N*-tosyl aniline 143e

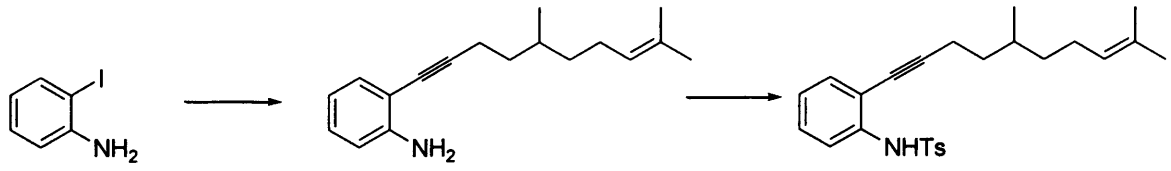


133 **142e** **143e**

According to the general procedure A, 2-methylbut-1-en-3-yne (0.75 ml, 11.4 mmol) was added to a solution of 2-iodoaniline **133** (1.00 g, 4.56 mmol), triphenylphosphine (0.24 g, 0.91 mmol), copper iodide (0.04 g, 0.23 mmol), and 10% palladium on carbon (0.19 g, 0.18 mmol) in a 1:2 mixture of water and triethylamine (15 ml) to give the *2-alkynyl aniline* **142e** as a yellow oil (0.65 g); δ_H 7.20 (1H, d, *J* 8.2, CH (Ar)), 7.00 (1H, t, *J* 8.2, CH (Ar)), 6.62 (1H, d, *J* 8.2, CH (Ar)), 6.61 (1H, t, *J* 8.2, CH (Ar)), 5.31-5.30 (1H, m, 4'-H_A), 5.22-5.21 (1H, m, 4'-H_B), 4.13 (2H, br s, NH_2), 1.94 (3H, app s, CH_3). According to the general procedure B, a solution of the crude precursor **142e** (0.60 g, 3.82 mmol) was stirred with *p*-TsCl (0.77 g, 4.01 mmol) and pyridine (0.61 ml, 7.63 mmol) in dry dichloromethane (20 ml) followed by work-up and column chromatography (89:11 hexane-ethyl acetate) gave the *2-alkynyl N-tosyl aniline* **143e** as a yellow solid (0.81 g, 68%); m.p. 104 °C; υ_{max}/cm^{-1} (DCM) 3322, 3055, 2983, 2924, 2306, 1598, 1490, 1401, 1341, 1265, 1166, 1092, 907, 813, 736; δ_H 7.67 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.61 (1H, d, *J* 8.2, CH (Ar)), 7.31-7.27 (2H, m, 2 x CH (Ar)), 7.22 (2H, d, *J* 8.3, 2 x CH (Ar)), 7.11 (1H, s, NH), 7.05 (1H, t, *J* 7.8, CH (Ar)), 5.42-5.41 (1H, m, 4'-H_A), 5.40-5.38 (1H, m, 4'-

H_B), 2.39 (3H, s, CH_3Ar), 1.99 (3H, s, CH_3); δ_C 144.1 (C), 137.7 (C), 136.2 (C), 131.9 (CH (Ar)), 129.6 (3 x CH (Ar)), 127.2 (2 x CH (Ar)), 125.9 (C), 124.5 (CH (Ar)), 123.4 (4'-CH_2), 120.1 (CH (Ar)), 97.2 (C≡C), 82.7 (C≡C), 23.4 (CH_3), 21.6 (CH_3Ar); *m/z* (ES) 312 ($M+H^+$, 100%); [Found: $[M+H]^+$, 312.1053. $C_{18}H_{18}NO_2S$ requires: *M+H*, 312.1058].

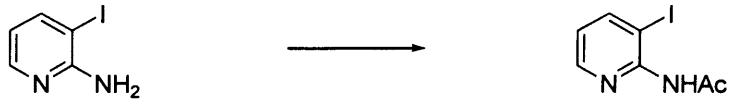
2-(5,9-Dimethyldec-8-en-1-yn-1-yl) *N*-tosyl aniline 143f



133 **142f** **143f**

According to the general procedure A, 5,9-Dimethyldec-8-en-1-yne **132** (0.75 ml, 4.53 mmol) was added to a solution of 2-iodoaniline **133** (1.00 g, 4.56 mmol), triphenylphosphine (0.24 g, 0.91 mmol), copper iodide (0.04 g, 0.23 mmol), and 10% palladium on carbon (0.19 g, 0.18 mmol) in a 1:2 mixture of water and triethylamine (15 ml) to give the crude 2-alkynyl aniline **142f** as a yellow oil (1.09 g) which was carried through to the next step. According to the general procedure B, a solution of the crude free aniline **142f** (0.60 g, 2.35 mmol) was stirred with *p*-TsCl (0.49 g, 2.58 mmol) and pyridine (0.38 ml, 4.70 mmol) in dry dichloromethane (15 ml), followed by work-up and column chromatography (95:5 hexane-ethyl acetate) gave the *2-alkynyl N-tosyl aniline* **143f** as a sweet smelling oil (2.01 g, 86%); υ_{max}/cm^{-1} (neat) 3263, 2920, 2223, 1599, 1574, 1491, 1453, 1399, 1341, 1290, 1168, 1092, 1044, 1019, 912; δ_H 7.68 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.57 (1H, d, *J* 8.2, CH (Ar)), 7.27-7.22 (2H, m, 2 x CH (Ar)), 7.22 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.00 (1H, t, *J* 7.7, CH (Ar)), 5.14 (1H, t, *J* 7.1, 8'-H), 2.48-2.39 (2H, m, CH_2), 2.39 (3H, s, CH_3Ar), 2.12-1.96 (2H, m, CH_2), 1.71 (3H, s, 9-Me), 1.68-1.58 (2H, m, CH_2), 1.64 (3H, s, 9-Me), 1.48-1.36 (2H, m, CH_2), 1.28-1.18 (1H, m, 5'-H), 0.97 (3H, d, *J* 6.5, 5'-CH_3); δ_C 143.9 (C), 137.5 (C), 136.1 (C), 131.9 (C), 131.5 (CH (Ar)), 129.6 (2 x CH (Ar)), 128.8 (CH (Ar)), 127.3 (2 x CH (Ar)), 124.6 (CH (Ar)), 124.2 (CH (Ar)), 119.3 (8-CH), 114.9 (C), 98.0 (C≡C), 75.2 (C≡C), 36.7 (CH_2), 35.7 (CH_2), 31.9 (5-CH), 25.8 (CH_3), 25.4 (CH_2), 21.6 (CH_3Ar), 19.1 (CH_3), 17.7 (CH_3), 17.3 (CH_2); *m/z* (ES) 427 ($M+NH_4^+$, 100%), 410 ($M+H^+$, 20%); [Found: $[M+H]^+$, 410.2152. $C_{25}H_{32}NO_2S$ requires: *M+H*, 410.2154].

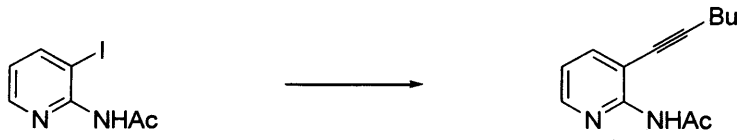
***N*-(3-Iodopyridin-2-yl)acetamide 145**



144 **145**

According to the established procedure[144] solution of pyridine **144** (1.00g, 4.54 mmol) in acetic anhydride (15 ml, excess) was refluxed for 20 h. The reaction mixture was cooled and poured into water (50 ml), followed by the addition of aqueous sodium bicarbonate (10 ml). The reaction mixture was then extracted with dichloromethane (3 x 30 ml). The combined organics were dried over sodium sulphate, filtered and evaporated to give clean *amide* **145** as a white fluffy solid (1.10 g, 92%); m.p. 88-89 °C ; δ_H 8.30 (1H, d, *J* 4.6, CH (Ar)), 8.04 (1H, app dd, *J* 7.9, 1.5, CH (Ar)), 7.83 (1H, br s, NH), 6.76 (1H, dd, *J* 7.9, 4.6, CH (Ar)), 2.32 (3H, s, CH_3Ac); δ_C 176.0 (C=O), 150.9 (C), 148.2 (CH (Ar)), 147.9 (CH (Ar)), 121.3 (CH (Ar)), 86.2 (C), 24.4 (CH_3Ac).

***N*-(3-(Hex-1-ynyl)pyridine-2-yl)acetamide 146**

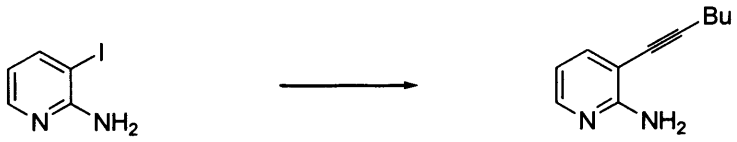


145 **146**

According to the established procedure[138] a solution of pyridine **145** (0.50 g, 1.91 mmol), palladium bis(triphenylphosphine) dichloride (0.05 g, 0.08 mmol), copper iodide (0.02 g, 0.10 mmol) and triethylamine (0.53 ml, 3.82 mmol) were stirred in tetrahydrofuran (30 ml) for 30 min. Followed by the addition of 1-hexyne (0.70 ml, 5.70 mmol) and heating the mixture to 50 °C. After 2 h the mixture was cooled and passed through a plug of celite and the solution was evaporated. This was followed by the addition of diethyl ether (20 ml) and water (10 ml). The aqueous layer was extracted with ether (3 x 20 ml) and the combined organics were washed with brine (2 x 20 ml), dried over sodium sulphate, filtered and evaporated to give the crude product. The crude material was then purified by column chromatography using 15-40% ethyl acetate in hexane to give the *2-alknynyl amino-pyridine* **146** as an orange oil (0.25 g, 61%); υ_{max}/cm^{-1} (neat) 3373, 2957, 2932, 2872, 2227, 1683, 1575, 1484, 1374, 1301, 1112; δ_H 8.18 (1H, dd, *J* 4.8, 1.8, CH (Ar)), 8.13 (1H, br s, NH), 7.57 (1H, dd, *J* 7.6, 1.8, CH (Ar)), 6.88 (1H,

dd, *J* 7.6, 4.8, CH (Ar)), 2.42 (3H, s, CH_3Ac), 2.40 (2H, t, *J* 7.2, 1'-CH_2), 1.54 (2H, *quintet*, *J* 7.2, 2'-CH_2), 1.41 (2H, *sextet*, *J* 7.2, 3'-CH_2), 0.88 (3H, t, *J* 7.2, 4'-CH_3); δ_C 170.9 (C=O), 151.6 (C), 146.6 (CH (Ar)), 140.3 (CH (Ar)), 118.4 (CH (Ar)), 109.2 (C), 99.8 (C≡C), 74.4 (C≡C), 30.5 (1'-CH_2), 25.0 (CH_3Ac), 22.1 (CH_2), 19.3 (CH_2), 13.6 (4'-CH_3); *m/z* (EI) 216 (M^+, 20%), 174 (40%), 132 (100%); [Found: $[M]^+$, 216.1264. $C_{13}H_{16}N_2O$ requires: *M*, 216.1263].

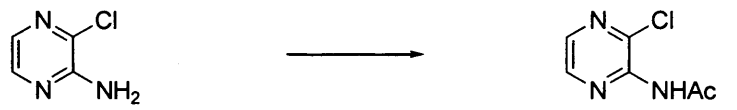
2-Amino-3-(hex-1-ynyl)pyridine 147[145]



144 **147**

A solution of pyridine **144** (0.50 g, 2.27 mmol), palladium(0) tetrakis triphenylphosphine (0.06 g, 0.09mmol), copper iodide (0.02 g, 0.11 mmol) and treithylamine (0.63 ml, 4.54 mmol) was stirred for 30 min. This was followed by the addition of 1-hexyne (0.78 ml, 6.82 mmol) and heating to 50 °C for 18 h. The resulting solution was filtered through celite and evaporated. The resulting residue was taken up in ether and washed with water (3 x 20 ml) and brine (2 x 20 ml), followed by dring over sodium sulphate, filtration and evaporation to give the crude product. Column chromatography using 50% ethyl acetate in hexane resulted in clean *2-alkynyl amino-pyridine* **147** as an orange oil (0.08 g, 20%); δ_H 7.96 (1H, br s, CH (Ar)), 7.45 (1H, dd, *J* 7.5, 1.7, CH (Ar)), 6.56 (1H, dd, *J* 7.5, 5.1, CH (Ar)), 5.17 (2H, br s, NH_2), 2.45 (2H, t, *J* 7.1, 1'-CH_2), 1.59 (2H, *quintet*, *J* 7.2, 2'-CH_2), 1.47 (2H, *sextet*, *J* 7.2, 3'-CH_2), 0.94 (3H, t, *J* 7.2, 4'-CH_3).

***N*-(3-Chloropyrazin-2-yl)acetamide 149**

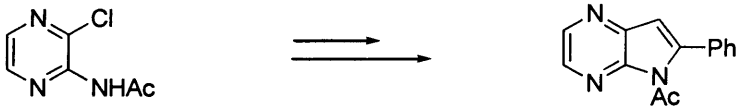


148 **149**

According to the established procedure[144] solution of pyrazine (1.00g, 7.72 mmol) **148** in acetic anhydride (15 ml, excess) was refluxed for 20 h. The reaction mixture was cooled and poured into water (50 ml), followed by the addition of aqueous sodium bicarbonate (10 ml). The

reaction mixture was then extracted with dichloromethane (3 x 30 ml). The combined organics were dried over sodium sulphate, filtered and evaporated to give clean *amide* **149** as a white fluffy solid (0.98 g, 74%); m.p. 93 °C; δ_H 8.22 (1H, d, *J* 2.5, CH (Ar)), 8.04 (1H, d, *J* 2.5, CH (Ar)), 2.40 (3H, s, CH_3Ac); δ_C 170.1 (C=O), 145.1 (C), 140.7 (CH (Ar)), 138.4 (CH (Ar)), 138.0 (C), 25.0 (CH_3Ac).

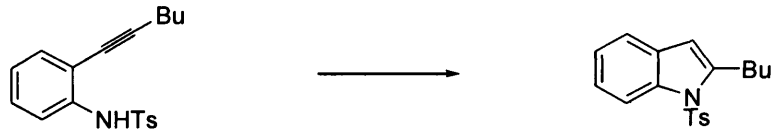
***N*-Acetyl-1-(6-phenyl-5*H*-pyrrole[2,3-*b*]pyrazin-5-yl) 151**



149 **151**

According to the established procedure[138] a solution of amino-pyrazine **149** (0.50 g, 2.92 mmol), palladium(0) tetrakis triphenylphosphine (0.14 g, 0.12 mmol), copper iodide (0.03 g, 0.15 mmol) and triethylamine (0.81 ml, 5.83 mmol) were stirred in tetrahydrofuran (25 ml) for 20 min. This was followed by the addition of phenylacetylene (0.64 ml, 5.83 mmol) and heating to 60 °C for 2 h. The resulting solution was passed through a plug of celite and the resulting solution was evaporated. The residue was taken up in ether and washed with water (3 x 20 ml) and brine (20 ml), followed by drying with sodium sulphate, filtration and evaporation to give crude product. Column chromatography using 30% to 40% ethyl acetate in hexane resulted in *aza-indole* **151** as a yellow solid (0.25 g, 36%); m.p. 128 °C; υ_{max}/cm^{-1} (DCM) 3054, 2933, 2857, 1734, 1553, 1490, 1381, 1371, 1360, 1301, 1257, 1163; δ_H 8.38 (1H, d, *J* 2.6, CH (Ar)), 8.16 (1H, d, *J* 2.6, CH (Ar)), 7.36-7.29 (5H, m, 5 x CH (Ar)), 6.70 (1H, s, 3-H), 2.93 (3H, s, CH_3Ac); δ_C 169.5 (C=O), 146.3 (C), 143.3 (C), 141.5 (C), 140.9 (CH (Ar)), 137.3 (CH (Ar)), 132.8 (C), 128.8 (CH (Ar)), 128.3 (2 x CH (Ar)), 128.2 (2 x CH (Ar)), 109.0 (3-CH), 27.8 (CH_3Ac); *m/z* (EI) 237 (M^+, 40%), 195 (100%); [Found: $[M]^+$, 237.0902. $C_{14}H_{11}N_3O$ requires: *M*, 237.0902].

2-Butyl-1-tosyl-*IH*-indole 152a[138]



143a **152a**

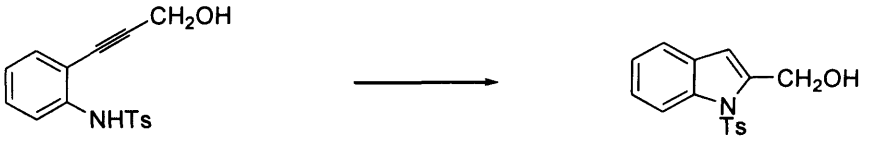
According to the general procedure C, 10% $AgNO_3.SiO_2$ (0.08 g, 0.05 mmol) was stirred with a solution of precursor **143a** (0.15 g, 0.46 mmol) in dichloromethane (3 ml) for 18 h to give *indole* **152a** as a yellow oil (0.15 g, 99%); δ_H; 8.09 (1H, d, *J* 8.3, CH (Ar)), 7.54 (2H, d, *J* 8.4, 2 x CH (Ar)), 7.33 (1H, d, *J* 7.4, CH (Ar)), 7.18-7.12 (2H, m, 2 x CH (Ar)), 7.11 (2H, d, *J* 8.4, 2 x CH (Ar)), 6.30 (1H, s, 3-H), 2.91 (2H, t, *J* 7.7, 1'-CH_2), 2.26 (3H, s, CH_3Ar), 1.66 (2H, *quintet*, *J* 7.8, 2'-CH_2), 1.37 (2H, *sextet*, *J* 7.7, 3'-CH_2), 0.88 (3H, t, *J* 7.5, 4'-CH_3); δ_C 144.6 (C), 142.5 (C), 137.2 (C), 136.2 (C), 129.9 (C), 129.8 (2 x CH (Ar)), 126.3 (2 x CH (Ar)), 123.8 (CH (Ar)), 123.5 (CH (Ar)), 120.1 (CH (Ar)), 114.8 (CH (Ar)), 108.6 (CH (Ar)), 31.0 (CH_2), 28.8 (CH_2), 22.5 (CH_2), 21.6 (CH_3Ar), 14.0 (CH_3).

2-Phenyl-1-tosyl-*IH*-indole 152b[138]

143b **152b**

According to the general procedure C, 10% $AgNO_3.SiO_2$ (0.05 g, 0.03 mmol) was stirred with a solution of precursor **143b** (0.10 g, 0.29 mmol) in dichloromethane (2 ml) for 18 h to give *indole* **152b** as a yellow oil (0.10 g, 99%); m.p. 144-145 °C (lit m.p.[138] 146-147 °C); δ_H 8.24 (1H, d, *J* 8.3, CH (Ar)), 7.45-7.41 (2H, m, 2 x CH (Ar)), 7.39-7.34 (4H, m, 4 x CH (Ar)), 7.31-7.25 (1H, m, CH (Ar)), 7.19-7.17 (3H, m, 3 x CH (Ar)), 6.97 (2H, d, J 8.3, 2 x CH (Ar)), 6.47 (1H, s, 3-H), 2.21 (3H, s, CH_3Ar); δ_C 144.6 (C), 142.2 (C), 138.3 (C), 134.6 (C), 132.4 (C), 130.6 (C), 130.4 (2 x CH (Ar)), 129.2 (2 x CH (Ar)), 128.7 (CH (Ar)), 127.5 (2 x CH (Ar)), 126.8 (2 x CH (Ar)), 124.8 (CH (Ar)), 124.4 (CH (Ar)), 120.7 (CH (Ar)), 116.7 (CH (Ar)), 113.7 (CH (Ar)), 21.6 (CH_3Ar).

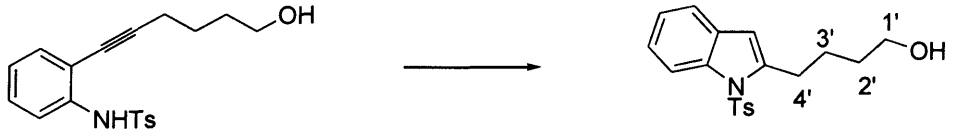
(1-Tosyl-*1H*-indol-2-yl)methanol 152c[138]



143c **152c**

According to the general procedure C, 10% $AgNO_3.SiO_2$ (0.06 g, 0.03 mmol) was stirred with a solution of precursor **143c** (0.10 g, 0.33 mmol) in dichloromethane (2 ml) for 3 h to give *indole* **152c** as a white solid (0.10 g, 99%); m.p. 88-90 °C (lit m.p.[138] 91-92 °C); δ_H; 7.98 (1H, d, *J* 8.7, CH (Ar)), 7.65 (2H, d, *J* 8.4, 2 x CH (Ar)), 7.41 (1H, d, *J* 8.4, CH (Ar)), 7.23 (1H, t, *J* 8.4, CH (Ar)), 7.18-7.12 (3H, m, 3 x CH (Ar)), 6.57 (1H, s, 3-H), 4.83 (2H, d, *J* 7.2, CH_2OH), 3.05 (1H, t, *J* 7.3, OH), 2.27 (3H, s, CH_3Ar); δ_C 145.2 (C), 140.3 (C), 137.0 (C), 135.5 (C), 130.0 (2 x CH (Ar)), 129.1 (C), 126.4 (2 x CH (Ar)), 125.0 (CH (Ar)), 123.8 (CH (Ar)), 121.2 (CH (Ar)), 114.4 (CH (Ar)), 111.2 (CH (Ar)), 58.6 (CH_2OH), 21.6 (CH_3Ar).

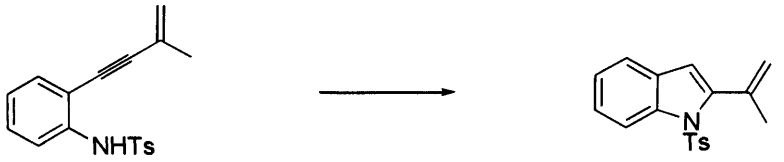
4-(1-Tosyl-1*H*-indol-2-yl)butan-1-ol 152d[34]



143d **152d**

According to the general procedure C, 10% $AgNO_3.SiO_2$ (0.03 g, 0.02 mmol) was stirred with a solution of precursor **143d** (0.05 g, 0.15 mmol) in dichloromethane (2 ml) for 18 h to give *indole* **152d** as a yellow oil (0.05 g, 99%); υ_{max}/cm^{-1} (neat) 3231, 2940, 2862, 1593, 1569, 1450, 1371, 1242, 1173, 1093; δ_H 8.08 (1H, d, *J* 8.2, CH (Ar)), 7.52 (2H, d, *J* 8.4, 2 x CH (Ar)), 7.32 (1H, d, *J* 8.2, CH (Ar)), 7.20-7.11 (2H, m, 2 x CH (Ar)), 7.09 (2H, d, *J* 8.4, 2 x CH (Ar)), 6.32 (1H, s, 3-H), 3.63 (2H, t, *J* 7.0, 1'-CH_2), 2.94 (2H, *J* 7.0, 4'-CH_2), 2.24 (3H, s, CH_3Ar), 1.77 (2H, *quintet*, *J* 7.0, 2' or 3'-CH_2), 1.61 (2H, *quintet*, *J* 7.0, 2' or 3'-CH_2), 1.56 (1H, s, OH); δ_C 144.7 (C), 142.0 (C), 137.2 (C), 136.0 (C), 129.8 (C), 129.8 (2 x CH (Ar)), 126.2 (2 x CH (Ar)), 123.9 (CH (Ar)), 123.6 (CH (Ar)), 120.2 (CH (Ar)), 114.9 (CH (Ar)), 109.1 (CH (Ar)), 62.5 (1'-CH_2), 32.3 (CH_2), 28.8 (CH_2), 25.3 (CH_2), 21.6 (CH_3Ar); *m/z* (EI) 343 (M^+, 50%), 170 (60%), 130 (100%); [Found: $[M]^+$, 343.1249. $C_{19}H_{21}NO_3S$ requires: *M*, 343.1242].

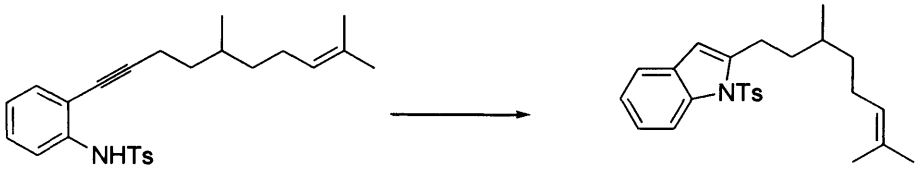
2-(Prop-1-en-2-yl)-tosyl-*1H*-indole 152e



143e **152e**

According to the general procedure C, 10% $AgNO_3.SiO_2$ (0.05 g, 0.03 mmol) was stirred with a solution of precursor **143e** (0.10 g, 0.32 mmol) in dichloromethane (2 ml) for 18 h to give the *indole* **152e** as a clear oil (0.10 g, 99%); υ_{max}/cm^{-1} (neat): 2921, 1631, 1597, 1451, 1367, 1192, 1121, 1090, 1016, 908, 812, 750; δ_H; 8.14 (1H, d, *J* 8.3, CH (Ar)), 7.51 (2H, d, *J* 8.4, 2 x CH (Ar)), 7.33 (1H, d, *J* 7.7, CH (Ar)), 7.25 (1H, t, *J* 7.4, CH (Ar)), 7.16 (1H, t, *J* 7.5, CH (Ar)), 7.03 (2H, d, *J* 8.4, 2 x CH (Ar)), 6.41 (1H, s, 3-H), 5.26-5.25 (1H, m, 2'-H_A), 5.14-5.13 (1H, m, 2'-H_B), 2.22 (6H, s, CH_3Ar and CH_3); δ_C 144.6 (C), 144.2 (C), 139.2 (C), 137.9 (C), 134.4 (C), 130.7 (C), 129.3 (2 x CH (Ar)), 126.8 (2 x CH (Ar)), 124.7 (CH (Ar)), 124.2 (CH (Ar)), 120.8 (CH (Ar)), 117.4 (2'-CH_2), 116.1 (CH (Ar)), 112.2 (CH (Ar)), 24.1 (CH_3), 21.5 (CH_3Ar); *m/z* (ES) 329 ($M+NH_4^+$, 20%), 312 ($M+H^+$, 100%); [Found: $[M+H]^+$, 312.1068. $C_{18}H_{18}NO_2S$ requires: *M+H*, 312.1058].

2-(3,7-Dimethyloct-6-en-1-yl)-1-tosyl-*1H*-indole 152f



143f **152f**

According to the general procedure C, 10% $AgNO_3.SiO_2$ (0.04 g, 0.02 mmol) was stirred with a solution of precursor **143f** (0.10 g, 0.24 mmol) in dichloromethane (2 ml) for 18 h to give the *indole* **152f** as a clear oil (0.10 g, 99%); υ_{max}/cm^{-1} (neat): 2924, 1597, 1452, 1369, 1219, 1175, 1146, 1119, 1091, 1050, 1022, 911, 811, 745, 706; δ_H 8.09 (1H, d, *J* 8.2, CH (Ar)), 7.53 (2H, d, *J* 8.4, 2 x CH (Ar)), 7.31 (1H, d, *J* 7.6, CH (Ar)), 7.18-7.10 (2H, m, 2 x CH (Ar)), 7.08 (2H, d, *J* 8.3, 2 x CH (Ar)), 6.29 (1H, s, 3-H), 5.03 (1H, tt, *J* 7.1, 1.3, 6'-H), 2.98-2.81 (2H, m, CH_2), 2.23 (3H, s, CH_3Ar), 1.92 (2H, m, CH_2), 1.73-1.62 (2H, m, CH_2), 1.61 (3H, s, 8'-Me), 1.53 (3H, s, 8'-Me), 1.52-1.44 (2H, m, CH_2), 1.37-1.28 (1H, m, 3'-H), 0.87 (3H, d, *J* 6.2, 3'-Me); δ_C

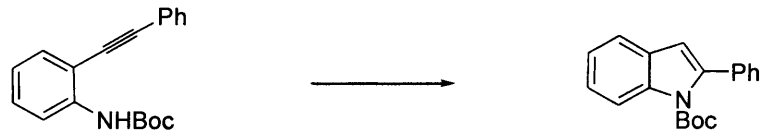
144.6 (C), 142.8 (C), 137.2 (C), 136.3 (C), 131.2 (C), 129.9 (C), 129.8 (2 x CH (Ar)), 126.3 (2 x CH (Ar)), 124.9 (CH), 123.8 (CH), 123.5 (CH), 120.1 (CH), 114.8 (CH), 108.5 (CH), 37.0 (CH_2), 36.0 (CH_2), 32.3 (3'-CH), 26.7 (CH_2), 25.8 (CH_3), 25.5 (CH_2), 21.6 (CH_3Ar), 19.5 (CH_3), 17.7 (CH_3); *m/z* (ES) 427 ($M+NH_4^+$, 55%), 410 ($M+H^+$, 100%); [Found: $[M + H]^+$, 410.2171. $C_{25}H_{32}NO_2S$ requires: *M+H*, 410.2154].

Methyl 2-butyl-*1H*-indole-1-carboxylate 153

137 **153**

According to the general procedure C, 10% $AgNO_3.SiO_2$ (0.07 g, 0.04 mmol) was stirred with a solution of precursor **137** (0.10 g, 0.43 mmol) in dichloromethane (2 ml) for 24 h to give *indole* **153** as a yellow oil (0.10 g, 99%); υ_{max}/cm^{-1} (neat): δ_H; 7.98 (1H, d, *J* 7.7, CH (Ar)), 7.35 (1H, d, *J* 7.6, CH (Ar)), 7.15 (1H, t, *J* 7.7, CH (Ar)), 7.10 (1H, t, *J* 7.4, CH (Ar)), 6.27 (1H, s, 3-H), 3.93 (3H, s, MeO_2C), 2.90 (2H, t, *J* 7.6, 1'-CH_2), 1.59 (2H, *quintet*, *J* 7.7, 2'-CH_2), 1.36 (2H, *sextet*, *J* 7.6, 3'-CH_2), 0.88 (3H, t, *J* 7.5, 4'-CH_3); δ_C 152.6 (C=O), 142.6 (C), 136.4 (C), 129.6 (C), 123.4 (CH (Ar)), 122.9 (CH (Ar)), 119.8 (CH (Ar)), 115.6 (CH (Ar)), 107.6 (CH), 53.4 (MeO_2C), 31.6 (CH_2), 29.6 (CH_2), 22.4 (CH_2), 14.0 (CH_3).

***tert*-Butyl-2-phenyl-*1H*-indole-1-carboxylate 154**[137]

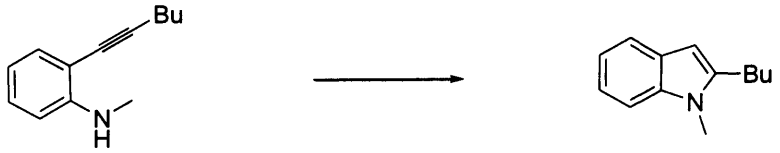


135 **154**

According to the general procedure C, 10% $AgNO_3.SiO_2$ (0.06 g, 0.04 mmol) was stirred with a solution of precursor **135** (0.11 g, 0.37 mmol) in dichloromethane (2 ml) for 24 h to give the *indole* **154** as a yellow oil (0.11 g, 99%); δ_H 8.14 (1H, d, *J* 8.3, CH (Ar)), 7.48 (1H, d, *J* 7.6, CH (Ar)), 7.34-7.24 (6H, m, 6 x CH (Ar)), 7.17 (1H, t, *J* 7.4, CH (Ar)), 6.48 (1H, s, 3-H), 1.23 (9H, s, 3 x CH_3C); δ_C 150.2 (C=O), 140.5 (C), 137.5 (C), 135.0 (C), 129.3 (CH (Ar)), 128.8 (2 x CH (Ar)), 127.8 (2 x CH (Ar)), 127.6 (C), 124.3 (CH (Ar)), 122.9 (CH (Ar)), 120.5 (CH (Ar)),

115.2 (CH (Ar)), 109.9 (CH (Ar)), 83.4 (C*t*Butyl), 27.6 (3 x CH_3C); *m/z* (ES) 293 (M^+, 20%), 237 (50%), 193 (100%); [Found $[M]^+$, 293.1425. $C_{19}H_{19}NO_2$ requires: *M*, 293.1416].

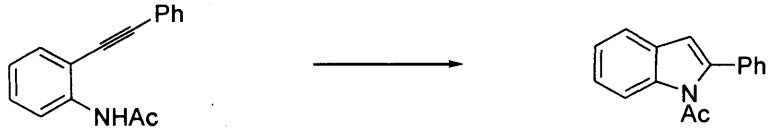
2-Butyl-1-methyl-*1H*-indole 155



141 **155**

According to the general procedure C, 10% $AgNO_3.SiO_2$ (0.27 g, 0.16 mmol) was stirred with a solution of precursor **141** (0.30 g, 1.60 mmol) in dichloromethane (6 ml) for 48 h to give *indole* **155** as a yellow oil (0.30 g, 99%); δ_H; 7.45 (1H, d, *J* 7.7, CH (Ar)), 7.18, (1H, d, *J* 7.8, CH (Ar)), 7.07 (1H, t, *J* 7.5, CH (Ar)), 6.98 (1H, t, *J* 7.5, CH (Ar)), 6.17 (1H, s, 3-H), 3.58 (3H, s, Me), 2.65 (2H, t, *J* 7.6, 1'-CH_2), 1.63 (2H, *quintet*, *J* 7.6, 2'-CH_2), 1.39 (2H, *sextet*, *J* 7.6, 3'-CH_2) 0.90 (3H, t, *J* 7.5, 4'-CH_3); δ_C 141.5 (C), 137.3 (C), 127.9 (C), 120.4 (CH (Ar)), 119.7 (CH (Ar)), 119.2 (CH (Ar)), 108.7 (CH (Ar)) 98.6 (CH (Ar)), 30.8 (NMe), 29.4 (1'-CH_2), 26.6 (2'-CH_2), 22.6 (3'-CH_2), 14.0 (4'-CH_3); *m/z* could not be obtained.

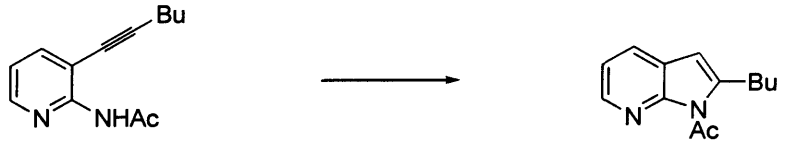
***N*-Acetyl-1-(2-phenyl-1H-indol-1-yl) 156**[146]



139 **156**

According to the general procedure C, 10% $AgNO_3.SiO_2$ (0.10 g, 0.06 mmol) was stirred with a solution of precursor **139** (0.13 g, 0.55 mmol) in dichloromethane (3 ml) for 24 h to give the *indole* **156** as a white solid (0.13 g, 99%); m.p. 77-79 °C (lit. m.p.[141] 80-82 °C); δ_H 8.29 (1H, d, *J* 8.3, CH (Ar)), 7.49 (1H, d, *J* 7.6, CH (Ar)), 7.41-7.35 (5H, m, 5 x CH (Ar)), 7.29 (1H, t, *J* 8.0, CH (Ar)), 7.22 (1H, t, *J* 7.5, CH (Ar)), 6.56 (1H, s, 3-H), 2.00 (3H, s, CH_3Ac); δ_C 171.5 (C=O), 139.7 (C), 137.7 (C), 134.2 (C), 129.0 (C), 129.1 (2 x CH (Ar)), 129.0 (2 x CH (Ar)), 128.8 (CH (Ar)), 125.1 (CH (Ar)), 123.7 (CH (Ar)), 120.4 (CH (Ar)), 116.0 (CH (Ar)), 111.6 (CH (Ar)), 28.0 (CH_3).

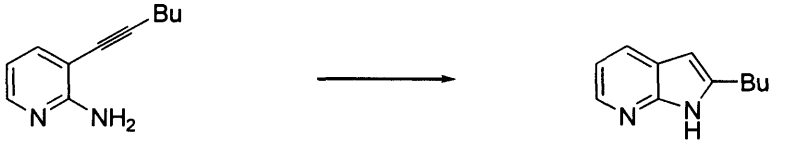
***N*-Acetyl-1-(2-butyl-1*H*-pyrrolo[2,3-*b*]pyridine-1-yl) 158**



146 **158**

According to the general procedure C, 10% $AgNO_3.SiO_2$ (0.24 g, 0.14 mmol) was stirred with a solution of precursor **146** (0.30 g, 1.39 mmol) in dichloromethane (6 ml) for 5 h to give the *aza-indole* **158** as a clear oil (0.30 g, 99%); υ_{max}/cm^{-1} (neat) 3054, 2960, 2933, 2873, 1713, 1589, 1563, 1406, 1378, 1302, 1195; δ_H 8.17 (1H, dd, *J* 4.9, 1.6, CH (Ar)), 7.64 (1H, dd, *J* 7.8, 1.6, CH (Ar)), 7.04 (1H, dd, *J* 7.8, 4.9, CH (Ar)), 6.23 (1H, s, 3-H), 2.99 (2H, t, *J* 7.6, 1'-CH_2), 2.99 (3H, s, CH_3Ac), 1.58 (2H, *quintet*, *J* 7.6, 2'-CH_2), 1.36 (2H, *sextet*, *J* 7.6, 3'-CH_2), 0.88 (3H, t, *J* 7.6, 4'-CH_3); δ_C 171.5 (C=O), 149.3 (C), 144.6 (C), 142.2 (CH (Ar)), 127.5 (CH (Ar)), 122.2 (C), 118.6 (CH (Ar)), 104.5 (CH (Ar)), 30.7 (CH_2), 30.3 (CH_2), 28.4 (CH_3Ac), 22.6 (CH_2), 14.0 (4'-CH_3); *m/z* (EI) 216 (M^+, 20%), 174 (30%), 132 (100%); [Found: $[M]^+$, 216.1262. $C_{13}H_{16}N_2O$ requires: *M*, 216.1263].

2-Butyl-1*H*-pyrrolo[2,3-*b*]pyridine 159[145]



147 **159**

According to the general procedure C, 10% $AgNO_3.SiO_2$ (0.03 g, 0.02 mmol) was stirred with a solution of precursor **147** (0.03 g, 0.17 mmol) in dichloromethane (1 ml) for 24 h to give a 1:1 crude mixture of *starting material* **147** and *aza-indole* **159** as a dark orange oil (0.03 g, 99%); δ_H 7.95 (1H, br d, *J* 5.2, CH (Ar)), 7.74 (1H, d, *J* 7.6, CH (Ar)), 6.88 (1H, dd, *J* 7.6, 5.3, CH (Ar)), 6.05 (1H, s, 3-H), 5.52 (1H, br s, NH), 2.71 (2H, t, *J* 7.6, 1'-CH_2), 1.42-1.24 (4H, m, 2' and 3'-CH_2), 0.82 (3H, t, *J* 7.6, 4'-CH_3).

5.3 Pyrazole experimental

General procedure D for the preparation of propargylic alcohols from aldehydes

To an ice-cold solution of an alkyne (1.05 equiv) in dry tetrahydrofuran (2-3 ml per mmol of alkyne) was added *n*-BuLi (2.5 M in hexanes, 1.05 equiv). The reaction mixture was allowed to stir at 0 °C for 0.5 h. The solution was then cooled to -78 °C and an aldehyde (1.00 equiv) was added dropwise, the resulting mixture was then stirred for 1.5 h. This was followed by the dropwise addition of water (1 x volume of mixture), and the tetrahydrofuran was evaporated. The residue was partitioned between aqueous ammonium chloride (1 x volume of mixture) and diethyl ether (1 x volume of mixture), and the separated aqueous layer was extracted with diethyl ether (2 x volume of mixture). The combined organics solutions were washed with brine (2 x volume of mixture), then dried with magnesium sulphate, filtered and evaporated to give the propargylic alcohol.

General procedure E for the preparation of propargylic alcohols by Sonogashira coupling

A suspension of halide (1.00 equiv), *bis*-triphenylphosphine palladium dichloride (0.06 equiv), copper iodide (0.03 equiv) and triethylamine (4.15 equiv) was stirred in dry tetrahydrofuran (2 ml per mmol halide) for 0.25 h. This was followed by the addition of 3-butyn-2-ol (1.20 equiv) and the reaction was heated to 40 °C for 5 h followed by cooling to an ambient temperature. The cooled reaction mixture was passed through a pad of celite and the tetrahydrofuran was evaporated. The residue was partitioned between diethyl ether (1 x volume of mixture) and water (1 x volume of mixture), and the separated aqueous layer was extracted with diethyl ether (3 x volume of mixture). The combined organics solutions were washed with brine (2 x volume of mixture), then dried with magnesium sulphate, filtered and evaporated to give the propargylic alcohol.

General procedure F for the phthalimide protection of a carbazate

A solution of phthalic anhydride (1.00 equiv) and carbazate (1.00 equiv) in dry tetrahydrofuran (12 ml per mmol of carbazate) was stirred at room temperature for 0.2 h, before the addition of *N,N'*-dicyclohexylcarbodiimide (1.20 equiv). The resulting reaction

mixture was stirred for a further 1 h. The white precipitate of dicyclohexylurea was removed by filtration. Acetic acid (2.00 equiv) and triethylamine (2.00 equiv) were added to the filtrate and the resulting mixture was refluxed for 1 h. The bulk of the solvent was then evaporated and the residue was partitioned between diethyl ether (50 ml per mmol of product) and water (50 ml per mmol product). The separated aqueous layer was extracted with diethyl ether (2 x volume of mixture), and the combined organic solutions were dried with sodium sulphate, filtered and evaporated to give the crude product as a white solid, which was purified by recrystalisation from ethyl acetate and hexane to give pure phthalimide.

General procedure G for the Mitsunobu reaction for the preparation of propargylic hydrazines[76]

To an ice-cold solution of triphenylphosphine (1.50 equiv) in dry tetrahydrofuran (15 ml per mmol of alcohol) diisopropyl azodicarboxylate (1.50 equiv) was added. The resulting mixture was allowed to stir for 0.25 h resulting in a white precipitate. This was followed by the addition of propargylic alcohol (1.00 equiv) and a further stirring period of 0.25 h. The phthalimide (1.50 equiv) was then added in one portion resulting in the disappearance of precipitate and the solution becoming clear orange in colour. The reaction mixture was then allowed to warm to room temperature overnight. The solvent was evaporated and the residue was partitioned between ethyl acetate (50 ml per mmol product) and water (50 ml per mmol product). The separated aqueous layer was extracted with ethyl acetate (2 x volume of mixture) and the combined organic solutions were dried with sodium sulphate, filtered and evaporated to give the crude product, which was then purified by column chromatography using the solvent specified to give clean propargylic phthalimide.

General procedure H for phthalimide deprotection using hydrazine

A solution of a phthalimide (1.00 equiv) and hydrazine hydrate (1.00 equiv) in ethanol (10 ml per mmol phthalimide) was refluxed for 1.5 h and then cooled. The solution was then further cooled to 0 °C and diethyl ether (1 x volume of mixture) was added. The resulting precipitate was filtered off and the filtrate was evaporated. The residue was then taken up in diethyl ether (50 ml per mmol product) and the solution washed with water (2 x volume of

mixture) and brine (1 x volume of mixture), then dried with sodium sulphate, filtered and evaporated to give the free hydrazine.

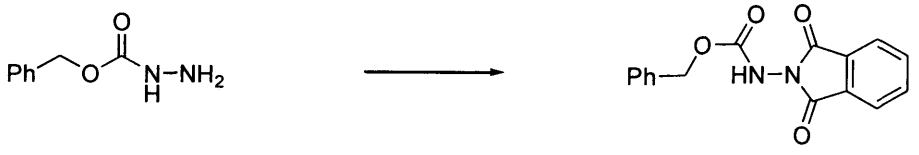
General procedure I for the 10% $AgNO_3$,SiO_2-catalysed cyclisation

In a flask wrapped with metal foil, 10% w/w silver nitrate on silica gel (0.10-1.00 equiv) was added to a stirred solution of hydrazine (1.00 equiv) in dichloromethane (20 mL g^{-1}). The resulting suspension was stirred for 4-8 h then filtered through a thin pad of celite and the solvent evaporated to yield the dihydropyrazole.

General procedure J for the mono-tosylation of a hydrazine

A solution of a monosubstituted hydrazine (1.00 equiv) in dichloromethane (2.6 ml per mmol of monosubstituted hydrazine) was stirred at -78 °C and pyridine (1.01 equiv) was added. The mixture was stirred for 0.2 h before the addition of *p*-TsCl (1.00 equiv) in one portion. The solution was allowed to warm up slowly over 8 h, then diluted with dichloromethane (1 x volume of mixture) and washed with water (4 x volume of mixture) and brine (2 x volume of mixture). The solution was then dried with sodium sulphate, filtered and evaporated to give crude tosylate. The crude product was then purified by recrystalisation from hot ethyl acetate and hexane to give pure mono-tosylate.

Benzyl oxycarbonylaminophthalimide 201a[76]

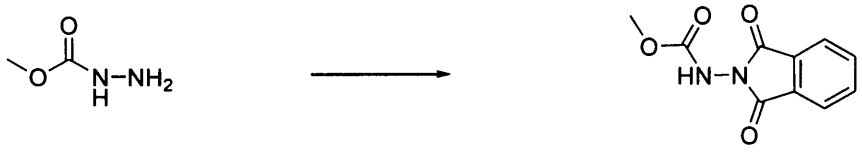


200a **201a**

According to the general procedure F, benzyl carbazate **200a** (4.00 g, 24.1 mmol), phthalic anhydride (3.57 g, 24.1 mmol), *N,N'*-dicyclohexylcarbodiimide (5.97 g, 28.9 mmol), acetic acid (2.77 ml, 48.2 mmol) and triethylamine (6.72 ml, 48.2 mmol) were added sequentially to dry tetrahydrofuran (290 ml). This was followed by work-up and recrystalisation to give pure *phthalimide* **201a** as a white solid (6.12 g, 85%); m.p. 141-142 °C (lit m.p.[76] 140°C); δ_H (500MHz) 7.88-7.82 (2H, m, 4-CH); 7.78-7.70 (2H, m, 2 x CH (Ar)); 7.35-7.20 (5H, m, 5 x CH (Ar)); 5.15 (2H, s, CH_2Ph); δ_C (125MHz) 165.3 (C=O), 154.7 (C=O), 135.1 (C),

134.8 (2 x CH (Ar)), 129.8 (C), 128.6 (3 x CH (Ar)), 128.4 (2 x CH (Ar)), 124.1 (2 x CH (Ar)), 68.6 (CH_2Ar).

Methyl oxycarbonylaminophthalimide 201b



200b **201b**

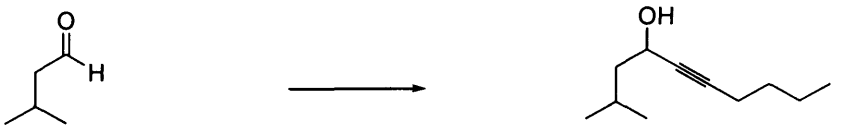
According to the general procedure F, methyl hydrazinocarboxylate **200b** (5.00 g, 55.5 mmol), phthalic anhydride (8.22 g, 55.5 mmol), *N,N'*-dicyclohexylcarbodiimide (13.75 g, 66.63 mmol), acetic acid (6.30 ml, 111 mmol) and triethylamine (15.90 ml, 111.0 mmol) were added sequentially to dry tetrahydrofuran (660 ml). This was followed by work-up and recrystalisation to give pure *phthalimide* **201b** as a white solid (11.00 g, 90%); m.p. 159-169 °C; υ_{max}/cm^{-1} (DCM) 3383, 2959, 2873, 1742, 1716, 1702, 1523, 1468, 1267, 1196, 1122; δ_H 7.87-7.85 (2H, m, 2 x CH (Ar)), 7.76-7.73 (2H, m, 2 x CH (Ar)), 6.75 (1H, br s, NH), 3.77 (3H, br s, Me); δ_C (DMSO) 165.2 (C=O), 165.0 (C=O), 155.5 (C=O), 135.4 (2 x CH (Ar)), 129.2 (C), 123.8 (2 x CH (Ar)), 52.9 (CH_3).

***tert*-Butyloxycarbonylaminophthalimide 201c**[147]

200c **201c**

According to the general procedure F, *tert*-butyl carbazate **200c** (5.00 g, 37.8 mmol), phthalic anhydride (5.60 g, 37.8 mmol), *N,N'*-dicyclohexyl-carbodiimide (9.35 g, 45.4 mmol), acetic acid (4.30 ml, 75.7 mmol) and triethylamine (5.60 ml, 75.7 mmol) were added sequencially to dry tetrahydrofuran (450 ml). This was followed by work-up and recrystalisation to give pure *phthalimide* **201c** as a white solid (9.80 g, 99%); mp 210-212 °C; δ_H (DMSO) 9.90 (1H, s, NH), 7.95-7.97 (4H, m, 4 x CH (Ar)), 1.44 (9H, s, 3 x CH_3C); δ_C (DMSO) 165.9 (C=O), 154.4 (C=O), 135.8 (2 x CH (Ar)), 129.7 (C), 124.2 (2 x CH (Ar)), 81.6 (C*t*Butyl), 28.3 (3 x CH_3C).

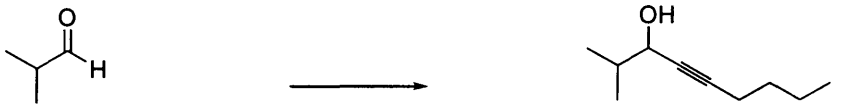
3-Methyldec-5-yn-4-ol 202a[148]



185a **202a**

According to the general procedure D, isovaleraldehyde **185a** (1.25 ml, 11.6 mmol) was added to a solution of 1-hexyne (1.40 ml, 12.2 mmol) and *n*-BuLi (2.5 M in hexanes, 4.88 ml, 12.2 mmol) in tetrahydrofuran (36 ml) at -78 °C, followed by work-up to give the *propargylic alcohol* **202a** as a yellow oil (1.82 g, 93%); δ_H 4.44-4.38 (1H, m 4-H), 2.21 (2H, td, *J* 6.8, 1.8, 7-CH_2), 1.89-1.78 (1H, m, 2-H), 1.71 (1H, d, *J* 5.3, OH), 1.65-1.57 (2H, m, 3-CH_2), 1.56-1.37 (4H, m, 8 and 9-CH_2), 0.93 (3H, t, *J* 7.7, 10-CH_3), 0.93 (6H, d, *J* 7.8, 2-Me, 1-CH_3).

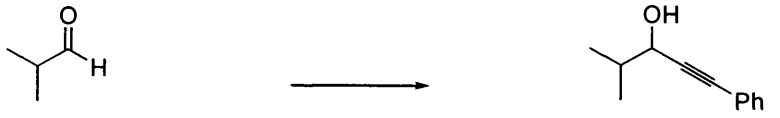
2-Methylnon-4-yn-3-ol 202b[149]



185b **202b**

According to the general procedure D, isobutyraldehyde **185b** (3.18 ml, 55.5 mmol) was added to a solution of 1-hexyne (6.69 ml, 58.2 mmol) and *n*-BuLi (2.5 M in hexanes, 23.30 ml, 58.24 mmol) in tetrahydrofuran (150 ml) at -78 °C, followed by work-up to give the *propargylic alcohol* **202b** as a yellow oil (7.93 g, 93%); δ_H 4.16 (1H, app dt, *J* 5.7, 2.0, 3-H), 2.22 (2H, td, *J* 6.9, 2.0, 6-CH_2), 1.88-1.79 (1H, m, 2-H), 1.66 (1H, br s, OH), 1.50 (2H, *quintet*, *J* 6.9, 7-CH_2), 1.42 (2H, *sextet*, *J* 6.9, 8-CH_2), 0.99 (3H, d, *J* 6.9, 2-Me), 0.97 (3H, d, *J* 6.9, 1-CH_3), 0.91 (3H, t, *J* 6.9, 9-CH_3).

4-Methyl-1-phenylpent-1-yn-3-ol 202c[150]

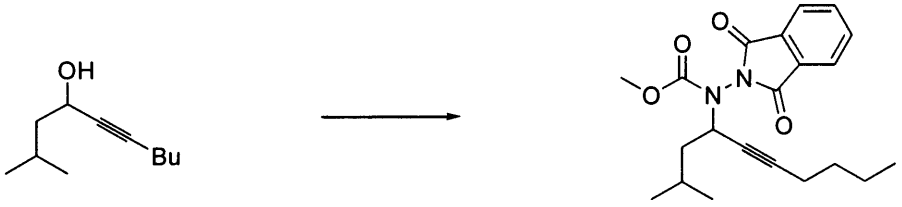


185b **202c**

According to the general procedure D, isobutyraldehyde **185b** (1.26 ml, 13.9 mmol) was added to a solution of phenylacetylene (1.60 ml, 14.6 mmol) and *n*-BuLi (2.5 M in hexanes, 5.82 ml, 14.6 mmol) in tetrahydrofuran (30 ml) at -78 °C, followed by work-up to give the

propargylic alcohol **202c** as an orange oil (2.31 g, 96%); δ_H 7.32-7.29 (2H, m, 2 x CH (Ar)), 7.20-7.17 (3H, m, 3 x CH (Ar)), 4.27 (1H, app t, *J* 5.6, 3-H), 1.85 (1H, hept, *J* 6.5, 4-H), 1.81 (1H, d, *J* 5.6, OH), 0.95 (3H, d, *J* 6.5, 4-CH_3), 0.93 (3H, d, *J* 6.5, 5-CH_3).

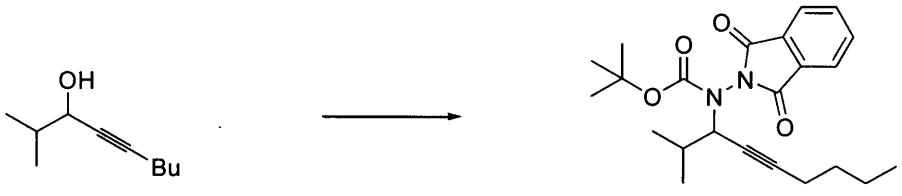
_N_-Methyloxycarbonyl-_N_-(2-methyldec-5-yn-4-yl)aminophthalimide 203a



202a **203a**

According to the general procedure G, triphenylphosphine (7.38 g, 28.1 mmol), diisopropyl azodicarboxylate (5.50 ml, 18.1 mmol), phthalimide **201b** (5.40 g, 28.1 mmol) and propargylic alcohol **202a** (3.15 g, 18.8 mmol) were added sequentially to tetrahydrofuran (280 ml), followed by work-up and purification by column chromatography using 20% ethyl acetate in hexane to give the *hydrazine* **203a** as a clear oil (4.40 g, 69%); υ_{max}/cm^{-1} (neat) 3056, 2959, 2935, 2872, 2305, 2241, 1799, 1740, 1618, 1445, 1335, 1309, 1266, 1215, 1109, 1081; δ_H 7.81-7.78 (2H, m, 2 x CH (Ar)), 7.70-7.67 (2H, m, 2 x CH (Ar)), 5.18-4.96 (1H, br m, 4-H), 3.72-3.53 (3H, br s, CH_3O), 1.94-1.89 (2H, m, 7-CH_2), 1.79-1.43 (3H, m, 3-CH_2, 2-H), 1.22-1.02 (4H, m, 8 and 9-CH_2), 0.85 (6H, br d, *J* 6.3, 1-CH_3, 2-Me), 0.62 (3H, br t, *J* 7.1, 10-CH_3); δ_C 165.8 (C=O), 154.2 (C=O), 134.7 (CH (Ar)), 130.1 (C), 123.9 (CH (Ar)), 123.8 (2 x CH (Ar)), 86.8 (C≡C), 75.7 (C≡C), 53.2 (CH_3O), 51.4 (4-CH), 43.9 (CH_2), 30.4 (CH_2), 25.1 (2-CH), 21.8 (CH_2), 21.5 (CH_3), 18.3 (CH_2), 13.5 (CH_3); *m/z* (EI) 370 (M^+, 20%), 315 (50%); [Found: $[M]^+$, 370.1881. $C_{21}H_{26}N_2O_4$ requires: M, 370.1893].

***N-tert*-Butyloxycarbonyl-_N_-(2-methylnon-4-yn-3-yl)aminophthalimide 203b**

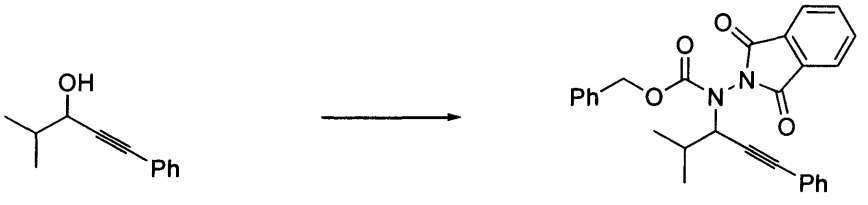


202b **203b**

According to the general procedure G, triphenylphosphine (2.04 g, 7.79 mmol), diisopropyl azodicarboxylate (1.51 ml, 7.79 mmol), phthalimide **201c** (2.04 g, 7.79 mmol) and

propargylic alcohol **202b** (0.80 g, 5.20 mmol) were added sequentially to tetrahydrofuran (80 ml), followed by work-up and purification by column chromatography using 20% ethyl acetate in hexane to give the *hydrazine* **203b** as a clear oil (1.62 g, 78%); υ_{max}/cm^{-1} (neat): 2960, 2932, 2872, 2361, 2239, 1799, 1741, 1608, 1466, 1399, 1369, 1317, 1297, 1258, 1161; δ_H 7.86-7.87 (2H, m, 2 x CH (Ar)), 7.7-7.72 (2H, m, 2 x CH (Ar)), 4.80 (1H, s, 3-H), 1.98-1.99 (3H, m, 2-H and 6-CH_2), 1.61-1.24 (9H, br. s, 3 x CH_3C), 1.11-1.24 (4H, m, 7 and 8-CH_2), 1.09 (6H, br d, *J 6.4,* 1-CH_3, 2-Me), 0.70 (3H, t, *J 7.0,* 9-CH_3); δ_C 165.9 (C=O), 165.3 (C=O), 152.9 (C=O), 135.8 (2 x CH (Ar)), 129.9 (C), 129.7 (C), 124.1 (CH (Ar)), 124.0 (CH (Ar)), 92.1 (C≡C), 82.3 (C≡C), 74.8 (C*t*butyl), 59.3 (3-CH), 33.4 (2-CH), 30.4 (CH_2), 28.1 (3 x CH_3C), 21.5 (CH_3), 20.0 (CH_2), 17.9 (CH_2), 13.4 (CH_3); *m/z* (APCI) 399 ($M+H^+$, 10%), 384 (60%), 357 (100%).

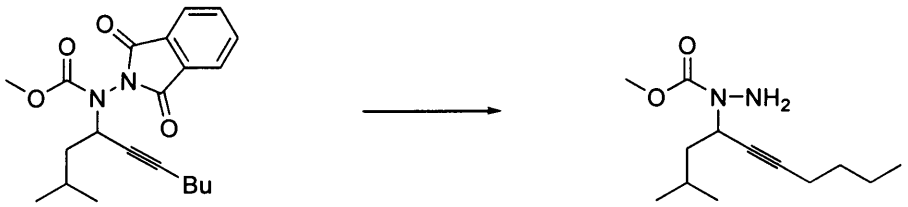
_N_-Benzyloxycarbonyl-_N_-(4-methyl-1-phenylpent-1-yn-3-yl)aminophthalimide 203c



202c **203c**

According to the general procedure G, triphenylphosphine (1.81 g, 6.90 mmol), diisopropyl azodicarboxylate (1.34 ml, 6.90 mmol), phthalimide **201a** (2.04 g, 6.90 mmol) and propargylic alcohol **202c** (0.80 g, 4.60 mmol) were added sequentially to tetrahydrofuran (70 ml), followed by work-up and purification by column chromatography using 20% ethyl acetate in hexane to give the *hydrazine* **203c** as a white solid (1.54 g, 76%); m.p. 89-93°C; υ_{max}/cm^{-1} (DCM): 3063, 2963, 2872, 2362, 2233, 1955, 1798, 1745, 1598, 1490, 1442, 1381, 1287; δ_H 7.89 (2H, d, *J* 4.4, 2 x CH (Ar)), 7.80 (2H, d, *J 4.5*, 2 x CH (Ar)), 7.4-7.19 (10H, m, 10 x CH (Ar)), 5.25 (3H, s, 3-H, CH_2Ph), 2.20-2.21 (1H, m, 4-H), 1.27 (3H, d, *J* 6.1, 5-CH_3), 1.21 (3H, d, *J* 6.54, 4-Me); δ_C 166.1 (C=O), 165.2 (C=O), 154.2 (C=O), 135.5 (C), 134.7 (CH (Ar)), 131.5 (CH (Ar)), 130.0 (C), 128.5 (C), 128.5 (CH (Ar)), 128.3 (CH (Ar)), 123.9 (CH (Ar)), 122.5 (CH (Ar)), 87.1 (C≡C), 84.2 (C≡C), 68.5 (CH_2Ph), 59.6 (3-CH), 33.3 (4-CH), 19.9 (5-CH_3), 19.3 (4-Me); *m/z* (ES) 453 ($M+H^+$, 100%); [Found: [M + H]$^+$, 453.1801. $C_{28}H_{25}N_2O_4$ requires: *M+H*, 453.1814].

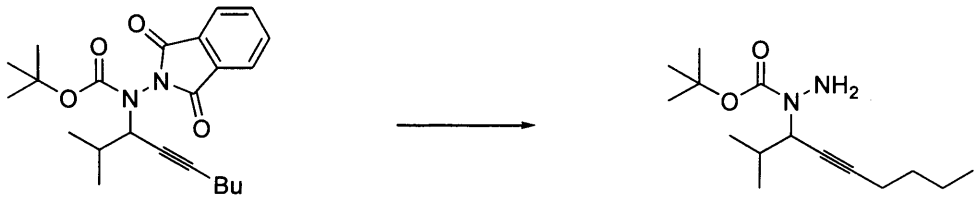
1-Methyloxycarbonyl-1-(2-Methyldec-5-yn-4-yl)hydrazine 206a



203a **206a**

According to the general procedure H, a solution of phthalimide **203a** (2.80 g, 8.19 mmol) and hydrazine hydrate (0.41 g, 8.19 mmol) in ethanol (80 ml) was refluxed for 1.5 h, followed by work-up resulted in crude *hydrazine* **206a** as a clear oil (1.50 g, 86%); υ_{max}/cm^{-1} (neat) 3410, 3054, 2987, 2959, 2872, 2305, 1696, 1447, 1385, 1266, 1104; δ_H 3.86-3.78 (1H, m, 4-H), 3.77 (3H, s, CH_3O), 2.20 (2H, td, *J* 7.1, 2.1, 7-CH_2), 1.72-1.55 (3H, m, 3-CH_2, 2-H), 1.48 (2H, *quintet*, *J* 7.1, 8-CH_2), 1.40 (2H, *sextet*, *J* 7.1, 9-CH_2), 0.93 (6H, d, *J* 6.2, 1-CH_3, 2-Me), 0.91 (3H, t, *J* 7.1, 10-CH_3); δ_C 159.1 (C=O), 53.3 (CH_3O), 48.8 (4-CH), 42.5 (CH_2), 30.8 (CH_2), 24.9 (2-CH), 22.4 (CH_3), 22.0 (CH_2), 18.4 (CH_2), 13.6 (CH_3); *m/z* (EI) 240 (M^+, 50%), 197 (30%), 183 (100%); [Found: $[M]^+$, 240.1832. $C_{13}H_{24}N_2O_2$ requires: *M*, 240.1838]. *Compound taken straight through to next step due to instability to column chromatography. C≡C quaternaries could not be detected in the ^{13}C-NMR possibly due to rotamers.*

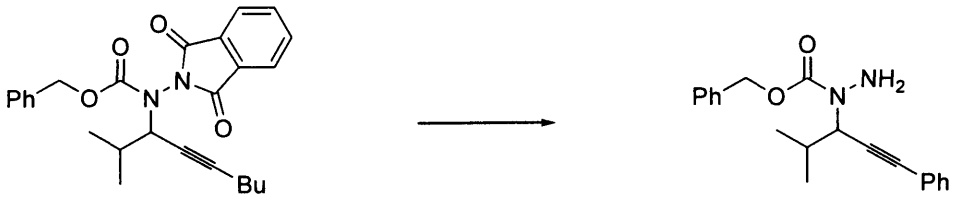
1-*tert*-Butoxycarbonyl-1-(2-methylnon-4-yn-3-yl)hydrazine 206b



203b **206b**

According to the general procedure H, a solution of phthalimide **203b** (0.40 g, 1.04 mmol) and hydrazine hydrate (0.05 ml, 1.04 mmol) in ethanol (10 ml) was refluxed for 1.5 h, followed by work-up resulted in crude hydrazine **206b** as a clear oil (0.20 g, 72%); δ_H 4.34-4.19 (1H, br m, 3-H), 3.66 (2H, br s, NH_2), 2.14 (2H, td, J 7.0, 2.1, 6-CH_2), 2.03-1.93 (1H, m, 2-H), 1.46-1.39 (2H, m, 7-CH_2), 1.41 (9H, s, 3 x CH_3C), 1.33 (2H, hex *J* 7.1, 8-CH_2), 0.98 (3H, d, *J* 7.0, 1-CH_3), 0.83 (3H, t, *J* 7.1, 9-CH_3), 0.79 (3H, d, *J* 7.0, 2-Me). *Compound taken through to next step due to instability to column chromatography.*

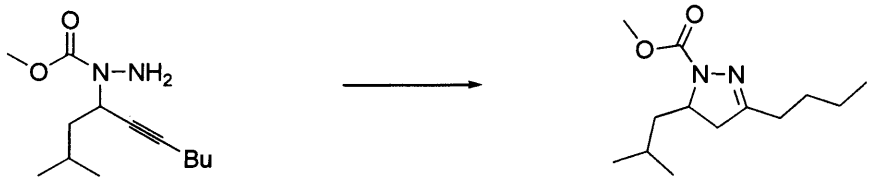
1-Benzyloxycarbonyl-1-(2-Methyldec-5-yn-4-yl)hydrazine 206c



203c **206c**

According to the general procedure H, A solution of phthalimide **203c** (0.65 g, 1.48 mmol) and hydrazine hydrate (0.07 ml, 1.48 mmol) in ethanol (15 ml) was refluxed for 1.5 h, followed by work-up resulted in crude hydrazine **206c** as a clear oil (0.45 g, 94%); δ_H 7.38-7.22 (10H, m, 10 x CH (Ar)), 5.14 (2H, s, CH_2Ph), 4.55-4.51 (1H, m, 3-H), 3.88 (2H, br s, NH_2), 2.21-2.12 (1H, m, 2-H), 1.08 (3H, d, *J* 6.7, 1-CH_3), 0.86 (3H, d, *J* 6.7, 2-Me). *Compound taken through to next step due to instability to column chromatography.*

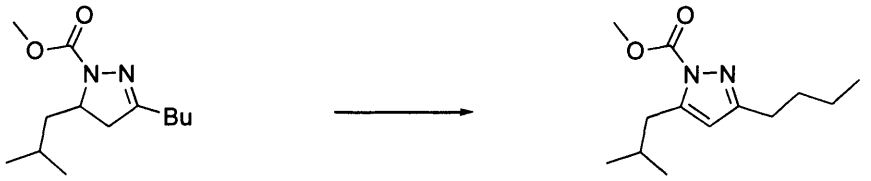
Methyl 3-butyl-5-isobutyl-4,5-dihydropyrazole-1-carboxylate 207a



206a **207a**

According to the general procedure I, 10% $AgNO_3.SiO_2$ (0.35 g, 0.21 mmol) was stirred with a solution of precursor **206a** (0.25 g, 1.04 mmol) in dichloromethane (5 ml) for 4 h to give the *dihydropyrazole* **207a** as a clear viscous oil (0.24 g, 96%); υ_{max}/cm^{-1} (neat) 2957, 2933, 2872, 2362, 2342, 1699, 1467, 1406, 1366, 1301, 1194, 1123, 1097; δ_H 4.27 (1H, app ddd, *J* 15.0, 10.0, 4.4, 5-H), 3.77 (3H, s, CH_3O), 2.93 (1H, dd, *J* 17.9, 10.9, 4-H_A), 2.43 (1H, dd, *J* 17.9, J 4.8, 4-H_B), 2.34 (2H, td, *J* 7.7, 2.4, 1'-CH_2), 1.84-1.73 (1H, br m, 2''-H), 1.64-1.55 (1H, m, 1''-H_A), 1.50 (2H, *quintet*, *J* 7.7, 2'-CH_2), 1.32 (2H, *sextet*, *J* 7.7, 3'-CH_2), 1.25 (1H, ddd, *J* 13.2, 10.0, 4.8, 1''-H_B), 0.91 (6H, dd, *J* 6.6, 1.3, 3''-CH_3, 2''-Me), 0.88 (3H, t, *J* 7.7, 4'-CH_3); δ_C 159.5 (C), 153.3 (C), 56.2 (CH_3O), 52.7 (5-CH), 43.0 (CH_2), 40.5 (CH_2), 30.0 (CH_2), 28.7 (CH_2), 25.0 (2''-CH), 23.5 (CH_3), 22.4 (CH_2), 21.6 (CH_3), 13.7 (CH_3); *m/z* (APCI) 503 ($2M+Na^+$, 100%), 304 ($M+MeCNNa^+$, 30%), 241 (80%).

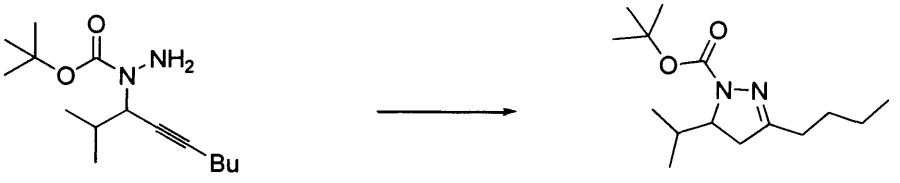
Methyl 3-butyl-5-isobutyl-1*H*-pyrazole-1-carboxylate 208



207a **208**

To a stirred solution of 4,5-dihydropyrazole **207a** (0.10 g, 0.42 mmol) in toluene (40 ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.28 g, 1.25 mmol) and the mixture was refluxed for 18 h. The mixture was then cooled to room temperature and the resulting precipitate was filtered off and the filtrate evaporated. The crude residue was then separated by column chromatography using 20% ethyl acetate in hexane to give the *pyrazole* **208** as a clear oil (0.07 g, 71%); υ_{max}/cm^{-1} (neat) 2957, 2931, 2871, 1750, 1576, 1467, 1441, 1373, 1306, 1208, 1115, 1075; δ_H 5.94 (1H, s, 4-H), 3.94 (3H, s, CH_3O), 2.75 (2H, d, *J* 6.9, 1''-CH_2), 2.55 (2H, t, *J* 7.6, 1'-CH_2), 1.90 (1H, *nonete*, *J* 6.8, 2''-H), 1.55 (2H, *quintet*, *J* 7.6, 2'-CH_2), 1.30 (2H, *sextet*, *J* 7.6, 3'-CH_2), 0.88 (6H, d, *J* 6.9, 3''-CH_3, 2''-Me), 0.85 (3H, t, *J* 7.6, 4'-CH_3); δ_C 157.2 (C), 150.8 (C), 148.7 (C), 109.6 (4-CH), 54.4 (CH_3O), 36.6 (CH_2), 31.2 (CH_2), 28.1 (CH_2), 27.5 (2''-CH), 22.5 (CH_2), 22.3 (CH_3), 13.9 (CH_3); *m/z* (ES) 499 ($2M+Na^+$, 25%), 302 ($M+MeCNNa^+$, 100%), 239 ($M+H^+$, 15%); [Found: $[M+H]^+$, 239.1759. $C_{13}H_{23}N_2O_2$ requires: *M+H*, 239.1760].

***tert*-Butyl 3-butyl-5-isopropyl-4,5-dihydropyrazole-1-carboxylate 207b**

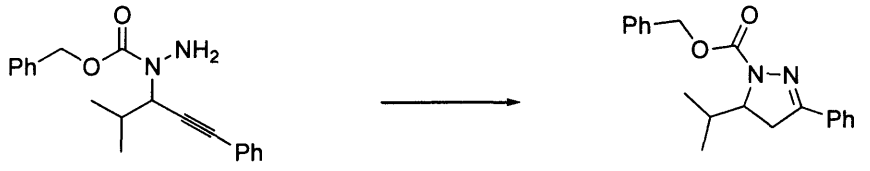


206b **207b**

According to the general procedure I, 10% $AgNO_3.SiO_2$ (0.04 g, 0.02 mmol) was stirred with a solution of precursor **206b** (0.06 g, 0.22 mmol) in dichloromethane (1 ml) for 4 h to give clean *dihydropyrazole* **207b** as a clear viscous oil (0.5 g, 83%); υ_{max}/cm^{-1} (DCM): 2958, 2932, 2872, 1719, 1685, 1421, 1365, 1320, 1280, 1254, 1224, 1168; δ_H 4.17-4.18 (1H, m, 5-H), 2.70 (1H, dd, *J*17.9, *J* 6.4, 4-H_A), 2.50 (1H, dd, *J* 18.0, *J* 4.8, 4-H_B), 2.30-2.31 (3H, m, 1'-CH_2, 1''-H), 1.48-1.45 (2H, m, 2'-CH_2), 1.48 (9H, s, 3 x CH_3C), 1.30-1.31 (2H, m, 3'-CH_2), 0.89 (3H, t, *J* 7.0, 4'-CH_3), 0.80 (3H, d, *J* 6.0, 2''-CH_3), 0.69 (3H, d, *J* 6.0, 1''-Me); δ_C 158.7 (C=O), 152.3 (3-C), 80.5 (C*t*Butyl), 62.1 (5-CH), 34.9 (4-CH_2), 30.1

(CH_2), 29.6 (1''-CH), 29.4 (CH_2), 28.2 (3 x CH_3C), 22.6 (CH_2), 17.5 (CH_3), 14.7 (CH_3), 13.8 (CH_3); *m/z* (EI) 268 (M^+, 5%), 168 (10%), 125 (100%); [Found: $[M]^+$, 268.2152. $C_{15}H_{28}N_2O_2$ requires: *M*, 268.2151].

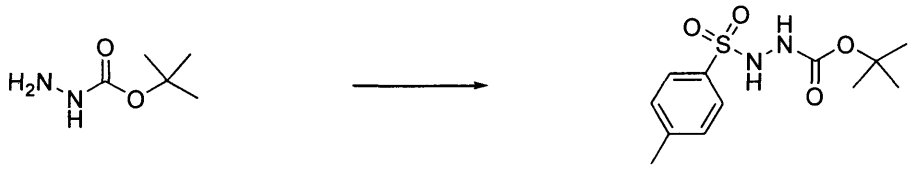
Benzyl 5-isopropyl-3-phenyl-4,5-dihydropyrazole-1-carboxylate 207c



206c **207c**

According to the general procedure I, 10% $AgNO_3.SiO_2$ (0.26 g, 0.16 mmol) was stirred with a solution of precursor **206c** (0.50 g, 1.55 mmol) in dichloromethane (10 ml) for 4 h to give clean *dihydropyrazole* **207c** as a clear viscous oil (0.47 g, 94%); υ_{max}/cm^{-1} (DCM): 2961, 2932, 1693, 1447, 1425, 1391, 1369, 1272; δ_H 7.68-7.69 (2H, m, 2 x CH (Ar)), 7.31-7.32 (2H, m, 2 x CH (Ar)), 7.29-7.19 (6H, m, 6 x CH (Ar)), 5.22-5.23 (2H, m, CH_2Ph), 4.34-4.35 (1H, m, 5-H), 3.10 (1H, dd, *J* 17.6, 6.0, 1H, 4-H_A), 2.89 (1H, dd, *J* 17.7, 4.9, 4-H_B), 2.40-2.33 (1H, m, 1'-H), 0.82 (3H, d, *J* 6.9, 2'-CH_3), 0.69 (3H, d, *J* 6.8, 1'-Me); δ_C 154.8 (C=O), 153.1 (C), 136.5 (C), 131.4 (C), 130.1 (CH (Ar)), 128.6 (4 x CH (Ar)), 128.1 (3 x CH (Ar)), 126.7 (2 x CH (Ar)), 67.4 (CH_2), 63.2 (5-CH), 32.9 (CH_2), 29.7 (1'-CH), 18.4 (CH_3), 15.3 (CH_3); *m/z* (ES) 323 ($M+H^+$, 100%), 279 (30%); [Found: $[M + H]^+$, 323.1766. $C_{20}H_{23}N_2O_2$ requires: *M+H*, 323.1760].

***N*-tert-Butoxycarbonyl-*N'*-(*p*-toluenesulfonyl)hydrazine 209**

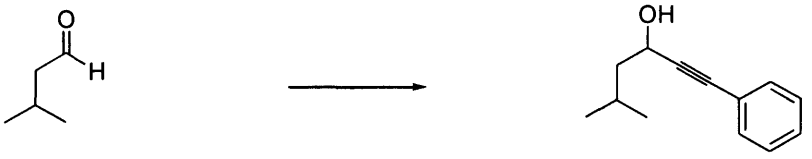


200c **209**

According to the general procedure J, *tert*-Butyl carbazate **200c** (12.50 g, 94.69 mmol), pyridine (7.70 ml, 95.6 mmol) and *p*-TsCl (18.05 g, 94.69 mmol) were added sequentially to dichloromethane (250 ml). Work-up and recrystalisation resulted in clean *tosylate* **209** as a white solid (20.20 g, 75%); m.p. 98-99 °C; υ_{max}/cm^{-1} ($CHCl_3$) 3325, 3250, 2981, 2932, 1718, 1598, 1495, 1370, 1341, 1290, 1256, 1160, 1092; δ_H 7.81 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.32 (2H, d, *J* 8.2, 2 x CH (Ar)), 6.57-6.49 (2H, br s, 2 x NH), 2.43 (3H, s, CH_3Ar), 1.25

(9H, s, 3 x CH_3C); δ_C 153.9 (C=O), 144.6 (C), 129.4 (2 x CH (Ar)), 128.9 (C), 128.5 (2 x CH (Ar)), 82.1 (C*t*Butyl), 27.3 (3 x CH_3C), 21.6 (CH_3Ar). *m/z* (EI) 286 (M^+, 2%), 230 (100%), 186 (90%); [Found: $[M]^+$, 286.0993. $C_{12}H_{18}N_2O_4S$ required: *M*, 286.0987]

5-Methyl-1-phenylhex-1-yn-3-ol 210[149]



185a **210**

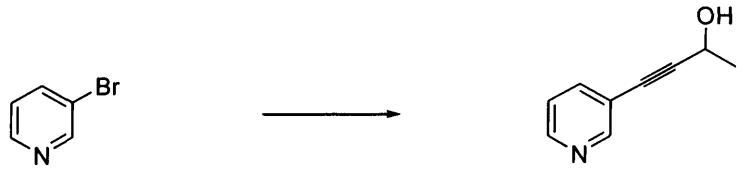
According to the general procedure D, isovaleraldehyde **185a** (1.25 ml, 11.6 mmol) was added to a solution of phenylacetylene (1.34 ml, 12.2 mmol) and *n*-BuLi (2.5 M in hexanes, 4.88 ml, 12.2 mmol) in tetrahydrofuran (30 ml) at -78 °C, followed by work-up to give the *propargylic alcohol* **210** as a yellow oil (1.99 g, 91%); δ_H 7.31-7.29 (2H, m, 2 x CH (Ar)), 7.21-7.17 (3 x CH (Ar)), 4.52 (1H, app td, *J* 7.5, 5.8, 3-H), 1.80 (1H, app hept, *J* 6.7, 5-H), 1.69 (1H, d, *J* 5.8, OH), 1.65-1.50 (2H, m, 4-CH_2), 0.86 (3H, d, J 5.8, 6-CH_3), 0.84 (3H, d, J 5.8, 5-Me).

1-(Thiophen-3-yl)but-2-yn-3-ol 213a[151]

211a **213a**

According to the general procedure E, bis triphenylphosphine palladium dichloride (0.19 g, 0.27 mmol), copper iodide (0.03 g, 0.14 mmol), 3-butyn-2-ol **212** (0.43 ml, 5.43 mmol), 2-iodothiophene **211a** (0.95 g, 4.52 mmol) and triethylamine (2.60 ml, 18.8 mmol) were stirred in dry tetrahydrofuran (10 ml), this was followed by work-up which gave clean *propargylic alcohol* **213a** as an orange oil (0.48 g, 70%); δ_H 7.28 (1H, dd, *J* 5.1, 1.1, CH (Ar)), 7.22 (1H, dd, *J* 3.6, 1.1, CH (Ar)), 6.99 (1H, dd, *J* 5.3, 3.6, CH (Ar)), 4.79 (1H, app q, *J* 6.0, 3-H), 2.05 (1H, d, *J* 6.0, OH), 1.57 (3H, d, *J* 6.0, 4-CH_3); δ_C 132.6 (CH (Ar)), 127.6 (CH (Ar)), 127.3 (CH (Ar)), 121.9 (C), 120.4 (C), 95.1 (C), 59.4 (3-CH), 24.6 (4-CH_3).

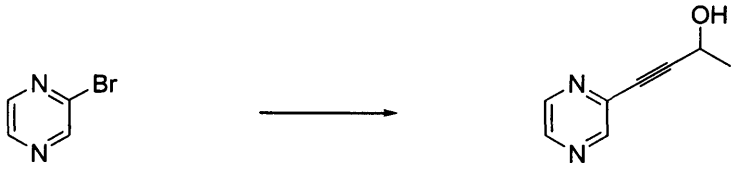
1-(Pyridine-2-yl)but-2-yn-3-ol 213b



211b **213b**

According to the general procedure E, bistriphenylphosphine palladium dichloride (0.22 g, 0.31 mmol), copper iodide (0.03 g, 0.16 mmol), 3-butyn-2-ol **212** (0.49 ml, 6.23 mmol), 3-bromopyridine **211b** (0.50 ml, 5.19 mmol) and triethylamine (3.00 ml, 21.5 mmol) were stirred in dry tetrahydrofuran (10 ml), this was followed by work-up which gave clean *propargylic alcohol* **213b** as a dark orange oil (0.50 g, 66%); δ 8.77 (1H, app. s, CH (Ar)), 8.52 (1H, app. s, CH (Ar)), 7.72 (1H, app. d, *J* 7.8, CH (Ar)), 7.27 (1H, app. dd, *J* 7.6, 4.9, CH (Ar)), 4.78 (1H, q, *J* 6.6, 3-CH), 4.65-4.62 (1H, br. s, OH), 1.57 (3H, d, *J* 6.6, 4-CH_3); δ_C 151.2 (CH (Ar)), 147.3 (CH (Ar)), 138.1 (CH (Ar)), 131.2 (C), 122.4 (CH (Ar)), 94.9 (C≡C), 79.2 (C≡C), 57.3 (3-CH), 23.3 (4-CH_3).

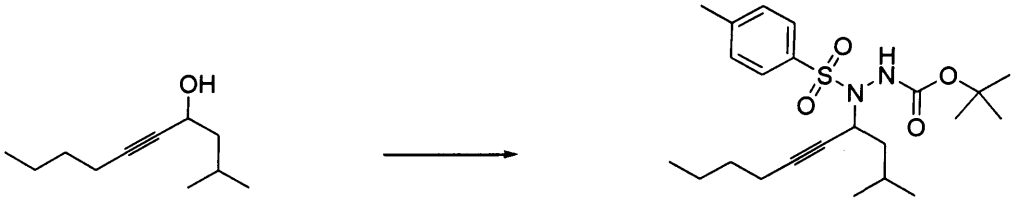
1-(Pyrazin-3-yl)but-2-yn-3-ol 213c



211c **213c**

According to the general procedure E, bis triphenylphosphine palladium dichloride (0.53 g, 0.76 mmol), copper iodide (0.07 g, 0.38 mmol), 3-butyn-2-ol **212** (0.85 ml, 15.1 mmol), 2-iodopyrazine **211c** (2.00 g, 12.6 mmol) and triethylamine (7.28 ml, 52.2 mmol) were stirred in dry tetrahydrofuran (25 ml), this was followed by work-up which gave clean *propargylic alcohol* **213c** as a brown oil (1.45 g, 78%); δ_H 8.68 (1H, app.d, *J* 1.4, CH (Ar)), 8.55 (1H, app. t, *J* 1.5, CH (Ar)), 8.51 (1H, app d, *J* 2.4, CH (Ar)), 4.82 (1H, app q, *J* 5.9, 3-CH), 2.20 (1H, d, *J* 5.9, OH), 1.61 (3H, d, *J* 5.9, 4-CH_3); δ_C 147.4 (CH (Ar)), 144.2 (CH (Ar)), 142.9 (CH (Ar)), 139.6 (C), 96.0 (C≡C), 79.9 (C≡C), 58.0 (3-CH), 23.7 (4-CH_3).

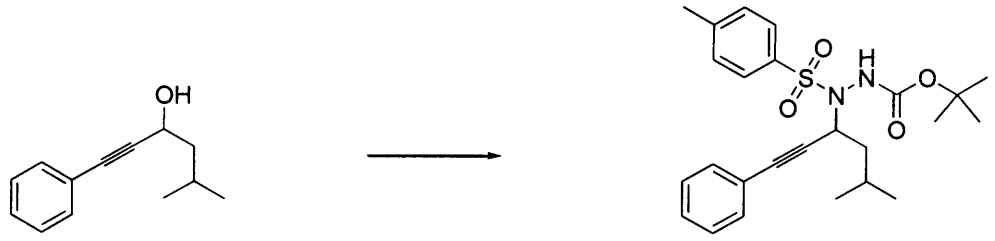
N-tert-Butyloxycarbonyl-_N_-(2-methyldec-5-yn-4-yl)-_p_-toluenesulfonylhydrazine 219a



202a **219a**

According to the general procedure G, triphenylphosphine (11.71 g, 44.64 mmol), diisopropyl azodicarboxylate (8.80 ml, 44.6 mmol), hydrazine **209** (11.52 g, 44.64 mmol) and propargylic alcohol **202a** (5.00 g, 29.8 mmol) were added sequentially to tetrahydrofuran (450 ml), followed by work-up and purification by column chromatography using 10% ethyl acetate in hexane to give the *substituted hydrazine* **219a** as a yellow solid (12.14 g, 91%); m.p. 59-60 °C; υ_{max}/cm^{-1} ($CHCl_3$) 3314, 2958, 2871, 1759, 1710, 1598, 1469, 1366, 1233, 1165, 1092; δ_H 7.76 (2H, d, *J* 8.0, 2 x CH (Ar)), 7.41 (2H, d, *J* 8.0, 2 x CH (Ar)), 4.65 (1H, app. t, *J* 7.4, 4-H), 2.42 (3H, s, CH_3Ar), 2.05-1.97 (2H, m, 7-CH_2), 1.95-1.81 (1H, m, 2-H), 1.56 (2H, *quintet*, *J* 7.4, 8-CH_2), 1.49-1.28 (4H, m, 9-CH_2, 3-CH_2), 1.37 (9H, s, 3 x CH_3C), 0.89 (3H, t, *J* 7.1, 10-CH_3), 0.88 (6H, d, *J* 7.0, 1-CH_3, 2-Me); δ_C 144.3 (C), 129.5 (C), 129.2 (2 x CH (Ar)), 128.5 (2 x CH (Ar)), 89.1 (C≡C), 81.3 (C≡C), 50.4 (4-CH), 43.1 (CH_2), 30.4 (CH_2), 27.9 (3 x CH_3C), 24.0 (2-CH), 21.9 (CH_2), 21.6 (CH_2), 21.4 (CH_3Ar), 18.1 (CH_3), 13.5 (CH_3); *m/z* (ES) 454 ($M+NH_4^+$, 100%), 381 (25%); [Found: $[M+NH_4]^+$, 454.2732. $C_{23}H_{40}N_3O_4S$ requires: *M+NH₄*, 454.2740]. *Boc quaternaries C=O and Ctbutyl could not be seen in the ^{13}C-NMR due to rotamers.*

_N-tert_butyloxycarbonyl-_N_-(5-methyl-1-phenylhex-2-yn-3-yl)-_p_toluenesulfonylhydrazine 219b

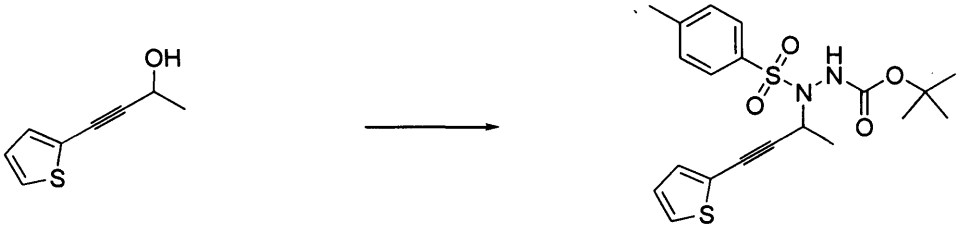


210 **219b**

According to the general procedure G, triphenylphosphine (2.47 g, 9.40 mmol), diisopropyl azodicarboxylate (1.83 ml, 9.40 mmol), hydrazine **209** (2.69 g, 9.40 mmol) and propargylic alcohol **210** (1.18 g, 6.27 mmol) were added sequentially to tetrahydrofuran (90 ml), followed by work-up and purification by column chromatography using 10% ethyl acetate

in hexane to give the *substituted hydrazine* **219b** as a white solid (1.40 g, 59%); m.p. 134-135 °C; υ_{max}/cm^{-1} ($CHCl_3$) 3357, 3056, 2960, 2866, 2359, 1754, 1718, 1598, 1479, 1367, 1265, 1166, 1091; δ_H 7.96 (1H, br. s, NH), 7.81 (2H, d, *J* 8.5, 2 x CH (Ar)), 7.38 (2H, d, *J* 8.5, 2 x CH (Ar)), 7.34-7.22 (5H, m, 5 x CH (Ar)), 4.90 (1H, t, *J* 7.4, 3-H), 2.44-2.38 (1H, m, 5-H), 2.36 (3H, s, CH_3Ar), 1.44-1.38 (2H, m, 4-CH_2), 1.39 (9H, s, 3 x CH_3C), 0.97 (3H, d, *J* 6.6, 6-CH_3), 0.93 (3H, d, *J* 6.6, 5-Me). δ_C 144.1 (C), 131.4 (CH (Ar)), 129.2 (CH (Ar)), 129.1 (C), 128.9 (3 x CH (Ar)), 128.4 (2 x CH (Ar)), 127.9 (2 x CH (Ar)), 85.6 (C≡C), 85.1 (C≡C), 77.8 (C*t*butyl), 50.4 (3-CH), 42.1 (4-CH_2), 27.7 (3 x CH_3C), 23.8 (5-CH), 22.7 (CH_3), 21.7 (CH_3), 21.6 (CH_3Ar); *m/z* (ES) 520 ($M+MeCNNa^+$, 15%), 474 ($M+NH_4^+$, 100%); [Found: $[M+NH_4]^+$, 474.2426. $C_{25}H_{36}N_3O_4S$ requires: *M+NH₄*, 474.2427]. *Boc C=O could not be seen in the ^{13}C-NMR due to rotamers.*

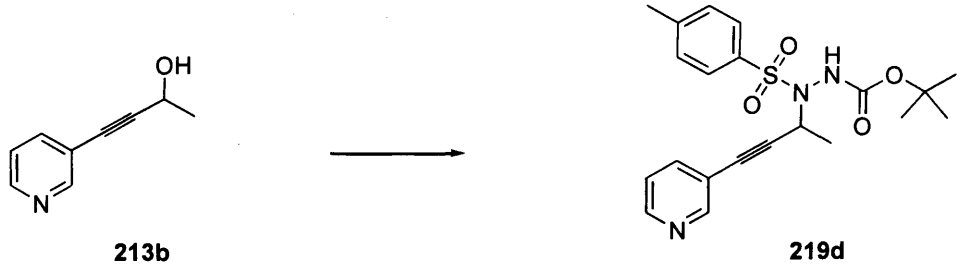
***N-tert*butyloxycarbonyl-*N*-(1-(thiophen-3-yl)but-2-yn-3-yl)-*p*toluenesulfonylhydrazine 219c**



213a **219c**

According to the general procedure G, triphenylphosphine (0.62 g, 2.37 mmol), diisopropyl azodicarboxylate (0.46 ml, 2.37 mmol), hydrazine **209** (0.68 g, 2.37 mmol) and propargylic alcohol **213a** (0.24 g, 1.58 mmol) were added sequentially to tetrahydrofuran (25 ml), followed by work-up and purification by column chromatography using 20% ethyl acetate in hexane to give the *substituted hydrazine* **219c** as a white solid (0.29 g, 44%); m.p. 98-99 °C; υ_{max}/cm^{-1} ($CHCl_3$) 3355, 3055, 2985, 2494, 2305, 1752, 1714, 1365, 1265, 1170, 1089; δ_H (DMSO, 392 K) 8.29 (1H, s, NH), 7.80 (2H, d, *J* 8.4, 2 x CH (Ar)), 7.49 (1H, dd, *J* 5.2, 1.2, CH (Ar)), 7.38 (2H, d, *J* 8.4, 2 x CH (Ar)), 7.13 (1H, dd, *J* 3.6, 1.2, CH (Ar)), 7.01 (1H, dd, *J* 5.1, 3.6, CH (Ar)), 5.06 (1H, q, *J* 6.9, 3-H), 2.39 (3H, s, CH_3Ar), 1.44 (3H, d, *J* 6.8, 4-CH_3), 1.36 (9H, s, 3 x CH_3C); δ_C (MeOD) 157.7 (C=O), 146.2 (C), 134.1 (C), 133.2 (CH (Ar)), 130.8 (CH (Ar)), 129.9 (2 x CH (Ar)), 128.7 (2 x CH (Ar)), 127.9 (CH (Ar)), 122.9 (C), 90.5 (C≡C), 82.1 (C≡C), 79.9 (C*t*butyl), 50.1 (3-CH), 28.4 (3 x CH_3C), 21.6 (CH_3Ar), 20.8 (4-CH_3); *m/z* (ES) 484 ($M+MeCNNa^+$, 20%), 459 ($M+K^+$, 10%), 438 ($M+NH_4^+$, 100%); [Found: $[M+NH_4]^+$, 438.1515. $C_{20}H_{28}N_3O_4S_2$ requires: *M+NH₄*, 438.1521].

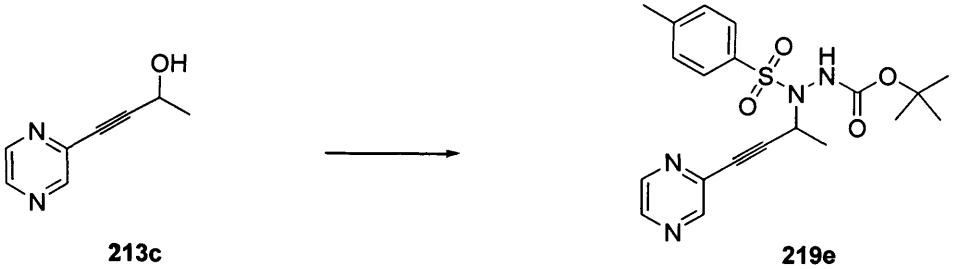
***N*-*tert*butyloxycarbonyl-*N*-(1-(3-pyridinyl)but-2-yn-3-yl)-*p*toluenesulfonylhydrazine 219d**



213b **219d**

According to the general procedure G, triphenylphosphine (0.67 g, 2.55 mmol), diisopropyl azodicarboxylate (0.50 ml, 2.55 mmol), hydrazine **209** (0.73 g, 2.55 mmol) and propargylic alcohol **213b** (0.25 g, 1.70 mmol) were added sequentially to tetrahydrofuran (25 ml), followed by work-up and purification by column chromatography using 30-50% ethyl acetate in hexane to give the *substituted hydrazine* **219d** as a white solid (0.31 g, 44%); m.p. 90-92 °C; υ_{max}/cm^{-1} ($CHCl_3$) 3432, 2980, 2931, 2367, 1745, 1704, 1640, 1476, 1363, 1166, 1089; δ_H (DMSO, 392 k) 8.51 (1H, dd, *J* 4.8, 1.6, 6-H), 8.44 (1H, d, *J* 1.9, 5-H), 8.40 (1H, br. s, NH), 7.81 (2H, d, *J* 8.3, 2 x CH (Ar)), 7.64 (1H, dt, *J* 7.9, 1.9, CH (Ar)), 7.36 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.36-7.31 (1H, m, CH (Ar)), 5.08 (1H, q, *J* 6.9, 3-H), 2.36 (3H, s, CH_3Ar), 1.46 (3H, d, *J* 6.9, 4-CH_3), 1.36 (9H, s, 3 x CH_3C); δ_C ($CDCl_3$) 157.1 (C=O), 152.7 (CH (Ar)), 149.2 (CH (Ar)), 146.3 (C), 140.6 (CH (Ar)), 134.5 (C), 130,7 (2 x CH (Ar)), 130.1 (2 x CH (Ar)), 124.6 (CH (Ar)), 121.2 (C), 90.1 (C≡C), 82.2 (C≡C), 79.8 (C*t*butyl), 54.2 (3-CH), 28.5 (3 x CH_3C), 21.5 (CH_3Ar), 20.5 (4-CH_3); *m/z* (ES) 479 ($M+MeCNNa^+$, 25%), 457 ($M+MeCNH^+$, 25%), 416 ($M+H^+$, 100%); [Found: $[M+H]^+$, 416.1657. $C_{21}H_{26}N_3O_4S$ requires: $M+NH_4$, 416.1644].

***N*-*tert*butyloxycarbonyl-*N*-(1-(2-pyrazinyl)but-2-yn-3-yl)-*p*-toluenesulfonylhydrazine 219e**



213c **219e**

According to the general procedure G, triphenylphosphine (0.53 g, 2.02 mmol), diisopropyl azodicarboxylate (0.39 ml, 2.02 mmol), hydrazine **209** (0.58 g, 2.02 mmol) and propargylic alcohol **213c** (0.20 g, 1.35 mmol) were added sequentially to tetrahydrofuran (20 ml), followed by work-up and purification by column chromatography using 30-50% ethyl

acetate in hexane to give the *substituted hydrazine* **219e** as a dark orange oil (0.07 g, 12%); υ_{max}/cm^{-1} ($CHCl_3$) 3225, 2979, 2349, 2240, 1748, 1710, 1365, 1163, 1090; δ_H (MeOD) 8.51 (2H, d, *J* 6.8, 2 x CH (Ar)), 8.38 (1H, s, CH (Ar)), 7.81 (2H, d, *J* 7.9, 2 x CH (Ar)), 7.33-7.26 (2H, m, 2 x CH (Ar)), 5.23-5.20 (1H, m, 3-H), 2.24 (3H, s, CH_3Ar), 1.48 (3H, d, *J* 7.1, 4-CH_3), 1.46 (9H, s, 3 x CH_3C); δ_C ($CDCl_3$) 157.6 (C=O), 148.9 (CH (Ar)), 146.2 (C), 145.4 (CH (Ar)), 144.8 (CH (Ar)), 140.8 (C), 135.2 (C), 130.6 (2 x CH (Ar)), 130.2 (2 x CH (Ar)), 91.9 (C≡C), 82.1 (C≡C), 78.9 (C*t*butyl), 51.2 (3-CH), 28.5 (3 x CH_3C), 21.5 (CH_3Ar), 20.5 (4-CH_3); *m/z* (ES) 417 ($M+H^+$, 10%), 361 (100%); [Found: $[M+H]^+$, 417.1588. $C_{20}H_{25}N_4O_4S$ requires: *M+H*, 417.1597].

_N_-(2-methyldec-5-yn-4-yl)_p_-toluenesulfonylhydrazide 219f

219a **219f**

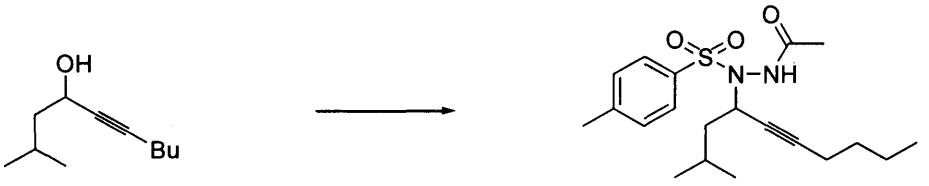
Boc-protected hydrazine **219a** (0.06 g, 0.14 mmol) was dissolved in dichloromethane (0.1 ml) and cooled to 0 °C. This was followed by the dropwise addition of 20% trifluoroacetic acid (0.03 ml, 0.41 mmol) in dichloromethane (0.12 ml) and allowed to stir at 0 °C for 4 h. The solution was diluted with dichloromethane (10 ml) and 2M sodium hydroxide (few drops) was added to neutralise. The organic layer was separated and was then washed with water (2 x 10 ml) and brine (10 ml). The organics were then dried over sodium sulphate, filtered and evaporated to give the *free hydrazine* **219f** as a crude yellow oil (0.03 g, 65%); υ_{max}/cm^{-1} (Neat) 3368, 2958, 2933, 2871, 2256, 1598, 1467, 1349, 1159, 1091; δ_H (500 MHz) 7.73 (2H, d, *J* 8.1, 2 x CH (Ar)), 7.24 (2H, d, *J* 8.1, 2 x CH (Ar)), 4.72 (1H, app t, *J* 7.6, 4-H), 3.51 (2H, br s, NH_2), 2.36 (3H, s, CH_3Ar), 1.76 (2H, app br t, *J* 6.6, 7-CH_2), 1.73-1.66 (1H, m, CH), 1.66-1.58 (1H, m, CH), 1.43-1.36 (1H, m, CH), 1.12-1.06 (4H, m, 2 x CH_2), 0.91 (3H, d, *J* 6.6, 1-CH_3), 0.87 (3H, d, *J* 6.6, 2-Me), 0.75 (3H, t, *J* 6.6, 10-CH_3). *Compound decomposed as was unstable.*

***N'*-Tosylacetohydrazide 222**[152]

221 **222**

According to the general procedure J, Acetic hydrazide **221** (5.00 g, 67.5 mmol), pyridine (5.50 ml, 68.2 mmol) and *p*-TsCl (12.74 g, 67.50 mmol) were added sequentially to dichloromethane (175 ml). Work-up and recrystalisation resulted in clean tosylate **222** as a clear solid (15.10 g, 98%); m.p. 160-162 (lit m.p.[152] 159 °C); δ_H 7.80 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.33 (2H, d, *J* 8.2, 2 x CH (Ar)), 2.45 (3H, s, CH_3Ar), 1.87 (3H, s, CH_3Ac).

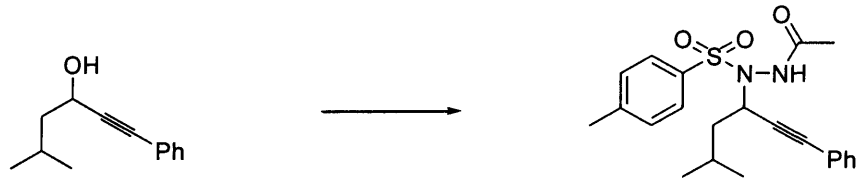
***N'*-(2-Methyldec-5-yn-4-yl)-*N'*-tosylacetohydrazide 223a**



202a **223a**

According to the general procedure G, triphenylphosphine (3.51 g, 13.4 mmol), diisopropyl azodicarboxylate (2.63 ml, 13.4 mmol), hydrazine **222** (3.06 g, 13.4 mmol) and propargylic alcohol **202a** (1.50 g, 8.93 mmol) were added sequentially to tetrahydrofuran (130 ml), followed by work-up and purification by column chromatography using 30% ethyl acetate in hexane to give the *Mitsunobu product* **223a** as a white solid (2.60 g, 77%); m.p. 62-63 °C; υ_{max}/cm^{-1} (DCM) 3196, 3107, 2958, 2933, 2871, 1688, 1598, 1362, 1163, 1090; δ_H 7.78 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.37 (2H, d, *J* 8.2, 2 x CH (Ar)), 6.42 (1H, s, NH), 4.81 (1H, tt, *J* 7.6, 2.1, 4-H), 2.47 (3H, s, CH_3Ar), 2.22 (3H, s, CH_3Ac), 1.83 (1H, *nonete*, *J* 6.6, 2-H), 1.77 (2H, td, *J* 7.2, 1.5, 7-CH_2), 1.60-1.52 (1H, m, 3-H_A), 1.49-1.41 (1H, m, 3-H_B), 1.22-1.08 (4H, m, 8 and 9-CH_2), 1.00 (3H, d, *J* 6.6, 1-CH_3), 0.96 (3H, d, *J* 6.6, 2-Me), 0.85 (3H, t, *J* 7.2, 10-CH_3); δ_C 175.5 (C=O), 145.1 (C), 131.4 (C), 129.4 (2 x CH (Ar)), 129.0 (2 x CH (Ar)), 89.2 (C≡C), 72.5 (C≡C), 52.5 (4-CH), 42.9 (CH_2), 30.3 (CH_2), 24.7 (2-CH), 22.4 (CH_3), 22.0 (CH_3), 22.0 (CH_2), 21.7 (CH_3), 20.6 (CH_3), 17.9 (CH_2), 12.9 (CH_3); *m/z* (APCI) 420 ($MeCNH^+$, 100%), 379 ($M+H^+$, 20%); [Found: $[M+H]^+$, 379.2068. $C_{20}H_{31}N_2O_3S$ requires: *M+H*, 379.2055].

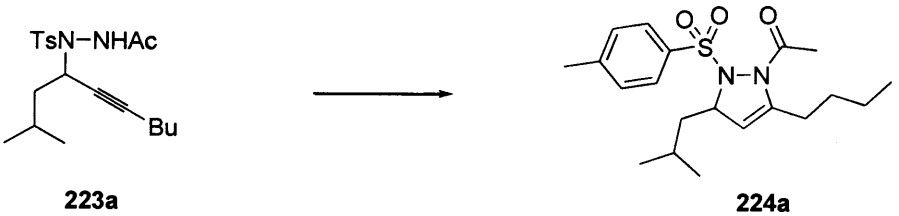
N'-(5-Methyl-1-phenylhex-1-yn-3-yl)-N'-tosylacetohydrazide 223b



210 **223b**

According to the general procedure G, triphenylphosphine (3.14 g, 12.0 mmol), diisopropyl azodicarboxylate (2.35 ml, 12.0 mmol), hydrazine **222** (2.73 g, 12.0 mmol) and propargylic alcohol **210** (1.50 g, 7.97 mmol) were added sequentially to tetrahydrofuran (120 ml), followed by work-up and purification by column chromatography using 30% ethyl acetate in hexane to give the *Mitsunobu product* **223b** as a yellow solid (1.82 g, 57%); m.p. 150-151 °C; υ_{max}/cm^{-1} (DCM) 3306, 3193, 2958, 2871, 2233, 1685, 1597, 1491, 1361, 1162, 1090; δ_H 7.80 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.31-7.18 (5H, m, 5 x CH (Ar)), 6.93 (2H, d, *J* 8.2, 2 x CH (Ar)), 6.75 (1H, s, NH), 5.03 (1H, t, *J* 7.5, 3-H), 2.29 (3H, s, CH_3), 2.24 (3H, s, CH_3), 1.90 (1H, *nonete*, *J* 6.6, 5-H), 1.68 (1H, dt, *J* 13.2, 7.5, 4-H_A), 1.59 (1H, dt, *J* 13.2, 7.5, 4-H_B), 1.03 (3H, d, *J* 6.6, 6-CH_3), 1.00 (3H, d, *J* 6.6, 5-Me); δ_C 175.6 (C=O), 145.5 (C), 131.6 (2 x CH (Ar)), 131.2 (C), 130.0 (2 x CH (Ar)), 129.2 (2 x CH (Ar)), 128.8 (CH (Ar)), 128.1 (2 x CH (Ar)), 121.1 (C), 88.1 (C≡C), 81.6 (C≡C), 52.7 (3-CH), 42.5 (CH_2), 24.8 (5-CH), 22.5 (CH_3), 22.1 (CH_3), 21.5 (CH_3), 20.0 (CH_3); *m/z* (APCI) 462 ($M+MeCNNa^+$, 50%), 440 ($M+MeCNH^+$, 100%), 399 ($M+H^+$, 15%); [Found: $[M+H]^+$, 399.1740. $C_{22}H_{27}N_2O_3S$ requires: *M+H*, 399.1742].

1-Tosyl-2-acetyl-3-butyl-5-isobutyl-2,5-dihydropyrazole 224a

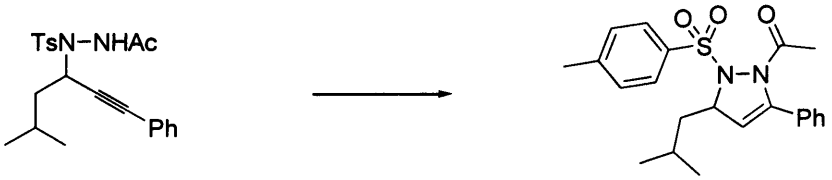


223a **224a**

According to the general procedure I, 10% $AgNO_3.SiO_2$ (2.69 g, 1.59 mmol) was stirred with a solution of precursor **223a** (0.20 g, 0.53 mmol) in dichloromethane (4 ml) for 18 h to give the *dihydropyrazole* **224a** as a clear viscous oil (0.10 g, 50%); υ_{max}/cm^{-1} (neat) 2957, 2932, 2871, 1704, 1683, 1597, 1468, 1357, 1167, 1090; δ_H 7.70 (2H, d, *J* 8.3, 2 x CH (Ar)), 7.28 (2H, d, *J* 8.3, 2 x CH (Ar)), 4.57 (1H, dt, *J* 3.0, 1.6, 4-H), 4.44 (1H, dddd, *J* 9.0, 6.4, 2.8, 1.6, 5-H), 2.60-2.47 (2H, m, 1'-CH_2), 2.45 (3H, s, CH_3), 2.43 (3H, s, CH_3), 2.13-2.06

(1H, m, 1''-H_A), 1.95-1.85 (1H, m, 1''-H_B), 1.37-1.28 (1H, m, 2''-H), 1.19-1.05 (4H, m, 2'-CH_2, 3'-CH_2), 1.02 (3H, d, *J* 6.4, 3''-CH_3), 0.97 (3H, d, *J* 6.4, 2''-Me), 0.81 (3H, t, *J* 7.0, 4'-CH_3); δ_C 176.7 (C=O), 145.5 (C), 145.0 (C), 131.8 (C), 129.5 (2 x CH (Ar)), 129.1 (2 x CH (Ar)), 109.7 (4-CH), 64.4 (5-CH), 43.4 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 24.8 (2''-CH), 23.8 (CH_3), 23.1 (CH_3), 22.3 (CH_2), 22.0 (CH_3), 21.6 (CH_3Ar), 14.0 (CH_3); *m/z* (APCI) 420 (M+MeCNH^+, 50%), 379 (M+H^+, 100%); [Found: [M+H]$^+$, 379.2063. $C_{20}H_{31}N_2O_3S$ requires: *M+H*, 379.2055].

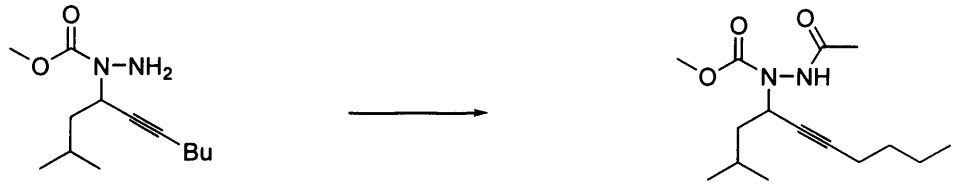
1-Tosyl-2-acetyl-3-phenyl-5-isobutyl-2,5-dihydropyrazole 224b



223b **224b**

According to the general procedure I, 10% $AgNO_3.SiO_2$ (1.74 g, 1.03 mmol) was stirred with a solution of precursor **223b** (0.20 g, 0.51 mmol) in dichloromethane (4 ml) for 18 h to give the *dihydropyrazole* **224b** as a clear viscous oil (0.08 g, 40 %); υ_{max}/cm^{-1} (neat) 3054, 2987, 2305, 1708, 1422, 1355, 1266, 1168, 896; δ_H 7.68 (2H, d, *J* 8.0, 2 x CH (Ar)), 7.16 (5H, app s, 5 x CH (Ar)), 7.02 (2H, d, *J* 8.0, 2 x CH (Ar)), 5.17 (1H, br s, 4-H), 4.56-4.50 (1H, m, 5-H), 2.43 (3H, s, CH_3Ar), 2.16 (3H, s, CH_3Ac), 1.98-1.87 (1H, m, 2'-H), 1.42-1.33 (1H, m, 1'-H_A), 1.25-1.14 (1H, m, 1'-H_B), 0.99 (3H, d, *J* 6.5, 3'-CH_3), 0.94 (3H, d, *J* 6.5, 2'-Me); δ_C 177.3 (C=O), 145.0 (C), 144.2 (C), 131.6 (C), 131.1 (C), 129.5 (2 x CH (Ar)), 128.8 (2 x CH (Ar)), 128.6 (CH (Ar)), 127.6 (2 x CH (Ar)), 126.6 (2 x CH (Ar)), 113.3 (4-CH), 65.0 (5-CH), 43.0 (1'-CH_2), 25.0 (2'-CH), 23.4 (CH_3), 23.1 (CH_3), 22.0 (CH_3), 21.5 (CH_3); *m/z* (APCI) 462 (M+MeCNNa^+, 80%), 399 (M+H^+, 100%); [Found: [M+H]$^+$, 399.1747. $C_{22}H_{27}N_2O_3S$ requires: *M+H*, 399.1742].

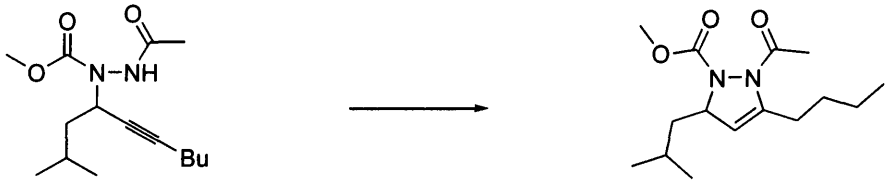
***N'*-(5-Methyl-1-phenylhex-1-yn-3-yl)-*N'*-methyloxycarbonylacetohydrazide 225**



206a **225**

A solution of free hydrazine **206a** (0.35 g, 1.46 mmol) in dichloromethane (15 ml) was stirred at -78 °C, followed by the dropwise addition of triethylamine (0.21 ml, 1.53 mmol). After 5 min acetyl chloride (0.10 ml, 1.47 mmol) was added and the solution was allowed to warm to room temperature overnight. The solution was then cooled to 0 °C and saturated aqueous sodium carbonate (5 ml) was added, followed by water (10 ml) and dichloromethane (20 ml). The separated solution was washed with water (3 x 10 ml) and brine (10 ml), then dried over sodium sulphate, filtered and evaporated to give crude product. The crude material was then purified using column chromatography using 40% ethyl acetate in hexane to give the *acyl hydrazine* **225** as a clear viscous oil (0.26 g, 63%); υ_{max}/cm^{-1} (neat) 3392, 3055, 2960, 2872, 2306, 1719, 1705, 1446, 1387, 1266, 1196, 1109, 909; δ_H (DMSO, 367 K) 9.43 (1H, s, NH), 4.85 (1H, br t, *J* 6.9, 4-H), 3.63 (3H, br s, CH_3O), 2.17 (2H, br t, *J* 7.0, 7-CH_2), 1.88 (3H, s, CH_3Ac), 1.74 (1H, *nonete*, *J* 6.9, 2-H), 1.57-1.33 (6H, m, 8 and 9-CH_2, 3-CH_2), 0.92 (6H, d, *J* 6.9, 1-CH_3, 2-Me), 0.89 (3H, t, *J* 7.0, 10-CH_3); δ_C ($CHCl_3$) 176.5 (C=O), 155.7 (C=O), 85.4 (C≡C), 75.3 (C≡C), 53.7 (CH_3O), 50.0 (4-CH), 42.4 (CH_2), 30.7 (CH_2), 24.8 (2-CH), 22.7 (CH_3), 22.0 (CH_3), 21.0 (CH_3), 19.2 (CH_2) 18.3 (CH_2), 13.6 (CH_3); *m/z* (ES) 321 ($M+K^+$, 100%), 305 ($M+Na^+$, 70%), 283 ($M+H^+$, 50%); [Found: $[M+H]^+$, 283.2025. $C_{15}H_{27}N_2O_3$ requires: *M+H*, 283.2022].

Methyl 2-acetyl-3-butyl-5-isobutyl-2,5-dihydropyrazole-1-carboxylate 226



225 **226**

According to the general procedure I, 10% $AgNO_3.SiO_2$ (0.22 g, 0.13 mmol) was stirred with a solution of precursor **225** (0.18 g, 0.64 mmol) in dichloromethane (4 ml) for 18 h to give the *dihydropyrazole* **226** as a clear viscous oil (0.07 g, 39%); υ_{max}/cm^{-1} (neat) 2958, 2932, 2872, 1713, 1530, 1447, 1393, 1368, 1277, 1126; δ_H 5.05 (1H, app s, 4-H), 4.64-4.58 (1H, m, 5-H), 3.75 (3H, s, CH_3O), 2.68 (1H, app pent d, *J* 7.7, 1.6, 1''-H_A), 2.52 (1H, app *quintet*, *J* 7.7, 1''-H_B), 2.17 (3H, s, CH_3Ac), 1.66 (1H, *nonete*, *J* 6.7, 2'-H), 1.43 (2H, t, *J* 7.4, 1'-CH_2), 1.30-1.15 (4H, m, 2''-CH_2, 3''-CH_2), 0.92 (3H, d, *J* 6.7, 3'-CH_3), 0.87 (3H, d, *J* 6.7, 2'-Me), 0.83 (3H, t, *J* 7.7, 4''-CH_3); δ_C 173.4 (C=O), 159.8 (C=O), 144.8 (C), 111.0 (4-CH), 62.9 (CH_3O), 53.8 (5-CH), 42.8 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 24.7 (2''-CH), 22.8 (CH_3), 22.7 (CH_3), 22.1 (CH_3) 22.1 (CH_2), 13.9 (CH_3); *m/z* (APCI) 283 ($M+H^+$, 100%), 241 (50%), 210 (25%).

5.4 Experimental for the synthesis of pyrroles

General procedure K for the preparation of acetylenic aldehydes[103]

To a stirred solution of an acetylene (1.00 equiv) in dry tetrahydrofuran (approx 3-4 ml per mmol) at -78 °C was added *n*-BuLi (2.5 M in hexanes, 1.00 equiv) and the resulting mixture was stirred for 0.5 h. This was followed by the dropwise addition of anhydrous dimethyl formamide (2.00 equiv). The cooling bath was removed and the reaction was allowed to warm to room temperature over 0.5 hours. The reaction was then quenched by pouring into a vigorously stirred biphasic mixture of 10% aqueous solution of potassium dihydrogen phosphate (4.00 equiv) and ether as a 1:1 v/v mixture at 0 °C. The separated organic solution was dried and evaporated under reduced pressure to give the crude acetylenic aldehyde that was purified by passing through a thin pad of silica using 10% ether in hexane as eluent or by Kugelrohr distillation.

General procedure L for the *N*-tosylation of glycinates

To a stirred solution of glycine ethyl ester hydrochloride (1.00 equiv) in dry dichloromethane (2-3 ml per mmol glycine) at ambient temperature was added either *p*-nitrobenzenesulfonyl chloride or *p*-TsCl (1.10 equiv) and a few crystals of DMAP. This was followed by the dropwise addition of triethylamine (2.50 equiv). The mixture was allowed to stir overnight before being diluted with DCM (2 ml per mmol glycine). The organics were then washed with 1M HCl (2 x volume of reaction mixture), water (3 x volume of reaction mixture) and brine (2 x volume of reaction mixture) before being dried over sodium sulphate, filtered and evaporated to give a viscous oil that solidified upon standing. The crude product was then purified by recrystalisation using ethyl acetate/hexane to give clean product.

General procedure M for the preparation of β-hydroxy amino esters using chelated glycine enolates[106]

To a stirred solution of diisopropylamine (2.20 equiv) in dry tetrahydrofuran (4-5 ml per mmol) at 0 °C *n*-BuLi (2.5 M in hexanes, 2.20 equiv) was added dropwise. The resulting mixture was allowed to warm to room temperature over 0.5 h. The solution was cooled to -78 °C and *N*-tosyl glycine ethyl ester (1.00 equiv) in tetrahydrofuran (1.00 ml per mmol) was added dropwise followed by the dropwise addition of tin(II) chloride (2.50 equiv) in tetrahydrofuran (0.50 ml per mmol). The mixture was allowed to stir at -78 °C for 0.5 h before the dropwise addition of acetylenic aldehyde or ketone (1.10 equiv) in tetrahydrofuran (1.00 ml per mmol). The reaction mixture was then allowed to stir at room temperature overnight. The resulting cloudy yellow solution was quenched with phosphate buffer (pH 7) and passed through a pad of silica. The bulk of the tetrahydrofuran was then evaporated, and the resulting residue extracted with ether (3 x volume of reaction mixture). The combined organic solutions were then dried over sodium sulphate, filtered and evaporated to give the crude β-hydroxy amino ester that was purified by recrystalisation or column chromatography.

General procedure N for the copper(II) acetate-catalysed cyclisation

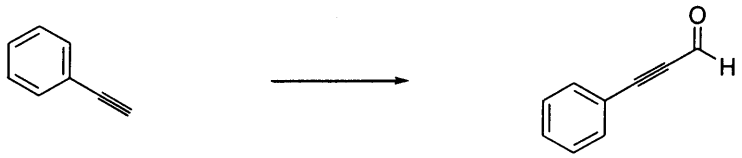
A solution containing precursor (1.00 equiv) and $Cu(OAc)_2$ (0.10 equiv) in toluene (10 ml g^{-1}) was refluxed. The resulting brown solution was allowed to cool followed by filtration through silica and washing through with ether to give clean pyrrole.

Hept-2-ynal 300a[153]

299a **300a**

According to the general procedure K, *n*-BuLi (2.5 M in hexanes, 14.6 mL, 36.3 mmol) and dimethylformamide (5.65 ml, 73.2 mmol) were added sequencially to 1-hexyne **299a** (4.20 ml, 36.3 mmol) in dry tetrahydrofuran (120 ml). Dipotassium hydrogen phosphate (25.29 g, 145.2 mmol) in water (250 ml) was added to quench. The work-up yielded the *aldehyde* **300a** as an orange oil (2.80 g, 66%); bp: 80 °C (at 0.5-0.75 mmHg); υ_{max}/cm^{-1} (neat): 2960, 2930, 2871, 2281, 2235, 2202, 1715, 1669, 1463, 1422, 1385, 1325, 1268, 1138, 1071, 980; δ_H 9.05 (1H, s, 1-H), 2.29 (2H, t, *J* 7.3, 4-CH_2), 1.45 (2H, *quintet*, *J* 7.3, 5-CH_2), 1.35 (2H, *sextet*, *J* 7.3, 6-CH_2), 0.81 (3H, t, *J* 7.3, 7-CH_3).

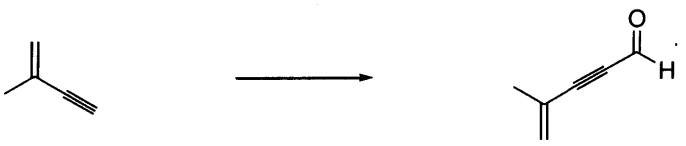
3-Phenylprop-2-ynal 300b[153]



299b **300b**

According to the general procedure K, *n*-BuLi (2.5 M in hexanes, 11.6 ml, 29.0 mmol) and dimethylformamide (4.49 ml, 58.0 mmol) were added sequencially to phenylacetylene **299b** (3.23 ml, 29.0 mmol) in dry tetrahydrofuran (90 ml). Dipotassium hydrogen phosphate (20.20 g, 116.0 mmol) in water (220 ml) was added to quench. The work-up yielded the *aldehyde* **300b** as an orange oil (2.81 g, 74%); bp; 190°C (at 0.5-0.75 mmHg); υ_{max}/cm^{-1} (neat): 3298, 3056, 2855, 2518, 2239, 2188, 1959, 1725, 1658, 1572, 1488, 1443, 1387, 1261, 1159, 1069, 1002; δ_H 9.30 (1H, s, 1-H), 7.49-7.26 (5H, m, 5 x CH (Ar)).

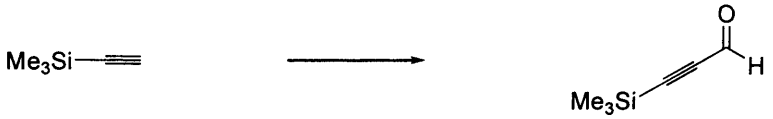
4-Methyl-pent-4-en-2-ynal 300c[154]



299c **300c**

According to the general procedure K, *n*-BuLi (2.5 M in hexanes, 18.20 ml, 45.45 mmol) and dimethylformamide (7.04 ml, 90.9 mmol) were added sequencially to 3-methyl but-3-en-1-yne **299c** (3.00 g, 45.5 mmol) in dry tetrahydrofuran (150 ml). Dipotassium hydrogen phosphate (31.67 g, 181.8 mmol) in water (310 ml) was added to quench. The work-up yielded the *aldehyde* **300c** as an orange oil (2.60 g, 60%); δ_H 9.29 (1H, s, 1-H), 5.60 (1H, s, 5-H_A), 5.53 (1H, s, 5-H_B), 1.96 (3H, s, 4-Me).

3-(Trimethylsilyl)prop-2-ynal 300d[155]



299d **300d**

According to the general procedure K, *n*-BuLi (2.5 M in hexanes, 8.10 ml, 20.4 mmol) and dimethylformamide (3.10 ml, 40.7 mmol) were added sequencially to trimethylsilylacetylene **299d** (2.90 ml, 20.4 mmol) in dry tetrahydrofuran (60 ml). Dipotassium hydrogen phosphate (14.18 g, 81.44 mmol) in water (140 ml) was added to quench. The work-up yielded the *aldehyde* **300d** as a orange oil (1.705 g, 66%); δ_H 9.01 (1H, s, 1-H), 0.11 (9H, s, 3 x CH_3Si).

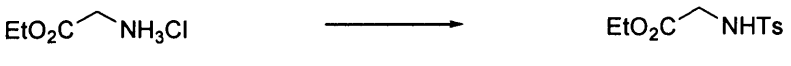
5-(*tert*-Butyldimethylsilyloxy)pent-2-ynal 300e[156]

299e **300e**

According to the general procedure K, *n*-BuLi (2.5 M in hexanes, 4.30 ml, 10.8 mmol) and dimethylformamide (1.70 ml, 21.7 mmol) were added sequencially to *tert*-butyltrimethylsilyl-butyn-1-ol **299e** (2.00 g, 10.8 mmol) in dry tetrahydrofuran (50 ml). Dipotassium hydrogen phosphate (7.60 g, 43.4 mmol) in water (76 ml) was added to quench. The work-up yielded the

aldehyde **300e** as a yellow oil (2.10 g, 87%); δ_H 9.09 (1H, s, 1-H), 3.72 (2H, t, *J* 6.7, 5-CH_2), 2.54 (2H, t, *J* 6.7, 4-CH_2), 0.82 (9H, s, 3 x CH_3C), 0.00 (6H, s, 2 x CH_3Si).

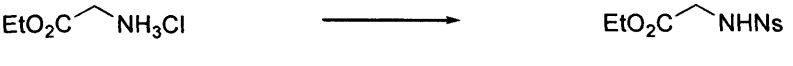
_N_-Tosyl-glycine ethyl ester 298a[157]



297 **298a**

According to the general procedure L, a solution of glycine ethyl ester hydrochloride **297** (5.00 g, 35.8 mmol), *p*-TsCl (7.51 g, 39.4 mmol), triethylamine (12.48 ml, 89.55 mmol) and a few crystals of DMAP were stirred in dry dichloromethane (100 ml) overnight. This was followed by work-up and recrystalisation to give the *tosyl-protected glycinate* **298a** as a white solid (8.87 g, 96%); m.p. 60-61 °C (lit. m.p.[26] 59-61 °C); υ_{max}/cm^{-1} (DCM): 3290, 2985, 1741, 1599, 1445, 1334, 1162, 1093; δ_H 7.74 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.33 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.11 (1H, t, *J* , NH), 4.09 (2H, q, *J* 7.1, **CH_2**O), 3.77 (2H, d, *J* 5.5, **CH_2**N), 2.42 (3H, s, CH_3Ar), 1.19 (3H, t, *J* 7.1, **CH_3CH_2**O); δ_C 168.8 (C=O), 143.9 (C), 136.1 (C), 129.8 (2 x CH (Ar)), 127.3 (2 x CH (Ar)), 62.0 (**CH_2**O), 44.2 (**CH_2**N), 21.6 (CH_3Ar), 14.0 (**CH_3CH_2**O).

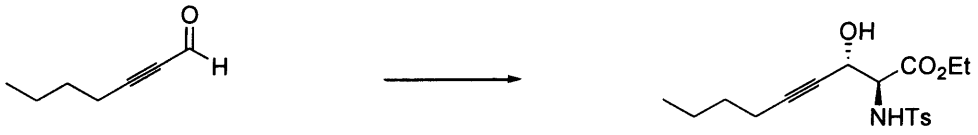
_N_-Nosyl-glycine ethyl ester 298b[158]



297 **298b**

According to the general procedure L, a solution of glycine ethyl ester hydrochloride **297** (10.00 g, 71.64 mmol), *p*-NsCl (17.47 g, 78.81 mmol), triethylamine (25.00 ml, 179.1 mmol) and a few crystals of DMAP were stirred in dry dichloromethane (200 ml) overnight. This was followed by work-up and recrystalisation to give the *nosyl-protected glycinate* **298b** as an orange solid (20.31 g, 98%); m.p. 112-114 °C (lit. m.p.[156] 118-120 °C); υ_{max}/cm^{-1} (DCM): 3419, 2980, 2873, 1723, 1645, 1526, 1352, 1312, 1249, 1174, 1091; δ_H 8.31 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.98 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.23 (1H, t, *J* 5.5, NH), 4.14 (2H, q, *J* 7.2, **CH_2**O), 3.77 (2H, d, *J* 5.5, **CH_2**N), 1.12 (3H, t, *J* 7.2, **CH_3CH_2**O); δ_C 168.5 (C=O), 145.3 (C), 138.9 (C), 128.5 (2 x CH (Ar)), 124.4 (2 x CH (Ar)), 62.3 (**CH_2**O), 44.1 (**CH_2**N), 14.1 (**CH_3CH_2**O); *m/z* (EI) 288 (M^+, 2%), 215 (70%), 103 (20%), 85 (100%); [Found: $[M]^+$, 288.0409. $C_{10}H_{12}N_2O_6S$ requires: *M*, 288.0416].

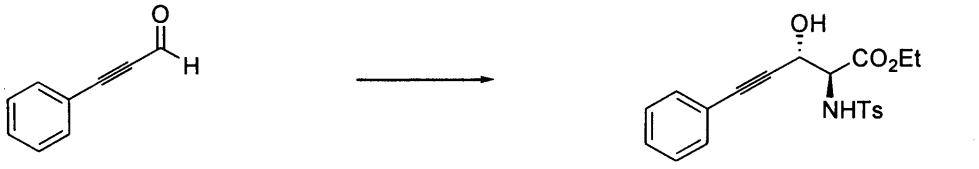
(2SR, 3SR)-Ethyl 2-(4-toluenesulfonylamino)-3-hydroxynon-4-ynoate 294a[4,104]



300a **294a**

According to the general procedure M, to a stirred solution of diisopropylamine (3.80 ml, 27.3 mmol) and *n*-BuLi (2.5 M in hexanes, 10.90 ml, 27.3 mmol) in tetrahydrofuran (200 ml), *N*-tosyl glycine ethyl ester (3.19 g, 12.4 mmol) in tetrahydrofuran (13 ml), tin(II) chloride (5.88 g, 31.0 mmol) in tetrahydrofuran (15.5 ml) and heptynal **300a** (1.50 g, 13.6 mmol) in tetrahydrofuran (14 ml) were added sequencially. After workup the crude product was recrystalised from ethyl acetate/petrol to give the *β-hydroxy amino ester* **294a** as a single diastereoisomer and as a yellow crystalline solid (3.60 g, 79%), m.p. 66-67 °C (lit m.p.[4] 66°C). δ_H 7.69 (2H, d, *J*, 8.3, 2 x CH (Ar)), 7.25 (2H, d, *J* 8.3, 2 x CH (Ar)), 5.45 (1H, d, *J* 9.3, NH), 4.59 (1H, br. m, 3-CH), 4.05 (1H, dd, *J* 9.3, 3.8, 2-H), 4.01-3.95 (2H, m, OCH_2), 2.70 (1H, d, *J* 10.3, OH), 2.41 (3H, s, CH_3Ar), 2.12 (2H, td, *J* 7.0, 2.0, 6-CH_2), 1.43-1.28 (4H, m, 7 and 8-CH_2), 1.09 (3H, t, *J* 7.0, $\mathbf{CH_3}CH_2O$), 0.83 (3H, t, *J* 7.1, 9-CH_3).

(2SR, 3SR)-Ethyl 3-hydroxy-2-(toluenesulfonylamido)-5-phenylpent-4-ynoate 294b[4,104]

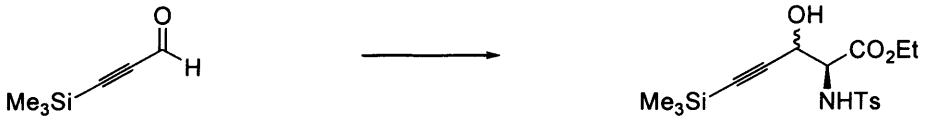


300b **294b**

According to the general procedure M, to a stirred solution of diisopropylamine (1.28 ml, 9.06 mmol) and *n*-BuLi (2.5 M in hexanes, 3.62 ml, 9.06 mmol) in tetrahydrofuran (100 ml), *N*-tosyl glycine ethyl ester (1.06 g, 4.12 mmol) in tetrahydrofuran (4 ml), tin(II) chloride (1.95 g, 10.3 mmol) in tetrahydrofuran (5 ml) and 3-phenylpropiolaldehyde **300b** (0.91 g, 4.28 mmol) in tetrahydrofuran (4.3 ml) were added sequencially. After workup the crude product was purified by recrystalisation using ethyl acetate and hexane to give the *β-hydroxy amino ester* **294b** as a single diastereoisomer and as a white solid (1.31 g, 82%), m.p. 119 °C (lit m.p.[4] 118-119°C). δ_H 7.79 (2H, d, *J* 8.3, 2 x CH (Ar)), 7.42-7.31 (5H, m, 5 x CH (Ar)), 7.33 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.60 (1H, d, *J* 9.5, NH), 4.92 (1H, dd, *J* 10.7, 3.9, 3-H), 4.24 (1H, dd, *J* 9.5, 3.9, 2-H),

4.08 (2H, q, *J* 7.2, OCH_2), 2.93 (1H, d, *J* 10.7, OH), 2.45 (3H, s, CH_3Ar), 1.17 (3H, t, *J* 7.2, $\mathbf{CH_3}CH_2O$); 167.9 (C=O), 144.1 (C), 136.2 (C), 131.8 (2 x CH (Ar)), 129.8 (2 x CH (Ar)), 129.0 (CH (Ar)), 128.4 (2 x CH (Ar)), 127.3 (2 x CH (Ar)), 121.4 (C), 87.5 (C≡C), 84.2 (C≡C), 63.6 (2 or 3-CH), 62.4 (OCH_2), 60.7 (2 or 3-CH), 21.6 (CH_3Ar), 14.0 ($\mathbf{CH_3}CH_2O$).

(2SR, 3SR)-Ethyl-2-amino-3-hydroxy-2-(4-toluenesulfonylamino)-5-(trimethylsilyl)pent-4-ynoate 294c



300d **294c**

According to the general procedure M, to a stirred solution of diisopropylamine (1.80 ml, 12.7 mmol) and *n*-BuLi (2.5 M in hexanes, 5.10 ml, 12.7 mmol) in tetrahydrofuran (100 ml), *N*-tosyl glycine ethyl ester (1.48 g, 5.77 mmol) in tetrahydrofuran (5.8 ml), tin(II) chloride (2.73 g, 14.4 mmol) in tetrahydrofuran (7 ml) and 3-(trimethylsilyl)propiolaldehyde **300d** (0.80 g, 6.34 mmol) in tetrahydrofuran (6.3 ml) were added sequencially. After workup the crude product was purified by column chromatography using 10% ethyl acetate in hexane to give the *β-hydroxy amino ester* **294c** as a 85:15 mixture of diastereoisomers and as a yellow oil (2.21 g, 83%); υ_{max}/cm^{-1} (DCM): 3343, 3055, 2986, 2358, 2341, 2307, 1740, 1421, 1347, 1266, 1164, 1093; δ_H 7.60 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.16 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.34 (1H, d, *J* 9.5, NH), 4.88-4.84 (1H, m, 3-CH), 4.52 (1H, dd, *J* 10.6, 3.9, 2-CH), 3.97-3.91 (2H, m, OCH_2), 2.63 (1H, d, *J* 10.6, OH), 2.28 (3H, s, CH_3Ar), 1.04 (3H, t, *J* 7.1, $\mathbf{CH_3}CH_2O$), 0.00 (9H, s, 3 x CH_3Si); 168.8 (C=O), 143.8 (C), 136.2 (C), 129.8 (2 x CH (Ar)), 127.3 (2 x CH (Ar)), 100.3 (C≡C), 93.0 (C≡C), 63.4 (2 or 3-CH), 62.3 (OCH_2), 60.3 (2 or 3-CH), 21.6 (CH_3Ar), 14.0 ($\mathbf{CH_3}CH_2O$), -0.4 (3 x CH_3Si); *m/z* (ES) 401 ($M+NH_4^+$, 100%), 384 ($M+H^+$, 30%); [Found: $[M+H]^+$, 384.1294. $C_{17}H_{26}NO_5SiS$ requires: *M+H*, 384.1301].

δ_H (distinguishable minor peaks (2SR/3RS)) 5.23 (1H, d, *J* 9.1, NH), 4.47 (1H, dd, *J* 8.0, 4.1, 2-H), 2.58 (1H, d, *J* 8.1, OH).

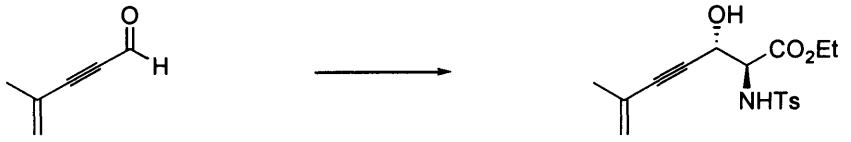
(2SR,3SR)-Ethyl-7-(*t*-butyldimethylsilyloxy)-3-hydroxy-2-(4-toluenesulfonylamino)hept-4-ynoate 294d

300e **294d**

According to the general procedure M, to a stirred solution of diisopropylamine (1.20 ml, 8.55 mmol) and *n*-BuLi (2.5 M in hexanes, 3.40 ml, 8.55 mmol) in tetrahydrofuran (80 ml), *N*-tosyl glycine ethyl ester (1.00 g, 3.89 mmol) in tetrahydrofuran (4 ml), tin(II) chloride (1.84 g, 9.72 mmol) in tetrahydrofuran (5 ml) and 5-(*tert*-butyldimethylsilyloxy)pent-2-ynal **300e** (0.91 g, 4.28 mmol) in tetrahydrofuran (4.3 ml) were added sequencially. After workup the crude product was purified using column chromatography using 25% ethyl acetate in hexane to give the *β-hydroxy amino ester* **294d** as a 86:14 mixture of diastereoisomer and as a clear colourless oil (1.51 g, 83%), υ_{max}/cm^{-1} (neat): 3490, 2925, 2357, 1736, 1654, 1598, 1458, 1338; δ_H 7.69 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.24 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.50-5.47 (1H, br. m, NH), 4.60-4.57 (1H, m, 3-H), 4.07-3.90 (3H, m, OCH_2, 2-H), 3.59 (2H, t, *J* 7.1, 7-CH_2), 2.75 (1H, d, *J* 10.1, OH), 2.36 (3H, s, CH_3Ar), 2.32 (2H, td, *J* 7.1, 2.0, 6-CH_2), 1.07 (3H, t, *J* 6.0, **CH_3CH_2O**), 0.83 (9H, s, 3 x CH_3C), 0.00 (6H, s, 2 x CH_3Si); δ_C 167.9 (C=O), 144.0 (C), 136.3 (C), 129.8 (2 x CH (Ar)), 127.4 (2 x CH (Ar)), 85.5 (C≡C), 76.7 (C≡C), 63.2 (3-CH), 62.2 (7-CH_2), 61.5 (OCH_2), 60.7 (2-CH), 25.9 (3 x CH_3C), 23.0 (6-CH_2), 21.6 (CH_3Ar), 18.1 (C-Si), 13.9 (**CH_3CH_2O**), -5.3 (2 x CH_3Si); *m/z* (ES) 487 ($M+NH_4^+$, 100%), 470 ($M+H^+$, 35%); [Found: $[M+H]^+$, 470.2010. $C_{22}H_{36}NO_6SSi$ requires: *M+H*, 470.2033].

δ_H (distinguishable minor peaks (2SR/3RS)) 2.64 (1H, d, *J* 7.5, OH).

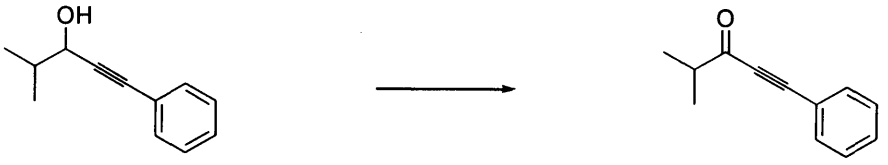
(2SR, 3SR)-Ethyl 3-hydroxy-6-methyl-2-(4-toluenesulfonylamino)hept-6-en-4-ynoate 294e[4,104]



300c **294e**

According to the general procedure M, to a stirred solution of diisopropylamine (4.50 ml, 31.9 mmol) and *n*-BuLi (2.5 M in hexanes, 19.90 ml, 31.91 mmol) in tetrahydrofuran (200 ml), *N*-tosyl glycine ethyl ester (3.73 g, 14.5 mmol) in tetrahydrofuran (14.5 ml), tin(II) chloride (6.87 g, 36.3 mmol) in tetrahydrofuran (18 ml) and 4-methyl-pent-4-en-2-ynal **300c** (1.50 g, 16.0 mmol) in tetrahydrofuran (16 ml) were added sequencially. After workup the crude product was recrystalised from ethyl acetate/petrol to give the *β-hydroxy amino ester* **294e** as a yellow crystaline solid (3.60 g, 71%), m.p. 74°C (lit m.p.[4] 72-73°C). δ_H 7.78 (2H, d, *J* 8.2, 2 x *CH* (Ar)), 7.33 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.54 (1H, d, *J* 9.0, NH), 5.31-5.28 (1H, br. m, 7-H_A), 5.29 (1H, m, 7-H_B), 4.80 (1H, dd, *J* 10.1, 3.9, 3-H), 4.16 (1H, dd, *J* 9.0, 3.9, 2-H), 4.05 (2H, m, OCH_2), 2.82 (1H, d, *J* 10.1, OH), 2.45 (3H, s, CH_3Ar), 1.86 (3H, app s, 6-Me), 1.16 (3H, t, *J* 7.0, $\mathbf{CH_3}CH_2O$).

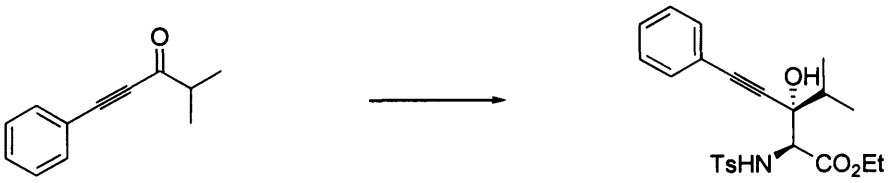
4-Methyl-1-phenylpent-1-yn-3-one 301[159]



202c **301**

To a mixture of propargylic alcohol **202c** (3.00 g, 17.2 mmol) and 4 Å molecular sieves (5.00 g) in dichloromethane (90 ml), pyridinium dichromate (12.97 g, 34.50 mmol) was added and the mixture was stirred overnight, then passed through a thick pad of silica and eluted with dichloromethane. The combined filtrates were evaporated to yield the *ketone* **301** as a yellow oil (2.60 g, 88%); 7.45 (2H, d, *J* 7.6, 2 x CH (Ar)), 7.36-7.24 (3H, m, 3 x CH (Ar)), 2.63 (1H, sept, *J* 7.0, 4-H), 1.14 (6H, d, *J* 7.0, 5-CH_3 and 4-Me).

(2SR,3SR)-Ethyl 3-hydroxy-3-(isopropyl)-5-phenyl-2-(4-toluenesulfonylamino)-pent-4-ynoate 294f[4,104]



301 **294f**

According to the general procedure M, to a stirred solution of diisopropylamine (3.30 ml, 23.3 mmol) and *n*-BuLi (2.5 M in hexanes, 9.30 ml, 23.3 mmol) in tetrahydrofuran (150 ml), *N*-tosyl glycine ethyl ester (3.05 g, 10.6 mmol) in tetrahydrofuran (10.6 ml), tin(II) chloride (5.00 g, 26.4 mmol) in tetrahydrofuran (13.2 ml) and ketone **301** (2.00 g, 11.6 mmol) in tetrahydrofuran (11.6 ml) were added sequencially. After work-up the crude product was recrystalised from ethyl acetate/petrol to give *the β-hydroxy amino ester* **294f** as an orange crystaline solid (4.02 g, 82%), m.p. 126-127 °C (lit m.p.[4] 127 °C). δ_H 7.76 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.38-7.27 (7H, m, 7 x CH (Ar)), 5.63 (1H, d, *J* 10.7, NH), 4.21 (1H, d, *J* 10.7, 2-H), 3.90 (1H, dq, *J* 10.8, 7.2, OCH*a*), 3.76 (1H, dq, *J* 10.8, 7.2, OCH*b*), 3.25 (1H, br s, OH), 2.43 (3H, s, CH_3Ar), 2.28 (1H, sept, *J* 6.7, CH-*i*Pr), 1.15 (3H, d, *J* 6.7, CH_3-*i*Pr), 1.05 (3H, d, *J* 6.7, CH_3-*i*Pr), 1.05 (3H, t, *J* 7.2, $\mathbf{CH_3}CH_2O$).

(2SR, 3SR)-Ethyl 3-dihydroxy-2-(4-toluenesulfonamino)pent-4-ynoate 294i

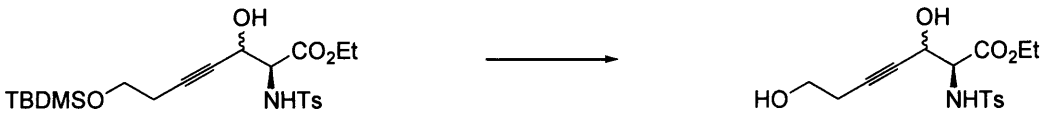
294c **294i**

Potassium carbonate (0.02 g, 0.14 mmol) was added to a solution of β-hydroxy aminoester **294c** (0.28 g, 0.73 mmol) in ethanol (3 ml) at 0 °C. The solution was stirred for 1.5 hours before warming up to room temperature. The solution was filtered and evaporated before being taken up in ether (10 ml). The organic layer was washed with water and brine followed by drying over sodium sulphate, filtered and then evaporated to give the crude desilylated product. The product was then purified by column chromatography using 30% ethyl acetate in hexane to give clean *β-hydroxy amino ester* **294i** as a clear oil (0.20g, 88%); υ_{max}/cm^{-1} (neat): 3277, 2961, 2898, 2346, 1736, 1453, 1310, 1266, 1162, 1093; δ_H 7.77 (2H, d, *J* 8.3, 2 x CH (Ar)), 7.32 (2H,

d, *J* 8.1, 2 x CH (Ar)), 5.42 (1H, d, *J* 8.0, NH), 4.69 (1H, ddd, *J* 16.0, 8.0, 4.0, 3-H), 4.08-4.17 (3H, m, OCH_2, 2-H), 2.73 (1H, d, *J* 8.0, OH), 2.49 (1H, d, *J* 4.0, 5-H), 2.44 (3H, s, CH_3Ar), 1.18 (3H, t, *J* 8.0, $\mathbf{CH_3}CH_2O$); δ_C 168.7 (C=O), 143.8 (C), 136.9 (C), 129.6 (2 x CH (Ar)), 127.4 (2 x CH (Ar)), 80.2 (**CH**≡C), 75.5 (C≡C), 63.7 (3-CH), 62.5 (OCH_2), 60.1 (2-CH), 21.6 (CH_3Ar), 13.9 ($\mathbf{CH_3}CH_2O$); *m/z* (APCI) 329 ($M+NH_4^+$, 70%), 312 ($M+H^+$, 100%), 294 ($M-H_2O$, 25%); [Found: $[M+H]^+$, 312.0920. $C_{14}H_{18}NO_5S$ requires: *M+H*, 312.0906].

δ_H (distinguishable minor peaks (2SR,3RS)) 5.56 (1H, d, *J* 9.4, NH), 2.96 (1H, d, *J* 10.8, OH), 2.51 (1H, d, *J* 2.3, 5-H).

(2SR, 3SR)-Ethyl 3,7-dihydroxy-2-(4-toluenesufonylamino)hept-4-ynoate 294j



294d **294j**

A solution of tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 1.17 ml, 1.17 mmol) was added dropwise to a stirred solution of β-hydroxyaminoester **294d** (0.50 g, 1.07 mmol) in dry tetrahydrofuran (10 ml) at 0 °C. The reaction was allowed to stir overnight without further cooling. The solution was then evaporated and the residue taken up in ether (20 ml) and the organic layer was washed with water (2 x 10 ml) and brine (10 ml). The solution was then dried over sodium sulphate, filtered and evaporated to give the crude product, which was then purified by column chromatography using 50% ethyl acetate in hexane to give the *alcohol* **294j** as a colourless oil (0.32 g, 85%); υ_{max}/cm^{-1} (neat): 3482, 2927, 2358, 1734, 1654, 1598, 1458, 1338, 1162; δ_H 7.69 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.33 (2H, d, *J* 8.2, 2 x CH (Ar)), 6.01-5.83 (1H, app s, NH), 4.62-4.59 (1H, m, 3-H), 4.10 (1H, app d, *J* 3.6, 2-H), 3.99-3.90 (2H, m, OCH_2), 3.74-3.69 (2H, m, 7-CH_2), 2.59 (2H, dt, *J* 7.5, 5.7, 6-CH_2), 2.33 (3H, s, CH_3Ar), 1.02 (3H, t, *J* 7.1, $\mathbf{CH_3}CH_2O$); δ_C 168.9 (C=O), 143.9 (C), 136.2 (C), 129.6 (2 x CH (Ar)), 127.1 (2 x CH (Ar)), 86.0 (C≡C), 77.8 (C≡C), 63.2 (3-CH), 62.3 (7-CH_2), 61.0 (2-CH), 60.6 (OCH_2), 22.9 (6-CH_2), 21.6 (CH_3Ar), 13.9 ($\mathbf{CH_3}CH_2O$); *m/z* (APCI) 378 ($M+Na^+$, 5%), 177 (60%), 130 (100%); [Found: $[M+Na]^+$, 378.1002. $C_{16}H_{21}NO_6SNa$ requires: *M+Na*, 378.0987]

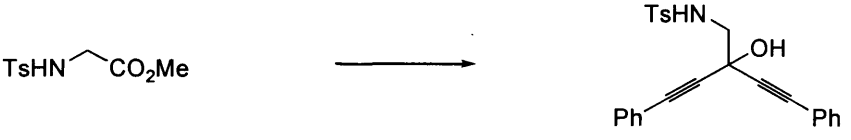
The minor diastereoisomer could not be clearly distinguished.

7-Hydroxy-7-(4-toluenesulfonylaminomethyl)trideca-5,8-diyne 303a

302 **303a**

A solution of 1-hexyne (1.70 ml, 14.4 mmol) in dry tetrahydrofuran (60 ml) was cooled to -78 °C and *n*-BuLi (2.5 M in hexanes, 5.80 ml, 14.4 mmol) was added dropwise and the mixture was then allowed to stir for 0.5 h at -78°C. This was followed by the dropwise addition of *N*-tosyl glycine methyl ester **302** (1.00 g, 4.11 mmol) in dry tetrahydrofuran (10 ml). The reaction mixture was then allowed to warm up to room temperature overnight. The reaction was then quenched by the addition of saturated ammonium chloride solution (5 ml) and the tetrahydrofuran was evaportated. The residue was then taken up in ether (30 ml) and washed with water (2 x 20 ml) and brine (20 ml). The solution was dried over sodium sulphate, filtered and evaporated to give clean *diyne* **303a** as an orange oil (1.51 g, 98%). υ_{max}/cm^{-1} (neat): 3456, 3283, 2931, 2872, 2360, 2239, 1686, 1598, 1455, 1331, 1161, 1094; δ_H 7.65 (2H, d, *J* 8.1, 2 x CH (Ar)), 7.18 (2H, d, *J* 8.1, 2 x CH (Ar)), 4.82 (1H, t, *J* 6.7, NH), 3.14 (2H, d, *J* 6.7, CH_2N), 2.30 (3H, s, CH_3Ar), 2.05 (4H, t, *J* 7.1, 4 and 10-CH_2), 1.51 (1H, br.s, OH), 1.38-1.20 (8H, m, 2, 3, 11 and 12-CH_2) 0.77 (6H, t, *J* 7.1, 1 and 13-CH_3); δ_C 143.9 (C), 137.1 (C), 129.7 (2 x CH (Ar)), 127.2 (2 x CH (Ar)), 86.0 (C≡C), 78.2 (C≡C), 62.7 (7-C), 53.9 (CH_2N), 30.3 (4 and 10-CH_2), 22.0 (CH_2), 21.6 (CH_3Ar), 18.3 (CH_2), 13.6 (1 and 13-CH_3); *m/z* (ES) 439 (M+MeCNNa$^+$, 90%), 414 (M+K$^+$, 30%), 393 (M+NH_4^+, 80%), 358 (M-H_2O, 100%); [Found: [M+NH_4]$^+$, 393.2208. $C_{21}H_{33}N_2O_3S$ requires: *M+NH*$_4$, 393.2212].

3-Hydroxy-3-(4-toluenesulfonylaminomethyl)1,5-diphenylpenta-1,4-diyne 303b

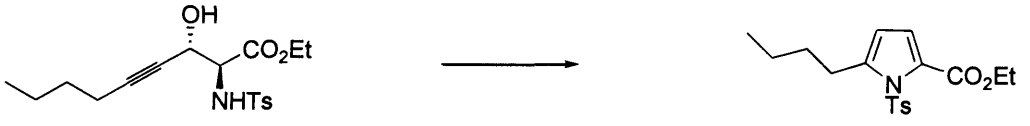


302 **303b**

A solution of phenylacetylene (1.60 ml, 14.4 mmol) in dry tetrahydrofuran (60 ml) was cooled to -78 °C and *n*-BuLi (2.5 M in hexanes, 5.80 ml, 14.4 mmol) was added dropwise and the mixture was then allowed to stir for 0.5 h at -78°C. This was followed by the dropwise addition of *N*-tosyl glycine methyl ester **302** (1.00 g, 4.11 mmol) in dry tetrahydrofuran (10 ml). The

reaction mixture was then allowed to warm up to room temperature overnight. The reaction was then quenched by the addition of saturated ammonium chloride solution (5 ml) and the tetrahydrofuran was evaportated. The residue was then taken up in ether (30 ml) and washed with water (2 x 20 ml) and brine (20 ml). The solution was dried over sodium sulphate, filtered and evaporated to give crude diyne that was purified by column chromatography using 10% ethyl acetate in hexane to give the *diyne* **303b** as an orange oil (1.31 g, 77%). υ_{max}/cm^{-1} (neat): 3404, 3287, 3059, 2984, 2931, 2234, 1598, 1470, 1443, 1374, 1332, 1257, 1161, 1092, 1044, 936; δ_H 7.69 (2H, d, *J* 8.1, 2 x CH (Ar)), 7.38-7.31 (4H, 4 x CH (Ar)), 7.22-7.19 (4H, m, 4 x CH (Ar)), 7.18 (2H, d, *J* 8.1, 2 x CH (Ar)), 7.06 (2H, d, *J* 8.1, 2 x CH (Ar)), 5.52-5.48 (1H, t, *J* 6.7, NH), 3.66 (1H, s, OH), 3.44 (2H, d, *J* 6.7, CH_2N), 2.20 (3H, s, CH_3Ar); δ_C 143.6 (C), 137.0 (C), 132.0 (CH (Ar)), 129.8 (CH (Ar)), 129.0 (CH (Ar)), 128.3 (CH (Ar)), 127.2 (CH (Ar)), 121.5 (C), 86.5 (C≡C), 85.1 (C≡C), 63.6 (3-C), 53.7 (CH_2N), 21.5 (CH_3Ar); *m/z* (APCI) 433 ($M+NH_4^+$, 30%), 243 (40%), 229 (100%); [Found: $[M+NH_4]^+$, 433.1598. $C_{25}H_{25}N_2O_3S$ requires: $M+NH_4$, 433.1586].

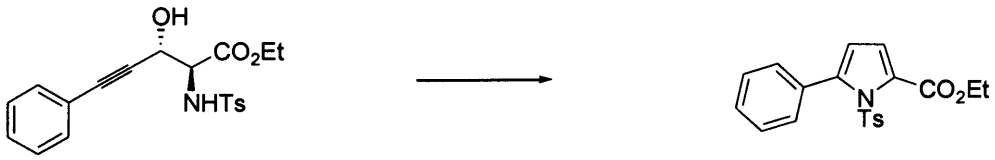
Ethyl 5-butyl-1-tosyl-1H-pyrrole-2-carboxylate 313a[4]



294a **313a**

According to the general procedure N, a solution containing β-hydroxy-α-amino ester **294a** (0.15 g, 0.41 mmol) and $Cu(OAc)_2$ (0.005 g, 0.04 mmol) in toluene (2 ml), was refluxed for 40 minutes. This was then followed by workup to give clean *pyrrole* **313a** (0.13 g, 91%); υ_{max}/cm^{-1} (neat): 3055, 2961, 1721, 1496, 1368, 1318, 1264, 1176, 1106, 895; δ_H 7.85 (2H, d, *J* 8.3, 2 x CH (Ar)), 7.25 (2H, d, *J* 8.3, 2 x CH (Ar)), 6.73 (1H, d, *J* 3.6, 3-H), 5.92 (1H, d, *J* 3.6, 4-H), 4.21 (2H, q, *J* 7.1, OCH_2), 2.76 (2H, t, *J* 7.8, 1'-CH_2), 2.36 (3H, s, CH_3Ar), 1.54-1.46 (2H, m, 2'-CH_2), 1.32-1.22 (2H, m, 3'-CH_2), 1.24 (3H, t, *J* 7.1, $\mathbf{CH_3}CH_2O$), 0.83 (3H, t, *J* 7.4, 4'-CH_3); δ_C 160.8 (C=O), 144.8 (C), 143.8 (C), 136.8 (C), 129.6 (2 x CH (Ar)), 127.9 (C), 127.4 (2 x CH (Ar)), 120.3 (3-CH), 110.8 (4-CH), 61.1 (OCH_2), 30.9 (CH_2), 29.7 (CH_2), 28.3, 22.5 (CH_3), 21.7 (CH_3Ar), 14.1 (CH_3), 13.8 (CH_3).

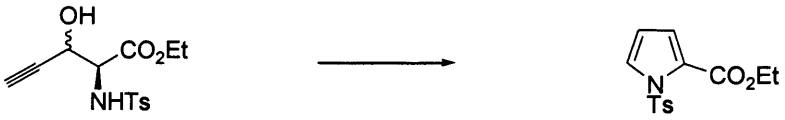
Ethyl 5-phenyl-1-tosyl-1*H*-pyrrole-2-carboxylate 313b[4]



294b **313b**

According to the general procedure N, a solution containing β-hydroxy-α-amino ester **294b** (0.24 g, 0.62 mmol) and $Cu(OAc)_2$ (0.008 g, 0.06 mmol) in toluene (2 ml), was refluxed for 70 minutes. This was then followed by workup to give clean *pyrrole* **313b**. (0.22 g, 97%) υ_{max}/cm^{-1} (neat): 3058, 2987, 1719, 1550, 1470, 1369, 1237, 1139, 1092; δ_H 7.32 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.29-7.08 (5H, m, 5 x CH (Ar)), 7.05 (2H, d, *J* 8.2, 2 x CH (Ar)), 6.28 (1H, d, *J* 3.4, 3-H), 6.04 (1H, d, *J* 3.4, 4-H), 4.33 (2H, q, *J* 7.2, OCH_2), 2.28 (3H, s, CH_3Ar), 1.35 (3H, t, *J* 7.1, $\mathbf{CH_3}CH_2O$).

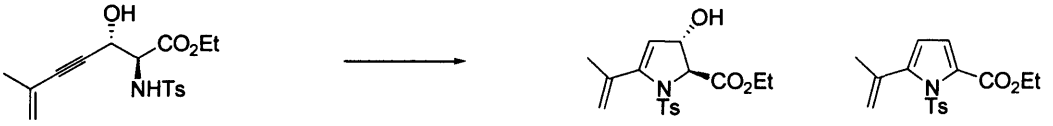
Ethyl 1-tosylpyrrole-2-carboxylate 313d[160]



294i **313d**

According to the general procedure N, a solution containing β-hydroxy-α-amino ester **294i** (0.05 g, 0.16 mmol) and $Cu(OAc)_2$ (0.03 g, 0.16 mmol) in toluene (1 ml), was heated to 90 °C for 18 h. This was then followed by workup to give almost clean *pyrrole* **313d** as a yellow oil (0.037 g, 79%); υ_{max}/cm^{-1} (neat): 3055, 2986, 2927, 1726, 1598, 1446, 1330, 1266, 1166, 1147, 1089; δ_H 7.86 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.70 (1H, dd, *J* 3.2, 1.8, CH), 7.25 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.04 (1H, dd, *J* 3.7, 1.8, CH), 6.30 (1H, m, CH), 4.19 (2H, q, *J* 7.0, OCH_2), 2.42 (3H, s, CH_3Ar), 1.26 (3H, t, $\mathbf{CH_3}CH_2O$).

Ethyl 3-hydroxy-5-(2-propenyl)-1-(4-toluenesulfonyl)-2,3-dihydropyrrole-2-carboxylate 312e[4] and Ethyl 5-(prop-1-en-2-yl)-1-tosyl-1*H*-pyrrole-2-carboxylate 313e[4]:



294e **312e** **313e**

According to the general procedure N, a solution containing β-hydroxy-α-amino ester **294e** (0.15 g, 0.43 mmol) and $Cu(OAc)_2$ (0.01 g, 0.04 mmol) in toluene (2 ml), was refluxed for 3.5 h. This was then followed by workup to give a mixture of *hydroxydihydropyrrole* **312e** and *pyrrole* **313e** in a 1:3 ratio respectively (0.12 g, 84%); **Ethyl 3-hydroxy-5-(2-propenyl)-1-(4-toluenesulfonyl)-2,3-dihydropyrrole-2-carboxylate 312e:** δ_H 7.65 (2H, d, *J* 8.3, 2 x CH (Ar)), 7.28 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.31 (1H, d, *J* 3.4, 4-H), 5.27 (1H, app. s, 2'-H_A), 5.13 (1H, br. m, 2'-H_B), 4.41 (1H, app. s, 2-H), 4.37 (1H, dd, *J* 9.7, 3.4, 3-H), 4.02 (2H, q, *J* 7.3, OCH_2), 2.36 (3H, s, CH_3Ar), 2.02 (3H, s, 1'-Me), 1.22 (3H, t, *J* 7.3, $\mathbf{CH_3}CH_2O$), 0.52 (1H, d, *J* 9.7, OH). **Ethyl 5-(prop-1-en-2-yl)-1-tosyl-1*H*-pyrrole-2-carboxylate 313e:** δ_H 7.71 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.17 (2H, d, *J* 8.2, 2 x CH (Ar)), 6.75 (1H, d, *J* 3.6, 3-H), 5.96 (1H, d, *J* 3.7, 4-H), 5.11 (1H, m, 2'-H_A), 4.86 (1H, m, 2'-H_B), 4.25 (2H, q, *J* 7.1, OCH_2), 2.34 (3H, s, CH_3Ar), 1.91 (3H, s, 1'-Me), 1.28 (3H, t, *J* 7.1, $\mathbf{CH_3}CH_2O$).

Ethyl 5-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1-tosyl-1*H*-pyrrole-2-carboxylate 313f

294d **313f**

According to the general procedure N, a solution containing β-hydroxy-α-amino ester **294d** (0.20 g, 0.44 mmol) and $Cu(OAc)_2$ (0.009 g, 0.04 mmol) in toluene (2 ml), was refluxed for 1.5 h. This was then followed by workup to give clean *pyrrole* **313f** as a yellow viscous oil (0.18 g, 95%); υ_{max}/cm^{-1} (neat): 2980, 2949, 2835, 2607, 1710, 1667, 1458, 1113, 1031; δ_H 7.90 (2H, d, *J* 8.4, 2 x CH (Ar)), 7.35 (2H, d, *J* 8.4, 2 x CH (Ar)), 6.77 (1H, d, *J* 3.3, 3-H), 6.08 (1H, d, *J* 3.3, 4-H), 4.29 (2H, q, *J* 7.0, $\mathbf{OCH_2}$), 3.83 (2H, t, *J* 6.5, 2'-CH_2), 3.08 (2H, t, *J* 6.5, 1'-CH_2), 2.42 (3H, s, CH_3Ar), 1.30 (3H, t, *J* 7.0, $\mathbf{CH_3}CH_2O$), 0.85 (9H, s, 3 x CH_3C), 0.00 (6H, s, 2 x CH_3Si); δ_C 161.0 (C=O), 144.5 (C), 140.0 (C), 137.0 (C), 129.9 (2 x CH (Ar)), 127.3 (2 x CH (Ar)),

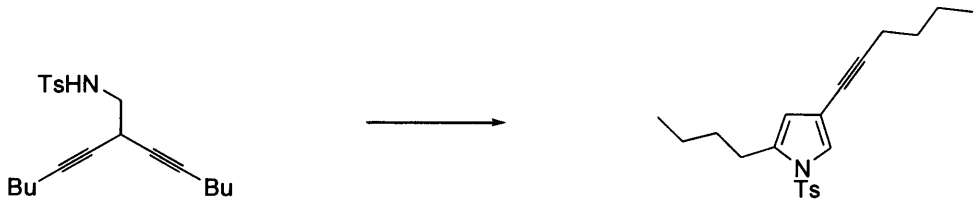
120.5 (3-CH), 112.4 (4-CH), 62.2 (CH_2), 61.2 (CH_2), 32.4 (1'-CH_2), 25.9 (3 x CH_3C), 21.8 (CH_3Ar), 18.1 (C*t*Butyl), 14.3 (**CH_3CH_2O**), -5.3 (2 x CH_3Si); [Found: $[M+H]^+$, 470.2010. requires: *M+H*, 470.2033].

Ethyl 5-(2-hydroxyethyl)-1-tosyl-1 *H*-pyrrole-2-carboxylate 313g

294j **313g**

According to the general procedure N, a solution containing β-hydroxy-α-amino ester **294j** (0.14 g, 0.39 mmol) and $Cu(OAc)_2$ (0.008 g, 0.04 mmol) in toluene (2 ml), was refluxed for 1 h. This was then followed by workup to give clean *pyrrole* **313g** as a yellow viscous oil (0.13g, 98%); υ_{max}/cm^{-1} (neat): 3427, 3057, 2962, 2921, 1733, 1638, 1493, 1265, 1109; δ_H 7.82 (2H, d, *J* 8.4, 2 x CH (Ar)), 7.23 (2H, d, *J* 8.1, 2 x CH (Ar)), 6.71 (1H, d, *J* 3.6, 3-H), 6.02 (1H, d, *J*, 3.6, 4-H), 4.19 (2H, q, *J* 7.1, OCH_2), 3.79-3.78 (2H, m, 2'-CH_2), 3.07 (2H, t, *J* 6.3, 1'-CH_2), 2.31 (3H, s, CH_3Ar), 1.94-1.85 (1H, m, OH), 1.16 (3H, t, *J* 7.1, **CH_3CH_2O**); δ_C 160.7 (C=O), 145.0, 139.6 and 136.6 (all C), 129.8 (2 x CH (Ar)), 128.4 (C), 127.4 (2 x CH (Ar)), 120.4 (3-CH), 112.4 (4-CH), 61.6 (CH_2), 61.3 (CH_2), 32.0 (1'-CH_2), 21.7 (CH_3Ar), 14.1 (**CH_3CH_2O**); *m/z* (APCI) 360 ($M+Na^+$, 50%), 355 ($M+NH_4^+$, 100%), 338 ($M+H^+$, 100%); [Found: $[M+H]^+$, 338.1062. $C_{16}H_{20}NO_5S$ requires: *M+H*, 338.1067].

2-butyl-4-(hex-1-ynyl)-1-tosyl-1*H*-pyrrole 313i

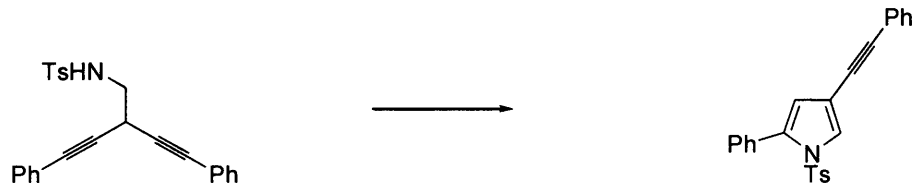


303a **313i**

According to the general procedure N, a solution containing diyne **303a** (0.36 g, 0.96 mmol) and $Cu(OAc)_2$ (0.02 g, 0.10 mmol) in toluene (4 ml), was refluxed for 0.75 h. This was then followed by workup to give clean *pyrrole* **313i** as an orange oil (0.30 g, 87%); υ_{max}/cm^{-1} (neat): 2931, 2871, 2754, 1596.4, 1464, 1367, 1174, 1091; δ_H 7.58 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.30

(1H, d, *J* 1.7, 2-H), 7.21 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.91 (1H, m, 3-H), 2.52 (2H, t, *J* 7.7, either 3'' or 1'-CH_2), 2.34 (3H, s, CH_3Ar), 2.29 (2H, t, *J* 6.9, either 3'' or 1'-CH_2), 1.50-1.18 (8H, m, 2', 3', 4'' and 5''-CH_2), 0.86 (3H, t, *J* 7.3, either 4' or 6''-CH_3), 0.79 (3H, t, *J* 7.3, either 4' or 6''-CH_3); δ_C 145.0 (C), 136.0 (C), 135.8 (C), 130.0 (2 x CH (Ar)), 126.9 (2 x CH (Ar)), 124.5 (C), 114.5 (C), 108.2 (C), 91.0 (C≡C), 30.8 (CH_2), 30.5 (CH_2), 26.6 (CH_2), 22.3 (CH_2), 22.0 (CH_2), 21.7 (CH_3Ar), 19.2 (CH_2), 13.8 (CH_3), 13.7 (CH_3); *m/z* (EI) 357 (M^+, 10%), 218 (30%), 171 (100%); [Found $[M]^+$, 357.1761. $C_{21}H_{27}NO_2S$ requires: *M*, 357.1763].

2-Phenyl-4-(2-phenylethynyl)-1-tosyl-1*H*-pyrrole 313j



303b **313j**

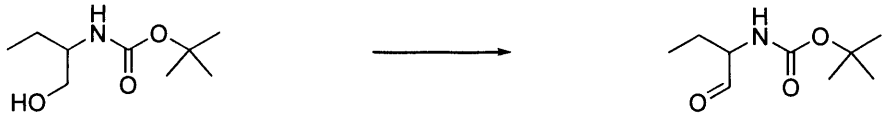
According to the general procedure N, a solution containing diyne **303b** (0.10 g, 0.24 mmol) and $Cu(OAc)_2$ (0.005 g, 0.02 mmol) in toluene (1 ml), was refluxed for 0.75 h. This was then followed by workup to give clean *pyrrole* **313j** as an orange oil (0.098 g, 98%); υ_{max}/cm^{-1} (neat): 3060, 2926, 2853, 1597, 1475, 1443, 1377, 1307, 1226, 1172, 1091, 1064, 909; δ_H 7.61 (1H, app d, *J* 1.8, CH), 7.43-7.40 (2H, m, 2 x CH (Ar)), 7.31-7.21 (6H, m 6 x CH (Ar)), 7.17-7.13 (4H, m, 4 x CH (Ar)), 7.02 (2H, d, *J* 8.2, 2 x CH (Ar)), 6.19 (1H, app d, *J* 1.8, CH), 2.28 (3H, s, CH_3Ar); δ_C 145.2 (C), 136.0 (C), 135.1 (C), 131.5 (2 x CH (Ar)), 131.0 (2 x CH (Ar)), 130.5 (C), 129.6 (2 x CH (Ar)), 128.7 (CH (Ar)), 128.4 (2 x CH (Ar)), 128.2 (CH (Ar)), 127.4 (2 x CH (Ar)), 126.7 (2 x CH (Ar)), 126.7 (CH (Ar)), 123.2 (C), 117.8 (CH (Ar)), 108.2 (C), 90.3 (C≡C), 82.4 (C≡C), 21.7 (CH_3Ar). *m/z* could not be obtained.

***tert*-Butyl 1-hydroxybutan-2-ylcarbamate 309**[161]

308 **309**

To a stirred solution of 2-aminobutan-1-ol **308** (10.00 g, 112.0 mmol) in dichloromethane (100 ml) at 0 °C dry triethylamine (17.08 ml, 123.0 mmol) was added dropwise. This was followed by the dropwise addition of di-*tert*-butyldicarbonate (24.72 g, 113.0 mmol) in dichloromethane (10.00 ml) and the reaction mixture was allowed to warm up overnight. The solution was then diluted with dichloromethane (100 ml) and washed with water (2 x 50 ml), brine (50 ml), followed by drying with sodium sulphate, filtration and evaporation to give the *boc-protected amino alcohol* **309** as a yellow oil (21.98 g, 99%); υ_{max}/cm^{-1} (neat): 3855, 3356, 2970, 2877, 1694, 1679, 1540, 1503, 1454, 1367, 1285, 1246, 1172, 1073; δ_H 4.63 (1H, br s, NH), 3.61-3.46 (1H, m, 2-H), 3.48 (2H, d, *J* 7.4, 1-CH_2), 2.73 (1H, s, OH), 1.56-1.47 (1H, m, 3-H*a*), 1.42-1.33 (1H, m, 3-H*b*), 1.38 (9H, s, 3 x CH_3C), 0.88 (3H, t, *J* 7.4, 4-CH_3).

***tert*-Butyl 1-oxobutan-2-ylcarbamate 310**[162]



309 **310**

To a solution of IBX (3.05 g, 10.8 mmol) in dimethylsulfoxide (50 ml), was added a solution of boc aminoalcohol **309** (0.80 g, 5.40 mmol) in dimethylsulfoxide (5 ml) and the reaction was allowed to stir for 2 h. The mixture was poured into a stirred biphasic mixture of diethyl ether (100 ml) and water (50 ml) at 0 °C and the solution was allowed to continue stirring for a further 15 mins. The layers were separated and the aqueous layer was extracted with ether (2 x 50 ml). The combined organics were then washed with water (3 x 50 ml) and brine (2 x 50 ml) and the solution was dried over sodium sulphate, filtered and evaporated to give clean *aldehyde* **310** as a viscous yellow oil (0.61 g, 77%); υ_{max}/cm^{-1} (neat): 3348, 2974, 2934, 1697, 1508, 1459, 1392, 1367, 1248, 1168, 1070; δ_H 9.37 (1H, s, 1-CH), 3.99 (1H, br s, 2-CH), 3.88 (1H, br

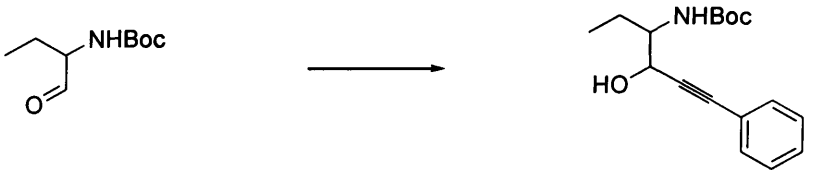
s, NH), 1.48-1.39 (2H, m, 3-CH_2), 1.23 (9H, s, 3 x CH_3C), 0.75 (3H, t, *J* 7.4, 4-CH_3); δ_C 200.1 (1-CHO), 155.6 (C=O), 79.8 (6-C), 60.8 (2-CH), 27.9 (3 x CH_3C), 22.2 (3-CH_2), 9.4 (4-CH_3).

***tert*-Butyl 4-hydroxydec-5-yn-3-ylcarbamate 311a**

310 **311a**

According to the procedure,[1] to a stirred solution of 1-hexyne (0.68 ml, 5.88 mmol) in tetrahydrofuran (20 ml) at 0 °C a 2.5M solution of *n*-BuLi (2.5 M in hexanes, 2.35 ml, 5.88 mmol) was added dropwise. The solution was the allowed to stir at this temperature for 0.5 h before cooling to -78 °C. A solution of aldehyde **310** (0.50 g, 2.67 mmol) in tetrahydrofuran (10 ml) was then added dropwise to the mixture and the mixture was allowed to warm up overnight. The solution was then cooled to 0 °C and was quenched with concentrated hydrochloric acid (1.2 ml, 2 ml g^{-1}) and the solution was allowed to warm to room temperature. The crude product was extracted into ether (2 x 20 ml) and the combined organics were washed with water (2 x 20 ml) and brine (20 ml), dried with sodium sulphate, filtered and evaporated to yield crude alcohol. The crude product was purified by column chromatography using 20% ethyl acetate in hexane to yield clean *propargylic alcohol* **311a** as a clear viscous oil of diastereoisomers with a 4:1 ratio (0.61 g, 85%); υ_{max}/cm^{-1} (neat): 3390, 2964, 2933, 2875, 2359, 1694, 1504, 1456, 1392, 1251, 1170, 1056; δ_H 5.01 (1H, br s, NH minor) 4.54 (1H, br s, NH major), 4.34 (1H, app s, 4-H minor), 4.25 (1H, d, *J* 5.0, 4-H major), 3.64-3.56 (1H, m, 3-H minor), 3.53-3.44 (1H, m, 3-H major), 2.11 (2H, app t, *J* 7.0, 3'-CH_2), 1.74-1.49 (2H, m, 2-CH_2), 1.45-1.27 (4H, m, 4'-CH_2, 5'-CH_2), 1.36 (9H, s, 3 x CH_3C), 0.88 (3H, app t, *J* 7.5, 1 or 6'-CH_3), 0.81 (3H, t, *J* 7.2, 1 or 6'-CH_3); δ_C 66.0 (4-CH), 65.4 (4-CH), 57.2 (3-CH), 56.9 (3-CH), 30.7 (CH_2), 30.6 (CH_2), 28.4 (3 x CH_3C), 28.3 (3 x CH_3C), 23.8 (CH_2), 23.7 (CH_2), 22.4 (CH_2), 22.0 (CH_2), 18.4 (CH_2), 14.2 (CH_3), 13.6 (CH_3), 10.7 (CH_3), 10.5 (CH_3). *m/z* (APCI) 561 ($2M+Na^+$, 30%), 333 ($M+MeCNNa^+$, 20%), 270 ($M+H^+$, 15%), 237 (100%); [Found: $[M+H]^+$, 270.2075. $C_{15}H_{28}NO_3$ requires: *M+H,* 270.2069]. *The quaternary boc peaks were not detected by ^{13}C-NMR due to rotomers.*

***tert*-Butyl 4-hydroxy-6-phenylhex-5-yn-3-ylcarbamate 311b**



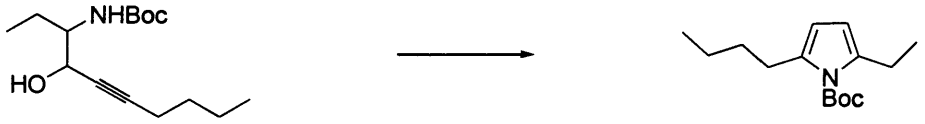
310 **311b**

According to the procedure,[1] to a stirred solution of phenylacetylene (0.65 ml, 5.88 mmol) in tetrahydrofuran (20 ml) at 0 °C a 2.5M solution of *n*-BuLi (2.5 M in hexanes, 2.35 ml, 5.88 mmol) was added dropwise. The solution was the allowed to stir at this temperature for 0.5 h before cooling to -78 °C. A solution of aldehyde **310** (0.50 g, 2.67 mmol) in tetrahydrofuran (10 ml) was then added dropwise to the mixture and the mixture was allowed to warm up overnight. The solution was then cooled to 0 °C and was quenched with concentrated hydrochloric acid (1.2ml, 2 ml g^{-1}) and the solution was allowed to warm to room temperature. The crude product was extracted into ether (2 x 20 ml) and the combined organics were washed with water (2 x 20 ml) and brine (20 ml), dried with sodium sulphate, filtered and evaporated to yield crude alcohol. The crude product was purified by column chromatography using 20% ethyl acetate in hexane to yield clean *alcohol* **311b** as a clear viscous oil of diastereoisomers with a 7:3 ratio (0.72 g, 93%); υ_{max}/cm^{-1} (neat): 3396, 2971, 2934, 2877, 1695, 1505, 1456, 1393, 1367, 1249, 1168, 1057; δ_H 7.38-7.34 (2H, m, 2 x CH (Ar)), 7.26-7.21 (3H, m, 3 x CH (Ar)), 4.68 (1H, br d, *J* 8.6, NH), 4.61 (1H, d, *J* 2.7, 4-H minor), 4.53 (1H, d, *J* 5.0, 4-H major), 3.80-3.71 (1H, m, 3-H minor), 3.70-3.59 (1H, m, 3-H major), 1.85-1.65 (1H, m, 2-H_A), 1.55-1.34 (1H, m, 2-H_B), 1.39 (9H, s, 3 x CH_3C minor), 1.38 (9H, s, 3 x CH_3C major), 0.96-0.91 (3H, m, 1-CH_3); δ_C 131.8 (2 x CH (Ar)), 131.8 (2 x CH (Ar)), 128.6 (CH (Ar)), 128.5 (CH (Ar)), 128.3 (2 x CH (Ar)), 128.3 (2 x CH (Ar)), 66.4 (4-CH), 65.6 (4-CH), 57.3 (3-CH), 56.9 (3-CH), 28.4 (3 x CH_3C), 24.5 (2-CH_2), 23.7 (2-CH_2), 10.8 (1-CH_3), 10.6 (1-CH_3); *m/z* (APCI) 290 ($M+H^+$, 15%), 216 (60%), 172 (100%); [Found: $[M+H]^+$, 290.1746. $C_{17}H_{24}NO_3$ requires: *M+H*, 290.1756]. *The quaternary boc peaks were not detected by ^{13}C-NMR due to rotomers.*

General procedure O for the 10% $AgNO_3.SiO_2$ cyclisation

In a flask wrapped with foil, 10% w/w silver nitrate on silica gel (0.10-1.00 equiv) was added to a stirred solution of precursor (1.00 equiv) in dichloromethane (10 mL g^{-1}). The resulting suspension was stirred for 4-24 h then filtered through celite and the solvent evaporated to yield the pyrrole.

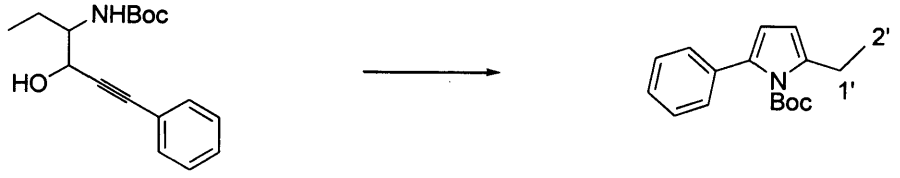
***tert*-Butyl 2-butyl-5-ethyl-1*H*-pyrrole-1-carboxylate 313o**



311a **313o**

According to the general procedure O, 10% $AgNO_3.SiO_2$ (0.23 g, 0.14 mmol) was stirred with a solution of precursor **311a** (0.18 g, 0.67 mmol) in dichloromethane (4 ml) for 4 h to give clean *pyrrole* **313o** as a clear viscous oil (0.16 g, 96%); υ_{max}/cm^{-1} (neat): 2971, 2933, 2873, 1738, 1534, 1457, 1323, 1266, 1171, 1123, 1024; δ_H 5.76 (2H, app s, 3-H, 4-H), 2.71 (4H, m, 1'-CH_2, 1''-CH_2), 1.55.1.46 (2H, m, 2'-CH_2), 1.31 (2H, *sextet*, *J* 7.6, 3'-CH_2), 1.12 (3H, t, *J* 7.6, 4'-CH_3 or 2''-CH_3), 0.85 (3H, t, *J* 7.6, 2''-CH_3 or 4'-CH_3); δ_C 150.5 (C=O), 137.6 (C), 136.1 (C), 109.0 (3 or 4-CH), 108.1 (3 or 4-CH), 83.2 (C*t*butyl), 31.4 (CH_2), 29.4 (CH_2), 28.0 (3 x CH_3C), 22.9 (CH_2), 22.6 (CH_2), 14.1 (CH_3), 13.5 (CH_3); *m/z* (EI) [Found: $[M]^+$, 251.1887. $C_{15}H_{25}NO_2$ requires: *M*, 251.1885].

***tert*-Butyl 2-phenyl-5-ethyl-1*H*-pyrrole-1-carboxylate 313p**



311b **313p**

According to the general procedure O, 10% $AgNO_3.SiO_2$ (0.13 g, 0.08 mmol) was stirred with a solution of precursor **311b** (0.11 g, 0.38 mmol) in dichloromethane (2 ml) for 4 h to give clean *pyrrole* **313p** as a clear viscous oil (0.1 g, 98%); υ_{max}/cm^{-1} (neat): 3063, 2978, 2934, 2878,

1739, 1606, 1527, 1483, 1370, 1311, 1258, 1146, 1078; δ_H 7.27-7.15 (5H, m, 5 x CH (Ar)), 6.02 (1H, d, *J* 3.3, 3-H) 5.91 (1H, d, *J* 3.3, 4-H), 2.79 (2H, q, *J* 7.5, 1'-CH_2), 1.19 (3H, t, *J* 7.5, 2'-CH_3), 1.16 (9H, s, 3 x CH_3C); δ_C 150.3 (C=O), 139.4 (C), 135.5 (C), 134.9 (C), 128.3 (2 x CH (Ar)), 127.8 (2 x CH (Ar)), 126.6 (CH (Ar)), 112.1 (3-CH), 108.3 (4-CH), 83.4 (C*t*butyl), 27.3 (3 x CH_3C), 22.0 (1'-CH_2), 13.3 (2'-CH_3). *m/z* (EI) 271 (M^+, 10%), 251 (M^+, 50%), 215 (30%), 156 (100%), 196 (100%); [Found: $[M]^+$, 271.1578. $C_{17}H_{21}NO_2$ requires: *M*, 271.1572].

General procedure P for the amino hydroxylation of alkenes[163]

A solution of alkene (1.00 equiv), chloroamine-T-hydrate (3.00 equiv), potassium osmate dehydrate (0.05 equiv) and $(DHQ)_2PHAL$ (0.04 equiv) were stirred in *tert*-butanol:water (3-4 ml per mmol of alkene combined as a 1:1 mixture) for 24-48 h. The resulting solution was then quenched by the addition of 1% sodium hydroxide in brine (1 x volume of mixture) and ethyl acetate (2 x volume of mixture) was also added. The organic phase was separated and washed with a further portion of 1% sodium hydroxide in brine (1 x volume of mixture) before passing through a pad of silica. The resulting solution was evaporated to yield crude amino alcohol that was purified by column chromatography using 20-30% ethyl acetate in hexane to give clean amino alcohol.

General procedure Q for the amino hydroxylation of alkenes[164]

To a stirred solution of alkene (1.00 equiv) in *t*BuOH:H_2O (1-2 ml per mmol of alkene as a 1:1 mixture) potassium osmate (0.01 equiv) was added resulting in a brown solution. A solution of chloroamine-T hydrate (1.50 equiv) and benzyltriethylammonium chloride (0.05 equiv) in water was added resulting in the dark brown solution turning green. The mixture was then allowed to stir overnight. The solvent was then evaporated and the residue was partitioned between water (1 x volume of mixture) and ethyl acetate (1 x volume of mixture). The aqueous layer was washed with ethyl acetate (2 x volume of mixture) and the combined organics were washed with water (2 x volume of mixture), followed by brine containing 1% sodium hydroxide (1 x volume of mixture). The organics were dried over sodium sulphate and filtered. The solvent was then evaporated to give the crude product as a solid. The crude product was

then purified by column chromatography or recrystalisation from hot chloroform to give clean β-hydroxy sulfonamide.

General procedure R for the pyridinium chlorochromate oxidation of amino alcohols

To a solution of amino alcohol (1.00 equiv) and 4 Å molecular sieves in dichloromethane (10 ml per mmol amino alcohol) pyridinium chlorochromate (1.80 equiv) was added and the mixture was stirred overnight. The resulting mixture was passed through a thick pad of silica and eluted with dichloromethane, followed by evaporation to yield the ketone.

General procedure S for the Jones oxidation of amino alcohols

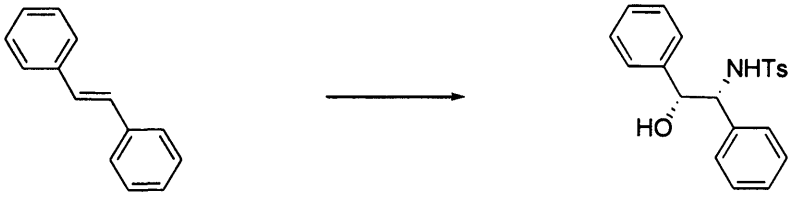
The β-hydroxy sulfonamide (1.00 equiv) was dissolved in acetone (2.3 ml per mmol) and the solution was cooled to 0 °C. This was followed by the dropwise addition of Jones reagent (2.67 M, 1.30 equiv) and the reaction mixture was stirred for 1.5 hours. The reaction mixture was then quenched with saturated potassium carbonate solution (~ 1 x volume of mixture). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x volume of reaction mixture). The combined organic solutions were then washed with water (2 x volume of reaction mixture), followed by brine (1 x volume of reaction mixture). The organics were dried over sodium sulphate, filtered and evaporated resulting in clean β-keto sulfonamide.

General procedure T for the lithio-acetylide addition to amino ketones

A solution of *n*-BuLi (2.5 M in hexanes, 2.20 equiv) was added dropwise to a stirred solution of alkyne (2.20 equiv) in tetrahydrofuran (~5 ml per mmol alkyne) at -78 °C. The reaction mixture was then allowed to stir for 30 minutes with the temperature was maintained. The resulting lithio-acetylide was then added dropwise to a stirred solution of β-keto sulfonamide (1.00 equiv) in tetrahydrofuran (~5 ml per mmol ketone) at -78 °C. The reaction mixture was then allowed to warm to room temperature overnight. The reaction was then quenched using saturated ammonium chloride solution (~ 1 x volume of mixture). The tetrahydrofuran was the evaporated and the resulting residue was extracted with diethyl ether (3 x volume of mixture).

The combined organics extracts then washed with water (2 x volume of mixture) and brine (1 x volume of mixture), followed by drying using sodium sulphate and filtration. The solvent was then evaporated to give the crude 2-alkynyl sulfonamide, which was then purified using column chromatography to give clean sulfonamide.

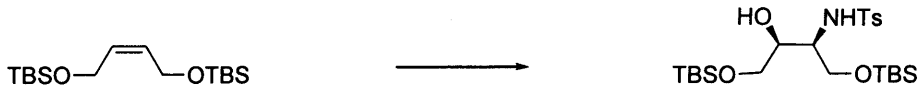
_N_-(2-Hydroxy-1,2-diphenylethyl)-4-toluenesulfonamide 305a[165]



304a **305a**

According to the general procedure P, trans-stilbene **304a** (1.00 g, 5.55 mmol), chloramine-T-hydrate (3.79 g, 16.6 mmol), potassium osmate dihydrate (0.10 g, 0.28 mmol) and $(DHQ)_2PHAL$ (0.18 g, 0.22 mmol) were stirred in a solution of *t*BuOH (20 ml) and water (20 ml) overnight. Upon aqueous workup the crude product was purified by column chromatography using 15% ethyl acetate in hexane to give the *amino alcohol* **305a** as a fluffy white solid (1.42 g, 70%); m.p. 117-118 °C; υ_{max}/cm^{-1} (DCM): 3408, 3054, 2987, 1641, 1421, 1265, 1161, 1093; δ_H 7.45 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.31-7.27 (4H, m, 4 x CH (Ar)), 7.12-7.01 (6H, m, 6 x CH (Ar)), 6.96-6.93 (2H, m, 2 x CH (Ar)), 5.42 (1H, d, *J* 6.2, NH), 4.72 (1H, app dd, *J* 6.1, 2.1, **CH**OH), 4.35 (1H, t, *J* 6.0, **CH**NH), 2.40 (1H, br d, *J* 2.6, OH), 2.26 (3H, br s, CH_3Ar); δ_C 142.9 (C), 139.5 (C), 137.8 (C), 137.4 (C), 129.2 (CH (Ar)), 128.7 (CH (Ar)), 128.3 (CH (Ar)), 127.7 (CH (Ar)), 127.6 (CH (Ar)), 127.4 (CH (Ar)), 126.5 (CH (Ar)), 126.4 (CH (Ar)), 76.9 (**CH**OH), 64.1 (**CH**NH), 21.4 (CH_3Ar); *m/z* (ES) 431 ($M+MeCNNa^+$, 100%), 406 ($M+K^+$, 10%); [Found: $[M+K]^+$, 406.0896. $C_{21}H_{21}NO_3SK$ requires: *M+K*, 406.0879].

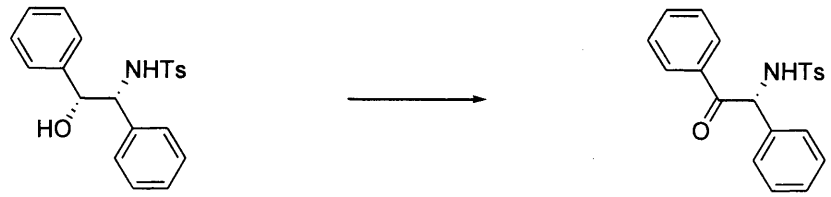
_N_-(1,4-Bis(*tert*-butyldimethylsilyloxy)-3-hydroxybutan-2-yl)-4-toluenesulfonamide 305b



304b **305b**

According to the general procedure P, alkene **304b** (10.00 g, 31.59 mmol), chloramine-T-hydrate (21.57 g, 94.76 mmol), potassium osmate dihydrate (0.58 g, 1.58 mmol) and $(DHQ)_2PHAL$ (0.98 g, 1.26 mmol) were stirred in a solution of *t*BuOH (100 ml) and water (100 ml) overnight. Upon aqueous workup the crude product was purified by column chromatography using 20% ethyl acetate in hexane to give the *amino alcohol* **305b** as a yellow viscous oil (11.65 g, 73%); υ_{max}/cm^{-1} (neat): 3510, 3280, 2929, 2857, 2872, 1599, 1472, 1407, 1336, 1255, 1164, 1090; δ_H 7.70 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.25 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.25 (1H, d, *J* 8.6, NH), 3.82 (1H, dd, *J* 10.2, 2.5, CH), 3.61 (1H, dd, *J* 10.2, 5.6, CH), 3.57 (1H, dd, *J* 10.2, 5.6, CH), 3.52-3.45 (1H, m, CH), 3.29 (1H, dd, *J* 10.2, 4.3, CH), 3.25-3.19 (1H, m, CH), 2.83 (1H, d, *J* 6.3, OH), 2.38 (3H, s, CH_3Ar), 0.83 (9H, s, 3 x CH_3C), 0.80 (9H, s, 3 x CH_3C), 0.00 (6H, s, 2 x CH_3Si), -0.04 (6H, s, 2 x CH_3Si); δ_C 143.4 (C), 137.8 (C), 129.7 (2 x CH (Ar)), 127.0 (2 x CH (Ar)), 70.7 (**C**HOH), 64.4 (CH_2), 62.0 (CH_2), 55.6 (**C**HNH), 25.9 (3 x CH_3C), 25.8 (3 x CH_3C), 21.5 (CH_3Ar), 18.2 (C*t*butyl), 18.1 (C*t*butyl), -5.5 (2 x CH_3Si), -5.6 (2 x CH_3Si); *m/z* (ES) 504 (M+H, 100%), 526 (M+Na, 80%), 567 (55%), 372 (10%); *m/z* (ES) 567 ($MeCNNa^+$, 50%), 526 ($M+Na^+$, 80%), 504 ($M+H^+$, 100%); [Found: $[M+H]^+$ 504.2639. $C_{23}H_{46}NO_5Si_2S$ requires: *M+H*, 504.2635].

4-Methyl-*N*-(2-oxo-1,2-diphenylethyl)toluenesulfonamide 306a

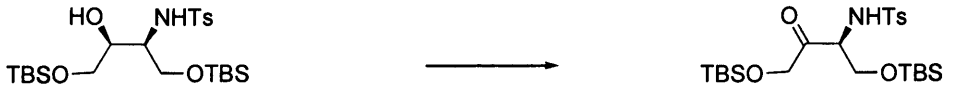


305a **306a**

According to the general procedure R, a solution containing amino alcohol **305a** (1.50 g, 4.09 mmol), pyridinium chlorochromate (1.59 g, 7.36 mmol) and 4 Å molecular sieves were stirred in dichlromethane (40 ml) for 24 h. Workup resulted in clean *amino ketone* **306a** as a white solid (1.31, 88%); m.p. 144-146 °C (lit. m.p.[164] 141-143 °C) υ_{max}/cm^{-1} (DCM): 3348, 3054,

2987, 2305, 1687, 1422, 1265, 1161, 1092; δ_H 7.81 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.54 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.52 (1H, t, *J* 7.6, CH (Ar)), 7.38 (2H, t, *J* 7.6, 2 x CH (Ar)), 7.20 (5H, s, 5 x CH (Ar)), 7.08 (2H, d, *J* 8.2, 2 x CH (Ar)), 6.23 (1H, br d, *J* 7.4, NH), 6.01 (1H, d, *J* 7.4, **CH**NH), 2.32 (3H, s, CH_3Ar).

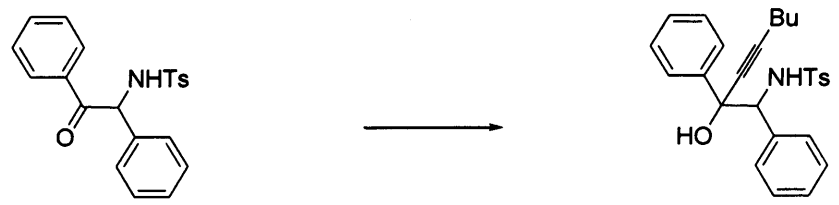
***N*-(1,4-bis(*tert*-butyldimethylsilyloxy)-3-oxobutan-2-yl)-4-toluenesulfonamide 306b**



305b **306b**

According to the general procedure R, a solution containing amino alcohol **305b** (1.00 g, 1.98 mmol), pyridinium chlorochromate (0.77 g, 3.57 mmol) and 4 Å molecular sieves were stirred in dichlormethane (20 ml) for 48 h. Workup resulted in clean *amino ketone* **306b** as a yellow viscous oil (0.89 g, 89%); υ_{max}/cm^{-1} (neat): 3286, 2929, 2873, 2857.3, 1736, 1598, 1471, 1341, 1257, 1166, 1092, 982; δ_H 7.69 (2H, d, *J* 7.9, 2 x CH (Ar)), 7.27 (2H, d, *J* 7.9, 2 x CH (Ar)), 5.60 (1H, d, *J* 7.6, NH), 4.23 (1H, m, **CH**NH), 4.16 (2H, s, $\mathbf{CH_2}$C=O), 4.08 (1H, dd, *J* 3.3, 10.3, $\mathbf{CH_A}$CHNH), 3.75 (1H, dd, *J* 3.8, 10.3, $\mathbf{CH_B}$CHNH), 2.41 (3H, s, CH_3Ar), 0.88 (9H, s, 3 x CH_3C), 0.82 (9H, s, 3 x CH_3C), 0.01 (6H, s, 2 x CH_3Si), 0.00 (6H, s, 2 x CH_3Si); δ_C 205.4 (C=O), 143.7 (C), 136.7 (C), 129.8 (2 x CH (Ar)), 127.2 (2 x CH (Ar)), 68.1 ($\mathbf{CH_A}$CHNH), 63.8 ($\mathbf{CH_B}$CHNH), 60.5 (**CH**NH), 25.7 (2 x (3 x CH_3C)), 21.5 (CH_3Ar), 18.2 (2 x C*t*butyl), -5.7 (4 x CH_3Si); *m/z* (ES) 565 ($M+MeCNNa^+$, 100%), 540 ($M+K^+$, 50%), 519 ($M+NH_4^+$, 60%), 502 ($M+H^+$, 40%); [Found: $[M+H]^+$ 502.2470. $C_{23}H_{44}NO_5Si_2S$ requires: *M+H*, 502.2479].

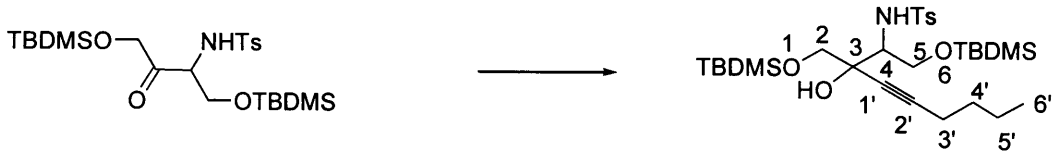
***N*-(2-Hydroxy-1,2-diphenyloct-3-ynyl)-4-toluenesulfonamide 307a**[166]



306a **307a**

According to the general procedure T, amino ketone **306a** (0.45 g, 1.23 mmol) in tetrahydrofuran (6.2 ml) was added dropwise to a solution of 1-hexyne (0.40 ml, 3.10 mmol) and *n*-BuLi (2.5 M in hexanes, 1.24 ml, 3.10 mmol) in tetrahydrofuran (16 ml). Following workup the crude amino alcohol was purified by column chromatography using 10% ethyl acetate in hexane to give clean *alcohol* **307a** as a yellow viscous oil as what appeared to be a single diastereoisomer (0.40 g, 73%); υ_{max}/cm^{-1} (DCM): 3375, 3283, 3065, 3033, 2960, 2932, 2873, 2362, 2253, 1455, 1329, 1162, 1091; δ_H 7.23 (2H, d, *J* 7.8, 2 x CH (Ar)), 7.13-7.00 (6H, m, 6 x CH (Ar)), 6.95 (2H, t, *J* 7.8, 2 x CH (Ar)), 6.89 (2H, d, *J* 7.8, 2 x CH (Ar)), 6.80 (2H, d, *J* 7.8, 2 x CH (Ar)), 5.08 (1H, d, *J* 7.9, NH), 4.33 (1H, d, *J* 7.9, **CH**NH), 2.21 (1H, s, OH), 2.14 (3H, s, CH_3Ar), 2.13 (2H, t, *J* 7.1, 3'-CH_2), 1.38 (2H, *quintet*, *J* 7.1, 4'-CH_2), 1.25 (2H, *sextet*, *J* 7.1, 5'-CH_2), 0.76 (3H, t, *J* 7.1, 6'-CH_3); δ_C 142.7 (C), 140.9 (C), 137.0 (C), 136.1 (C), 129.1 (2 x CH (Ar)), 128.9 (2 x CH (Ar)), 128.1 (CH (Ar)), 127.9 (2 x CH (Ar)), 127.7 (CH (Ar)), 127.5 (2 x CH (Ar)), 126.9 (2 x CH (Ar)), 126.5 (2 x CH (Ar)), 90.5 (C≡C), 79.3 (C≡C), 75.3 (**C**OH), 66.9 (**CH**NH), 30.4 (CH_2), 22.1 (CH_2), 21.4 (CH_3Ar), 18.5 (CH_2), 13.6 (CH_3); *m/z* (EI) 429 (M-H_2O, 50%), 274 (100%), 232 (90%); [Found: [M-H_2O], 429.1761. $C_{27}H_{27}NO_2S$ requires: *M-H_2O*, 429.1763].

***N*-(1-(*tert*-butyldimethylsilyloxy)-3-((*tert*-butyldimethylsilyloxy)methyl)-3-hydroxynon-4-yn-2-yl)-4-toluenesulfonamide 307b**

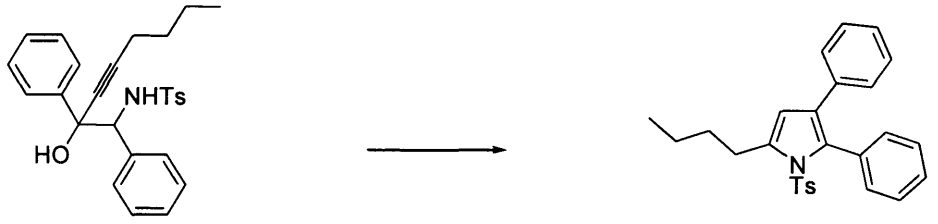


306b **307b**

According to the general procedure T, amino ketone **306b** (1.40 g, 2.79 mmol) in tetrahydrofuran (14 ml) was added dropwise to a solution of 1-hexyne (1.00 ml, 8.38 mmol)

and *n*-BuLi (2.5 M in hexanes, 3.30 ml, 8.38 mmol) in tetrahydrofuran (42 ml). Following workup the crude amino alcohol was purified by column chromatography using 15% ethyl acetate in hexane to give clean *alcohol* **307b** as a viscous yellow oil as what appeared to be a single diastereoisomer (1.02 g, 63%); υ_{max}/cm^{-1} ($CHCl_3$): 3485, 3286, 2943, 2910, 2857, 2238, 1597, 1470, 1409, 1338, 1252, 1161, 1080, 1004; δ_H 7.73 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.23 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.24 (1H, d, *J* 8.8, NH), 4.20 (1H, dd, *J* 2.5, 10.5, 5-H_A), 3.82 (2H, s, 2-CH_2), 3.74 (1H, dd, *J* 4.1, 10.5, 5-H_B), 3.54-3.41 (1H, m, 4-H), 2.37 (3H, s, CH_3Ar), 2.12 (2H, t, *J* 6.4, 3'-CH_2), 1.40 (2H, *quintet*, *J* 6.3, 4'-CH_2), 1.34 (2H, *sextet*, *J* 6.4, 5'-CH_2), 0.84 (9H, s, 3 x CH_3C), 0.83 (9H, s, 3 x CH_3C), 0.87-0.80 (3H, t, *J* 6.4, 6'-CH_3), 0.00 (6H, s, 2 x CH_3Si), -0.04 (6 H, s, 2 x CH_3Si); δ_C 143.1 (C), 138.3 (C), 129.6 (2 x CH (Ar)), 127.0 (2 x CH (Ar)), 87.2 (C≡C), 79.8 (C≡C), 73.8 (3-C), 66.4 (2-CH_2), 65.4 (5-CH_2), 56.4 (4-CH), 30.5 (3'-CH_2), 25.8 (3 x CH_3C), 25.7 (3 x CH_3C), 22.0 (4'-CH_2), 21.5 (CH_3Ar), 18.4 (5'-CH_2), 18.2 (C*t*butyl), 18.1 (C*t*butyl), 13.6 (6'-CH_3), -3.58 (4 x CH_3Si); *m/z* (APCI) 584 ($M+H^+$, 80%), 395 (100%); [Found: $[M+H]^+$, 584.3254. $C_{29}H_{54}NO_5Si_2S$ requires: *M+H*, 584.3261].

5-Butyl-2,3-diphenyl-1-tosyl-1*H*-pyrrole 313k



307a **313k**

According to the general procedure O, 10% $AgNO_3.SiO_2$ (0.04 g, 0.02 mmol) was stirred with a solution of precursor **307a** (0.10 g, 0.22 mmol) in dichloromethane (2 ml) for 18 h to give clean *pyrrole* **313k** as a clear oil (0.09 g, 94%); υ_{max}/cm^{-1} (neat): 3062, 3028, 2959, 2928, 2857, 1597, 1536, 1495, 1442, 1361, 1264, 1170, 1150, 1095; δ_H 7.26-7.21 (1H, m, CH (Ar)), 7.19 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.15 (2H, t, *J* 7.6, 2 x CH (Ar)), 7.06 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.04-6.99 (5H, m, 5 x CH (Ar)), 6.91-6.88 (2H, m, 2 x CH (Ar)), 6.20 (1H, s, 4-H), 2.92 (2H, t, *J* 7.6, 1'-CH_2), 2.29 (3H, s, CH_3Ar), 1.69 (2H, *quintet*, *J* 7.6, 2'-CH_2), 1.40 (2H, *sextet*, *J* 7.6, 3'-CH_2), 0.91 (3H, t, *J* 7.6, *4'-CH_3*); δ_C 144.3(C), 138.7 (C), 137.0 (C), 134.5 (C), 132.5 (2 x CH (Ar)), 132.0 (C), 131.8 (C), 129.4 (2 x CH (Ar)), 128.1 (CH (Ar)), 128.0 (4 x CH (Ar)), 127.4 (2 x CH (Ar)), 127.0 (C), 126.6 (2 x CH (Ar)), 126.2 (CH (Ar)), 113.1 (4-CH), 31.6 (1'-CH_2), 29.2

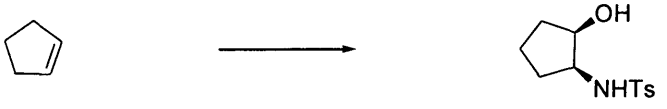
(2'-CH_2), 21.6 (3'-CH_2), 21.6 (CH_3Ar), 14.1 (4'-CH_3); *m/z* (APCI) 430 ($M+H^+$, 100%); [Found: $[M+H]^+$, 430.1823. $C_{27}H_{28}NO_2S$ requires: *M+H*, 430.1841].

5-Butyl-2,3-bis((*tert*-butyldimethylsilyloxy)methyl)-1-tosyl-1*H*-pyrrole 313l

307b **313l**

According to the general procedure O, 10% $AgNO_3.SiO_2$ (0.13 g, 0.08 mmol) was stirred with a solution of precursor **307b** (0.11 g, 0.38 mmol) in dichloromethane (2 ml) for 4 h to give clean *pyrrole* **313l** as a clear viscous oil (0.1 g, 98%); υ_{max}/cm^{-1} ($CHCl_3$): 2928, 2894, 2856, 1597, 1460, 1428, 1365, 1254, 1180, 1090, 837, 777, 704; δ_H 7.71 (2H, d, *J* 8.3, 2 x CH (Ar)), 7.15 (2H, d, *J* 8.3, 2 x CH (Ar)), 5.95 (1H, s, 4-H), 4.84 (2H, s, CH_2O), 4.53 (2H, s, CH_2O), 2.58 (2H, t, *J* 7.6, 1'-CH_2), 2.32 (3H, s, CH_3Ar), 1.45 (2H, *quintet*, *J* 7.6, 2'-CH_2), 1.26 (2H, *sextet*, *J* 7.6, 3'-CH_2), 0.84 (18H, s, 2 x (3 x CH_3C)), 0.81 (3H, t, *J* 7.6, 4'-CH_3), 0.03 (6H, s, 2 x CH_3Si), 0.00 (6H, s, 2 x CH_3Si); δ_C 144.1 (C), 137.5 (C), 130.7 (C), 129.5 (2 x CH (Ar)), 127.3 (C), 126.8 (2 x CH (Ar)), 111.5 (4-CH), 57.9 (CH_2O), 55.3 (CH_2O), 30.8 (1'-CH_2), 28.1 (2'-CH_2), 26.0 (2 x (3 x CH_3C)), 22.4 (3'-CH_2), 21.6 (CH_3Ar), 18.5 (C*t*butyl), 18.4 (C*t*butyl), 13.9 (4'-CH_3), -3.98 (4 x CH_3Si); *m/z* molecular ion is not observed.

(1S,2R)-*p*-Toluenesulfonylamino(cyclopentan-2-ol) 318a



317a **318a**

According to the general procedure Q, cyclopentene **317a** (1.36 g, 20.0 mmol), potassium osmate dihydrate (0.07 g, 0.20 mmol), chloramine-T-hydrate (6.82 g, 30.0 mmol) and benzyltriethylammonium chloride (0.23 g, 1.00 mmol) were stirred in a mixture of *t*BuOH (25 ml) and water (25 ml) overnight. Following aqueous workup the crude product was purified by column chromatography using 40% ethyl acetate in hexane to give clean *amino alcohol* **318a** as a powdery white solid (1.81 g, 36%); δ_H 7.71 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.25 (2H, d, *J* 8.2, 2 x CH (Ar)), 4.81 (1H, d, *J* 7.6, NH), 3.94-3.90 (1H, m, 2-H), 3.34 (1H, app ddt, *J* 12.1, 7.5, 4.8,

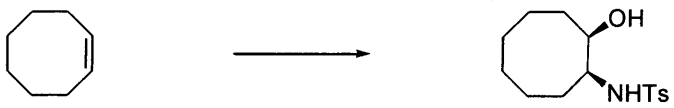
1-H), 2.37 (3H, s, CH_3Ar), 1.79-1.64 (3H, m, 3 of 3-H*a*/H*b* and 5-H*a*/H*b*), 1.72 (1H, d, *J* 3.7, OH), 1.60-1.53 (1H, m, 1 of 3-H*a*/H*b* and 5-H*a*/H*b*), 1.48-1.33 (2H, m, 4-CH_2); δ_C 143.6 (C), 137.4 (C), 129.8 (2 x CH (Ar)), 127.1 (2 x CH (Ar)), 72.2 (2-CH), 57.9 (1-CH), 30.1 (3-CH_2 or 5-CH_2), 29.3 (3-CH_2 or 5-CH_2), 21.6 (CH_3Ar), 19.9 (4-CH_2).

(1S,2R)-*p*-Toluenesulfonylamino(cyclohexan-2-ol) 318b[164]

317b **318b**

According to the general procedure Q, cyclohexene **317b** (1.64 g, 20.0 mmol), potassium osmate dihydrate (0.07 g, 0.20 mmol), chloramine-T-hydrate (6.82 g, 30.0 mmol) and benzyltriethylammonium chloride (0.23 g, 1.00 mmol) were stirred in a mixture of *t*BuOH (25 ml) and water (25 ml) overnight. Following aqueous workup the crude product was purified by column chromatography using 40% ethyl acetate in hexane to give clean *amino alcohol* **318b** as a powdery white solid (2.36 g, 44%); m.p. 154-156 °C (lit m.p.[164] 158-159 °C); δ_H 7.78 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.32 (2H, d, *J* 8.2, 2 x CH (Ar)), 4.79 (1H, d, *J* 7.3, NH), 3.82-3.77 (1H, m, 2-H), 3.28-3.22 (1H, m, 1-H), 2.36 (3H, s, CH_3Ar), 1.74-1.67 (1H, m, CH), 1.67 (1H, d, J 4.6, OH), 1.63-1.49 (3H, m, 3 x CH), 1.48-1.41 (1H, m, CH), 1.41-1.31 (1H, m, CH), 1.30-1.22 (2H, m, 2 x CH).

(1S,2R)-*p*-Toluenesulfonylamino(cyclooctan-2-ol) 318c[164]

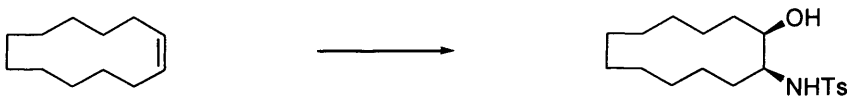


317c **318c**

According to the general procedure Q, cyclooctene **317c** (2.20 g, 20.0 mmol), potassium osmate dihydrate (0.07 g, 0.19 mmol), chloramine-T-hydrate (6.82 g, 30.0 mmol) and benzyltriethylammonium chloride (0.23 g, 1.00 mmol) were stirred in a mixture of *t*BuOH (25 ml) and water (25 ml) overnight. Following aqueous workup the crude product was purified by column chromatography using 40% ethyl acetate in hexane to give clean *amino alcohol* **318c** as a powdery white solid (3.52 g, 59%); 120-121 °C (lit. m.p.[164] 118-119 °C); δ_H 7.70 (2H, d, *J*

8.2, 2 x CH (Ar)), 7.24 (2H, d, *J* 8.2, 2 x CH (Ar)), 4.80 (1H, d, *J* 8.1, NH), 3.70 (1H, app ddd, *J* 10.0, 4.5, 3.2, 2-H), 3.45-3.39 (1H, app ddt, *J* 10.0, 7.9, 2.9, 1-H), 2.37 (3H, s, CH_3Ar), 1.74-1.64 (3H, m, 3 x CH), 1.63-1.56 (1H, m, CH), 1.47-1.38 (5H, m, 5 x CH), 1.37-1.29 (3H, m, 3 x CH); δ_C 143.2 (C), 137.8 (C), 129.8 (2 x CH (Ar)), 127.0 (2 x CH (Ar)), 72.4 (2-CH), 56.2 (1-CH), 31.4 (CH_2), 29.4 (CH_2), 27.1 (CH_2), 25.6 (CH_2), 25.3 (CH_2), 22.4 (CH_2), 21.6 (CH_3Ar).

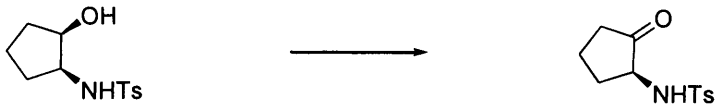
(1S,2R)-*p*-Toluenesulfonylamino(cyclododecan-2-ol) 318d



317d **318d**

According to the general procedure Q, cyclododecene **317d** (0.85 g, 5. 11 mmol), potassium osmate dihydrate (0.02 g, 0.05 mmol), chloramine-T-hydrate (1.74 g, 7.50 mmol) and benzyltriethylammonium chloride (0.06 g, 0.25 mmol) were stirred in a mixture of *t*BuOH (25 ml) and water (25 ml) overnight. Following aqueous workup the crude product was purified by column chromatography using 40% ethyl acetate in hexane to give clean *amino alcohol* **318d** as a yellow viscous oil (0.90 g, 50%); δ_H 7.75 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.25 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.55 (1H, br d, *J* 6.7, NH), 4.02-3.95 (2H, m, 1-H, 2-H), 2.37 (3H, s, CH_3Ar), 2.07-2.01 (2H, m, 2 x CH), 1.40-1.17 (18H, m, 9 x CH_2).

***p*-Toluenesulfonylamino(cyclopentan-2-one) 319a**[167]



318a **319a**

According to the general procedure S, amino alcohol **318a** (0.57 g, 2.33 mmol) in acetone (5.3 ml) and Jones reagent (1.09 ml, 2.90 mmol) were stirred for 1.5 h. Following this workup was carried out resulting in clean *ketone* **319a** as a white powdery solid (0.41 g, 73%); m.p. 93-95 °C; υ_{max}/cm^{-1} (DCM): 3419, 3057, 2985, 1752, 1640, 1421, 1335, 1266, 1163, 1094; δ_H 7.70 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.25 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.01 (1H, app s, NH), 3.37 (1H, ddd, *J* 11.9, 8.2, 2.9, 1-H), 2.53-2.42 (1H, m, CH), 2.36 (3H, s, CH_3Ar), 2.29 (1H, app dd, *J* 18.8, 8.9, CH), 2.04 (1H, app dd, *J* 19.0, 9.6, CH), 2.00-1.93 (1H, m, CH), 1.74-1.56 (2H, m,

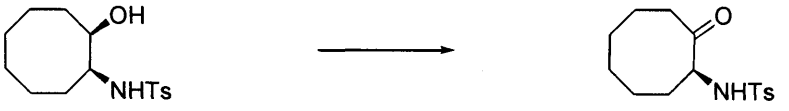
CH_2); δ_C 212.1 (C=O), 142.9 (C), 135.2 (C), 128.7 (2 x CH (Ar)), 126.2 (2 x CH (Ar)), 59.2 (1-CH), 33.2 (CH_2), 29.9 (CH_2), 20.5 (CH_3Ar), 16.6 (4-CH_2).

_p_-Toluenesulfonylamino(cyclohexan-2-one) 319b[168]

318b **319b**

According to the general procedure S, amino alcohol **318b** (2.36 g, 8.76 mmol) in acetone (20.1 ml) and Jones reagent (4.30 ml, 11.5 mmol) were stirred for 0.5 h. Following this workup was carried out resulting in clean *ketone* **319b** as a white powdery solid (2.32 g, 99%); m.p. 120-121 °C (lit. m.p.[168] 116-118 °C); υ_{max}/cm^{-1} (DCM): 3306, 3054, 2987, 2358, 1718, 1422, 1265, 1165, 1093; δ_H 7.65 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.21 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.71 (1H, d, *J* 4.8, NH), 3.68 (1H, app dt, *J* 11.9, 5.5, 1-H), 2.47 (1H, app ddd, *J* 12.9, 6.1, 3.0, CH), 2.44-2.39 (1H, m, CH), 2.35 (3H, s, CH_3Ar), 2.16 (1H, tdd, *J* 13.6, 6.6, 0.9, CH), 2.00 (1H, app ddt, *J* 13.0, 6.5, 2.8, CH), 1.83-1.77 (1H, m, CH), 1.67-1.46 (3H, m, 3 x CH); δ_C 205.8 (C=O), 143.6 (C), 136.9 (C), 129.8 (2 x CH (Ar)), 127.0 (2 x CH (Ar)), 60.6 (1-CH), 40.8 (CH_2), 36.9 (CH_2), 27.4 (CH_2), 23.9 (CH_2), 21.6 (CH_3Ar).

_p_-Toluenesulfonylamino(cyclooctan-2-one) 319c



318c **319c**

According to the general procedure S, amino alcohol **318c** (3.50 g, 11.8 mmol) in acetone (27.1 ml) and Jones reagent (5.70 ml, 15.3 mmol) were stirred for 1.5 h. Following this workup was carried out resulting in clean *ketone* **319c** as a white powdery solid (2.44 g, 70%); m.p. 68-69 °C; υ_{max}/cm^{-1} (DCM): 3304, 3056, 2958, 2930, 2867, 1707, 1453, 1335, 1266, 1164, 1093; δ_H 7.65 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.21 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.65 (1H, br d, *J* 4.6, NH), 3.75 (1H, ddd, *J* 7.3, 4.6, 3.0, 1-H), 2.42-2.35 (1H, m, CH), 2.34 (3H, s, CH_3Ar), 2.25 (1H, ddt, *J* 14.8, 11.4, 3.4, CH), 2.10 (1H, ddd, *J* 12.7, 6.7, 3.5, CH), 1.97 (1H, dddd, *J* 16.6, 9.6, 5.7, 3.8, CH), 1.88-1.81 (1H, m, CH), 1.75-1.48 (4H, m, 4 x CH), 1.34-1.17 (3H, m, 3 x CH); δ_C 212.7

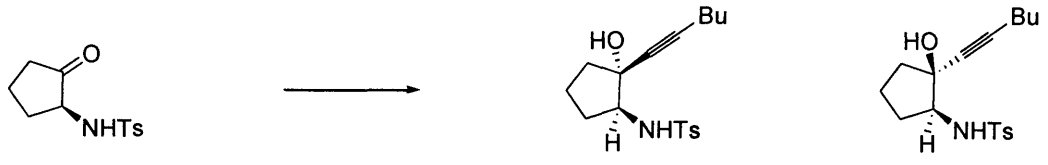
(C=O), 143.7 (C), 136.4 (C), 129.7 (2 x CH (Ar)), 127.0 (2 x CH (Ar)), 60.9 (1-CH), 38.9 (CH_2), 29.3 (CH_2), 28.2 (CH_2), 26.0 (CH_2), 24.2 (CH_2), 22.5 (CH_2), 21.6 (CH_3Ar); *m/z* (EI) 295 (M^+, 20%), 267 (90%), 224 (85%), 210 (100%); [Found: $[M]^+$, 295.1241. $C_{15}H_{21}NO_3S$ requires: *M*, 295.1242].

p-Toluenesulfonylamino(cyclododecan-2-one) 319d

318d **319d**

According to the general procedure S, amino alcohol **318d** (0.57 g, 2.33 mmol) in acetone (5.4 ml) and Jones reagent (1.09 ml, 2.90 mmol) were stirred for 1.5 h. Following this workup was carried out resulting in clean *ketone* **319d** as a clear viscous oil (0.41 g, 73%); υ_{max}/cm^{-1} ($CHCl_3$): 3387, 2958, 2930, 2867, 1715, 1454, 1406, 1305, 1274, 1166, 1091; δ_H 7.61 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.20 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.55 (1H, d, *J* 6.7, NH), 4.00 (1H, m, 1-H), 2.69 (2H, m, 3-CH_2), 2.38 (3H, s, CH_3Ar), 2.05-1.00 (18H, m, 9 x CH_2); δ_C 213.0 (C=O), 139.5 (C), 137.2 (C), 129.7 (2 x CH (Ar)), 127.0 (2 x CH (Ar)), 61.3 (1-CH), 34.3 (CH_2), 30.7 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 23.9 (CH_2), 22.7 (CH_2), 22.4 (CH_2), 22.0 (CH_2), 21.4 (CH_3Ar), 21.3 (CH_2), 18.7 (CH_2); *m/z* (APCI) [Found: $[M+H]^+$, 352.1943. $C_{19}H_{30}NO_3S$ requires: *M+H*, 352.1946].

(1S,2R) and (1S,2S) 4-toluenesulfonylamino-2-(hex-1-yn-1-yl)cyclopentan-2-ol 320a



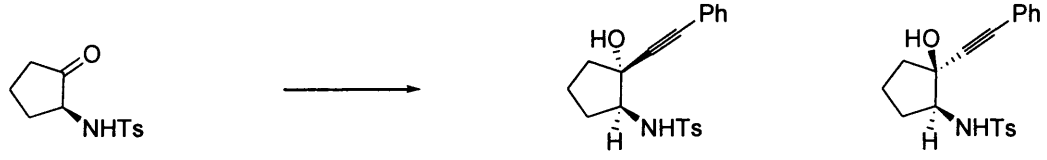
319a **320a**

According to the general procedure T, amino ketone **319a** (0.40 g, 1.58 mmol) in dry tetrahydrofuran (8 ml) was added droppwise to a solution of 1-hexyne (0.40 ml, 3.47 mmol) and *n*-BuLi (2.5 M in hexanes, 1.39 ml, 3.47 mmol) in tetrahydrofuran (18 ml) at -78 °C. Following workup the crude product was purified by column chromatography using 33% ethyl acetate in hexane to give clean *amino alcohol* as a yellow oil and a 91:9 mixture of

diastereoisomers (0.36 g, 70%); υ_{max}/cm^{-1} ($CHCl_3$): 3489, 3278, 2957, 2933, 2872, 2240, 1452, 1379, 1322, 1305, 1161, 1094, 988; δ_H (Major 1S,2R) 7.73 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.24 (2H, d, *J* 8.2, 2 x CH (Ar)), 4.78 (1H, d, *J* 9.2, NH), 3.33 (1H, app q, *J* 9.3, 1-H), 2.75 (1H, s, OH), 2.36 (3H, s, CH_3Ar), 2.18 (2H, t, *J* 7.1, 3'-CH_2), 2.02 (2H, app ddd, *J* 17.5, 8.7, 4.6, CH_2), 1.86-1.73 (2H, m, CH_2), 1.67-1.55 (2H, m, CH_2), 1.44 (2H, *quintet*, *J* 7.2, 4'-CH_2), 1.35 (2H, *sextet*, *J* 7.1, 5'-CH_2), 0.86 (3H, t, *J* 7.2, 6'-CH_3); δ_C (Major) 143.7 (C), 137.3 (C), 129.7 (2 x CH (Ar)), 127.3 (2 x CH (Ar)), 88.9 (C≡C), 79.4 (C≡C), 77.1 (2-C), 63.5 (1-CH), 38.1 (CH_2), 30.7 (CH_2), 29.6 (CH_2), 22.0 (CH_2), 21.6 (CH_3Ar), 18.5 (CH_2), 18.4 (CH_2), 13.6 (6'-CH_3); *m/z* (APCI) 318 (M-H_2O, 100%); [Found: [M]-H_2O, 318.1529. $C_{18}H_{24}NO_2S$ requires: *M-H_2O*, 318.1528].

δ_H (distinguishable minor peaks 2S,1S) 4.90 (1H, br d, *J* 8.3, NH), 3.50 (1H, q, *J* 8.4, 1-H).

(1S,2R) and (1S,2S) 4-Toluenesulfonylamino-2-(phenylethynyl)cyclopentan-2-ol 320b



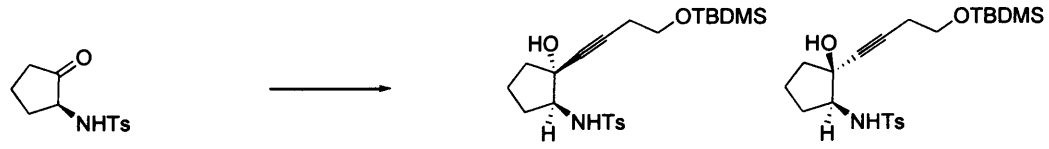
319a **320b**

According to the general procedure T, amino ketone **319a** (0.30 g, 1.18 mmol) in dry tetrahydrofuran (6 ml) was added droppwise to a solution of phenylacetylene (0.28 ml, 2.60 mmol) and *n*-BuLi (2.5 M in hexanes, 1.04 ml, 2.60 mmol) in tetrahydrofuran (13 ml) at -78 °C. Following workup the crude product was purified by recrystalisation using ethyl acetate/hexane to give pure *amino alcohol* **320b** as a yellow crystalline solid and a 84:16 mixture of diastereoisomers (0.36 g, 85%), m.p. 135-138 °C; υ_{max}/cm^{-1} ($CHCl_3$): 3491, 3272, 2924, 2854, 2254, 1634, 1599, 1495, 1456, 1335, 1261, 1160, 1093, 1019; δ_H (Major 1S,2R) 7.75 (2H, d, *J* 8.3, 2 x CH (Ar)), 7.73-7.59 (3H, m, 3 x CH (Ar)), 7.27-7.20 (4H, m, 4 x CH (Ar)), 4.75 (1H, d, *J* 9.7, NH), 3.38 (1H, ddd, *J* 12.7, 7.8, 2.4, 1-H), 3.01 (1H, s, OH), 2.36 (3H, s, CH_3Ar), 1.84-1.44 (6H, m, 6 x CH); δ_C (Major) 143.6 (C), 137.1 (C), 131.9 (2 x CH (Ar)), 129.9 (2 x CH (Ar)), 128.9 (CH (Ar)), 128.4 (2 x CH (Ar)), 127.4 (2 x CH (Ar)); 81.9 (C), 77.2 (2-C), 63.9 (1-CH), 38.2 (CH_2), 29.9 (CH_2), 21.6 (CH_3Ar), 18.6 (CH_2); *m/z* (APCI) 338 (M-

H_2O, 100%), 238 (35%); [Found: [M]-H_2O, 338.1208. $C_{20}H_{20}NO_2S$ requires: *M-H_2O*, 338.1215].

δ_H (distinguishable minor peaks 2S,1S) 4.90 (1H, br s, NH).

(1S,2R) and (1S,2S) 4-Toluenesulfonylamino-2-(*tert*butyldimethylsilyloxy-but-1-yn-1-yl)cyclopentan-2-ol 320c

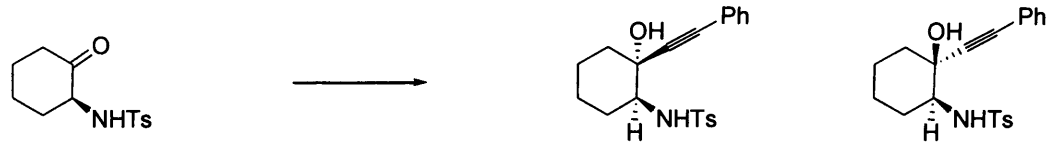


319a **320c**

According to the general procedure T, amino ketone **319a** (0.40 g, 1.58 mmol) in dry tetrahydrofuran (8 ml) was added droppwise to a solution of silyl protected alkyne (0.73 g, 3.95 mmol) and *n*-BuLi (2.5 M in hexanes, 1.58 ml, 3.95 mmol) in tetrahydrofuran (20 ml) at -78 °C. Following workup the crude product was purified by column chromatography using 33% ethyl acetate in hexane to give clean *amino alcohol* **320c** as a yellow oil as a 98:2 mixture of diastereoisomers (0.37 g, 53%); υ_{max}/cm^{-1} ($CHCl_3$): 3483, 3276, 2955, 2928, 2883, 2857, 2362, 2432, 1599, 1472, 1387, 1335, 1161, 1095, 1006, 918; δ_H (Major 1S,2R) 7.70 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.22 (2H, d, *J* 8.2, 2 x CH (Ar)), 4.87 (1H, d, *J* 9.6, NH), 3.66 (2H, ddd, *J* 13.5, 6.8, 2.8, 4'-CH_2), 3.32 (1H, td, *J* 9.7, 7.5, 1-H), 2.87 (1H, s, OH), 2.38 (2H, t, *J* 6.8, 3'-CH_2), 2.34 (3H, s, CH_3Ar), 2.01 (1H, ddd, *J* 15.1, 8.6, 4.4, CH), 1.81-1.72 (2H, m, 2 x CH), 1.62-1.53 (1H, m, CH), 1.43-1.35 (2H, m, 2 x CH), 0.82 (9H, s, 3 x CH_3C), 0.00 (6H, s, 2 x CH_3Si); δ_C (Major) 143.7 (C), 137.3 (C), 129.7 (2 x CH (Ar)), 127.3 (2 x CH (Ar)), 86.0 (C≡C), 80.7 (C≡C), 76.9 (2-C), 63.7 (1-CH), 61.8 (4'-CH_2), 37.9 (CH_2), 29.6 (CH_2), 25.9 (3 x CH_3C), 23.2 (CH_2), 21.6 (CH_3Ar), 18.4 (C*t*butyl), 18.4 (CH_2), -5.1 (2 x CH_3Si); *m/z* (APCI) 438 ($M+H^+$, 15%), 420 (100%); [Found: $[M+H]^+$, 438.2140. $C_{22}H_{36}NO_4SiS$ requires: *M+H*, 438.2134].

δ_H (distinguishable minor peaks 2S,1S) 5.05 (1H, br s, NH).

(1S,2R) and (1S,2S) 4-Toluenesulfonylamino-2-(phenylethynyl)cyclohexan-2-ol 320d

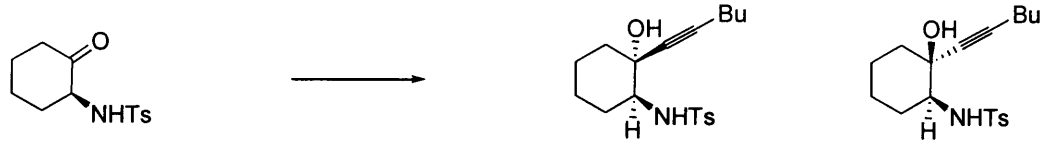


319b **320d**

According to the general procedure T, amino ketone **319b** (0.21 g, 0.79 mmol) in dry tetrahydrofuran (4 ml) was added droppwise to a solution of phenylacetylene (0.19 ml, 1.73 mmol) and *n*-BuLi (2.5 M in hexanes, 0.69 ml, 1.73 mmol) in tetrahydrofuran (9 ml) at -78 °C. Following workup the crude product was purified by column chromatography using 33% ethyl acetate in hexane to give clean *amino alcohol* **320d** as a crystalline white solid and a 86:14 mixture of diastereoisomers (0.21 g, 73%), m.p. 139-141 °C; υ_{max}/cm^{-1} ($CHCl_3$): 3821, 3475, 3263, 2936, 2860, 2238, 1598, 1490, 1442, 1328, 1161, 1082, 1037, 919; δ_H (Major 1S,2R) 7.74 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.39-7.36 (2H, m, 2 x CH (Ar)), 7.29-7.24 (5H, m, 5 x CH (Ar)), 4.62 (1H, d, *J* 9.9, NH), 3.08 (1H, ddd, *J* 11.8, 9.9, 4.1, 1-H), 2.37 (3H, s, CH_3Ar), 2.14-2.10 (1H, m, CH), 1.64-1.54 (3H, m, 3 x CH), 1.43-1.32 (2H, m, 2 x CH), 1.23-1.11 (2H, m, 2 x CH); δ_C (Major) 143.8 (C), 137.5 (C), 131.8 (2 x CH (Ar)), 129.9 (2 x CH (Ar)), 128.8 (CH (Ar)), 128.4 (2 x CH (Ar)), 127.1 (2 x CH (Ar)), 122.0 (C), 88.2 (C≡C), 87.5 (C≡C), 72.3 (2-C), 61.6 (1-CH), 38.4 (CH_2), 31.4 (CH_2), 24.8 (CH_2), 23.0 (CH_2), 21.6 (CH_3Ar); *m/z* (APCI) [Found: $[M]^+$-OH, 352.1382. $C_{21}H_{22}NO_2S$ requires: *M-OH*, 352.1371].

δ_H (distinguishable minor peaks 2S,1S) 5.19 (1H, br d, J 7.4, NH).

(1S,2R) and (1S,2S) 4-Toluenesulfonylamino-2-(hex-1-yn-1-yl)cyclohexan-2-ol 314



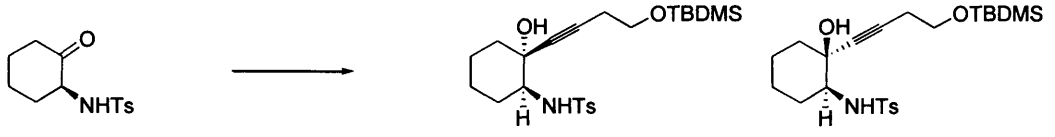
319b **314**

According to the general procedure T, amino ketone **319b** (0.40 g, 1.50 mmol) in dry tetrahydrofuran (7.5 ml) was added droppwise to a solution of 1-hexyne (0.38 ml, 3.29 mmol) and *n*-BuLi (2.5 M in hexanes, 1.31 ml, 3.29 mmol) in tetrahydrofuran (17 ml) at -78 °C. Following workup the crude product was purified by column chromatography using 25% ethyl

acetate in hexane to give clean *amino alcohol* **314** as a yellow oil and as a 86:14 mixture of diastereoisomers (0.33 g, 83%); υ_{max}/cm^{-1} ($CHCl_3$): 3489, 3270, 2935,2860, 2238, 1599, 1559, 1496, 1448, 1328, 1290, 1266, 1160, 1090, 1038, 931; δ_H (Major 1S,2R) 7.72 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.24 (2H, d, *J* 8.2, 2 x CH (Ar)), 4.59 (1H, d, *J* 9.9, NH), 2.98 (1H, ddd, *J* 11.8, 9.9, 4.0, 1-CH), 2.77 (1H, br s, OH), 2.36 (3H, s, CH_3Ar), 2.16 (2H, t, *J* 7.1, 3'-CH_2), 1.59-1.50 (5H, m, 5 x CH), 1.47-1.39 (3H, m, 4'-CH_2, 1 x CH), 1.38-1.25 (4H, m, 5'-CH_2, 2 x CH), 0.85 (3H, t, *J* 7.1, 6'-CH_3); δ_C (Major) 143.6 (C), 137.9 (C), 129.8 (2 x CH (Ar)), 127.2 (2 x CH (Ar)), 88.4 (C≡C), 79.3 (C≡C), 71.8 (2-C), 61.5 (1-CH), 38.6 (CH_2), 31.5 (CH_2), 30.7 (CH_2), 24.8 (CH_2), 23.0 (CH_2), 22.0 (CH_2), 21.5 (CH_3Ar), 18.3 (CH_2), 13.6 (6'-CH_3); *m/z* (APCI) [Found: [M]-H_2O, 332.1682. $C_{19}H_{26}NO_2S$ requires: *M-H_2O*, 332.1684].

δ_H (distinguishable minor peaks 2S,1S) 4.88 (1H, d, *J* 7.0, NH), 3.19 (1H, ddd, *J* 9.1, 7.0, 4.1, 1-H).

(1S,2R) and (1S,2S) 4-Toluenesulfonylamino-2-(*tert*butyldimethylsilyloxy-but-1-yn-1-yl)cyclohexan-2-ol 315



319b **315**

According to the general procedure T, amino ketone **319b** (0.29 g, 1.08 mmol) in dry tetrahydrofuran (5 ml) was added droppwise to a solution of silyl protected alkyne (0.44 g, 2.39 mmol) and *n*-BuLi (2.5 M in hexanes, 0.95 ml, 2.39 mmol) in tetrahydrofuran (12 ml) at -78 °C. Following workup the crude product was purified by column chromatography using 25% ethyl acetate in hexane to give clean *amino alcohol* **315** as a yellow solid and a 94:6 mixture of diastereoisomers (0.21 g, 43%); m.p. 88-90 °C; υ_{max}/cm^{-1} ($CHCl_3$): 3501, 3270, 2936, 2861, 2349, 2251, 1599, 1495, 1449, 1328, 1289, 1160, 1090, 1038; δ_H (Major 1S,2R) 7.71 (2H, d, *J* 8.1, 2 x CH (Ar)), 7.23 (2H, d, *J* 8.1, 2 x CH (Ar)), 4.63 (1H, d, *J* 9.8, NH), 3.64 (2H, t, *J* 6.9, 4'-CH_2), 2.97 (1H, ddd, *J* 12.0, 9.7, 3.9, 2-CH), 2.36 (2H, t, *J* 6.8, 3'-CH_2), 2.35 (3H, s, CH_3Ar), 2.13-1.88 (2H, m, 2 x CH), 1.61-1.12 (6H, m, 6 x CH), 0.81 (9H, s, 3 x CH_3C), 0.00 (6H, s, 2 x CH_3Si); δ_C (Major) 143.6 (C), 137.9 (C), 129.8 (2 x CH (Ar)), 127.1 (2 x CH

(Ar)), 71.9 (2-C), 61.8 (4'-CH_2), 61.5 (1-CH), 38.5 (CH_2), 31.6 (CH_2), 25.9 (3 x CH_3C), 24.8 (CH_2), 23.1 (CH_2), 22.9 (CH_2), 21.6 (CH_3Ar), 18.1 (C*t*butyl), -5.2 (2 x CH_3Si); *m/z* (APCI) [Found: $[M+H]^+$, 452.2278. $C_{23}H_{38}NO_4SiS$ requires: *M+H*, 452.2291].

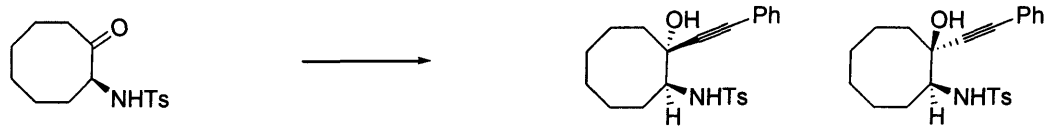
δ_H (distinguishable minor peaks 2S,1S) 4.83 (1H, br d, *J* 7.5, NH), 3.23-3.13 (1H, m, 1-H).

(1S,2R) and (1S,2S) 4-Toluenesulfonylamino-2-(hex-1-yn-1-yl)cyclooctan-2-ol 320e

319c **320e**

According to the general procedure T, amino ketone **319c** (0.40 g, 1.35 mmol) in dry tetrahydrofuran (7 ml) was added droppwise to a solution of 1-hexyne (0.34 ml, 2.97 mmol) and *n*-BuLi (2.5 M in hexanes, 1.19 ml, 2.97 mmol) in tetrahydrofuran (15 ml) at -78 °C. Following workup the crude product was purified by column chromatography using 33% ethyl acetate in hexane to give a the clean *amino alcohol* **320e** as a yellow oil and a 1:1 mixture of diastereoisomers (0.39 g, 77%); υ_{max}/cm^{-1} ($CHCl_3$): 3501, 3274, 2928, 2859, 2251, 1918, 1598, 1466, 1446, 1332, 1290, 1240, 1162, 1093, 1040, 913; δ_H (1S,2R and 1S,2S) 7.77-7.71 (2H, m, 2 x CH (Ar)), 7.28-7.22 (2H, m, 2 x CH (Ar)), 5.12 (1H, d, *J* 8.0, NH), 4.72 (1H, d, *J* 10.1, NH), 3.43 (1H, t, *J* 8.0, 1-H), 3.36 (1H, t, *J* 10.1, 1-H), 2.37 (3H, br s, CH_3Ar), 2.11 (2H, t, *J* 7.0, 3'-CH_2), 2.00-1.25 (16H, m, 8 x CH_2), 0.84 (3H, t, *J* 7.0, 6'-CH_3); δ_C (1S,2R and 1S,2S) 143.6 (C), 142.8 (C), 138.3 (C), 137.5 (C), 129.9 (2 x CH (Ar)), 129.4 (2 x CH (Ar)), 127.2 (2 x CH (Ar)), 127.2 (2 x CH (Ar)), 85.9 (C≡C), 85.4 (C≡C), 81.7 (C≡C), 80.6 (C≡C), 73.4 (2-C), 73.1 (2-C), 60.8 (1-CH), 59.7 (1-CH), 38.9 (CH_2), 36.9 (CH_2), 36.6 (CH_2), 32.4 (CH_2), 31.1 (CH_2), 30.7 (CH_2), 29.3 (CH_2), 28.2 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 24.6 (CH_2), 24.2 (CH_2), 22.7 (CH_2), 22.5 (CH_2), 22.0 (CH_2), 22.0 (CH_2), 21.6 (CH_3Ar), 21.5 (CH_3Ar), 18.3 (CH_2), 18.2 (CH_2), 13.6 (6'-CH_3), 13.6 (6'-CH_3); *m/z* (EI) 359 (M-H_2O, 10%), 335 (35%), 222 (100%); [Found: [M]-H_2O, 359.1912. $C_{21}H_{29}NO_2S$ requires: *M-H_2O*, 359.1919].

(1S,2R) and (1S,2S) 4-Toluenesulfonylamino-2-(phenylethynyl)cyclooctan-2-ol 320f

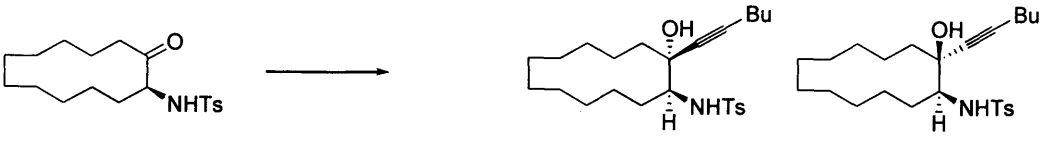


319c **320f**

According to the general procedure T, amino ketone **319c** (0.40 g, 1.35 mmol) in dry tetrahydrofuran (7 ml) was added droppwise to a solution of phenylacetylene (0.33 ml, 2.97 mmol) and *n*-BuLi (2.5 M in hexanes, 1.19 ml, 2.97 mmol) in tetrahydrofuran (15 ml) at -78 °C. Following workup the crude product was purified by column chromatography using 25% ethyl acetate in hexane to give *amino alcohol* **320f** as a white solid and a 73:27 mixture of diastereoisomer (0.28 g, 52%); m.p. 140-142 °C; υ_{max}/cm^{-1} ($CHCl_3$): 3487, 3268, 3062, 2925, 2856, 2251, 1598, 1574, 1490, 1465, 1443, 1332, 1162, 1092, 1049, 911; δ_H (Major 1S,2R) 7.75 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.36-7.32 (2H, m, 2 x CH (Ar)), 7.28-7.22 (5H, m, 5 x CH (Ar)), 4.76 (1H, d, *J* 10.0, NH), 3.47 (1H, td, *J* 9.9, 1.4, 1-H), 3.13 (1H, d, *J* 2.0, OH), 2.37 (3H, s, CH_3Ar), 2.11 (1H, m, CH), 1.98-1.90 (1H, m, CH), 1.88-1.70 (2H, m, 2 x CH), 1.83-1.69 (1H, m, CH), 1.64-1.58 (2H, m, 2 x CH), 1.54-1.49 (1H, m, CH), 1.42-1.22 (4H, m, 4 x CH); δ_C (Major) 144.0 (C), 137.2 (C), 131.8 (2 x CH (Ar)), 130.0 (2 x CH (Ar)), 128.6 (CH (Ar)), 128.3 (2 x CH (Ar)), 127.3 (2 x CH (Ar)), 122.1 (C), 89.5 (C≡C), 85.2 (C≡C), 73.5 (2-C), 59.7 (1-CH), 36.7 (CH_2), 32.5 (CH_2), 28.3 (CH_2), 25.7 (CH_2), 24.6 (CH_2), 21.6 (CH_3Ar), 21.1 (CH_2); *m/z* (APCI) 380 (M-H_2O, 20%), 296 (100%); [Found: [M]-H_2O, 380.1679. $C_{23}H_{26}NO_2S$ requires: *M-H_2O*, 380.1684].

δ_H (distinguishable minor peaks 2S,1S) 5.19 (1H, br d, *J* 8.4, NH), 3.59 (1H, t, *J* 8.4, 1-H).

(1S,2R) and (1S,2S) 4-Toluenesulfonylamino-2-(hex-1-yn-1-yl)cyclododecan-2-ol 320g



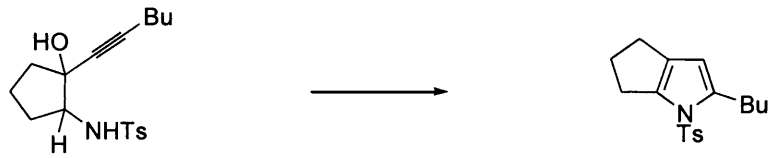
319d **320g**

According to the general procedure T, amino ketone **319d** (0.30 g, 0.85 mmol) in dry tetrahydrofuran (5 ml) was added droppwise to a solution of 1-hexyne (0.39 ml, 3.41 mmol) and *n*-BuLi (2.5 M in hexanes, 1.36 ml, 3.41 mmol) in tetrahydrofuran (17 ml) at -78 °C.

Following workup the *amino alcohol* **320g** was isolated as a crude yellow oil and a 7:3 mixture of diastereoisomers (0.34 g, 92%); υ_{max}/cm^{-1} ($CHCl_3$): 3471, 2930, 2861, 2246, 1598.22, 1495, 1468, 1236, 1179, 1119, 1093, 957; δ_H 7.73 (2H, d, *J* 8.3, 2 x CH (Ar)), 7.24 (2H, d, *J* 8.3, 2 x CH (Ar)), 4.46 (1H, d, *J* 9.7, NH), 3.11 (1H, ddd, *J* 18.6, 12.3, 2.9, 1-H), 2.36 (3H, s, CH_3Ar), 2.28 (2H, t, *J* 7.3, 3'-CH_2), 2.00-1.20 (24H, m, 12 x CH_2), 0.85 (3H, t, *J* 7.3, 6'-CH_3). *Product was carried through crude to the next step.*

δ_H (distinguishable minor peaks 2S,1S) 4.78 (1H, d, *J* 8.4, NH).

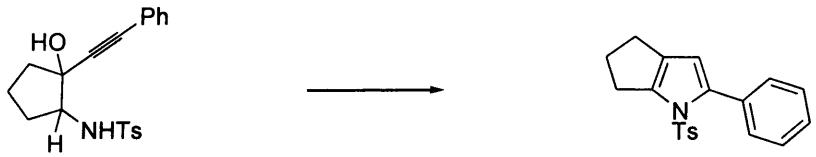
2-Butyl-1-tosyl-1,4,5,6-tetrahydrocyclopent[*b*]pyrrole 321a



320a **321a**

According to the general procedure O, 10% $AgNO_3.SiO_2$ (0.73 g, 0.46 mmol) was stirred with a solution of precursor **320a** (0.15 g, 0.46 mmol) as a 91:9 mixture of diastereoisomers in dichloromethane (5 ml) for 18 h to give clean *pyrrole* **321a** as a clear oil (0.13 g, 92%); υ_{max}/cm^{-1} ($CHCl_3$): 2956, 2861, 2360, 2342, 1598, 1521, 1495, 1487, 1418, 1365, 1174, 1126, 1089, 1032; δ_H 7.53 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.20 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.75 (1H, s, 3-H), 2.88 (2H, t, *J* 6.5, CH_2Ar), 2.61 (2H, t, *J* 7.6, CH_2Ar), 2.43 (2H, tt, *J* 5.4, 1.6, CH_2Ar), 2.33 (3H, s, CH_3Ar), 2.28 (2H, *quintet*, *J* 7.2, CH_2), 1.46 (2H, *quintet*, *J* 7.1, 2'-CH_2), 1.28 (2H, *sextet*, *J* 7.1, 3'-CH_2), 0.82 (3H, t, *J* 7.1, 4'-CH_3); δ_C 144.3 (C), 139.8 (C), 138.4 (C), 137.2 (C), 129.9 (2 x CH (Ar)), 129.7 (C), 126.4 (2 x CH (Ar)), 107.9 (3-CH), 30.5 (CH_2), 28.3 (CH_2), 28.0 (CH_2), 27.8 (CH_2), 25.3 (CH_2), 22.4 (CH_2), 21.6 (CH_3Ar), 13.9 (4'-CH_3); *m/z* (EI) 317 (M^+, 40%), 274 (100%); [Found $[M]^+$, 317.1457. $C_{18}H_{23}NO_2S$ requires: *M*, 317.1450].

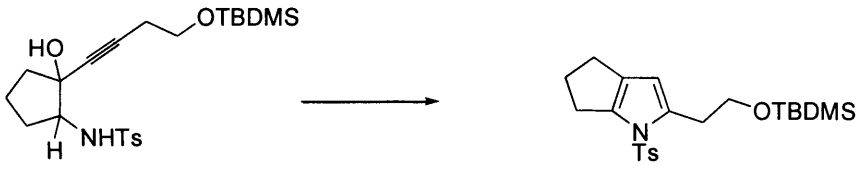
2-Phenyl-1-tosyl-1,4,5,6-tetrahydrocyclopent[*b*]pyrrole 321b



320b **321b**

According to the general procedure O, 10% $AgNO_3.SiO_2$ (0.34 g, 0.20 mmol) was stirred with a solution of precursor **320b** (0.07 g, 0.20 mmol) as a 84:16 mixture of diastereoisomers in dichloromethane (2 ml) for 3.5 h to give clean *pyrrole* **321b** as a clear oil (0.06 g, 96%); υ_{max}/cm^{-1} ($CHCl_3$): υ_{max}/cm^{-1} ($CHCl_3$): 2955, 2924, 2854, 1598, 1451, 1337, 1162; δ_H 7.47 (2H, s, *J* 8.2, 2 x CH (Ar)), 7.28-7.18 (5H, m, 5 x CH), 7.17 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.91 (1H, s, 3-H), 3.01 (2H, tt, *J* 7.1, 1.5, 6 or 8-CH_2), 2.48 (2H, tt, *J* 7.1, 1.5, 8 or 6-CH_2), 2.29 (CH_3Ar), 1.79-1.72 (2H, m, 2 x CH); δ_C 144.4 (C), 140.9 (C), 139.8 (C), 136.1 (C), 132.5 (C), 131.3 (C), 130.8 (2 x CH (Ar)), 129.4 (2 x CH (Ar)), 127.9 (CH (Ar)), 127.3 (2 x CH (Ar)), 126.8 (2 x CH (Ar)), 112.4 (3-CH), 28.8 (CH_2), 27.9 (CH_2), 25.2 (CH_2), 21.6 (CH_3Ar). *m/z* could not be obtained.

2-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-1-tosyl-1,4,5,6-tetrahydrocyclopent[*b*]pyrrole 321c

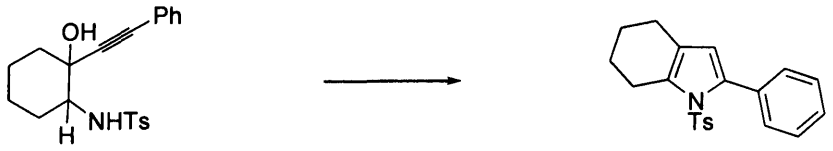


320c **321c**

According to the general procedure O, 10% $AgNO_3.SiO_2$ (1.00 g, 0.59 mmol) was stirred with a solution of precursor **320c** (0.26 g, 0.59 mmol) as a 98:2 mixture of diastereoisomers in dichloromethane (5 ml) for 18 h to give clean *pyrrole* **321c** as a clear oil (0.25 g, 99%); υ_{max}/cm^{-1} ($CHCl_3$): 2957, 2928, 2858, 1598, 1519, 1495, 1471, 1463, 1368, 1306, 1252, 1174, 1093, 1033; δ_H 7.58 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.26 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.87 (1H, s, 3-H), 3.77 (2H, t, *J* 7.0, 2'-CH_2), 2.95-2.89 (4H, m, 2 x CH_2Ar), 2.48 (2H, t, *J* 7.0, 1'-CH_2), 2.39 (3H, s, CH_3Ar), 2.34 (2H, *quintet*, *J* 7.2, 7-CH_2), 0.86 (9H, s, 3 x CH_3C), 0.00 (6H, s, 2 x CH_3Si); δ_C 147.3 (C), 138.7 (C), 137.1 (C), 135.7 (C), 130.0 (C), 127.7 (2 x CH (Ar)), 126.4 (2 x CH (Ar)), 110.0 (3-CH), 63.0 (2'-CH_2), 32.1 (CH_2), 28.3 (CH_2), 27.8 (CH_2), 25.7 (3 x CH_3C),

21.6 (CH_3Ar), 18.3 (C*t*butyl), -3.6 (2 x CH_3Si); *m/z* (APCI) 420 ($M+H^+$, 100%); [Found: $[M+H]^+$, 420.2036. $C_{22}H_{35}NO_3SiS$ requires: *M+H*, 420.2029].

2-Phenyl-1-tosyl-4,5,6,7-tetrahydro-1*H*-indole 321d



320d **321d**

According to the general procedure O, 10% $AgNO_3.SiO_2$ (0.09 g, 0.05 mmol) was stirred with a solution of precursor **320d** (0.02 g, 0.05 mmol) as a 86:14 mixture of diastereoisomers in dichloromethane (2 ml) for 3 h to give clean *pyrrole* **321d** as a clear oil (0.02 g, 99%); υ_{max}/cm^{-1} ($CHCl_3$): 2927, 2851, 2257, 1914, 1803, 1598.22, 1532, 1495, 1403, 1372, 1175, 1092; δ_H 7.30-7.28 (5H, m, 5 x CH (Ar)), 7.24-7.19 (2H, m, 2 x CH (Ar)), 7.07 (2H, d, *J* 8.3, 2 x CH (Ar)), 5.88 (1H, s, 3-H), 2.86 (2H, tt, *J* 6.2, 1.9, CH_2Ar), 2.29 (3H, s, CH_3Ar), 2.19 (2H, tt, *J* 6.3, 1.9, CH_2Ar), 1.75-1.69 (2H, m, 2 x CH), 1.64-1.58 (2H, m, 2 x CH); δ_C 130.5 (2 x CH (Ar)), 129.4 (2 x CH (Ar)), 127.8 (CH (Ar)), 127.2 (2 x CH (Ar)), 126.5 (2 x CH (Ar)), 117.1 (3-CH), 25.3 (CH_2), 23.3 (CH_2), 23.2 (CH_2), 22.6 (CH_2), 21.6 (CH_3Ar); *m/z* (APCI) [Found: $[M+H]^+$, 352.1355. $C_{21}H_{22}NO_2S$ requires: *M+H*, 352.1371].

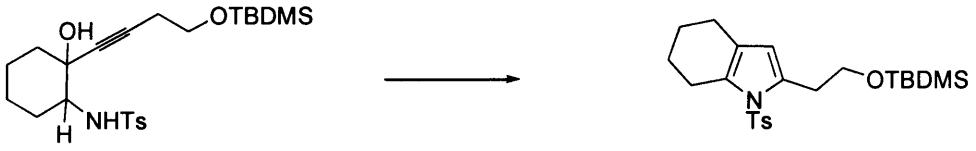
2-Butyl-1-tosyl-4,5,6,7-tetrahydro-1*H*-indole 313m

314 **313m**

According to the general procedure O, 10% $AgNO_3.SiO_2$ (0.39 g, 0.21 mmol) was stirred with a solution of precursor **314** (0.15 g, 0.42 mmol) as an 86:14 mixture of daistereoisomers in dichloromethane (2 ml) for 27 h to give clean *pyrrole* **313m** as a clear oil (0.12 g, 85%); υ_{max}/cm^{-1} ($CHCl_3$): 2924, 1597, 1539, 1495, 1465, 1410, 1363, 1251, 1200, 1159, 1139, 1092, 1019, 936; δ_H 7.44 (2H, d, *J* 8.2, 2 x CH (Ar)), 7.19 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.72 (1H, s, 3-H), 2.70 (4H, m, 2 x CH_2Ar), 2.29 (2H, tt, *J* 6.1, 1.6, CH_2Ar), 1.70-1.66 (2H, m, 2 x CH), 1.63-1.56 (2H, m, 2 x CH), 1.50 (2H, *quintet*, *J* 7.2, 2'-CH_2), 1.30 (2H, *sextet*, *J* 7.2, 3'-CH_2), 0.84

(3H, t, *J* 7.2, 4'-CH_3); δ_C 144.1 (C), 137.8 (C), 136.5 (C), 130.5 (C), 129.8 (2 x CH (Ar)), 126.0 (2 x CH (Ar)), 122.1 (C), 112.0 (3-CH), 31.0 (CH_2), 28.3 (CH_2), 24.7 (CH_2), 23.4 (CH_2), 23.2 (CH_2), 22.7 (CH_2), 22.5 (CH_2), 21.6 (CH_3Ar), 14.0 (4'-CH_3); *m/z* (APCI) [Found: $[M+H]^+$, 332.1676. $C_{19}H_{26}NO_2S$ requires: *M+H*, 332.1684].

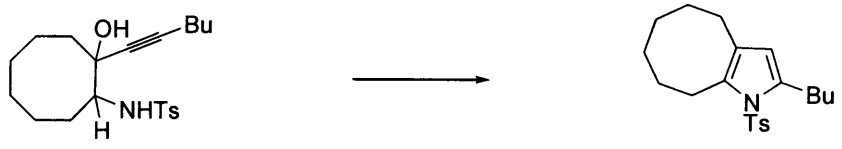
2-(2-*Tert*-butyldimethylsilyloxy)ethyl)-4,5,6,7-tetrahydro-1*H*-indole 313n



315 **313n**

According to the general procedure O, 10% $AgNO_3.SiO_2$ (0.43 g, 0.26 mmol) was stirred with a solution of precursor **315** (0.12 g, 0.26 mmol) as an 94:6 mixture of diastereoisomers in dichloromethane (2 ml) for 48 h to give clean *pyrrole* **313n** as a clear oil (0.08 g, 74%); υ_{max}/cm^{-1} ($CHCl_3$): 2929, 2855, 1914, 1538, 1471, 1367, 1306, 1291, 1180, 1093, 1059, 1018, 1007, 987; δ_H 7.50 (2H, d, *J* 8.2, d, 2 x CH (Ar)), 7.24 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.84 (1H, s, 3-H), 3.81 (2H, t, *J* 6.7, 2'-CH_2), 2.98 (2H, t, *J* 6.8, CH_2Ar), 2.74 (2H, t, *J* 6.2, CH_2Ar), 2.38 (3H, s, CH_3Ar), 2.33 (2H, tt, *J* 6.0, 1.6, CH_2Ar), 1.74-1.68 (2H, m, 2 x CH), 1.64-1.58 (2H, m, 2 x CH), 0.86 (9H, s, 3 x CH_3C), 0.00 (6H, s, 2 x CH_3Si); δ_C 143.1 (C), 136.6 (C), 131.4 (C), 129.7 (C), 128.8 (2 x CH (Ar)), 125.0 (2 x CH (Ar)), 121.3 (C), 113.0 (3-CH), 62.0 (2'-CH_2), 31.3 (CH_2), 25.4 (CH_2), 24.9 (3 x CH_3C), 23.7 (CH_2), 22.4 (CH_2), 22.1 (CH_2), 21.6 (CH_3Ar), 17.3 (C*t*butyl), -3.7 (2 x CH_3Si); *m/z* (APCI) [Found: $[M+H]^+$, 434.2171. $C_{23}H_{36}NO_3SiS$ requires: *M+H*, 434.2185].

2-Butyl-1-tosyl-4,5,6,7,8,9-hexahydro-1*H*-cycloocta[*b*]pyrrole 321e

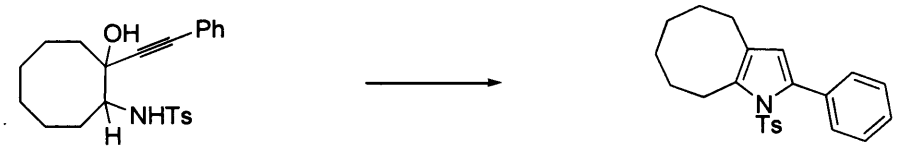


320e **321e**

According to the general procedure O, 10% $AgNO_3.SiO_2$ (1.03 g, 0.61 mmol) was stirred with a solution of precursor **320e** (0.23 g, 0.61 mmol) as a 1:1 mixture of diastereoisomers in dichloromethane (5 ml) for 18 h to give clean *pyrrole* **321e** as a yellow solid (0.20 g, 91%);

m.p. 61 °C; υ_{max}/cm^{-1} ($CHCl_3$): 2926, 2857, 1914, 1598, 1535, 1461, 1406, 1362, 1179, 1151, 1093; δ_H; 7.41 (2H, d, *J* 8.3, 2 x CH (Ar)), 7.17 (2H, d, *J* 8.3, 2 x CH (Ar)), 5.73 (1H, s, 3-H), 2.82 (2H, t, *J* 6.3, 2 x CH), 2.69 (2H, app t, *J* 7.7, 2 x CH), 2.37-2.31 (2H, m, 2 x CH), 2.31 (3H, s, CH_3Ar), 1.59-1.44 (6H, m, 6 x CH), 1.36-1.25 (6H, m, 6 x CH), 0.83 (3H, t, *J* 7.3, 4'-CH_3); δ_C 144.0 (C), 136.5 (C), 131.6 (C), 126.0 (C), 112.8 (3-CH), 31.5 (CH_2), 31.2 (CH_2), 30.0 (CH_2), 28.6 (CH_2), 26.7 (CH_2), 26.4 (CH_2), 25.6 (CH_2), 24.0 (CH_2), 22.5 (CH_2), 21.6 (CH_3), 14.2 (4'-CH_3); *m/z* (EI) 359 (M^+, 40%), 331 (50%), 204 (50%); [Found; $[M]^+$, 359.1922. $C_{21}H_{29}NO_2S$ requires: *M*, 359.1919].

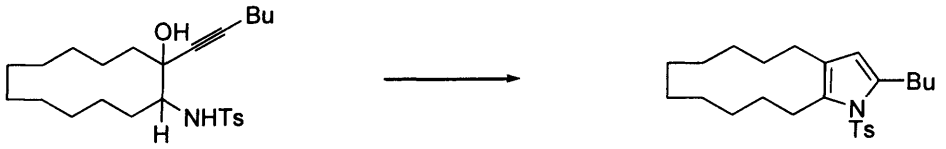
2-Phenyl-1-tosyl-4,5,6,7,8,9-hexahydro-1*H*-cycloocta[*b*]pyrrole 321f



320f **321f**

According to the general procedure O, 10% $AgNO_3.SiO_2$ (0.81 g, 0.48 mmol) was stirred with a solution of precursor **320f** (0.19 g, 0.48 mmol) as an 73:27 mixture of diastereoisomers in dichloromethane (5 ml) for 23 h to give clean *pyrrole* **321f** as a yellow solid (0.15 g, 83%); m.p. 112 °C; υ_{max}/cm^{-1} ($CHCl_3$): 3062, 2925, 2854, 1597, 1450, 1368, 1291, 1187, 1176, 1092, 1071; δ_H 7.28-7.20 (7H, m, 7 x CH (Ar)), 7.07 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.89 (1H, s, 3-H), 2.98 (2H, t, *J* 6.3, CH_2Ar), 2.35 (2H, t, J 5.7, CH_2Ar), 2.29 (3H, s, CH_3Ar), 1.70 (2H, *quintet*, *J* 6.1, CH_2), 1.49 (2H, ddt, *J* 13.4, 5.9, 3.3, CH_2), 1.37 (2H, *quintet*, *J* 5.1, CH_2), 1.29-1.22 (2H, m, CH_2); δ_C 144.0 (C), 137.0 (C), 136.7 (C), 133.9 (C), 133.5 (C), 130.5 (2 x CH (Ar)), 129.3 (2 x CH (Ar)), 128.0 (C), 127.6 (CH (Ar)), 127.2 (2 x CH (Ar)), 126.4 (2 x CH (Ar)), 117.9 (3-CH), 31.4 (CH_2), 30.1 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 25.7 (CH_2), 24.5 (CH_2), 21.6 (CH_3Ar); *m/z* (EI) 379 (M^+, 10%); 224 (50%), 171 (60%); [Found: $[M]^+$, 379.1597. $C_{23}H_{25}NO_2S$ requires: *M*, 379.1606].

2-Butyl-1-tosyl-4,5,6,7,8,9,10,11,12,13-decahydro-1*H*-cyclododeca[*b*]pyrrole 321g



320g **321g**

According to the general procedure O, 10% $AgNO_3.SiO_2$ (2.34 g, 1.38 mmol) was stirred with a solution of precursor **320g** (0.20 g, 0.46 mmol) as a 7:3 mixture of diastereoisomers in dichloromethane (10 ml) for 3 h followed by column chromatography using 10% ethyl acetate in hexane to give the clean *pyrrole* **321g** as a clear oil (0.16 g, 84%); υ_{max}/cm^{-1} (DCM): 2930, 2860, 1676, 1466, 1341, 1162, 1092; δ_H 7.34 (2H,d, *J* 8.2, 2 x CH (Ar)), 7.15 (2H, d, *J* 8.2, 2 x CH (Ar)), 5.78 (1H, s, 3-H), 2.69 (2H, t, *J* 7.2, CH_2Ar), 2.62 (2H, t, *J* 7.5, CH_2Ar), 2.41-2.32 (2H, m, CH_2Ar), 2.31 (3H, s, CH_3Ar), 2.24-2.11 (6H, m, 6 x CH), 2.08-2.02 (2H, m, 2 x CH), 1.76-1.60 (6H, m, 6 x CH), 1.56-1.26 (6H, m, 6 x CH), 0.82 (3H, t, *J* 7.0, 4'-CH_3); δ_C 143.8 (C), 137.6 (C), 133.5 (C), 129.7 (2 x CH (Ar)), 126.2 (C), 125.6 (2 x CH (Ar)), 113.1 (3-CH), 106.9 (C), 32.7 (CH_2), 31.0 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 26.3 (CH_2), 26.1 (CH_2), 25.6 (CH_2), 25.4 (CH_2), 25.0 (CH_2), 24.4 (CH_2), 23.8 (CH_2), 23.0 (CH_2), 22.5 (CH_2), 21.6 (CH_3Ar), 14.00 (4'-CH_3); *m/z* (EI) 415 (M^+, 15%), 260 (30%), 171 (55%); [Found: $[M]^+$, 415.2536. $C_{25}H_{37}NO_2S$ requires: *M*, 415.2545].

General procedure U for the Swern oxidation of alcohol to aldehyde[108]

A solution of DMSO (2.20 equiv) dissolved in dichloromethane (0.2 ml per mmol DMSO) was added dropwise to a stirred solution of oxalyl chloride (1.20 equiv) in dichloromethane (2 ml per mmol oxalyl chloride) at -63 °C. After 10 min a solution of prolinol (1.00 equiv) in dichloromethane was added dropwise over 15 min followed by 30 min of stirring. DIPEA (4.00 equiv) was then added over 4 min and the mixture was allowed to warm to room temperature over 30 min. The mixture was then washed with 0.5 % HCl (3 x volume of mixture), water (3 x volume of mixture), brine (1 x volume of mixture), dried over sodium sulphate, filtered and evaporated to give an oil.

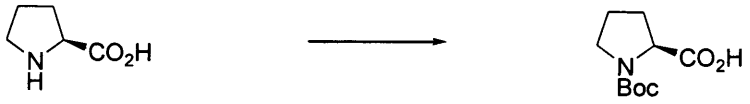
General procedure V for the Addition of Grignard to aldehyde[108]

Alkyne (1.20-1.30 equiv) was added dropwise to a stirred solution of ethyl magnesium bromide (1.0 M in tetrahydrofuran, 1.20-1.30 equiv) dissolved in etrahydrofuran (~3 ml per mmol of alkyne) at 0 °C and stirred at this temperature for 1 h. The reaction was then allowed to warm to room temperature over 15 min, followed by addition of prolinal (1.00 equiv) in tetrahydrofuran (2 ml per mmol aldehyde) over 30 min. The reaction was then allowed to stir for 0.5-1.5 h before being quenched with aq NH_4Cl (~1 x volume of mixture) and concentrated. The resulting residue was dissolved in diethyl ether (3 x volume of mixture) and washed with aq NH_4Cl (2 x volume of mixture), brine (2 x volume of mixture), dried over sodium sulphate, filtered and evaporated to give product that was purified by column chromatography.

General procedure W for Boc-deprotection

To a stirred solution of N-Boc compound (1.00 equiv) in dichloromethane (1-2 ml per mmol of Boc compound) at 0 °C a 20% v/v TFA (4.00 equiv) in dichloromethane was added dropwise. The mixture was stirred at 0 °C and monitored by TLC and upon completion was basified with 2M sodium hydroxide solution. The solution was the extracted with dichloromethane (3 x volume of mixture), washed with brine (2 x volume of mixture), water (1 x volume of mixture), dried over sodium sulphate, filtered and evaporated. The crude material was then purified by column chromatography with a mixture of DCM: MeOH: Et_3N resulting in a pungent smelling free amine

***N*-Boc-(L)-proline 325**



324 **325**

(L)-Proline **324** (3.00 g, 26.1 mmol) was dissolved in dichloromethane (60 ml) and treithylamine (4.70 ml, 33.9 mmol) was added dropwise, followed by the addition of Boc_2O (8.25 g, 37.8 mmol) in dichloromethane (3 ml). The reaction was stirred at room temperature for 2.5 h and then quenched with sat citric acid solution (15 ml). The mixture was then washed

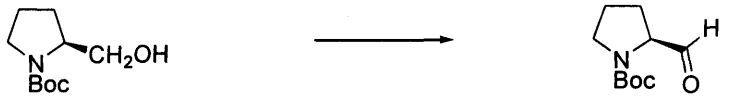
with water (2 x 20 ml) and the brine (1 x 20 ml), dried, filtered and evaporated to give a white semi solid. The residue was then dissolved in hot ethyl acetate (7 ml) and hexane was added dropwise (60 ml). The mixture was then cooled to -25 °C and the crystals that formed were filtered resulting in the *boc-protected proline* **325** as white crystalline solid (5.30 g, 94%); m.p. 131-132 °C (lit m.p.[169] 133-134 °C); υ_{max}/cm^{-1} (DCM): 3419, 3055, 2986, 1694, 1422, 1267, 1162, 1131; δ_H 4.40-4.25 (1H, br m, 2-H), 3.60-3.33 (2H, br m, CH_2), 2.45-2.28 (1H, br m, CH), 2.10-1.89 (3H, br m, CH, CH_2) two singlets at 1.51 and 1.45 (9H, s, 3 x CH_3C).

_N_-Boc-(L)-prolinol 326[108]

325 **326**

A solution of *N*-boc proline **325** (2.00 g, 9.30 mmol) in tetrahydrofuran (50 ml) was cooled to 0 °C and $BH_3.SMe_2$ (1.10 ml, 12.1 mmol) was added dropwise over 30 min. As soon as gas evolution had ceased the mixture was gently warmed to reflux for 1 h. Followed by cooling to room temperature and evaporation of solvent. The residue was dissolved in a mixture of dichloromethane (100 ml) and water (30 ml). The organic layer was isolated and washed with $NaHCO_3$ (30 ml), brine (2 x 30 ml), dried filtered and evaporated to give *prolinol* **326** as a clear oil (1.85 g, 99%); υ_{max}/cm^{-1} (DCM): 3382, 3054, 2980, 2882, 1742, 1683, 1408, 1368, 1266, 1168, 1112; δ_H 3.92-3.85 (1H, m, 2-H), 3.56 (1H, dd, *J* 11.2, 3.6, 1-H_A), 3.51 (1H, dd, *J* 11.2, 7.4, 1-H_B), 3.43 (1H, br. s, OH), 3.39 (1H, dt, *J* 10.8, 7.0, 4-H_A), 3.24 (1H, dt, *J* 10.8, 6.7, 4-H_B), 1.94 (1H, ddd, *J* 14.9, 12.4, 7.3, 6-H_A), 1.83-1.66 (2H, m, 5-CH_2), 1.59-1.48 (1H, m, 6-H_B), 1.40 (9H, s, 3 x CH_3C).

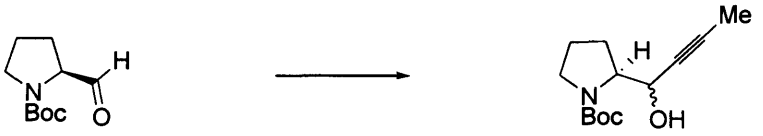
***N*-Boc-(L)-prolinal 328**[108]



326 **328**

According to the general procedure U, a solution of DMSO (7.90 ml, 111 mmol) in dichloromethane (25 ml) was added dropwise to a stirred solution of oxalyl chloride (5.30 ml, 61.0 mmol) in dichloromethane (125 ml) at -63 °C. After 10 min N-boc prolinol **326** (10.16 g, 50.50 mmol) in dichloromethane (50 ml) was added dropwise over 15 min and the reaction was stirred for a further 30 min. Quenching with DIPEA (35.00 ml, 202.0 mmol) and work-up resulted in *prolinal* **328** as a clear oil (9.70 g, 96%) as a 2:1 mixture of rotomers; δ_H 9.49 and 9.39 (1H, d, *J* 2.6, 1-CHO), 4.16-4.11 and 4.01-3.95 (1H, m, 2-H), 3.54-3.33 (2H, m, 4-CH_2), .210-1.86 (2H, m, CH_2), 1.85-1.76 (2H, m, CH_2), 1.41 and 1.36 (9H, s, (3 x CH_3C).

(2S,IR) and (2S,1S) 2-(1-Hydroxybut-2-yn-1-yl)*N*-Boc-pyrrolidine 331a

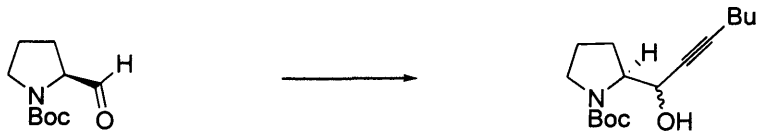


328 **331a**

A solution of (L)-prolinal **328** (1.50 g, 7.54 mmol) in tetrahydrofuran (15 ml) was added dropwise over 30 min, to a stirred solution of 1-propynyl magnesium bromide (0.5 M, 30.14 ml, 15.07 mmol) in tetrahydrofuran followed by column chromatograpghy (70:30 hexane-ethyl acetate) resulted in *2-propargylic pyrrolidine* **331a** as a 63:37 mixture of diastereoisomers (1S:1R) as a yellow oil (1.40 g, 83%); υ_{max}/cm^{-1} ($CHCl_3$): 3423, 2976, 2934, 2885, 2289, 2243, 1668, 1412, 1367, 1166, 1126, 1064, 1038; δ_H (500 MHz) (Major, 2S,1S) 5.21 (1H, s, OH), 4.30-4.26 (1H, br m, **CH**OH), 4.00-3.94 (1H, m, 2-H), 3.57-3.30 (2H, m, 5-CH_2), 2.11-1.71 (4H, m, 3-CH_2, 4-CH_2), 1.84 (3H, br s, 3'-CH_3), 1.47 (9H, s, 3 x CH_3C); (2S,1R) δ_H (Minor, 2S,1R) 5.87 (1H, s, OH), 4.41-4.38 (1H, br m, **CH**OH), 4.05-4.00 (1H, m, 2-H), 3.57-3.30 (2H, m, 5-CH_2), 2.11-1.71 (4H, m, 3-CH_2, 4-CH_2), 1.83 (3H, br s, 3'-CH_3), 1.47 (9H, s, 3 x CH_3C); δ_C (125MHz) (2S,1S and 2S,1R) 157.6 (C=O), 157.1 (C=O), 81.2 (C), 81.1 (C), 80.6 (C), 80.3 (C), 78.7 (C), 77.5 (C), 67.5 (**CH**OH), 67.1 (**CH**OH), 63.1 (2-CH), 63.0 (2-CH), 48.3 (CH_2),

47.7 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.4 (3 x CH_3C), 28.4 (3 x CH_3C), 24.0 (CH_2), 23.8 (CH_2), 3.6 (3'-CH_3), 3.6 (3'-CH_3).

(2S,IR) and (2S,1S) 2-(1-Hydroxyhept-2-yn-1-yl)*N*-Boc-pyrrolidine 331b



328 **331b**

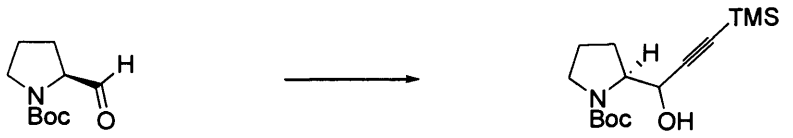
According to the general procedure V, a solution of (L)-prolinal **328** (0.50 g, 2.51 mmol) in tetrahydrofuran (5 ml) was added to a solution of 1-hexyne (0.35 ml, 3.01 mmol) and ethyl magnesium bromide (1.0 M in tetrahydrofuran, 3.10 ml, 3.10 mmol) in tetrahydrofuran (10ml) at 5°C. This was followed by aqueous workup and column chromatography (70:30 hexane-ethyl acetate) to give the clean *2-propargylic pyrrolidine* **331b** as a 56:44 mixture of diastereoisomers (1S:1R) as a yellow oil (0.64 g, 91%); δ_H (500MHz) (Major, 2S,1S) 5.96 (1H, d, *J* 8.7, OH), 4.39 (1H, d, *J* 8.7, **CH**OH), 4.03 (1H, app t, *J* 6.8, 2-H), either 3.56-3.51 (1H, m, 5-H_A) or 3.46-3.40 (1H, m, 5-H_A), 3.36-3.28 (1H, m, 5-H_B), 2.22-2.18 (2H, m, 3'-CH_2), 2.13-1.68 (4H, m, 3-CH_2, 4-CH_2), 1.52-1.37 (4H, m, 4'-CH_2, 5'-CH_2), 1.50 (9H, s, 3 x CH_3C), 0.90 (3H, t, *J* 7.4, 6'-CH_3); (2S,1R) δ_H (Minor 2S,1R) 5.09 (1H, app s, OH), 4.33-4.30 (1H, m, **CH**OH), 4.00-3.96 (1H, m, 2-H), either 3.56-3.51 (1H, m, 5-H_A) or 3.46-3.40 (1H, m, 5-H_A), 3.36-3.28 (1H, m, 5-H_B), 2.22-2.18 (2H, m, 3'-CH_2), 2.13-1.68 (4H, m, 3-CH_2, 4-CH_2), 1.52-1.37 (4H, m, 4'-CH_2, 5'-CH_2), 1.50 (9H, s, 3 x CH_3C), 0.90 (3H, t, J 7.4, 6'-CH_3); δ_C (125MHz) (2S,1S and 2S,1R) 157.6 (C=O), 157.1 (C=O), 85.7 (C), 85.6 (C), 80.5 (C), 80.31 (C), 79.5 (C), 78.4 (C), 67.4 (**CH**OH), 67.2 (**CH**OH), 63.3 (2-CH), 63.0 (2-CH), 48.3 (CH_2), 47.7 (CH_2), 30.8 (CH_2), 30.6 (CH_2), 29.2 (CH_2), 28.8 (CH_2), 28.4 (3 x CH_3C), 28.4 (3 x CH_3C), 24.0 (CH_2), 23.8 (CH_2), 21.9 (CH_2), 21.8 (CH_2), 18.4 (CH_2), 18.4 (CH_2), 13.6 (6'-CH_3), 13.6 (6'-CH_3); *m/z* (APCI) 282 ($M+H^+$, 30%), 267 (50%), 249 (100%); [Found: $[M+H]^+$, 282.2060. $C_{16}H_{28}NO_3$ requires: *M+H*, 282.2069].

(2S,IR) and (2S,1S) 2-(Hydroxy-3-phenylprop-2-yn-1-yl)*N*-Boc-pyrrolidine 331c[170]

328 **331c**

According to the general procedure V, a solution of (L)-prolinal **328** (1.50 g, 7.54 mmol) in tetrahydrofuran (15 ml) was added to a solution of phenylacetylene (0.91 ml, 8.29 mmol) and ethyl magnesium bromide (1.0 M in tetrahydrofuran, 8.30 ml, 8.29 mmol) in tetrahydrofuran (60 ml) at 5 °C. This was followed by aqueous workup and column chromatography (70:30 hexane-ethyl acetate) to give the *2-propargylic pyrrolidine* **331c** as a 63:37 mixture of diastereoisomers (1S,1R) as a viscous orange oil (1.70 g, 75%); υ_{max}/cm^{-1} ($CHCl_3$): 3395, 3078, 2977, 2931, 2882, 2230, 1671, 1490, 1407, 1367, 1255, 1165, 1123, 1048, 910; δ_H (500 MHz) (Major, 2S,1S) 7.47-7.41 (2H, m, 2 x CH (Ar)), 7.33-7.30 (3H, m, 3 x CH (Ar)), 6.26 (1H, d, *J* 8.9, OH), 4.65 (1H, d, *J* 8.9, **CH**OH), 4.19-4.14 (1H, m, 2-H), 3.61-3.38 (2H, m, 5-CH_2), 2.22-1.73 (4H, m, 3-CH_2, 4-CH_2), 1.50 (9H, s, 3 x CH_3C); (2S,1R) δ_H (Minor) 7.47-7.41 (2H, m, 2 x CH (Ar)), 7.33-7.30 (3H, m, 3 x CH (Ar)), 5.31 (1H, s, OH), 4.62-4.58 (1H, m, **CH**OH), 4.15-4.11 (1H, m, 2-H), 3.61-3.38 (2H, m, 5-CH_2), 2.22-1.73 (4H, m, 3-CH_2, 4-CH_2), 1.50 (9H, s, 3 x CH_3C); δ_C (125 MHz) (2S,1S and 2S,1R) 157.6 (C), 157.3 (C), 131.7 (4 x CH (Ar)), 128.3 (2 x CH (Ar)), 128.2 (4 x CH (Ar)), 123.0 (C), 122.8 (C), 88.7 (C), 87.7 (C), 85.0 (C), 80.7 (C), 80.5 (C), 67.8 (**CH**OH), 67.6 (**CH**OH), 63.4 (2-CH), 62.9 (2-CH), 48.4 (5-CH_2), 47.7 (5-CH_2), 29.3 (CH_2), 28.8 (CH_2), 28.5 (3 x CH_3C), 24.0 (CH_2), 23.9 (CH_2); *m/z* (APCI) 302 ($M+H^+$, 10%), 269 (50%), 228 (100%), 184 (70%); [Found: $[M+H]^+$, 302.1762. $C_{18}H_{24}NO_3$ requires: *M+H*, 302.1756].

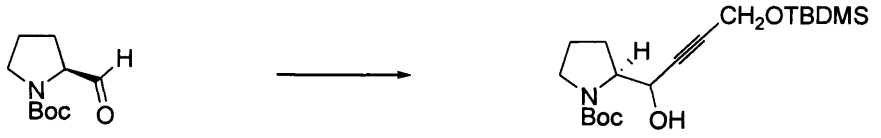
(2S,IR) and (2S,1S) 2-(1-Hydroxy-3-trimethylsilylprop-2-yn-1-yl)*N*-Boc-pyrrolidine 331d[108]



328 **331d**

According to the general procedure V, a solution of (L)-prolinal **328** (1.50 g, 7.54 mmol) in tetrahydrofuran (15 ml) was added to a solution of trimethylsilyl acetylene (1.40 ml, 9.80 mmol) and ethyl magnesium bromide (1.0 M in tetrahydrofuran, 9.80 ml, 9.80 mmol) in tetrahydrofuran (60ml) at 5 °C. This was followed by aqueous workup and column chromatograpghy (70:30 hexane-ethyl acetate) to give clean *2-propargylic pyrrolidine* **331d** as a 67:33 mixture of diastereoisomers (1S:1R) as a yellow oil (1.47 g, 66%); υ_{max}/cm^{-1} ($CHCl_3$): 3403, 2975, 2882, 2172, 1696, 1673, 1407, 1367, 1166, 1053, 843; δ_H (500 MHz) (Major, 2S,1S) 4.98 (1H, s, OH), 4.23-4.14 (1H, m, **CH**OH), 3.91-3.82 (1H, m, 2-H), 3.46-3.12 (2H, m, 5-CH_2), 2.00-1.53 (4H, m, 3-CH_2, 4-CH_2), 1.33 (9H, s, 3 x CH_3C); 0.00 (9H, s, 3 x CH_3Si); (2S,1R) δ_H (Minor, 2S,1R) 6.02 (1H, s, OH), 4.48-4.39 (1H, m, **CH**OH), 3.98-3.93 (1H, m, 2-H), 3.46-3.12 (2H, m, 5-CH_2), 2.00-1.53 (4H, m, 3-CH_2, 4-CH_2), 1.33 (9H, s, 3 x CH_3C); 0.00 (6H, s, 2 x CH_3Si); *m/z* (APCI) 298 ($M+H^+$, 5%), 242 (100%), 224 (20%), 180 (50%); [Found: $[M+H]^+$, 298.1836. $C_{15}H_{28}NO_3Si$ requires: *M+H*, 298.1838].

(2S,IR) and (2S,1S) 2-(1-Hydroxy-4-*tert*butyldimethylsilyloxybut-2-yn-1-yl)*N*-Boc-pyrrolidine 331e[171]



328 **331e**

According to the general procedure V, a solution of (L)-prolinal **328** (1.50 g, 7.54 mmol) in tetrahydrofuran (15 ml) was added to a solution of TBDMS-protected propargyl alcohol (1.28 g, 7.54 mmol) and ethyl magnesium bromide (1.0 M in tetrahydrofuran, 7.54 ml, 7.54 mmol) in tetrahydrofuran (60 ml) at 5 °C, followed by aqueous workup and column chromatograpghy (70:30 hexane-ethyl acetate) resulted in *2-propargylic pyrrolidine* **331e** as a

6:4 mixture of diastereoisomers (1S,1R) as a yellow oil (1.90 g, 68%); υ_{max}/cm^{-1} ($CHCl_3$): 3415, 2957, 2930, 2859, 2341, 1696, 1672, 1458, 1404, 1363, 1255, 1167, 1126, 1090, 837; δ_H (500 MHz) (Major, 2S,1S) 5.02 (1H, br s, OH), 4.42-4.26 (1H, br m, **CH**OH), 4.23 (2H, s, 3'-CH_2), 3.97-3.88 (1H, br m, 2-H), 3.44-3.22 (2H, m, 5-CH_2), 2.03-1.57 (4H, m, 3-CH_2, 4-CH_2), 1.36 (9H, s, 3 x CH_3C), 0.79 (9H, s, 3 x CH_3CSi), 0.00 (6H, s, 2 x CH_3Si); δ_H (Minor, 2S,1R) 5.93 (1H, d, *J* 8.1, OH), 4.42-4.26 (1H, br m, **CH**OH), 4.22 (3H, s, 3'-CH_3), 3.97-3.88 (1H, br m, 2-H), 3.44-3.22 (2H, m, 5-CH_2), 2.03-1.57 (4H, m, 3-CH_2, 4-CH_2), 1.36 (9H, s, 3 x CH_3C), 0.79 (9H, s, 3 x CH_3CSi), 0.00 (6H, s, 2 x CH_3Si); δ_C (125MHz) (2S,1R and 2S,1S) 157.6 (C=O), 157.3 (C=O), 84.2 (C), 83.7 (C), 83.1 (C), 80.6 (C), 80.5 (C), 67.2 (2 x **CH**OH), 63.0 (2-CH), 62.6 (2-CH), 51.8 (3'-CH_2), 51.7 (3'-CH_2), 48.3 (5-CH_2), 47.6 (5-CH_2), 29.0 (CH_2), 28.7 (CH_2), 28.4 (3 x CH_3C), 25.8 (3 x CH_3C), 23.9 (CH_2), 23.8 (CH_2), 18.2 (C*t*butyl), -5.1 (2 x CH_3Si), -5.2 (2 x CH_3Si); *m/z* (APCI) 370 ($M+H^+$, 10%), 337 (20%), 314 (100%); [Found: $[M+H]^+$, 370.2401. $C_{19}H_{36}NO_4Si$ requires: *M+H*, 370.2414].

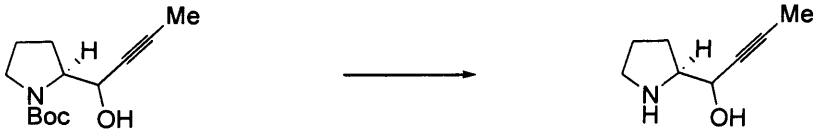
(2S,IR) and (2S,1S) 2-(1-Hydroxy-3-methoxycarbonylprop-2-yn-1-yl)*N*-Boc-pyrrolidine 331f

328 **331f**

According to the general procedure V, a solution of (L)-prolinal **328** (1.50 g, 7.54 mmol) in tetrahydrofuran (15 ml) was added to a solution of methyl propiolate (0.80 ml, 9.04 mmol) and ethyl magnesium bromide (1.0 M in tetrahydrofuran, 9.00 ml, 9.00 mmol) in tetrahydrofuran (60ml) at -30 °C, followed by aqueous workup and column chromatograpghy (70:30 hexane-ethyl acetate) resulted in clean *2-propargylic pyrrolidine* **331f** as a 73:27 mixture of diastereoisomers (1S,1R) as a yellow oil (1.10 g, 51%); υ_{max}/cm^{-1} ($CHCl_3$): 3404, 2978, 2878, 2237, 1719, 1696, 1670, 1406, 1368, 1253, 1165, 1124, 1062, 911; δ_H (500 MHz) (Major, 2S,1S) 5.46 (1H, s, OH), 4.47 (1H, br d, *J* 8.1, **CH**OH), 4.15-4.07 (1H, m, 2-H), 3.79 (3H, s, **CH_3O_2C**), 3.59-3.35 (2H, m, 5-CH_2), 2.19-1.75 (4H, m, 3-CH_2, 4-CH_2), 1.49 (9H, s, 3 x CH_3C); (2S,1R) δ_H (Minor, 2S,1R) 6.48 (1H, d, *J* 7.4, OH), 4.55-4.53 (1H, m, **CH**OH), 4.15-4.07 (1H, m, 2-H), 3.78 (3H, s, **CH_3O_2C**), 3.59-3.35 (2H, m, 5-CH_2), 2.19-1.75 (4H, m, 3-CH_2, 4-CH_2),

1.49 (9H, s, 3 x CH_3C); δ_C (125MHz) (2S,1R and 2S,1S) 157.7 (C=O), 157.4 (C=O), 153.7 (C=O), 86.7 (C), 86.2 (C), 81.1 (C), 67.3 (**CH**OH), 67.0 (**CH**OH), 62.9 (2-CH), 62.0 (2-CH), 52.8 ($\mathbf{CH_3}O_2C$), 52.7 ($\mathbf{CH_3}O_2C$), 48.3 (5-CH_2), 47.7 (5-CH_2), 29.2 (CH_2), 28.6 (CH_2), 28.4 (3 x CH_3C), 23.8 (CH_2); *m/z* (ES) [Found: $[M+Na]^+$, 306.1317. $C_{14}H_{21}NO_5Na$ requires: *M+Na*, 298.1838].

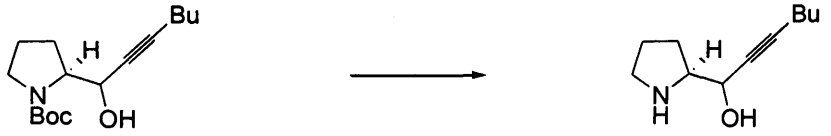
(2S,IR) and (2S,1S) 2-(1-Hydroxybut-2-yn-1-yl)pyrrolidine 333a



331a **333a**

According to the general procedure W, a solution of 2-propargylic pyrrolidine **331a** (0.55 g, 2.29 mmol) in dichloromethane (2.5 ml) was cooled to 0 °C and a solution of trifluoroacetic acid (0.71 ml, 9.17 mmol) in dichloromethane (2.83 ml) was added dropwise, and stirred for 8 h. Followed by column chromatography (85:14:1 DCM-methanol-triethylamine) resulted in *free amine* **333a** as a 63:37 mixture of diastereoisomer (1S,1R) as a pungent orange oil (0.31 g, 96%);υ_{max}/cm^{-1} ($CHCl_3$): 3292, 2966, 2929, 2873, 1624, 1540, 1411, 1355, 1143, 1036, 922; δ_H (500 MHz) (Major, 2S,1S) 4.76 (2H, br s, OH, NH), 4.02 (1H, dq, *J* 7.5, 2.2, **CH**OH), 3.20 (1H, app q, *J* 7.5, 2-H), 2.94-1.85 (2H, m, 5-CH_2), 1.89-1.51 (4H, m, 3-CH_2, 4-CH_2), 1.77 (3H, app d, *J* 2.2, 3'-CH_3); (2S,1R) δ_H (Minor, 2S,1R) 4.76 (2H, br s, OH, NH), 4.33 (1H, app *sextet*, *J* 2.1, **CH**OH), 3.25 (1H, app td, *J* 7.3, 4.3, 2-H), 3.01-2.94 (2H, m, 5-CH_2), 1.89-1.51 (4H, m, 3-CH_2, 4-CH_2), 1.78 (3H, app d, *J* 2.1, 3'-CH_3); δ_C (125MHz) (2S,1R and 2S,1S) 81.0 (C), 80.4 (C), 79.2 (C), 78.6 (C), 64.3 (CH), 63.9 (CH), 63.5 (CH), 63.1 (CH), 46.8 (5-CH_2), 46.0 (5-CH_2), 27.8 (CH_2), 26.7 (CH_2), 25.6 (CH_2), 25.2 (CH_2), 3.5 (3'-CH_3), 3.5 (3'-CH_3); *m/z* (EI) 121 (M-H_2O, 40%), 84 (100%); [Found: [M]-H_2O, 121.0894. $C_8H_{11}N$ requires: *M-H_2O*, 121.0891].

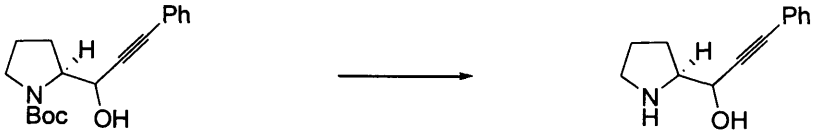
(2S,IR) and (2S,1S) 2-(1-Hydroxyhept-2-yn-1-yl)pyrrolidine 333b



331b **333b**

According to the general procedure W, a solution of 2-propargylic pyrrolidine **331b** (0.40 g, 1.42 mmol) in dichloromethane (2.00 ml) was cooled to 0°C and a solution of trifluoroacetic acid (0.43 ml, 5.67 mmol) in dichloromethane (1.77 ml) was added dropwise, and stirred for 8 h. Followed by column chromatography (85:14:1 DCM-methanol-triethylamine) resulted in *free amine* **333b** as a 56:44 mixture of diastereoisomer (1S,1R) as a pungent orange oil (0.25 g, 99%); υ_{max}/cm^{-1} ($CHCl_3$): 3294, 2960, 2934, 2873, 2243, 1459, 1431, 1380, 1328, 1300, 1140, 1037, 909; δ_H (500 MHz) (Major, 2S,1S) 5.18 (2H, br s, OH, NH), 4.10 (1H, dt, *J* 7.9, 1.6, **CH**OH), 3.25 (1H, app q, *J* 7.9, 2-H), 3.04-2.89 (2H, m, 5-CH_2), 2.15-2.11 (2H, m, 3'-CH_2), 1.92-1.53 (4H, m, 3-CH_2, 4-CH_2), 1.44-1.38 (2H, m, 4'-CH_2), 1.33 (2H, *sextet*, *J* 7.4, 5'-*CH_2)*, 0.83 (3H, t, *J* 7.4, 6'-CH_3); (2S,1R) δ_H (Minor, 2S,1R) 5.18 (2H, br s, OH, NH), 4.44 (1H, app dt, *J* 3.6, J 1.8, **CH**OH), 3.34 (1H, app td, *J* 7.1, J 4.0, 2-H), 3.04-2.89 (2H, m, 5-CH_2), 2.15-2.11 (2H, m, 3'-CH_2), 1.92-1.53 (4H, m, 3-CH_2, 4-CH_2), 1.44-1.38 (2H, m, 4'-CH_2), 1.33 (2H, *sextet*, *J* 7.4, 5'-*CH_2)*, 0.83 (3H, t, *J* 7.4, 6'-CH_3); δ_C (125MHz) (2S,1R and 2S,1S) δ_C 85.7 (C), 85.1 (C), 79.8 (C), 78.9 (C), 64.2 (**CH**OH), 64.1 (**CH**OH), 63.1 (2-CH), 63.1 (2-CH), 46.8 (5-CH_2), 45.9 (5-CH_2), 30.6 (CH_2), 30.6 (CH_2), 27.9 (CH_2), 26.5 (CH_2), 25.5 (CH_2), 25.1 (CH_2), 21.8 (CH_2), 21.8 (CH_2), 18.3 (CH_2), 18.3 (CH_2), 13.4 (6'-CH_3) 13.4 (6'-CH_3); *m/z* (EI) 163 (M-H_2O, 8%), 120 (40%); [Found: [M]-H_2O, 163.1360. $C_{11}H_{17}N$ requires: *M-H_2O*, 163.1361].

(2S,IR) and (2S,1S) 2-(Hydroxy-3-phenylprop-2-yn-1-yl)pyrrolidine 333c

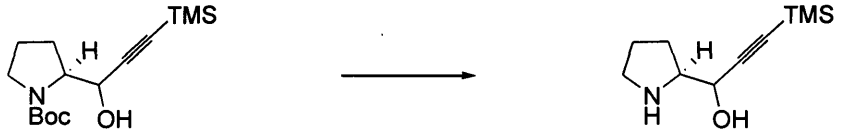


331c **333c**

According to the general procedure W, a solution of 2-propargylic pyrrolidine **331c** (0.50 g, 1.66 mmol) in dichloromethane (2.00 ml) was cooled to 0°C and a solution of trifluoroacetic acid (0.51 ml, 6.62 mmol) in dichloromethane (2.04 ml) was added dropwise, and stirred for

8 h. Followed by column chromatography (85:14:1 DCM-methanol-triethylamine) resulted in *free amine* **333c** as a 63:37 mixture of diastereoisomer (1S,1R) as a pungent orange oil (0.29 g, 87%); υ_{max}/cm^{-1} ($CHCl_3$): 3298, 3259, 2966, 2243, 1598, 1489, 1441, 1324, 1200, 1072, 909; δ_H (500 MHz) (Major, 2S,1S) 7.33-7.30 (2H, br m, 2 x CH (Ar)), 7.18-7.14 (3H, br m, 3 x CH (Ar)), 4.73 (2H, br s, OH, NH), 4.27 (1H, d, *J* 7.6, **CH**OH), 3.36-3.29 (1H, m, 2-H), 2.99-2.80 (2H, m, 5-CH_2), 1.88-1.56 (4H, m, 3-CH_2, 4-CH_2); (2S,1R) δ_H (Minor, 2S,1R) 7.33-7.30 (2H, br m, 2 x CH (Ar)), 7.18-7.14 (3H, br m, 3 x CH (Ar)), 4.73 (2H, br s, OH, NH), 4.57 (1H, d, *J* 4.3, **CH**OH), 3.36-3.29 (1H, m, 2-H), 2.99-2.80 (2H, m, 5-CH_2), 1.88-1.56 (4H, m, 3-CH_2, 4-CH_2); δ_C (125MHz) (2S,1R and 2S,1S) δ_C 131.7 (4 x CH (Ar)), 128.2 (6 x CH (Ar)), 122.8 (2 x C), 89.7 (C), 89.2 (C), 84.9 (C), 84.4 (C), 64.9 (**CH**OH), 64.2 (**CH**OH), 63.8 (2-CH), 63.1 (2-CH), 47.1 (5-CH_2), 46.2 (5-CH_2), 28.0 (CH_2), 27.1 (CH_2), 25.9 (CH_2), 25.4 (CH_2); *m/z* (APCI) 243 (M +MeCNH$^+$, 10%), 202 (M+H$^+$, 100%); [Found: [M+H]$^+$, 202.1224. $C_{13}H_{16}NO$ requires: *M+H*, 202.1232].

(2S,IR) and (2S,1S) 2-(1-Hydroxy-3-trimethylsilylprop-2-yn-1-yl)pyrrolidine 333d[108]



331d **333d**

According to the general procedure W, a solution of 2-propargylic pyrrolidine **331d** (0.35 g, 1.17 mmol) in dichloromethane (2 ml) was cooled to 0 °C and a solution of trifluoroacetic acid (0.36 ml, 4.69 mmol) in dichloromethane (1.45 ml) was added dropwise, and stirred for 8 h. Followed by column chromatography (85:14:1 DCM-methanol-triethylamine) resulted in *free amine* **333d** as a 67:33 mixture of diastereoisomers (1S,1R) as a pungent orange oil (0.21 g, 90%); υ_{max}/cm^{-1} ($CHCl_3$): 3280, 2961, 2898, 2875, 2171, 1559, 1409, 1250, 1053, 843; δ_H (500 MHz) (Major, 2S,1S) 5.06 (2H, br s, OH, NH), 4.01 (1H, d, *J* 7.7, **CH**OH), 3.19 (1H, app q, *J* 7.7, 2-H), 2.85 (2H, app ddt, *J* 19.5, 10.4, 7.0, 5-CH_2), 183-1.46 (4H, m, 3-CH_2, 4-CH_2), 0.00 (9H, s, 3 x CH_3Si); (2S,1R) δ_H (Minor, 2S,1R) 5.06 (2H, br s, OH, NH), 4.34 (1H, d, *J* 3.9, **CH**OH), 3.28 (1H, app td, *J* 7.3, 3.9, 2-H), 2.95-2.89 (2H, m, 5-CH_2), 183-1.46 (4H, m, 3-CH_2, 4-CH_2), 0.00 (9H, s, 3 x CH_3Si); δ_C (125MHz) (2S,1R and 2S,1S) δ_C 105.9 (C), 105.2 (C), 89.5 (C), 88.9 (C), 64.4 (CH), 63.7 (CH), 63.4 (CH), 62.7 (CH), 46.9 (5-CH_2), 46.0 (5-CH_2), 27.9

(CH_2), 26.6 (CH_2), 25.6 (CH_2), 25.1 (CH_2), -0.2 (3 x CH_3Si), -0.2 (3 x CH_3Si); *m/z* (ES) 198 ($M+H^+$, 100%), 180 (20%); [Found: $[M+H]^+$, 198.1313. $C_{10}H_{20}NOSi$ requires: *M+H*, 198.1314].

5-Methyl-2,3-dihydro-1*H*-pyrrolizine 335a[172]

333a **335a**

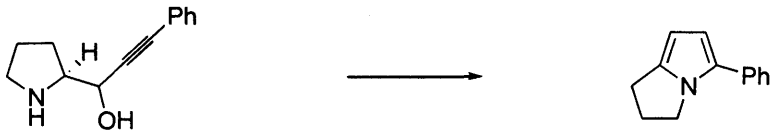
According to the general procedure O, 10% $AgNO_3.SiO_2$ (0.08 g, 0.57 mmol) was stirred with a solution of precursor **333a** (0.10 g, 0.06 mmol) as a 63:37 mixture of diastereoisomers in dichloromethane (2 ml) for 24 h to give clean *pyrrolizine* **335a** as a clear oil (0.07 g, 80%); δ_H 5.80 (1H, d, J 3.0, 3-H or 4-H), 5.61 (1H, d, *J* 3.0, 3-H or 4-H), 3.72 (2H, t, *J* 7.3, CH_2), 2.76 (2H, t, *J* 7.3, CH_2), 2.40 (2H, app *quintet*, *J* 7.3, CH_2), 2.13 (3H, s, 1'-CH_3).

5-Butyl-2,3-dihydro-1*H*-pyrrolizine 335b

333b **335b**

According to the general procedure O, 10% $AgNO_3.SiO_2$ (0.07 g, 0.04 mmol) was stirred with a solution of precursor **333b** (0.07 g, 0.38 mmol) as a 56:44 mixture of diastereoisomers in dichloromethane for 3 h gave the *pyrrolizine* **335b** as a yellow oil (0.06 g, 100%); υ_{max}/cm^{-1} ($CHCl_3$): 2959, 2931, 2874, 2861, 2253,2235, 1505, 1466, 1428, 1379, 1305, 1290, 1097, 907; (500MHz) δ_H 5.80 (1H, d, *J* 3.1, 4-H), 5.63 (1H, d, *J* 3.1, 3-H), 3.73 (2H, t, *J* 7.1, 6-CH_2), 2.74 (2H, t, *J* 7.1, 8-CH_2), 2.45 (2H, t, *J* 7.6, 1'-CH_2), 2.40 (2H, *quintet*, *J* 7.1, 7-CH_2); 1.51 (2H, *quintet*, *J* 7.6, 2'-CH_2), 1.32 (2H, *sextet*, *J* 7.6, 3'-CH_2), 0.86 (3H, t, *J* 7.6, 4'-CH_3); (125 MHz) δ_C 135.1 (C), 128 (C), 108.2 (3-CH or 4-CH), 97.9 (3-CH or 4-CH), 44.3 (6-CH_2), 31.5 (CH_2), 27.9 (CH_2), 26.6 (CH_2), 24.3 (CH_2), 22.5 (CH_2), 14.0 (4'-CH_3); *m/z* (EI) 163 (M^+, 30%), 120 (100%); [Found: $[M]^+$, 163.1361. $C_{11}H_{17}N$ requires: *M*, 163.1361].

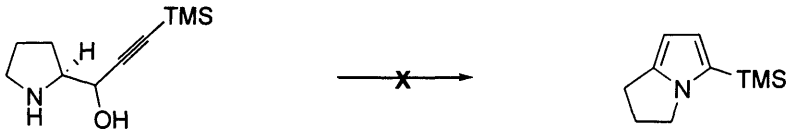
5-Phenyl-2,3-dihydro-1*H*-pyrrolizine 335c



333c **335c**

According to the general procedure O, 10% $AgNO_3.SiO_2$ (0.11 g, 0.06 mmol) was stirred with a solution of precursor **333c** (0.13 g, 0.62 mmol) as a 63:37 mixture of daistereoisomers in dichloromethane (5 ml) for 2 h to give a the *pyrrolizine* **335c** as a clear viscous oil (0.12 g, 100%); υ_{max}/cm^{-1} ($CHCl_3$): 2960, 2926, 2853, 1603, 1512, 1452, 1389, 1283, 1168, 1072, 908; (500MHz) δ_H 7.37 (2H, dd, *J* 8.2, 1.4, 2 x *o*-CH (Ar)), 7.25 (2H, t, *J* 8.2, 2 x *m*-CH (Ar)), 7.09 (1H, tt, *J* 7.4, 1.4, *p*-CH (Ar)), 6.33 (1H, d, *J* 3.4, 4-H), 5.81 (1H, d, *J* 3.4, 3-H), 4.02 (2H, t, *J* 7.1, 6-CH_2), 2.79 (2H, t, *J* 7.1, 8-CH_2), 2.41 (2H, *quintet*, *J* 7.1, 7-CH_2); (125 MHz) δ_C 139.0 (2-C), 133.9 (*i*-C), 128.7 (2 x *o*-CH (Ar)), 128.6 (5-C), 125.6 (2 x *m*-CH (Ar)), 125.6 (2 x *o*-CH (Ar)), 110.9 (4-CH), 100.1 (3-CH), 46.8 (6-CH_2), 26.8 (7-CH_2), 22.8 (8-CH_2); *m/z* (APCI) 184 ($M+H^+$, 100%); [Found: $[M+H]^+$, 184.1130. $C_{13}H_{14}N$ requires: *M+H*, 184.1126].

5-(Trimethylsilyl)-2,3-dihydro-1*H*-pyrrolizine 335d



333d **335d**

According to the general procedure O, 10% $AgNO_3.SiO_2$ (0.05 g, 0.03 mmol) was stirred with a solution of precursor **333d** (0.10 g, 0.29 mmol) as a 67:33 mixture of diastereoisomers in dichloromethane for 24 h to give predominantly starting material **333d**.

(2S,IR) and (2S,1S) 2-(1-Hydroxyprop-2-yn-1-yl)*N*-Boc-pyrrolidine 338

331d **338**

To a stirred solution of **331d** (1.00 g, 3.35 mmol) in methanol (10 ml) cooled to 0 °C solid potassium carbonate (0.07 g, 0.50 mmol) was added. The mixture was stirred for 3 h, followed by the addition of water (10 ml) and extraction with diethyl ether, then dried, filtered and evaporated to give *terminal acetylene* **338** as a yellow oil (0.61 g, 81%); υ_{max}/cm^{-1} (DCM): 3383, 3055, 2982, 2885, 2305, 1658, 1408, 1368, 1266, 1166, 1107, 1047; (2S,1S) δ_H (Major) 5.18 (1H, br d, *J* 3.2, OH), 4.20-4.16 (1H, br m, **CH**OH), 3.94-3.77 (1H, br m, 2-H), 3.43-3.17 (2H, m, 5-CH_2), 2.29 (1H, d, *J* 2.1, 3'-CH), 2.02-1.56 (4H, m, 3-CH_2, 4-CH_2), 1.32 (9H, s, 3 x CH_3C); (2S,1R) δ_H (Minor) 6.09 (1H, d, *J* 8.9, OH), 4.27 (1H, app d, *J* 8.9, **CH**OH), 3.94-3.77 (1H, br m, 2-H), 3.43-3.17 (2H, m, 5-CH_2), 2.21 (1H, d, *J* 1.9, 3'-CH_3), 2.02-1.56 (4H, m, 3-CH_2, 4-CH_2), 1.32 (9H, s, 3 x CH_3C); (2S,1R and 2S,1S) δ_C 83.4 (3'-CH), 82.4 (3'-CH), 80.9 (C), 80.7 (C), 73.2 (C), 67.1 (**CH**OH), 67.0 (**CH**OH), 63.0 (2-CH), 62.6 (2-CH), 48.4 (5-CH_2), 47.7 (5-CH_2), 29.1 (CH_2), 28.7 (CH_2), 28.4 (3 x CH_3C), 28.4 (3 x CH_3C), 23.9 (CH_2), 23.8 (CH_2); *m/z* (APCI) 226 ($M+H^+$, 40%), 211 (100%); [Found: $[M+H]^+$, 226.1451. $C_{12}H_{20}NO_3$ required: *M+H*, 226.1443].

***N*-Boc piperidine 2-methanol 327[173]**

337 **327**

To a stirred solution of piperidine 2-methanol **327** (2.00 g, 17.4 mmol) in dichloromethane (40 ml) at 0 °C triethylamine (3.20 ml, 24.3 mmol) was added dropwise, followed by the dropwise addition of *t*butyl dicarbonate (5.31 g, 22.6 mmol). The reaction was then allowed to warm to room temperature overnight. The solution was then diluted with dichloromethane (100 ml) and washed with 0.2M hydrochloric acid (3 x 20 ml), water (2 x 20 ml) and brine (20 ml). Followed by drying with sodium sulphate, filtration and evaporation to yield clean *boc-protected amine*

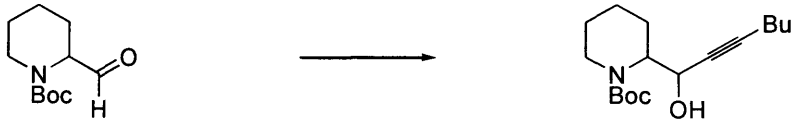
327 (3.32 g, 89%) as a yellow oil; υ_{max}/cm^{-1} (DCM): 3443, 3054, 2982, 2942, 2869, 1741, 1676, 1420, 1366, 1266, 1164, 1050; δ_H 4.23 (1H, ddt, *J* 11.1, 5.9, 2.6, 2-H), 3.90-3.85 (1H, m, OH), 3.74 (1H, dd, *J* 11.1, 9.1, **CH_A**OH), 3.54 (1H, *J* 11.1, 5.9, **CH_B**OH), 2.80 (1H, t, *J* 12.1, CH), 2.21-2.18 (1H, m, CH), 1.66-1.49 (4H, m, 2 x CH_2), 1.46 (4H, s, CH_3C), 1.42-1.34 (2H, m, CH_2), 1.39 (5H, s, CH_3C); δ_C 146.7 (C=O), 85.2 (C*t*butyl), 61.8 (CH_2OH), 52.5 (2-CH), 40.0 (CH_2), 28.4 (3 x CH_3C), 27.4 (3 x CH_3C), 25.3 (CH_2), 25.2 (CH_2), 19.6 (CH_2).

***Tert*-Butyl 2-formylpiperidine-1-carboxylate 329[173]**

327 **329**

According to the general procedure U, a solution of DMSO (2.90 ml, 40.9 mmol) in dichloromethane (10 ml) was added dropwise to a stirred solution of oxalyl chloride (1.90 ml, 22.7 mmol) in dichloromethane (45 ml) at -63 °C. After 10 min N-boc piperidine 2-methanol **327** (4.00 g, 18.6 mmol) in dichloromethane (20 ml) was added dropwise over 15 min and the reaction was stirred for a further 30 min. Quenching with triethylamine (10.60 ml, 74.36 mmol) followed by aqueous workup gave clean *aldehyde* **329** (3.67 g, 93%) as a yellow oil; δ_H 9.52 (**CH**O), 4.59-4.40 (1H, m, 2-H), 4.00-3.78 (1H, m, 6-H_A), 2.91-2.75 (1H, m, 6-H_B), 2.13-2.07 (1H, m, 3-H_A), 1.66-1.51 (5H, m, 3-H_B, 4-CH_2, 5-CH_2), 1.46 (9H, s, 3 x CH_3C).

2-(1-Hydroxyhept-2-yn-1-yl)*N*–Boc-piperidine 332a



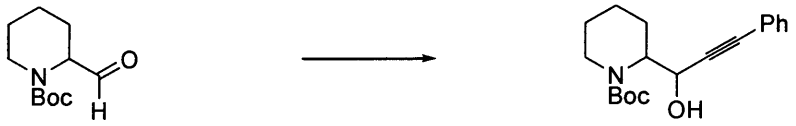
329 **332a**

According to the general procedure V, a solution of piperidine 2-aldehyde **329** (2.00 g, 9.38 mmol) in tetrahydrofuran (20 ml) was added to a solution of 1-hexyne (2.15 ml, 18.8 mmol) and ethyl magnesium bromide (1.0 M in tetrahydrofuran, 18.76 ml, 18.76 mmol) in tetrahydrofuran (80 ml) at 5 °C, followed by aqueous workup and column chromatography (70:30 hexane-ethyl acetate) resulted in *2-propargylic piperidine* **332a** (2.00 g, 72%) as a 85:15

mixture of diastereoisomers as a yellow oil; υ_{max}/cm^{-1} (DCM): 3418, 3053, 2934, 2867, 2246, 1739, 1674, 1422, 1366, 1276, 1166, 1032; δ_H 4.62 (1H, app d, *J* 6.8, **CH**OH), 4.20-4.15 (1H, m, 2-H), 4.06-3.95 (1H, m, 6-H_A), 3.05-2.93 (1H, m, 6-H_B), 2.20 (2H, td, *J* 7.0, 1.9, 3'-CH_2), 2.06-1.95 (2H, m, OH, 3-H_A), 1.74-1.57 (6H, m, 4-CH_2, 5-CH_2, 3-H_B), 1.54-1.46 (2H, m, 4'-CH_2), 1.49 (9H, s, 3 x CH_3C), 1.40 (2H, *sextet*, *J* 7.0, 5'-CH_2), 0.92 (3H, t, *J* 7.0, 6'-CH_3); δ_C 155.5 (C=O), 86.1 (C), 79.9 (C), 79.4 (C), 62.6 (**CH**OH), 55.4 (2-CH), 40.2 (6-CH_2), 30.7 (CH_2), 28.4 (3 x CH_3C), 24.8 (CH_2), 24.3 (CH_2), 22.9 (CH_2), 19.2 (CH_2), 18.5 (CH_2), 13.5 (6'-CH_3); *m/z* (APCI) 296 ($M+H^+$, 10%), 263 (100%), [Found: $[M+H]^+$, 296.2227. $C_{17}H_{30}NO_3$ requires: *M+H*, 296.2226].

δ_H distinguishable minor peak (1S,2R and 1R,2S) 4.52-4.46 (1H, m, **CH**OH).

2-(Hydroxy-3-phenylprop-2-yn-1-yl)*N*-Boc-piperidine 332b

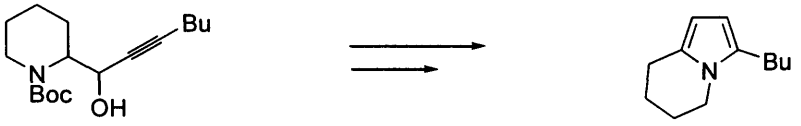


329 **332b**

According to the general procedure V, a solution of piperidine 2-aldehyde **329** (2.00 g, 9.38 mmol) in tetrahydrofuran (20 ml) was added to a solution of phenylacetylene (1.10 ml, 10.3 mmol) and ethyl magnesium bromide (1.0M in tetrahydrofuran, 10.32 ml, 10.32 mmol) in tetrahydrofuran (80 ml) at 5 °C, followed by aqueous workup and column chromatograpghy (70:30 hexane-ethyl acetate) resulted in *2-propargylic piperidine* **332b** (2.01 g, 68%) as a 76:24 mixture of diastereoisomer as a yellow solid; m.p. 91-92 °C; υ_{max}/cm^{-1} (DCM): 3396, 3054, 2987, 2305, 1735, 1681, 1421, 1266, 1162, 1038; δ_H 7.47-7.42 (2H, m, 2 x CH (Ar)), 7.35-7.30 (3H, m, 3 x CH (Ar)), 4.88-4.82 (1H, m, **CH**OH), 4.47-4.31 (1H, m, 2-H), 4.09-3.96 (1H, m, 6-H_A), 3.13-2.99 (1H, m, 6-H_B), 2.17-2.02 (2H, m, OH, 3-H_A), 1.75-1.62 (5H, m, 4-CH_2, 5-CH_2, 3-H_B), 1.50 (3H, s, CH_3C), 1.44 (6H, s, 2 x CH_3C); δ_C 155.6 (C=O), 131.7 (2 x CH (Ar)), 128.2 (3 x CH (Ar)), 122.8 (C), 91.3 (C), 80.2 (C), 79.6 (C), 63.0 (**CH**OH), 55.5 (2-CH), 40.4 (6-CH_2), 28.4 (3 x CH_3C), 24.8 (CH_2), 24.5 (CH_2), 19.4 (CH_2); *m/z* (APCI) 316 ($M+H^+$, 50%), 283 (80%), 242 (100%); [Found: $[M+H]^+$, 316.1901. $C_{19}H_{26}NO_3$ requires: *M+H*, 316.1913].

δ_H distinguishable minor peaks (1S,2R and 1R,2S) 4.83-4.78 (1H, m, **CH**OH).

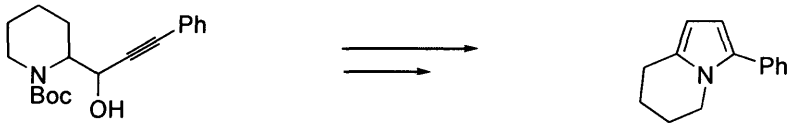
3-butyl-5,6,7,8-tetrahydroindolizine 336a



332a **336a**

According to the general procedure W, a solution of 2-propargylic piperidine **332a** (0.35 g, 1.18 mmol) in dichloromethane (2 ml) was cooled to 0 °C and a solution of trifluoroacetic acid (0.36 ml, 4.73 mmol) in dichloromethane (1.46 ml) was added dropwise, and stirred for 8 h. The reaction then underwent a typical workup procedure for boc-deprotection to give crude free amine (0.18 g, 80% crude) as a yellow oil and the crude product was used directly in the next step. Using the general procedure E, 10% $AgNO_3.SiO_2$ (0.15 g, 0.09 mmol) was stirred with a solution of the crude free amine **334a** (0.18 g, 0.92 mmol) in dichloromethane (2 ml) for 4 h to give crude product that was then purified by column chromatography using 7% ethyl acetate in hexane to give clean *indolizine* **336a** (0.14 g, 86%) as a yellow oil; υ_{max}/cm^{-1} ($CHCl_3$): 2934, 2862, 2234, 1508, 1449, 1424, 1334, 1290, 1253, 1159, 909; δ_H 5.75 (1H, d, *J* 3.4, 3-H or 4-H), 5.68 (1H, d, *J* 3.4, 3-H or 4-H), 3.69 (2H, t, *J* 6.2, 6-CH_2), 2.69 (2H, t, *J* 6.2, 9-CH_2), 2.41 (2H, t, *J* 7.6, 1'-CH_2), 1.86 (2H, dtd, *J* 8.8, 6.2, 2.6, 7-CH_2 or 8-CH_2), 1.70 (2H, dtd, *J* 8.8, 6.2, 2.6, 7-CH_2 or 8-CH_2), 1.52 (2H, *quintet*, *J* 7.6, 2'-CH_2), 1.34 (2H, *sextet*, *J* 7.6, 3'-CH_2), 0.86 (3H, t, *J* 7.6, 4'-CH_3); δ_C 131.6 (C), 128.2 (C), 104.0 (3-CH or 4-CH), 102.9 (3-CH or 4-CH), 42.7 (6-CH_2), 30.8 (CH_2), 25.9 (CH_2), 23.8 (CH_2), 23.7 (CH_2), 22.7 (CH_2), 21.1 (CH_2), 14.0 (4'-CH_3); *m/z* (APCI) 178 ($M+H^+$, 100%); [Found: $[M+H]^+$, 178.1589. $C_{12}H_{20}N$ requires: *M+H*, 178.1596].

3-Phenyl-5,6,7,8-tetrahydroindolizine 336b[174]



332b **336b**

According to the general procedure W, a solution of 2-propargylic piperidine **332b** (0.30 g, 0.95 mmol) in dichloromethane (3 ml) was cooled to 0 °C and a solution of trifluoroacetic acid (0.29 ml, 3.80 mmol) in dichloromethane (1.17 ml) was added dropwise, and stirred for 8 h. The

reaction then underwent a typical workup procedure for boc-deprotection to give crude free amine (0.20 g, 98% crude) as a brown solid and the crude product was used directly in the next step. Using the general procedure O, 10% $AgNO_3.SiO_2$ (0.16 g, 0.09 mmol) was stirred with a solution of the crude free amine **334b** (0.20 g, 0.93 mmol) in dichloromethane (2 ml) for 4 h to give crude product that was then purified by column chromatography using 7% ethyl acetate in hexane to give clean *indolizine* **336b** (0.13 g, 71%) as a yellow oil; υ_{max}/cm^{-1} ($CHCl_3$): 2948, 2872, 2253, 2238, 1601, 1510, 1479, 1449, 1334, 1226, 1027, 908; δ_H 7.56-7.49 (4H, m, 2 x *o*-CHAr, 2 x *m*-CH (Ar)), 7.39 (1H, tt, *J* 7.2,.1.4, *p*-CH (Ar)), 6.40 (1H, d, *J* 3.4, 4-H), 6.09 (1H, d, *J* 3.4, 3-H), 4.08 (2H, t, *J* 6.1, 6-CH_2), 3.03 (2H, t, *J* 6.1, 9-CH_2), 2.07-2.01 (2H, m, 7-CH_2), 2.00-1.95 (2H, m, 8-CH_2); δ_C 133.7 (C), 132.5 (C), 130.5 (C), 128.6 (2 x CH (Ar)), 128.3 (2 x CH (Ar)), 126.3 (CH (Ar)), 108.0 (3-CH or 4-CH), 104.7 (3-CH or 4-CH), 44.8 (6-CH_2), 24.1 (CH_2), 23.8 (CH_2), 21.0 (CH_2); *m/z* (APCI) 198 ($M+H^+$, 100%); [Found: $[M+H]^+$, 198.1286. $C_{14}H_{16}N$ requires: *M+H*, 198.1283].

Methyl 2, 2-dimethoxyethylcarbamate 394[175]

393 **394**

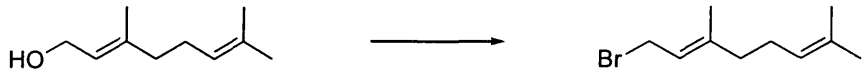
To a solution of amino acetaldehyde dimethyl acetal **393** (20.72 ml, 190.2 mmol) in dichloromethane (500 ml) at 0 °C triethylamine (58.30 ml, 418.5 mmol) was added dropwise, followed by the dropwise addition of methyl chloroformate (17.64 ml, 228.3 mmol). The solution was allowed to warm to room temperature overnight. The solution was then diluted by the addition of dichloromethane and the organics were washed with 0.2M hydrochloric acid (3 x 50 ml), water (4 x 50 ml) and brine (20 x 50 ml). The organics were then dried over sodium sulphate, filtered and evaporated to give *clean carbamate* **394** as an orange oil (29.85 g, 96%); υ_{max}/cm^{-1} (DCM): 3355, 3057, 2992, 2949, 2837, 1717, 1538, 1464, 1367, 1267, 1194, 1131, 1065; δ_H 4.92 (1H, br s, NH), 4.31 (1H, app t, *J* 5.4, **CH**O_2), 3.61 (3H, br s, **C**H_3O_2C), 3.33 (6H, s, 2 x O**C**H_3), 3.25 (2H, app td, *J* 5.4, 2.1, **C**H_2N).

Methyl (1, 3-dithian-2-yl)ethylcarbamate 395[124]

394 **395**

To a stirred solution of carbamate **394** (16.32 g, 100.0 mmol) in dichloromethane (200 ml) at 0 °C propanedithiol (10.04 ml, 100.0 mmol) was added dropwise followed by the addition of boron trifluoride diethyl ethearate (24.61 ml, 200.1 mmol). The mixture was allowed to stir for 6 h before warming to room temperature. The mixture was then poured into a 2M potassium hydroxide solution (400 ml) and the organic layer was separated. The organic layer was washed with brine (3 x 100 ml), dried with sodium sulphate, filtered and evaporated to give *dithiane* **395** (18.15 g, 88%) as a chalky white solid; m.p. 73-75 °C (lit. m.p.[9] 79-80 °C); υ_{max}/cm^{-1} (DCM): 3441, 3054, 2987, 2305, 1724, 1518, 1422, 1266, 1072; δ_H 5.49 (1H, br s, NH), 3.95 (1H, t, *J* 7.1, **CH**S_2), 3.57 (3H, s, **C**H_3O_2C), 3.46 (2H, t, *J* 6.4, **C**H_2N), 2.81 (2H, ddd, *J* 14.0, 7.0, 2.4, 2 x S**C**H_{Ax}), 2.66 (2H, td, *J* 9.6, 2.4, 2 x S**C**H_{Eq}), 2.01-1.94 (1H, m, SCH_2**C**H_A), 1.87-1.79 (1H, m, SCH_2**C**H_B); δ_C 156.9 (C=O), 52.2 (**C**H_3O_2C), 45.4 (**C**HS_2), 44.3 (CH_2N), 28.0 (2x CH_2), 25.6 (CH_2).

(E)-1-Bromo-3, 7-dimethylocta-2, 6-diene 396

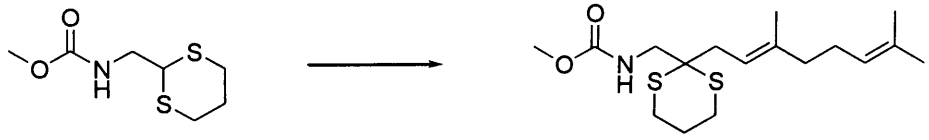


380 **396**

A solution of geraniol **380** (5.60 ml, 32.4 mmol) in dichloromethane (80 ml) was stirred at -30 °C before the addition of triphenylphosphine (9.35 g, 35.7 mmol). This was followed by the addition of *N*-bromo-succinimide (6.35 g, 35.7 mmol) in portions over 20 min and followed by allowing to warm to room temperature overnight. The solution was then evaporated and the triphenylphosphine oxide by-product was separated by the addition of petrol (150 ml) at 0 °C. The resulting mixture was filtered and the filtrate was washed with water (3 x 50 ml), followed by drying, filtering and evaporating to give the *bromide* **396** as a yellow oil (6.00g, 86%); δ_H 5.46 (1H, app tq, *J* 8.5, 1.2, 2-H), 5.03-4.98 (1H, m, 6-H), 3.96 (2H, d, *J* 8.5, 1-CH_2), 2.08-1.96

(4H, m, 4-CH_2, 5-CH_2), 1.66 (3H, d, *J* 1.2, 3*a*-CH_3), 1.62 (3H, br s, 7*a*-CH_3), 1.53 (3H, s, 7*b*-CH_3).

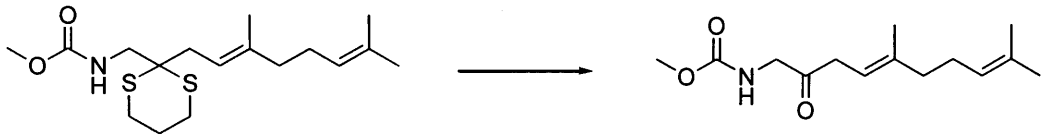
(E)-Methyl (2-(3, 7-dimethylocta-2, 6-dienyl)-1, 3-dithiane-2-yl)methylcarbamate 397



395 **397**

To a stirred solution of dithiane **395** (2.86 g, 13.8 mmol) in tetrahydrofuran (75 ml) at -40 °C was added 2.5M solution of *n*-BuLi in hexanes (11.40 ml, 28.55 mmol). The resulting solution was stirred for 2 h with the temperature maintained at -40 to -20 °C. The solution was then cooled to -78 °C and DMPU (6.65 ml, 55.3 mmol) was added dropwise and the solution was stirred for a further 1 h at this temperature. The solution was then carefully transferred by cannula to a solution of the bromide **380** (2.00 g, 9.21 mmol) in tetrahydrofuran (40 ml) at -78 °C. The reaction mixture was stirred at this temperature for 4 h followed by warming slowly to -20 °C and stirring for 12 h. The reaction mixture was then poured into ice water (200 ml) and the aqueous layer was extracted with ether (5 x 50 ml). The combined organics were dried over sodium sulphate then filtered and evaporated to give the crude dithiane. The crude mixture was separated by column chromatography using 15 % ethyl acetate in hexane as eluent to give clean *dithiane* **397** (2.81 g, 89%) as a pungent viscous orange oil; υ_{max}/cm^{-1} (neat): 3353, 2913, 2856, 1729, 1511, 1447, 1375, 1244, 1194, 1109, 1061, 908; δ_H 5.28 (1H, app t, *J* 6.9, 2-H), 5.11-5.07 (1H, m, 6-H), 5.02 (1H, s, NH), 3.69 (3H, s, $\mathbf{CH_3O_2C}$), 3.66 (2H, app d, *J* 6.0, CH_2N), 3.01 (2H, app t, *J* 12.9, 2 x $\mathbf{SCH_{Ax}}$), 2.66 (2H, dq, *J* 15.0, 3.2, 2 x $\mathbf{SCH_{Eq}}$), 2.45 (2H, d, *J* 7.2, 1-CH_2), 2.13-2.03 (6H, m, $\mathbf{CH_2}(CH_2)_2S$, 4 and 5-CH_2), 1.68 (3H, s, 3-Me), 1.64 (3H, s, 7-Me), 1.61 (3H, s, 7-Me); δ_C 157.0 (C=O), 139.5 (3-C), 131.5 (7-C), 124.1 (6-CH), 117.1 (2-CH), 53.2 ($\mathbf{CS_2}$), 52.2 ($\mathbf{CH_3}CO_2C$), 45.1 (CH_2N), 39.9 ($\mathbf{CH_2}(CH_2)_2S$), 37.0 (1-CH_2), 26.5 (2 x $\mathbf{CH_2}S$), 26.1 (4 or 5-CH_2), 25.7 (7-Me), 24.93 (4 or 5-CH_2), 17.7 (7-Me), 16.5 (3-Me); *m/z* (APCI) 344 ($M+H^+$, 80%), 170 (45%); [Found: $[M+H]^+$, 344.1735. $C_{17}H_{30}NO_2S_2$ required: *M+H*, 344.1718].

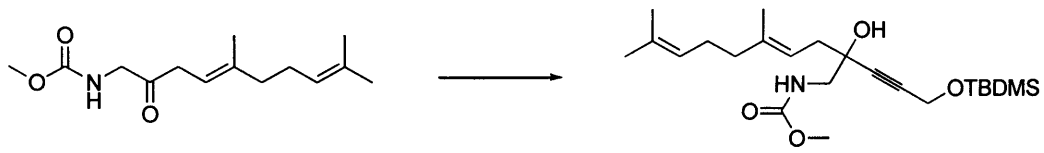
(E)-Methyl 5, 9-dimethyl-2-oxadeca-4, 8—dienylcarbamate 398



397 **398**

To a vigorously stirred solution of silver nitrate (2.22 g, 13.1 mmol) and *N*-chlorosuccinimide (1.75 g, 13.1 mmol) in a mixture of acetonitrile (160 ml) and water (40 ml) a solution of dithiane **397** (1.00 g, 2.91 mmol) in acetonitrile (60 ml) was added in one portion. The mixture was then stirred for 3 min as the solution went from a clear to a milky white solution. After 3 min the solution was quenched by the addition of aqueous brine (130 ml) and the resulting mixture was passed through a plug of celite. This was followed by passing brine (150 ml), water (150 ml) and ethyl acetate (300 ml) through the celite. The resulting biphasic mixture was separated and the organic layer was washed with 10% aqueous sodium sulphite solution (50 ml), water (4 x 50 ml) and brine (2 x 50 ml) before drying with sodium sulphate, followed by filtration and evaporation to give clean *ketone* **398** (0.71 g, 96%) as a yellow oil; υ_{max}/cm^{-1} (neat): 3361, 2966, 2924, 2856, 1717, 1520, 1452, 1356, 1257, 1195, 1107, 1045, 915; δ_H 5.37 (1H, br s, NH), 5.22 (1H, app tq, *J* 7.3, 1.2, 4-H), 5.00 (1H, app tt, *J* 6.8, 1.2, 8-H), 4.03 (2H, d, *J* 4.8, 1-CH_2), 3.61 (3H, s, $\mathbf{CH_3}CO_2C$), 3.09 (2H, d, *J* 7.3, 3-CH_2), 2.05-1.96 (4H, m, 6 and 7-CH_2), 1.61 (3H, app d, *J* 1.2, 5-Me), 1.57 (3H, s, 9-Me), 1.53 (3H, s, 9-Me); δ_C 203.9 (2-C=O), 156.8 (C=O), 140.7 (5 or 9-C), 131.8 (5 or 9-C), 123.8 (8-CH), 114.4 (4-CH), 52.3 ($\mathbf{CH_3}CO_2C$), 50.0 (1-CH_2), 40.1 (3-CH_2), 39.6 (6 or 7-CH_2), 26.4 (6 or 7-CH_2), 25.6 (5-Me), 17.7 (9-Me), 16.4 (9-Me); *m/z* (EI) 253 (M^+, 5%), 184 (20%), 88 (100%); [Found: $[M]^+$, 253.1686. $C_{14}H_{23}NO_3$ requires: *M*, 253.1678].

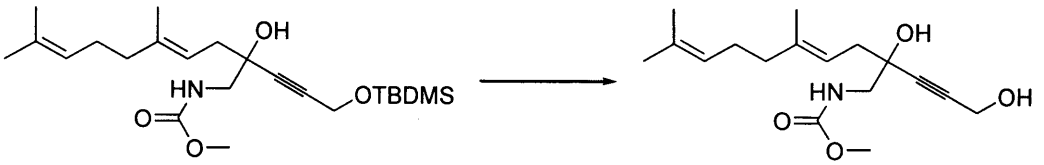
(E)-Methyl-2-(3-(*tert*-butyldimethylsilyloxy)prop-1-ynyl)-2-hydroxy-5,9-dimethyldeca-4, 8-dienylcarbamate 399



398 **399**

A solution ethyl magnesium bromide (1.0 M in tetrahydrofuran, 6.23 ml, 6.23 mmol) was added dropwise to a stirred solution of TBDMS-protected propargyl alcohol **389** (1.06 g, 6.23 mmol) in tetrahydrofuran (18 ml) at -15 °C and the solution was allowed to stir for 0.75 h. This was followed by the dropwise addition of ketone **398** (0.75 g, 2.96 mmol) in tetrahydrofuran (15 ml) at -15 °C. The solution was allowed to stir maintaining the temperature for 12 h. The solution was then quenched by the dropwise addition of glacial acetic acid (0.36 ml, 6.23 mmol) and the solution was evaporated. The resulting residue was dissolved in ethyl acetate (30 ml) and washed with aqueous ammonium chloride (10 ml), water (2 x 20 ml) and brine (10 ml). The solution was then dried over sodium sulphate, filtered and evaporated. The residue was dissolved in dichloromethane and passed through a plug of silica using pure hexane to pure ethyl acetate as eluent to give a 2:1 mixture of *desired alcohol* **399** and starting *ketone* **398** as a yellow oil (0.92 g, 49% crude yield); δ_H 5.21-5.15 (1H, m, 4 or 8-H), 4.99-4.91 (2H, br m, 4 or 8-H and NH), 4.22 (2H, app s, **CH_2O**), 3.57 (3H, s, **CH_3CO_2C**), 3.29-3.25 (2H, m, 1-CH_2), 2.33 (1H, dd, *J* 14.1, *J* 8.5, 3-H_A), 2.24 (1H, dd, *J* 14.4, *J* 7.2, 3-H_B), 2.01-1.94 (4H, m, 6 and 7-CH_2), 1.56 (3H, s, 5-Me), 1.51 (3H, s, 9-Me), 1.48 (3H, s, 9-Me), 0.79 (9H, s, 3 x CH_3CSi), 0.00 (6H, s, 2 x CH_3Si).

(E)-Methyl 2-hydroxy-2-(3-hydroxyprop-1-ynyl)-5,9-dimethyldeca-4,8-dienylcarbamate 401

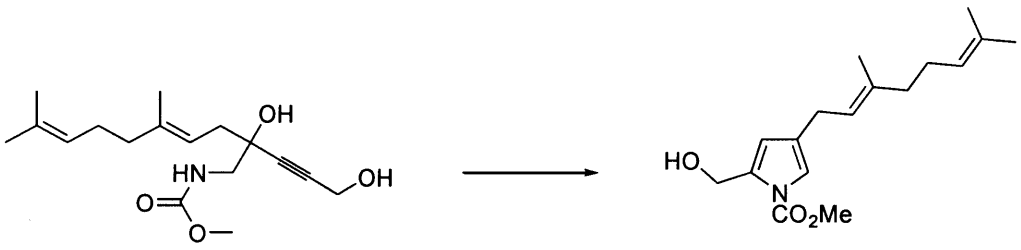


399 **401**

To a stirred solution of the crude tertiary alcohol **399** (0.70 g, 1.65 mmol) in dichloromethane (7 ml) at 0 °C a solution of tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 1.65 ml,

1.65 mmol) was added dropwise. The solution was allowed to warm to room temperature overnight and the solution was then evaporated. The crude mixture was separated using column chromatography (30-100% ethyl acetate in hexane) to give the *diol* **401** (0.28g, 54%) as a yellow viscous oil; δ_H 5.46 (1H, app t, *J* 6.0, 4 or 8-H), 5.20 (1H, app t, *J* 7.2, 4 or 8-H), 5.02-4.97 (1H, br s, NH), 4.17 (2H, br s, **CH$_2$**OH), 3.60 (5H, br s, **CH$_3$**CO$_2$C and 2 x OH), 3.37-3.22 (2H, m, 1-CH$_2$), 2.37-2.26 (2H, m, 3-CH$_2$), 2.04-1.94 (4H, m, 6 and 7-CH$_2$), 1.59 (3H, s, 5-Me), 1.54 (3H, s, 9-Me), 1.51 (3H, s, 9-Me); δ_C 158.1 (C=O), 140.2 (5 or 9-C), 131.7 (5 or 9-C), 124.1 (4 or 8-CH), 117.7 (4 or 8-CH), 86.5 (C≡C), 83.4 (C≡C), 70.9 (2-C), 52.5 (**CH$_3$**CO$_2$C), 50.7 (**CH$_2$**OH), 49.9 (1-CH$_2$), 39.9 (CH$_2$), 38.1 (CH$_2$), 26.5 (CH$_2$), 25.7 (5-Me), 17.7 (9-Me), 16.4 (9-Me); *m/z* (ES) 348 (M+K$^+$, 50%), 332 (M+Na$^+$, 100%), 310 (M+H$^+$, 50%); [Found: [M+H]$^+$, 310.2018. $C_{17}H_{28}NO_4$ requires: *M+H*, 310.2018].

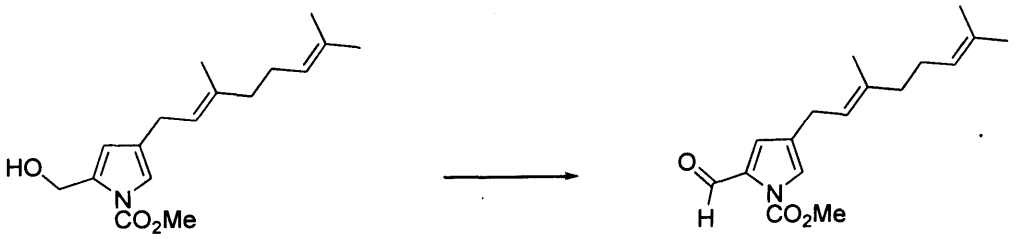
(E)-Methyl 4-(3, 7-dimethylocta-2, 6-dienyl)-2-(hydroxymethyl)-1*H*-pyrrole-1-carboxylate 402



401 **402**

According to the general procedure O, 10% $AgNO_3.SiO_2$ (0.07 g, 0.04 mmol) was stirred with a solution of diol **401** (0.12 g, 0.38 mmol) in dichloromethane (2 ml) for 3 h to give clean *pyrrole* **402** as an orange oil (0.11 g, 100%); υ_{max}/cm^{-1} ($CHCl_3$): 3408, 2962, 2919, 2854, 1733, 1444, 1349, 1280, 1252, 1100; δ_H 6.95 (1H, s, 5-H), 6.09 (1H, s, 3-H), 5.29 (1H, t, *J* 6.7, 2'-H), 5.12 (1H, t, *J* 6.8, 6'-H), 4.64 (2H, s, **CH$_2$**OH), 3.97 (3H, s, **CH$_3$**CO$_2$C), 3.70 (1H, br s, OH), 3.10 (2H, d, *J* 7.2, 1'-CH$_2$), 2.16-2.02 (4H, m, 4' and 5'-CH$_2$), 1.71 (3H, s, 3' or 7'-Me), 1.67 (3H, s, 3' or 7'-Me), 1.63 (3H, s, 3' or 7'-Me); δ_H 151.9 (C=O), 136.4 (C), 135.1 (C), 131.5 (C), 126.4 (C), 124.2 (CH), 121.9 (CH), 118.0 (CH), 115.3 (CH), 57.6 (**CH$_2$**OH), 54.1 (**CH$_3$**O$_2$C), 39.6 (1'-CH$_2$), 26.5 (4' or 5'-CH$_2$), 25.7 (CH$_3$), 25.3 (4' or 5'-CH$_2$), 17.7 (CH$_3$), 16.0 (CH$_3$); *m/z* (APCI) 274 (M-H$_2$O, 100%); [Found: [M]-H$_2$O, 274.1811 $C_{17}H_{24}NO_2$ requires: *M-H$_2$O*, 274.1807].

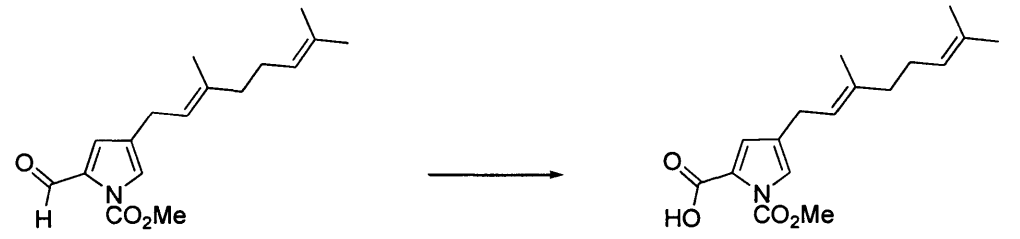
(E)-Methyl 4-(3, 7-dimethylocta-2, 6-dienyl)-2-formyl-1*H*-pyrrole-1-carboxylate 408



402 **408**

A solution of pyrrole-2-methanol **402** (0.05g, 0.17 mmol) and activated manganese dioxide (0.30 g, 3.44 mmol) in hexane (8 ml) was stirred for 3 h. The solution was then filtered and evaporated to give the *pyrrole-2-aldehyde* **408** (0.05 g, 100%) as a yellow oil; υ_{max}/cm^{-1} ($CHCl_3$): 2958, 2923, 2854, 1756, 1721, 1444, 1353, 1255, 1138, 1104; δ_H 10.24 (1H, s, CHO), 7.14 (1H, s, 5-H), 5.20 (1H, t, *J* 7.2, 2' or 6'-H), 5.02 (1H, t, *J* 7.3, 2' or 6'-H), 7.00 (1H, s, 3-H), 3.95 (3H, s, $\mathbf{CH_3}CO_2C$), 3.08 (2H, d, *J* 7.3, 1'-CH_2), 2.07-1.95 (4H, m, 4' and 5'-CH_2), 1.62 (3H, s, 3' or 7'-Me), 1.59 (3H, s, 3' or 7'-Me), 1.54 (3H, s, 3' or 7'-Me); *m/z* (APCI) 290 ($M+H^+$, 10%), 115 (100%); [Found: $[M+H]^+$, 290.1762. $C_{17}H_{24}NO_3$ requires: *M+H*, 290.1756].

(E)-4-(3, 7-Dimethylocta-2, 6-dienyl)-1-(methoxycarbonyl)-1*H*-pyrrole-2-carboxylic acid 410

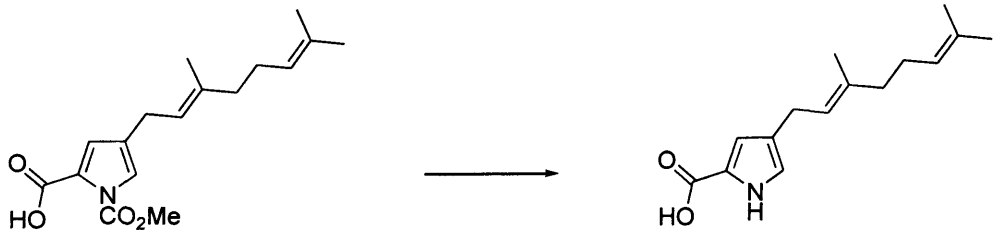


408 **410**

According to a reported procedure,[129] a solution of sodium chlorite (0.02 g, 0.26 mmol) and potassium dihydrogen phosphate (0.04 g, 0.30 mmol) in water (0.5 ml) was added dropwise to a stirred solution of aldehyde **408** (0.05 g, 0.17 mmol) and 2-methyl-but-2-ene (0.09 ml) in *t*-butanol (2 ml) at 0 °C and the solution was allowed to warm to room temperature overnight. The *tert*-butanol was evaporated and water (5 ml) was added, followed by the addition of a few drops of 2M hydrochloric acid. The aqueous layer was then extracted with dichloromethane (4 x 10 ml) and the combined extracts dried over sodium sulphate, filtered and evaporated to give

the *pyrrole-2-carboxylic acid* **410** as a yellow oil (0.04 g, 80%). Purification was deemed unnecessary as the product was clean. υ_{max}/cm^{-1} ($CHCl_3$): 3367, 2962, 2922, 2854, 1755, 1709, 1443, 1373, 1337, 1260, 1073, 1018; δ_H 7.21 (1H, s, 3-H or 5-H), 7.12 (1H, s, 3-H or 5-H), 5.18 (1H, t, *J* 7.3, 2'-H), 5.02 (1H, t, *J* 6.8, 6'-H), 4.00 ($\mathbf{CH_3O_2C}$), 3.06 (2H, d, *J* 7.3, 1'-CH_2), 2.07-1.94 (4H, m, 4' and 5'-CH_2), 1.62 (3H, s, 3' or 7'-Me), 1.59 (3H, s, 3' or 7'-Me), 1.54 (3H, s, 3' or 7'-Me); δ_C 159.6 (C=O), 152.2 (C=O), 137.5 (C), 131.7 (C), 129.0 (2 x CH (Ar)), 127.5 (C), 126.4 (C), 124.0 (CH (Ar)), 120.7 (CH (Ar)), 55.7 ($\mathbf{CH_3CO_2C}$), 39.6 (1'-CH_2), 26.5 (4' or 5'-CH_2), 25.7 (CH_3), 25.0 (4' or 5'-CH_2), 17.7 (CH_3), 16.1 (CH_3).

(E)-4-(3, 7-Dimethylocta-2, 6-dienyl)-1*H*-pyrrole-2-carboxylic acid (Pyrrolostatin) 379[123]



410 **379**

According to the known procedure,[123] to a solution of lithium hydroxide (0.007 g, 0.30 mmol) in water (0.2 ml) a solution of pyrrole **410** (0.04 g, 0.12 mmol) in dioxane (0.2 ml) was added dropwise. The mixture was then warmed to 40 °C under nitrogen overnight. The solution was then allowed to cool to room temperature and buffer solution (pH 3.5, 3 ml) was added dropwise. This was followed by the addition of diethyl ether (10 ml) and saturated brine (5 ml). The separated aqueous layer was then extracted with ether (3 x 10 ml) and the combined organic solutions were washed with water (2 x 10 ml) and brine (10 ml), then dried over sodium sulphate, filtered and evaporated to give *pyrrolostatin* **379** as a dark yellow solid (0.02 g, 70%); m.p. 110-112 °C (lit m.p.[123] 117-119 °C); δ_H 8.97 (1H, br s, OH), 6.80 (1H, s, 3 or 5-H), 6.72 (1H, s, 3 or 5-H), 5.26 (1H, m, 2' or 6'-H), 5.03 (1H, m, 2' or 6'-H), 3.13 (2H, d, *J* 7.2, 1'-CH_2), 2.07-1.94 (4H, m, 4' and 5'-CH_2), 1.62 (1H, s, 3' or 7'-Me), 1.61(1H, s, 3' or 7'-Me), 1.54 (1H, s, 3' or 7'-Me); δ_C 165.2 (C=O), 136.0 (C), 131.5 (C), 126.4 (C), 124.3 (CH), 122.8 (CH), 121.4 (C), 116.8 (CH), 39.6 (1'-CH_2), 26.6 (4' or 5'-CH_2), 25.8 (CH_3), 25.3 (4' or 5'-CH_2), 17.7 (CH_3), 16.0 (CH_3). *Data given matches the data reported for pyrrolostatin in the literature.*[123]

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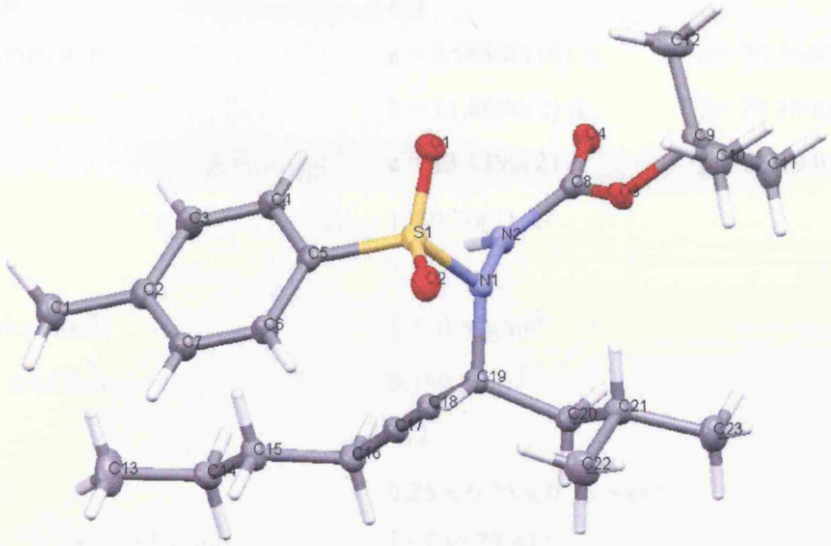
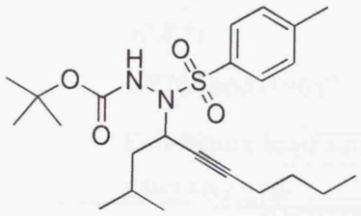
Appendix

X-ray Data

X-ray crystal structure of hydrazine **219a**





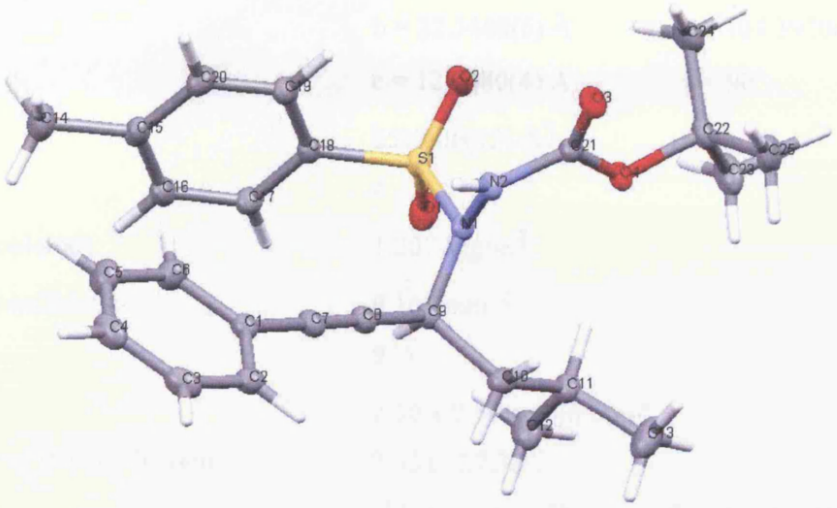
$C_{23}H_{36}N_2O_4S$

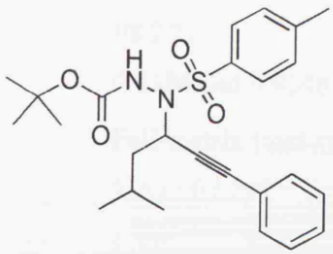
CCDC number 783430

Table 1. Crystal data and structure refinement for dwk0913.

Identification code	dwk0913	
Empirical formula	C23 H36 N2 O4 S	
Formula weight	436.60	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.58800(10) Å	α= 70.3660(10)°.
	b = 11.8690(2) Å	β= 79.3600(10)°.
	c = 13.1390(2) Å	γ = 86.1940(10)°.
Volume	1239.70(3) $Å^3$	
Z	2	
Density (calculated)	1.170 Mg/m^3	
Absorption coefficient	0.159 mm^{-1}	
F(000)	472	
Crystal size	0.25 x 0.25 x 0.15 mm^3	
Theta range for data collection	3.02 to 27.44°.	
Index ranges	-11<=h<=11, -15<=k<=15, -15<=l<=17	
Reflections collected	8998	
Independent reflections	5592 [R(int) = 0.0317]	
Completeness to theta = 27.44°	98.8 %	
Max. and min. transmission	0.9765 and 0.9612	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5592 / 0 / 278	
Goodness-of-fit on F^2	1.030	
Final R indices [I>2sigma(I)]	R1 = 0.0467, wR2 = 0.1174	
R indices (all data)	R1 = 0.0592, wR2 = 0.1257	
Extinction coefficient	0.092(8)	
Largest diff. peak and hole	0.332 and -0.378 $e.Å^{-3}$	

X-ray crystal structure of hydrazine **219b**





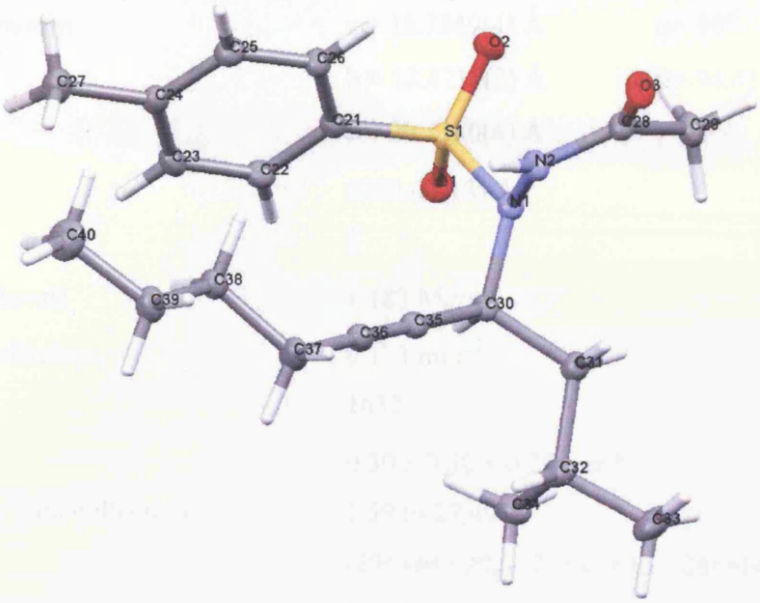
$C_{25}H_{32}N_2O_4S$

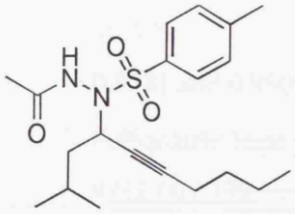
CCDC number 783431

Table 1. Crystal data and structure refinement for dwk0914.

Identification code	dwk0914	
Empirical formula	C25 H32 N2 O4 S	
Formula weight	456.59	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/a	
Unit cell dimensions	a = 8.9670(2) Å	α= 90°.
	b = 22.3460(6) Å	β= 104.3920(10)°.
	c = 12.9480(4) Å	γ = 90°.
Volume	2513.06(12) $Å^3$	
Z	4	
Density (calculated)	1.207 Mg/m^3	
Absorption coefficient	0.161 mm^{-1}	
F(000)	976	
Crystal size	0.50 x 0.50 x 0.40 mm^3	
Theta range for data collection	2.52 to 27.36°.	
Index ranges	-11<=h<=11, -28<=k<=28, -16<=l<=16	
Reflections collected	10414	
Independent reflections	5584 [R(int) = 0.0340]	
Completeness to theta = 27.36°	98.2 %	
Max. and min. transmission	0.9386 and 0.9240	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5584 / 0 / 295	
Goodness-of-fit on F^2	1.025	
Final R indices [I>2sigma(I)]	R1 = 0.0537, wR2 = 0.1362	
R indices (all data)	R1 = 0.0727, wR2 = 0.1476	
Largest diff. peak and hole	0.404 and -0.529 $e.Å^{-3}$	

X-ray crystal structure of hydrazine **223a**





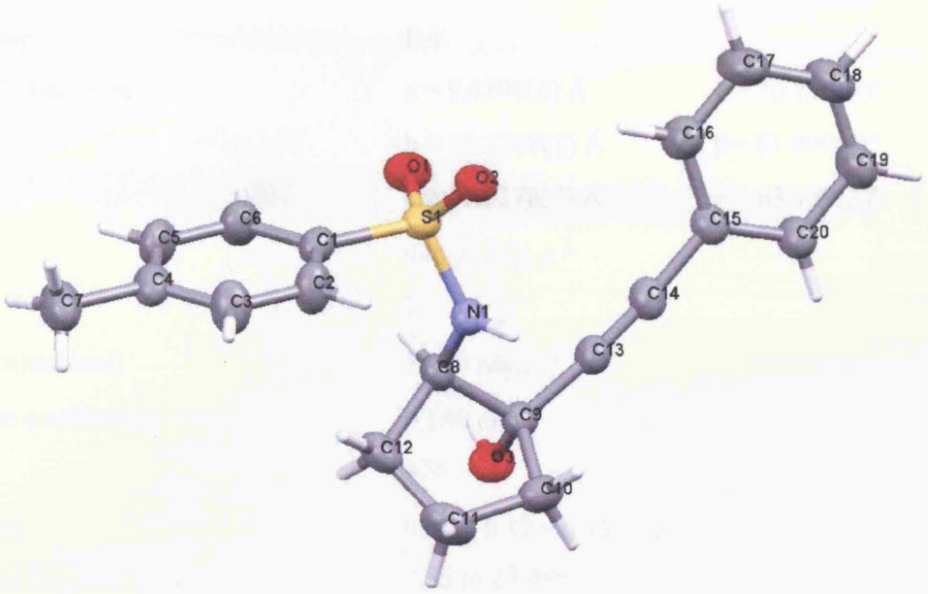
$C_{20}H_{30}N_2O_3S$

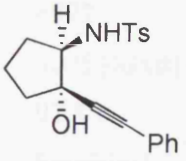
CCDC number 783434

Table 1. Crystal data and structure refinement for dwk1008.

Identification code	dwk1008	
Empirical formula	C20 H30 N2 O3 S	
Formula weight	378.52	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/n	
Unit cell dimensions	a = 15.7349(4) Å	α= 90°.
	b = 13.4711(2) Å	β= 94.4130(10)°.
	c = 20.1130(6) Å	γ = 90°.
Volume	4250.64(18) $Å^3$	
Z	8	
Density (calculated)	1.183 Mg/m^3	
Absorption coefficient	0.173 mm^{-1}	
F(000)	1632	
Crystal size	0.30 x 0.30 x 0.25 mm^3	
Theta range for data collection	1.59 to 27.49°.	
Index ranges	-20<=h<=20, -17<=k<=15, -26<=l<=26	
Reflections collected	17617	
Independent reflections	9712 [R(int) = 0.0505]	
Completeness to theta = 27.49°	99.3 %	
Max. and min. transmission	0.9581 and 0.9500	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9712 / 0 / 479	
Goodness-of-fit on F^2	1.035	
Final R indices [I>2sigma(I)]	R1 = 0.0586, wR2 = 0.1291	
R indices (all data)	R1 = 0.1001, wR2 = 0.1495	
Largest diff. peak and hole	0.244 and -0.408 $e.Å^{-3}$	

X-ray crystal structure of 2-alkynyl-2-hydroxysulfonamide **320b**





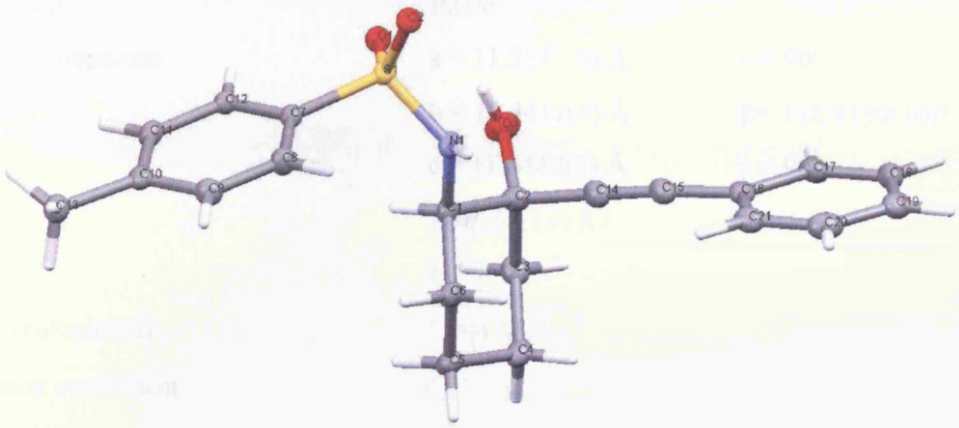
$C_{20}H_{21}NO_3S$

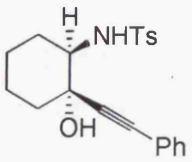
CCDC number 783433

Table 1. Crystal data and structure refinement for dwk1007.

Identification code	dwk1007	
Empirical formula	C20 H21 N O3 S	
Formula weight	355.44	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.6896(8) Å	α= 70.776(4)°.
	b = 10.2208(8) Å	β= 81.999(4)°.
	c = 11.3278(7) Å	γ = 63.173(3)°.
Volume	945.23(12) $Å^3$	
Z	2	
Density (calculated)	1.249 Mg/m^3	
Absorption coefficient	0.189 mm^{-1}	
F(000)	376	
Crystal size	0.30 x 0.12 x 0.12 mm^3	
Theta range for data collection	2.36 to 27.48°.	
Index ranges	-10<=h<=12, -13<=k<=13, -14<=l<=12	
Reflections collected	6377	
Independent reflections	4245 [R(int) = 0.0424]	
Completeness to theta = 27.48°	97.8 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9777 and 0.9455	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4245 / 0 / 228	
Goodness-of-fit on F^2	1.025	
Final R indices [I>2sigma(I)]	R1 = 0.0735, wR2 = 0.1550	
R indices (all data)	R1 = 0.1496, wR2 = 0.1913	
Largest diff. peak and hole	0.267 and -0.271 $e.Å^{-3}$	

X-ray crystal structure of 2-alkynyl-2-hydroxysulfonamide **320d**





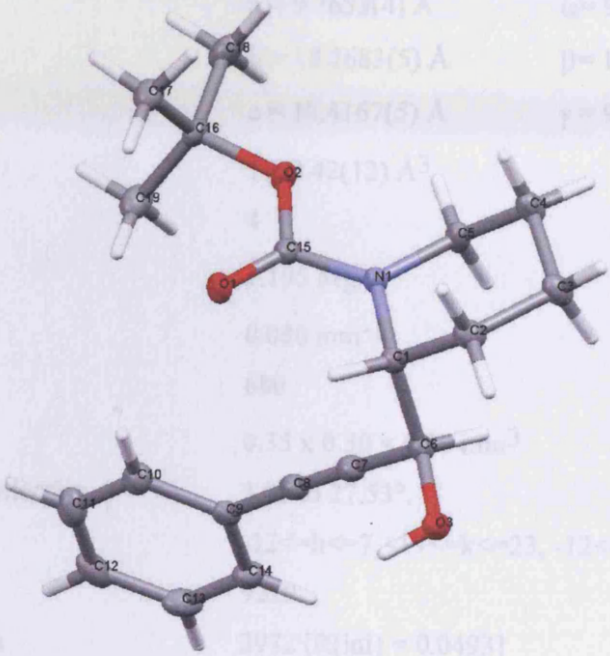
$C_{21}H_{23}NO_3S$

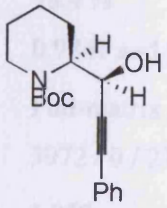
CCDC number 783432

Table 1. Crystal data and structure refinement for dwk1005.

Identification code	dwk1005	
Empirical formula	C21 H23 N O3 S	
Formula weight	369.46	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 11.3142(6) Å	α= 90°.
	b = 16.4417(4) Å	β= 118.9150(10)°.
	c = 11.6442(5) Å	γ = 90°.
Volume	1896.08(14) $Å^3$	
Z	4	
Density (calculated)	1.294 Mg/m^3	
Absorption coefficient	0.191 mm^{-1}	
F(000)	784	
Crystal size	0.20 x 0.20 x 0.06 mm^3	
Theta range for data collection	2.35 to 27.46°.	
Index ranges	-14<=h<=14, -21<=k<=16, -15<=l<=15	
Reflections collected	7572	
Independent reflections	4277 [R(int) = 0.0627]	
Completeness to theta = 27.46°	98.9 %	
Max. and min. transmission	0.9886 and 0.9628	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4277 / 1 / 241	
Goodness-of-fit on F^2	1.017	
Final R indices [I>2sigma(I)]	R1 = 0.0674, wR2 = 0.1509	
R indices (all data)	R1 = 0.1154, wR2 = 0.1777	
Largest diff. peak and hole	0.598 and -0.444 $e.Å^{-3}$	

X-ray crystal structure of piperidine **332b**





$C_{19}H_{25}NO_3$

CCDC number 783435

Table 1. Crystal data and structure refinement for dwk1009.

Identification code	dwk1009	
Empirical formula	C19 H25 N O3	
Formula weight	315.40	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 9.7653(4) Å	α= 90°.
	b = 18.2683(5) Å	β= 109.434(2)°.
	c = 10.4167(5) Å	γ = 90°.
Volume	1752.42(12) $Å^3$	
Z	4	
Density (calculated)	1.195 Mg/m^3	
Absorption coefficient	0.080 mm^{-1}	
F(000)	680	
Crystal size	0.35 x 0.30 x 0.20 mm^3	
Theta range for data collection	3.05 to 27.53°.	
Index ranges	-12<=h<=7, -19<=k<=23, -12<=l<=13	
Reflections collected	9220	
Independent reflections	3972 [R(int) = 0.0493]	
Completeness to theta = 27.53°	98.4 %	
Max. and min. transmission	0.9841 and 0.9725	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3972 / 0 / 212	
Goodness-of-fit on F^2	1.052	
Final R indices [I>2sigma(I)]	R1 = 0.0586, wR2 = 0.1283	
R indices (all data)	R1 = 0.0982, wR2 = 0.1486	
Largest diff. peak and hole	0.229 and -0.279 $e.Å^{-3}$	