A Flow System for Heterocyclic Synthesis

Thesis submitted in accordance with the requirements of the University of Cardiff for the degree of Doctor in Philosophy by

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Abstract

The potential of the silver-catalysed cyclisation has been illustrated by the synthesis of furans, pyrroles and pyrazole-*N*-oxides. With yields predominantly being >95%, and ubiquitous high purity, the results herein show the compatibility of many substituents including alkyl, aryl and silyl, to name but a few. Extended investigations have improved our understanding of reaction rates, the effect of stereochemistry and the use of protection strategies as well as identifying a handful of limitations.

With the above results in hand, and a desire to recognise the practical advantages of a metal-catalysed procedure, we have further described two continuous flow systems for heterocyclic synthesis. The first, a trickle-bed reactor, produces heterocycles in excellent yields (>95% except where volatile products were produced) and has been shown to exhibit < 1 ppm silver leaching. Our understanding of the optimal flow rates, catalyst loading and practical attributes associated with such a reactor is then described. The second, a supercritical carbon dioxide : ionic liquid system, has been shown to produce furans in excellent yields (>95%), when used in batch mode, and in slightly lower yield (>70%) when used in a continuous fashion. Once again silver leaching was seen to be <1 ppm. The success of these two systems, and the speed in which their success was achieved, clearly demonstrates the ease of working with silver-catalysed cyclisations. In a further brief foray, the use of heat and microwave irradiation is discussed in view of potential applications to other continuous systems.

Finally, several specific applications of the silver-catalysed cyclisation have been shown. It is seen that this procedure is suitable for the synthesis of scented furans and has uses in the preparation of heterocyclic substrates, which can be used for bigger and better things. One such example, which is described in Chapter 6, is the formation of oxepan-4-ones, oxepin-4-ones and oxocins-5-ones from their corresponding furyl alcohols.

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Abbreviations

$AgNO_3.SiO_2$	Silver nitrate on silica gel
bmim	1-Butyl-3-methylimidazonium
Boc	*tert*-Butyloxycarbonyl
bp	Boiling point
COSY	Correlation spectroscopy
CSTR	Continuous Stirred Tank Reactor
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCCI	*N,N'*-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEPT	Distortionless Enhancement by Polarisation Transfer
DHQD	Dihydroquinidine
DIBAL	Diisobutylaluminium hydride
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMPU	*N,N'*-Dimethylpropyleneurea
DMSO	Dimethyl Sulphoxide
EDA	Ethylenediamine
EWG	Electron withdrawing group
FDA	Federal Drug Agency
HMBC	Heteronuclear Multiple Bond Correlation
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
IBX	2-Iodoxybenzoic acid
ICPMS	Inductively Coupled Plasma Mass Spectrometry
IL	Ionic liquid
IR	Infra-red
LDA	Lithium diisopropylamide

m-CPBA	*meta*-Chloroperoxybenzoic acid
Moc	Methoxycarbonyl
mp	Melting point
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
Nuc	Nucleophile
omim	1-Octyl-3-methylimidazolium
ompy	1-*N*-Octyl-3-methylpyridinium
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PHAL	Phthalazine
PT	Proton transfer
PTSA	*para*-Toluenesulphonic acid
R_f	Retention factor
$scCO_2$	Supercritical carbon dioxide
SF	Supercritical fluid
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TBS	Tributylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate

Chapter 1: Introduction

1.1: Introduction

Heterocycles (Figure 1) are inherently important in many modern pharmaceuticals, being found in >70% of such commercial products. Why heterocycles? One of the prevalent features in a heterocycle is the presence of at least one lone pair of electrons (*e.g.* O, N, S), which provides a basis for electronic co-ordination, hydrogen-bonding, reactivity and resonance. Such electronic properties are crucial to a heterocycle's ability to exhibit biological activity. With many aromatic heterocycles being electron excessive, these become ideal candidates for coordination and electrophilic substitution, a property which is vital to the synthesis of substituted examples. Indeed, the presence of heterocycles in many biological systems means their use should contribute to providing a therapeutic which is biologically stable.

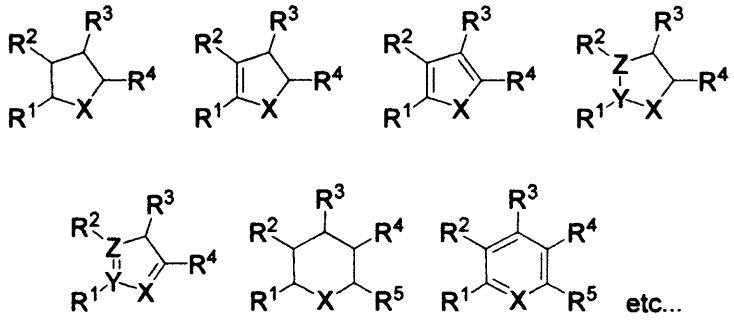
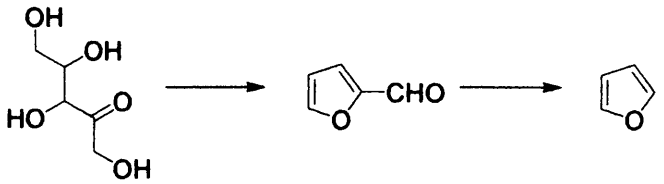


Figure 1: Heterocyclic compounds.

Many traditional synthetic approaches to heterocycles have been discussed in Comprehensive Heterocyclic Chemistry, 1996,[1] with many featuring ring closures through the nucleophilic addition of a heteroatom to an electron deficient carbon atom. These electron deficient centres can be present 'naturally' in, for example, carbonyls, nitriles and alkyl halides or can be generated *in situ* from unsaturated linkages by coordination with an intermolecularly-delivered electrophilic species. Classical examples of this latter methodology include halo-etherification and halo-lactonisation, amongst many others.

1.1.1: Furans

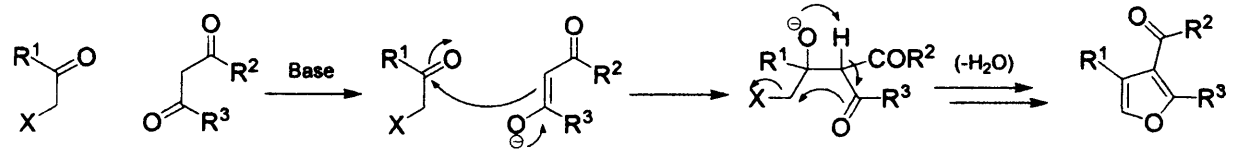
Furans have attracted much interest with particular uses in therapeutics and further applications within fragrance chemistry. Industrially, furan itself, **3**, a clear colourless oil, is obtained from the nickel-catalysed decarbonylation of furfural **2** (Scheme 1), itself a product of the acidic dehydration of pentose sugars **1**.



1 **2** **3**

Scheme 1: Industrial preparation of furan **3**.

A typical synthesis of functionalized furans is the Feist-Benary method.[2] Here, a 1,3-dicarbonyl compound **5** adds to an α-halo-carbonyl **4** *via* its enolate **6**. The resulting 1,3-dicarbonyl **7** can then undergo cyclisation and dehydration to yield a substituted furan **8** in high yield (90%) (Scheme 2), but with the requirement for a β-carbonyl substituent in the final product. This latter type of cyclisation **[7]** proceeds in a similar fashion to the Paal-Knorr furan synthesis, in which a 1,4-dione undergoes acid-catalysed cyclisation.

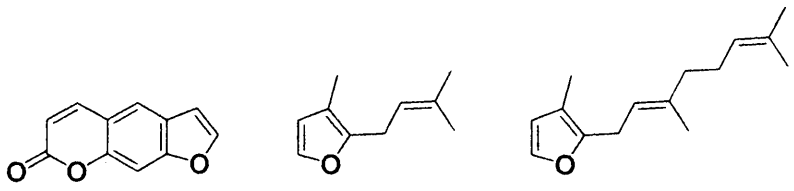


4 **5** **6** **7** **8**

(X = Cl, Br, I)

Scheme 2: Feist-Benary furan synthesis.[2]

With a host of other procedures available, furans including furocoumarins **9**, rosefuran **10** [3,4] and sesquirosefuran **11** [4] have been synthesised (Scheme 3).

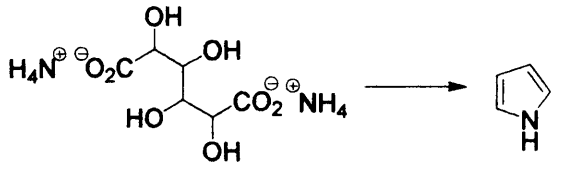


9 **10** **11**

Scheme 3: Important furans.

1.1.2: Pyrroles

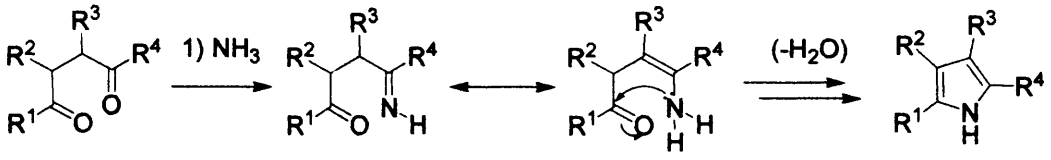
Another important class of heterocycles, especially in the context of this thesis, are the pyrroles. Pyrrole itself, **13**, also a clear colourless oil, is held in high regard by synthetic chemists. It too has vast numbers of applications in many industries, with particular uses in therapeutics and materials science, and has been synthesised from the dry distillation of the ammonium salt of D-galactaric acid **12** (Scheme 4).



12 **13**

Scheme 4: Industrial preparation of pyrrole **13**.

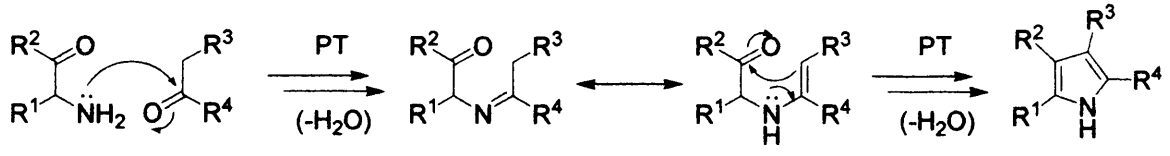
A classic example of a substituted pyrrole synthesis is seen in the Paal-Knorr cyclocondensation [5,6] of a 1,4-dicarbonyl precursor **14** with ammonia (Scheme 5). Here the nucleophilic lone pair of the nitrogen heteroatom ring closes **[16]** with a carbonyl situated in its γ-position to yield a fully substituted pyrrole **17**.



14 **15** **16** **17**

Scheme 5: Paal-Knorr synthesis [5,6] of pyrroles **17**.

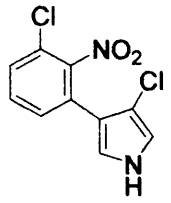
A derivative of this procedure is the Knorr pyrrole synthesis, [7-9] where an α-aminoketone **18** condenses with an α-methylene-ketone **19**. The product of the condensation, **20**, then undergoes intramolecular ring closure **[21]** to form the aromatic pyrrole **22** (Scheme 6). This reaction involves a heteroatom driven carbon-carbon bond formation between an enamine and a ketone.



18 **19** **20** **21** **22**

Scheme 6: Knorr synthesis [7-9] of pyrroles **22**.

Pyrrole rings are found in the therapeutics pyrrolnitrin **23** and zomepirac **24**, and in haemoglobin. which is based on the tetrapyrrole porphyrin ring system **25** (Scheme 7). They are also used in the formation of polypyrrole polymers **26**, often referred to as 'pyrrole blacks'.



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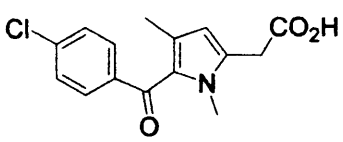

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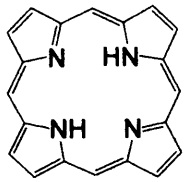

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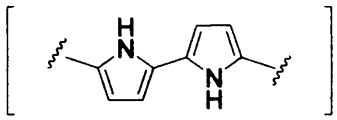
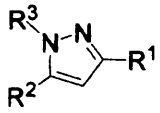


26

Scheme 7: Important pyrroles.

1.1.3: Pyrazoles

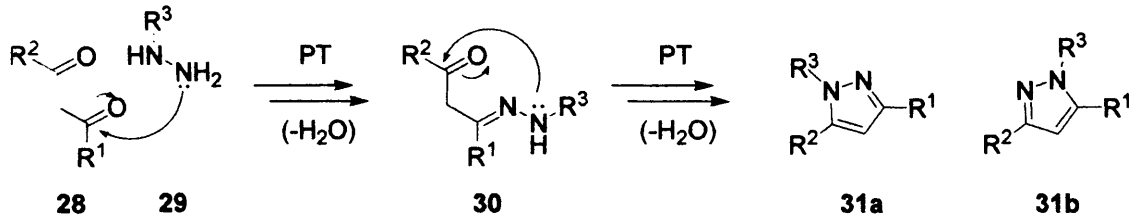
The final class of aromatic heterocycles that will be featured during the course of this project are pyrazoles **27** (Scheme 8). These too take the form of a 5-membered ring but, unlike furan **3** and pyrrole **13**, contain two adjacent nitrogen heteroatoms. This arrangement provides pyrazole with both a pyrrole-like nitrogen, whose lone pair provides aromaticity, and a pyridine-like nitrogen, which has an exposed lone pair giving pyrazole a degree of basicity comparable with tertiary amine bases.



27

Scheme 8: Pyrazole.

Its electron-rich π system readily undergoes electrophilic substitution, preferably at the 4-position, and nucleophilic substitution at the 3 and 5-positions. A typical synthesis of the pyrazoles **31a** and **31b** [10] incorporates the addition of hydrazine **29** to a 1,3-dicarbonyl **28** to give, upon cyclisation of **30**, good to excellent yields of the regioisomers of the expected pyrazoles **31a, 31b** (Scheme 9). Some regioselectivity can be achieved through the use of appropriate substituents, for example through steric bulk.



28 **29** **30** **31a** **31b**

Scheme 9: Knorr synthesis [10] of pyrazoles **31a** and **31b**.

1.2: Aims of the project

With the basics of furan **3**, pyrrole **13** and pyrazole **27** syntheses having been described, the focus of this work now turns towards Knight's interest in the synthesis of heterocycles.[11-16] With a previous interest in the silver-catalysed synthesis of pyrroles **17** (R^3 = H) [17] and furans **3**,[18] our attention turned towards providing a broadly applicable continuous flow system for heterocyclic synthesis.

Often, as with all approaches, traditional techniques have their limitations, be it in terms of substituent compatibility, regioselectivity or reaction conditions. There is also the problem that many of these techniques show subtle differences in their starting materials as well as in their conditions. It would therefore be desirable to present a practical approach which can produce heterocycles regiospecifically *via* a common scheme and set of conditions.

Chapter 2: Results and Discussion

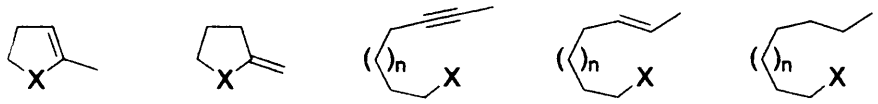
Synthesis of Furans

2.1: Introduction

There is significant interest in furans and their applications as therapeutics for a range of diseases. Therefore a broadly applicable, fast and efficient synthesis is crucial to their successful use. Many previous synthetic approaches suffered from low yields, the need for forcing conditions or require convoluted synthetic approaches to attain suitable starting materials. The few approaches that provide a more practicable mode of synthesis are often extremely good for their desired purpose but, like most synthetic procedures, do have significant limitations.[19] By drawing comparisons with previous literature, it will be shown that we have developed a powerful procedure for the synthesis of a broad range of furans from commercially available starting materials.

2.1.1: Baldwin's rules

Almost all cyclisation reactions adhere to a set of rules devised by Baldwin,[20-22] often referred to as Baldwin's Rules, (Figure 2 (X=Nuc)). There are several conditions which a transformation must usually obey in order to allow a successful reaction. The rules predict the feasibility of a cyclisation reaction for a range of *sp* (digonal) **34**, sp^2 (trigonal) **35** and sp^3 (tetrahedral) **36** carbon centres (Figure 2). It also accounts for the relative positions of bond formation and breakage in relation to a particular carbon centre. If the broken bond is within the newly formed ring, then *endo* **32** attack has ensued whereas if the converse is true, *i.e.* the bond is broken outside the newly formed ring, then *exo* **33** attack has ensued. The final piece of nomenclature deals with the size of the final ring structure, *i.e.* the number of ring atoms (R). Thus, a number of transformations can be written as being R-*endo/exo*-dig/trig/tet.

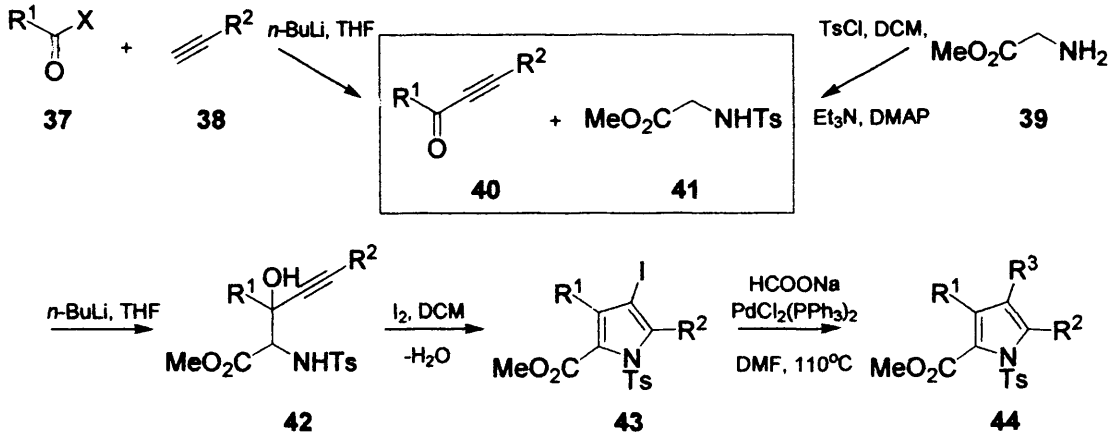


32 *endo* | **33** *exo* | **34** *sp* | **35** sp^2 | **36** sp^3

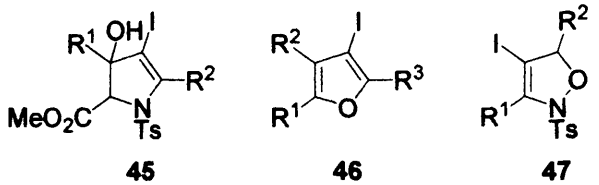
Figure 2: Baldwin's rules for ring closure.[20-22]

2.1.2: Iodocyclisation

According to Baldwin's rules, 5-*endo*-dig ring closures are favoured and indeed recently there has been much activity in this area.[16, 23-29] One of the most common stoichiometric approaches uses iodine to activate the alkyne bond such that a formal 5-*endo*-dig cyclisation can proceed. Indeed, the Knight group held a previous interest in this field with investigations into the use of stoichiometric iodine [11, 15] to effect the cyclisation of 3-alkyne-2-hydroxy-1-sulfonamides **42**. Unpublished results [30] showed high conversions which yielded 3-iodopyrroles **43** and, with an additional step, pyrroles **44**. These results were achieved through the addition of tosyl glycine methyl ester **41** to alkynones **40**, synthesised from carbonyls **37** (or DMF) and alkynes **38** to yield the desired 3-alkyne-1,2-sulfonamide **42**, which is then cyclised to the 3-iodopyrrole **43** (Scheme 10). Indeed, the success of the technique also found uses in the synthesis of dihydro-3-iodopyrroles **45**, [31] a complete surprise, of 3-iodofurans **46** [15] from 3-alkyne-1,2-diols and of 4-iodo-3-isoxazolines **47** [32] (Scheme 11).



Scheme 10: Synthesis of 3-iodopyrroles using the iodocyclisation protocol.

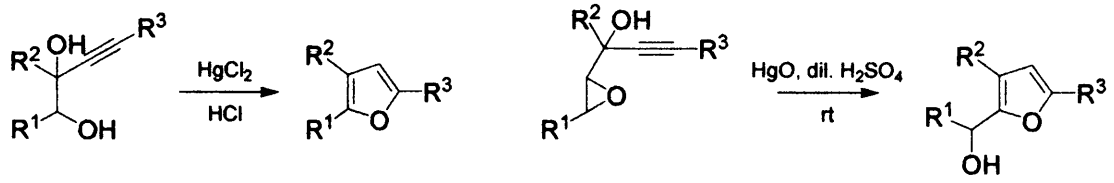


Scheme 11: Dihydro-3-iodopyrroles, 3-iodofurans and 4-iodo-3-isoxazolines.

Although very successful procedures, these iodocyclisations suffer the drawback of occasional side-product formation, *e.g. bis*-iodination of the alkyne, and the more serious requirement of excess iodine (3 eq). Interest therefore moved towards investigating the use of catalytic variants of these cyclisation procedures, especially the possibility of developing a heterogeneous catalyst.

2.1.3: Catalytic synthesis of furans

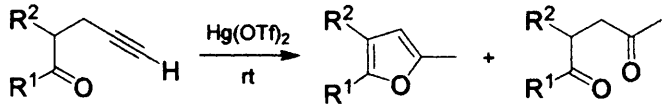
Previous literature [23-29, 33-48] had shown the use of several transition metal salts in effecting the cyclisation of similar compounds, in both a 5-*endo*-dig and 5-*exo*-dig fashion, but with varying yields and sometimes harsh conditions. Indeed, some of the earliest examples saw the use of mercury salts, which were employed to effect the cyclisation of 3-alkyne-1,2-diols **48** [33] and 1-alkynyl-2,3-epoxyalcohols **50** [34] to their corresponding furans **49, 51** in good yields (55-85%) (Scheme 12).



48 **49** **50** **51**

Scheme 12: Mercury-catalysed furan synthesis.

More recently, Nishizawa has used mercuric triflate, in the most successful mercury-catalysed procedure to date, to effect the cyclisation of 1-alkyn-5-ones **52**.[35] He showed that furans **53** could be obtained in excellent yields (70-100%), under very mild conditions, when using a terminal alkyn-5-one **52** (Scheme 13). There were however several drawbacks with this procedure: for instance, side product formation – the diones **54** - was often observed. More significantly, it was also not possible to cyclise aldehydes or non-terminal alkynes and there was a need to use benzene as solvent to obtain good yields.



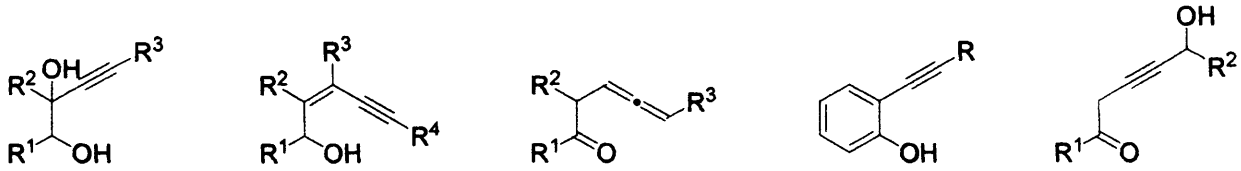
52 **53** **54**

Scheme 13: Nishizawa's mercury-catalysed furan synthesis.[35]

Another general problem which affects all mercury-catalysed procedures is the toxicity of these salts, which makes their use very undesirable, especially in industrial preparations.

In the mid-1980s, and again more recently, the trend moved towards the use of palladium in the catalytic cyclisation of 3-alkyne-1,2-diols **55**,[23] (*Z*)-2-en-4-yn-1-ols **56**,[36-38] allenyl ketones **57**,[39, 40] *O*-alkynylphenols **58** [25] and alkynones **59** [41] (Scheme 14). These procedures were often

coupled with carbonylation, using carbon monoxide, and are distinguished by their ability to produce tetrasubstituted furans.

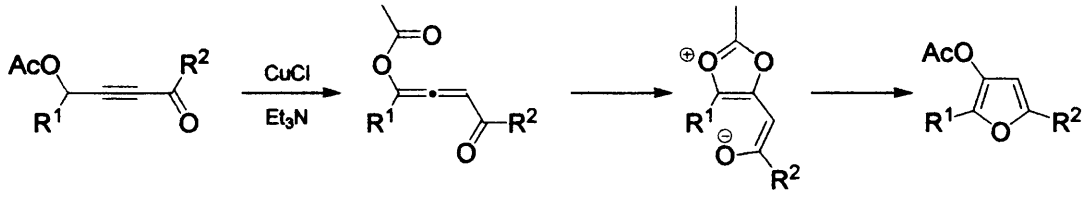


55 **56** **57** **58** **59**

Scheme 14: Substrates for palladium-catalysed furan synthesis.

These approaches seem ideal at face value, often giving good to excellent yields, and exhibiting low toxicity and the potential for broad substitution. In many cases however, they suffer from the need for extended reaction times and elevated temperatures, as well as inconsistency, given the varied yields which are obtained even with relatively basic substituent alterations. Further drawbacks are associated with the use of palladium itself, as it is notoriously expensive, sensitive and difficult to remove but, at least, it is usually required only in catalytic amounts.

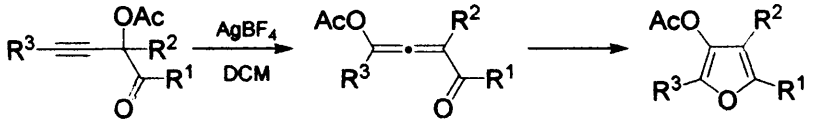
More recently, a novel 1,2-migration has been shown by Gevorgyan to yield tri- and tetra-substituted furans by the use of a copper-catalysed cyclo-isomerisation and a silver-catalysed sequence respectively.[42] The first incorporates a base-assisted propargyl-allenyl isomerisation of α-acyloxyalkynones **60** to give allenones **61**, which can undergo nucleophilic Ad_N-E attack **[62]** to form the furans **63** (Scheme 15).



60 **61** **62** **63**

Scheme 15: Gevorgyan's copper-catalysed furan synthesis.[42]

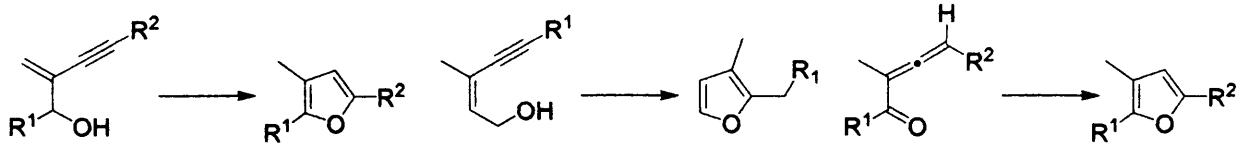
Gevorgyan's other cyclo-isomerisation procedure sees the use of silver tetrafluoroborate for the synthesis of furans *via* a [3,3]-shift, 1,2-migration and cyclo-isomerisation sequence.[42] Addition of catalytic silver tetrafluoroborate to a solution of α-acyloxy-β-ketoalkynes **64** in dichloromethane promotes the [3,3]-shift and 1,2-migration to yield the acyloxyallenones **65**, which then readily cyclise to yield tetrasubstituted furans **66** (Scheme 16). The procedure can also be used with other hetero-migrating groups such as phosphatyloxy and tosyloxy analogues.



64 **65** **66**

Scheme 16: Gevorgyan's silver-catalysed furan synthesis.[42]

Marshall had previously shown that it was possible to effect the cyclisation of β-alkynyl allylic alcohols **67**, 5-*endo*-dig, and γ-alkynyl allylic alcohols **69**,[26, 43] 5-*exo*-dig, as well as allenones **71**,[26, 44-45] by using various silver salts, to yield the corresponding furans **68**, **70** and **72** in excellent yields (>86%) (Scheme 17). This was achieved by the addition of commercially available 10% w/w silver nitrate on silica gel (henceforth referred to as 10% $AgNO_3.SiO_2$) to a solution of the heterocyclic precursor, to yield furans in excellent yields (up to 96%) within 1 h.

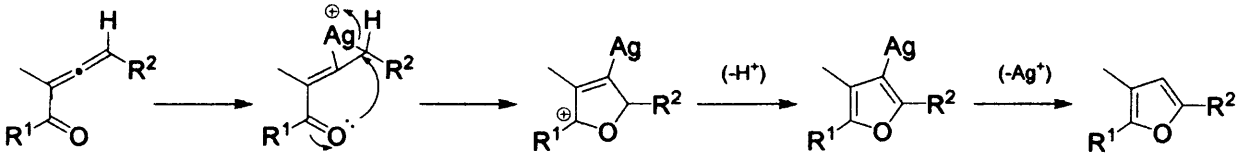


67 **68** **69** **70** **71** **72**

Scheme 17: Marshall's silver-catalysed furan synthesis.[26, 43-45]

Having found great success with this procedure, Marshall invested time in optimising the reaction conditions and understanding the mode of action. He showed that the most efficient cyclisations of allenones **71** used 20% $AgNO_3.SiO_2$, with acetone as the solvent, to yield furans **72** (90%) within 1 h.[26] Further developments saw the improved conversion of alkynyl allylic alcohols **67** and **69** with 10% $AgNO_3.SiO_2$ in hexane, to yield furans **68** and **70** (96%), still within 1 h.[26]

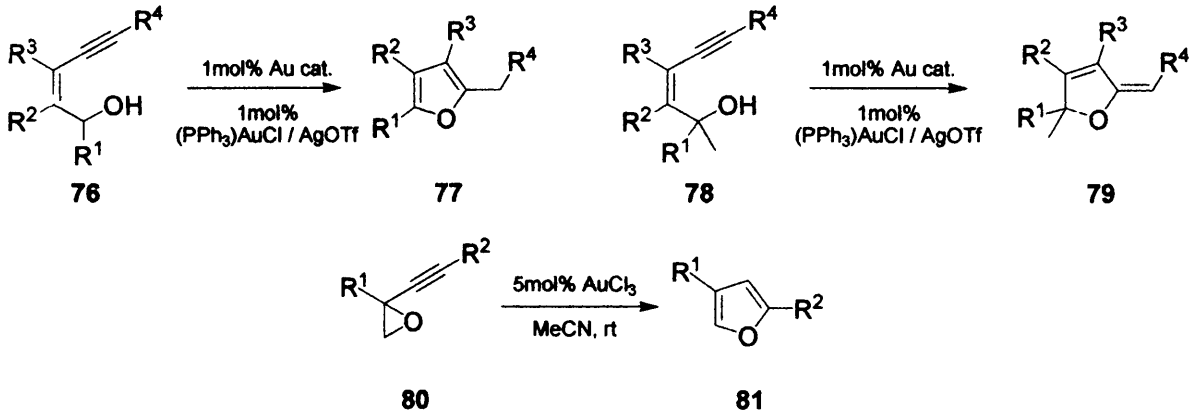
With this optimisation of the reaction conditions, Marshall then assessed the mode of action of the allenone cyclisation (Scheme 18). Using deuterium labelling, he was able to show that allene coordination to silver **[73]** allowed ring closure to proceed *via* lone pair donation from the carbonyl oxygen. Deprotonation of the resulting silver complex followed by Ag^+/H^+ exchange of the silver derivative **74** afforded furan **75** in the usual excellent yields (92%).



71 **73** **74** **75**

Scheme 18: Marshall's proposed silver cyclisation pathway.

In a final development, more recent interest has focused on the use of gold(III) salts and gold(I) complexes.[46-48] It was shown by Liu that both gold(III) chloride and the cationic gold(I) complex (PPh_3)AuCl/AgOTf could be used.[46] He successfully cyclised a range of (*Z*)-2-en-4-yn-1-ols **76** to yield the corresponding furans **77**, or dihydrofurans **79** in the case of tertiary alcohols **78**, in excellent yields (>83%) (Scheme 19), *via* a 5-*exo*-dig pathway.



76 **77** **78** **79**

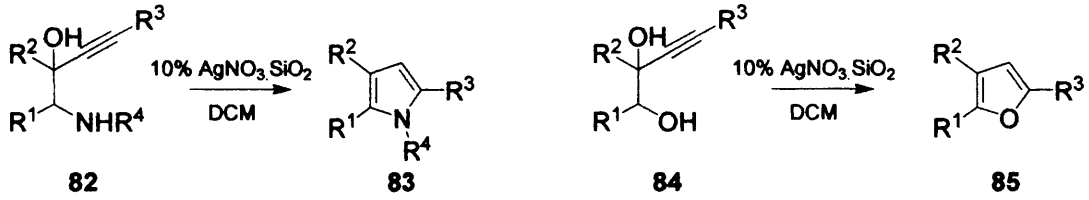
80 **81**

Scheme 19: Liu's and Hashmi's gold-catalysed furan syntheses.

Liu found that these reactions could be performed at room temperature within 3 h when using just 1 mol% of catalyst, although he did acknowledge that the presence of air did reduce yields slightly. Unsurprisingly, his use of silver triflate with the gold(I) catalyst appears to show a marked effect. Previously, the best yields (77%) were obtained when using (PPh_3)AuCl under reflux in acetonitrile for five days. The addition of 1 mol% silver triflate to this catalyst was found to not only improved yields (82%) but, more importantly, allow the cyclisations to proceed at room temperature within 3 h. This result is perhaps expected given that Marshall had already demonstrated the use of silver nitrate, amongst other silver salts, in effecting the cyclisation of (*Z*)-2-en-4-yn-1-ols **69** (Scheme 17).[26] The use of silver with gold is interesting and, in view of Marshall's results, it appears that the combination of the two are critical to lowering the required amount of catalyst to just 1 mol%.

Hashmi also spent some time investigating the use of gold(III) chloride.[48] He found that he could catalyse the isomerisation of alkynyl epoxides **80** to furans **81** in moderate to high yields (25-85%) under mild conditions (Scheme 19). Tolerating a range of functional groups including alkyl, aryl, aryl halide and hydroxyl groups, this work highlighted the strength of gold-catalysed cyclisations for the synthesis of furans. With predominantly high yields, its inert nature and the successes seen when using low levels of the catalyst, the use of gold is highly attractive.

Knight had already seen some success with the use of copper and protons [17] in the synthesis of pyrroles **83** and, less successfully, furans **85** (Scheme 20) but publications by Marshall inspired investigations into the use of silver. Sharland, a previous member of the Knight group, assessed the use of 10% $AgNO_3.SiO_2$, amongst other transition metal salts, in the cyclisation of a small number of 3-alkyne-2-hydroxy-1-sulfonamides **82**. Hoping to find a heterogeneous system, he found that the addition of 10% $AgNO_3.SiO_2$ to a solution of **82** screened from daylight, so as not to reduce silver(I), yielded the corresponding pyrroles **83** in excellent yields (>95%) and in high purity. With this result in hand, Menzies attempted the cyclisation of another class of substrate, the 3-alkyne-1,2-diols **84**, with 10% $AgNO_3.SiO_2$ and found, once again, the formation of furans **85** to occur in excellent yields (>95%) and in high purity. In view of these early results, it was felt that an equally strong procedure for the synthesis of a range of furans **85** from 3-alkyne-1,2-diols **84** had been found.



82 **83** **84** **85**

Scheme 20: Substituted pyrroles **83** and furans **85**.

As the above results were very much 'initial observations' which had been by no means comprehensively investigated, no great effort had been made to optimise the system, and at the time it was not known for certain what the best conditions were. It was known that with the advent of gold catalysts in this field, a viable competitor had been discovered, however a competitor which also suffers a major drawback: gold catalysts act in a homogeneous fashion. This renders the use of gold catalysts in continuous synthetic production awkward to say the least, given that product contamination was unavoidable and purification often quite difficult. It is here where silver could gain some ground.

At the outset of the present project, the silver nitrate system had the great advantage over gold catalysts of being heterogeneous and hence much more easily removed. However, leaching of silver(I) species into the products was a problem in all systems. There was however a belief that the heterogeneous nature of the silver catalysts might provide an opportunity through which leaching could be prevented, and a flow system formed. This belief formed a fundamental aim for this present project.

2.1.4: Silver cyclisation

With the isolation of such pure products, it was felt that the silver cyclisation procedure may have applications to a range of other heterocycles including dihydrofurans **86**, dihydropyrroles **87**, isoxazolidines **88**, isoxazolines **89, 90, 91**, isoxazoles **92**, pyrazoles **93**, pyrazole-*N*-oxides **94**, benzofurans **95**, indoles **96** and triazoles **97** (Figure 3), all continuing with the 5-*endo*-dig theme. Clearly, it may be anticipated that similar 5- and 6-*exo*-dig versions could also be discovered. It was at this point that this work commenced. With research by Song having shown a further application in the synthesis of pyrazoles **93**,[49] the aim of this project became orientated towards the synthesis of a comprehensive range of furans **85**, pyrroles **83** and pyrazole-*N*-oxides **94** through the development of a flow system (Figure 4), once the basic viability of these particular cyclisations had been demonstrated.

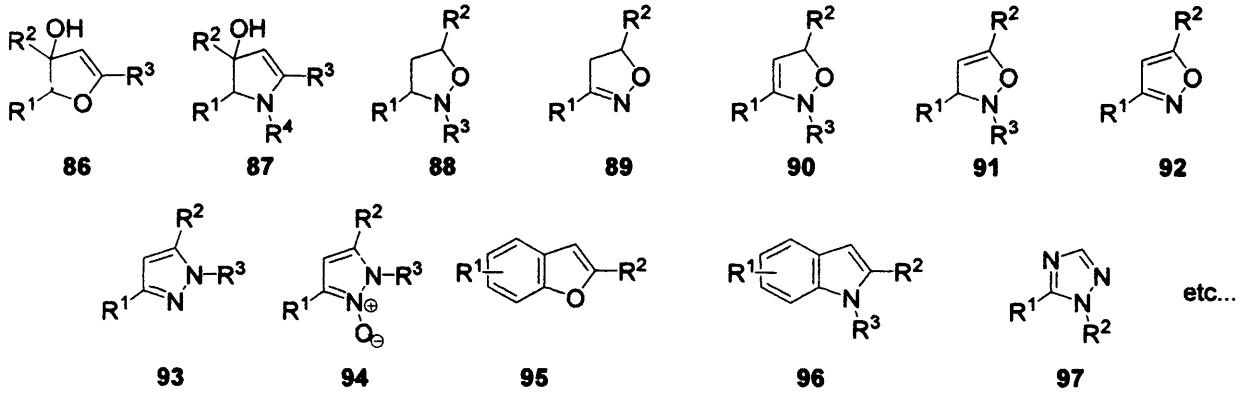


Figure 3: Possible heterocyclic targets.

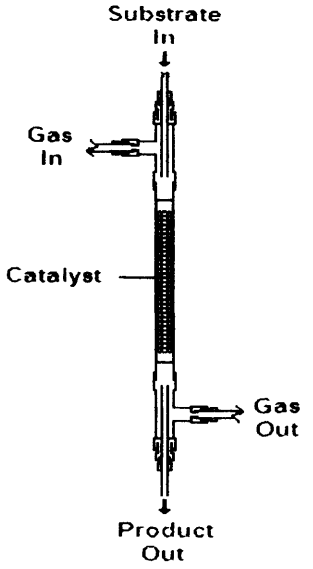
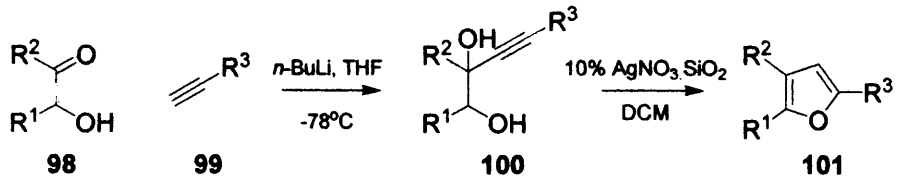


Figure 4: Principle of a continuous flow system.

2.2: Silver-catalysed synthesis of furans

2.2.1: α-Hydroxycarbonyl pathway

Following the work of Menzies[18] and with the use of additional synthetic approaches, a comprehensive range of 2,4-disubstituted, 2,5-disubstituted and 2,3,5-trisubstituted furans were synthesised (Table 1 and 2 - p 17 and 30). A few of these results were repeated, from the original work of Menzies[18] in an attempt to confirm and optimise the overall yields, and many others were performed to complete a thorough assessment of substituent effects and compatibilities. Addition of excess alkyne **99** (2.2 eqs), an arguably justified atom efficiency in view of the time and cost of using protection strategies (see later; Chapter 2.2.1 – p 23), to a commercially available α-hydroxycarbonyl compound **98**, as utilised by Menzies, yielded the desired 3-alkyne-1,2-diols **100a-o**. The addition of 10% $AgNO_3.SiO_2$, commercially available from Aldrich, to a stirred solution of the diols **100a-o** in dichloromethane (3-24 h) yielded the pure furans **101a-o** (>95%) (Scheme 21) (Table 1). It is worth highlighting that the vast majority of the successful cyclisation reactions exhibited >95% conversion and isolated yield. Only in a few specific cases were isolated yields seen to be lower, at around 50-60%, usually a result of product volatility, a likely explanation given that, in all of these instances, conversion remained high at >95%. As such, we feel it a fairer reflection to discuss each cyclisation herein with respect to its conversion. As a result of the observed high conversions, the purity shown by these cyclisations was seen to be outstanding, indeed in the majority of cases, there were no indications of by-product formation whatsoever (other than water). The few cases which did exhibit a degree of by-product formation are interesting in their own right (Chapters 2.2.1, 2.2.3 and 5.2.4 – p 24, 32, 97 and 100). Perhaps one of the most impressive aspects of this synthetic transformation was the isolation of such pure products, as shown by the represented ^{1}H NMR spectra (Spectrum 1, 2 and 3).

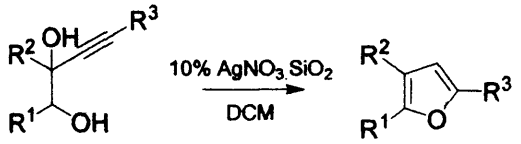


Scheme 21: α-Hydroxycarbonyl approach to furans.

Further aspects of this project have shown that a successful cyclisation can be attempted even in the presence of trace impurities. This, although usually avoided, does hint at the robustness of the technique, and hence provides greater scope for its practical use. It is worth mentioning that

when furans **101** are the desired end point, it is recommended that purification is attempted at the diol stage. This often simplifies column chromatography given the larger difference in polarity observed between many of the alkynes **99** and diols **100**, as well as other impurities. Obviously this recommendation is case-dependent, but for a large number of alkynes it remains true.

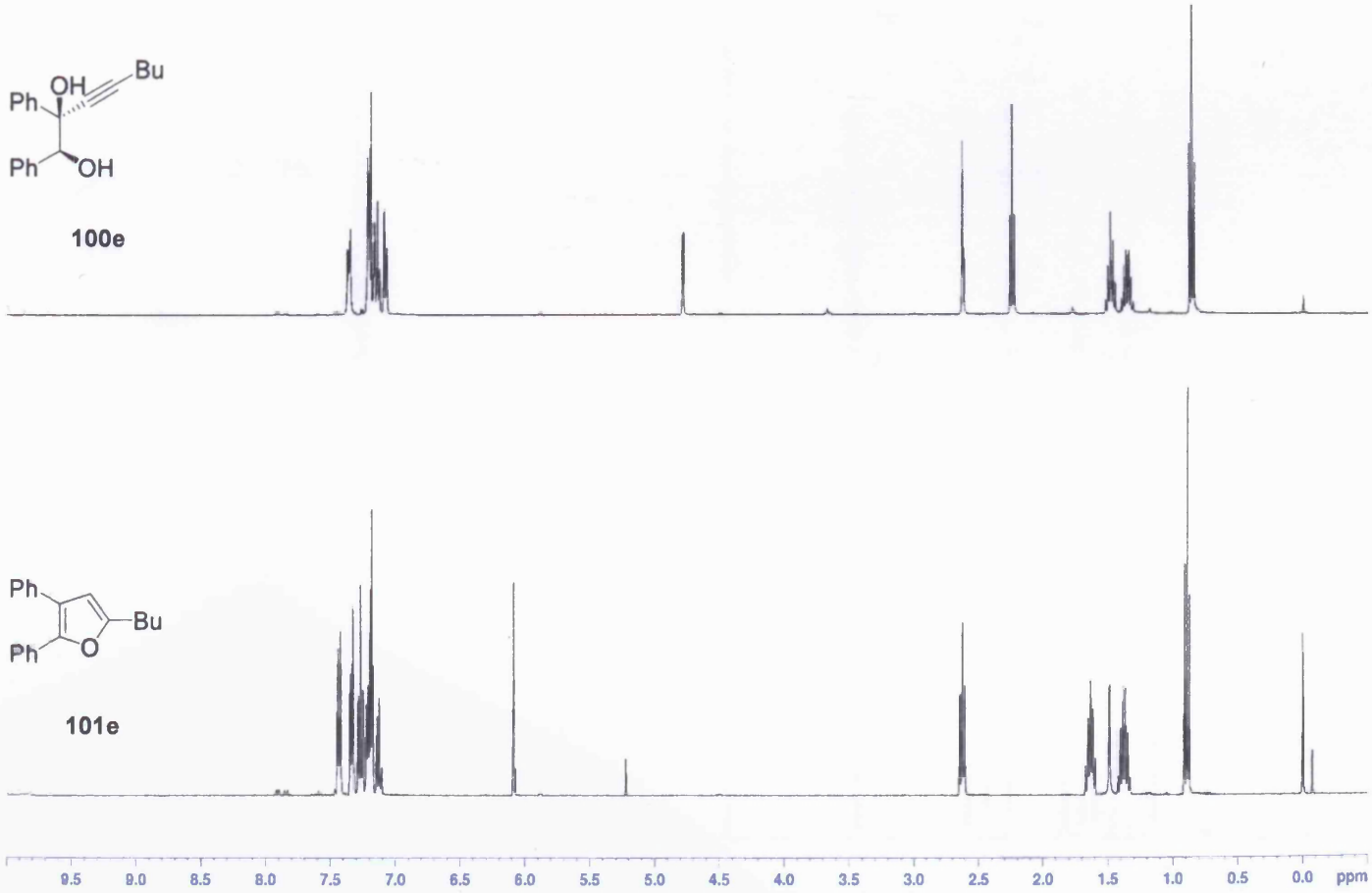
Table 1: Silver(I)-catalysed synthesis of furans.



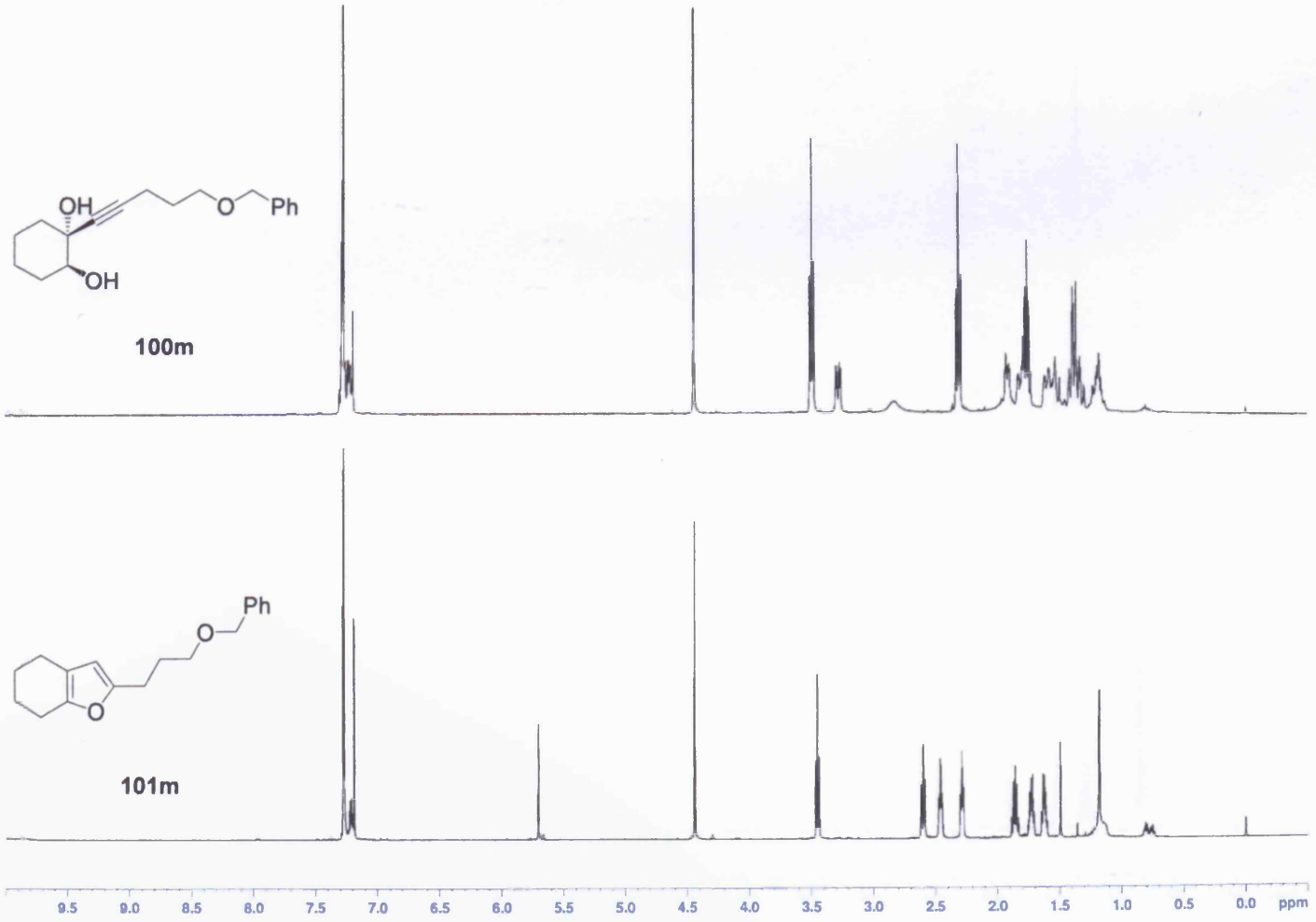
100, 126 **101, 127**

3-alkyne-1,2-diol	R^1	R^2	R^3	Furan	Isolated Yield (%)
100a	Me	Me	Bu	**101a** [c]	67
100b	Me	Me	Ph	**101b**	95
100c	Me	Me	$(CH_2)_2OTIPS$	**101c**	63
100d	Me	Me	$(CH_2)_3OBn$	**101d**	96
100e	Ph	Ph	Bu	**101e** [c]	99
100f	Ph	Ph	Ph	**101f**	95
100g	Ph	Ph	*t*-Bu	**101g**	97
100h	Ph	Ph	$(CH_2)_2OTIPS$	**101h**	96
100i	Ph	Ph	$(CH_2)_3OBn$	**101i**	98
100j	Ph	Ph	$(C{=}CH_2)CH_3$	**101j**	0
100k	Cy [a]		Bu	**101k** [c]	96
100l	Cy [a]		Ph	**101l**	95
100m	Cy [a]		$(CH_2)_3OBn$	**101m**	80
100n	H	Me	Bu	**101n**	48
100o	H	Me	Ph	**101o** [c]	85
126a	Ph	H	Bu	**127a** [c]	83
126b	Ph	H	$(CH_2)_3OTBDMS$ [b]	**127b** [b]	95
126c	Me	H	$(CH_2)_2OTIPS$	**127c**	98
126d	Me	H	$(CH_2)_3OTBDMS$ [b]	**127d** [b]	94

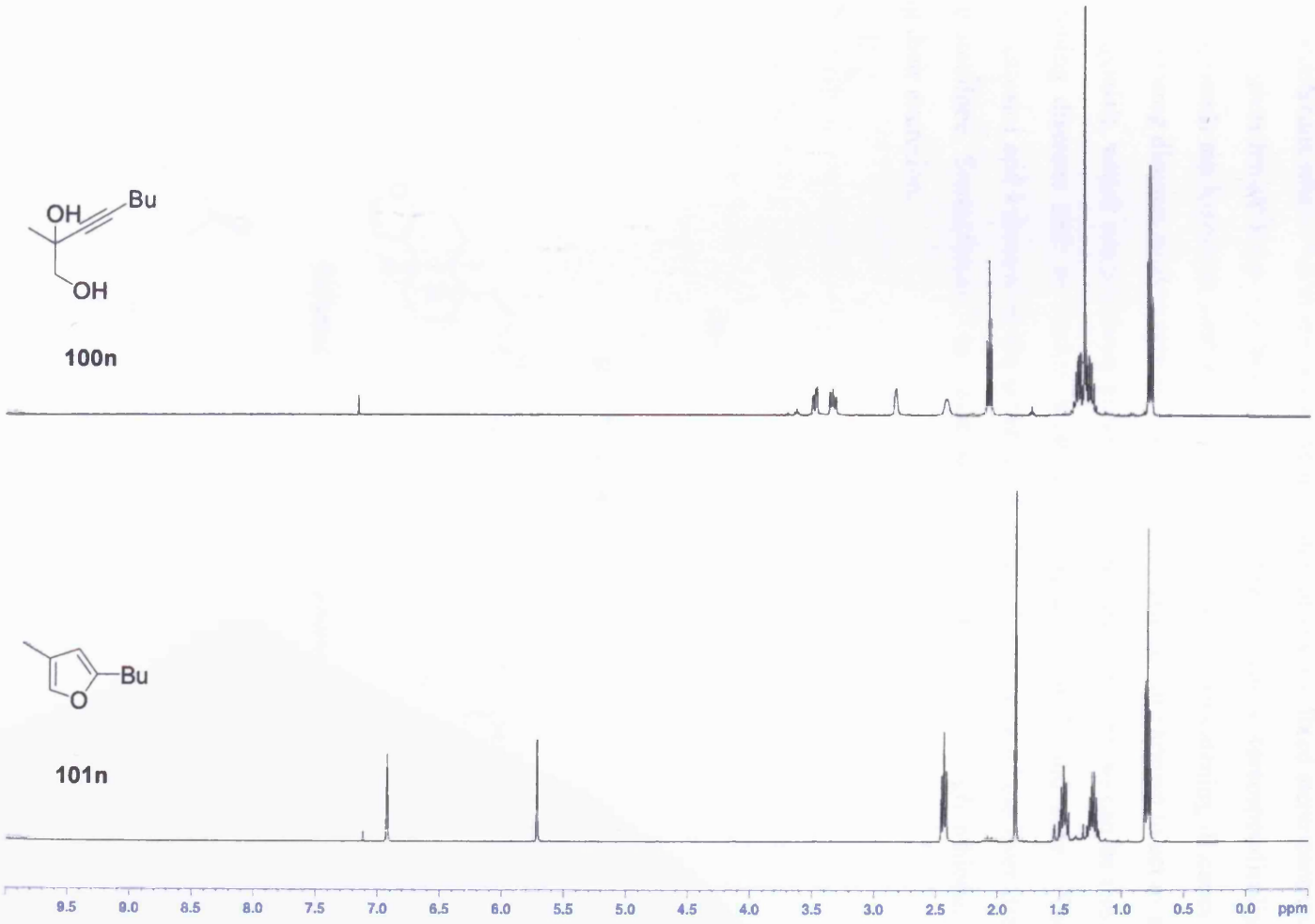
[a] Cy = Fused cyclohexanyl ring. [b] silyl group was partially removed during cyclisation to yield $R^3{=}(CH_2)_nOH$ (~2:1 in favour of proto-desilylated). [c] confirmation and optimisation of yields obtained by Menzies. [18]



Spectrum 1: ^{1}H NMR spectrum of diol **100e** ($CDCl_3$) and furan **101e** ($CDCl_3$).



Spectrum 2: ^{1}H NMR spectrum of diol **100m** ($CDCl_3$) and furan **101m** ($CDCl_3$).



Spectrum 3: ^{1}H NMR spectrum of diol **100n** ($CDCl_3$) and furan **101n** ($CDCl_3$).

Results of particular importance are the elaboration of the bicyclic ring systems **101k-m,** the 2,4-disubstituted furans **101n-o** and the ability to protect against competing 5-*exo*-dig ring closures (Scheme 25 and 26 – p 24). By inclusion of a cyclohexanyl moiety, it was possible to synthesise tetrahydrobenzofurans which would allow for the inclusion of several fixed stereocentres. This is important as it gives the ability to synthesise a range of furanosteroids stereospecifically (Figure 5); such compounds are known to treat not only common non-life-threatening diseases but also rapidly proliferating diseases such as cancer. [3,2]-Furanosteroids[50] are known to act as androgen receptor antagonists, which competitively prevent the action of androgen, so can be used to treat less threatening diseases such as benign prostatic hyperplasia (BPH) and acne. The coffee constituents cafestol and kahweol on the other hand induce the activity of the liver detoxifying enzyme glutathione S-transferase[51] to increase binding of toxins to glutathione, thereby facilitating their excretion.

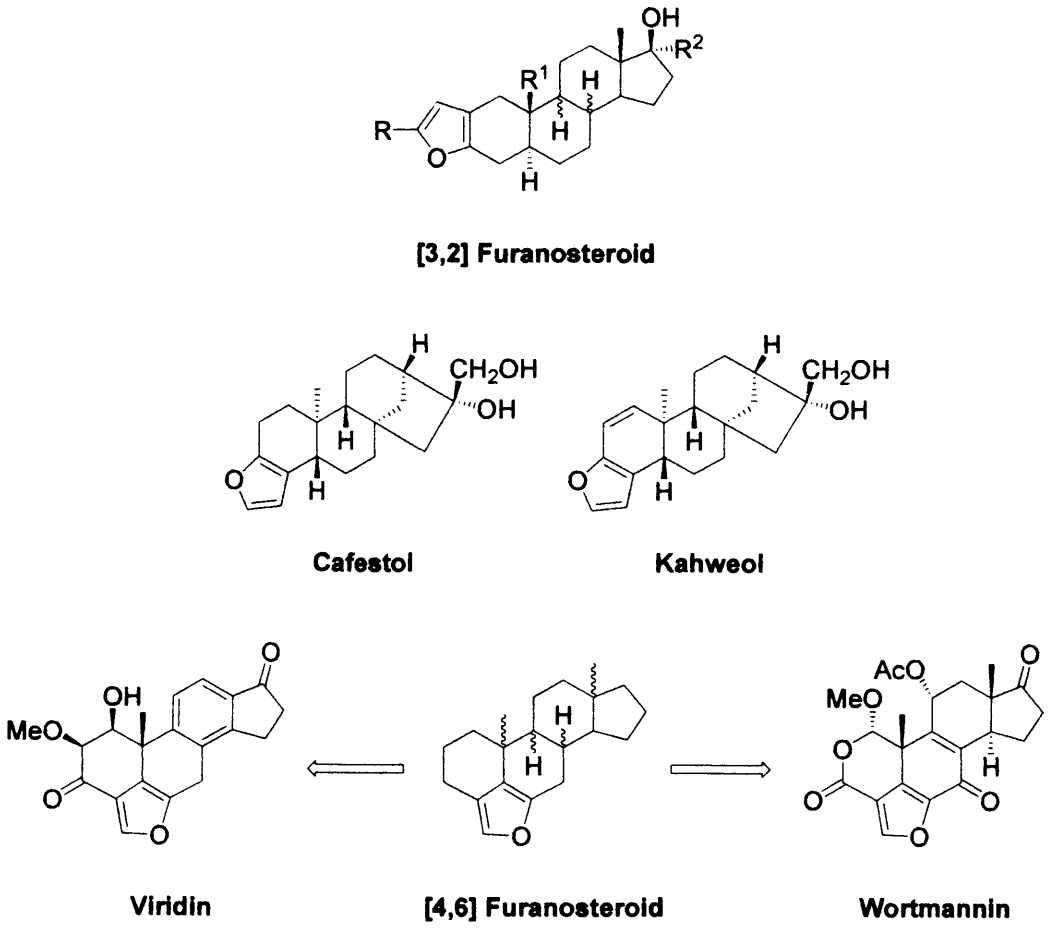
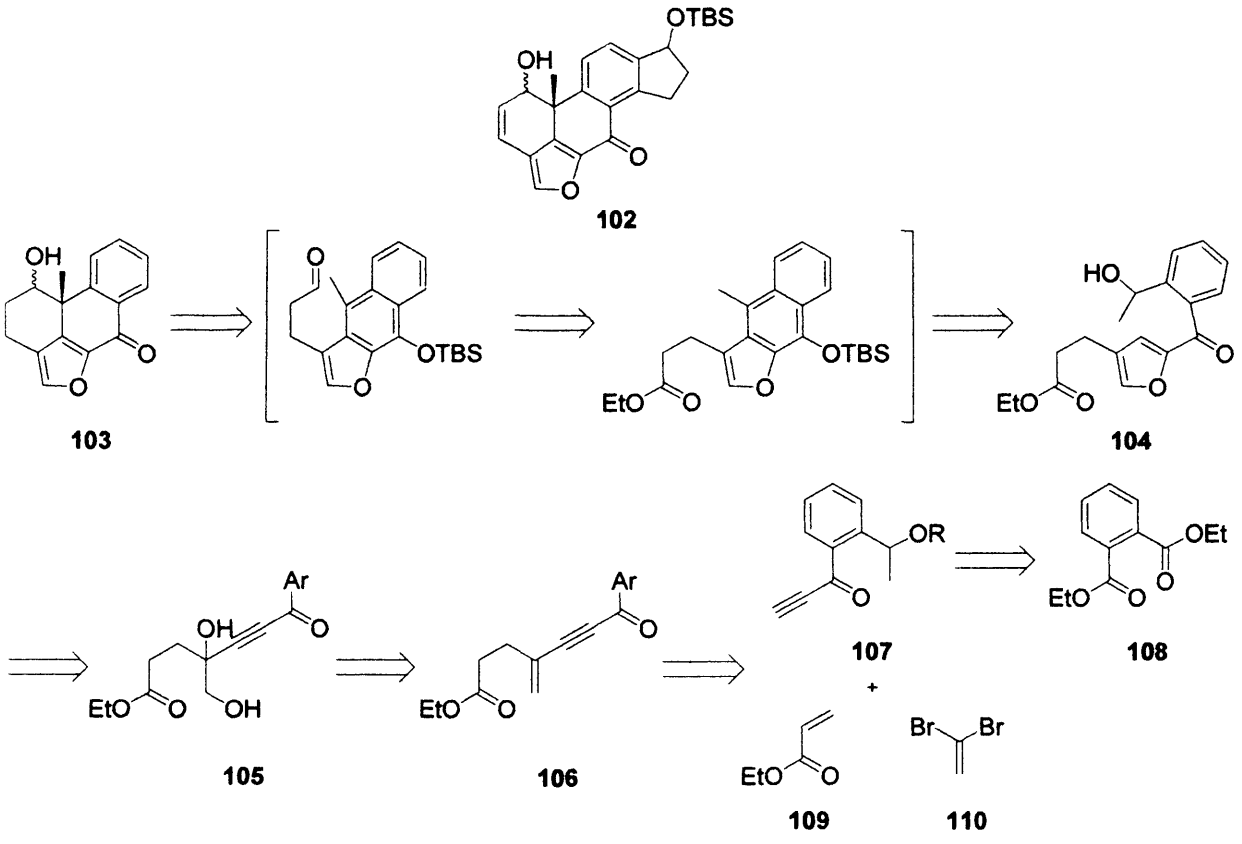


Figure 5: Furanosteroids.

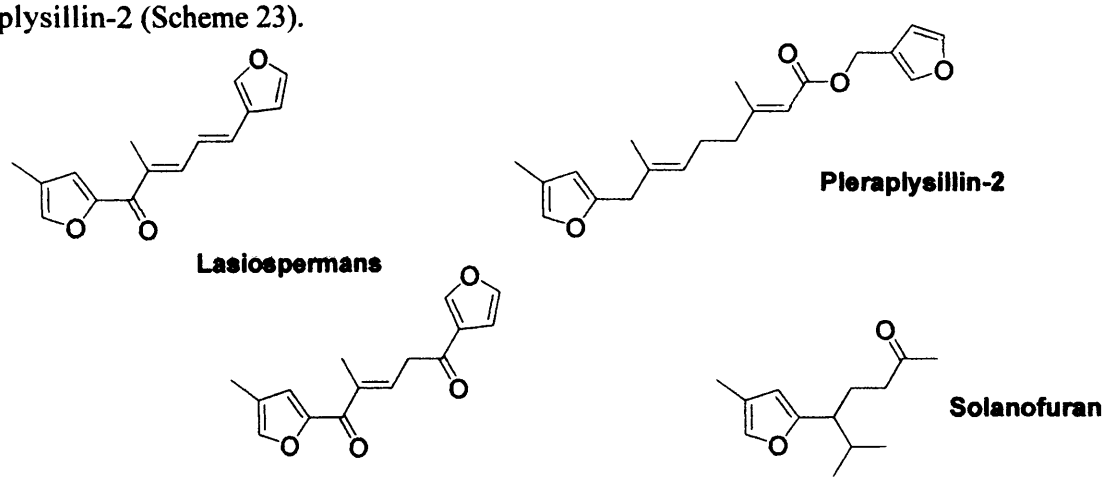
Finally, the [4,6]-furanosteroids[52] have perhaps attracted the most interest given their potential to act as anti-cancer agents. Traditionally known for their potent anti-inflammatory properties, these compounds have recently been shown to selectively block certain intracellular signalling pathways associated with cell growth and development, through their irreversible inhibition of P13-Kinase. One of the most common examples of a P13-inhibitor is Wortmannin (Figure 5), which is used in cell biology to inhibit DNA repair and cell proliferation.[53]

Of the other [4,6]-furanosteroids Viridin, which has the same order of activity as organomercurials,[54] has also attracted much interest, with a recent publication by Jacobi[52] describing a model study of its synthesis (Figure 5). Targeting Jacobi's model **103** of a viridin precursor **102** previously prepared by Sorensen,[55] and using some of Jacobi's previous approach work, it seems plausible that **103** can be synthesised from the 2,4-disubstituted furan **104**. One could perhaps imagine furan **104** being readily synthesised from the 3-alkyne-1,2-diol **105** *via* our silver cyclisation procedure (Scheme 22). The diol itself could be synthesised in a number of ways, with one particularly attractive approach featuring an alkynenone ester **106** derived from alkynone **107**, obtainable from commercially available diethyl phthalate **108**, together with ethyl acrylate **109** and 1,1-dibromoethene **110**.



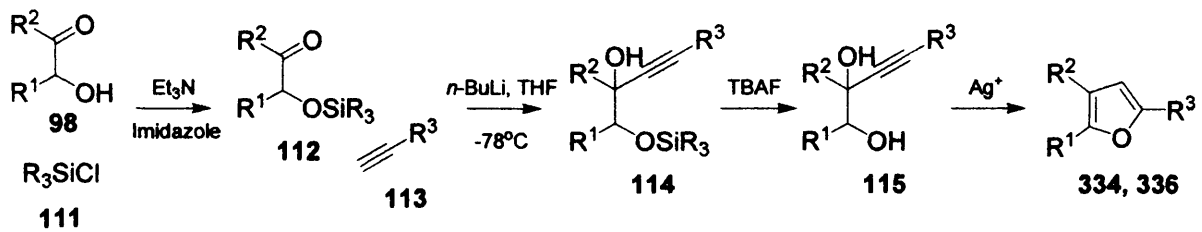
Scheme 22: Proposed retrosynthetic analysis of model viridin compound **102**.

Traditionally, the synthesis of 2,4-substituted furans has often been troublesome.[56-58] Their presence in natural terpenoids[59] and other natural products[60] has generated interest in their synthesis yet many previous efforts have failed to be broadly applicable. Knight and Rustidge presented one of the first syntheses of 2,4-disubstituted furans, which was of some generality, with the use of 4-methyl-2-furyl-lithium but this approach was one which was limited to 4-methyl-2-substituted furans.[59] Their procedure allowed for the synthesis of a range of 2,4-disubstituted terpenoid furans in good yields (50-65%) including the natural sponge metabolite pleraplysillin-2 (Scheme 23).



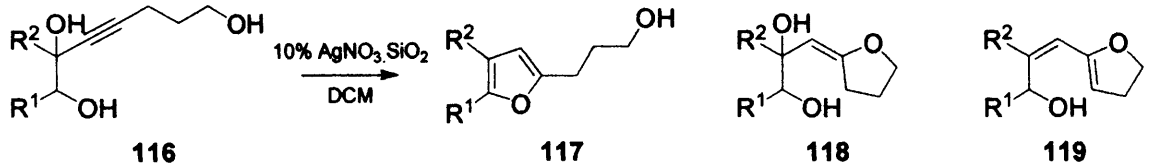
Scheme 23: Naturally occurring 2,4-disubstituted furans.

Using our new approach, it was possible to obtain several 2,4-disubstituted furans in the usual excellent conversions (>95%) with the only significant reduction in yield being observed with 2-butyl-4-methylfuran **101n** (isolated 48%), which can readily explained by extreme product volatility. Given the simplicity of this approach, we feel that we have defined a highly efficient way to synthesise the troublesome 2,4-disubstituted furans, and one which is truly general. Indeed, with silyl protection and deprotection strategies allowing for the use of just one equivalent of precious alkynes **113** (Scheme 24), it was possible to synthesise a series of more complex 2,4-disubstituted **[334; R^1 = H]** and 2,3,5-trisubstituted **336** furans (Chapter 6.2 – p 117). This made it possible to access a range of substituted furans which contained both stereogenic centres and olefinic bonds.



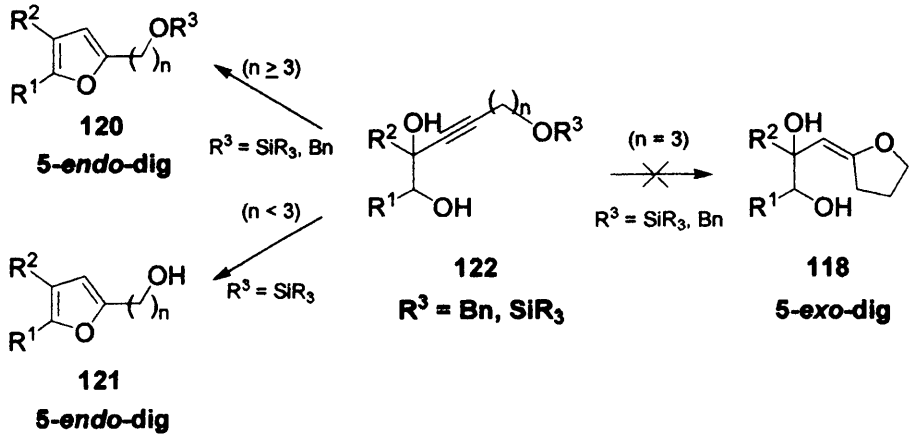
Scheme 24: Silyl protection during α-hydroxycarbonyl approach to furans **334** and **336**.

The final series of results, which sparked particular interest, centred around the ability to both effect and prevent 5-*exo*-dig ring closures. Attempts to cyclise pentyn-1-ol-based 3-alkyne-1,2-diols **116** led to a 4:2:1 mixture of the expected "5-*endo*-dig" furan **117** together with the alternative "5-*exo*-dig" tetrahydrofuran-2-ylidene **118** and dihydrofuran **119**, resulting from a 1,4-elimination, products (Scheme 25). Spectrum 4 highlights the key peaks between 5.00 and 7.00 ppm which allude to the proposed structures.

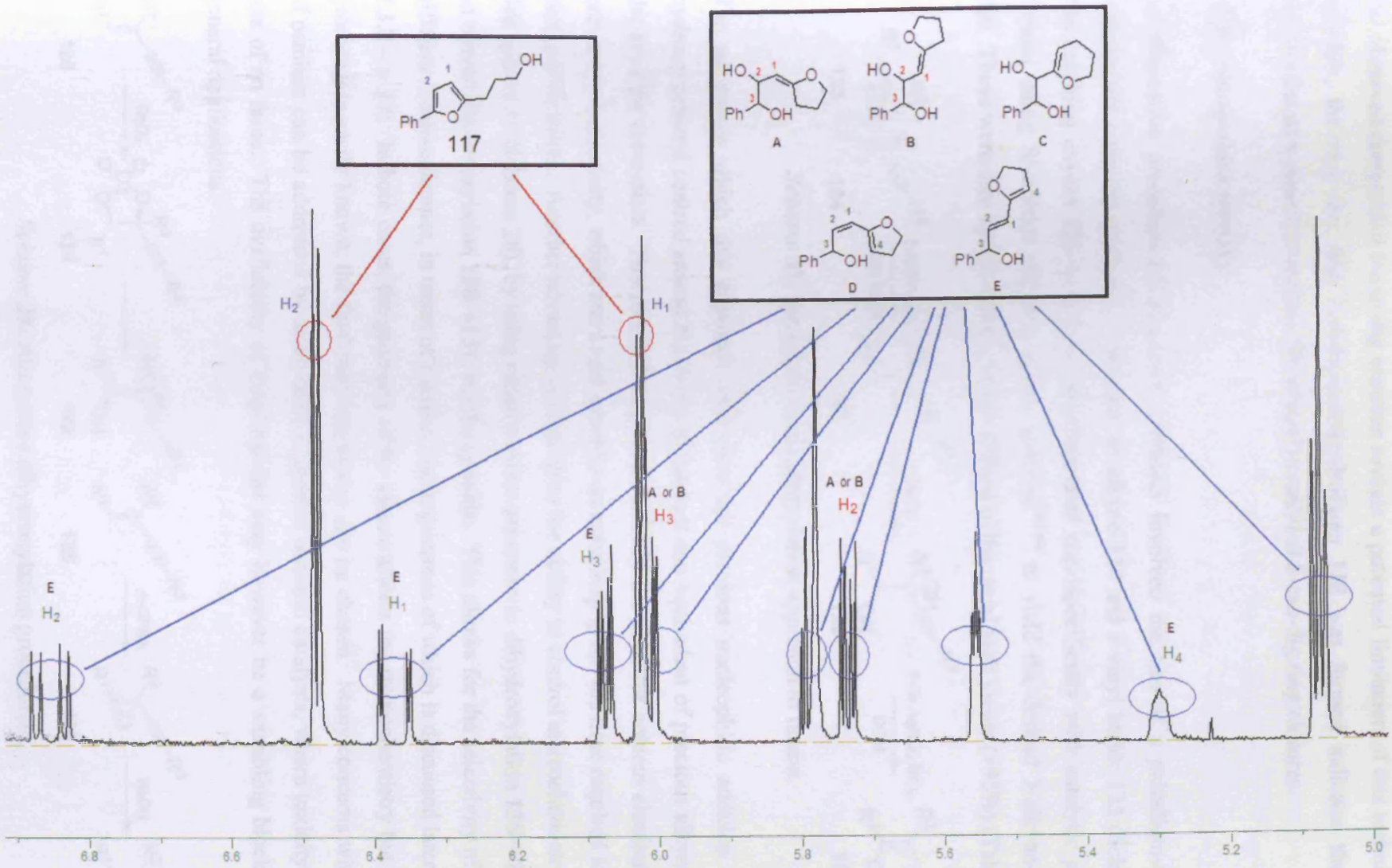


Scheme 25: 5-*endo* vs 5-*exo* ring closures.

Fortunately, simple masking of the "5-*exo*" hydroxyl of triol **116**, through the application of standard protection strategies, allowed for this competitive cyclisation mode to be blocked. Examples using both R^3 = benzyl **122** ($R^1 = R^2$ = Ph) (98%) and R^3 = silyl **122** (R^1 = Ph, R^2 = H) (60-98%) protecting groups were both shown to be successful in preventing 5-*exo*-dig ring closure **118**, despite their potential lability in the presence of a nearby electrophilic centre. Unlike analogous results from the iodocyclisation reaction,[61] the desired 5-*endo*-dig closure **120** was observed exclusively when using benzyl and silyl protecting groups (Scheme 26). The spontaneous deprotection of shorter chain silyl ethers **121** ($n < 3$) was observed in some cases after successful cyclisation; fortunately in these examples, competitive cyclisation was not likely. It would appear that this was not the case for longer chain lengths ($n \geq 3$) **120**, where successful prevention of 5-*exo*-dig ring closures **118** was possible with silyl and benzyl protecting groups.



Scheme 26: Protection strategies allow 5-*endo* **120**, **121** and prevent 5-*exo* **118** ring closures.

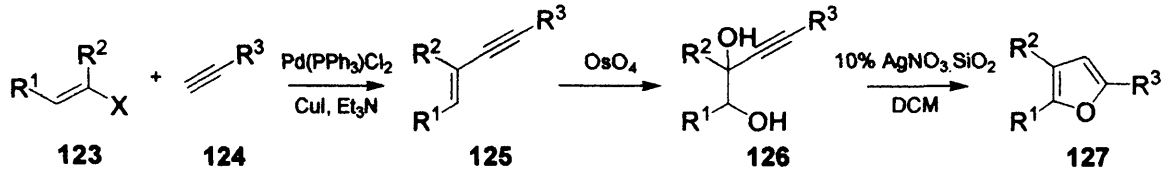


Spectrum 4: ^{1}H NMR spectrum of possible products from the cyclisation of unprotected diol **116** ($CDCl_3$).

The observed competitive 5-*exo*-dig reaction reveals a potential limitation of this technique but, naturally, the very fact that 2-ylidenetetrahydrofuran **118** was formed indicates the further possibilities of a general procedure for silver(I)-catalysed 5-*exo*-dig ring closures.

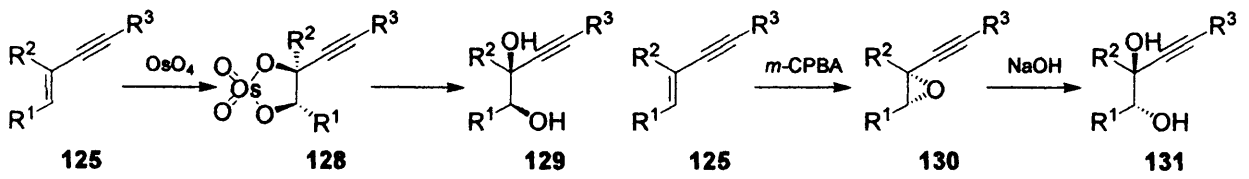
2.2.2: Sonogashira strategy

An alternative procedure for precursor synthesis involved the use of a palladium-catalysed Sonogashira coupling reaction[62, 63] between an alkyne **124** and a vinyl halide **123** (Scheme 27). The resulting enynes **125** were then dihydroxylated regiospecifically with catalytic potassium osmate, using Sharpless' dihydroxylation protocol,[64-66] to yield the desired 3-alkyne-1,2-diols **126**. These were then cyclised to the furans **127a-d** in the usual high yields (>95%) (Table 1).



Scheme 27: Sonogashira, dihydroxylation approach to furans.

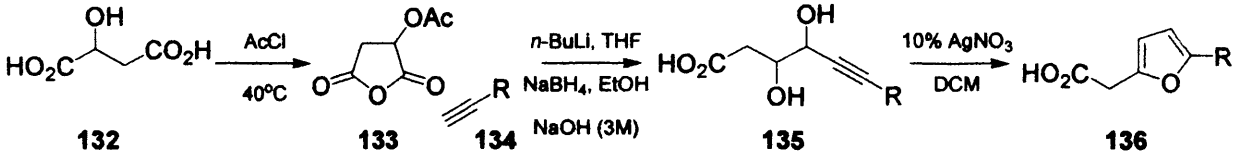
The advantage which this approach held over the previous nucleophilic addition to an α-hydroxycarbonyl centred around the ability to use just one equivalent of precious alkyne without the need for protection. This reduced waste and removed the need for column chromatography, previously a necessity, which one could consider an extra step given the time required to perform such purifications. Another advantage is clear from the ability to control stereochemistry through this approach (Scheme 28), by using either a direct asymmetric dihydroxylation **128**→**129**[64-66] or an overall dihydroxylation **130**→**131**, *via* the epoxide. This allows for the selectivity of the more efficient diastereoisomer, in terms of kinetics, the importance of which is discussed later (Chapter 2.3.2 – p 37). In both cases, the geometry of the alkene affects the stereochemistry but since this geometry is easily known, the final stereochemistry can be chosen. Many concerns with the use of osmium can be addressed by using solid-supported osmium catalysts, where toxicity becomes less of an issue. The availability of vinyl halides may however be a stumbling block for very general applications.



Scheme 28: Alternative dihydroxylation procedures.

2.2.3: Furylacetic acids

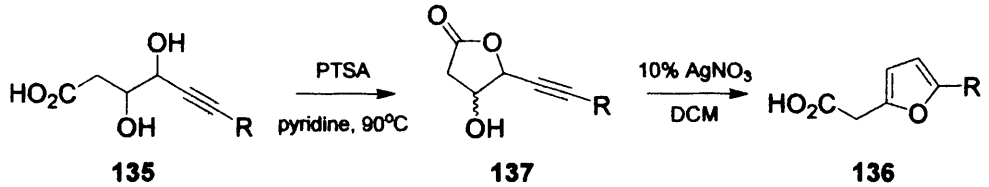
A further application of the 5-*endo*-dig cyclisation method was aimed at accessing a range of furylacetic acids **136**, a functionality present in the natural product Plakorsin A,[67-70] which itself will be discussed in more detail later (Chapter 6.3.2.1 – p 130). Using a literature procedure presented by Lavallée,[71] it was possible to regiospecifically add an alkyne **134** to the more electrophilic ring carbonyl of 2-acetoxysuccinic anhydride **133**, synthesised from malic acid **132**, since this is also the less hindered site. *In situ* sodium borohydride reduction was followed by sodium hydroxide-induced removal of the acetate group to yield the desired 3-alkyne-1,2-diols **135a-b** (>60%). These diols **135a-b** were then directly cyclised under standard conditions to yield the target furylacetic acids **136a-b** (>95%) (Scheme 29) (Table 2). It can be seen in Spectrum 5 that this transformation was effected cleanly once again.



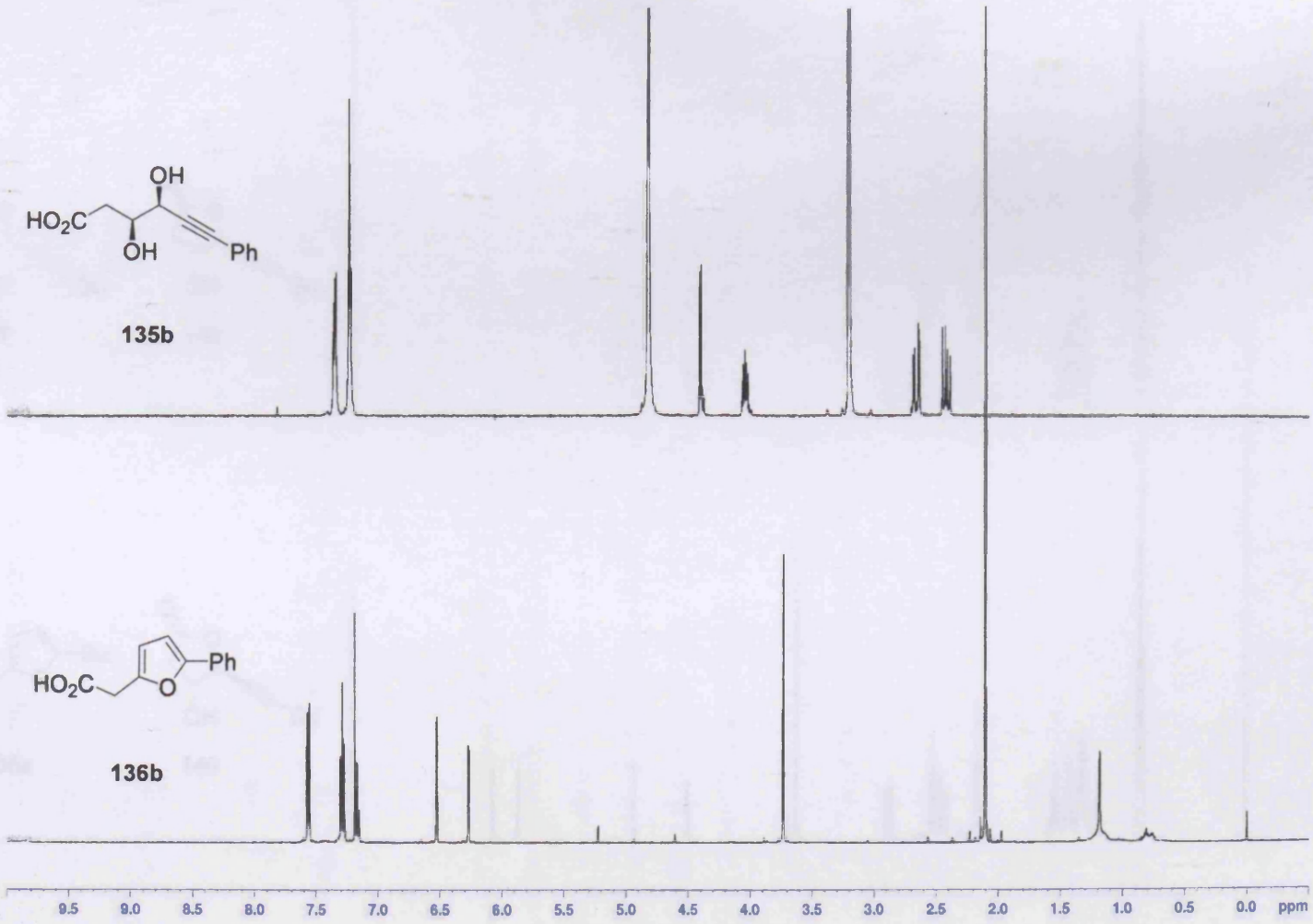
Scheme 29: Synthesis of furylacetic acids **136a-b**.

The lack of literature references surrounding the synthesis of 2-furylacetic acids[67-70] alludes to the difficulties associated with accessing this class of furans and this result therefore provided a major bonus and another beneficial application for the silver(I)-catalysed cyclisation procedure. With both alkyl and aryl functionalities being compatible, this procedure formed the basis of our attempts to synthesise the natural functionalised furylacetic acid **351** (Chapter 6.3.2 – p 130).

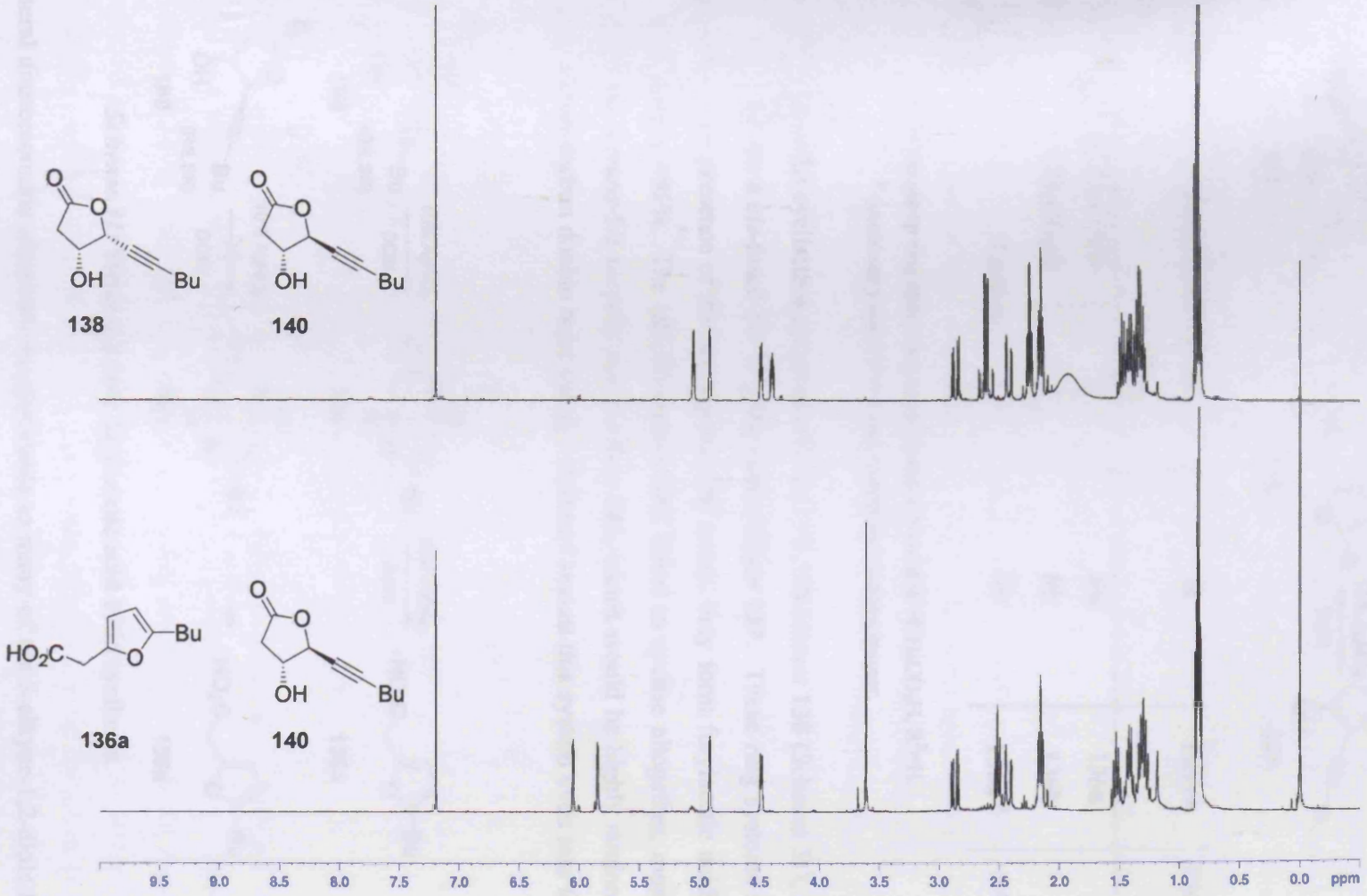
In a slight modification to the existing procedure, it was also possible to lactonise diols **135a-b** with *para*-toluenesulfonic acid in refluxing pyridine to yield a mixture of two cyclic diastereomers **137** (Scheme 30).[71] Exposure of this mixture to 10% $AgNO_3.SiO_2$ permitted the cyclisation of just one of these (Scheme 31) (Table 2) (Spectrum 6). The successful conversion of this diastereomer into its cyclic product was found to occur in >95% yield.



Scheme 30: Hydroxylactone **137** 5-*endo*-dig cyclisation.

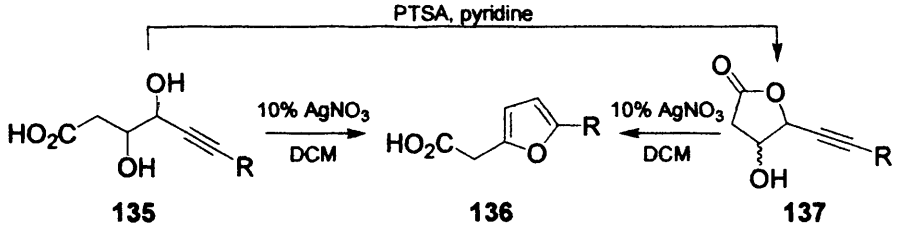


Spectrum 5: ^{1}H NMR spectrum of diol **135b** (MeOD) and furan **136b** ($CDCl_3$).



Spectrum 6: ^{1}H NMR spectrum of lactone **138** and **140** ($CDCl_3$) cyclising to furan **136a** ($CDCl_3$).

Table 2: Synthesis of furylacetic acids.

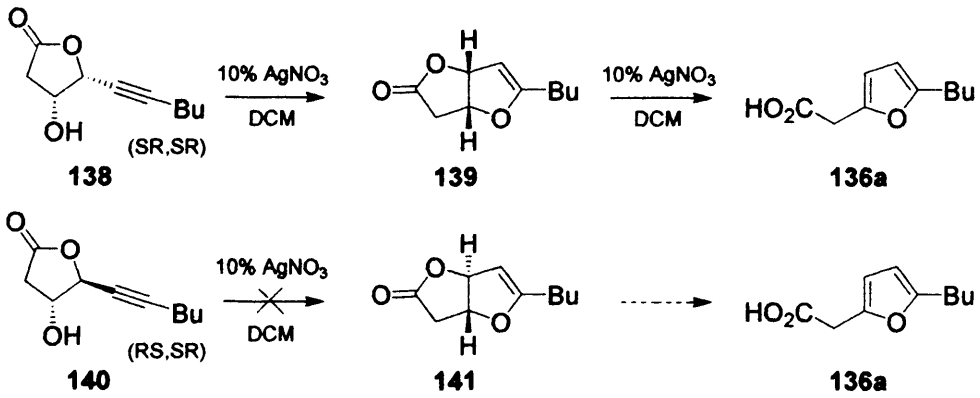


3-alkyne-1,2-diol	Functional Group		R	Furan	Yield (%)
135a	CH_2CO_2H	H	Bu	**136a**	96
135b	CH_2CO_2H	H	Ph	**136b**	93
137	Lactone [a]		Bu	**136a** [a]	*ca.* 84 [b]

[a] lactone group ring opens during cyclisation to yield R^1=CH_2CO_2H, R^2=H.

[b] combined yield of furan and uncyclised lactone isomer.

It is likely that successful cyclisation occurred with the (*SR,SR*)-isomer **138** (Scheme 31), to yield furylacetic acid **136** *via* a *cis*-fused 5/5 bicyclic intermediate **139**. These ring systems are less strained and, with the presence of the acetoxy leaving group, they form furylacetic acid **136** in excellent conversions, >95%. The (*RS,SR*)-isomer **140** failed to cyclise altogether, most likely due to the need for a *trans*-5/5 bicyclic intermediate **141**, which would be highly strained. The presence of a carbon-carbon double bond and sp^2 carbonyl makes this system even less likely to form.



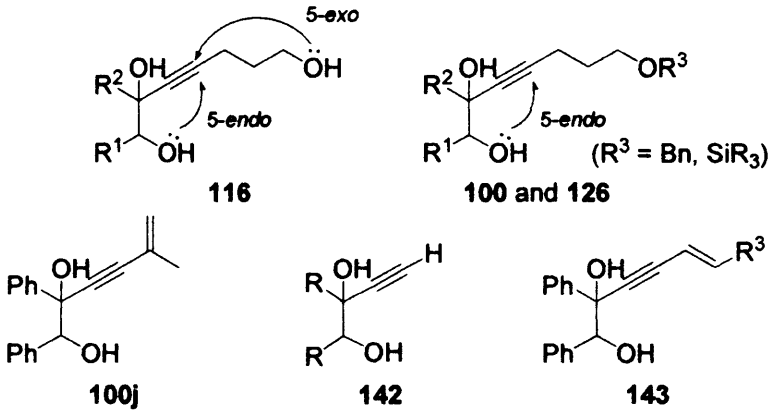
Scheme 31: Stereoselective furylacetic acid **136a** synthesis.

More general diastereomeric observations, applicable to many of the 3-alkyne-1,2-diols **100a-o, 126a-d** and **136a-b** discussed in Tables 1-2, are addressed later (Chapter 2.3.2 – p 37).

2.2.4: Limitations

Throughout the course of this project, it has been shown that there are, as with the vast majority of synthetic procedures, certain limitations. It had been previously shown that divalent sulfur is not compatible with this cyclisation procedure and it is obvious that tetrasubstituted furans are unattainable directly through the silver(I)-catalysed cyclisation. Another general observation seen previously, and still apparent in these results, was that of silver leaching. It was apparent at this stage that a 'pure' product could not be obtained without filtration through celite, thus preventing the re-use of the silver(I) salt. Investigations into resolving the issue of the immobilisation of silver(I) are discussed later (Chapter 5 – p 81).

Other results of this study highlighted the risk of a competitive 5-*exo*-dig cyclisation [see **116**] in appropriate cases, but this has been shown to be avoidable with the implementation of benzyl **100d,i,m** or silyl **100c,h** and **126b-d** protection strategies (Scheme 32) (Chapter 2.2.1 – p 24). Despite this incurring an additional cost to the procedure, the use of protecting groups often has further benefits to the success of other steps, namely in the improved efficiency of addition of alkynols **99** ($R^3 = (CH_2)_nOH$) to α-hydroxycarbonyls **98** (Scheme 21 – p 16).

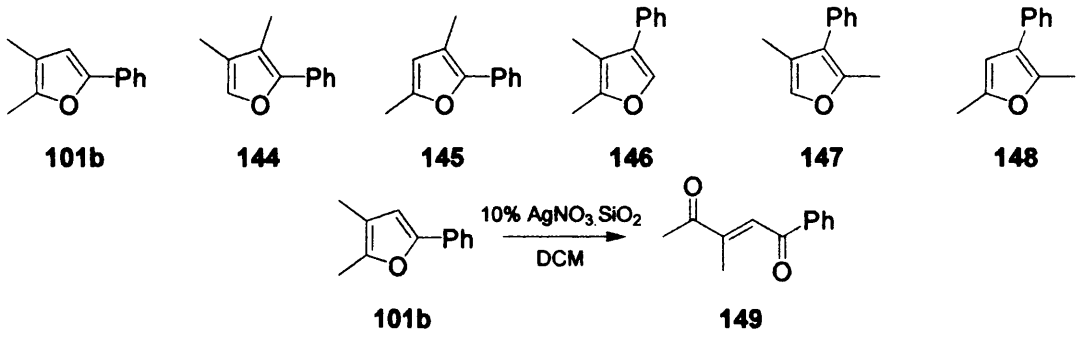


Scheme 32: Limitations of the silver cyclisation.

The inability to cyclise diol **100j** also appeared to show a limitation. Addition of 10% $AgNO_3.SiO_2$ to a solution of diol **100j** failed to produce the desired furan **101j**. Instead the complex nature of the ^1H NMR spectrum meant that no firm conclusions could be drawn to as what actually did happen. A possible explanation is the nucleophilic addition (by water, or other molecules) to the terminus of the exposed enyne system when activated by silver(I). If the adjacent hydroxyl were also to be lost, one could envisage cumulene formation. Terminal alkyne diols **142** (R = Me or Ph) also failed to cyclise, with only starting material recovered. It is

however expected that the use of non-terminal alkene substituents **143** may still be compatible with the silver(I)-catalysed cyclisation (Scheme 32), in view of a similar result seen with the iodocyclisation.[11-15] Indeed, evidence described later suggests that this is the case (Chapter 6.2 – p 117) however, an example where the proposed non-terminal alkene substituent is in conjugation with the alkyne **[143]** has not been tested as yet.

A final observation is offered as a caveat. It was seen, particularly in the synthesis of 2,3-dimethyl-5-phenylfuran **101b**, that, upon prolonged exposure to 10% $AgNO_3.SiO_2$, cyclisation produced a second product. With a singlet at 6.75 ppm (J = 1.6 Hz) and a full set of aromatic peaks, as well as a fresh pair of methyl singlets at 2.30 ppm and 2.05 ppm (J = 1.6 Hz), it seemed plausible that the product was closely related to the furan **101b** formed initially. Thus, it was felt that the product might be either a "migrated" furan derivative **144→148** or the product of oxidation **149** (Scheme 33).



Scheme 33: Methyl migration and oxidation.

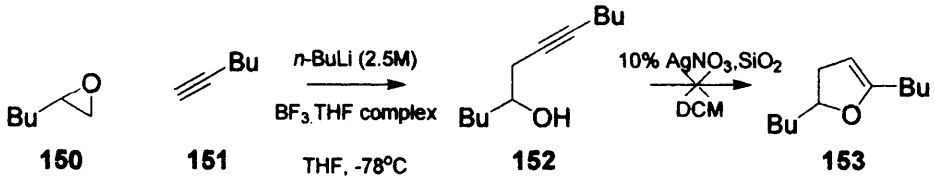
Interestingly, there had been some further evidence of such transformations when using either a heated flow system (Chapter 5.2.4 – p 97) and/or microwave irradiation (Chapter 5.2.4 – p 100). Literature ^1H NMR data[72] had suggested that this product may indeed be a furan **[*e.g.* 144]**. Further investigation into the literature, with particular focus on ^{13}C NMR data, helped identify its true nature. Using the data available,[72] and the further evidence from ^{13}C NMR, it was shown that 1,4-dione **149** was the species formed. Therefore, with careful monitoring, it was possible to synthesise a clean sample of the desired furan **101b** in excellent yield (>95%). Prolonged exposure of furan **101b** to 10% $AgNO_3.SiO_2$, over a period of several weeks, led to the observation of a third product at the expense of dione **149**. It is felt that this third product may in fact be one of the migrated furans **144→148**; however, with the lack of literature ^{13}C NMR data, these "migrated" structures can only be tentatively proposed.

In a recent development, with the help of Taheri, the synthesis of pure dione **149** has now been robustly achieved. It was shown that microwave irradiation of furan **101b** in THF at elevated temperature (130°C), in the presence of 10%$AgNO_3.SiO_2$ (1 eq), successfully yielded dione **149** in excellent yields (>95%) within 1 h. Exposure of other furans **101** to the same conditions yielded analogous products, but high yields were only observed with furans which contained an α-phenyl substituent. As a result of these studies, it can be recommended that care be taken when performing the silver(I)-catalysed cyclisations at higher temperatures, and completed reactions carried out at ambient temperature should be worked up immediately.

2.3: Silver-catalysed cyclisation

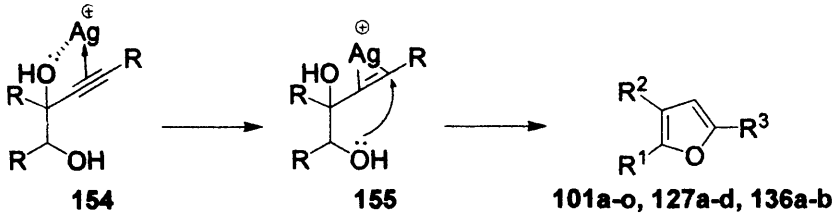
2.3.1: Mechanistic elucidation

Given the success of the silver-catalysed cyclisations, efforts were made to try to ascertain how and why the cyclisation proceeds. With previous literature having alluded to the "remarkable accelerating effect of a propargylic C-O bond"[73] in silver-catalysed cyclisations of other acetylenic alcohols, it seemed prudent to investigate the effect of the propargylic C-O bond on our system. Addition of 1-hexyne **151** to 1,2-epoxyhexane **150** yielded the required β-alkynol **152** in excellent yield (97%) (Scheme 34).[74] Upon addition of 10% $AgNO_3.SiO_2$, only starting material **152** was recovered.



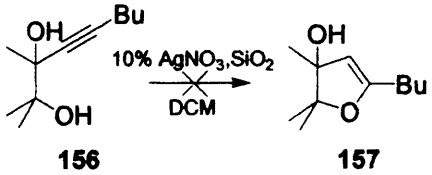
Scheme 34: The importance of propargyl alcohol.

This suggests that the propargylic alcohol functionality is required to instigate a successful cyclisation reaction, as suggested by Dalla and Pale (Scheme 35).[73, 75] According to their rationalisation, it seems likely that the propargylic oxygen coordinates the silver within close proximity to the alkyne bond **154**, which allows attack by the β-heteroatom **155** to yield furan **101a-o**, **127a-d** and **136a-b**, at least in the case of furan formation when the nucleophile is a primary or secondary alcohol.



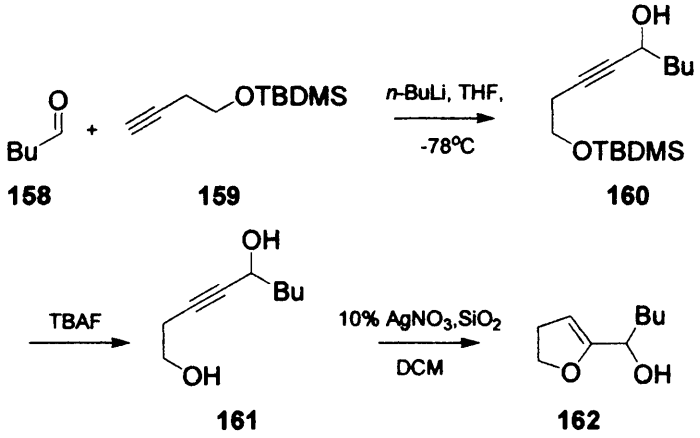
Scheme 35: Silver co-ordination by propargylic alcohol.

In another approach to determine the driving force of the reaction, the diol β-hydrogens were replaced with methyl groups to prevent aromatisation. Addition of 10% $AgNO_3.SiO_2$ to a solution of the β-*gem*-dimethyl-1,2-diol **156** in dichloromethane, resulted in no cyclisation, but rather yielded an unknown product that might be due to degradation.[76] The inability of diol **156** to cyclise to the dihydrofuran **157** (Scheme 36) suggested that aromatisation is a requirement for a successful cyclisation, possibly by providing a thermodynamic 'sink' for the furan product.



Scheme 36: β-gemdimethyl-1,2-diol **156** cyclisation.

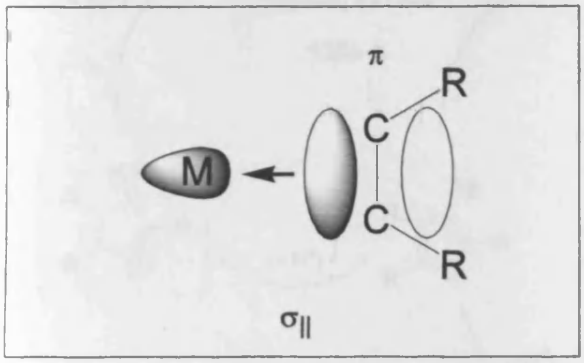
To test this, a final modification involved the movement of the propargyl alcohol to an *exo* position **161**. In this position, the propargyl alcohol would still be present to encourage co-ordination of the silver to the alkyne bond, but it would not be situated in a position where aromatisation could occur, without additional rearrangement. Addition of *O*-TBDMS-3-butyn-1-ol **159** to valeraldehyde **158** (80%), followed by deprotection of the resulting homopropargylic alcohol **160**, yielded the desired 3-alkyne-1,5-diol **161** (88%) (Scheme 37).



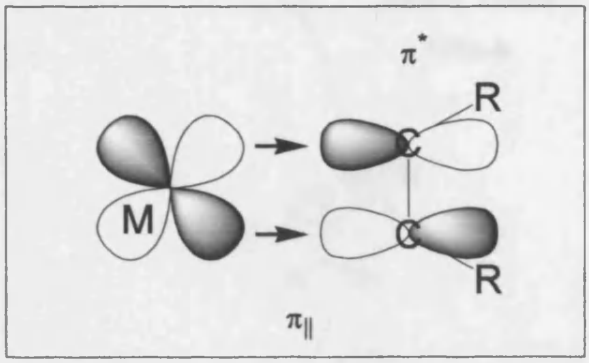
Scheme 37: *Exo* propargyl alcohol **161**.

Cyclisation with 10% $AgNO_3.SiO_2$ led to the formation of dihydrofuran **162**, containing unreacted starting diol **161**. Prolonged exposure, in an attempt to achieve complete cyclisation, saw decomposition of the initial product **162** to unknown products.[76] This observation deserves further attention, but clearly is not currently a viable dihydrofuran synthesis. It does however suggest that aromatisation may not be critical to a successful cyclisation but may be a requirement for robust, stable reaction products.

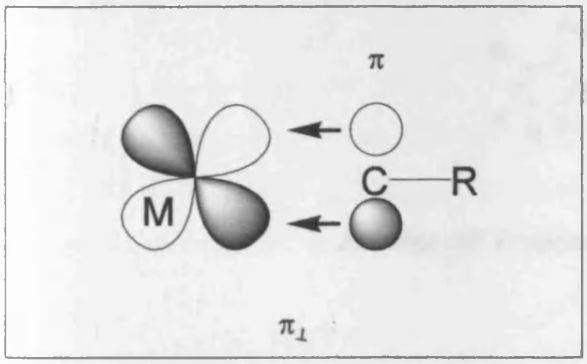
With the above observations in hand, we propose a mechanistic pathway through which the silver cyclisation of 3-alkyne-1,2-diols proceeds. Starting with the known coordinating abilities of the propargyl alcohol, one would expect the silver to be directed into a position where it bridges the alkyne bond through acceptance of π-electrons into its lowest unoccupied molecular orbital, in the case of silver, a σ-orbital. Molecular orbital theory then suggests that an occupied d-orbital, most likely a d_{xy}, d_{xz} or d_{yz} orbital, donates electrons to the empty π^*-orbital of the alkyne to help form a stronger interaction. This phenomenon is known as back bonding and is best shown by the Dewar-Chatt-Duncanson model (Figure 6).



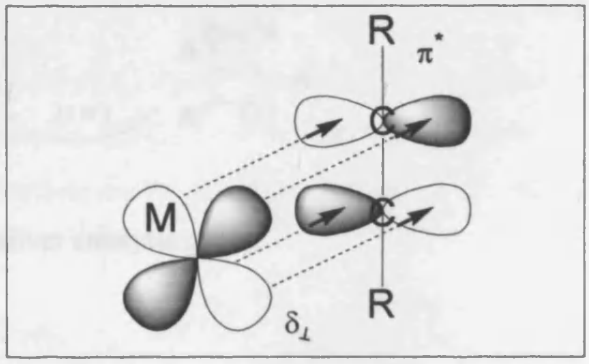
(1) π-electron donation to metal $\sigma_{||}$-orbital.



(2) d-orbital back bonding to alkyne π-orbital.



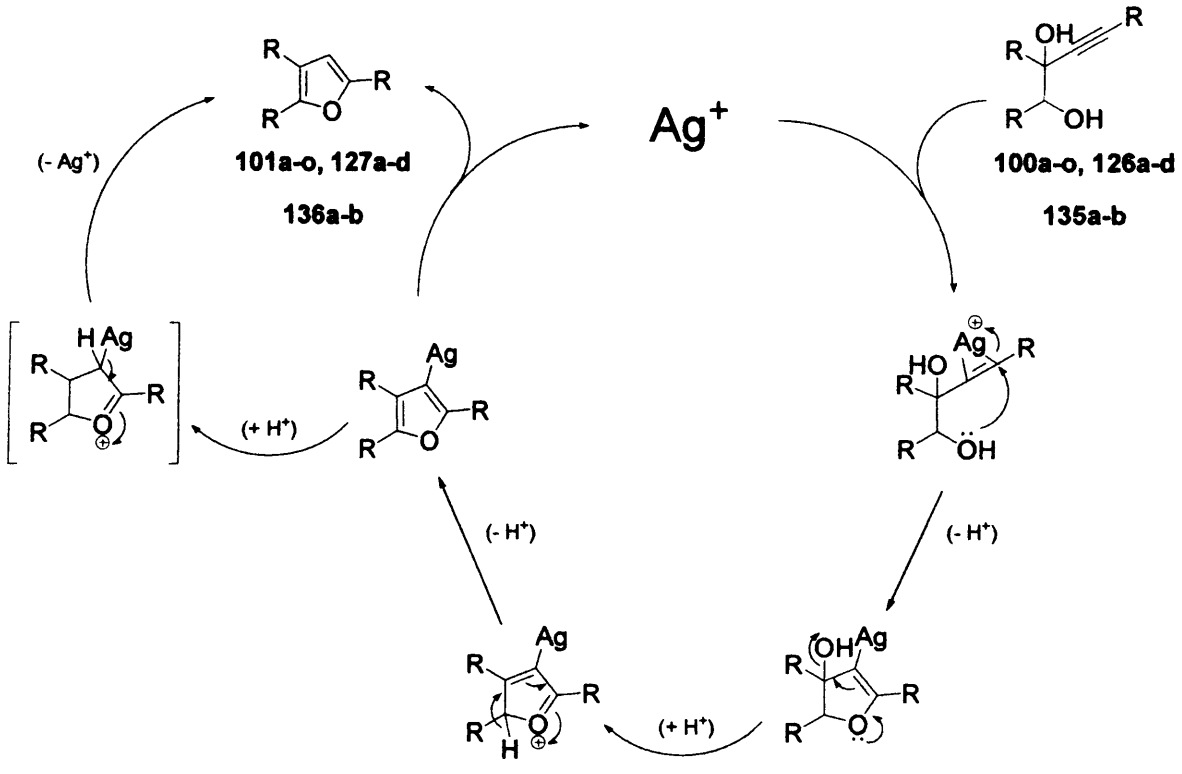
(3) π-electron donation to metal d-orbital.



(4) d-orbital back bonding to alkyne π-orbital.

Figure 6: Dewar-Chatt-Duncanson model: Four-bonding interactions of an alkyne and metal.

The effect of donation of the alkyne π-electrons to the silver σ-orbital is to make the alkyne electron deficient, which in turn makes it amenable to nucleophilic attack. Attack of the β-heteroatom results in ring closure *via* a formal 5-*endo*-dig transformation. Donation of the ring heteroatoms' lone pair into the newly formed cycle allows for elimination of the α-hydroxyl group. This results in the formation of an oxonium ion which readily loses a proton to form the observed furan (Scheme 38). Finally, it is believed that the silver undergoes Ag^+/H^+ exchange. Although it is not clear when or exactly how this happens, this concept seems plausible given both the acidic nature of the support and the presence of the nitrate counter ion, which together can be used to abstract the silver atom from the furan intermediate. Further evidence is provided by Nishizawa's investigations into the use of mercury triflate, where he proposed a similar exchange concept.[35, 77]

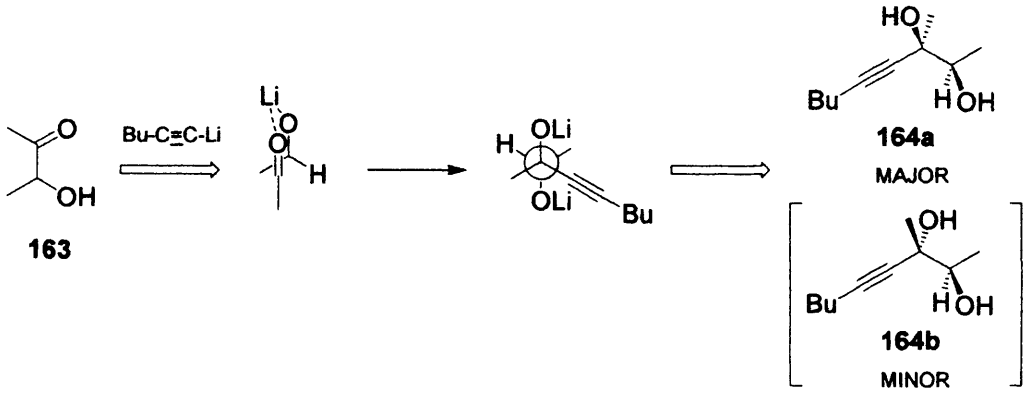


Scheme 38: Proposed silver catalytic cycle.

2.3.2: Stereochemistry

Stereochemical control is crucial to many chemical transformations, and is equally true for this work. As already identified, stereochemistry had an effect not only on the rate of cyclisation, but in one particular case, on the ability to cyclise altogether. In the case of the lactone cyclisation, it was clear that the required *trans*-5/5 bicyclic intermediate **141** of the (*RS,SR*) isomer was too strained to permit cyclisation, (Scheme 31 – p 30). All other general examples **100a-m, 126a-d, 135a-b and 137** did not have this large ring strain and thus only their rate of cyclisation, rather than their ability to cyclise, was seen to be affected.

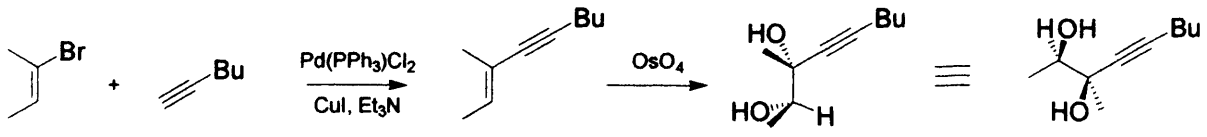
Thus, to understand the effects of stereochemistry on the rate of cyclisation, it is first necessary to confirm the nature of the major isomer formed. In the case of 3-methylnon-4-yne-2,3-diol **164**, a 68:32 ratio of isomers was observed. Assuming chelation control prevails, a provisional Felkin-Anh assessment alluded to the stereochemistry of the major isomer **164a** to be *syn* and the minor isomer **164b** to be *anti* (Scheme 39).



163 **164a** MAJOR **164b** MINOR

Scheme 39: Felkin-Anh elucidation of stereochemistry - Chelation control.

In a bid to confirm the above, 3-methylnon-4-yne-2,3-diol **164a** was stereoselectively synthesised. A Sonogashira coupling of (*E*)-2-bromobut-2-ene **165** with 1-hexyne **166** yielded an enyne **167** (Scheme 40). Sharpless asymmetric dihydroxylation with the $(DHQD)_2$-PHAL ligand allowed for isolation of the *syn*-diol **164a** (Scheme 40).[64-66]

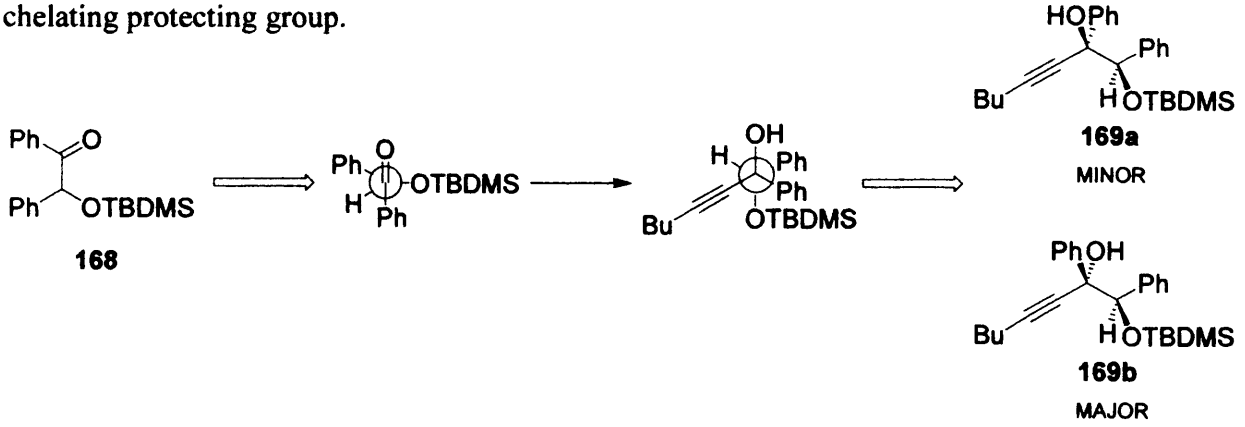


165 **166** **167** **164a**

Scheme 40: Stereoselective approach to *syn*-3-methylnon-4-yne-2,3-diol **164a**.

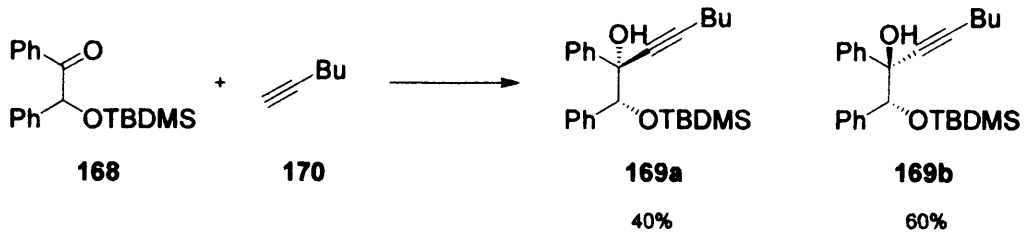
The ^{1}H NMR spectra of the diastereomeric mixture obtained through the addition of lithiated-1-hexyne to 3-hydroxybutan-2-one **163** (Scheme 39) showed the presence of two isomers, with the 2-H proton seen at 3.70ppm for the major isomer and 3.52ppm for the minor isomer. Comparison with the ^{1}H NMR spectra of the stereoselectively synthesised *syn*-3-methylnon-4-yne-2,3-diol **164a**, where 2-H was seen at 3.70ppm, confirmed the major diastereomer from the mixture to be the *syn*-diol **164a**. This result appears to agree with the Felkin-Anh model analysis (Scheme 39), if chelation control is indeed true.

Therefore, to test whether this was the case, the effect of protection groups was assessed. One would expect that if chelation control is predominant, then the presence of a non-chelating protecting group on the α-hydroxy group should change the selectivity of the addition. A good example would be the use of a silyl protection strategy. With the direct addition of 1-hexyne to benzoin having been seen to be almost stereospecific (99:1) in favour of the presumed *syn*-type diastereomer **169a** (OH in place of *O*-TBDMS = **100e**), a Felkin-Anh model with TBDMS-benzoin **168** was used (Scheme 41). This suggests that the previously observed minor *anti*-type isomer **169b** would now be favoured over the *syn*-type isomer **169a** upon the use of a non-chelating protecting group.



Scheme 41: Felkin-Anh elucidation of stereochemistry - Non-chelation control.

It was found that addition of 1-hexyne **170** to *O*-TBDMS-benzoin **168** resulted in the observation of the proposed stereochemistry with a ratio of *syn*- **169a** to *anti*- **169b** being 40:60 (Scheme 42).



Scheme 42: Addition of 1-hexyne **170** onto *O*-TBDMS-benzoin **168**.

This observation was important as the enforcement of non-chelation control successfully inverted the selectivity, of what was a highly selective addition, in favour of the minor isomer. As a result, this appears to support the previous concept of chelation control in the formation of unprotected 3-alkyne-1,2-diols **164a,b**.

Final confirmation came from the successful procurement of an X-ray crystal structure (Appendix A) for the major isomer of diol **100f**, obtained *via* the chelation control pathway. It can be seen clearly that, as predicted, the hydroxyl groups are situated *syn* to one another (Figure 7). All bond angles and lengths appear normal and there appears to be hydrogen bonding between O1 and the hydrogen attached to O2, which has further implications (Scheme 43).

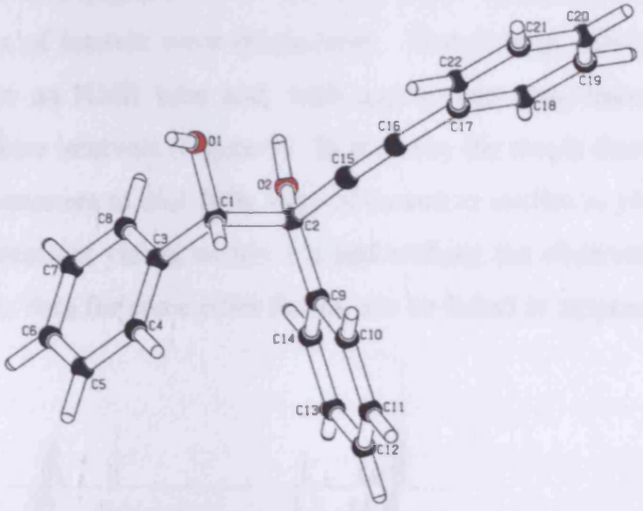
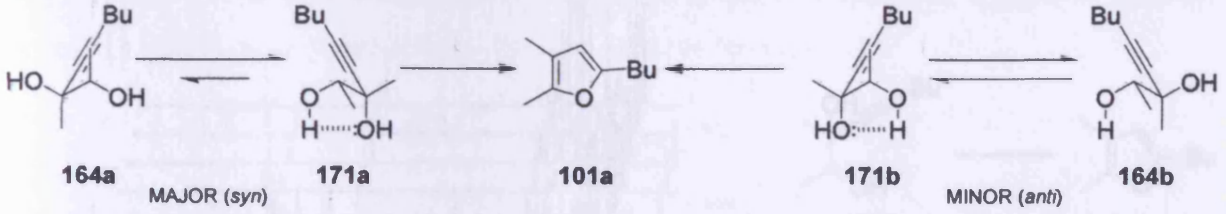


Figure 7: X-ray structure of *syn*-diastereomer of diol **100f**.

Having determined the issues of selectivity upon addition to an α-hydroxyketone, it is now possible to consider the effect of stereochemistry on the rate of cyclisation. The synthesis of both *syn*- **164a** and *anti*- **164b** diastereomers implies two possible cyclisation alignments (Scheme 43).



Scheme 43: Cyclisation of *syn*- **164a** and *anti*- **164b** diastereomers.

It can be seen in Scheme 43 that the more stable conformation of the major *syn*-isomer **171a**, where the bulky side groups (2 x Me) reside in equatorial positions, provides the required

alignment for cyclisation. It also presents a beneficial axial alignment of the propargylic hydroxyl, which perhaps aids proton abstraction from the ring closing heteroatom. The minor *anti*-isomer **164b**, on the other hand, has a sterically demanding axially aligned substituent in both of its alignments **164b** and **171b**, thus the equilibrium is not as one sided towards the beneficial axially aligned hydroxyl groups **171b**. With consideration of these factors, one would expect the *syn*-isomer **164a** to cyclise faster, particularly when the methyl substituents are replaced by larger groups, to give furan **101a**.

One of the best ways of assessing the rates of cyclisation is to use continuous monitoring. The use of thin layer chromatography (TLC) to qualitatively analyse the cyclisation of 3-alkyne-1,2-diols in different solvents (Chapter 2.3.3 – p 41) was less applicable to this situation since some of the diastereomers of interest were inseparable. Fortuitously, silver(I)-catalysed cyclisations can be performed in an NMR tube and, with appropriate programming, can be continuously analysed at regular time intervals (Figure 8). In this way the single diastereomer of diol **100e** and the combined diastereomers of diol **100a** were observed to cyclise to yield their respective furans **101a** and **101e** in excellent yields, within 4 h and without the observation of any intermediates. Further spectroscopic data for some other furans can be found in Appendix B and C

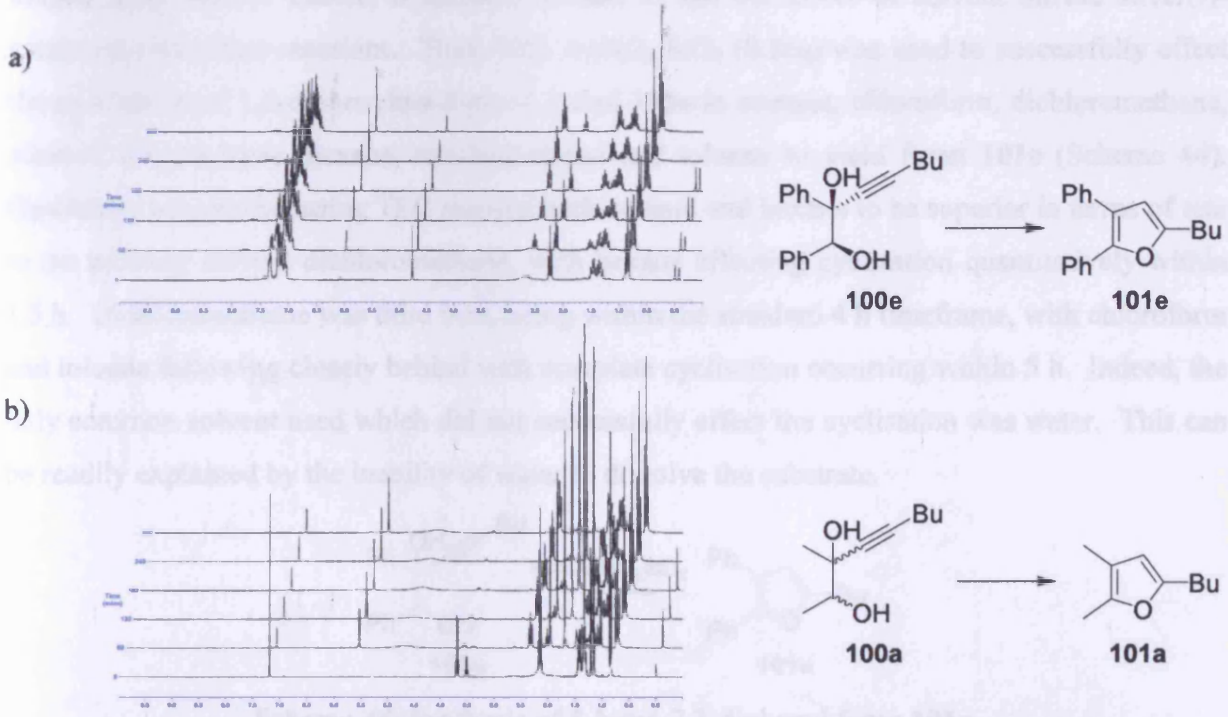


Figure 8: Continuous *in situ* monitoring by ^{1}H NMR spectroscopy.

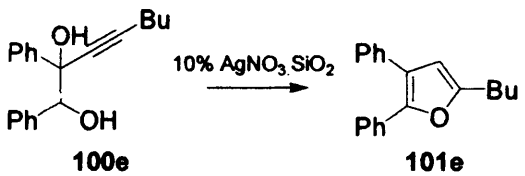
a)1,2-diphenyloct-3-yne-1,2-diol **100e** ($CDCl_3$). b) 3-methylnon-4-yne-2,3-diol **100a** ($CDCl_3$).

Performing a similar analysis on the mixture of diastereomers of 3-methylnon-4-yne-2,3-diol **100a** allowed for the relative rates of cyclisation of the *syn*- **164a** and *anti*- **164b** isomers to be continuously monitored (Figure 8b). It was found that in a 2:1 mixture, the major *syn*- **164a** isomer cyclised faster than the minor *anti*- **164b** isomer, as expected. Indeed, the cyclisation is seen to proceed at approximately twice the rate of the *anti*-isomer **164b**, a significant time saving.

Thus, with the above results in hand, it can be confirmed that the observed stereochemistry occurs as a result of chelation control, except where protection strategies are used. Unsurprisingly this has been shown to have important implications on the overall rate of cyclisation, and should certainly be considered when choosing whether or not to implement protection strategies. It adds purpose to the use of a Sonogashira pathway given the reliability of Sharpless dihydroxylation.

2.3.3: Solvent effect

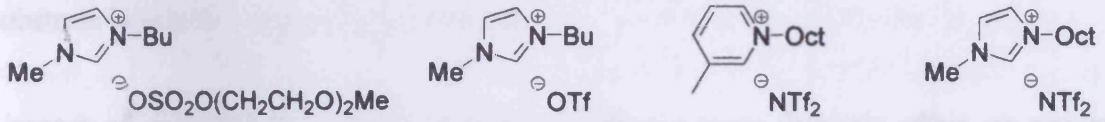
Historically, dichloromethane had been the chosen solvent for these cyclisations. With the previous experience of other group members having shown that certain iodocyclisation reactions hinged upon solvent choice, it seemed prudent to test the effect of solvent on the silver(I)-catalysed cyclisation reactions. Thus, 10% $AgNO_3.SiO_2$ (0.2eq) was used to successfully effect the cyclisation of 1,2-diphenyloct-3-yne-1,2-diol **100e** in acetone, chloroform, dichloromethane, ethanol, ethyl acetate, hexane, tetrahydrofuran and toluene to yield furan **101e** (Scheme 44). Qualitative monitoring using TLC showed both ethanol and hexane to be superior in terms of rate to the existing solvent dichloromethane, with hexane effecting cyclisation quantitatively within 1.5 h. Dichloromethane was third best, being within the standard 4 h timeframe, with chloroform and toluene following closely behind with complete cyclisation occurring within 5 h. Indeed, the only common solvent used which did not successfully effect the cyclisation was water. This can be readily explained by the inability of water to dissolve the substrate.



100e **101e**

Scheme 44: Synthesis of 5-butyl-2,3-diphenyl furan **101e**.

Additionally, a short time was spent assessing the use of ionic liquids. In preparation for work which was performed with David Cole-Hamilton (Chapter 5.3 – p 105),[78] the ionic liquids [bmim][$OSO_2O(CH_2CH_2O)_2Me$] **172** and [bmim][OTf] **173** (Scheme 45) were successfully employed for the cyclisation of 1,2-diphenyloct-3-yne-1,2-diol **100e** to its corresponding furan **101e** in similarly essentially quantitative yields (>95%) (Scheme 44).



172 **173** **174** **175**

Scheme 45: Ionic liquids to effect cyclisation.

The further successful use of [omim][NTf_2] **174** and [ompy][NTf_2] **175** (Scheme 45) had important implications for use in our second novel flow system for heterocyclic synthesis (Chapter 5.3 – p 105).

2.3.4: Rate studies

At this point, having been able to make some suggestions for the mechanism and the stereochemical behaviour, efforts were made to optimise the reaction kinetics using our existing dichloromethane system. Using 1,2-diphenyloct-3-yne-1,2-diol **100e** as a standard (Scheme 44), 100μL samples were taken at frequent intervals and assayed using ^{1}H NMR spectroscopy. The data generated allowed an assessment of the effect of both substrate concentration and catalyst equivalence on the rate of reaction to be made (Chart 1).

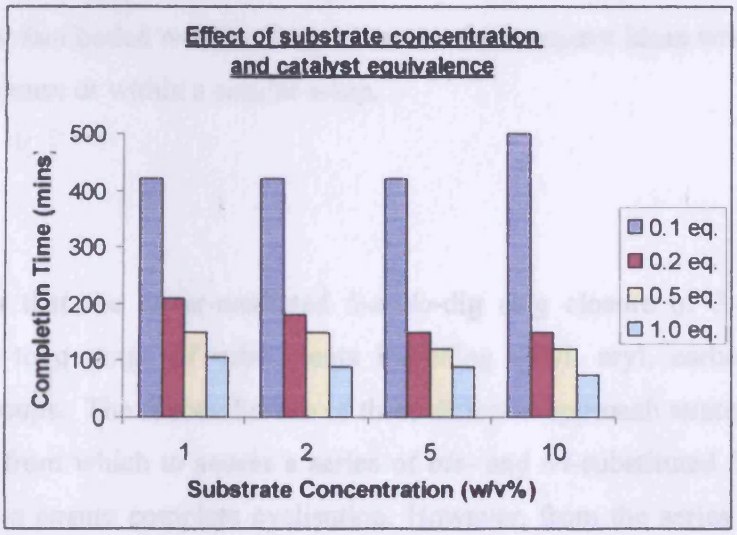


Chart 1: Conversion data: Effect of substrate concentration and catalyst equivalence.

Consideration of the variation in substrate concentration showed that, on the whole, the more concentrated the solution and the more catalyst present then the shorter the overall reaction time. This can be seen clearly in Chart 1 with complete conversion occurring between 75-150 mins for the most concentrated solutions tested. Interestingly the reaction profile of each solution showed the expected concentration dependent curve, where maximal conversion is seen early on when the substrate is in effect saturating the catalyst.

The impact of catalyst concentration seemed to induce a more dramatic effect, as one might expect, given that even a slight increase in catalyst equivalence was enough to accelerate cyclisation significantly. In fact, this acceleration was most dramatic between lower catalytic boundaries, i.e. between 10 mol% and 20 mol% catalyst use, where the 20 mol% catalytic reactions were all seen to achieve completion in less than half the time of the corresponding 10 mol% reactions. Beyond a catalyst equivalence of 20 mol%, there were marginal improvements in rate relative to the increase seen between 10 mol% and 20mol%. Indeed, when using stoichiometric $AgNO_3.SiO_2$ catalyst, the rate was seen to increase by a factor of two relative to the rate shown when using 20 mol% catalyst, yet the molar equivalence of silver had increased by a factor of five.

It is of note that any change in concentration appears to be much less significant than a change in the equivalence of catalyst, with regard to the rate of reaction. Indeed the data shows an overall increase in rate of cyclisation, across the range tested, by a factor of 1.4 for a 10-fold increase in substrate concentration compared to a change of 6.7 for a 10-fold increase in the amount of catalyst. All of this data boded well for the pursuance of subsequent ideas where the catalyst was to be placed in a column or within a similar setup.

2.4: Conclusion

It has been shown that the silver-mediated 5-*endo*-dig ring closure of 3-alkyne-1,2-diols is broadly applicable to a range of substituents including alkyl, aryl, carboxyl, hydroxyl and substituted vinyl groups. The successful use of three different approach strategies has provided a variety of avenues from which to access a series of *bis*- and *tri*-substituted furans. Many were cyclised overnight to ensure complete cyclisation. However, from the series of rate studies one would expect the majority of these to be complete within 4-6 h. In a handful of cases the

prolonged exposure to 10% $AgNO_3.SiO_2$ caused ring opening, and perhaps methyl migration, however under standard conditions this was not an issue in the majority of cases.

The observed competitive 5-*exo*-dig cyclisation reaction is of interest. Although an undesired side reaction in the synthesis of furans **127b'**, this observed transformation has great potential. For instance one could imagine, given appropriate substrates, the use of the silver(I)-catalysed cyclisation in the synthesis of a series of 2-alkylidenetetrahydrofurans **118**, and perhaps even a series of pyrrolidine-2-ylidenes.

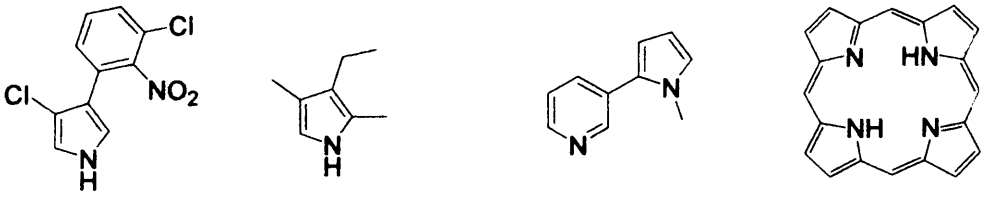
With the effects of stereochemistry and solvent nature having been assessed, as well as substrate and catalyst concentration dependence, a range of operation conditions have been identified. It appears that optimal cyclisation is observed when using the *syn* diastereomer as a highly concentrated solution in hexane or dichloromethane. The use of 10% $AgNO_3.SiO_2$ in differing amounts had a marked effect on the overall rate, with an optimum of 20 mol% perhaps being seen as the most efficient relative to the amount of catalyst required. With the above work displaying the vast potential of this technique, a solid foundation, from where the rest of this project is built, has been laid.

Chapter 3: Results and Discussion

Synthesis of Pyrroles

3.1: Introduction

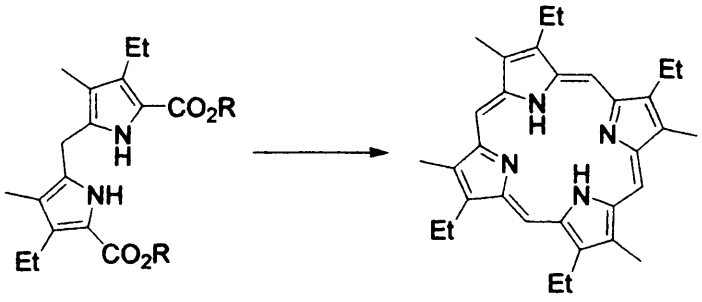
Like furans, pyrroles **83** are important targets in drug development and elsewhere. They, and their derivatives, are used in a range of highly successful therapeutics and are found throughout nature, *e.g.* pyoluteorin **176**, kryptopyrrole **177**, *β*-nicotyrine **178** and the porphyrin ring system **179** (Scheme 46).



176 **177** **178** **179**

Scheme 46: Important examples of substituted pyrroles.

Porphyrins **179** and **181**, found in haem and chlorophyll derivatives, have long been a target of many synthetic chemists. Traditionally, these were synthesised through the condensation of dipyrrolic intermediates **180** (Scheme 47),[80] but suffered from the need for symmetry in order to avoid complex mixtures of isomers.

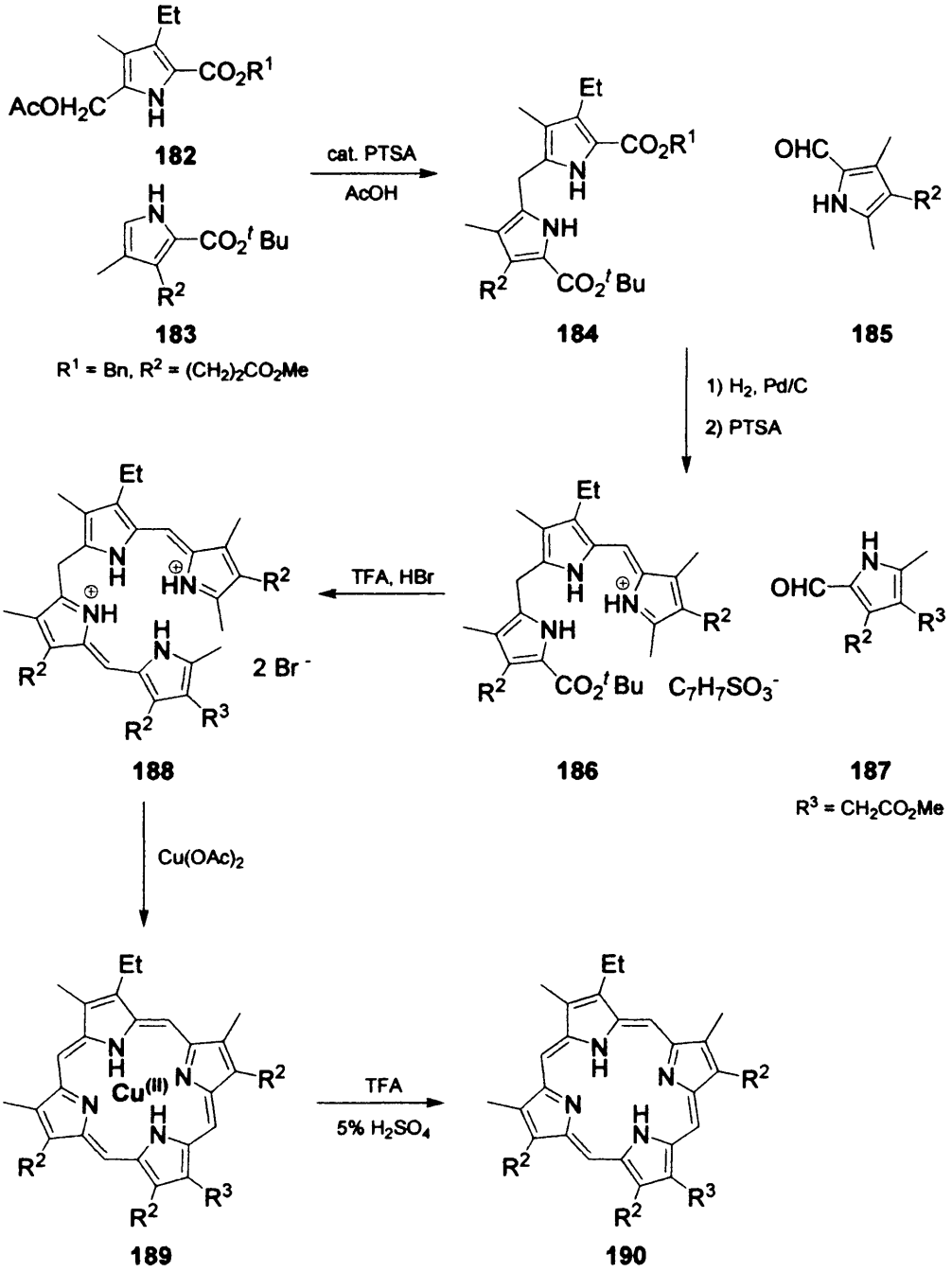


180 **181**

Scheme 47: Classic synthesis of porphyrins **181**.

Following this work, Kenner described the stepwise synthesis of unsymmetrically substituted porphyrins, *via* the progressive synthesis of pyrrole **182**, **183**, **185** and **187**, dipyrrole **184** (72%), tripyrrole **186** (76%) and tetrapyrrole **188** (89%) subunits.[81, 82] Cyclisation of tetrapyrrole **188** in the presence of copper(II) acetate in DMF yielded the copper(II) complex of porphyrin **189**

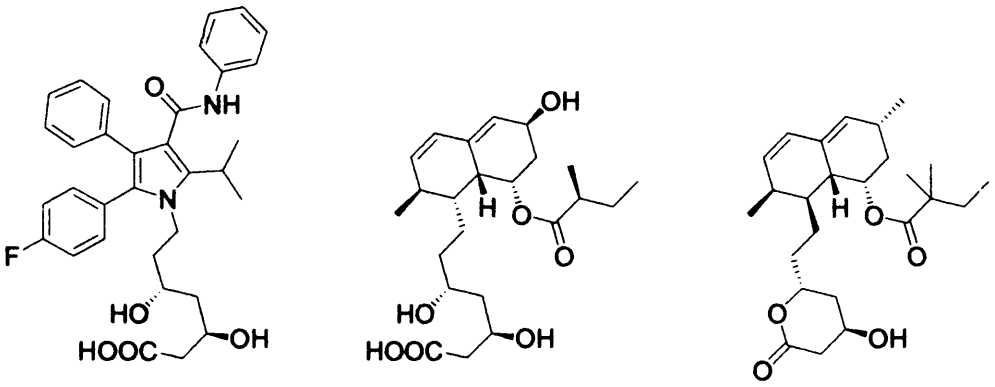
(Scheme 48). Demetallation was effected by the addition of trifluoroacetic acid containing 5% sulfuric acid to yield porphyrin **190** in moderate yield (30%).



Scheme 48: Kenner's porphyrin **190** synthesis.

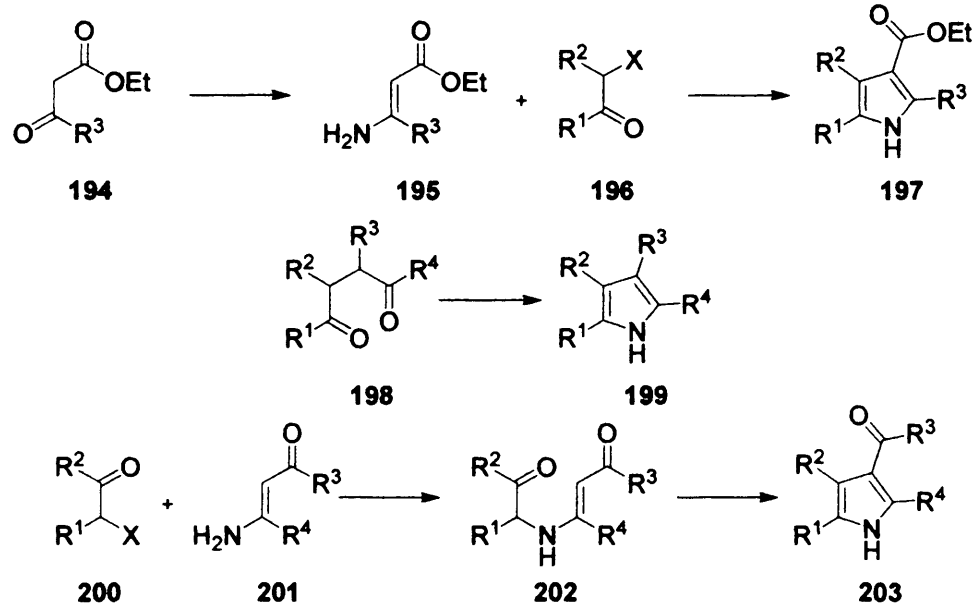
One of the most significant synthetic applications of a pyrrole functionality in recent years has seen its use in atorvastatin **191** (Scheme 49). Like statins **192** and **193**, it acts as a competitive inhibitor of the enzyme HMG-CoA reductase to help lower levels of LDL-cholesterol in the blood.[83] Unlike other statins, for example Pravastatin **192**[84] and Simvastatin **193**,[85] atorvastatin

191 is an entirely synthetic compound and in 2005 traded under the name Lipitor to produce annual sales of $12.2 billion, making it the largest selling drug in the world that year.[83]



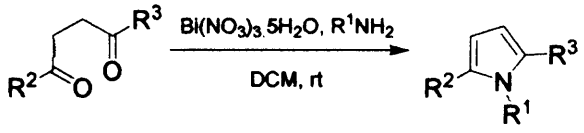
Scheme 49: Atorvastatin **191**, Pravastatin **192** and Simvastatin **193**.

Despite the importance of pyrroles, there are only a few broadly applicable synthetic strategies available to a synthetic chemist. Perhaps the best known of these are the Hantzsch **194→197**[86], Paal-Knorr **198→199**[5-6] and Knorr **200→203**[7-9] syntheses (Scheme 50). These are classic "textbook" reactions, but unfortunately their efficiency and lack of very broad applicability do not reflect as kindly as their fame may suggest. A common example of this is that in many pyrrole syntheses, there is often a requirement for the inclusion of an ester group around the ring as in **197** and **203**. It is further seen, in many examples, that precursor synthesis is more of a problem than the key reaction itself.



Scheme 50: Hantzsch **194→197**, Paal-Knorr **198→199** and Knorr **200→203** pyrrole syntheses.

Despite its limitations, the reputation of the Paal-Knorr reaction **198→199** means that it still attracts much interest. Many have focused on trying to improve the yields of what on paper looks like an appealingly straightforward transformation. A good example of this is seen in a recent modification presented by Banik.[87] He used bismuth nitrate and obviated the need for previous modifications which required acid and/or microwave irradiation (Scheme 51).[88-90]



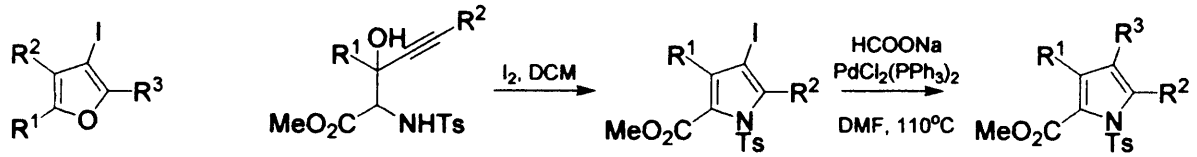
204 **205**

Scheme 51: Banik's modified *Paal-Knorr* synthesis of pyrroles **205**.

With high yields of pyrroles **205** (70-98%), and mild conditions, this approach has certainly made an improvement on many of the previous attempts but still suffers from the major drawback of the *Paal-Knorr* reaction, the relative difficulty in synthesising 1,4-dicarbonyls **204**. While there are very many routes, atom efficiency is often a problem as well as overall yields. Fortunately, there are several less well known synthetic methodologies that are of greater practical interest and, as such, these have found use in the synthesis of several important targets.

3.1.1: Iodocyclisation

Knight's interest in the synthesis of 3-iodofurans **206**[15] had been extended to the synthesis of 3-iodopyrroles **208**[12] *via* the cyclisation of 3-alkyne-2-hydroxy-1-sulfonamides **207** (Chapter 2.1.2 – p 9). Using this method, Singkhonrat was able to successfully synthesise a range of substituted 3-iodopyrroles **208** in high yields (65-85%), which could further be converted into the analogous pyrroles **209** using one of the many Pd ^{0} catalysed coupling reactions now available (Scheme 52).[91]



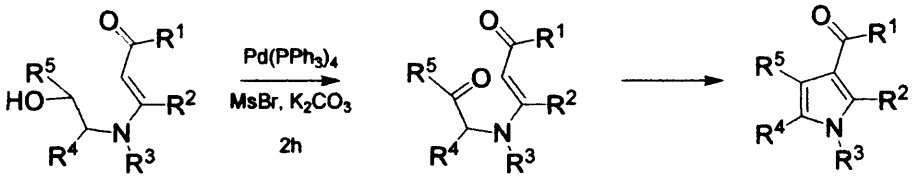
206 **207** **208** **209**

Scheme 52: Synthesis of 3-iodopyrroles **208** using the iodocyclisation protocol.

With complete regioselectivity and high yields, this technique certainly provided a useful approach to a series of synthetically useful pyrroles **208** and **209**. Unfortunately, there were some limitations with this technique, with the need for three equivalents of iodine being of particular concern. There was therefore still a reliance on other techniques for the synthesis of many other substituted pyrroles **209**.

3.1.2: Catalytic synthesis of pyrroles

As with furans, there are a variety of catalysed procedures for the synthesis of pyrroles. Both copper[92, 94] and palladium[93, 94] salts are good examples of this but, as with most synthetic approaches to pyrroles, their success is often restricted to only a handful of examples. For instance, Takeya has described a palladium-catalysed oxidation of hydroxy-enamines **210** to keto-enamines **211**, which then yielded polysubstituted pyrroles **212** in mixed yields (36-84%) (Scheme 53).[93]

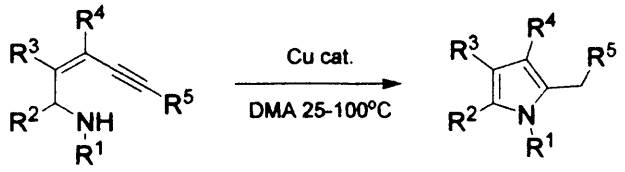


210 **211** **212**

Scheme 53: Takeya's synthesis of polysubstituted pyrroles **212**.

With the need for elevated temperatures (150°C), the required β-ester substituent and the 'moderate' yields, this procedure has severe limitations. Despite allowing for the inclusion of a range of substituents, the overriding limitations prevent this technique from being widely used.

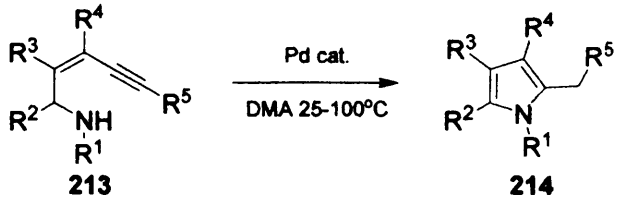
Gabriele has investigated the copper- and palladium-catalysed cycloisomerisation of (*Z*)-2-en-4-yn-1-amines **[213;** $R^3 \neq H$**]**.[94] In a similar transformation to that featuring the previously discussed (*Z*)-2-en-4-yn-1-ols **56**[26, 26-38, 43] (Chapter 2.1.3 – p 10), the corresponding amines **213** undergo cyclisation to yield polysubstituted pyrroles **[214;** $R^3 \neq H$**]** (Scheme 54).



213 **214**

Scheme 54: Gabriele's copper-mediated synthesis of poly-substituted pyrroles **[214;** $R^3 \neq H$**]**.

The conversions in many of these copper-catalysed transformations were found to be excellent (often 100%), however isolation was a problem with somewhat lower yields (63-91%) often being obtained. Alkyl, substituted vinyl and *t*-butyl substituents were all compatible with this cyclisation but there was a requirement in each example that R^3 could not be a proton. The same palladium-catalysed transformations of enynes [**213**; $R^3 \neq H$], in the presence of a co-salt *e.g.* KI or KCl, were not as efficient as their copper counterparts with pyrroles [**214**; $R^3 \neq H$] being isolated in usually moderate yields (25-80%) (Scheme 55).

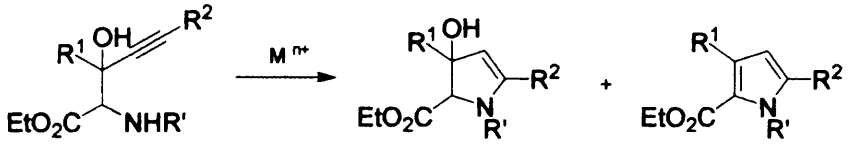


213 **214**

Scheme 55: Gabriele's palladium-mediated synthesis of polysubstituted pyrroles [**214**; $R^3 = H$].

Unlike the copper-catalysed cyclisation, it was found that the palladium-catalysed system was far more suited to enynes [**213**; $R^3 = H$]. In such cases, conversions were excellent (~100%) and isolated yields only fell slightly to 82-87%. With this proven ability to synthesise 2-substituted, 2,4-disubstituted and both 2,3,4- and 2,3,5-trisubstitued pyrroles [**214**; $R^3 = H$], these approaches present a system which has the potential for very broad applications. The variable yields are perhaps somewhat of an issue, but this work marks a significant contribution in a difficult field.

The final significant contributions, regarding the catalysed synthesis of pyrroles, have been described by Knight and Sharland. They successfully cyclised several 3-alkyne-2-hydroxy-1-sulfonamides **215** (R' = Ts) with copper(I) (6 h), palladium(II) (5 h) and mercury(II) (16 h) salts to give 3-hydroxy dihydropyrroles **216a** and pyrroles **216b** in good yields (76-84%), often with selectivity leaned towards the 3-hydroxy dihydropyrroles **216a** (Scheme 56).[16] These reactions were carried out in pyridine-ether mixtures at reflux.



215 **216a** **216b**

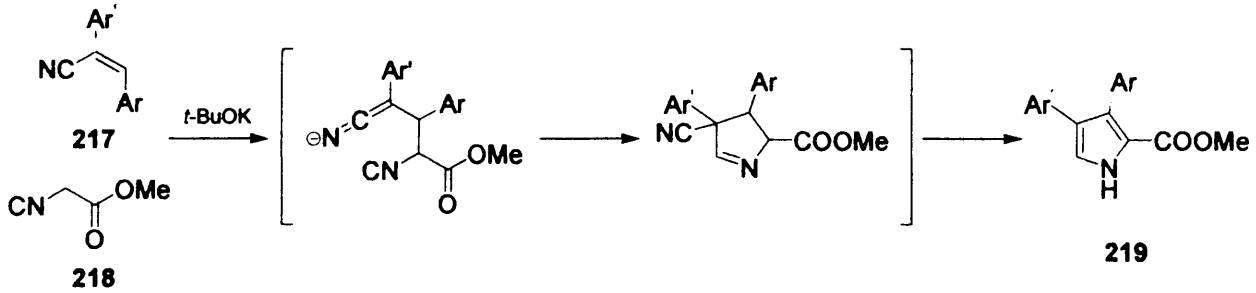
Scheme 56: Metal-catalysed synthesis of pyrrole-2-carboxylates **216**.

Following this work, they successfully employed 10% $AgNO_3.SiO_2$ in the synthesis of a series of pyrrole-2-carboxylates **216b**, which were obtained in excellent yields (>95%) (Scheme 56). Not only were pyrroles **216b** formed selectively but the reaction no longer required pyridine and it proceeded successfully at ambient temperature within 4 h. This was the first example of a silver-catalysed cyclisation of a 3-alkyne-2-hydroxy-1-sulfonamide **215** and formed the basis of the work performed towards the synthesis of the furans **101a-o** **127a-d** and **136a-b** (Chapter 2.2 – p 16). With the high yields came high purity: the only observed side product was water. Furthermore, the reaction conditions were mild and, as has been shown by the work towards the synthesis of furans **101a-o**, **127a-d** and **136a-b**, the reaction itself was very robust and has the potential to be manipulated by temperature, solvent and a range of other variables. With few limitations, and without as strong a competitor as gold in this field, generalisation of this synthesis of pyrroles has the potential to make a considerable impact.

3.1.3: Nitriles in pyrrole synthesis

As a final point of discussion for the synthesis of pyrroles, nitriles and isonitriles are well known for their uses in cycloaddition reactions. Containing both nucleophilic and electrophilic functionalities, they are involved in two bond-forming transitions, which ultimately results in the formation of a nitrogen-containing heterocycle. They have traditionally found applications in the synthesis of pyrazoles but more recently they have also been used in the synthesis of pyrroles.

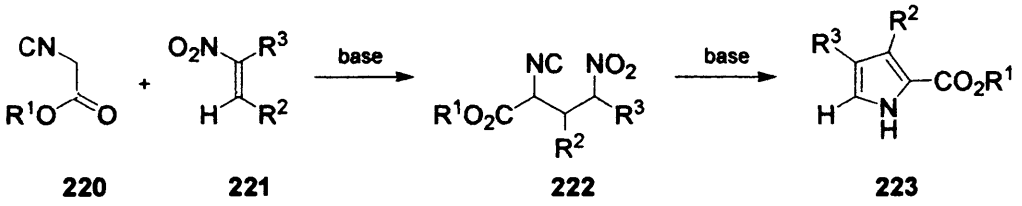
With there being such an interest in developing a simple and broadly applicable synthesis of pyrroles, several groups have looked to utilise nitriles or isonitriles. A good example, presented by Bullington,[95] incorporates the use of isocyanoacetates **218**. Here, an α,β-unsaturated nitrile **217** is coupled with methyl isocyanoacetate **218**, in the presence of potassium *t*-butoxide, to yield a 2,3,4-trisubstituted pyrrole **219** (51-60%) (Scheme 57).



Scheme 57: Bullington's methyl isocyanoacetate [2,3] strategy.

Addressing perhaps one of the most difficult tasks in the synthesis of pyrroles, that of regioselectivity, this technique does have its advantages. Many others require quite varied and convoluted approaches to obtain the desired regioisomers. Despite this, and the simplicity, there is still an untested limitation with the use of only non-enolisable aryl α,β-unsaturated nitriles **217**. The generation of potassium cyanide is of course another concern, one which could limit this technique to preparative scales.

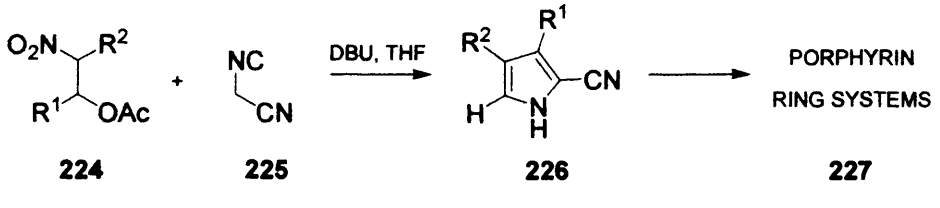
One of the most successful syntheses, which utilises isonitriles, is the Barton-Zard reaction. This reaction has generated much interest and as a result there have been several publications which are based around this reaction. First reported in 1990,[96] Barton and Zard described the synthesis of pyrroles **223** in good yield (55-97%) from nitroalkenes **221** and *α*-isocyanoacetate esters **220** using a procedure which is now widely regarded as one of the most competitive pyrrole syntheses (Scheme 58).



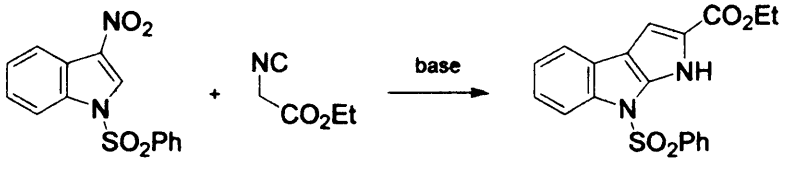
220 **221** **222** **223**

Scheme 58: The Barton-Zard synthesis of pyrroles.

Having shown compatibility with alkyl, aryl and hydroxyl substituents, this procedure has broad applications towards the synthesis of substituted pyrroles **223**. Further successes of the Barton-Zard reaction include its use in the synthesis of *β*-substituted porphyrins **227**[97] and the synthesis of pyrrole[2,3-*b*]indole ring systems **230** (Scheme 59).[98]



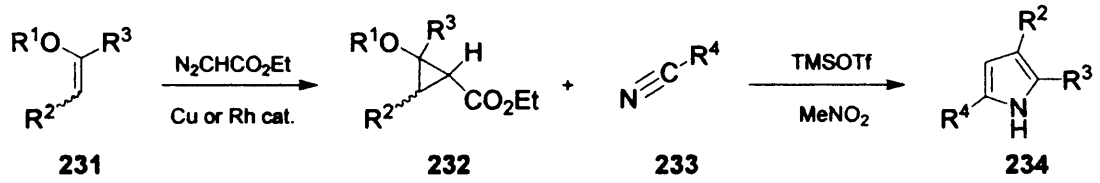
224 **225** **226** **227**



228 **229** **230**

Scheme 59: Synthesis of substituted porphyrins **227** and pyrrole[2,3-*b*]indoles **230**.

The alternative procedure exemplifying the use of nitriles, presented by Pagenkopf,[99] utilises both nitriles **233** and α,β-unsaturated nitriles **217** in combination with cyclopropanes **232** in a [2,3]-cycloaddition (Scheme 60). He showed that pyrroles **234** could be synthesised, *via* a novel cascade [2,3]-dipolar cycloaddition, dehydration and tautomerisation sequence, in often respectable yields (52-93%).



231 **232** **233** **234**

Scheme 60: Pagenkopf's synthesis of pyrroles.

This sequence allows for the inclusion of aryl, alkyl and substituted vinyl groups around the ring system. With further regioselectivity, this procedure has all the makings of an approach which can be used for the efficient synthesis of a vast array of substituted pyrroles. There are of course occasional examples which are not as efficiently synthesised but, even with these in mind, this procedure is perhaps another major competitor in the field of substituted pyrrole synthesis.

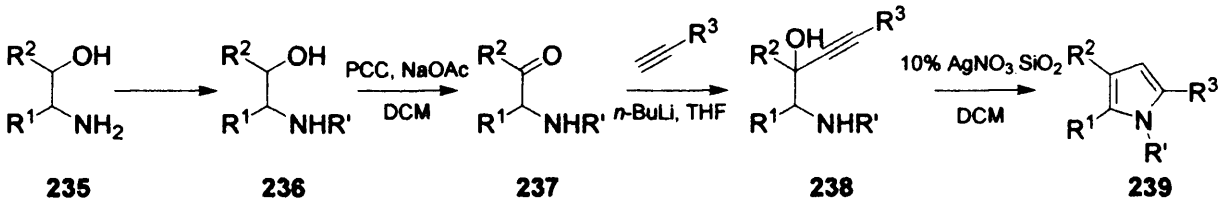
3.2 Silver-catalysed synthesis of pyrroles

3.2.1: Aim

Given the broad successes of the furan cyclisations, it was felt that similar efforts could be made to secure the synthesis of a broad range of pyrroles. As shown previously, the Knight group had applied two different 5-*endo*-dig cyclisations to the synthesis of pyrroles: the iodocyclisations investigated by Singkhonrat,[91] and the silver(I)-catalysed cyclisation, described briefly by Sharland.[17] With much of the work by Sharland having been focused around syntheses of the substituted pyrrole-2-carboxylates **216b** (Scheme 56), it seemed prudent to attempt to prepare a more expansive series of alkyl, aryl and *N*-protected pyrroles **239** (Scheme 61). It was also of interest to assess the effect of protecting groups[100a] and stereochemistry,[100b] with the aim of forging a compatibility with both acid- and base-sensitive approach strategies, as well as determining their compatibility with the cyclisation itself.

3.2.2: α-Aminocarbonyl pathway

Following on from the approach work to 3-alkyne-1,2-diols **100a-o**, **126a-d** and **135a-b** (Chapter 2.2 – p 16), a simple approach was devised, one in which an alkyne would be coupled to an α-aminocarbonyl compound **237**. With nitrogen being trivalent there came a further requirement to use a protection strategy. Coupled with the fact that commercially available α-aminocarbonyls **237** (R' = H) are few and far between, it meant that, unfortunately, this strategy had to be taken back to a synthetically early stage with the addition of two extra steps (Scheme 61).



Scheme 61: α-Aminocarbonyl approach to protected pyrroles.

The first step incorporates protection of the more nucleophilic nitrogen of a commercially available 1,2-aminoalcohol **235** to yield the protected amine derivative **236** (>95%). Overnight PCC oxidation, with purification through a flash column, yielded the desired protected α-aminoketones **237** in excellent yields (>80%). Next, *n*-BuLi-mediated alkyne addition (2.2 eqs) yielded the corresponding protected-3-alkyne-2-hydroxyamines **238**, the key cyclisation precursors. Starting with a tosyl protected α-aminocarbonyl **237a** (R^1 = Me, R^2 = Ph, R' = Ts), several alkynes were successfully employed to yield a series of tosyl-3-alkyne-2-hydroxysulfonamides **238a-d** (Table 3).

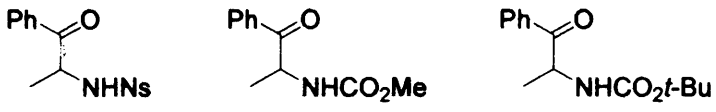
Table 3: Synthesis of tosyl protected-3-alkyne-2-hydroxyamines.

Protected α-aminocarbonyl	R^1	R^2	R^3	Protecting Group (R')	Protected-3-alkyne-2-hydroxyamine	Yield (%)
237a	Me	Ph	Bu	Ts	**238a**	82
237a	Me	Ph	Ph	Ts	**238b**	80
237a	Me	Ph	TMS	Ts	**238c** [a]	22 [a]
237a	Me	Ph	H	Ts	**238d** [a]	18 [a]

[a] Obtained from the same crude mixture. Yields reflect contribution in crude composition.

Where TMS-acetylene **238c,d** (R^3 = TMS) was used, it was found that two products were isolated, the TMS-alkyne **238c** (R^3 = TMS) and the deprotected terminal alkyne **238d** (R^3 = H). With a combined isolated yield of ~40%, this addition was not as efficient as previous examples, but provided two tosyl-3-alkyne-2-hydroxysulfonamides **238c** and **238d**, both suitable candidates for cyclisation.

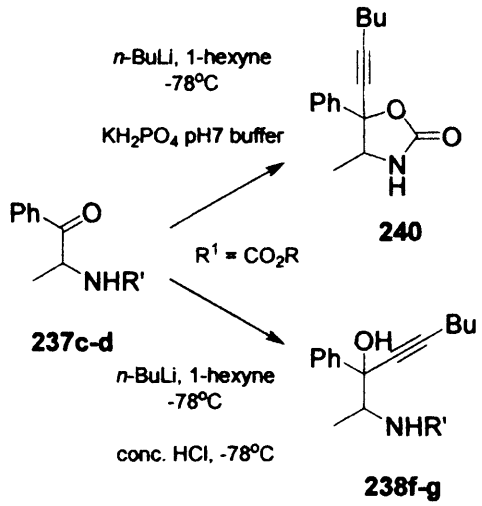
In view of the ease of work-up associated with the use of 1-hexyne, the synthesis of a series of protected-2-aminonon-4-yn-3-ols **238a-h** (R^1 = Me, R^2 = Ph, R^3 = Bu) was targeted. Protection of the α-amino group and concurrent oxidation were found to be equally successful in the cases of the precursors **237b-d** having 4-nosyl, Moc and Boc protecting groups respectively (Scheme 62).



237b **237c** **237d**

Scheme 62: Protected α-aminoketones.

Addition of 1-hexyne to the respective protected α-aminoketones **237b-d** yielded the desired protected-2-aminonon-4-yn-3-ols **238e-h** (65-83%) (Table 4), with any stereochemical implications of the protecting groups being discussed later (Chapter 3.2.4 – p 64). It was found that when using Moc **237c** and Boc **237d** protecting groups, there was a requirement to modify the work-up procedure upon the addition of 1-hexyne to the protected α-aminoketone **237c-d** (Scheme 63).



Scheme 63: Modified work-up procedure for Moc and Boc protection strategies.

This modification was required given the electrophilic nature of the carbamate functionality. If not used, then it was found that a significant amount of oxazolidin-2-one **240** was formed when quenching with the usual aqueous phosphate buffer, upon warming to room temperature. This was still the case even when this quench was carried out at -78°C, probably a result of the frozen water not providing a sufficient proton source. Thus, the decision was taken to add concentrated hydrochloric acid (few mL) at -78°C to ensure an immediate termination to the reaction (Scheme 63). It was found that the products of this reaction contained only the desired 3-alkyne-2-hydroxy-1-aminocarbonyls **238f-g**, which were obtained in high yield (65-83%). Importantly, despite the presence of concentrated acid, the Boc protecting group remained in place.

With the above series of 3-alkyne-2-hydroxyamines **238a-h** in hand, 10 mol% silver nitrate on silica gel was added to a solution of each in dry dichloromethane, screened from daylight using aluminum foil. Reaction times between 3 and 24 h cleanly delivered the expected pyrroles **239a-g**, in mostly excellent yields (>95%) (Table 4) and in high purity (Spectrum 7 and 8).

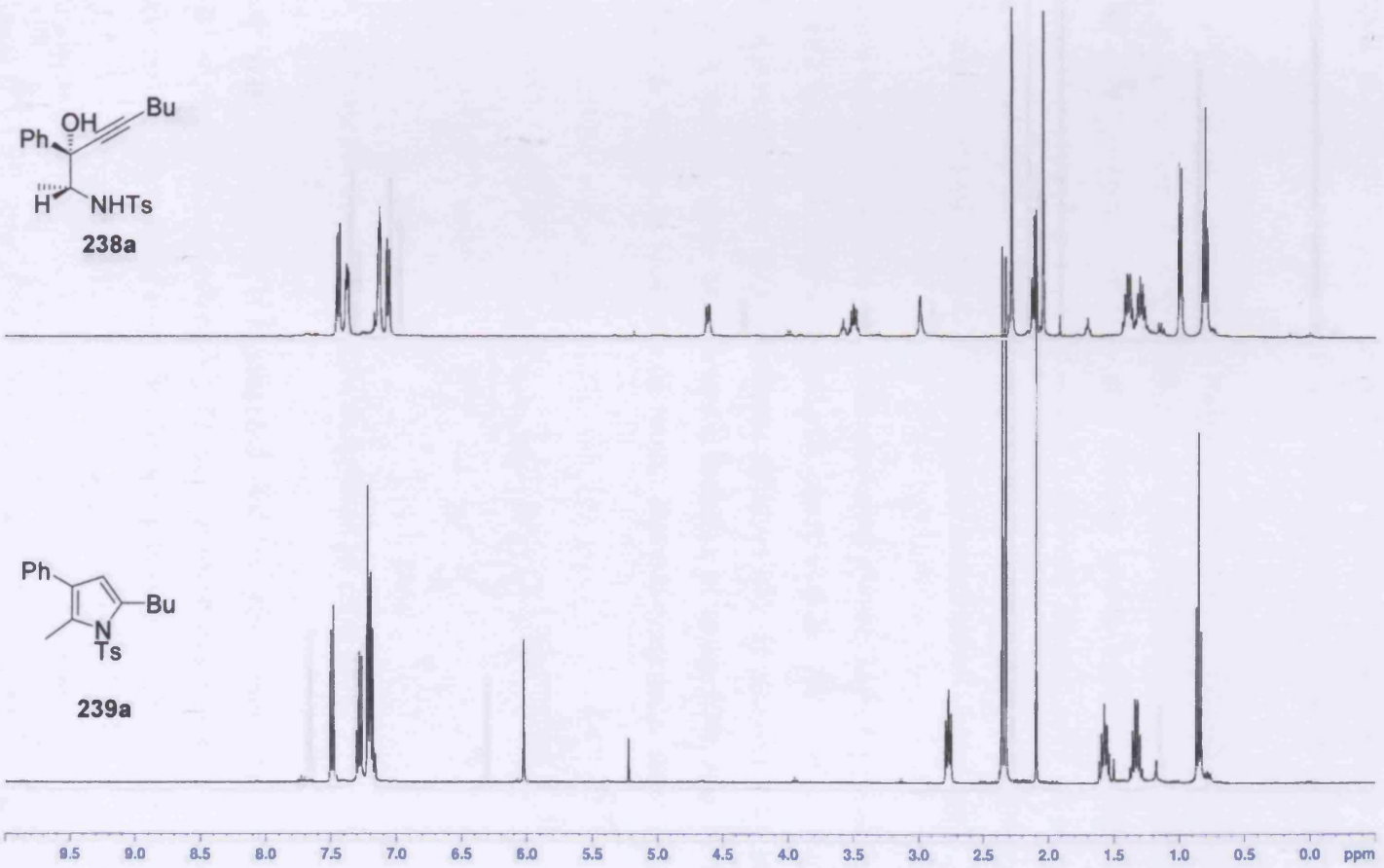
Table 4: Silver(I)-catalysed synthesis of pyrroles.

238a-h **239a-g**

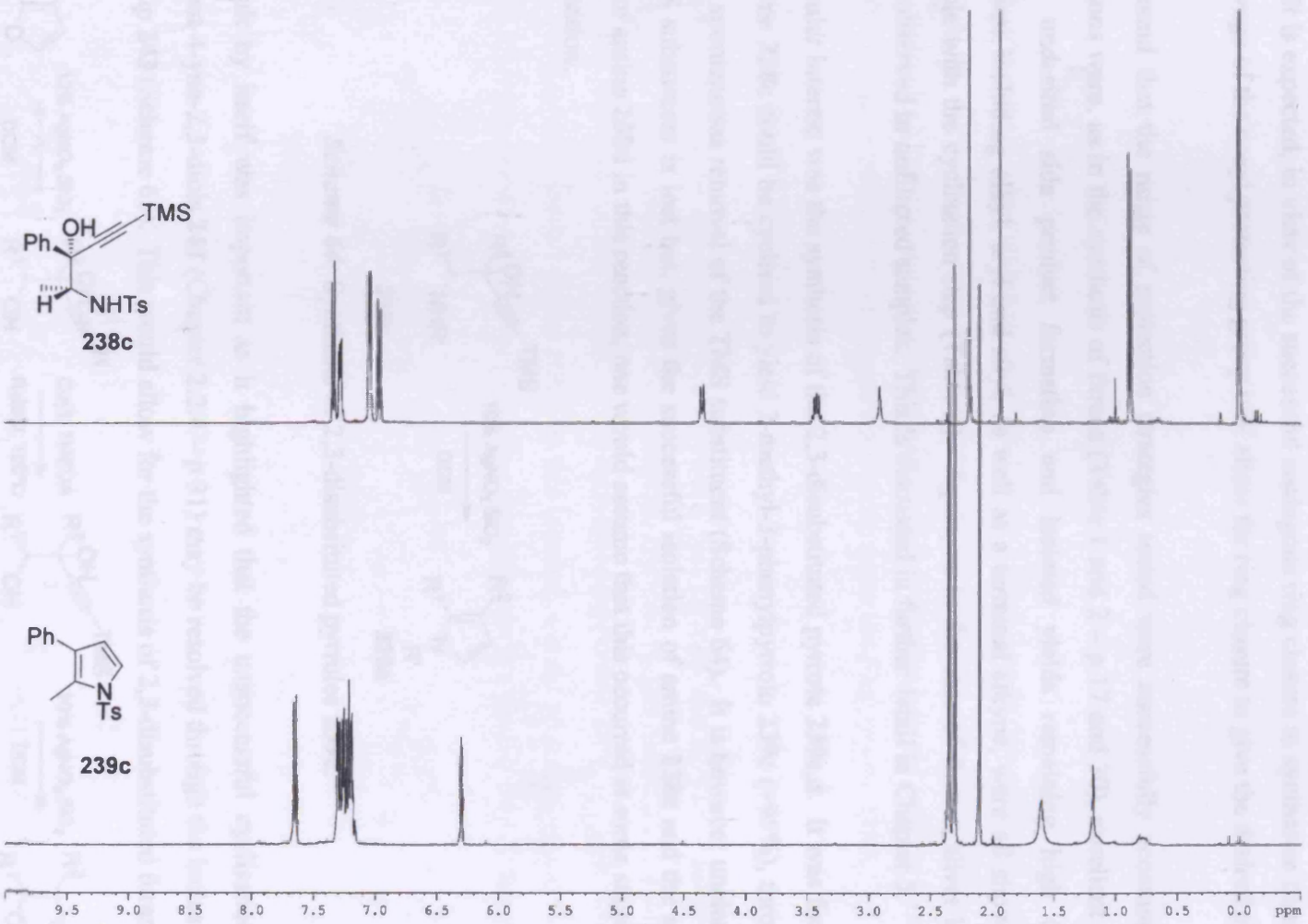
Protected-3-alkyne-2-hydroxyamine	R^1	R^2	R^3	Protecting Group (R')	Pyrrole	Yield (%)
238a	Me	Ph	Bu	Ts	**239a**	94
238b	Me	Ph	Ph	Ts	**239b**	97
238c	Me	Ph	TMS	Ts	**239c** [a]	95
238d	Me	Ph	H	Ts	**239d**	100
238e	Me	Ph	Bu	Ns	**239e** [b]	96
238f	Me	Ph	Bu	CO_2Me	**239f**	98
238g	Me	Ph	Bu	CO_2t-Bu	**239g**	90
238h	Me	Ph	*t*-Bu	Ns	**239h**	x

[a] TMS group was removed during cyclisation to yield R^3=H

[b] Dihydrohydroxypyrrole **244** formed *en route* to the corresponding pyrrole.



Spectrum 7: ^{1}H NMR spectrum of amine **238a** ($CDCl_3$) and pyrrole **239a** ($CDCl_3$).

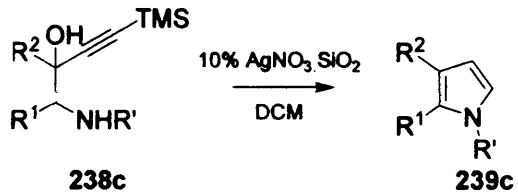


Spectrum 8: ^{1}H NMR spectrum of amine **283c** ($CDCl_3$) and pyrrole **239c** ($CDCl_3$).

The only amine which failed to cyclise was 3-alkyne-2-hydroxyamine **238h**. In hindsight this result was not that surprising, this given the strain associated with the steric repulsion of the 4-nosyl protecting group trying to ring close against the bulky *t*-butyl substituent attached to the alkyne. It is expected, in view of the successful analogous ring closure to synthesise furan **101g**, that cleavage of the nosyl protecting group will allow for ring closure to give the desired pyrrole.

It was found that the range of protection strategies tested were successfully accommodated. Conversions were, as in the synthesis of furans (Table 1 and 2 – p 17 and 30), excellent (>95%) with no undesired side product formation and isolated yields remaining high (>90%). Substituents including alkyl, aryl and silyl, as well as a terminal alkyne, were all shown to be compatible with the cyclisation step (Table 4). Again, as in the case of furans, silver leaching was still observed in unfiltered samples. This is discussed in further detail in Chapter 5.

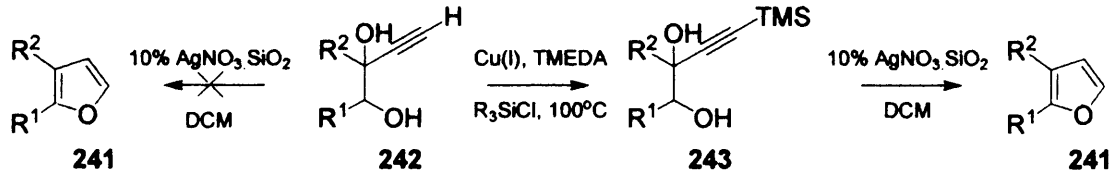
Of particular interest was the synthesis of the 2,3-disubstituted pyrrole **239c,d**. It was found that silyl alkyne **238c** could be cyclised to yield 2-methyl-3-phenylpyrrole **239c** (>95%), through the apparent spontaneous removal of the TMS substituent (Scheme 64). It is however unclear when this TMS substituent is lost but, given the successful isolation of amine **238c** and the apparent absence of amine **238d** in this reaction, one would assume that this occurred at some stage during the cyclisation.



238c **239c**

Scheme 64: Synthesis of 2,3-disubsituted pyrroles **239c**.

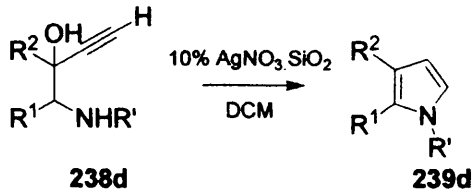
This result by itself was important as it highlighted that the unsuccessful cyclisation of 3-methylpent-4-yne-2,3-diols **242** (Chapter 2.2.4 – p 31) may be resolved through the inclusion of a silyl group **243** (Scheme 65). This would allow for the synthesis of 2,3-disubstituted furans **241**.



241 **242** **243** **241**

Scheme 65: *Proposed* synthesis of 2,3-disubstituted furans **241**.

This proposal was somewhat discredited with the observation that the terminal 3-alkyne-2-hydroxyamine **238d** was successfully cyclised to the same 2-methyl-3-phenylpyrrole **239d** in equally high yields (>95%) (Scheme 66).

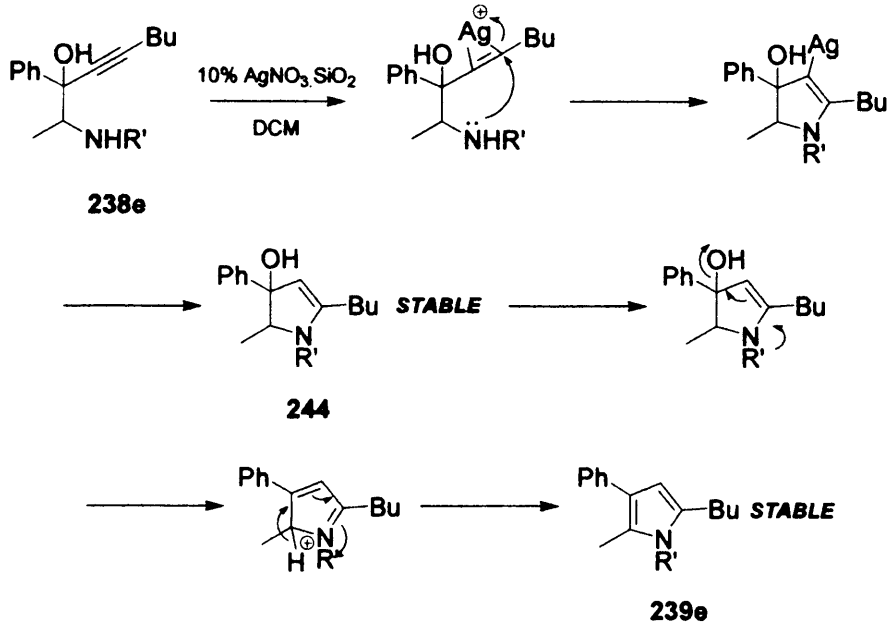


Scheme 66: Synthesis of 2,3-substituted pyrrole **239d**.

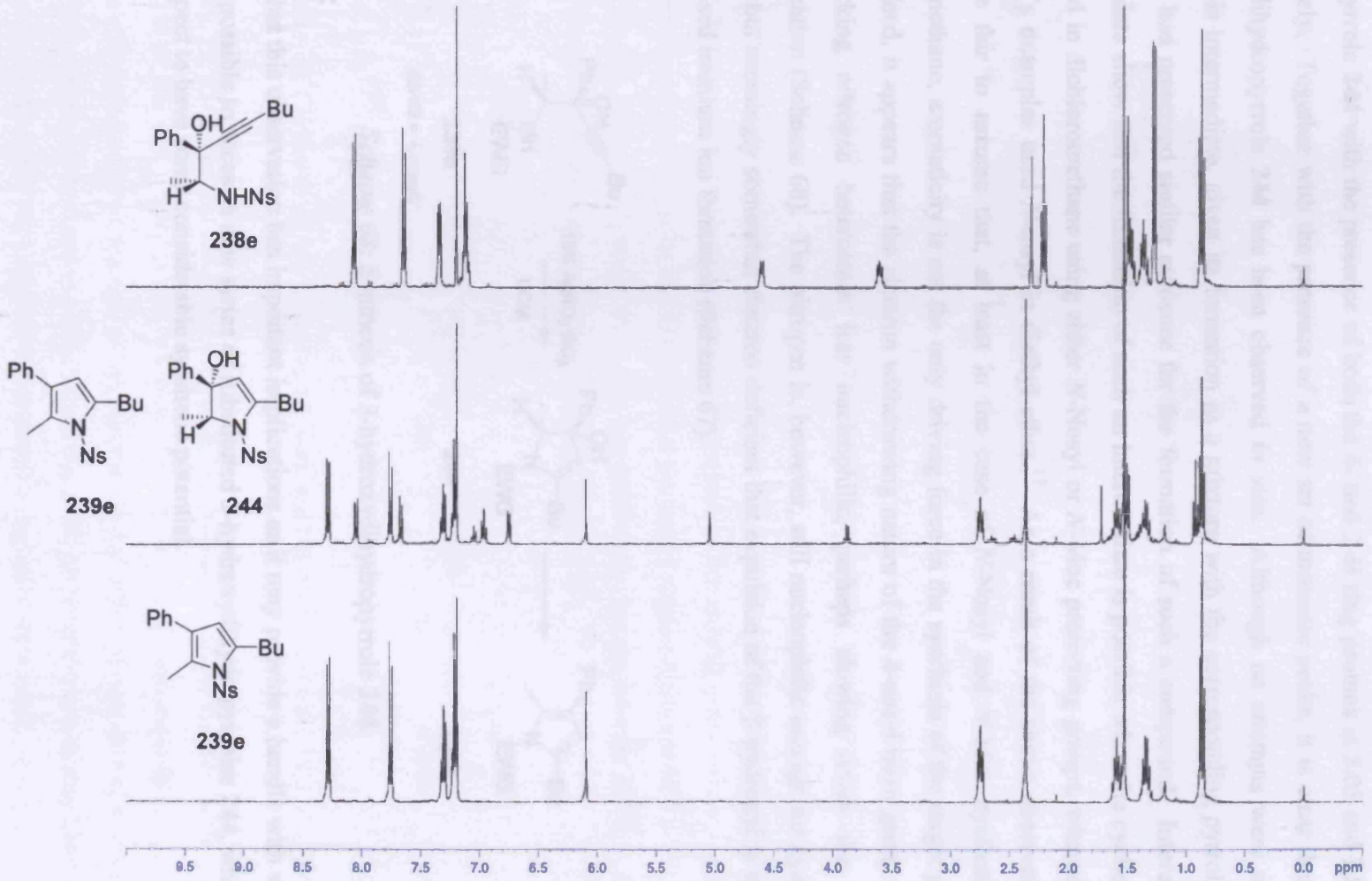
Given the success of this cyclisation, and the failure of the 3-methylpent-4-yne-2,3-diol **242** cyclisations, no effort was made to synthesise and cyclise silyl diol **243** (Scheme 65). By no means a proven fact, but perhaps the nucleophilicity of the nitrogen was the driving force in the successful cyclisation of the terminal alkyne **238d** to its corresponding pyrrole **239d**.

3.2.3: 3-Hydroxy-2,3-dihydropyrroles

A final observation from the above series of results was directly related to the nature of the protecting group. It was seen that there was significant evidence for the formation of a 3-hydroxy dihydropyrrole intermediate **244**, *en route* to the corresponding pyrrole **239e**, in the cyclisation of protected 3-alkyne-2-hydroxy-1-amine **238e**. In this instance, a nosyl protecting group was used, but there is also some evidence that Moc protection strategies act in a similar way (Scheme 67).

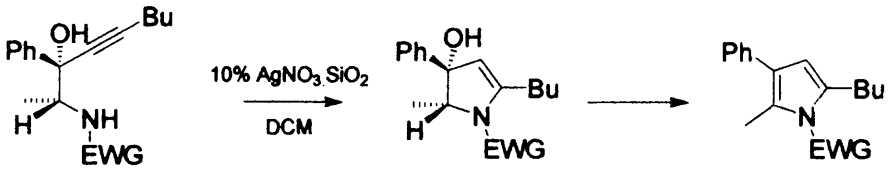


Scheme 67: 3-Hydroxy dihydropyrrole intermediate **244** formation.



Spectrum 9: ^{1}H NMR spectrum of amine **238e** ($CDCl_3$), 3-hydroxydihydropyrrole **244** ($CDCl_3$) and pyrrole **239e** ($CDCl_3$).

Unlike any case from the synthesis of furans, there was clear evidence for the presence of such an intermediate **244**, at least when using a 4-nosyl protecting group. Indeed, the central plot of Spectrum 9, obtained by *in situ* ^{1}H NMR, clearly shows the formation of 3-hydroxy dihydropyrrole **244** with the presence of both the 4- and 2-H ring protons at 5.05 and 3.88 ppm respectively. Together with the presence of a new set of aromatic peaks, it is clear that the 3-hydroxydihydropyrrole **244** has been observed *in situ*. Although no attempts were made to isolate this intermediate, given its formation as a mixture with the corresponding pyrrole **239e**, Sharland had presented similar evidence for the formation of such a compound. Interestingly, our own data show that the formation of such an intermediate is possible when the cyclisation is performed in dichloromethane using either *N*-Nosyl or *N*-Moc protecting groups, whereas all of Sharland's examples used *N*-tosyl in diethyl ether.[17] As a result of the above observations, it would be fair to assume that, at least in the case of *N*-Nosyl and *N*-Moc cyclisations in dichloromethane, aromaticity is not the only driving force in the synthesis of the target pyrroles **239**. Indeed, it appears that the electron withdrawing nature of the 4-nosyl nitro group renders the attacking nitrogen heteroatom less nucleophilic, perhaps slowing down the overall transformation (Scheme 68). The nitrogen is, however, still nucleophilic enough for cyclisation to occur, but seemingly somewhat electron deficient that expulsion of the β-hydroxyl is slow *via* the proposed iminium ion formation (Scheme 67).



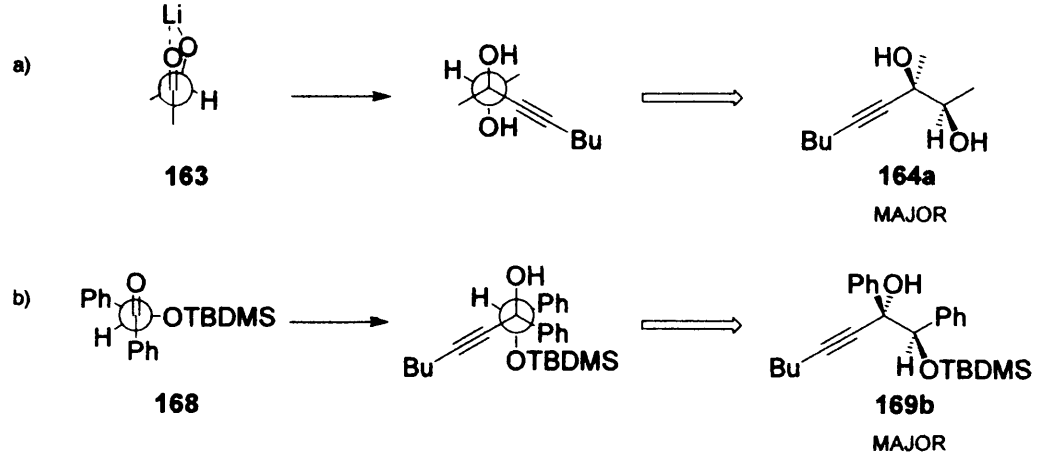
238e (EWG = 4-nosyl) **244** **239e**

Scheme 68: Synthesis of 3-hydroxydihydropyrrole **244**.

It is felt that this observation has important implications as it may provide a handle with which it might be possible to access a new series of substituted 3-hydroxydihydropyrroles **244**, which one would expect to have some considerable synthetic potential.

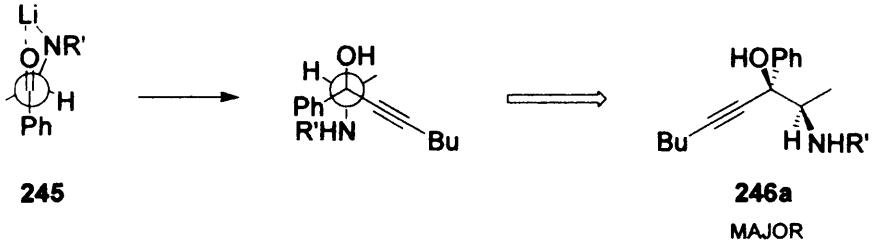
3.2.4: Stereochemistry

Stereochemistry has an important effect on the synthesis of furans (Chapter 2.3.2 – p 37). It was shown that the stereochemistry of the major isomers **164a** could be altered upon introduction of a protection strategy such that the major isomer became *anti* **169b** (Scheme 69).



Scheme 69: a) Chelation and b) non-chelation control in diol synthesis.

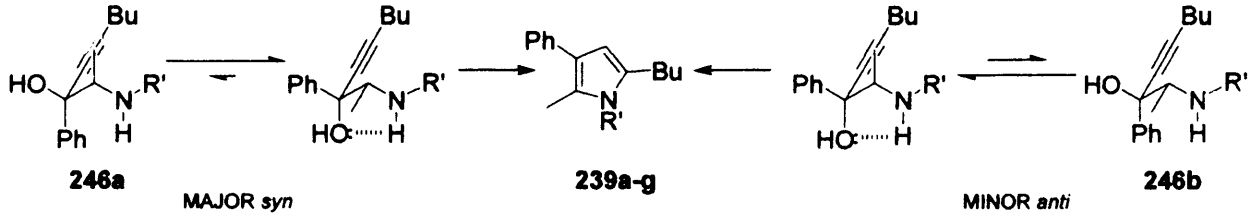
This had important implications on the cyclisation reaction as the *syn*-isomer **164a** was shown to cyclise faster, given it exhibited the required alignment of the attacking heteroatom, which was aided by hydrogen bonding with the adjacent axial propargyl alcohol (Scheme 43 – p 39). In the case of pyrroles, the major isomers were also expected to be the *syn*-isomers **246a**, a result of chelation control[100b] given nitrogen anion formation (Scheme 70).



Scheme 70: Chelation control in protected 3-alkyne-2-hydroxy-1-amine **246a** synthesis.

Indeed, the ^{1}H NMR spectra of all the protected 3-alkyne-2-hydroxy-1-amines **238a-h** suggest the presence of just one isomer, which one could assume to be the *syn*-isomer **246a**. As a result of the use of mono-protected amines, no assessment of the effect of non-chelation control was made for this model. However, one would expect the preference for the *syn*-isomer **246a** to cross over in favour of the *anti*-isomer **246b** if *bis*-protection strategies were used.

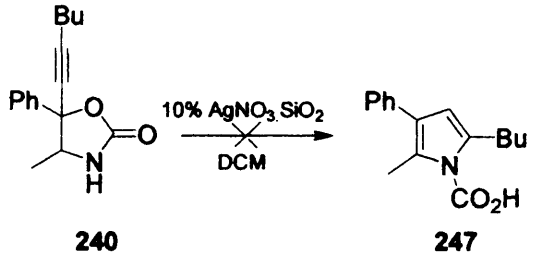
With the presence of primarily only one isomer, it was difficult to assess the rate of cyclisation of such isomers. It can only be assumed that, as in the case of diols **246a**, the *syn*-isomer would cyclise faster, given the further stability seen with all bulky substituents being equatorial in the desired hydrogen bonded alignment, including the protecting group (Scheme 71). Interestingly, in the example below, the difference in rate may be very small given the preference of the phenyl group of the *anti*-isomer **246b** to lie equatorially.



Scheme 71: Cyclisation of *syn*- **246a** and *anti*- **246b** diastereomers.

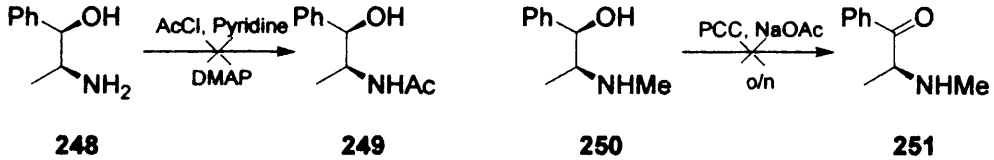
3.2.5: Limitations

As already stated, the silver-catalysed cyclisation of **238f-g** (R' = Moc and Boc) proceeded with normal efficiency; however attempts to cyclise oxazolidin-2-one **240** were unsuccessful, not surprising given the misalignment of the nitrogen heteroatom and alkyne (Scheme 72).



Scheme 72: Cyclisation of oxazolidin-2-one **240**.

The use of acetyl protection **[248→249]** and the oxidation of *N*-methylephedrine **[250→251]** were also unsuccessful (Scheme 73), although no great effort was made to optimise these systems as the above four protection strategies appeared to provide an adequate choice. It is felt that with further effort, there should be no problems implementing these two other protection strategies.



Scheme 73: Acetyl protection **249** and attempted oxidation of *N*-methylephedrine **250**.

3.3: Conclusions

In conclusion, it has been shown that it is possible to use alkyl, aryl and silyl substituents in the silver-catalysed synthesis of pyrroles. With the successes seen in the synthesis of furans, and previous work having been performed in this field, a representative series of pyrroles has been synthesised using silver(I). The successful implementation of a range of protection strategies has helped broaden the applications of this procedure, with both acid- and base-labile protecting groups being accommodated in the approach strategy. Problems observed with the use of acetyl and methyl protecting groups are thought to be easily solved with further investigations.

The observed increase in rate of reaction, relative to the cyclisation of diols **100a-o**, **126a-d** and **136a-b**, is of interest. It is felt that the increased nucleophilicity of nitrogen is responsible, which hints towards the fact that ring closure may be the rate limiting step. Indeed, this may well be the case in view of the infrequent observations of the 3-hydroxy dihydropyrrole intermediates **244** which, given their absence in most of the 'crude' products, appear to aromatise to the target pyrrole **239** with great ease. Further evidence is provided by the highly successful cyclisation of the amine **238d** (R^1 = Me, R^2 = Ph, R^3 = H), where the nitrogen heteroatom successfully ring closed onto a terminal alkyne, a transformation which was not possible with diol **142** (R^1 = R^2 = Ph, R^3 = H), to give a 2,3-disubstituted furan. With the greater nucleophilicity of the nitrogen being a significant factor in the success of this cyclisation, it would seem be fair to conclude that nitrogen nucleophilicity is responsible for both the rate and success of pyrrole **239** formations.

The discovery of the 3-hydroxy dihydropyrrole **244** is very encouraging. Importantly, it suggests that our proposed mechanism is feasible, since allene formation would not allow for such intermediates to be formed. It further draws our attention to the possibility of accessing a series of 3-hydroxy dihydropyrroles, perhaps themselves valuable synthetic intermediates.

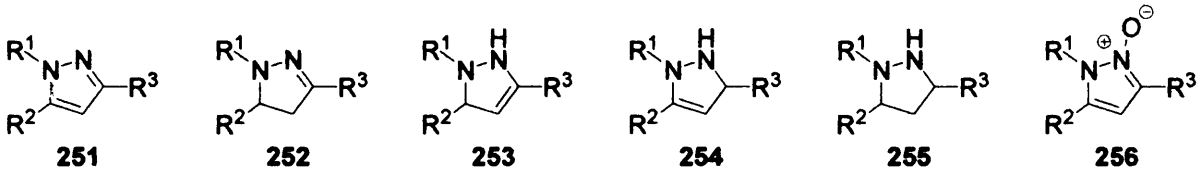
With the limited commercial availability of α-aminocarbonyl compounds, future work could see the use of Sharpless aminohydroxylation chemistry, which would allow for the selective formation of the more efficient, in terms of the parent cyclisation, *syn*-isomer. Although the desired *syn*-stereochemistry is apparently attainable using our current protected approach, Sharpless' methodology would, more importantly, allow access to a wider range of substituted pyrroles.

Chapter 4: Results and Discussion

Synthesis of Pyrazole-N-oxides

4.1: Introduction

Pyrazoles **251** are important heterocyclic targets and their synthesis is by no means trivial. Although not being known to occur naturally, they are highly prized for their therapeutic activity. With derivatives including dihydropyrazoles **252-254**, tetrahydropyrazoles **255** and pyrazole-*N*-oxides **256** (Scheme 74), there is much interest in a broadly applicable, fast and efficient synthesis of this class of heterocycles.



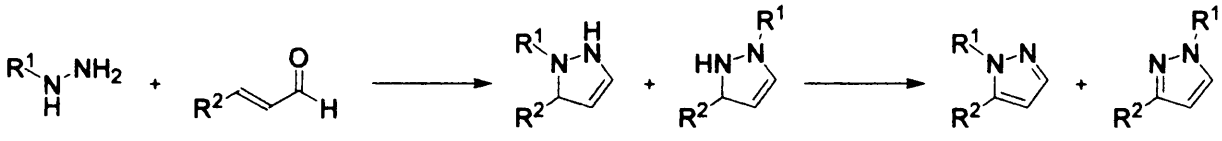
251 **252** **253** **254** **255** **256**

Scheme 74: Pyrazole derivatives.

Many methods for the synthesis of this class of compounds suffer in terms of regioselectivity, with several being limited in their general applications. The key structural feature of pyrazole is seen to be the presence of two adjacent nitrogen ring atoms. This provides a very specific handle from which one can design a synthesis, with many approaches taking advantage of readily available hydrazines.[101-105]

4.1.1: Hydrazine-based synthesis of pyrazoles

Procedures which use hydrazine are exposed to the possibility of regioisomer formation (*e.g.* Chapter 1.1.3 – p 5). Often, when used as a general procedure, the outcome of such approaches is extremely dependent on the nature of the substrate substituents. However, despite such complications, hydrazines have found broad uses in accessing these heterocycles. One such approach sees the 2+3 addition of hydrazines **257** to an α,β-unsaturated carbonyl **258**.[106, 107] Subsequent dehydrogenation of the dihydropyrazole intermediates **259** and **260** yields the corresponding pyrazoles **261** and **262** (Scheme 75).

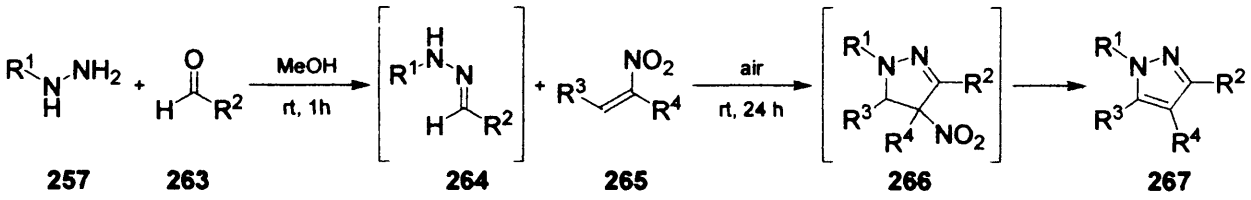


257 **258** **259** **260** **261** **262**

Scheme 75: Synthesis of pyrazoles **261** and **262**.

Unfortunately, the drawback of this simple transformation is seen in its susceptibility to regioisomer formation when using unsymmetrical reagents. In the above example, this results in a mixture of 1,3- **262** and 1,5- **261** disubstituted pyrazoles, and with regioisomers being difficult to separate, this is quite problematic. It means that this procedure is limited primarily to symmetrical reagents and, perhaps most importantly, it cannot therefore be used as a generic approach.

Another stoichiometric approach which employs hydrazine has been reported by Deng and Mani.[105] They coupled monosubstiuted hydrazines **257** with aldehydes **263** to produce hydrazones **264**. Addition of a substituted nitro-olefin **265** permitted regioselective formation of the substituted pyrazoles **267** in low to high yields (26-92%) (Scheme 76). They propose that this reaction proceeds *via* 'a key nitropyrazolidine intermediate' **266**, which appears to account for the observed regioselectivity, and is believed to result from the reversible cycloaddition of a 1,3-dipolar intermediate, generated *in situ*.



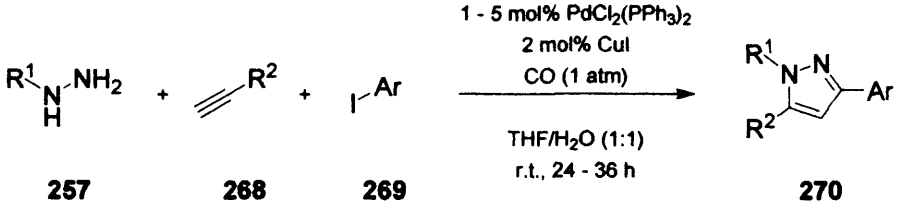
257 **263** **264** **265** **266** **267**

Scheme 76: Deng and Mani's pyrazole **267** synthesis.

This one-pot approach, given some higher yields (26-92%) and the observed regioselectivity, means the method has the potential to make a significant impact. Its ability to produce tetrasubstituted pyrazoles **267** means that it could well have applications in parallel synthesis. However, there is evidence that this cycloaddition occurs in competition with the irreversible conjugate addition of the more nucleophilic secondary amine centre of hydrazone **264**. The product of the conjugate addition is known not to undergo cyclisation and as a result resides as a contaminant in the isolated product. The toxic nature of nitro compounds, and the limited availability of nitro-olefins **265**, highlight some further limitations.

Of the catalysed hydrazine additions, palladium has been employed in a four-component coupling reaction for the synthesis of pyrazoles **270** and isoxazoles. Very recently, Mori showed the use of 1-5 mol% $PdCl_2(PPh_3)_2$, in the presence of 2 mol% CuI, in successfully coupling hydrazine

257, a terminal alkyne **268**, an aryl iodide **269** and carbon monoxide (Scheme 77).[103] He showed that pyrazoles **270** could be synthesised in good yields (59-93%) at ambient temperatures and pressures.

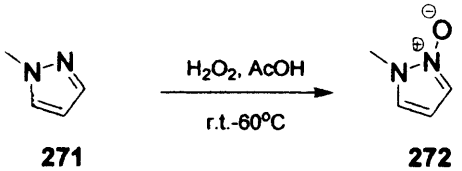


Scheme 77: Palladium-catalysed synthesis of pyrazoles **270**.

Proceeding *via* the palladium-catalysed coupling of an aryl iodide **269** with carbon monoxide and an alkyne **268**, the resultant propargyl ketone readily reacts with hydrazine **257**, which subsequently cyclises to form a substituted pyrazole **270**. As a result, this procedure benefits from being one-pot and catalytic, but it does also produce large quantities of waste given the need for excess hydrazine **257** (3 eq). Furthermore, with the need for prolonged reaction times and the compatibility with only aryl iodides, there are limitations to its broad applicability. Finally, the need for carbon monoxide and the use of hydrazines, which have a limited availability, is not desirable given issues of containment and toxicity.

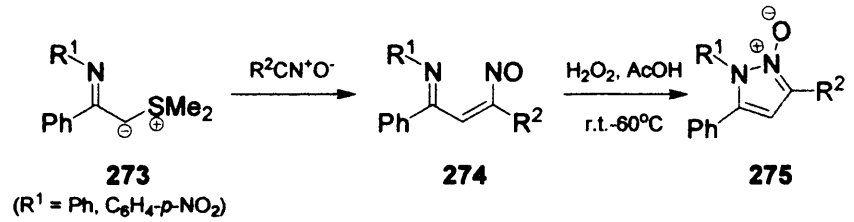
4.1.2: Pyrazole-*N*-oxides

One of the key derivatives of pyrazoles **271** are the pyrazole-*N*-oxides **272**. They are an important class of compounds, and are themselves useful in the synthesis of substituted pyrazoles. Despite the demand for an efficient synthesis, there are few reports of such approaches to pyrazole-*N*-oxides **272**. Often these are derived from the oxidation of pyrazoles **271** (Scheme 78),[108] but in these reactions, yields are usually low (<20%), with the presence of electron withdrawing ring substituents preventing any oxidation.



Scheme 78: Oxidation of pyrazoles **271**.

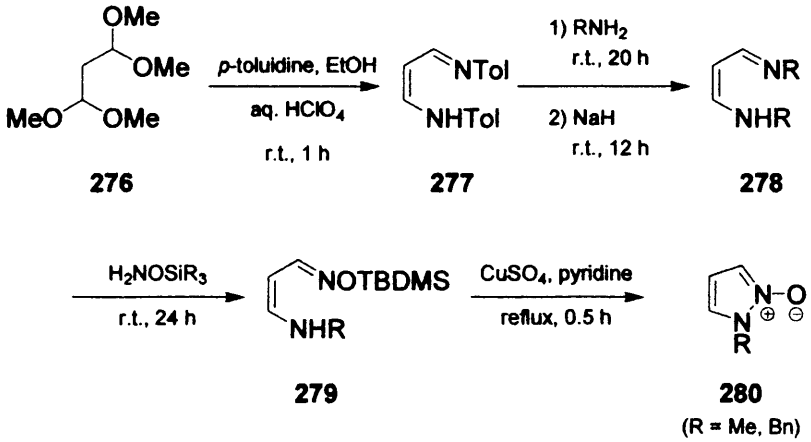
Another approach, reported by Gilchrist, sees the cyclisation of 1-imino-2-nitrosoalkenes **274** to yield pyrazole-*N*-oxides **275** (Scheme 79).[109]



Scheme 79: Gilchrist's synthesis of pyrazole-*N*-oxides **275**.

In a different tactic to those described before, Gilchrist, and others since, utilised a N-N bond forming step. Prepared from ylides **273**, 1-imino-2-nitrosoalkenes **274** undergo successful cyclisations in mixed yields (9-75%), with the electron-poor *N*-oxide **275** ($R^1 = C_6H_4$-*p*-NO_2, $R^2 = CO_2Et$) being formed in the highest yield (75%). In fact, it appears that there is a requirement to have electron withdrawing groups in both positions around the ring. This procedure is further limited to the synthesis of 3,5-disubstituted pyrazole-*N*-oxides **275** and attempts to extend the range of *N*-substituents were unsuccessful.

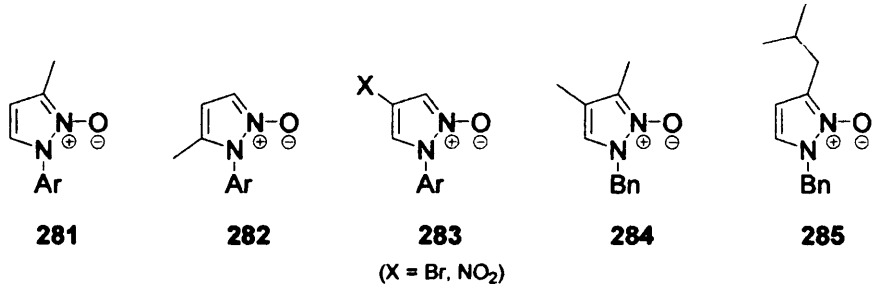
Following this work, Begtrup *et al.* synthesised a series of 4-hydroxylamino-1-azabuta-1,3-dienes **279** from commercially available 1,1,3,3-tetramethoxypropane **276**.[110, 111] He was able to cyclise these dienes **279** to yield 2-substituted pyrazole-*N*-oxides **280** (Scheme 80).



Scheme 80: Begtrup's synthesis of pyrazole-*N*-oxides **280**.

Although providing access to pyrazole-*N*-oxides **280**, the yields of the key cyclisation were always low (3-36%) and often resulted in mixtures being obtained. There was however some

evidence of the potential to use these *N*-oxides **280** to access a range of alkyl and aryl substituted pyrazole-*N*-oxides **281-285** (Scheme 81), however yields were low once again.



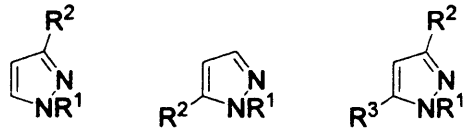
281 **282** **283** **284** **285**

(X = Br, NO_2)

Scheme 81: Begtrup's other pyrazole-*N*-oxides **281-285**.

4.1.3: Synthesis of substituted pyrazoles from pyrazole-*N*-oxides

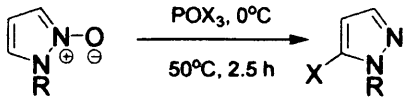
Pyrazole-*N*-oxides *e.g.* **261**, **262** and **270**, as stated above, can be used in the synthesis of substituted pyrazoles **286→288**, *via* the use of a deoxygenation procedure. Recent literature points towards the use of deoxygenation, following alkylation and halogenation reactions, in the synthesis of 1,3-, 1,5- and 1,3,5-substituted pyrazoles **286-288** (Scheme 82).[112]



286 **287** **288**

Scheme 82: Substituted pyrazoles **286-288**.

A good example of such a transformation has been presented by Vedsø and Begtrup.[112] They synthesised a range of 1-alkyl-5-halopyrazoles **289** regiospecifically using phosphorus oxychloride and phosphorus oxybromide in high yield (70-98%) (Scheme 83).



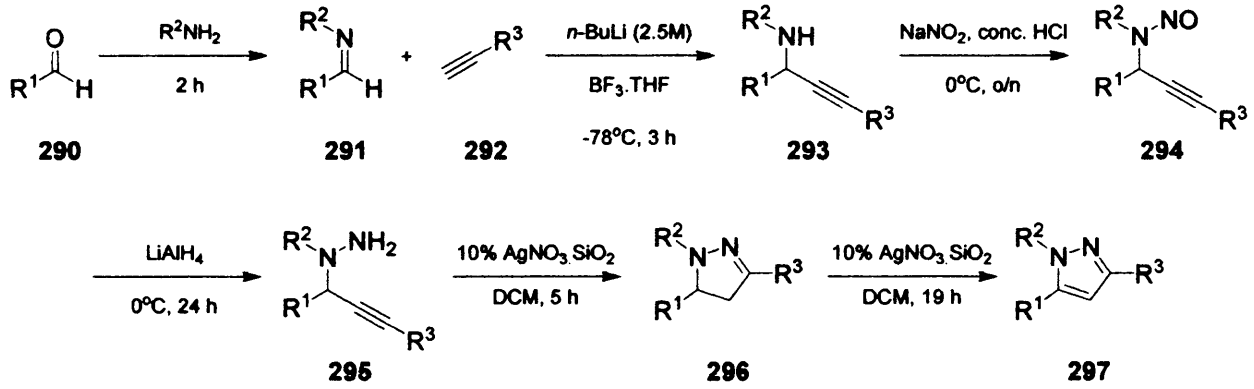
280 **289**

Scheme 83: Synthesis of 1-alkyl-5-halopyrazoles **289**.

Proceeding *via* $POCl_3$ activation of the N-O bond, the halide ion, generated *in situ*, attacks at the 5-position to effect deoxygenation. With the opportunity to apply palladium chemistry, and the ability to selectively alkylate at the 5-position, this procedure becomes of synthetic importance to the synthesis of a range of substituted pyrazoles **286-288** (Scheme 82).

4.1.4: Silver-catalysed synthesis of pyrazoles

With the above work in mind, and with the silver-mediated cyclisation in hand, Knight and Song recently assessed the silver-catalysed synthesis of pyrazoles **297**.[113] Starting with the addition of a 1-alkyne **292** to imine derivatives **291** of aldehydes **290**, they formed a series of propargylamines **293**. Nitrosation of these with nitrous acid yielded *N*-nitroso propargylamines **294**, which in turn were reduced to propargyl hydrazines **295** with $LiAlH_4$. Addition of stoichiometric 10% $AgNO_3.SiO_2$ successfully effected cyclisation to the pyrazoles **297** in excellent yields (>95%), *via* the oxidation of their corresponding dihydropyrazoles **296** by silver(I) (Scheme 84).



Scheme 84: Silver-catalysed synthesis of pyrazoles **297**.

With the usual attributes of high yields, cleanliness and speed, this work showed yet another application of the silver-mediated cyclisation reaction, with the necessary regiospecificity displayed by this approach being a key strength. Interestingly, it was expected that dihydropyrazoles **296** would be the end point of these silver(I)-catalysed cyclisations, not the observed pyrazoles **297**. The use of catalytic 10% $AgNO_3.SiO_2$ did however often lead to the preparation of a mixture of pyrazoles **297** and dihydropyrazoles **296**. The subsequent oxidation to pyrazoles appeared to be catalytic in the presence of silver(I) with *N*-alkyl substituents, but did not proceed at all with *N*-COR substituents. This observation does however highlight the greater potential of this transformation. There were however two prevailing limitations to this technique: *N*-nitroso propargylamines **294** are known to be highly toxic and their reduction is often somewhat low yielding. Nonetheless, perhaps most importantly, this procedure is unrivalled in terms of efficiency and regioselectivity.

4.2: Silver-catalysed synthesis of pyrazole-N-oxides

4.2.1: *N*-Nitroso propargylamine pathway

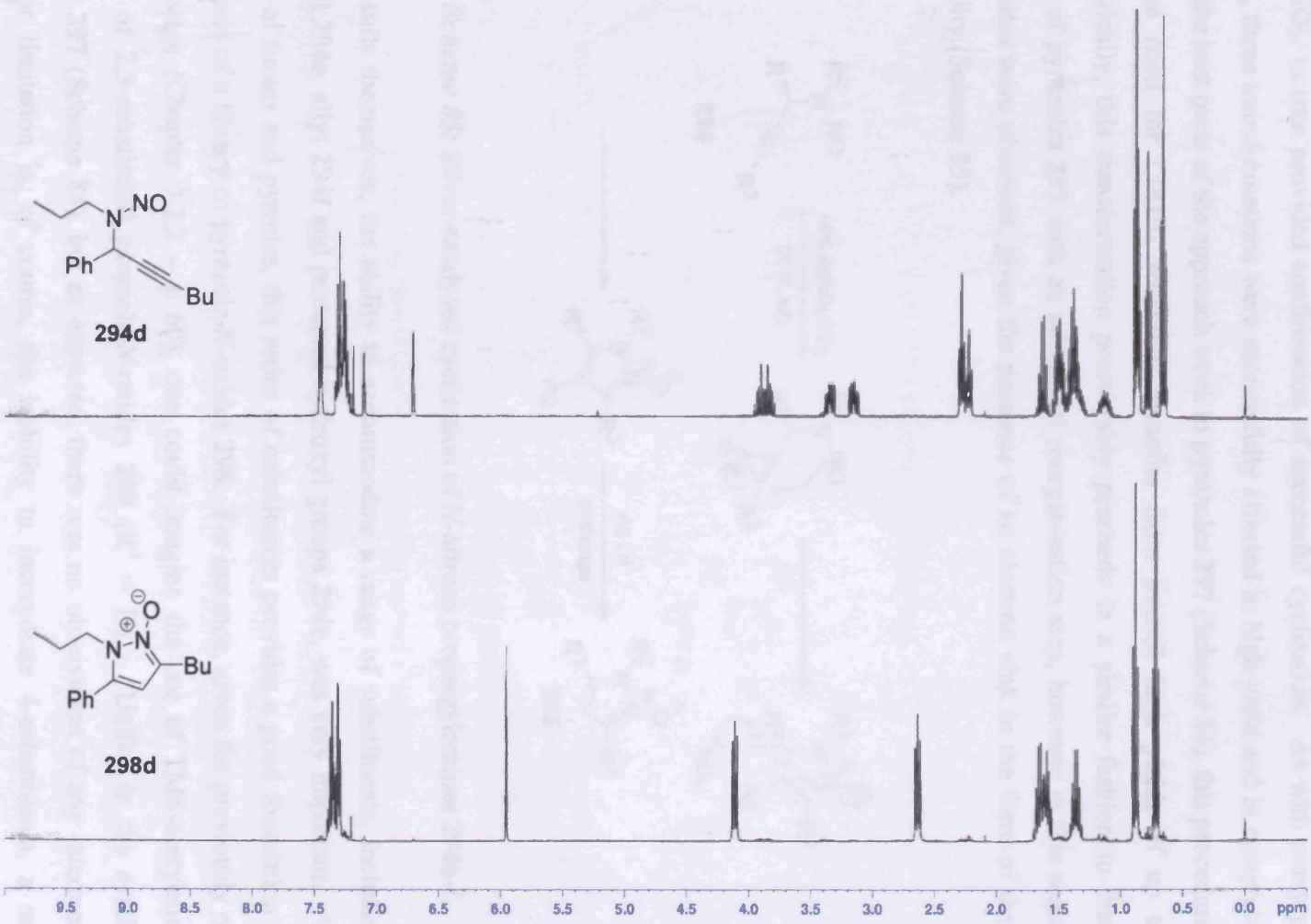
We wondered if a change of order would be possible *i.e.* cyclisation prior to reduction. Thus, during further investigations into the field of pyrazoles **297**, an opportunity arose to test this possibility. With the help of a project student, Pickering, and using Song's approach work, it was found that 10% $AgNO_3.SiO_2$ successfully induces the cyclisation of *N*-nitroso propargylamines **294a-f** to yield the corresponding pyrazole-*N*-oxides **298a-f** in excellent yield (>95%) (Table 5). As with pyrroles and furans, silver leaching was observed in unfiltered products.

Table 5: Silver(I)-catalysed synthesis of pyrazole-*N*-oxides.

294a-f **298a-f**

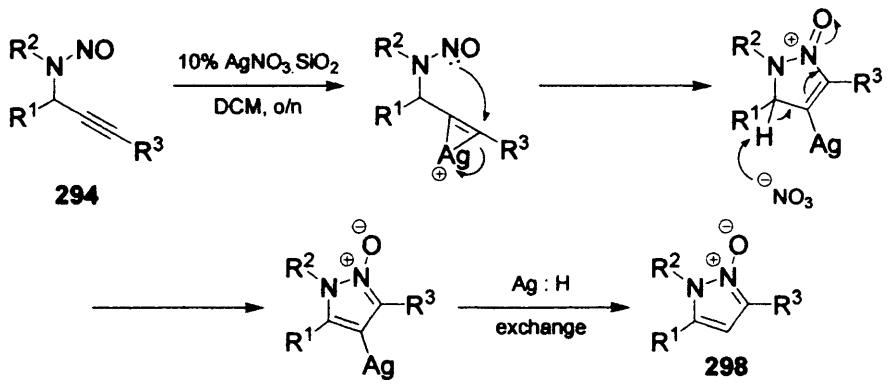
N-nitroso propargylamine	R^1	R^2	R^3	Pyrazole-*N*-oxide	Yield (%)
294a	*i*-Bu	CH_2Ph	Bu	**298a**	>95
294b	*i*-Bu	CH_2Ph	Ph	**298b**	>95
294c	*i*-Bu	CH_2Ph	$(CH_2)_2OTBDPS$	**298c**	>95
294d	Ph	Pr	Bu	**298d**	>95
294e	Ph	Pr	Ph	**298e**	>95
294f	*i*-Bu	$CH_2CH{=}CH_2$	Ph	**298f**	>95

Given the toxicity of the products, these cyclisations were carried out in NMR tubes and the quoted yields are therefore a reflection of the conversion seen by ^1H NMR analysis (Spectrum 10). Both ^{13}C NMR and mass spectrometry were used in conjunction with the above data to confirm the successful formation of the pyrazole-*N*-oxides **298a-f**. Mass spectrometric data for the *N*-nitroso propargylamines **294a-f** were inconclusive, with each *N*-nitroso propargylamine appearing to form some sort of unknown dimer. In the case of amine **294b**, a [2M-NO] dimer appeared to form (M = 552), however in the case of some of the other amines *e.g.* **294d**, there was no tangible explanation for the observed high molecular weight fragment (M = 516).



Spectrum 10: ^{1}H NMR spectrum of *N*-nitrosoamine **294d** ($CDCl_3$) and pyrazole-*N*-oxide **298d** ($CDCl_3$).

There was therefore a reliance on the characteristic ^{1}H NMR signals of the rotameric *N*-nitroso propargylamines **294a-f** to confirm their successful formation. Indeed, their replacement by a single set of peaks consistent with the cyclic pyrazole-*N*-oxides **298a-f**, upon the addition of 10% $AgNO_3.SiO_2$, in turn provided confirmation of successful cyclisation. As with many previous examples, these transformations were successfully effected in high yield and in complete purity. Utilising the best parts of the approach work to pyrazoles **297** (Scheme 84), this procedure, which avoids the need for $LiAlH_4$ reduction, benefits from overall high yields of up to 70%. Mechanistically, this transformation presumably proceeds in a similar fashion to that of the synthesis of pyrazoles **297** with an additional reorganisation step, however in this sequence no intermediates were observed, given the presence of an electron sink in the form of the nitrone functionality (Scheme 85).



Scheme 85: Silver-catalysed cyclisation of *N*-nitroso propargylamines **294a-f.**

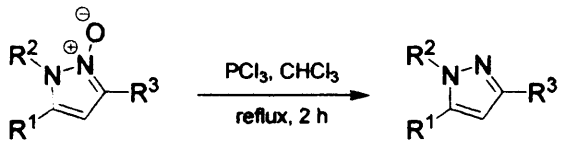
Of the results themselves, the ability to accommodate a range of substituents, including alkyl **294a**, aryl **294e**, allyl **294f** and protected hydroxyl groups **294c**, was very important. As in the synthesis of furans and pyrroles, this series of substituents provides a good foundation towards the synthesis of a library of pyrazole-*N*-oxides **298**. For instance, given the previously observed silyl cleavage (Chapter 3.2.2 – p 60), one could imagine the use of TMS-acetylene in the synthesis of 2,3-substituted pyrazole-*N*-oxides **298** (R^3 = H). Unlike in the synthesis of pyrazoles **297** (Scheme 84), but as expected, there was no observation of any intermediate(s). The major limitation is, of course, the inability to incorporate 4-substituents, a necessary limitation with the silver-catalysed cyclisations but one which may be overcome through similar work to that of Nozaki.[23] However, with the vast commercial availability of amines, aldehydes **290** and terminal alkynes **292**, this procedure is still of probable synthetic importance. Indeed,

given the cyclisation proceeds in excellent yields (>95%), this transformation is arguably the best pyrazole-*N*-oxide **298** synthesis to date, in terms of yield, compatibility and cleanliness. Finally, a further benefit is seen with the use much milder conditions, *i.e.* ambient temperatures, in the key cyclisation step.

4.2.2: Synthesis of pyrazoles

Following this work, and with literature alluding to the use of phosphorus trichloride for the deoxygenation of pyrazole-*N*-oxides **298**, it became apparent that it would also be possible to access substituted pyrazoles **297** from this approach (Table 6).[112, 114]

Table 6: Synthesis of pyrazoles.

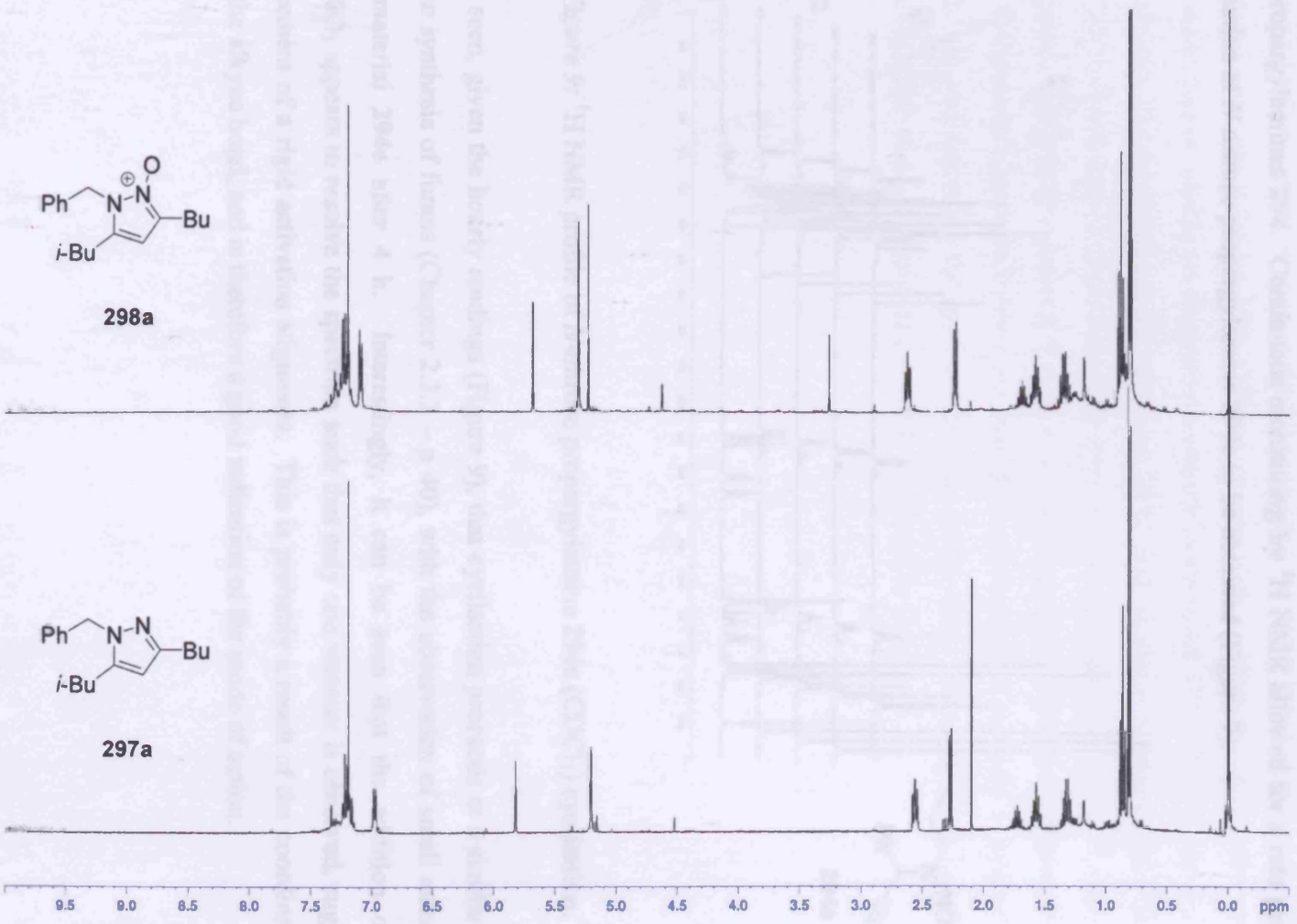


298a,c **297a,b**

Pyrazole-*N*-oxide	R^1	R^2	R^3	Pyrazole	Yield (%)
298a	*i*-Bu	CH_2Ph	Bu	**297a**	99
298c	*i*-Bu	CH_2Ph	$(CH_2)_2OTBDPS$ [a]	**297b** [a]	92

[a] silyl group was removed during deoxygenation to yield R^3=$(CH_2)_2OH$.

It was found that deoxygenation could be effected in excellent yields (92-99%), with the isolation of pyrazole **297a,b** (Spectrum 11). Having avoided the need for $LiAlH_4$ reduction, which was at times low yielding, this synthesis of pyrazoles **297a-b** provided a further improvement on the overall yields of the original approach to these heterocycles.[113] Interestingly, where a silyl-protected hydroxyl substituents were used [*e.g.* **298c**], deprotection was observed, yielding the free hydroxyl pyrazole derivative **297b**. This was perhaps not very surprising given the harsh conditions used to deoxygenate the pyrazole-*N*-oxide **298c**.



Spectrum 11: ^{1}H NMR spectrum of pyrazole-*N*-oxide **298a** ($CDCl_3$) and pyrazole **297a** ($CDCl_3$).

4.2.3: Rate of cyclisation

As with the previous cyclisations, we held an interest in assessing the rate of cyclisation of *N*-nitroso propargylamines **294**. Continuous monitoring by ^{1}H NMR allowed for a rate profile of the cyclisation of *N*-nitroso propargylamine **294e** to be obtained (Figure 9).

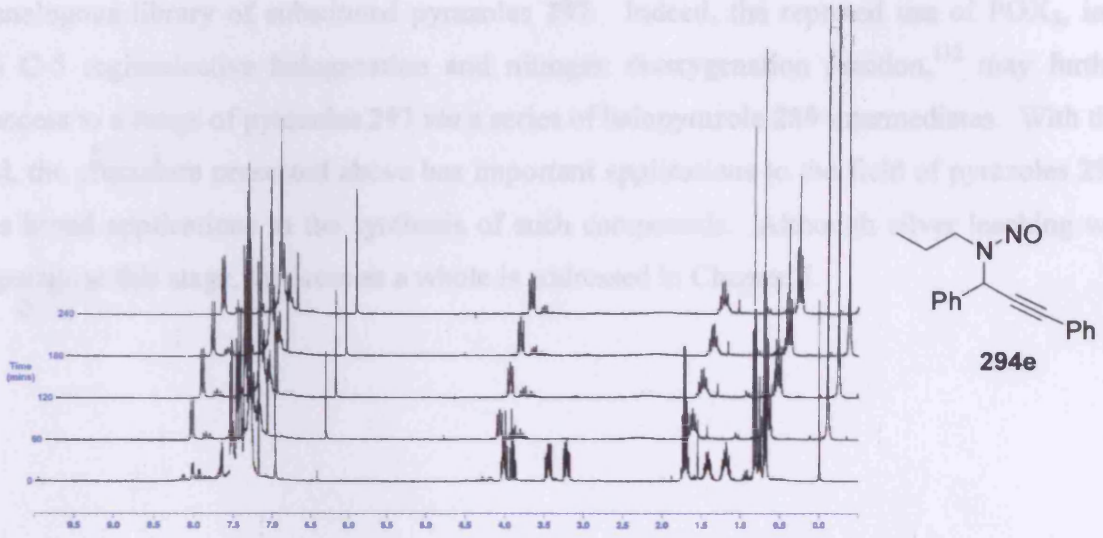


Figure 9: ^{1}H NMR profile of *N*-nitroso propargylamine **294e** ($CDCl_3$) cyclisation.

It can be seen, given the hourly readings (Figure 9), that cyclisation proceeds at a similar rate to that of the synthesis of furans (Chapter 2.3.2 – p 40), with the observation of small amounts of starting material **294e** after 4 h. Interestingly, it can be seen that the addition of 10% $AgNO_3.SiO_2$ appears to resolve the spectrum such that only one rotamer is observed, suggesting the inducement of a rigid activation alignment. This is probably a result of the coordination of silver to the alkyne bond, and is therefore a good indication of the mode of action.

4.3: Conclusions

A novel approach to the synthesis of pyrazole-*N*-oxides **298** has been developed. Being effected in high yields (>95%), this procedure is thought to be a class leader in the regiospecific synthesis of substituted pyrazole-*N*-oxides **298**. With a proven high yielding deoxygenation step (92-99%),[114] it can also be used in an alternative approach to pyrazoles **297**, which allows one access to an analogous library of substituted pyrazoles **297**. Indeed, the reported use of POX_3, in a tandem C-5 regioselective halogenation and nitrogen deoxygenation reaction,[112] may further allow access to a range of pyrazoles **297** *via* a series of halopyrazole **289** intermediates. With this in mind, the procedure presented above has important applications to the field of pyrazoles **297**, and has broad applications to the synthesis of such compounds. Although silver leaching was still apparent at this stage, the issue as a whole is addressed in Chapter 5.

Chapter 5: Results and Discussion

A Flow System for Heterocyclic Synthesis

5.1: Introduction

Traditionally, the manufacturing industry has used batch processing as the chosen method of synthesis in a range of procedures. Favoured for the production of a broad range of different compounds on both small and large scales, and because these lend themselves to the development of new catalytic procedures, batch processes have found frequent uses. Recently however, with the desire and need for industry to improve productivity, increase safety and lower wastage, there has been much focus on the use of continuous processes. With the advantage of decreased downtime, risk and spatial requirements coupled with an increase in efficiency, turnover and safety, these systems are seen by many to be the future of the manufacturing industry. With the common limitation of batch process being single sample fixation, there has been an even greater desire to develop continuous processes which have much broader applications.

There are many non-commercial and commercially used continuous flow reactor systems which are utilised in a bid to achieve continuous processing. Often, continuous processing is used in bulk chemical processing, primarily within petrochemical industries. The complexity and greater demands associated with pharmaceutical processes has, until recently, presented a difficult hurdle to overcome for the applications of this technique to the pharmaceutical industry. Indeed, only some are accepted as being truly continuous but these can be found in many processes worldwide today; others however are still subject to scrutiny surrounding the role they might play in continuous processing.

5.1.1: Continuous stirred tank reactor

One type of continuous flow system is known as a continuous stirred tank reactor (CSTR), which is closely related to a batch reactor (Figure 10). They use conjoined series of batch reactors, into which the reactants are added at the same rate as the partially reacted material is removed.[115-116]

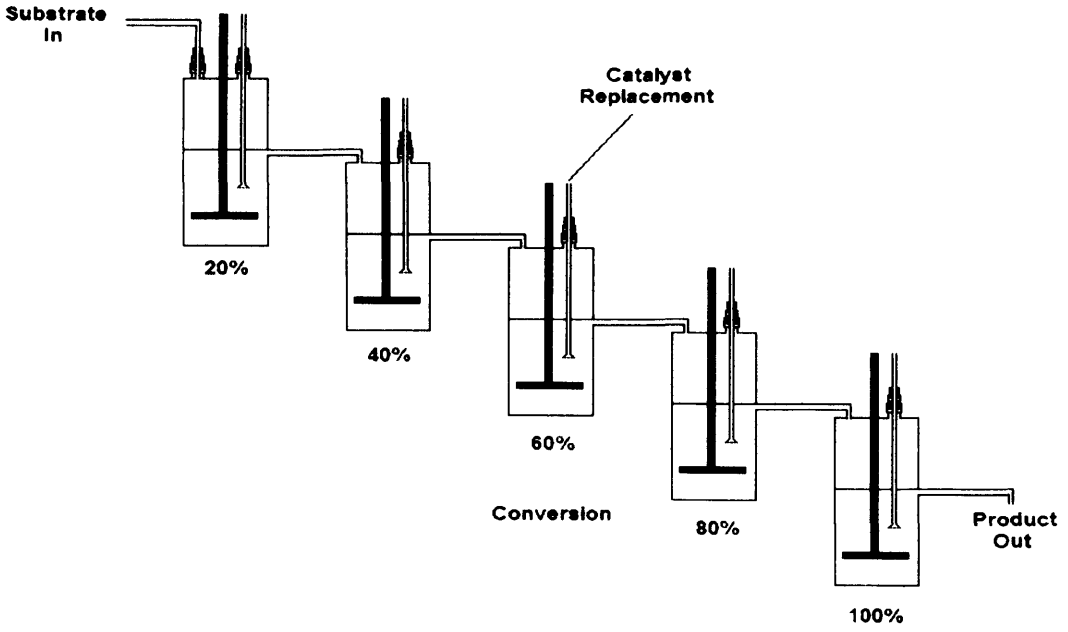


Figure 10: Continuous stirred tank reactor.[115-116]

For example, if each reactor contains catalyst, a progressive increase in product formation is achieved which ultimately results in high levels of conversion. Unfortunately there is a major drawback associated with this technique when fine powder catalysts are used. Often in cases such as these, the effluent passing between reactors contains catalyst as well as partially reacted material, which has the effect to reduce the activity of each sequential reactor over time. This problem can be eliminated by using a coarser catalyst contained within a 'basket' but this removes the advantages gained by having a large surface area exposed.

5.1.2: Fixed bed reactor

Given the problems associated with the use of CSTRs, there has been much more emphasis on the use of fixed bed reactors, the most common of which is arguably the trickle-bed reactor (Figure 11).[117-119] In its crudest form, this comprises of a tube containing catalyst which can effect the transformation of a stream of reactant into the desired product. With the potential for use with both gaseous and liquid reagents, this system has found many applications. A good example is its application in a three phase reaction such as a hydrogenation.[120, 121] With the use of a baffled thermocouple, it is possible to control temperatures reliably such that both vapour and liquid phase reactions can be performed. The only limiting factor to this reactor is particle size: if too small, there comes a requirement to use high pressures which, although manageable, are often preferably avoided. Thus, surface area is usually slightly compromised in the interests of reducing pressures whilst still maintaining the required flow rate. Many have found applications for this system due to its major strength: simplicity.

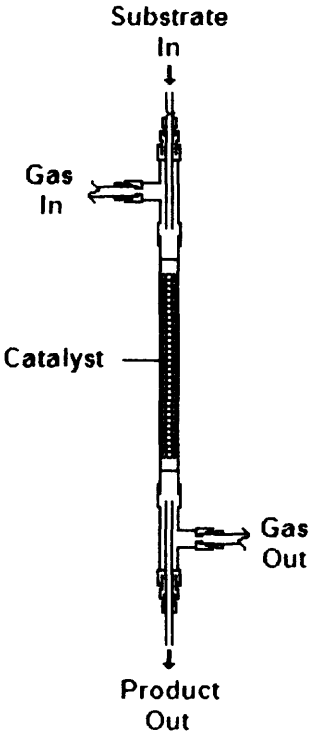


Figure 11: Three-phase trickle-bed reactor.

5.2: Silver-catalysed flow system for heterocyclic synthesis

5.2.1: Silica gel flow system

With the overwhelming success of the batch silver cyclisation reactions, which had been observed when using commercially available 10% w/w $AgNO_3.SiO_2$ as the catalyst, it was felt that it would be possible to apply this catalyst to a continuous flow reactor system. Using the trickle-bed model (Figure 11), 10% $AgNO_3.SiO_2$ catalyst was packed in a foil-lagged glass column (18 x 0.5 inches), with a bed volume of 10 inches and a protecting sand layer of 0.5 inch, with dichloromethane as the mobile phase (Figure 12). The flow was maintained with the application of positive pressure from an air line into the solvent reservoir.

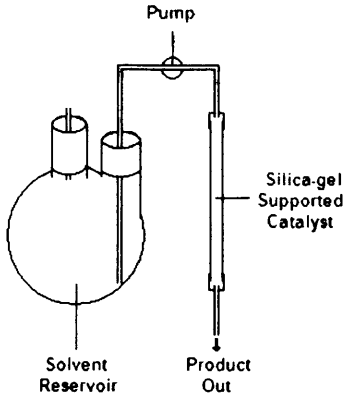
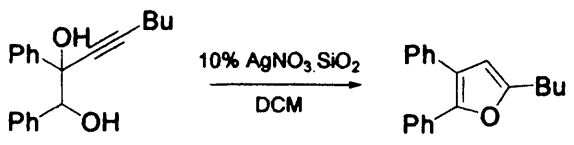


Figure 12: Trickle-bed flow system (10% w/v $AgNO_3.SiO_2$ catalyst).

Given the polarity of the silica-gel, it was apparent that a polar diol **100** would progress through the column at a slower rate than the derived non-polar furan **101** (Scheme 86), providing a potential advantage by increasing the contact time of the diol **100** with the catalyst. Thus, a 10% w/v solution of diol **100e** in dichloromethane (1 mL) was loaded onto the column and mobilised with a dichloromethane wash (50-100 mL). In this way, furan **101e** was prepared over the course of 1 h by passage of the solution of diol **100e** through the column at a flow rate of ~1 mL/min.



100e **101e**

Scheme 86: Synthesis of 5-butyl-2,3-diphenylfuran **101e**.

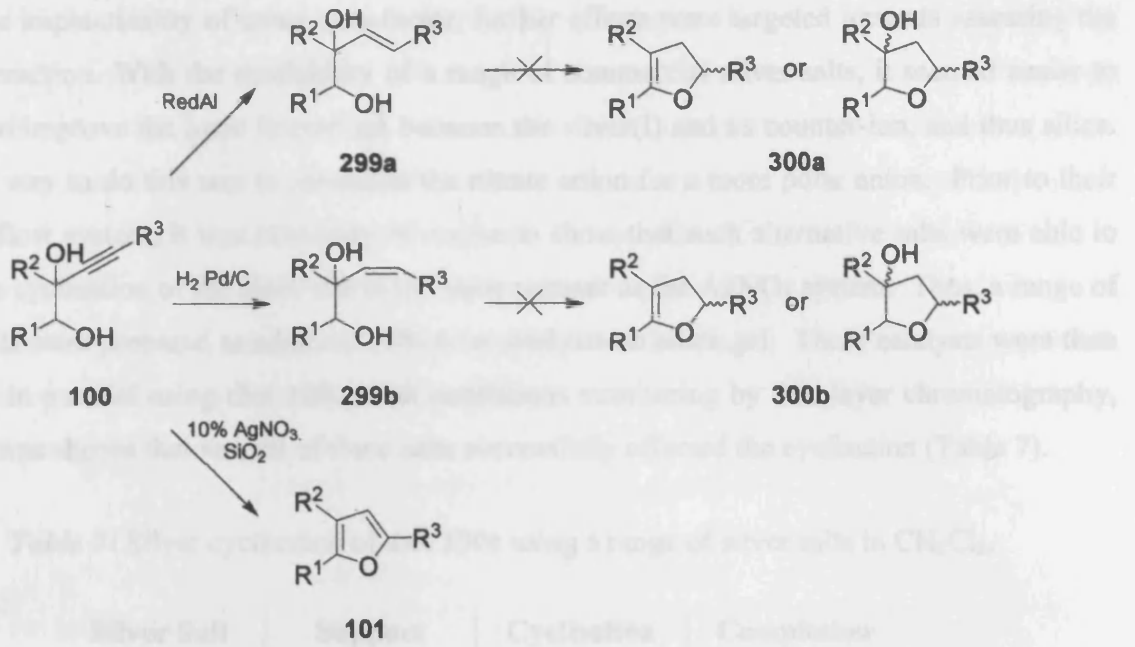
Analysis of the residue after evaporation of the filtrate showed the isolation of product in high yields (>95%) and complete conversion into the desired furan **101e**. Unfortunately, there was one major drawback with this particular catalyst: relatively high levels of silver were seen to have leached with the product. This was clear from the fact that a stark silver mirror was deposited upon exposure of the product to light. Incorporation of an additional bed of silica gel beneath the 10% $AgNO_3.SiO_2$ catalyst contained within the glass column, designed to reduce silver leaching, failed to have any affect, which was very disappointing.

With this result in hand, it had been shown that although it was possible to effect cyclisation using our standard catalyst, 10% $AgNO_3.SiO_2$, embedded within a trickle-bed reactor, it was not possible to prevent leaching of the catalyst. The alternative option to remove silver by passage through a separate celite column, as shown in the batch reactions, was not a viable solution. Not only would this detract from the advantages of this method, but it would merely treat the symptoms of the issue instead of the cause, and further lead to a short operational lifetime.

5.2.2: Studies towards a flow system for heterocyclic synthesis

It seemed that the fundamental success of the cyclisations within a trickle-bed reactor did warrant its continued use, but the inability to completely retain silver questioned the use of our current catalyst. An understanding of why the catalyst was leaching silver was required. Either the interaction between the $AgNO_3$ salt and silica support or the ionic bond between Ag^+ and its NO_3^- counter-ion, which itself interacts with silica, were weak enough to allow silver to leave the system.

To address the first scenario, a cofactor was used in an attempt to "glue" the silver salt to the silica support. Serendipitously, it had been seen that in the failed cyclisation of a mixture of the 3-alkene-1,2-diols **299a-b** in the presence of the precursor 3-alkyne-1,2-diol **100**, it was possible to isolate pure furan **101**. This purification was achieved with the decantation of the organic solution from the 10% w/w $AgNO_3.SiO_2$. It appeared that this left all unreacted 3-alkene-1,2-diols **299a-b** behind, adsorbed on the catalyst (Scheme 87), given their absence in the ^1H NMR spectra of the evaporated organic solution. Furthermore, it seemed as though the unreacted diols **299a-b** had an affinity for the 10% w/w $AgNO_3.SiO_2$ catalyst, to the extent that there was a visible reduction in silver leaching into the product **101**, this given the absence of a silver mirror.



Scheme 87: Reaction of 3-alkyne-1,2-diols **100** and 3-alkene-1,2-diols **299a-b**.

As it is well established that silver(I) interacts with alkenes (Figure 13),[122-123] it seemed most likely that the catalyst was interacting with the substituted allylic alcohol functionality. This interaction arises from donation of π-electrons from the alkene into the σ-orbital of the metal, and is further strengthened by d-orbital back donation into the alkenes' π^*-orbital (Figure 13). Thus, addition of equimolar 3-penten-2-ol, relative to the silver(I)-catalyst, a commercially available substituted allylic alcohol and clearly NOT a cyclisation precursor, appeared to reduce silver leaching when performing the same simple decantation. Unfortunately, it was found that the use of such a cofactor within the trickle-bed reactor seemed impractical as varying amounts were often observed to be admixed with the reaction products obtained (despite the initial observations – *see above*). Other alcohols were tested, including allyl alcohol itself (10 mol%), but once again product contamination was an issue, despite this additive having a much lower boiling point.

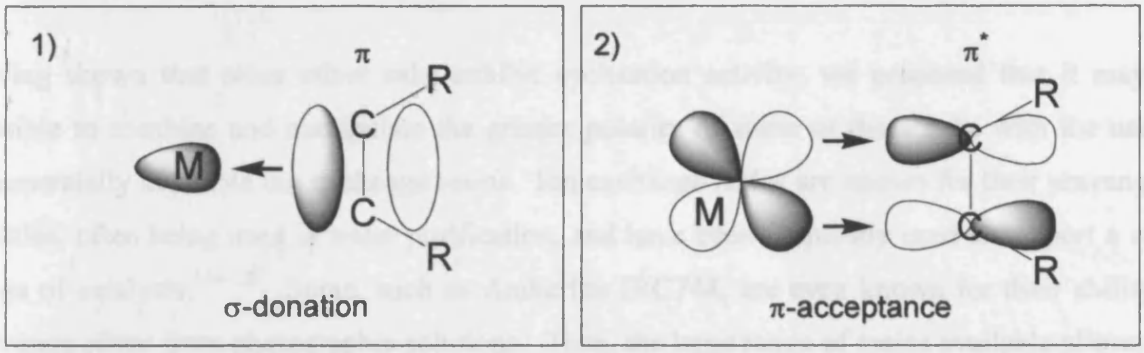
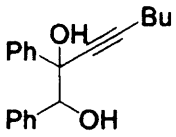


Figure 13: *Dewar-Chatt-Duncanson* model: Two-bonding interactions of an alkene to metal.

Given the impracticality of using a co-factor, further efforts were targeted towards assessing the ionic interaction. With the availability of a range of commercial silver salts, it seemed easier to attempt to improve the ionic interaction between the silver(I) and its counter-ion, and thus silica. The best way to do this was to substitute the nitrate anion for a more polar anion. Prior to their use in a flow system, it was necessary of course to show that such alternative salts were able to effect the cyclisation of the diols **100** in the same manner as the $AgNO_3$ system. Thus, a range of silver salts were prepared as admixed 10% w/w catalysts on silica gel. These catalysts were then screened in parallel using diol **100e**, with continuous monitoring by thin layer chromatography, where it was shown that several of these salts successfully effected the cyclisation (Table 7).

Table 7: Silver cyclisation of diol **100e** using a range of silver salts in CH_2Cl_2.

Silver Salt	Support	Cyclisation	Completion Time (h)
$AgNO_3$	Silica	✓	4
Ag_2CO_3	Silica	✓	18
AgI	Silica	✗	>48 (0%)
$AgBF_4$	Silica	✓	6
AgOTf	Silica	✓	4



100e

It was clear from this simple screen that silver tetrafluoroborate and silver triflate gave comparable rates of cyclisation to the previously used silver nitrate catalyst. Silver iodide was not expected to permit cyclisation as silver halides are not very soluble in organic solvents. Interestingly, a side study showed that silver carbonate on celite did not induce cyclisation, probably due to the use of neutral celite, which is used to remove silver from the cyclisation solutions. It should be noted that at this stage we were most interested in activity and thus leaching was not quantified.

Having shown that other silver salts exhibit cyclisation activity, we proposed that it may be possible to combine and manipulate the greater polarity of some of these salts with the use of commercially available ion exchange resins. Ion exchange resins are known for their scavenging abilities, often being used in water purification, and have been frequently used to support a wide range of catalysts.[124-127] Some, such as Amberlite IRC748, are even known for their ability to scavenge silver from photographic solutions. Thus, the large range of resins available allows for almost any catalyst to be accommodated, and as such many reactions have been seen to be

performed in the presence of such resins. Hence, as a starting point, it was proposed that an ion-exchange resin could be used as a pad at the bottom of our existing column in a bid to scavenge any leaching silver (Figure 12 – p 85). The thought then occurred that the silver cations, when bound to an ion-exchange resin, could themselves be effective in inducing cyclisation, but without leaching. The mode of action is as follows. Many resins present surface areas covered in a wide range of simple anions or cations, which are attracted to an immobilised charged site of opposite charge. These charged sites can be readily exchanged to remove an appropriately charged ion from a reaction medium (Table 8).

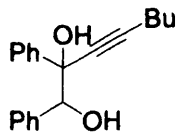
Table 8: Amberlite ion exchange resins.

Resin	Surface ion	Counter ion	Classification
Amberlite IRC50	RCO_2^-	H^+	Weakly acid
Amberlite IRC748	$RN(CH_2CO_2^-)_2$	Na^+	Weakly acid
Amberlite 200C	RSO_3^-	Na^+	Strongly acid
Amberlite IRA95	RNH_2	free base	Weakly basic
Amberlite IRA400	RNH_3^+	Cl^-	Strongly basic

Known as scavenging, this exchange is pH dependent, therefore to absorb a cationic metal, a resin must present a negative charge.[115] To ensure efficient absorption, the pH of the impregnating solution has to be controlled. Thus, it was possible to impregnate the acidic amberlite IRC50, IRC748 and 200C supports by percolation of an acidic aqueous silver nitrate solution (pH 3.5-5), through a column of the solid resin (Table 9).

Table 9: Silver cyclisation using a range of support conditions.

Resin	Active Surface	Cyclisation	Cost (£/kg)
Silica	SiO_2	✓	122
No support [a]	-----	✗	0
Celite	SiO_2, Fe_2O_3, Al_2O_3	✗	14
Amberlite IRC50	RCO_2^-	✓	46
Amberlite IRC748	$RN(CH_2CO_2^-)_2$	✓	55
Amberlite 200C	RSO_3^-	✓	27



100e

[a] When using silver nitrate by itself in DCM it was found that cyclisation did not proceed.

The results from a screen of these silver impregnated resins, and those of other supports, showed effective cyclisation in the expected cases, *i.e.* in cases where an acidic, but non-retentive, support is present.

An unfortunate consequence of the above 'wet impregnation' is that solution concentration, salt nature, solvent and contact time can all affect the distribution of the catalyst on the support (Figure 14).[115] These distributions are further effected by the nature of the support used and as such allow for the formation of several, very different, types of supported catalyst, each of which can present slightly different activities.

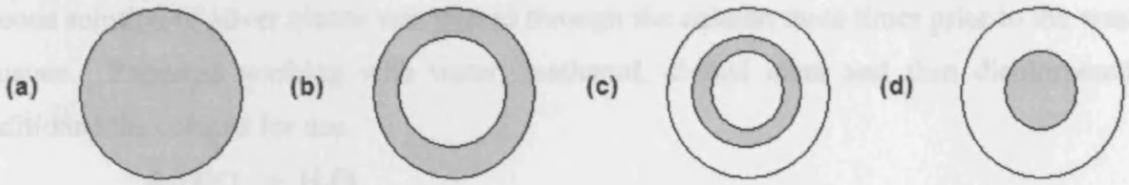


Figure 14: Different modes of catalyst distribution (catalyst in grey)[115]
(a) Uniform (b) Egg shell (c) Egg white (d) Egg yolk.

Uniform distributions, formed by saturation of the support with catalyst solution, allow for increased contact time between the reagent and the catalyst. This increases the likelihood of side reactions occurring, and as such they are only used in specialised cases.[115] For the silver cyclisation, one may expect an 'egg shell' distribution to be most appropriate. This would allow the alkyne access to the active metal, but minimise contact time, allowing for the furan to be readily displaced without the threat of undergoing side reactions. So how does one go about forming such a distribution? 'Egg shell' distributions are often seen when using strongly absorbing resins, for instance strongly acidic resins such as amberlite 200C. Such resins absorb the metal on their surface first and then as all the surface sites become occupied the resin gradually impregnates towards its core. Thus, both the concentration of the impregnating solution and contact time can then be adjusted to determine how thick this shell becomes. In the case of this system, the decision was taken to pack the resin within a stainless steel column, to form a light-free environment, and to then flush saturated aqueous silver nitrate quickly through the column five times. It was felt that this would have the effect of lowering contact time, to ensure mainly surface absorption, but at the same time would provide enough silver to ensure that this surface became sufficiently impregnated.

5.2.3: Ion-exchange flow system

With the assessment of counter-ions and supports having been performed, and in an attempt to mimic the triflate counter-ion, amberlite 200C, the cheapest resin tested, was chosen to act as both the counter-ion and support. With strongly acidic resins having an isoelectric point far below pH 7, it was expected that this resin would load with the most efficiency and desired distribution. It was found that amberlite 200C, in its sodium form, packed in a stainless steel column (8 x 0.5 inches) (Figure 16) and with a bed volume of 50 cm^3, successfully exchanged Ag^+ from an aqueous solution of silver nitrate (Figure 15). In practice 50 mL of a 10% w/v aqueous solution of silver nitrate was passed through the column three times prior to the washing sequence. Repeated washing with water, methanol, diethyl ether and then dichloromethane conditioned the column for use.

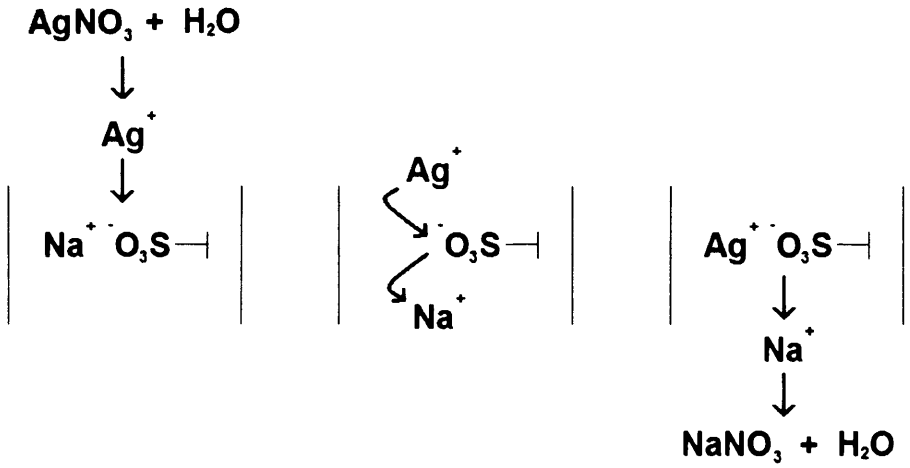


Figure 15: Silver exchange by an ion exchange resin.

Analysis of silver content on this resin, by ICPMS, showed there to be 7.65% w/w silver on this column, with very little difference between the top and bottom of the column. With the dry weight of the impregnated resin being 8.8 g, it can be calculated that there was a total of 0.67 g of silver contained within the column, which would be equivalent to 1.05 g of $AgNO_3$. Unfortunately we were not able to obtain data surrounding the % loading of sodium on the parent resin, but it is thought that the desired 'egg shell' distribution was at least partly achieved given the short contact time associated with the passage of aqueous silver nitrate solution down the amberlite packed column.

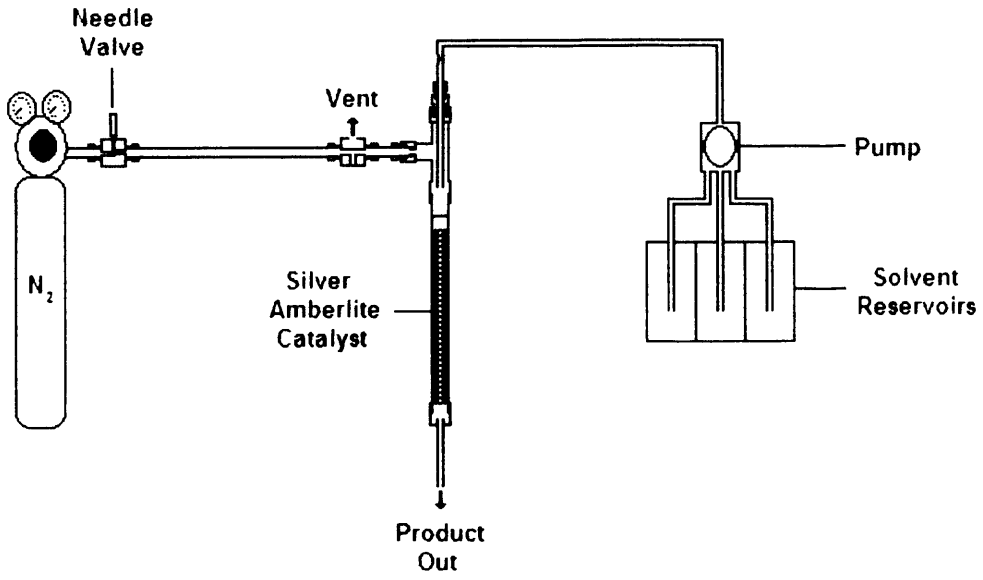
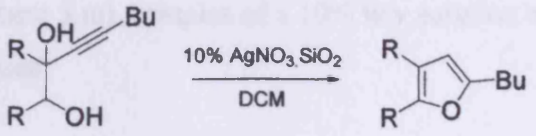


Figure 16: A flow system for heterocyclic synthesis.

As before, passage of a 10% solution of diol **100e** through the column (Figure 16, Appendix D) at a flow rate of 1mL/min, with N_2 pressure being set to 1 bar, yielded pure furan **101e** (Scheme 86) in excellent yields (>95%). Over a 30 min run this equated to the preparation of > 2.67 g of furan **101e** from 3 g of diol **100e**. This formed our first truly effective 'Flow System for Heterocyclic Synthesis'. The major advantage observed with this new column was the complete absence of silver leaching. Analysis of metal content in a range of product samples, determined by ICPMS at an independent GSK facility, showed silver content to be <1 ppm in all cases. This is a strong indication that minimal silver leaching, if any, is observed from this new amberlite 200C supported silver column. Indeed, the strictest FDA limit for any transition metal in an active pharmaceutical is 5 ppm for oral doses, a figure applied to platinum, palladium, iridium, rhodium, ruthenium and osmium.[128] The consistency of the column was also very high, with the same result being repeated in the proceeding two experiments, as well as 6 months later, even after 40, quite varied, runs in between. Such was the success of the system that it was able to form part of the patent[129] which was secured for the broader applications of the silver cyclisation procedure.

5.2.4: Optimisation

Having proven the concept of a successful flow system for heterocyclic synthesis, efforts were then made to optimise several parameters. Perhaps the easiest parameter to adjust was the flow rate, thus the flow rate of a known concentration of diols **100a, 100e** was increased until ^{1}H NMR analysis showed that complete cyclisation to the furans **101a, 100e** was not being attained (Scheme 88).



100a,e (R = Me, Ph) **101a,e**

Scheme 88: Synthesis of 5-butyl-2,3-disubstituted furans **101a, 101e**.

It was shown that at flow rates of 0.5 < 1.5 mL/min, cyclisation of a 10% w/v solution of diol **100e** went through to completion (Figure 17). Above 1.5 mL/min, cyclisation did not go to completion, with NMR showing the presence of some unreacted starting material in the case of a 2mL/min experiment, where conversion was 48%.

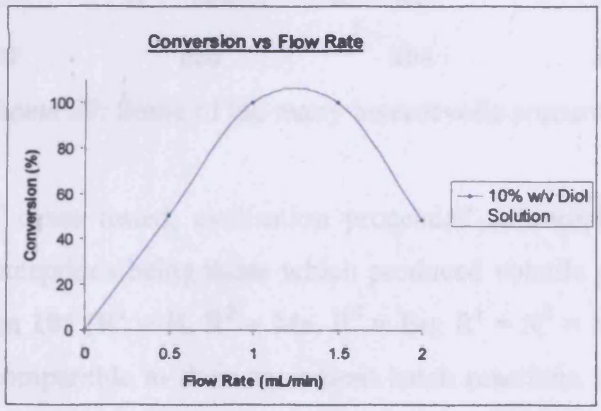
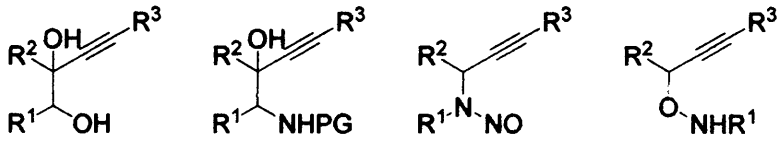


Figure 17: Effect of flow rate on amberlyst-supported silver cyclisations.

The above observations relate to the fact that given the 5 mL liquid capacity of the column, one would expect there to be in the region of 0.5 g of diol **100** contained within the column at any one time. With it being known that the column contains 0.67g silver, this equates to 365 mol% silver being present in the case of 1,2-diphenyloct-3-yne-1,2-diol **100e** and 211 mol% silver in the case of 3-methylnon-4-yne-2,3-diol **100a**. This amount is more than enough to effect cyclisation quickly provided an adequate contact time is allowed, which is what a flow rate of < 1.5 mL/min appears to provide.

In view of these results, and their reproducibility, a standard protocol was developed. This took the form of a programmed HPLC pump timetable, where the substrate was introduced for 5 mins, followed by a dichloromethane wash for 15 mins and then finally reconditioning with methanol then dichloromethane, for 5 mins each. For the first 20 mins, a conservative flow rate of 1 mL/min was maintained, which equates to a resonance time of around 5 mins, before the flow rate was increased to 5 mL/min during the reconditioning period. This protocol formed the basis of an automated system where 5 mL samples of a 10% w/v solution of any heterocyclic precursor could be consistently cyclised.

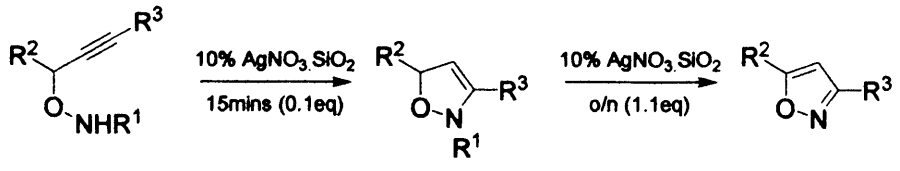
To test this claim, a series of different heterocyclic precursors were passed through the column as 10% w/v solutions and the above protocol used. These precursors included 3-alkyne-1,2-diols **100** (R^1 = R^2 = Ph, Me, H, R^3 = Bu), 3-alkyne-2-hydroxy-1-sulfonamides **238a-f** (R^1 = Me, R^2 = Ph, R^3 = Bu, PG = Boc), *N*-nitroso propargylamines **294** (R^1 = Bn, R^2 = *i*-Bu, R^3 = Bu) and *O*-propargylhydroxylamines **301**[130] (R^1 = H, R^2 = *i*-Bu, R^3 = Bu) (Scheme 89).



100 **238** **294** **301**

Scheme 89: Some of the many heterocyclic precursors.

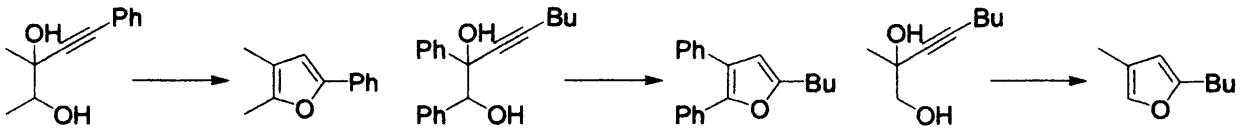
In the vast majority of cases tested, cyclisation proceeded to completion in excellent yield (>95%), with the only exceptions being those which produced volatile products. In these cases, the isolated yield of furan **101** [R^1 = H, R^2 = Me, R^3 = Bu; R^1 = R^2 = Me, R^3 = Bu] were lower (60-66%), but directly comparable to their equivalent batch reactions, and one would expect to obtain yields of >95% when handled with appropriate equipment. Pleasingly, the difficult *O*-propargylhydroxylamines **301** appeared to form isoxazolines **302a** and did not oxidise to the corresponding isoxazoles **302b** (Scheme 90), a common side reaction known to occur in the presence of silver nitrate on silica gel.[130]



301 **302a** **302b**

Scheme 90: Oxidation of *O*-propargylhydroxylamines **301** to isoxazoles **302b**.

In a further experiment, one which was designed to test the competitive nature of these cyclisations, a mixture of three different diols **100b**, **100e** and **100n** was cyclised (Scheme 91). All three substrates were successfully transformed into their corresponding furans **101b**, **101e** and **101n**, and there was no suggestion of the formation of any side products.

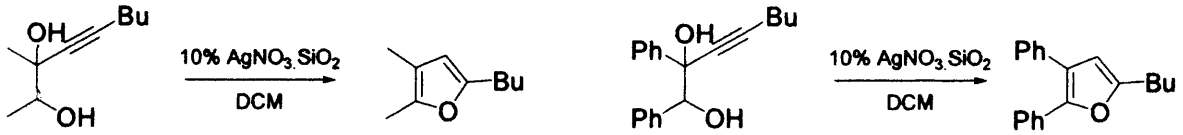


100b **101b** **100e** **101e** **100n** **101n**

Scheme 91: Silver-catalysed cyclisation of a mixture of diols **100b**, **100e** and **100n**.

This is an important result as it gives an indication of the robustness of this technique and of the potential to use just a single column to cyclise a variety of different substrates, without the risk of side product formation with any contaminants. Important commercial implications can be drawn from this result, given that it allows for the possibility of a "general use column" to be sold for standard laboratory research use.

Another avenue of investigation, in view of the successful use of several substrates, sought to test a range of substrate concentrations. Given the varying physical form of many of these substrates it was clear that, in the case of liquid precursors *e.g.* **100a**, it may not be necessary to use a solvent at all. In the case of solids *e.g.* **100e**, it was felt that it may be possible to use more concentrated solutions, after all 10% was originally chosen arbitrarily. Thus, to test this, a neat sample of 3-methylnon-4-yne-2,3-diol **100a** (Scheme 92) was passed through a column (8 x 1/8 inches) at a flow rate of 0.5 mL/min for 15 mins. Analysis of the product showed complete conversion to the furan **101a** in excellent yield (85%), higher than had been previously seen when using solvent, a result of there not being a need to remove any solvent, with attendant loss of product through volatilisation.



100a **101a** **100e** **101e**

Scheme 92: Synthesis of 5-butyl-2,3-dimethylfuran **101a** and 5-butyl-2,3-diphenylfuran **101e**.

The above observation was based upon a one-off result where the column contained minimal amounts of dichloromethane. Given the narrower dimension of the column used, one can be fairly confident that passage of the substrate through the system for 15 mins allows for the majority, if not all, of the dichloromethane to be removed. With cyclisation still proceeding to completion, it is reasonable to state that solvents are not required for the reaction to occur, although granted they are still needed to clean the column afterwards. This result has therefore provided an improvement on the system, for this particular compound, since this time there was not the requirement for solvent during the reactive stage.

Having already shown the positive effect of more concentrated solutions of 1,2-diphenyloct-3-yne-1,2-diol **100e** (Scheme 92) in increasing the rate of cyclisation (Chapter 2.3.4 – p 42), it seemed prudent to test more concentrated solutions through the flow system. Thus a 20% w/v solution in dichloromethane was prepared. Passage of the 20% w/v solution at a flow rate of < 1.5 mL/min allowed for complete cyclisation to the furan (> 95%) with incomplete cyclisation (67%) being observed for a flow rate of 2 mL/min (Figure 18).

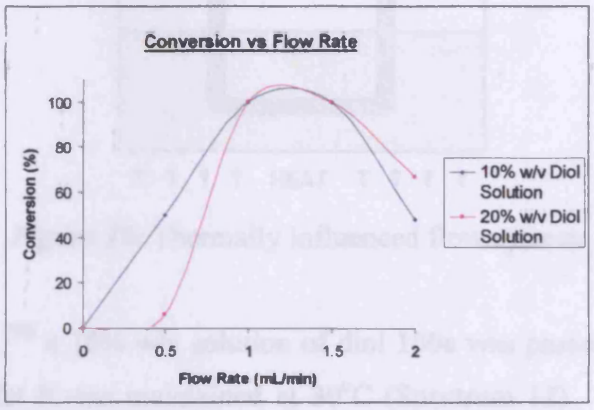


Figure 18: Effect of flow rate on amberlyst-supported silver cyclisations.

Although the results in Figure **18** are comparable to the results seen with the 10% w/v solutions, a subtle increase in conversion with the more concentrated 20% solution was observed. This suggested that concentration may contribute towards a minor improvement in the efficiency of cyclisation in our continuous flow system. This difference appears to be only very small and needs further investigation to understand its actual significance. For instance, a more detailed study with more sample points may be considered.

The final optimisation centred around studies into thermal influences on the flow system. This work also incorporated investigations into the use of microwave irradiation, given the findings described in recent literature articles.[131-136] Previous operations of the flow system had been successfully performed under ambient conditions. It was recognised therefore, that there was a clear opportunity to assess the affect of higher temperatures on the function of this system. Preliminary studies by John[79a] using heated batch reactions showed there to be an acceleration in rate upon an increase of temperature, as one would expect. Indeed, these studies showed that when using 20 mol% of 10% $AgNO_3.SiO_2$, it was possible to effect the cyclisation of a 10% w/v substrate solution in $1/6^{th}$ of the time at 40°C. This positive result prompted the preparation of a 'U' shaped column (Figure 19) with which it was possible to assess such affects on continuous flow production.

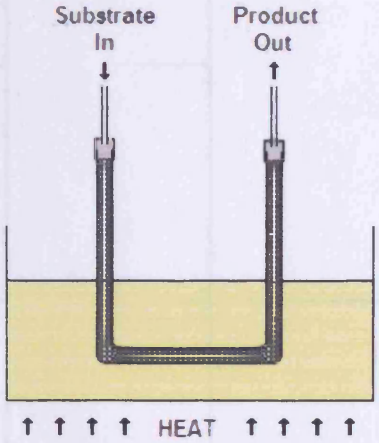
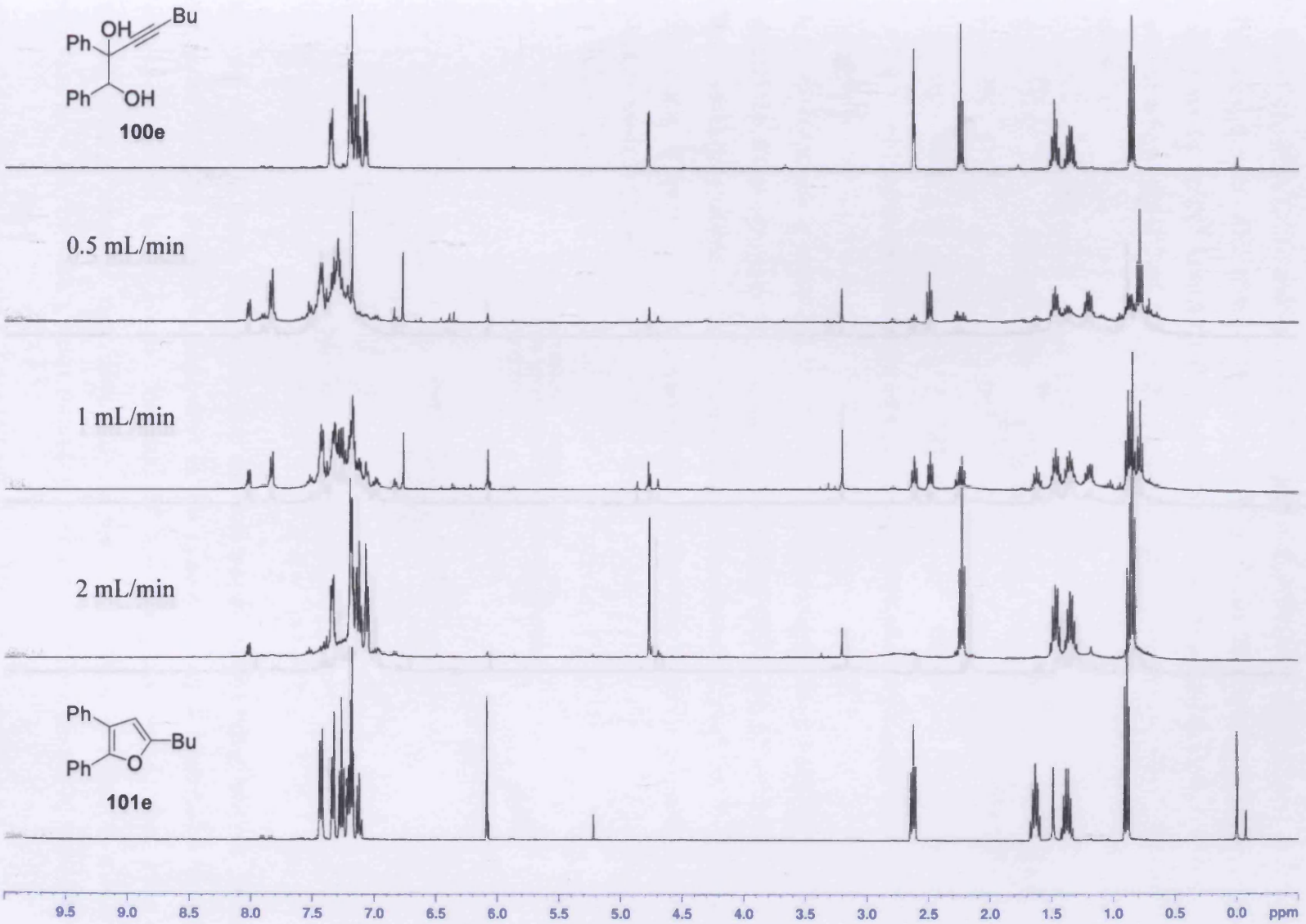
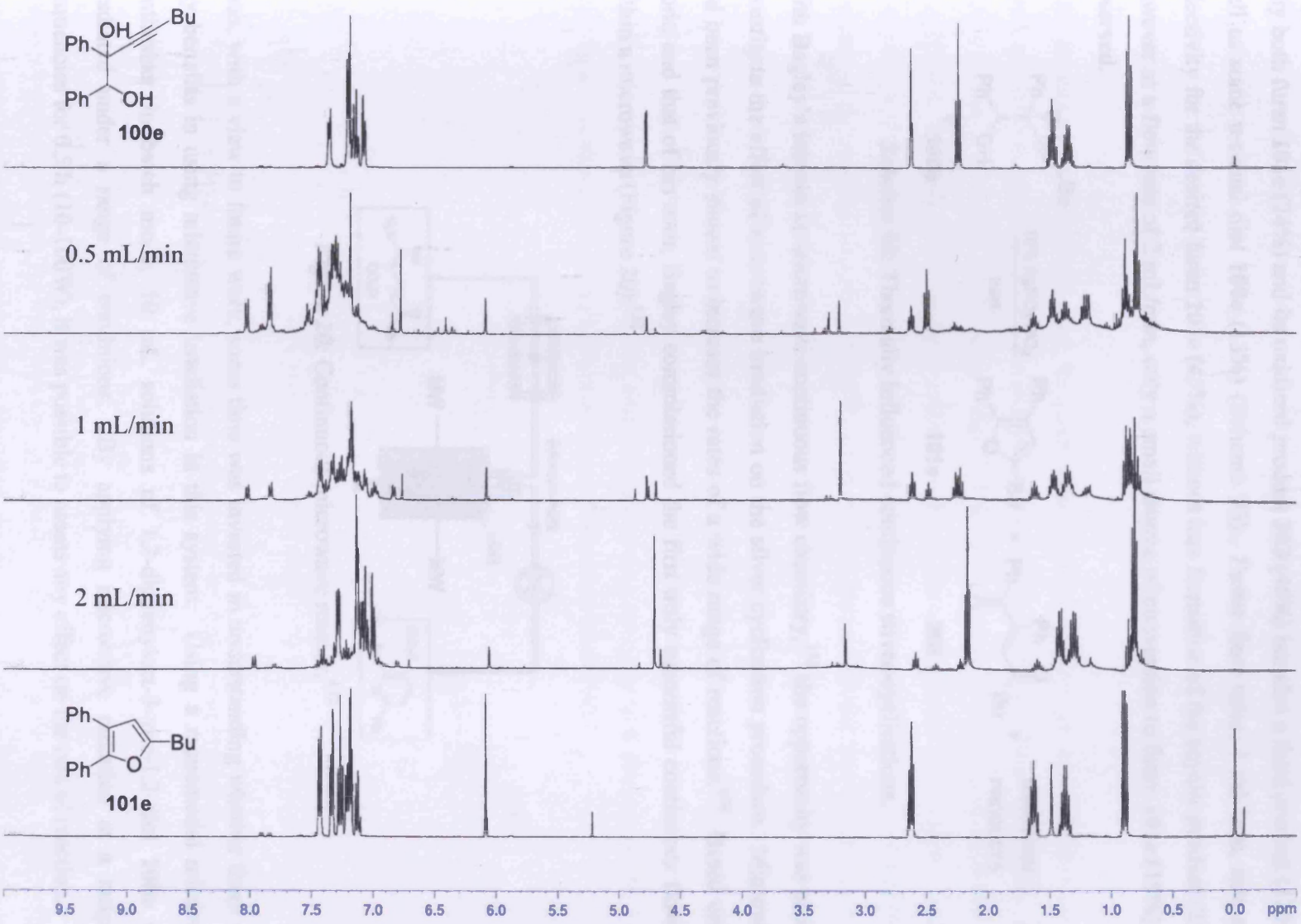


Figure 19: Thermally influenced flow system.

With the help of Knight,[79b] a 10% w/v solution of diol **100e** was passed through this column at different flow rates whilst it was maintained at 30°C (Spectrum 12). It was found that under continuous flow conditions, at a flow rate of 0.5 mL/min, consumption of the diol **100e** was successfully achieved. However, unfortunately, under these conditions a mixture of furan **101e** (Scheme 92) and a suspected ring opened adduct were obtained, this in view of similar previous observations (Chapter 2.2.4 – p 32). At faster flow rates, incomplete cyclisation became apparent, with a flow rate of 2 mL/min effecting only slight cyclisation (3%). This was likely to be a result of there having been too short a contact time between the substrate and the catalyst in this smaller column. A flow rate of 1 mL/min did show some conversion to the furan **101e** but equal quantities of ring opened product were also observed. These results provided a reference point from which to work.

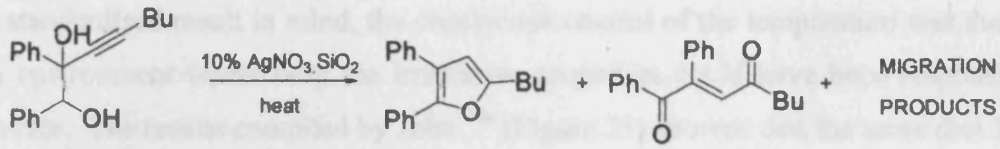


Spectrum 12: ^{1}H NMR spectrum comparison of flow rates of the cyclisation of diol **100e** to furan **101e** at 30 °C (in $CDCl_3$).



Spectrum 13: ^{1}H NMR spectrum comparison of flow rates of the cyclisation of diol **100e** to furan **101e** at 50 °C (in $CDCl_3$).

Using the results from these 30 °C cyclisations it was possible to assess the effect of increased temperature. It was found shown that at 50 °C (Spectrum 13), a flow rate of 0.5 mL/min gave not only both furan **101e** (24%) and its oxidised product **303** (46%) but also a third product (17%) as well as some residual diol **100e** (13%) (Scheme 93). Faster flow rates, 1 mL/min, saw more selectivity for the desired furan **101e** (45%), without less formation of the acyclic product (25%), however at a flow rate of 2 mL/min, only a small degree of conversion to furan **101e** (15%) was observed.



100e **101e** **303**

Scheme 93: Thermally influenced continuous silver-cyclisations.

With Bagley's interest in microwave continuous flow chemistry,[132] the opportunity was taken to investigate the effect of microwave irradiation on the silver cyclisation procedure. Microwaves had been previously shown to increase the rates of a wide range of reactions.[136] Based on this work, and that of his own, Bagley commissioned the first truly successful continuous flow cell within a microwave (Figure 20).[132]

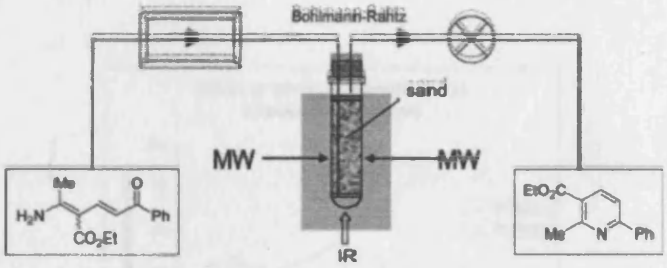


Figure 20: Continuous microwave reactor.[132]

Thus, with a view to future work, some time was invested in understanding whether there were any benefits in using microwave irradiation in this system. Using a monomodal microwave synthesiser in batch mode, 10 mL solutions of 1,2-diphenyloct-3-yne-1,2-diol **100e** were irradiated under a range of conditions. By applying microwave radiation at a range of frequencies for 0.5 h (10-100W), it was possible to assess any effect on the rate of reaction.

Given the potential thermal contribution of microwaves, control measures had to be introduced to ensure that we were truly assessing the effect of the microwave radiation. These took the form of continuous temperature control and use of a standardised sample to act as a reference point from which to judge the success of any microwave irradiation. The standardised 2% w/v solution of diol **100e** was fully cyclised with 0.5 equivalents of 10% $AgNO_3.SiO_2$ catalyst at 40°C within 1h and without any influence from microwave irradiation (Chapter 5.2.4 – p 97).

With the standardised result in mind, the continuous control of the temperature was then used to create an environment where only the irradiative properties could have been responsible for a change in rate. The results compiled by John [79a] (Figure 21) showed that the same diol **100e**, also as a 2% w/v solution, could be fully cyclised to furan **101e** at ambient temperature (external vessel temperature maintained by air cooling) within 1h when using 50W microwave irradiation. Irradiation of the same solution with 30W microwave radiation effected the cyclisation of diol **100e** in 98% conversion. This suggests that the optimum wattage lies around 30W, a reasonable improvement on the use of elevated temperatures, but still quite energy demanding. Further studies into the use of a 1% w/v solution of diol **100e** proved to be less effective with 100W irradiation being required to effect complete cyclisation. Further problems were also seen with this 1% w/v solution given its apparent susceptibility to ring opening, with the product of a 30W experiment containing the previously observed acyclic product **303** (8%).

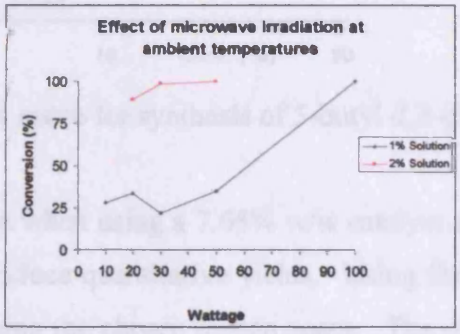


Figure 21: Effect of adjusting wattage on degree of conversion (%) (1h reaction time).

It would appear from the data shown in Figure 21 that microwave irradiation does produce a positive influence on the speed of the silver cyclisation reaction for batch cyclisations. Further studies are needed to assess the true influence of such irradiation but on the basis of this study the results look promising. However, given the apparent problem of ring opening when applying

heat to our ion-exchange continuous flow system, it would seem that early indications of a similar transformation resulting from microwave irradiation may just complicate an already efficient system. The further expense and effort required when using such a system, when compared to an established and simple flow system, is perhaps not worth the trouble. It should of course be recognised that if a robust synthesis of the ring opened products can be achieved, then the use of microwaves may be pivotal to their continuous synthesis.

5.2.5: Discussion

With all of the above optimisations in hand, it seemed prudent to draw a series of reasonable comparisons. This was achieved using a "design space" representation (Figure 22). Correlation of three variables, concentration, flow rate and catalyst loading, allowed an overall perspective to be drawn. Temperature was not a chosen variable given the observed ring opening.

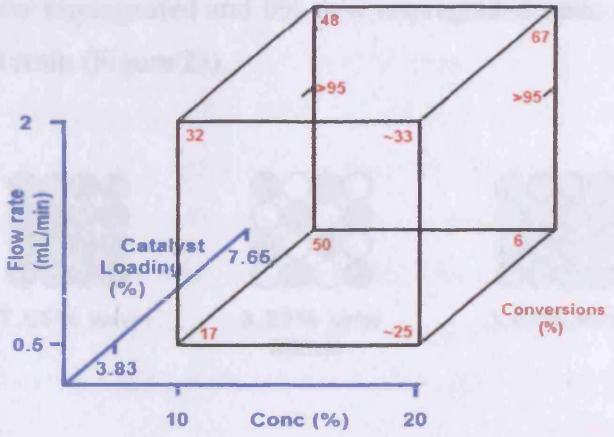


Figure 22: Design space for synthesis of 5-butyl-2,3-diphenylfuran **101e**.

It had already been shown that when using a 7.65% w/w catalyst at a flow rate of 1.5 mL/min, it was possible to repeatedly produce quantitative yields. Using the largest flow system, (8 x 0.5 inches), we went about assessing the chosen design space. The results of this study highlighted that at reduced flow rates, conversion is often very low (< 25%). This is an expected consequence of the reactor design as it is felt that at flow rates < 0.5mL/min, the diol fails to bridge the initial cotton wool plug efficiently. Thus, the comparatively high conversion (50%) seen when using a 0.5mL/min flow rate at 10% concentration and 7.65% w/w catalyst loading, is most likely to be representative of the inconsistencies attributed to passage through such a plug of cotton wool.

At flow rates above 1.5 mL/min, the degree of conversion was seen to drop, as expected; this a result of a decrease in contact time. Indeed, the degree of reduction in conversion allows us to view another previously formed conclusion regarding concentration more clearly. It had been suggested that the 20% w/v solution was slightly more efficient beyond its optimal flow rate than its 10% w/v counterpart (Chapter 2.3.4 – p 43). This can now be seen clearly with just a 28% drop in activity when using a 20% solution at higher flow rates, as opposed to the 47% drop seen with the more dilute solution.

The final area of interest enables an assessment of the effect of catalyst loading to be made. Given the time taken to obtain ICPMS data, a decision was taken to assess catalyst loading by replacing half of the catalyst present in the tube with non-impregnated amberlite 200C. To ensure consistency, the retained half of the column resin was thoroughly dry blended with the fresh amberlite 200C to ensure even distribution. This repackaged resin was then used as a 50:50 distribution of 7.65% w/w impregnated and 0% w/w impregnated resin to mimic the action of a 3.83% w/w impregnated resin (Figure 23).

Figure 23: Catalyst distribution of the 3.83% w/w mimic catalyst.

The effect that this mimicked catalyst had can clearly be seen in Figure 22, where conversions were down by up to 35%. With evidence from the batch reactions showing that marked changes in reaction time occur upon alteration of the catalyst molar equivalence, this result seems reasonable.

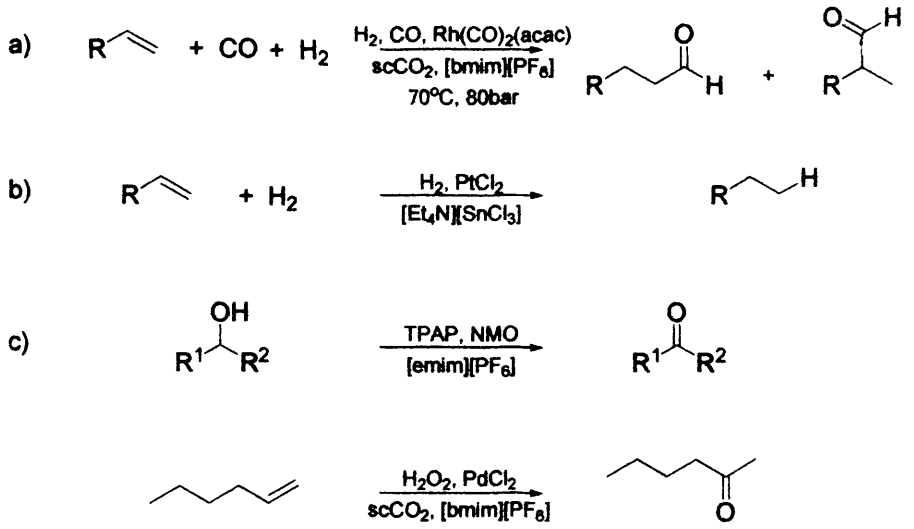
5.2.6: Trickle-Bed Conclusions

Overall, it was confirmed that silica had a potential use as a support in a continuous flow system with excellent yields (> 95%) of furan **101e**. However, despite our best efforts, we were unable to control silver leaching from this system, which gave the catalyst a distinctly finite lifetime and gave the added requirement of a separate product purification step. With investigations focusing on the causes of this leaching, our attention was turned down another avenue, the use of alternative supports. It was found that use of the ion exchange resin amberlite 200C provided a solution to the silver leaching, with quantification of product metal content showing the presence of < 1 ppm silver. Not only had silver leaching been prevented but the excellent product yields (> 95%) were maintained. This was a truly remarkable result, with further successes including the use of a range of other heterocyclic precursors; even neat diol **101a** could be cyclised uneventfully. To date, we have neared 100 experimental runs over the course of a year and the system appears to be functioning as well as ever. An approximate turnover number of between 20 and 35 mmol/g has been calculated, per gram of loaded resin, a number which is still improving with every result that is run. With mixed results from thermal and microwave investigations, there may be further scope for development of this system but as it stands, it forms a very powerful and novel flow system for heterocyclic synthesis, one which may have industrial applications. And with these views in mind, one would propose the use of a shorter but wider column. This would allow for maximal flow rates to be achieved, providing correct substrate distribution, given that there would be a far greater surface area of catalyst upon first contact of the substrate.

5.3: $scCO_2$ continuous extraction from ionic liquids

5.3.1: Introduction

On the back of the interest in continuous synthesis, there have recently been determined efforts to incorporate and develop novel continuous extraction systems. A key example originates from investigations into the uses of supercritical carbon dioxide ($scCO_2$) and ionic liquids (ILs) in hydroformylation,[137-143] hydrogenation[144-146] and oxidation[147-151] reactions (Scheme 94). As a result of the robustness, high yields and in some respects environmental advantages, recent interest has turned to expanding the applications of such systems. In view of this, it was felt that there may be an application of the silver chemistry in such a combined $scCO_2$:IL system. Discussions with Prof. David Cole-Hamilton,[78, 143] University of St Andrews, led us to believe that our proposal was reasonable.



Scheme 94: a) Hydroformylation,[141] b) hydrogenation[144] and c) oxidation in $scCO_2$.[147-151]

Supercritical carbon dioxide belongs to a class of solvents known as supercritical fluids (SFs), which are formed at and above the critical point of a compound. This critical point consists of a critical temperature (T_c) and a critical pressure (P_c) at which the compound exhibits gas- and liquid-like properties. This gives the SF a unique advantage, since SFs are usually gases in their natural state, they can be readily removed from a system upon simple decompression. With $scCO_2$ having a T_c of 31.1°C and a P_c of 73.8 bar (Figure 24), it is possible to remove any CO_2 from the product under atmospheric pressure and at ambient temperature.[152, 153]

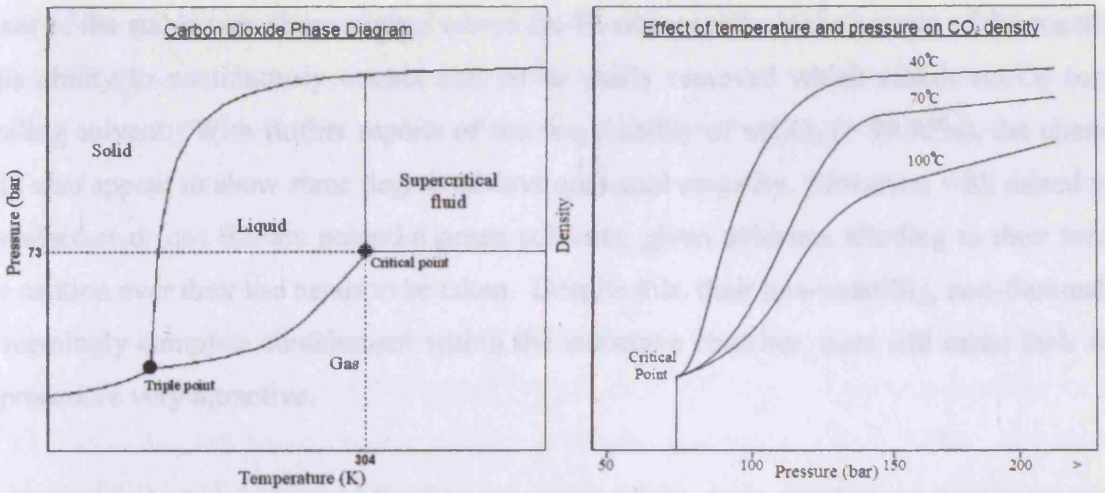


Figure 24: Phase diagram of $scCO_2$ and effect of temperature and pressure on density.

By adjusting both the temperature and pressure of the system, it is possible to alter the solvation power of the $scCO_2$. As a general rule of thumb, it can be seen that an increase in temperature causes density to lower and an increase in pressure causes density to increase (Figure 24), although beyond a certain point the effect of pressure becomes less significant.

The non-polar nature of $scCO_2$ makes it formally immiscible with an IL as a liquid, allowing for a two phase system (Figure 25). Its gaseous properties on the other hand allow it to partially mix with, but not to dissolve anything ionic.

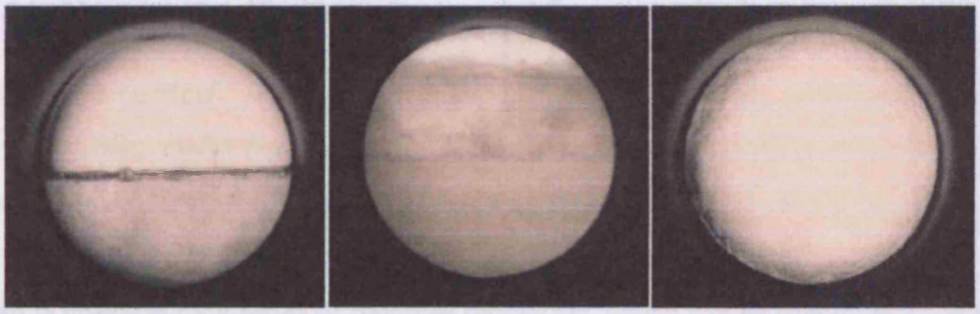


Figure 25: Phase photographs of CO_2 transforming into $scCO_2$.

In tandem with the polar nature of the ILs, it has been broadly shown that transition metal catalyst leaching can therefore be kept to a minimum,[137, 143, 152, 153] with ICPMS figures often seen to be <100ppb. As a result of these findings, it has been shown that it is possible to cleanly extract organic matter from a metal-catalysed reaction carried out in an IL. Indeed, the relative ease in maintaining a continuous flow of $scCO_2$ also makes it is possible to extract continuously,

a result of the stable two-phase system where the IL sits securely at the bottom of the reactor. It is this ability to continuously extract and be so easily removed which makes $scCO_2$ such an appealing solvent. With further reports of the recyclability of $scCO_2$ (> 99.95%), the chemistry would also appear to show some degree of environmental empathy. However, with mixed views as to whether or not ILs are potential green solvents, given evidence alluding to their toxicity, some caution over their use needs to be taken. Despite this, their low-volatility, non-flammability and seemingly complete containment within the autoclave chamber, does still make their use in this procedure very attractive.

To comprehend the function of such a system, it is best to first understand previous hydroformylation reactions. The nature of this reaction meant that elevated pressures and temperatures were a requirement. As a result, this procedure employed a rig which consisted of the $scCO_2$ generator, a HPLC pump, an autoclave and a decompression chamber (Figure 26).[143, 154, 155]

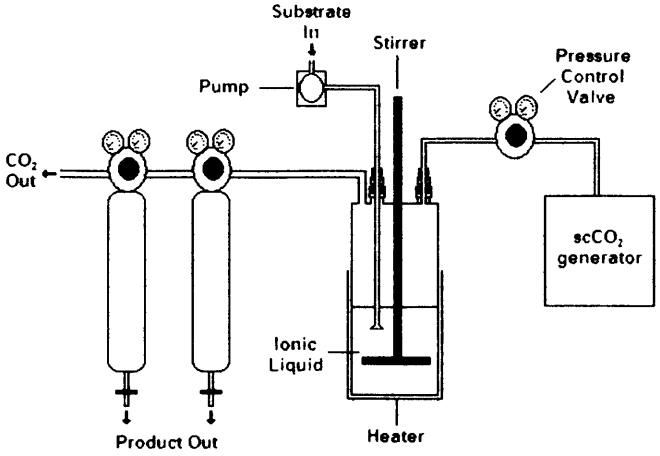


Figure 26: $scCO_2$: IL reactor.

The system is operated by a series of pressure regulators, which can be manipulated to accurately control the pressure of individual compartments whilst maintaining a continuous flow of mobile phase. This allows for continuous decompression of the $scCO_2$ such that $CO_{2\,(g)}$ is vented off to leave behind the organic product. It is here that the inherent complexity of these hydroformylation reactions raises an issue of desired product retrieval, this given that the polarity of the product is greater than the starting material. To be successful, the system is required to act counter intuitively *i.e.* the $scCO_2$ is being asked to extract the more polar species, something it is not set up to do. By manipulating both pressure and temperature, and choosing the correct IL, it

is possible to give the $scCO_2$ a helping hand. Thus, it was found that application of elevated temperatures (100 °C) and pressures (200 bar) allowed for an efficient reaction where the product was formed rapidly and continuous extraction occurred with good isolated yields (76%).[143] The highest yields were obtained when using 1-alkyl-3-methylimidazolium bis(trifluoromethanesulfonyl)amides, for example [omim][NTf_2].

With the knowledge that furan products are generally considerably *less* polar than their starting diols, it was expected that extraction would present little difficulty. This was expected to allow for an efficient extraction under more moderate conditions than those required for hydroformylation. The objective of this part of the project was therefore to effect a successful silver-catalysed cyclisation in such a continuous extraction system. All of the following experiments were carried out during a two week period at St Andrews University.

5.3.2: $scCO_2$ batch silver cyclisation

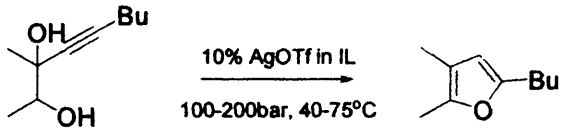
It had been previously proven (Chapter 2.3.3 – p 42) that 3-alkyne-1,2-diols **100** could be successfully cyclised when using an ionic liquid as a solvent. With such a variety of commercially available ILs, the question arose as to which would be the best one to use in this continuous system. Clearly, given the nature of the reaction, a water stable IL was necessary. It was suggested by the Cole-Hamilton group that the ILs [ompy][NTf_2] **304** and [omim][NTf_2] **305** (Scheme 95) may be suitable candidates. These had previously been used in their own hydroformylation reaction[156] and had been shown to be both thermally stable and water tolerant. An initial assessment of the ability of these ILs to solvate a handful of silver salts revealed that silver triflate dissolved better than silver nitrate. It was found that of the two, [ompy][NTf_2] solvated silver better, so this IL was used in the model system (Figure 26).

304 **305**

Scheme 95: [ompy][NTf_2] **304** and [omim][NTf_2] **305** ionic liquids.

To first understand the proposed process, the autoclave chamber was charged with [ompy][NTf_2] (12 mL) containing 10 w/w % silver triflate and to this 3-methylnon-4-yne-2,3-diol **100a** (1 g)

was added (Scheme 96). The chamber was then heated to 50 °C and pressurised, in three separate experiments, with $scCO_2$ to 100, 130 and 200 bar. The mixture was stirred for 1h and then continuously extracted with a flow of $scCO_2$ for 30 min.



100a **101a**

Scheme 96: Synthesis of 5-butyl-2,3-dimethylfuran.

The resultant oil was identified as the expected furan **101a** and found to contain no trace of [ompy][NTf_2] **304** in all cases, as determined by ^{1}H NMR analysis. Yields were excellent in view of product volatility with the best result, from this set of batch experiments, achieved at 200bar (> 95%). Given the one-off nature of each experiment, as a result of limited time and starting diol **100a** availability, these provisional results were entirely unoptimised and were used only as an indication of the success of the proposed principle.

5.3.3: $scCO_2$ Continuous flow system for heterocyclic synthesis

With the optimised batch results in hand, efforts were focused on the use of this catalyst under continuous flow conditions. Optimal pressurisation and heating of the stirred autoclave chamber, charged with just the 10% IL-silver catalyst solution (12 mL), primed the system for use. Opening to the HPLC pump allowed for a controlled flow of the substrate **100a** to be introduced at a rate of 0.05-0.2 mL/min. Coupled with the steady release of $scCO_2$ from the system (1mL/min), furan **101a** was successfully extracted every 0.25 h in good yields (> 70%) under conditions of 150bar, 50°C and at a substrate flow rate of 0.1mL/min. As with the batch procedure, ^{1}H NMR analysis showed there to be no presence of diol **100a** or [ompy][NTf_2] **304** as contaminants in the extracted product. Further analysis was carried out by GC, which showed that all samples obtained from the cyclisation contained only furan **101a**. Analysis for silver content by ICPMS showed there to be < 1ppm silver in every sample assayed, which was comparable to the ion exchange resin method and repeatable once again.

5.3.4: Optimisation

With continuous sampling for 1.5 to 2 h, it was possible to show that consistent levels of furan were extracted once the observed start-up time had been completed (Figure 27). This start-up time was set as the point at which product was first extracted and is seen to be both pressure and temperature dependent, ranging between 0.25 and 0.75 h.

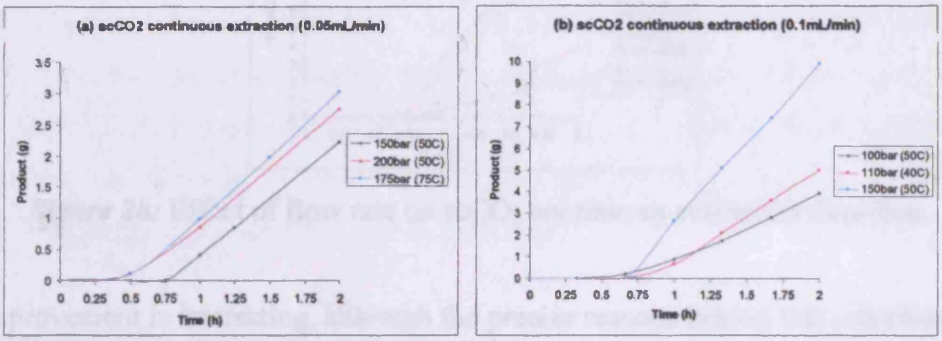


Figure 27: $scCO_2$ continuous extraction time lines for (a) 0.05 mL/min (b) 1mL/min flow rates.

It can be seen from the data displayed in Figure 27 that there is an approximate trend, which is dependent on both pressure and temperature, even when using different flow rates: as pressure increases, the start-up time of the extraction decreases. It was also found, not surprisingly, that an increase in temperature had a similar effect. This observation is illustrated by the profile of the reaction run at 175 bar and 75 °C, the reaction being comparable to that of the 200 bar and 50 °C reaction, despite the drop in pressure (Figure 27a). It is worth noting that with the emphasis on identifying 'candidate' reaction conditions, given the tight time restrictions, these results of course show a degree of experimental error. It is clear however that a general trend has been identified, where an improvement in start-up time occurs when both pressure and temperature increase. At the same time, it can also be seen that pressure and temperature have an effect on the overall efficiency of the reaction. Temperature increases have already been used to improve profiles of lower pressure runs, as shown in Figure 27a, such that they match the profiles of their higher pressure counterparts. Pressure effects are best represented by a 50 bar increase in pressure, from 100 to 150 bar, seen in Figure 27b, where overall yields are seen to increase by nearly three fold.

Having assessed the effect of temperature and pressure, efforts then focused on the effect of diol **100a** flow rates, given the previous variations found in the ion exchange system. It was shown that doubling the flow rate at 100 bar and 50 °C, and again at 150 bar and 50 °C, decreased the start-up time (Figure 28) by up to 20mins.

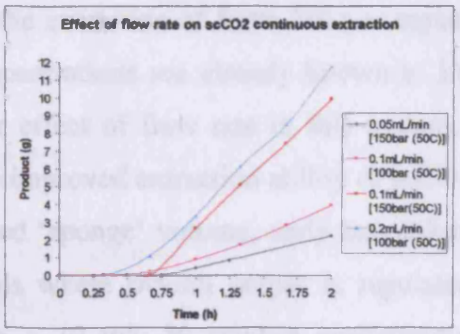


Figure 28: Effect of flow rate on $scCO_2$ continuous extraction time-line.

Such an improvement is interesting, although the precise reasons behind this induction period are not clear; perhaps the concentration of diol **100a** within the IL has a marked affect. If this is true, then it is possible to draw comparisons with the effects of concentration observed in the dichloromethane batch reactions (Chapter 2.3.4 – p 42). Previously, it had been observed that in these standard batch reactions, a higher concentration of diol **100a** had the effect of increasing the rate of cyclisation. Therefore, it would be reasonable to assume that the observed improvements in start-up time resulted from an increase in flow rate which may be linked to a concentration dependency.

A final area of investigation saw the effect of the IL volume being assessed. In previous runs, silver triflate (1.36 g) dissolved in [ompy][NTf_2] **304** (12 mL) was used. Using conditions of 150 bar and 50 °C at a flow rate of 1 mL/min, it has been found that halving the amount of silver triflate and [ompy][NTf_2] **304**, causes a lower conversion rate (Figure 29), not surprisingly.

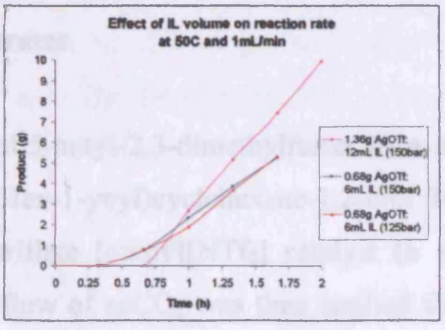


Figure 29: Effect of IL volume on $scCO_2$ extraction time line.

It was also clear that an improved start-up time of 20 mins was apparent when using reduced volumes of [ompy][NTf_2] **304**, an improvement on the previous time of 40 mins. Indeed, this improvement was also observed when using 125 bar pressure. The reason for this reduction in start-up time may be as follows. When using lower volumes of IL, the diol **100a** concentration can increase much faster and the extraction of furan **101a** is arguably easier with less stationary phase present. Increased concentrations are already known to improve reaction efficiency, as seen with the studies into the effect of flow rate in this system, and therefore improve furan production. Together with the improved extraction ability of $scCO_2$ when reduced amounts of IL are present, given the decreased 'sponge' volume, early extraction would be expected to occur. A limiting factor then prevails where overall output is regulated by the physical amount of catalyst present, *i.e.* although a 10 w/v % catalyst concentration has been maintained, the equivalence of silver in the system has still been halved.

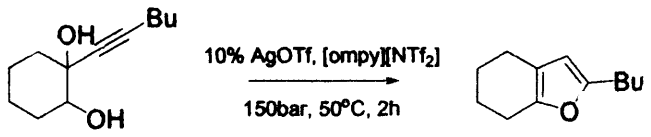
5.3.5: Operational considerations

The main difficulty observed was associated with the control of $scCO_2$ decompression. With the large change in pressure came problems of evaporative cooling, which in time led to crystallisation of furan **101a** within the decompression regulator valve. With intermittent blockages forming in this valve, it was difficult to control $scCO_2$ flow rate at times and, as a result, the efficiency of extraction was affected. To counteract this, the regulator was heated, quite vigorously, with heating tape. This solved the problem of crystallisation, but led to the loss of some of the highly volatile product, 5-butyl-2,3-dimethylfuran **101a**. Crude cooling (0 °C) beyond the regulator did improve yields (>70%), however a degree of product evaporation was still observed even with this cooling in place. It is expected that the addition of a condenser to the rig should allow the product to re-condense more efficiently.

5.3.6: Use of alternative substrates

With the successful synthesis of 5-butyl-2,3-dimethylfuran **101a** in hand, attempts were made to cyclise another substrate. 1-(Hex-1-ynyl)cyclohexane-1,2-diol **100k** (2.5 g) (Scheme 97) was dissolved in the 10% silver triflate [ompy][NTf_2] catalyst (6 mL), and held under 150 bar pressure at 50 °C for 2 h. A flow of $scCO_2$ was then applied for 30 mins so as to extract the

product **101k**. This reaction was run in batch mode due to the limited quantity of diol **100j** that had been prepared for the visit.



100k **101k**

Scheme 97: Synthesis of 2-butyl-4,5,6,7-tetrahydrobenzofuran **101k**.

It was found that 2-butyl-4,5,6,7-tetrahydrobenzofuran **101k** could be isolated cleanly and in high yields (80%). Extraction did not present any problems and ^{1}H NMR analysis showed there to be no contamination by either the starting diol **100k** or the IL [ompy][NTf_2] **304**.

5.3.7: $scCO_2$ Conclusions

In summary, it has been shown that a $scCO_2$ continuous extraction system, with an appropriate ionic liquid, can be successfully employed for the novel continuous synthesis of 5-butyl-2,3-dimethylfuran **101a** and 2-butyl-4,5,6,7-tetrahydrobenzofuran **101k**. Yields were high (>70%) and conditions were optimised to a system which uses a 10% w/w silver [ompy][NTf_2] catalyst under conditions of 150bar and 50°C. A range of substrate flow rates were successfully employed with optimal yields being obtained when using a 0.1 mL/min flow. Further benefits were seen through the removal of organic solvents and the quantification of silver leaching as being < 1ppm. With possible environmental benefits and much interest from industry, this procedure may contribute a great number of synthetic procedures. The anticipated ability to selectively extract the much less polar furan product had clearly been shown to be correct.

It is believed that there is plenty of scope for the synthesis of pyrroles, pyrazoles and isoxazoles in the future, but these will perhaps be limited to non-polar examples. Furthermore, with the successes of this procedure having been based on partially optimised conditions, given the short timeframe available, a promising foundation has surely been laid.

5.4: Conclusions

Investigations into the immobilisation of silver have led us to discover two novel flow systems for heterocyclic synthesis. The first, a more traditional trickle-bed reactor, takes the form of a simplistic and low expense approach, with advantages of high yields (>95%) and seemingly no silver leaching. Indeed, the robust nature of this first system, as shown by its continuous use over the past 18 months, attests to the attractiveness of such a simple system. The alternative $scCO_2$:IL system provides a more intricate and expensive approach, but one which is potentially more lucrative, and like its counterpart, benefits from only trace silver leaching and the observed high, if unoptimised yields (>70%). The further potential for the use of alternative flow rates, substrate concentrations, solvents, supports, ionic liquids, pressures and temperatures in these systems make both of their discoveries all the more important. Perhaps the overriding factor in the choice comes from the pharmaceutical sector's interest in new technologies, where there may well be more of a demand for the $scCO_2$ system. With this in mind, the immediate future interest would lie in the optimisation of the $scCO_2$ process, with the further application of alternative mobile phases, of differing polarities. Some work on the effect of the use of industrially proportioned, short and fat columns for the trickle-bed system should also be undertaken.

Chapter 6: Results and Discussion

Studies into the Applications of the Silver Cyclisation Procedure

6.1: Synopsis

Discussions up to this point have primarily been focused on core aspects of this project. It has been shown that a range of furans, pyrroles and pyrazole-*N*-oxides have been successfully cyclised *via* a formal silver-mediated 5-*endo*-dig ring closure. Yields were high (>95%) in the vast majority of cases and further developments saw the successful use of both amberlite 200C and ionic liquid-immobilised catalysts in novel flow systems for heterocyclic synthesis.

6.1.1: Aim

The next step was to illustrate the strength of these results by applying our findings to the synthesis of several target compounds. Given the identification of several approaches to the silver-catalysed synthesis of substituted furans, we identified a series of targets, which contained a furan moiety at their core. These targets included a range of potentially scented furans **307** to **311** and the natural products plakorsin A [**312**; R=$C_{16}H_{33}$] and B [**313**; R=$C_{16}H_{33}$] (Figure 30).

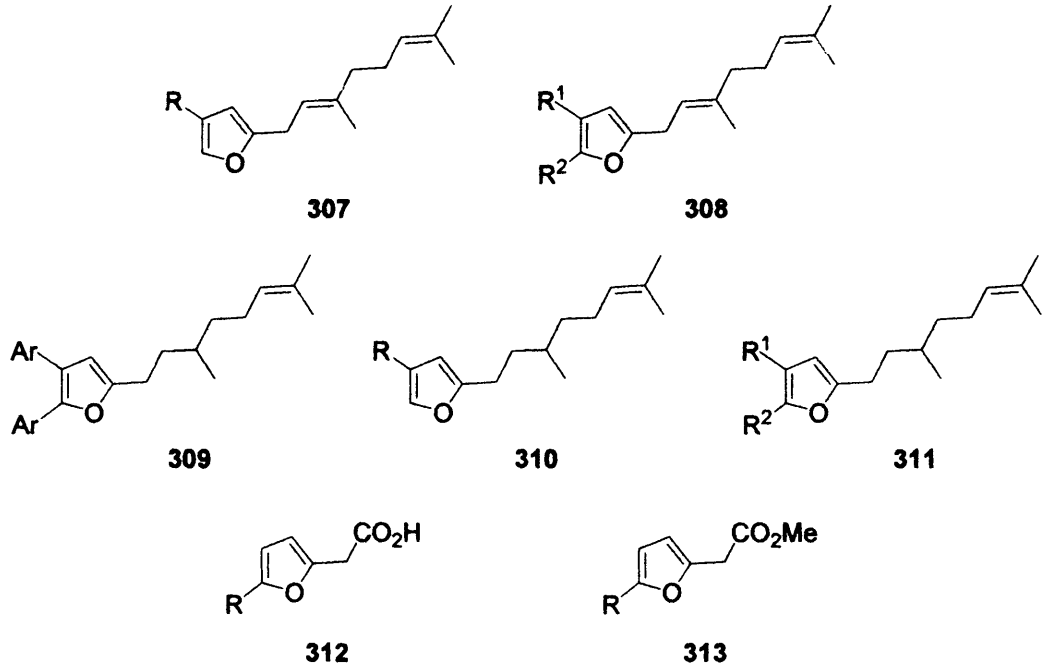
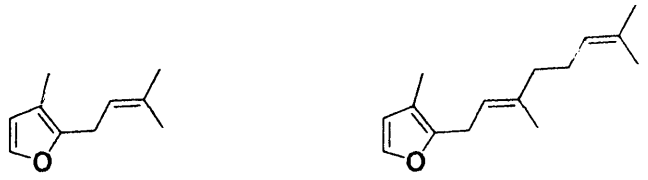


Figure 30: Targeted compounds

6.2: Scented furans

6.2.1: Introduction

In the past, there has been much interest in the synthesis of "scented furans",[3, 4, 157-159] so classed due to their possession of quite distinct aromas. This aroma is often highly prized and together with the tuneable nature of each scent, this draws attention to their potential use as fragrances. Indeed, the more succulent of these fragrances are seen to omit odours which are suitable for use within the cosmetics industry, the best examples being rosefuran **314** and sesquirosefuran **315** (Scheme 98).

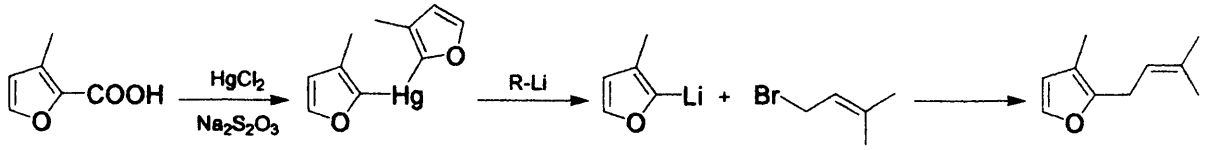


314 **315**

Scheme 98: Rosefuran **314** and sesquirosefuran **315**.

Rosefuran **314**, a colourless oil with a boiling point of just 39-40 °C at 1mmHg, presents an aroma not too dissimilar to roses, as its name might suggest. Sesquirosefuran **315**, also a colourless oil, displays a slightly heavier scent than rosefuran, reminiscent of geraniol, as one might expect. Their synthesis has been widely studied, as highlighted by Salerno,[3] with recent efforts focused towards an improved synthesis of rosefuran, given its commercial interest.

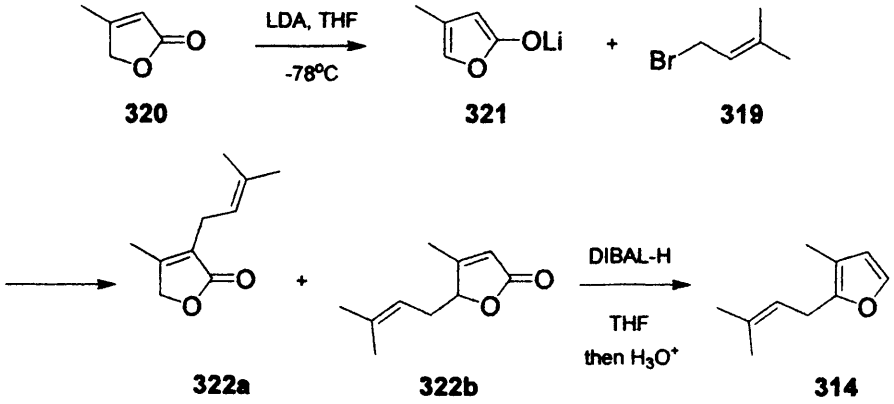
One of the first syntheses[160] saw the use of mercuric chloride and sodium thiosulfate to decarboxylate 3-methyl-2-furoic acid **316** and then produce the corresponding difurylmercury dimer **317**. Transmetalation with lithium yielded 2-lithio-3-methylfuran **318** which was alkylated with 1-bromo-3-methyl-2-butene **319** to yield rosefuran **314** in relatively low yields (35%) (Scheme 99). Being a simple approach, it has its attractions, however the toxicity of mercury salts and the low yield make this approach unacceptable for use in large scale production.



316 **317** **318** **319** **314**

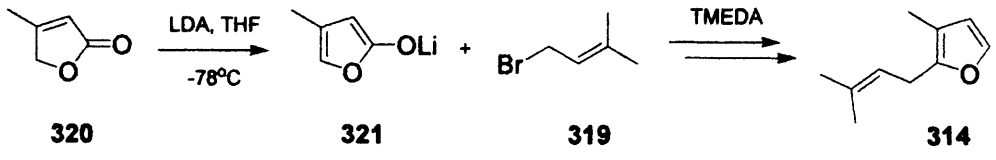
Scheme 99: Buechi's mercury chloride-based synthesis of rosefuran **314**.

Subsequent contributions saw gradual improvements with Pattenden's mercury-free approach providing the foundations for other successes.[4] He showed that 4-methylfuran-2-one **320** acts as a better nucleophile, *via* its enolate **321**, for 1-bromo-3-methyl-2-butene **319** to yield a (1:2) mixture of the separable regioisomers **322a,b** (60%) (Scheme 100), together with smaller amounts of *bis*-alkylated adducts. Reduction of **322b** with DIBAL-H at -30°C, followed by acidification, yielded rosefuran **314** (80%).



Scheme 100: Pattenden's synthesis of rosefuran **314**.

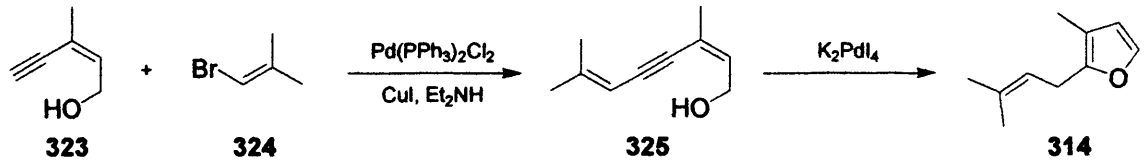
Using the above procedure, it was also possible to synthesise the homologous compound sesquirosefuran **315**, however it too had overall yields of just 32-34%, comparable to those observed in Buechi's synthesis. It was clear that these yields were being affected by the formation of undesired *mono*- and *bis*-alkylated regioisomers. It was not until 1983 that this approach showed its true potential when Hoffmann[161] was able to limit the *bis*-alkylation and improve regioselectivity through the use of tetramethylethylenediamine (TMEDA), a sterically encumbered metal ligand. Hoffmann found that when using his modified procedure, it was possible to isolate rosefuran **314** in greater yields (up to 80%) (Scheme 101).



Scheme 101: Hoffmann's synthesis of rosefuran **314**.

More recently, with much interest in metal catalysed procedures, palladium has been used to catalyse a cycloisomerisation of (*Z*)-2-en-4-yn-1-ols **56**,[36-38] as previously discussed in Chapter 2.1.3. One such case reported by Salerno[3] has highlighted the use of this isomerisation procedure

for the synthesis of rosefuran **314**. This group have shown that it is possible to cycloisomerise (*Z*)-3,7-Dimethylocta-2,6-dien-4-yn-1-ol **325**, obtained in 78% yield from (*Z*)-enynol **323**, to yield rosefuran **314** in an overall yield of 60% (Scheme 102).



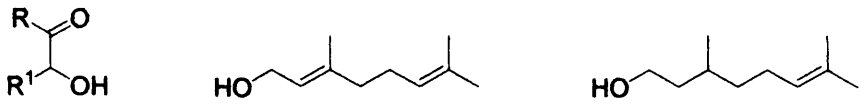
323 **324** **325** **314**

Scheme 102: Salerno's synthesis of rosefuran **314**.

Given the volatility of rosefuran **314**, it should be acknowledged that yields such as those reported by Salerno and Hoffmann are quite acceptable. Thus, given these optimisations have provided efficient syntheses of rosefuran **314**, one which is equally applicable to the synthesis of sesquirosefuran **315**,[162] our efforts turned to the synthesis of several analogues in the hope of generating potential perfume components.

6.2.2: Synthesis of *iso*-sesquirosefuran

Having already addressed one of the greatest difficulties associated with the synthesis of 2,4-disubstituted furans (Chapter 2.2.1 – p 23), it was proposed that it would be possible to synthesise a range of 2,4-disubstituted, potentially scented, furans using the silver-catalysed cyclisation procedure. Using sesquirosefuran as our model, one could imagine using an α-hydroxyketone **98** combined with geraniol **326** or citronellol **327**, as core building blocks (Scheme 103). This would further test the silver-catalysed method in the presence of a non-terminal but potentially labile alkene.

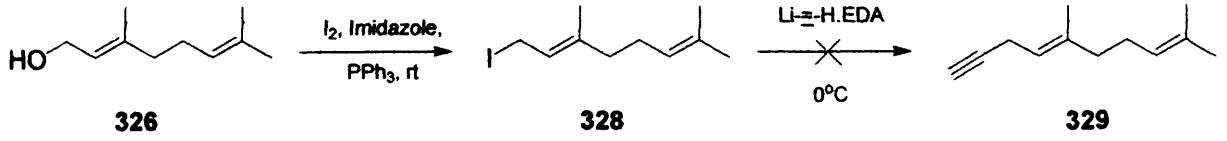


98 **326** **327**

Scheme 103: Core building blocks for synthesis of *iso*-sesquirosefuran analogues.

With the help of undergraduates Haynes, Petherbridge and Williams, efforts were made to synthesise the targeted scented furans. Early attempts to mimic an *iso*-form of sesquirosefuran **315** were troubled. The required synthesis of geranyl acetylene **329** from geranyl iodide **328**[163] (itself synthesised in high yield (97%) from geraniol **326** by exposure to iodine, imidazole and triphenylphosphine) was unsuccessful for reasons unknown (Scheme 104). Significantly, geranyl

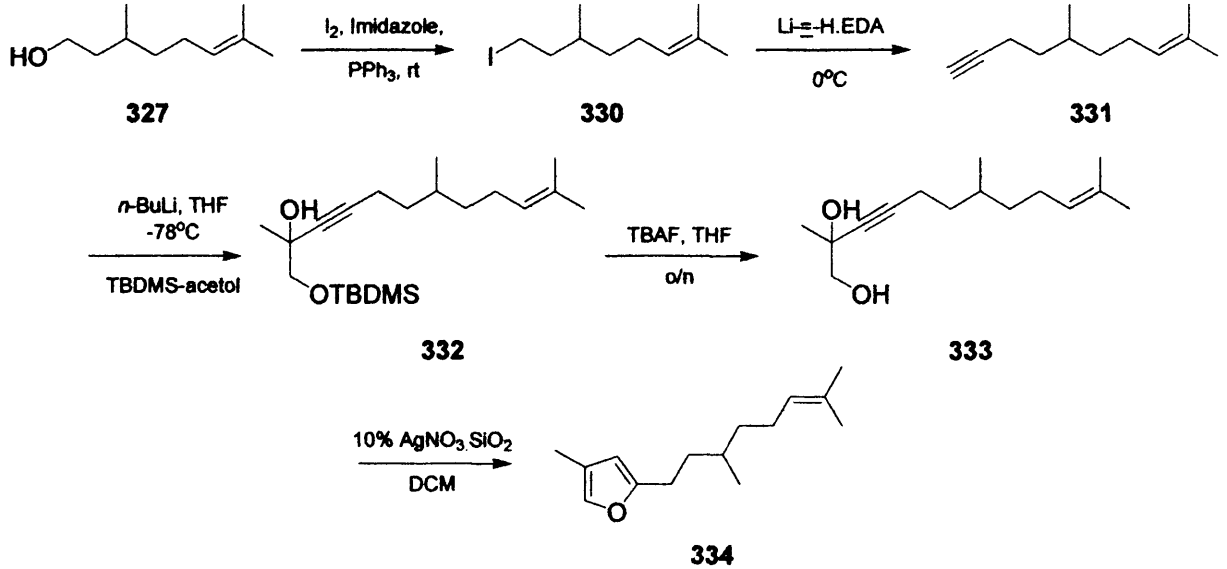
acetylene **329** is not recorded in the literature, a sign, perhaps, that it is in some way unstable or difficult to prepare.



326 **328** **329**

Scheme 104: Synthesis of geranyl acetylene **329**.

To test this conclusion, lithium acetylide-ethylene diamine complex was added to a solution of citronellyl iodide **330**,[163] synthesised from commercially available racemic citronellol **327** in excellent yields (97%). Using the same procedure, the citronellyl acetylene **331** was successfully isolated as an oil in 78% yield. Deprotonation using *n*-BuLi allowed for successful addition to a slight excess of TBDMS-acetol to yield crude propargyl alcohol **332** (97%). Addition of TBAF (1M in THF) to a solution of the crude alcohol **332** in THF allowed for the isolation of crude diol **333**. Any excess TBDMS-acetol from the original mixture was also deprotected in this step to yield acetol, a water soluble component which was successfully washed out during a standard aqueous work-up. Column chromatography of the crude mixture allowed for further purification to yield pure diol **333** in lower than expected, but unoptimised, yields of 37-55%. Addition of 10% $AgNO_3.SiO_2$ successfully induced cyclisation of diol **333** to yield furan **334** in excellent yield (95%) (Scheme 105).



327 **330** **331**

332 **333**

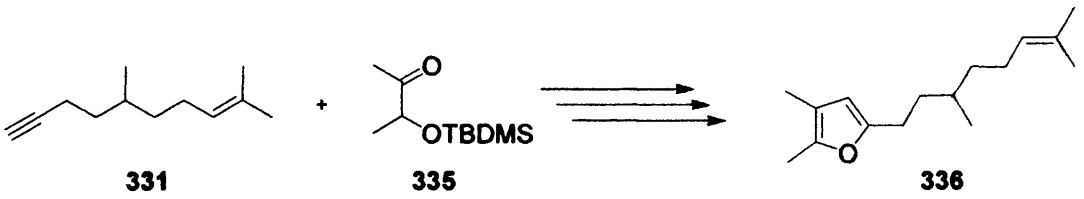
334

Scheme 105: Synthesis of 4-methyl-2-(3,7-dimethyloct-6-enyl)furan **334**.

It is significant that this cyclisation proceeded cleanly, given the presence of a sensitive prenyl group in citronellyl. Overall yields for this approach were moderate (43%) but it is expected that

with further optimisation of this procedure these yields would increase. The aroma which this furan **334** displayed is best described as being fresh lemon in nature, perhaps expected given that citronellol smells of lemons.

With the above result in hand, efforts were made to test the effect of furan substituents. Addition of citronellyl acetylene **331** to *O*-TBDMS-3-hydroxybutan-2-one **335**, followed by deprotection, purification and cyclisation yielded the corresponding furan **336** (Scheme 106). The key cyclisation step once again proceeded cleanly and in excellent yield (93%).



331 **335** **336**

Scheme 106: Synthesis of 2,3-dimethyl-5-(3,7-dimethyloct-6-enyl)furan **336**.

Again, lower than expected overall yields (28%) were observed but the high yields resulting from the key cyclisation were very encouraging. This furan **336** displayed a heavier aroma, more reminiscent of an earthy lemon scent. Given the trisubstituted nature of this furan **336**, it is perhaps not surprising that a more subtle aroma was detected, given the decreased volatility associated with increased substitution.

The final scented furan to be synthesised used benzoin **337** as the source of substituents. Here citronellyl acetylene **331** was used to synthesise furan **338** in high yield (95%) (Scheme 107).

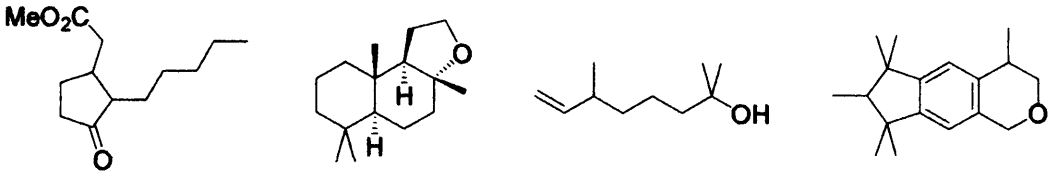
331 **337** **338**

Scheme 107: Synthesis of 2,3-diphenyl-5-(3,7-dimethyloct-6-enyl)furan **338**.

In this instance, furan **338** displayed what can be described as a mild, heavy, smokey lemon scent, perhaps not unexpected given the presence of two bulky aryl substituents. With this result we had again moved away from the more inviting and purer scent of furan **334**. Overall it can be said that these results have shown a successful foray into the field of the synthesis of potential fragrances. From this provisional work we saw an opportunity to assess the formation of an enantiomerically pure furan.

6.2.3: Stereochemistry in fragrances

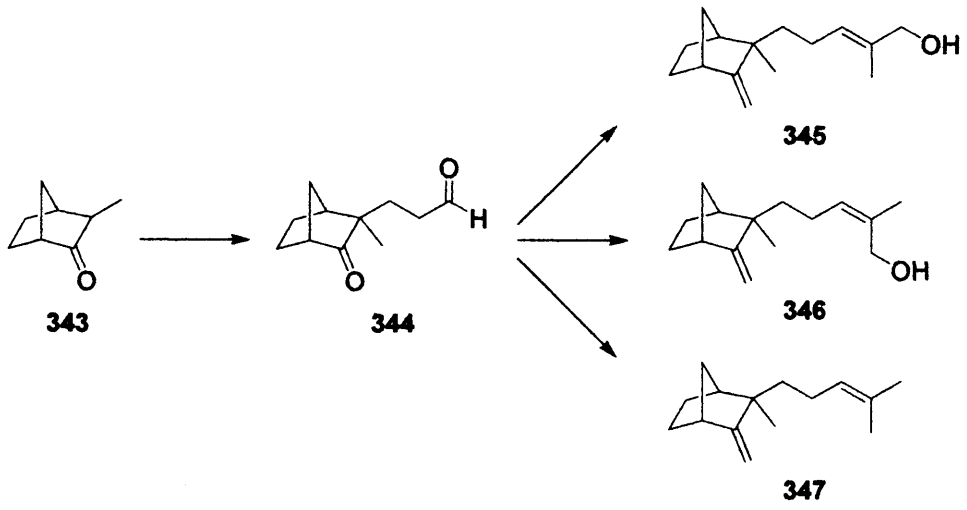
Based on detailed reviews on the effect of stereochemistry on aroma,[158] our final investigation in this field sought the implementation of fixed stereochemistry. Unsurprisingly, numerous examples have shown that stereochemistry can have a marked effect on the aromas of a broad range of compounds. For example, the isomers of Hedione ™ **339** are renowned for their floral jasmine fragrance and have been used in Christian Dior's Eau Sauvage ™. Other examples include Ambrox ™ **340**, Dihydromyrcenol ™ **341** and Galaxolide ™ **342** (Scheme 108), all of which contain crucial stereogenic centers that can be used to tailor the overall scent.



339 **340** **341** **342**

Scheme 108: Hedione ™ **339**, Ambrox ™ **340**, Dihydromyrcenol ™ **341** and Galaxolide ™ **342**.

A more generic ingredient in perfumes is sandalwood oil, a complex mixture of scented organic compounds.[157-159] With its wide use and composition of multiple active ingredients, there has been much interest in identifying its key odorant. In 1990 Krotz and Helmchen identified (*Z*)-(-)-*β*-santalol **346**, which contributes up to 25% of the weight of the oil, as the major sandalwood odour. They synthesised enantiomerically pure (*Z*)-*β*-santalol **346**, together with the minor constituents (*E*)-*β*-santalol **345** and *β*-santalene **347**, from enantiomerically pure 3-methyl-2-norbornanones **343** and **344** (Scheme 109).[164]



343 **344** **345** **346** **347**

Scheme 109: Synthesis of enantiomerically pure sandalwood oil components.

It was found that **(-)-346** displayed a scent reminiscent of sandalwood oil, whereas **(+)-346** was shown to be odourless. As for the enantiomers of (*E*)-*β*-santalol **345** and *β*-santalene **347**, it was found that only **(-)-345** displayed an odour similar to **(-)-346**, but notably milder. Remarkably all of the other enantiomers prepared, **(+)-345** and **(+/-)-347**, were found to be odourless (Scheme 110).

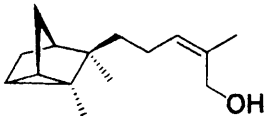
(-)-345 **(+)-345**

(-)-346 **(+)-346**

(-)-347 **(+)-347**

Scheme 110: Isomers of (*E*)-*β*-santalol **345**, (*Z*)-*β*-santalol **346** and *β*-santalene **347**.

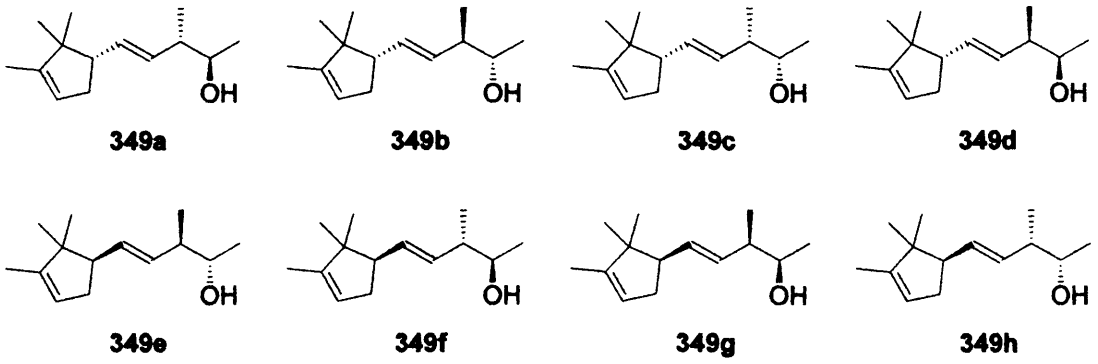
Interestingly, some view (*Z*)-(+)-*α*-santalol **348** (Scheme 111), which contributes some 47% to the composition of sandalwood, as key to the displayed aroma; however, this view is still open to debate.[159]



348

Scheme 111: (*Z*)-(+)-*α*-sanatol **348**.

Prior to the acceptance of (*Z*)-(-)-*β*-Santalol **345** as the main odour, many others looked at some of the other components in sandalwood oil. Naipawer[165] showed that Ebanol ™ **349** displayed a relevant odour, with a racemic mixture of diastereomers **349a-h** presenting the strongest odour ever reported at the time (Scheme 112). Bajgrowicz[166] later showed that of the eight possible isomers of Ebanol ™ **349**, only two exhibited the desired lucrative aroma attributed to sandalwood oil. These were the (1'*S*, 2*S*, 3*R*)- **349b** and (1'*R*, 2*S*, 3*R*)- **349e** isomers.



349a **349b** **349c** **349d**

349e **349f** **349g** **349h**

Scheme 112: The eight stereoisomers of Ebanol ™ **349**.

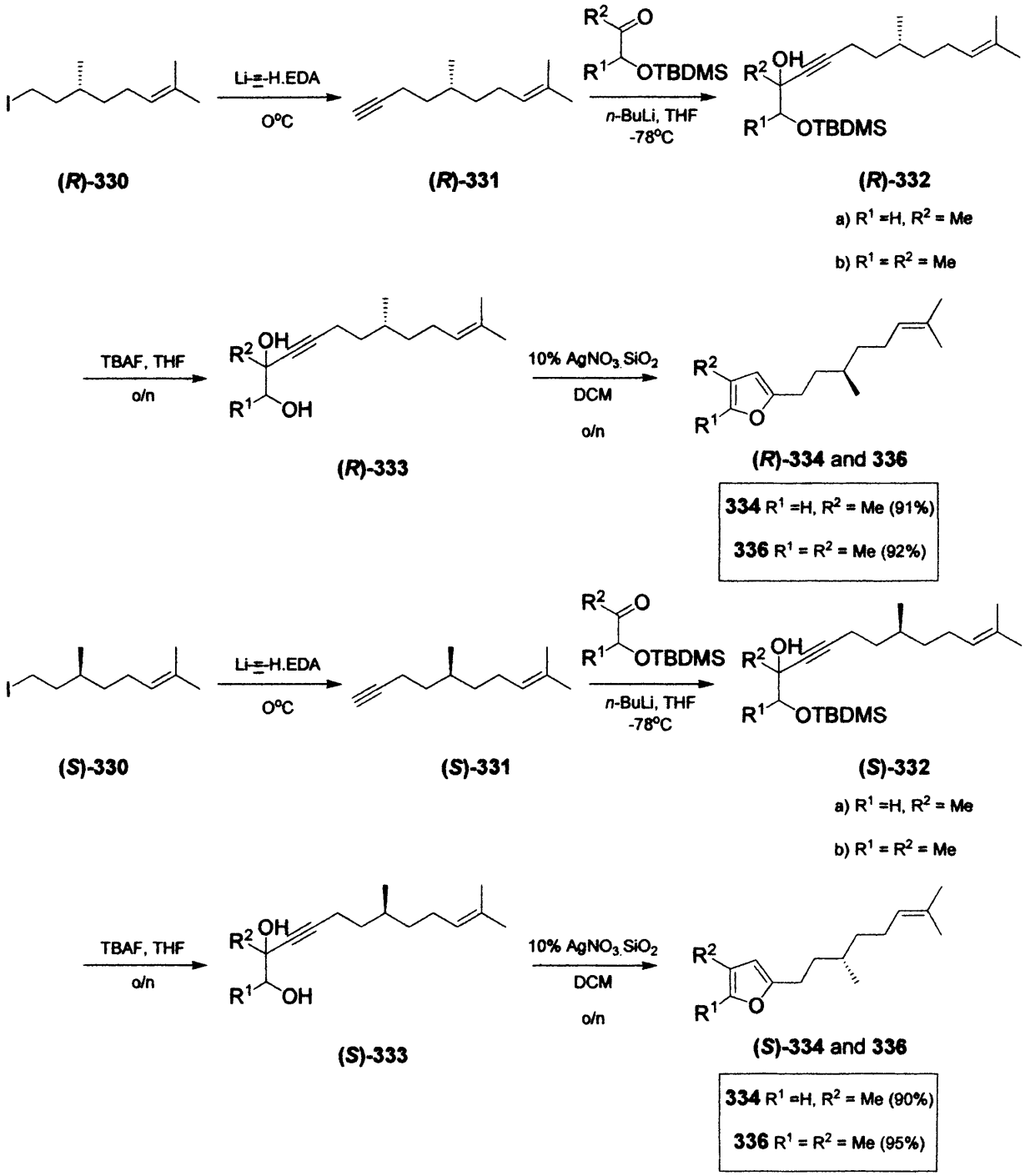
All of the above examples, just a small number from what is a vast library of compounds, illustrate the powerful effect which stereochemistry can have on the aroma of a compound. Citronellol contains a stereogenic centre at its core and therefore has two possible enantiomeric forms, the (*R*)-enantiomer **(*R*)-327** and the (*S*)-enantiomer **(*S*)-327** (Scheme 113).[167] With the change from geraniol to citronellol introducing this stereochemical feature, the opportunity was taken to assess any stereochemically related changes in the aroma of furans **334** and **336**.

(*R*)-327 **(*S*)-327**

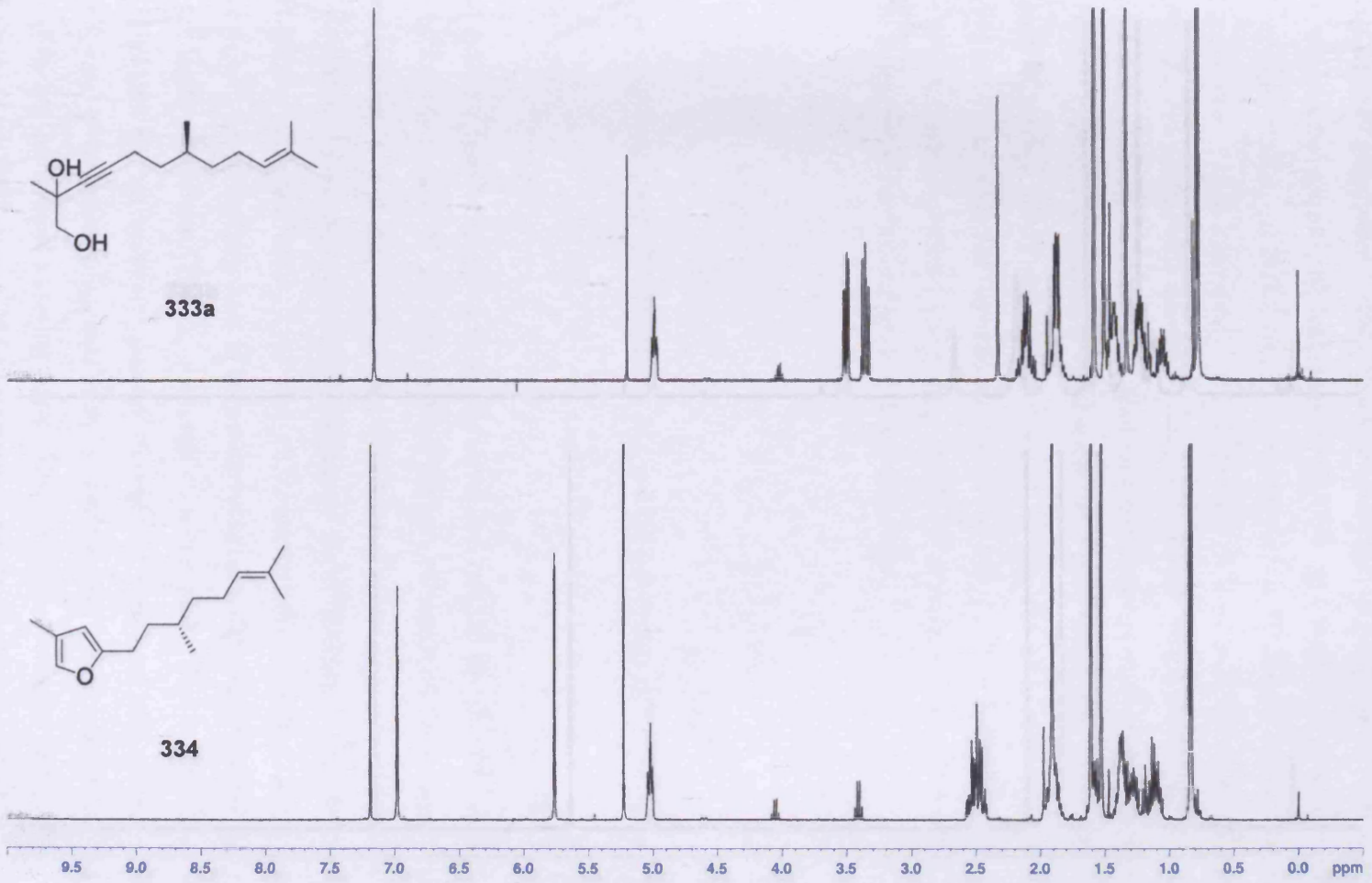
Scheme 113: (*R*)- and (*S*)- citronellol **327**.

With the help of Williams,[168] commercially available enantiomerically pure (*R*)- and (*S*)-citronellyl bromide was used to synthesise pure (*R*)- and (*S*)-citronellyl acetylene **331** (71%). [163] With the yields being a little low, the decision was made to take a step back and synthesise (*R*)- and (*S*)-citronellyl iodide **330** (Scheme 114) from enantiomerically pure (*R*)- and (*S*)- citronellol **327** (Scheme 113). The corresponding (*R*)- and (*S*)-citronellyl acetylenes **331** were obtained in marginally improved yields (79%). Addition to both TBDMS-acetol and TBDMS-3-hydroxybutan-2-one **335**, which were used in excess once again, yielded the corresponding propargyl (*R*)- and (*S*)- silyl ethers **332a,b** which were successfully deprotected to give the diols **333a,b** which were finally cyclised to yield the (*R*)- and (*S*)- forms of both furans **334** and **336** in excellent yields (>90%). Spectra 14 and 15 show the (*S*)-enantiomers of furans **334** and **336** and their respective (*S*)-diols **333a** and **333b**. The purity of each furan can be seen clearly from their respective images (Spectrums 14 and 15), and given $[\alpha]_D^{291}$ values of +6.3° and +11.4° for the

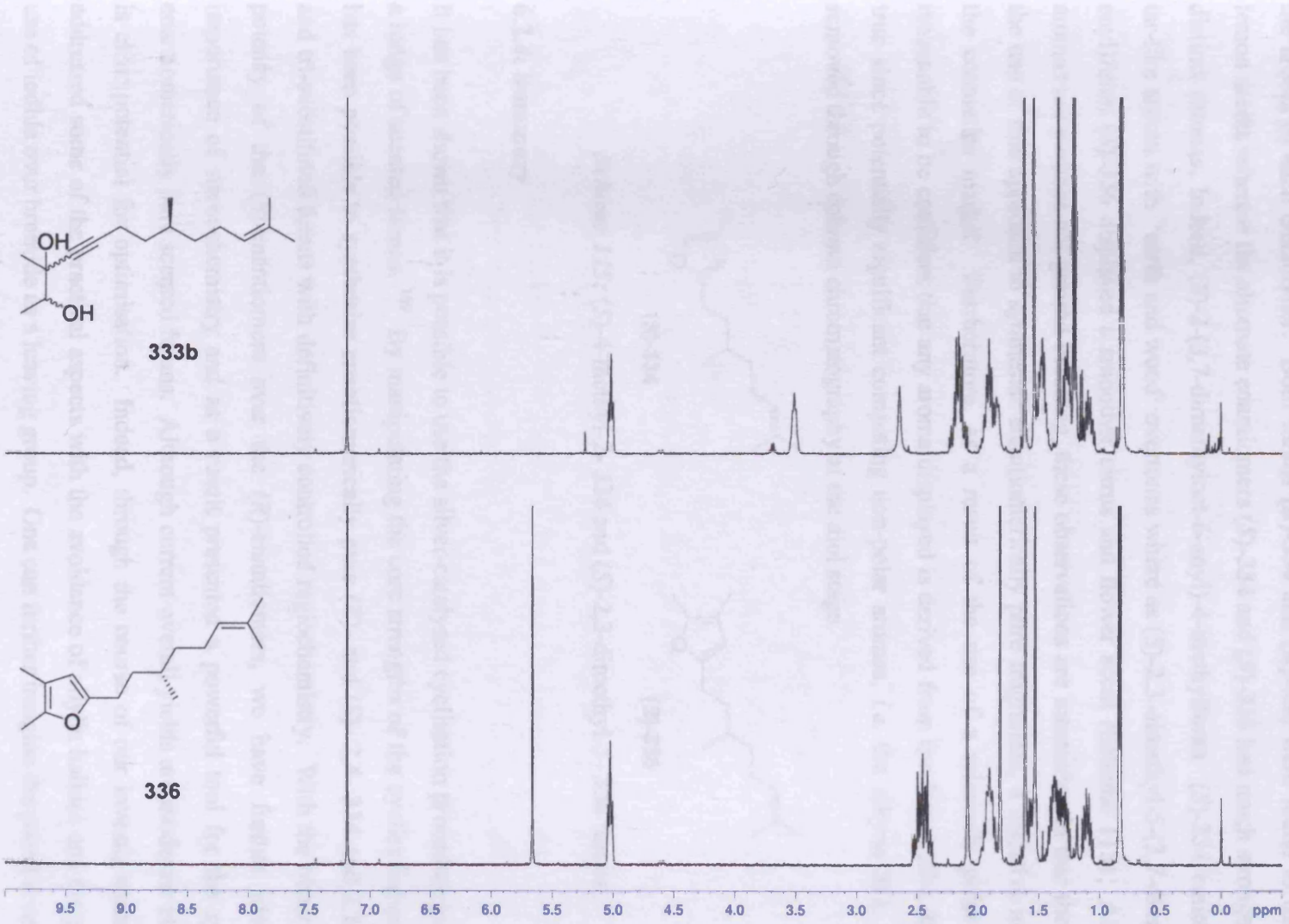
furans (*S*)-**334** and (*S*)-**336**, and -7.8° and -8.9° for the furans (*R*)-**334** and (*R*)-**336**, it appears that enantiomeric selectivity/purity has been maintained.



Scheme 114: Synthesis of enantiomerically pure (*R*)- and (*S*)- furans **334** and **336**.



Spectrum 14: ^{1}H NMR spectrum of (*S*)-diol **333a** ($CDCl_3$) and (*S*)-furan **334** ($CDCl_3$).



Spectrum 15: ^{1}H NMR spectrum of (*S*)-diol **333b** ($CDCl_3$) and (*S*)-furan **336** ($CDCl_3$).

Overall yields were varied (24-43%), but importantly each furan **(*R*/*S*)-334** and **(*R*/*S*)-336** shows the defined optical activity. Interestingly, it was found that there were noticeable differences in the aroma of each enantiomer. Both furans **(*R*)-334** and **(*R*)-336** were found to display weak lemon scents whereas the alternate enantiomers **(*S*)-334** and **(*S*)-336** had much stronger and more distinct aromas. Indeed, (*S*)-2-(3,7-dimethyloct-6-enyl)-4-methylfuran **(*S*)-334** emitted a sharp tar-like aroma with 'earth and wood' overtones where as (*S*)-2,3-dimethyl-5-(3,7-dimethyloct-6-enyl)furan **(*S*)-336** displayed a smoother citrus and flower scent (Scheme 115). Although the aromas are perhaps not ground-breaking, these observations are interesting in that they highlight the use of this approach to synthesise enantiomerically pure fragrances, a lucrative niche within the cosmetics market. Furthermore, as a result of the use of a relatively polar diol, it is reasonable to be confident that any aroma displayed is derived from the furans **334, 336**. This is true since potentially significant competing non-polar aromas, *i.e.* the alkyne **331**, are readily removed through column chromatography at the diol stage.

(*S*)-334 **(*S*)-336**

Scheme 115: (*S*)-4-methyl-2- **334** and (*S*)-2,3-dimethyl-5- **336** furans.

6.2.4: Summary

It has been shown that it is possible to use the silver-catalysed cyclisation procedure to synthesise a range of scented furans. [169] By manipulating the core strengths of the cyclisation procedure, it has been possible to synthesise enantiomerically pure (*R*)- and (*S*)- 2,4- **334** and 2,3,5- **336** di- and tri-substituted furans with definitively controlled regiochemistry. With the observed greater potency of the (*S*)-enantiomers over the (*R*)-enantiomers, we have further identified the importance of stereochemistry and as a result presented a powerful tool for the synthesis of enantiomerically pure scented furans. Although current overall yields are moderate at best, there is clear potential for optimisation. Indeed, through the course of our investigations, we have addressed some of the practical aspects with the avoidance of allylic halides and the preferential use of iodide over bromide as a leaving group. One can further imagine the possible use of Lewis acids to improve the efficiency of the addition step. In summary, it would be fair to say that the successes shown here have the potential to impact, in some way, on the field of fragrances.

6.3: Plakorsin A and B

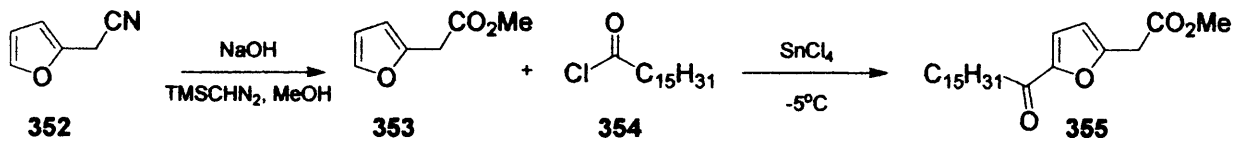
6.3.1: Introduction

With much of the focus in synthetic organic chemistry having been, and still being, orientated towards the synthesis of natural products, there has been a growth in the number of naturally occurring targets. These targets can range in complexity from simple, non-stereogenic motifs to complex scaffolds containing multiple stereogenic centers. At first sight, Plakorsin A **350** and Plakorsin B **351** would appear to be amongst the easiest of natural products to synthesise, given their simplicity and lack of stereogenic centers (Scheme 116). Their use in the synthesis of manzamenones,[67-68] which are known to inhibit DNA-polymerase, makes them particularly desired targets. The lack of research around this area however uncovers the truth, particularly in the case of Plakorsin B **351**: furylacetic acids are not easy to synthesise.

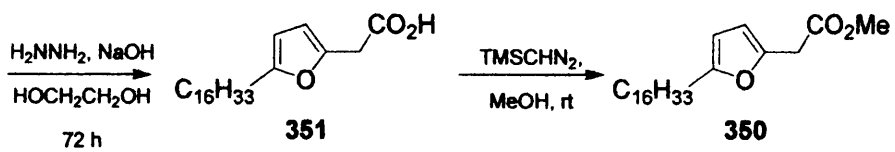
350 **351**

Scheme 116: Plakorsin A **350** and Plakorsin B **351**.

Previous attempts to synthesise Plakorsin A **350** and Plakorsin B **351** are sparse with the only significant studies undertaken by Whitehead.[67-70] His group synthesised both Plakorsin A **350** and Plakorsin B **351** from 2-(furan-2-yl)acetonitrile **352**.[67] Addition of sodium hydroxide then TMS-diazomethane in MeOH yielded the methyl ester **353** of 2-furanylacetic acid in variable yields. Friedel-Crafts acylation with palmitoyl chloride **354** yielded furyl ketone **355** (98%), which was reduced using a Wolff-Kishner reaction to yield Plakorsin B **351** (60%). Esterification of acid **351** with TMS-diazomethane yielded Plakorsin A **350** in good yields (72%) (Scheme 117). Such decent yields were obtained only after extensive optimisations.



352 **353** **354** **355**



351 **350**

Scheme 117: Whitehead's synthesis of Plakorsin A and B **350** and **351**.

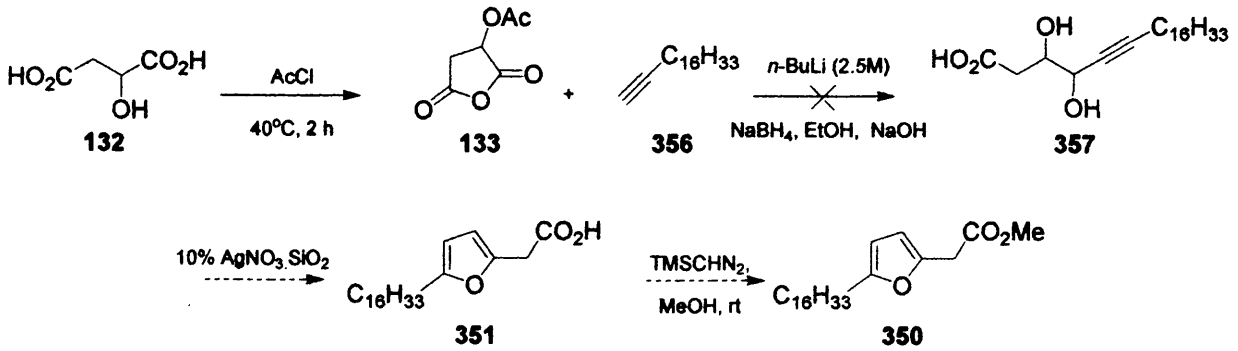
This procedure was effective for the synthesis of both Plakorsin A and B **350** and **351**, taking on a 4-step approach, with the overall yields of Plakorsin B **351** (59%) being respectable, although lower for Plakorsin A **350** (42%). A recent modification has since improved the yield of Plakorsin A **350** (43-58%), with the use of DCCI to improve esterification of Plakorsin B **351**.[69] With applications to the synthesis of other important products,[67-70] Whitehead should be given credit for having successfully tackled this difficult synthetic target, perhaps best appreciated by the six years taken to optimise this procedure to its current level.

6.3.2: New approaches towards Plakorsin A and B.

With the silver-catalysed cyclisation procedure in hand, it seemed that it might be possible to synthesise both Plakorsin A **350** and Plakorsin B **351** (Scheme 118) *via* two of our approach strategies. It was clear that the chemistry involved in some of our previous approaches (Chapter 2.2.2 and 2.2.3) lent itself to the synthesis of these two targets.

6.3.2.1: 2-Acetoxysuccinic anhydride approach to Plakorsin B.

Having shown the use of 2-acetoxysuccinic anhydride **133** (Chapter 2.2.3 – p 27), synthesised from malic acid **132** (98%),[169] as a starting point for the synthesis of furylacetic acids **136a-b** (>57% overall yields), it seemed that we held a competitive solution to the above targets. Thus, using our standard procedure (Scheme 118),[71] *n*-BuLi was added dropwise to a solution of commercially available 1-octadecyne **356** in THF. After stirring for 0.5h, this solution was then added dropwise to a solution of 2-acetoxysuccinic anhydride **133** in THF, and then treated with sodium borohydride in ethanol and deprotected with sodium hydroxide solution (2M). A yellow wax was obtained, which was identified as 1-octadecyne **356**.



Scheme 118: 2-Acetoxysuccinic anhydride **133** approach to Plakorsin A and B **350** and **351**.

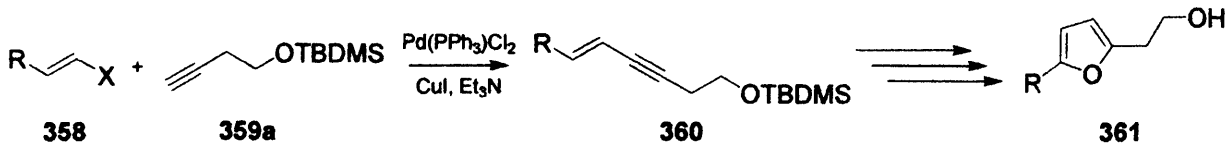
This result was disappointing to say the least, especially since there had not been any previous problems with this type of addition. In a bid to counteract this setback, we implemented a range of addition strategies, which included the use of Lewis acids, co-solvents and Grignard regents. Indeed, a brief foray into the compatibility of cerium trichloride[170] with our additions to α-hydroxycarbonyls had shown that addition was able to proceed as normal. It was therefore felt that application of this methodology might aid the addition of 1-octadecyne **356** to the anhydride **133**; however, once again, only 1-octadecyne **356** was recovered. Reference to the literature highlighted the use of other Lewis acids such as boron trifluoride,[171] silver iodide[172] and zinc triflate,[173] but as with cerium chloride, each attempt was unsuccessful. Changing tack slightly, isopropylmagnesium chloride was used to form octadecylmagnesium chloride. Grignard reagents[174] are known to have good affinity for anhydrides and it was felt that this may provide the best hope for this addition. Unfortunately, this Grignard reagent was equally unsuccessful.

With the above observations in hand, perhaps the problem was not related to the addition itself but possibly to the formation of micelles, given the fatty nature of 1-octadecyne **356**. To rule out such a problem, DMPU was used in a (1:6) mixture with THF,[175] to evenly distribute the chains throughout the solution such that their anions were more exposed. Yet again, successful addition was not observed.

At this juncture, we terminated this approach, citing the use of extended alkynes as a limitation to our furylacetic acid synthetic procedure, and instead focused our efforts on our alternative approach using the Sonogashira pathway.

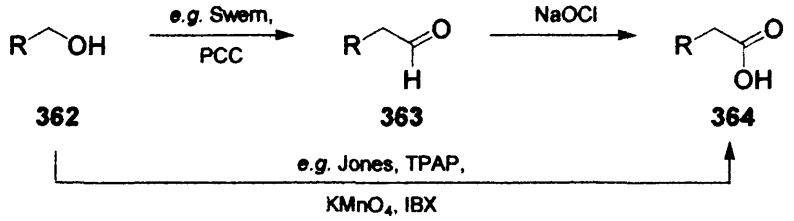
6.3.2.2: Sonogashira approach to Plakorsin B.

This previously defined approach (Chapter 2.2.2 – p 26) featured the synthesis of conjugated enynes **360** using a Sonogashira coupling reaction,[61-63] followed by osmium-catalysed regiospecific *bis*-hydroxylation.[64-66] Substituents including alkyl, aryl and silyl ethers were all accommodated in this approach. It was further shown that this procedure was successful with TBDMS protected 3-butyn-1-ol **359a** to produce 5-substituted-2-furylalcohols **361** (Scheme 119).



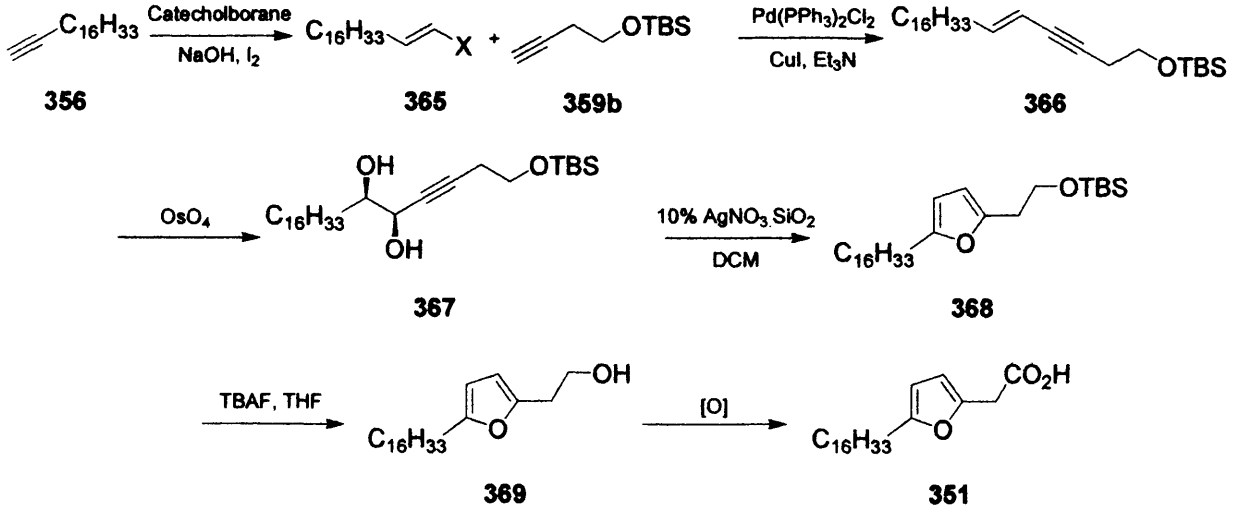
Scheme 119: Synthesis of 5-substituted-2-furylalcohols **361**.

With this in mind, it was felt that it should be possible to oxidise the 2-furylethanol **361** (R = $C_{16}H_{33}$) using one of the very many literature oxidation procedures.[176-190] Having performed a comprehensive review of the literature, there appeared to be little, if anything, in the field of 2-furylethanol **361** oxidation. A broader review identified a number of general oxidation procedures **362**, some leading directly to the desired carboxylic acid **364**[176-180, 184-190] and others pausing at the aldehyde stage **363**[181-183, 186] (Scheme 120). We were particularly attracted to the use of PDC in DMF,[185] Jones reagent,[176-178] regarded by many as an "all or nothing" reagent given its strength, and the equally effective but milder oxidants TPAP,[189] potassium permanganate[187, 188] and IBX.[186] Other oxidants including PCC[183] and the Swern protocol[182] stood out given that they could be combined with sodium chlorite[184] to promote a 2-step oxidation to the acid **364**.



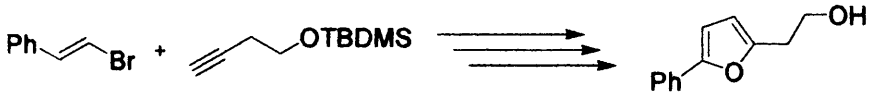
Scheme 120: Oxidation procedures.

Thus, 1-octadecyne **356** was treated with catecholborane and iodine to yield 1-iodooctadec-1-ene **365** (46%). Sonogashira coupling with **359b** then yielded enyne **366** in good yield (79%), which was converted into the corresponding diol **367** by selective *bis*-hydroxylation. Cyclisation with 10% $AgNO_3.SiO_2$ successfully yielded furan **368** in excellent yield (95%) (Scheme 121).



Scheme 121: Sonogashira approach to Plakorsin B **351**.

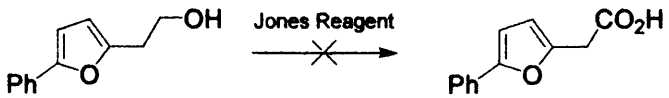
At this point, with a small amount of furan **368** in hand and the expected greater stability of the furan with the silyl group still present, it was felt that a previously prepared model compound should first be used to determine suitable oxidative conditions. This model, 5-phenyl-2-furylethanol **371**, was synthesised from β-bromostyrene **370** and *O*-TBDMS protected 3-butyn-1-ol **359a** (Scheme 122).



370 **359a** **371**

Scheme 122: Synthesis of 5-phenyl-2-furylethylalcohol **371.**

With this model compound **371**, the decision was made to attempt to carry out a direct oxidation to give furan **136b**, an alternative synthesis of which has been previously described in Chapter 2.2.3. Given the highly acidic nature of Jones reagent, and the sensitivity of furans to strong acids, some of the alternative oxidative procedures were implemented first. It was found that TPAP,[189] basic potassium permanganate[187-188] and PDC in DMF[185] were all unsuccessful with each yielding an array of unexpected products in the presence of starting material **371**. Despite some reservations, Jones' reagent[176-178] was also used in the interest of completeness. Although a potentially risky strategy, given the sensitivity of furans, Jones oxidations are usually easy to perform and can often be highly effective. It was found that the addition of a few drops of Jones reagent to a solution of furylethanol **371** in acetone failed to effect the desired oxidation to the corresponding furylacetic acid **136b** (Scheme 123).



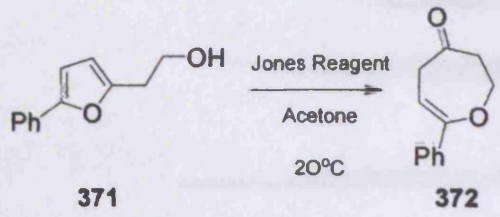
371 **136b**

Scheme 123: Oxidation of 5-phenyl-2-furylethylalcohol **371**.

Attempts to perform a two step oxidation *via* the mild conditions of a Swern oxidation[182] provided yet another set-back. Yet again, we had been unsuccessful in obtaining the desired furylacetic acid **136b**. Instead, what had become apparent, at this stage, was the presence of an unidentified product in the mixtures produced from the PDC, Jones and Swern oxidation procedures. Indeed Jones reagent appeared to provide a remarkably clean passage to this unknown product.

6.3.3: A new approach to oxepin-4-ones

With the difficulties encountered in our attempts to oxidise a furylethanols **361** we stumbled upon a quite remarkable transformation. To our surprise, addition of a slight excess of Jones reagent (120 mol%) to a solution of 5-phenylfuran-2-ethanol **371** in acetone at 20 °C had in fact produced 2,3-dihydro-7-phenyloxepin-4(5H)-one **372** in moderate yield (50%) (Scheme 124).



371 **372**

Scheme 124: Synthesis of 2,3-dihydro-7-phenyloxepin-4(5H)-one **372**.

The enclosed ^{1}H NMR data (Spectrum 16) suggested that the product formed is cyclic, this given the nature of the signals between 4.50 and 2.00 ppm. Careful interpretation of the coupling constants provided confidence in the proposed structure given the grouping of the apparent ring protons into one group of three, the 5- and 6-H 's, and one group of four, the 2- and 3-H 's. Further structural confirmation was achieved through the use of COSY (Figure 31) and HMBC analysis (Figure 32), and with the determination of the molecular weight of 188, consistent with structure **372**. Infrared spectroscopy further showed the presence of a carbonyl and enol ether peak at 1756 and 1686 cm^{-1}. Yields were later optimised (81%) by cooling to 0 °C and improving the work-up protocol.

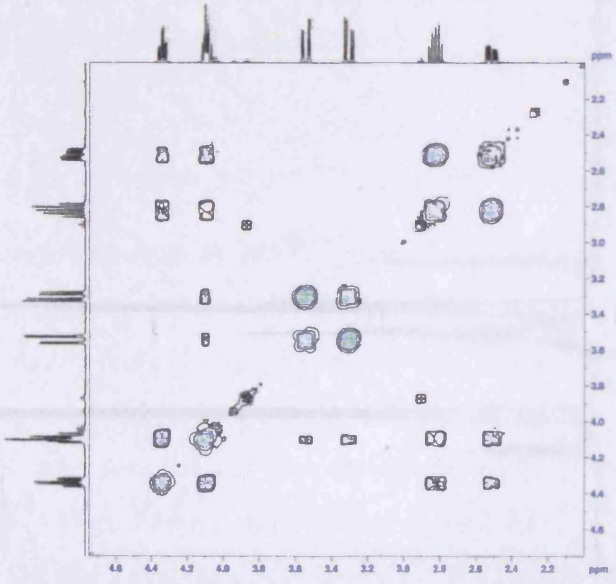
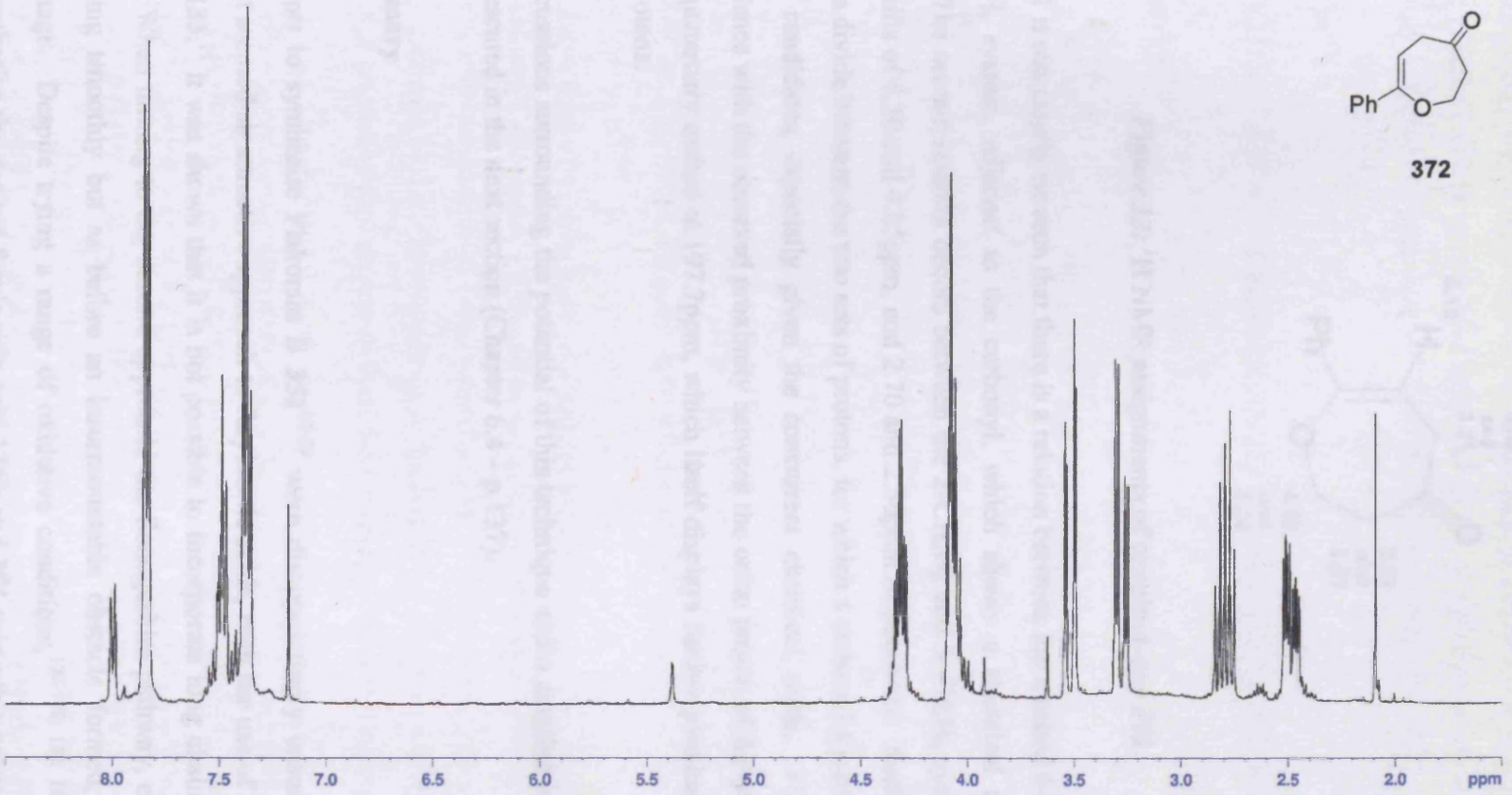


Figure 31: COSY analysis of 2,3-dihydro-7-phenyloxepin-4-one **372**.



Spectrum 16: ^{1}H NMR spectrum of oxepin-4-one **372** ($CDCl_3$).

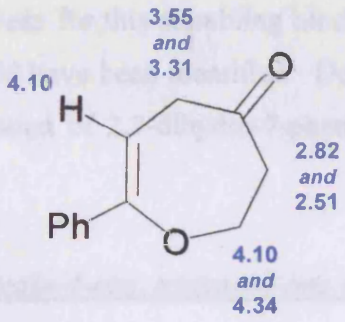


Figure 32: ^{1}H NMR assignments of oxepin-4-one **372**.

In Figure 31 it can clearly be seen that there is a relation between the masked 6-H at 4.10ppm and the 5-CH_aH_b system, adjacent to the carbonyl, which shows a chemical shift of 3.55 and 3.30ppm. The second relation occurs between the 2-CH_aH_b and 3-CH_aH_b systems, which have chemical shifts of 4.30 and 4.05ppm, and 2.70 and 2.50ppm respectively. Such relations suggest there to be a divide between the two sets of protons, for which a carbonyl group and ether oxygen are perfect candidates, especially given the concurrent chemical shifts. Figure 32 provides further evidence with the observed proximity between the ortho proton of the phenyl ring and the enol ether quaternary carbon at 197.7ppm, which itself displays further proximity to the 6-H and 5-CH_aH_b protons.

Further discussions surrounding the potential of this technique and a detailed introduction to this field are presented in the next section (Chapter 6.4 – p 137).

6.3.4: Summary

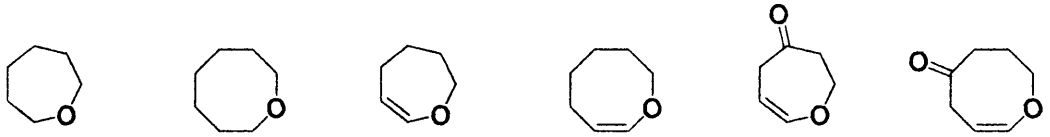
Both attempts to synthesise Plakorsin B **351**[67-70] were disappointingly unsuccessful. Despite having what seemed an attractive approach to furylacetic acids, with the use of 2-acetoxysuccinic anhydride **133**,[71] it was shown that it is not possible to incorporate long chain alkynes into this procedure. When turning to our second approach, the Sonogashira pathway, everything seemed to be running smoothly but as before an insurmountable obstacle formed, in this case the oxidation stage. Despite trying a range of oxidative conditions,[176-178, 182, 185, 187-189] we were unable to synthesise the desired furylacetic acid **136b** and **351** using this approach. In hindsight

perhaps the literature had a hidden message, given the lack of reports of the successful oxidation of furylethanols **361**. Had it not been for this stumbling block, then we believe that an efficient synthesis of Plakorsin B **351** would have been identified. Despite these set backs, the pleasing, but completely unexpected, formation of 2,3-dihydro-7-phenyloxepin-4(5H)-one **372** had been realised.

6.4: Synthesis of cyclic ethers - oxepin-4-one, oxepan-4-one and oxocin-5-one

6.4.1: Introduction

Oxepanes **373** and oxocanes **374** are 7- and 8-membered oxygen-containing heterocycles (Scheme 125). They are known to have important practical and medicinal applications and can be functionalised further with unsaturated bonds to give oxepins **375** and oxocins **376**, as well as with carbonyl groups to give oxepinones **377** and oxocinones **378**.



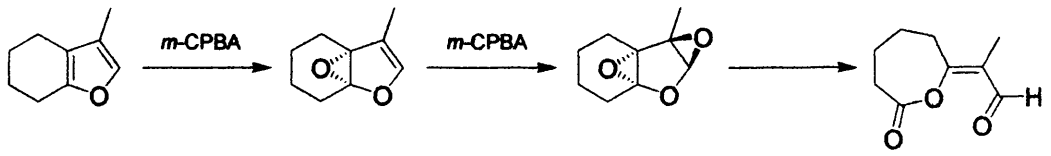
373 **374** **375** **376** **377** **378**

Scheme 125: Functionalised and non-functionalised oxepanes **373** and oxocanes **374**.

With the relative ease of synthesis of non-functionalised cyclic lactone derivatives, there have been some industrial preparations with perhaps the best example being the use of ε-caprolactone as monomer for the production of poly-ε-caprolactone.[191] Whilst there have been successes in this area, the synthesis of more functionalised derivatives is by no means trivial. The synthesis of oxocanes **374** is particularly troublesome given the required energies to permit cyclisation.

Many synthetic approaches to oxepanes **372** incorporate either a displacement reaction, with elimination of an activated leaving group, or a ring expansion reaction such as a Beckmann rearrangement.[192] Indeed, one of the best approaches to a functionalised oxepane involves the rearrangement of a *bis*-epoxidized furan **381**, obtained from the epoxidation of a substituted furan **379** with *m*-CPBA.[193] Here it is seen that epoxidation occurs in two stages **380** and **381**, with the latter epoxidation activating ring expansion to the oxepanone **382** (Scheme 126). Yields for this

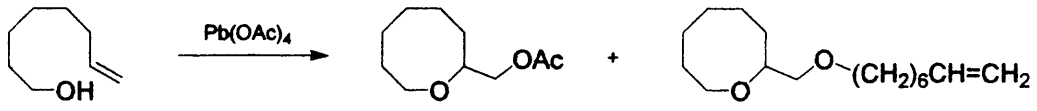
transformation are high (>95%) and furthermore successfully exemplify the effectiveness of using heterocyclic substrates.



379 **380** **381** **382**

Scheme 126: Synthesis of (Z)-2-(7-oxooxepan-2-ylidene)propanal **382**.

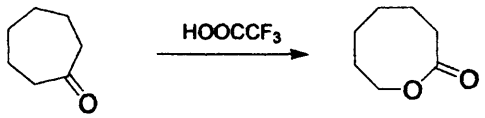
Approaches to functionalised oxocanes **385** tend to be fixed to ring expansion reactions, and often result in low yields. One of the few cyclisation procedures uses lead tetraacetate to effect ring closure of Δ^7-octene-1-ol **383**,[194] however yields of the 2-substituted oxocanes isomers **384, 385** are low (10-11%) and contain mixtures of alternative products (Scheme 127).



383 **384** **385**

Scheme 127: Synthesis of 2-substituted oxocanes from Δ^7-octene-1-ol **383**.

Finally, a high yielding ring expansion has also been described by Closson.[195] In this procedure, cycloheptanone **386** was reacted with peroxytrifluoroacetic acid to yield oxocan-2-one **387** in good yields (72%) (Scheme 128).

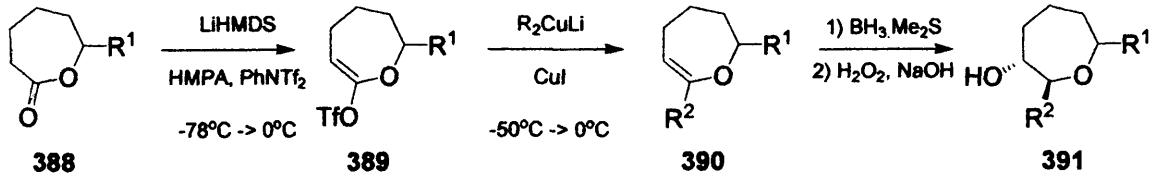


386 **387**

Scheme 128: Closson's synthesis of oxocan-2-one **387**.

All in all, the literature around the synthesis of these compounds is quite varied, with the best results reported through ring expansion procedures,[195-196] with a significant proportion of these ring expansions seeing the synthesis of oxepan-2-ones **382** and oxocan-2-ones **387**. Although a little limited, it is possible to convert oxepane-2-ones **388** into the corresponding 2-substituted cyclic ethers, through a series of simple transformations. Indeed, Murai has shown that it is possible to convert oxepan-2-one **388** into a substituted cyclic ether **391** *via* the formation of its enol triflate **389**.[197] Thus, addition of lithium hexamethyldisilazide, HMPA and *N*-phenyl triflimide to a solution of oxepane-2-one **388** in THF successfully yielded the enol triflates **389** in

excellent yields (89-95%). These enol triflates **389** could then be coupled with lithium dialkylcuprates to give the 7-substituted tetrahydrooxepines **390** in good yields (58-72%). Further functionalisation was shown with hydroboration and oxidation to yield the β-hydroxyoxepane **391** in low yields (30%) (Scheme 129).

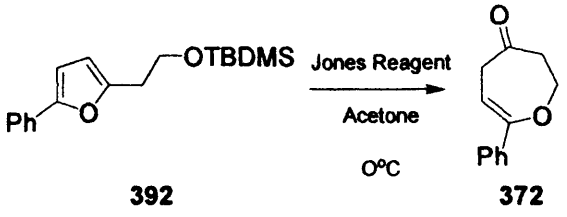


Scheme 129: Functionalisation of oxepane-2-ones **388**.

Murai's work shows the potential manipulations of oxepan-2-ones **388** and, provides access to 'various marine natural products with cyclic ether ring systems'[197] *e.g.* hemibrevetoxin B.[198]

6.4.2: Synthesis of oxepin-4-ones and oxepan-4-ones

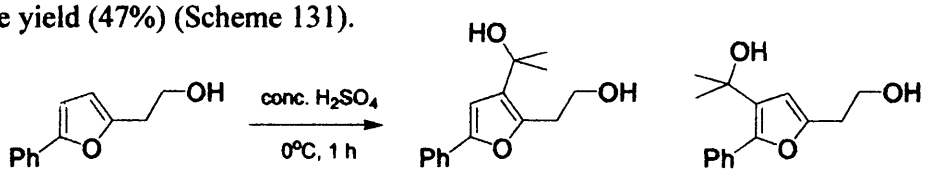
In view of the successful synthesis of 2,3-dihydro-7-phenyloxepin-4(5H)-one **372** from 5-phenylfuran-2-ethanol **371** (Scheme 124), we looked to assess the need for deprotection prior to this transformation. Further investigations into the effect of protection strategies saw the successful transformation of the *O*-TBDMS-protected 2-furylalcohol **392** into the (*Z*)-oxepin-4-one **372** (Scheme 130).



Scheme 130: Synthesis of 2,3-dihydro-7-phenyloxepin-4(5H)-one **372**.

In this one-off experiment, yields were lower (15%), as purification was required to remove traces of silyl residues, but it had been shown that separate deprotection of the protected 2-furylalcohol **393** was not essential and can be replaced by *in situ* removal of the silyl group. This allows the number of steps in this sequence to be reduced to five. It also lowers time and wastage as, in this case, deprotection required overnight stirring in the presence of 400 mol% TBAF to ensure complete cleavage.

With these results in hand, and in an effort to optimise the reaction conditions, the components of Jones reagent were tested individually. Addition of 25% sulfuric acid to a solution of furan **371** in acetone failed to induce the transformation, and somewhat surprisingly had no effect on furan **371** as this starting material was recovered, even after exposure to the acidic solution for 1 h. The use of concentrated sulfuric acid did have an effect, but once again did not yield the now expected oxepinone **372**. Instead, the acid sensitive furan **371** had undergone a Friedel-Crafts alkylation at its β-position. The highly acidic conditions had allowed for the addition of acetone, traditionally used as the solvent, to yield trisubstituted furan **393a**, seemingly regioselectively but in moderate yield (47%) (Scheme 131).

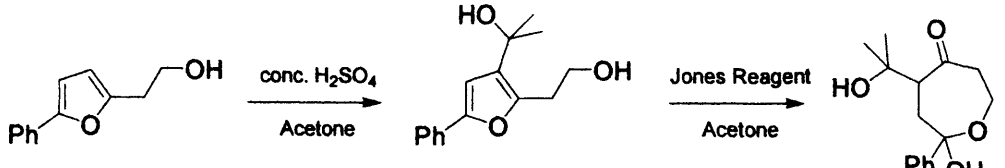


371 **393a** **393b**

Scheme 131: β-acylation of furylethanol **371**.

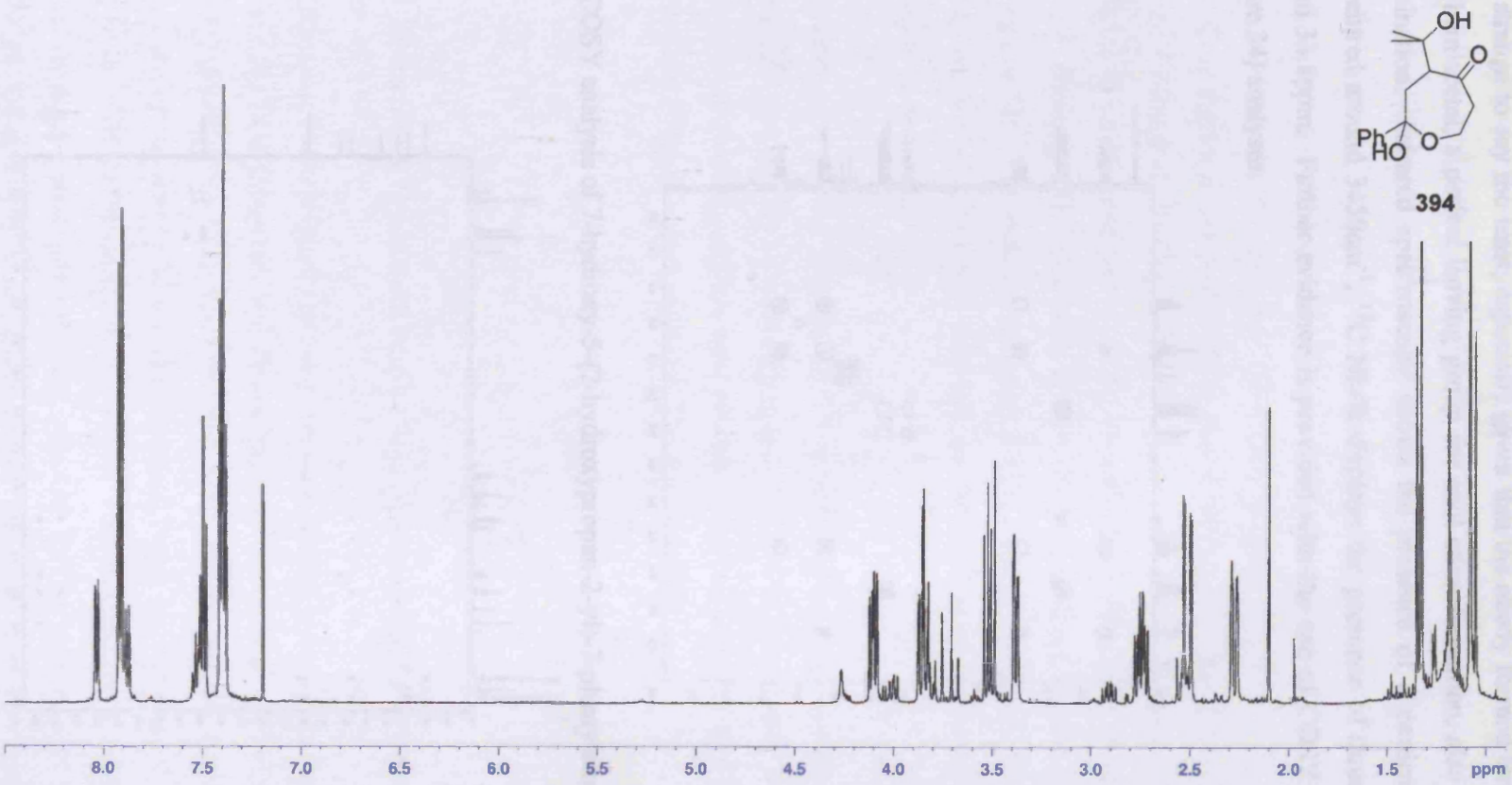
NOESY correlations provided some evidence that the regioselective addition of acetone had occurred at the 3-position of furan **371**, this given the distinct absence of any overlap between the newly incorporated *gem*-dimethyl group and the existing phenyl *ortho*-protons. Although not definitive, this evidence does provide our best estimate of the correct regiochemistry, and the addition itself confirmed through further elucidation with a second transformation to the corresponding oxepin-4-one **394**. With the regiochemistry tentatively proposed a second curiosity is obviously the presence of an apparently acid-stable tertiary alcohol. It would be normal for such an "allylic" tertiary alcohol to undergo easy elimination, forming a conjugated 3-vinylfuran, especially with the furan heteroatom being perfectly aligned to activate this. Instead this alcohol remains intact.

The addition of Jones reagent to this modified furyl alcohol **393** then yielded oxepan-4-one **394** (27%) (Scheme 132). Interestingly, the image presented in Spectrum 17 appears to suggest that this product consisted of both diastereoisomers in a 4:1 ratio.



371 **393** **394**

Scheme 132: Synthesis of 7-hydroxy-5-(2-hydroxypropan-2-yl)-7-phenyloxepan-4-one **394**.



Spectrum 17: ^{1}H NMR spectrum of furan **393** and oxepan-4-one **394** ($CDCl_3$).

It appeared that water has not been eliminated from the product, despite the acidic conditions. This seemed strange to say the least, especially given that the newly formed tertiary 7-hydroxyl group of the hemiacetal, a perfect leaving group for enol ether formation, also appeared to not undergo elimination. Infrared spectroscopy shows the presence of a particularly broad OH absorbance centred around 3450cm^{-1}, ^{13}C NMR displays the presence of three CH_2 groups at 61.6, 42.2 and 33.8ppm. Further evidence is provided with the use of COSY (Figure 33) and HMBC (Figure 34) analyses.

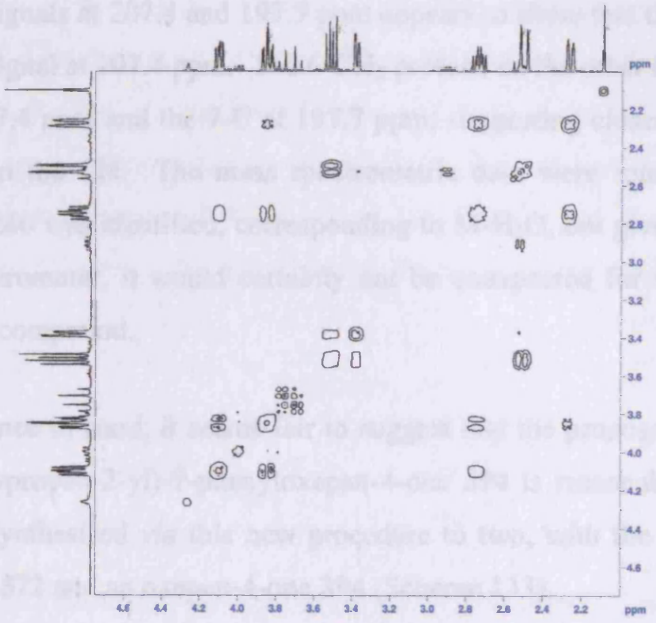


Figure 33: COSY analysis of 7-hydroxy-5-(2-hydroxypropan-2-yl)-7-phenyloxepan-4-one **394**.

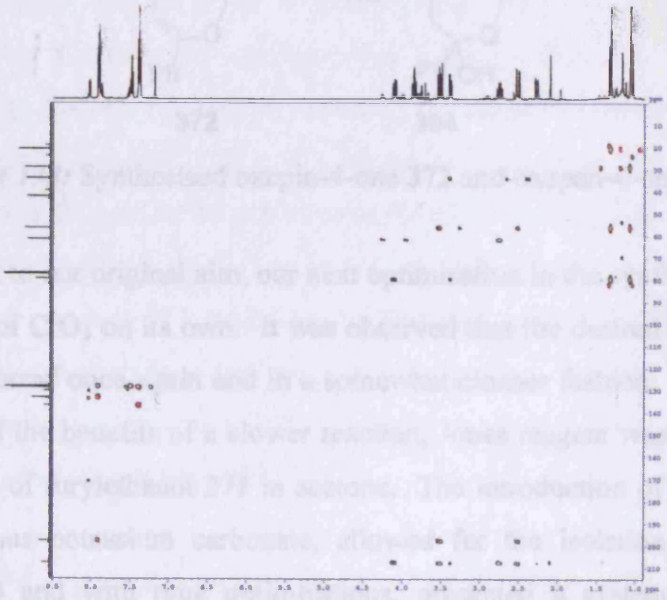
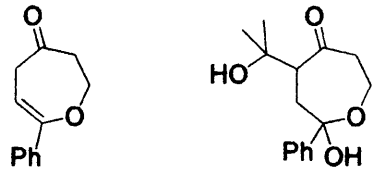


Figure 34: HMBC analysis of 7-hydroxy-5-(2-hydroxypropan-2-yl)-7-phenyloxepan-4-one **394**.

Figure 33 shows coupling between the 2-CH_aH_b system, with a chemical shift of 4.10 and 3.83 ppm, and the 3-CH_aH_b system, which has a chemical shift of 2.73 and 2.30 ppm. It also shows a separate series of couplings between the signals at 3.50, 3.35 and 2.50 ppm, which appear to belong to the 5-H and 6-CH_aH_b protons. With reference to Figure 34, it can be seen that the clear J_1 coupling of the proton at 3.35ppm to the CH carbon at 56.2 ppm, pinpoints this peak as the 5-CH group. The further J_1 coupling of the 3.50 and 2.50ppm signals to the 6-CH_2 carbon at 33.8 ppm adds further weight to the presence of a CH_2 group at the 6-position. Finally, close interpretation of the signals at 207.4 and 197.7 ppm appears to show that the 5-CH group couples only to the carbonyl signal at 207.4 ppm. The 6-CH_2 protons on the other hand couple to both the carbonyl signal at 207.4 ppm and the 7-C at 197.7 ppm, suggesting closer proximity of the CH_2 group to the 7-C than the CH. The mass spectrometric data were somewhat ambiguous. A molecular weight of 246 was identified, corresponding to M-H_2O, but given the harsh conditions within the mass spectrometer, it would certainly not be unexpected for water to be eliminated from such a sensitive compound.

With the above evidence in hand, it seems fair to suggest that the proposed transformation to 7-hydroxy-5-(2-hydroxypropan-2-yl)-7-phenyloxepan-4-one **394** is reasonable. It also brings the tally of compounds synthesised *via* this new procedure to two, with the apparent formation of both an oxepin-4-one **372** and an oxepan-4-one **394** (Scheme 133).



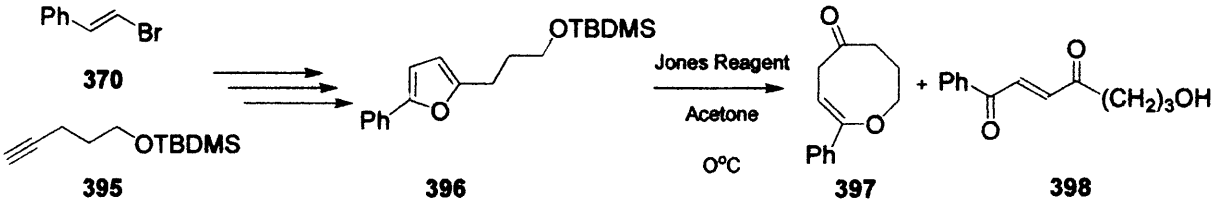
372 **394**

Scheme 133: Synthesised oxepin-4-one **372** and oxepan-4-one **394**.

Finally, reverting back to our original aim, our next optimisation in the synthesis of our oxepin-4-one **372**, saw the use of CrO_3 on its own. It was observed that the desired transformation to the oxepin-4-one **372** occurred once again and in a somewhat cleaner fashion, but at a much slower rate. Thus, in view of the benefits of a slower reaction, Jones reagent was added dropwise to a cooled (0 °C) solution of furylethanol **371** in acetone. The introduction of a neutralisation step, using saturated aqueous potassium carbonate, allowed for the isolation of pure product in excellent yield (81%) and with time optimisations, presented a system which effected the transformation to oxepinone **372** in just 0.5 h when using just a slight excess of Jones reagent.

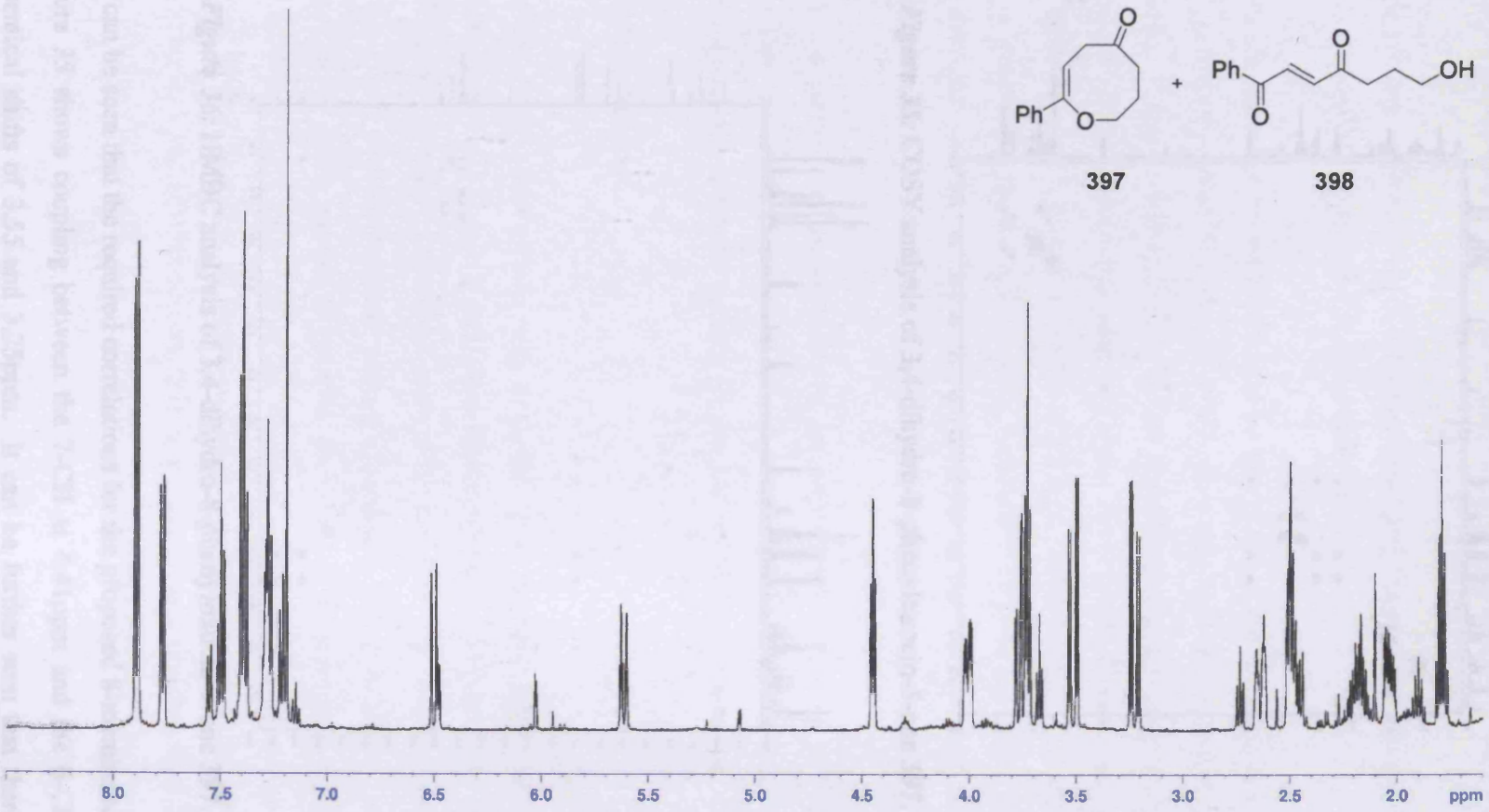
6.4.3: A new approach to oxocin-5-ones

With the above results in hand, it was then proposed that it would be possible to synthesise an oxocin-5-one **397**. With the compatibility of silyl protection groups having already been shown, it was possible to use our standard synthetic approach (Chapter 2.2.1 – p 24) to synthesise *O*-TBDMS protected 5-phenylfuran-2-propanol **396** (60%) from β-bromostyrene **370** and *O*-TBDMS protected 4-pentyn-1-ol **395**. Addition of Jones reagent (120 mol%) to this protected 5-phenylfuran-2-propanol **396** yielded a mixture of products containing oxocin-5-one **397**, dione **398** and the carboxylic acid derivative of furan **396** as the major products in a ratio of 5 : 2 : 25. This result was more reflective of a traditional Jones oxidation, given the predominant formation of the furyl acid, however interestingly we were able to form at least some of the targeted 8-membered ring. Column chromatography led to the isolation of 3,4-dihydro-8-phenyl-2H-oxocin-5(6H)-one **397** (10%) in a 3:2 mixture with the ring opened product **398** (6%) of furan **396** (Scheme 134).



Scheme 134: Synthesis of 3,4-dihydro-8-phenyl-2H-oxocin-5(6H)-one **397**.

Although product formation did not occur as cleanly as in the previous example, a columned yield of 10% did provide a satisfactory starting point. The ^{1}H NMR data (Spectrum 18) shows clearly that there are two distinct compounds, including the oxocins-5-one **397** with what are now characteristic cyclic signals between 4.50 and 2.00ppm and the dione **398** with its acyclic CH_2 groups at 3.73, 2.50 and 1.79 ppm in the presence of the *cis*-alkene signals at 6.50 and 5.62 ppm. Together with the evidence from COSY (Figure 35) and HMBC (Figure 36) analyses, it seems likely that the suggested structure of 3,4-dihydro-8-phenyl-2H-oxocin-5(6H)-one **397** may indeed be correct. Mass spectrometry showed two major molecular ions, one with a mass of 202, which corresponds to the proposed oxocin-5-one **397**, and the other with a mass of 218, which correlates with the ring-opened and oxidised dione **398**.



Spectrum 18: ^{1}H NMR of oxocin-5-one **397** ($CDCl_3$).

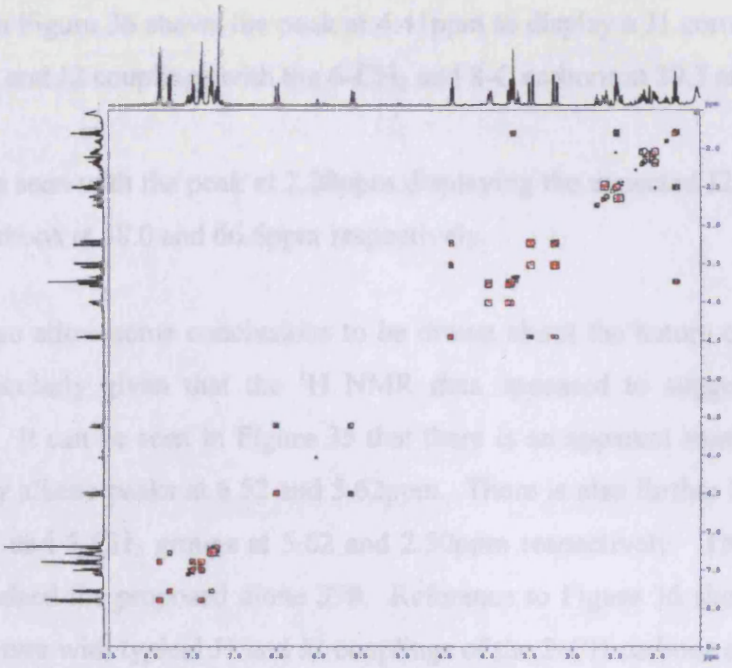


Figure 35: COSY analysis of 3,4-dihydro-8-phenyloxocin-5-one **397**.

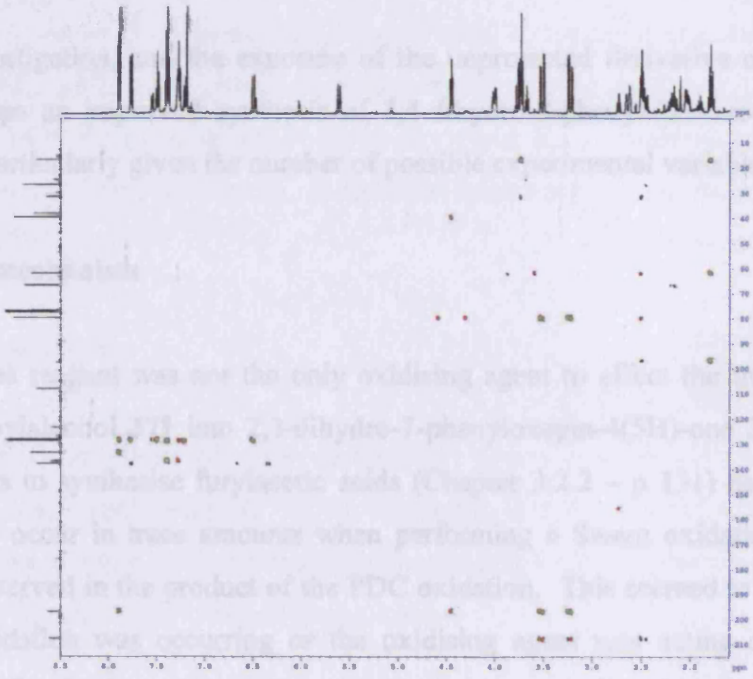


Figure 36: HMBC analysis of 3,4-dihydro-8-phenyloxocin-5-one **397**.

Once again it can be seen that the required correlations for the proposed 8-membered ring **397** are present. Figure 35 shows coupling between the 7-CH at 4.41ppm and the 6-CH_aH_b system, which has chemical shifts of 3.55 and 3.25ppm. It can be further seen that there is coupling between the 2-, 3- and 4-CH_aH_b protons at 4.01, 3.83, 2.63, 2.48, 2.18 and 2.04ppm. The HMBC

profile presented in Figure 36 shows the peak at 4.41ppm to display a J1 correlation with the CH carbon at 79.6ppm and J2 couplings with the 6-CH_2 and 8-C carbons at 39.3 and 196.8ppm.

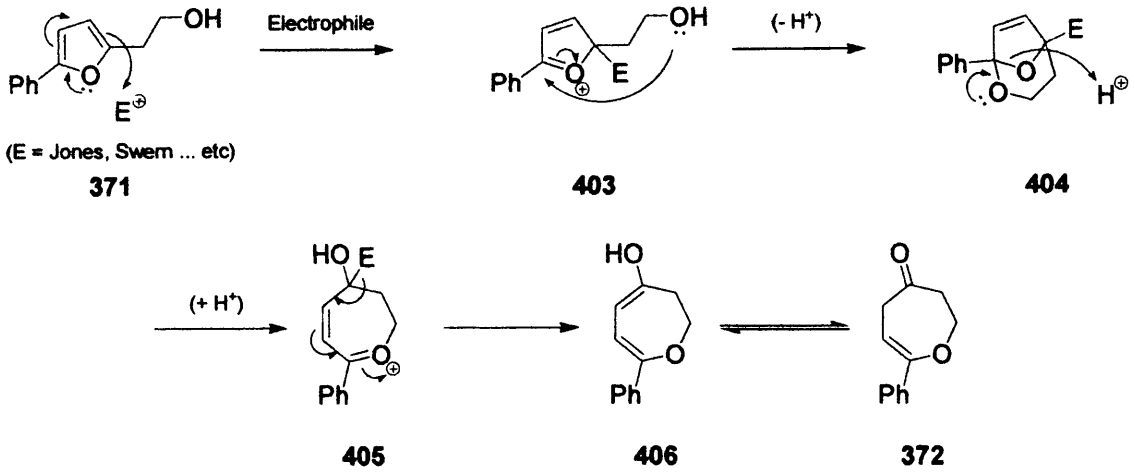
Further evidence is seen with the peak at 2.28ppm displaying the expected J2 couplings to the 2-CH_2 and 4-CH_2 carbons at 38.0 and 66.6ppm respectively.

The above data also allow some conclusions to be drawn about the nature of the other isolated product **398**, particularly given that the ^1H NMR data appeared to suggest that this second product is acyclic. It can be seen in Figure 35 that there is an apparent *trans*-coupling between what are seemingly alkene peaks at 6.52 and 5.62ppm. There is also further long range coupling between the 3-CH and 5-CH_2 groups at 5.62 and 2.50ppm respectively. This suggests that the other product is indeed the proposed dione **398**. Reference to Figure 36 shows further proof of this proposed structure with typical J1 and J2 couplings of the 2-CH carbons and characteristic J1 and J2 couplings for the 5-, 6- and 7-CH_2 carbons.

With further investigation, and the exposure of the unprotected derivative of **396** to the same conditions, perhaps an improved synthesis of 3,4-dihydro-8-phenyl-2H-oxocin-5(6H)-one **397** can be realised, particularly given the number of possible experimental variables.

6.4.4: Proposed mechanism

Interestingly Jones reagent was not the only oxidising agent to effect the transformation of 5-phenylfuran-2-ethylalcohol **371** into 2,3-dihydro-7-phenyloxepin-4(5H)-one **372** (Scheme 124). Our earlier efforts to synthesise furylacetic acids (Chapter 3.2.2 – p 131) had shown the same transformation to occur in trace amounts when performing a Swern oxidation, and significant amounts were observed in the product of the PDC oxidation. This seemed to suggest that either some sort of oxidation was occurring or the oxidising agent was acting as an electrophilic activating group. On the face of it, no formal oxidation is required to form the proposed product **372**, thus the chromium- and DMSO-derived species present in such reagents must be involved in activating ring closure. To this effect, it is proposed that the following happens (Scheme 135):

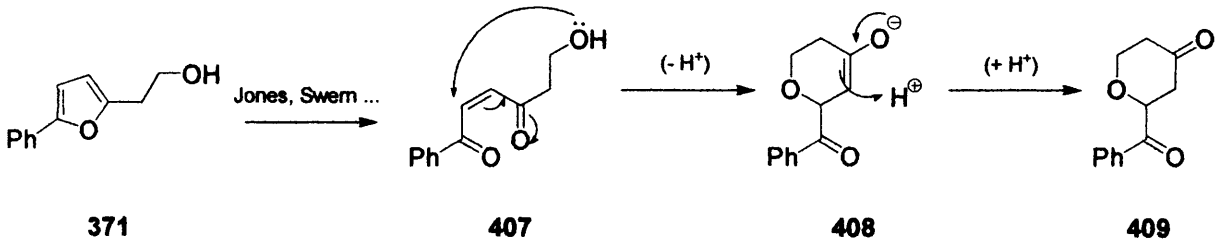


Scheme 135: Electrophile-mediated synthesis of 7- and 8-membered cyclic ethers.

It seems plausible that the addition of an electrophile at the 2-position **[403]**, perhaps assisted by ethyl alcohol co-ordination, would allow for ring closure by the 2'-hydroxyl substituent and newly formed oxonium ion to form a bicyclic intermediate **404**. This intermediate does not contravene Bredt's rule as there are no bridgehead double bonds and one could imagine oxonium ion formation **[405]**, elimination **[406]** and tautomerisation to occur to yield oxepin-4-one **372**. Given the possibilities for the addition of water at various stages throughout this mechanism it would not be so unsurprising to observe related hemi-acetal derivatives, as seen in the synthesis of oxepane-4-one **394**.

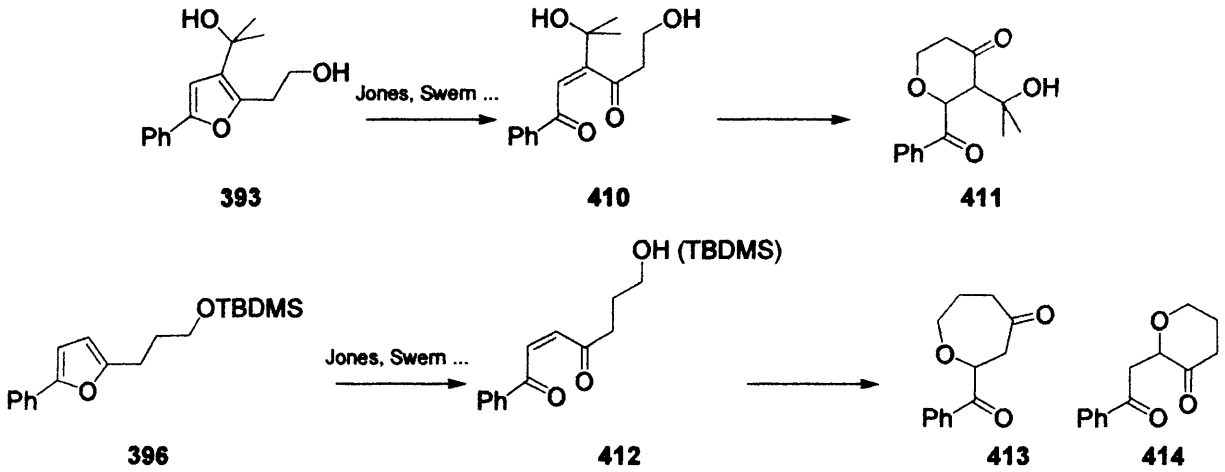
6.4.5: Alternative Pathway

Recently, it has been proposed that this reaction may proceed *via* an alternative pathway, one which produces a different product. It is suggested that the 5-phenylfuran-2-ethanol **371** undergoes oxidation to dione **407**, which then cyclises using the 2'-hydroxyl substituent to form a substituted tetrahydropyran-4-one **409** (Scheme 136).



Scheme 136: Alternative oxidative-transformation of 5-phenylfuran-2-ethanol **371**.

Whilst this mechanism does incorporate a formal oxidation, the data available does not conclusively fit the proposed structure. Mass spectrometry does give a molecular ion of 227, which could correspond to the sodium adduct of **409**, and both ^{1}H- and ^{13}C-NMR can relate to the above, with the lower chemical shift of the 2-CH group now attributable to its alkylic nature. The infra-red spectrum is less conclusive with signals at 1686 and 1756cm^{-1} being perhaps too low given the presence of two ketone functionalities. The alternative structures for the transformation of furans **393** and **396** are shown in scheme 137.



Scheme 137: Alternative oxidative-transformation products.

The data for these products is less conclusive. The ^{1}H- and ^{13}C-NMR suggest the presence of three CH_2 functionalities and one CH for the proposed formation of dihydropyran-4-one **411** from furan **393**, where as there are only two CH_2 groups in the above structure. For the transformation of furan **396** there are two potential products, oxepan-4-one **413** and dihydropyran-3-one **414**, for which there is a molecular ion ($M+H^+$) of 219. The ^{1}H- and ^{13}C-NMR data show agreement with both of the proposed structures, with the intermediate dione **412** showing ^{1}H-NMR signals at 6.50 and 5.62ppm. Reference to the HMBC (Figure 36) highlights that oxepane-4-one **413** is the more likely of these two given the observed coupling of the 2-CH proton to the aryl ketone at 196.8cm^{-1}, yet this would be perhaps the least favoured on first sight. The final piece of data available is the infra-red, which shows two signals at 1639 and 1748cm^{-1}. The lower of these signals is perhaps too low for a ketonic functionality and again draws a degree of uncertainty over such a transformation.

Whilst this proposal presents an alternative pathway, which produces potentially more viable products **409**, **411** and **414**, the data available does not completely agree with the proposal.

Tetrahydropyran-4-one **409** appears plausible however dihydropyran-4-one **411** appears to lack a CH_2 group and dihydropyran-3-one **414** appears not to be formed. Clearly an X-ray crystal structure will answer this question once and for all however a disruption to departmental facilities have meant that the data has not been obtainable. Once the proposed data is available then a firm conclusion should be drawn on the precise nature of this transformation.

6.4.6: Summary

The transformation of 5-phenylfuran-2-ethanol **371** into 2,3-dihydro-7-phenyloxepin-4(5H)-one **372** was a pleasant surprise. The cleanliness and high yields of the reaction hinted towards the discovery of a novel synthetic methodology. Thus, with further experimentation, it was also shown that other 7- and 8-membered cyclic ethers **394** and **397** could be synthesised through the use of this procedure. Unfortunately the yields of these reactions were lower (27% and 10%) than in the synthesis of 2,3-dihydro-7-phenyloxepin-4(5H)-one **372** (83%), and in the case of the 8-membered ether **397**, a competitive reaction was observed, to yield what is thought to be a ring opened furan derivative **398**.

With the potential to use 5-alkylfurylalcohols **127** and tri-substituted furylalcohols **101**, there is great scope for this technique. There are still several avenues for optimisation and much work which still needs doing, but the results from this brief study are promising. Indeed, with optimised conditions in hand, one could imagine accessing a large library of other 7- and even 8-membered heterocycles, and perhaps even a series of 9-membered ring systems. If this can be achieved then a significant synthetic procedure would have been formed.

6.5: Conclusions

The work in this Chapter has shown the potential of the silver-catalysed cyclisation. Despite the mixed successes in achieving the overall outcomes it was found, that in all cases where the cyclisation procedure had been used to synthesise furans (±)-**334**, (±)-**336**, **371** and **396** were obtained in high yields. Indeed the most successful result saw the synthesis of a series of enantiospecific scented furans (±)-**334** and (±)-**336** (>95%), which displayed a mixed array of aromas. With the vast range of substituents accommodated by the silver cyclisation, one could imagine the compilation of an extensive library of scented compounds from this technique alone.

The attempted syntheses of Plakorsin A and B were unsuccessful. With the implementation of two quite different synthetic approaches there was great hope in obtaining the desired products. Unfortunately, despite best efforts, the unsuccessful addition of 1-octadecyne **356** onto 2-acetoxysuccinic anhydride **133** proved a stumbling block. The insurmountable problems found when oxidising substituted furylethanols **361** further meant that progress towards the synthesis of Plakorsin A and B became stalled. With the above failings in mind, we were able to highlight the importance of our existing approach to furylacetic acids **136** (Chapter 2.2.3 – p 27), be it with the limitation of not being able to use fatty alkyne chains. Ominously there is sparse literature around the synthesis of furylacetic acids **136**, and therefore the simplicity and high yields of our approach certainly has its merits.

The unsuccessful oxidation of furan **371** did however identify an unforeseen use for the products of the silver-catalysed cyclisation reactions. It was shown that Jones reagent, specifically chromium(VI) trioxide although slow by itself, can be used to effect the synthesis of substituted oxepin-4-ones **372** and **394** and oxecin-5-ones **397**. With the potential synthesis of a series of substituted cyclic ethers, *via* the preparation of required substrates through the use of the silver cyclisation, it is felt that this procedure may have important applications. Although yields are varied (10-83%), there is much hope for the optimisation of this procedure through further investigation.

Chapter 7: Conclusions

7.1 Conclusions

The silver(I)-catalysed synthesis of furans, pyrroles and pyrazole-*N*-oxides has been described. It has been shown that all are formed from their respective substrates with excellent conversions (>95%), and isolated yields are equally high (>95%) in the majority of cases. The few observations of an impurity can be clearly related to the purity of the starting material or, in a handful of cases, further but preventable side reactions.

In the scope of this project, the procedure was successfully used to synthesise a series of 2,4-, 2,5- and 2,3,5-substituted furans, which included the troublesome furylacetic acids and 2,3- and 2,3,5-substituted pyrroles, pyrazole-*N*-oxides and pyrazoles. Through this work it was shown that there is compatibility with a range of substituents including alkyl, allyl, aryl, hydroxyl and silyl groups, as well as a series of protecting groups, which include alkyl, benzyl and silyl for hydroxyl groups and Boc, Moc, 4-nosyl and tosyl groups for amines. Many of these substituents appear to be broadly applicable to each heterocycle; this has important future implications, as it is likely that this will be the case for the many other possible heterocyclic targets which are attainable through this kind of approach.

Efforts to understand the mode of reaction, including stereochemistry, key functionalities and *in situ* ^{1}H NMR studies, have helped to elucidate the proposed mechanism. From the evidence in hand, we can be reasonably confident in our conclusions and go some way towards optimising the overall procedure. Of particular note was the observation that the *syn*-isomer cyclises the faster, a result which may influence the choice of approach towards a chosen heterocyclic target, be it chelation or non-chelation control or the use of an appropriate stereoselective approach.

As with all procedures there are of course limitations; fortunately in this instance, there have only been a handful of such constraints identified thus far. These include the use of allylic alkenes, divalent sulfur, unprotected propyl alcohol substituents and the synthesis of dihydrofurans. Some of these issues have been resolved and it is believed that with further work will help to address many of the others in time. Interestingly in the case of propyl alcohol substituents, competitive 5-*exo*, and possibly 6-*endo*, transformations were observed. Although a limitation in the synthesis of the required furan, this observation is in fact of great interest as it highlights the possibility of using the silver(I)-catalysed method for the synthesis of other heterocyclic products.

With the above results in hand, and with a view towards the continuous use of the silver(I) catalyst, it was possible to engineer a flow system for heterocyclic synthesis. Early attempts using the existing catalyst, 10% $AgNO_3.SiO_2$, although high yielding (>95%), were troubled by silver leaching. By considering what was known about the chemistry, and further assessing the active state of the catalyst, amberlite 200C was identified as a candidate for catalyst support. The results from this supported catalyst were remarkable. By placing the supported catalyst in a stainless steel column, we were able to successfully synthesise a series of furans, pyrroles, pyrazole-*N*-oxides and isoxazoles in high yield (>95%). Quantification of the levels of metal within the products obtained from this column, showed silver content to be <1ppm in all samples tested. Furthermore, the highly repeatable nature of the results and large number of runs to date are an indication of the robustness of the column, and show the potential value of such a simple piece of equipment. Finally, in another positive move, it has been shown that the column can be operated without solvents when using liquid diols. This is important as it means the turnover from such a column greatly increases and processing is kept to a minimum.

With the help of David Cole-Hamilton, investigations into the use of a second flow system proved to be equally fruitful, with it being shown that this chemistry can be applied to a $scCO_2$:IL continuous flow system. It was possible to contain the silver catalyst within a polar ionic liquid such that upon application of a continuous feed of diol, cyclisation could proceed. Using a second continuous feed of $scCO_2$, and by manipulating its gas and liquid-like properties, it was possible to continuously extract the newly prepared non-polar furan cleanly and in high yield (>70%). Yields were a little lower than the existing flow system but this can confidently be put down to product volatility, given the upstream condensation of the product. With the high recyclability of CO_2 and there not being a specific need for organic solvents, this process has great potential and is seen by many as part of the future of continuous manufacturing.

Finally, having achieved our original aims, we were able to demonstrate specific uses of the silver(I)-catalysed cyclisation procedure. As part of this work the individual enantiomers of the sesquirosefuran analogues **334** and **336** were successfully prepared, with the key cyclisation step proceeding in high yield (>90%). Having taken measures to ensure the removal of competing aromas, it was shown that the (*S*)-isomers of both furans **334** and **336** presented the most pleasant scent. Indeed, given the range of compatible substituents, and the successful development of our flow system, one could imagine the preparation of a library of similarly scented compounds.

Further work towards the applications of the silver(I)-catalysed cyclisation saw the attempted synthesis of the natural products Plakorsin A and B. Unfortunately, in this instance, it was not possible to synthesise the desired targets however, with regard to the silver(I) cyclisation, these approaches were successful. Instead these approaches failed as a result of the unsuccessful nucleophilic addition of 1-octadecyne and the failure to oxidise the furyl ethyl alcohol to the desired furyl acetic acid. The results of the oxidation did however highlight our final synthetic transformation, the synthesis of 7- and 8-membered cyclic ethers. It was shown that several oxidising agents successfully effected the transformation of furyl alcohols to their corresponding 7- or 8-membered cyclic ether. By far the best of these was Jones reagent, with oxepin-4-one **372** being obtained in high yield (81%). Using this procedure, it was also possible to synthesise the larger 8-membered cyclic ether, oxocin-5-one **397**.

Future work should expand the range of heterocycles prepared by the silver(I)-catalysed cyclisation. With there being evidence for competitive 5-*exo* ring closures, as well as the formation of dihydrohydroxy pyrroles, it seems prudent to investigate these areas in particular. Given the range of compatible substituents, it may be of interest to attempt the synthesis of other natural products, perhaps the furanosteroids. Finally further investigations are required into the synthesis of 7- and 8-membered cyclic ethers using Jones reagent. With the provisional successes in hand there is potential to expand and optimised this field still further, perhaps into the synthesis of 9-membered rings.

Chapter 8: Experimental

Experimental

8.1: General Details

All non-aqueous reactions, unless otherwise stated, were conducted in oven- or flame-dried glassware under an atmosphere of dry nitrogen with magnetic stirring. Solid carbon dioxide and an acetone bath (-78 °C) or an ice-water bath (0 °C) were used to obtain low temperatures. Heated reactions were conducted in a stirred oil bath heated on a magnetically stirred hotplate.

Dried: Refers to addition of dried magnesium sulfate ($MgSO_4$) to remove trace amounts of water.

Filtered: Refers to removal of $MgSO_4$ by filtration of organic solutions through filter paper.

Evaporated: Refers to the distillation of solvent using a Bűchi rotary evaporator, typically between 20 and 40 °C.

Overnight: 18-24hrs.

When required, solvents were dried and purified prior to use. Tetrahydrofuran was distilled from sodium. Dichloromethane and toluene were distilled from calcium hydride. Triethylamine, diisopropylamine, pyridine and Hűnigs base were distilled over sodium hydroxide containing 4Å molecular sieves. Diethyl ether was distilled from sodium benzophenone ketyl. All solutions of crude products were dried by brief exposure to dried magnesium sulfate ($MgSO_4$), unless otherwise stated, then filtered and evaporated under reduced pressure (Bűchi rotary evaporator attached to a 20 L Charles Austen pump and using a warm water bath). Column chromatography was carried out over matrix silica gel (35-70 μm mesh), sourced from Biotage, as the stationary phase, and with an elution gradient of ethyl acetate: petrol (40-60 °C) solutions (ranging from 2.5 - 30% ethyl acetate). All reactions, where appropriate, were monitored by tlc using Merck silica gel 60 F_{254} precoated aluminium backed plates, which were visualised with ultraviolet light or ammonium molybdenate. Retention factor values (R_f) are reported in the appropriate solvent system.

All melting points (mp °C) were determined using a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 1600 series Fourier Transform

Infrared Spectrometer, as liquid films on sodium chloride plates [film], as a solution in dichloromethane [DCM] or as nujol mulls on sodium chloride plates [nujol].

Proton (^{1}H) NMR spectra were recorded on a Bruker DPX 400 instrument at 400 MHz, unless otherwise stated, in which case they were performed on a Bruker DPX 250 or 500 instrument operating at 250 and 500 MHz respectively. Spectra were obtained as dilute solutions in deuteriochloroform, unless otherwise stated. The chemical shifts are recorded relative to residual chloroform (7.17 ppm) as an internal standard. Abbreviations used for the multiplicities are s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), m (unresolved multiplet), *app.* (apparent) or as a combination of these multiplicities. All coupling constants (*J*) are recorded in Hertz (Hz). Carbon (^{13}C) spectra were recorded on the same instruments, but were operated at 100, 62.5 and 125 MHz respectively. Chemical shifts are reported relative to residual chloroform (77.0 ppm) as an internal standard. Assignments were made on the basis of chemical shift and coupling constant data using DEPT-90, DEPT-135, COSY, NOESY and HMBC experiments where required.

Mass spectra were recorded on a Varion Platform II Quadrupole low resolution instrument using electron ionisation [EI], atmospheric pressure chemical ionisation [APCI] and electrospray techniques [ES]. *m/z* values are reported with the percentage abundance in parentheses. Accurate high resolution mass spectrometric data were determined using the HRMS Service, Cardiff University, with the molecular formula corresponding to the observed signal using the most abundant isotopes of each element. All molecular formulae are given as values quoted as either molecule (M), molecule + hydrogen $(M+H)^+$, molecule + potassium $(M+K)^+$, molecule + sodium $(M+Na)^+$ or molecule – water $(M-H_2O)$.

A literature reference associated with title of compound means it is not a novel compound and any data recorded in this thesis matches well with those reported in the associated references, unless otherwise stated.

General procedure for the synthesis of furans

Alkyne additions to α-hydroxycarbonyls: [18]

n-BuLi (2.5 – 250 mmol of a 2.5M solution in hexanes, 2.2 eq) was added dropwise to a solution of 1-alkyne (2.5 - 250 mmol, 2.2 eq) dissolved in THF (10 mL g^{-1}) maintained at -78 °C. The solution was stirred for 0.5 h before being transferred dropwise to a second flask containing an α-hydroxyketone (1.1 – 113 mmol, 1 eq) dissolved in THF (10 mL g^{-1}), which was also maintained at -78°C for the first 3 h. After overnight stirring, with slow warming to ambient temperature, the mixture was quenched by the addition of aqueous 0.1M KH_2PO_4 pH 7 buffer, and any emulsion broken up by the dropwise addition of 2M hydrochloric acid. The product was extracted with diethyl ether (3 x 25 mL g^{-1}) and the combined organic layers washed with water (1 x 50 mL g^{-1}) then brine (1 x 50 mL g^{-1}). The ether layer was then dried, filtered and evaporated, with any excess 1-alkyne being removed through column chromatography when necessary, to give the diol.

Sonogashira couplings: [61-63]

Palladium(II) *bis*-(triphenylphosphine)dichloride (0.3 mmol, 0.05 eq), copper iodide (0.6 mmol, 0.1 eq) and a vinyl halide (6 mmol, 1 eq) were suspended in dry diisopropylamine (10 mL g^{-1}). The mixture was heated to 50°C for 5 mins. Upon cooling to ambient temperature, a 1-alkyne (6 mmol, 1 eq) was added and the solution left to stir overnight. The metal content was removed by filtration through silica with hexane (3 x 50 mL g^{-1}) and the filtrate washed with 2M hydrochloric acid (25 mL g^{-1}), water (100 mL g^{-1}) and brine (100 mL g^{-1}) then dried, filtered and carefully evaporated to yield the enyne.

Dihydroxylation of enynes: [64-66]

Potassium ferricyanide (1.2 – 9.3 mmol, 3 eq), potassium carbonate (1.2 – 9.3 mmol, 3 eq) and $DHQD_2$-PHAL (30 - 170 μmol, 0.01 eq) were dissolved in a 1:1 mixture of *t*-butanol and water (10 mL g^{-1}). To this mixture, an enyne (0.4 – 3.1 mmol, 1 eq) was added followed by potassium osmate (VI) dihydrate (6 – 30 μmol, 0.002 eq). The resulting solution was stirred overnight then quenched with sodium sulfite (0.1 g mL^{-1}), with stirring for 0.5 h. The product was extracted

with ethyl acetate (3 x 25 mL g^{-1}) and the combined organic layers washed with water (1 x 50 mL g^{-1}) and brine (1 x 50 mL g^{-1}). The ethyl acetate layer was then dried, filtered and evaporated to yield the diol.

Cyclisations using 10% $AgNO_3.SiO_2$: [18]

In a foil-wrapped flask, 10% w/w silver nitrate on silica gel (0.01 – 0.66 mmol, 0.1 - 0.5 eq) was added to a stirred solution of a 3-alkyne-1,2-diol (0.06 – 1.32 mmol, 1 eq) in dichloromethane (10 mL g^{-1}). The resulting suspension was stirred for 3-48 h then filtered through celite and the solvent evaporated to yield the furan.

Experiments and Data

(*RS*,*RS*)- and (*RS*,*SR*)-3-Methylnon-4-yne-2,3-diol (100a)[18]

100a

Using the general procedure, 1-hexyne (28.7 mL, 0.250 mol) was added to 3-hydroxybutan-2-one (10g, 0.113 mol) to give the *diol* **100a** as a colourless oil (18.498g, 96%), containing a ratio of 68:32 of diastereomers: R_f 0.21 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3396, 2958, 2211, 1457, 1372, 1075, 929; δ_H 3.70 (0.68H, q, J 6.4, 2-H), 3.52 (0.32H, q, J 6.4, 2-H), 2.16 (1.36H, t, J 7.0, 5-CH_2), 2.12 (0.64H, t, J 6.1, 5-CH_2), 1.50-1.38 (2H, m, 6-CH_2), 1.38-1.26 (2H, m, 7-CH_2), 1.34 (0.96H, s, 3-Me), 1.33 (2.04H, s, 3-Me), 1.21 (0.96H, d, J 6.4, 1-Me), 1.15 (2.04H, d, J 6.4, 1-Me), 0.85 (0.96H, t, J 7.2, 9-Me), 0.84 (2.04H, t, J 7.2, 9-Me); δ_c *minor* 85.8 (4-C), 80.7 (5-C), 74.3 (2-CH), 71.9 (3-C), 30.7 (6-CH_2), 24.9 (3-Me), 21.9 (7-CH_2), 19.5 (1-Me), 18.3 (9-Me), 18.2 (8-CH_2); δ_c *major* 85.2 (4-C), 82.3 (5-C), 73.7 (2-CH), 71.0 (3-C), 30.6 (6-CH_2), 23.1 (3-Me), 21.9 (7-CH_2), 18.2 (8-CH_2), 16.8 (1-Me), 13.6 (9-Me); *m/z* (EI) 152 ([M] - H_2O) 27%, 125 (100), [Found ([M]-H_2O), 152.1197. $C_{10}H_{16}O$ requires *M-H_2O*, 152.1201]. All data obtained matched that previously reported in the literature.

5-Butyl-2,3-dimethylfuran (101a)[18]

100a **101a**

Using the general procedure (3 h), 10% $AgNO_3.SiO_2$ (0.25g, 0.147 mmol) was stirred with a solution of diol **100a** (0.05g, 0.294 mmol) in dichloromethane to yield the *furan* **101a** as a pale yellow oil (0.030g, 67%): R_f 0.74 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 2927, 2863, 1643, 1578, 1457, 1386, 1263, 1225, 1161, 1129, 1081, 992, 950, 796, 739, 629; δ_H 5.67 (1H, s, 4-H), 2.41 (2H, t, J 7.6, 1'- CH_2), 2.09 (3H, s, 2-Me), 1.79 (3H, s, 3-Me) 1.50 (2H, m, 2'-CH_2), 1.30 (2H, m, 3'-CH_2), 0.83 (3H, t, J 7.3, 4'-Me); δ_c 153.5 (C), 145.1 (C), 114.1 (C), 107.7 (4-CH), 30.4 (1'-CH_2), 27.7 (2'-CH_2), 22.3 (3'-CH_2), 13.9 (4'-Me), 11.3 (2-Me), 9.9 (3-Me); *m/z* (APCI) 153 $[M+H]^+$ 100%. All data obtained matched that previously reported in the literature.

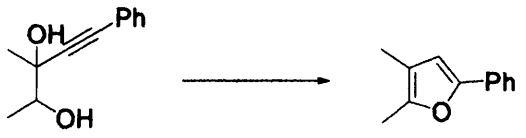
(*RS*,*RS*)- and (*RS*,*SR*)-3-Methyl-5-phenylpent-4-yne-2,3-diol (100b)

100b

Using the general procedure, phenylacetylene (6.85 mL, 62.4 mmol) was added to 3-hydroxybutan-2-one (2.5g, 28.4 mmol) to give a crude oily solid (6.913g). This was purified by column chromatography (10:90 ethyl acetate - petroleum ether) to give the *diol* **100b** as a yellow solid (5.4g, 100%, mp = 56-57 °C), containing a ratio of 69:31 of diastereoisomers: R_f 0.21 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (DCM) 3382, 2980, 2247, 1598, 1488, 1372, 1265, 1070, 938, 756, 691; δ_H 7.39-7.33 (2H, m, 2 x Ar-H), 7.28-7.21 (3H, m, 3 x Ar-H), 3.85 (0.69H, qd, J 6.4 and 2.7, 2-H), 3.64 (0.31H, dq, 7.0 and 6.3, 2-H), 2.91 (0.31H, bs, OH), 2.41 (0.69H, bs, OH), 2.30 (0.69H, bs, OH), 1.97 (0.31H, bs, OH), 1.46 (0.93H, s, 3-Me), 1.45 (2.07H, s, 3-Me), 1.31 (0.93H, d, J 6.3, 1-Me), 1.23 (2.07H, d, J 6.4, 1-Me); δ_c *minor* 131.8 (2 x Ar-CH), 128.5 (2 x Ar-CH), 128.3 (Ar-CH), 122.3 (C), 89.6 (4-C), 85.3 (5-C), 74.6 (2-CH), 72.4 (3-C), 25.8 (3-Me),

16.8 (1-Me); δ_c *major* 131.7 (2 x Ar-CH), 128.6 (2 x Ar-CH), 128.3 (Ar-CH), 122.2 (C), 91.1 (4-C), 84.7 (5-C), 73.7 (2-CH), 71.5 (3-C), 31.0 (3-Me), 18.6 (1-Me); *m/z* (APCI) 173 ($[M+H]^+$ - H_2O) 100%;

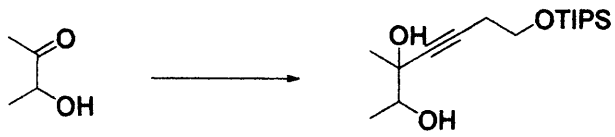
2,3-Dimethyl-5-phenylfuran (101b)[199]



100b **101b**

Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.224 g, 0.132 mmol) was stirred with a solution of diol **100b** (0.25g, 1.32 mmol) in dichloromethane to yield the *furan* **101b** as a pale yellow oil (0.213 g, 95%): R_f 0.80 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 2921, 1601, 1554, 1487, 1447, 1149, 1072, 936, 759, 691; δ_H (125MHz) 7.59 (2H, dd, J 8.2 and 1.2, 2 x Ar-H), 7.33 (2H, dd, J 8.2 and 7.5, 2 x Ar-H), 7.19 (1H, tt, J 7.5 and 1.2, Ar-H), 6.44 (1H, s, 4-H), 2.27 (3H, s, 2-Me), 1.97 (3H, s, 3-Me); δ_c (125MHz) 150.9 (C), 147.4 (C), 131.3 (C), 128.6 (2 x Ar-CH), 126.6 (Ar-CH), 123.2 (2 x Ar-CH), 116.3 (C), 108.4 (4-CH), 11.5 (2-Me), 10.0 (3-Me); *m/z* 172 [M] 100%, 157 (26), 128 (36), 77 (21). All data obtained matched that previously reported in the literature.

(*RS*,*RS*)- and (*RS*,*SR*)-7-(Triisopropylsilyloxy)-3-methylhept-4-yne-2,3-diol (100c)

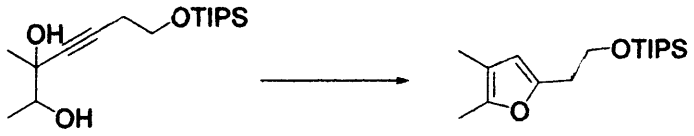


100c

Using the general procedure, *O*-TIPS-3-butyn-1-ol (2.8g, 12.5 mmol) was added to 3-hydroxybutan-2-one (0.5g, 5.67 mmol) to give the *diol* **100c** as a crude yellow oil (2.958g), containing a ratio of 57:43 of diastereoisomers, which was purified by column chromatography (30:70 ethyl acetate – petroleum ether) to yield the *diol* **100c** as a pale yellow oil (1.152g, 65%), containing a ratio of 54:46 of diastereoisomers: υ_{max}/cm^{-1} (film) 3399, 2941, 2242, 1639, 1464,

1383, 1334, 1258, 1211, 1106, 1013, 996, 920, 882, 792, 737, 683, 659; δ_H 3.76-3.66 (2.54H, m, 6-CH_2 and 2-H), 3.52 (0.46H, dq, J 6.3 and 2.0, 2-H), 2.71 (0.46H, bs, OH), 2.41 (0.92H, t, J 6.9, 7-CH_2), 2.39 (1.08H, t, J 6.9, 7-CH_2), 2.24 (0.54H, bs, OH), 2.11 (0.54H, s, OH), 1.89 (0.46H, bs, OH), 1.34 (1.38H, s, 3-Me), 1.33 (1.62H, s, 3-Me), 1.21 (1.38H, d, J 6.3, 1-Me), 1.15 (1.62H, d, J 6.4, 1-Me), 1.02-0.98 (21H, m, TIPS); δ_c *major* 83.3 (4-C), 82.6 (5-C), 73.8 (2-CH), 71.2 (3-C), 61.9 (7-CH_2), 23.4 (3-Me), 23.1 (1-Me), 18.0 (TIPS-Me), 11.9 (TIPS-CH); δ_c *minor* 83.2 (4-C), 81.6 (5-C), 74.6 (2-CH), 72.1 (3-C), 62.0 (7-CH_2), 25.6 (3-Me), 23.2 (1-Me), 18.0 (TIPS-Me), 11.9 (TIPS-CH).

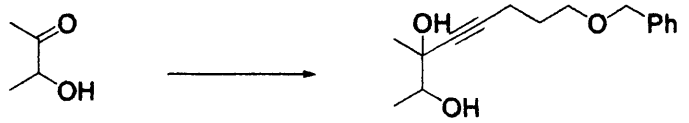
(2-(4,5-Dimethylfuran-2-yl)ethoxy)triisopropylsilane (101c)



100c **101c**

Using the general procedure (16 h), 10% $AgNO_3.SiO_2$ (0.287g, 0.169 mmol) was stirred with a solution of diol **100c** (0.5g, 1.69 mmol) in dichloromethane to yield the *furan* **101c** as a pale yellow oil (0.298g, 63%): R_f 0.81 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 2943, 2893, 1642, 1577, 1541, 1464, 1385, 1367, 1249, 1224, 1105, 1069, 1013, 995, 909, 883, 804, 735, 678; δ_H 5.76 (1H, s, 3-H), 3.80 (2H, t, J 7.3, 2'-CH_2), 2.72 (2H, t, J 7.3, 1'-CH_2), 2.07 (3H, s, 5-Me), 1.81 (3H, s, 4-Me), 1.00-0.96 (21H, m, OTIPS); δ_c 150.0 (C), 145.5 (C), 114.3 (C), 109.3 (3-CH), 62,3 (2'-CH_2), 32.1 (1'-CH_2), 18.0 (5-Me), 17.7 (TIPS-Me), 12.3 (TIPS-CH), 12.0 (4-Me); *m/z* (EI) 296 [M] 1%, 253 (4), 131 (61), 103 (71), 75 (100), [Found ([M]-*i*Pr), 253.1615. $C_{14}H_{25}O_2Si$ requires *M-iPr*, 253.1624].

(*RS*,*RS*)- and (*RS*,*SR*)-8-(Benzyloxy)-3-methyloct-4-yne-2,3-diol (100d)



100d

Using the general procedure, *O*-benzyl-4-pentyn-1-ol (1.09g, 6.24 mmol) was added to 3-hydroxybutan-2-one (0.25g, 2.84 mmol) to give a crude yellow oil (1.022g), containing a ratio of

55:45 of diastereoisomers, which was purified by column chromatography (20:80 ethyl acetate – petroleum ether) to yield the *diol* **100d** as a yellow oil (0.258g, 35%), containing a ratio of 66:34 of diastereoisomers: R_f 0.23 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3416, 3055, 3033, 2983, 2935, 2869, 2241, 1453, 1367, 1268, 1105, 1077, 928, 738 700: δ_H 7.39-7.31 (4H, m, 4 x Ar-H), 7.31-7.27 (1H, m, Ar-H), 4.51 (2H, s, Bn-CH_2), 3.72 (0.66H, q, J 6.4, 2-H), 3.56 (0.34H, q, J 6.1, 2-H), 3.54 (2H, t, J 6.0, 8-CH_2), 2.35 (0.68H, t, J 7.0, 6-CH_2), 2.33 (1.32H, t, J 7.0, 6-CH_2), 1.86-1.76 (2H, m, 7-CH_2), 1.37 (1.02H, s, 3-Me), 1.36 (1.98H, s, 3-Me), 1.24 (1.02H, d, J 6.1, 1-Me), 1.19 (1.98H, d, J 6.4, 1-Me); δ_c *minor* 138.3 (C), 128.4 (2 x Ar-CH), 127.7 (2 x Ar-CH), 127.7 (Ar-CH), 85.2 (4-C), 81.0 (5-C), 74.5 (2-CH), 72.9 (Bn-CH_2), 72.0 (3-C), 68.7 (8-CH_2), 28.8 (6-CH_2), 25.9 (3-Me), 16.6 (1-Me), 15.6 (7-CH_2); δ_c *major* 138.3 (C), 128.4 (2 x Ar-CH), 127.7 (2 x Ar-CH), 127.7 (Ar-CH), 84.7 (4-C), 82.7 (5-C), 73.8 (2-CH), 72.9 (Bn-CH_2), 71.1 (3-C), 68.7 (8-CH_2), 28.7 (6-CH_2), 23.4 (3-Me), 18.4 (1-Me), 15.6 (7-CH_2); *m/z* (EI) 244 ([M] - H_2O) 3%, 173 (100), [Found ([M]-H_2O), 244.1465. $C_{16}H_{20}O$ requires *M-H_2O*, 244.1463].

5-(3-(Benzyloxy)propyl)-2,3-dimethylfuran (101d)

100d **101d**

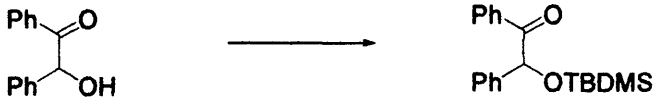
Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.2g, 0.118 mmol) was stirred with a solution of diol **100d** (0.05g, 0.191 mmol) in dichloromethane to yield the *furan* **101d** as a yellow oil (0.045g, 96%): R_f 0.76 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 2923, 2859, 1673, 1636, 1454, 1364, 1273, 1104, 945, 807, 736, 698; δ_H 7.35-7.15 (5H, m, 5 x Ar-CH), 5.63 (1H, s, 4-H), 4.42 (2H, s, Bn-CH_2), 3.42 (2H, t, J 6.4, 3'-CH_2), 2.52 (2H, t, J 7.5, 1'-CH_2), 2.07 (3H, s, 2-Me), 1.89-1.80 (2H, m, 2'-CH_2), 1.83 (3H, s, 3-Me); δ_c 152.6 (C), 145.4 (C), 138.6 (C), 128.4 (2 x Ar-CH), 127.7 (2 x Ar-CH), 127.6 (Ar-CH), 114.2 (C), 109.2 (4-CH), 72.9 (PhCH_2), 69.5 (3'-CH_2), 28.3 (1'-CH_2), 24.7 (2'-CH_2), 11.3 (2-Me), 9.9 (3-Me).

(*RS,RS*)- and (*RS,SR*)-1,2-Diphenyloct-3-yne-1,2-diol (100e)[18]

100e

Using the general procedure, 1-hexyne (28.7 mL, 0.250 mol) was added to benzoin (24.1g, 0.113 mol) to give the *diol* **100e** as a pale yellow solid (32.020g, 96%), containing a ratio of 99:1 of diastereoisomers. Recrystallisation from methanol : water yielded the *diol* **100e** as a fluffy pale yellow solid (30.111g, 90%, mp = 95-97°C): R_f 0.30 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} 3443, 2958, 1652, 1457, 1372, 1129, 929; δ_H 7.40-7.30 (2H, m, 2 x Ar-H), 7.25-7.00 (8H, m, 8 x Ar-H), 4.80 (1H, d, J 3.1, 1-H), 2.65-2.60 (2H, m, 2 x OH), 2.25 (2H, t, J 7.1, 5-CH_2), 1.54-1.44 (2H, m, 6-CH_2), 1.40-1.31 (2H, m, 7-CH_2), 0.86 (3H, t, J 7.3, 8-Me); δ_c (125MHz) 140.5 (C), 137.7 (C), 128.1 (2 x Ar-CH), 128.0 (Ar-CH), 128.0 (Ar-CH), 127.7 (2 x Ar-CH), 127.3 (2 x Ar-CH), 126.7 (2 x Ar-CH), 89.0 (3-C), 81.2 (1-CH), 80.8 (4-C), 76.4 (2-C), 30.6 (5-CH_2), 22.1 (6-CH_2), 18.6 (7-CH_2), 13.6 (8-Me); *m/z* (EI) 276 ([M] - H_2O) 100%. All data obtained matched that previously reported in the literature.

***O*-(*t*-Butyldimethylsilyl)benzoin (168)**[200]

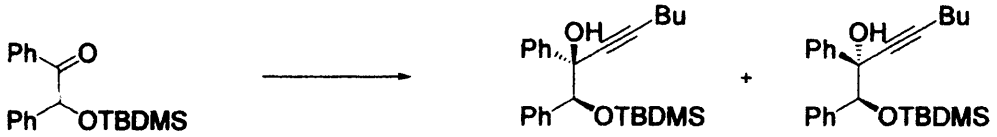


168

t-Butyldimethylsilyl chloride (0.71g, 4.71 mmol, 2 eq), imidazole (0.64g, 9.42 mmol, 4 eq) and DMAP (0.03g, 0.24 mmol, 0.1 eq) were added to a solution of benzoin (0.5g, 2.36 mmol, 1 eq) in dry dichloromethane (20 mL). The resulting solution was then stirred at ambient temperature overnight before being transferred to a separating funnel containing saturated aqueous sodium hydrogen carbonate (20 mL) and petroleum ether (20 mL). The mixture was shaken and separated and the aqueous layer was extracted with petroleum ether (2 x 20 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), then dried, filtered and evaporated to yield *TBDMS-benzoin* **168**, as a pale yellow oil (0.77g, 100%): υ_{max}/cm^{-1} (film)

3170, 2850, 2830, 1680, 1600, 1450, 1225, 1120, 1070, 865, 835, 780, 695; δ_H 8.03-8.00 (2H, m, 2 x Ar-H), 7.55-7.51 (2H, m, 2 x Ar-H), 7.48-7.43 (1H, m, Ar-H), 7.37-7.31 (4H, m, 4 x Ar-H), 7.28-7.22 (1H, m, Ar-H), 5.74 (1H, s, 1-H), 0.89 (9H, s, *t*-Bu Me), 0.00 (6H, s, Si-Me); δ_c 199.2 (C=O), 138.9 (C), 134.4 (C), 132.9 (Ar-CH), 130.0 (2 x Ar-CH), 128.7 (2 x Ar-CH), 128.1 (2 x Ar-CH), 127.7 (Ar-CH), 125.7 (2 x Ar-CH), 80.4 (1-CH), 25.8 (*t*-Bu Me), 18.2 (C), -4.9 (Si-Me); *m/z* (APCI) 327 $[M+H]^+$ 8%, 211 (100), [Found $[M+H]^+$, 327.1770. $C_{20}H_{27}O_2Si$ requires *M+H*, 327.1780]. All data obtained matched that previously reported in the literature.

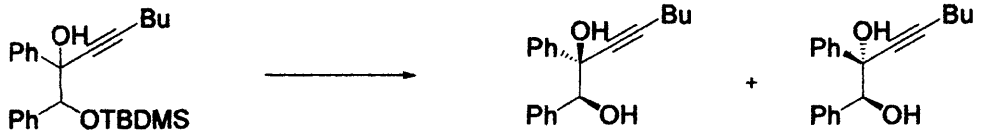
(*RS*,*RS*)- and (*RS*,*SR*)-1,2-Diphenyl-2-hydroxy-1-*O*-(*t*-butyldimethylsilyl)oct-3-yne (169a and 169b)



168 **169a** **169b**

Using the general procedure, 1-hexyne (0.1 mL, 0.842 mmol, 1.1 eq) was added to TBDMS-benzoin **168** (0.25g, 0.766 mmol, 1 eq) to give *propargylic alcohols* **169a,b** as a pale yellow oil (0.262g, 84%) and a 39:61 mixture of diastereoisomers: δ_H 7.57-7.21 (8.78H, m, 18 x Ar-H), 7.18-7.12 (1.22H, m, 2 x Ar-H), 4.78 (0.39H, s, 1-H), 4.75 (0.61H, s, 1-H), 3.49 (0.61H, bs, OH), 3.01 (0.39H, bs, OH), 2.38 (0.78H, t, J 7.0, 5-CH_2), 2.32 (1.22H, t, J 6.9, 5-CH_2), 1.69-1.44 (4H, m, 6- and 7-CH_2), 0.99-0.95 (8.49H, m, 2 x 8-Me and *t*-Bu Me), 0.93 (3.51H, s, *t*-Bu Me), 0.16 (1.83H, s, Si-Me), 0.00 (1.83H, s, Si-Me), -0.12 (1.17H, s, Si-Me), 0.23H (1.17H, s, Si-Me); δ_c *minor* 141.6 (C), 139.6 (C), 128.5 (Ar-CH), 128.3 (2 x Ar-CH), 127.6 (Ar-CH), 127.3 (2 x Ar-CH), 127.1 (2 x Ar-CH), 126.9 (2 x Ar-CH), 91.8 (3-C), 85.4 (4-C), 82.3 (1-CH), 76.4 (2-C), 30.7 (5-CH_2), 25.7 (*t*-Bu Me), 22.1 (6-CH_2), 18.5 (7-CH_2), 18.1 (C), 13.4 (8-Me), -4.9 (Si-Me), -5.6 (Si-Me); δ_c *major* 141.4 (C), 139.2 (C), 130.2 (Ar-CH), 128.3 (2 x Ar-CH), 127.6 (Ar-CH), 127.3 (2 x Ar-CH), 127.0 (2 x Ar-CH), 126.9 (2 x Ar-CH), 94.7 (3-C), 88.3 (4-C), 82.3 (1-CH), 77.2 (2-C), 30.5 (5-CH_2), 25.8 (*t*-Bu Me), 21.9 (6-CH_2), 18.6 (7-CH_2), 18.2 (C), 13.6 (8-Me), -4.8 (Si-Me), -5.4 (Si-Me); *m/z* (EI) 390 ([M] - H_2O) 37%.

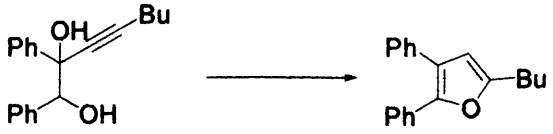
(*RS,RS*)- and (*RS,SR*)-1,2-Diphenyloct-3-yne-1,2-diol (100e)



169a-b **100e**

Tetrabutylammonium fluoride (0.16 mL of a 1M solution in THF, 0.538 mmol, 1.1 eq) was added to a solution of propargylic alcohol **169a,b** (0.2g, 0.489 mmol, 1.1 eq) in tetrahydrofuran (5 mL) and the resulting solution stirred overnight at ambient temperature. The mixture was diluted with water (25 mL) and extracted with diethyl ether (3 x 25 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), then dried, filtered and evaporated to give the *diol* **100e** as a pale yellow solid (0.135g, 94%), containing a 39:61 mixture of diastereoisomers: δ_H 7.42-7.32 (2H, m, 4 x Ar-H), 7.28-7.05 (8H, m, 16 x Ar-H), 4.83 (0.39H, s, 1-H), 4.75 (0.61H, s, 1-H), 3.04 (0.39H, bs, OH), 2.93 (0.61H, bs, OH), 2.67 (0.61H, bs, OH), 2.29 (0.78H, t, J 7.1, 5-CH_2), 2.27 (1.22H, t, J 7.0, 5-CH_2), 1.58-1.31 (4H, m, 6- and 7-CH_2), 0.90 (1.17H, t, J 7.2, 8-Me), 0.89 (1.83H, t, J 7.3, 8-Me); δ_c *minor* 140.5 (C), 137.9 (C), 128.1 (2 x Ar-CH), 128.0 (Ar-CH), 128.0 (Ar-CH), 127.7 (2 x Ar-CH), 127.3 (2 x Ar-CH), 126.7 (2 x Ar-CH), 89.3 (3-C), 81.2 (1-CH), 80.8 (4-C), 76.4 (2-C), 30.6 (5-CH_2), 22.1 (6-CH_2), 18.5 (7-CH_2), 14.2 (8-Me); δ_c *major* 141.0 (C), 135.0 (C), 129.9 (Ar-CH), 128.0 (Ar-CH), 127.9 (2 x Ar-CH), 127.8 (2 x Ar-CH), 127.2 (2 x Ar-CH), 126.8 (2 x Ar-CH), 89.0 (3-C), 81.7 (1-CH), 79.3 (4-C), 77.6 (2-C), 30.5 (5-CH_2), 22.0 (6-CH_2), 18.5 (7-CH_2), 13.6 (8-Me). All other data collected was in accord with that previously obtained from the direct addition of 1-hexyne to benzoin.

5-Butyl-2,3-diphenylfuran (101e) [18,201]



100e **101e**

Using the general procedure (4 h), 10% $AgNO_3.SiO_2$ (1.5g, 0.675 mmol) was stirred with a solution of diol **100e** (0.5g, 1.75 mmol) in dichloromethane to yield *furan* **101e** as an orange oil

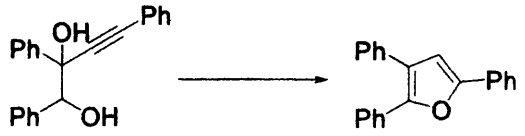
(0.463g, 99%): R_f 0.76 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3451, 2931, 2250, 1671, 1450, 1380, 1266, 1181, 1060, 903, 734; δ_H 7.46-7.41 (2H, m, 2 x Ar-H), 7.36-7.31 (2H, m, 2 x Ar-H), 7.30-7.24 (2H, m, 2 x Ar-H), 7.23-7.16 (3H, m, 3 x Ar-H), 7.15-7.09 (1H, m, Ar-H), 6.09 (1H, s, 4-H), 2.63 (2H, t, J 7.5, 1'- CH_2), 1.69-1.59 (2H, m, 2'- CH_2), 1.43-1.32 (2H, m, 3'-CH_2), 0.86 (3H, t, J 7.3, 4'-Me); δ_c 155.1, 146.3, 132.2, 128.4, 126.2, 125.2, 122.5, 108.8, 31.7, 30.2, 30.0, 29.3, 27.8, 26.0, 22.6, 22.3, 14.1, 13.9; *m/z* (EI) 276 $[M]^+$ 100%, [Found $[M]^+$, 276.1499. $C_{20}H_{20}O$ requires *M*, 276.1515]. All data obtained matched that previously reported in the literature.

(*RS*,*RS*)- and (*RS*,*SR*)-1,2,4-Triphenylbut-3-yne-1,2-diol (100f)

100f

Using the general procedure, phenylacetylene (0.57 mL, 5.18 mmol) was added to benzoin (0.5g, 2.36 mmol) to give the *diol* **100f** as a yellow solid (0.704g, 95%, mp = 138-140°C), containing a ratio of 87:13 of diastereoisomers: R_f 0.5 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (DCM) 3442, 2100, 1643, 1489, 1450, 1175, 1060, 930, 729; δ_H 7.48-7.39 (4H, m, 4 x Ar-H), 7.30-7.16 (11H, m, 11 x Ar-H), 4.91 (0.87H, d, J 3.4, 1-H), 4.80 (0.13H, d, J 3.9, 1-H), 3.25 (0.13H, s, OH), 2.98 (0.13H, d, J 3.9, OH), 2.83 (0.87H, s, OH), 2.64 (0.87H, d, J 3.4, OH); δ_c (125MHz) 140.1 (C), 137.6 (C), 131.8 (2 x Ar-CH), 128.9 (Ar-CH), 128.4 (2 x Ar-CH), 128.3 (2 x Ar-CH), 128.1 (2 x Ar-CH), 127.9 (2 x Ar-CH), 127.5 (2 x Ar-CH), 126.8 (2 x Ar-CH), 122.1 (C), 89.5 (3-C), 87.9 (4-C), 81.2 (1-CH), 77.0 (2-C); *m/z* (APCI) 297 ($[M+H]^+ - H_2O$) 100%.

2,3,5-Triphenylfuran (101f)[202]

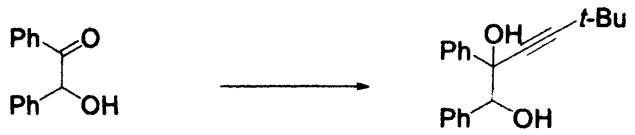


100f **101f**

Using the general procedure (4 h), 10% $AgNO_3.SiO_2$ (0.2g, 0.118 mmol) was stirred with a solution of diol **100f** (0.05g, 0.159 mmol) in dichloromethane to yield the *furan* **101f** as a oil

(0.045g, 95%): R_f 0.85 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3060, 2248, 1949, 1882, 1810, 1675, 1593, 1488, 1449, 1146, 1073, 1054, 1026, 953, 909, 816, 762, 736, 695; δ_H 7.65 (2H, d, J 8.56, 2 x Ar-CH), 7.52 (2H, d, J 8.2, 2 x Ar-CH), 7.37 (2H, d, J 8.0, 2 x Ar-CH), 7.35-7.10 (9H, m, 9 x Ar-CH), 6.73 (1H, s, 4-H); δ_c 152.6 (C), 147.9 (C), 134.3 (C), 131.1 (C), 130.5 (C), 128.8 (2 x Ar-CH), 128.7 (4 x Ar-CH), 128.5 (2 x Ar-CH), 127.6 (Ar-CH), 127.6 (Ar-CH), 127.4 (Ar-CH), 126.2 (2 x Ar-CH), 124.6 (C), 123.9 (2 x Ar-CH), 109.5 (4-CH); *m/z* (APCI) 297 $[M+H]^+$ 100%, [Found $[M+H]^+$, 297.1327. $C_{22}H_{27}O$ requires $M+H^+$, 297.1301]. All data obtained matched that previously reported in the literature.

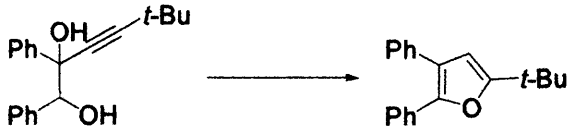
(*RS*,*RS*)- and (*RS*,*SR*)-5,5-Dimethyl-1,2-diphenylhex-3-yne-1,2-diol (100g)



100g

Using the general procedure, 3,3-dimethyl-1-butyne (0.63 mL, 5.18 mmol) was added to benzoin (0.5g, 2.36 mmol) to give the *diol* **100g** as a pale yellow solid (0.619 g, 89%, mp = 126-127 °C), containing a ratio of 91:9 of diastereoisomers: υ_{max}/cm^{-1} (DCM) 3487, 3065, 2971, 2232, 1682, 1449, 1363, 1265, 1173, 1058, 939, 889, 739, 697; δ_H 7.40-7.34 (2H, m, 2 x Ar-H), 7.25-7.05 (8H, m, 8 x Ar-H), 4.78 (0.91H, d, J 3.2, 1-H), 4.68 (0.09H, d, J 4.2, 1-H), 2.95 (0.09H, s, OH), 2.89 (0.09H, d, J 4.2, OH), 2.57 (0.91H, d, J 3.2, OH), 2.55 (0.91H, s, OH), 1.21 (8.19H, s, *t*-Bu), 1.18 (0.81H, s, *t*-Bu); δ_c *minor* 141.3 (C), 138.0 (C), 128.2 (2 x Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 127.6 (2 x Ar-CH), 127.2 (2 x Ar-CH), 127.0 (2 x Ar-CH), 97.5 (2-C), 81.7 (1-CH), 77.9 (3-C), 76.1 (4-C), 30.9 (*t*-Bu Me), 25.6 (*t*-Bu C); δ_c *major* 140.5 (C), 137.8 (C), 128.2 (Ar-CH), 128.0 (Ar-CH), 128.0 (Ar-CH), 127.6 (Ar-CH), 127.2 (Ar-CH), 127.0 (Ar-CH), 97.1 (2-C), 81.1 (1-CH), 79.3 (3-C), 76.2 (4-C), 30.9 (*t*-Bu Me), 27.6 (*t*-Bu C); *m/z* (APCI) 277 ($[M+H]^+$ - H_2O) 100%, [Found ($[M+H]^+$ - H_2O), 277.1588. $C_{20}H_{21}O$ requires *[M+H] - H_2O*, 277.1592].

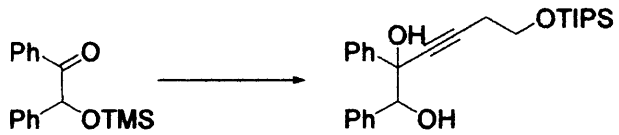
5-*tert*-Butyl-2,3-diphenylfuran (101g)



100g **101g**

Using the general procedure (24 h) 10% $AgNO_3.SiO_2$ (0.031g, 0.018 mmol) was stirred with a solution of diol **100g** (0.053g, 0.180 mmol) in dichloromethane to yield the *furan* **101g** as a yellow oil (0.050g, 97%): υ_{max}/cm^{-1} (film) 2965, 1601, 1552, 1501, 1444, 1362, 1258, 1143, 1070, 962, 762, 694; δ_H 7.47-7.42 (2H, d, J 7.6, 2 x Ar-H), 7.36-7.32 (2H, d, J 7.5, 2 x Ar-H), 7.28-7.22 (2H, m, 2 x Ar-H), 7.22-7.16 (3H, m, 3 x Ar-H), 7.15-7.08 (1H, m, Ar-H), 6.09 (1H, s, 4-H), 1.32 (9H, s, *t*-Bu-Me); δ_c 163.3 (C), 146.3 (C), 134.9 (C), 131.7 (C), 128.7 (2 x Ar-CH), 128.6 (2 x Ar-CH), 128.3 (2 x Ar-CH), 127.0 (Ar-CH), 126.9 (Ar-CH), 125.9 (2 x Ar-CH), 122.7 (C), 106.7 (4-CH), 32.8 (*t*-Bu C), 29.1 (*t*-Bu-Me); *m/z* (APCI) 277 $[M+H]^+$ 100%, [Found $[M+H]^+$, 277.1583. $C_{20}H_{21}O$ requires *M+H*, 277.1592].

(*RS*,*RS*)- and (*RS*,*SR*)-6-(Triisopropylsilyloxy)-1,2-diphenylhex-3-yne-1,2-diol (100h)

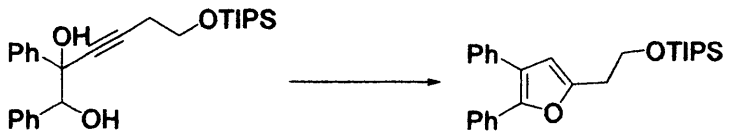


100h

Using the general procedure, TIPS-3-butyn-1-ol (0.8g, 3.52 mmol, 1 eq) was added to TMS-benzoin (1g, 3.52 mmol) to give the *diol* **100h** as a yellow oil (1.101g), containing a ratio of 80:20 of diastereoisomers. The residue was purified by column chromatography (20:80 ethyl acetate – petroleum ether) to yield the major *anti-diol* **100h** as a yellow wax (0.158g, 10%): υ_{max}/cm^{-1} (DCM) 3435, 3062, 3032, 2943, 2867, 2245, 1494, 1450, 1385, 1192, 1109, 1058, 910, 882, 733, 698; δ_H 7.37-7.33 (2H, m, 2 x Ar-H), 7.22-7.03 (8H, m, 8 x Ar-H), 4.78 (1H, d, J 3.3, 1-H), 3.78 (2H, dt, J 7.1 and 1.3, 6-CH_2), 2.71 (1H, d, J 3.3, OH), 2.68 (1H, s, OH), 2.49 (2H, t, J 7.1, 5-CH_2), 1.00-0.95 (21H, m, OTIPS); δ_c (125MHz) 140.3 (C), 137.5 (C), 128.0 (3 x Ar-CH), 128.0 (Ar-CH), 127.7 (2 x Ar-CH), 127.3 (2 x Ar-CH), 126.7 (2 x Ar-CH), 85.8 (3-C), 82.0 (4-

C), 81.2 (1-CH), 61.9 (6-CH_2), 23.4 (5-CH_2), 18.0 (TIPS-Me), 12.0 (TIPS-CH); *m/z* (EI) 420 ([M] - H_2O) 4%, 377 (59), 287 (47), 105 (100), 77 (72).

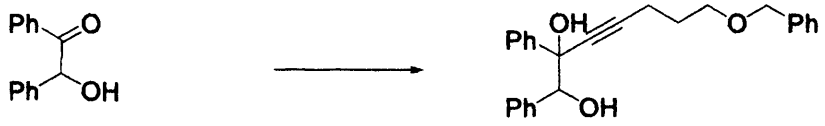
(2-(4,5-Diphenylfuran-2-yl)ethoxy)triisopropylsilane (101h)



100h **101h**

Using the general procedure (16 h), 10% $AgNO_3.SiO_2$ (0.047g, 0.027 mmol) was stirred with a solution of diol **100h** (0.12g, 0.274 mmol) in dichloromethane to yield the *furan* **101h** as a pale yellow oil (0.11g, 96%): υ_{max}/cm^{-1} (film) 3062, 2942, 2865, 1672, 1601, 1502, 1464, 1383, 1365, 1249, 1218, 1176, 1107, 1071, 995, 953, 911, 882, 763; δ_H 7.42 (2H, dd, J 7.2 and 1.5, 2 x Ar-H), 7.34-7.10 (8H, m, 8 x Ar-H), 6.18 (1H, s, 3-H), 3.94 (2H, t, J 6.9, 2'-CH_2), 2.89 (2H, t, J 6.9, 1'-CH_2), 1.00-0.95 (21H, m, OTIPS); δ_c 152.6 (C), 146.9 (C), 134.7 (C), 131.5 (C), 128.6 (2 x Ar-CH), 128.6 (2 x Ar-CH), 128.3 (2 x Ar-CH), 127.1 (Ar-CH), 126.9 (Ar-CH), 126.0 (2 x Ar-CH), 123.1 (C), 110.9 (3-CH), 62.0 (2'-CH_2), 32.1 (1'-CH_2), 18.0 (TIPS-Me), 12.0 (TIPS-CH); *m/z* (APCI) 421 $[M+H]^+$ 12%, 263 (52), 255 (100), 198 (59), 115 (71), [Found $[M+H]^+$, 421.2583. $C_{27}H_{37}O_2Si$ requires *M+H*, 421.2563].

(*RS*,*RS*)- and (*RS*,*SR*)-7-(Benzyloxy)-1,2-diphenylhept-3-yne-1,2-diol (100i)

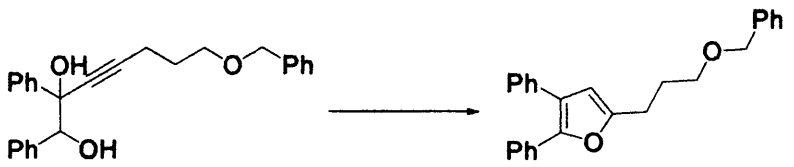


100i

Using the general procedure, *O*-benzyl-4-pentyn-1-ol (0.45g, 2.59 mmol) was added to benzoin (0.25g, 1.18 mmol) to give the *diol* **100i** as a crude red oil (0.519g). This was purified by column chromatography (10:90 ethyl acetate – petroleum ether) to yield the *diol* **100i** as a pale orange wax (0.217g, 48%) containing only one diastereoisomer: R_f 0.33 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (DCM) 3395, 3027, 2867, 2246, 1493, 1450, 1366, 1195, 1026, 697; δ_H 7.40-7.05 (15H, m, 15 x Ar-H), 4.78 (1H, s, 1-H), 4.47 (2H, s, Bn-CH_2), 3.52 (2H, t, J 6.1, 7-

CH_2), 3.03 (1H, s, OH), 2.99 (1H, bs, OH), 2.40 (2H, t, J 7.0, 5-CH_2), 1.88-1.78 (2H, m, 6-CH_2); δ_c 140.5 (C), 138.3 (C), 137.8 (C), 128.5 (2 x Ar-CH), 128.1 (2 x Ar-CH), 127.9 (Ar-CH), 127.9 (Ar-CH), 127.8 (2 x Ar-CH), 127.7 (Ar-CH), 127.7 (2 x Ar-CH), 127.3 (2 x Ar-CH), 126.8 (2 x Ar-CH), 88.0 (3-C), 81.5 (4-C), 81.2 (1-CH), 76.3 (2-C), 73.0 (Bn-CH_2), 68.8 (7-CH_2), 28.7 (5'-CH_2), 15.9 (6'-CH_2); *m/z* (APCI) 369 ([M+H^+] – H_2O) 100%, 278 (27).

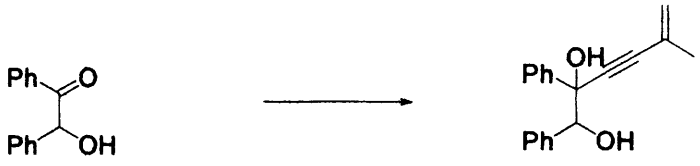
5-(3-(Benzyloxy)propyl)-2,3-diphenylfuran (101i)



100i **101i**

Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.2g, 0.118 mmol) was stirred a solution of diol **100i** (0.05g, 0.129 mmol) in dichloromethane to yield the *furan* **101i** as a yellow oil (0.047g, 98%): R_f 0.82 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3061, 2926, 2855, 1703, 1600, 1557, 1502, 1448, 1364, 1271, 1216, 1103, 1026, 910, 813, 763, 734, 696; δ_H 7.41 (2H, d, J 8.6, 2 x Ar-CH), 7.35-7.05 (13H, m, 13 x Ar-CH), 6.08 (1H, s, 4-H), 4.43 (2H, s, Bn-CH_2), 3.49 (2H, t, J 6.3, 3'-CH_2), 2.74 (2H, t, J 7.5, 1'-CH_2), 1.95 (2H, dt, J 7.5 and 6.3, 2'-CH_2); δ_c 154.9 (C), 146.8 (C), 138.5 (C), 134.7 (C), 131.5 (C), 128.6 (2 x Ar-CH), 128.6 (2 x Ar-CH), 128.5 (2 x Ar-CH), 128.4 (2 x Ar-CH), 127.8 (2 x Ar-CH), 127.6 (Ar-CH), 127.1 (Ar-CH), 127.0 (Ar-CH), 126.0 (2 x Ar-CH), 123.0 (C), 109.7 (4-CH), 73.0 ($PhCH_2$), 69.4 (3'-CH_2), 28.2 (1'-CH_2), 24.8 (2'-CH_2); *m/z* (APCI) 369 $[M + H]^+$ 92%, 277 (95), 134 (54).

(*RS*,*RS*)- and (*RS*,*SR*)-5-Methyl-1,2-diphenylhex-5-en-3-yne-1,2-diol (100j)

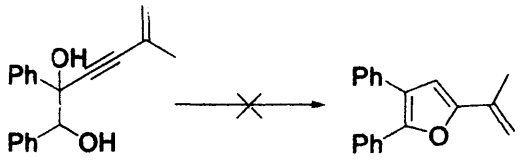


100j

Using the general procedure, freshly distilled 2-methyl-1-butene-3-yne (0.7 mL, 7.26 mmol) was added to benzoin (0.7g, 3.30 mmol) to give the *diol* **100j** as a crude yellow solid (0.721g) in a

ratio of 99:1, which was purified by column chromatography (10:90 ethyl acetate – petroleum ether) to yield the *diol* **100j** as a yellow solid (0.50g, 54%, mp 110-111 °C): R_f 0.45 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (DCM) 3442, 2145, 1709, 1494, 1364, 1288, 1228, 1092, 1058, 904, 845, 703; δ_H 7.41-7.36 (2H, m, 2 x Ar-H), 7.25-7.20 (4H, m, 4 x Ar-H), 7.18-7.10 (4H, m, 4 x Ar-H), 5.31 (1H, dq, J 1.9 and 1.0, 6-H), 5.24 (1H, dq, J 1.9 and 1.5, 6-H), 4.83 (1H, d, J 3.2, 1-H), 2.69 (1H, s, OH), 2.56 (1H, d, J 3.2, OH), 1.86 (3H, dd, J 1.5 and 1.0, 5-Me); δ_c 140.1 (C), 137.6 (C), 128.1 (2 x Ar-CH), 128.0 (2 x Ar-CH), 127.8 (2 x Ar-CH), 127.4 (2 x Ar-CH), 126.8 (2 x Ar-CH), 126.0 (5-C), 123.0 (6-CH_2), 89.0 (3-C), 88.5 (4-C), 81.1 (1-CH), 76.6 (2-C), 23.3 (6-Me); *m/z* (EI) 260 ([M] - H_2O) 1%, 229 (42), 171 (100), 105 (92), 77 (93), [Found ([M] - H_2O), 260.1189. $C_{19}H_{18}O$ requires *M-H_2O*, 260.1201].

2,3-Diphenyl-5-(prop-1-en-2-yl)furan (101j)



100j **101j**

Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.12g, 0.072 mmol) was stirred with a solution of diol **100j** (0.2g, 0.72 mmol) in dichloromethane to yield an unidentified product.

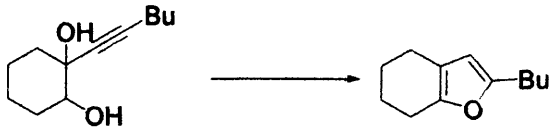
(*RS*,*RS*)- and (*RS*,*SR*)-1-(Hex-1-ynyl)cyclohexane-1,2-diol (100k)[18]

100k

Using the general procedure, 1-hexyne (1.1 mL, 9.64 mmol, 4.4 eq) was added to 2-hydroxycyclohexanone dimer (0.5g, 2.19 mmol) to give the *diol* **100k** as a crude yellow oil (0.333g), containing a ratio of 64:36 of diastereoisomers. The two diastereoisomers were separated by column chromatography (20:80 ethyl acetate – petroleum ether) to give the major *syn*-isomer as a colourless solid (0.103g, 12%, mp = 65-66 °C): R_f 0.21 (30 : 70 ethyl acetate – petroleum ether): υ_{max}/cm^{-1} (DCM) 3150, 2936, 1446 and 1060; δ_H 3.32 (1H, dd, J 11.2 and 4.3,

2-H), 2.19 (2H, t, J 7.1, 3'-CH_2), 1.98-1.92 (1H, m, 6-H), 1.87-1.80 (1H, m, 3-H), 1.70-1.50 (2H, m, 3- and 6-H), 1.50-1.10 (8H, m, 4-, 5-, 4'- and 5'-CH_2), 0.85 (3H, t, J 7.2, 6'-Me); δ_c 88.3 (1'-C), 79.4 (2'-C) , 77.2 (2-CH), 74.1 (1-C), 37.9 (6-CH_2), 32.2 (3-CH_2), 30.8 (3'-CH_2), 24.2 (5-CH_2), 23.3 (4-CH_2), 22.0 (4'-CH_2), 18.4 (5'-CH_2), 13.6 (6'-Me); *m/z* (EI) 178 ([M] - H_2O) 3%, [Found ([M] - H_2O), 178.1359. $C_{12}H_{18}O$ requires *M-H_2O*, 178.1358]; and the minor *anti*-isomer as a colourless solid (0.088g, 10%): R_f 0.26 (30 : 70 ethyl acetate – petroleum ether); δ_H 3.61 (1H, dd, J 7.9 and 3.8, 2-H), 2.36-2.22 (1H, m, 6-H), 2.15 (2H, t, J 7.0, 3'-CH_2), 1.97-1.87 (1H, m, 3-H), 1.75-1.15 (9H, m, 3- and 6-H; 4-, 5-, 4'- and 5'-CH_2), 0.84 (3H, t, J 7.3, 6'-Me); δ_c 85.4 (1'-C), 82.5 (2'-C), 74.1 (2-CH), 70.2 (1-C), 35.5 (6-CH_2), 30.7 (3'-CH_2), 28.6 (3-CH_2), 21.9 (4'- and 5-CH_2), 21.6 (4-CH_2), 18.3 (5'-CH_2), 13.6 (6'-Me); *m/z* (EI) 178 ([M] - H_2O) 5%, 165 (45), 93 (48), 79 (100), [Found ([M]-H_2O), 178.1359. $C_{12}H_{18}O$ requires *M-H_2O*, 178.1358]. The remainder of the compound was isolated as a white solid (0.120g, 15%) containing a mixture of both isomers. All data obtained matched that previously reported in the literature.

2-Butyl-4,5,6,7-tetrahydrobenzofuran (101k)[18]



100k **101k**

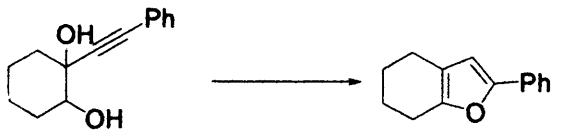
Using the general procedure (3 h minor isomer, 16 h major isomer), 10% $AgNO_3.SiO_2$ (0.22g, 0.127 mmol) was stirred with a solution of diol **100k** (0.05g, 0.255 mmol) in dichloromethane to yield the *furan* **101k** as a pale yellow oil (0.043g, 96%): R_f 0.75 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3558, 3054, 2939, 1603, 1422, 1061, 896; δ_H 5.68 (1H, s, 3-H), 2.43 (4H, m, 4-CH_2 and 7-CH_2) 2.29 (2H, tt, J 6.0 and 1.8, 1'- CH_2), 1.78-1.68 (2H, m, 6-CH_2), 1.67-1.59 (2H, m, 5-CH_2), 1.56-1.47 (2H, m, 2'- CH_2), 1.34-1.24 (2H, m, 3'-CH_2), 0.83 (3H, t, J 7.3, 4'-Me); δ_c (125MHz) 154.2 (C), 148.6 (C), 117.1 (C), 105.4 (3-CH), 30.5 (1'-CH_2), 27.9 (2'-CH_2), 23.3 (4-CH_2), 23.2 (7-CH_2), 23.1 (5-CH_2), 22.4 (6-CH_2), 22.2 (3'-CH_2), 13.9 (4'-Me); *m/z* (APCI) 179 $[M+H]^+$ 100%, [Found $[M+H]^+$, 179.1432. $C_{12}H_{19}O$ requires *M*, 179.1434]. All data obtained matched that previously reported in the literature.

(*RS*,*RS*)- and (*RS*,*SR*)-1-(2-Phenylethynyl)cyclohexane-1,2-diol (100l)

100l

Using the general procedure, phenylacetylene (0.26mL, 2.41 mmol) was added to 2-hydroxycyclohexanone dimer (0.25g, 1.10 mmol) to give the *diol* **100l** as a crude yellow oil (0.212g), in a ratio of 63:37 of diastereoisomers. The two isomers were separated by column chromatography (10:90 and 20:80 ethyl acetate – petroleum ether) to give the major *syn*-isomer as a yellow oil (0.058g, 12%): R_f 0.23 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3419, 2939, 2246, 1645, 1495, 1451, 1378 1070, 756; δ_H 7.39-7.33 (2H, m, 2 x Ar-H), 7.27-7.20 (3H, m, 3 x Ar-H), 3.77 (1H, dd, J 7.9 and 3.8, 2-H), 2.58 (1H, bs, OH), 2.38 (1H, bs, OH), 2.08-2.00 (1H, ddd, J 13.3, 7.0 and 3.7, 6-H), 1.85-1.20 (7H, m, 6-H; 3-, 4- and 5-CH_2); δ_c 131.8 (2 x Ar-CH), 128.5 (Ar-CH), 128.3 (2 x Ar-CH), 122.4 (C), 91.3 (1'-C), 84.6 (2'-C), 74.1 (2-CH), 70.7 (1-C), 35.5 (6-CH_2), 28.6 (3-CH_2), 21.7 (5-CH_2), 21.3 (4-CH_2); and the minor *anti*-isomer as a yellow oil (0.063g, 13%), which was successfully recrystallised from ethyl acetate : petroleum ether to yield the *anti-diol* as a white solid (0.050g, mp = 93-94 °C): R_f 0.27 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3388, 2937, 2244, 1490, 1444, 1371, 1060, 756; δ_H 7.39-7.35 (2H, m, 2 x Ar-H), 7.21-7.16 (3H, m, 3 x Ar-H), 4.02 (1H, bs, OH), 3.44 (1H, dd, 11.0 and 3.2, 2-CH), 3.04 (1H, bs, OH), 2.08-2.01 (1H, m, 6-H), 1.88-1.78 (1H, m, 3-H), 1.64-1.40 (5H, m, 3-, 4- and 6-H; 5-CH_2), 1.20-1.04 (1H, m, 4-H); δ_c 131.9 (2 x Ar-CH), 128.5 (Ar-CH), 128.3 (2 x Ar-CH), 122.5 (C), 88.7 (1'-C), 87.4 (2'-C), 76.9 (2-CH), 74.5 (1-C), 37.9 (6-CH_2), 32.1 (3-CH_2), 24.2 (5-CH_2), 23.3 (4-CH_2); *m/z* (ES) 239 $[M+Na]^+$ 91%, 199 (100).

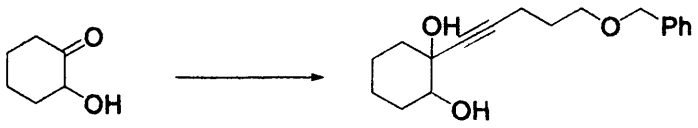
2-Phenyl-4,5,6,7-tetrahydrobenzofuran (101l)[203,204]



100l **101l**

Using the general procedure (6 h), 10% $AgNO_3.SiO_2$ (0.05g, 0.03 mmol) was stirred with a solution of diol **1001** (0.02g, 0.06 mmol) in dichloromethane to yield the *furan* **1011** as a yellow oil (0.018 g, 95%): R_f 0.82 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 1600, 1485, 1440, 1300; δ_H 7.52 (2H, d, J 8.4 Ar-CH), 7.26 (2H, *app.* t, Ar-CH), 7.13 (2H, t, J 7.2, Ar-CH), 6.38 (1H, s, 3-H), 2.54 (2H, t, J 6.2, 7-CH_2), 2.37 (2H, t, J 6.0 and 1.7, 4-CH_2), 1.82-1.75 (2H, m, 6-CH_2), 1.70-1.64 (2H, m, 5-CH_2); δ_c 152.3, 151.5, 132.1, 129.2, 127.2, 123.9, 119.6, 106.7, 24.0, 23.8, 22.8; *m/z* (EI) 198 [M] 100%. All data obtained matched that previously reported in the literature.

(*RS*,*RS*)- and (*RS*,*SR*)-1-(5-(Benzyloxy)pent-1-ynyl)cyclohexane-1,2-diol (100m)

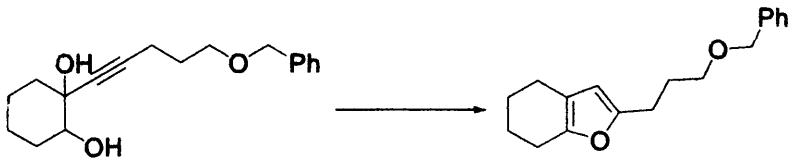


100m

Using the general procedure, *O*-benzyl-4-pentyn-1-ol (0.42g, 2.41 mmol) was added to 2-hydroxycyclohexanone dimer (0.25g, 1.10 mmol) to give the *diol* **100m** as a crude yellow oil (0.275g), containing a ratio of 60:40 of diastereoisomers. The two isomers were separated by column chromatography (20:80 ethyl acetate – petroleum ether) to give the major *syn*-isomer as a pure yellow wax (0.023g, 4%): R_f 0.30 (20 : 80 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (DCM) 3419, 3056, 2306, 1644, 1422, 1265, 1114, 896, 738 and 705; δ_H 7.29-7.25 (4H, m, 4 x Ar-H), 7.25-7.20 (1H, m, Ar-H), 4.44 (2H, s, Bn-CH_2), 3.56 (1H, dd, J 8.0 and 3.8, 2-CH), 3.48 (2H, t, J 6.3, 5'-CH_2), 2.35 (1H, bs, OH), 2.28 (2H, t, J 6.9, 3'-CH_2), 1.93-1.83 (1H, m, 6-H), 1.74 (2H, tt, J 6.9 and 6.3, 4'-CH_2), 1.70-1.20 (7H, m, 6-H; 3-, 4- and 5-CH_2); δ_c 138.4 (C), 128.4 (2 x Ar-CH), 127.7 (2 x Ar-CH), 127.6 (Ar-CH), 84.7 (1'-C), 82.9 (2'-C), 74.3 (2-CH), 73.0 (Bn-CH_2), 70.2 (1-C), 68.7 (5'-CH_2), 35.6 (6-CH_2), 29.3 (3-CH_2), 28.8 (3'-CH_2), 28.5 (5-CH_2), 21.3 (4-CH_2), 15.7 (4'-CH_2); *m/z* could not be obtained; and the minor *anti*-isomer as a pure yellow oil (0.018g, 3%): R_f 0.32 (20 : 80 ethyl acetate – petroleum ether); δ_H 7.29-7.25 (4H, m, 4 x Ar-H), 7.25-7.20 (1H, m, Ar-H), 4.45 (2H, s, Bn-CH_2), 3.50 (2H, t, J 6.2, 5'-CH_2), 3.28 (1H, dd, J 11.2 and 4.2, 2-CH), 2.84 (1H, bs, OH), 2.32 (2H, t, J 7.0, 3'-CH_2), 1.96-1.79 (2H, m, 6- and 3-H), 1.77 (2H, tt, J 7.0 and 6.2, 4'-CH_2), 1.70-1.10 (6H, m, 3- and 6-H; 4- and 5-CH_2); δ_c 138.3 (C), 128.4 (2 x Ar-CH), 127.7 (2 x Ar-CH), 127.7 (Ar-CH), 87.5 (1'-C), 79.9 (2'-C), 77.2 (2-CH),

74.0 (1-C), 73.0 (Bn-CH_2), 68.8 (5'-CH_2), 37.7 (6-CH_2), 32.1 (3-CH_2), 28.9 (3'-CH_2), 24.2 (5-CH_2), 23.3 (4-CH_2), 15.8 (4'-CH_2); *m/z* could not be obtained.

2-(3-(Benzyloxy)propyl)-4,5,6,7-tetrahydrobenzofuran (101m)



100m **101m**

Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.012g, 0.007 mmol) was stirred with a solution of *syn*-diol **100m** (0.020g, 0.070 mmol) in dichloromethane to yield the *furan* **101m** as a yellow oil (0.015g, 80%): R_f 0.82 (20 : 80 ethyl acetate – petroleum ether); δ_H (125MHz) 7.29-7.26 (4H, m, 4 x Ar-CH), 7.24-7.19 (1H, m, Ar-CH), 5.71 (1H, s, 3-H), 4.43 (2H, s, Bn-CH_2), 3.45 (2H, t, J 6.4, 3'-CH_2), 2.61 (2H, t, J 7.5, 1'-CH_2), 2.46 (2H, t, J 6.2, 7-CH_2), 2.28 (2H, td, J 6.0 and 1.8, 4-CH_2), 1.83 (2H, dt, J 7.5 and 6.4, 2'-CH_2), 1.76-1.70 (2H, m, 6-CH_2), 1.65-1.60 (2H, m, 5-CH_2); δ_c (125MHz) 153.3 (C), 148.9 (C), 138.6 (C), 128.4 (2 x Ar-CH), 127.7 (2 x Ar-CH), 127.5 (Ar-CH), 117.5 (C), 105.9 (3-CH), 72.9 (PhCH_2), 69.5 (3'-CH_2), 29.7 (1'-CH_2), 28.4 (2'-CH_2), 23.2 (7-CH_2 and 5-CH_2), 23.1 (4-CH_2), 22.1 (6-CH_2); *m/z* (APCI) 271 $[M+H]^+$ 100%, 179 (12), [Found $[M+H]^+$, 271.1686. $C_{18}H_{23}O_2$ requires *M+H*, 271.1698].

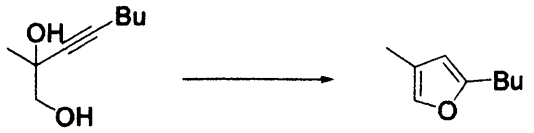
2-Methyloct-3-yne-1,2-diol (100n)[205]

100n

Using the general procedure, 1-hexyne (1.89 mL, 16.4 mmol) was added to acetol (0.5 mL, 7.48 mmol) to give the *diol* **100n** as a colourless oil (0.82g, 70%): R_f 0.17 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3374, 2956, 2244, 1640, 1458, 1377, 1052, 949; δ_H 3.54 (1H, d, J 11.0, 1-H_a), 3.39 (1H, d, J 11.0, 1-H_b), 2.14 (2H, t, J 7.1, 5-CH_2), 1.47-1.38 (2H, m, 6-CH_2),

1.37 (3H, t, 2-Me), 1.36-1.26 (2H, m, 7-CH_2), 0.84 (3H, t, J 7.3, 8-Me); δ_c 85.4 (3-C), 81.5 (4-C), 70.9 (1-CH_2), 68.7 (2-C), 30.7 (5-CH_2), 25.6 (2-Me), 22.0 (6-CH_2), 18.3 (7-CH_2), 13.6 (8-Me); *m/z* (EI) 138 ([M] - H_2O) 1%, 130 (100), [Found ([M]-H_2O), 138.1043. $C_9H_{14}O$ requires *M-H_2O*, 138.1045]. All data obtained matched that previously reported in the literature.

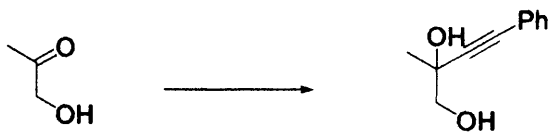
2-Butyl-4-methylfuran (101n)[205]



100n **101n**

Using the general procedure (3 h), 10% $AgNO_3.SiO_2$ (0.054g, 0.032 mmol) was stirred with a solution of diol **100n** (0.05g, 0.320 mmol) in dichloromethane to yield the *furan* **101n** as a pale yellow oil (0.021g, 48%): R_f 0.73 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 2958, 2872, 1619, 1552, 1459, 1379, 1269, 1122, 947, 914, 799, 739 and 602; δ_H (125MHz) 6.91 (1H, s, 5-H), 5.72 (1H, s, 3-H), 2.43 (2H, t, J 7.6 1'- CH_2), 1.85 (3H, s, 4-Me), 1.52-1.42 (2H, m, 2'-CH_2), 1.29-1.18 (2H, m, 3'-CH_2), 0.79 (3H, t, J 7.3, 4'-Me); δ_c (125MHz) 156.6 (C), 137.2 (5-CH), 120.4 (C), 107.4 (3-CH), 30.2 (1'-CH_2), 27.8 (2'-CH_2), 22.3 (3'-CH_2), 13.8 (4'-Me), 9.8 (4-Me); *m/z* (EI) 138 [M] 100%. All data obtained matched that previously reported in the literature.

2-Methyl-4-phenylbut-3-yne-1,2-diol (100o)[18,206]

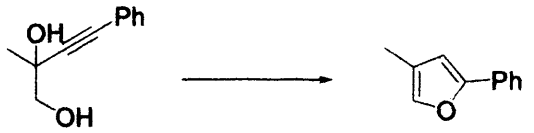


100o

Using the general procedure, phenylacetylene (0.88 mL, 8.03 mmol) was added to acetol (0.25mL, 3.65 mmol) to give a crude yellow solid (0.359). This residue was purified by column chromatography (30: 70 ethyl acetate – petroleum ether) to yield *diol* **100o** as a yellow solid (0.145g, 23%, mp 88-90 °C) *(lit. mp. = 85-86 °C)*: R_f 0.14 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (DCM) 3399, 2247, 1651, 1376, 1283, 1050, 908, 733; δ_H 7.39-7.33 (2H, m, 2 x

Ar-H), 7.27-7.21 (3H, m, 3 x Ar-H), 3.70 (1H, d, J 11.0, 1-H_a), 3.51 (1H, dd, J 11.0 and 3.4, 1-H_b), 2.71 (1H, bs, OH), 2.14 (1H, bs, OH), 1.49 (3H, s, 2-Me); δ_c (125MHz) 131.8 (2 x Ar-CH), 128.6 (Ar-CH), 128.3 (2 x Ar-CH), 122.2 (C), 90.3 (3-C), 84.5 (4-C), 70.8 (1-CH_2), 69.1 (2-C), 25.4 (2-Me); *m/z* (EI) 158 [M – H_2O] 100%. All data obtained matched that previously reported in the literature.

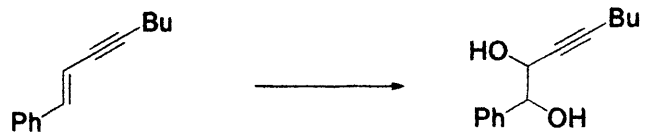
4-Methyl-2-phenylfuran (101o)[18,207]



100o **101o**

Using the general procedure (3 h), 10% $AgNO_3.SiO_2$ (0.029g, 0.017 mmol) was stirred with a solution of diol **100o** (0.03g, 0.17mmol) in dichloromethane to yield *furan* **101o** as a pale yellow oil (0.023g, 85%): R_f 0.70 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 1597, 1538, 1484, 1445, 914, 763; δ_H (125MHz) 7.58 (2H, d, J 7.1, 2 x Ar-CH), 7.31-7.27 (2H, m, 2 x Ar-CH), 7.19-7.14 (2H, m, Ar-CH and 5-H), 6.43 (1H, s, 3-H), 2.00 (3H, d, J 1.0, 4-Me); δ_c (125MHz) 153.9 (C), 138.9 (5-CH), 131.1 (C), 128.6 (2 x Ar-CH), 127.1 (Ar-CH), 123.7 (2 x Ar-CH), 122.0 (C), 107.7 (3-CH), 9.9 (4-Me); *m/z* (EI) 158 [M] 100%, [Found [M], 158.0728. $C_{11}H_{10}O$ requires *M*, 158.0727]. All data obtained matched that previously reported in the literature.

(*RS*,*RS*)-1-Phenyloct-3-yne-1,2-diol (126a)[18]



125a **126a**

Using the general procedure, (*E*)-1-phenyloct-1-en-3-yne[208] **125a** (0.182g, 1 mmol) was dihydroxylated with potassium osmate (VI) dihydrate (5mg, 19.8 μmol) to yield the *diol* **126a** as a yellow-brown oil (0.144g, 67%): R_f 0.24 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1}

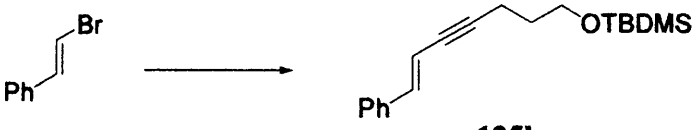
(film) 3404, 3033, 2958, 2872, 2249, 1548, 1494, 1454, 1380, 1227, 1260, 1198, 1142, 1057, 909, 842, 734, 700, 649; δ_H 7.36 (2H, d, J 7.4, 2 x Ar-H), 7.33-7.20 (3H, m, 3 x Ar-H), 4.61 (1H, d, 6.9, 1-H), 4.31 (1H, dt, J 6.9 and 2.0, 2-H), 2.75 (1H, bs, OH), 2.26 (1H, bs, OH), 2.09 (2H, td, J 7.2 and 2.0, 5-CH_2), 1.40-1.30 (2H, m, 6-CH_2), 1.29-1.17 (2H, m, 7-CH_2), 0.80 (3H, t, J 7.3, 8-Me); δ_c 139.4 (C), 128.2 (2 x Ar-CH), 127.1 (Ar-CH), 123.3 (2 x Ar-CH), 88.1 (3-C), 77.8 (4-C), 77.7 (1-CH), 67.7 (2-CH), 30.4 (5-CH_2), 21.8 (6-CH_2), 18.3 (7-CH_2) and 13.6 (8-Me); *m/z* (APCI) 219 $[M+H]^+$ 89%. All data obtained matched that previously reported in the literature.

2-Butyl-5-phenylfuran (127a)[18]

126a **127a**

Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.2g, 0.115 mmol) was stirred with a solution of diol **126a** (0.05g, 0.230 mmol) in dichloromethane to yield *furan* **127a** as an orange oil (0.038g, 83%): R_f 0.73 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3019, 2926, 1448, 1215, 755, 669; δ_H 7.56 (2H, d, J 7.6, 2 x Ar-H), 7.25 (2H, t, J 7.6, 2 x Ar-H), 7.17-7.11 (1H, m, Ar-H), 6.47 (1H, d, J 3.2, 4-H), 5.97 (1H, d, J 3.2, 3-H), 2.61 (2H, t, J 7.6, 1'- CH_2), 1.65-1.56 (2H, m, 2'- CH_2), 1.40-1.29 (2H, m, 3'-CH_2), 0.86 (3H, t, J 7.3, 4'-Me); δ_c 156.5 (C), 152.1 (C), 131.3 (C), 128.6 (2 x Ar-CH), 126.7 (Ar-CH), 123.3 (2 x Ar-CH), 106.9 (3-CH), 105.7 (2-CH), 30.3 (1'-CH_2), 27.9 (2'-CH_2), 22.3 (3'-CH_2), 13.9 (4'-Me); *m/z* (EI) 200 $[M]^+$ 97%, [Found [M], 200.1195. $C_{14}H_{16}O$ requires *M*, 200.1201]. All data obtained matched that previously reported in the literature.

(*E*)- and (*Z*)-(7-Phenylhept-6-en-4-ynyloxy)(*tert*-butyl)dimethylsilane (125b)



125b

Using the general procedure, *O*-TBDMS-4-pentyn-1-ol (3.1 g, 15.6 mmol) was added to β-bromostyrene (2 mL, 15.6 mmol) to give the *enyne* **125b** as a crude yellow oil (4.76 g),

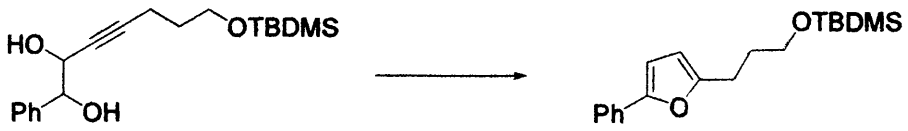
containing a ratio of 96:4 of isomers: R_f 0.25 (5 : 95 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 2953, 2856, 2213, 1651, 1492, 1471, 1447, 1388, 1361, 1255, 1105, 1006, 953, 836, 777, 747, 691, 664; δ_H 7.78 (0.08H, d, J 7.6, 2 x Ar-H), 7.32-7.15 (4.92H, m, 8 x Ar-H), 6.79 (0.96H, d, J 16.3, 7-H), 6.48 (0.04H, d, J 11.9, 7-H), 6.07 (0.96H, dt, J 16.3 and 2.1, 6-H), 5.62 (0.04H, dt, J 11.9 and 2.4, 6-H), 3.66 (1.92H, t, J 6.0, 1-CH_2), 3.60 (0.08H, t, J 6.0, 1-CH_2), 2.45 (0.08H, dt, J 7.0 and 2.4, 3-CH_2), 2.38 (1.92H, dt, J 7.0 and 2.1, 3-CH_2), 1.77-1.62 (2H, m, 2-CH_2), 0.84-0.82 (9H, s, *t*-Bu), 0.00 (6H, s, Si Me); δ_c 140.1 (7-CH), 136.5 (C), 128.7 (2 x Ar-CH), 128.3 (Ar-CH), 126.1 (2 x Ar-CH), 108.8 (6-CH), 92.5 (5-C), 79.9 (4-C), 61.7 (1-CH_2), 31.8 (3-CH_2), 26.0 (*t*-Bu Me), 18.4 (C), 16.1 (2-CH_2), -5.3 (Si Me) (minor isomer was not observed by ^{13}C-NMR); *m/z* (EI) 300 [M] 2%, 243 (96), 141 (71), 89 (100) [Found [M], 300.1916. $C_{19}H_{28}OSi$ requires *M*, 300.1909].

(*RS*,*RS*)-7-((*tert*-Butyl)dimethylsilyloxy)-1-phenylhept-3-yne-1,2-diol (126b)

125b **126b**

Using the general procedure, enyne **125b** (4g, 13.3 mmol) was dihydroxylated with potassium osmate(VI) dihydrate (8mg, 30 μmol) to yield crude *diol* **126b** as a yellow oil (3.842g, 94%) containing a ratio of 96:4 of isomers, which was purified by column chromatography (20:80 ethyl acetate – petroleum ether) to give the *diol* **126b** as a pale yellow oil (3.842g, 86%) and as a single isomer: R_f 0.26 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3372, 2953, 2896, 2857, 2234, 1672, 1599, 1495, 1471, 1389, 1361, 1326, 1255, 1198, 1104, 1065, 968, 836, 776; δ_H 7.39 (2H, dd, J 7.8 and 1.3, 2 x Ar-H), 7.36-7.26 (3H, m, 3 x Ar-H), 5.04 (1H, bs, OH), 4.63 (1H, d, J 7.2, 1-H), 4.34 (1H, dt, J 7.2 and 1.8, 2-H), 3.54 (2H, t J 6.0, 7-CH_2), 2.21 (2H, dt, J 1.8 and 7.2, 5-CH_2), 1.65-1.55 (2H, m, 6-CH_2), 0.86 (9H, s, *t*-Bu), 0.00 (6H, s, Si Me); δ_c 139.3 (C), 128.2 (Ar-CH), 128.2 (2 x Ar-CH), 127.1 (2 x Ar-CH), 87.7 (3-C), 77.8 (4-C), 77.6 (1-CH), 67.6 (2-CH), 61.5 (7-CH_2), 31.4 (5-CH_2), 25.9 (*t*-Bu Me), 18.3 (C), 15.1 (6-CH_2), -5.3 (Si Me).

(3-(5-Phenylfuran-2-yl)propoxy)(*tert*-butyl)dimethylsilane (127b)



126b **127b**

Using the general procedure (48 h), 10% $AgNO_3.SiO_2$ (2 g, 1.20 mmol) was stirred with a solution of diol **126b** (2 g, 5.98 mmol) in dichloromethane to yield the *furan* **127b** as a pale yellow oil (1.799g, 95%): R_f 0.77 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3335, 3054, 2955, 2857, 1667, 1597, 1548, 1471, 1448, 1389, 1265, 1102, 1017, 974.8, 837, 778, 740, 704; δ_H 7.57 (2H, d, J 7.2, 2 x Ar-H), 7.32-7.26 (2H, m, 2 x Ar-H), 7.14 (1H, t, J 7.3, Ar-H), 6.48 (1H, d, J 3.3, 4-H), 6.00 (1H, d, J 3.3, 3-H), 3.63 (2H, t, J 6.2, 3'-CH_2), 2.70 (2H, t, J 7.6, 1'-CH_2), 1.89-1.80 (2H, m, 2'-CH_2), 0.85 (9H, s, *t*-Bu), 0.00 (6H, s, Si-Me); δ_c 155.8 (C), 152.2 (C), 131.2 (C), 128.6 (2 x Ar-CH), 126.8 (Ar-CH), 123.3 (2 x Ar-CH), 107.1 (4-CH), 105.7 (Ar-CH), 62.2 (3'-CH_2), 31.4 (1'-CH_2), 26.0 (*t*-Bu Me), 24.6 (2'-CH_2), 18.4 (C), -5.2 (Si-Me); *m/z* (EI) 316 [M] 5%, 259 (100), [Found [M], 316.1873. $C_{19}H_{28}O_2Si$ requires *M*, 316.1859].

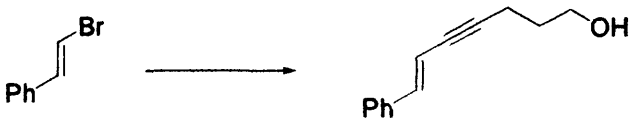
3-(5-Phenylfuran-2-yl)propan-1-ol (117)

127b **117**

Tetrabutylammonium fluoride (15 mL of a 1M solution in THF, 14.7 mmol, 4.4 eq) was added to a solution of furan **127b** (1.1g, 3.35 mmol, 1 eq) in dichloromethane (20 mL). The resulting solution stirred overnight at ambient temperature, then diluted with water (50 mL) and extracted into dichloromethane (3 x 50 mL). The combined organic layers were washed with water (200 mL) and brine (200 mL), then dried, filtered and evaporated to give a brown oil (1.105g), which was purified twice by column chromatography (30:70 ethyl acetate – petroleum ether) to yield the *furan* **117** as a yellow oil (0.166g, 25%) containing an apparent decomposition product: R_f

0.28 (30 : 70 ethyl acetate – petroleum ether): δ_H *furan* 7.54 (2H, d, J 7.2, Ar-H), 7.28-7.24 (2H, m, Ar-H), 7.14 (1H, t, J 7.1, Ar-H), 6.48 (1H, d, J 3.2, 4-H), 6.02 (1H, dt, J 3.2 and 0.8, 3-H), 3.66 (2H, t, J 6.4, 3'-CH_2), 2.72 (2H, t, J 7.4, 1'-CH_2), 1.89 (2H, tt, J 7.4 and 6.4, 2'-CH_2), 1.39 (1H, bs, OH); δ_c *furan* 162.7 (C), 151.1 (C), 142.4 (C), 128.6 (2 x Ar-CH), 126.9 (Ar-CH), 123.4 (2 x Ar-CH), 107.3 (4-CH), 105.7 (3-CH), 62.2 (3'-CH_2), 31.1 (1'-CH_2) and 24.5 (2'-CH_2).

(*E*)- and (*Z*)-7-Phenylhept-6-en-4-yn-1-ol (125b')



125b'

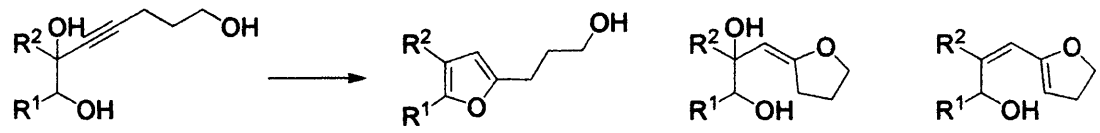
Using the general procedure, 4-pentyn-1-ol (1.45 mL, 15.6 mmol) was added to β-bromostyrene (2 mL, 15.6 mmol) to give the *enyne* **125b'** as a crude red oil (3.12 g), containing a ratio of 96:4 of isomers. Pure sample recovered as a result of purification in the following step (20:80 ethyl acetate – petroleum ether) (0.223g): R_f 0.30 (30 : 70 ethyl acetate – petroleum ether): υ_{max}/cm^{-1} (film) 3350, 3027, 2948, 2211, 1952, 1597, 1492, 1447, 1326, 1179, 1055, 955, 930, 844, 787, 749, 692; δ_H 7.77 (0.08H, d, J 7.4, 2 x Ar-H), 7.31-7.15 (4.92H, m, 8 x Ar-H), 6.80 (0.96H, d, J 16.3, 7-H), 6.50 (0.04H, d, J 11.4, 7-H), 6.07 (0.96H, dt, J 16.3 and 2.3, 6-H), 5.61 (0.04H, dt, J 11.8 and 2.5, 6-H), 3.71 (1.92H, t, J 6.2, 1-CH_2), 3.66 (0.08H, t, J 6.2, 1-CH_2), 2.49 (0.08H, dt, J 6.9 and 2.5, 3-CH_2), 2.43 (1.92H, dt, J 7.0 and 2.3, 3-CH_2), 1.79-1.70 (2H, m, 2-CH_2), 1.65 (0.96H, bs, OH); δ_c *E-isomer* 140.4 (7-CH), 136.4 (C), 128.7 (2 x Ar-CH), 128.4 (Ar-CH), 126.1 (2 x Ar-CH), 108.5 (6-CH), 91.9 (5-C), 80.3 (4-C), 61.8 (1-CH_2), 31.4 (3-CH_2), 16.3 (2-CH_2); δ_c *Z-isomer* 137.2 (7-CH), 135.9 (C) 128.4 (2 x Ar-CH), 128.2 (Ar-CH), 126.1 (2 x Ar-CH), 106.6 (6-CH), 91.9 (5-C), 80.3 (4-C), 61.8 (1-CH_2), 31.3 (3-CH_2), 16.5 (2-CH_2); *m/z* (EI) 186 [M] 40%, 141 (67), [Found [M], 186.1039. $C_{13}H_{14}O$ requires *M*, 186.1045].

(*RS,RS*)-1-Phenylhept-3-yne-1,2,7-triol (116)

125b' **116**

Using the general procedure, enyne **125b'** (1g, 5.37 mmol) was dihydroxylated with potassium osmate(VI) dihydrate (3mg, 10 μmol) to yield a crude mixture (1.629g) containing *diol* **116**, enyne **125b'** and *t*-butanol. The residue was purified by column chromatography (30:70 ethyl acetate – petroleum ether) to yield the *diol* **116** as a yellow oil (0.133g), comprising solely of the *syn-diol* **116**: R_f 0.25 (40 : 60 ethyl acetate – petroleum ether): υ_{max}/cm^{-1} (film) 3419, 2930, 2251, 1640, 1496, 1263, 1143, 1056, 909, 733, 700; δ_H 7.36-7.23 (5H, m, 5 x Ar-H), 4.68 (1H. bs, OH), 4.60 (1H, d, J 7.0, 1-H), 4.32 (1H, dt, J 7.0 and 1.8, 2-H), 3.55 (2H, t, J 6.0, 7-CH_2), 2.20 (2H, dt, J 6.8 and 1.8, 5-CH_2), 1.71 (1H, bs, OH), 1.64-1.56 (2H, m, 2-CH_2), 1.48 (1H, bs, OH); δ_c 139.3 (C), 128.3 (Ar-CH), 128.3 (2 x Ar-CH), 127.1 (2 x Ar-CH), 87.2 (3-C), 77.6 (1-CH), 77.2 (4-C), 67.5 (2-CH), 61.5 (7-CH_2), 30.8 (5-CH_2), 15.3 (6-CH_2); *m/z* (EI) 202 ([M] – H_2O) 5%, 105 (89), 77 (100), [Found ([M]-H_2O), 202.1000. $C_{13}H_{14}O_2$ requires *M-H_2O*, 202.0994].

Cyclisation of (*RS,RS*)-1-phenylhept-3-yne-1,2,7-triol (116)



116 **117** **118** **119**

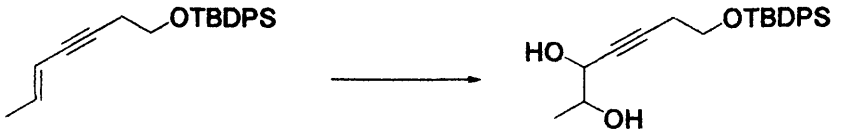
Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.077 g, 0.045 mmol) was stirred with a solution of the *syn*-diol **116** (0.1 g, 0.454 mmol) in dichloromethane to yield a crude mixture of products as a pale yellow oil (0.088g) containing the *furan* **117** (57%), *5-exo diol* **118** (29%) and *dihydrofuran* **119** (24%). Key selected data: δ_H *furan* 6.48 (1H, d, J 3.1, 4-H), 6.03 (1H, d, J 3.1, 3-H), 3.66 (2H, t, J 6.3, 3'-CH_2), 2.73 (2H, t, J 7.2, 1'-CH_2), 1.89 (2H, tt, J 7.2 and 6.3, 2'-CH_2); δ_H *5-exo diol* 6.02 (1H, dd, J 5.8 and 1.7, 3'-H), 5.80 (1H, m, 1'-H), 5.74 (1H, dd, J 5.8 and 2.3, 2'-H); δ_H *dihydrofuran* 6.87 (1H, dd, J 15.8 and 5.1, 2'-H), 6.38 (1H, dd, J 15.8 and 1.7, 1'-H), 6.08 (1H, dd, J 5.1 and 1.7, 3'-H), 5.31 (1H, m, 3-H).

(*E*)-(Hept-5-en-3-ynyloxy)(*tert*-butyl)diphenylsilane (125c)

125c

Using the general procedure, *O*-TBDPS-3-butyn-1-ol (1.7g, 6.01 mmol) was added to (*E*)-1-bromoprop-1-ene (0.5 mL, 6.01 mmol) to give a yellow oil (1.538g), which was purified by column chromatography (10:90 ethyl acetate – petroleum ether) to yield the *enyne* **125c** as a yellow oil (1.258g), containing residual *O*-TBDPS-3-butyn-1-ol. The product **125c** showed: R_f 0.30 (5 : 95 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 2931, 2857, 2327, 1510, 1428, 1112, 813, 765, 702; δ_H *enyne* 7.66-7.52 (4H, m, Ar-H), 7.39-7.22 (6H, m, Ar-H), 5.80 (1H, dq, J 10.7 and 6.8, 6-H), 5.35 (1H, d, J 10.7, 5-H), 3.67 (2H, t, J 6.8, 1-CH_2), 2.41 (2H, t, J 6.8, 2-CH_2), 1.74 (3H, d, J 6.8, 7-Me), 0.97 (9H, s, *t*-Bu); δ_c (125MHz) *enyne* 137.5 (5-CH), 133.7 (C), 135.7 (4 x Ar-CH), 133.5 (C), 129.7 (2 x Ar-CH), 127.8 (4 x Ar-CH), 110.3 (6-CH), 78.3 (4-C), 74.6 (3-C), 62.7 (1-CH_2), 26.9 (*t*-Bu Me), 23.8 (2-CH_2), 19.3 (C), 15.9 (7-Me).

(*RS,RS*)-*O*-(*tert*-Butylphenylsilyloxy)-hept-4-yne-2,3-diol (126c)



125c **126c**

Using the general procedure, crude *enyne* **125c** (1g, 3.12 mmol), containing 0.7g of *O*-TBDPS-3-butyn-1-ol, was dihydroxylated with potassium osmate(VI) dihydrate (2mg, 6 μmol) to give a yellow oil (0.997g), which was purified by column chromatography (20:80 ethyl acetate – petroleum ether) to yield the *diol* **126c** as a yellow oil (0.175g, 54%): R_f 0.29 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3385, 2931, 2342, 1472, 1428, 1390, 1112, 910, 823, 735, 702; δ_H 7.60-7.56 (4H, m, 4 x Ar-H), 7.32-7.24 (6H, m, 6 x Ar-H), 4.16 (1H, dt, J 3.5 and 1.9, 3-H), 3.71 (1H, dq, J 6.4 and 3.5, 2-H), 3.67 (2H, t, J 6.9, 7-CH_2), 2.38 (2H, dt, J 6.9 and 1.9, 6-CH_2), 1.09 (3H, d, J 6.4, 1-Me), 0.96 (9H, s, *t*-Bu Me); δ_c (125MHz) 135.6 (4 x Ar-H), 133.4 (2

x C), 129.8 (2 x Ar-CH), 127.8 (4 x Ar-CH), 84.8 (4-C), 78.6 (5-C), 70.3 (3-CH), 67.3 (2-CH), 62.3 (7-CH_2), 26.8 (*t*-Bu Me), 22.9 (6-CH_2), 19.2 (1-Me), 18.3 (C).

(3-(5-Methylfuran-2-yl)ethoxy)(*tert*-butyl)diphenylsilane (127c)

126c **127c**

Using the general procedure (48 h), 10% $AgNO_3.SiO_2$ (0.088g, 0.052 mmol, 0.2 eq) was stirred with a solution of diol **126c** (0.1g, 0.261 mmol) in dichloromethane to yield the *furan* **127c** as a yellow oil (0.093g, 98%): δ_H 7.58-7.53 (4H, m, 4 x Ar-H), 7.38-7.26 (6H, m, 6 x Ar-H), 5.84 (1H, d, J 2.8, 4-H), 5.77 (1H, d, J 2.8, 3-H), 3.80 (2H, t, J 6.8, 2'-CH_2), 2.77 (2H, t, J 6.8, 1'-CH_2), 2.16 (3H, s, 5-Me), 0.95 (9H, s, *t*-Bu Me); δ_c (125MHz) 151.4 (C), 150.4 (C), 135.6 (4 x Ar-CH), 133.8 (2 x C), 129.6 (2 x Ar-CH), 127.6 (4 x Ar-CH), 106.9 (4-CH), 105.9 (3-CH), 62.6 (2'-CH_2), 31.7 (1'-CH_2), 26.8 (*t*-Bu Me), 19.2 (C), 13.5 (5-Me).

2-(5-methylfuran-2-yl)ethanol (127c')

127c **127c'**

Furan **127c** (0.093g, 0.250 mmol, 1 eq) was dissolved in THF (10 mL). TBAF (1.3 mL of a 1M solution in THF, 1.20 mmol, 4.8 eq) was added and the resulting solution stirred overnight, then poured into a mixture of dichloromethane (25 mL) and water (25 mL). The separated aqueous layer was extracted with dichloromethane (2 x 25 mL) and the combined organic layers washed with water (100 mL), then dried, filtered and evaporated to give a yellow oil (0.109g), which was purified by column chromatography (20:80 ethyl acetate – petroleum ether) to yield the *furan* **127c'** as a yellow oil (0.004g, 12%): R_f 0.39 (20 : 80 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3413, 2925, 1646, 1046, 909, 733; δ_H 5.91 (1H, d, J 2.8, 4-H), 5.81 (1H, d, J 2.8, 3-H), 3.78 (2H, t, J 6.2, 2'-CH_2), 2.78 (2H, t, J 6.2, 1'-CH_2), 2.19 (3H, s, 5-Me), 1.69 (1H, bs, OH); δ_c

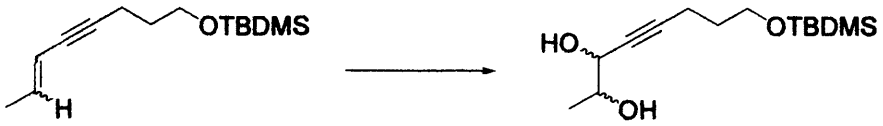
151.2 (C), 151.1 (C), 107.3 (4-CH), 106.1 (3-CH), 61.2 (2'-CH_2), 31.7 (1'-CH_2), 13.6 (5-Me); *m/z* (EI) 126 [M] 22%, 95 (100), [Found [M], 126.0683. $C_7H_{10}O_2$ requires *M*, 126.0681].

(*E*)- and (*Z*)-Oct-6-en-4-ynyloxy)(*tert*-butyl)dimethylsilane (125d)

125d

Using the general procedure, *O*-TBDMS-4-pentyn-1-ol (1.64g, 8.27 mmol) was added to 1-bromoprop-1-ene (1g, 8.27 mmol) to give a yellow solid (1.207g), containing a ratio of 77:23 of the *trans* : *cis* isomers. This mixture was then purified by column chromatography to yield the *enyne* **125d** as a pale yellow oil (0.123g, 6%), containing a ratio of 69:31 of the *trans* : *cis* isomers: υ_{max}/cm^{-1} (film) 2954, 2929, 2857, 2206, 1673, 1471, 1388, 1255, 1106, 972, 837, 777, 735; δ_H 5.99 (0.69H, dq, J 15.7 and 6.7, 2-CH), 5.83 (0.31H, dq, J 10.6 and 6.8, 2-CH), 5.40 (1H, *app.* doubled hextet, J 15.7 and 1.8, 3-CH), 3.66 (0.62H, t, J 6.0, 8-CH_2), 3.64 (1.38H, t, J 6.0, 8-CH_2), 2.38 (0.62H, dt, J 7.0 and 2.0, 6-CH_2), 2.31 (1.38H, dt, J 7.0 and 1.8, 6-CH_2), 1.79 (0.93H, dd, J 6.8 and 1.6, 1-Me), 1.70 (2.07H, dd, J 6.7 and 1.8, 1-Me), 1.71-1.61 (2H, m, 7-CH_2), 0.84 (9H, s, *t*-Bu), 0.00 (6H, s, Si-Me); δ_c *trans* 138.1 (3-CH), 111.0 (2-CH), 88.0 (4-C), 79.3 (5-C), 61.7 (8-CH_2), 31.8 (6-CH_2), 26.0 (*t*-Bu-Me), 18.5 (1-Me), 18.4 (C), 15.7 (7-CH_2), -5.3 (Si-Me); δ_c *cis* 137.0 (3-CH), 110.3 (2-CH), 94.4 (4-C), 88.0 (5-C), 61.7 (8-CH_2), 31.9 (6-CH_2), 26.0 (*t*-Bu Me), 18.5 (1-Me), 18.4 (C), 16.0 (7-CH_2), -5.3 (Si-Me).

(*RS*,*RS*)- and (*RS*,*SR*)-8-((*tert*-Butyl)dimethylsilyloxy)-oct-4-yne-2,3-diol (126d)

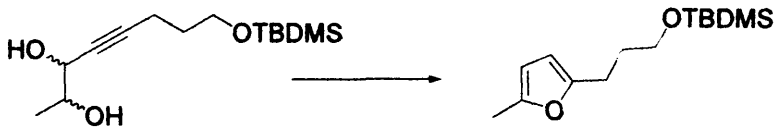


125d **126d**

Using the general procedure, *enyne* **125d** (0.1g, 0.42 mmol) was dihydroxylated with potassium osmate (VI) dihydrate (2mg, 6 μmol) to give the *diol* **126d** as a yellow oil (0.109g, 96%), containing a ratio of 69:31 of diastereoisomers: υ_{max}/cm^{-1} (film) 3375, 2928, 2857, 2233, 1576,

1471, 1362, 1326, 1255, 1154, 1106, 975, 837, 777, 738, 662; δ_H 4.23 (0.31H, d, J 3.5, 3-H), 4.03 (0.69H, dt, J 6.9 and 1.8, 3-H), 3.79 (0.31H, dq, J 6.2 and 3.5, 2-H), 3.71 (0.69H, *app.* quintet, 2-H), 3.63 (0.62H, t, J 6.0, 8-CH_2), 3.62 (1.38H, t, J 6.0, 8-CH_2), 2.31-2.22 (0.62H, m, 6-CH_2), 2.26 (1.38H, dt, J 7.2 and 1.8, 6-CH_2), 1.70-1.61 (2H, m, 7-CH_2), 1.21 (2.07H, d, J 6.2, 1-Me), 1.20 (0.93H, d, J 6.2, 1-Me), 0.84 (9H, s, *t*-Bu), 0.00 (6H, s, Si-Me); δ_c *syn* 77.2 (4-C), 74.9 (5-C), 71.4 (3-CH), 67.7 (2-CH), 61.5 (8-CH_2), 43.5 (1-Me), 31.5 (6-CH_2), 26.0 (*t*-Bu Me), 18.5 (C), 15.1 (7-CH_2), -5.3 (Si-Me), δ_c *anti* 76.8 (4-C), 73.6 (5-C), 70.4 (3-CH), 67.3 (2-CH), 61.6 (8-CH_2), 43.6 (1-Me), 31.6 (6-CH_2), 26.0 (*t*-Bu Me), 18.4 (C), 15.2 (7-CH_2), -5.3 (Si-Me); *m/z* (EI) 141 ([M] - TBDMS - H_2O) 46%, 169 (99), 95 (52), 75 (100).

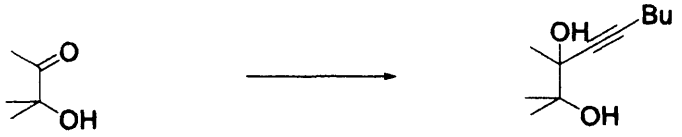
(3-(5-Methylfuran-2-yl)propoxy)(*tert*-butyl)dimethylsilane (127d)



126d **127d**

Using the general procedure (48 h), 10% $AgNO_3.SiO_2$ (0.062g, 0.037 mmol) was stirred with a solution of diol **126d** (0.1g, 0.367 mmol) in dichloromethane to yield the *furan* **127d** as a pale yellow oil (0.087g, 94%): υ_{max}/cm^{-1} (film) 2927, 2856, 1571, 1463, 1362, 1255, 1103, 1020, 965, 910,837, 777, 735; δ_H 5.80 (2H, bs, 3- and 4-H), 3.60 (2H, t, J 6.3, 3'-CH_2), 2.59 (2H, t, J 7.6, 1'-CH_2), 2.20 (3H, s, 5-Me), 1.78 (2H, m, 2'-CH_2), 0.85 (9H, s, *t*-Bu), 0.00 (6H, s, Si-Me); δ_c 154.2 (C), 150.2 (C), 105.8 (4-CH), 105.3 (3-CH), 62.3 (3'-CH_2), 31.2 (1'-CH_2), 26.0 (*t*-Bu Me), 24.4 (2'-CH_2), 18.4 (C), 13.5 (5-Me), -5.3 (Si-Me).

2,3-Dimethylnon-4-yne-2,3-diol (156)

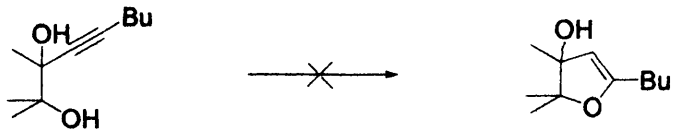


156

Using the general procedure, 1-hexyne (0.5 mL, 4.31 mmol) was added to 3-hydroxy-3-methylbutan-2-one (0.21 mL, 1.96 mmol) to give the *diol* **156** as a clear oil (0.194g, 53%):

υ_{max}/cm^{-1} (film) 3434, 2935, 2873, 2245, 1639, 1460, 1370, 1266, 1083, 959, 915, 851, 794, 735; δ_H 2.49 (1H, s, OH), 2.15 (2H, t, J 7.0, 6-CH_2), 1.97 (1H, s, OH), 1.48-1.30 (4H, m, 7- and 8-CH_2), 1.37 (3H, s, 2-Me), 1.30 (3H, s, 1-Me), 1.20 (3H, s, 3-Me), 0.84 (3H, t, J 7.2, 9-Me); δ_c 85.5 (4-C), 82.2 (5-C), 75.3 (3-C), 74.1 (2-C), 30.7 (6-CH_2), 25.7 (1-Me), 24.5 (2-Me), 22.7 (3-Me), 22.0 (7-CH_2), 18.3 (8-CH_2), 13.6 (9-Me), *m/z* (EI) 184 [M] 100%.

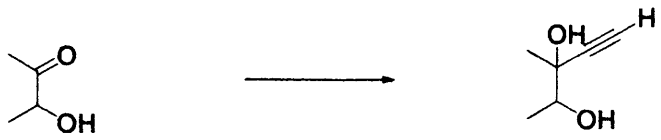
Attempted cyclisation of 2,3-dimethylnon-4-yne-2,3-diol (156)



156 **157**

Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.184g, 0.11 mmol) was stirred a solution of diol **157** (0.1g, 0.54 mmol) in dichloromethane to yield an unidentified product.

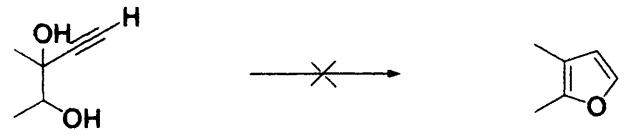
(*RS*,*RS*)- and (*RS*,*SR*)- 3-Methylpent-4-yne-2,3-diol (142a)



142a

Using the general procedure, TMS-acetylene (0.7 mL, 4.99 mmol) was added to 3-hydroxybutan-2-one (0.2g, 2.27 mmol) to give the *diol* **142a** as a pale yellow oil (0.074g). The residue was purified by column chromatography (20:80 ethyl acetate – petroleum ether) to yield the *diol* **142a** as a clear oil (0.027g, 11%), containing a ratio of 69:31 of diastereoisomers: υ_{max}/cm^{-1} (film) 3350, 3297, 2985, 2359, 1640, 1450, 1375, 1069, 1009, 935, 874; δ_H 3.77 (0.69H, q, J 6.2, 2-H), 3.57 (0.31H, *app. quintet*, J 6.0, 2-H), 3.22 (0.69H, bs, OH), 2.84 (0.69H, bs, OH), 2.72 (0.31H, bs, OH), 2.44 (1H, s, 5-H), 2.40 (0.31H, bs, OH), 1.37 (0.93H, s, 3-Me), 1.36 (2.07H, s, 3-Me), 1.24 (0.93H, d, J 6.4, 1-Me), 1.17 (2.07H, d, J 6.2, 1-Me); δ_c *major and minor* 86.2 (5-CH), 84.6 (5-CH), 74.2 (2-CH), 73.4 (2-CH), 72.8 (4- and 3-C), 71.8 (3-C), 70.8 (4-C), 25.6 (3-Me), 23.1 (3-Me), 18.3 (1-Me), 16.6 (1-Me).

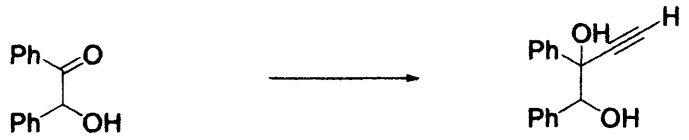
Attempted cyclisation of 3-methylpent-4-yne-2,3-diol (142a)



142a **407**

Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.7g, 0.45 mmol) was stirred a solution of diol **157** (0.1g, 0.90 mmol) in dichloromethane. Starting material was recovered.

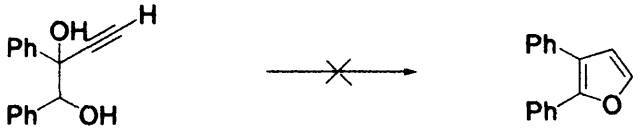
(*RS*,*RS*)-1,2-Diphenylbut-3-yne-1,2-diol (142b)[18]



142b

Using the general procedure, TMS-acetylene (0.72 mL, 5.18 mmol) was added to benzoin (0.5g, 2.36 mmol) to give the *diol* **142b** as a yellow solid (0.673g), which was purified by column chromatography (20:80 ethyl acetate – petroleum ether) to yield the *diol* **142b** as a yellow solid (0.235g, 42%, mp 114-115 °C) and as an apparent single diastereoisomer: υ_{max}/cm^{-1} (DCM) 3435, 3326, 3055, 2962, 2137, 1641, 1494, 1450, 1421, 1265, 1192, 1089, 1053, 846, 738; δ_H 7.24-7.18 (2H, m, 2 x Ar-H), 7.10-6.92 (8H, m, 8 x Ar-H), 5.65 (1H, d, J 2.9, 1-H), 2.55 (1H, s, 4-H), 2.46 (1H, d, J 2.9, OH), 1.34 (1H, s, OH); δ_c 139.8 (C), 137.9 (C), 132.3(2 x Ar-CH), 128.9 (Ar-CH), 128.7 (Ar-CH), 128.7 (2 x Ar-CH), 127.7 (2 x Ar-CH), 127.0 (2 x Ar-CH), 84.7 (3-C), 80.8 (4-CH), 76.3 (2-C), 76.1 (1-CH); *m/z* (APCI) 239 $(M+H)^+$ 100%. All data obtained matched that previously reported in the literature.

Attempted cyclisation of 1,2-diphenylbut-3-yne-1,2-diol (142b)



142b **408**

Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.142g, 0.08 mmol) was stirred a solution of diol **157** (0.1g, 0.42 mmol) in dichloromethane. Starting material was recovered.

2-Acetoxysuccinicanhydride (133)[209]

133

Racemic malic acid (10g, 75 mmol) was dissolved in acetyl chloride (37 mL) and the resulting solution heated to 40°C for 2 h, then, using a water pump, acetic acid and any excess acetyl chloride were removed under reduced pressure. The viscous residue obtained was recrystallised from ethanol-free chloroform to yield *2-acetxoysuccinic anhydride* **133** (10.686g, 91%, mp = 55-57 °C (lit. mp. (S) = 54-56 °C[209]; (R) = 56-58 °C[209])): δ_H 5.47 (1H, dd, J 9.6, 6.4, 2-H), 3.32 (1H, dd, J 18.9 and 9.6, 3-H_a), 2.97 (1H, dd, J 18.9 and 6.4, 3-H_b), 2.13 (3H, s, Me). All data obtained matched that previously reported in the literature.

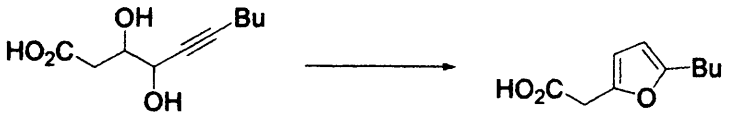
(*RS*,*RS*)- and (*RS*,*SR*)-3,4-Dihydroxydec-5-ynoic acid (135a)

133 **135a**

n-BuLi (2.5 mL of a 2.5M solution in hexanes, 6.32 mmol, 1 eq) was added dropwise to a solution of 1-hexyne (0.72 mL, 6.32 mmol, 1 eq) in THF (10 mL) and maintained at -78°C. The solution was stirred for 0.5 h before being transferred dropwise to a second flask containing a stirred solution of 2-acetoxysuccinic anhydride **133** (1.00 g, 6.32 mmol, 1 eq) in THF (10 mL), which was also maintained at -78 °C. After stirring for 0.5 h, sodium borohydride (0.25 g) in ethanol (5 mL) was added to the solution which was then stirred for a further 0.25 h. Aqueous 1M sodium hydroxide (6 mL) was added and the solution warmed to 0 °C. After stirring for 1 h, sufficient 2M hydrochloric acid was added carefully to acidify the solution to pH 4. The product

was extracted with ethyl acetate (3 x 25 mL) and the combined organic layers washed with water (50 mL) and brine (50 mL) then dried, filtered and evaporated to yield a yellow wax, the *diol* **135a** (0.73g, 58%), which was of suitable quality for all proceeding transformations and contained a mixture of two diastereomers in a 51:49 ratio. Recrystallisation of a small portion (0.1 g) from methanol yielded pure *diol* **135a** as a colourless solid (0.09g): R_f 0.10 (40 : 60 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (nujol) 3422, 2962, 2930, 2864, 2234, 1710, 1460, 1420, 1398, 1318, 1266, 1156, 1062, 1020, 972, 932, 736, 700; δ_H 5.06 (0.49H, dt, J 4.0 and 2.0, 4-H), 4.95 (0.51H, dt, J 3.4 and 1.8, 4-H), 4.48 (0.51H, ddd, J 5.7, 3.4 and 1.7, 3-H), 4.41 (0.49H, ddd, J 5.3, 4.0 and 2.2, 3-H), 2.86 (0.51H, dd, J 17.8 and 5.7, 2-H_a), 2.66 (0.49H, dd, J 17.7 and 5.3, 2-H_a), 2.58 (0.49H, dd, J 17.7 and 2.2, 2-H_b), 2.45 (0.51H, dd, J 17.8 and 1.7, 2-H_b), 2.25 (0.98H, dt, J 7.1 and 2.0, 7-CH_2), 2.15 (1.02H, dt, J 7.0 and 1.8, 7-CH_2), 1.55-1.25 (4H, m, 8- and 9-CH_2), 0.89-0.81 (3H, m, 10-Me); δ_c *major* 176.6 (C), 90.7 (5-C), 77.5 (4-CH), 73.9 (6-C), 73.5 (3-CH), 36.9 (2-CH_2), 30.2 (7-CH_2), 21.9 (8-CH_2), 18.4 (9-CH_2), 13.6 (10-Me); δ_c *minor* 174.6 (C) 93.7 (5-C), 75.3 (4-CH), 71.1 (6-C), 68.5 (3-CH), 37.2 (2-CH_2), 30.5 (7-CH_2), 22.0 (8-CH_2), 18.4 (9-CH_2), 13.6 (10-Me); *m/z* (EI) 182 ([M] - H_2O) <1%, 111 (100) [Found ([M]-H_2O), 182.0948. $C_{10}H_{14}O_3$ requires *M-H_2O*, 182.0943].

2-(5-Butylfuran-2-yl)acetic acid (136a)



135a **136a**

Using the general procedure (4 h), 10% $AgNO_3.SiO_2$ (0.21g, 0.125 mmol) was stirred with a solution of diol **135a** (0.05g, 0.25 mmol) in dichloromethane to yield the *furan* **136a** as an orange oil (0.044g, 96%): υ_{max}/cm^{-1} (film) 3422, 2960, 2873, 1716, 1566, 1466, 1420, 1232, 1015, 906, 733, 650; δ_H 6.06 (1H, d, J 3.0, 3-H), 5.85 (1H, d, J 3.0, 4-H), 3.62 (2H, s, 1'-CH_2), 2.52 (2H, t, J 7.6, 1''-CH_2), 1.58-1.48 (2H, m, 2''-CH_2), 1.36-1.24 (2H, m, 3''-CH_2), 0.85 (3H, t, J 7.3, 4''-Me); δ_c 175.6 (C), 156.5 (C), 144.8 (C), 108.9 (3-CH), 105.5 (4-CH), 33.9 (1'-CH_2), 30.1 (1''-CH_2), 27.7 (2''-CH_2), 22.3 (3''-CH_2) and 13.8 (4''-Me); *m/z* (EI) 182 [M] 50%, 137 (100), [Found [M], 182.0946. $C_{10}H_{14}O_3$ requires *M*, 182.0943].

(*RS,SR*)-3,4-Dihydroxy-6-phenylhex-5-ynoic acid (135b)[71]

133 **135b**

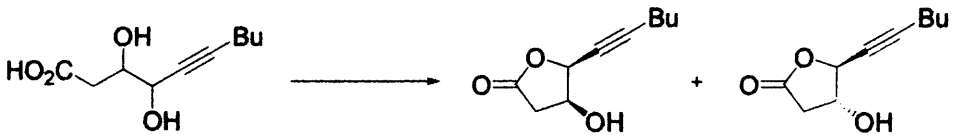
n-BuLi (2.5mL of a 2.5M solution in hexanes, 6.32 mmol, 1 eq) was added dropwise to a solution of phenylacetylene (0.7 mL, 6.32 mmol, 1 eq) in THF (10 mL) maintained at -78 °C. The solution was stirred for 0.5 h before being transferred dropwise to a second flask containing a stirred solution of 2-acetoxysuccinic anhydride **133** (1 g, 6.32 mmol, 1 eq) in THF (10 mL), which was also maintained at -78°C. After stirring for 0.5 h, sodium borohydride (0.25 g) in ethanol (5 mL) was added and stirring continued for a further 0.25 h. Aqueous 1M sodium hydroxide (6 mL) was added and the solution warmed to 0 °C. After stirring for 1 h, sufficient 2M hydrochloric acid was added carefully to acidify the solution to pH 4. The product was extracted with ethyl acetate (3 x 25 mL) and the combined organic layers washed with water (50 mL) and brine (50 mL) then dried, filtered and evaporated to yield the *diol* **135b** (0.216 g) as a mixture of diastereomers in a 1:2 ratio. The product was recrystallised from chloroform to yield the *diol* **135b** as a yellow solid (0.216g, 16%, mp =103-105 °C), which contained a single diastereoisomer: R_f 0.10 (0 : 60 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (nujol) 3409, 1703, 1490, 1176, 1101, 1039; δ_H (MeOD) 7.37-7.34 (2H, m, 2 x Ar-H), 7.27-7.20 (3H, m, 3 x Ar-H), 4.41 (1H, d, J 4.9, 4-H), 4.05 (1H, ddd, J 9.0, 4.9 and 3.8, 3-H), 2.67 (1H, dd, J 15.7 and 3.8, 2-H_a), 2.42 (1H, dd, J 15.7 and 9.0, 2-H_b); δ_c (125MHz) (MeOD) 178.1 (C), 135.2 (Ar-CH), 132.1 (Ar-CH), 132.0 (Ar-CH), 126.7 (C), 91.3 (6-C), 89.1 (5-C), 75.0 (4-CH), 69.0 (3-CH), 41.2 (2-CH_2); *m/z* (APCI) 243 $[M+Na]^+$ 100%, 221(15), [Found $[M+Na]^+$, 243.0644. $C_{12}H_{12}O_4Na$ requires *M+Na*, 243.0633]. All data obtained matched that previously reported in the literature.

2-(5-Phenylfuran-2-yl)acetic acid [210] **(136b)**

135b **136b**

Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.012g, 0.007 mmol) was stirred with a solution of diol **135b** (0.015g, 0.25 mmol), as a 2:1 mixture of diastereoisomers, in dichloromethane to yield the *furan* **136b** as a colourless solid (0.013g, 93%, mp = 78-79°C): R_f 0.35 (30 : 70 ethyl acetate – petroleum ether); δ_H (MeOD) 7.57 (2H, d, J 8.3, 2 x Ar-H), 7.31-7.25 (2H, m, 2 x Ar-H), 7.17 (1H, tt, J 7.4 and 1.1, Ar-H), 6.53 (1H, d, J 3.3, 4-H), 6.27 (1H, d, J 3.3, 3-H), 3.74 (2H, s, 1'-CH_2); δ_c (125MHz) (MeOD)179.1 (C), 153.8 (C), 146.6 (C), 130.7 (C), 128.6 (2 x Ar-CH), 127.3 (Ar-CH), 123.7 (2 x Ar-CH), 110.6 (4-CH), 106.0 (3-CH), 30.9 (1'-CH_2); *m/z* (APCI) 203 $[M+H]^+$ 100%, 157(37), [Found $[M+H]^+$, 203.0714. $C_{12}H_{11}O_3$ requires *M+H*, 203.0708]. All data obtained matched that previously reported in the literature.

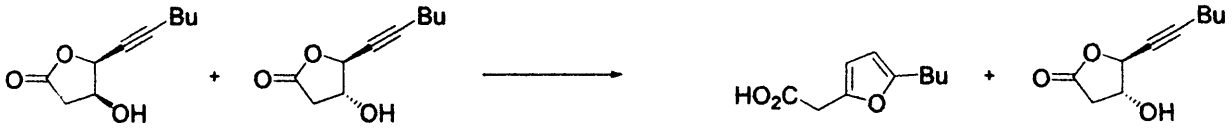
(*RS,RS*)- and (*RS,SR*)-5-(Hex-1-ynyl)-dihydro-4-hydroxyfuran-2(3H)-one (138 and 140)



135a **138** **140**

In a dry flask, diol **135a** (0.1 g, 0.5 mmol, 1 eq) and *para*-toluenesulfonic acid (few crystals) were dissolved in toluene (10 mL) at ambient temperature and the resulting solution warmed to 50°C for 1.5 h. Upon cooling, pyridine (2.25 mL) was added and the mixture then washed with saturated copper sulfate (25 mL), water (25 mL) and brine (25 mL) then dried, filtered and evaporated to yield the *lactones* **138** and **140** (0.063g, 69%) as a colourless oil, in a ratio of 51:49: υ_{max}/cm^{-1} (film) 3434, 1787, 1642, 1156; δ_H 5.05 (0.51H, dt, J 4.0 and 2.0, 5-H), 4.92 (0.49H, dt, J 2.0 and 1.9, 5-H), 4.49 (0.49H, *app.* dt, J 5.8 and 1.9, 4-H), 4.40 (0.51H, ddd, J 5.1, 4.0 and 2.4, 4-H), 2.87 (0.49H, dd, J 17.7 and 5.8, 3-H_a), 2.65 (0.51H, dd, J 17.6 and 5.1, 3-H_a), 2.58 (0.51H, dd, J 17.6 and 2.4, 3-H_b), 2.42 (0.49H, dd, J 17.7 and 1.9, 3-H_b), 2.25 (1.02H, dt, J 7.1 and 2.0, 1'-CH_2), 2.16 (0.98H, dt, J 7.0 and 2.0, 1'-CH_2), 1.55-1.25 (4H, m, 2'- and 3'-CH_2), 0.86 (1.53H, t, J 7.4, 4'-Me), 0.84 (1.47H, t, J 7.4, 4'-Me); δ_c *major* and *minor* 174.9 (C), 90.7 (1'-C), 80.0 (2'-C), 77.3 (5-CH), 73.6 (4-CH), 36.9 (3-CH_2), 30.2 (3'-CH_2), 21.9 (4'-CH_2), 18.4 (5'-CH_2) and 13.6 (6-Me).

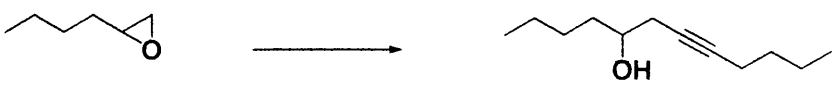
2-(5-Butylfuran-2-yl)acetic acid (136a and 140)



138 **140** **136a** **140**

Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.233g, 0.137 mmol) was stirred with a solution of lactones **138** and **140** (0.05g, 0.274 mmol) in dichloromethane to yield a 1:1 mixture of *furan* **136a** and uncyclised (*RS,SR*) isomer **140**, as an orange oil (0.042g, *ca.* 84%): The data obtained was identical to the respective preparations detailed above.

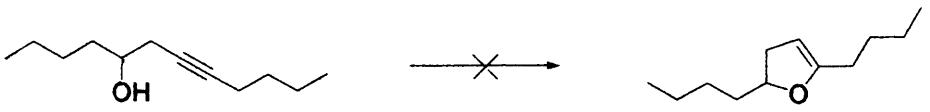
Dodec-7-yn-5-ol (152)



152

n-BuLi (4.43 mL, 11.1 mmol of a 2.5M solution in hexanes) was added dropwise to a solution of 1-hexyne (1.27 mL, 11.1 mmol) dissolved in THF (10 mL) maintained at -78 °C. After stirring for 15 mins, boron trifluoride-THF complex (1.28 mL, 11.6 mmol) was added slowly and the solution stirred for a further 15 mins. The solution was then transferred dropwise to a second flask containing 1,2-epoxyhexane (1 mL, 8.31 mmol) dissolved in THF (10 mL), which was also maintained at -78°C. After 3 h at this temperature, saturated aqueous ammonium chloride (20 mL) was added and the resulting mixture allowed to warm to ambient temperature. The product was extracted into ethyl acetate (3 x 50 mL) and the combined organic layers washed with water (75 mL) and brine (75 mL), then dried, filtered and evaporated to give the *β-hydroxy-alkyne* **152** (1.458g, 97%), as a pale yellow oil: δ_H 3.62 (1H, ddt, J 12.7, 6.8 and 4.5, 5-H), 2.34 (1H, ddt, J 16.5, 4.5 and 2.4, 6-H_a), 2.20 (1H, ddt, J 16.5, 6.8 and 2.4, 6-H_b), 2.11 (2H, tt, J 6.9 and 2.4, 9-CH_2), 1.50-1.20 (10H, m, 2-, 3-, 4-, 10- and 11-CH_2), 0.87-0.81 (6H, m, 1- and 12-Me); *m/z* (EI) 164 ([M] - H_2O) 100%. All data obtained matched that previously reported in the literature.

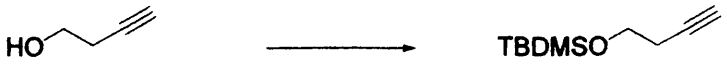
Attempted cyclisation of alkynol (152)



152 **153**

Using the general procedure (3 h), 10% $AgNO_3.SiO_2$ (0.466g, 0.27 mmol) was stirred with a solution of the β-hydroxy alkyne **152** (0.1g, 0.55 mmol) in dichloromethane. Unreacted *β-hydroxy alkyne* **152** (0.097g, 97%) was recovered as a pale yellow oil.

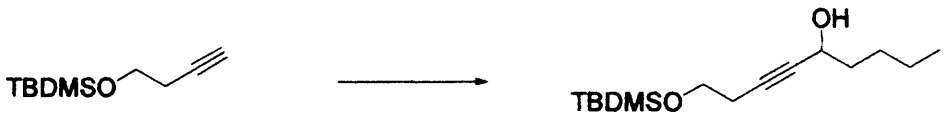
***tert*-Butyl(but-3-ynyloxy)dimethylsilane (159)**



159

t-Butyldimethylsilyl chloride (3.98g, 26 mmol), imidazole (3.60g, 53 mmol) and DMAP (0.161g, 1.3 mmol) were added to a solution of 3-butyn-1-ol (1 mL, 13 mmol) in dry dichloromethane (20 mL). The resulting solution was then stirred at ambient temperature overnight before being transferred to a separating funnel containing saturated aqueous sodium hydrogen carbonate (20 mL) and petroleum ether (20 mL). The mixture was shaken and separated and the aqueous layer extracted with petroleum ether (2 x 20 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), then dried, filtered and evaporated to yield *O-TBDMS-3-butyn-1-ol* **159** (2.39g, 98%), as a colourless oil: δ_H 3.67 (2H, t, J 7.2, 1-CH_2), 2.33 (2H, dt, J 7.2 and 2.8, 2-CH_2), 1.89 (1H, t, J 2.8, 4-H), 0.82 (9H, s, *t*-Bu Me), 0.00 (6H, s, Si-Me); δ_c 81.5 (3-C), 69.3 (1-CH_2), 61.7 (4-CH), 25.9 (*t*-Bu Me), 22.9 (2-CH_2), 18.4 (C), -5.1 (Si-Me); *m/z* (EI) 184 [M] 87%, 69 (100). All data obtained matched that previously reported in the literature.

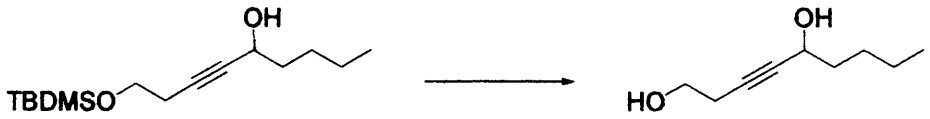
tert-Butyl(5-hydroxynon-3-ynyloxy)dimethylsilane (160)[211]



159 **160**

n-BuLi (2.17 mL, 5.42 mmol of a 2.5M solution in hexanes) was added dropwise to a solution of *O*-TBDMS-3-butyn-1-ol **159** (1g, 5.42 mmol) in THF (10 mL) maintained at -78 °C. The solution was stirred for 0.5 h before being transferred dropwise to a second flask containing pentanal (0.58 mL, 5.42 mmol) dissolved in THF (10 mL), which was also maintained at -78°C. After overnight stirring, with slow warming to ambient temperature, the mixture was quenched with the addition of aqueous KH_2PO_4 pH 7 buffer (10 mL). The product was extracted with diethyl ether (3 x 25 mL) and the combined organic layers washed with water (50 mL) then brine (50 mL). The ether layer was then dried, filtered and evaporated to give *propargylic alcohol* **160** (1.17g, 80%), as a pale yellow oil: δ_H 4.27 (1H, tt, J 6.4 and 1.9, 5-H), 3.64 (2H, t, J 7.3, 1-CH_2), 2.36 (2H, dt, J 7.3 and 1.9, 2-CH_2), 1.67-1.52 (2H, m, 6-CH_2), 1.40-1.20 (4H, m, 7- and 8-CH_2), 0.84 (3H, t, J 7.2, 9-Me), 0.82 (9H, s, *t*-Bu Me), 0.00 (6H, s, Si Me); δ_c 82.5 (3-C), 69.3 (4-C), 62.6 (5-CH), 61.9 (1-CH_2), 37.8 (2-CH_2), 27.4 (6-CH_2), 25.9 (*t*-Bu Me), 23.1 (7-CH_2), 22.4 (8-CH_2), 18.3 (C), 14.0 (9-Me), -5.3 (Si-Me). All data obtained matched that previously reported in the literature.

Non-3-yne-1,5-diol (161)

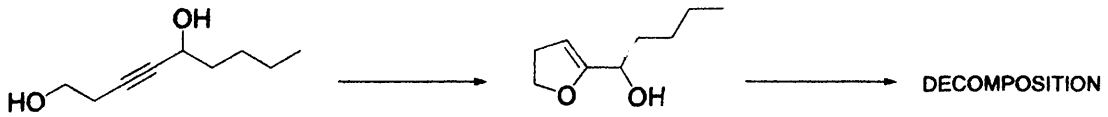


160 **161**

Tetrabutylammonium fluoride (4.07 mL of a 1M solution in THF, 4.07 mmol) was added to a solution of propargylic alcohol **160** (0.25g, 0.924 mmol) in tetrahydrofuran (10 mL) and the resulting solution stirred overnight at ambient temperature. The mixture was diluted with water (25 mL) then extracted with diethyl ether (3 x 25 mL). The combined organic layers were washed with water (150 mL) and brine (150mL) then dried, filtered and evaporated to give the

diol **161** as a colourless oil (0.126g, 88%): δ_H 4.27 (1H, dt, J 6.6 and 1.8, 5-H), 3.63 (2H, t, J 6.2, 1-CH_2), 2.40 (2H, dd, J 6.2 and 1.8, 2-CH_2), 1.65-1.52 (2H, m, 6-CH_2), 1.37-1.13 (4H, m, 7- and 8-CH_2), 0.82 (3H, t, J 7.2, 9-Me). All data obtained matched that previously reported in the literature.

1-(4,5-Dihydrofuran-2-yl)pentan-1-ol (162)[76]



161 **162**

In a foil wrapped NMR tube, 10% w/w $AgNO_3$ on silica gel (0.033g, 0.019 mmol) was added to a solution of diol **161** (0.015g, 0.096 mmol) in deuteriochloroform (1 mL), and the resulting suspension monitored over a period of 24 h with occasional shaking. The solution was analysed by ^{1}H NMR spectroscopy periodically to show the formation of *dihydrofuran* **162** (33%) in the presence of diol **161**, followed by decomposition. The *dihydrofuran* **162** was identified by δ_H *dihydrofuran* 4.74 (1H, t, J 2.5, 3-H), 4.10-4.04 (1H, m, 1'-H), 3.61-3.54 (2H, m, 5-CH_aH_b), 2.57 (1H, ddd, J 12.0, 9.3, and 1.2, 4-H_a), 2.55 (1H, ddd, J 12.0, 9.5 and 1.0, 4-H_b), 1.64-1.55 (2H, m, 2'-CH_2), 1.35-1.20 (4H, m, 3'- and 4'-CH_2), 0.88 (3H, t, J 7.4, 5'-Me).

Amino alcohol protection

Triethylamine (6 - 88 mmol, 1.1eq) was added slowly to a solution of an amino-alcohol (5 - 80 mmol, 1 eq) dissolved in dichloromethane (10 mL g^{-1}) at 0 °C. After stirring for 0.5 h, DMAP (few crystals) and the desired protecting group precursor (6 - 88 mmol, 1.1 eq) were added and the solution left to stir overnight at ambient temperature. The resultant mixture was neutralized with aqueous 2M hydrochloric acid and the product extracted into dichloromethane (3 x 25 mL g^{-1}). The combined organic layers were washed with water (1 x 50 mL g^{-1}) and brine (1 x 50 mL g^{-1}) then dried, filtered and evaporated, with any excess protecting group being removed through column chromatography when necessary, to give the protected amino alcohol.

General procedure for the synthesis of pyrroles

Protected amino-alcohol oxidation

A protected amino-alcohol (2 – 5 mmol, 1 eq) was dissolved in dichloromethane (10 mL g^{-1}) containing 4 Å molecular sieves (0.1 g ml^{-1}). Upon cooling to 0 °C, sodium acetate (0.6 – 1.4 mmol, 0.3 eq) and PCC (3 – 7.2 mmol, 1.5 eq) were added and the resulting mixture left to stir at ambient temperature overnight. The metal content was then removed by filtration through silica gel, using dichloromethane (100-250 mL) to wash through the organic product, and the filtrate was then evaporated to yield the protected-α-aminocarbonyl.

Alkyne addition onto a 4-nosyl or tosyl protected-α-aminocarbonyl

n-BuLi (1 – 3.6 mmol of a 2.5M solution in hexanes, 2.2 eq) was added dropwise to a solution of a 1-alkyne (1 – 3.6 mmol, 2.2eq) in THF (10 mL g^{-1}) maintained at -78 °C. The solution was stirred for 0.5 h before being transferred dropwise to a second flask containing a protected-α-aminocarbonyl (0.4 – 1.6 mmol, 1 eq) dissolved in THF (10 mL g^{-1}), which was also maintained at -78 °C for the first 3 h. After overnight stirring at ambient temperature, the mixture was quenched with the dropwise addition of aqueous 0.1M KH_2PO_4 pH 7 buffer, and any emulsion broken up by the addition of 2M hydrochloric acid. The product was extracted with diethyl ether (3 x 25 mL g^{-1}) and the combined organic layers washed with water (1 x 50 mL g^{-1}) then brine (1 x 50 mL g^{-1}). The ether layer was then dried, filtered and evaporated to yield 3-alkyne-2-hydroxy-1-sulfonamide. Any excess 1-alkyne, and other impurities, were removed through column chromatography when necessary.

Alkyne addition onto a Moc or Boc protected-α-aminocarbonyl

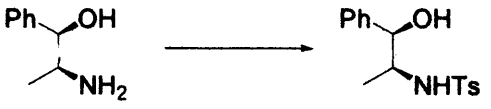
n-BuLi (1.9 – 5.3 mmol of a 2.5M solution in hexanes, 2.2eq) was added dropwise to a solution of 1-alkyne (1.9 – 5.3 mmol, 2.2eq) in THF (10 mL g^{-1}) maintained at -78 °C. The solution was stirred for 0.5 h before being transferred dropwise to a second flask containing protected-α-aminocarbonyl (0.8 – 2.4 mmol, 1eq) in THF (10 mL g^{-1}), which was also maintained at -78 °C. After stirring for 3 h the mixture was quenched by the dropwise addition of concentrated hydrochloric acid at -78 °C (2 mL g^{-1}). After 10 mins stirring, the resulting solution was allowed

to warm to ambient temperature and the product then extracted into diethyl ether (3 x 25 mL g^{-1}). The combined organic layers were washed with water (1 x 50 mL g^{-1}) and brine (1 x 50 mL g^{-1}) then dried, filtered and evaporated to yield 3-alkyne-2-hydroxy-1-amide. Any excess 1-alkyne, and other impurities, were removed through column chromatography where necessary.

Cyclisation [17]

In a, foil-wrapped flask 10% w/w silver nitrate on silica (0.003 – 0.05 mmol, 0.1 eq) was added to a stirred solution of a 3-alkyne-2-hydroxy-1-amide or sulfonamide (0.03 – 0.5 mmol, 1 eq) in dichloromethane (10 mL g^{-1}) with stirring. The resulting suspension was stirred for 3-48 h then filtered through celite and the solvent evaporated to yield a pyrrole.

(1*R*,2*S*)-1-Phenyl-2-(tosylamino)propan-1-ol (236a)[212]



236a

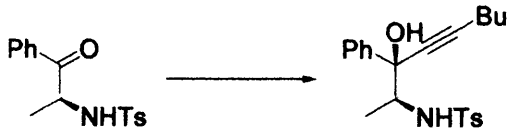
Using the general procedure, tosyl chloride (16.8 g, 88 mmol) was added to (1*R*,2*S*)-norephedrine hydrochloride (15 g, 80 mmol) to give the *tosyl-amino alcohol* **236a** as a colourless solid (19.645g, 80%, mp = 93-95°C (lit. mp = 93-95°C[212]): υ_{max}/cm^{-1} (KBr) 3504, 3257, 1591, 1457, 1324, 1160; δ_H 7.77 (2H, d, J 8.3, 2 x Ar-H), 7.33-7.29 (7H, m, 7 x Ar-H), 5.16 (1H, d, J 8.8, 1-H), 4.79 (1H, d, J 3.4, NH), 3.58-3.52 (1H, m, 2-H), 2.86 (1H, bs, OH), 2.41 (3H, s, Ts-Me), 0.82 (3H, d, J 6.8, 3-Me); δ_c 143.6 (C), 140.0 (C), 137.7 (C), 129.8 (2 x Ar-CH), 128.4 (2 x Ar-CH), 127.8 (Ar-CH), 127.0 (2 x Ar-CH), 126.1 (2 x Ar-CH), 75.7 (1-CH), 54.8 (2-CH), 21.6 (Ts-Me), 15.0 (3-Me); *m/z* (ES) 328 $[M+Na]^+$ 34%, 288 (100), 155 (90), 133 (50), [Found $[M+Na]^+$, 328.0968. $C_{16}H_{19}NNaO_3S$ requires *M+Na*, 328.0963]. All data obtained matched that previously reported in the literature.

(*S*)-1-Phenyl-2-(tosylamino)propan-1-one [213] (237a)

236a **237a**

Using the general procedure, PCC (0.611 g, 3 mmol) and sodium acetate (0.05 g, 0.6 mmol) were added to tosyl-amino alcohol **236a** (0.647 g, 2 mmol) to yield the *N-tosyl-α-aminoketone* **237a** as a colourless solid (0.547g, 85%, mp = 103-104°C (lit. mp = 100-101°C[213])): R_f 0.76 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (DCM) 3315, 3054, 2986, 1687, 1598, 1343, 1165, 1093, 970, 896, 815, 704; δ_H 7.70 (2H, d, J 7.2, 2 x Ar-H), 7.63 (2H, d, J 8.2, 2 x Ar-H), 7.53 (1H, m, Ar-H), 7.38 (2H, m, 2 x Ar-H), 7.09 (2H, Ar-H, J 8.2, 2 x Ar-H), 5.71 (1H, d, J 7.9, NH), 4.84 (1H, dq, J 7.9 and 7.2, 2-H), 2.27 (3H, s, Ts-Me), 1.32 (3H, d, J 7.2, 3-Me); δ_c 198.1 (C), 148.7 (C), 143.5 (C), 137.0 (C), 134.1 (Ar-CH), 129.7 (2 x Ar-CH), 128.9 (2 x Ar-CH), 128.5 (2 x Ar-CH), 127.1 (2 x Ar-CH), 53.4 (2-CH), 21.5 (Ts-Me), 21.2 (3-Me); *m/z* (APCI) 304 $[M+H]^+$ 48%, 155 (100), 148 (100). All data obtained matched that previously reported in the literature.

(2*S*,3*S*)-3-Phenyl-2-(tosylamino)non-4-yn-3-ol (238a)



237a **238a**

Using the general procedure (4 h), 1-hexyne (0.42 mL, 3.63 mmol) was added to the *N*-tosyl-α-aminoketone **237a** (0.5 g, 1.65 mmol) to give the *3-alkyne-2-hydroxy-1-sulfonamide* **238a** as a beige solid (0.635 g, 82%, mp = 79-80 °C) and as a single isomer: R_f 0.52 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (DCM) 3482, 3280, 2957, 1707, 1599, 1448, 1331, 1161, 1092, 668; δ_H 7.45 (2H, d, J 8.2, 2 x Ar-H), 7.39 (2H, dd, J 7.1 and 2.4, 2 x Ar-H), 7.15-7.11 (3H, m, 3 x Ar-H), 7.05 (2H, d, J 8.2, 2 x Ar-H), 4.63 (1H, d, J 9.0, NH), 4.50 (1H, dq, J 9.0 and 6.6, 2-H), 2.99 (1H, bs, OH), 2.27 (3H, s, Ts-Me), 2.12 (2H, t, J 7.1, 6-CH_2), 1.40 (2H, m, 7-CH_2), 1.30 (2H, m, 8-CH_2), 1.01 (3H, d, J 6.6, 1-Me), 0.79 (3H, t, J 7.2, 9-Me); δ_c (125MHz) 143.0 (C), 141.5 (C), 137.7 (C), 129.5 (2 x Ar-CH), 127.9 (2 x Ar-CH), 127.9 (Ar-CH), 127.0 (2 x Ar-CH), 126.5 (2 x

Ar-CH), 88.6 (4-C), 80.3 (5-C), 75.2 (3-C), 58.8 (2-CH), 30.6 (6-CH_2), 22.1 (7-CH_2), 21.5 (Ts-Me), 18.4 (8-CH_2), 17.3 (1-Me), 13.6 (9-Me); *m/z* (ES) 408 $[M+Na]^+$ 55%, 368 (100), 213 (92), 155 (42).

5-Butyl-2-methyl-3-phenyl-1-tosyl-1H-pyrrole (239a)

238a **239a**

Using the general procedure (6 h), 10% $AgNO_3.SiO_2$ (0.041 g, 0.024 mmol) was stirred with a solution of 3-alkyne-2-hydroxy-1-sulfonamide **238a** (0.093 g, 0.241 mmol) in dichloromethane to yield pyrrole **239a** as a yellow oil (0.084g, 94%): R_f 0.70 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 2957, 2929, 2871, 1597, 1541, 1495, 1442, 1362, 1253, 1194, 1171, 1096, 1032, 812, 764, 703; δ_H 7.51 (2H, d, J 8.3, 2 x Ar-H), 7.27 (2H, d, J 7.6, 2 x Ar-H), 7.2 (2H, d, J 8.3, 2 x Ar-H), 7.20-7.16 (3H, m, 3 x Ar-H), 6.01 (1H, s, 4-H), 2.78 (2H, t, J 7.7, 1'-CH_2), 2.33 (3H, s, Ts-Me), 2.31 (3H, s, 2-Me), 1.58 (2H, m, 2'-CH_2), 1.33 (2H, m, 3'-CH_2), 0.85 (3H, t, J 7.3, 4'-Me); δ_c (125MHz) 144.4 (C), 137.6 (C), 137.2 (C), 135.4 (C), 130.0 (2 x Ar-CH), 128.7 (2 x Ar-CH), 128.6 (2 x Ar-CH), 127.7 (C), 126.5 (Ar-CH), 126.1 (2 x Ar-CH), 126.0 (C), 112.4 (4-C), 31.3 (1'-CH_2), 28.7 (2'-CH_2), 22.6 (3'-CH_2), 21.6 (Ts-Me), 14.0 (2-Me), 13.6 (4'-Me); *m/z* (ES) 368 $[M+H]^+$ 100%, [Found $[M+H]^+$, 368.1697. $C_{22}H_{26}NO_2S$ requires *M+H*, 368.1684].

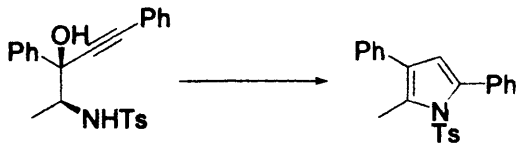
(2*S*,3*S*)-1,3-Diphenyl-4-(tosylamino)pent-1-yn-3-ol (238b)

237a **238b**

Using the general procedure (4 h), phenylacetylene (0.4 mL, 3.63 mmol) was added to the *N*-tosyl α-aminoketone **237a** (0.5 g, 1.65 mmol) to give the *3-alkyne-2-hydroxy-1-sulfonamide* **238b** as a yellow solid (0.533g, 80%, mp = 138-140 °C) and as a single isomer: R_f 0.42 (30 : 70 ethyl

acetate – petroleum ether); υ_{max}/cm^{-1} (DCM) 3410, 1598, 1325, 1150, 756, 665; δ_H 7.55 (2H, d, J 8.2, 2 x Ar-H), 7.54 (2H, d, J 7.8, 2 x Ar-H), 7.39 (2H, d, J 7.8, 2 x Ar-H), 7.34-7.24 (6H, m, 6 x Ar-H), 7.08 (2H, d, J 8.2, 2 x Ar-H), 4.52 (1H, d, J 9.3, NH), 3.69 (1H, dq, J 9.3 and 6.6, 4-H), 2.88 (1H, bs, OH), 2.28 (3H, s, Ts-Me), 1.05 (3H, d, J 6.6, 5-Me); δ_c (125MHz) 143.2 (C), 140.8 (C), 137.6 (C), 131.9 (2 x Ar-CH), 129.6 (2 x Ar-CH), 128.9 (Ar-CH), 128.4 (2 x Ar-CH), 128.2 (Ar-CH), 128.2 (2 x Ar-CH), 127.0 (2 x Ar-CH), 126.4 (2 x Ar-CH), 121.0 (C), 89.3 (1-C), 87.3 (2-C), 75.7 (3-C), 58.8 (4-CH), 21.5 (Ts-Me), 17.3 (5-Me); *m/z* (ES) 428 $[M+Na]^+$ 48%, 388 (100), 233 (100), 155 (19).

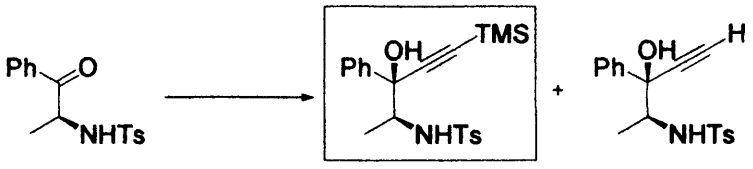
2-Methyl-3,5-diphenyl-1-tosyl-1H-pyrrole (239b)



238b **239b**

Using the general procedure (3 h), 10% $AgNO_3.SiO_2$ (0.054 g, 0.032 mmol) was stirred with a solution of 3-alkyne-2-hydroxy-1-sulfonamide **238b** (0.13 g, 0.321 mmol) in |dichloromethane to yield *pyrrole* **239b** as a pale yellow-orange wax (0.120g, 97%): R_f 0.60 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3062, 2965, 2927, 1643, 1598, 1537, 1495, 1443, 1365, 1306, 1240, 1190, 1176, 1145, 1094, 1028, 910, 812, 734; δ_H 7.35-7.15 (12H, m, 12 x Ar-H), 7.10 (2H, d, J 8.2, 2 x Ar-H), 6.20 (1H, s, 4-H), 2.51 (3H, s, 5-Me), 2.27 (3H, s, Ts-Me); δ_c (125MHz) 144.7 (C), 137.4 (C), 136.3 (C), 134.9 (C), 133.1 (C), 130.5 (2 x Ar-CH), 129.7 (C), 129.5 (2 x Ar-CH), 128.8 (2 x Ar-CH), 128.4 (2 x Ar-CH), 128.0 (Ar-CH), 127.9 (C), 127.3 (2 x Ar-CH), 126.8 (Ar-CH), 126.6 (2 x Ar-CH), 117.1 (4-CH), 21.6 (Ts-Me), 14.2 (2-Me).

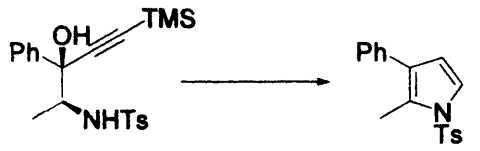
(2*S*,3*S*)-1-(Trimethylsilyl)-3-phenyl-4-(tosylamino)pent-1-yn-3-ol (238c)



237a **238c** **238d**

Using the general procedure (24 h), TMS-acetylene (0.5 mL, 3.63 mmol) was added to tosyl α-aminoketone **237a** (0.5 g, 1.65 mmol) to yield a brown oil (0.357 g), containing a mixture of both silylated **238c** and desilylated **238d** alkynes. The two products were separated by column chromatography (10:90 and 20:80 ethyl acetate – petroleum ether) to yield the *silylated-sulfonamide* **238c** as a colourless solid (0.142 g, 22%, mp = 140-142 °C): R_f 0.30 (30 : 70 ethyl acetate – petroleum ether): υ_{max}/cm^{-1} (DCM) 3475, 3276, 2960, 2254, 2168, 1599, 1332, 1250, 1163, 1092, 910, 846, 734; δ_H 7.34 (2H, d, J 8.2, 2 x Ar-H), 7.29-7.25 (2H, m, 2 x Ar-H), 7.06-7.01 (3H, m, 3 x Ar-H), 6.96 (2H, d, J 8.2, 2 x Ar-H), 4.35 (1H, d, J 9.2, NH), 3.41 (1H, dq, J 9.0 and 6.6, 4-H), 2.91 (1H, bs, OH), 2.19 (3H, s, Ts-Me), 0.89 (3H, d, J 6.6, 5-Me), 0.0 (9H, s, $SiMe_3$); δ_c (125MHz) 143.2 (C), 140.4 (C), 137.5 (C), 129.6 (2 x Ar-CH), 128.1 (Ar-CH), 128.0 (2 x Ar-CH), 127.0 (2 x Ar-CH), 126.6 (2 x Ar-CH), 105.2 (2-C), 92.8 (1-C), 75.5 (3-C), 58.5 (4-CH), 21.5 (Ts-Me), 17.3 (5-Me); *m/z* (ES) 440 $[M+K]^+$ 30%, 424 (41), 384 (100), 229 (26), [Found $[M+K]^+$, 440.1111. $C_{21}H_{27}KNO_3SiS$ requires *M+K*, 440.1118].

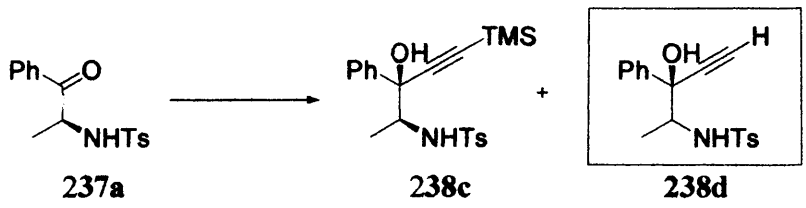
2-Methyl-3-phenyl-1-tosyl-1H-pyrrole (239c)



238c **239c**

Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.011 g, 0.007 mmol) was stirred with a solution of 3-alkyne-2-hydroxy-1-sulfonamide **238c** (0.027 g, 0.067 mmol) in dichloromethane to yield the *pyrrole* **239c** as a pale yellow oil (0.020g, 95%): R_f 0.56 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3148, 3059, 2925, 1597, 1501, 1443, 1365, 1270, 1175, 1121, 1090, 1027, 814, 768, 703, 687; δ_H; 7.65 (2H, d, J 8.3, 2 x Ar-H), 7.35-7.10 (8H, m, 8 x Ar-H), 6.30 (1H, d, J 3.5, 4-H), 2.35 (3H, s, Ts-Me), 2.30 (3H, s, 2-Me); δ_c (125MHz) 144.9 (C), 136.3 (C), 135.1 (C), 130.1 (2 x Ar-CH), 128.5 (2 x Ar-CH), 128.4 (2 x Ar-CH), 127.4 (C), 127.1 (2 x Ar-CH), 126.6 (Ar-CH), 126.2 (C), 121.4 (5-CH), 112.5 (4-CH), 21.7 (Ts-Me), 11.9 (2-Me); *m/z* (ES) 312 $[M+H]^+$ 93%, 155 (100).

(2*S*,3*S*)-3-Phenyl-4-(tosylamino)pent-1-yn-3-ol (238d)



237a **238c** **238d**

Using the general procedure (24 h), TMS-acetylene (0.5 mL, 3.63 mmol) was added to the *N*-tosyl α-aminoketone **237a** (0.5 g, 1.65 mmol) to yield a crude brown oil (0.357 g), containing a mixture of both silylated **238c** and desilylated **238d** alkynes. The two products were separated by column chromatography to yield the *desilylated-sulfonamide* **238d** as a yellow oil (0.099g, 18%): R_f 0.27 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3453, 3276, 2254, 2113, 1598, 1325, 1158, 1091, 910, 733; δ_H 7.36 (2H, d, J 8.2, 2 x Ar-H), 7.31-7.27 (2H, m, 2 x Ar-H), 7.08-7.02 (3H, m, 3 x Ar-H), 6.99 (2H, d, J 8.2, 2 x Ar-H), 4.60 (1H, bs, NH), 3.48 (1H, *app.* quintet, J 6.8, 4-H), 3.15 (1H, bs, OH), 2.48 (1H, s, 1-H), 2.17 (3H, s, Ts-Me), 0.83 (3H, d, J 6.8, 5-Me); δ_c (125MHz) 143.2 (C), 140.3 (C), 137.6 (C), 129.6 (2 x Ar-CH), 128.2 (Ar-CH), 128.1 (2 x Ar-CH), 127.1 (2 x Ar-CH), 126.3 (2 x Ar-CH), 84.2 (1-CH), 75.5 (2-C), 75.0 (3-C), 58.7 (4-CH), 21.6 (Ts-Me), 17.0 (5-Me); *m/z* (ES) 352 $[M+Na]^+$ 63%, 312 (100).

2-Methyl-3-phenyl-1-tosyl-1H-pyrrole (239d)

238d **239d**

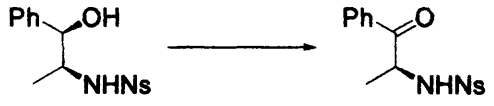
Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.013 g, 0.008 mmol) was stirred with a solution of 3-alkyne-2-hydroxy-1-sulfonamide **238d** (0.025 g, 0.076 mmol) in dichloromethane to yield *pyrrole* **239d** as a pale yellow oil (0.024g, 100%): δ_H 7.65 (2H, d, J 8.3, 2 x Ar-H), 7.35-7.10 (8H, m, 8 x Ar-H), 6.30 (1H, d, J 3.5, 4-H), 2.35 (3H, s, Ts-Me), 2.30 (3H, s, 2-Me), all other data was in agreement with the previously prepared compound.

(1*R*,2*S*)-1-Phenyl-2-(4-nosylamino)propan-1-ol [214] (236b)

236b

Using the general procedure, 4-nosyl chloride (1.3 g, 5.86 mmol) was added to (1*R*,2*S*)-norephedrine hydrochloride (1 g, 5.33 mmol) to yield the *N-nosyl amino-alcohol* **236b** as a yellow solid (1.563g, 87%, mp = 147-148°C): R_f 0.18 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (DCM) 3512, 3243, 3105, 1606, 1529, 1445, 1290, 1222, 1159, 1085, 1066, 907, 854, 736; δ_H 8.26 (2H, d, J 8.8, 2 x Ar-H), 7.97 (2H, d, J 8.8, 2 x Ar-H), 7.30-7.15 (5H, m, 5 x Ar-H), 5.11 (1H, bs, NH), 4.72 (1H, d, J 3.5, 1-H), 3.61 (1H, bs, 2-H), 2.43 (1H, bs, OH), 0.87 (3H, d, J 6.8, 3-Me); δ_c 147.0 (C), 139.9 (C), 131.9 (C), 128.6 (2 x Ar-CH), 128.2 (3 x Ar-CH), 126.0 (2 x Ar-CH), 124.4 (2 x Ar-CH), 76.1 (1-CH), 55.3 (2-CH), 15.4 (3-Me); *m/z* (APCI) 319 ($[M+H]^+$ - H_2O) 32%, 186 (12), 133 (100).

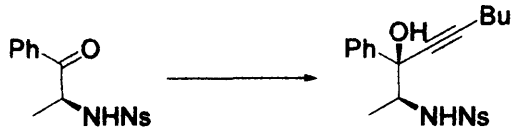
(*S*)-1-Phenyl-2-(4-nosylamino)propan-1-one (237b)



236b **237b**

Using the general procedure, PCC (1.3 g, 6.04 mmol) and sodium acetate (0.1 g, 1.21 mmol) were added to *N*-nosyl amino-alcohol **236b** (1.5 g, 4.46 mmol) to yield the *N-nosyl-α-aminoketone* **237b** as a yellow solid (0.406g, 27%, mp = 154-155°C): R_f 0.70 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (DCM) 3289, 3107, 1694, 1608, 1526, 1454, 1351, 1318, 1267, 1227, 1163, 1096, 963, 861, 739, 703; δ_H 8.17 (2H, d, J 8.8, 2 x Ar-H), 7.93 (2H, d, J 8.8, 2 x Ar-H), 7.70 (2H, d, J 7.1, 2 x Ar-H), 7.55 (1H, t, J 7.4, Ar-H), 7.41-7.37 (2H, t, m, 2 x Ar-H), 5.87 (1H, d, J 8.0, NH), 4.95 (1H, dq, J 8.0 and 7.2, 2-H), 1.39 (3H, d, J 7.2, 3-Me); δ_c (125MHz) 197.2 (C), 146.0 (C), 140.3 (C), 134.6 (Ar-CH), 133.0 (C), 129.1 (2 x Ar-CH), 128.5 (2 x Ar-CH), 128.3 (2 x Ar-CH), 124.4 (2 x Ar-CH), 53.7 (2-CH), 21.2 (3-Me); *m/z* (ES) 335 $[M+H]^+$ 29%, 186 (27), 149 (100).

(2*S*,3*S*)-3-Phenyl-2-(4-nosylamino)non-4-yn-3-ol (238e)



237b **238e**

Using the general procedure (3 h), 1-hexyne (0.17 mL, 1.48 mmol) was added to the *N*-nosyl-α-aminoketone **237b** (0.25 g, 0.674 mmol) to give the *3-alkyne-2-hydroxy-1-sulfonamide* **238e** as a yellow solid (0.258g, 83%, mp = 144-145 °C) and as a single isomer: R_f 0.41 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (DCM) 3492, 3318, 2931, 2361, 1524, 1443, 1338, 1265, 1165, 1089, 1022, 855, 737; δ_H 8.06 (2H, d, J 8.9, 2 x Ar-H), 7.64 (2H, d, J 8.9, 2 x Ar-H), 7.33-7.31 (2H, m, 2 x Ar-H), 7.15-7.05 (3H, m, 3 x Ar-H), 4.58 (1H, d, J 9.5, NH), 3.60 (1H, dq, J 9.5 and 6.4, 2-H), 2.20 (2H, t, J 7.2, 6-CH_2), 1.49 (2H, m, 7- CH_2), 1.35 (2H, m, 8-CH_2), 1.27 (3H, d, J 6.4, 1-Me), 0.87 (3H, t, J 7.3, 9-Me); δ_c (125MHz) 149.6 (C), 146.3 (C), 141.7 (C), 128.3 (Ar-CH), 128.2 (2 x Ar-CH), 128.0 (2 x Ar-CH), 126.2 (2 x Ar-CH), 124.0 (2 x Ar-CH), 89.9 (4-C), 79.2 (5-C), 75.3 (3-C), 59.3 (2-CH), 30.6 (6-CH_2), 22.1 (7-CH_2), 18.4 (8-CH_2), 18.2 (1-Me), 13.6 (9-Me); *m/z* (APCI) 399 ($[M+H]^+$ - H_2O) 32%, 213 (73), 197 (39), 170 (73), 135 (100).

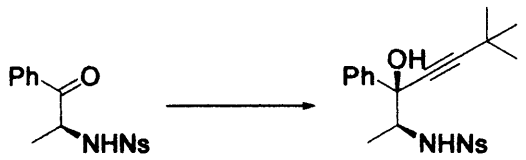
5-Butyl-2-methyl-3-phenyl-1-(4-nosyl)-1H-pyrrole (239e)

238e **239e**

Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.026 g, 0.015 mmol) was stirred with a solution of 3-alkyne-2-hydroxy-1-sulfonamide **238e** (0.063 g, 0.151 mmol) in dichloromethane to yield the *pyrrole* **239e** as a yellow oil (0.060g, 96%): υ_{max}/cm^{-1} (film) 3100, 1607, 1532, 1349, 1169, 1095, 741, 686; δ_H 8.29 (2H, d, J 8.9, 2 x Ar-H); 7.76 (2H, d, J 8.9, 2 x Ar-H), 7.27 (2H, t, J 7.5, 2 x Ar-H), 7.25-7.10 (3H, m, 3 x Ar-H), 6.08 (1H, s, 4-H), 2.80 (2H, t, J 7.7, 1'-CH_2), 2.35 (3H, s, 2-Me), 1.60 (2H, m, 7-CH_2), 1.35 (2H, m, 8-CH_2), 0.87 (3H, t, J 7.4, 9-Me); δ_c (125MHz) 147.3 (C), 137.5 (C), 134.7 (C), 128.8 (C), 128.7 (2 x Ar-CH), 128.5 (2 x Ar-CH), 127.9 (C),

127.4 (2 x Ar-CH), 127.0 (Ar-CH), 124.7 (2 x Ar-CH), 124.5 (C), 113.8 (4-CH), 31.3 (1'-CH_2), 28.8 (2'-CH_2), 22.5 (3'-CH_2), 14.0 (2-Me), 13.8 (4'-Me); *m/z* (ES) 399 $[M+H]^+$ 28%, 228 (37), 184 (100), [Found $[M+H]^+$, 399.1376. $C_{21}H_{23}N_2O_4S$ requires *M+H*, 399.1379].

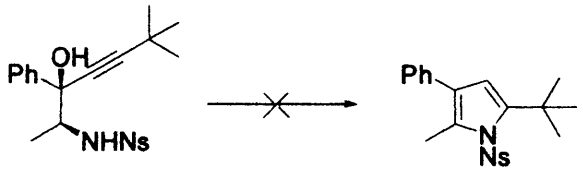
(2*S*,3*S*)-6,6-Dimethyl-3-phenyl-2-(4-nosylamino)hept-4-yn-3-ol (238h)



237b **238h**

Using the general procedure (3 h), 3,3-dimethyl-1-butyne (0.12 mL, 0.990 mmol) was added to the *N*-nosyl-α-aminoketone **237b** (0.15 g, 0.450 mmol) to give the *3-alkyne-2-hydroxy-1-sulfonamide* **238h** as a yellow solid (0.122g, 65%, mp = 151-153°C) and as a single isomer: R_f 0.48 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (DCM) 3496, 3335, 2961, 2226, 1523, 1416, 1338, 1164, 1042, 854, 736, 685; δ_H 8.05 (2H, d, J 8.8, 2 x Ar-H); 7.64 (2H, d, J 8.8, 2 x Ar-H), 7.3 (2H, t, J 7.0, 2 x Ar-CH), 7.20-7.05 (3H, m, 3 x Ar-CH), 4.66 (1H, d, J 9.5, NH), 3.59 (1H, dq, J 9.5 and 6.5, 2-H), 2.58 (1H, bs, OH), 1.22 (12H, bs, 1-Me and *t*-Bu); δ_c 149.5 (C), 146.3 (C), 141.6 (C), 128.3 (Ar-CH), 128.1 (2 x Ar-CH), 127.9 (2 x Ar-CH), 126.3 (2 x Ar-CH), 124.1 (2 x Ar-CH), 98.2 (4-C), 77.6 (5-C), 75.2 (3-C), 59.1 (2-CH), 30.8 (*t*-Bu Me), 27.6 (*t*-Bu C), 18.2 (1-Me); *m/z* (APCI) 399 ($[M+H]^+$ - H_2O) 22%, 229 (64), 213 (88), 198 (100), 186 (90).

5-*tert*-Butyl-2-methyl-3-phenyl-1-(4-nosyl)-1H-pyrrole (239h)



238i **239i**

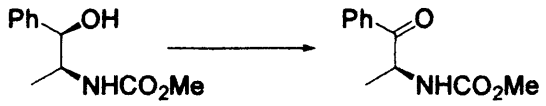
Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.02 g, 0.01 mmol) was stirred with a solution of 3-alkyne-2-hydroxy-1-sulfonamide **238h** (0.02 g, 0.05 mmol) in dichloromethane to give unreacted *3-alkyne-2-hydroxy-1-sulfonamide* **239h** as a yellow solid.

(1*R*,2*S*)-Methyl 1-hydroxy-1-phenylpropan-2-ylcarbamate [215] (236c)

236c

Using the general procedure, methyl chloroformate (0.82 mL, 10.7 mmol) was added to (1*R*,2*S*)-norephedrine hydrochloride (2 g, 10.7 mmol) to yield the *Moc amino-alcohol* **236c** as a colourless oil (1.070g, 48%): υ_{max}/cm^{-1} (film) 3414, 2983, 1698, 1519, 1452, 1346, 1253, 1064, 911, 734, 702; δ_H 7.31-7.26 (4H, m, 4 x Ar-H), 7.21-7.18 (1H, m, Ar-H), 4.80 (2H, bs, NH and 1-H), 3.95 (1H, bs, 2-H), 3.63 (3H, s, OMe), 2.75 (1H, bs, OH), 0.9 (3H, d, J 6.9, 3-Me); δ_c 157.2 (C), 140.6 (C), 128.3 (3 x Ar-CH), 127.6 (Ar-CH), 126.2 (Ar-CH), 76.3 (1-CH), 52.3 (2-CH), 52.3 (OMe), 14.5 (3-Me); *m/z* (APCI) 192 ($[M+H]^+$ - H_2O) 42%, 160 (91), 148 (56), 133 (49), 117 (100). All data obtained matched that previously reported in the literature.

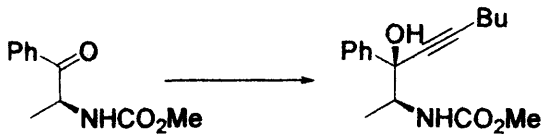
(*S*)-Methyl 1-oxo-1-phenylpropan-2-ylcarbamate [216] (237c)



236c **237c**

Using the general procedure, PCC (1.55 g, 7.17 mmol) and sodium acetate (0.12 g, 1.43 mmol) were added to Moc amino alcohol **236c** (1 g, 4.78 mmol) to yield the *Moc-α-aminoketone* **237c** as a colourless solid (0.693g, 70%, mp = 54-56°C): υ_{max}/cm^{-1} (DCM) 3339, 2984, 1705, 1692, 1526, 1450, 1356, 1229, 1068, 972, 702; δ_H 7.9 (2H, d, J 7.6, 2 x Ar-H), 7.55 (1H, t, J 7.4, Ar-H), 7.40 (2H, t, 7.7, 2 x Ar-H), 5.73 (1H, d, J 5.2, NH), 5.25 (1H, *app.* quintet, J 7.2, 2-H), 3.60 (3H, s, OMe), 1.37 (3H, d, J 7.2, 3-Me); δ_c 199.0 (C), 156.3 (C), 133.9 (Ar-CH), 130.1 (C), 128.9 (3 x Ar-CH), 128.7 (Ar-CH), 52.3 (OMe), 51.6 (2-CH), 20.1 (3-Me); *m/z* (APCI) 208 $[M+H]^+$ 5%, 132 (100). All data obtained matched that previously reported in the literature.

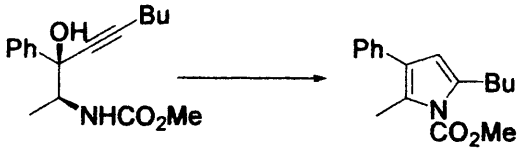
(2*S*,3*S*)-Methyl 3-hydroxy-3-phenylnon-4-yn-2-ylcarbamate (238f)



237c **238f**

Using the general procedure with the modified work-up, 1-hexyne (0.6 mL, 5.31 mmol) was added to Moc-α-aminoketone **237c** (0.5 g, 2.41 mmol) to give the *3-alkyne-2-hydroxy-1-aminocarbonyl* **238f** as a colourless solid (0.579g, 83%) and as a single isomer: R_f 0.25 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (DCM) 3410, 2957, 1710, 1698, 1517, 1449, 1377, 1236, 1068, 701; δ_H 7.61 (2H, d, J 7.2, 2 x Ar-H), 7.35 (2H, t, J 7.3, 2 x Ar-H), 7.29 (1H, t, J 7.3, Ar-H), 4.80 (1H, bs, NH), 4.13 (1H, dq, J 6.7 and 6.1, 2-H), 3.62 (3H, s, OMe), 3.06 (1H, bs, OH), 2.29 (2H, t, J 7.0, 6-CH_2), 1.54 (2H, m, 7-CH_2), 1.44 (2H, m, 8-CH_2), 1.11 (3H, d, J 6.1, 1-Me), 0.93 (3H, t, J 7.3, 9-Me); δ_c (125MHz) 156.7 (C), 141.5 (C), 128.9 (Ar-CH), 127.9 (2 x Ar-CH), 127.9 (Ar-CH), 126.4 (Ar-CH), 87.5 (4-C), 81.4 (5-C), 75.9 (3-C), 56.1 (2-CH), 52.2 (OMe), 30.7 (6-CH_2), 22.0 (7-CH_2), 18.4 (8- CH_2), 16.3 (1-Me), 13.6 (9-Me); *m/z* (APCI) 272 ($[M+H]^+$ - H_2O) 14%, 197 (52), 155 (100), 141 (49), 132 (32).

Methyl 5-butyl-2-methyl-3-phenyl-1H-pyrrole-1-carboxylate (239f)



238f **239f**

Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.088 g, 0.052 mmol) was stirred with a solution of 3-alkyne-2-hydroxy-1-aminocarbonyl **238f** (0.150 g, 0.518 mmol) in dichloromethane to yield the *pyrrole* **239f** as a colourless oil (0.138g, 98%): υ_{max}/cm^{-1} (film) 2956, 2930, 2861, 1744, 1598, 1547, 1509, 1442, 1332, 1263, 1193, 1141, 1110, 764, 701; δ_H 7.35-7.20 (4H, m, 4 x Ar-H), 7.18 (1H, tt, J, 6.8 and 2.0, Ar-H), 5.98 (1H, s, 4-H), 3.88 (3H, s, OMe), 2.74 (2H, t, J 7.6, 1'-CH_2), 2.38 (3H, s, 2-Me), 1.53 (2H, m, 2'-CH_2), 1.35 (2H, m, 3'-CH_2), 0.87 (3H, t, J 7.4, 4'-Me); δ_c 152.7 (C), 136.0 (C), 135.8 (C), 128.7 (2 x Ar-CH), 128.3 (2 x Ar-CH), 126.8 (C), 126.2

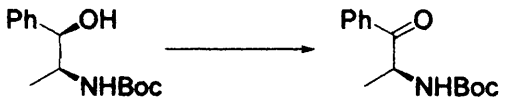
(Ar-CH), 125.1 (C), 111.4 (4-CH), 53.4 (OMe), 31.3 (1'-CH_2), 29.1 (2'-CH_2), 22.6 (3'-CH_2), 14.2 (2-Me), 14.0 (4'-Me); *m/z* (ES) 272 $[M+H]^+$ 100%, [Found $[M+H]^+$, 272.1646. $C_{17}H_{22}NO_2$ requires *M+H*, 272.1651].

(1*R*,2*S*)-*tert*-Butyl 1-hydroxy-1-phenylpropan-2-ylcarbamate [217] (236d)

236d

Using the general procedure, Boc anhydride (1.28 g, 5.86 mmol) was added to (1*R*,2*S*)-norephedrine hydrochloride (1 g, 5.33 mmol) to yield the *Boc-amino alcohol* **236d** as a colourless solid (1.338g, 100%, mp = 95-97°C (lit. mp = 90-92°C[216])): υ_{max}/cm^{-1} (DCM) 3435, 3055, 2981, 1700, 1505, 1453, 1368, 1166, 1051, 704; δ_H 7.30-7.26 (3H, m, 3 x Ar-H), 7.22-7.18 (2H, m, 2 x Ar-H), 4.80 (1H, bs, NH), 4.54 (1H, bs, 1-H), 3.96 (1H, bs, 2-H), 3.16 (1H, bs, OH), 1.40 (9H, s, *t*-Bu), 0.93 (3H, d, J 6.8, 3-Me); δ_c 156.3 (C), 141.0 (C), 128.1 (3 x Ar-CH), 127.3 (Ar-CH), 126.3 (Ar-CH), 79.7 (*t*-Bu C), 76.5 (1-CH), 52.0 (2-CH), 28.4 (*t*-Bu Me), 14.5 (3-Me); *m/z* (APCI) 274 $[M+Na]^+$ 100%, 134 (70). All data obtained matched that previously reported in the literature.

(*S*)-*tert*-Butyl 1-oxo-1-phenylpropan-2-ylcarbamate [216] (237d)

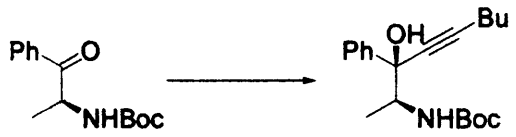


236d **237d**

Using the general procedure, PCC (0.65 g, 3.01 mmol) and sodium acetate (0.05 g, 0.60 mmol) were added to the Boc amino-alcohol **236d** (0.5 g, 1.99 mmol) to yield the *Boc-α-aminoketone* **237d** as a colourless solid (0.324 g, 65%, mp = 82-83°C (lit. mp = 70-72°C[216])): R_f 0.66 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (DCM) 3423, 1710, 1637, 1265, 738; δ_H 7.92 (2H, d, J 7.5, 2 x Ar-H), 7.54 (1H, t, J 7.5, Ar-H), 7.42 (2H, t, J 7.5, 2 x Ar-H), 5.50 (1H, d, J 7.2, NH), 5.23 (1H, *app.* quintet, J 7.2, 2-H), 1.38 (9H, s, *t*-Bu), 1.33 (3H, d, J 7.2, 3-Me); δ_c 199.5 (C), 155.2 (C), 134.2 (C), 133.8 (Ar-CH), 128.9 (3 x Ar-CH), 128.7 (Ar-CH), 79.8 (*t*-Bu C), 51.1 (2-

CH), 28.4 (*t*-Bu), 20.0 (3-Me); *m/z* (APCI) 250 $[M+H]^+$ 18%, 194 (23), 150 (100). All data obtained matched that previously reported in the literature.

(2*S*,3*S*)-*tert*-Butyl 3-hydroxy-3-phenylnon-4-yn-2-ylcarbamate (238g)



237d **238g**

Using the general procedure, 1-hexyne (0.22 mL, 1.90 mmol) was added to Boc-α-aminoketone **237d** (0.2 g, 0.802 mmol) to give the *3-alkyne-2-hydroxy-1-aminocarbonyl* **238g** as a colourless solid (0.178g, 67%) and as a single isomer: υ_{max}/cm^{-1} (DCM) 3432, 2962, 2933, 2873, 2248, 1699, 1505, 1449, 1392, 1367, 1249, 1166, 1106, 1057, 1024, 909, 860, 735, 701; δ_H 7.51 (2H, d, J 7.2, 2 x Ar-H), 7.28-7.25 (2H, m, 2 x Ar-H), 7.20-7.17 (1H, m, Ar-H), 4.59 (1H, bs, NH), 4.00 (1H, bs, 2-H), 2.22 (2H, t, J 7.0, 6-CH_2), 2.02 (9H, s, *t*-Bu), 1.48 (2H, m, 7-CH_2), 1.33 (2H, m, 8-CH_2), 1.05 (3H, bs, 1-Me), 0.86 (3H, t, J 7.2, 9-Me).

***tert*-Butyl 5-butyl-2-methyl-3-phenyl-1H-pyrrole-1-carboxylate (239g)**

238g **239g**

Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.05 g, 0.003 mmol) was stirred with a solution of *3-alkyne-2-hydroxy-1-aminocarbonyl* **238g** (0.1 g, 0.030 mmol) in dichloromethane to yield *pyrrole* **239g** as a colourless oil (0.09g, 90%): R_f 0.86 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 2981, 2253, 1733, 1457, 1370, 1330, 1140, 1115, 908, 733, 650; δ_H 7.35-7.15 (5H, m, 5 x Ar-H), 5.95 (1H, s, 4-H), 2.74 (2H, t, J 7.7, 1'-CH_2), 2.37 (3H, s, 2-Me), 1.53 (9H, s, *t*-Bu), 1.40-1.25 (4H, m, 2'- and 3'-CH_2), 0.88 (3H, t, J 7.3, 4'-Me); δ_c (125MHz) 150.6 (C), 136.3 (C), 135.4 (C), 128.7 (2 x Ar-CH), 128.3 (2 x Ar-CH), 126.5 (C), 126.0 (Ar-CH), 124.5 (C), 110.7 (4-CH), 83.5 (*t*-Bu C), 31.4 (1'-CH_2), 29.2 (2'-CH_2), 28.1 (*t*-Bu), 22.6 (3'-CH_2), 14.4 (2-Me), 14.1 (4'-Me).

General procedure for the synthesis of pyrazole-*N*-oxides

General procedure for imine formation[49]

An amine (22 - 51 mmol, 1.1 eq) was added dropwise to a solution of aldehyde (20 - 47 mmol, 1 eq) in diethyl ether (10 mL g^{-1}). The solution was stirred overnight before being dried, filtered and evaporated to yield the desired imine as a yellow oil (>95%).

General procedure for propargylamine formation[49]

n-BuLi (17 - 24 mmol of a 2.5M solution in hexanes, 1.3eq) was added dropwise to a solution of 1-alkyne (17 - 24 mmol, 1.3 eq) dissolved in THF (10 mL g^{-1}) maintained at -78 °C. The solution was stirred for 0.5 h. Boron trifluoride-THF complex (17 - 24 mmol, 1.3 eq) was added slowly to the mixture which was then stirred for a further 0.25 h at -78 °C. The resulting solution was then added dropwise to a solution of imine (5.7 - 8 mmol, 1 eq) in THF (10 mL g^{-1}) at -78 °C. After stirring for 3 h, the mixture was quenched by the addition of 0.1M KH_2PO_4 pH 7 buffer (10 mL g^{-1}). The product was then extracted into diethyl ether (3 x 25 mL g^{-1}), and the combined extracts washed with water (1 x 50 mL g^{-1}) and brine (1 x 50 mL g^{-1}), then dried, filtered and evaporated to yield the propargyl amine. Any excess 1-alkyne, and other impurities, were removed through column chromatography when necessary.

General procedure for *N*-nitrosation[49]

A propargylamine (0.9 – 1.1 mmol, 1 eq) was cooled to 0°C and treated with 32% hydrochloric acid (1.8 – 2.2 mmol, 2 eq) with stirring for 5 mins. The resulting mixture was diluted with diethyl ether (10 mL g^{-1}), before a solution of sodium nitrite (1.1 – 1.3 mmol, 1.2 eq) in water (10 mLg^{-1}) was added and the resulting mixture stirred at ambient temperature for 3 h. The product was extracted with diethyl ether (3 x 25 mL g^{-1}) and the combined organic extracts washed with water (1 x 25 mL g^{-1}) and brine (1 x 25 mL g^{-1}), then dried, filtered and evaporated to yield the *N*-nitroso propargylamine. No purification was usually required.

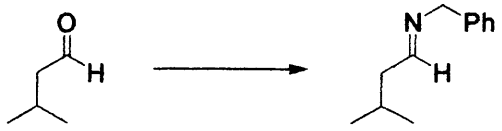
General procedure for synthesis of pyrazole-*N*-oxides

In a foil wrapped NMR tube, 10% w/w silver nitrate on silica gel (0.02 - 0.04 mmol, 0.2eq) was added to a solution of a propargyl-*N*-nitrosoamine (0.1 – 0.2 mmol, 1eq) in deuteriochloroform (1 mL), and the resulting suspension left for 6-24 h with occasional shaking. The solution was then analysed by ^{1}H NMR spectroscopy to show the formation of a pyrazole-N-oxide.

General procedure for pyrazole-*N*-oxide deoxygenation[112, 114]

The pyrazole-*N*-oxide (0.35 - 0.5 mmol, 1 eq) was dissolved in dry, ethanol free, chloroform (5 mL) at ambient temperature. Phosphorus trichloride (1.9 – 2.7 mmol, 5.5eq) was added dropwise and the solution heated to reflux for 2 h. Upon cooling, water was added and the product extracted from the aqueous layer into chloroform (3 x 15 mL) and then washed with water (1 x 25 mL) and brine (1 x 25 mL). The combined organic layers were then dried, filtered and evaporated to yield pyrazole.

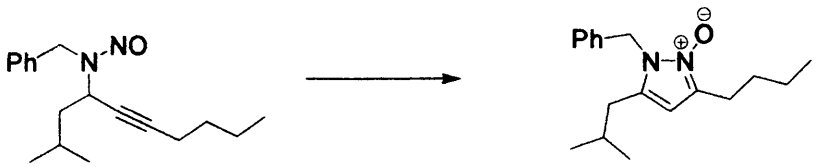
(*E*)-1-Phenyl-2-aza-5-methylhex-2-ene (291a)[218]



291a

Using the general procedure, benzylamine (5.6 mL, 51.3 mmol) was added to isovaleraldehyde (5 mL, 46.6 mmol) to give the *imine* **291a** (7.928 g, 97%) as a clear oil: δ_H 7.79 (1H, t, J 5.5, 3-H), 7.40-7.20 (5H, m, 5 x Ar-H), 4.58 (2H, s, 1-CH_2), 2.21 (2H, dd, J 6.6 and 5.5, 4-CH_2), 1.95 (1H, *app.* nonet, J 6.6, 5-H), 0.98 (6H, d, J 6.6, 3- and 6-Me); δ_c 166.0 (3-CH), 139.4 (C), 128.5 (2 x Ar-CH), 127.9 (2 x Ar-CH), 126.9 (Ar-CH), 65.3 (1-CH_2), 44.8 (4-CH_2), 26.4 (5-CH), 22.6 (6-Me). All data obtained matched that previously reported in the literature.

N-Benzyl-3-isobutyl-5-butylpyrazole-N-oxide (298a)[79c]

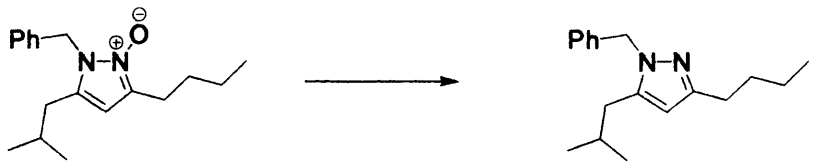


294a **298a**

Preparative Scale:

Using material provided by Pickering,[79c] and to test the true efficiency of these experiments prior to further investigation, one isolation experiment was performed. Thus, 10% $AgNO_3.SiO_2$ (0.059g, 0.035 mmol, 0.1 eq) was added to a stirred solution of *N*-nitroso propargylamine **294a** (0.1g, 0.349 mmol) in dichloromethane (5mL) for 18 h. The resulting suspension was filtered through celite and the solvent removed to give the *pyrazole-N-oxide* **298a** as a orange-yellow oil (0.090g, 96%): δ_H 7.25-7.18 (3H, m, 3 x Ar-H), 7.10 (2H, d, J 7.0, 2 x Ar-H), 5.71 (1H, s, 4-H), 5.30 (2H, s, 1'-CH_2), 2.63 (2H, t, J 7.8, 1'''-CH_2), 2.22 (2H, d, J 7.2, 1''-CH_2), 1.72-1.62 (1H, m, 1''-H), 1.59-1.50 (2H, m, 2'''-CH_2), 1.37-1.26 (2H, m, 3'''-CH_2), 0.90 (3H, t, J 7.5, 4'''-Me), 0.80 (6H, d, J 6.6, 2''-Me); *m/z* (APCI) 287 $[M+H]^+$ 100%.

N-Benzyl-3-butyl-5-isobutylpyrazole (297a)



298a **297a**

Using the general procedure, pyrazole-*N*-oxide **298a** (0.1g, 0.350 mmol) was treated with phosphorus trichloride (0.17mL, 1.92 mmol) to yield the *pyrazole* **297a** as a brown oil (0.093g, 99%): R_f 0.69 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 2958, 1707, 1545, 1496, 1455, 1388, 1076, 701; δ_H 7.26-7.15 (3H, m, Ar-H), 6.98 (2H, d, J 7.4, Ar-H), 5.82 (1H, s, 4-H), 5.21 (2H, s, 1'-CH_2), 2.56 (2H, t, J 7.7, 1''-CH_2), 2.27 (2H, d, J 7.2, 1'''-CH_2), 1.80-1.65 (1H, m, 2'''-H), 1.62-1.52 (2H, m, 2''-CH_2), 1.38-1.27 (2H, m, 3''-CH_2), 0.87 (3H, t, J 7.4, 4''-Me), 0.81 (6H, d, J 6.6, 2'''-Me); δ_c 152.2 (C), 143.5 (C), 137.3 (C), 128.7 (2 x Ar-CH), 127.5 (Ar-CH),

126.6 (2 x Ar-CH), 104.3 (4-CH), 52.5 (1'-CH_2), 34.7 (1'''-CH_2), 31.9 (1''-CH_2), 28.1 (2'''-CH), 27.7 (2''-CH_2), 22.5 (3''-CH_2), 22.5 (2 x 2'''-Me), 13.9 (4''-Me); *m/z* (APCI) 271 $[M+H]^+$ 100%.

_N_-(5-Methyl-1-phenylhex-1-yn-3-yl)-_N_-phenylmethylamine (293b)

291a **293b**

Using the general procedure, phenylacetylene (1.9 mL, 17.1 mmol) was added to imine **291a** (1 g, 5.70 mmol) to give a brown oil (2.126 g), which was purified by column chromatography to give the *propargylamine* **293b** (0.72g, 45%) as a yellow oil. υ_{max}/cm^{-1} (film) 3308, 3060, 2954, 2866, 2226, 1946, 1874, 1804, 1666, 1598, 1490, 1452, 1364, 1168, 1070, 970, 756, 692; δ_H 7.50-7.20 (10H, m, 10 x Ar-H), 4.15 (1H, d, J 12.9, 1'-H_a), 3.90 (1H, d, J 12.9, 1'-H_b), 3.63 (1H, dd, J 7.8 and 7.2, 3-H), 2.04-1.92 (1H, m, 5-H), 1.64-1.58 (2H, m, 4-CH_2), 1.40 (1H, bs, NH), 0.93 (6H, d, J 6.7, 5-Me); δ_c 140.2 (C), 131.7 (2 x Ar-CH), 128.4 (4 x Ar-CH), 128.3 (2 x Ar-CH), 127.9 (Ar-CH), 127.0 (Ar-CH), 123.5 (C), 91.2 (1-C), 83.9 (2-C), 51.5 (1'-CH_2), 48.5 (3-CH), 45.3 (4-CH_2), 25.3 (5-CH), 23.0 (5-Me), 22.3 (6-Me); *m/z* (APCI) 278 $[M+H]^+$ 100%.

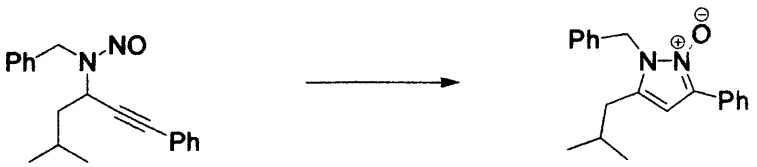
_N_-Nitroso-_N_-(5-methyl-1-phenylhex-1-yn-3-yl)-_N_-phenylmethylamine (294b)

293b **294b**

Using the general procedure, sodium nitrite (0.07 g, 1.08 mmol) was added to propargylamine **293b** (0.25 g, 0.90 mmol) to give the *N-nitroso propargylamine* **294b** (0.127 g, 46%) as an orange oil, which showed a mixture of two rotamers in a ratio of 45:55. δ_H 7.40-7.15 (10H, m, 10 x Ar-H), 5.93 (0.45H, dd, J 8.0 and 7.2, 3-H), 5.74 (0.55H, *app.* t, J 7.9, 3-H), 5.49 (0.45H, d, J 14.9, 1'-H_a), 5.32 (0.45H, d, J 14.9, 1'-H_b), 4.93 (0.55H, d, J 14.7, 1'-H_a), 4.74 (0.55H, d, J 14.7,

1'-H_b), 1.76-1.70 (1.1H, m, 4-CH_2), 1.62-1.50 (0.55H, m, 5-H), 1.50-1.40 (0.45H, m, 5-H), 1.20-1.12 (0.9H, m, J 7.1, 4-CH_2), 0.89 (1.65H, d, J 6.6, 5-Me), 0.87 (1.35H, d, J 6.6, 5-Me), 0.80 (1.35H, d, J 6.6, 5-Me), 0.78 (1.65H, d, J 6.6, 5-Me); δ_c (125MHz) 136.1 (C), 135.2 (C), 131.7 (2 x Ar-CH), 131.7 (2 x Ar-CH), 128.8 (Ar-CH), 128.7 (2 x Ar-CH), 128.6 (2 x Ar-CH), 128.5 (3 x Ar-CH), 128.4 (Ar-CH), 128.3 (2 x Ar-CH), 128.2 (Ar-CH), 128.1 (2 x Ar-CH), 127.5 (2 x Ar-CH), 122.2 (C), 122.0 (C), 87.0 (1-C), 86.1 (1-C), 85.2 (2-C), 84.8 (2-C), 54.5 (3-CH), 53.7 (1'-CH_2), 45.4 (1'-CH_2), 44.4 (3-CH), 43.9 (4-CH_2), 42.1 (4-CH_2), 25.3 (5-CH), 24.8 (5-CH), 22.8 (5-Me), 22.1 (5-Me), 22.0 (5-Me), 21.4 (5-Me).

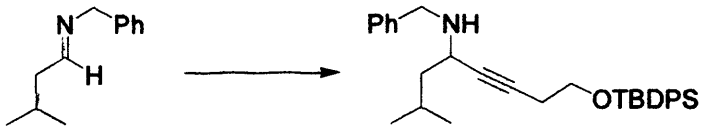
_N_-Benzyl-3-isobutyl-5-phenylpyrazole-_N_-oxide (298b)



294b **298b**

Using the general procedure, 10% $AgNO_3.SiO_2$ (0.055g, 0.033 mmol, 0.2 eq) was mixed with a solution of *N*-nitroso propargylamine **294b** (~0.05g, 0.163 mmol) in deuteriochloroform (0.75mL). Analysis by ^{1}H NMR showed complete conversion to the *pyrazole-N-oxide* **298b** in 6 h. δ_H 8.15 (2H, dd, J 8.5 and 1.3, 2 x Ar-H), 7.37 (2H, m, 2 x Ar-H), 7.31-7.19 (4H, m, 4 x Ar-H), 7.15 (2H, dd, J 8.0 and 1.4, 2 x Ar-H), 6.17 (1H, s, 4-H), 5.38 (2H, s, 1'-CH_2), 2.32 (2H, d, J 7.3, 1''-CH_2), 1.83-1.70 (1H, m, 2''-H), 0.85 (6H, d, J 6.7, 2''-Me); δ_c 135.7 (C), 132.2 (C), 128.9 (2 x Ar-CH), 128.6 (2 x Ar-CH), 128.5 (C), 128.4 (Ar-CH), 128.4 (C), 127.9 (Ar-CH), 127.0 (2 x Ar-CH), 126.4 (2 x Ar-CH), 98.3 (4-CH), 45.5 (1'-CH_2), 35.3 (1''-CH_2), 27.6 (2''-CH), 22.3 (2 x 2''-Me); *m/z* (APCI) 307 $[M+H]^+$ 100%, [Found $[M+H]^+$, 307.1802. $C_{20}H_{23}N_2O$ requires *M+H*, 307.1810].

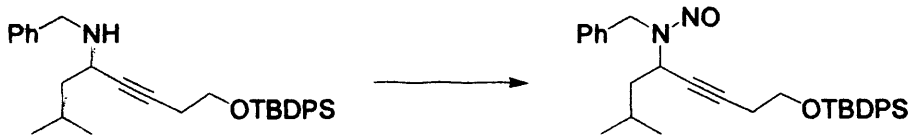
O-(*t*-Butyldiphenylsilyl)-7-Methyl-5-phenylmethylaminooct-3-yn-1-ol (293c)



291a **293c**

Using the general procedure, *O*-TBPDS 3-butyn-1-ol (5.28 g, 17.1 mmol) was added to imine **291a** (1 g, 5.70 mmol) to give a crude product (6.132 g) as an orange oil, which was purified by column chromatography (40:60 ethyl acetate – petroleum ether) to give the *propargylamine* **293c** (1.443 g, 52%) as a yellow oil: R_f 0.41 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3306, 3070, 2954, 2928, 2224, 1958, 1886, 1820, 1590, 1472, 1428, 1384, 1362, 1262, 1104, 916, 822, 736, 698; δ_H 7.69 (2H, d, J 7.9, 2 x Ar-H), 7.68 (2H, d, J 7.9, 2 x Ar-H), 7.46-7.26 (11H, m, 11 x Ar-H), 3.99 (1H, d, J 12.9, 1'-H_a), 3.78 (2H, t, J 7.0, 1-CH_2), 3.76 (1H, d, J 12.9, 1'-H_b), 3.37 (1H, dt, J 7.5 and 1.9, 5-H), 2.50 (2H, td, J 7.0 and 1.9, 2-CH_2), 1.94-1.82 (1H, m, 7-H), 1.49-1.43 (2H, m, 6-CH_2), 1.03 (9H, s, *t*-Bu Me), 0.89 (3H, d, J 6.6, 7-Me), 0.88 (3H, d, J 6.6, 7-Me); δ_c 140.3 (C), 135.6 (4 x Ar-CH), 133.7 (C), 129.7 (2 x Ar-CH), 128.4 (2 x Ar-CH), 128.3 (2 x Ar-CH), 128.3 (4 x Ar-CH), 126.9 (1 x Ar-CH), 82.7 (4-C), 80.7 (3-C), 62.8 (1-CH_2), 51.4 (1'-CH_2), 48.0 (5-CH), 45.5 (2-CH_2), 26.8 (*t*-Bu Me), 25.1 (7-CH), 23.0 (6-CH_2), 23.2 (7-Me), 22.9 (7-Me), 22.2 (*t*-Bu C); *m/z* (APCI) 484 $[M+H]^+$ 100%, [Found $[M+H]^+$, 484.3052. $C_{32}H_{42}NOSi$ requires *M+H*, 484.3036].

O-(*t*-Butyldiphenylsilyl)-*N*-nitroso-7-Methyl-5-phenylmethylaminooct-3-yn-1-ol (294c)



293c **294c**

Using the general procedure, sodium nitrite (0.09 g, 1.24 mmol) was added to propargylamine **293c** (0.5 g, 1.03 mmol) to give the *N-nitroso propargylamine* **294c** (0.369 g, 70%) as a yellow oil, which showed a mixture of two rotamers in a ratio of 30:70. δ_H 7.63-7.00 (15H, m, 15 x Ar-H), 5.68 (0.3H, *app.* t, J 6.7, 5-H), 5.47 (0.7H, *app.* tt, J 7.9 and 2.0, 5-H), 5.36 (0.3H, d, J 14.9,

1'-H_a), 5.21 (0.3H, d, J 14.9, 1'-H_b), 4.85 (0.7H, d, J 14.7, 1'-H_a), 4.61 (0.7H, d, J 14.7, 1'-H_b), 3.61 (2H, t, J 6.9, 1-CH_2), 2.35 (1.4H, dt, J 6.9 and 2.0, 2-CH_2), 2.33 (0.6H, dt, J 6.9 and 2.0, 2-CH_2), 1.60-1.54 (1.4H, m, 6-CH_2), 1.52-1.40 (1.3H, m, 6-CH_2 and 7-H), 1.39-1.29 (0.3H, m, 7-H), 0.98 (9H, s, *t*-Bu CH_3), 0.80 (1.8H, d, J 6.5, 7-Me), 0.69 (4.2H, d, J 6.7, 7-Me); δ_c 135.6 (4 x Ar-CH), 135.3 (C), 133.4 (2 x C), 129.8 (2 x Ar-CH), 128.4 (2 x Ar-CH), 128.0 (2 x Ar-CH), 127.8 (4 x Ar-CH), 127.4 (Ar-CH), 84.8 (3-C), 83.8 (3-C), 77.3 (4-C), 76.7 (4-C), 62.2 (1-CH_2), 62.1 (1-CH_2), 54.3 (5-CH), 53.4 (1'-CH_2), 45.2 (1'-CH_2), 44.0 (5-CH), 43.9 (2-CH_2), 42.1 (2-CH_2), 26.8 (*t*-Bu Me), 25.0 (7-CH), 24.6 (7-CH), 22.9 (2 x 6-CH_2), 22.0 (7-Me), 21.3 (7-Me), 15.3 (2 x C).

_N_-Benzyl-3-isobutyl-5-_O_-(_t_-Butyldiphenylsilyl)ethan-2-ol-pyrazole-_N_-oxide (298c)

294c **298c**

Using the general procedure, 10% $AgNO_3.SiO_2$ (0.033g, 0.019 mmol, 0.2 eq) was mixed with a solution of *N*-nitroso propargylamine **294c** (~0.05g, 0.097 mmol) in deuteriochloroform (0.75mL). Analysis by ^1H NMR showed complete conversion to the *pyrazole-N-oxide* **298c** in 8 h. δ_H 7.57 (2H, d, J 8.0, 2 x Ar-H), 7.56 (2H, d, J 8.0, 2 x Ar-H), 7.38-7.19 (9H, m, 9 x Ar-H), 7.08 (2H, dd, J 8.2 and 1.6, 2 x Ar-H), 5.86 (1H, s, 4-H), 5.32 (2H, s, 1'-CH_2), 3.90 (2H, t, J 6.1, 2'''-CH_2), 2.90 (2H, t, J 6.1, 1'''-CH_2), 2.25 (2H, d, J 7.2, 1''-CH_2), 1.76-1.61 (1H, m, 2''-H), 0.96 (9H, s, *t*-Bu Me), 0.80 (6H, d, J 6.7, 2''-Me); δ_c 135.6 (C), 135.6 (4 x Ar-CH), 133.5 (C), 132.3 (C), 129.7 (2 x Ar-CH), 128.9 (2 x Ar-CH), 127.9 (Ar-CH), 127.7 (4 x Ar-CH), 127.7 (C), 126.9 (2 x Ar-CH), 101.0 (4-CH), 61.0 (1'-CH_2), 45.9 (2'''-CH_2), 35.1 (1'''-CH_2), 28.4 (1''-CH_2), 27.6 (2''-CH), 26.8 (*t*-Bu Me), 22.3 (2 x 2''-Me), 19.2 (C).

N-Benzyl-5-isobutyl-3-O-(t-Butyldiphenylsilyl)ethan-2-ol-pyrazole (297b)

298c **297b**

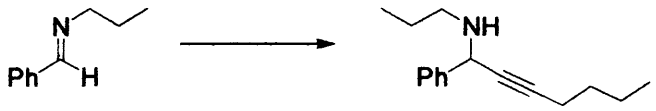
Using the general procedure, pyrazole-*N*-oxide **298c** (0.25g, 0.487 mmol) was treated with phosphorus trichloride (0.23mL, 2.68 mmol) to yield the *pyrazole* **297b** as a yellow oil (0.222g, 92%): R_f 0.67 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3340, 2959, 1710, 1589, 1471, 1473, 1235, 1113, 1028, 859, 821, 703; δ_H 7.65 (4H, dd, 7.6 and 1.6, 4 x Ar-H), 7.36-7.23 (11H, m, 11 x Ar-H), 6.16 (1H, s, 4-H), 5.54 (2H, s, 1'-CH_2), 3.92 (2H, t, J 4.5, 2''-CH_2), 3.00 (2H, t, J 4.5, 1''-CH_2), 2.38 (2H, d, J 6.7, 1'''-CH_2), 1.84-1.72 (1H, m, 2'''-H), 0.99 (9H, s, *t*-Bu), 0.83 (6H, d, J 6.3, 2'''-Me); δ_c 147.0 (C), 135.5 (C), 135.3 (2 x C), 134.8 (6 x Ar-CH), 129.6 (2 x Ar-CH), 129.3 (Ar-CH), 129.1 (C), 127.2 (6 x Ar-CH), 107.2 (4-CH), 59.4 (1'-CH_2), 52.3 (2''-CH_2), 34.0 (1''-CH_2), 29.2 (1'''-CH_2), 27.7 (2'''-CH), 26.6 (*t*-Bu Me), 22.3 (2 x 2'''-Me), 19.1 (C); *m/z* (ES) 497 $[M+H]^+$ 34%, 259 (100), [Found $[M+H]^+$, 497.2982. $C_{32}H_{41}N_2OSi$ requires *M+H*, 497.2988].

(*E*)-1-Phenyl-2-azapent-1-ene (291b)[49, 219]

291b

Using the general procedure, propylamine (1.8 mL, 21.8 mmol) was added to benzaldehyde (2 mL, 19.8 mmol) to give the *imine* **291b** (2.753 g, 94%) as a clear oil: δ_H 8.26 (1H, *app.* s, 1-H), 7.78-7.75 (2H, m, 2 x Ar-H), 7.42-7.40 (3H, m, 3 x Ar-H), 3.59 (2H, td, J 6.9 and 1.2, 3-CH_2), 1.77 (2H, *app.* sext, J 7.2, 4-CH_2), 0.99 (3H, t, J 7.4, 5-Me); δ_c 160.3 (1-CH), 136.1 (C), 130.1 (Ar-CH), 128.0 (2 x Ar-CH), 127.7 (2 x Ar-CH), 63.3 (3-CH_2), 23.8 (4-CH_2), 11.6 (5-Me). All data obtained matched that previously reported in the literature.

N-(1-Phenylhept-2-yn-1-yl)-N-propylamine (293d)[49]



291b **293d**

Using the general procedure, 1-hexyne (2.4 mL, 20.9 mmol) was added to imine **291b** (1 g, 6.98 mmol) to give a crude mixture (1.426g) as a yellow oil, which was purified by column chromatography (20:80 ethyl acetate – petroleum ether) to give the *propargylamine* **293d** (1.204 g, 77%) as a pale yellow oil: R_f 0.46 (30:70 ethyl acetate - petroleum ether): δ_H 7.49 (2H, d, J 7.2, 2 x Ar-H), 7.32-7.21 (3H, m, 3 x Ar-H), 4.57 (1H, s, 1-H), 2.64 (1H, ddd, J 11.2, 8.2 and 6.6, 1'-H_a), 2.59 (1H, dd, J 11.2, 8.2, 6.6, 1'-H_b), 2.20 (2H, dt, J 7.0 and 2.0, 4-CH_2), 1.56-1.30 (6H, m, 2'-, 5- and 6-CH_2), 0.85 (3H, t, J 7.3, 3'-Me), 0.84 (3H, t, J 7.4, 7-Me); δ_c 141.3 (C), 128.5 (3 x Ar-CH), 127.9 (2 x Ar-CH), 87.1 (2-C), 79.8 (3-C), 54.1 (1-CH), 48.5 (1'-CH_2), 30.8 (4-CH_2), 22.0 (2'-CH_2), 18.5 (5- and 6-CH_2), 13.6 (7-Me), 11.8 (3'-Me); *m/z* (ES) 230 $[M+H]^+$ 22%, 171 (100) [Found $[M+H]^+$, 230.1909. $C_{16}H_{24}N$ requires *M+H*, 230.1909]. All data obtained matched that previously reported in the literature.

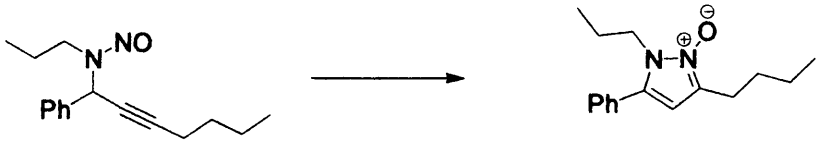
N-Nitroso-N-(1-phenylhept-2-yn-1-yl)-N-propylamine (294d)[49]

293d **294d**

Using the general procedure, sodium nitrite (0.09 g, 1.33 mmol) was added to propargylamine **293d** (0.25 g, 1.10 mmol) to give the *N-nitroso propargylamine* **294d** (0.221 g, 78%) as a yellow oil, which showed a mixture of two rotamers in a ratio of 38:62: δ_H 7.48-7.20 (5H, m, 5 x Ar-H), 7.11 (0.38H, t, J 2.2, 1-H), 6.71 (0.62H, t, J 2.2, 1-H), 3.92 (0.38H, dt, J 13.9 and 7.5, 1'-H_a), 3.83 (0.38H, dt, J 13.9 and 7.4, 1'-H_b), 3.35 (0.62H, ddd, J 13.1, 10.4 and 5.4, 1'-H_a), 3.15 (0.62H, ddd, J 13.1, 10.5 and 5.3, 1'-H_b), 2.29 (1.24H, dt, J 7.0 and 2.2, 4-CH_2), 2.23 (0.76H, dt, J 7.0 and 2.2, 4-CH_2), 1.70-1.58 (0.76H, m, J 7.5, 5-CH_2), 1.56-1.44 (2H, m, 2'- and 6-CH_2), 1.44-1.34 (2.48H, m, 5- and 6-CH_2), 1.20-1.07 (0.76H, m, 2'-CH_2), 0.89 (1.86H, t, J 7.2, 3'-Me), 0.88

(1.14H, t, J 7.2, 3'-Me), 0.78 (1.14H, t, J 7.4, 7-Me), 0.66 (1.86H, t, J 7.5, 7-Me); δ_c 135.7 (C), 135.6 (C), 128.8 (2 x Ar-CH), 128.7 (2 x Ar-CH), 128.6 (Ar-CH), 128.3 (Ar-CH), 127.7 (2 x Ar-CH), 127,6 (2 x Ar-CH), 90.2 (2-C), 87.4 (2-C), 74.0 (3-C), 73.8 (3-C), 58.5 (1-CH), 51.2 (1'-CH_2), 46.1 (1-CH), 44.4 (1'-CH_2), 30.6 (4-CH_2), 30.5 (4-CH_2), 22.9 (2'-CH_2), 22.0 (2 x 5-CH_2), 20.1 (2'-CH_2), 18.5 (6-CH_2), 18.4 (6-CH_2), 13.6 (2 x 7-Me), 11.7 (3'-Me), 11.3 (3'-Me). All data obtained matched that previously reported in the literature.

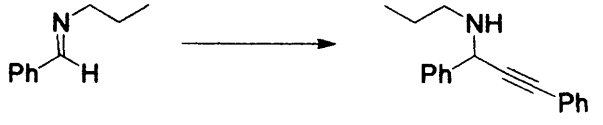
_N_-Propyl-5-butyl-3-phenylpyrazole-_N_-oxide (298d)



294d **298d**

Using the general procedure, 10% $AgNO_3.SiO_2$ (0.066 g, 0.039 mmol, 0.2 eq) was mixed with a solution of *N*-nitroso propargylamine **294d** (~0.05g, 0.193 mmol) in deuteriochloroform (0.75mL). Analysis by ^1H NMR showed complete conversion to the *pyrazole-N-oxide* **298d** in 24 h: δ_H 7.41-7.28 (5H, m, 5 x Ar-H), 5.96 (1H, s, 4-H), 4.11 (2H, t, J 7.5, 1'-CH_2), 2.64 (2H, t, J 7.8, 1'''-CH_2), 1.66 (2H, sextet, J 7.5, 2'-CH_2), 1.64-1.56 (2H, m, 2'''-CH_2), 1.42-1.31 (2H, m, 3'''-CH_2), 0.88 (3H, t, J 7.3, 4'''-Me), 0.72 (3H, t, J 7.5, 3'-Me); δ_c 132.6 (C), 132.5 (C), 129.8 (C), 129.0 (2 x Ar-CH), 128.7 (Ar-CH), 128.2 (2 x Ar-CH), 100.4 (4-CH), 45.7 (1'-CH_2), 29.0 (1'''-CH_2), 24.4 (2'-CH_2), 22.5 (2'''-CH_2), 22.1 (3'''-CH_2), 13.9 (4'''-Me), 10.9 (3'-Me); *m/z* (APCI) 259 $[M+H]^+$ 100%, [Found $[M+H]^+$, 259.1799. $C_{16}H_{23}N_2O$ requires *M+H*, 259.1810].

_N_-(1,3-Diphenylprop-2-yn-1-yl)-_N_-propylamine (293e)[49]



291b **293e**

Using the general procedure, phenylacetylene (2.3 mL, 20.9 mmol) was added to imine **291b** (1 g, 6.98 mmol) to give the *propargylamine* **293e** (1.50g, 88%) as a yellow oil: R_f 0.52 (30:70 ethyl acetate - petroleum ether): δ_H 7.59 (2H, d, J 7.2, 2 x Ar-H), 7.50-7.26 (8H, m, 8 x Ar-H), 4.80

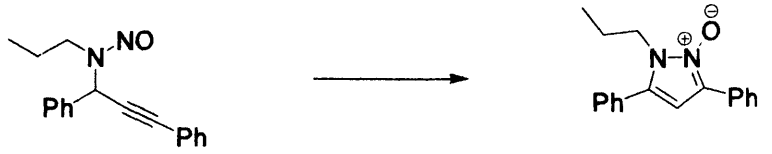
(1H, s, 1-H), 2.81 (1H, ddd, J 11.2, 8.0 and 6.8, 1'-H_a), 2.69 (1H, ddd, J 11.2, 8.0 and 6.4, 1'-H_b), 1.82 (1H, bs, NH), 1.62-1.50 (2H, m, 2'-CH_2), 0.94 (3H, t, J 7.4, 3'-Me); δ_c 140.6 (C), 131.8 (2 x Ar-CH), 128.6 (2 x Ar-CH), 128.3 (2 x Ar-CH), 128.2 (Ar-CH), 127.8 (Ar-CH), 127.7 (2 x Ar-CH), 123.2 (C), 89.6 (3-C), 85.3 (2-C), 54.7 (1-CH), 49.3 (1'-CH_2), 23.2 (2'-CH_2), 11.9 (3'-Me); *m/z* (APCI) 250 $[M+H]^+$ 2%, 191 (100), 113 (28). All data obtained matched that previously reported in the literature.

_N_-Nitroso-_N_-(1,3-diphenylprop-2-yn-1-yl)-_N_-propylamine (294e)[49]

293e **294e**

Using the general procedure, sodium nitrite (0.08 g, 1.22 mmol) was added to propargylamine **293e** (0.25 g, 1.02 mmol) to give the *N-nitroso propargylamine* **294e** (0.243 g, 87%) as an orange oil, which showed a mixture of two rotamers in a ratio of 42:58: δ_H 7.60-7.23 (10.42H, m, 10 x Ar-H and 1-H), 6.97 (0.58H, s, 1-H), 4.06-3.85 (0.84H, m, 1'-CH_2), 3.45 (0.58H, ddd, J 13.2, 10.3 and 5.4, 1'-H_a), 3.22 (0.58H, ddd, J 13.2, 10.4 and 5.3, 1'-H_b), 1.71 (0.84H, *app.* sextet, J 7.5, 2'-CH_2), 1.50-1.34 (0.58H, m, 2'-H_a), 1.27-1.12 (0.58H, m, 2'-H_b), 0.82 (1.26H, t, J 7.4, 3'-Me), 0.69 (1.74H, t, J 7.4, 3'-Me); δ_c 135.2 (C), 135.0 (C), 131.8 (Ar-CH), 131.8 (Ar-CH), 129.2 (Ar-CH), 129.1 (Ar-CH), 128.9 (Ar-CH), 128.8 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 127.7 (Ar-CH), 127.6 (Ar-CH), 122.0 (C), 121.8 (C), 89.1 (3-C), 86.3 (3-C), 83.0 (2 x 2-C), 58.9 (1-CH), 51.4 (1'-CH_2), 46.3 (1-CH), 44.6 (1'-CH_2), 22.9 (2'-CH_2), 20.2 (2'-CH_2), 11.8 (3'-Me), 11.3 (3'-Me). All data obtained matched that previously reported in the literature.

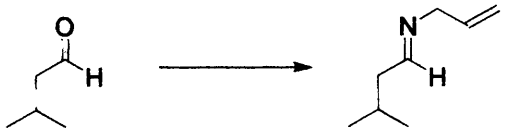
_N_-Propyl-3,5-diphenylpyrazole-_N_-oxide (298e)



294e **298e**

Using the general procedure, 10% $AgNO_3.SiO_2$ (0.061g, 0.036 mmol, 0.2 eq) was mixed with a solution of *N*-nitroso propargylamine **294e** (~0.05g, 0.180 mmol) in deuteriochloroform (0.75mL). Analysis by ^1H NMR showed complete conversion to the *pyrazole-N-oxide* **298e** in 8 h. δ_H 8.14 (2H, m, 2 x Ar-H), 7.43-7.36 (8H, m, 8 x Ar-H), 6.42 (1H, s, 4-H), 4.19 (2H, t, J 7.5, 1'-CH_2), 1.73 (2H, sextet, 2'-CH_2), 0.76 (3H, t, J 7.5, 3'-Me); δ_c (125MHz) 133.8 (C), 132.3 (C), 129.1 (2 x Ar-CH), 128.6 (2 x Ar-CH), 128.5 (Ar-CH), 128.4 (2 x Ar-CH), 128.2 (C), 127.7 (C). 126.5 (Ar-CH), 126.4 (2 x Ar-CH), 99.1 (4-CH), 45.7 (1'-CH_2), 22.2 (2'-CH_2), 11.1 (3'-Me).

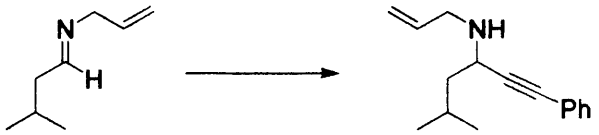
(*E*)-4-Aza-7-methylocta-1,4-diene (291c)[49]



291c

Using the general procedure, allylamine (5.6 mL, 51.3 mmol) was added to isovaleraldehyde (5 mL, 46.6 mmol) to give the *imine* **291c** (7.928 g, 97%) as a clear oil. The spectroscopic data obtained were in accord with those previously reported in the literature.

***N*-(5-Methyl-1-phenylhex-1-yn-3-yl)-*N*-allylamine (293f)**



291c **293f**

Using the general procedure, phenylacetylene (2.63 mL, 23.9 mmol) was added to imine **291c** (1 g, 7.98 mmol) to give a crude mixture (2.717 g) as an orange oil. The residue was purified by column chromatography (30:70 ethyl acetate – petroleum ether) to give the *propargylamine* **293f** (0.67g, 37%) as a pale yellow oil: R_f 0.59 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3315, 3080, 2956, 2869, 1643, 1599, 1490, 1467, 1385, 1366, 1315, 1102, 1069, 1028, 993, 919, 756, 691; δ_H 7.51-7.27 (5H, m, 5 x Ar-H), 5.95 (1H, dddd, J 17.0, 10.6, 6.3 and 5.7, 2'-H), 5.24 (1H, ddt, J 17.0, 3.1 and 1.4, 3'-H_a), 5.12 (1H, ddt, J 10.6, 3.1 and 1.4, 3'-H_b), 3.66 (1H,

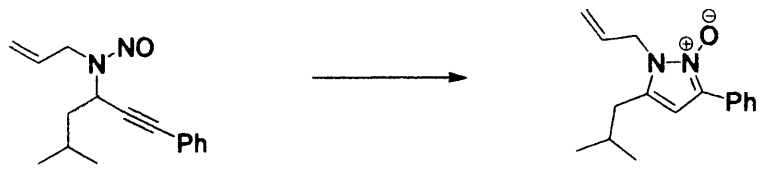
dd, J 8.7 and 6.5, 3-H), 3.57 (1H, ddt, J 13.8, 5.7 and 1.4, 1'-H_a), 3.35 (1H, ddt, J 13.8, 6.3 and 1.4, 1'-H_b), 2.04-1.89 (1H, m, 5-H), 1.67-1.51 (2H, m, 4-CH_2), 1.27 (1H, bs, NH), 0.93 (3H, d, J 6.7, 5-Me), 0.92 (3H, d, J 6.7, 5-Me); δ_c 136.6 (Ar-CH), 132.1 (Ar-CH), 131.7 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 127.9 (2'-CH), 123.4 (C), 116.3 (3'-CH_2), 91.0 (1-C), 83.8 (2-C), 50.1 (1'-CH_2), 48.5 (3-CH), 45.3 (4-CH_2), 25.3 (5-CH), 23.2 (5-Me), 22.1 (5-Me); *m/z* (APCI) 228 $[M+H]^+$ 36%, 171 (100), [Found $[M+H]^+$, 228.1763. $C_{16}H_{22}N$ requires *M+H*, 228.1752].

_N_-Nitroso-_N_-(5-methyl-1-phenylhex-1-yn-3-yl)-_N_-allylamine (294f)

293f **294f**

Using the general procedure, sodium nitrite (0.09 g, 1.32 mmol) was added to propargylamine **293f** (0.5 g, 1.10 mmol) to give the *N-nitroso propargylamine* **294f** (0.089 g, 32%) as a yellow oil, which showed a mixture of two rotamers in a ratio of 25:75: δ_H 7.37-7.20 (5H, m, 5 x Ar-H), 5.98 (0.25H, dddd, J 17.1, 10.0, 7.2 and 5.6, 2'-H), 5.91 (0.25H, dd, J 9.2 and 6.0, 3-H), 5.71 (0.75H, *app.* t, J 8.0, 3-H), 5.68 (0.75H, dddd, J 17.1, 10.1, 6.6 and 5.4, 2'-H), 5.35 (0.25H, ddt, J 17.1, 2.5 and 1.3, 3'-H_a), 5.23 (0.25H, ddt, J 10.0, 2.5 and 1.1, 3'-H_b), 5.14 (0.75H, ddt, J 17.1, 2.6 and 1.4, 3'-H_a), 5.10 (0.75H, ddt, J 10.1, 2.6 and 1.1, 3'-H_b), 4.85 (0.25H, ddt, J 15.2, 5.6 and 1.3, 1'-H_a), 4.76 (0.25H, ddt, J 15.2, 7.2 and 1.1, 1'-H_b), 4.27 (0.75H, ddt, J 14.9, 5.4 and 1.4, 1'-H_a), 4.14 (0.75H, ddt, J 14.9, 6.6 and 1.2, 1'-H_b), 1.83-1.77 (1.50H, m, 4-CH_2), 1.73-1.60 (1H, m, 5-H), 1.55 (0.25H, ddd, J 13.0, 9.2 and 5.6, 4-H_a), 1.37 (0.25H, ddd, J 13.0, 8.3 and 6.0, 4-H_b), 0.94 (2.25H, d, J 6.6, 5-Me), 0.90 (2.25H, d, J 6.7, 5-Me), 0.90 (0.75H, d, J 6.6, 5-Me), 0.87 (0.75H, d, J 6.6, 5-Me); δ_c 133.3 (2'-CH), 131.7 (2 x Ar-CH), 130.2 (Ar-CH), 128.9 (2'-CH), 128.8 (Ar-CH), 128.4 (6 x Ar-CH), 122.1 (C), 122.0 (C), 119.6 (3'-CH_2), 118.8 (3'-CH_2), 86.6 (1-C), 85.7 (1-C), 84.9 (2-C), 84.5 (2-C), 54.5 (3-CH), 52.6 (1'-CH_2), 45.2 (1'-CH_2), 44.1 (3-CH), 43.6 (4-CH_2), 41.9 (4-CH_2), 25.4 (5-CH), 24.8 (5-CH), 23.0 (5-Me), 22.1 (5-Me), 22.0 (5-Me), 21.5 (5-Me).

N-Allyl-3-isobutyl-5-phenylpyrazole-N-oxide (298f)



294f **298f**

Using the general procedure, 10% $AgNO_3.SiO_2$ (0.068g, 0.040 mmol, 0.2 eq) was mixed with a solution of *N*-nitroso propargylamine **294f** (~0.05g, 0.201 mmol) in deuteriochloroform (0.75mL). Analysis by ^1H NMR showed complete conversion to the *pyrazole-N-oxide* **298f** in 24 h: δ_H 8.08 (2H, m, 2 x Ar-H), 7.37-7.31 (2H, m, 2 x Ar-H), 7.27-7.21 (1H, m, Ar-H), 6.14 (1H, s, 4-H), 5.84 (1H, ddt, J 17.1, 10.3 and 5.1, 2'-H), 5.14 (1H, ddt, J 10.3, 1.4 and 1.0, 3'-H_a), 4.97 (1H, ddt, J 17.1, 1.4 and 1.0, 3'-H_b), 4.77 (2H, dt, J 5.1 and 1.4, 1'-CH_2), 2.36 (2H, d, J 7.2, 1''-CH_2), 1.93-1.79 (1H, m, 2''-H), 0.90 (6H, d, J 6.7, 2''-Me); δ_c 132.8 (C), 131.2 (Ar-CH), 130.0 (C), 128.6 (2 x Ar-CH), 128.2 (C), 126.5 (2 x Ar-CH), 117.8 (3'-CH_2), 98.4 (2'-CH), 44.8 (1'-CH_2), 35.1 (1''-CH_2), 27.7 (2''-CH), 22.4 (2 x 2''-Me); *m/z* (APCI) 257 $[M+H]^+$ 100%, [Found $[M+H]^+$, 257.1643. $C_{16}H_{21}N_2O$ requires *M+H*, 257.1654].

Preparation of (*R*)- and (*S*)-334 and 336.

Both (*R*)- and (*S*)-enantiomers were treated in an identical fashion. All ^1H, ^{13}C, IR and *m/z* data collected was seen to be identical for each enantiomerically pure intermediate. $[\alpha]_D^{291}$ values were used to determine the optical activity of each enantiomer of the final furans **334** and **336.**

8-Iodo-2,6-dimethyloct-2-ene (330)

330

Iodine (3.35g, 1.32 mmol, 1.2 eq) was added to a stirred solution of triphenylphosphine (3.46g, 1.32 mmol, 1.2 eq) and imidazole (0.898g, 1.32 mmol, 1.2 eq) dichloromethane (30 mL). Citronellol (2 mL, 1.10 mmol, 1 eq) was added dropwise after 15 mins, and the resulting mixture

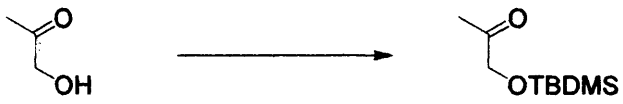
stirred at room temperature overnight. The reaction was quenched with water (30 mL) and the product extracted into dichloromethane (3 x 50 mL), washed with water (100 mL) and brine (100 mL), then dried, filtered and evaporated to yield a pale orange oil. Hexane (25 mL) was then added to crystallise the triphenylphosphine oxide, which was then removed by filtration through a sintered funnel. Evaporation of the solvent gave *citronellyl iodide* **330** (2.41g, 82%) as a pale orange oil: υ_{max}/cm^{-1} (film) 3226, 2962, 2923, 1437, 1377, 1180, 1119, 972, 722, 694; δ_H 5.10 (1H, t heptet, J 6.4 and 1.2, 3-H), 3.18 (1H, ddd, J 9.5, 8.6 and 5.6, 8-H_a), 3.10 (1H, ddd, J 9.5, 8.2 and 7.1, 8-H_b), 2.00-1.85 (2H, m, 4-CH_2), 1.60 (3H, d, J 1.2, 1-Me), 1.60-1.54 (1H, m, 6-H), 1.54 (3H, d, J 1.2, 2-Me), 1.50-1.42 (2H, m, 7-CH_2), 1.31-1.04 (2H, m, 5-CH_2), 0.80 (3H, d, J 6.5, 6-Me); δ_c 131.9 (2-C), 124.4 (3-CH), 40.9 (7-CH_2), 36.4 (5-CH_2), 33.5 (6-CH), 25.7 (6-Me), 25.3 (4-CH_2), 18.6 (1-Me), 17.7 (2-Me), 5.2 (8-CH_2).

5,9-Dimethyldec-8-en-1-yne (331)

330 **331**

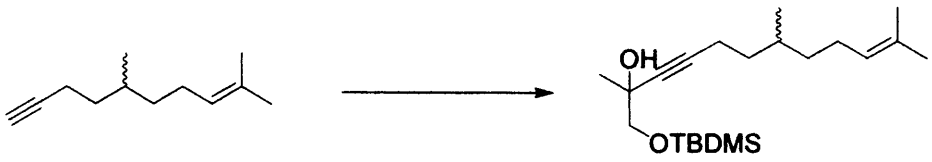
A solution of lithium acetylide ethylene diamine complex (0.955g, 10.37 mmol, 1.2 eq) in DMSO (20 mL) was stirred at 0°C for 10 mins. Citronellyl iodide **330** (2.3g, 8.64 mmol, 1 eq) was then added dropwise and the reaction allowed to warm to room temperature with stirring for 1 h. Water was added to quench the reaction, the product extracted into hexane (3 x 25 mL) and the combined organic extracts washed with water (100 mL) and brine (100 mL), then dried, filtered and evaporated to yield a pale orange oil, *acetylene* **331** (1.13g, 78%): R_f 0.65 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3304, 2929, 2358, 1668, 1531, 1436, 1377, 1264, 1079, 895, 739; δ_H 5.00 (1H, t heptet, J 7.1 and 1.3, 8-H), 2.11 (2H, dt, J 6.1 and 1.8, 3-CH_2), 1.90 (2H, m, 7-CH_2), 1.85 (1H, t, J 1.8, 1-H), 1.61 (3H, d, J 1.3, 9-Me), 1.54 (3H, d, J 1.3, 10-Me), 1.45 (2H, m, 4-CH_2), 1.27 (2H, m, 6-CH_2), 1.09 (1H, m, 5-H), 0.80 (3H, d, J 6.6, 5-Me); δ_c 131.2 (9-C), 124.7 (8-CH), 84.9 (2-C), 67.9 (1-CH), 36.6 (5-CH), 35.5 (3-CH_2), 31.6 (7-CH_2), 25.7 (5-CH_2), 25.4 (4-CH_2), 19.0 (9-Me), 17.6 (10-Me), 16.1 (6-CH_2).

O-TBDMS acetol[220]



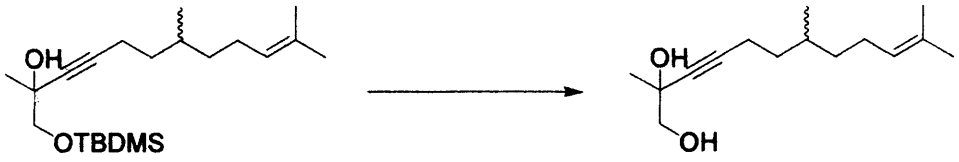
Imidazole (11.37g, 48.9 mmol, 3 eq), TBDMS-chloride (7.34g, 48.9, 3 eq) and DMAP (0.28g, 2.24 mmol, 0.1 eq) were added to a solution of acetol (1.21g, 16.3 mmol, 1 eq) in dichloromethane (15 mL) and stirred overnight at ambient temperature. The reaction was quenched with water (25 mL), the product extracted into petroleum ether (3 x 50 mL) and the combined organic layers washed with water (100 mL) and brine (100 mL), then dried, filtered and evaporated to yield *O-TBDMS acetol* (2.98g, 97%) as a yellow oil. The product was subsequently distilled at 0.5mmHg (b.p. 28-32°C), to yield a colourless oil (2.67g, 87%): υ_{max}/cm^{-1} (film) 3445, 2954, 2857, 1720, 1472, 1360, 1254, 1119, 1071, 1005, 837, 778, 669; δ_H 4.06 (2H, s, 1-CH_2), 2.11 (3H, s, 3-Me), 0.84 (9H, s, *t*-Bu Me), 0.00 (6H, s, Si-Me); δ_c 209.4 (C), 69.5 (1-CH_2), 25.9 (3-Me), 25.6 (*t*-Bu Me), 18.1 (C), -5.5 (Si-Me). All data obtained matched that previously reported in the literature.

2,7,11-Trimethyldodec-10-en-3-yne-1,2-diol (333a)



331 **332a**

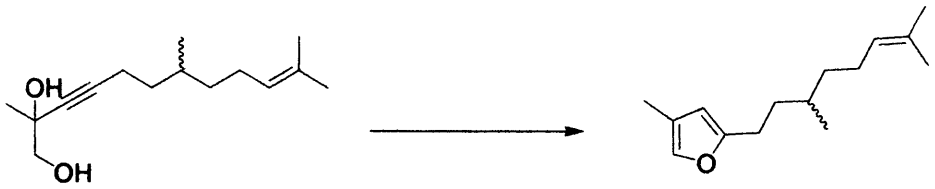
Using the general procedure, citronellyl acetylene **331** (0.25g, 1.52 mmol, 1 eq) was added to *O*-TBDMS acetol (0.315g, 1.67 mmol, 1.1 eq) to give a crude yellow oil (0.419g) containing *propargyl alcohol* **332a**. Key selected data: δ_H 5.00-4.94 (1H, m, 10-H), 3.51-3.45 (2H, m, 1-CH_2), 1.59 (3H, s, 11-Me), 1.51 (3H, s, 12-Me), 1.30 (3H, s, 2-Me), 0.82 (9H, s, *t*-Bu Me), 0.00 (6H, s, Si-Me). The propargyl alcohol **332a** was used without further purification.



332a **333a**

Tetrabutylammonium fluoride (3.54 mL of a 1M solution in THF, 3.54 mmol, 4 eq) was added to a solution of propargyl alcohol **332a** (0.291g, 0.88 mmol, 1 eq) in dichloromethane (10 mL). The resulting solution was stirred overnight at ambient temperature, then diluted with water (25 mL) and extracted into dichloromethane (3 x 25 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), then dried, filtered and evaporated to give a thick yellow oil (0.311g), which was purified by column chromatography (30:70 ethyl acetate – hexane) to yield the *diol* **333a** (0.08g, 37%) as a colourless oil with a weak nondescript odour: R_f 0.28 (30 : 70 ethyl acetate – hexane): υ_{max}/cm^{-1} (film) 3411, 2918, 2359, 2224, 1618, 1438, 1361, 1221, 1166; δ_H 5.09 (1H, t. heptet, J 7.1 and 1.4, 10-H), 3.61 (1H, dd, J 10.9 and 4.9, 1-H_a), 3.46 (1H, d, J 10.9 and 8.9, 1-H_b), 2.48 (1H, s, OH), 2.30-2.15 (2H, m, 5-CH_2), 2.05-1.91 (2H, m, 9-CH_2), 1.68 (3H, s, 11-Me), 1.60 (3H, d, J 1.4, 12-Me), 1.60-1.48 (2H, m, 6-CH_2), 1.41 (3H, d, J 1.4, 2-Me), 1.39-1.29 (2H, m, 8-CH_2), 1.20-1.10 (1H, m, 7-H), 0.88 (3H, d, J 6.5, 7-Me); δ_c 131.4 (11-C), 124.6 (10-CH), 85.6 (3-C), 81.3 (4-C), 71.0 (1-CH_2), 68.7 (2-C), 36.6 (5-CH_2), 35.7 (9-CH_2), 31.7 (7-CH), 25.8 (11-Me), 25.5 (12-Me), 25.4 (6-CH_2), 19.1 (7-Me), 16.4 (8-CH_2).

4-Methyl-2-(3,7-dimethyloct-6-enyl)furan (334)



333a **334**

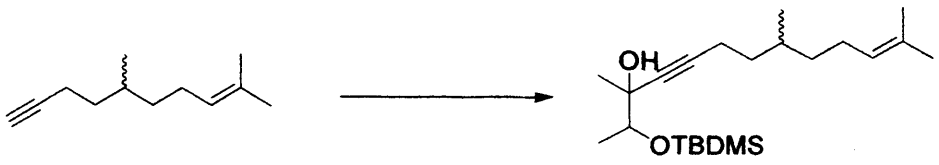
Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.114g, 0.067 mmol) was stirred with a solution of diol **333a** (0.08g, 0.336 mmol) in dichloromethane to yield the *furan* **334** (0.067g, 91 and 90%) as a clear oil: υ_{max}/cm^{-1} (film) 3465, 2931, 2336, 1617, 1551, 1453, 1376, 1270, 1121, 947, 884; δ_H 6.98 (1H, s, 5-H), 5.77 (1H, s, 3-H), 5.02 (1H, t heptet, J 7.1 and 1.4, 6'-H), 2.55-2.35 (2H, m, 1'-CH_2), 2.00-1.82 (2H, 5'-CH_2), 1.91 (3H, s, 4-Me), 1.61 (3H, s, 7'-Me), 1.53 (3H, s, 8'-Me), 1.42-1.31 (4H, 2'- and 4'-CH_2), 1.19-1.09 (1H, m, 3'-H), 0.83 (3H, d, J 6.3, 3'-Me); δ_c

156.8 (2-C), 137.2 (5-CH), 131.2 (7'-C), 124.9 (6'-CH), 120.4 (4-C), 107.3 (3-CH), 36.9 (1'-CH_2), 35.3 (5'-CH_2), 32.0 (3'-CH), 25.7 (4-Me), 25.7 (2'-CH_2), 25.4 (4'-CH_2), 19.4 (7'-Me), 17.7 (8'-Me), 9.8 (3'-Me). $[\alpha]_D^{291}$ *(R)-enantiomer* -7.8° (oily scent). $[\alpha]_D^{291}$ *(S)-enantiomer* +6.3° (some woody, earthy overtones).

O-TBDMS 3-hydroxybutan-2-one

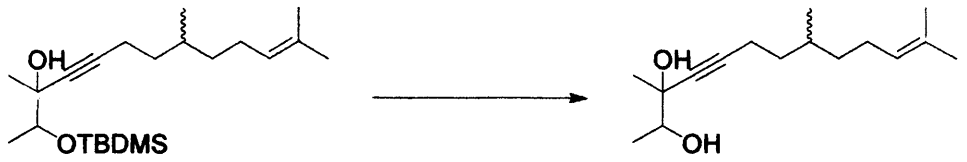
Imidazole (6.1g, 90.0 mmol, 4 eq), TBDMS-chloride (6.63g, 45.0 mmol, 2 eq) and DMAP (0.28g, 2.24 mmol, 0.1 eq) were added to a solution of 3-hydroxybutan-2-one (2g, 22.7 mmol, 1 eq) in dichloromethane (20 mL) and stirred overnight at ambient temperature. The reaction was quenched with water (25 mL), the product extracted into petroleum ether (3 x 50 mL) and the combined organic layers washed with water (100 mL) and brine (100 mL), then dried, filtered and evaporated to yield *O-TBDMS 3-hydroxybutan-2-one* (4.59g, 99%) as a colourless oil: υ_{max}/cm^{-1} (film) 3306, 2929, 2358, 1668, 1531, 1436, 1377, 1264, 1079, 895, 739; δ_H 4.04 (1H, q, J 6.8, 2-H), 2.11 (3H, s, 4-Me), 1.20 (1H, d, J 6.8, 1-Me), 0.84 (9H, s, *t*-Bu Me), 0.00 (6H, s, Si-Me); δ_c 208.5 (C), 75.0 (2-CH), 25.7 (4-Me), 24.8 (*t*-Bu Me), 20.7 (1-Me), 18.0 (C), -3.0 (Si-Me).

3,8,12-Trimethyltridec-11-en-4-yne-2,3-diol (333b)



331 **332b**

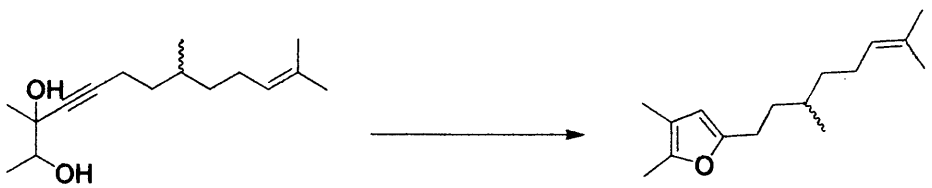
Using the general procedure, citronellyl acetylene **331** (0.33g, 2.01 mmol, 1 eq) was added to *O*-TBDMS 3-hydroxybutan-2-one (0.488g, 2.41 mmol, 1.2 eq) to give a crude yellow oil (0.652g) containing *propargyl alcohol* **332b**. Key selected data: δ_H 5.02 (1H, bt, J *ca* 7, 11-H), 3.58 (1H, q, J 6.0, 2-H), 2.64 (1H, bs, OH), 2.10 (3H, s, 3-Me), 1.60 (3H, s, 12-Me), 1.53 (3H, s, 13-Me), 0.84 (9H, s, *t*-Bu Me), 0.00 (6H, s, Si-Me). The propargyl alcohol **332b** was used without further purification.



332b **333b**

Tetrabutylammonium fluoride (4.86 mL of a 1M solution in THF, 4.86 mmol, 4 eq) was added to a solution of propargyl alcohol **332b** (0.440g, 1.22 mmol, 1 eq) in dichloromethane (10 mL). The resulting solution was stirred overnight at ambient temperature, then diluted with water (25 mL) and extracted into dichloromethane (3 x 25 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), then dried, filtered and evaporated to give a thick yellow oil (0.498g), which was purified by column chromatography (30:70 ethyl acetate – hexane) to yield a colourless oil, the *diol* **333b** (0.135g, 35%) as a mixture of two diastereoisomers in a ratio of 89:11, which together displayed a weak nondescript odour: R_f 0.40 (30 : 70 ethyl acetate – hexane): υ_{max}/cm^{-1} (film) 3425, 2925, 2254, 1652, 1465, 1383, 1097, 911; δ_H 5.01 (1H, bt, J *ca* 7.1, 11-H), 3.69 (0.11H, q J 6.6, 2-H), 3.58-3.51 (0.89H, m, 2-H), 2.65 (1H, bs, OH), 2.25-2.05 (2H, m, 6-CH_2), 2.00-1.80 (3H, m, 10-CH_2 and OH), 1.62 (3H, s, 12-Me), 1.54 (3H, s, 13-Me), 1.52-1.41 (2H, m, 7-CH_2), 1.33 (2.67H, s, 3-Me), 1.32 (0.33H, s, 3-Me), 1.31-1.22 (2H, m, 9-CH_2), 1.20 (2.67H, d, J 6.3, 1-Me), 1.15 (0.33H, d, J 6.6, 1-Me), 1.13-1.03 (1H, m, 8-H), 0.82 (3H, d, J 6.7, 8-Me); 131.5 (C), 124.7 (11-CH), 86.4 (4-C), 80.4 (5-C), 77.3 (2-CH), 74.5 (2-CH), 72.1 (3-C), 36.7 (6-CH_2), 35.8 (10-CH_2), 31.7 (8-CH), 25.9 (1-Me), 25.8 (3-Me), 25.4 (7-CH_2), 19.1 (12-Me), 18.5 (13-Me), 17.7 (8-Me), 16.4 (9-CH_2).

2,3-Dimethyl-5-(3,7-dimethyloct-6-enyl)furan (336)



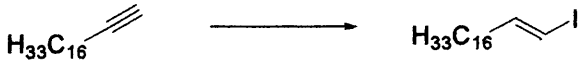
333b **336**

Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.182g, 0.117 mmol) was stirred with a solution of diol **333b** (0.135g, 0.535 mmol) in dichloromethane to yield the *furan* **334** (0.117g, 92 and 95%) as a clear oil: υ_{max}/cm^{-1} (film) 3451, 2918, 2567, 2242, 1642, 1578, 1448, 1376, 1260,

1223, 1164, 1123, 992, 858; δ_H 5.67 (1H, s, 4-H), 5.03 (1H, t heptet, J 7.0 and 1.3, 6'-H), 2.53-2.38 (2H, m, 1'-CH_2), 2.09 (3H, s, 2-Me), 2.00-1.82 (2H, 5'-CH_2), 1.82 (3H, s, 3-Me), 1.68 (3H, s, 7'-Me), 1.60 (3H, s, 8'-Me), 1.46-1.35 (4H, 2'- and 4'-CH_2), 1.21-1.05 (1H, m, 3'-H), 0.83 (3H, d, J 6.4, 3'-Me); δ_c 153.7 (5-C), 145.1 (2-C), 131.2 (7'-C), 124.9 (6'-CH), 114.1 (3-C), 107.6 (4-CH), 36.9 (1'-CH_2), 35.2 (5'-CH_2), 32.0 (3'-CH), 25.8 (3-Me), 25.6 (2'-CH_2), 25.5 (4'-CH_2), 19.4 (7'-Me), 17.7 (8'-Me), 11.3 (2-Me), 9.9 (3'-Me). $[\alpha]_D^{291}$ *(R)-enantiomer* -8.9° (oily scent). $[\alpha]_D^{291}$ *(S)-enantiomer* +11.4° (fruity flowery scent).

Towards the synthesis of Plakorsin A and B

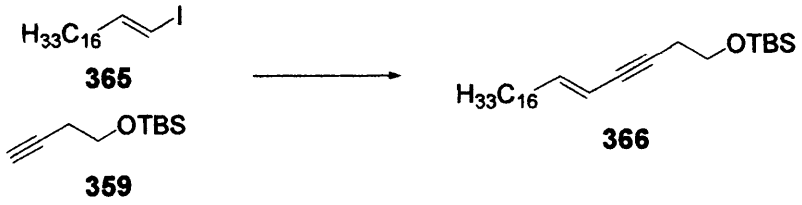
(*E*)-1-Iodooctadec-1-ene (365)



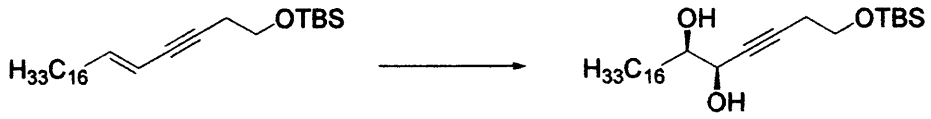
365

Catecholborane (0.42 mL, 3.99 mmol, 1 eq) was added dropwise to 1-octadecyne (1g, 3.99 mmol, 1 eq) and the mixture heated to 70°C for 2 h, then cooled to ambient temperature and stirred with water (5 mL) for a further 2 h. The resulting white solid was collected by filtration and washed free of catechol with ice-cold water (5 mL). Next, 3M sodium hydroxide (5 mL) was added slowly to a solution of the white solid, (*E*)-1-octadecenylboronic acid, in diethyl ether (10 mL), which was maintained at 0 °C. After stirring for 0.25 h, iodine (1.2g, 4.79 mmol, 1.2 eq) in diethyl ether (10 mL) was added with stirring for 0.5 h. Saturated aqueous sodium thiosulfate (few mL) was added and the product extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with water (2 x 50 mL) and brine (1 x 50 mL) then dried, filtered and evaporated to yield a pale yellow wax, *(E)-1-iodooctadec-1-ene* **365** (0.679g, 45%): υ_{max}/cm^{-1} (DCM) 3419, 2926, 2854, 2305, 1639, 1466, 1377, 1264, 1099, 947, 896, 740; δ_H 6.43 (1H, dt, J 14.4 and 7.3, 2-H), 5.89 (1H, dt, J 14.4 and 1.3, 1-H), 1.97 (2H, *app. dt*, J 7.3 and 1.3, 3-CH_2), 1.49-1.41 (2H, m, 4-CH_2), 1.24-1.14 (26H, m, 5 → 17-CH_2), 0.81 (3H, t, J 6.9, 18-Me); δ_c 146.8 (2-CH), 74.3 (1-CH), 36.1 (3-CH_2), 32.0 (4-CH_2), 30.0-28.3 (12 x CH_2), 22.7 (17-CH_2), 14.2 (18-Me).

(*RS,RS*)-Docos-5,6-dihydroxy-3-ynyloxytributylsilane (367)

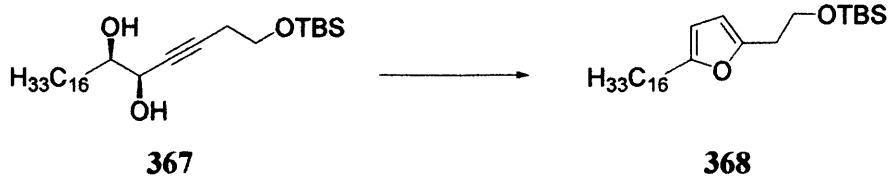


Using the general procedure, *O*-TBS-3-butyn-1-ol **359** (0.35g, 1.32 mmol, 1 eq) was added to (*E*)-1-iodooctadecene **365** (0.5g, 1.32 mmol, 1 eq) to give the *enyne* **366** as a crude yellow solid (0.542g), which was immediately dihydroxylated to give *diol* **367**.



Using the general procedure, enyne **366** (0.5g, 0.96 mmol) was dihydroxylated with potassium osmate (VI) dihydrate (5mg, 20 μmol) to give crude *diol* **367** as a yellow wax (0.450g). The product was purified by column chromatography to give the *syn-diol* **367** as a pure yellow wax (0.037g): υ_{max}/cm^{-1} (film) 3438, 2960, 2237, 1724, 1404, 1266, 1163, 1066, 978, 933, 738, 703; δ_H 4.06 (1H, d, J 6.1, 5-H), 3.63 (2H, t, J 7.2, 1-CH_2), 3.51 (1H, ddt, J 8.1, 6.1 and 3.6, 6-H), 2.37 (2H, dt, J 7.2 and 1.9, 2-CH_2), 1.64-1.52 (2H, m, 7-CH_2), 1.48-1.35 (2H, m, 8-CH_2), 1.27-1.21 (6H, m, Si 1'-CH_2), 1.20-1.14 (26H, m, 9 → 21-CH_2), 0.86-0.78 (15H, m, 22-Me, Si 2'- and 3'-CH_2), 0.57-0.50 (9H, m, Si 4'-Me); δ_c 84.1 (4-C), 79.9 (3-C), 75.1 (5-CH), 66.4 (6-CH), 61.3 (1-CH_2), 32.4 (2-CH_2), 32.0 (2 x CH_2), 29.7 (7 x CH_2), 29.4 (2 x CH_2), 26.6 (3 x Si 1'-CH_2), 25.6 (CH_2), 26.4 (3 x 2'-CH_2), 23.1 (CH_2), 22.7 (2 x CH_2), 14.2 (22-Me), 13.8 (Si 3 x 4'-Me), 13.2 (Si 3 x 3'-CH_2); *m/z* (EI) 534 ([M] - H_2O) 2%.

(2-(5-Hexadecylfuran-2-yl)ethoxy)tributylsilane (368)



Using the general procedure (24 h), 10% $AgNO_3.SiO_2$ (0.018g, 0.010 mmol, 0.2 eq) was added to a solution of diol **367** (0.03g, 0.054 mmol) in DCM to yield *furan* **368** as a yellow oil (0.025g, 86%): δ_H 5.91 (1H, d, J 2.8, 3-H), 5.81 (1H, d, J 2.8, 4-H), 3.78 (2H, t, J 6.7, 2'-CH_2), 2.77 (2H, t, J 6.7, 1'-CH_2), 2.50 (2H, t, J 7.2, 1''-CH_2), 1.55 (6H, m, Si 1'-CH_2), 1.22 (31H, m, 14 x CH_2 and 16''-Me), 0.81 (18H, m, 9 x CH_2), 0.50 (9H, m, Si 4'-Me); δ_c 154.9 (C), 151.2 (C), 106.4 (3-CH), 105.0 (4-CH), 61.5 (2'-CH_2), 31.9 (1'-, 1''-CH_2 and CH_2), 29.7 (6 x CH_2), 29.3 (2 x CH_2), 26.5 (3 x CH_2), 25.3 (3 x CH_2), 22.7 (2 x CH_2), 14.8 (3 x CH_2), 14.1 (16''-Me), 13.8 (3 x Si 4'-Me), 13.3 (2 x CH_2).

Preparation of 7- and 8-membered cyclic ethers

2,3-Dihydro-7-phenyloxepin-4(5H)-one (372)

371 **372**

Method 1:

In an open flask, furan **371** (1 g, 5.32 mmol, 1 eq) was dissolved in acetone (10 mL) at ambient temperature. Jones reagent[178] (3 mL, 6.38 mmol, 1.2 eq) was added dropwise and the solution stirred for 0.5 - 1 h. Sufficient sodium sulfite was added to quench the reaction and the slurry filtered through silica with ethyl acetate (200 mL). The solvent was removed to yield the *oxepin-4-one* **372** as an orange oil (0.497 g, 50%). In a slight modification to this procedure, the reaction was run at 0 °C and basified by the addition of sufficient saturated aqueous potassium carbonate solution after 0.5 h, and the product extracted into ethyl acetate (3 x 25 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL) then dried, filtered and evaporated to yield the *oxepin-4-one* **372** as an orange oil (0.812g, 81%). Recrystallisation from methanol: water yielded orange crystals (0.653 g, mp = 48-50 °C): R_f 0.56 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (DCM) 1756, 1686, 1597, 1449, 1370, 1268, 1219, 1150, 1092, 736, 689; δ_H 7.86 (2H, d, J 7.2, 2 x Ar-H), 7.51 (1H, t, J 7.3, Ar-H), 7.42-7.38 (2H, m, 2 x Ar-H), 4.34 (1H, dt, J 9.2 and 4.2, 2-H_a), 4.13-4.05 (2H, m, 2-H_b and 6-H), 3.55 (1H, dd, J 18.0 and 3.4, 5-

H_a), 3.31 (1H, dd, J 18.0 and 5.5, 5-H_b), 2.82 (1H, dt, J 18.0 and 9.0, 3-H_a), 2.51 (1H, ddd, J 18.0, 7.5 and 4.2, 3-H_b); δ_c (125MHz) 215.8 (C), 196.1 (C), 136.2 (C), 133.6 (Ar-CH), 128.7 (2 x Ar-CH), 128.2 (2 x Ar-CH), 75.5 (6-CH), 65.3 (2-CH_2), 40.6 (5-CH_2), 36.6 (3-CH_2); *m/z* (ES) 227 $[M+K]^+$ 100%.

Method 2:

In an open flask, furan **371** (0.2g, 1.06 mmol) was dissolved in acetone (10 mL) and the solution cooled to 0 °C. Chromium trioxide (0.128g, 1.28 mmol) was added and the solution stirred for 1 h. Sodium sulfite (1 g) was used to quench the reaction and the slurry filtered through silica with ethyl acetate (25 mL). Saturated aqueous potassium carbonate solution (10 mL) was added to neautralise the reaction mixture and the product extracted into ethyl acetate (3 x 25 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL) then dried, filtered and evaporated to yield a 1:1 mixture of *oxepin-4-one* **372** and *furan* **371** (0.162g). All data obtained was in accord with that previously obtained from our conventional approach.

Method 3:

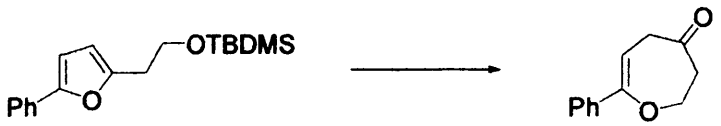
Furan **371** (0.2g, 1.06 mmol) was dissolved in DMF (2 mL) and cooled to 0 °C. Pyridinium dichromate (1.4g, 3.72 mmol) in DMF (4 mL) was added and the solution stirred at ambient temperature overnight. Sodium sulfite (1 g) was used to quench the reaction and the slurry filtered through silica with ethyl acetate (25 mL). Saturated aqueous potassium carbonate solution (few mL) was added to neautralise the reaction mixture and the product extracted into ethyl acetate (3 x 25 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL) then dried, filtered and evaporated to yield a crude product containing primarily *furan* **371** together with trace amounts of *oxepin-4-one* **372** (0.037g). All data obtained was in accord with that previously obtained from our conventional approach.

Method 4:

Dimethyl sulfoxide (0.21mL, 2.93 mmol) was added carefully to a solution of oxalyl chloride (0.13mL, 1.46 mmol) in dichloromethane, cooled to -78 °C and stirred for 10 mins. Furan **371** (0.25g, 1.33 mmol) was added dropwise and the mixture stirred for 15 mins. Finally

triethylamine (0.93mL, 6.65 mmol) was added with further 15 mins, at which point the solution was allowed to warm to 0 °C. The reaction mixture was then filtered through a plug of silica and washed with 30:70 ethyl acetate: hexane. The organic solution was then dried, filtered and evaporated to yield a crude yellow oil (0.123g). The data obtained showed the formation of oxepin-4-one **372** (5%) amongst other products.

Method 5:



392 **372**

In an open flask, furan **392** (0.1 g, 0.314 mmol, 1 eq) was dissolved in acetone (10 mL) and cooled to 0 °C. Jones reagent (0.15 mL, 0.314 mmol, 1 eq) was added dropwise and the solution stirred for 1 h. Sufficient sodium sulfite was added to quench the reaction and the slurry filtered through silica with ethyl acetate (200 mL). The solvent was removed to yield *oxepin-4-one* **372** as an orange oil (0.045 g, 76%). All data obtained was in accord with that previously obtained from our conventional approach.

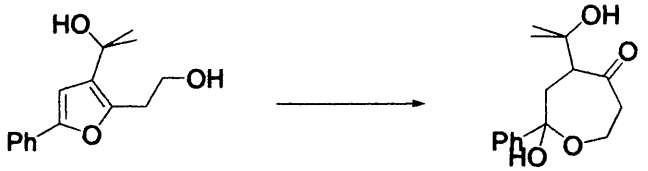
2-(2-(2-Hydroxyethyl)-5-phenylfuran-3-yl)propan-2-ol (393a)

371 **393a**

In an open flask, furan **371** (0.42 g, 2.13 mmol, 1 eq) was dissolved in acetone (10 mL) and cooled to 0 °C. Concentrated sulfuric acid (5 mL) was added dropwise and the solution stirred for 8 h at ambient temperature. Upon re-cooling to 0°C, sufficient aqueous saturated K_2CO_3 was added carefully to neautralise the solution. Next, 2M hydrochloric acid was added dropwise to acidify the solution to pH 4, and the product extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL) then dried, filtered and evaporated to yield a crude brown oil (0.654g). The residue was purified by column

chromatography (30:70 ethyl acetate – petroleum ether) to yield the *furan* **393a** as a yellow oil (0.246 g, 47%): R_f 0.22 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3344, 2972, 1632, 1553, 1486, 1448, 1405, 1379, 1335, 1250, 1224, 1170, 1114, 1092, 1053, 947, 930, 869, 817, 760, 724, 691, 671, 654; δ_H 7.55 (2H, d, J 7.1, 2 x Ar-H), 7.32-7.25 (2H, m, 2 x Ar-H), 7.15 (1H, t, J 7.5, Ar-H), 6.37 (1H, s, 4-H), 3.95 (2H, t, J 5.5, 2'-CH_2), 2.69 (2H, t, J 5.5, 1'-CH_2), 1.39 (6H, s, 1''-Me); δ_c (125MHz) 152.2 (C), 146.4 (C), 131.0 (C), 128.7 (2 x Ar-CH), 127.0 (Ar-CH), 126.4 (C), 123.4 (2 x Ar-CH), 102.5 (4-CH), 73.0 (C), 59.6 (2'-CH_2), 28.1 (2 x 1''-Me), 24.7 (1'-CH_2); *m/z* (ES) 269 $[M+Na]^+$ 100%.

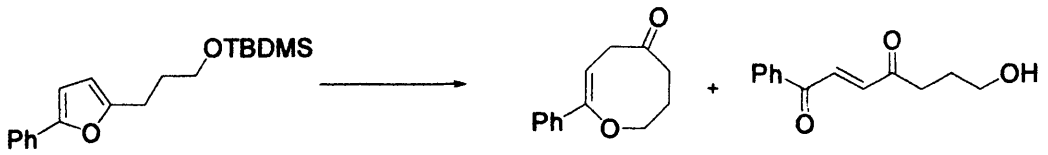
7-Hydroxy-5-(2-hydroxypropan-2-yl)-7-phenyloxepan-4-one (394)



393a **394**

In an open flask, furan **393a** (0.1 g, 0.406 mmol, 1 eq) was dissolved in acetone (10 mL) and cooled to 0°C. Jones reagent (0.23 mL, 0.487 mmol, 1.2 eq) was added dropwise and the solution stirred for 1 h. Sufficient sodium sulfite was added to quench the reaction and the slurry filtered through silica with ethyl acetate (100 mL). The solvent was removed to a crude yellow oil (0.09 g) containing the desired *oxepane-4-one* **394** together with oxepin-4-one **372**, formed from previous trace impurities of furan **371**. The product was purified by column chromatography (30:70 ethyl acetate – petroleum ether) to yield the *oxepan-4-one* **394** as a yellow oil (0.029 g, 27%): R_f 0.46 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3450, 2977, 2926, 1715, 1687, 1598, 1581, 1449, 1372, 1330, 1281, 1216, 1173, 1148, 1095, 1071, 1003, 912, 851, 734, 690, 648; δ_H 7.92 (2H, d, J 7.3, 2 x Ar-H), 7.50 (1H, t, J 7.3, Ar-H), 7.43-7.38 (2H, m, 2 x Ar-H), 4.10 (1H, ddd, J 11.9, 7.9 and 1.5, 2-H_a), 3.85 (1H, *app.* dt, J 11.9 and 3.1, 2-H_b), 3.52 (1H, dd, J 17.3 and 9.7, 6-H_a), 3.38 (1H, dd, J 9.7 and 2.3, 5-H), 2.75 (1H, dddd, J 13.5, 11.9, 7.9 and 0.8, 3-H_a), 2.51 (1H, dd, J 17.3 and 2.3, 6-H_b), 2.27 (1H, ddd, J 13.5, 3.1 and 1.5, 3-H_b), 1.33 (3H, s, 2'-Me), 1.08 (3H, s, 2'-Me); δ_c (125MHz) 207.4 (C), 197.7 (C), 136.9 (C), 133.1 (Ar-CH), 128.6 (2 x Ar-CH), 128.1 (2 x Ar-CH), 79.4 (C), 61.6 (2-CH_2), 56.2 (5-CH), 42.2 (3-CH_2), 33.8 (6-CH_2), 28.9 (2'-Me), 20.6 (2'-Me); *m/z* (EI) 246 ([M] – H_2O) 2%, 231 (8), 187 (8), 141 (40), 122 (36), 105 (100), 83 (38), 77 (70), [Found [M-H_2O], 246.1265. $C_{15}H_{18}O_3$ requires *M-H_2O*, 246.1256].

3,4-Dihydro-8-phenyl-2H-oxocin-5(6H)-one (397) and **(*E*)-7-hydroxy-1-phenylhept-2-ene-1,4-dione (398)**



396 **397** **398**

In an open flask, furan **396** (0.2 g, 0.630 mmol, 1 eq) was dissolved in acetone (10 mL) and cooled to 0 °C. Jones reagent (0.3 mL, 0.756 mmol, 1.2 eq) was added dropwise and the solution stirred for 1 h. Sufficient sodium sulfite was added to quench the reaction and the slurry filtered through silica with ethyl acetate (200 mL). The solvent was removed to yield a residue (0.129 g), which was purified by column chromatography (20:80 ethyl acetate – petroleum ether) to give a yellow oil (0.020g), which contained *oxecin-5-one* **397** (10%) and *dione* **398** (6%): R_f 0.35 and 0.26 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 2928, 1748, 1639, 1577, 1448, 1210, 1110, 1002, 751, 691; δ_H *oxecin-5-one* 7.90 (1.26H, dd, J 7.2 and 1.4, Ar-H), 7.53-7.48 (0.63H, m, Ar-H), 7.42-7.37 (1.26H, m, Ar-H), 4.45 (0.63H, dd, J 6.0 and 4.7, 7-H), 4.01 (0.63H, ddd, 11.6, 7.1 and 2.1, 2-CH_a), 3.78 (0.63H, *app. dd*, 11.6 and 2.9, 2-CH_b), 3.52 (0.63H, dd, J 17.6 and 4.7, 6-H_a), 3.23 (0.63H, dd, J 17.6 and 6.0, 6-H_b), 2.64 (0.63H, ddd, J 16.1, 7.5 and 2.8, 4-H_a), 2.48 (0.63H, *app. dd*, J 16.1 and 6.7, 4-H_b), 2.18 (0.63H, m, 3-H_a), 2.04 (0.63H, m, 3-H_b); δ_H *dione* 7.77 (0.74H, dd, J 7.4 and 1.3, 2 x Ar-H), 7.32-7.25 (0.74H, m, 2 x Ar-H), 7.24-7.20 (0.37H, m, Ar-H), 6.50 (0.37H, d, J 12.0, 2-H), 5.62 (0.37H, dt, J 12.0 and 2.5, 3-H), 3.73 (0.74H, t, J 6.2, 7-CH_2), 2.50 (0.74H, dt, J 6.7 and 2.5, 5-CH_2), 1.83-1.75 (0.74H, m, 6-CH_2); δ_c (125MHz) *oxecin-5-one* 207.7 (C), 196.8 (C), 136.6 (C), 128.6 (2 x Ar-CH), 128.4 (Ar-CH), 128.2 (2 x Ar-CH), 79.5 (7-CH), 66.6 (2-CH_2), 39.3 (6-CH_2), 38.0 (4-CH_2), 26.5 (3-CH_2); δ_c (125MHz) *dione* 188.2 (C), 180.7 (C), 144.0 (C), 137.7 (2-CH), 133.3 (3 x Ar-CH), 128.3 (2 x Ar-CH), 123.3 (3-CH), 61.8 (7-CH_2), 31.2 (5-CH_2), 16.5 (6-CH_2); *m/z* (ES) 203 $[M+H]^+$ 5% and 219 [*Dione* $M+H]^+$ 100%.

General procedure for the operation of the resin bound flow system

Catalyst Preparation and Formal Priming:

Amberlyst 200C was suspended in water and then packed into a stainless steel column (8 x 0.5 inches), plugged lightly at both ends with cotton wool, using positive pressure. A t-piece joint was fitted to the top of the column so as to allow the introduction of reagent and nitrogen inlets. A saturated aqueous solution of silver nitrate was then passed through the column five times using positive pressure. Water (1L) was then used to wash of any unbound silver from the column. Acetone (250mL), methanol (250mL), hexane (250mL) and dichloromethane (250mL) were then passed through the column to condition it for use.

Continuous cyclisation reaction:

A heterocyclic precursor (e.g. diols **100, 126**) was dissolved in dichloromethane (typically 10 mL g^{-1}). The resulting solution was passed through the column at a flow rate of 1mL/min, and the output collected into a round- bottomed flask. The solvent was removed to yield product in excellent purity and yield (>95%). The column was then washed and re-primed.

Washing:

Methanol (50mL), hexane (50mL) and dichloromethane were passed sequentially through the column (5mL/min) to remove any organics. The flow rate was then adjusted to 0.1mL/min in preparation for additional runs.

General procedure for the operation of the $scCO_2$: IL flow system

Catalyst Preparation:

Silver triflate was dissolved in the required ionic liquid (10g/g) and stirred in a foil-wrapped flask at 40°C until dissolved (*ca.* 1h). The solution was then transferred to the autoclave chamber and, with stirring, heated to the desired reaction temperature and placed under pressure.

$scCO_2$ Cyclisation Reaction:

Once at temperature and pressure, the output pressure regulator was adjusted to maintain a continuous flow of CO_2 (1mL/min). Diol **100a** was then added at a steady flow rate (0.05-0.2mL/min). Samples were collected every 30mins by shutting the output pressure regulator momentarily and then releasing the pressure in the decompression chamber. Pure furan **101a** was then collected into a small vial, *via* a tap at the bottom of the decompression chamber, and then the flow of CO_2 restored. Once finished, CO_2 was used to flush the system and the catalyst used again, if desired.

General procedure for the use of the microwave reactor

Diol **100e** was dissolved in dichloromethane (10ml g^{-1}) and placed inside a microwave tube fitted with a stirrer bar. 10% w/w silver nitrate on silica gel (0.1 - 0.5eq) was then added to the stirred solution, which was then immeadiately irradiated with microwave radiation for 1h. The resulting suspension was then filtered through celite and the solvent evaporated to yield furan **101e** in excellent yield (>95%).

Chapter 9: References

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Chapter 10: Appendix

Supplementary Information

Appendix A: X-Ray Data for Chelation Control Diol **100f.**

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Table 1. Crystal data and structure refinement.

Identification code	**2007src0348 (MG002)**	
Empirical formula	$C_{22}H_{18}O_2$	
Formula weight	314.36	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	$a = 15.5139(3)$ Å	$\alpha = 90°$
	$b = 5.63200(10)$ Å	$\beta = 93.0380(10)°$
	$c = 18.7366(4)$ Å	$\gamma = 90°$
Volume	1634.80(6) Å^3	
Z	4	
Density (calculated)	1.277 Mg / m^3	
Absorption coefficient	0.081 mm^{-1}	
F(000)	664	
Crystal	Prism; colourless	
Crystal size	0.50 × 0.20 × 0.20 mm^3	
θ range for data collection	3.32 – 27.49°	
Index ranges	$-18 \le h \le 20$, $-7 \le k \le 7$, $-24 \le l \le 21$	
Reflections collected	18952	
Independent reflections	3754 [$R_{int} = 0.0757$]	
Completeness to $\theta = 27.49°$	99.7 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9841 and 0.9608	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3754 / 0 / 219	
Goodness-of-fit on F^2	1.124	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0598$, $wR2 = 0.1408$	
R indices (all data)	$R1 = 0.0879$, $wR2 = 0.1548$	
Largest diff. peak and hole	0.242 and –0.344 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SADABS Version 2.10.* (G. M. Sheldrick (2003)) Bruker AXS Inc., Madison, Wisconsin, USA. **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** *PLATON* (A.L. Spek, J. Appl. Crystallogr. 2003, 36, 7).

Special details:
C1 = C2 = S Chirality

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	1006(1)	1949(3)	9373(1)	19(1)	1
C2	1554(1)	3415(3)	9938(1)	20(1)	1
C3	1097(1)	2803(3)	8616(1)	19(1)	1
C4	1601(1)	1509(4)	8163(1)	23(1)	1
C5	1700(1)	2262(4)	7465(1)	29(1)	1
C6	1294(1)	4303(4)	7216(1)	29(1)	1
C7	783(1)	5604(4)	7661(1)	26(1)	1
C8	686(1)	4860(3)	8359(1)	22(1)	1
C9	2505(1)	3207(3)	9775(1)	19(1)	1
C10	2962(1)	1156(4)	9965(1)	24(1)	1
C11	3826(1)	941(4)	9813(1)	29(1)	1
C12	4237(1)	2745(4)	9463(1)	28(1)	1
C13	3785(1)	4774(4)	9265(1)	28(1)	1
C14	2921(1)	5004(4)	9419(1)	24(1)	1
C15	1421(1)	2507(4)	10666(1)	23(1)	1
C16	1355(1)	1912(4)	11277(1)	23(1)	1
C17	1325(1)	1384(3)	12027(1)	20(1)	1
C18	1695(1)	2990(4)	12522(1)	26(1)	1
C19	1689(2)	2516(4)	13246(1)	33(1)	1
C20	1314(2)	460(4)	13489(1)	32(1)	1
C21	942(2)	−1141(4)	13000(1)	33(1)	1
C22	952(1)	−695(4)	12274(1)	27(1)	1
O1	121(1)	2103(2)	9568(1)	24(1)	1
O2	1326(1)	5865(2)	9896(1)	24(1)	1

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

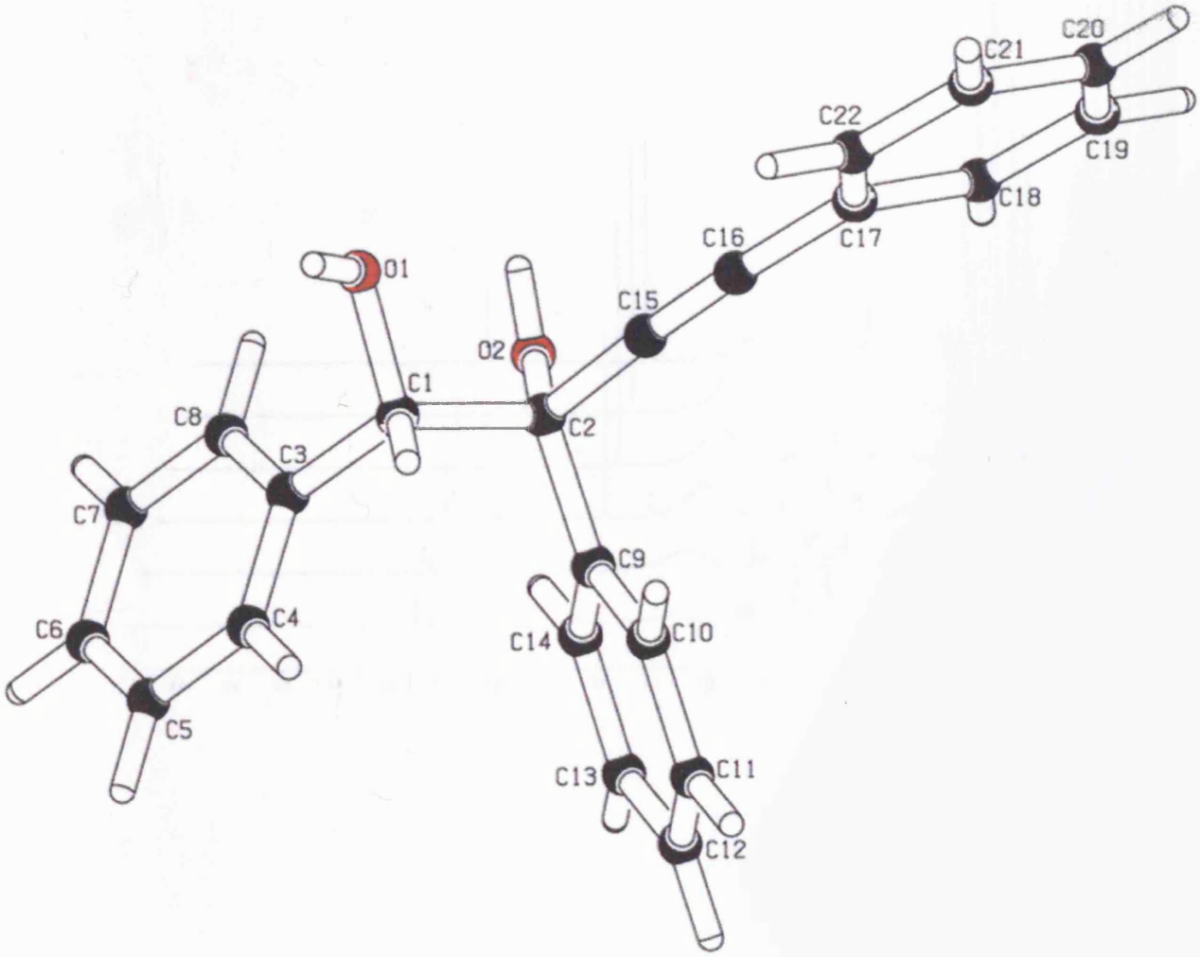
C1–O1	1.442(2)	C9–C10	1.392(3)
C1–C3	1.511(3)	C10–C11	1.390(3)
C1–C2	1.559(3)	C11–C12	1.383(3)
C2–O2	1.425(2)	C12–C13	1.382(3)
C2–C15	1.481(3)	C13–C14	1.391(3)
C2–C9	1.528(3)	C15–C16	1.202(3)
C3–C4	1.391(3)	C16–C17	1.440(3)
C3–C8	1.396(3)	C17–C22	1.395(3)
C4–C5	1.391(3)	C17–C18	1.398(3)
C5–C6	1.381(3)	C18–C19	1.384(3)
C6–C7	1.390(3)	C19–C20	1.383(3)
C7–C8	1.388(3)	C20–C21	1.388(3)
C9–C14	1.390(3)	C21–C22	1.385(3)

O1–C1–C3	110.86(15)
O1–C1–C2	106.79(15)
C3–C1–C2	113.22(15)
O2–C2–C15	109.82(15)
O2–C2–C9	107.61(15)
C15–C2–C9	109.97(16)
O2–C2–C1	110.50(15)
C15–C2–C1	110.17(16)
C9–C2–C1	108.74(15)
C4–C3–C8	118.98(18)
C4–C3–C1	119.39(17)
C8–C3–C1	121.63(17)
C3–C4–C5	120.59(19)
C6–C5–C4	120.04(19)
C5–C6–C7	119.98(19)
C8–C7–C6	120.05(19)
C7–C8–C3	120.36(18)
C14–C9–C10	118.93(18)
C14–C9–C2	121.25(17)
C10–C9–C2	119.79(17)
C11–C10–C9	120.22(19)
C12–C11–C10	120.48(19)
C13–C12–C11	119.65(19)
C12–C13–C14	120.1(2)
C9–C14–C13	120.57(19)
C16–C15–C2	174.8(2)
C15–C16–C17	174.8(2)
C22–C17–C18	119.09(18)
C22–C17–C16	122.18(18)
C18–C17–C16	118.73(18)
C19–C18–C17	120.1(2)
C20–C19–C18	120.6(2)
C19–C20–C21	119.6(2)
C22–C21–C20	120.3(2)
C21–C22–C17	120.3(2)

Symmetry transformations used to generate equivalent atoms:

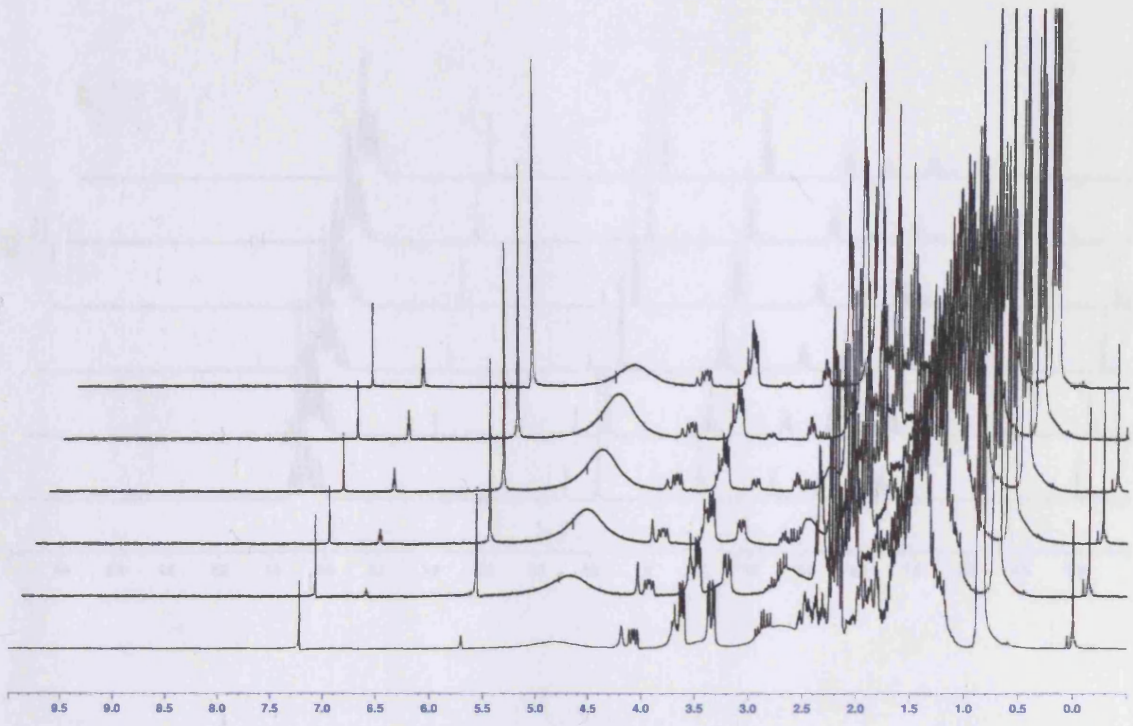
Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	18(1)	15(1)	23(1)	2(1)	3(1)	1(1)
C2	23(1)	14(1)	22(1)	0(1)	2(1)	1(1)
C3	18(1)	18(1)	20(1)	1(1)	−1(1)	−3(1)
C4	23(1)	23(1)	23(1)	1(1)	−1(1)	2(1)
C5	29(1)	36(1)	22(1)	−2(1)	4(1)	3(1)
C6	30(1)	36(1)	21(1)	7(1)	1(1)	−5(1)
C7	26(1)	23(1)	27(1)	7(1)	−4(1)	−2(1)
C8	24(1)	19(1)	25(1)	0(1)	1(1)	0(1)
C9	21(1)	19(1)	16(1)	−1(1)	−1(1)	−1(1)
C10	28(1)	22(1)	21(1)	2(1)	0(1)	2(1)
C11	27(1)	28(1)	30(1)	3(1)	−3(1)	7(1)
C12	20(1)	35(1)	29(1)	−2(1)	−1(1)	−1(1)
C13	24(1)	29(1)	31(1)	4(1)	1(1)	−5(1)
C14	24(1)	20(1)	27(1)	3(1)	−1(1)	0(1)
C15	24(1)	21(1)	24(1)	−2(1)	2(1)	2(1)
C16	22(1)	23(1)	24(1)	−2(1)	1(1)	2(1)
C17	19(1)	22(1)	19(1)	−1(1)	1(1)	3(1)
C18	28(1)	23(1)	26(1)	−3(1)	2(1)	−2(1)
C19	39(1)	36(1)	23(1)	−7(1)	−1(1)	0(1)
C20	33(1)	43(1)	20(1)	6(1)	5(1)	9(1)
C21	31(1)	32(1)	36(1)	10(1)	7(1)	2(1)
C22	26(1)	27(1)	28(1)	−1(1)	−1(1)	−2(1)
O1	21(1)	20(1)	30(1)	0(1)	7(1)	−5(1)
O2	25(1)	15(1)	32(1)	−1(1)	5(1)	2(1)

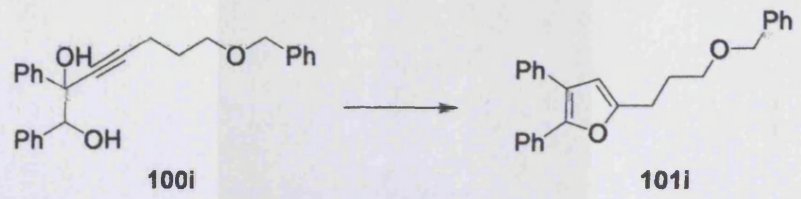

C21
C20
C22
C19
C18
C16
C17
O1
C15
O2
C1
C2
C8
C3
C7
C9
C6
C4
C14
C10
C5
C13
C11
C12

Appendix B: ^{1}H NMR profile of 3-alkyne-1,2-diol **100k** cyclisation.

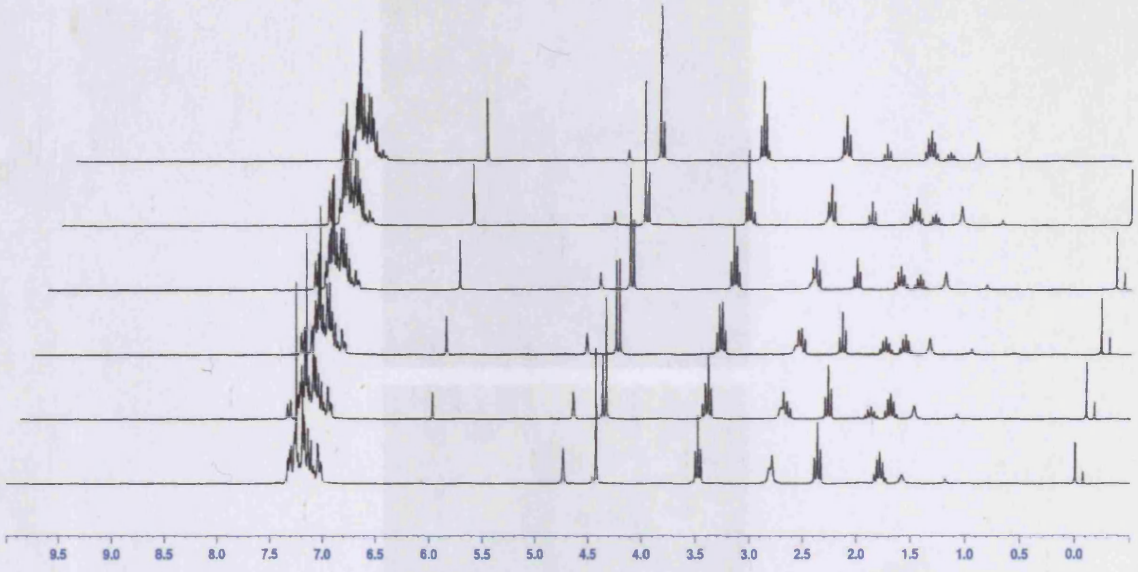
100k **101k**



Appendix C: ^{1}H NMR profile of 3-alkyne-1,2-diol **100i** cyclisation.



100i **101i**



Appendix D: A Flow System for Heterocyclic Synthesis.