5-*Endo*-Dig Approaches to Pyrroles

A thesis submitted to Cardiff University

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BSc, MSc

In candidature of

Doctor of Philosophy

September 2004

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Abstract

This project required developing new practical routes towards pyrroles and could help the project of total synthesis of *(-)-rhazinilam*. In chapter one, the most widely used methods for constructing the pyrrole ring system are reviewed. The origins of this project were to investigate further uses for the iodocyclization reactions developed previously. In chapter 2, a new approach to such highly substituted pyrroles in which the key step is a 5-*endo*-dig halocyclisation of substituted homopropargylic sulfonamides was successfully achieved. Key to the success of this novel method is the rapid preparation of suitable starting materials, from 1-alkynes by sequential formylation and condensation with a tin(II) enolate of *N*-tosyl glycinate.

Also, in chapter 2, a transition metal-catalyzed cyclisation using silica-supported silver nitrate was investigated and found to be effective. The reaction is clean and proceeds in quantitative yields. Obviously this fundamental research project is of a great interest because *(-)-rhazinilam* acts as an antimitotic agent like taxol, which are powerful anticancer agents. Different strategies of this approach are reviewed in chapter 3.

In chapter 4 and 5, various aspects of separate approaches to the anti-tumor compound *rhazinilam* are described. In the former, both the synthesis of suitable 3-arylpyrrole cores and strategies for extending this methodology by the incorporation of a suitable substituent based on a cleavable cyclohexene are outlined. In the second section, chapter 5, similar issues are addressed but, in contrast, the Ag(I) methodology is used to construct a suitable arylpyrrole, the synthesis of which also features construction of the key precusor by aziridine ring hydrolysis. An efficient route to an enantiopure precusor of the necessary side chain is also described.

This thesis is completed by a full experimental section and reference list.

Acknowledgements

I would like to take this opportunity to thank my supervisor Professor David W. Knight for his enthusiasm, guidance and support throughout this project. I am very grateful to all members of the academic staff and the technicians of the chemistry department at Cardiff university, especially Mr. Rob Jenkins and Rob for their assistance and to Prof.Knight's secretary, Mrs Fran Godwin, for her encouragement and constant support.

I would like also to thank Dr. K. M. A. Malik and Dr. Liling Ooi for their help on the X-ray crytal structures; all other students of the department, past and present, especially Chris, Lilian, Amjad, John, Emily, Nick, Mel, Xu, Charlie boy, Ian, Heizi, Lars, Shaista, and any others for making my time at Cardiff so pleasurable. I am so grateful to my great friends, Charlie, Siân and Nigel for proofreading my Thai-english thesis.

I must thank my family for their great support; my mother for her belief, my father for his encouragement, my sister and my brother for their enthusiasm, and finally my sweetest guy, Edmond for being here and helped me through a difficult time in my life.

Finally, I could not make it without the help from Royal Thai Government and EPRSC for financial support.

Thank you so much.

JIRADA

CONTENTS

Chapter two: Results and Discussion

Chapter three : (-)-Rhazinilam

Abbreviations

AcOH	acetic acid
APcI	atmospheric pressure chemical ionisation
Bn	benzyl
Bu	butyl
BOC	*t*-butoxycarbonyl
bp	boiling point
Bz	benzoyl
c	concentrated
COSY	correlation spectroscopy
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer
DIBAL-H	di-*iso*-butylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N'*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2[1H]-pyrimidinone
DMSO	dimethyl sulphoxide
ee	enantiomeric excess
EDCI	1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide
EI	electron ionization
eq	equivalents
ES	electrospray
EtOAc	ethyl acetate
Δ	heat
h	hours
HOBT	1-Hydroxybenzotriazole, monohydrate
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
LiAlH	lithium aluminium hydride
LHMDS	lithium bis(trimethylsilyl) amide
LDA	lithium diisopropylamine
M	molar
mp	melting point

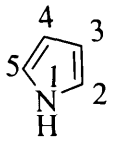
min	minutes
mol	mole
n-BuLi	normal butyl lithium
Ms	methanesulphonyl
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
PCC	pyridinium chlorochromate
PPTS	pyridinium *p*-toluenesulphonate
pyr	pyrrole
r.t.	room temperature
R_f	retention factor values
TBAF	tetrabutylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TEOA	triethyl orthoacetate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Tlc	thin layer chromatography
TMSCl	trimethylsilyl choride
Tr/trityl	triphenylmethyl
Ts/tosyl	*p*-toluenesulphonyl

Chapter 1

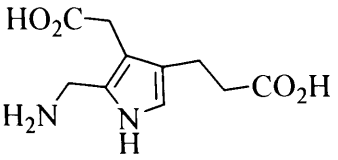
Classical Pyrrole Syntheses

1.1 Introduction

Many heterocyclic compounds are biosynthesized by plants and animals and many are biologically active. These compounds play a vital role in life, medicine and industry. The biological properties of heterocycles make them of prime interest to the pharmaceutical and biotechnology industries. Our interest focuses on one of the most important groups of heterocycles, the five-membered cyclic compounds based upon the pyrrole nucleus **1**.



Pyrrole
[1*H*-pyrrole] **1**



porphobilinogen **2**

Figure 1.1

Pyrrole[1] is commercially available, and is manufactured by alumina-catalysed gas-phase reaction of furan with ammonia. Pyrroles are fundamental to life; compounds such as haemderivatives in blood, the chlorophylls essential for photosynthesis, and related natural products such as vitamin B_{12}, all play key roles in general metabolism. Chlorophyll and haem are synthesised in living cells from porphobilinogen **2**, the only pyrrole to play a function in fundamental metabolism. These compounds provided the impetus for much of the early work on the preparation and reactions of pyrroles. The synthesis of pyrroles related to these naturally occurring complex molecules continues to be a very active area of research, in which the natural structures have inspired the design and preparation of potentially bioactive but non-natural derivatives.

1.2 Synthesis of pyrroles

This review focuses on the syntheses of highly substituted pyrroles and the more commonly used methods. When the formation of pyrrole is considered retrosynthetically, it exhibits the function of a double enamine and can be dissected retroanalytically in three major ways (from **A**, see Figure 1.2). The classical pyrrole syntheses usually involve polar cyclo-

condensations in which nucleophilic and electrophilic centers react through one or more addition-elimination steps. Usually, nitrogen and/or the nucleophilic carbon of an enol, enolate or enamine are the nucleophilic components. A carbonyl, an imine, or an electron-deficient carbon-carbon double bond is usually the electrophilic component.

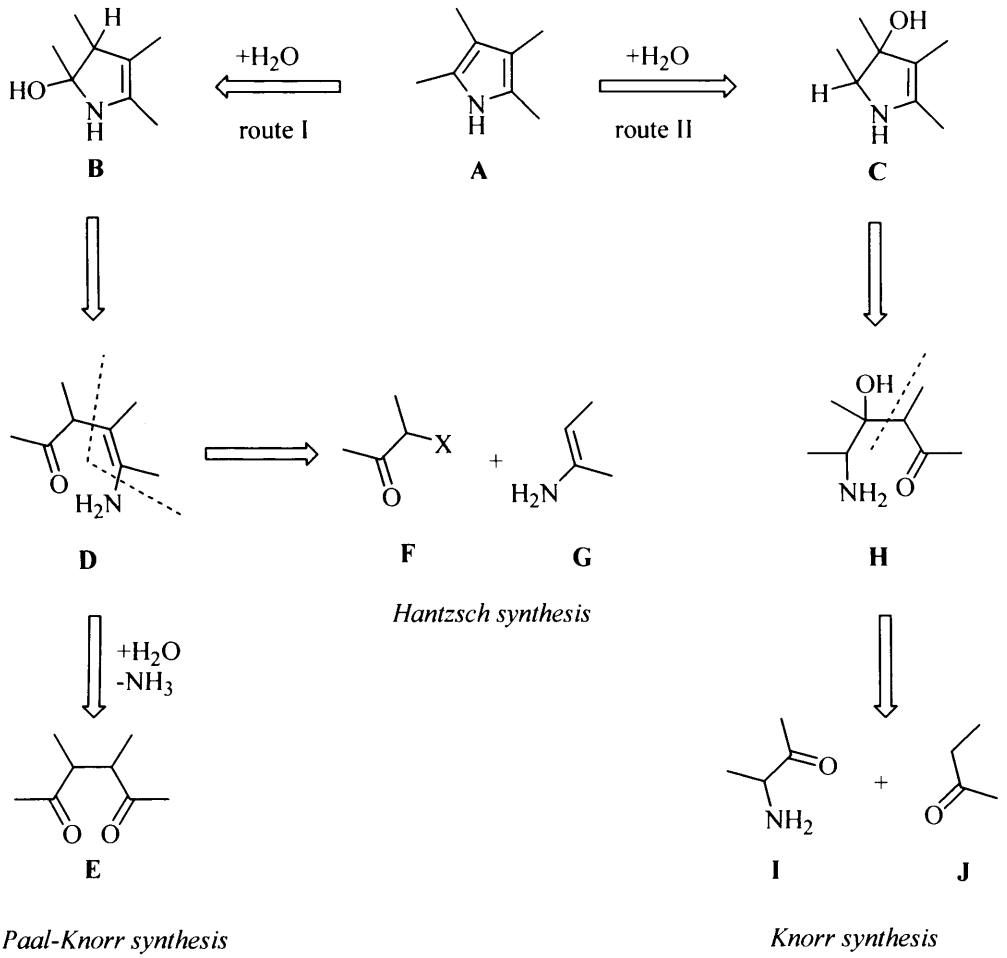
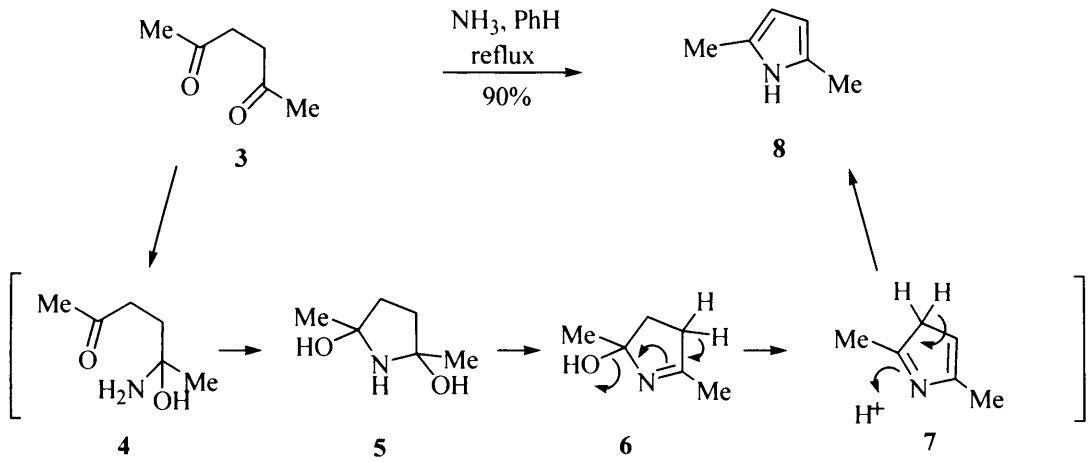


Figure 1.2: Retrosynthesis of pyrrole.

1.2.1 Paal-Knorr synthesis

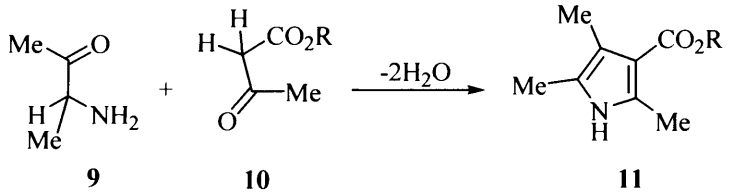
1,4-Dicarbonyl compounds, **3**, react with ammonia or primary amines to give pyrroles. Successive nucleophilic additions of the amine nitrogen to the two carbonyl carbon atoms and the loss of two equivalents of water represent the net course of the synthesis; a reasonable sequence for this is shown below in the synthesis of 2,5-dimethylpyrrole, **8** (Scheme 1.1).[2] A variety of more complex 1,4-dicarbonyl compounds have been used in the synthesis of substituted pyrroles.



Scheme 1.1

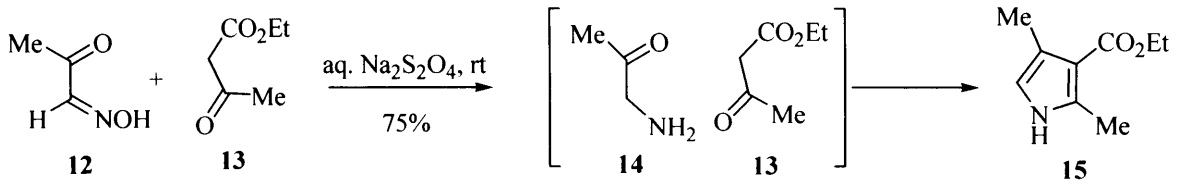
1.2.2 Knorr synthesis

This widely used, general approach to pyrroles utilizes two components: an α–aminocarbonyl component **9**, which supplies the nitrogen, C-2 and C-3, and a second component which supplies C-4 and C-5, and which must have an activated C-H bond adjacent to a ketone such as the β–keto ester **10** shown below (Scheme 1.2). The cyclisation normally proceeds by an initial enamine formation. However, in general, only 3-carboxy- or 3-acylpyrroles can be made using this method.



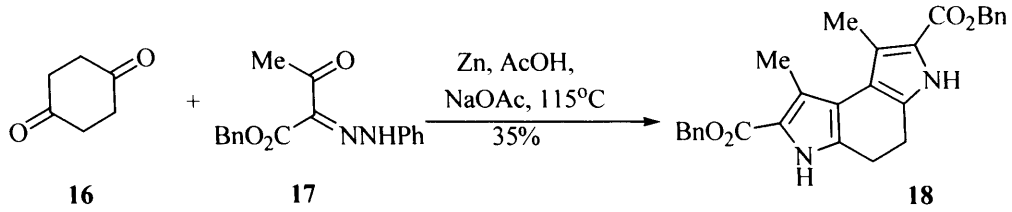
Scheme 1.2

A way of avoiding the difficulty of handling α–aminocarbonyl compounds is to prepare them in the presence of the second component with which they are to react. For example, zinc-acetic acid or sodium dithionite[3] can be used to selectively reduce an oxime group to an amine, leaving ketone and ester groups untouched (Scheme 1.3). Thus, such a selective reduction of the pyruvaldehyde monoxime **12** is possible in the presence of ethyl acetoacetate **13** to give the amino ketone **14** and then the pyrrole **15**.



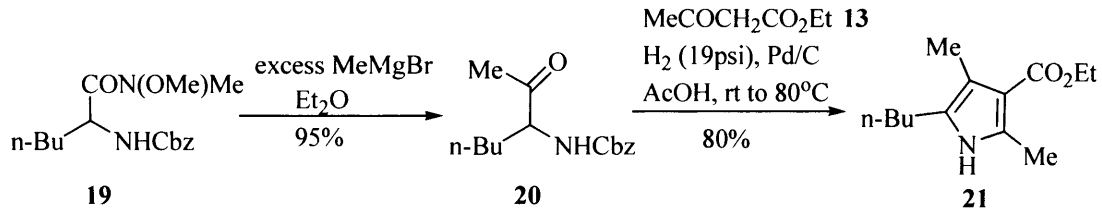
Scheme 1.3

Another interesting example in which two pyrrole rings are formed using phenylhydrazone **17** as a precursor of the α–aminocarbonyl component is illustrated in Scheme 1.4.[4] Although the yield of the pyrrole **18** is relatively poor, this is not so low considering the number of transformations involved.



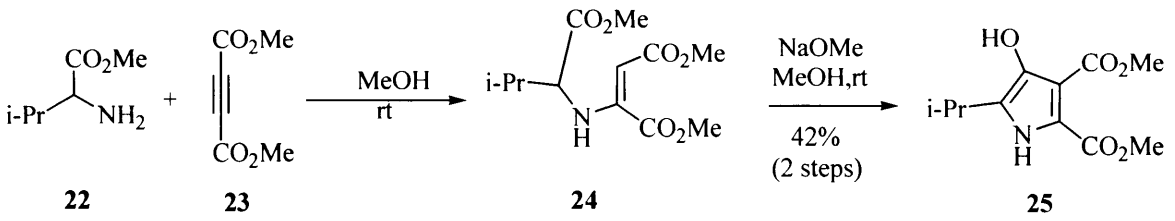
Scheme 1.4

Modern alternatives for the assembly of the α–aminocarbonyl components feature the reaction of a Weinreb amide of an *N*-protected α-amino acid **19** with a Grignard reagent to form an *N*-protected amino ketone **20**. Release of the amino group in the presence of the second component, ethyl acetoacetate **13**, enables the desired condensation leading to the pyrrole to compete effectively with self-condensation of the free amino-ketone (Scheme 1.5).[5]



Scheme 1.5

In a related alternative, the enamine **24**, produced by the addition of an α-amino ester **22** to dimethyl acetylenedicarboxylate **23**, form 3-hydroxypyrroles **25** by a Claisen Ester-type ring closure (Scheme 1.6).[6]

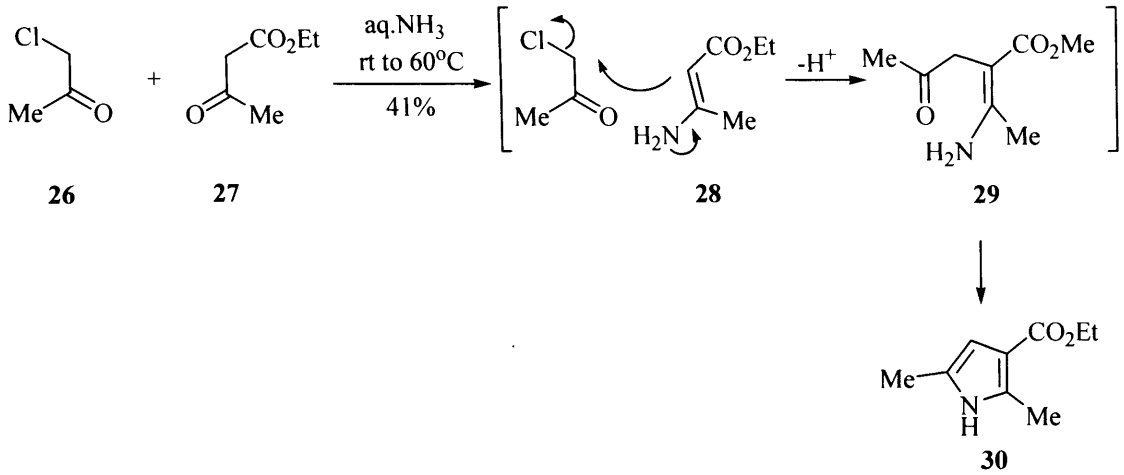


22 23 24 25

Scheme 1.6

1.2.3 Hantzsch synthesis

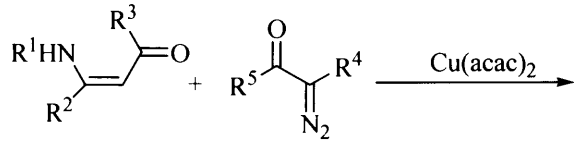
As a modification of the Feist-Benary synthesis of furans, ammonia or a primary amine is incorporated. This strategy employs an α–halocarbonyl compound **26**, a β–keto-ester **27** and ammonia.[7]



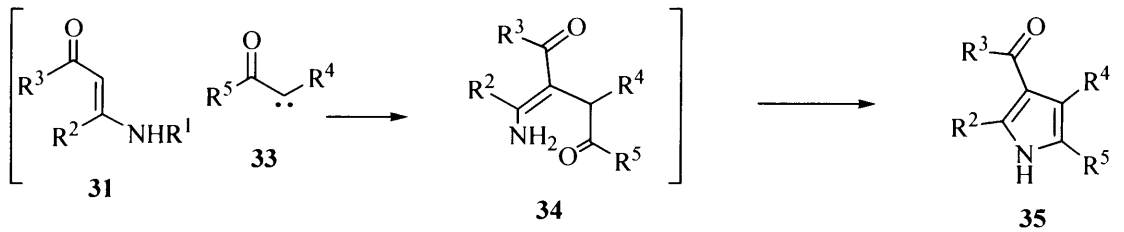
26 27 28 29 30

Scheme 1.7

Similar intermediates can also be obtained when the keto carbene **33**, formed from the decomposition of α-diazoketone **32** in the presence of copper(II) acetylacetonate, is reacted with stabilized enaminone **31** to give pyrroles **35**, as shown in Scheme 1.8.[8]



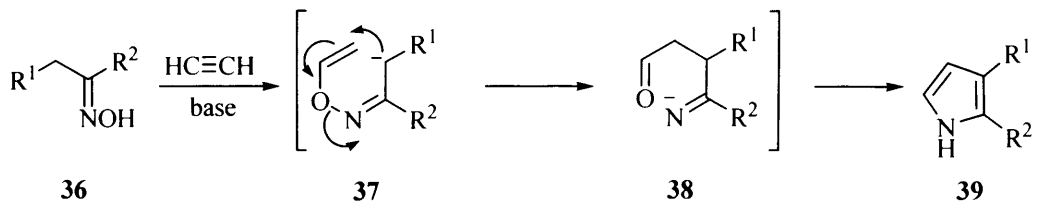
31 32



31 33 34 35

Scheme 1.8

Trofimov and co-workers[9] have developed a pyrrole synthesis that involves reactions of ketoximes **36** with alkynes under strongly basic conditions. A sigmatropic rearrangement of the resulting *O*-vinyloximes **37** is a key step in this reaction, which is then followed by a typical imine-carbonyl condensation.



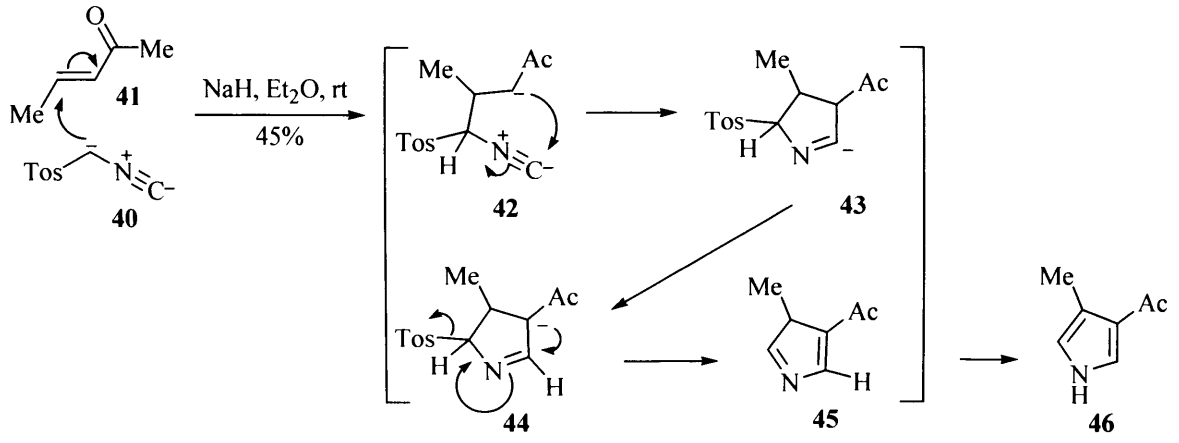
36 **37** **38** **39**

Scheme 1.9

1.2.4 By using dipoles with a potential leaving group, cycloadditions can lead directly to pyrroles. Appropriate dipolarophiles include unsaturated ketones, esters, nitriles, and nitro compounds, as well as electrophilic alkynes.

The van Leusen synthesis

The tosylmethyl isocyanide **40** reacts with the α,β–unsaturated ketone **41**, as well as with related ketones or sulfones, by Michael addition; subsequent closure onto the isocyanide carbon then generates the cyclic imine **43**. Subsequent loss of toluenesulfinate[10] from intermediate **44** and tautomerisation to the aromatic system of pyrrole **46** then completes the synthesis (Scheme 1.10).

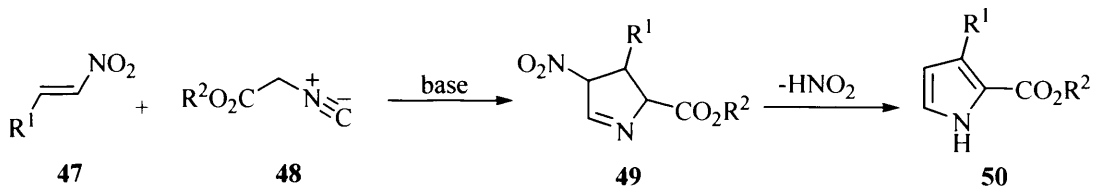


41 **40** **42** **43** **44** **45** **46**

Scheme 1.10

The Barton-Zard synthesis

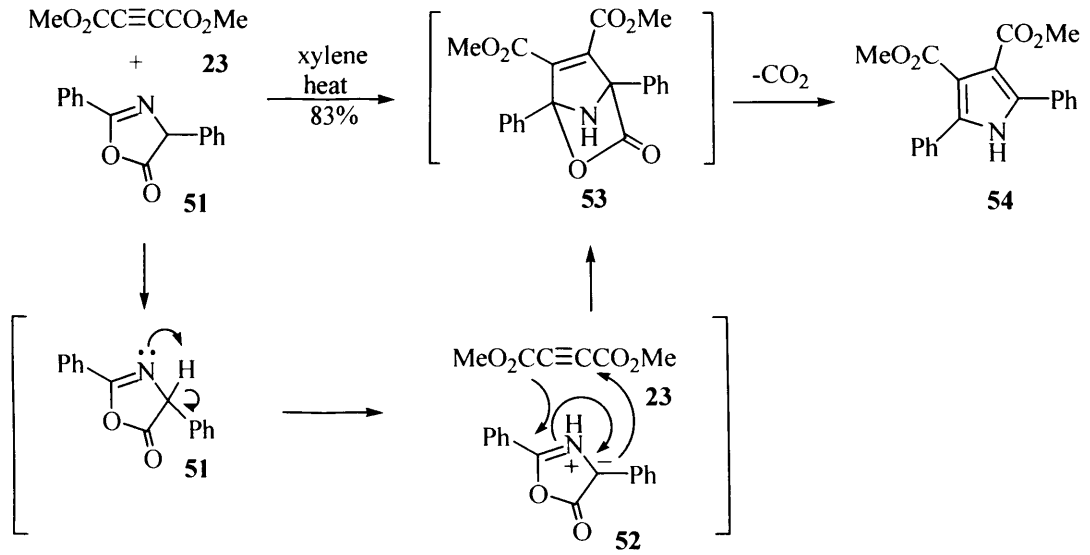
Nitroalkenes are useful reactants for isocyanoacetates, with pyrroles being formed by elimination of nitrous acid (Scheme 1.11).[11]



Scheme 1.11

The cycloaddition of oxazolium oxides

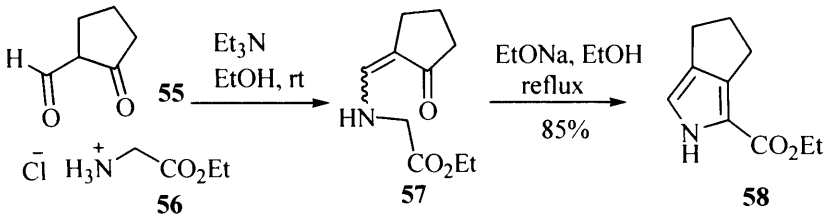
Dehydration of *N*-acylamino acids can be carried out by heating an α–amino acid in acetic anhydride to generate azalactones **51**. In the presence of a dipolarophile such as dimethyl acetylene dicarboxylate **23**, an unstable adduct **53** is presumably formed, which then undergoes decarboxylation to provide a pyrrole **54** (Scheme 1.12).[12] Although this synthesis is efficient, it is limited to electron-deficient alkynes.



Scheme 1.12

1.2.5 From 1,3-dicarbonyl compounds and glycine esters

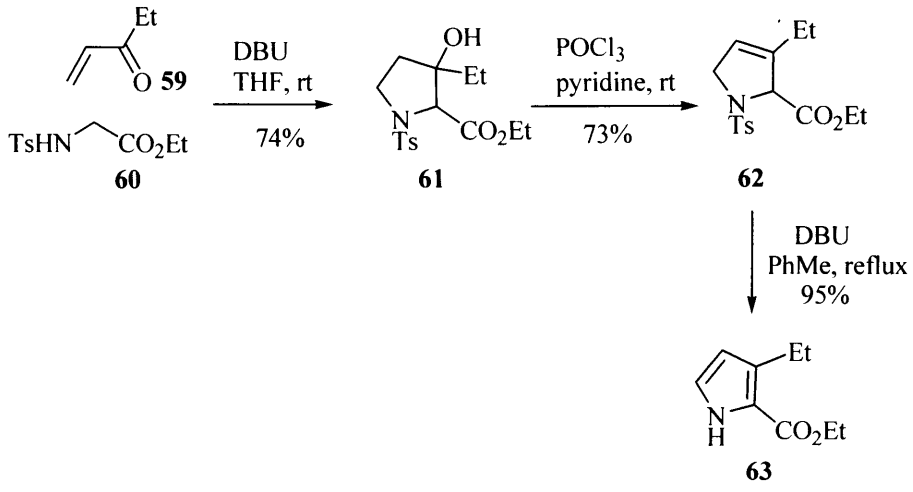
1,3-Dicarbonyl compounds and their synthetic equivalents can give pyrroles by condensation with amines that possess an α-electron-withdrawing substituent, such as an ester or a ketone. Such condensations have the potential for producing two isomeric products when the dicarbonyl component is unsymmetrical. The regioselectivity is usually governed by an initial condensation of the amino group with the more reactive carbonyl group. The simplest is condensation using triethylamine as base to produce an intermediate enamino-ketone **57**, which then undergoes ring closure in a second step (Scheme 1.13). [13]



Scheme 1.13

The Kenner synthesis

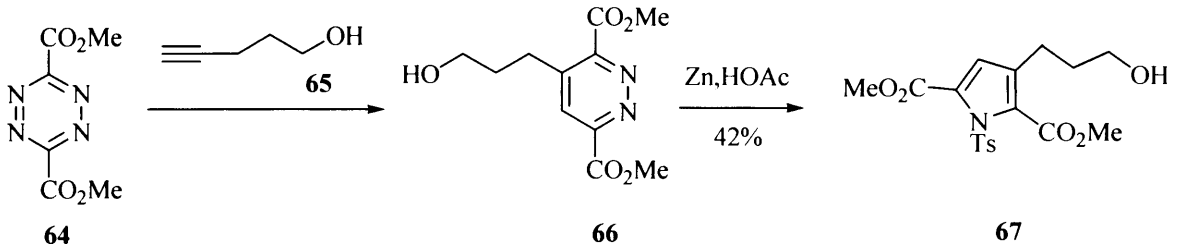
By Michael addition and a similar intramolecular aldol condensation, an α,β–unsaturated ketone **59**, generates compound **61**; subsequent chlorination and elimination forms compound **62**. The pyrrole oxidation level is achieved by treating compound **62** with DBU. The tosyl group is eliminated as toluensulfinate (Scheme 1.14).[14]



Scheme 1.14

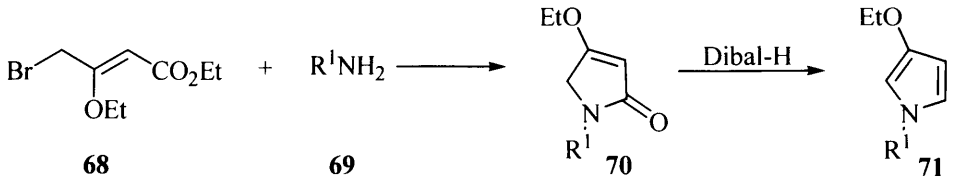
1.2.6 Synthesis by reduction of existing rings

Pyrroles can be obtained by reduction of 1,2-diazines **66**. This reaction has been used in conjunction with inverse electron demand Diels-Alder reactions. Herein, the use of alkynes **65**, as the dienophile, and a tetrazine **64** allows for the synthesis of 3-alkylpyrrole-2,5-dicarboxylate ester **67**, as shown in Scheme 1.15.[15]



Scheme 1.15

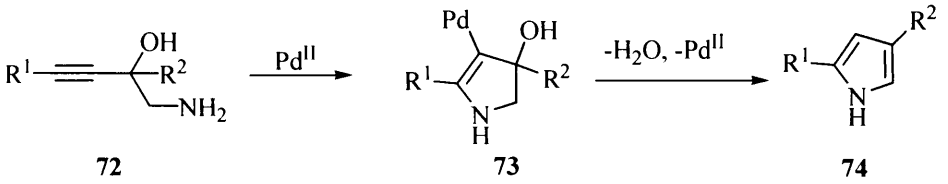
Reductive formation of pyrroles[16] from pyrrolenones is also feasible. For example, Dibal-H reduction of 4-alkoxy-3-pyrrolin-2-ones **70** provides a route to 3-alkoxypyrroles **71**.



Scheme 1.16

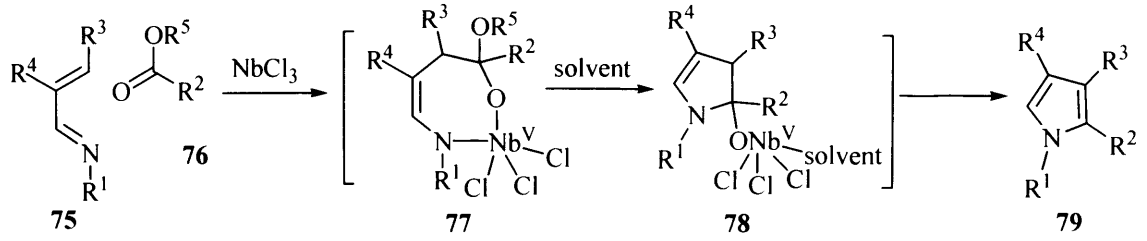
1.2.7 Metal-mediated cyclizations

1-Aminomethyl-1-alkynyl carbinols **72** are cyclized to pyrroles by palladium(II) salts,[17] which presumably form electrophilic palladium(II)-alkyne complexes, which then aromatize by the elimination of palladium(II) and water from intermidiate **73**, as shown below.



Scheme 1.17

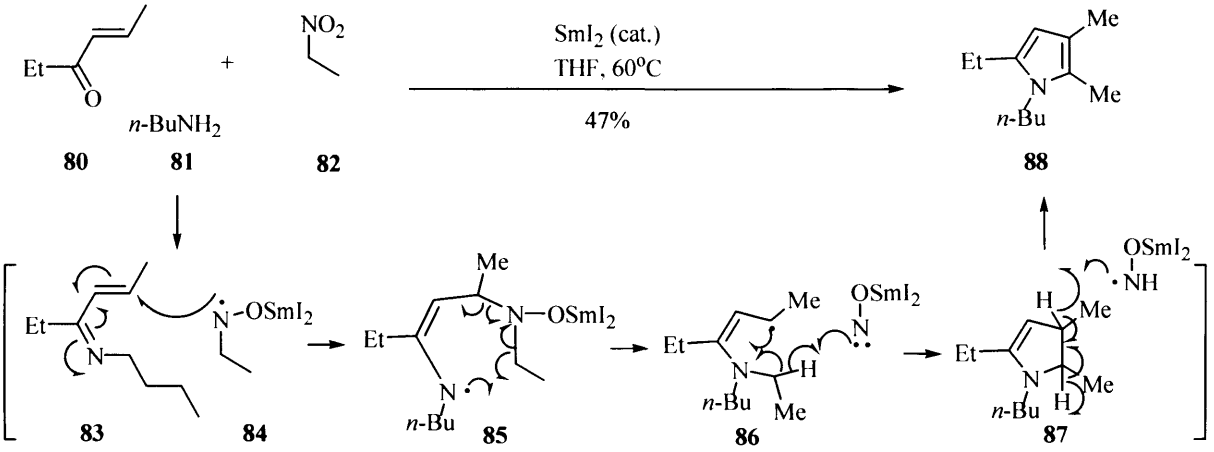
α,β-Unsaturated imines **75** react with esters **76** to give pyrrole derivatives **79** in the presence of $NbCl_3$.[18] Presumably, the niobium functions both to form a complex **77** and to effect the reductive formation of the C-C bond.



Scheme 1.18

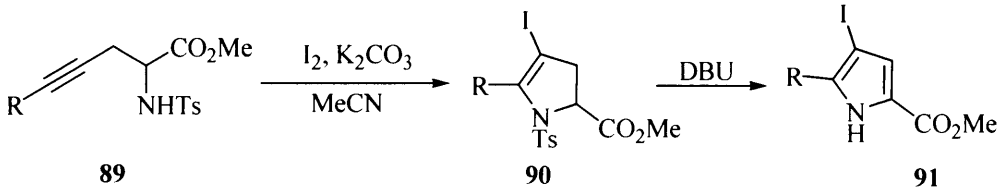
1.2.8 Electrophile-induced cyclisation

Samarium(II) iodide is a reagent for single electron transfer and, in this case, the single electron is delivered to nitro compounds **82**, which then form a samarium radical **84**. The radical **84** then reacts in a Michael fashion with the unsaturated imine **83**, generated from aldehydes **80** and amine **81**, to give pyrrole derivative **88** (Scheme 1.19).[19]



Scheme 1.19

The 5-*endo*-dig closure of 4-tosylaminoalkynes **89** generates dihydropyrroles **90**; the elimination of toluenesulfinate then produces the aromatic system, the pyrroles **91**.[20]



89 90 91

Scheme 1.20

1.3 5-*endo*-dig cyclisation

Baldwin's rules[21] are based on the stereochemical requirements for the transition states of the various *tetrahedral*, *trigonal*, and *digonal* ring closure processes. The ring forming process is described with the prefix *exo*, when the breaking bond is exocyclic to the smallest forming ring, and *endo* when the bond that breaks is endocyclic. The *favoured* ring closures are determined by the length and nature of the linking chain, which enables the achievement of the required trajectories for the terminal atoms to form the final ring bond, as illustrated in Figure 1.3. In the *disfavoured* cases, bond angles and distances require severe distortion to achieve such trajectories; alternative reaction pathways can then dominate and the desired ring closures will be difficult.

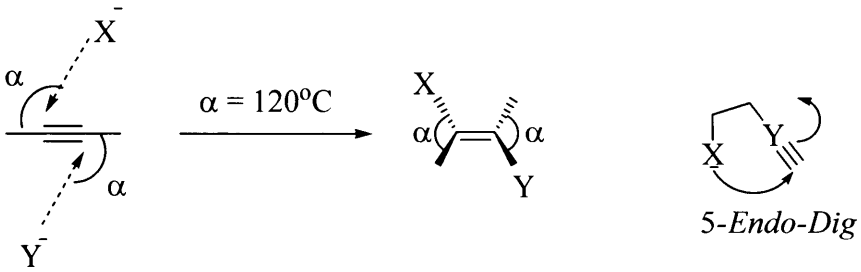


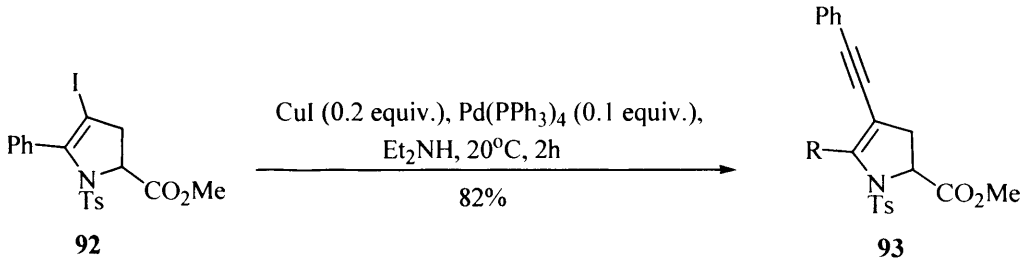
Figure 1.3: the digonal case

Since Heilbron and co-workers[22] reported the preparation of 2,5-dimethylfuran from 3-hexen-5-yn-2-ol, by the catalytic action of mercuric sulphate, substituted furans have been synthesized from acetylenic intermediates. Further, palladium catalysts have been found to be effective for the intramolecular addition of an amine, or an alcohol to an acetylene (Scheme 1.17).[17]

The recently developed methods for the overall 5-*endo*-dig cyclization of 3-alkyne-1,2-diols to give β–iodofurans[23] have opened up a new approach to iodopyrroles,[20] by inducing iodocyclization of sulfonamides upon treatment with three equivalents each of iodine and base in acetonitrile, followed by elimination of *p*–toluenesulfinic acid using 2.1 equivalents

of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); this was successful when R was a simple alkyl or aryl group (Scheme 1.20).

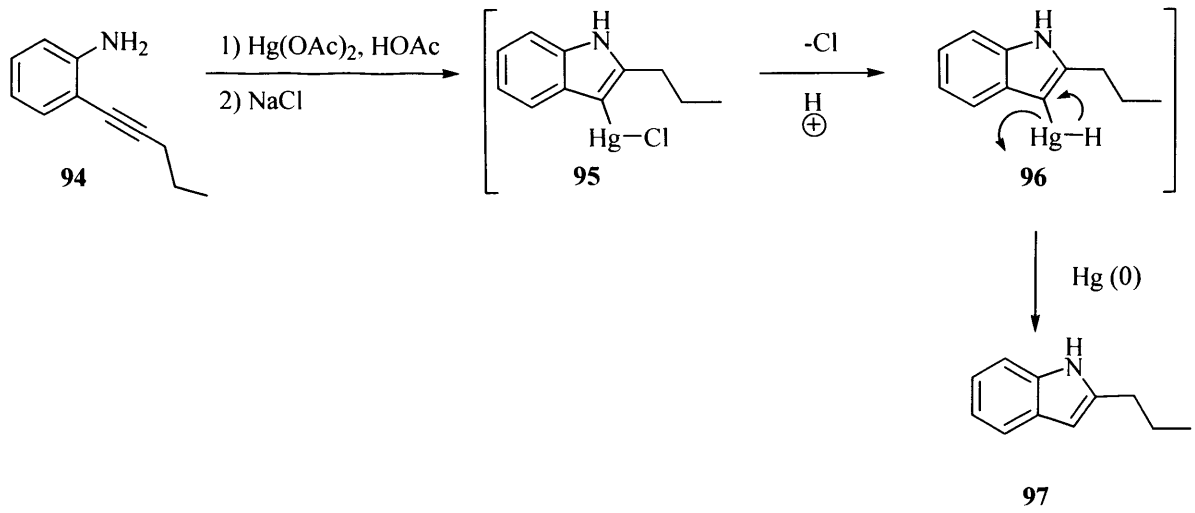
According to this system, the iodine atom can readily be used as a handle for further elaboration, making it easy to make more highly-substituted pyrroles. For instance, the β-iodo-dihydropyrroles **92** have been shown to undergo Sonogashira palladium-catalyzed coupling reactions (Scheme 1.21).



92 **93**

Scheme 1.21

Although favoured processes, 5-*endo*-dig cyclizations to achieve pyrroles have scarcely been reported in the literature. However, other groups have used related ring closing reactions. In 1984, Larock[24a] reported the cyclization of nitrogen-containing aryl acetylenes to mercurated indoles. This used one equivalent of mercuric acetate in acetic acid for 30 min at room temperature followed by an aqueous sodium chloride workup (Scheme 1.22). Larock[24a] suggested that the anticipated heterocyclic mercurials were readily protodemercurated by acetic acid present in the reaction mixture.

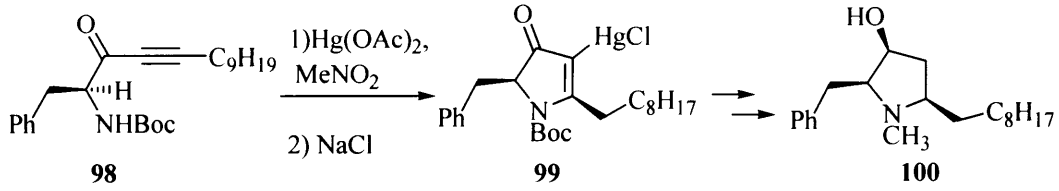


94 **95** **96** **97**

Scheme 1.22

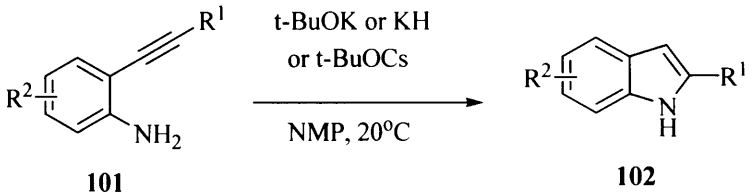
A more recent application of 5-*endo*-dig mercury-cyclisation was employed during a synthesis of the natural product (+)-preussin **100**.[24b] Despite conjugation to the keto group,

the alkyne **98** remains sufficiently nucleophilic to interact with the electrophilic mercury. The intermediate ketone **99** is stable to racemization and the N-Boc group did not interfere.



Scheme 1.23

In 2000, Knochel[25] reported a 5-*endo*-dig cyclisation of *ortho*-alkynylanilines **101** to give indoles **102**. This cyclisation was achieved using caesium or potassium bases in *N*-methylpyrrolidinone (NMP), as shown in Scheme 1.24.



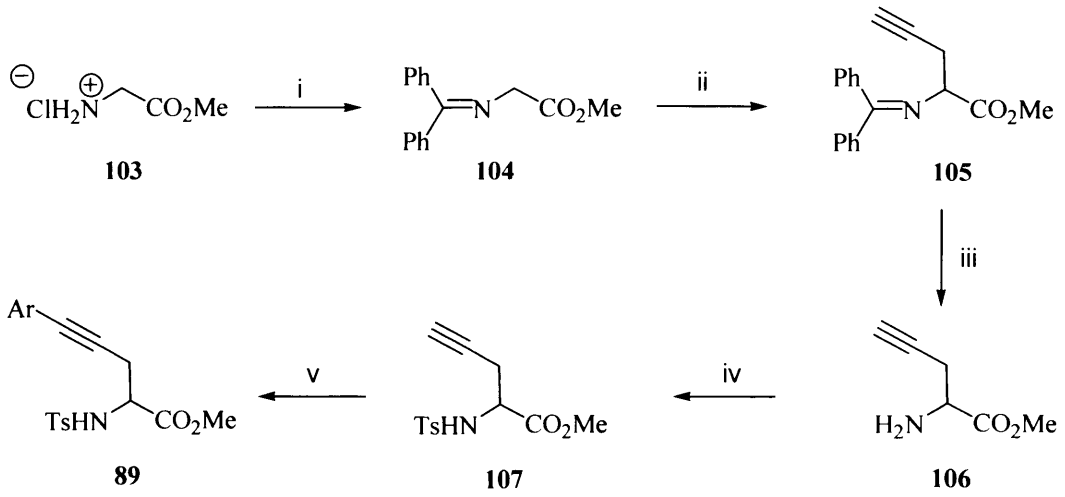
Scheme 1.24

1.3.1 Iodocyclisation

The advantage of the 5-*endo*-dig methodology is that the formation of the heterocycle is an intramolecular reaction, the competing reactions are Baldwin disfavoured 4-*exo*-dig cyclizations and, in the case of iodocyclization, addition of iodine across the triple bond. The described classical methods, except for the Paal-Knorr synthesis, require the condensation of two smaller fragments, which can lead to problems of regioselectivity. The fragments can also cause problems in their own right. They may be highly reactive, unstable and harmful intermediates, for example isocyanides.

Following on from the successful results of Knight and Redfern in 1998[20] in preparing the dihydropyrroles **90** and pyrroles **91** by iodocyclization (Scheme 1.20), it was a primary aim of this present project to assess the practical applications of the methodology already developed and study various applications. According to the formation of the starting

materials, Redfern had presented the best results, achieved for individual steps as shown in Scheme 1.25.



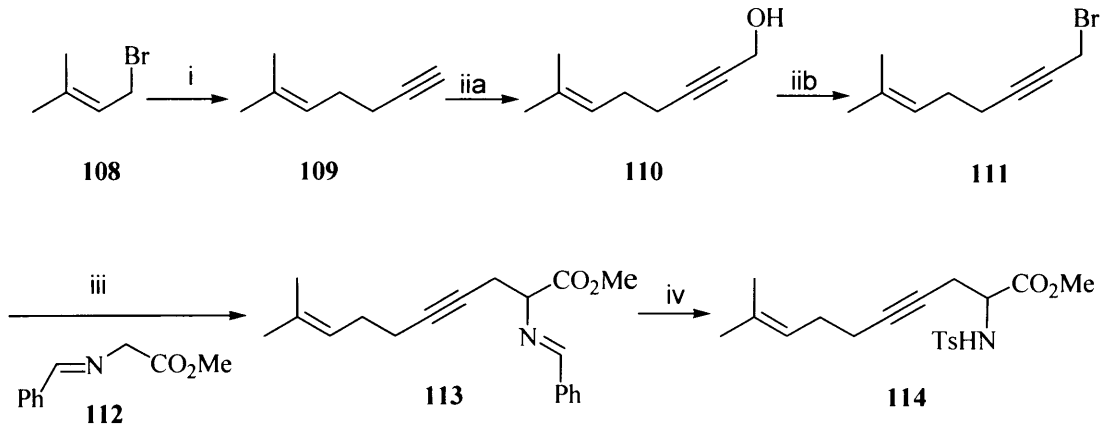
103 **104** **105** **89** **107** **106**

i)1eq. Benzophenone imine, DCM, 25°C, 48h, 99%; ii) 3eq. K_2CO_3, 0.1eq. Bu_4NI, 2.2eq. propargyl bromide, MeCN, reflux, 16h; iii) 2M HCl (aq.)/Et_2O, 25°C, 1.5h, 83% (2 steps); iv) 1.1eq. tosyl chloride, DMAP (cat.), 1.5eq. Et_3N, DCM, 25°C, 16h, 96%; v) 1.2eq. ArX, 0.05eq. CuI, 0.05eq. $(Ph_3P)_4Pd(0)$, Et_2NH, reflux, 16h, 77-92%.

Scheme 1.25

Steps i) and iv) were reliably good. However, it was a major drawback to synthesize the acetylenic-amino ester **89** from glycine methyl ester hydrochloride **103** due to requirement of the propargyl glycine **107** in large amounts. The glycines **107**, at best, gave 83% combined yields (from compound **104**), but these were often 20-30%. The problem step is the protecting group exchange, seemingly at the *N*-tosylation stage. The Sonogashira cross coupling (step v) was variable, being dependent upon the purity of the propargyl glycine **107**; it also required a considerable mass of $(Ph_3P)_4Pd(0)$.

Exposure of the sulfonamides **89** to three equivalents of I_2 and K_2CO_3 in dry acetonitrile at room temperature resulted in slow but clean cyclisation to give excellent isolated yields (71-78%) of the iododihydropyrroles **90** (Scheme 1.20), suggesting that will be prove to be useful synthetic intermediates. These aspects and further studies of the scope and this chemistry are then being pursued.

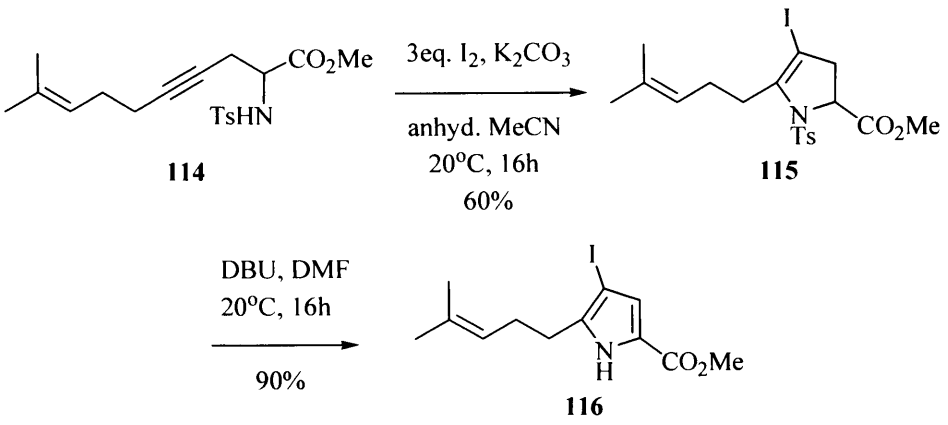


i) $HCCCH_2MgBr$, $HgCl_2$, CuCl, Et_2O, 20°C, 16h; ii) a) BuLi, THF, -78°C then add $(CH_2O)_n$, warm to 20°C, 16h; b) NBS, PPh_3, DMF, -30°C; iii) LDA, THF, -78°C then add bromide and slowly warm to 20°C; iv) a) 1M HCl, Et_2O, 20°C, 1h; b) TsCl, Et_3N, DMAP, DCM, 20°C, 16h.

Scheme 1.26

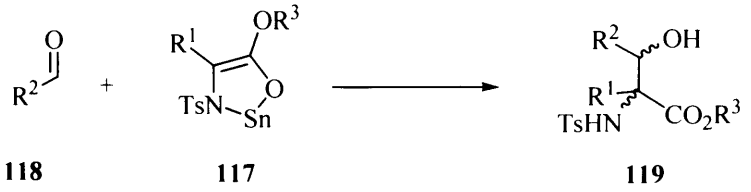
Later, in 1999[26], Fagan and Knight reported an alternative method to prepare the key starting materials **114**, in which the enolate of *N*-benzylidene glycinate **112** was reacted with the propargylic bromide **111** to give compound **114** in good overall yields (Scheme 1.26). However, a lengthy synthesis is still involved and would in any case detract from the synthetic utility of the scheme.

Treatment of this enynoate **114** with iodine in dry acetonitrile in the presence of potassium gave 60% isolated yields of the expected iodo-dihydropyrrole **115**, which was then treated with DBU to give the iodopyrrole **116** in 90% yield (Scheme 1.27).



Scheme 1.27

We reasoned that, by working at a higher oxidation level, the whole process could be made more efficient. A new route was suggested, based on the report of Kazmaier *et al.*[27] This group reported the addition of tin(II)-chelated amino ester enolates **117** to conjugated alkynyl aldehydes **118** to give α-amino-β-hydroxy ester **119** (Scheme 1.28).

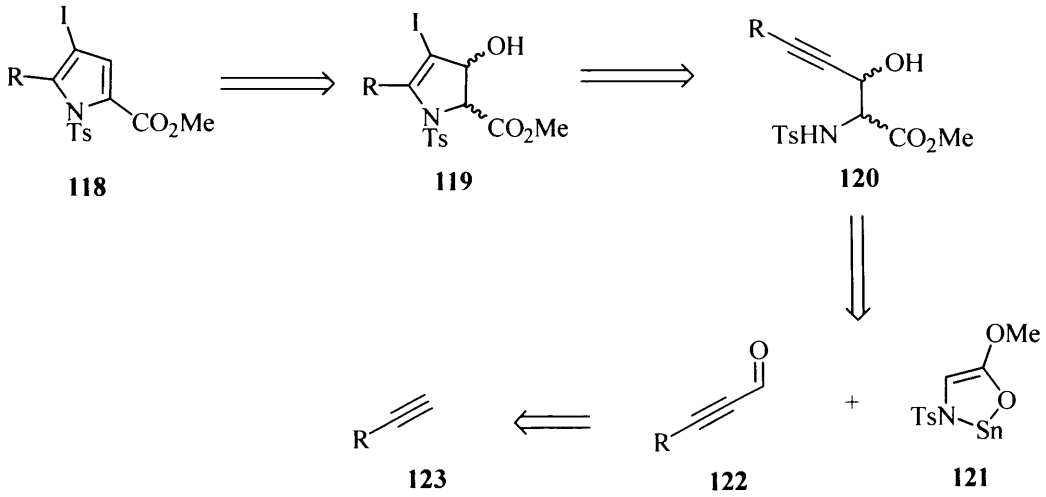


118 **117** **119**

Scheme 1.28

In fact, as we were intending to form pyrroles eventually, and thus destroying the stereogenic centers, the diastereoselectivity of the reaction was unimportant to us. This would also have the great advantage of avoiding the protecting group exchange, which is a weak step in the previous approaches described above (Scheme 1.25 and 1.26).

The idea was to develop a synthesis of the iodopyrroles **118**, which could be formed by the elimination of water from the 3-hydroxy-2,3-dihydropyrroles **119**, prepared by iodocyclization of the α-amino-β-hydroxy esters **120** (Scheme 1.29).



118 **119** **120**

123 **122** **121**

Scheme 1.29

Following on from an aldol addition of an enolate **121** of glycinate to an acetylenic aldehyde **122**, all that was now required was a facile synthesis of such acetylenic aldehydes in order to access a quantity of the α-amino-β-hydroxy esters **120**. Accordingly, we found that Larsen[28]

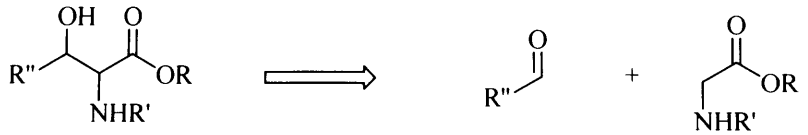
had reported a successful formylation methodology to achieve an excellent yield of acetylenic aldehydes **122** from terminal acetylene **123** by using 10% aqueous potassium dihydrogen phosphate in a reverse work-up, as outlined below.

1.3.2 Synthesis of β-hydroxy-α-amino esters

β-hydroxy-α-amino esters are the key starting material in our cyclisations. In fact, *N*-protected β-hydroxy-α-amino esters are very important compounds in synthetic organic chemistry. They are interesting as intermediates in natural product synthesis and as starting materials for nitrogen-containing heterocycles; amongst many other potential applications.[29]

1.3.2.1 Glycine Enolate Aldol Reactions

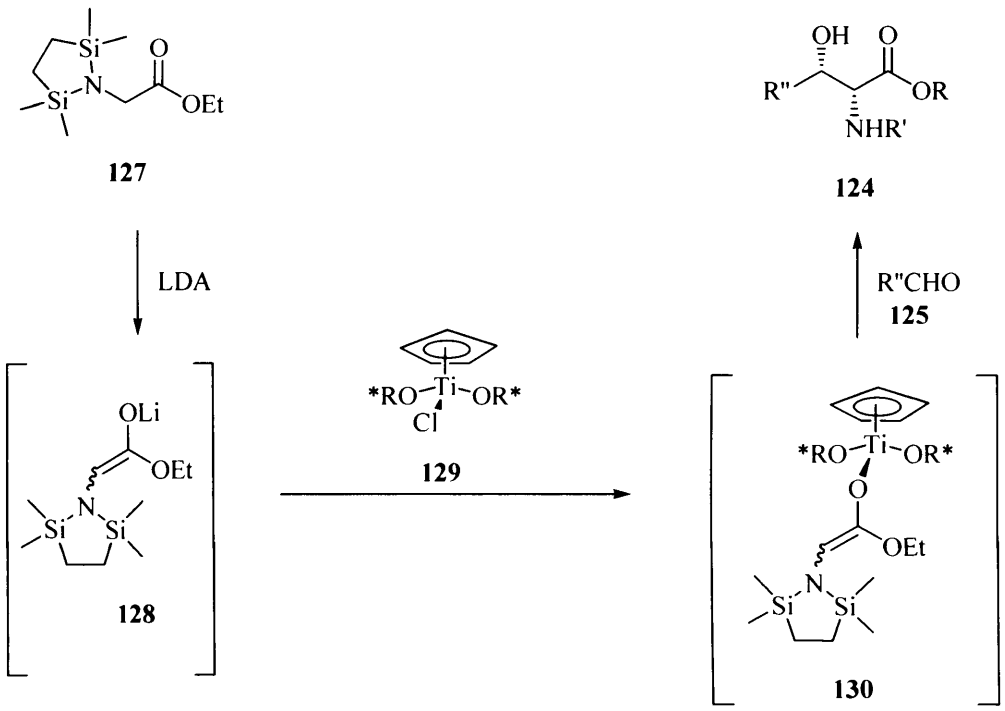
Reactions of glycine derivatives have proven particularly successful. The aldol reaction plays an especially significant role, since it leads to the important class of β–hydroxy-α-amino acids. The development of the glycine enolate and its participation in the desired aldol bond construction (Figure 1.4) was established well by Bold's work in 1989.[30]



124 **125** **126**

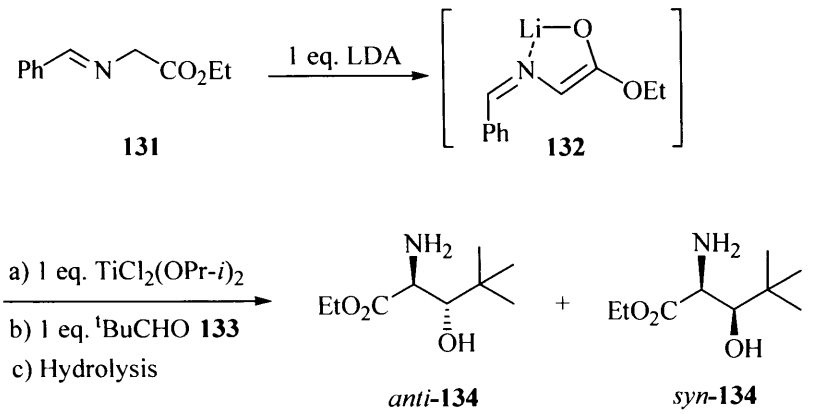
Figure 1.4: Aldol bond construction of β–hydroxy-α-amino acids.

Bold applied titanium complex **129** to achieve stereochemical control in condensations of lithium enolates of *N-bis*-silylated glycine esters **128**, however only moderate yields (43-70%) and levels of *syn*-diastereoselectivity (87-98%) of β–hydroxy-α-amino acid esters were observed (Scheme 1.30).



Scheme 1.30

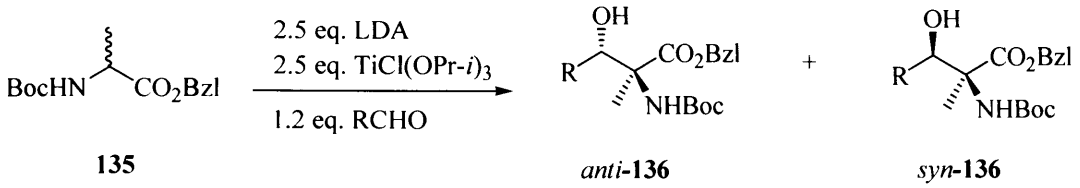
The chelated enolates **130** show higher stability than the corresponding lithium enolates **128**. In addition, because of the fixed enolate geometry, their reactions are more selective than those of the lithium enolates. In 1993, a very high diastereoselectivity of >99% was obtained in the reaction of *N*-benzylideneglycinate **131** in the presence of one equivalent of $TiCl_2(OPr\text{-}i)_2$ with pivaldehyde **133** (Scheme 1.31).[31] This high *anti*-selectivity was only observed when bulky aldehyde acceptors were employed.



Scheme 1.31

Kazmaier and co-workers[32] reported a high *anti*-diastereoselectivity in the aldol reactions of *N*- (benzyloxycarbonyl)-protected amino acid esters **135** with aliphatic aldehydes, which were

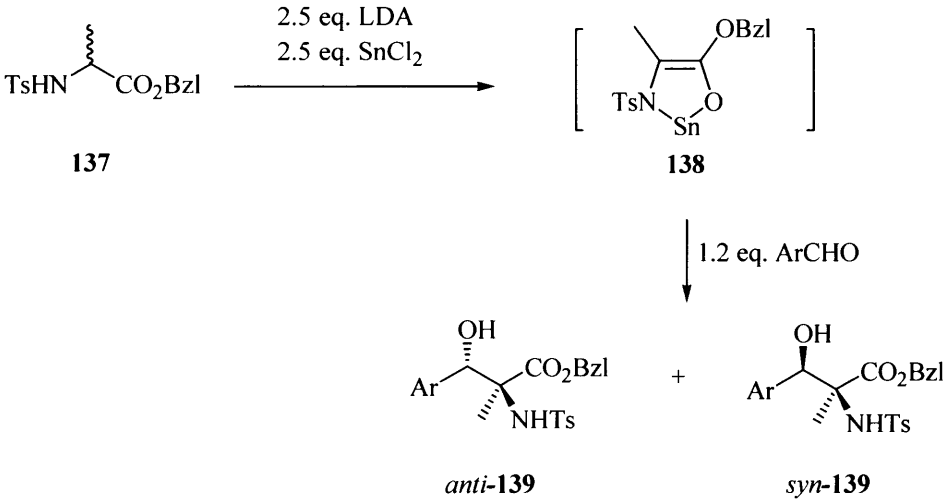
obtained by adding 2.5 equivalents of $TiCl(OPr\text{-}i)_3$. This study also showed similar results with other chelating metals such as $ZnCl_2$, $MgCl_2$, $Al(OPr\text{-}i)_3$, $NiCl_2$ and $CoCl_2$. In contrast, the addition of 2.5 equivalents of $SnCl_2$ led to extremely high diastereoselectivity and improved yields (Scheme 1.32). Also, both *N*-tosyl and benzyl esters of alanine could be used to obtain the *anti*-diastereoisomers; however, this was not applicable to aromatic aldehydes.



135 *anti*-**136** *syn*-**136**

Scheme 1.32

In 1998,[27] they presented the results of aldol reactions of tin enolates of *N*-(methylphenylsulfonyl)-protected amino acid esters **137** with various aromatic aldehydes (Scheme 1.33). The tosyl-protecting group proved to be particularly valuable in such aldol reactions of tin chelated enolates, concerning both yield (60-91%) and *anti*-diastereoselectivity (85-99%) of β–hydroxy-α-amino acid esters **139**.



137 **138** *anti*-**139** *syn*-**139**

Scheme 1.33

Deprotonation of *N*-tosyl alanine ester **137** with LDA at –78°C and subsequent addition of $SnCl_2$ presumably results in the formation of chelated enolate **138**, which is then trapped with the aldehyde. It became clear that condensation of the tin enolates **138** with the aldehyde required at least two equivalents of tin(II) chloride to achieve good selectivity. This high *anti*-diastereoselectivity arises from the fixed enolate geometry and chelation control on the

aldehyde (Figure 1.5). Complex **140** is more favorable than complex **142**, presumably because of steric hindrance between the R group and the *N*-tosyl, and/or the R group and Me group.

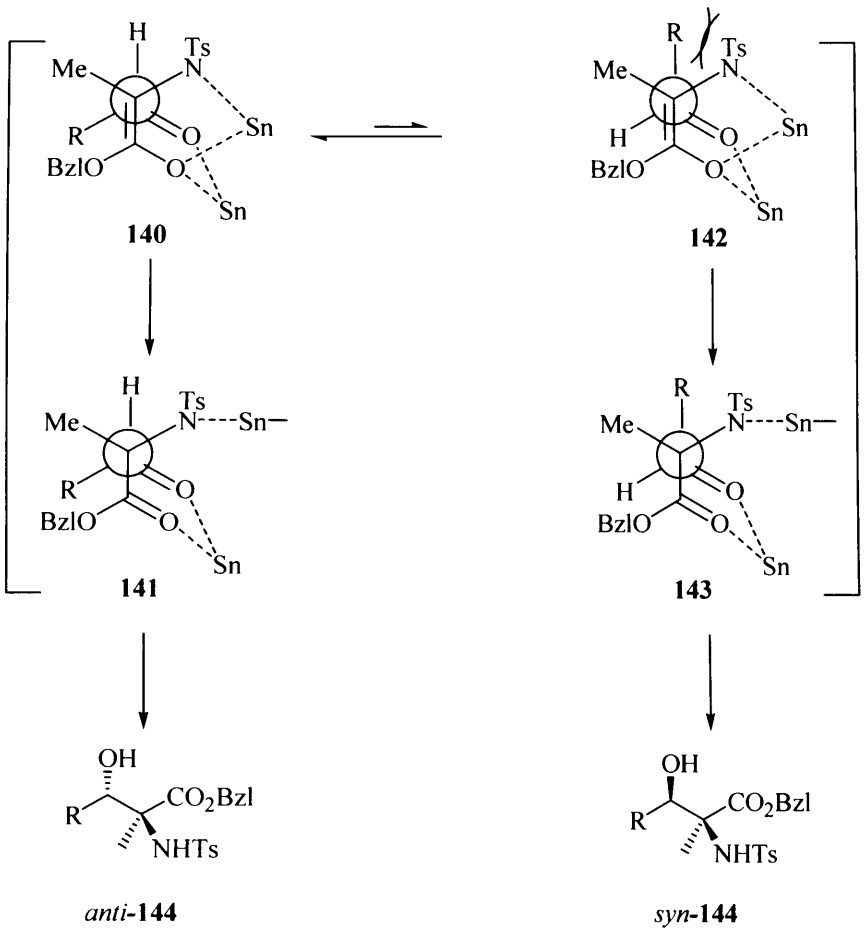
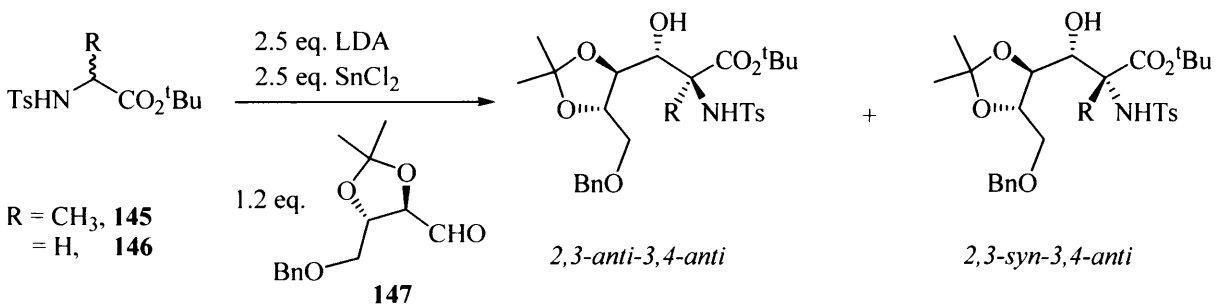


Figure 1.5

Later, Kazmaier[33] showed the aldol reactions of tosylated amino acid ester enolates **145** with chiral aldehydes **147** give rise to polyhydroxylated amino acid esters **148** with high levels of stereoselectivity (Scheme 2.4).



R = CH_3, **148**	78	22
= H, **149**	50	50

Scheme 1.34

In contrast, the reaction of glycine enolates **146** gave a 1:1 diastereomeric mixture at the α-center of polyhydroxylated amino acid esters **149**, probably because of epimerization. This inversion of configuration can be explained by examining the planar enolate **152**, where the hydrogen can be delivered from the left face **151** or from the right face **153** (Figure 1.6).

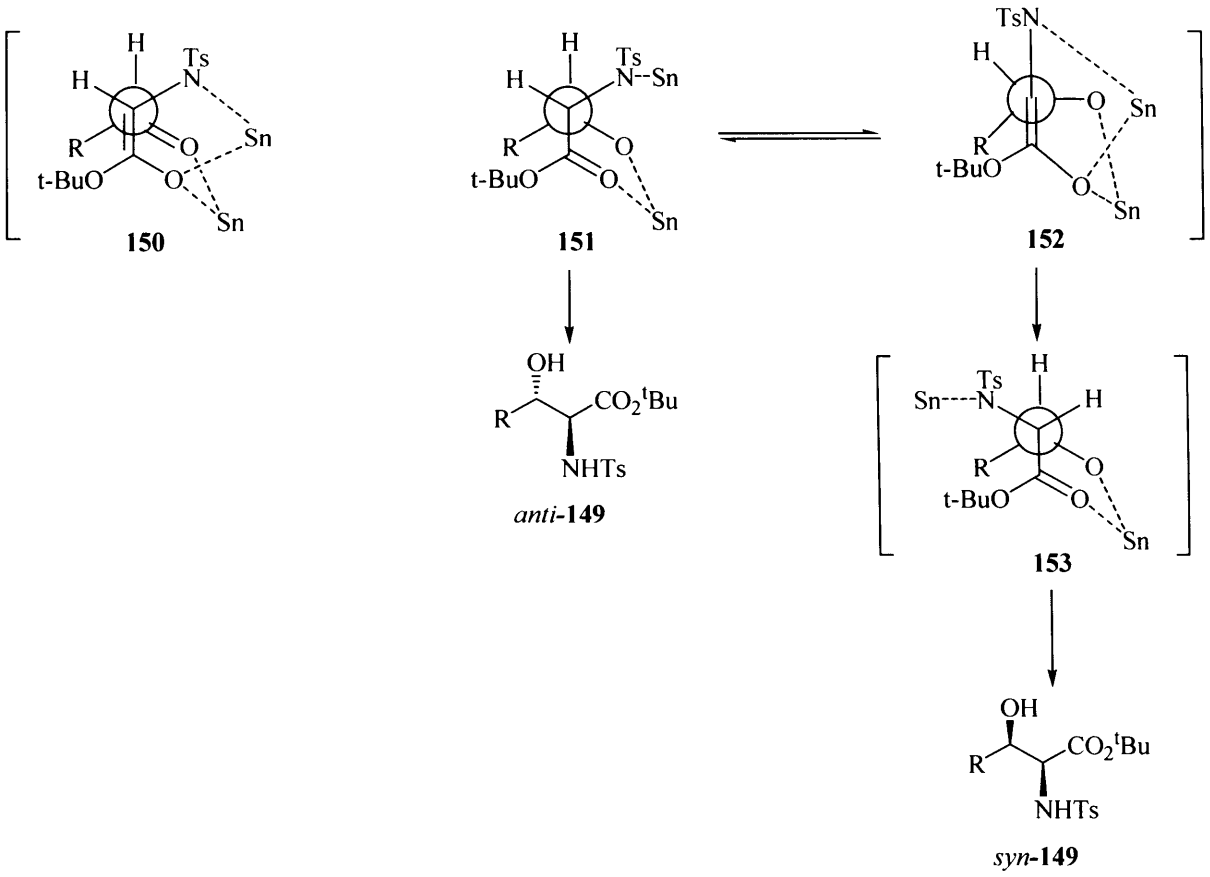


Figure 1.6

1.3.2.2 Retrosynthesis Analysis

According to our projected 5-*endo* dig cyclisation, this methodology could be applied to achieve our key precursors, alkynyl-β-hydroxy-α-amino esters **120**, by condensations between *N*-tosyl protection amino esters **154** and α,β–acetylenic aldehydes **122** (Figure 1.7). We proposed this route to obtain any diastereoisomers, which was of little concern, as both stereogenic centers would be destroyed to form pyrroles eventually, we anticipated.

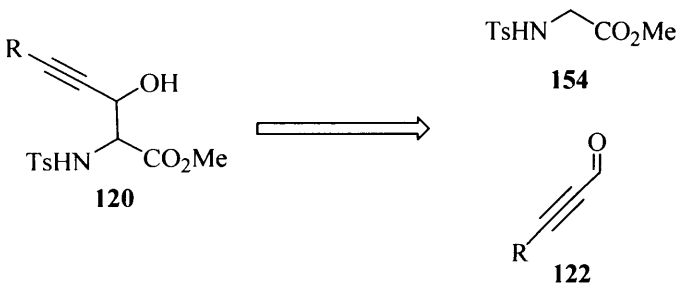
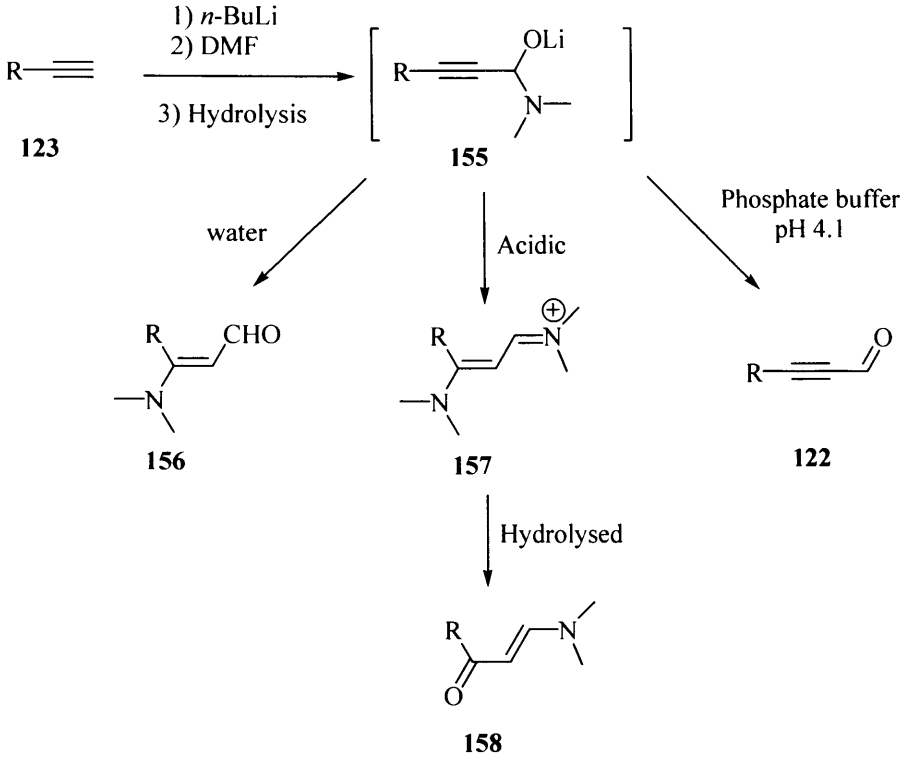


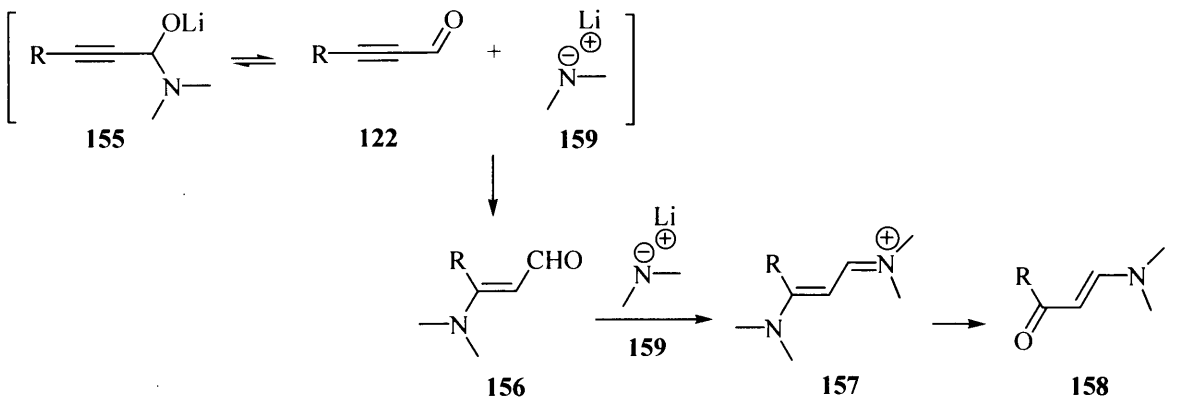
Figure 1.7

This requires a facile synthesis of the aldehydes **122**. Larsen reported in 1989 that the direct formylation of an acetylide with DMF gave excellent yields of α,β–acetylenic aldehyde **122**, but only when the intermediate hemiaminal salts **155** are decomposed in such a way as to prevent various side reactions (Scheme 1.35).[28]



Scheme 1.35

In fact, the intermediate **155** could release the strong nucleophile dimethylamide **159**, which can subsequently react with the alkynal **122** to form Michael adduct **156**; this could then react with more nucleophilic dimethylamide to form the iminium salt **157** which could then form the ketone **158** (Scheme 1.36).

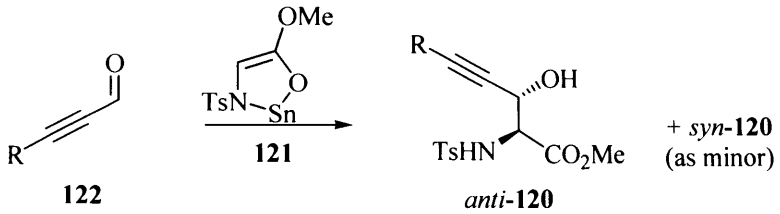


Scheme 1.36

The possibility of these side reaction was eliminated by a reverse quench into a monobasic phosphate solution, trapping the dimethylamine as its salt, to afford the α,β–acetylenic aldehydes **122** without any trace of Michael adducts **156**, **157** and **158** (Scheme 1.34).

1.3.2.3 Initial Studies

Indeed, the aldol condensation was smoothly applied to condense the acetylenic aldehydes **122** and the glycinate enolate **121** in very useful levels of *anti*-stereoselection and yields, as shown briefly in Scheme 1.37 (see Chapter 2).[34]



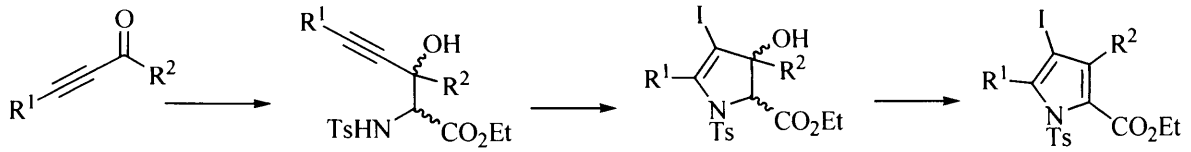
122 **121** *anti*-**120**

R = Ph (76%); 90:10	**160**
^{n}Bu (64%); 94:6	**161**
^{t}Bu (65%); 99:1	**162**
$TBSO(CH_2)_3$ (60%); 92:8	**163**
$TBSO(CH_2)_4$ (60%); 90:10	**164**

Scheme 1.37

This provided a methodology to access our key precursors, the α-amino-β-hydroxy esters **120**. Surprisingly, the results of Kazmaier's study suggested very low stereoselectivity would be obtained at the new α-position by using glycine enolate.[27] This was reasoned to be due to epimerization under the reaction conditions, assisted by acidification of the α-position by the electron withdrawing sulfonyl and especially ester functionalities.

In addition, Sharland had studied this 5-*endo*-cyclisation methodology with various conjugated ynals, and achieved a broader application in order to prepare highly substituted pyrroles, as shown in Table 1.1.[35a] These results were taken together with those obtained during the present project (see Chapter 2), and according to these results, it showed that the R^2 group (R^2 = H < Me < *i*Pr) had little effect upon the stereochemical outcome of α-amino-β-hydroxy ester **165** formation (see Chapter 2).



166 165 167 168

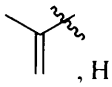
R^1, R^2	**166** %Yield	**165** %Yield, *anti:syn*	**167** %Yield	**168** %Yield
^{n}Bu, H	81	83, 88:12	93	53
 , H	74	63, 93:7	not isolated	56
Ph, H	67	58, 94:6	not isolated	98
Ph, Me	Commercially available	79, 92:8	95	67
Ph, C_7H_{15}	51	80, 90:10	71	not isolated
Ph, ^{i}Pr	32 (2 steps)	76, 84:16	not isolated	82 (2 steps)

Table 1.1

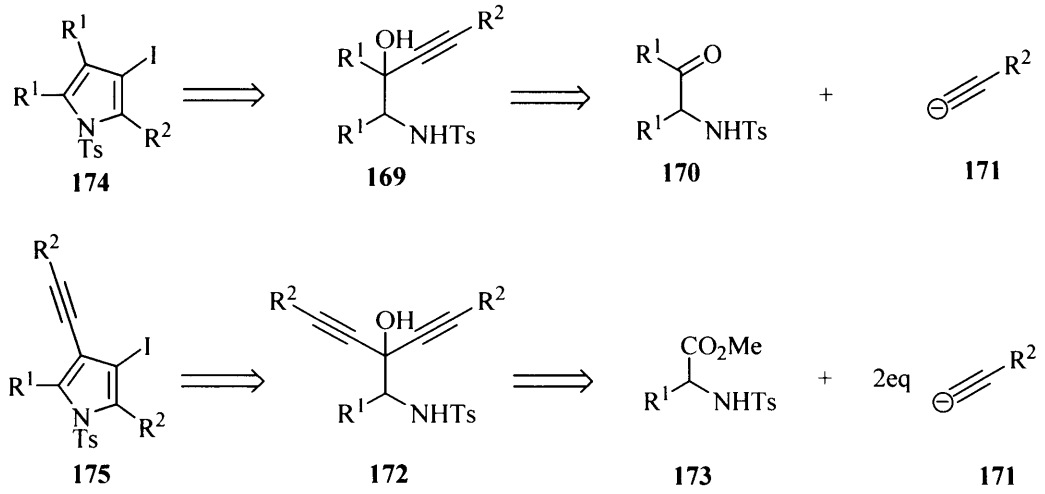
The iodocyclization of these precursors appeared to be much faster than those used in previous studies (Scheme 1.20)[20] and elimination to the pyrrole **168** could be achieved by treatment with methanesulfonyl chloride and pyridine in dichloromethane. Also, this report found that the use of idodine monobromide in dichloromethane tended to give better results to obtain the pyrroles **168**.

1.3.2.4 A generally applicable method for pyrrole synthesis

The work in this section was carried out in collaboration with an Erasmus student, Heinz Rost from Clausthal University.[35b] We were keen to access alternative approaches to seemingly suitable precursors in order to extend this generality even further. Thus, until now, all examples contained a 2-carboxylate group. As this is one of the key constraints associated with some of the 'classical' approaches to pyrroles, the motivation for this section of the

project is clear. Though it seemed unlikely that the ester group was necessary for the cyclisation, it is also well worthwhile to confirm this.

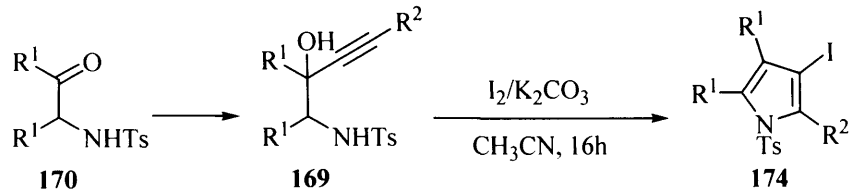
Knowing that the more generalized substrates **169** were required, we therefore sought to access this model system from an *N*-tosyl ketone **170** and an acetylide **171** (Scheme 1.38). Amino-hydroxylation, involving symmetric starting materials such as *trans*-stilbene and 2-butene, and followed by oxidation of the resulting alcohols was used to prepare the ketone **170** (Chapter 2).



Scheme 1.38

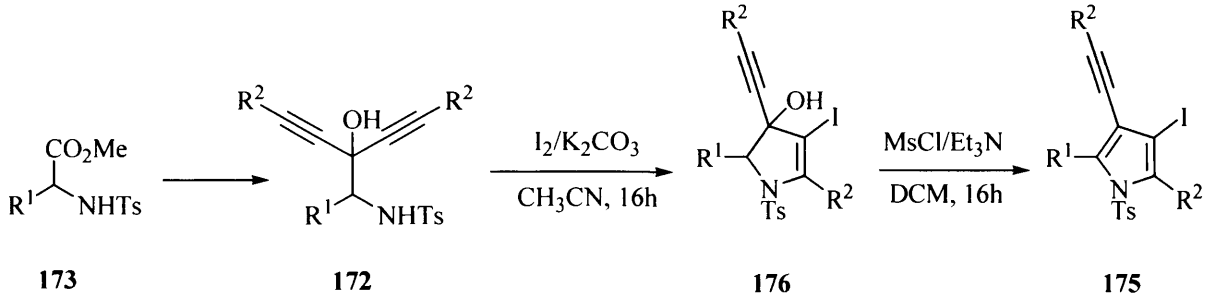
At the same time, we reasoned that symmetrical precursors **172** could be readily obtained by exposure of an *N*-tosyl-α-amino ester **173** to two equivalents of an acetylide **171**. If these precursors **169** and **172** could be cyclised successfully, this could lead to the *pseudo*-symmetrical iodopyrroles **174** and **175**, respectively.

Rost[35c] tested this methodology by preparing α-amino ketone **170** and α-amino esters **173** as starting materials, with a view to carrying a second alkyne function through the key cyclisation step (see Chapter 2). As detailed in Table 1.2 and Table 1.3, these underwent smooth cyclisation in acetonitrile to achieve excellent yields of the highly substituted iodopyrroles without the need for a subsequent elimination step.



R^1, R^2	**170** %Yield	**169** %Yield	**174** %Yield
Ph, Ph	55	99	73
Ph, ^{n}Bu	55	96	83
Me, ^{n}Bu	54	83	67

Table 1.2



R^1, R^2	**172** %Yield	**176** %Yield	**175** %Yield
*i*Pr, Ph	92	52	69
^{i}Pr, ^{n}Bu	68	76	67
Me, Ph	91	not isolated	85

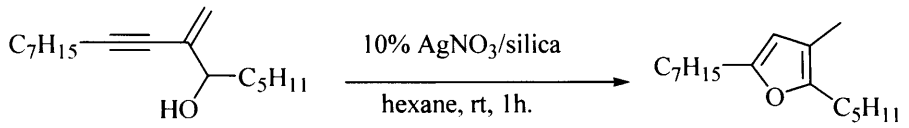
Table 1.3

The α-amino-alcohol **169** worked well in our standard iodocyclisation. Following on from this, Rost tested this methodology on α-amino alcohols **172** under the same condition as α-

amino ketone **169** (Table 1.3). Again, the results were excellent, although generally the dihydropyrroles **176** were formed, so a further elimination step was required.

1.4 Silver-mediated cyclisation

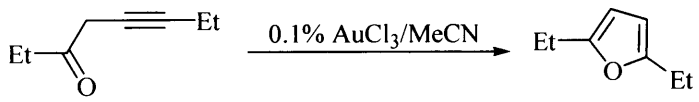
According to Section 1.2.7, the transition metal-catalyzed cyclisation of disubstituted alkynes possessing a nucleophile in proximity to the triple bond by either copper or palladium reagents has been shown to be extremely effective for the synthesis of a wide variety of carbo- and heterocycles.[17,18,36] In 1995, Marshall[37] reported a clean and high yielding synthesis of furans by Ag(I)-catalyzed cyclisation (Scheme 1.39).



177 96% **178**

Scheme 1.39

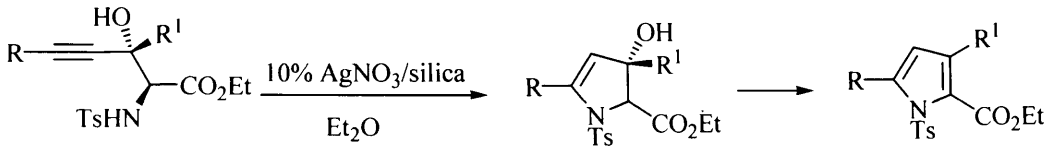
However, the reactions of propargyl ketones **179,** failed with Ag(I) as catalyst.[38] In 2000, Hashmi reported a new gold-catalyzed C-C bond formation in which the Au(III) catalyst readily transformed propargyl ketones **179** into furans **180** within minutes at room temperature in quantitative yields (Scheme 1.40).[39]



179 **180**

Scheme 1.40

Following on from Christopher Sharland's work,[35a] the α-amino-β-hydroxy ester **181** was dissolved in anhydrous diethyl ether and to this was added one equivalent of 10 % wt/wt silver(I) nitrate on silica and the mixture was stirred vigorously, in the dark, at room temperature for 2 hours. After removal of the catalyst by filtration and evaporation of the ether, dihydropyrroles **182** were obtained in excellent yield (Table 1.4).[35a] The dihydropyrroles **182** were very sensitive to elimination, and dehydration was observed on standing in deuteriochloroform to give the corresponding pyrroles **183.**



181 **182** **183**

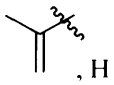
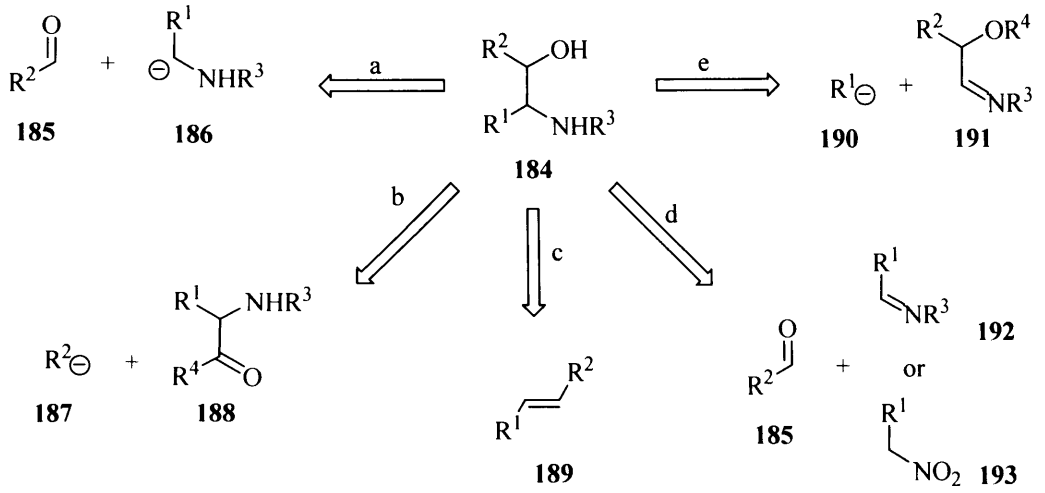
R, R^1	Time	**183** %Yield
^{n}Bu, H	3h	98
	3h	96
Ph, H	2h	87
Ph, Me	48h	91
Ph, ^{i}Pr	48h	94

Table 1.4

We aimed to study the scope and limitations of the chemistry in iodocyclisation and silver-mediated cyclisation, such as an influence of iodine-functionalised pyrrole with a various side chains and an application to different terminal alkynes.

1.5 Alternative syntheses of α-amino alcohols

The development of syntheses providing high diastereoseletivity of α-amino alcohols **184** has intrigued generations of chemists and been the subject of intense research. This effort has provided a diversity of methodologies, which have reviewed briefly here. Several strategically different approaches toward α-amino alcohols **184** involving a carbon-carbon bond-forming event are conceivable (Scheme 1.41).



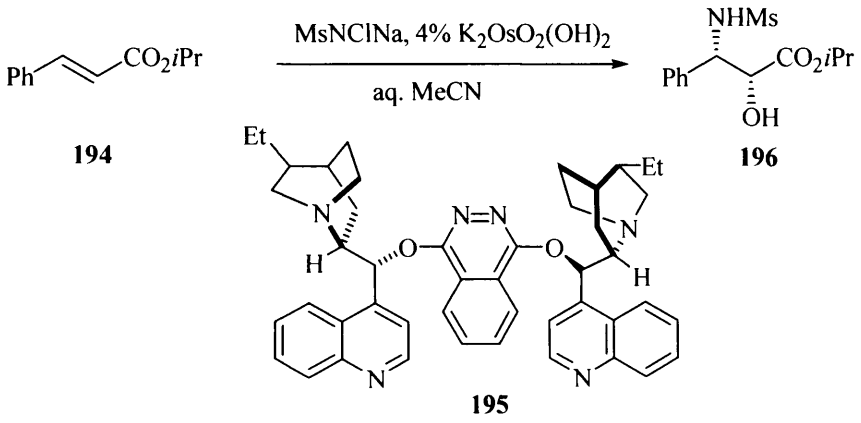
Scheme 1.41

1.5.1 Addition to α-aminocarbonyls

An attractive solution (route *a*) consists of the addition of electrophiles to glycine enolate derivatives **186** (R^1=CO_2Me, R^3=Ts), which has been used successfully as a methodology to access the β-hydroxy-α-amino ester **184** (see page 16). Another fast route (route *b*) to achieve α-amino alcohols **184** rapidly is the addition of two nucleophiles, such as the acetylide **187** to electrophilic carbonyl group of *N*-tosyl-α-amino ester **188** (see Section 1.3.2.4, page 24).

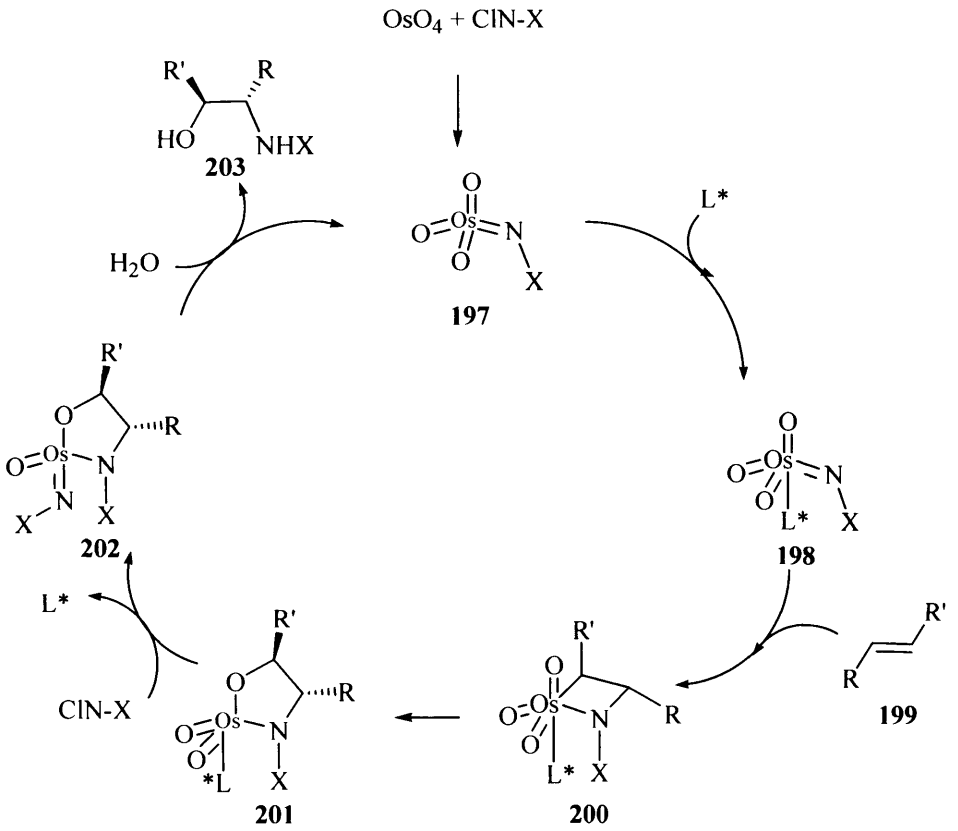
1.5.2 Asymmetric aminohydroxylation

Osmylation is an attractive method (route *c*) for the conversion of alkenes into α-amino alcohols. Sharpless introduced what is now called the *Sharpless asymmetric aminohydroxylation reaction*. When cinnamate **194** was treated with nitrogen reagents in the presence of $(DHQ)_2PHAL$ **195** using what provides facial selectivity (bottom (α)-attack), optically pure amino alcohol **196** was formed. The nitrogen sources include TsNClNa, MsNClNa, CbzNClNa, and BocNClNa. In a typical example, cinnamate **194** was treated with $(DHQ)_2PHAL$ **195**, 4% $K_2OsO_2(OH)_4$ and MsNClNa, in aqueous acetonitrile, and a 65% yield of **196** was obtained, in 94% ee (Scheme 1.42).[40] Normally, the products are solid, and enantioselectivity can be increased by recrystallisation.



Scheme 1.42

Osmium tetroxide (OsO_4) had a relatively high reduction potential in acidic media and the primary use is for the conversion of alkenes to 1,2-diols. Osmium tetroxide reacts with a nitrogen source to generate an osmium(VIII) complex **197**, followed by addition of L* (a ligand) to form a chiral osmate intermediate **198** (Scheme 1.43).

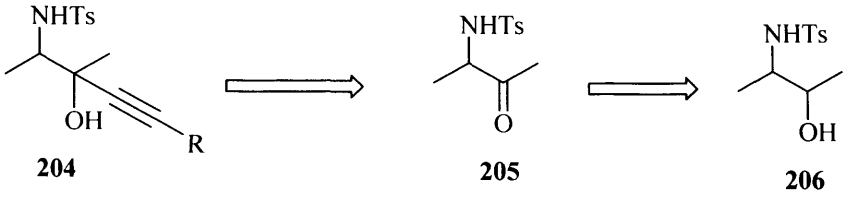


Scheme 1.43

Aminohydroxylation is proceeded by an allowed [2+2]-cycloaddition reaction with the alkene **199** to generate a complex **200**. The nitrogen atom is generally located in the position adjacent to the most electron-withdrawing group. Following reductive insertion of the Os-C bond into

an Os=O bond, a rearrangement occurs to form a [3+2]-cyclo-complex **201**, which is delivered to the same face as the nitrogen, to generate a complex **202**. Reoxidation of the nitrogen source and dissociation of the ligand L* occurs, which is followed by hydrolysis to give the α-amino acohol **203** and regenerate the complex **197**. The reaction proceeds with high enantioselectivity but often with moderate yields due to poor regioselectivity and, when sulfonamide is used as the nitrogen source, the problem of removing the sulfonyl group has to be considered.

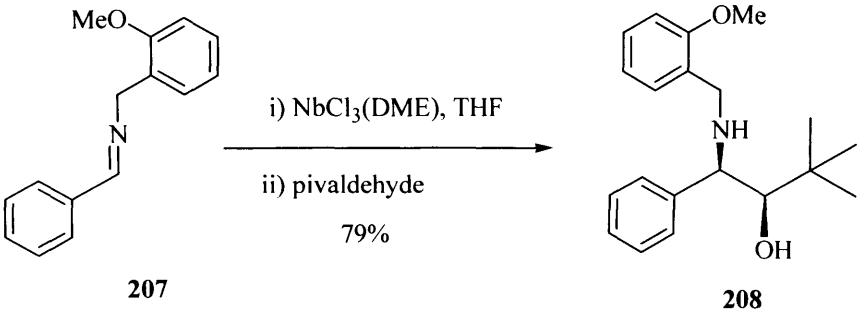
This was found however to be an attractive route to prepare the desired α-amino alcohols **204**, which were required as a precursor in our silver-mediated cyclisation (Section 1.4). We obtained α-amino alcohol **206** in good yields as precursors of amino alcohols **204** (Scheme 1.44).



Scheme 1.44

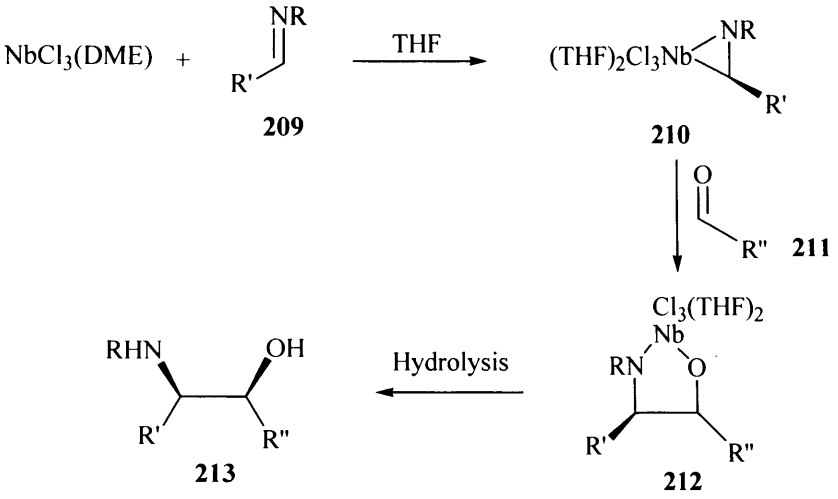
1.5.3 Pinacol Coupling

The pinacol coupling reaction is a powerful method for forming from two carbonyl groups a doubly functionalized carbon-carbon bond. Most pinacol coupling reactions are believed to proceed through the radical-radical coupling of ketyl anions, which are formed upon treatment of the carbonyl compound with a reducing agent. In 1987, Pedersen[41] developed new routes to functionalized amines employing transition-metal reagents (Scheme 1.45).



Scheme 1.45

He suggested that the niobium-imine reagent **210** was behaving like an N,C-dianion that should react with carbonyl groups **211** (*via* coordination and insertion into the metal-carbonyl bond) to give amino alcohols **213** after hydrolysis (Scheme 1.46). However, the coupling between $PhCH_2N{=}CHCMe_3/NbCl_3(DME)$ and octanal or between *t*-butyl methyl ketone and $PhCH_2N{=}CHPh/\ NbCl_3(DME)$ was not observed.

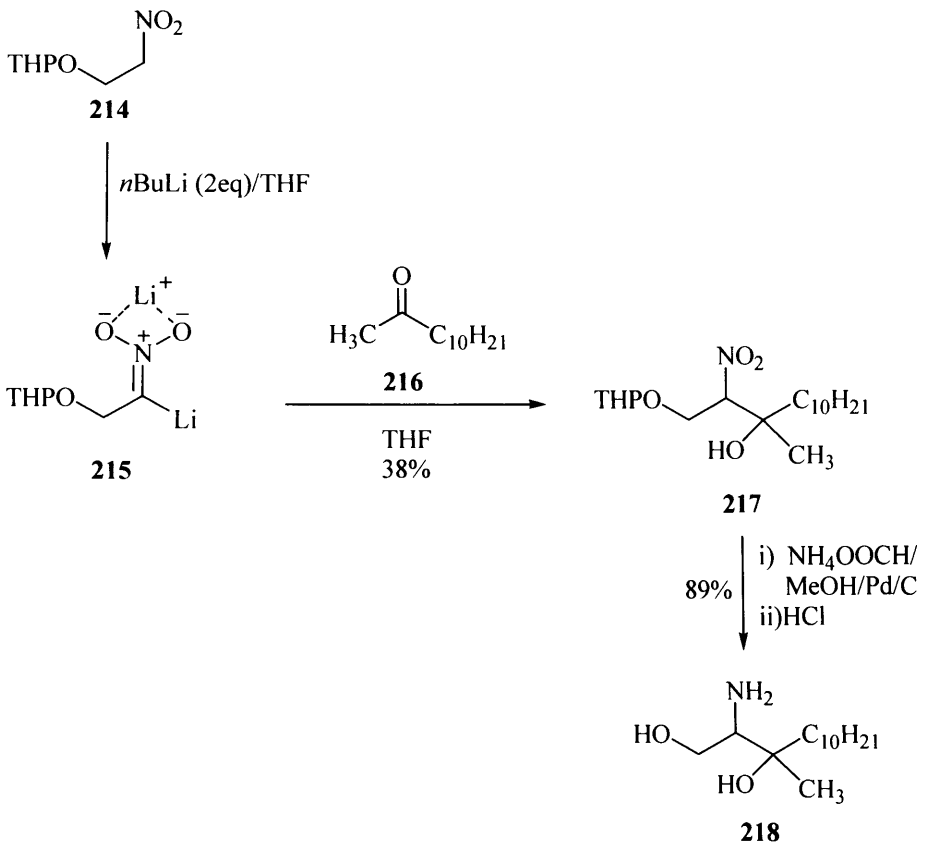


Scheme 1.46

1.5.4 Addition of Nitronates (Henry reaction)

The nitroaldol reaction of nitronates with aldehydes or ketones is a versatile method of synthesizing α-amino alcohols (route *d*). The nitronates are generated by catalytic amounts of base, such as sodium hydroxide, or by an equivalent amount of lithium diisopropylamide. The types of conditions, which are employed for the reaction, will largely depend on the type of functionality present, the solubility of the reactants and the ease to which the nitronate is generated.

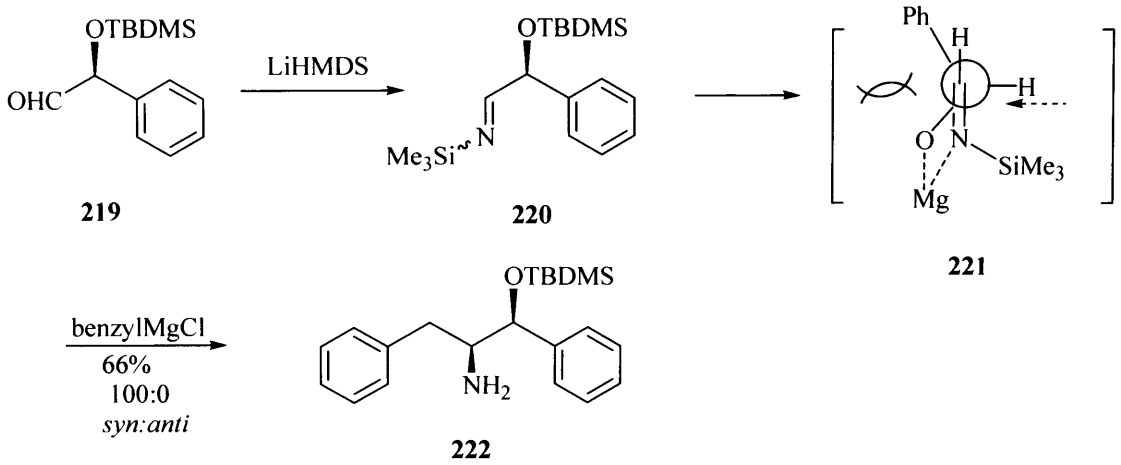
Sandhoff and co-workers[42] employed the dilithionitronate derivative of THP nitroethanol **215** in conjunction with 2-dodecanone **216** thereby providing the THP nitroalcohol **217** in low yield (38%). Phase-transfer reduction of the THP nitroalcohol **217** followed by direct hydrolysis with acid furnished the aminodiol **218** (Scheme 1.47).



Scheme 1.47

1.5.5 Nucleophile addition to imines

Cainelli[43] has demonstrated the synthetic usefulness of *N*-metallo imines to synthesis amino alcohols. α-Hydroxy-*N*-trimethylsilylimine **220** can be easily prepared from the corresponding aldehyde **219** *via* an addition-elimination reaction with lithium hexamethyldisilylamide (LiHMDS), to give clean conversion to the desired adduct **222** (Scheme 1.48). The diastereoselectivity is controlled by a chelation in the addition of the nucleophile to imines with a formation of the cyclic intermediate **221**.



Scheme 1.48

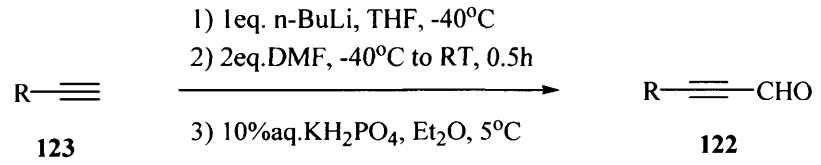
Chapter 2

Results and Discussion

2.1 Synthesis of α-amino alcohols

2.1.1 Initial Studies

Following on from Larsen's successful work,[28] we began with readily available phenyl acetylene **223** and reacted it with n-butyllithium in anhydrous tetrahydrofuran at –40°C followed by the addition of two equivalents of dimethylformamide. Reverse work-up into a phosphate buffer gave 3-phenyl-2-propynal **224** in ca. 100% crude yields (Table 2.1). From the infrared spectrum, the product showed the carbon-carbon triple bond at 2182 cm^{-1} and the carbonyl group at 1659 cm^{-1}. This showed an excellent result with the facile method to achieve our precursors for alkynyl-β-hydroxy-α-amino esters. We therefore applied this synthetic method to various alkynes.

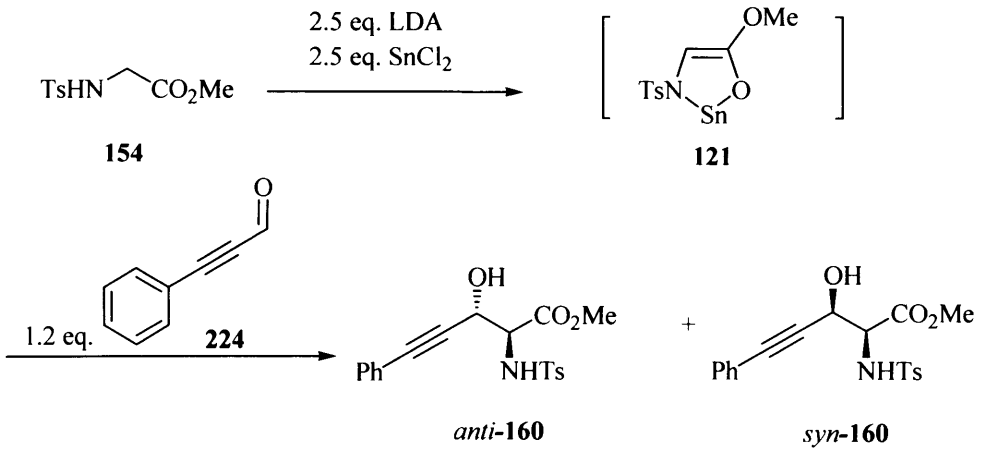


123 **122**

R	Alkyne	Ynal	Yields%	IR (cm^{-1}) C≡C, C=O	^{1}H NMR (CHO)
Ph	**223**	**224**	100	2182, 1659	9.36
n-Bu	**225**	**226**	100	2201, 1672	9.07
t-Bu	**227**	**228**	100	2220, 1685	9.09
TBDMSO$(CH_2)_3$	**229**	**230**	82	2203, 1671	9.16
TBDMSO$(CH_2)_4$	**231**	**232**	80	2201, 1672	9.13

Table 2.1

Commercially available 4-pentyn-1-ol and 5-hexyn-1-ol were protected with a TBDMS group (TBDMSCl, DMAP, imidazole, THF, 16 hours, r.t.) to give the corresponding silyl ethers **229** and **231** in relatively high yields of about 90%. As shown in Table 2.1, a range of α,β–acetylenic aldehydes were made in excellent yields without the need for further purification and were stored in the freezer until use.



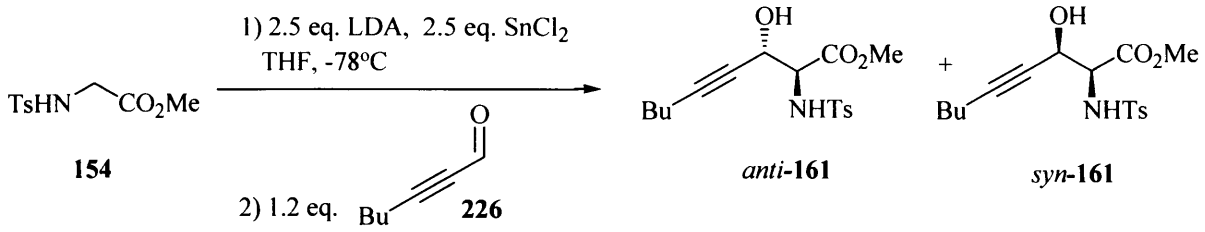
Scheme 2.1

We prepared these precursors in quantity in order to test the aldol reaction with *N*-(4-toluenesulfonyl) glycine methyl ester **154**, which was easily synthesized from commercial glycine methyl ester and purified by recrystallisation to give a crystalline white solid. 3-Phenyl-2-propynal **224** was first reacted with the tin enolate **121**, formed by deprotonation of the ester **154** by 2.5 equivalents of lithium diisopropylamine at –78°C in the presence of 2.5 equivalents of tin(II) chloride. After work-up, the crude β-ynyl-β-hydroxy-α-amino ester **160** was obtained as a yellow solid. From ^{1}H NMR spectroscopic data, the ratio of diastereoisomers was showed to be approximately 90:10. The crude product was purified by column chromatography to give analytically pure β-hydroxy-α-amino ester **160** in 76% yield (Scheme 2.1).

According to Sharland's report his results, taken together with those obtained during the present project, based on an X-ray crystal structure of a pure β-hydroxy-α-amino ester showed it to be the *anti*-diastereoisomer.[35a] We were therefore convinced that the same *anti*-diastereoisomer was the major diastereomer.

In the ^{1}H NMR spectroscopic data of β-hydroxy-α-amino ester **160**, a characteristic resonance for the proton α to the ester group was positioned at 4.18 ppm as an apparent broad singlet and the β-proton at 4.82 ppm as a double doublet (J = 10.2 and 3.4 Hz). This ester **160** was also confirmed by ^{13}C NMR (α- and β-carbon at 53.5 and 61.0 ppm), IR (broad absorbance at 3328 cm^{-1}), low resolution MS (374 $[M+H]^+$), and high-resolution MS (391.1322 $[M+NH_4]^+$).

To complete the study, examples of aliphatic aldehydes were tested in this aldol reaction. Firstly, the 2-heptynal **226** was used to give pure β-hydroxy-α-amino ester **161** in 64% yield and in a 96:4 ratio of diastereoisomers (Scheme 2.2). It was worth noting that the larger the scale of this aldol reaction, the more difficult the work-up. Due to large amounts of tin residues, these somehow absorbed the product; therefore the crude product required dividing into batches, which were filtered through a short plug of celite separately. Otherwise, it required approximately one hour for every 200 mL of crude solution to pass through the celite.



Scheme 2.2

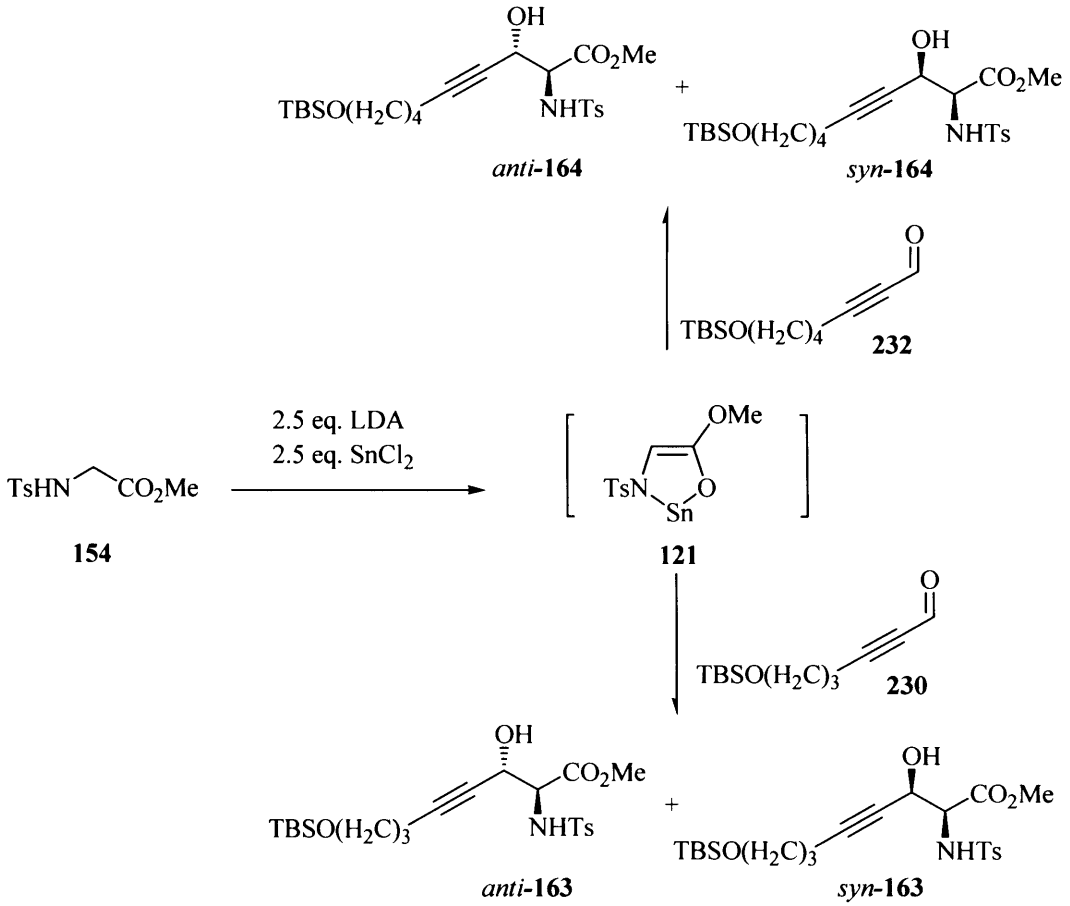
The structure of the β-hydroxy-α-amino ester **161** was confirmed by ^{1}H NMR (the proton α to the ester group at 4.06 ppm as a double doublet [J = 9.6 and 3.6 Hz], and the β-proton at 4.57 ppm as a double double triplet [J = 10.5, 3.6 and 1.8 Hz, also coupling with two protons of $CH_2C{\equiv}C$ and a proton of hydroxy group]), ^{13}C NMR (carbon β and α at 59.8 and 63.8 ppm), IR, low resolution MS (354 $[M+H]^+$) and CHN microanalysis.

2.1.2 Further studies

Followed on the previous condensations, it was decided to attempt the condensation with more complicated aliphatic aldehydes, such as silyloxy aldehydes **230** and **232**, which have a potential competition by attack the iodine by *O*-functionalised side chains. Both were successfully used in this aldol reaction to form the β-hydroxy-α-amino esters **163** and **164** in around 60% yields (Scheme 2.3). According to these slightly decreased yields, it was suggested that the tin enolate **121** was inadequately trapped with these silyloxy aldehydes. However, it still maintained good diastereoselectivity.

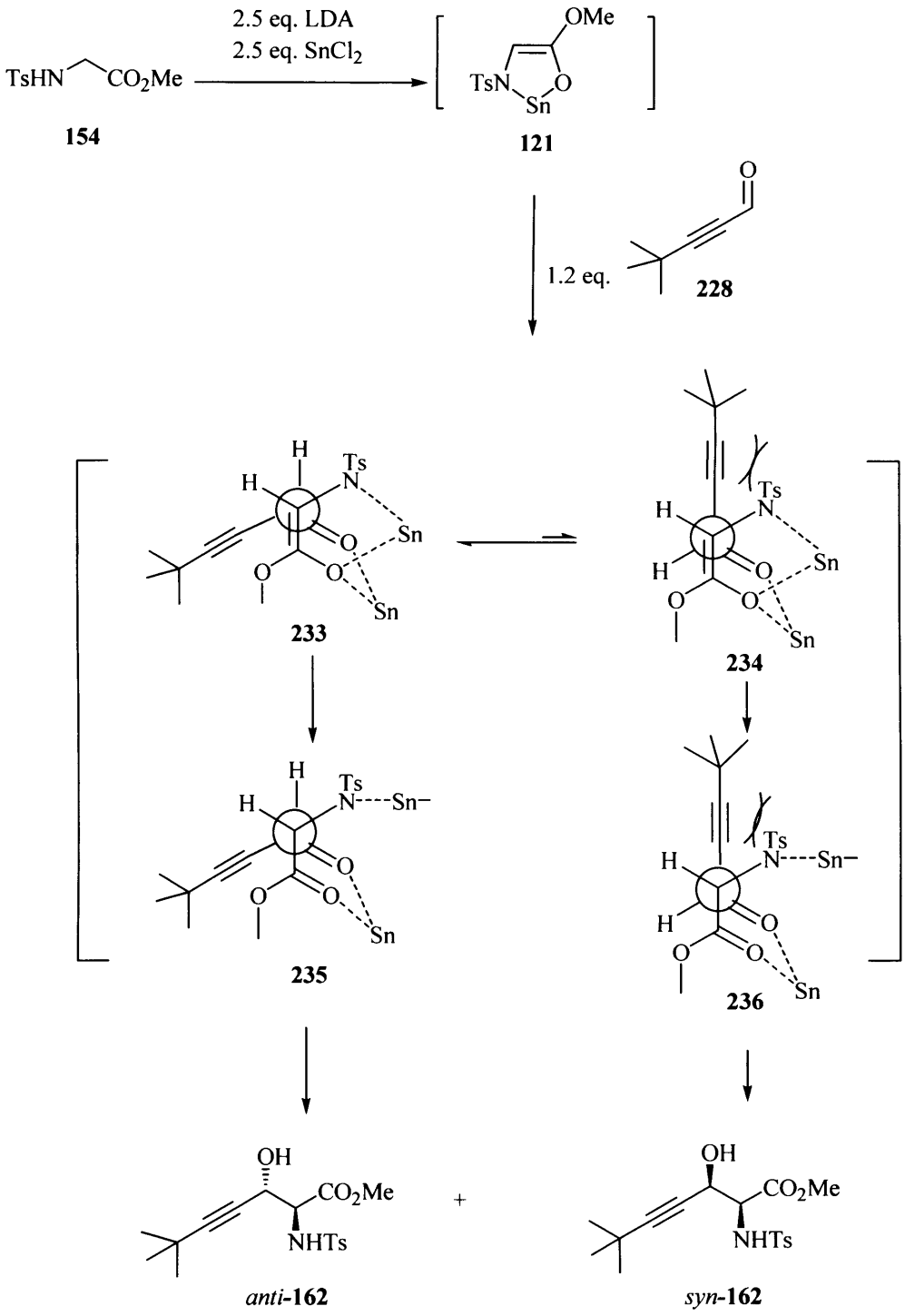
β-Hydroxy-α-amino ester **163** showed consistent ^{1}H NMR data (the proton α to the ester group at 4.11-4.16 ppm as a multiplet, and the proton β at 4.64 ppm as a double double triplet [J = 10.0, 3.7 and 2.0 Hz, also coupling with two protons of $CH_2C{\equiv}C$ and a proton of hydroxy

group]), ^{13}C NMR (carbon β and α at 61.0 and 63.5 ppm), IR, low resolution MS (470 $[M+H]^+$) and CHN microanalysis. From the ^1H NMR spectroscopic data, the ratio of diastereoisomers was shown to be approximately 92:8.



Scheme 2.3

The ^1H NMR spectroscopic data of β-hydroxy-α-amino ester **164** showed the characteristic resonance for the proton α to the ester group at 4.13 ppm as a double doublet (J = 9.5 and 3.7 Hz, also coupling with a proton of NH) and the proton β at 5.51 ppm as a double doublet (J = 10.4 and 3.7 Hz, also coupling with a proton of hydroxy group). This ester **164** was also confirmed by ^{13}C NMR (carbon α and β at 60.7 and 63.8 ppm), IR (broad at 3488 and 3288 cm^{-1}), low resolution MS (484 $[M+H]^+$) and CHN microanalysis. From the ^1H NMR spectroscopic data, the ratio of diastereoisomers was approximately 90:10.



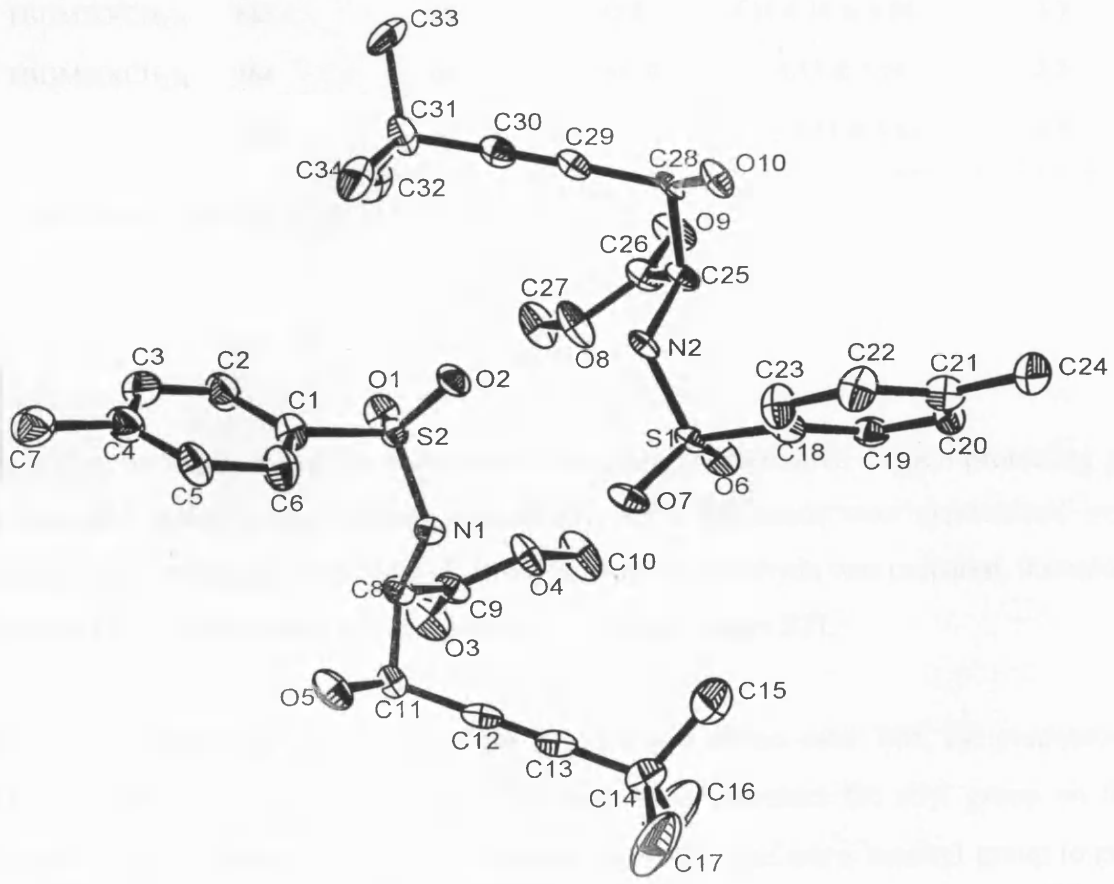
Scheme 2.4

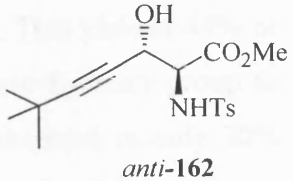
As we were interested in what effect a large substituent might have on the pyrrole synthesis, the aliphatic aldehyde **228** was also tested in this aldol reaction to form the β-hydroxy-α-amino ester *anti*-**162** (Scheme 2.4). Due to the bulky butyl group, complex **233** is more favorable than complex **234**, and this yielded the expected product **162** as a 65% yield as a single diastereoisomer which was isolated as a white solid.

From the ^{1}H NMR spectroscopic data of β-hydroxy-α-amino ester **162**, the characteristic resonance for the proton α to the ester group appeared at 4.13 ppm as a double doublet (J = 9.6 and 3.9 Hz, also coupling with a proton of NH) and the proton β at 4.63 ppm as a double doublet (J = 10.4 and 3.9 Hz, also coupling with a proton of hydroxy group). The structure was also confirmed by ^{13}C NMR (carbon α and β at 60.6 and 62.9 ppm), IR (broad at 3267 cm^{-1}), low resolution MS (354 $[M+H]^{+}$), CHN microanalysis and an X-ray crystal structure of two unitcells (Figure 2.1, full data on p. 235-242). Despite the previous X-ray determination by Sharland, we wished to be absolutely certain of the *anti*-stereochemical assignment.

Figure 2.1: X-Ray crystallographic Analysis

Methyl (*2SR,3SR*)-3-hydroxy-6,6-dimethyl-2-(4-methylphenylsulfonylamino)-hept-4-ynoate 162

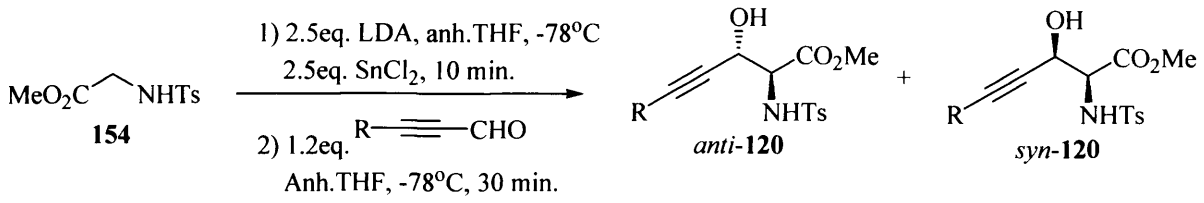




anti-**162**

We have found that the glycine enolate **121** and α,β–acetylenic aldehydes performed admirably in the desired aldol process, to provide the *anti*-products **160-164** as easily handled

solids; the results are shown in Table 2.2.[34] Multiple crystallisation of the crude products were however required to remove a small amount of the *N*-tosylated methyl ester **154** to afford pure products.



R	Compound	Yields%	*anti/syn**	2-H & 3-H (ppm)	*J value* (Hz)
Ph	**160**	76	90/10	4.18 & 4.82	3.4
n-Bu	**161**	64	96/4	4.06 & 4.57	3.6
TBDMSO$(CH_2)_3$	**163**	60	92/8	4.11-4.16 & 4.64	3.7
TBDMSO$(CH_2)_4$	**164**	60	90/10	4.13 & 5.51	3.7
t-Bu	**162**	65	100/0	4.13 & 4.63	3.9

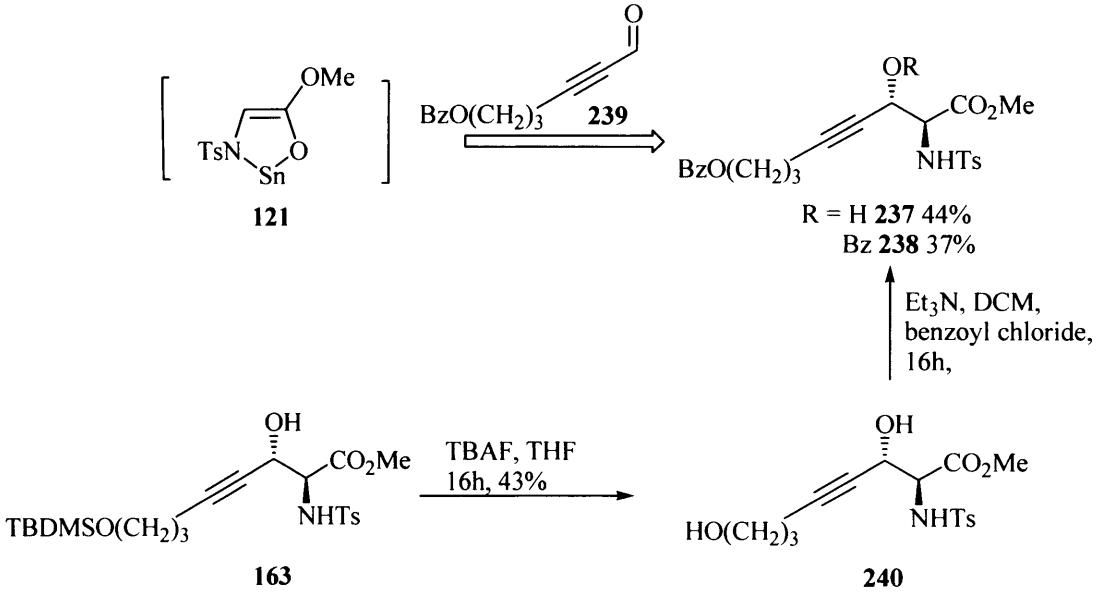
*Determined by integration of the ^{1}H NMR spectra.

Table 2.2[34]

We wanted to also test whether a substrate containing an alternative oxygen-protecting group in the side chain would cyclise successfully, so a precursor was synthesized with a benzoyloxy-protecting compound **237**. If the benzoyloxy aldehyde was prepared, it could then be used in the aldol reaction to form β-hydroxy-α-amino esters **237**.

Since we obtained a good amount of the β-hydroxy-α-amino ester **163**, the preparation of aldehyde **239** had been avoided. Thus, we decided to deprotect the silyl group on the β-hydroxy-α-amino esters **163** to form the amino esters **240** and use a benzoyl group to protect the primary hydroxy group to form the amino esters **237** (Scheme 2.10). This yielded 44% of the desired product **237**, and gave also over protection of the secondary hydroxy group to form the α-amino ester **238** in 37% yield. The desired product was obtained in only 20% overall yield. However, the obtained quantities of the amino ester **237** were sufficient to test the iodocyclization (Scheme 2.32).

From the ^{1}H NMR spectroscopic data of the amino esters **240**, **237** and **238**, the ratio of diastereoisomers were approximately 80:20, which showed a little epimerization due to the basic fluoride when cleaved the silyl group to obtain the amino esters **240**.

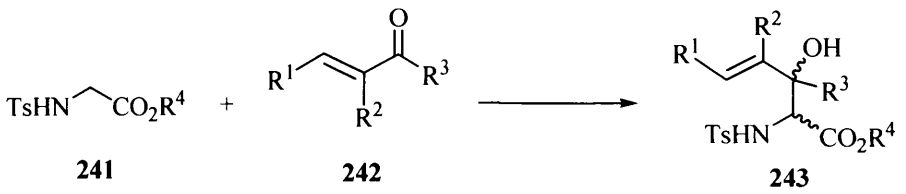


Scheme 2.10

2.1.3 Further studies of this aldol reaction

It should be noted that Sharland[35a] has extended the use of this aldol reaction to the α,β-unsaturated ketones or aldehydes **242**. These were performed in the same manner as the previous condensations. After work-up and purification by column chromatography, the β-hydroxy-α-amino esters **243** were obtained as a mixture of diastereoisomers (Table 2.3).

From the results, the condensation showed low diastereoselectivity when R^1 and R^3 become equal in size. During this present study, no further examples were done in this area, but it is noted that the products **243** could also be useful as pyrrole precursors. Williams's results[35d] showed similar diastereoisomer ratios of **248** and **249** with similar yields when these unsaturated aldehydes condensed with the *N*-tosylglycine methyl ester **154**.



241 **242** **243**

243	R^1	R^2	R^3	R^4	%Yield, *anti:syn*
244	Ph	H	H	Et	67, 80:20
245	Me	H	H	Et	69, 63:37
246	^{n}Bu	H	Me	Et	79, 71:29
247	Me	Me	Me	Et	91, 53:47
248	Ph	H	H	Me	67, 80:20
249	Me	H	H	Me	69, 63:37

Table 2.3

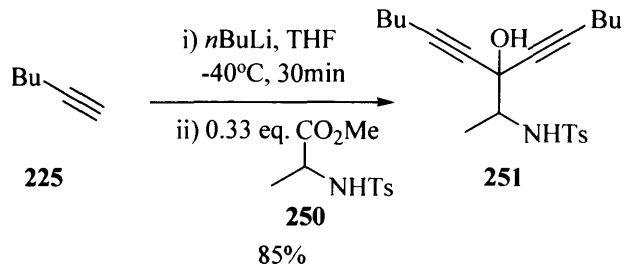
2.2 Alternative synthesis of α-amino alcohols

2.2.1 Addition to α-Aminocarbonyls

In order to extend the scope of the iodocyclisation (see page 24), a rapid preparation of symmetrical precursor was observed. The *N*-tosyl-alanine methyl ester **250** was prepared from commercial alanine methyl ester, followed by adding to two equivalents of the acetylide **225**, which was formed using *n*-buthyllithium at –40°C for 30 min to give a desired symmetrical precursor **251** in 85% yield (Scheme 2.11). The ^{1}H NMR spectroscopic data showed a singlet of a hydroxy group at 2.27 ppm and a singlet of a methyl group (Ts-CH_3) at 2.30 ppm.

From the ^{1}H NMR spectroscopic data of the α-amino alcohol **251**, the characteristic resonance for the proton α to the NH group appeared at 3.35 ppm as a double quartet (J = 9.1 and 6.6 Hz, also coupling with a proton of NH). The structure was also confirmed by ^{13}C NMR (carbon α to the NH group at 58.9 ppm), IR (broad at 3465 and 3274 cm^{-1}), low resolution MS (372 $[M\text{-}H_2O]^+$) and CHN microanalysis. This proved to be a facile route to

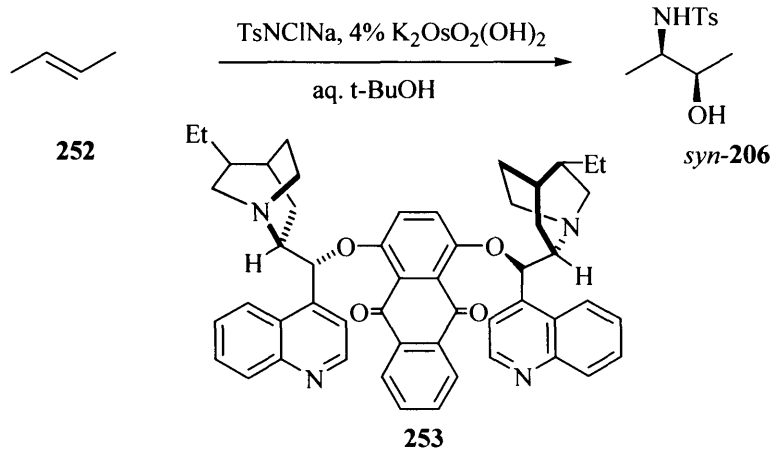
prepare the symmetrical precursors for the iodocyclisation. Rost also reported more examples on this synthetic route (see page 26).



Scheme 2.11

2.2.2 Asymmetric Aminohydroxylation

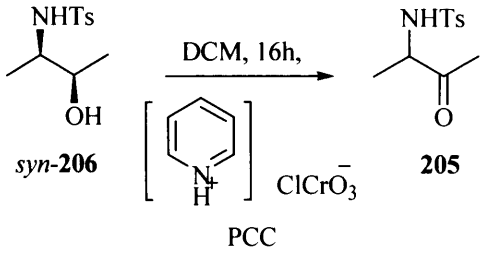
We firstly approached the reaction with the chemical reagents that were available in our research laboratory. Condensed 2-butene **252** was treated with $(DHQD)_2AQN$ **253**, 4% $K_2OsO_2(OH)_4$ and TsNClNa (chloramine-T), in aqueous *t*-butanol, to give a 66% yield of amino alcohol **206** (Scheme 2.12).



Scheme 2.12

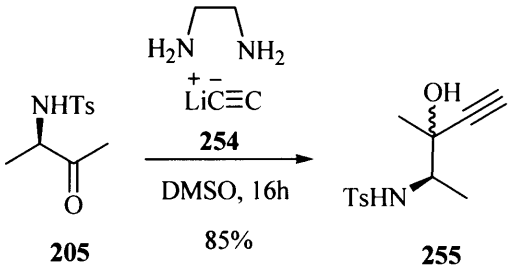
We faced difficulties in attempting to separate the product from the decomposition product of chloramine-T, tosylsulfonamide, $TsNH_2$, and obtained this product as a mixture of the amino alcohol **206** and the sulfonamide in a ratio of 2:1. From ^1H NMR spectroscopic data clearly indicated a CHN proton at 3.07 as a sextet (J = 7.0 Hz) and a CHO proton at 3.54 as a sextet (J = 7.0).

As the starting material was not pure, it was fortunate that the sulfonamide impurity did not affect the subsequent PCC oxidation and that the resulting ketone **205** could easily be separated from the impurity. After purification by flash chromatography, the ketone **205** was obtained as a white solid in 80% yield. The carbonyl group was observed in the ^{13}C NMR at 206.4 ppm and in the IR a strong absorbance at 1682 cm^{-1} was visible.



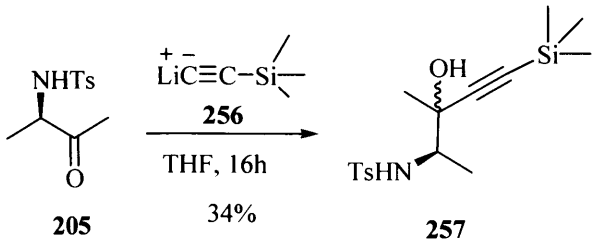
Scheme 2.13

To access examples of the desired α-amino alcohols **204** (page 31), the ketone **205** was first treated with three equivalents of lithium acetylide-ethylenediamine **254** in anhydrous dimethyl sulfoxide at room temperature for 16 hours (Scheme 2.14).



Scheme 2.14

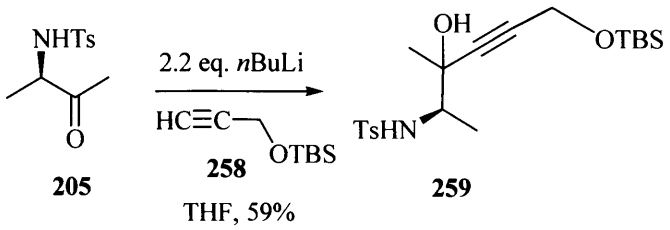
The amino alcohol **255** was isolated in 85% yield (**204,** R = H) and showed the ratio of 52:48 diastereoisomers according to two doublets due to the CH_3 group at 0.95 and 0.98 ppm (J = 6.7 Hz) and two singlets due to $CH_3C(OH)$ at 1.35 and 1.37 ppm in the ^1H NMR spectrum data. The ketone was also treated with the acetylide **256**, which was formed by addition of *n*-buthyllithium at –40°C (Scheme 2.15).



Scheme 2.15

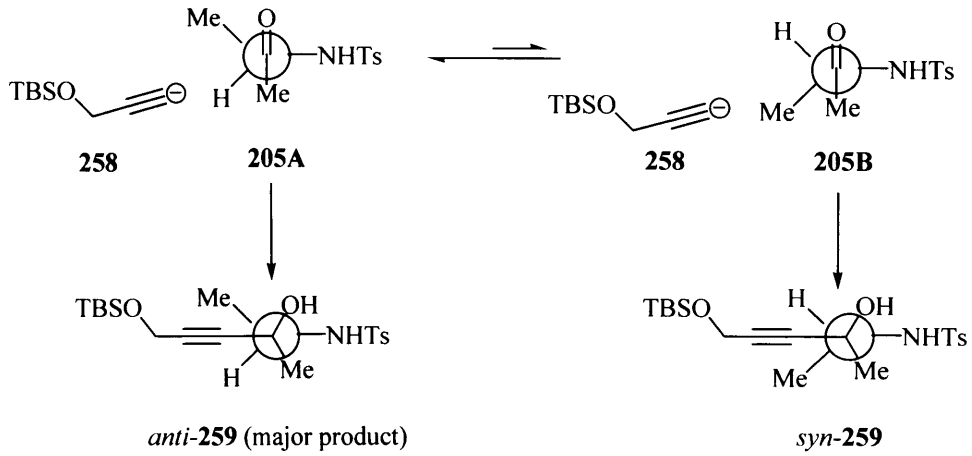
It yielded only 34% of the amino alcohol **257** (**204,** R = $SiMe_3$); this might be achieved by using more polar solvent. The ^1H NMR spectroscopic data showed a diastereisomer ratio of 61:39, corresponding to two doublets for CH_3 at 0.90 and 0.94 ppm (J = 6.9 Hz) and two singlets for CH_3 at 1.25 and 1.26 ppm. This proved to be the desired protected acetylene **257**.

To synthesise the α-amino alcohols **259** (**204**, R = CH_2OTBS), propynyloxysilane was prepared from commercially available propargyl alcohol, which was protected with a TBDMS group (TBDMSCl, DMAP, imidazole, THF, 16 hours, room temperature) to give the corresponding silyl ether **258** in excellent yields of about 99%. This was treated with *n*-butyl lithium at –40°C, followed by the addition of the ketone **205** (Scheme 2.16).



Scheme 2.16

In the ^1H NMR spectroscopic data of the α-amino alcohols **259**, both diastereoisomers were identified in a *anti:syn* ratio of 55:45. The Felkin-Anh model has been used to suggest a major diastereoisomer (Scheme 1.17).



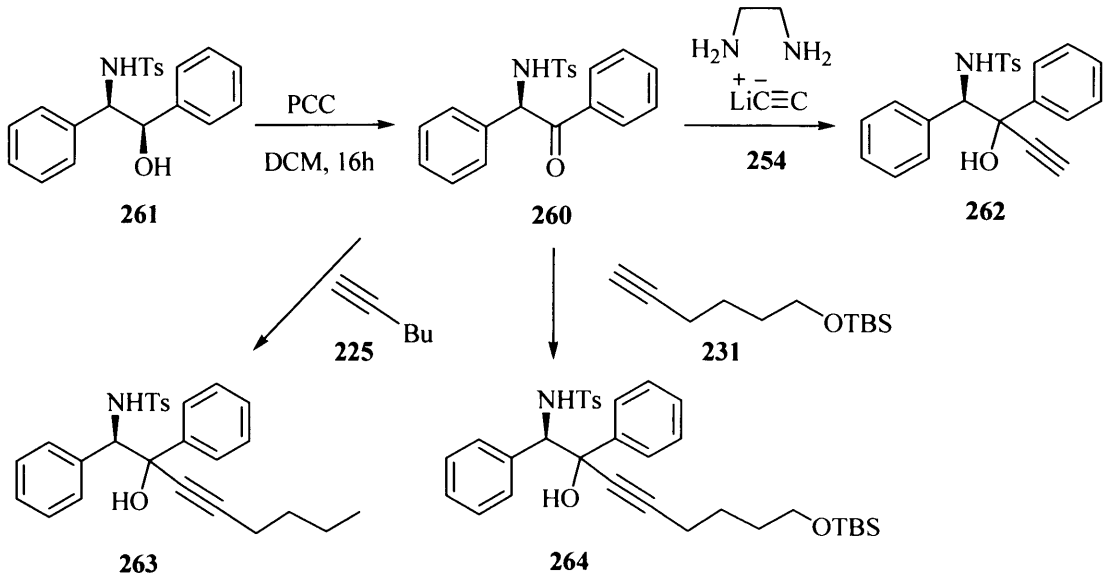
anti-**259** (major product) *syn*-**259**

Scheme 1.17

The transition states are favoured when nucleophilic attack occurs from an orientation antiperiplanar to an adjacent σ–bond group. In this way, the transition state is staggered and the largest group is *anti* to the incoming nucleophile. Also, the most favoured transition conformation was considered to have the medium group position near the carbonyl oxygen.

Purification by column chromatography gave the amino alcohols **259** in 59% yield as a mixture of diastereomers (55:45) according to ^{1}H NMR spectroscopic data, corresponding to two doublets of CH_3 at 0.93 and 0.98 ppm (J = 6.7 Hz) and two singlets of CH_3 at 1.31 and 1.33 ppm. This was also confirmed by ^{13}C NMR (CHN at 58.5 ppm and C(OH) at 70.5 ppm), IR, low resolution MS (412 $[M+H]^+$) and high resolution MS (412.1976 $[M+H]^+$).

An undergraduate student, L. Dando had prepared an amino alcohol **261** in good yield, which was then available for our further use. Thus, the amino acohol **261** then treated with PCC in dichloromethane for 16 hours gave the corresponding ketone **260** in 80% yield (Scheme 2.18). Various precursors were prepared to test the silver-mediated cyclisation (Section 1.4), which were acetylenes with an unprotected acetylenic substituent **262**, a saturated aliphatic substituent **263**, and a protected-alcohol aliphatic substituent **264**.



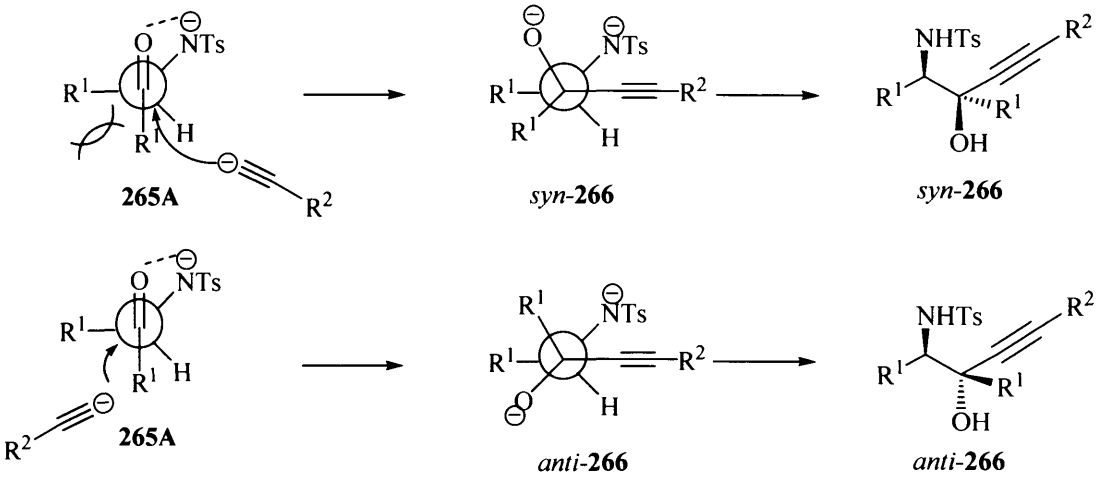
Scheme 2.18

The ketone **260** was first treated with three equivalents of lithium acetylide-ethylenediamine **254** in anhydrous dimethyl sulfoxide at room temperature for 16 hours to yield 67% of the amino alcohol **262.** The amino alcohol **262** showed only one diastereisomer according to a singlet for C≡CH at 2.54 ppm and a doublet of CHN at 4.51 ppm (J = 8.6 Hz) in the ^{1}H NMR spectroscopic data.

The acetylene **225** was treated with *n*-butyl lithium at –40°C and followed by the ketone **260**. Purification by column chromatography gave the amino alcohols **263** in 58% yield with only one diasteromer by ^{1}H NMR analysis, corresponding to a triplet of CH_3 at 0.84 ppm (J = 7.3 Hz) and a doublet of CHN at 4.43 ppm (J = 8.1 Hz). This was also confirmed by ^{13}C NMR (CHN at 67.4 ppm and HOC at 75.9 ppm), IR, and low resolution MS (430 $[M\text{-}OH]^+$).

Finally, the acetylene **231** was treated with *n*-butyl lithium at –40°C and followed by the ketone **260**. Purification by column chromatography gave the amino alcohols **264** in only 25% yield with a mixture of diasteroisomers (4:1) by ^{1}H NMR spectroscopic data, corresponding to a doublet corresponding to the CHN at 4.45 ppm and 4.47 ppm (J = 8.2 Hz) and a doublet corresponding to the NH at 5.42 ppm and 5.45 ppm (J = 8.2 Hz).

According to Scheme 2.19, a chelated model of the ketone **265** would be likely to form an intermediate **265A**, which prefers to be trapped by the acetylene on a less hindrance and, if R^1 is a phenyl group, the left-side, between R^1 groups, is very hindered. To support this suggestion, the summary of the results has showed in the Table 2.4.



Scheme 2.19

Ketone, R^1	Amino alcohol, R^2	Yield%	CHN(ppm), *J* (Hz)	Diastereoisomer ratio
205, CH_3	**255**, H	85	3.19 & 3.28, 9.1 & 6.7	52:48
205, CH_3	**257**, $SiMe_3$	34	3.23, multiplet	61:39
205, CH_3	**259**, CH_2OTBS	59	3.22, multiplet	55:45
260, Ph	**262**, H	67	4.51, 8.6	99:1
260, Ph	**263**, *n*Bu	58	4.43, 8.1	99:1
260, Ph	**264**, $(CH_2)_4OTBS$	25	4.45 & 4.47, 8.2	80:20

Table 2.4

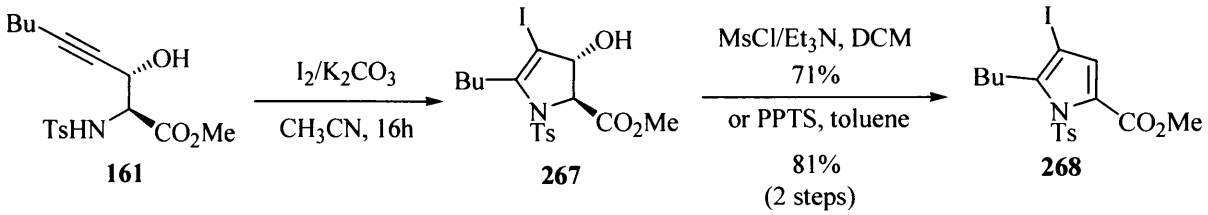
The diastereofacial selectivity is increased dramatically when the R^1 is phenyl group. Also, when the R^2 is more hindered, it would be more difficult to attack the ketone that causes decreasing yields. However, this methodology provided the desired protected acetylene precursors **266** in four steps with overall yields of 10-40%.

2.3 Studies of Iodocyclization

2.3.1 Initial Studies

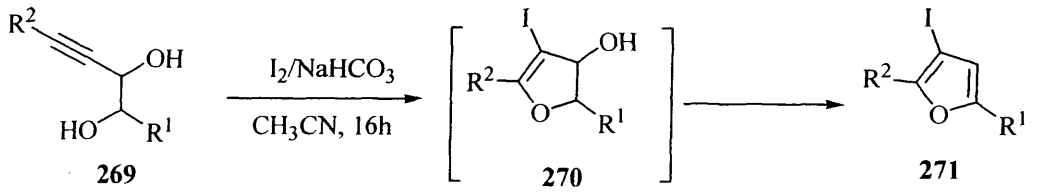
Having an idea to generalize and further develop by applying iodocyclization to α-amino-β-hydroxy esters, firstly, we aimed to check Sharland's result[35a] and tried to optimize the elimination process. Secondly, we aimed to extend to examples having functionality in the side chains, which could potentially interfere with the iodocycilzation. We chose to use toluene-*p*-sulfonamides to protect the amino groups, and in addition simple methyl esters rather than any more elaborate derivatives as these might interfere with the relatively favoured and desired 5-*endo* process.

A typical example of the key step is an iodine-induced 5-*endo*-dig cyclisation of the acetylenic α-amino-β-hydroxy ester **161**, which gave excellent yields of the 2-hydroxy-2,3-dihydropyrroles **267**, together with iodopyrroles **268**, by treatment with three equivalents of iodine and three equivalents of potassium carbonate in anhydrous acetonitrile at 0°C, and then at room temperature for 16 hours. Dehydration occurred under either basic condition (1.1 equivalent of methanesulfonyl chloride and 1 equivalent of triethylamine in dichloromethane for 16 hr) or acidic conditions (0.01 equivalent of pyridinium-*p*-toluenesulfonate in toluene for 16 hr); good yields of the iodopyrroles **268** were isolated (Scheme 2.20).



Scheme 2.20

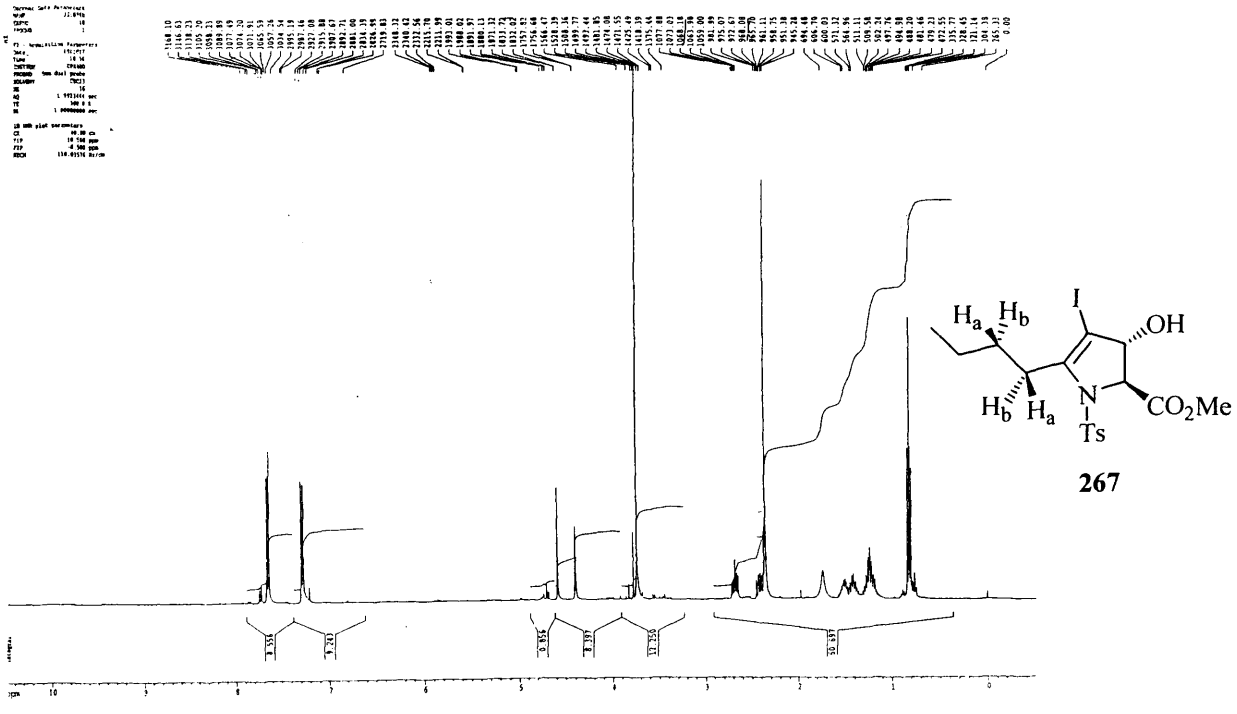
2-Hydroxy-2,3-dihydropyrrole **267** was not the expected product. According to Jones's work,[22b] the iodocyclization of related alkyne-1,2-diols **269** to β–iodofurans **271** with iodine and sodium hydrogen carbonate in acetonitrile, was successful achieved in good yield without ever observing the intermediate 3-hydroxy-2,3-dihydrofuran **270,** despite attempts to do so (Scheme 2.21). Therefore, it was assumed that the iodocyclisation step was the slower, not unreasonably in view of the generation of an aromatic system in the second step.



Scheme 2.21

However, the ^{1}H NMR spectroscopic data of 5-*n*-butyl-3-hydroxy-4-iodo-2,3-dihydropyrrole **267** showed the characteristic resonances for a proton α to the ester group at 4.39 ppm and for a proton α to the alcohol at 4.68 ppm (Figure 2.2). These both appeared as doublets with a small coupling constant of 1.4 Hz. It was known that the predominant stereochemistry of the acetylenic α-amino-β-hydroxy ester **161** was *anti*, which many explain the stability of the 5-*n*-butyl-3-hydroxy-4-iodo-2,3-dihydropyrrole **267**.

Figure 2.2: ^{1}H NMR spectroscopic data of Methyl (*2SR,3RS*)-5-butyl-3-hydroxy-4-iodo-1-(4-methylphenylsulfonyl)-2,3-dihydro-pyrrole-2-carboxylate, 267.



The iodopyrrole **268** also appeared in this spectrum data, considering two main resonances of a proton β to the NH group at 6.80 ppm and another one for CH_3 at 3.73 ppm, in

approximately 5% along with the major product **267**, suggesting that the *syn*-ester **161** was converted directly to form the iodopyrrole **268** as in Jones's report.[22b]

In the ^{1}H NMR spectroscopic data of the dihydropyrrole **267**, diastereotopic hydrogens from two pairs of hydrogens ($CH_3CH_2C\boldsymbol{H_aH_b}C\boldsymbol{H_cH_d}$ = *n*-Bu), were observed, presumably due to restricted rotation caused by the large iodine and sulfonyl substituents. The spectrum showed each proton separately at 1.39-1.44 ppm, 1.50-1.53 ppm, 2.41-2.46 ppm and 2.64-2.68 ppm as multiplets.

In the elimination process, it is important that the four atoms involved in the more facile E_2 elimination reaction lie in the same plane; the *anti*-periplanar configuration is preferred, as in *syn*-**267**. The *anti*-periplanar configuration is necessary for the orbital overlap, which must occur for the π bond to be generated in the pyrrole **268** (route a). If this cannot be achieved, then the elimination will normally proceed by an E_1 mechanism, which requires either loss of the hydroxy group to generate intermediate **272**, which can then lose a proton to form the pyrrole **268** (route b), or the deprotonation of *anti*-**161** to give the enolate **273**, which can eliminate the hydroxy group to form the pyrrole **268** as shown (route c, Figure 2.3).

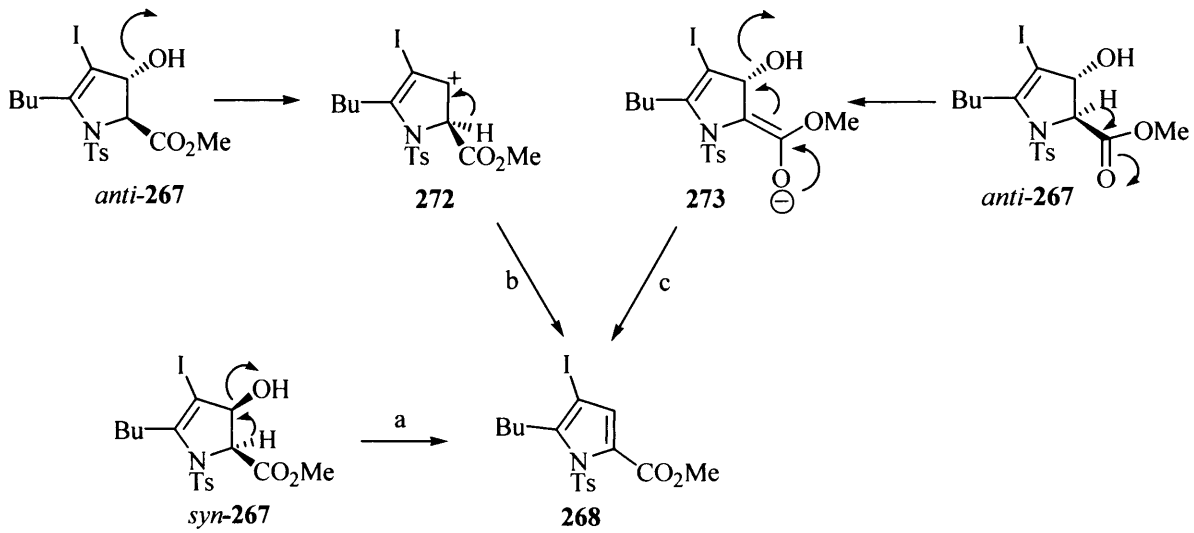
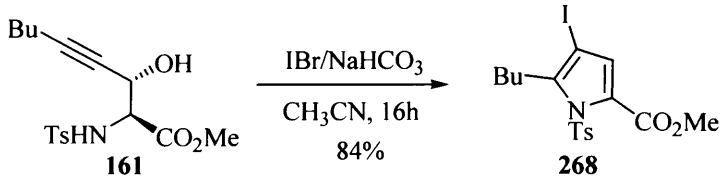


Figure 2.3: Elimination process.

Moreover, the acetylenic α-amino-β-amino ester **161** was successfully and directly converted into the iododpyrrole **268**, upon treatment with three equivalents of iodine monobromide and sodium hydrogen carbonate in acetronitrile at 0°C for 2 hours, followed by 14 hours at room temperature (Scheme 2.22). We achieved an excellent yield at this point, but not for all substrates, which will be discussed later on.



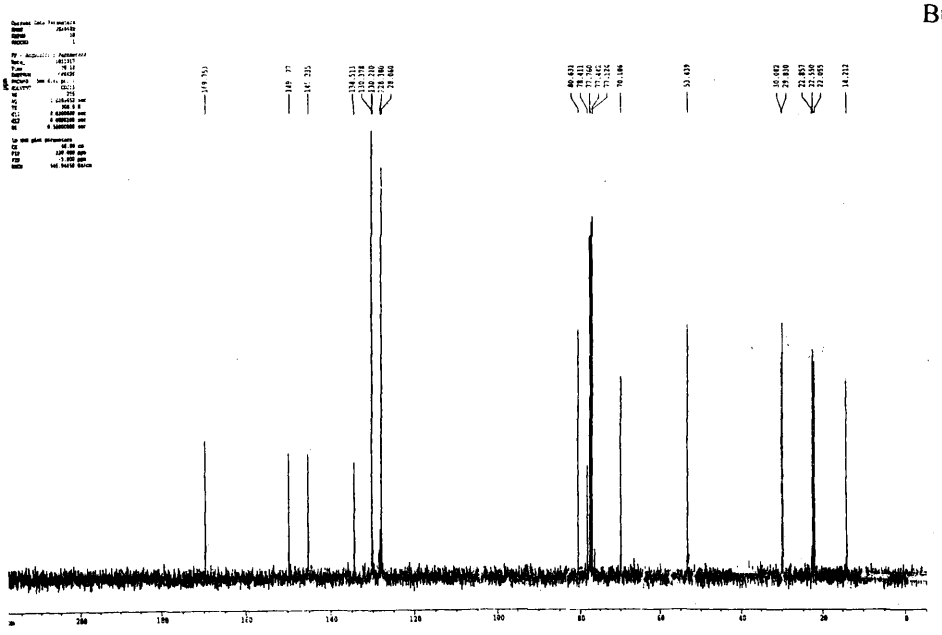
Scheme 2.22

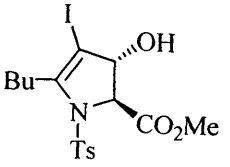
The full experimental method and data for the iodopyrrole **268** can be found in Chapter six. The ^{13}C NMR spectra (Figure 2.4) showed carbon-2 (CHN) and –3 (CHOH) of the dihydropyrrole **267** at 70.1 and 80.6 ppm, and carbon-3 (CH) of the iodopyrrole **268** at 125.6 ppm. The latter spectra also demonstrates the effect of electronegative atom (I) on the carbon-4 (CI) of the dihydropyrrole **267**, which resonates at 78.4 ppm and in the iodopyrrole **268**, at 68.9 ppm, due to the heavy atom effect.

In both spectra, the carbons of all methyl groups and CH_2s in the butyl group appear in the region of 12.6-53.4 ppm; CHs in the tosyl group was clearly showed at 128.0 and 130.3 ppm for the dihydropyrrole **267** and 126.5 and 128.8 ppm for the iodopyrrole **268**; three quaternary carbons of the dihydropyrrole **267** were showed at 134.5, 149.8 and 149.8 ppm, and four quaternary carbons of the iodopyrrole **268** were showed at 127.3, 135.2, 142.1 and 144.3 ppm; the carbonyl group of the dihydropyrrole **267** resonated at 169.8 ppm and in the iodopyrrole **268**, at 159.4 ppm.

Figure 2.4: ^{13}C NMR spectroscopic data

a) Methyl (*2SR,3RS*)-5-butyl-3-hydroxy-4-iodo-1-(4-methylphenylsulfonyl)-2,3-dihydro-pyrrole-2-carboxylate, 267.

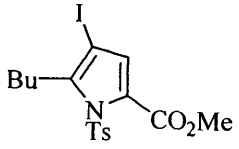




267

and

b) Methyl 5-butyl-4-iodo-1-(4-methylphenylsulfonyl)-pyrrole-2-carboxylate, 268.



268

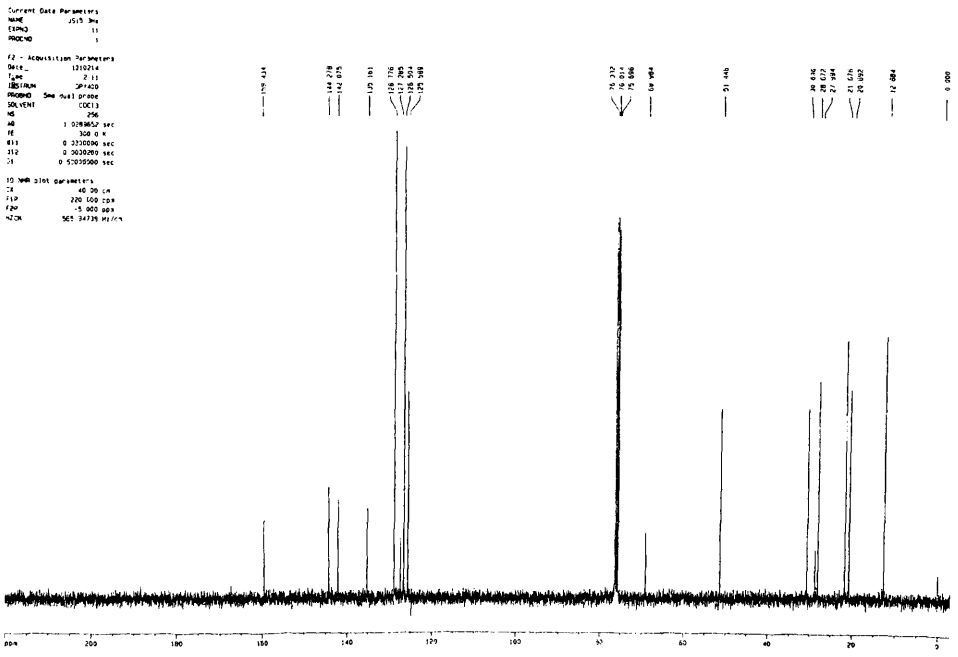
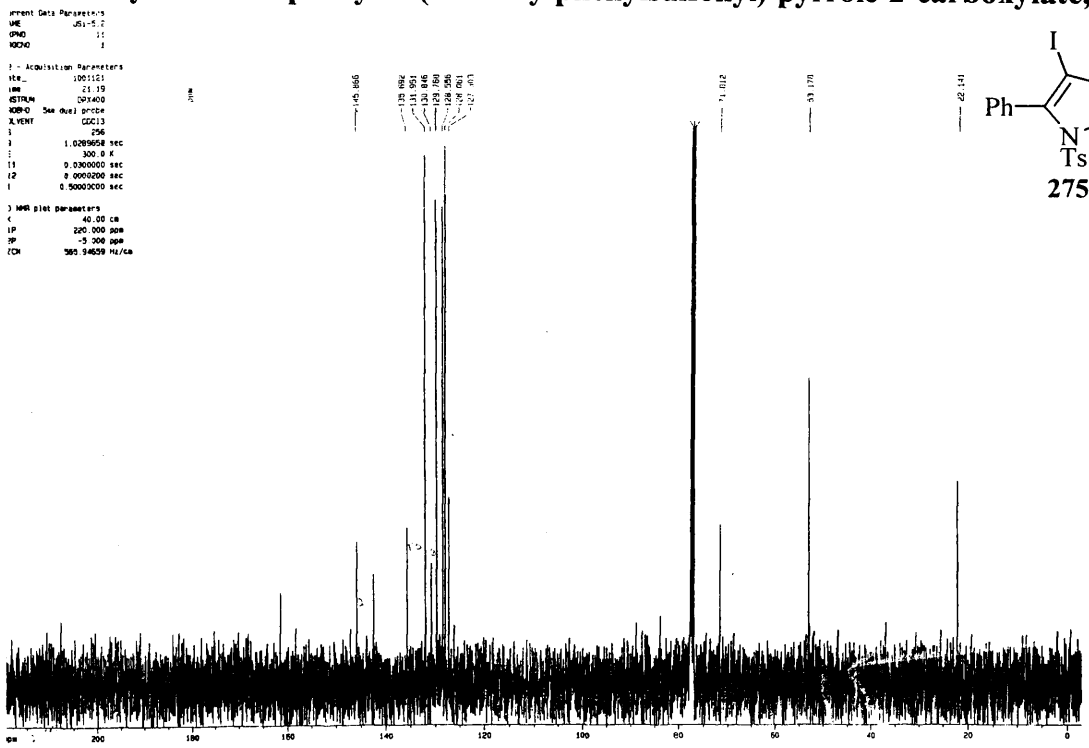
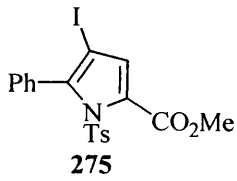


Figure 2.6: ^{13}C NMR spectroscopic data

Methyl 4-iodo-5-phenyl-1-(4-methylphenylsulfonyl)-pyrrole-2-carboxylate, 275

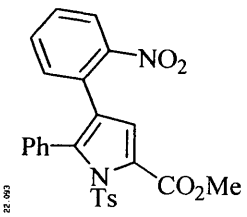




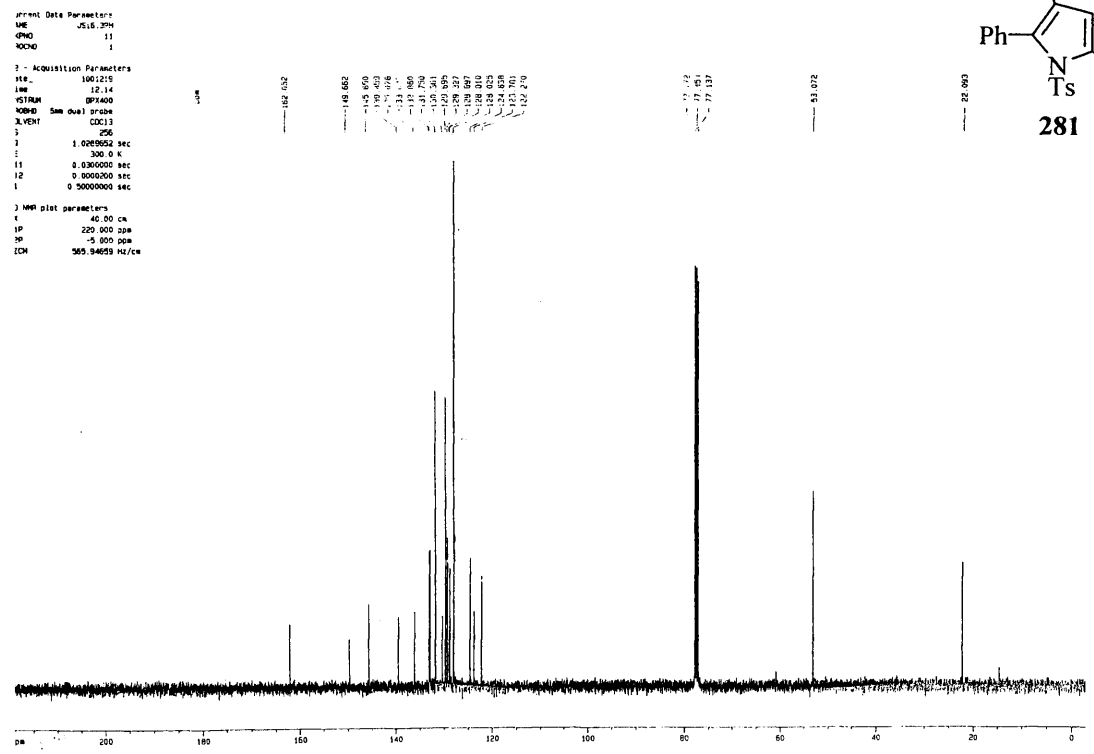
275

And

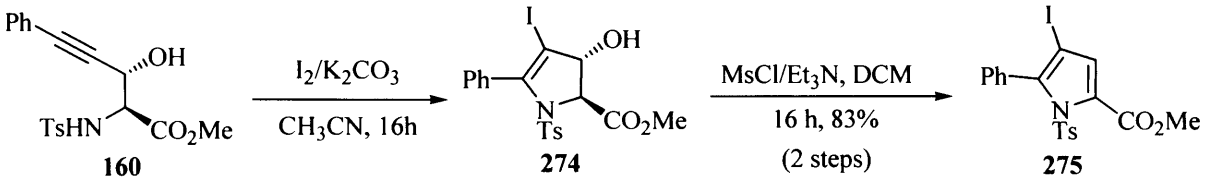
Methyl 4-(2-nitro-phenyl)-5-phenyl-1-(4-methylphenylsulfonyl)-1H-pyrrole-2-carboxylate, 281.



281



To approach iodopyrrole **275**, the cyclization of the acetylenic α-amino-β-hydroxy ester **160** was carried out smoothly, using three equivalents of iodine and three equivalents of potassium carbonate in acetonitrile at 0°C, then at room temperature for 16 hours to give the 2-hydroxy-2,3-dihydropyrrole **274** together with small amount of the iodopyrrole **275** in overall yield of 83%.



Scheme 2.23

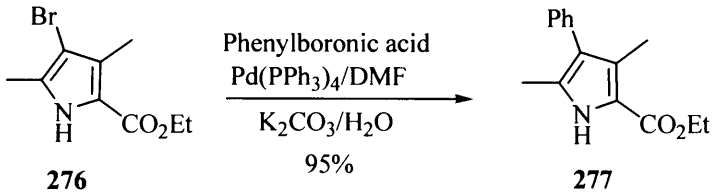
After elimination under basic conditions and isolation by column chromatography, the pyrrole **275** was obtained in 83% yield from α-amino-β-hydroxy ester **160** (Scheme 2.23). The resonance in the ^{13}C NMR spectroscopic data was remarkable, again indicating a heavy atom effect of I at 71.8 ppm, and the ^{1}H NMR spectroscopic data also showed a sharp peak for the 3-H proton in the pyrrole as a singlet at 6.92 ppm.

We were thus delighted to find that by simply exposing these *n*-butyl- and phenyl- substituted precursors to three equivalents of iodine and potassium carbonate in dry acetonitrile at 0°C, led smoothly to an excellent crude yield of the intermediate hydroxy-dihydropyrroles. Subsequently, these crude intermediate dihydropyrroles underwent elimination upon treatment with methanesulfonyl chloride and triethylamine in dichloromethane at 0°C, followed by stirring at room temperature for 16 hours. As our project aim was to develop the synthesis of highly substituted pyrroles, we carried out investigations for the possible applications of this new methodology, having confirmed the initial results reported by Sharland.[35a]

2.3.2 Suzuki coupling

Obviously, the availability of the iodopyrroles **268** and **275** offered the opportunity to also study methods for further homologation, especially using Pd-catalysed couplings. The Suzuki method was chosen for this, bearing in mind a particular target, *Rhazinilam*, the synthesis of which was planned for later in this present project.

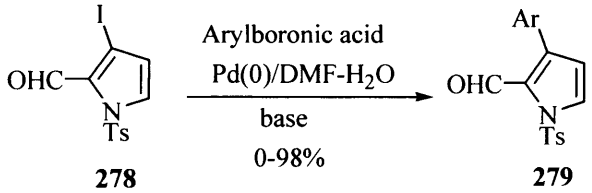
The Suzuki cross coupling conditions seemed to offer a high yielding and convenient approach to various highly substituted pyrroles. In 1995, Chang reported the Pd(0)-catalyzed cross coupling of the bromopyrrole **276** with phenylboronic acid to give 4-phenylpyrrole **277** as an optimum route to prepare this precursors for their studies on porphyrin synthesis (Scheme 2.24).[44]



276 **277**

Scheme 2.24

In 1999, Ghosez[45] reported the palladium-catalysed coupling of 2-formyl-3-iodopyrrole **278** with various arylboronic acids as an easy and convergent access to 2-substitued-3-arylpyrroles **279** (Scheme 2.25).



278 **279**

Scheme 2.25

This report had a very similar interest to our own project; therefore we decided to follow up on this coupling method in order to achieve our aim smoothly, the projected approach to (-)-*Rhazinilam.*

For the Suzuki coupling, which generally has to be performed under basic conditions, hydroxide plays a crucial role in the catalytic cycle in the formation of the borate species $RB(OH)_3^-$, which occurs prior to the transmetallation step, and the cycle is completed by reductive elimination, to give the desired coupling product. The specific cycle for this coupling reaction is shown in Figure 2.5.

As the Suzuki coupling gives high yields of products (Scheme 2.25), this was applied to the iodopyrroles **268** and **275**. The *ortho*-nitrophenylboronic acid was chosen, as the product could be useful in later plans for rhazinilam synthesis.

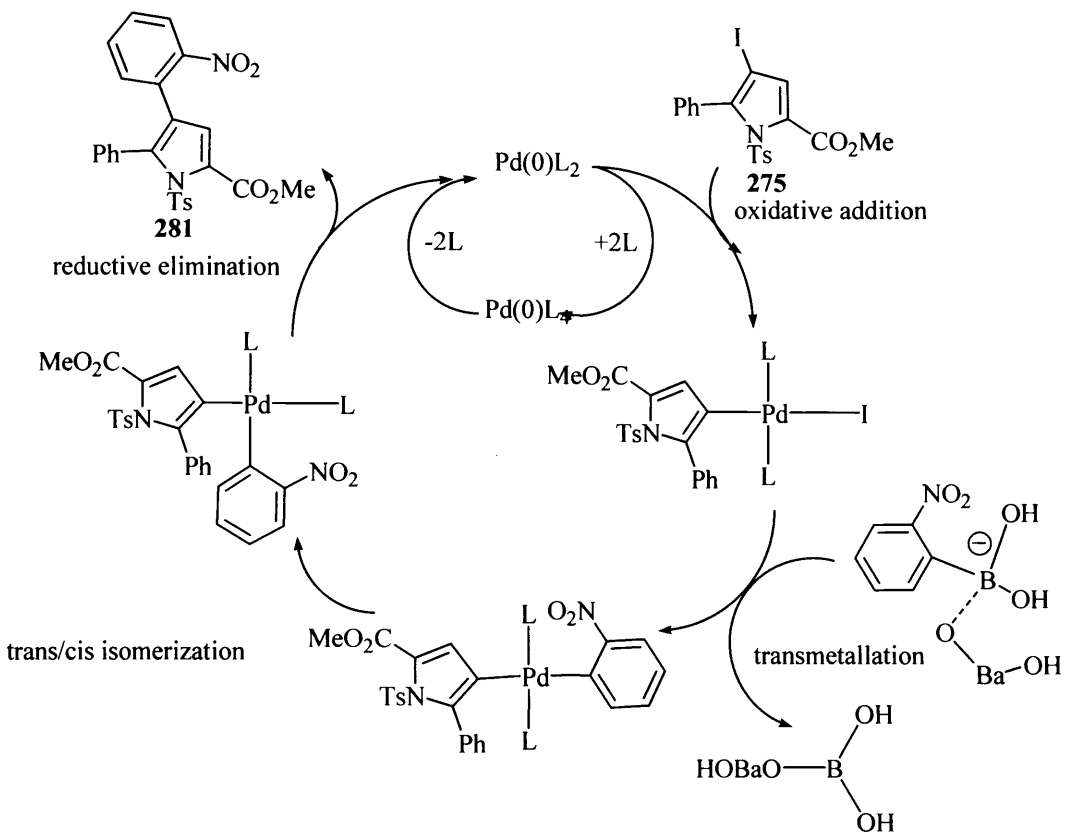
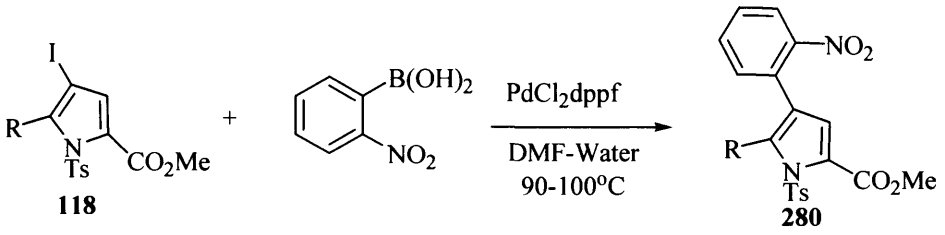


Figure 2.5



R = Ph **275**
= *n*-Bu **268**

R = Ph **281**
= *n*-Bu **282**

Entry	R	%$PdCl_2$dppf	Base	time	%yield
1	Ph	10	$Ba(OH)_2.8H_2O$	5 min.	10
2	Ph	18	$Ba(OH)_2.8H_2O$	30min.	53
3	Ph	20	$Ba(OH)_2.8H_2O$	2 hr.	60
4	Ph	20	Na_2CO_3	2 hr.	61
5	*n*-Bu	20	$Ba(OH)_2.8H_2O$	2 hr.	42
6	*n*-Bu	20	$Ba(OH)_2.8H_2O$	3 hr.	58
7	*n*-Bu	20	Na_2CO_3	2.5 hr.	69

Table 1.5: Coupling of 2-substituted-3-iodopyrrole with *0*-nitrophenylboronic acid.

Following on from Ghosez's report,[45] the Suzuki reaction was first performed at 80°C in DMF-H_2O (4:1) with 10% of $PdCl_2$dppf in the presence of $Ba(OH)_2.8H_2O$ over 5 minutes. The coupled product was obtained in only 10% yield (Table 1.5, entry 1). It can be clearly indicated by ^{13}C NMR: the CI signal at 71.8 ppm of the iodopyrrole **275** disappears to reveal a complicated aryl-carbon region at 122.2-149.6 ppm of *o*-nitrophenyl-pyrrole **281** (Figure 2.6). The *o*-nitrophenyl-pyrrole **281** is also indicated by ^1H NMR (one proton of 3-H at 6.82 ppm as a singlet), IR, low resolution MS (445 $[M+H]^+$), and CHN microanalysis.

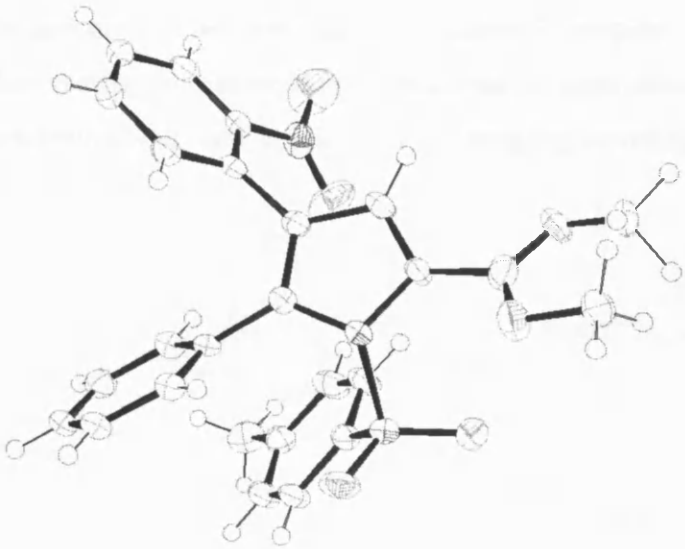
It has been reported that the addition of base exerts a remarkable effect on the transmetalation rate of organoboron reagents. In fact, the addition of a strong base exerts a remarkable effect on the acceleration of the coupling rate for stericly hindered arylboronic acids, such as mesitylboronic acid.[46]

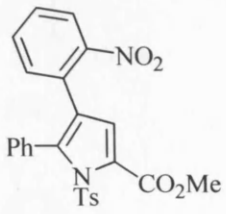
Herein, our coupling conditions preferred weaker bases, such Na_2CO_3, to give yields of **282**, ranging from 58% to 69%, for the coupling of 2-butyl-3-iodopyrrole **268** with *o*-nitrophenylboronic acid (Table1.5, entry 7). However, when R = Ph as in **275**, the choice of base seems to make no difference to the yield of the *o*-nitrophenyl-pyrrole **281** isolated.

The structure of the pyrroles (**281** and **282**) were confirmed by X-ray crystallographic analysis; the structure of **282** has the methyl ester disordered, as shown in Figure 2.7 (full data on p. 243 for the pyrrole **281** and p.249 for the pyrrole **282**). We noted that the nitrophenyl ring at C(4) and the methylphenylsulfonyl group at N(1) were both found to lie on the different side of the pyrrole.

Figure 2.7: X-Ray crystallographic Analysis

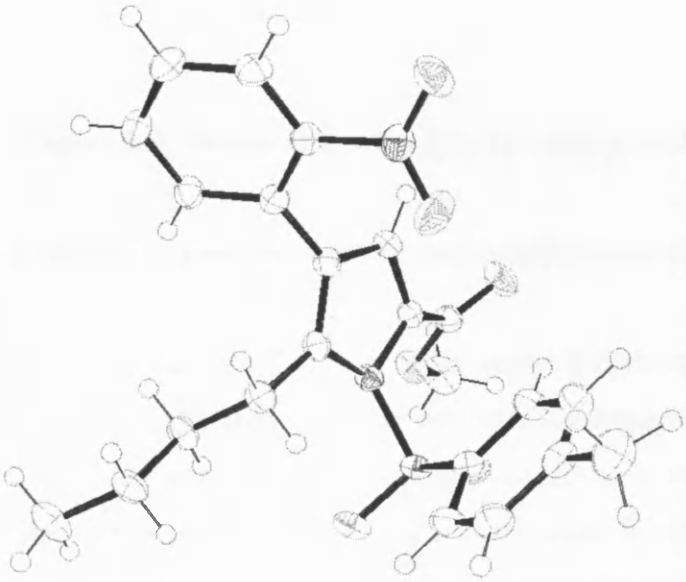
Methyl 4-(2-nitro-phenyl)-5-phenyl-1-(4-methylphenylsulfonyl)-1H-pyrrole-2-carboxylate, 281

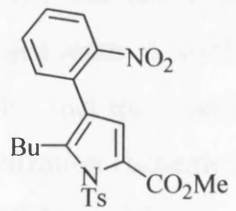




281

Methyl 5-butyl-4-(2-nitro-phenyl)-1-(toluene-4-sulfonyl)-1H-pyrrole-2-carboxylate, 282.





282

2.3.3 Further studies

We reasoned that this approach was ideal for the rapid preparation of *(-)-Rhazinilam* **283** and analogs (Chapter 3), if we could apply this methodology to our key models according to four rings of *(-)-Rhazinilam* **283**. To test the generality of this methodology in preparing these simple precursors, we designed four different pyrroles **284**, **285**, **286**, and **287** at the 5-position varying in substitution (considered to piperidine ring, nine-membered lactam ring, hindered substitute, and application on coupling reaction, respectively, as shown in Figure 2.8).

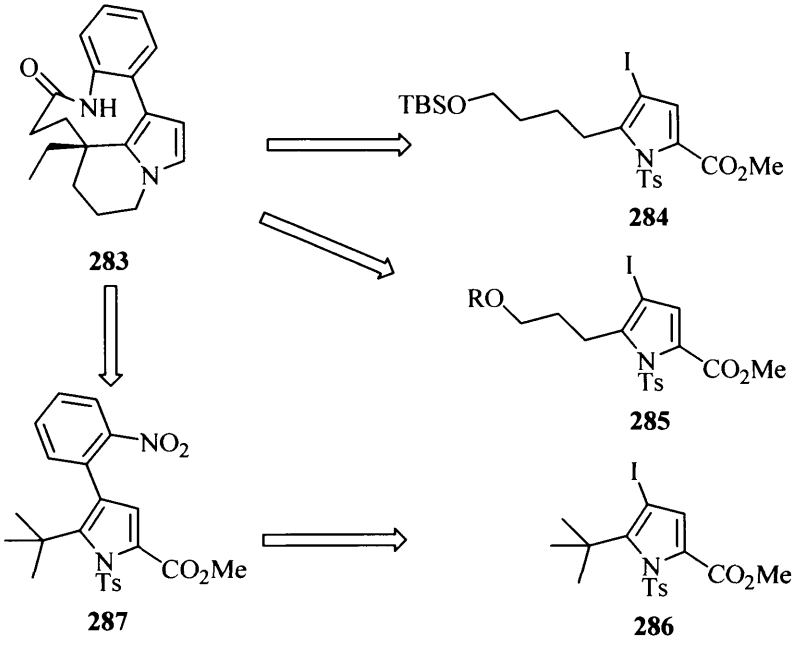
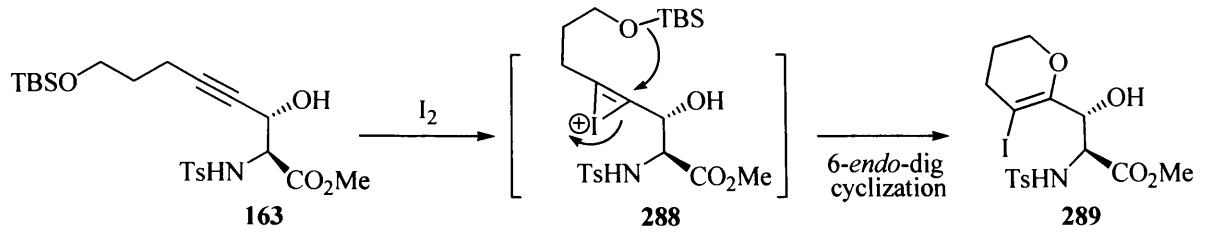


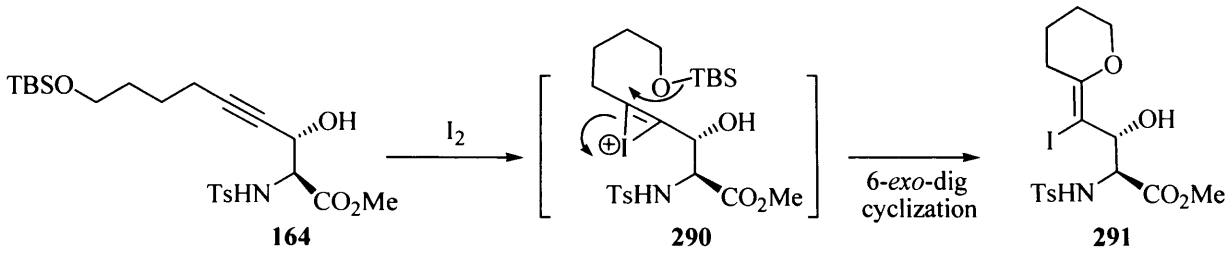
Figure 2.8: Design of the key models to approach *(-)-Rhazinilam* 283

2.3.2.1 An attempt to establish models to piperidine and nine-membered lactam ring

The iodocyclization (Section 1.3.1) of the α-amino-β-hydroxy esters **163** and **164** revealed a major concern in the synthesis, as these side chains contained an oxygen atom. According to Baldwin's rules, along with the 5-*endo*-dig cyclization, it was possible that the α-amino-β-hydroxy ester **164** might favor 6-*exo*-dig or, especially, 5-*exo*-dig cyclization (Scheme 2.26), and α-amino-β-hydroxy ester **163** might favor 6-*endo*-dig cyclization (Scheme 2.27).[20]



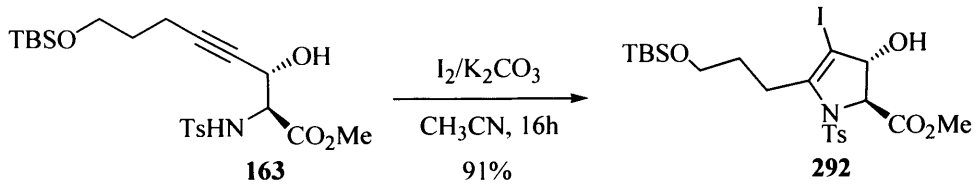
Scheme 2.26



Scheme 2.27

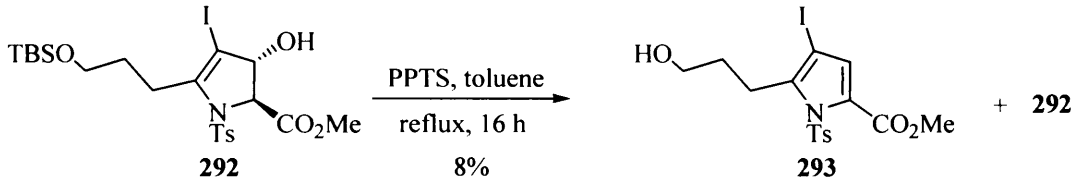
To test this concern, α-amino-β-hydroxy ester **163** was prepared on a large scale and treated with three equivalents of iodine and three equivalents of potassium carbonate in acetonitrile at 0°C, then at room temperature for 16 hours. It was pleasing to find that this worked well to give 3-hydroxy-4-iodo-dihydropyrrole **292** in 91% yield (Scheme 2.28) without any trace of other possible cyclizations.

The ^{1}H NMR spectroscopic data of 3-hydroxy-4-iodo-2,3-dihydropyrrole, **292** showed the characteristic resonance for the proton β to the ester group at 4.38 ppm as a double doublet, (J = 7.9 and 1.5 Hz, also coupling with a proton of hydroxy group) and the proton α at 4.56 ppm as a doublet (J = 1.5 Hz). The structure was also confirmed by ^{13}C NMR (CI at 78.2 ppm), IR, low resoluion MS (578 $[M-H_2O]^+$), and high-resolution MS (596.0997 $[M+H]^+$).



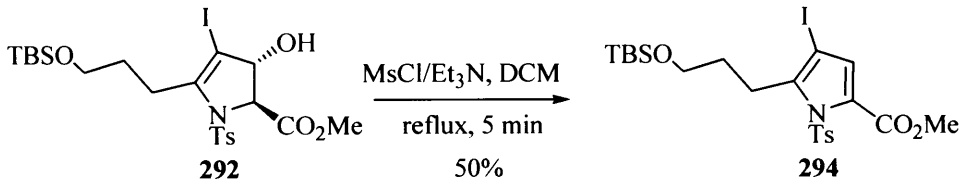
Scheme 2.28

Dehydration was somewhat less successful under either basic conditions (1.1 equivalent of methanesulfonyl chloride and 1 equivalent of triethylamine in dichloromethane for 16 hr), or acidic conditions (0.01 equivalent of pyridinium-p-toluenesulfonate in toluene for 16 hr). There was a tiny amount of the expected pyrrole (a proton of the pyrrole at 6.80 ppm), but the quantities were too small to isolate; instead, the alcohol protecting group had been removed to give iodopyrrole **293**, which was isolated in low yield (Scheme 2.29).



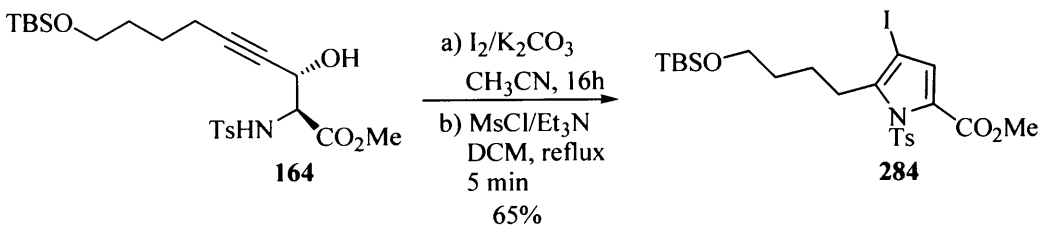
Scheme 2.29

Some optimization studies were carried out briefly to gain the desired pyrrole **294**; as a result, the dihydropyrrole **292** was refluxed in dichloromethane, followed by the addition of triethylamine and methanesulfonyl chloride. The reaction was observed to be complete within 5 minutes (Scheme 2.30) and gave the pyrrole **294** in 50% isolated yield.



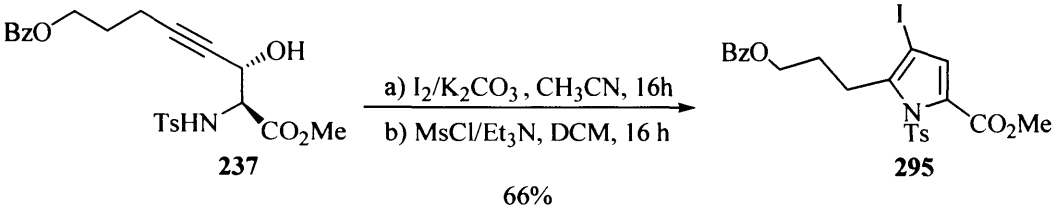
Scheme 2.30

The homologous α-amino-β-hydroxy ester **164** was also successfully converted into the iodopyrrole **284** using the same condition as the iodopyrrole **294**, in 65% isolated yield (Scheme 2.31). Due to limited time, this reaction has not been optimized to achieve even better conversion to the iodopyrrole **294**.



Scheme 2.31

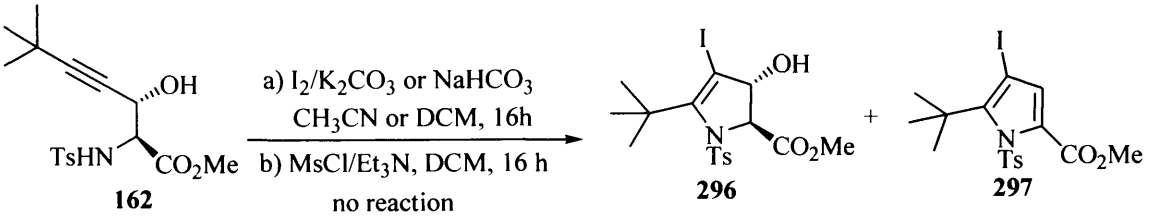
During the optimization attempts to prepare the iodopyrrole **294**, it was suggested to use a different protecting group for the hydroxy function. Subsequently, the benzoyl-protected α-amino-β-hydroxy ester **237** was prepared, and treated with three equivalents of iodine and three equivalents of potassium carbonate in acetonitrile at 0°C, then at room temperature for 16 hours. The crude product was then treated with 1.1 equivalents of methanesulfonyl chloride and 1 equivalent of triethylamine in dichloromethane for 16 hr at room temperature, to give smoothly the iodopyrrole **295** in 66% overall isolated yield (Scheme 2.32).



Scheme 2.32

2.3.2.2 Hindered substitution on the iodopyrrole

In order to apply this route to *(-)-Rhazinilam* **283**, a challenge of this project is the smooth application of this methodology to pyrroles with very bulky substituents in the 5-position, such as a *tert*-butyl group, which could be regarded as a model substrate. Therefore, α-amino-β-hydroxy ester **162** was prepared in a large amount and treated with three equivalents of iodine and three equivalents of either potassium carbonate or sodium hydrogen carbonate in acetonitrile or in dichloromethane at 0°C, then at room temperature for 16 hours (Scheme 2.33). As expected, this model was hindered by the *tert*-butyl substituent to form 2,3-dihydro-3-hydroxy-4-iodopyrrole **296** and cyclizations were poor yielding.



Scheme 2.33

Entry	Reagent	Solvent	Time (hr)	%Yield	%Recovery[c]
1	3eq. I_2	CH_3CN-K_2CO_3	16	-	-
2	3eq. I_2	DCM-K_2CO_3	16	-	-
3	3eq. IBr	DCM-K_2CO_3	16	-	-
4	3eq. IBr	CH_3CN-$NaHCO_3$	16	-	-
5	4eq. I_2	CH_3CN-K_2CO_3	16	-	-
6[a]	2eq. I_2	DCM-H_2O	16	18	50
7[a]	3eq. I_2	DCM-H_2O	192	50	-
8[a]	2eq. IBr	CH_3CN-H_2O	144	10	50
9[b]	3eq. I_2	DCM-H_2O	96	40	40
10[a]	5eq. I_2	DCM-H_2O	72	36	-
11[a]	3eq. I_2	CH_3CN-H_2O	72	50	20

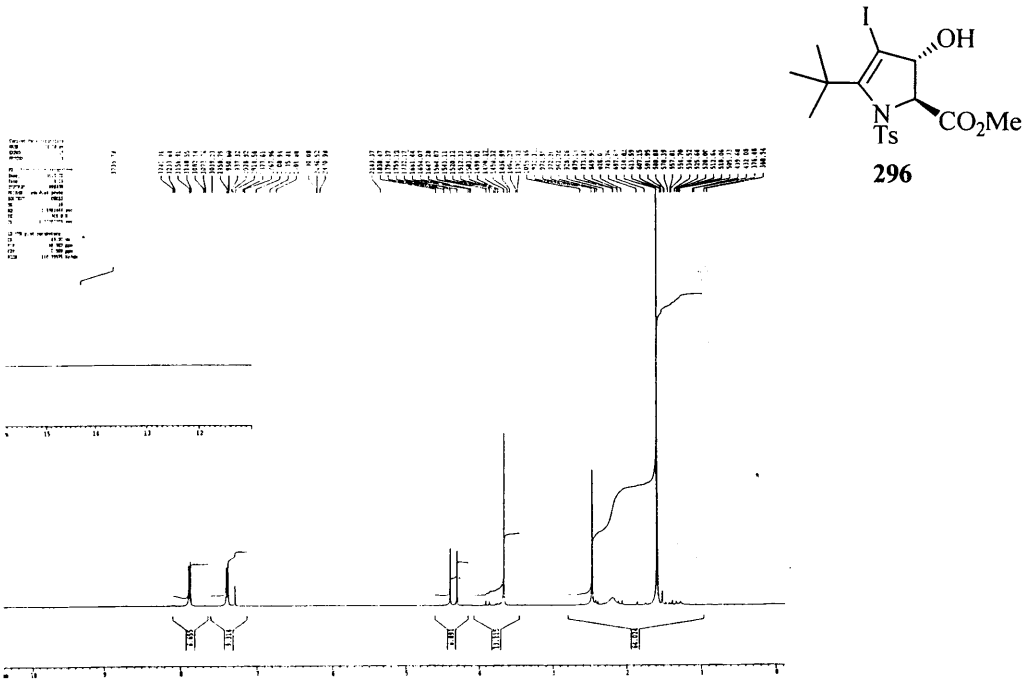
Table 1.6: Iodocyclisation conditions of 5-*tert*-butyl-4-iodo-2,3-dihydropyrrole **156**.
Note: [a] Using $NaHCO_3$ as base; [b] Using $NaHCO_3$ as base and 20% tetrabutylammonium bromide, as a phase transfer catalyst; [c] Recovery of the starting material **162**.

After optimization, we found that it was essential, in order to obtain reasonable yields of intermediate dihydropyrrole **296**, to use water in this iodocyclization. The use of K_2CO_3 in both dry acetonitrile and dry dichloromethane gave no cyclisation product (Table 1.3; entry 1 and 2); therefore $NaHCO_3$ was introduced into the study of this particular iodocyclisation. Attempts were made to drive the reaction by increasing the concentration of iodine, changing the temperature and solvent, but rather than the expected dihydropyrrole **296** being obtained, at a certain point, the starting material began to decompose. No improvement was obtained until biphasic conditions were applied and the dihydropyrrole **296** was first observed by ^{1}H-NMR with resonances at 4.30 and 4.38 ppm for the two CHs (Table 1.6, entry 6, Figure 2.7).

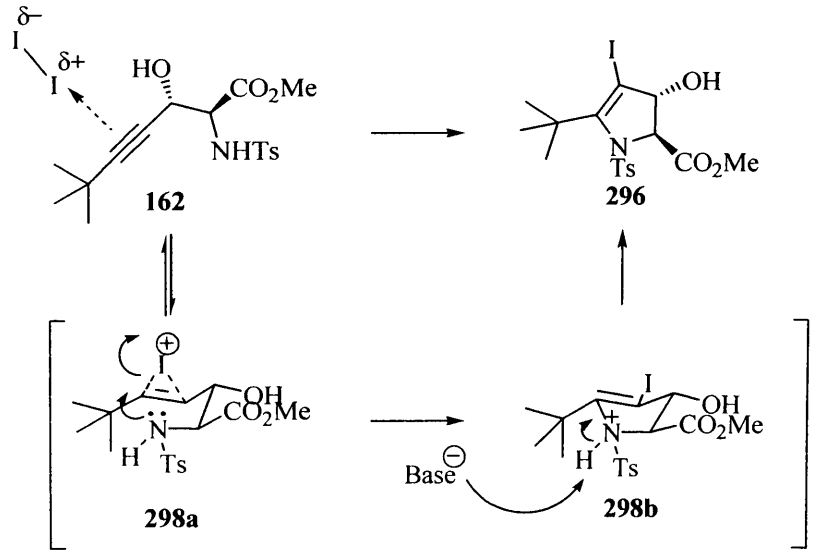
According to an earlier study, iodine monobromide was successfully used to obtain iodopyrrole **268** (84% yield, Scheme 2.22) under conventional cyclisation conditions and without further elimination. However, this was not applicable to the preparation of the hindered dihydropyrrole **296** (Table 1.6, entry 3, 4 and 8).

Figure 2.7: ^{1}H NMR spectroscopic data

Methyl (*2SR,3RS*)-5-tert-butyl-3-hydroxy-4-iodo-1-(toluene-4-sulfonyl)-2,3-dihydro-1H-pyrrole-2-carboxylate, 296.



With the advantage of the two-phase reaction (Table 1.6, entry 6-11), we suggested that the formation of cationic intermediate **298a** and/or **298b** in a two-phase environment was more favourable in a more polar solvent system (Scheme 2.34). We have no definite explanation, but suggest that syntheses of this type of molecule are possible using these more polar conditions. However, the longer reaction time and moderate yield gave us a concerned about using this route for our target compound, *(-)-Rhazinilam* **283**.

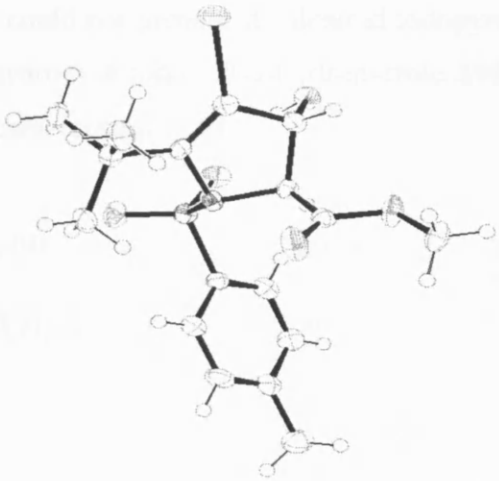


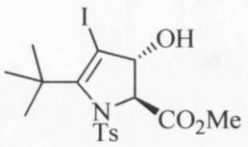
Scheme 2.34

Although a range of dehydrations was attempted under various conditions, the desired pyrrole **297** was never obtained from dihydropyrrole **296** and the reason for this difficulty was unclear. The elimination step is dependent on conformation, as discussed earlier; the hydrogen must be *anti* to the leaving group or the reaction will not occur easily. This problem was solved for the dihydro-iodopyrrole **292** (see Section 2.3.3.1). X-Ray crystallographic analysis confirmed that only the *syn*-configuration of the hydrogen and alcohol was present and in addition, the hydrogen atom of the hydroxy group and an oxygen atom on the sulfonyl group were both found to lie on the same direction, suggesting that their interaction could have interfered with the desired iodopyrrole **297** (Figure 2.8, full data on p. 256-260).

Figure 2.8: X-ray crystallographic Analysis

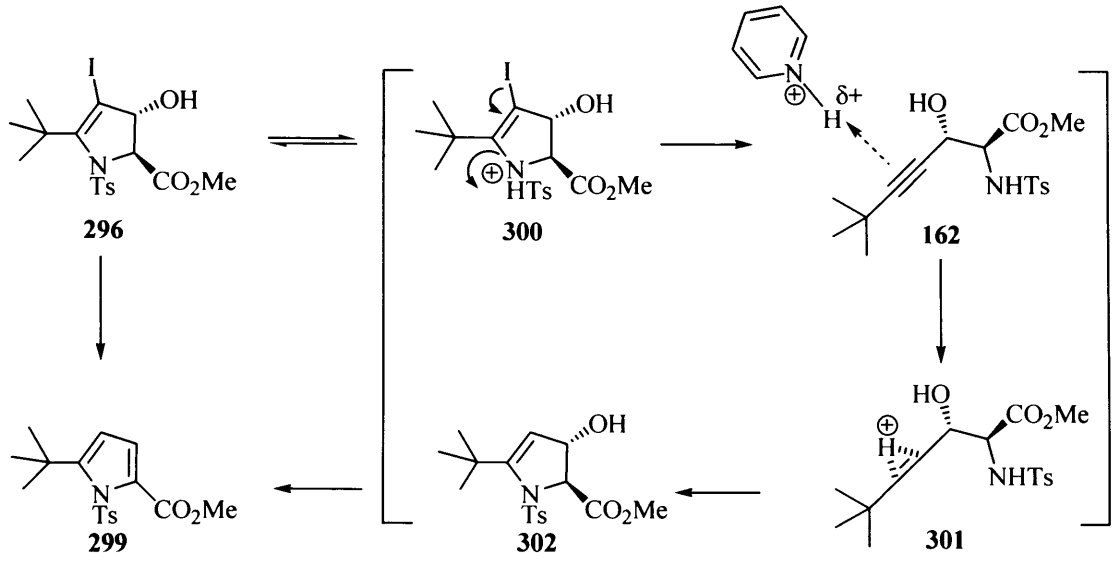
Methyl (*2SR,3RS*)-5-tert-butyl-3-hydroxy-4-iodo-1-(4-methylphenylsulfonyl)-2,3-dihydro-1H-pyrrole-2-carboxylate, 296.





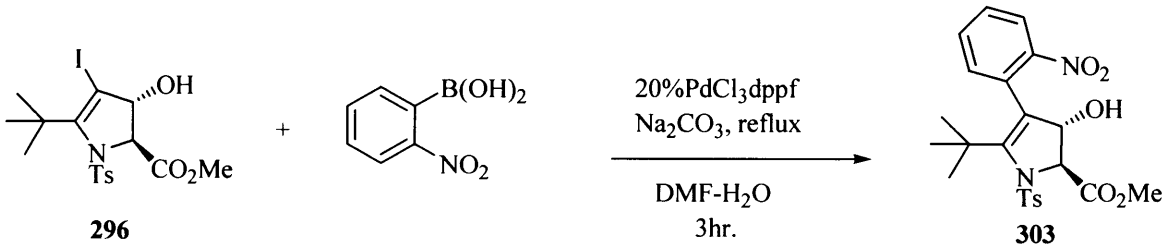
296

Interestingly, dehydration of the intermediate dihydropyrrole **296** when carried out in toluene and in the presence of PPTS led to isolation of the de-iodopyrrole **299** (two CHs at 6.12 and 6.65 ppm as doublets with coupling constants of 3.6 and 3.6 Hz respectively). This structure was confirmed using IR, mass spectral, ^{1}H NMR, ^{13}C NMR data and high-resolution MS (336.1266 $[M+H]^{+}$). However, the question of what was occurring still remained. Protonation of the nitrogen of the dihydropyrrole **296** could lead to *cycloreversion*, which would regenerate the acetylene **162**. Subsequent, acid-catalysed cyclization, shown in Scheme 1.47, would produce the pyrrole **299**.[35e]



Scheme 2.35

Although we could not prepare the desired iodopyrrole **297**, as a model substrate, coupling 5-*tert*-butyl-3-hydroxy-4-iodo-2,3-dihydropyrrole **296** with *o*-nitrophenylboronic acid was also clearly of interest (scheme 2.36).

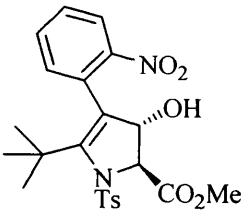


Scheme 2.36

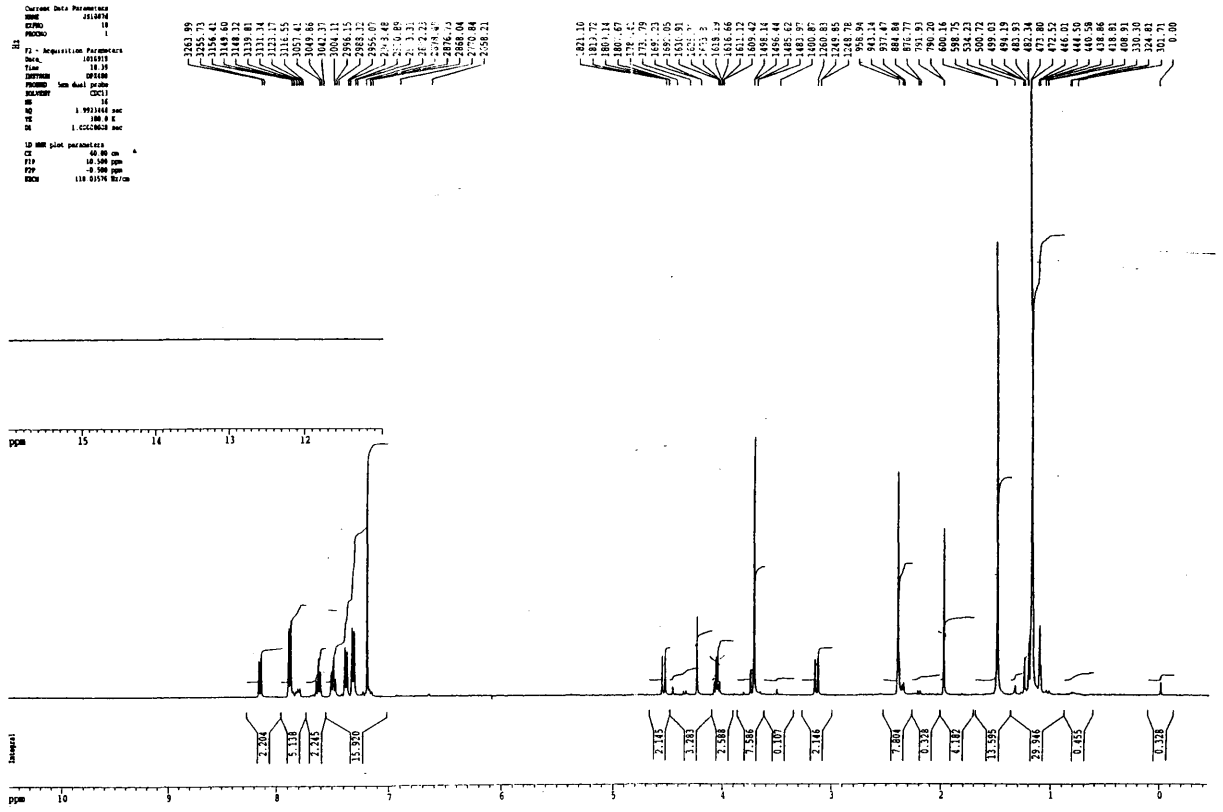
To test this coupling, we decided to carry out a Suzuki reaction on 3-hydroxy-2,3-dihydropyrrole **296** at 90°C in DMF-H_2O (4:1) with 20% $PdCl_2dppf$ in the presence of sodium carbonate over 3 hours. 2-*tert*-Butyl-3-*o*-nitrophenyl-dihydropyrrole **303** was isolated in only 15% yield (Figure 2.9); the ^1H NMR spectroscopic data showed the characteristic resonance for the proton-β to the ester group at 4.53 ppm as a double doublet (J = 11.8 and 1.2 Hz, also coupling with a proton of hydroxy group) and the α-proton at 4.23 ppm as a doublet (J = 1.2 Hz).

Figure 2.9: ^{1}H NMR spectroscopic data

Methyl (*2SR,3RS*)-5-tert-butyl-3-hydroxy-4-(2-nitro-phenyl)-1-(4-methylphenylsulfonyl)-2,3-dihydro-pyrrole-2-carboxylate, 303.



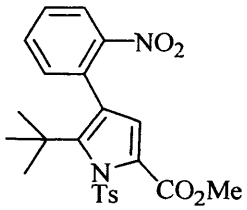
303



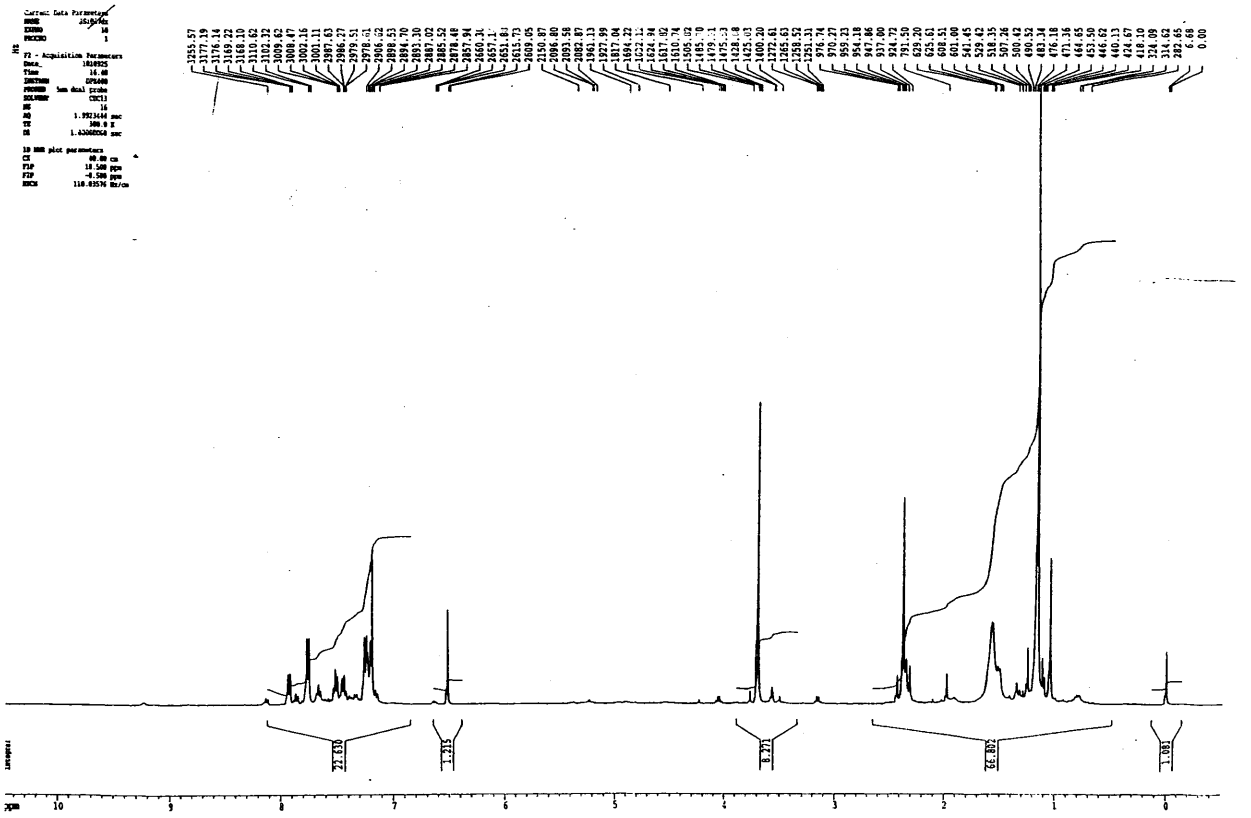
No other data could be obtained, because in the time taken to run ^{13}C and NOE spectra, dehydration occurred in $CDCl_3$ as shown by ^{1}H-NMR analysis; the resonances corresponding to two CHs at 4.23 and 4.53 ppm disappeared and were replaced by one proton of the pyrrole **304** at 6.54 ppm (Figure 2.10).

Figure 2.10: ^{1}H NMR spectroscopic data

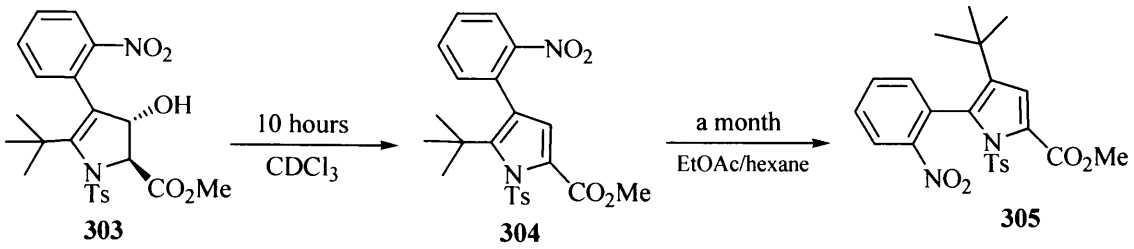
5-tert-Butyl-4-(2-nitro-phenyl)-1-(4-methylphenylsulfonyl)-pyrrole-2-carboxylic acid methyl ester, 304.



304

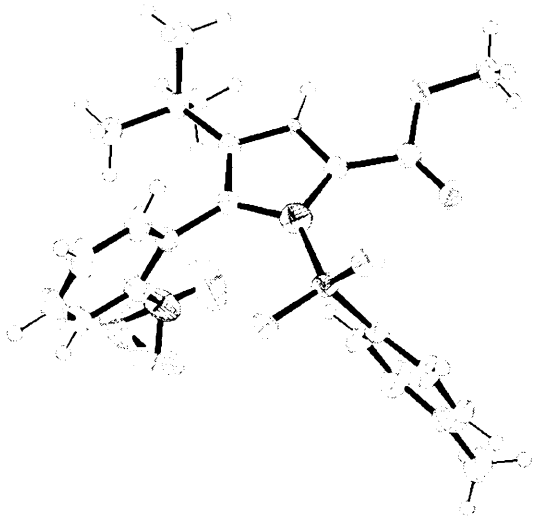


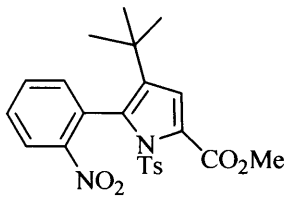
As we had only a small amount of the *o*-nitrophenyl-pyrrole **304**, we decided to obtain a crystal for X-ray crystallographic analysis, as this pleasing result appeared to be a solution to the problem.. Surprisingly, an unexpected rearrangement of the pyrrole **304** to pyrrole **305** (Scheme 2.37) was observed by ^{1}H-NMR, (the CH proton shifted from 6.54 ppm to 9.19 ppm) and was confirmed by a selected X-ray crystallographic analysis having the nitro group disordered (Figure 2.11) and repeated ^{1}H NMR spectroscopic data of the crystal. Using the desired iodopyrrole **297** might solve this problem; however, the problem of the elimination of the dihydropyrrole **296** to give the pyrrole **297** still remained.



Scheme 2.37

Figure 2.11: X-ray crystallographic Analysis
Methyl 4-tert-butyl-5-(2-nitro-phenyl)-1-(4-methylphenylsulfonyl)-pyrrole-2-carboxylate, 305.





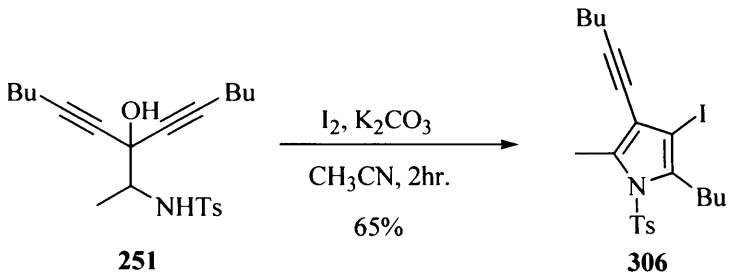
305

We first suggested that proton at 9.19 ppm was more likely to be identifiable as NH. To understand this ^{1}H NMR spectroscopic data, we carried out an experiment to observe this proton at different temperature. As NH at higher temperature, the peak should be broader or shift position, but no change in the ^{1}H NMR spectroscopic data was observed, whether obtained at 25°C or 50°C. This was not an NH peak, but one CH of the pyrrole **305** was confirmed by a selected X-ray crystallographic analysis (Figure 2.11, full data p. 261-267).

Unfortunately, an explanation of this rearrangement has not been studied. Also, it was not appropriate to apply this route to *(-)-Rhazinilam* **283** as we had expected, and better methodology was required.

2.4 A generally applicable method for pyrrole synthesis

Interestingly, the iodocyclisation had also been scaled up to 53-mmol scales in this study (Scheme 2.38). The reaction was carried out smoothly with 3 equivalents each of iodine and potassium carbonate at 0°C for 2 hours and at room temperature over 12 hours. At work-up stage, adding aqueous sodium thiosulphate, we experienced an extreme increase in the temperature of the reaction mixture. It is therefore essential to cool down the reaction mixture before adding the sodium thiosulphate to destroy the excess iodine.



251 **306**

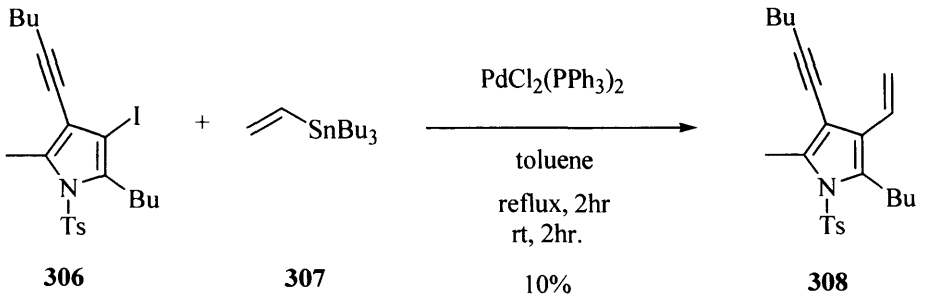
Scheme 2.38

2.4.1 Palladium-catalysed Coupling Reactions

Following on from the results above, the project investigated the possible applications of this new methodology to other palladium-mediated reactions. Generally, the palladium coupling cycle involves oxidative addition, followed by transmetalation, and the cycle is completed by reductive elimination. This study on further elaboration of the iodopyrroles, was not a main target of the research project; therefore, no optimization was carried out to achieve better yields. We synthesised the iodopyrroles **308**, **310**, and **311** using Stille, Heck, and Suzuki coupling reactions, respectively.

2.4.2 Stille Coupling Reaction

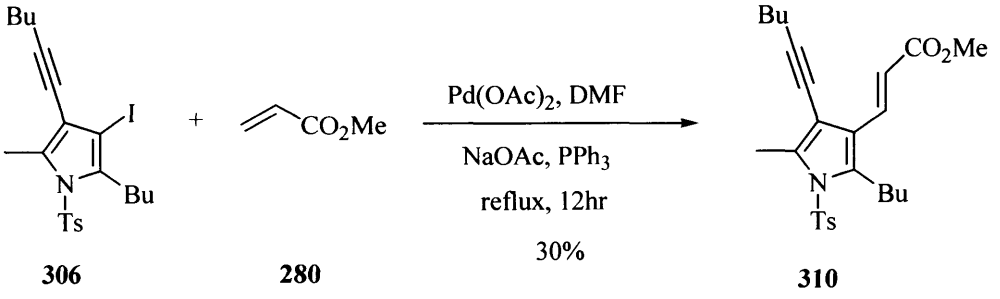
In 1995, Scott[47] successfully prepared several 3-vinylpyrroles by treatment of 3-iodopyrroles with commercial vinyltributyltin **307** in the presence of *bis*-(triphenylphosphine)palladium(II) chloride as catalyst. The iodopyrrole **306** was applied to this reaction (Scheme 1.53) and gave only 10% yield of 3-vinylpyrrole **308**, This structure of which was confirmed by ^{1}H NMR, ^{13}C NMR, IR, low-resolution MS (398 $[M+H]^+$), and High-resolution MS (398.2150 $[M+H]^+$).



Scheme 2.38

2.4.3 Heck reaction

The aryl palladium complexes formed *via* oxidative coupling of aryl halides with palldium(0) can undergo the Heck reaction with a suitable olefin. Aryl halides differ greatly in their reactivity, aryl iodides being the most reactive, followed by aryl bromide. In general, aryl chlorides are very unreactive in the Heck reaction. Conjugate addition is usually preferred when the alkene contains an electron-withdrawing group. Consequently, Reetz and co-workers[48a] developed an efficient system for the Heck reaction of unreactive aryl halides. We now tested 3-iodopyrrole **306** under these simple reaction conditions[48b] to prepare the pyrrole **310** (Scheme 2.39), but only a low yield was obtained. This pyrrole **310** was confirmed by ^{1}H NMR, ^{13}C NMR, IR, low resolution MS (456 $[M+H]^{+}$), and high-resolution MS (456.2204 $[M+H]^{+}$).

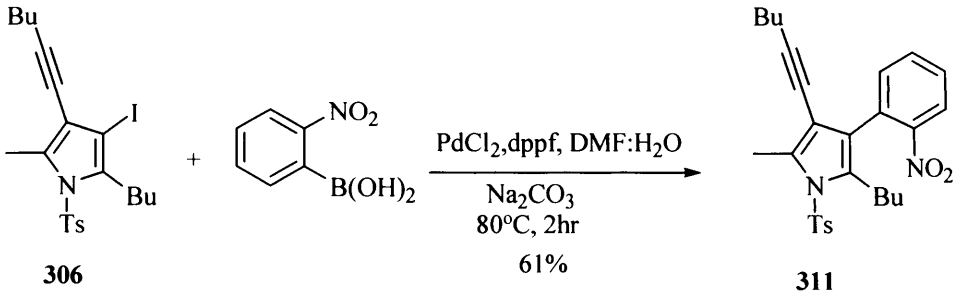


Scheme 2.39

2.4.4 Suzuki Reaction

Coupling of 3-iodopyrrole **306** with *o*-nitrophenylboronic acid is of real interest in this project. To test this coupling reaction, the iodopyrrole was treated with the boronic acid in DMF-H_2O (4:1) in the presence of sodium hydrogen carbonate and 20% $PdCl_2$dppf at 80°C

over 2 hours (Scheme 2.40). We successfully obtained the *o*-nitrophenyl-pyrrole **311** in 61% isolated yield, but this showed low stability at room temperature and was therefore only confirmed by ^{1}H NMR, ^{13}C NMR, IR, and low resolution MS (493 $[M+H]^{+}$).

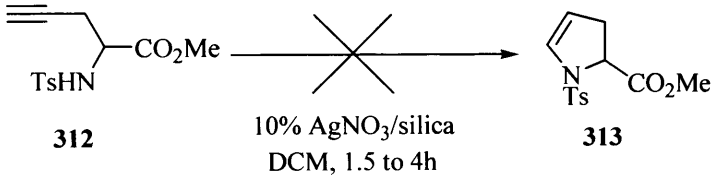


Scheme 2.40

2.5 Silver-mediated cyclisation

According to Section 1.4, having a range of substrates available, we have tested this alternative methodology for inducing 5-*endo*-dig cyclisation of amino-alkynes to pyrroles. Following Sharland's report (see page 28), we extended this generality even further.

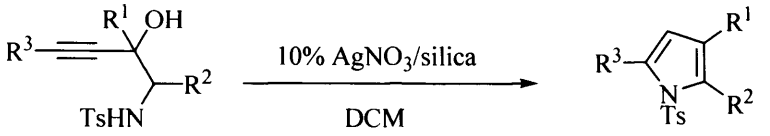
As a starting point, we subjected the *β*-alkynyl tosylamide **312**, which was available within our research group, to $AgNO_3$/silica gel in dichloromethane in the absence of light (Scheme 2.41). No cyclisation was observed. According to related work, it seems to be essential to also have a hydroxy group at the *β*-position of the nucleophilic nitrogen to successfully form an intermediate in order to achieve the cyclisation, (Scheme 1.17).



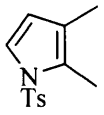
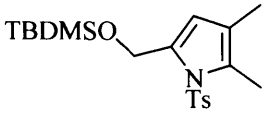
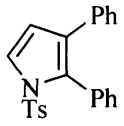
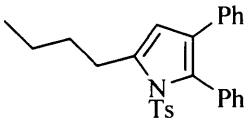
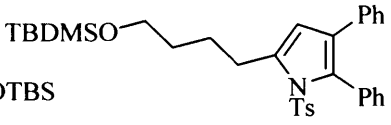
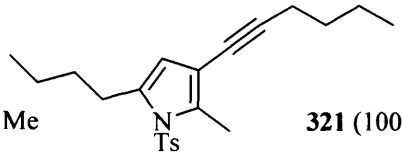
Scheme 2.41

Despite this failure, we carried on with the idea and exposed a range of *γ*-alkynyl-*β*-hydroxy tosylamides **314**, which were prepared in good yield (see Section 2.2, page 42), to 0.5 equivalent of 10% $AgNO_3$ on silica gel in dichloromethane at room temperature in the absence of light. We were delighted to find that from pure starting materials **314**, after work-

up simply by filtration through a short plug of silica gel, the pyrroles **315** were obtained cleanly in excellent yields (Table 1.7).



314 **315**

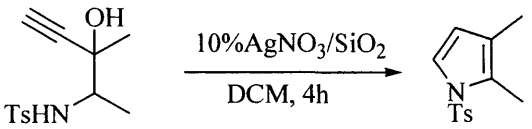
314: R^1, R^2, R^3	**315**, % yield*		Time (h)
255: CH_3, CH_3, H		**316** (75%)	4
257: CH_3, CH_3, TMS		(72%)	16
259: CH_3, CH_3, CH_2OTBS		**317** (93%)	16
262: Ph, Ph, H		**318** (100%)	16
263: Ph, Ph, $(CH_2)_3CH_3$		**319** (100%)	16
264: Ph, Ph, $(CH_2)_4OTBS$		**320** (58%)	16
251: ≡ $C(CH_2)_3CH_3$, $(CH_2)_3CH_3$, Me		**321** (100%)	4

*Crude yield (reaction mixture was worked-up by filtration through short plug of silica gel).

Table 1.7: Ag(I)-catalysed cyclisation of γ-alkynyl-β-hydroxy tosylated amine, **314**.

Firstly, the γ-alkynyl-β-hydroxy tosylsulfonamide **255** was dissolved in anhydrous dichloromethane and to this was added 0.5 equivalent of 10 % wt/wt silver(I) nitrate on silica and the mixture was stirred vigorously, in the dark, at room temperature for 4 hours (Scheme 2.42). After removal of the catalyst by filtration and evaporation of the ether, 2,3-dimethylpyrroles **316** were obtained in good yield. The ^1H NMR spectroscopic data of the

pyrrole **316** showed the characteristic resonance for the 4-and 5-proton at 5.99 and 7.13 ppm respectively as a pair of doublets (J = 3.3 Hz). This was also confirmed by ^{13}C NMR (CH at 113.9 and 120.6 ppm), IR, and low resolution MS (250 $[M+H]^+$).

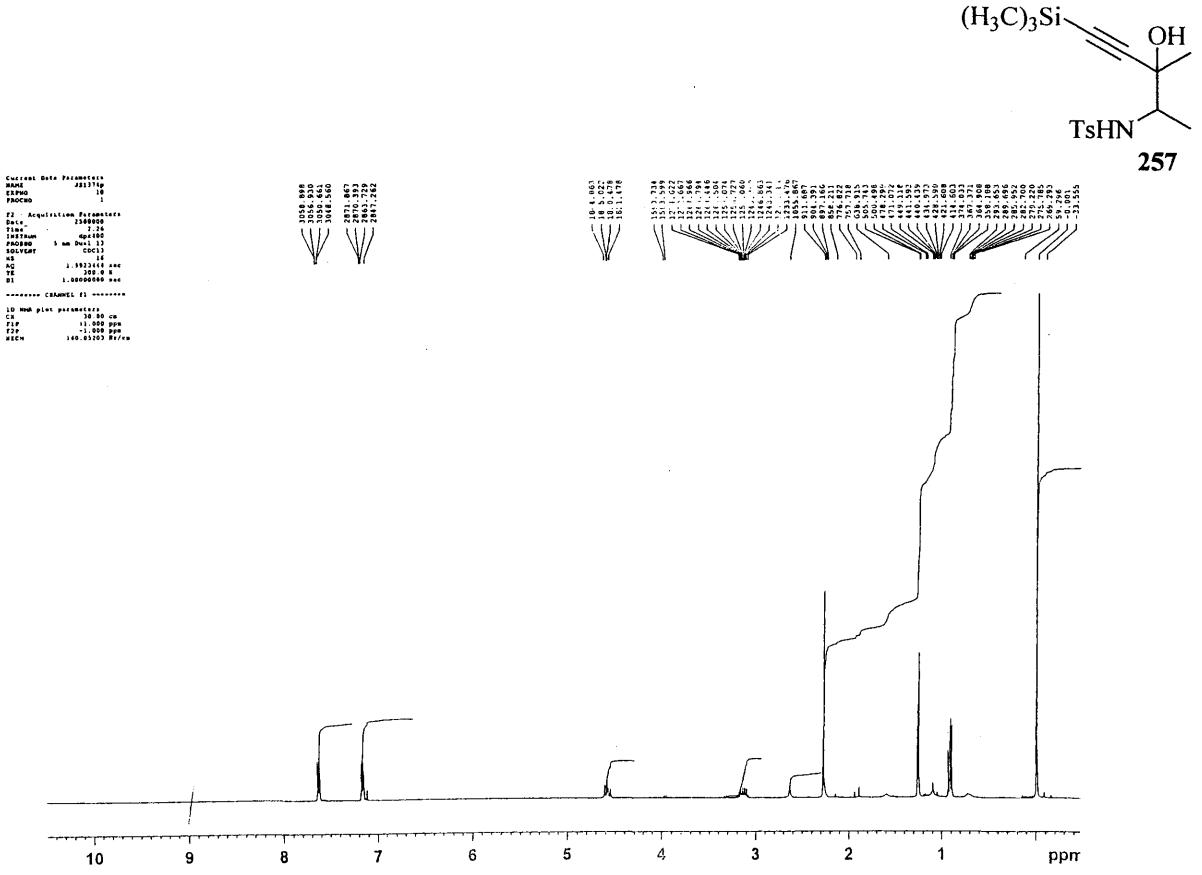


255 **316**

Scheme 2.42

The mechanism of this cyclisation is still unknown. We attempted to observe the cyclisation of γ-alkynyl-β-hydroxy tosylsulfonamide **257**. The ^1H NMR spectroscopic data (Figure 2.12) of the tosylsulfonamide **257**, showed both methyl groups at 0.90 and 1.26 ppm and the resonance due to CH can be seen at 3.10 ppm. It noted that small amount of impurity at 2.64 ppm was also observed.

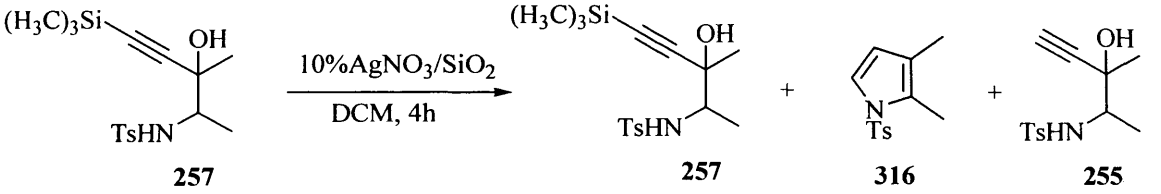
Figure 2.12: ^1H NMR spectroscopic data
N-(2-Hydroxy-1,2-dimethyl-4-trimethylsilanyl-but-3-ynyl)-4-methylphenylsulfonamide, 257



As shown in Figure 2.13, after 4 hours, some of the tosylamide **257** had cyclised. Two methyl groups as single peaks at 1.83 and 2.11 ppm, and the occurrence of two CHs of the pyrrole as doublets (J = 3.3 Hz) at 5.91 and 7.06 ppm (similar to the pyrrole **316**, Scheme 2.42) was observed. By comparing the integrations to one proton of NH at 4.66-4.80 ppm, the ^{1}H NMR spectroscopic data showed that the three methyl groups did not integrate for nine protons. This suggests that deprotection of the silyl group on the terminal acetylene occurred prior to cyclisation since the tosylamide **255** was observed in the ^{1}H NMR, showing the terminal acetylene at 1.94 ppm (Scheme 2.43). An additional 12 hours of this cyclisation gave overall 72% yield of pyrrole **316** from **257**.

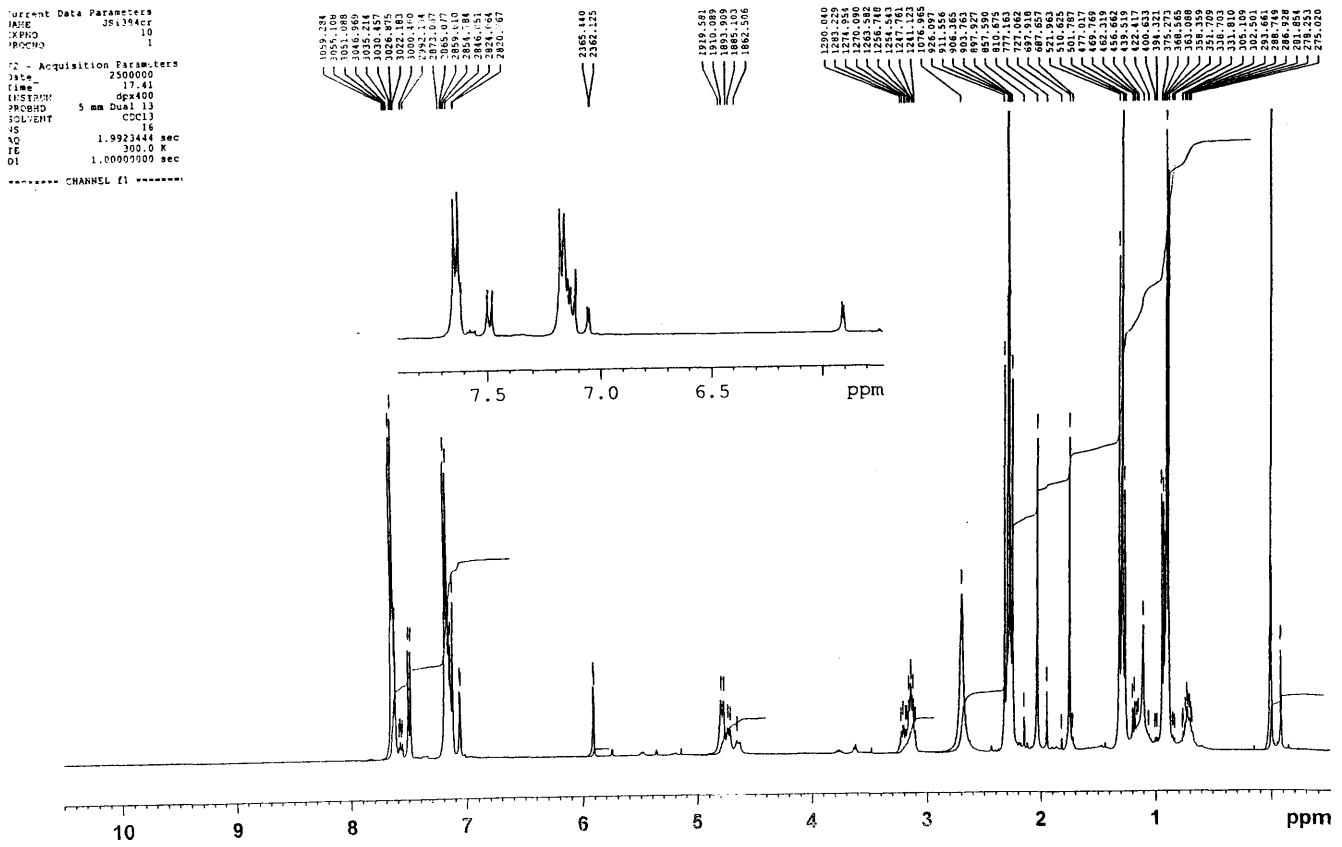
Figure 2.13: ^{1}H NMR spectroscopic data

Four-hour cyclisation of N-(2-Hydroxy-1,2-dimethyl-4-trimethylsilanyl-but-3-ynyl)-4-methylphenylsulfonamide, 257 (Scheme 2.43)

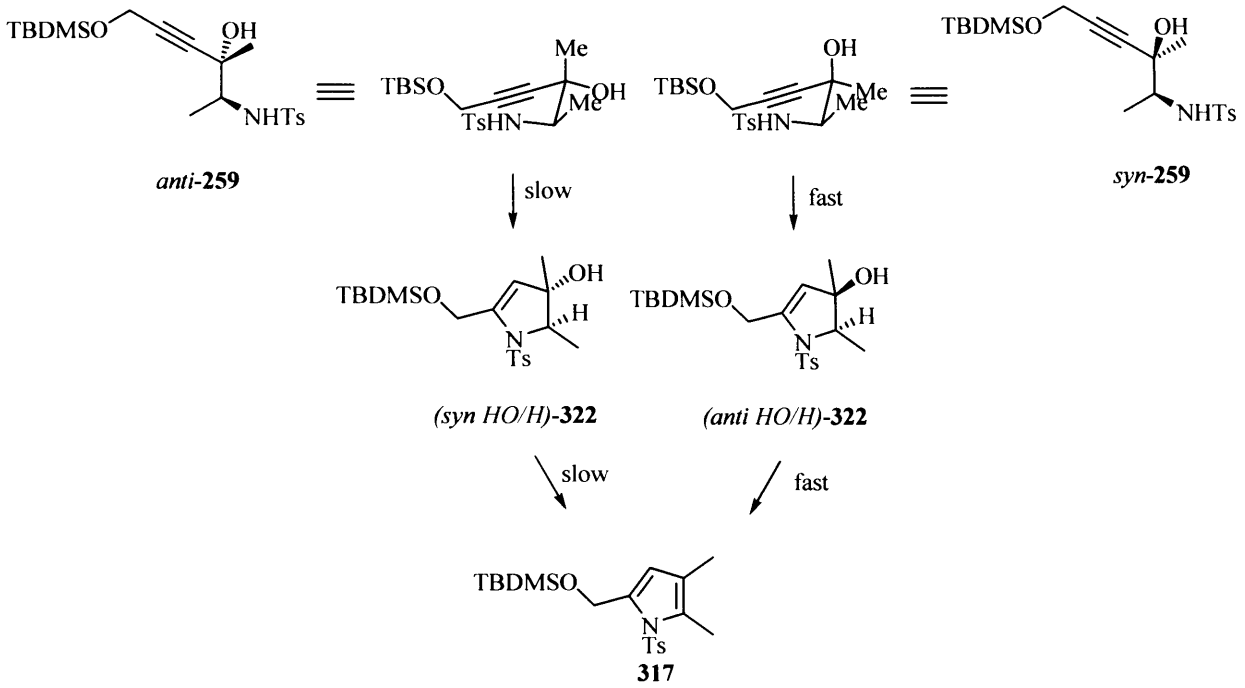


257 **257** **316** **255**

Scheme 2.43



Interestingly, the formation of pyrrole **317** from the two diastereoisomers of tosylamides **259**, in a *anti:syn* ratio of 55:45, presumably the cyclisation of *syn*-**259**, occurred faster. According to transition conformation of dihydropyrrole **322**, it was predicted that the reacting conformation of the *syn*-isomer was more favourable, with the two methyl groups 'equatorial' to minimise both torsional and steric strain. E_2 elimination was set up to obtain the pyrrole **317** (Scheme 2.44).

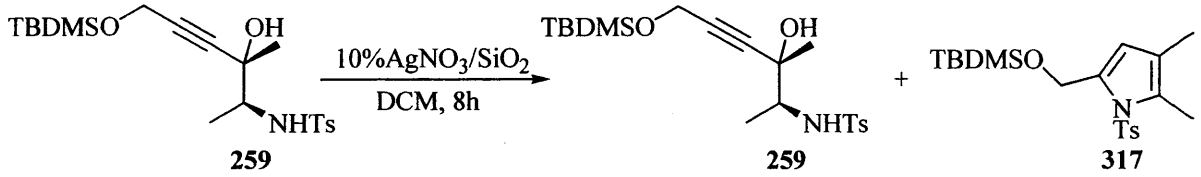


Scheme 2.44

Indeed, the ^{1}H NMR spectroscopic data of the eight-hour cyclisation of tosylamide **259**, showed that the majority of the minor isomer of the precursor (*syn*-**259**) was cyclised faster by losing two CH_3s at 0.98 and 1.33 ppm rapidly (Figure 2.14). The pyrrole **317** was also observed, by the appearance at two new CH_3s at 1.79, and 2.08 ppm and one CH at 5.98 ppm as a singlet. Also, a multiplet of CH in the tosylamide **259** at 3.18-3.22 ppm was disappearing, the OCH_2 of the pyrrole **317** at 4.79 ppm was appearing, and dichloromethane at 5.21 ppm was only a trace of solvent in use. After a further twelve-hour cyclisation, the reaction was complete according to the ^{1}H NMR of pyrrole **317** (Figure 2.15). This was also confirmed by ^{13}C NMR (4-CH at 113.6 ppm), IR, and low resolution MS (392 $[M+H]^+$ and 262 $[M\text{-}TMS]^+$).

Figure 2.14: ^{1}H NMR spectroscopic data

Eight-hour cyclisation of N-[5-(tert-Butyl-dimethyl-silanyloxy)-2-hydroxy-1,2-dimethyl-pent-3-ynyl]-4-methylphenylsulfonamide, 259



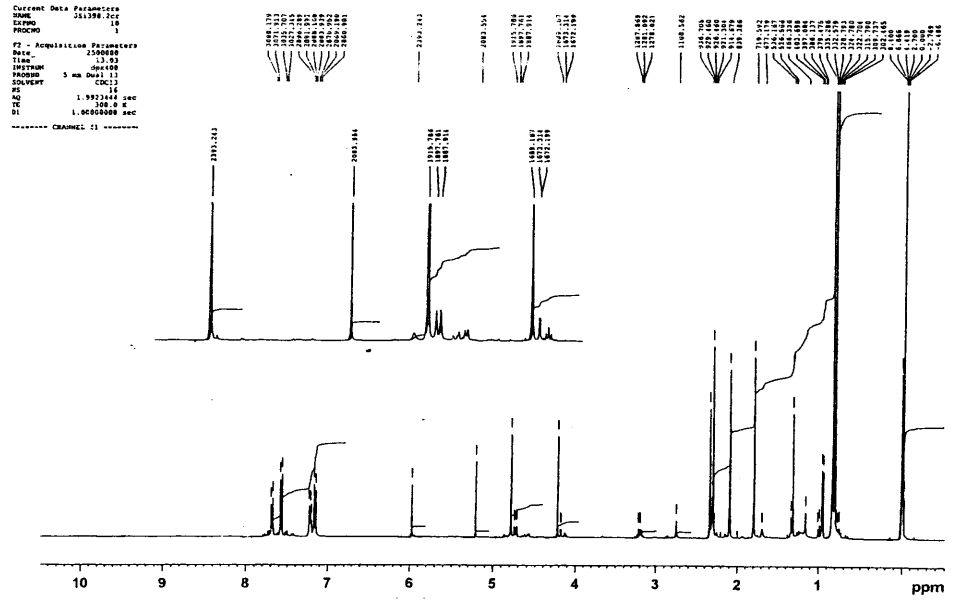
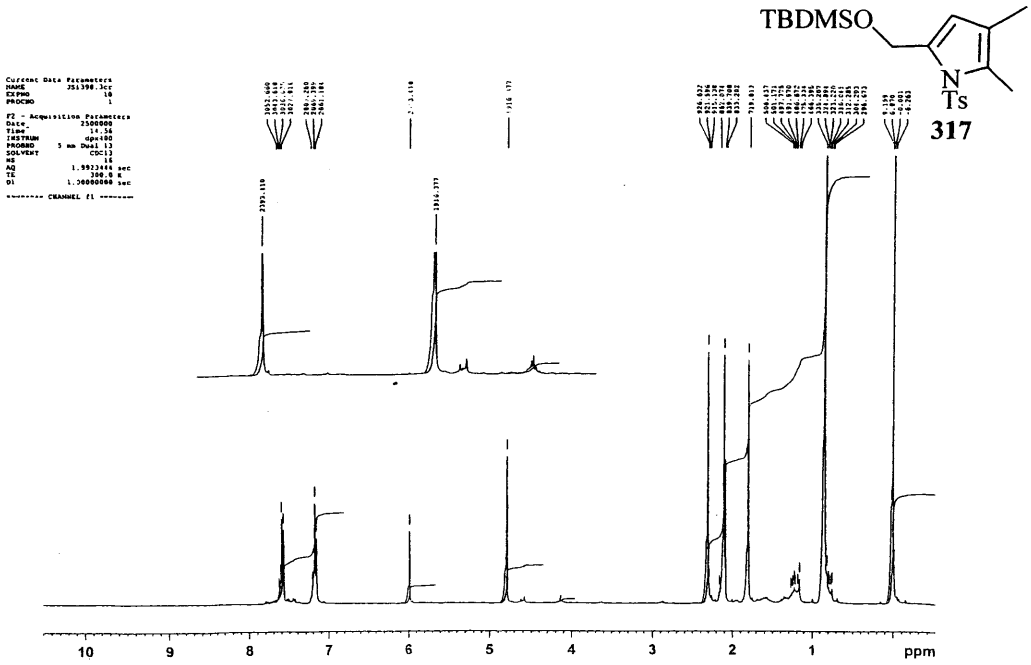


Figure 2.15: ^{1}H NMR spectroscopic data

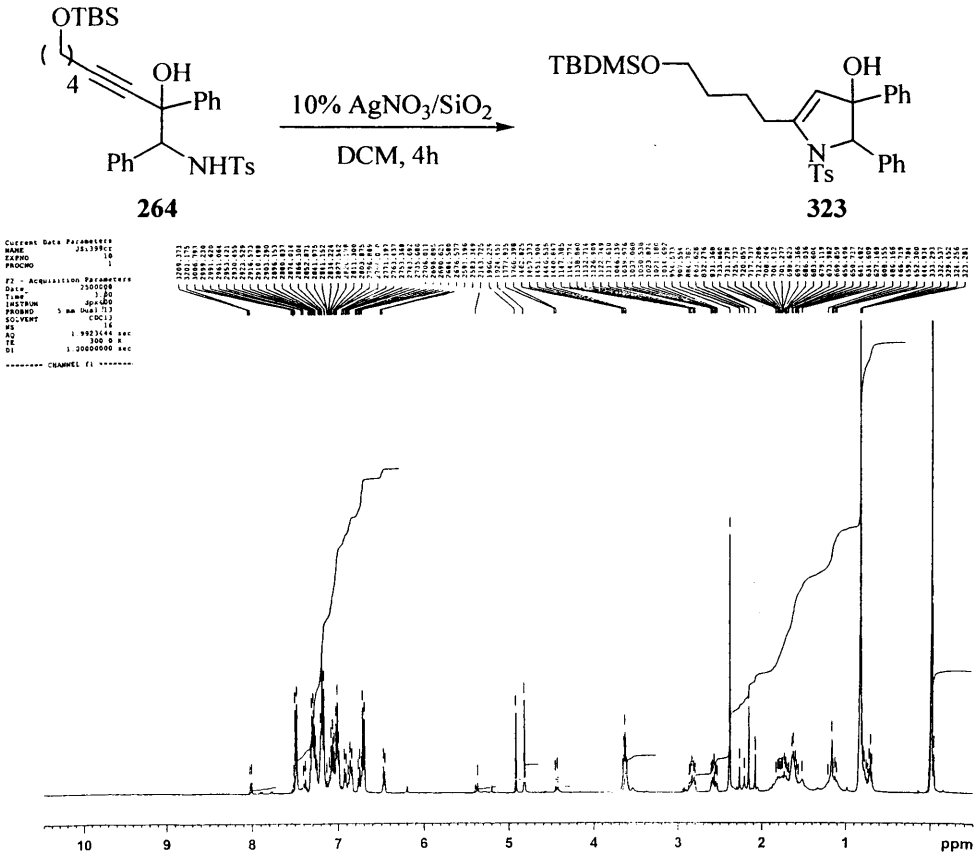
5-(tert-Butyldimethylsilanyloxymethyl)-2,3-dimethyl-1-(4-methylphenylsulfonyl)-pyrrole



As shown by the results in Table 1.7, the more substituted or hindered the precursor is, the longer reaction time is required for complete cyclisation. The tosylamides **262** and **263** were cyclized successfully within 16 hours to give the pyrroles **318** and **319**, respectively, in excellent yield (>99%). Interestingly, the tosylamide **264** was treated with 10% wt/wt $AgNO_3$ on silica in dichloromethane in the dark for 4 hours, and the dihydropyrrole **323** was observed in the ^1H NMR spectrum as the OH and CH appeared at 4.81 and 4.92 ppm as singlets (Figure 2.16). No precursor was evident. Diastereotopic hydrogens ($TBSOCH_2CH_2CH_2C\boldsymbol{H_aH_b}$) were showed each proton separately at 2.54-2.62 ppm and 2.79-2.87 ppm as multiplets.

Figure 2.16: ^1H NMR spectroscopic data

Four-hour cyclisation of N-[8-(tert-butyl-dimethyl-silanyloxy)-2-hydroxy-1,2-diphenyl-oct-3-ynyl]-4-methylphenylsulfonamide, 264.

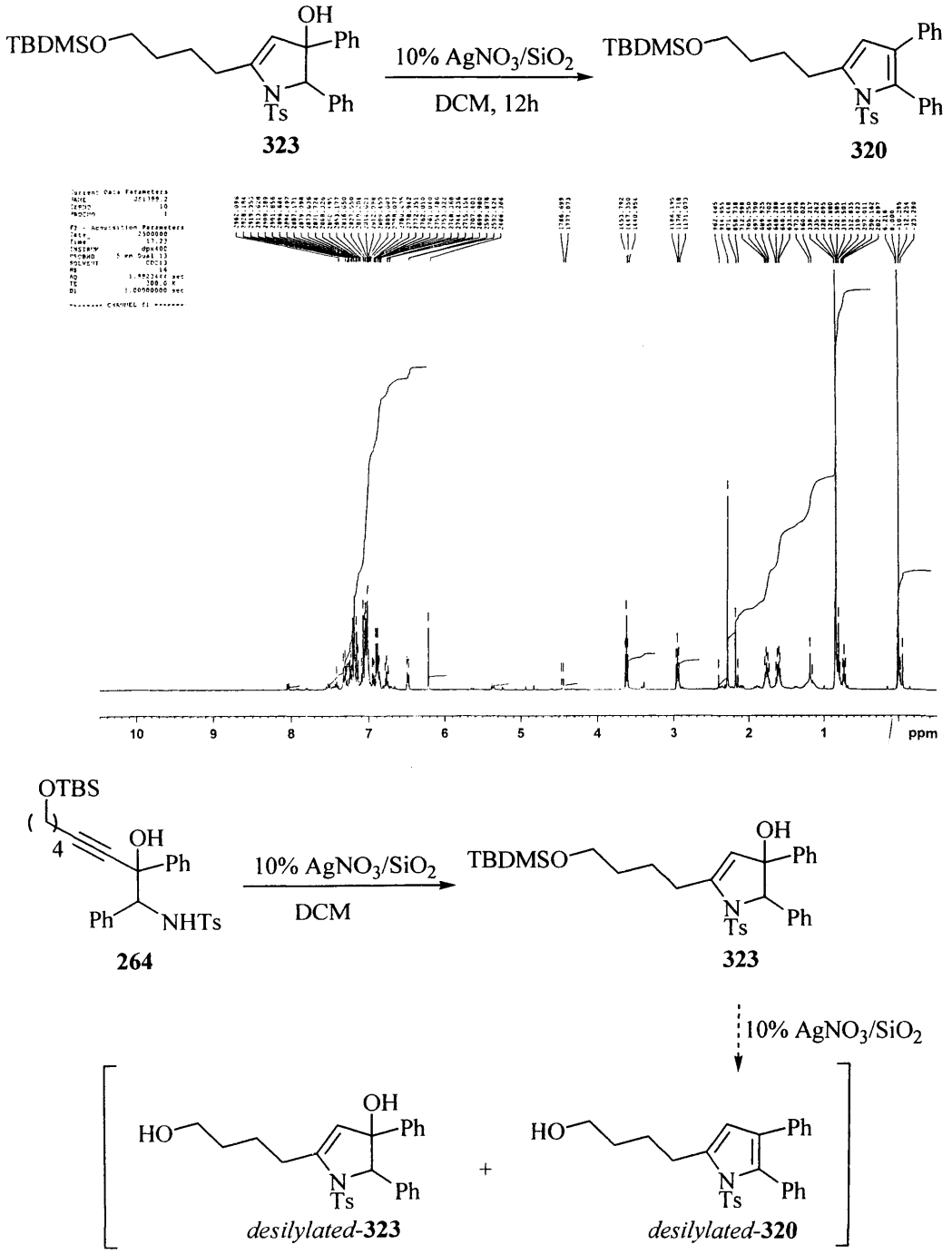


The cyclisation was completed within a 4-hour period, but it required more reaction time for the elimination process to obtain the desired pyrrole **320**. We decided to carry on the reaction further in 10% wt/wt silver nitrate on silica gel using the same reaction condition. After a further 12 hours, the expected pyrrole **320** (Figure 2.17) was obtained, in 58% yield, observing one CH of the pyrrole at 6.22 ppm. The moderate yield suggested the loss of the large TBDMS protecting group after cyclisation (Scheme 2.45). Due to filtration through a

plug of silica gel in the standard work-up, this has not been confirmed by the crude mixture ^{1}H NMR spectroscopic data.

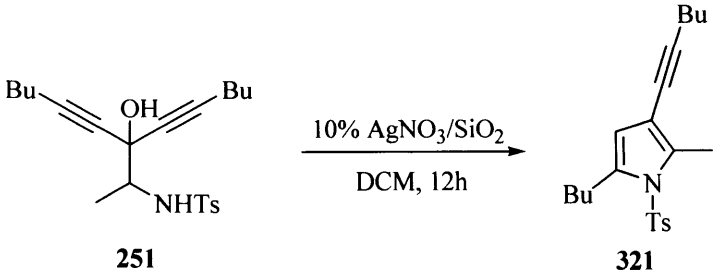
Figure 2.17: ^{1}H NMR spectroscopic data

5-[4-(*tert*-Butyldimethylsilanyloxy)-butyl]-2,3-diphenyl-1-(4-methylphenylsulfonyl)-pyrrole 320



Scheme 2.45

The cyclization of tosylamide **251** was completed within a 4-hour period to obtain the pyrrole **321** in quantitative yield (>99%, Scheme 2.46).



251 **321**

Scheme 2.46

2.6 Conclusion

The tin-mediated aldol addition of *N*-tosyl glycine to related α-β-unsaturated aldehydes and ketones was successfully achieved. However, a range of alternative methodologies showed the possibilities of different approaches to a variety of α-amino alcohols. To determine the better route, the ease of precursor preparation should be taken into consideration.

Such 'practical' syntheses are known for several important heterocycles. They are usually limited to certain substitution patterns in the target molecules. Also, yields seldom exceed 60%. Several side products are observed because several intermediates may react in different ways. We have been very successful in developing a novel synthesis of iodopyrroles *via* 5-*endo*-dig cyclisations of acetylenic tosylamides. These reactions require mild conditions, using a relatively simple two-step strategy to acquire the desired starting materials (see Section 2.1). Moreover, it is possible for the iodopyrroles to undergo subsequent palladium-catalysed couplings. For further work, it is suggested the use of thallium(I) ethoxide to promote Suzuki cross coupling reactions could be beneficial.[49] In addition, we have developed a synthesis of 2,3-disubstituted pyrroles and 2,3,5-trisubstituted pyrroles by silver-mediated cyclisations of similar acetylenic tosylamides. This required very mild conditions and gave pyrroles cleanly and in excellent yields (usually close to 100%). Further, the silver(I) was used catalytically. The possibilities of catalyst re-use and scale-up using either batch or flow technique remain to be assessed but appear to have considerable potential.

Chapter 3

(-)-Rhazinilam

3.1 Introduction

(-)-Rhazinilam **283** was first isolated in 1965 from *Melodinus Australia*,[50] then again in 1970 from *Rhazya stricta* (Apocynaceae) by A. Chatterjee,[51] who found it to contain an amide function and ethyl group. The structure of Rhazinilam **324** was firstly established in 1972. [52,53] Its structure strongly suggested a derivation from a relative simple alkaloid, 5,21-dihydrorhazinilam **325** as the natural precursor.[52] Most recently (1987),[54] (-)-Rhazinilam **283** was isolated from the Malaysian plant, *Kopsia singapurensis* (Ridley).

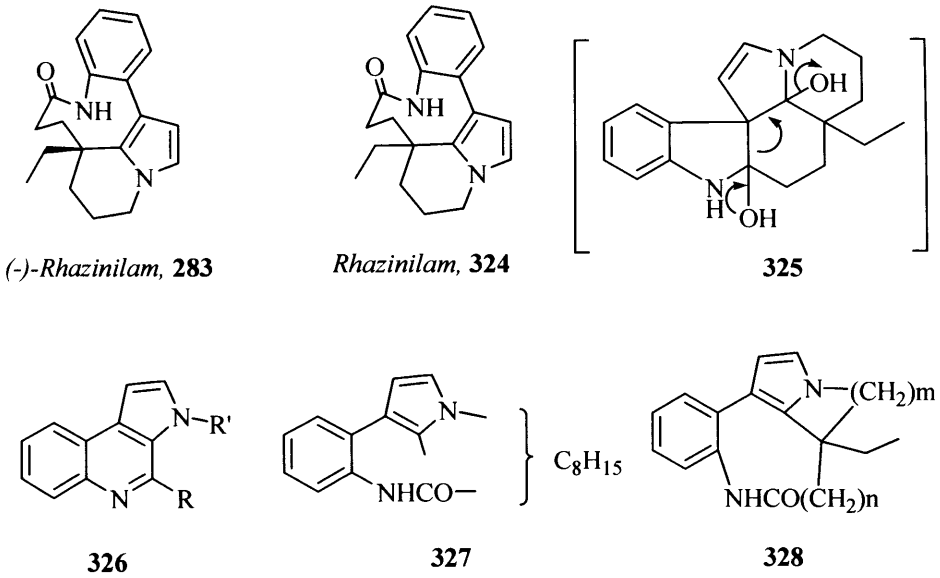


Figure 3.1

Smith and co-workers[52] found that the electronic absorption and fluorescence spectra of rhazinilam **324** were very closely similar to those of 3H-3,4-dimethylpyrrolo(2,3-c)quinoline **326** (R, R' = Me), also the ^{1}H NMR spectrum showed six aromatic protons. The weak electronic absorption showed steric inhibition of conjugation of all three chromophores (amide, benzene, and pyrrole). It then became evident that rhazinilam **324** must posses part-structure **327** in which the amide group was part of a medium-sized ring.

The ^{1}H NMR spectrum of rhazinilam **324** showed only one methyl group, and the most intense peak in the mass spectrum was M-C_2H_5, which suggested stabilization involving the

pyrrolic nitrogen (Figure 3.2). Therefore, the partial structure for rhazinilam **324** could then be extended to **328** (m+n = 5).

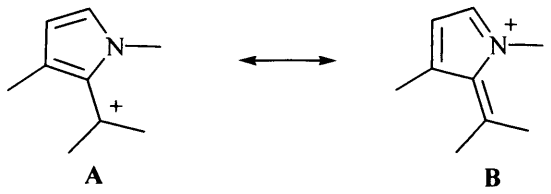


Figure 3.2

To disconnect the amide bond, treatment of rhazinilam **324** with acetic acid yielded an amino acid, converted into a carboxylic acid. According to the base peak in the mass spectrum of which corresponds to M-$CH_2CH_2CO_2H$, this was only compatible with attachment of the propionyl residue to the same quaternary atom as the ethyl group. The assignment of structure **324** to rhazinilam was then possible.

At the same time, Abraham and Rosenstein[53] reported the structure of rhazinilam **324** by single crystal X-ray diffraction studies. Structurally, rhazinilam **324** is characterized by four rings: the phenyl A-ring, the nine-membered lactam B-ring, the pyrrole C-ring, and the piperidine D-ring. Although the absolute configuration of their enantiomer was not determined in this X-ray structural analysis, the A-C dihedral angle of (-)-rhazinilam **283** was 95° and the amide bond seemed to possess a *cis*-conformation.

3.2 Biological activity [55]

3.2.1 Antimitotic agent

Antimitotic agents are active against solid tumors. In order to predict clinical responses, it is important to clarify the factors responsible for the antitumor effects of these agents. Antimitotic agents bind to tubulin and inhibit cancer cell proliferation. Two well-known examples of antimitotic agents are Vinblastine, which inhibits the polymerization of tubulin and Taxol, which inhibits the depolymerization of tubulin.

Using the tubulin test to screen antimitotic activities of plant extracts, the biological activity of rhazinilam has been demonstrated as responsible for the antitubulin activity of a Malaysian plant, *Kopsia singapurensis*. (-)-Rhazinilam **283** is an antimitotic agent, which mimics the

action of both Vinblastine and Taxol. Indeed, Taxol is the most promising antitumor agent developed in the past three decades.

3.2.2 Taxol

In the early 1960s, the National Cancer Institute (NCI) in the United States initiated a programme of biological screening of extracts taken from a wide variety of natural sources. One of these extracts was found to exhibit marked antitumour activity against a broad range of rodent tumours. Although this discovery was made in 1962, it was not until five years later that two researchers, Wall and Wani, of the Research Triangle Institute, North Carolina, isolated the active compound, from the bark of the Pacific yew tree (*Taxus brevifolia*). In 1971, Wall and Wani[55a,b] published the structure of this promising new anti-cancer lead compound, a complex poly-oxygenated diterpene.

Despite its well-documented biological activity, very little interest was shown in taxol until scientists at the Albert Einstein Medical College[55c] reported that its mode of action was totally unique. Until this finding in 1980, it was believed that the cytotoxic properties of taxol were due to its ability to destabilise microtubules, which are important structures involved in cell division (mitosis). In fact, taxol was found to induce the assembly of tubulin into microtubules, and more importantly, that the drug actually stabilizes them to the extent that mitosis is disrupted. Such a novel mode of action was believed to make taxol a prototype for a new class of anticancer drugs.

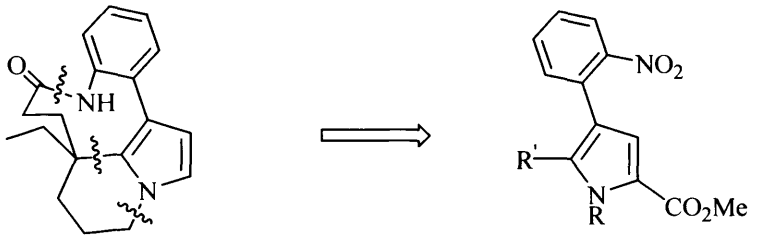
Renewed interest in taxol led to major problems, since many groups wished to conduct clinical trials, and so large quantities of this material were required. The natural source, the Pacific yew tree, is an environmentally protected species, which is also one of the slowest growing trees in the world. Isolation of the compound, which is contained in the bark, involves killing the tree, and the quantities available by this method are pitifully small. It would take six 100-year old trees to provide enough taxol to treat just one patient.

In 1994, taxol was approved for the treatment of breast cancer, one of the newer chemotherapy drugs, following surgery and radical techniques of radiotherapy. The cost of producing sufficient quantities of this new wonder drug, however, is a severely limiting factor. Synthetic organic chemistry may provide a solution to this problem in the years to come.

3.3 Synthesis

3.3.1 An Overview

Rhazinilam **324** had been the subject of two successful total synthetic studies reported by Smith and co-workers in 1973.[56] They used 3-(*o*-nitrophenyl)-pyrrole **329** as a key intermediate to establish the subsequent structure elements (Figure 3.3). To develop new practical routes towards heterobiaryls, this generated interests in building 3-arylpyrrole framework *via* a Suzuki coupling, such as in the reports of Ghosez in 1999,[57] and Guerritte in 2000.[58a,b] According to Guerritte's studies, his intent was to have a rapid and efficient construction of a library of analogues for biological screening proposes.



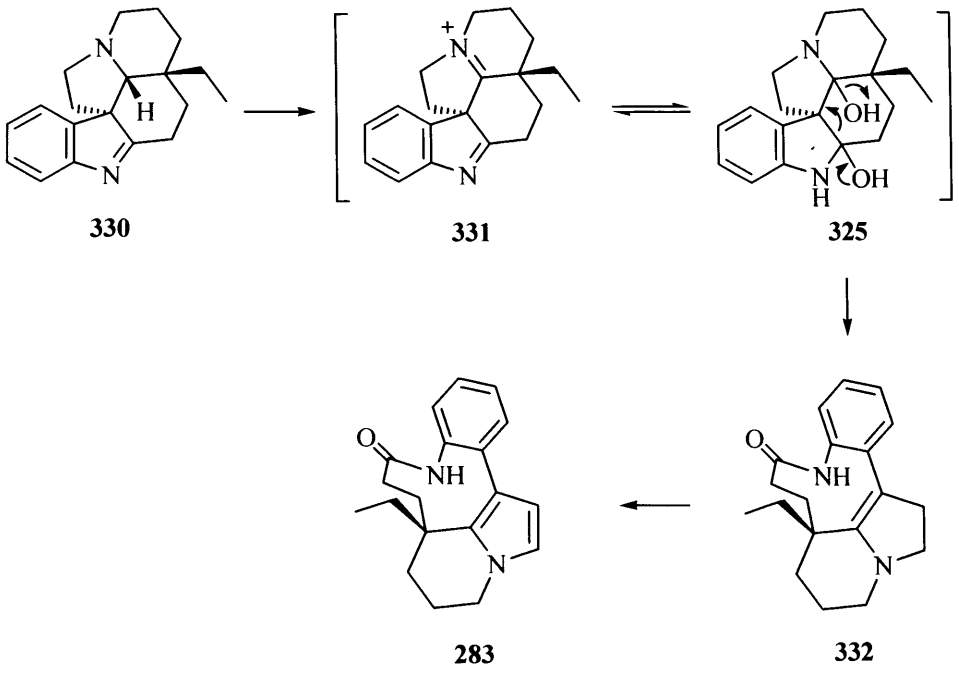
324 **329**

Figure 3.3

Guenard and Guerritte[59a,b,c] had reported the syntheses of rhazinilam analogues during 1998-2001, and M. Banwell[60] reported a convergent synthesis of (±)-B-norrhazinilam in 2000, which has been characterized and subjected to a preliminary biological evaluation. Finally in 2000, Johnson and Sames[61] had achieved the total synthesis of (-)-rhazinilam **283** through C-H bond activation of hydrocarbon segments.

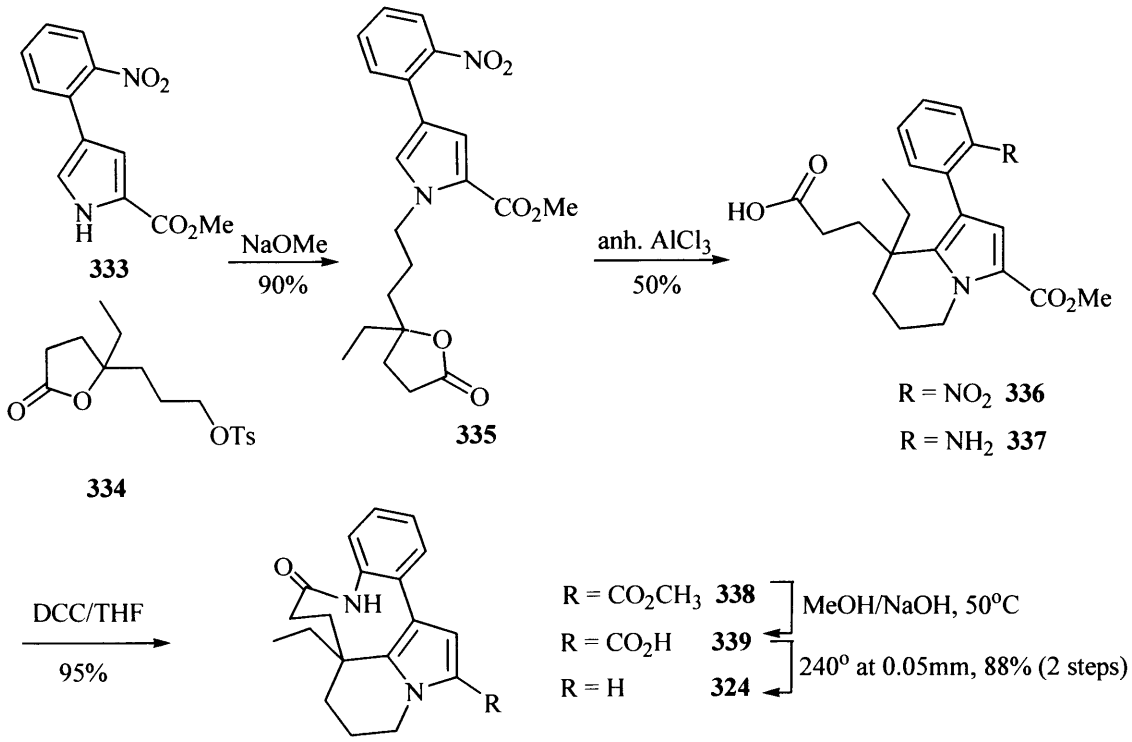
3.3.2 First Total Synthesis of Rhazinilam 324 [56]

Smith and co-workers[56] had reported a partial synthesis of (-)-Rhazinilam **283** from (+)-1,2-didehydroaspidospermidine **330**, and a total synthesis of rhazinilam **324** in 1973. After (+)-1,2-didehydroaspidospermidine **330** was oxidised by *m*-chloroperbenzoic acid, 5,21-dihydrorhazinilam **332** then treated with aqueous iron(II) sulphate to give a moderate yield of (-)-Rhazinilam **283** (30%, Scheme 3.1). However, the reactions were not always reproducible and poor yields were obtained due to work up difficulties.



Scheme 3.1

To have the entire carbon skeleton in their total synthesis involved the direct alkylation of 2-methoxycarbonyl-4-2-nitrophenyl pyrrole **333** by 4-ethyl-4-hydroxy-7-tosyloxyheptanoic acid γ–lactone **334** to give the pyrrole heptanoic acid γ–lactone **335**, in 90% yield (Scheme 3.2).

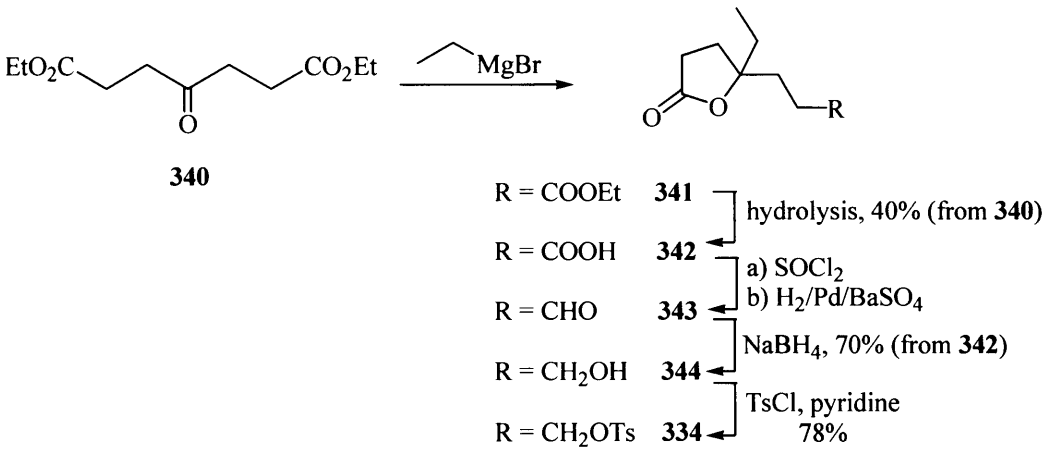


Scheme 3.2

To obtain the piperidine D-ring, the lactone **335** was treated with anhydrous aluminium chloride in nitromethane to give the tetrahydroindolizinyl propanoic acid **336** in 50% yield. The synthesis was then completed in four steps: reduction of the nitro group (86% yield), lactamisation by using DCC (>95% yield), saponification of the ester function and decarboxylation (88% yield from 5-methoxycabonylrhazinilam **338**).

However, this route probably could not be used to obtain pure enantiomers. The stereogenic center at the γ-lactone position would be destroyed during cyclisation onto the pyrrole to obtain **336**. Perhaps a chiral Lewis acid could be used in place of aluminium trichloride in order to control the stereogenic center.

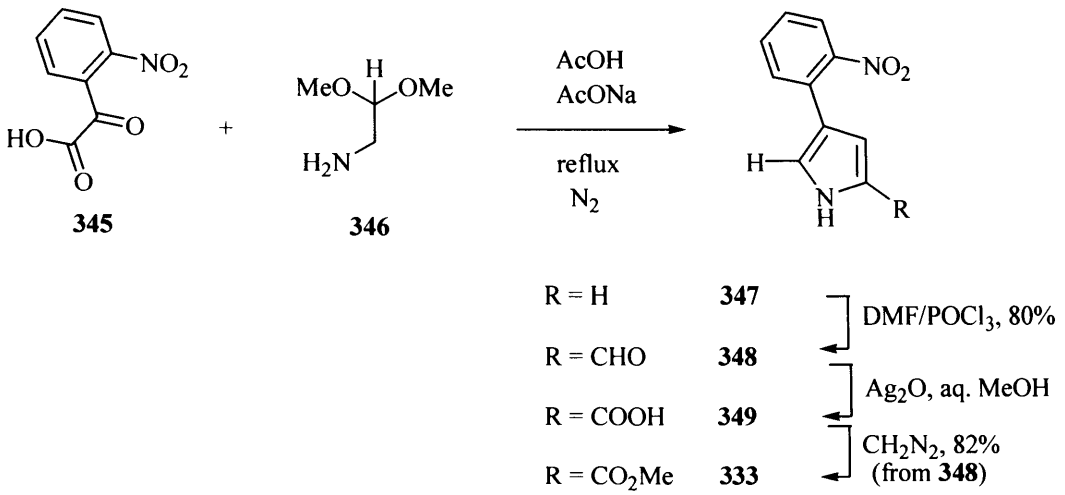
Their starting point for the synthesis of the lactone **334** was the interaction of diethyl 4-ketopimelate **340** and ethylmagnesium bromide (Scheme 3.3).



Scheme 3.3

After hydrolysis, the corresponding acid **342** was obtained 40% yield. The acid was reduced by the Rosenmund method, followed by sodium·borohydride to obtain the alcohol **344** with 70% yield. Tosyl choride in pyridine at 25°C converted this alcohol into the tosylate **334**.

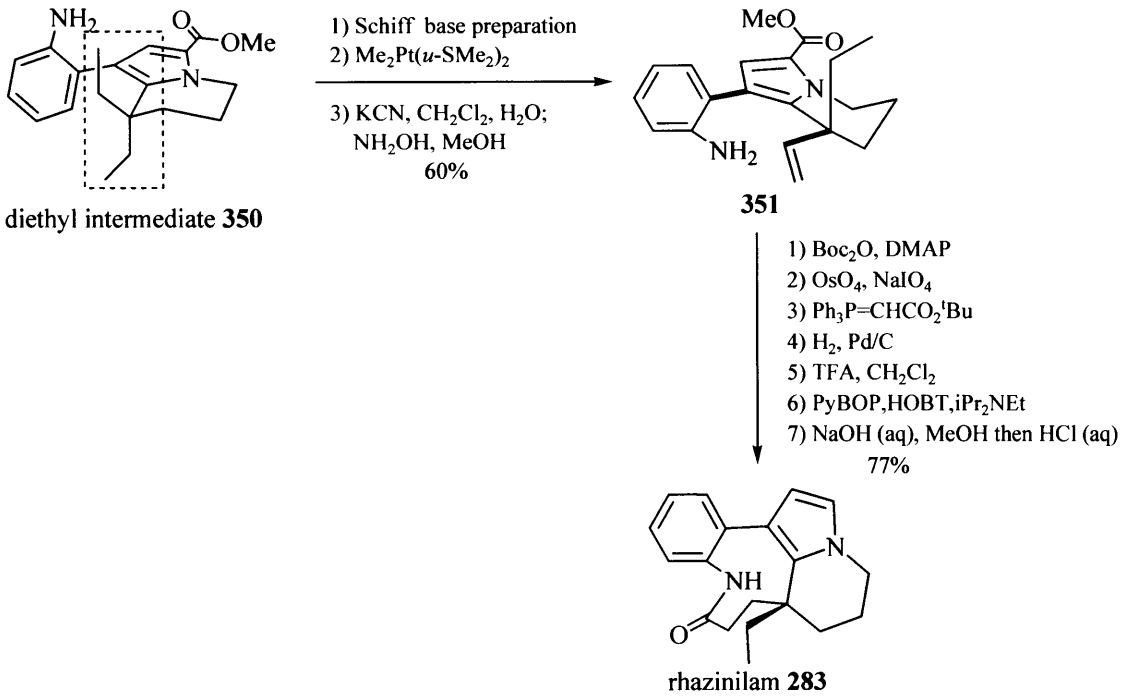
Synthesis of the pyrrole **333** started with the ring synthesis of 3-(*o*-nitrophenyl)-pyrrole **347**, which was then formylated by the Vilsmeier method to give 2-formyl-4-(*o*-nitrophenyl)-pyrrole **348** (60% yield). The pyrrole **348** was then treated with silver oxide to give the pyrrole acid **349** and followed by diazomethane to give the pyrrole **329** with 82% yield (Scheme 3.4). This therefore gave an overall yield of Rhazinilam **324** of >20%.



Scheme 3.4

3.3.3 Total Synthesis of (-)-Rhazinilam 283 using C-H bond activation [61]

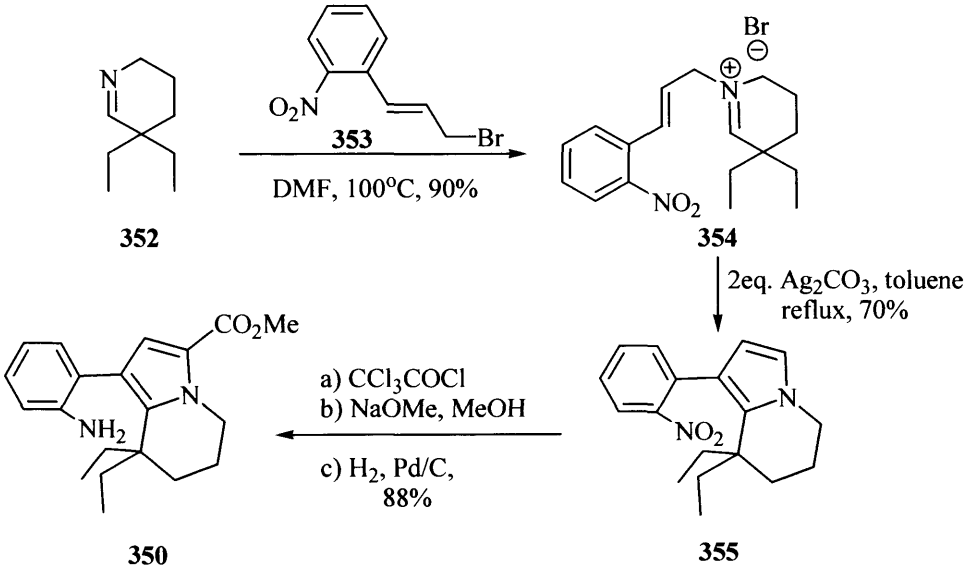
C-H σ-bond activation of alkane and aromatic compounds is of considerable interest in recent organometallic chemistry, because this can introduce several functional groups into alkane and aromatic compounds through the σ-bond activation. Johnson and Sames[61] had reported a directed C-H activation to obtain the pyrrole **351** in 60% yield, which was influenced by the proximity of the amino group to the ethyl groups in the diethyl intermediate **350** (Scheme 3.5).



Scheme 3.5

Dehydrogenation of the ethyl group, mediated by a platinum complex, was accomplished in the presence of a variety of functional groups including the ester group, pyrrole and arene rings. To complete the total synthesis of rhazinilam **324**, a one-carbon extension of the vinyl group and the subsequent macrocycle closure was required. The alkene double bond of **351** was transformed to an aldehyde, followed by Wittig reaction, catalytic hydrogenation, *t*-butyl ester and Boc deprotection, and finally a macrolactam formation with >30% yield from **351**.

To obtain the intermediate **350**, iminium salt **354** was generated from readily available imine **352** and *o*-nitrocinnamyl bromide **353**, followed by cyclisation and aromatization by heating the salt **354** in the presence of silver carbonate to give the pyrrole **355** in 70% yield. The carboxylate group was then installedto stabilize the electrophile-sensitive pyrrole ring, and finally the nitro group was reduced to furnish amine **350** in 88% yield (Scheme 3.6). This gave an overall yield of Rhazinilam **324** >10%.

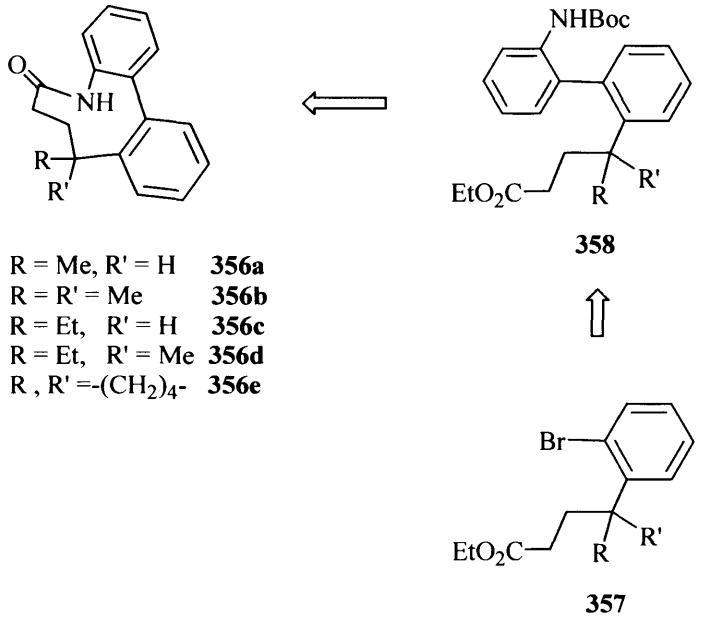


Scheme 3.6

3.3.4 The synthesis of new substituted biphenyl analogs [59a,b,c]

Guenard and Guerritte' s studies[59a,b,c] had focused on the replacement of the phenylpyrrole by a biphenyl unit, and a range of candidates for structure-activity relationship studies were prepared. According to Guenard's previous studies,[62] the presence of the aromatic units as well as the lactam function was essential for good binding to tubulin. Also, the size of the lactam ring and the bulkiness of the substituents present on the ring had an influenece in the interaction with microtubules.

In 1998,[59a] they reported the synthesis of new *o*-substituted bridge biphenyls **356a** to **356e**, and showed that the more or less hindered substitution at carbon 9 affected the interaction with tubulin. Their approach was based on a cross-coupling reaction of a protected aniline derivative with *o*-substituted aryl bromide **357**. This led to the key biphenyl intermediate **358**, which was cyclized into a nine-membered ring after deprotection of the amine and acid groups followed by intramolecular cyclization in the presence of EDCI and HOBT to obtain **356a-e** in good yields (Figure 3.4).



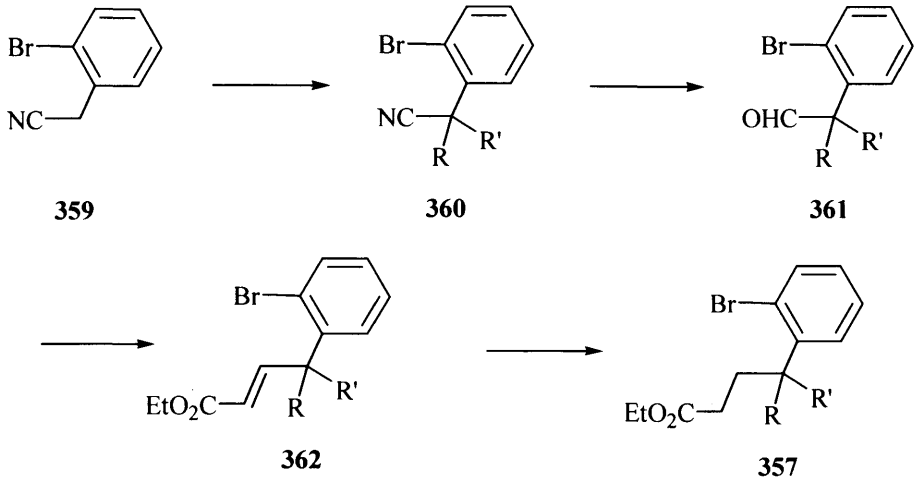
R = Me, R' = H **356a**
R = R' = Me **356b**
R = Et, R' = H **356c**
R = Et, R' = Me **356d**
R , R' =-$(CH_2)_4$- **356e**

Figure 3.4

According to their results, the compounds **356a-e** had the capacity to interact with tubulin in the same fashion as (-)-rhazinilam **283**. However, compounds **356b**, **356c**, **356d**, and **356e** were respectively 20, 17, 8, and 16 times less active than (-)-rhazinilam **283** and compounds **356a** was inactive. The decrease of the conformational freedom along the biphenyl axis seemed to increase the activity of the compounds **356**. This was not relevant to **356e**, which suggested a direct interaction of the alkyl groups with tubulin.

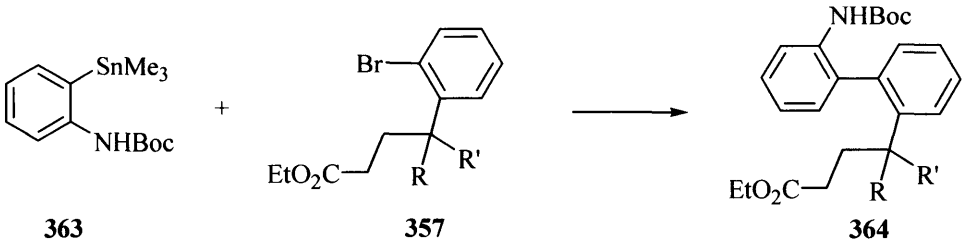
To obtain compound **357**, monoalkylation and dialkylation of commercially available 2-bromophenylacetonitrile **359** was carried out, and this led to nitriles **360a-e**, which then were reduced into the corresponding aldehydes **361a-e**. These unstable aldehydes **361a-e** were immediately subjected to the Horner-Wadsworth-Emmons (HWE) condition to afford

selectively *trans*-alkenes **362a-e** with good yields, followed by catalytic hydrogenation to give the aryl bromides **357a-e** (Scheme 3.7).



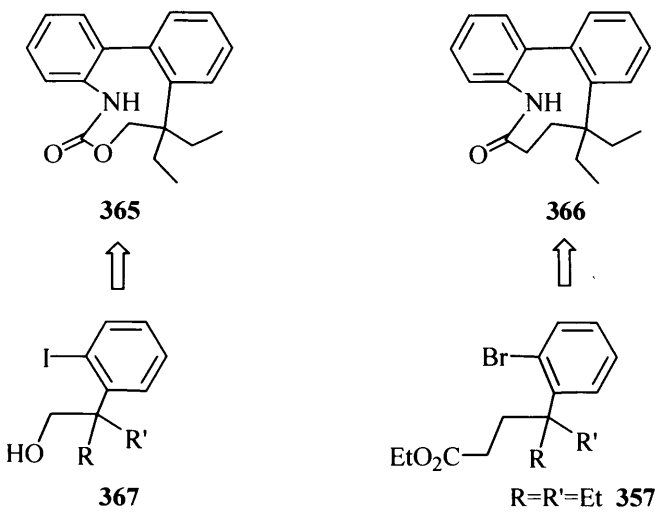
Scheme 3.7

Cross-coupling reaction of *N*-(*t*-butoxycarbonyl)-2-(trimethylstannyl)aniline **363** and the arylbromides **357a-e** gave **364a-e** in yields ranging from 64% to 3% depending on the amount of steric hindrance in the arylbromides **357** (Scheme 3.8).



Scheme 3.8

Later on, more analogs[59b] had been prepared in the similar way to show the conformation of the B-ring (lactam), which could play a role in the binding (Scheme 3.9). Such an analog (-)-**365** showed that the replacement of the lactam by a urethane function was favourable for the binding with tubulin by possessing a better interaction than (-)-rhazinilam **283** and lactam **366**. This work established the first features needed for maximum antitubulin activity.

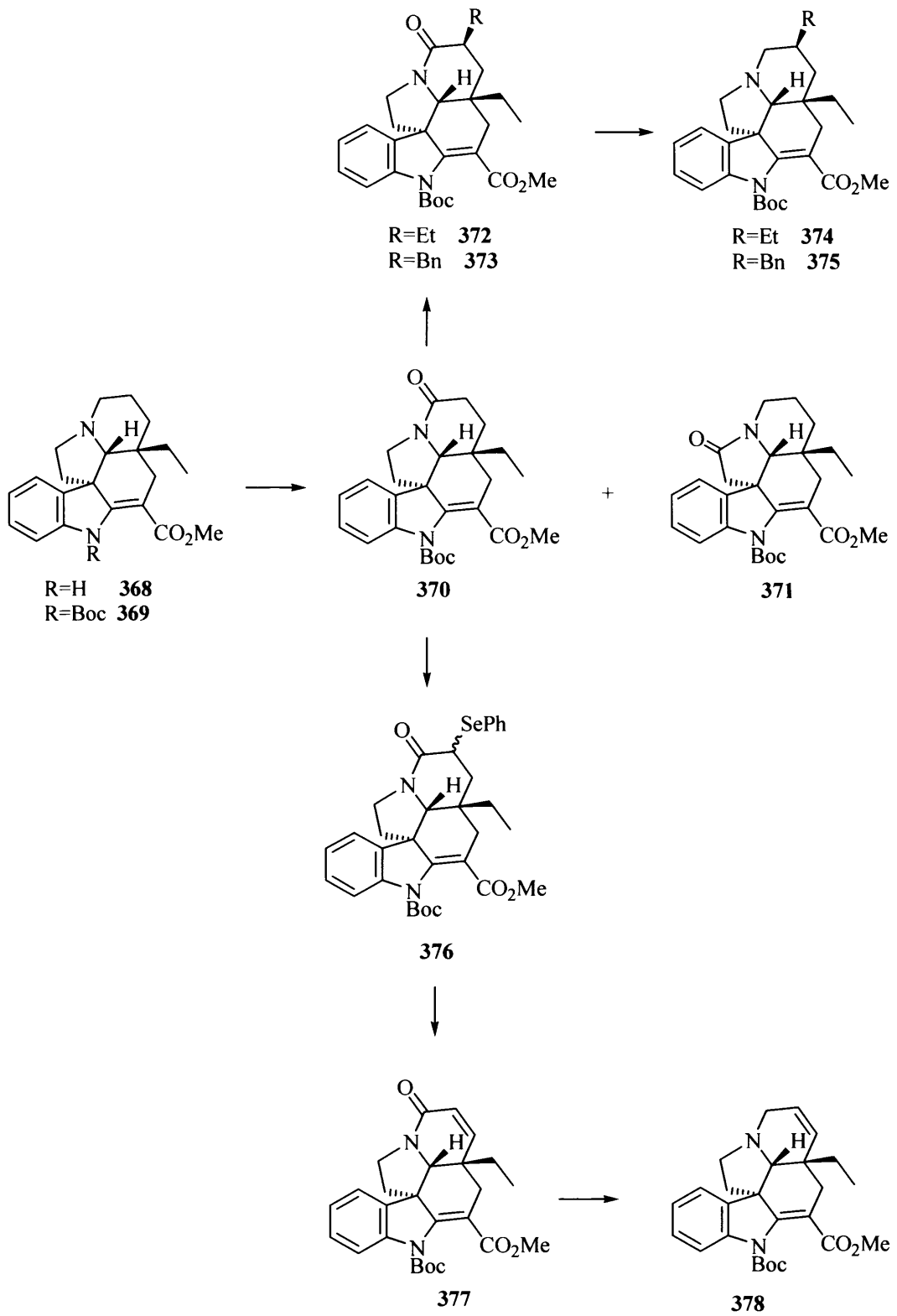


Scheme 3.9

In 1999, Guenard and Guerritte[63] further reported chemical modifications of the D-ring and the biological activity evaluation of these new D-ring substituted rhazinilam analogs. The synthesis strategy, using the semisynthetic pathway, starts from (+)-vincadifformine **368** affording easily (+)-1,2-didehydroaspidospermidine **330** after acid treatment. By treating with *m*-chloroperoxybenzoic acid, and using a classical Polonovski conditions (Ac_2O, triethylamine), a reproducible 'one pot' semisynthesis from **330** afforded (-)-rhazinilam **283** in 50% yield. This allowed the easy preparation of (-)-rhazinilam analogues substituted on the D-ring.

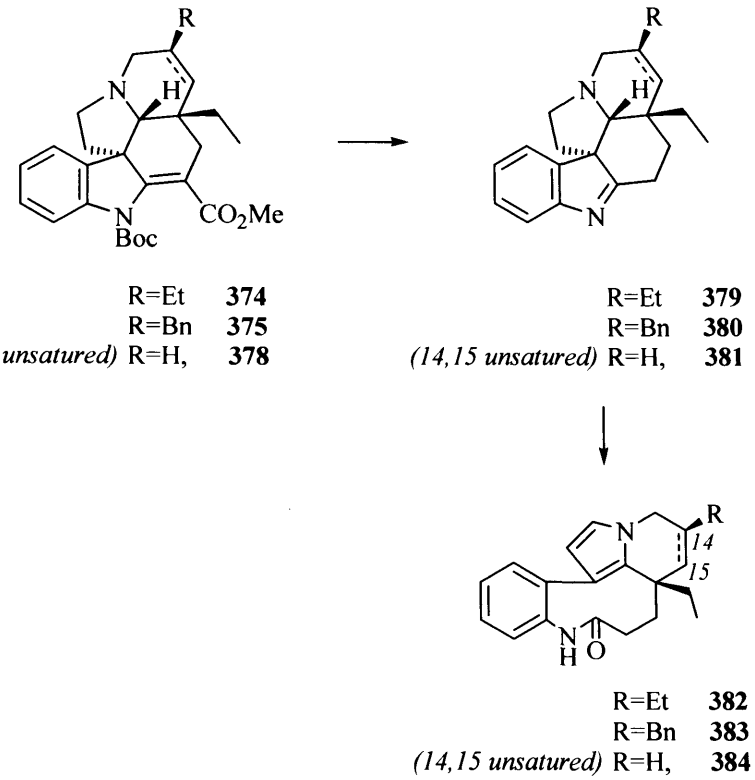
(+)-Vincadifformine **368** was protected by a Boc group to yield **369**, which then oxidized with bromine in THF:water to obtain **370** along with **371**. Alkylation of **370** with ethyl iodide and benzyl bromide afforded the kinetically favoured **372** and **373**, respectively. The selective reduction of the **372** and **373** was performed with borane-THF complex at 0°C to obtain **374** and **375** in quantitative yield.

Compound **370** was also reacted with phenylselenenyl chloride and led to **376** in 80% yield. Elimination of the selenoxide group occurred smoothly to afford the α,β-unsaturated amide **377**, which then reduced selectively with diisobutylaluminium hydride to give **378** (Scheme 3.10).



Scheme 3.10

Decarboxylation and Boc-deprotection of **374**, **375**, and **378** with hydrochloric acid gave 1,2-didehydroaspidospermidine derivatives **379**, **380**, and **381** in high yields. The 'one pot' semisynthesis was finally performed to give (-)-14β-ethylrhazinilam **382**, (-)-14β-benzylrhazinilam **383**, and (-)-14,15-didehydrorhazinilam **384** (Scheme 3.11).



Scheme 3.11

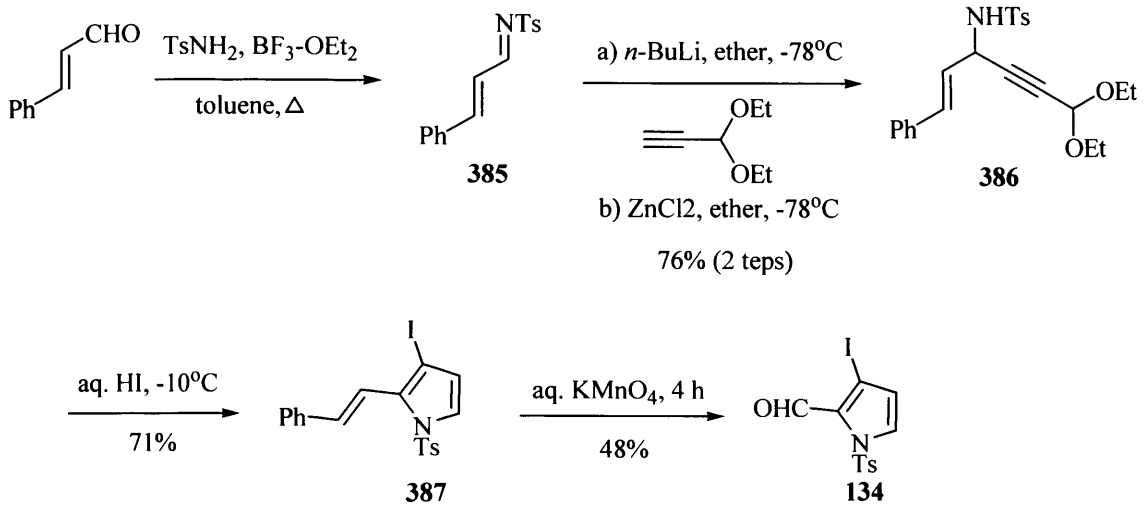
This work provided information on the structure-activity relationship in the rhazinilam series. The substitution at position *14* with the hydrophobic ethyl and benzyl groups, **382** and **383**, resulted in a clear decrease of the antitubulin activity comparing to (-)-rhazinilam **283**. The unsaturated D-ring **384** was 2 times less active than (-)-rhazinilam **283**. They suggested that these modified C-14 compounds might be in interaction with the binding site, related to a mode of action different from a direct interaction with microtubules.

3.3.5 Hetero-ring cross coupling

By means of a rapid and efficient construction of a library of analogues, a Suzuki cross-coupling reaction had influenced Ghosez[45] (see Section 2.3.2, page 54), Guenard, and Guerritte[58a,b,59c] to use this reaction as a key step, when approaching analogues of (-)-rhazinilam **283**.

Ghosez and co-workers[45] reported the successful results in Suzuki coupling of 2-formyl-3-iodopyrrole **134** with various arylboronic acids. The pyrrole **134** had been prepared in four steps from cinnamaldehyde, which was firstly converted into amide **386**, followed by

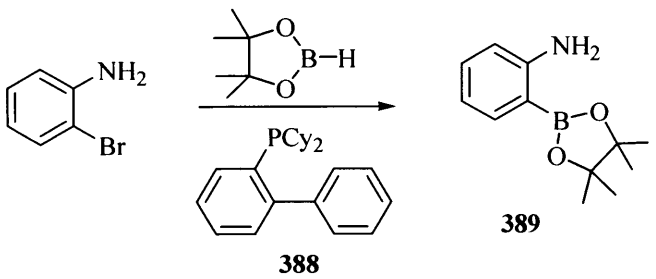
cyclisation to give the pyrrole **387**, and finally oxidative cleavage of the double bond using potassium permanganate to give the iodopyrrole **134** in 48% yield (Scheme 3.12).



Scheme 3.12

To access 2-substituted-3-arylpyrrole **279** (Scheme 2.25, Section 2.32), a Suzuki reaction was performed with 1,1'-*bis*-(diphenylphosphino)ferrocene (dppf) in the presence of barium hydroxide in DMF:H_2O (4:1) at 80°C in order to achieved high yields of coupling products.

In 2000, Guenard, and Guerritte[58b] reported the borylation of *o*-substitued aryl halides and 'one-pot' Suzuki cross-coupling reactions with *o*-substitued aryl iodides, yielding sterically hindered 2,2'-disubstituted biphenyls. They showed that use of biphenylphosphine ligand **388** improved dramatically in the borylation process the presence of 5% mol of palladium acetate and four equivalents of triethylamine in dioxane (Scheme 3.13). This afforded the boronate **389** in 81% yield within an hour.



Scheme 3.13

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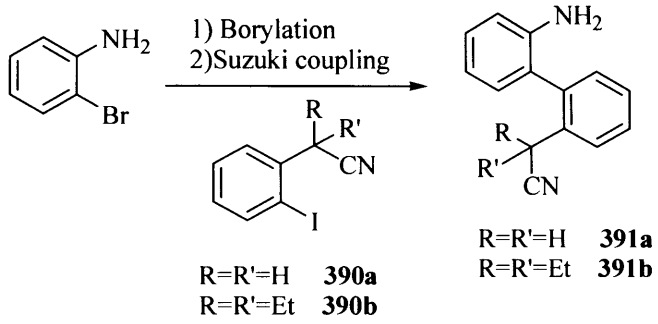
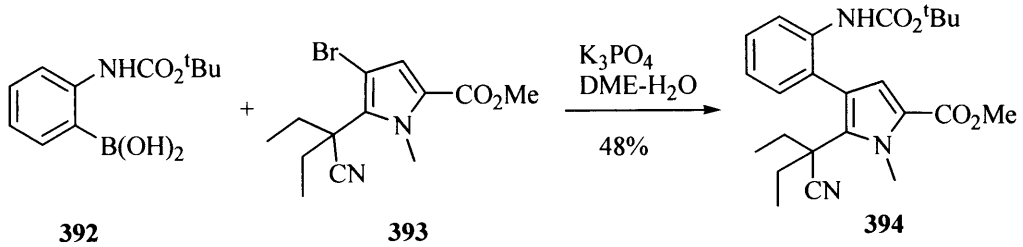
With these good results, they also extended this methodology to the synthesis of 2,2'-biphenyls *via* 'one-pot' Suzuki cross-coupling reactions. After the boronation of 2-bromoaniline was followed by addition of water, an equivalent of 2-iodophenylacetonitrile **390**, excess barium hydroxide, and heating for an hour at 100°C. The cross-coupling products **391a** and **391b** were obtained in 73% and 66%, respectively (Scheme 3.14), which then could be further elaborated to give rhazinilam biphenyl analogues **365** (see Scheme 3.6, 3.7, and 3.8).



Scheme 3.14

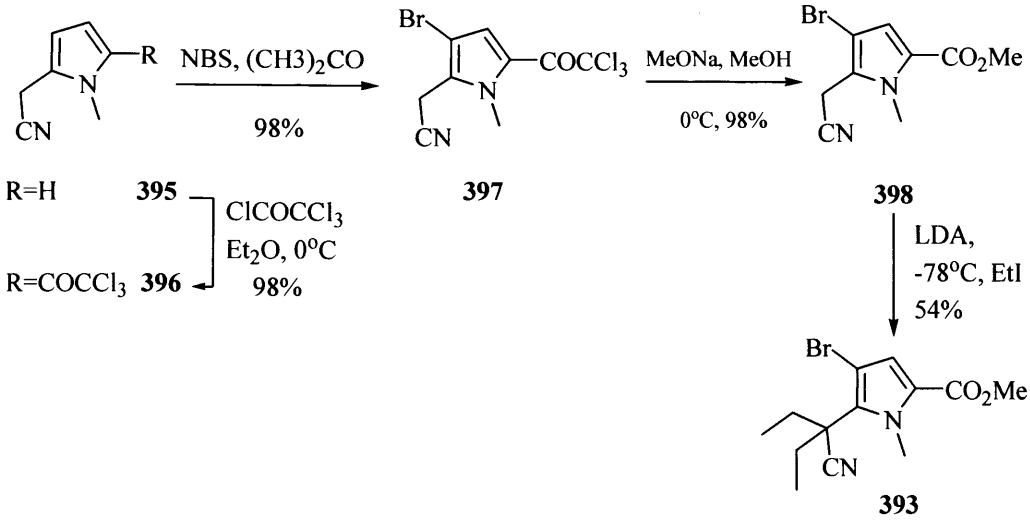
In the same year, Guenard, and Guerritte[58a] also reported the Suzuki cross-coupling reaction between 1,2,5-trisubstituted pyrrole halides and 2-*N*-(*t*-butoxycarbonyl)aminophenyl boronic acid. In this highly hindered coupling, the reactions were performed with benzyl[bis(triphenylphosphine)]palladium(II) chloride ($PdBnCl(PPh_3)_2$) in a DMF:H_2O solution in the presence of potassium phosphate. Under this condition reaction, the coupling between arylboronic acid **392** and pyrrole bromine **393** gave the 3-phenylpyrrole derivative **394** in a modest yield (48%, Scheme 3.15).



Scheme 3.15

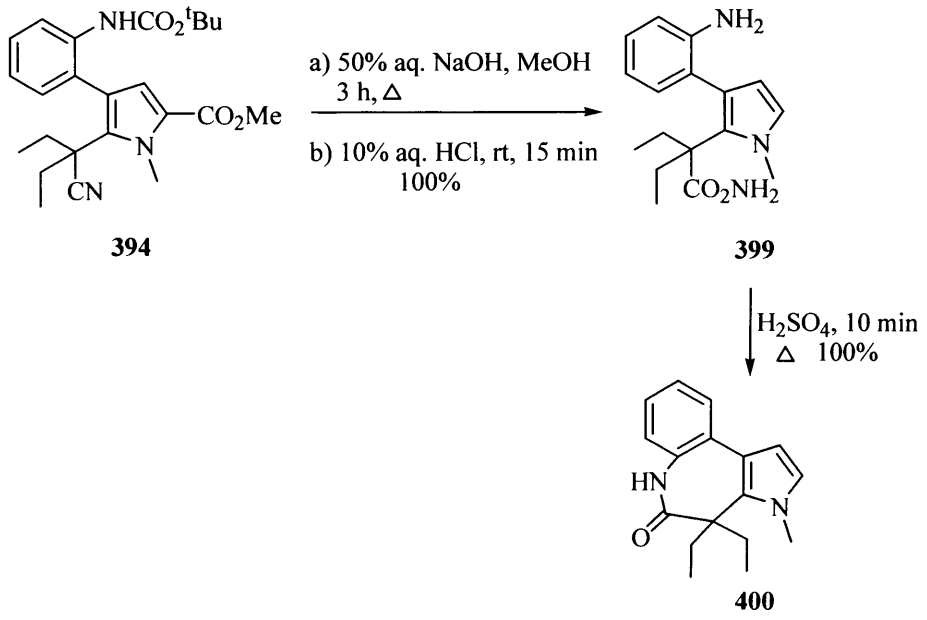
The pyrrole **393** was prepared from commercial 1-methyl-2-pyrroleacetonitrile **395**, which was protected at carbon 5 with a trichloroacetyl group, followed by converting into bromide to give 3-bromopyrrole **397** in quantitative yield. Treatment of the 3-bromopyrrole **397** with

sodium methoxide led to **398** which was dialkylated to yield pyrrole **393** in 54% yield (Scheme 3.16).



Scheme 3.16

Finally, the phenylpyrrole **394** was treated with a 10% aqueous solution of hydrochloric acid to give the primary amide **399**, which was then converted into the analogue **400** after lactamization (Scheme 3.17). The phenylpyrrole was found to be inactive. This confirmed that the size of the lactam ring was playing an essential role in the inhibition of tubulin. So far, Guenard, and Guerritte suggested that the presence of a biaryl unit sustaining a nine-membered ring was crucial, as well as a quaternary center at the 13 position.

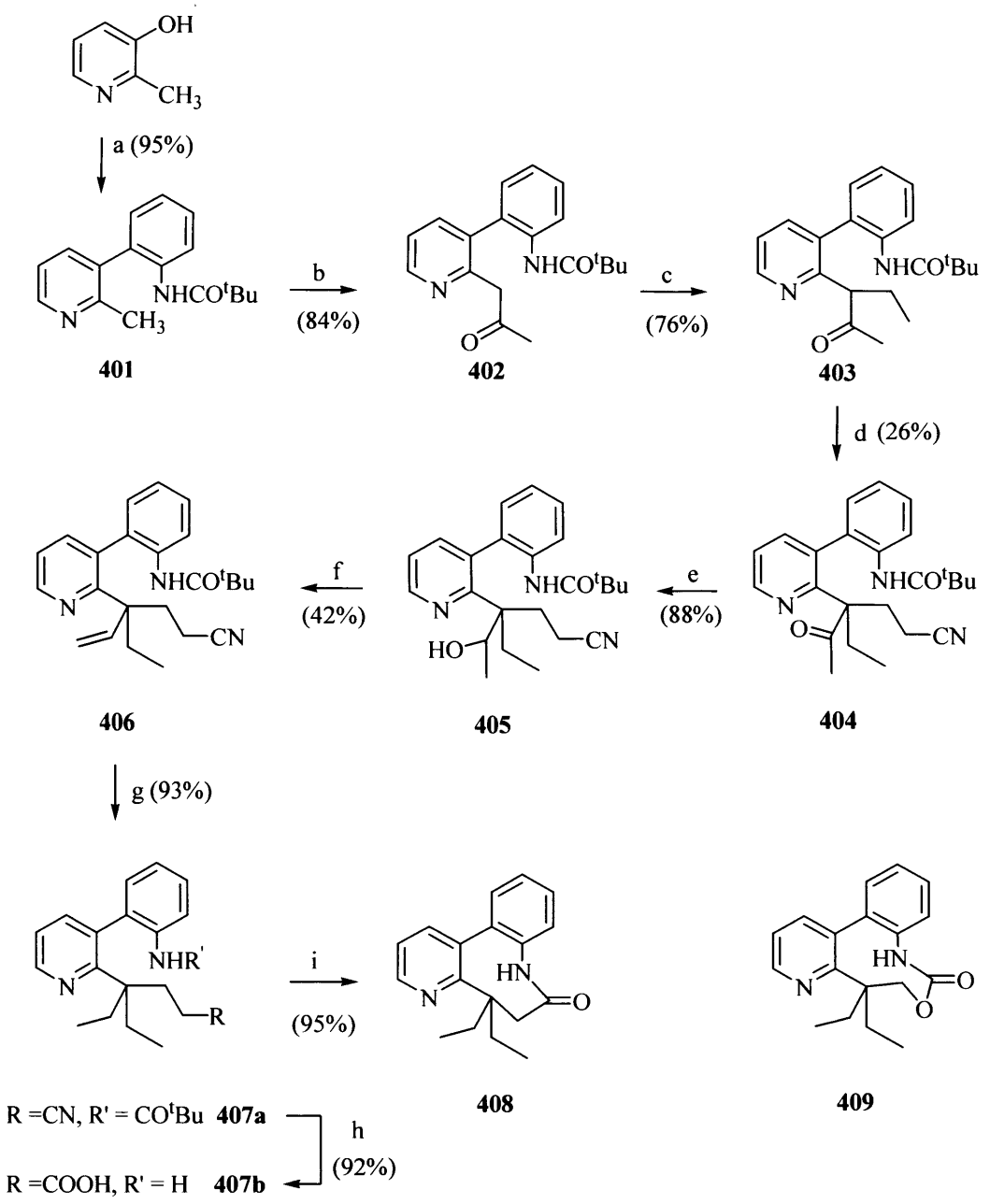


Scheme 3.17

In 2001, Guenard, and Guerritte[59c] also reported the first total synthesis of phenylpyridine analogues, using Suzuki cross-coupling reactions as one of the key steps. Under a 'one-pot' procedure, commercially available 3-hydroxy-2-methylpyridine was used as starting material to synthesize the biaryl system by treating with triflic anhydride in pyridine for 45 minutes, then with 2-pivaloylaminophenylboronic acid, tetrakis(triphenylphosphine)palladium(0) in the presence of potassium carbonate in toluene:EtOH, to yield the biaryl **401** in 95% (Scheme 3.18).

The biaryl **401** was then treated with *n*-BuLi and dimethyl acetamide leading to the pyridylacetone **402**, which was followed by alkylation to afford the ketone **403** in good yield. The ketone **403** was then treated with acrylonitrile in the presence of benzyltrimethylammonium hydroxide to give the quaternary picolinic compound **404** in low yield, along with a byproduct. Compound **404** was reduced to the alcohol **405** with sodium borohydride and then dehydrated to vinyl compound **406** in hot HMPA and a presence of a small amount of sulfuric acid. The vinyl compound **406** was then converted into alkane **407a** by catalytic hydrogenation. The lactam **408** was obtained in good yield by deprotecting the amine **407a** to obtain amino acid **407b** by aqueous sulfuric acid treatment followed by cyclization using the HOBT/EDCI system (Scheme 3.18).

The biological result showed the low activity of the lactam **408**. According to the acidic character of tubulin, this might be due to protonation of the pyridine ring leading to an unfavorable charge distribution for the interaction with tubulin. Their best result was obtained for cyclic carbamate **409**, which was synthesized using a similar strategy and had three times less active than (-)-rhazinilam **283**.



a) Tf_2O, pyridine, 20°C, 45 min; then 1.2 eq. 2-pivaloylaminophenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, toluene, EtOH, 80°C, 3h. b) *n*-BuLi, THF, -20°C; then DMF, -70°C, 30 min. c) *n*-BuLi, THF –70°C to 20°C, 40 min; EtI, reflux, 16 h. d) acrylonitrile, $BnMe_3N^+OH^-$, *t*-BuOH, 25°C, 7 days. e) $NaBH_4$, EtOH, 20°C, 16 h. f) HMPA, H_2SO_4, 220-225°C, 1.5 h. g) H_2, Pd/C, MeOH, 1 atm, 20°C, 1 h. h) 30% H_2SO_4, 160°C, 2 h; then 25% NH_4OH. i) HOBT, EDCI, NEt_3, $CHCl_3$, 36 h, 50°C.

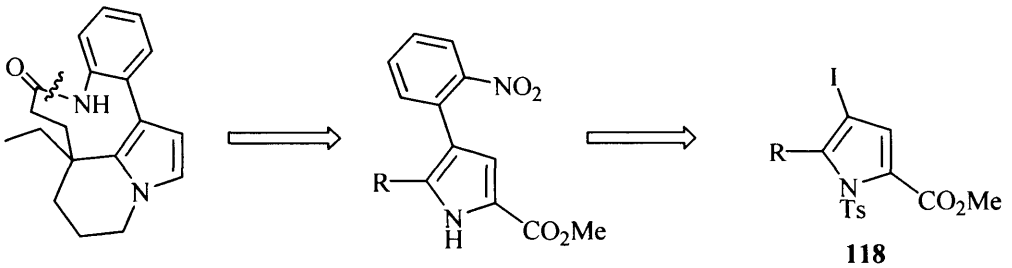
Scheme 3.18

Chapter 4

The first synthetic approach to Rhazinilam

4.1 Introduction

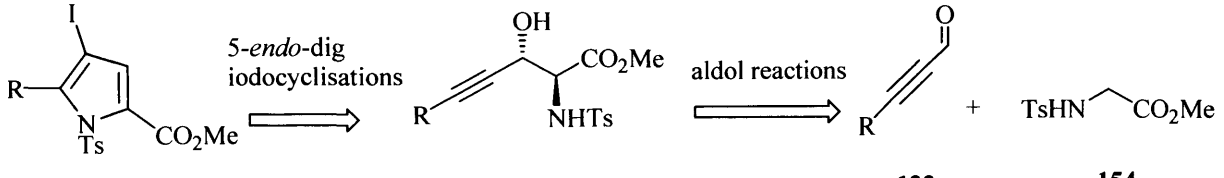
As shown in the previous Chapter, many groups have attempted to synthesise Rhazinilam **324** and its analogues. One well-designed route was based on the 3-(*o*-nitrophenyl)-pyrrole **280**, as a key intermediate to establish the remainder of the structure elements (Chapter 3). To achieve a rapid and efficient access to the pyrrole **280**, other new approaches are required. We were interested in the synthesis of (-)-Rhazinilam **139**, not only for its potential antitumor activity, but also in providing us with a synthetic challenge in applying two methodologies developed by our group: aldol reactions and 5-*endo*-dig iodocyclisations.



324 **280** **118**

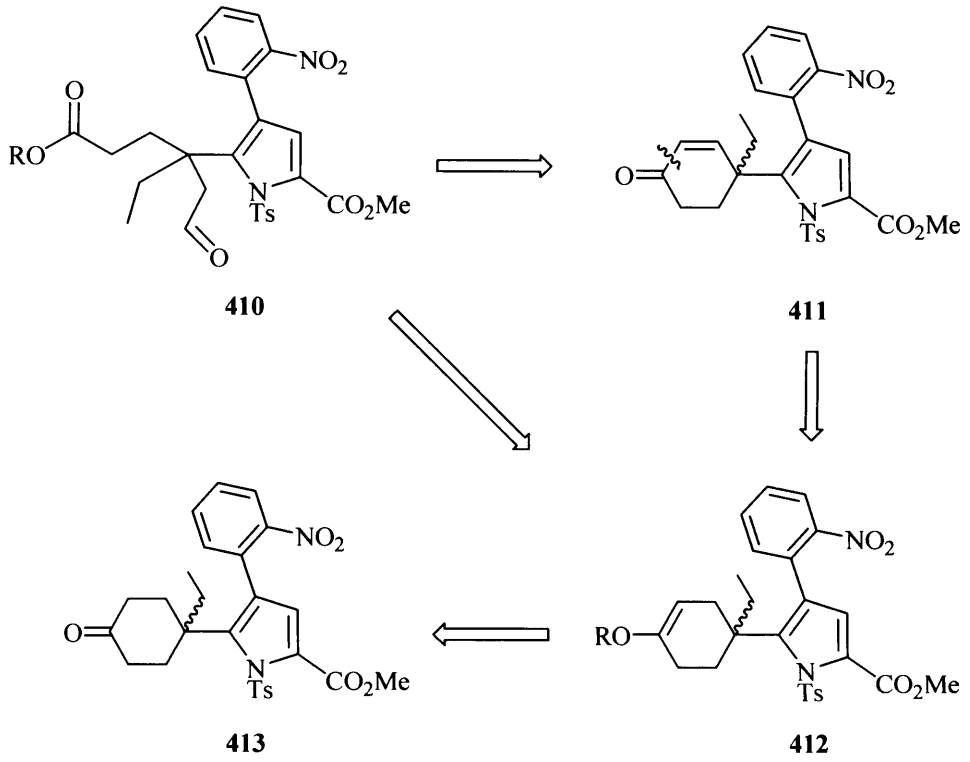
Scheme 4.1

According to the retrosynthetic study of Rhazinilam **324**, the disconnection of the amide functionality, followed by cleavage of the *o*-nitrophenyl group would lead to the iodopyrrole **118** (Scheme 4.1). It has previously been shown that the Suzuki reaction works successfully in this coupling. To obtain the iodopyrrole **118**, 5-*endo*-dig iodocyclisation would apply to the alkynyl-β-hydroxy-α-amino ester **120**, only if the aldol reaction could be applied successfully to a suitable α,β–acetylenic aldehyde **122** (Scheme 4.2).



118 **120** **122** **154**

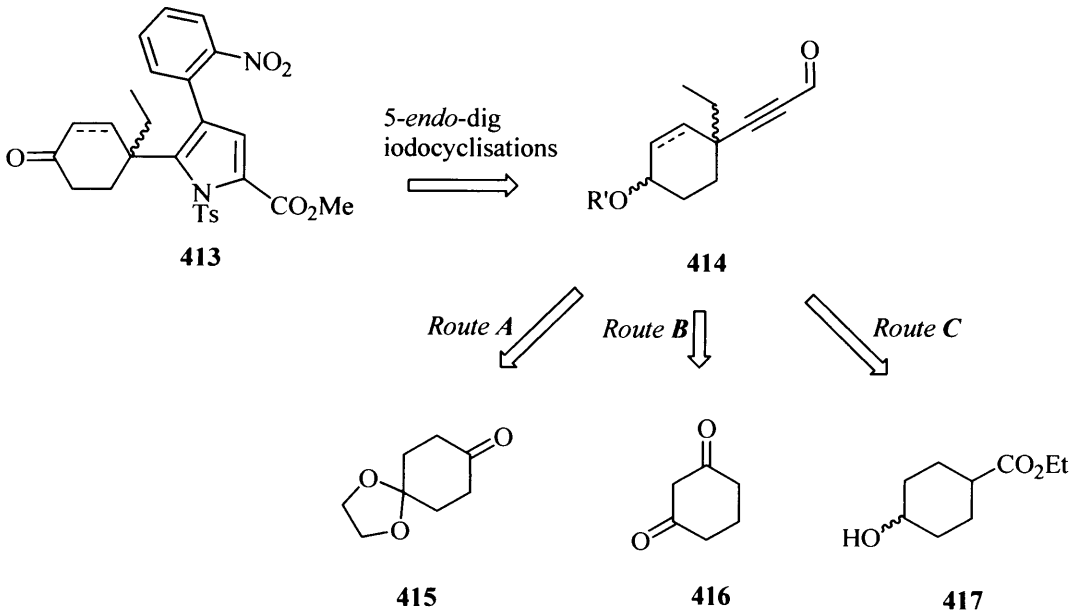
Scheme 4.2



Scheme 4.3

To establish the entire structure elements, we planned to convert the enol ester **412** into the ester **410** by using one of three ring-opening approaches (Scheme 4.3): a) the direct ozonolysis of enol ester **412** (e.g.in MeOH/DCM then Ph_3P), b) Baeyer-Villiger oxidation of enone **411** (urea-hydrogen peroxide, trifluoroacetic anhydride, sodium hydrogen phophate in DCM), or c) the epoxidation of the enol ester **412** followed by rearrangement and oxidative cleavage (MCPBA, acetic acid and sodium iodate).[64] With Tsuji's oxidative rearrangement (methyl lithium, TMSCl, phenylselenenyl chloride, H_2O_2), the enone **411** could directly be prepared from the enol ester **412**, which would be derived easily from the ketone **413**.

To access the pyrrole **413**, we believed that our previous studies (see Section 1.3.3 and 2.1.5) had established a promising route. We attempted to synthesize our key precursor, α,β–acetylenic aldehyde **414**, from **415**, **416**, or **417** as starting materials (Scheme 4.4), which then could be condensed with *N*-tosyl protected amino esters **154** (Chapter 2).

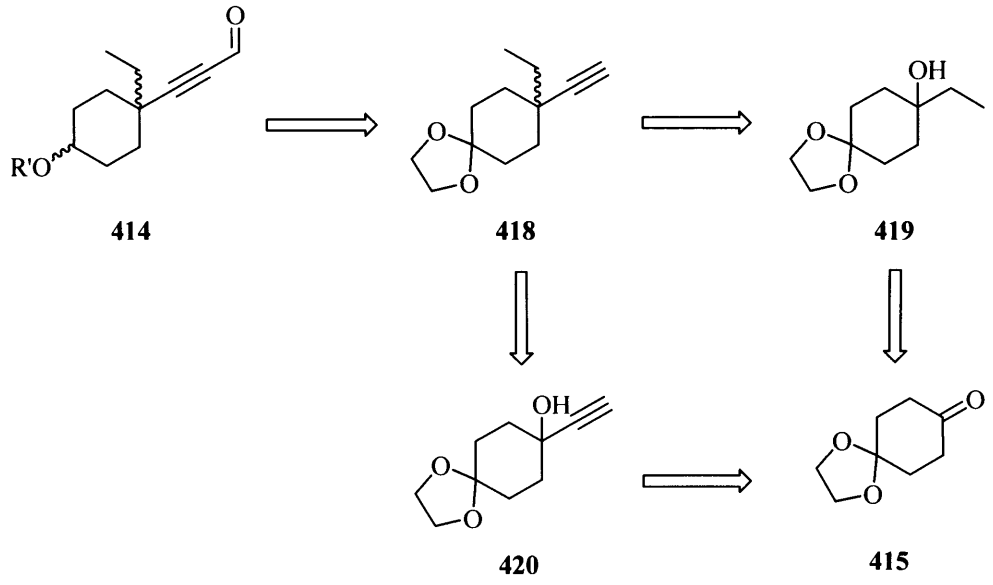


Scheme 4.4

4.2 Synthesis

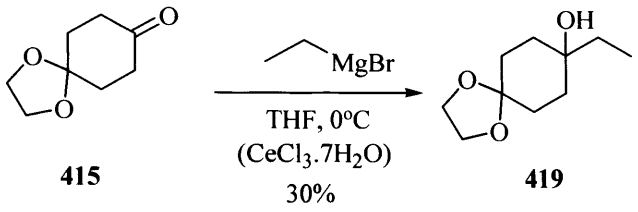
4.2.1 Route A

This seemed to be a direct approach to the aldehyde **414**, using formylation of an acetylide (from **418**) with DMF (Section 2.1.3). To access a quantity amount of the acetylene **418**, we believed that a Grignard reaction would achieve a good result.



Scheme 4.5

Starting from commercially available ketone **415**, we attempted to obtain a tertiary alcohol **419** by using ethylmagnesium bromide. The ketone was treated with ethylmagnesium bromide at 0°C, then at room temperature for 16 hours to give the alcohol **419** in moderate yield (10-30%). The ^{1}H NMR spectrum of the alcohol **419** showed the characteristic resonance for the protons of ethyl group at 0.89 ppm as a triplet (CH_3, J = 7.5 Hz) and 1.48 ppm as a quartet (CH_2, J = 7.5 Hz). This also confirmed by ^{13}C NMR (8-C, quaternary carbon, at 65.0 ppm), and IR at 3456 cm^{-1}.



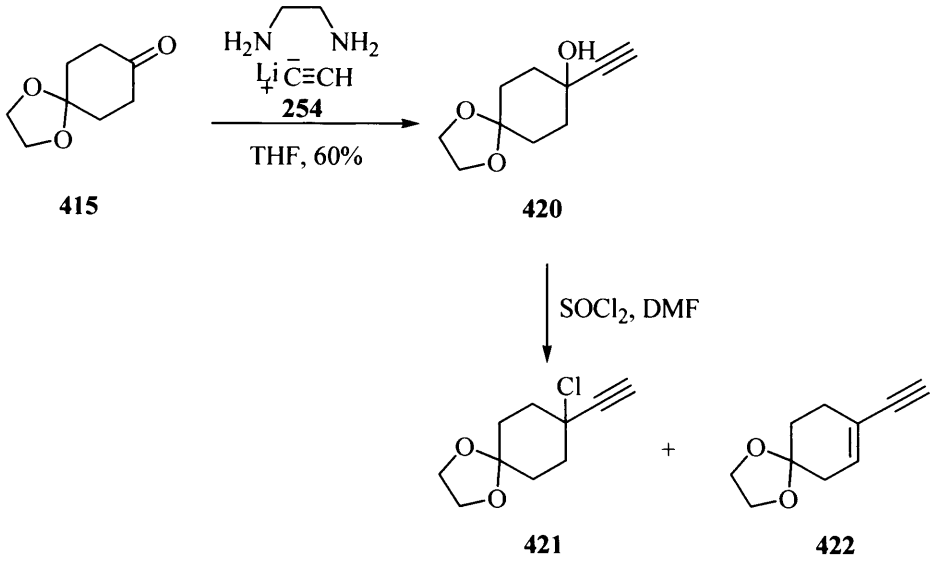
Scheme 4.6

However, we faced the difficulty of purifying the alcohol **419**. It is well recognized that the Grignard reaction is often accompanied by side reactions such as enolization and condensation. In 1989, Imamoto and co-workers[65] found that anhydrous cerium chloride significantly promoted additions of Grignard reagents to carbonyl compounds with remarkable suppression of side reactions.

Imamoto and co-workers also prepared the similar alcohol and achieved a 30% yield along with 30% of by-product, using the cyclohexanone as a starting material. Herein, we were interested in enhancing the yields of the alcohol by using this method. Firstly, cerium chloride was finely ground to powder, and then heated gradually to 140°C with evacuation for an hour and an additional hour with a magnetic stirrer bar. After cooling the flask with nitrogen and an ice bath, tetrahydrofuran was added, and the suspension was vigorously stirred for 16 hours. This was ready to use in the Grignard reaction to give the alcohol **419** in reproducible yield of 30%, but then problem of purification of the product remained (Scheme 4.6).

Although the reaction had been heated to reflux, it was still difficult to achieve a better yield of tertary alcohol **419**. It was, therefore, desired to try an alternative approach to the acetylene **418**. The alcohol **420** was prepared in 60% yield by using a modified procedure,[66] treating the ketone **415** with lithium acetylide/ethylenediamine complex in THF (Scheme 4.7). To introduce into this compound an ethyl group, the hydroxy group of **420** was converted into the chloride **421**, using thionyl chloride in DMF, in 34% yield (Scheme 4.7).[67] This chloride **421**

was confirmed by 8-C, quaternary carbon in ^{13}C NMR, which shifted to high field from 66.3 ppm (COH) to 55.7 ppm (CCl).

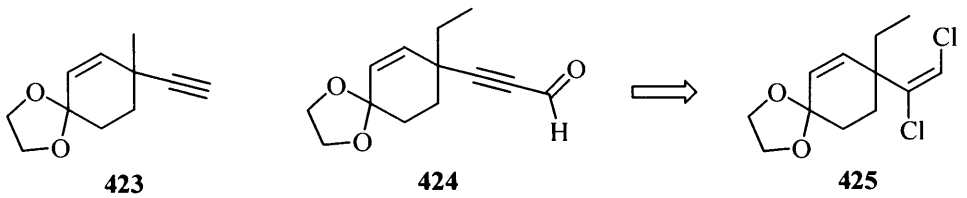


415 420 421 422

Scheme 4.7

These was also obtained an undesired compound **422** in 40% yield which showed, in the ^{1}H NMR spectrum, a proton of the double bond at 6.31-6.33 ppm as a multiplet and 8-C in ^{13}C NMR at 132.7 ppm. By following the tlc during the reaction, it was suggested that dehydration mainly occurred during the reaction along with chlorination. Unfortunately, we found that the chloride **421** failed to react with the Grignard reagent, ethylmagnesium bromide.[68] So, this route was stopped at this stage to investigate a better approach to the acetylene **418**.

4.2.2 Route B



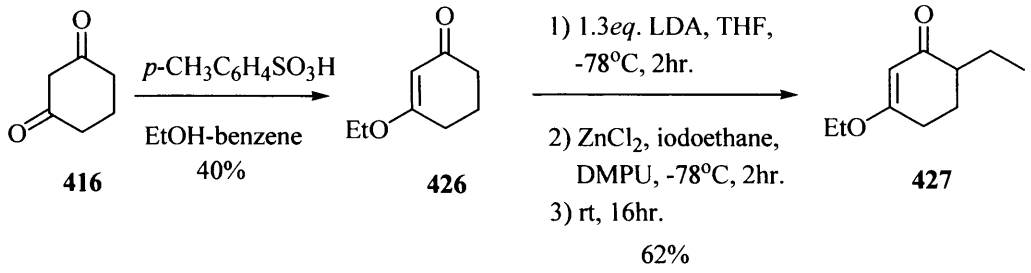
423 424 425

Scheme 4.8

In 1990, Kende and Fludzinki[69a,b] demonstrated the conversion of cyclohexane-1,3-dione **416** into 8-methynyl-8-methyl-1,4-dioxa-spiro[4.5]dec-6-ene **423** in good yield. This would be a

rather straightforward approaching to the alkynal **424** (Scheme 4.8), after elimination of the dichloride of dichlorovinyl compound **425**, using *n*-butyllithium, and then direct formylation.

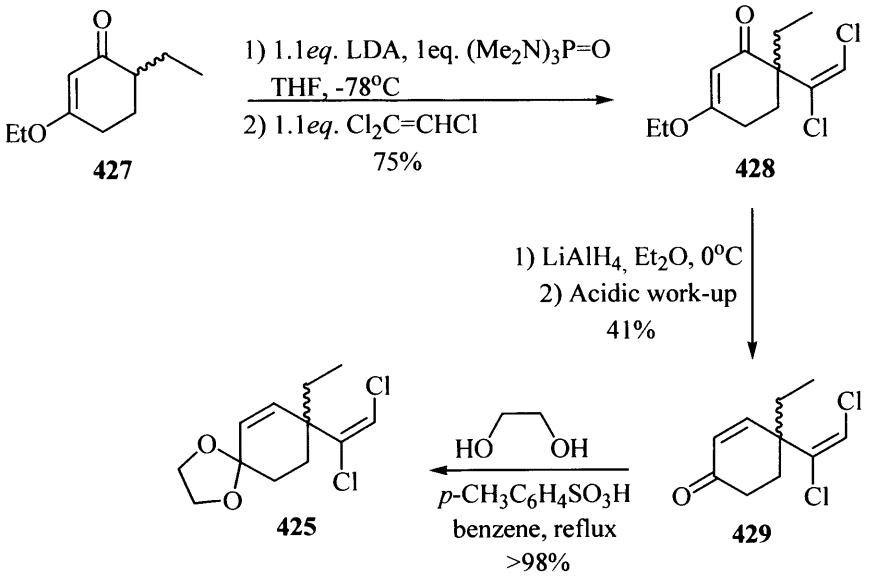
Cyclohexenone **426** can be formed in a yield of about 40% by heating a solution of cyclohexane-1,3-dione **416**, ethanol, and *p*-toluenesulfonic acid in benzene (Scheme 4.9).[69c] Ethylation between the lithium enolate derived from **426** and iodoethane gave 6-ethyl cyclohexenone **427** in 62% yield, which was obtained only when zinc chloride and DMPU[70] were used as a mild Lewis acid and a co-solvent, respectively.



416 **426** **427**

Scheme 4.9

By using HPMA in the alkylation of the cyclohexenone **427**, the 6-dichlorovinyl-6-ethyl cyclohexenone **428**, was obtained in 75% yield, having the quaternary carbon on C-6 (at 54.8 ppm in ^{13}C NMR).



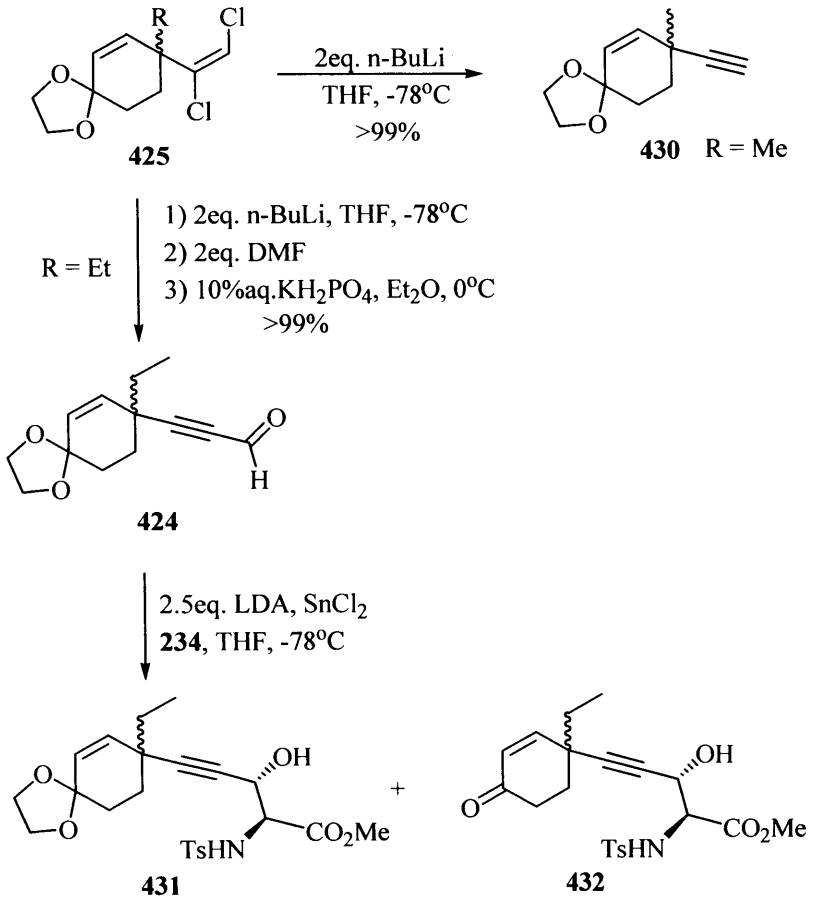
427 **428** **425** **429**

Scheme 4.10

The sequential action of lithium aluminium hydride followed by an acidic work-up, on compound **428**, gave the ketone **429** (41% yield); subsequent treatment with ethylene glycol then gave the protected ketone **425** in excellent yield (Scheme 4.10).[69a]

Compound **425** was confirmed by ^{1}H NMR (CHs of the double bonds showed CH=CH at 5.55 and 6.18 ppm as doublets with J = 10.4 Hz and CHCl at 6.30 ppm as a singlet), ^{13}C NMR (8-C, quaternary carbon showed at 34.8 ppm and CHs of the double bonds showed CH=CH at 125.7, 135.9 ppm and ClC=CHCl at 125.7, 143.1 ppm), IR, low resolution MS (263 $[M+H]^+$), and high-resolution MS (263.0607 $[M+H]^+$).

To prepare a 1-alkyne (e.g. **430**) from the corresponding 1,2-dichloro-alkene, Kende and Fludzinki[69b] used two equivalents of *n*-butyllithium. Similarly, exposure of 8-dichlorovinyl compound **425** to two equivalents of *n*-butyllithium, followed by two equivalents of *N,N*-dimethylformamide accomplished a one-pot formylation and led to the facile formation of our key precursor **424** (Scheme 4.11).

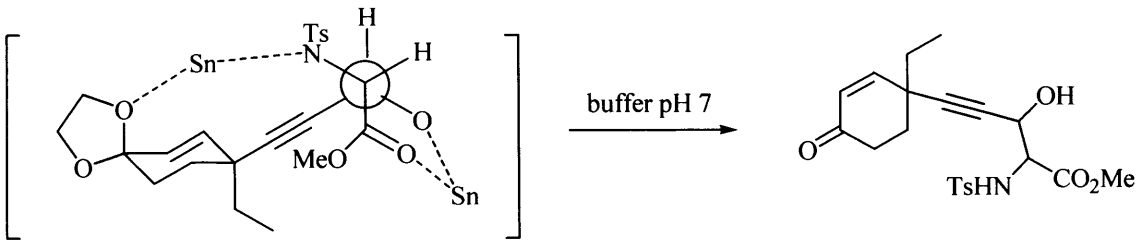


Scheme 4.11

This aldehyde **424** was confirmed using IR (1666 cm^{-1}), mass spectrometric (221 $[M+H]^+$), ^1H NMR (CHO at 7.79 ppm as a singlet), ^{13}C NMR (a triple bond at 71.5, 82.8 ppm and the carbonyl group at 176.9 ppm) data and high-resolution MS (221.1173 $[M+H]^+$).

Treatment of the *N*-tosyl protection amino ester **234** and tin(II) chloride with lithium diisopropylamide resulted in the formation of the tin enolate **121** which was subsequently employed in an aldol condensation with the propynal **424** (Section 2.1). This provided a 2:3 mixture of adducts **431** and **432** in 24% yield. After purification by chromatography, β-hydroxy-α-amino ester **431** was identified by ^{13}C NMR (β- and α-carbon at 60.8 and 63.4 ppm), IR (broad at 3464 cm^{-1}, strong at 2232, 1745, 1668 cm^{-1}), low resolution MS (464 $[M+H]^+$), and high-resolution MS (481.2005 $[M+NH_4]^+$). We observed an *anti:syn* ratio of diastereoisomers that was approximately 76:24 according to the ^1H NMR spectrum.

The ^{13}C NMR spectrum of β-hydroxy-α-amino ester **432** showed the characteristic resonance of α- and β-carbons at 60.7, 63.8 ppm and the carbonyl group (ketone) at 199.2 ppm, IR (broad at 3488 cm^{-1}, strong at 1744, 1662 cm^{-1}), low resolution MS (420 $[M+H]^+$), and High-resolution MS (420.1478 $[M+H]^+$). From ^1H NMR spectrum, an *anti:syn* ratio of diastereoisomers was approximately 83:17.

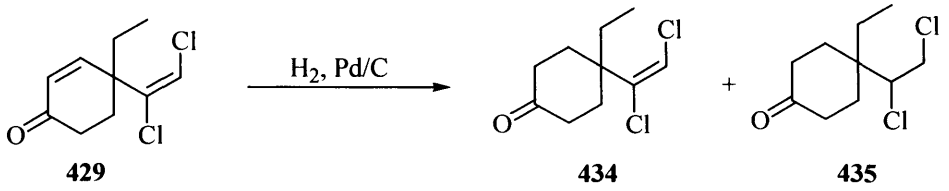


433 **432**

Scheme 4.12

The ketone **432** had presumably arisen from the intermediate **433**, a process that was likely induced by one of the ketal oxygen atoms trapping the proton from the buffer solution and then being ready cleavage by water (Scheme 4.12). Although this route provided a reasonable yield of the propynal **424**, the aldol condensation obtained the desired adduct **431** in low yield (10%), mixed with the ketone **432** as a major adduct (14% yield). It was thus shown that the propynal **424** was not compatible with this aldol condensation.

It was suggested that hydrogenation of the 4-dichlorovinyl cyclohex-2-enone **429** to the 4-dichlorovinyl cyclohexanone **434** might provide a solution in this aldol reaction. The action of palladium (Pd/C) in methanol on the cyclohex-2-enone **429** gavethe desired cyclohexanone **434**, and also further reduction of the vinyl group to give cyclohexanone **435**. This mixture was difficult to separate; therefore, this route was stopped to focus on the last precursor **417** (Scheme 4.13).

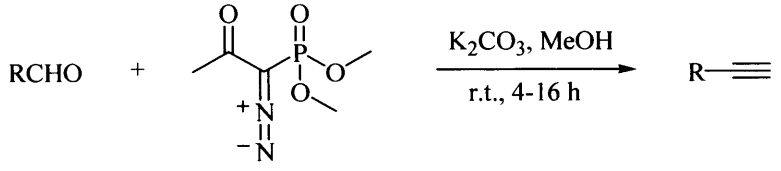


429 **434** **435**

Scheme 4.13

4.2.3 Route C

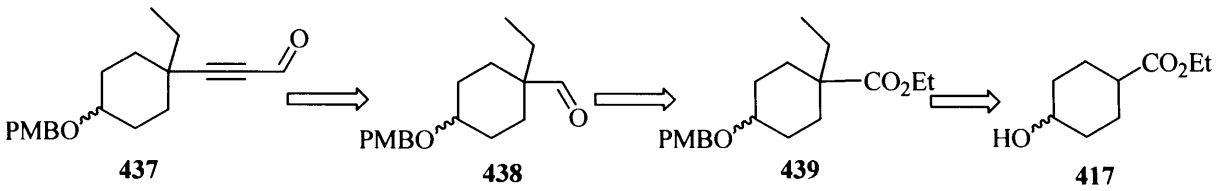
In 1996, Bestmann and co-workers[71] reported the transformation of aldehydes into terminal alkynes using the reagent dimethyl 1-diazo-2-oxopropylphosphonate **436** (Scheme 4.14). The key reagent **436** can be obtained in good yield from commercially available dimethyl-2-oxopropylphosphnate in a single step by diazo transfer with TsN_3.[72]



436

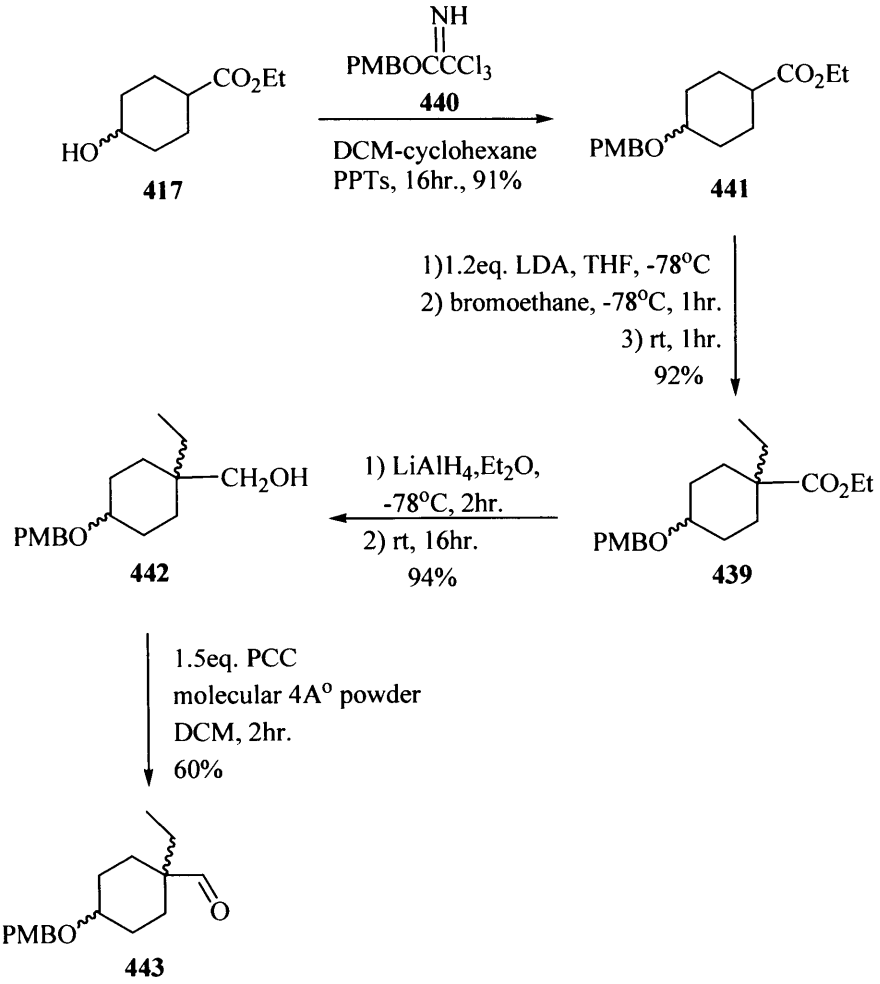
Scheme 4.14

If this could be applied to the aldehyde **438**, direct formylation would then furnish the propynal **437** as a potential precursor. In the synthetic direction, an oxidation of the alcohol derived from the ester **439** could afford the aldehyde **438**, while the ester **439** could arise through alkylation of *p*-methoxybenzyl (PMB) ether, which can be produced by protecting the commercial available alcohol **417**, with bromoethane (Scheme 4.15). The application of this basic plan is described below.



Scheme 4.15

Ethyl 4-hydroxy-cyclohexanecarboxylate **417** was treated with PMB trichloroacetimidate **440** and a small amount of PPTS to give a PMB ether **441** in 91% yield.[73] Exposure of the ether **441** to 1.2 equivalents of LDA and bromoethane resulted in the formation of the desired ester **439**, having a C-1 quaternary carbon (at 47.3 ppm in ^{13}C NMR spectrum), in 92% yield (Scheme 4.16). The action of lithium aluminium hydride in diethyl ether at –78°C induced smooth reduction of the ethyl ester **439** and gave the alcohol **442** in an excellent yield of 94%.



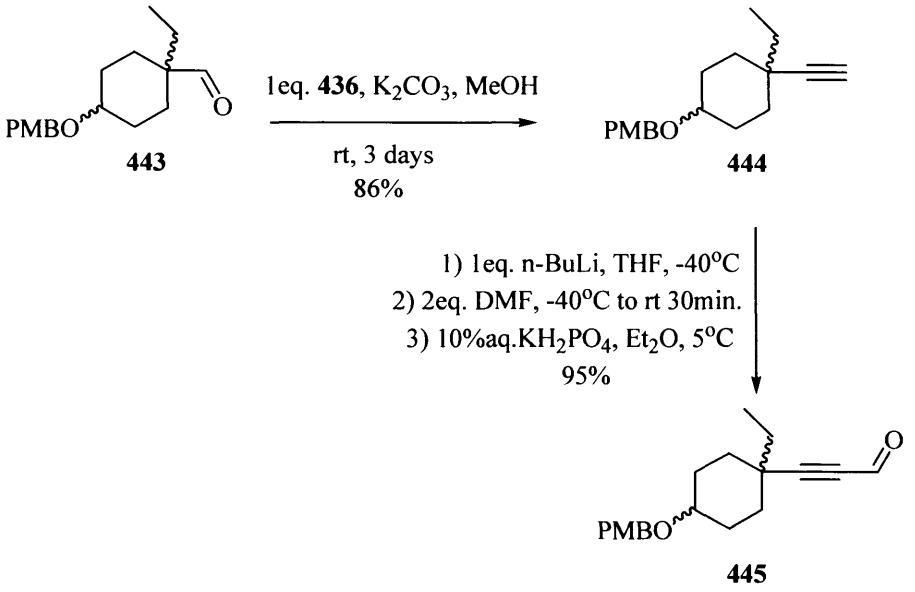
Scheme 4.16

The ^1H NMR spectrum of the alcohol **442** showed the characteristic resonance for CH_2 protons next to the hydroxy group at 3.45 ppm as a singlet. The structure **442** was also

confirmed by ^{13}C NMR (quaternary carbon at 36.6 ppm), IR (broad at 3414 cm^{-1}), low resolution MS (279 $[M+H]^+$) and high-resolution MS (296.2228 $[M+NH_4]^+$).

Oxidation of the primary alcohol in **442** with PCC gave the aldehyde **443** in 60% yield and the carbonyl group was indicated at 212.3 ppm in the ^{13}C NMR spectrum. When the aldehyde **443** was stirred in the presence of the reagent **436** and potassium carbonate for 3 days, acetylene **444** was formed in 86% yield (Scheme 4.17).

The acetylene **444** was indicated by ^1H NMR (a proton of the terminal alkyne at 2.08 ppm as a singlet, ^{13}C NMR (carbons of the triple bond at 69.3 and 88.7 ppm), IR (at 2105 cm^{-1}), and low resolution MS (273 $[M+H]^+$). The completion of the synthesis of the aldehyde **445** only required the direct formylation, which was achieved in an excellent yield of 95%. This was confirmed by ^{13}C NMR (the carbonyl group at 177.2 ppm), IR (1665 cm^{-1}), low resolution MS (301 $[M+H]^+$) and high-resolution MS (318.2065 $[M+NH_4]^+$).

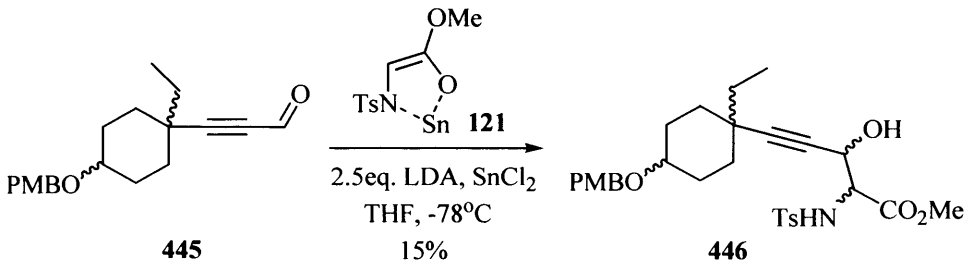


Scheme 4.17

We are now in a position to address the crucial aldol condensation of the aldehyde **445** with a tin enolate **121**. After repeating this condensation several times, it was found that the optimum yield of aldol adducts **446** was 15% as a 75:25 ratio of *anti:syn* diastereoisomer (Scheme 4.18). Only small amount of this compound was obtained, and it was used for full characterization only.

The β-hydroxy-α-amino ester **446** indicated by ^1H NMR (the α-proton to the ester group at 4.06 ppm as a double doublet [J = 9.3 and 3.6Hz, also coupling with a proton of amino

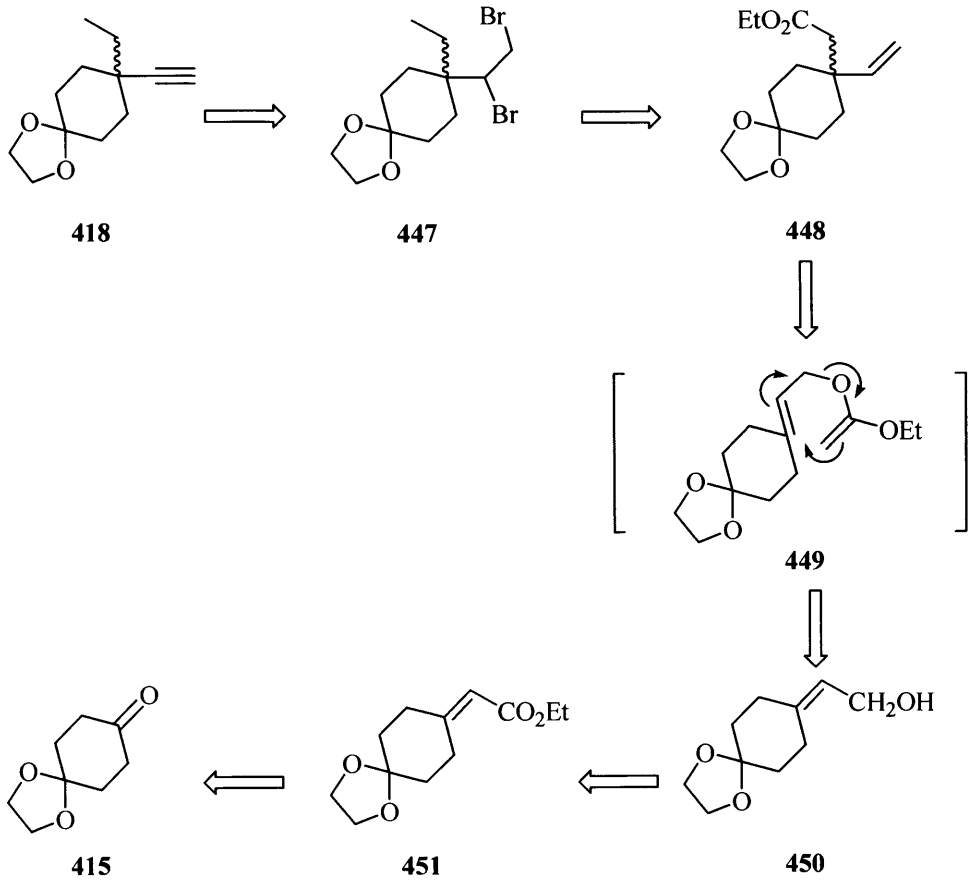
group]), and the β-proton at 4.61 ppm as double doublets [J = 10.5 and 3.6 Hz, also coupling with a proton of hydroxy group]), ^{13}C NMR (β- and α-carbon at 52.8 and 58.1 ppm), IR (broad at 3286^{-1}, strong at 1514, 1248, 1164 cm^{-1}), low resolution MS (544 $[M+H]^+$) and high-resolution MS (544.2371 $[M+H]^+$).



445 446

Scheme 4.18

4.2.4 Route D (alternative to route A)



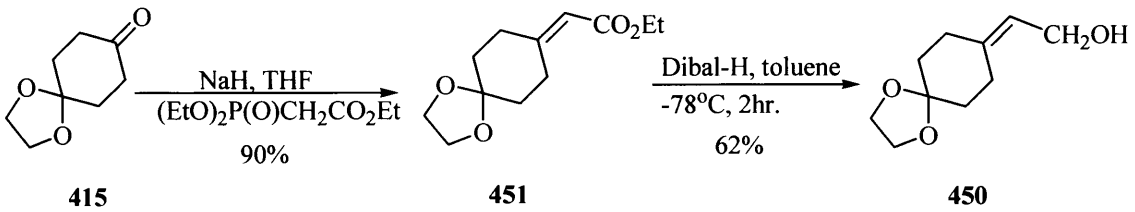
418 447 448 449 450 451 415

Scheme 4.19

We investigated this approach along with route B and C due to the apparent easy access of this route, which might provide a good result. It was anticipated that acetylene **418** derived from the dibromo compound **447** would be ready to perform the direct formylation. After elimination of the ester **448**, a double bond would then undergo bromination to give the dibromo compound **447**. Claisen rearrangement of the mixed-ketene acetal **449** was expected to play a key role in the synthesis of the ester **448**. A Wittig or a related reaction of commercially available ketone **415** could be relied upon to establish the unsaturated ester **451**. Through reduction of the ester **451**, alcohol **450** could be derived (Scheme 4.19).

It has been considered that the advantages of the microwave in organic synthesis are to accelerate organic reactions and reduce the reaction times substantially.[74] In conventional condition of Claisen rearrangement, a reaction mixture in a sealed tube would be heated up to 180°C for 48 hours, while using the microwave oven could provide a much more simple and convenient procedure. Srikrishna and Nagaraju[75] reported the use of a commercial microwave oven for this ortho-ester Claisen rearrangement. However, in our facility, we used a microwave designed for laboratory use, and it was therefore necessary to investigate various conditions to achieve a suitable outcome.

The ketone **415** was converted into the intermediate ester **451** by a Wadsworth-Emmons reaction. Reduction of the ester **451** using lithium aluminium hydride afforded the alcohol **450** in low yield, but the action of Dibal-H in toluene at –78°C induced a better yield of the alcohol **450** (62%; Scheme 4.20).[76]

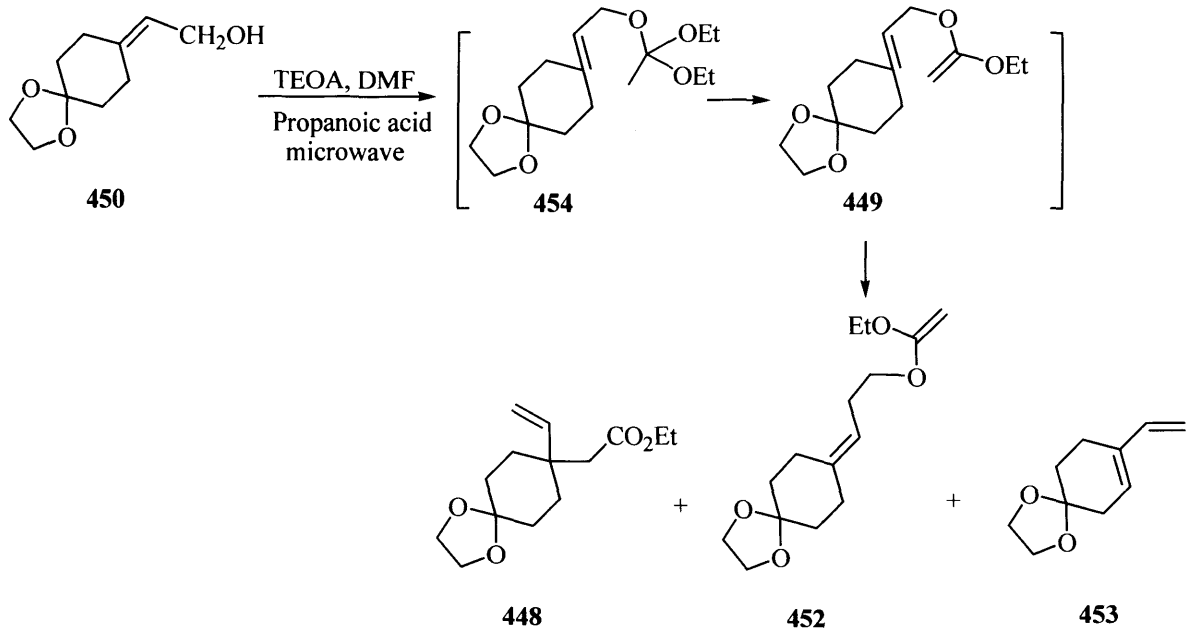


415 **451** **450**

Scheme 4.20

When a solution of unsaturated alcohol **450** and triethyl orthoacetate in DMF[75] was placed in a sealed tube under microwave conditions (optimized conditions: power 30 W, 100°C, pressure 250 psi, 15 min.), the ortho ester Claisen rearrangement proceeded to give an intermediate **452** (20% yield) and a dehydration product **453** (18% yield) mixed with the desired ester **448** (51% yield, Scheme 4.21). The optimization of the microwave conditions, to achieve either only or mainly the ester **448**, are shown in Table 4.1.

According to Srikrishna and S. Nagaraju's report,[75] their procedure could accelerate the three-step ortho ester Claisen rearrangement (from **450** to **448**), but, under our reaction conditions, elimination of water to give **453** and uncompleted rearrangement of the intermediate **452** was observed in high ratio at 90°C and 120°C (entry 1 and 6, Table 1).



Scheme 4.21

Table 4.1: The optimization of the microwave condition for the ortho ester Claisen rearrangement.

Entry	temperature(°C)	time(min.)	**448**	**452**	**453**
1	120	10	1	1.2	2
2	100	10	2.5	1.25	1
3	100	15	3.5	1	1
4	100	20	3	1	2
5	100	30	4	1	3
6	90	15	1	2	3
7*	100	15	1.4	2.8	1
8*	100	20	2	14	1

Note: the reaction was on 100mg scale. * for entry 7-8 on a gram scale.

In addition, the diene **453** was produced in all the tested conditions. We could only minimize this by-product **453** by reducing the reaction times from 30 min to 15 min (entry 3, 4 and 5, Table 1). The results of varying times showed that the rearrangement required more than 10 min to give a satisfying portion of the desired products, a mixture of **448**:**452**:**453** at 3.5:1:1 (entry 2 and 3, Table 1). We attempted to scale-up this reaction from 0.1-gram to one-gram scale, and the expected product mixtures had changed. In fact, the reaction also varied on the scale of the reaction. This brought an obstacle to access to the dibromo compound **447**. We therefore stopped this route at this stage.

4.3 Conclusion

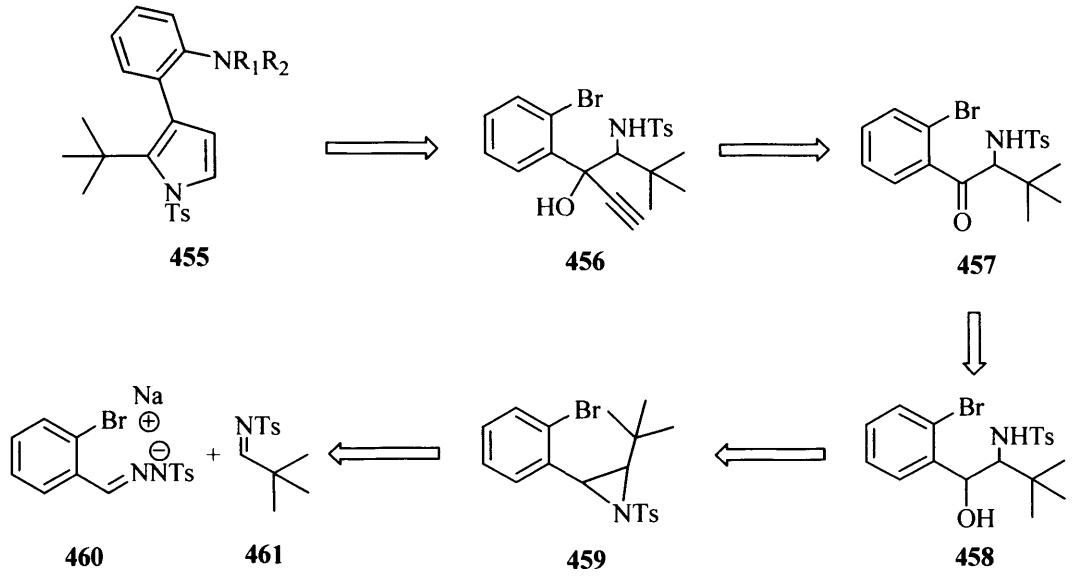
We had adopted, what we thought, were convenient routes to the acetylene aldehyde **414** and related structures. However, through the our course of our syntheses, route A and B proved unproductive strategies *via* Grignard reagent or Claisen rearrangement, but route B and C proved high-yielding approaches to our desired precursor, the aldehyde **414**. Unfortunately, neither of the derived ynals **424** nor **445** performed well in the aldol reaction. It may be due to the complexity of both compounds. Nevertheless, route C provided the most appealing strategy according to the ease of each reaction and low-toxic reagents used. At this time of despair, a new methodology of metal-mediated cyclization was developed in Sector 2.5 and this appeared to offer an alternative approach to our target molecule. The project still intended to achieve at least the key pyrrole **280**.

Chapter 5

The second synthetic approach to Rhazinilam

5.1 Application of Silver-Mediated Cyclization

We reasoned that a silver-mediated cyclization would be ideal for the alternative preparation of *(-)-Rhazinilam* **283** (Section 2.5). To test the generality of this methodology in preparing a simple precursor **456**, we designed a pyrrole **455** with a bulky substituent, a *tert*-butyl group, in the 2-position and a *o*-nitrophenyl or other nitrogen group in the 3-position. Alternatively, to avoid N-protection, a bromine could be incorporated to allow late introduction of the nitrogen by a Buchwald-Harwig method.



Scheme 5.1

To obtain the pyrrole **455**, silver-mediated cyclization would have to be applied to the γ-alkynyl-β-hydroxy tosylamide **456**. This could be generated by the addition of acetylene to the amino ketone **457**, which is derived from an oxidation of an amino alcohol **458**. The alcohol **458** can be prepared, it appeared, in a productive fashion by ring opening of an aziridine **459** using acid hydrolysis. Compound **459** could conceivably be formed in one step through coupling of intermediates **460** and **461** using Aggarwal's aziridination technology (Scheme 5.1).[77] In section 5.3, which follows, the reaction sequences culminating in the synthesis of the pyrrole **455** are presented.

5.2 Aziridination

These are two direct routes to aziridines that also lend themselves to asymmetric catalysis: the addition of nitrenoids to alkenes (route A) and the addition of carbenes/carbenoids to the imines (route B), as shown in Figure 5.1.

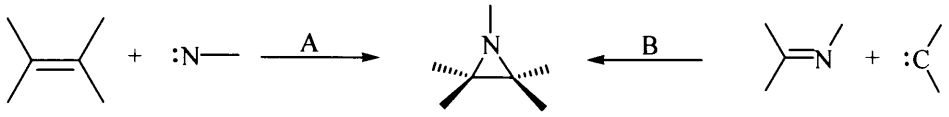
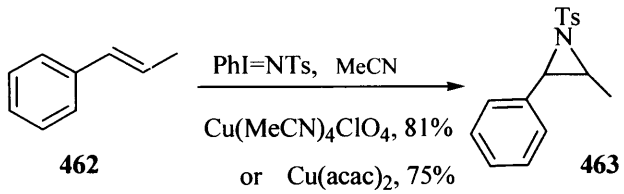


Figure 5.1

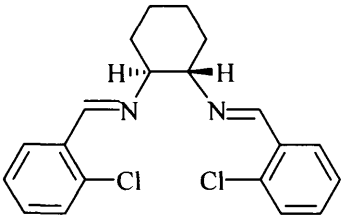
5.2.1 Alkene Aziridination

Nitrogen atom transfer reactions constitute an important area of research in bioinorganic and organic chemistry. The importance of alkene aziridination reactions in the construction of carbon-nitrogen bonds is well documented in the literature.[78] The Cu^{I} or Mn^{III} complexes discovered by Evans,[78a] Jacobsen,[78b] and Katsuki[78c] represent efficient catalysts for asymmetric aziridinations when [N-(p-toluenesulfonyl)imino]phenyliodinane, PhI=NTs, is used as a nitrogen source. Evans and co-workers reported that, under standard conditions (acetonitrile, 5-10% Cu-catalyst, 1 equiv of PhI=NTs, 5 equiv of olefin, 0.4 M, 25°C), the catalyzed aziridination reaction proceeded in good yields with both aromatic and aliphatic olefins. For example, with phenyl substituted olefins **462**, both Cu^{I} and Cu^{II} afforded high yields of aziridine **463** (Scheme 5.2).

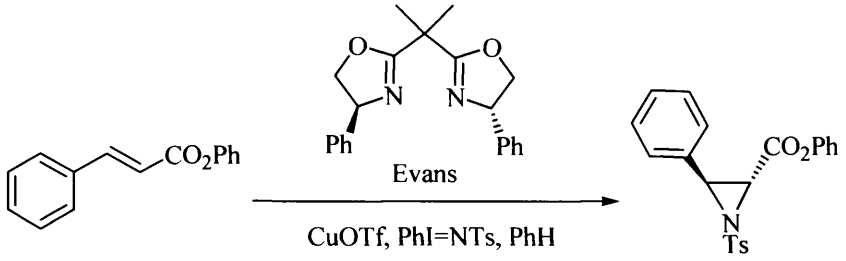


Scheme 5.2

Chiral ligands have since been developed to generate chiral copper catalysts and achieve high enantiopurity in the resulting aziridines (Scheme 5.3).[79]



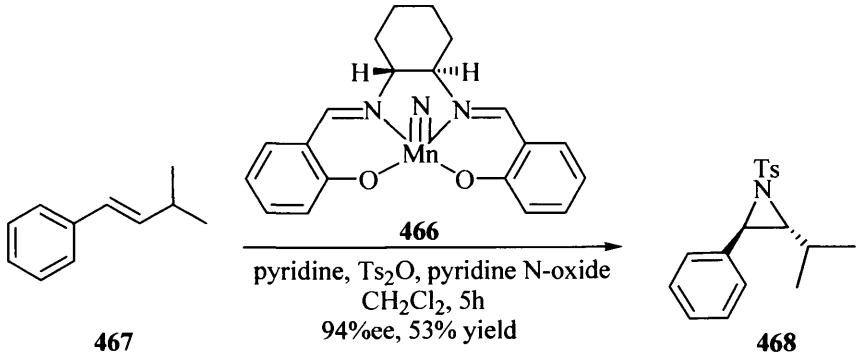
Jacobsen



464 465

Scheme 5.3

Komatsu[78d] reported the asymmetric aziridination of styrene derivatives by transfer of a nitrogen atom from a chiral nitridomangenese complex **466** (Scheme 5.4).

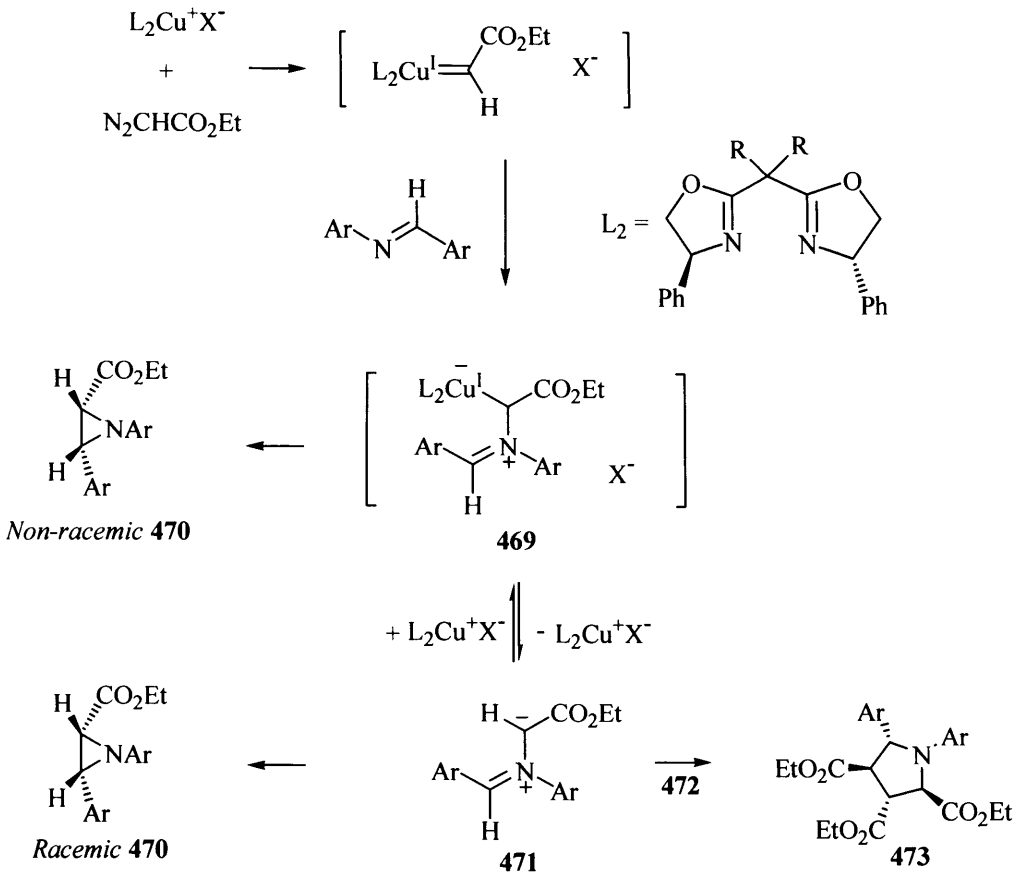


467 468

Scheme 5.4

5.2.2 Ylide Mediated Catalytic Aziridination

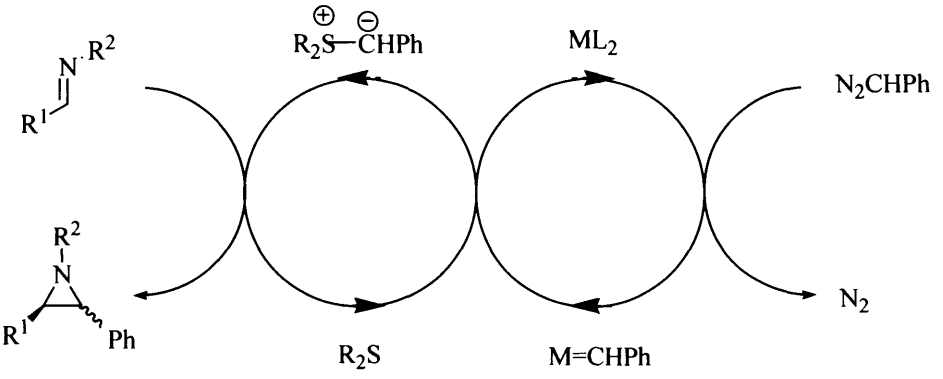
In a series of elegant experiments, Jacobsen and co-workers[80] showed that there are two pathways leading to the aziridine **470** (Scheme 5.5): one bearing the chiral metal species **469** which yielded the non-racemic aziridine and the second a planar azomethine ylide **471** which gave the racemic aziridine.



Scheme 5.5

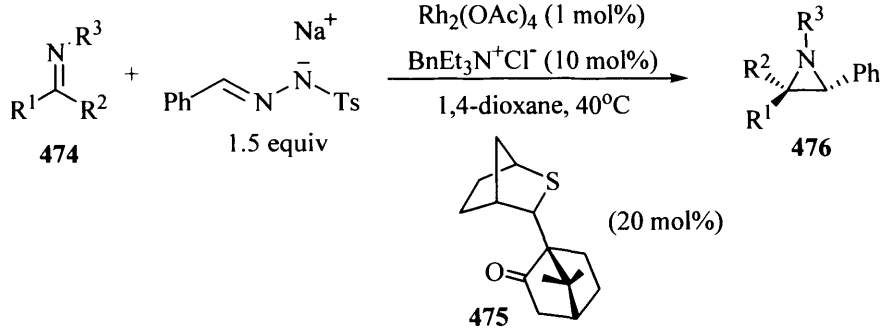
Jacobsen and co-workers[80] further proved this by trapping the azomethine ylide **471** with dipolarophile, $EtO_2CCH{=}CHCO_2Et$ **472**. Evidently, the problem with the addition of metal carbenes to imines is that the C-N bond is formed before the C-C bond, which leads to a planar azomethine ylide **471** if the metal is lost. If the C-C bond could be formed ahead of the C-N bond, then it would not be possible to form the achiral azomethine ylide **469**.

One approach, which allows C-C bond formation ahead of C-N formation is the reaction of a sulfur ylide with an imine. In 1996, Aggarwal and co-workers reported aziridination process mediated by sulfur ylides.[81a] Their proposed catalytic cycle for aziridination involves the slow addition of a diazo compound to solution of a suitable metal salt, sulfide, and imine. The reaction proceeds through the intermediacy of diazocompounds, metal carbenes and sulfur ylide as shown in Scheme 5.6. High yields of aziridines were achieved using 1% mol of $Rh_2(OAc)_4$ and one equiv of dimethyl sulfide; high enantioselectivity came from the use of enantiomerically pure sulfides.



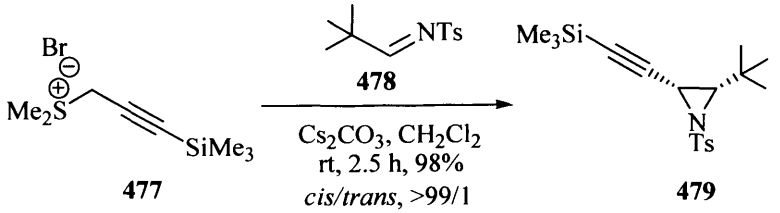
Scheme 5.6

In 2001,[81b] a highly effective catalytic asymmetric process for the aziridination of imines was developed, which can be applied to a broad range of electrophiles **474** and diazo precursors (Scheme 5.7). High enantioselectivity of the aziridines **476** is obtained by using a chiral sulfide **475**.



Scheme 5.7

In 1998, Dai and co-workers reported the ylide aziridination of *N*-sulfonylimines with sulfonium propargylide under mild reaction conditions.[82] The best base/solvent combination for this reaction was found to be Cs_2CO_3/CH_2Cl_2 allowing both high yield and high *cis* selectivity could be achieved (Scheme 5.8).

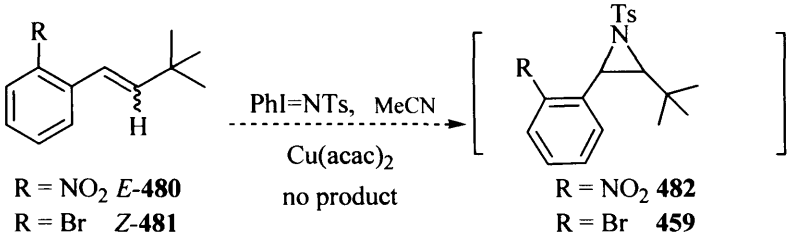


Scheme 5.8

5.3 Synthesis

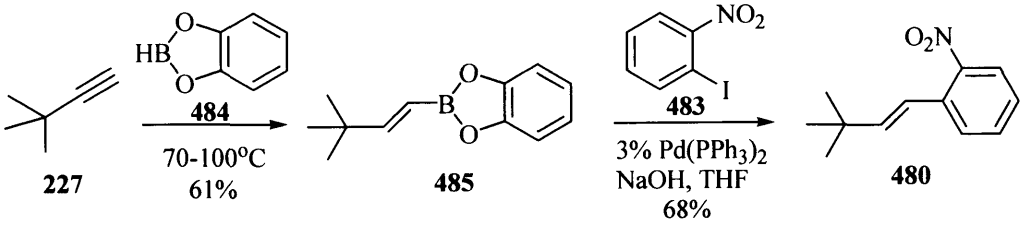
5.3.1 Approaching the aziridine 459

It was our intention to develop a convenient route to access the γ-alkynyl-β-hydroxy tosylamide **456** starting from an aziridine. Firstly, copper-catalyzed aziridination[72a] of olefins **480** and **481** using PhI=NTs was explored. According to Evans methodology, the olefins **475a** or **475b** was treated with PHI=NTs, and a catalytic amount of $Cu(acac)_2$ in acetonitrile at room temperature for 16 hours, but the desired aziridines **482** or **476** were not obtained (Scheme 5.9).This may be due to the highly hindered nature of the olefins.



Scheme 5.9

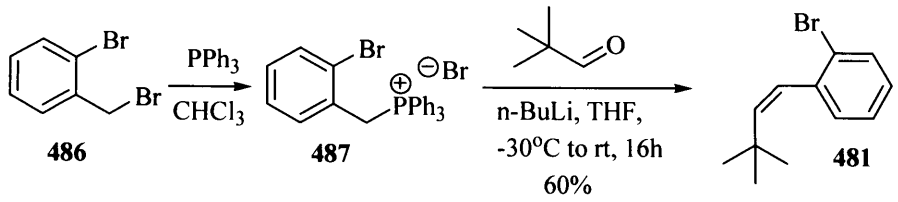
A Suzuki coupling reaction has been used to prepare the olefin **480**.[83] Treatment of iodonitrobenzene **483** with dioxaborole **485** (prepared by hydroboration of the 3,3-dimethyl-but-1-yne **227** with catecholborane **484**) in tetrahydrofuran with 3% $Pd(PPh_3)_4$ in the presence of NaOH under reflux generated the olefin **480** in 68% yield (Scheme 5.10). This olefin **480** confirmed by ^1H NMR (CHs of the double bonds showed resonances at 6.15 and 6.71 ppm as doublets with J = 16 Hz), ^{13}C NMR (CHs of the double bonds showed resonances at 121.8, and 139.6 ppm), IR, low resolution MS (206 $[M+H]^+$)and high-resolution MS (223.1447 $[M+NH_4]^+$).



Scheme 5.10

A Wittig reaction, however, was used to prepare the olefin **481**.[84] Pivaldehyde was simply treated with the phosphonium salt derived from 2-bromobenzyl bromide and

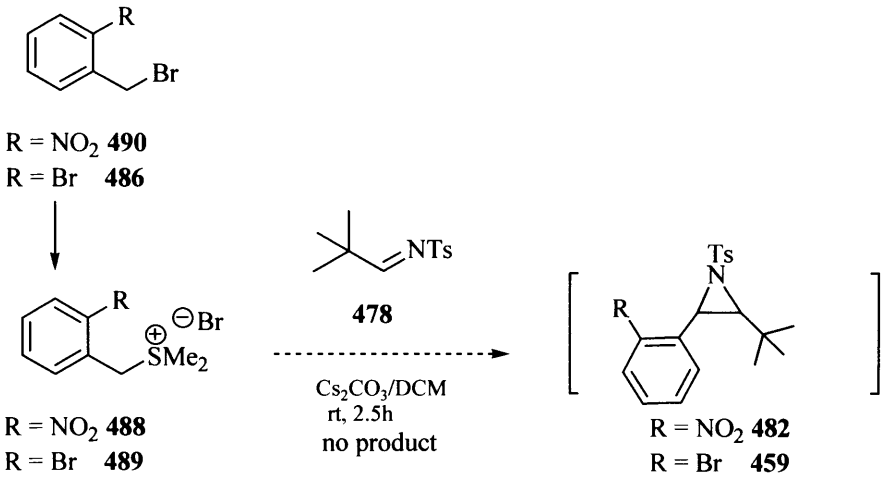
triphenylphosphine yielding desired olefin **481** in 60% yield (Scheme 5.11). In the ^{1}H NMR spectrum, the protons of the double bond appear as doublets at 5.58 and 6.13 ppm with J = 12.5 Hz.



486 **487** **481**

Scheme 5.11

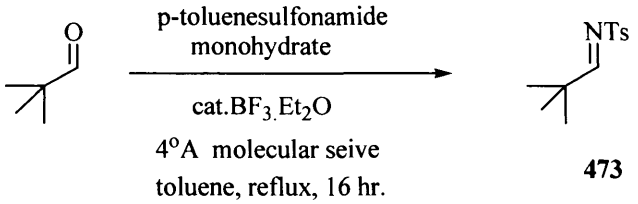
The aziridination through the reaction of an imine with an ylide has recently shown great promise in obtaining various functionalized aziridines (Scheme 5.7 and 5.8).[81,82] An aziridination of *N*-sulfonylimine **478** with sulfonium ylide **488** or **489** derived from benzyl bromide **490** and **486**, respectively, with dimethyl sulfide in water under reflux, has been explored by their reaction with Cs_2CO_3 in dichloromethane. Unfortunately, neither of the desired aziridines **459** nor **476** could be obtained (Scheme 5.12).



Scheme 5.12

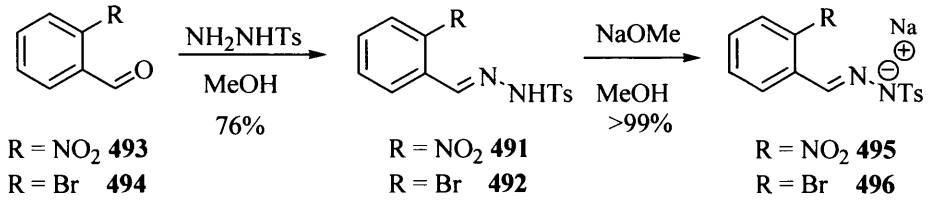
Finally, Aggarwal's aziridination technology[81b] was applied to the preparation of the aziridines **459** or **482**. In order to follow on this procedure, an imine **478** and diazo precursors **491** and **492** were required. Treatment of commercially available pivaldehyde with *p*-toluenesulfonamide monohydrate, 4Å molecular sieves and a catalytic amount of boron trifluoride etherate in toluene under reflux for 16 hours resulted in the formation of the imine **478** in 93% yield (Scheme 5.13).[85] The synthesis of the tosylhydrazone sodium salt

commences with the formation of tosylhydrazones **491** and **492**, followed by formation of the sodium salts **493** and **494**.



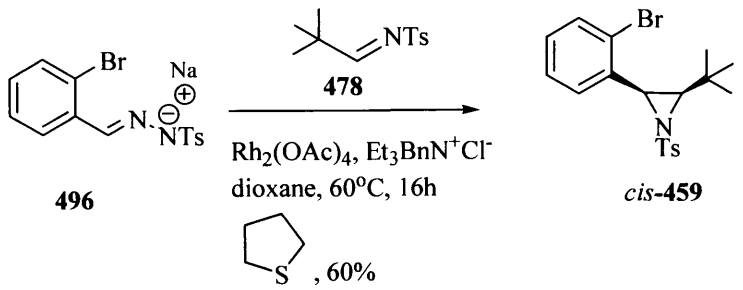
Scheme 5.13

Benzaldehydes **493** and **494** can be condensed in a straightforward manner by treatment with *p*-toluenesulfonylhydrazide in methanol. The tosylhydrazone **482** is then collected by Büchner filtration as a colourless solid in good yield (Scheme 5.14).[86] Exposure of dry tosylhydrazone **491** and **492** with a solution of 25% sodium methoxide in methanol results the formation of the intermediate **495** and **496**, respectively.



Scheme 5.14

Construction of the key intermediates **459** and **482** could now be examined. The aziridination of the tosylhydrazone sodium salt **496** with the imine **478** in the presence of a catalytic amount of rhodium acetate, $BnEt_3N^+Cl^-$ [as a phase transfer catalyst], and tetrahydrothiophene in dioxane at 60°C furnished the desired *cis*-aziridine **459** in a yield of 60% (Scheme 5.15). Unfortunately, exposure of the tosylhydrazone sodium salt **495** to the same condition gave no trace of the aziridine **482**.



Scheme 5.15

The ^{1}H NMR spectrum of the aziridine **459** showed characteristic resonances for the two protons of the aziridine ring at 2.84 and 3.81 ppm as doublets (J = 7.4 Hz, showing *cis*-conformation). This was also confirmed by ^{13}C NMR (these two carbons of the aziridine ring at 47.4 and 55.2 ppm), low resolution MS (408 $[M(^{79}Br)+H]^{+}$) and high-resolution MS (408.0631 $[M(^{79}Br)+H]^{+}$).

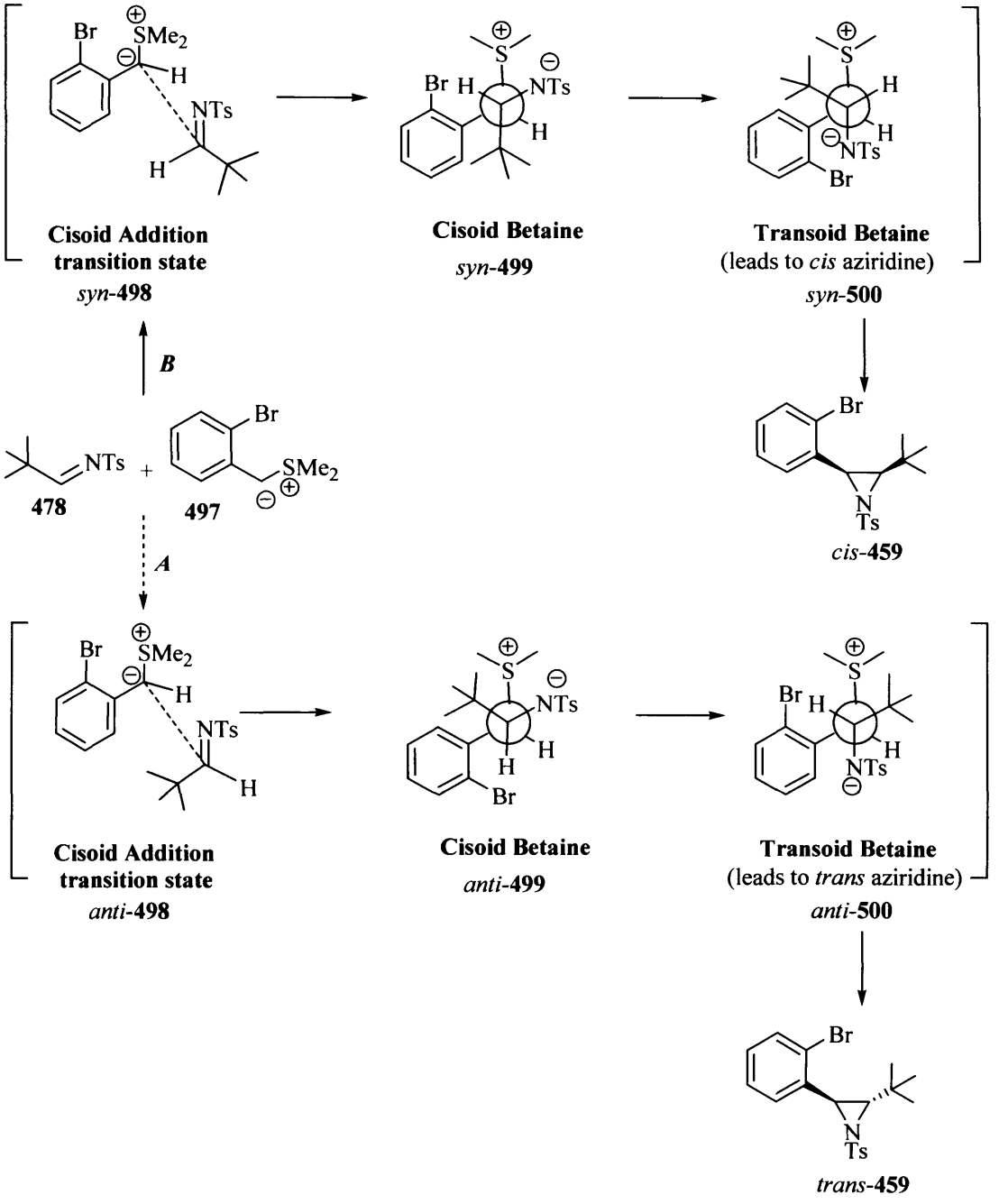


Figure 5.1: Approach of the ylide to the imine.

Aggarwal's studies on the mechanism of epoxide formation,[87] which we applied to aziridine formation (Figure 5.1), suggest that the overall reaction mechanism consists of two separate steps: initial rotation around the C-C single bond of the initially formed cisoid betaine *anti-*

499 to form its transoid rotamer *anti*-**500**; and ring-forming elimination *via* S_N2-like substitution from the latter (route A, Figure 5.1).

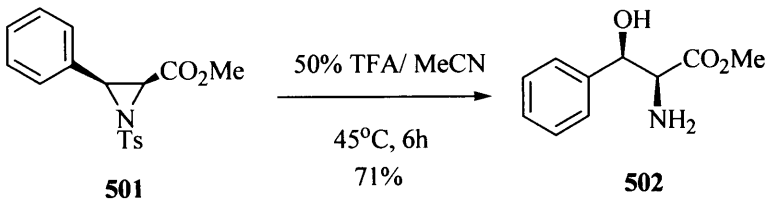
According to the ^1H NMR spectrum of the aziridine **459**, the observed *cis*-diastereoselectivity can be explained by comparing the two possible transition state having the two developing charges in an electronically favored gauche arrangement, as shown in routes A and B (Figure 5.1). That leading to the *trans*-**459** is less favoured, as it possesses three sterically demanding gauche interactions.

5.3.2 Ring Opening of the aziridine 459

The chemistry of aziridines continues to attract the attention of the synthetic community.[88] This interest is driven by the useful properties of aziridines centered on their ring-opening transformations. The reactivity of aziridines as carbon electrophiles makes them versatile nitrogen-containing building blocks for the synthesis of biologically important compounds.[89]

Figure 5.2. Activated and nonactivated aziridines

Aziridines can be divided into two classes depending on the nature of the *N*-substituent (Figure 5.2). Activated aziridines, such as *N*-tosyl and *N*-acyl aziridines, contain a strongly electronegative substituent that facilitates their ring-opening chemistry. Nonactivated aziridines, such as alkyl aziridines, do not have a substituent that is capable of stabilizing the anion resulting from the ring opening.

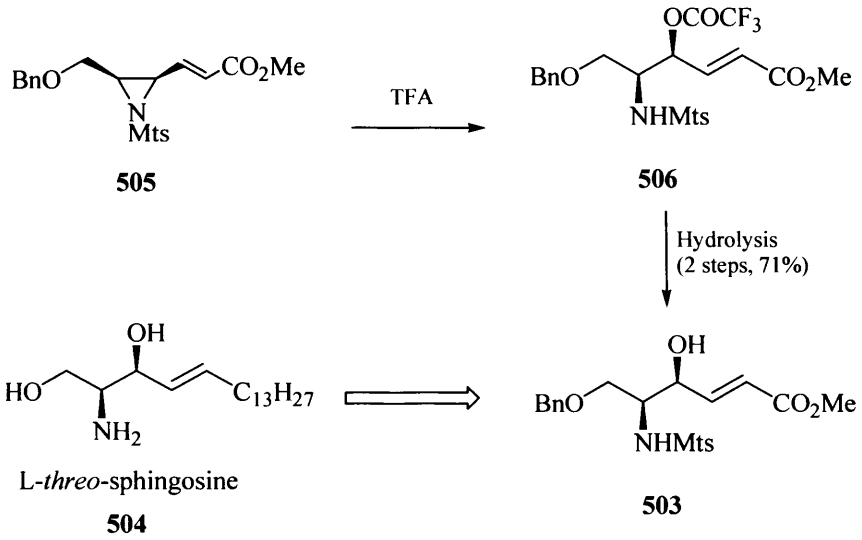


Scheme 5.16

In 1994, Davis and co-workers reported the regioselective ring opening of a 3-phenyl-2-carbomethoxyaziridine **501** by heating at 45°C for 6 hours in 50% aqueous TFA, and then

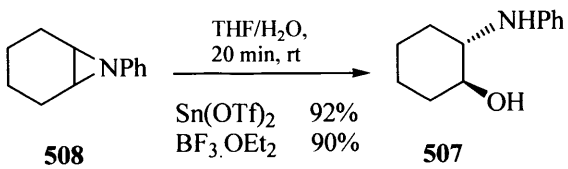
neutralizing with concentrated ammonium hydroxide to obtain *syn*-β-phenylserine derivative **502** as a 93:7 mixture of diastereoisomers (Scheme 5.16).[90a]

Also, in 1999, Tamamura and co-workers showed that the TFA-mediated ring-opening reaction was useful for the convenient synthesis of the diastereomerically pure δ–aminated γ–hydroxy α,β–enolates, such as **503**, as the key intermediates for several bioactive compounds, such as sphingosine **504** (Scheme 5.17).[90b]



Scheme 5.17

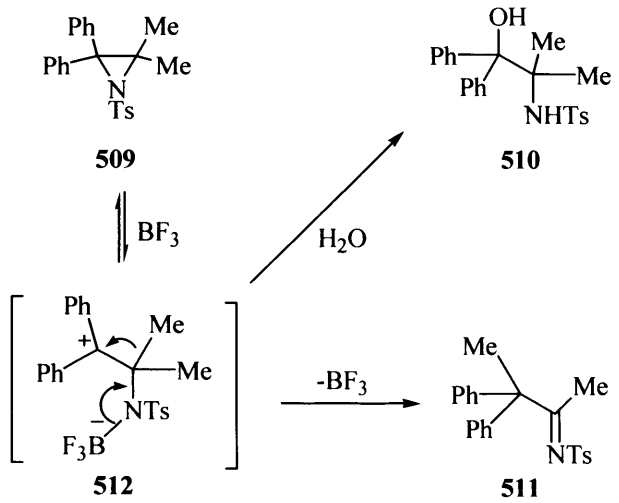
Later, in 2000, Singh and co-workers reported the Lewis acid-induced ring opening of *N*-substituted aziridines with water, primary, allylic, and propargylic alcohols. Since both $Sn(TfO)_2$ and $BF_3.OEt_2$ turned out to be highly effective for the aziridine opening, the reaction was extended to the use of water and the product **507** was obtained in high yield (90-92%, Scheme 5.18).[90c]



Scheme 5.18

In 2001, Nakayama and coworkers[90d] found that *N*-tosylaziridines undergo an acid-catalyzed aza-pinacol rearrangement under mild conditions to give the corresponding *N*-tosylimines.[90d] When the reaction of **509** with $BF_3.OEt_2$, carried out at –18°C, was quenched after 6 hours by addition of aqueous sodium hydrogen carbonate, the amino alcohol **498** was isolated in 39%

yield in addition to the *N*-tosylimine **511** in 55% yield (Scheme 5.19). Thus, this chemistry is not as simple as it might appear!



Scheme 5.19

In the mechanism of the rearrangement of aziridine **509**, the initial step would involve the formation of carbocation intermediate **512**, which yields amino alcohol **510** by hydrolysis. The carbocation **512** is stable enough to suppress fluoride migration; hence imine **511** is directly formed by methyl migration. Although an β-amino alcohol could potentially be derived in short order from the aziridine **459**, an intermediate **513** is rather different, particularly with a *tert*-butyl substituent, which is a very good migratory group.

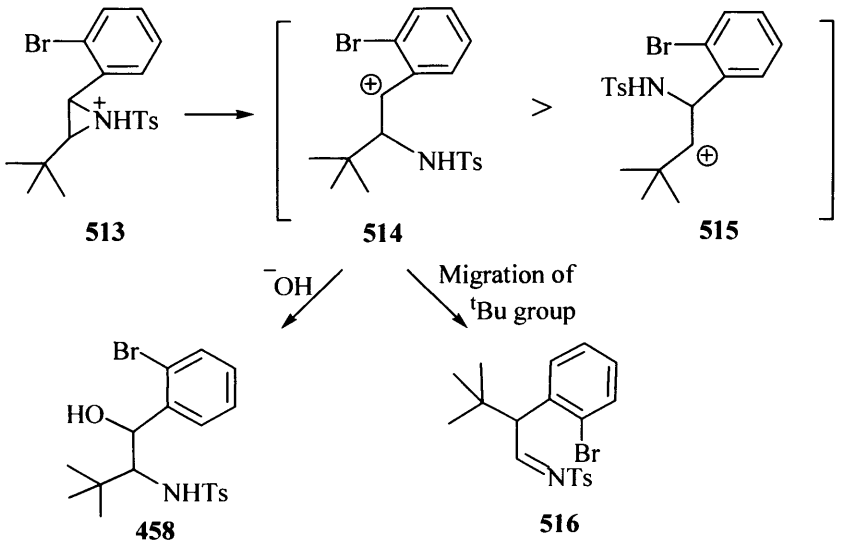
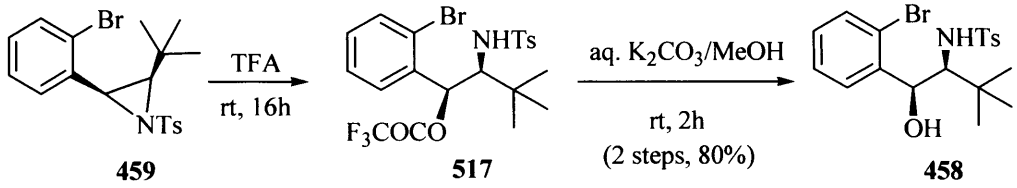


Figure 5.3. Regiochemistry.

A carbocation intermediate **514** should be highly favoured, due to the benzene ring stabilizing the cation, when compared with the alternative carbocation intermediate **515** (Figure 5.3). This could permit the formation of the β-amino alcohol **458**, when a nucleophilic attack takes place; however, a formation of an imine **516** would be expected, to some extent at least.

Subjection of the aziridine **459** to the action of trifluoroacetic acid resulted in the formation of trifluoroacetate **517**, which is afforded by a regiospecific ring-opening reaction (Scheme 5.20). The intermediate **517** is stable enough for chromatographic purification and characterization. The ^{1}H NMR spectrum of the trifluoroacetate **517** showed the resonance for the proton β to the ester group at 3.72 ppm as a double doublet (J = 10.4 and 1.0 Hz) and the proton α at 4.73 ppm as a doublet (J = 10.4 Hz). This was further confirmed by low resolution MS (525 $[M+H]^+$). Fortunately, no products arising from the alternative aza-pinacol process were observed.



459 **517** **458**

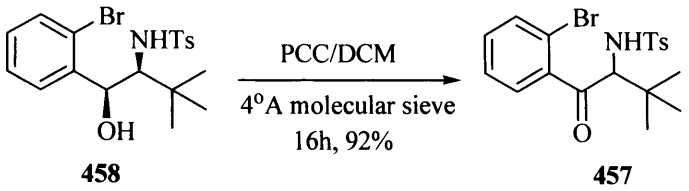
Scheme 5.20

The subsequent hydrolysis of trifluoroacetate **517** yielded the β-amino alcohol **458** in 80% yield based upon aziridine **459**. The ^{1}H NMR spectrum of **458** showed the resonance for the proton β to the hydroxy group at 4.18 ppm as a double doublet (J = 9.6 and 1.1 Hz) and the proton α at 5.04 ppm as a doublet (J = 9.6 Hz). Surprisingly, we observed one proton at 5.33 ppm as a sharp singlet, which must be due to the NH group. It was surprising to observe no coupling with the proton α in this case. However, the structure of **458** was also confirmed by ^{13}C NMR (the carbons α and β appearing at 64.9 and 71.2 ppm), IR (broad at 3504 cm^{-1}), low resolution MS (407 $[M(^{79}Br)-H_2O]^+$) and high-resolution MS (443.1004 $[M(^{79}Br)+NH_4]^+$).

5.3.3 Approaching the pyrrole 455

Oxidation of the hydroxy group in **458** with pyridinium chlorochromate in dichloromethane furnished the corresponding ketone **457** (Scheme 5.21). The ketone **457** was indicated by ^{1}H NMR (the α-proton to the carbonyl group at 4.33 ppm as a doublet [J = 10 Hz]), ^{13}C NMR

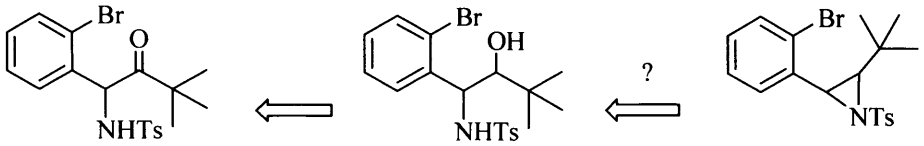
(the α-carbon at 70.0 ppm and the carbonyl carbon at 201.1 ppm), IR (medium at 1697 cm^{-1}), low resolution MS (424 $[M(^{79}Br)+H]^+$)and high-resolution MS (424.0576 $[M(^{79}Br)+H]^+$).



458 457

Scheme 5.21

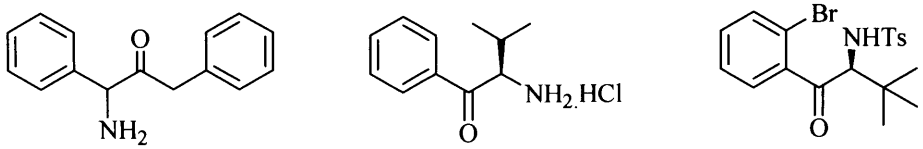
These data confirm the structure of ketone **457**, and, importantly, the success of the overall synthesis towards this ketone **457**. It was difficult to show whether the ring-opening reaction generated the desired β-amino alcohol **458** or its regioisomer **519**. The carbonyl group of the corresponding ketone shows a difference between the two isomers, confirming the structure as the ketone **457**.



518 519 459

Figure 5.4

According to similar ketones, reported by Kasai[91a] and Najera,[91b] these IR spectra provide promising results comparing to our data, which are similar to the ketone **521** as shown below.



520[15a] **521**[15b] **457**

1730 cm^{-1} 1680 cm^{-1} 1697 cm^{-1}

Table 5.1: C=O stretching of amino ketones

The ketone **521** contains an aromatic substitute α to the carbonyl group, similar to the ketone **457** (Table 5.1). Later, we obtained of X-ray crystallographic analysis data (Appendix, p.269-272), which confirmed the structure of the ketone **457** (Figure 5.5).

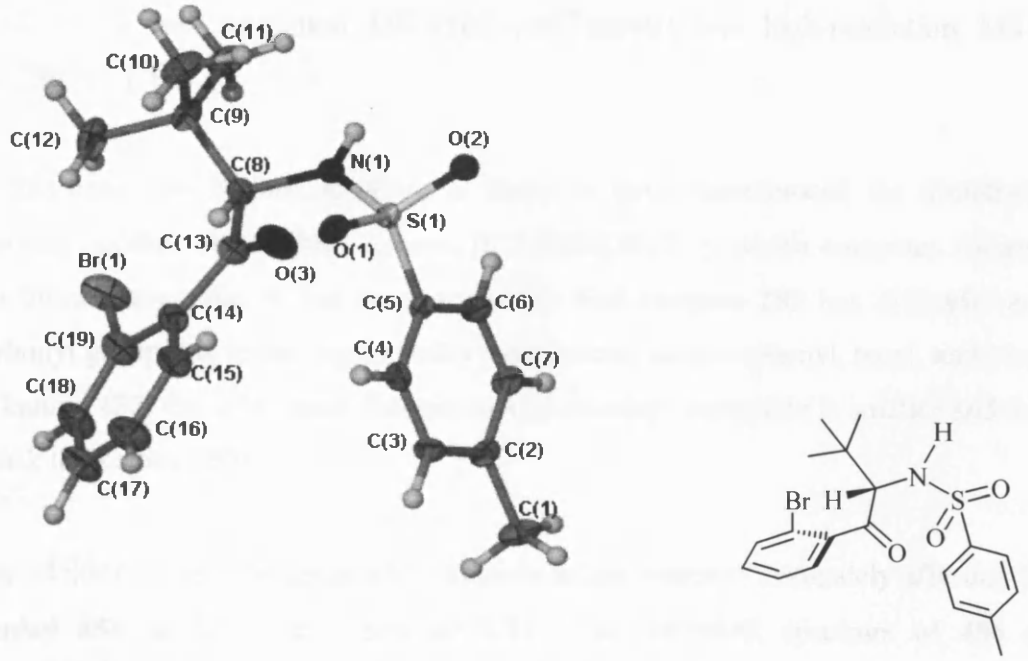
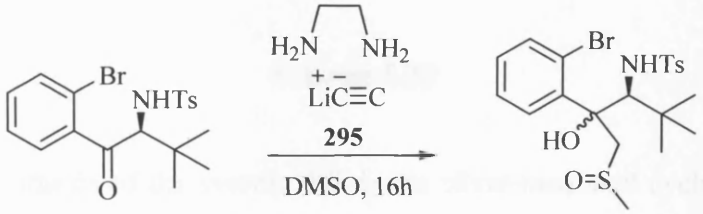


Figure 5.5: X-ray Analysis of 1-(o-Bromophenyl)-3,3-dimethyl-2-(tosylamino)-butanone 457

The completion of the synthesis of the key intermediate **456** required only an apparently straightforward acetylene addition (Section 2.2.2, Scheme 2.16). Ketone **457** was first treated with five equivalents of lithium acetylide-ethylenediamine **295** in anhydrous dimethyl sulfoxide at room temperature for 16 hours (Scheme 5.22).



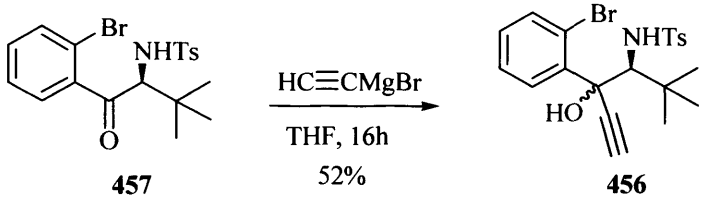
Scheme 5.22

Surprisingly, a β-amino alcohol **522** was isolated in 85% as a single diastereoisomer. The ^{1}H NMR spectrum of the amino alcohol **522** showed the resonance for the proton β to the hydroxy group at 4.53 ppm as a double doublet (J = 9.8 and 1.8 Hz, coupling with a proton of NH and long-range coupling with the hydroxy group) and two protons of the methylsulphinyl methyl group at 3.21 and 4.09 ppm as doublets (J_{AB} = 13.4 Hz). This was further confirmed

by ^{13}C NMR (the α-carbon at 65.1 ppm and quarternary carbon at 37.8 ppm), IR (broad at 3267 cm^{-1}), low resolution MS (502 $[M(^{79}Br)+H]^+$)and high-resolution MS (502.0719 $[M(^{79}Br)+H]^+$).

In this case, the lithium acetylide is likely to have deprotonated the dimethyl sulfoxide, deriving another nucleophilic species $[CH_3S(O)CH_2^-Li^+]$, which competes successfully with the lithium acetylide. It has been suggested that complex **295** has difficulty attacking the carbonyl group due to the highly bulky substitutents (*o*-bromphenyl, tosyl, and *t*-butyl groups) of ketone **457**. On other hand, lithium methylsulphinyl methylide is smaller and this is able to attack the ketone **457**.

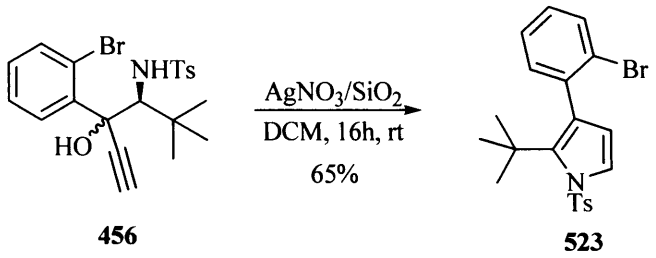
The addition of ethynylmagnesium bromide to the carbonyl fortunately afforded the β-amino alcohol **456** in 52% yield (Scheme 5.23). The ^1H NMR spectrum of **456** showed the resonance for the β-proton to the hydroxyl group at 4.64 ppm as a doublet (J = 9.8 Hz) and the proton of the alkyne at 3.09 ppm as a singlet. This was confirmed by ^{13}C NMR (a quaternary carbon at 37.6 ppm and the β-carbon at 65 ppm), IR (broad at 3486 cm^{-1}), low resolution MS (432 $[M(^{79}Br)-H_2O]^+$)and high-resolution MS (467.1004 $[M(^{79}Br)+NH_4]^+$).



457 **456**

Scheme 5.23

A key step in the synthesis of the pyrrole **455** is the silver-mediated cyclization (see Section 1.4). The intermediate **456** was dissolved in anhydrous dichloromethane to which was added one equivalent of 10 % wt/wt silver(I) nitrate on silica and the mixture was stirred vigorously in the dark at room temperature for 16 hours (Scheme 5.24). After removal of the catalyst by filtration and evaporation of the ether, the desired pyrrole **523** was obtained in 65% yield. The intermediate **456** could also be treated with 0.5 equivalent of 10 % wt/wt silver(I) nitrate on silica, but the reaction required 36 hours to achieve a good yield.



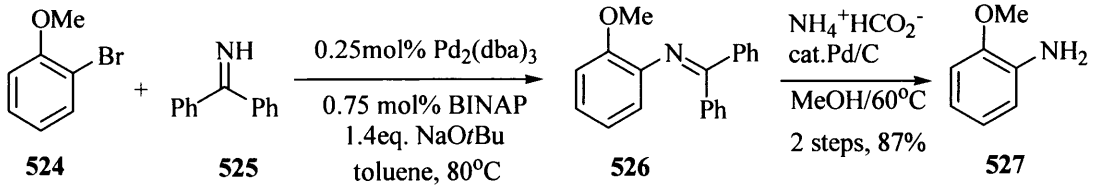
456 523

Scheme 5.24

The ^{1}H NMR spectrum of the pyrrole **508** showed the resonances for the 4-and 5-pyrrole protons at 5.95 and 7.40 ppm respectively as a pair of doublets (J = 3.5 Hz). This was confirmed by ^{13}C NMR (CH-pyrrole at 114.7 and 128.7 ppm), IR, low resolution MS (432 $[M(^{79}Br)+H]^{+}$) and high-resolution MS (432.0629 $[M(^{79}Br)+H]^{+}$).

5.3.4 Carbon-nitrogen bond formation

An important task remaining is the amination of the aryl halide, a key C-N bond-forming process. Arylamines are attractive targets for chemical synthesis because of their prevalence and wide utility. They are found in many biologically active compounds such as our target molecule, rhazinilam, and are also employed as ligands for transition metals,[92a] and other electronically interesting materials.[92b] Traditional routes for the synthesis of these compounds such as electrophilic nitration and subsequent reduction, nucleophilic aromatic substitution, and Ullmann-type couplings often suffer from relatively harsh conditions and limited generality.[92c]

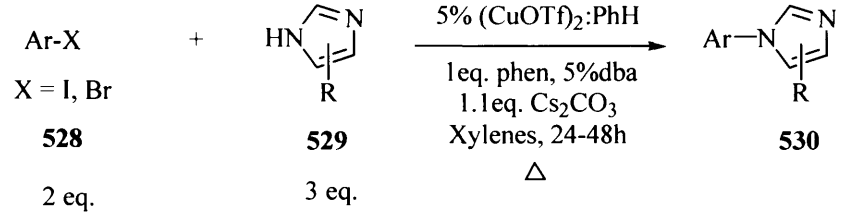


524 525 526 527

Scheme 5.25

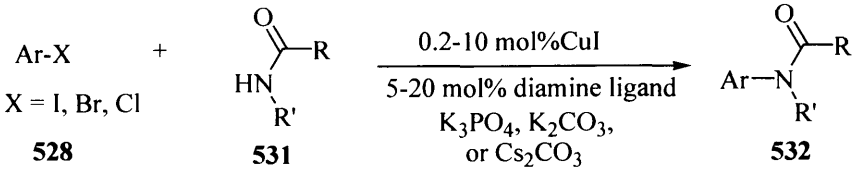
In 1997, Buchwald demonstrated the utility of employing benzophenone imine **525** as a substitute for ammonia in the palladium-catalyzed amination of aryl halides and triflates (Scheme 5.25).[93a] The coupling and subsequent deprotections proceed in uniformly high yields.

Buchwald also reported a fairly smooth copper-catalyzed coupling reaction.[93b] Copper-catalyzed *N*-arylation of imidazole could be completed using $Cu(OTf)_2$.benzene as a catalyst precursor and Cs_2CO_3 as a base in xylene at 110°C~120°C (Scheme 5.26). The addition of 1,10-phenanthroline (phen) and *trans, trans*-dibenzylideneacetone (dba) was crucial to the success of the process. The authors assumed that dba prevented undesirable disproportionation or in some way stabilized the catalytically active copper(I) species, but the effects of 1,10-phenanthroline were unclear.



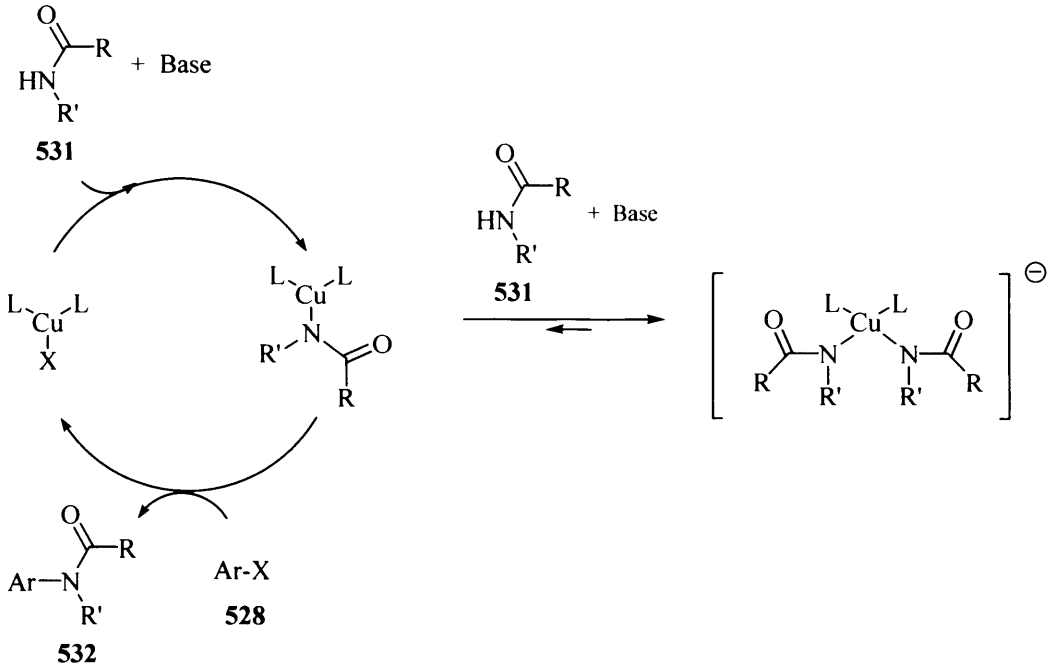
Scheme 5.26

This finding led to the examination of the efficiency of other chelating nitrogen ligands in copper-catalyzed C-N bond forming process. Buchwald recently reported an enhanced version of the Goldberg reaction-the copper-catalyzed amidation of aryl and heteroaryl halides.[93c] The combination of air stable CuI and 1,2-diamine ligands in the presence of K_3PO_4, K_2CO_3 or Cs_2CO_3 comprised an extremely efficient and general catalytic system for *N*-amidation of aryl and heteroaryl iodides and bromides and in some cases even unactivited aryl chlorides (scheme 5.27).



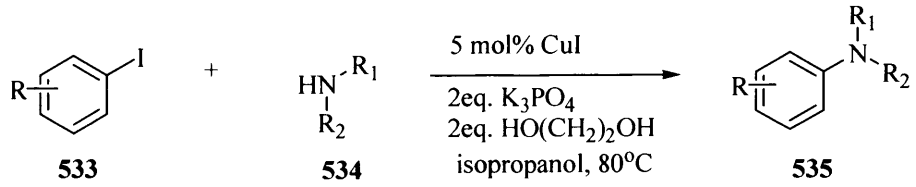
Scheme 5.27

The reaction is tolerant of a variety of functional groups. The degree of substitution and consequently the steric bulk of the diamine ligands played the most important role. *N,N'*-dimethylethylenediamine and *trans-N,N'*-dimethyl-1,2-cyclohexanediamine gave the best results. Strong base impedes the desired aryl amidation reaction *via* formation of unreactive cuprate complexes (Scheme 5.28). The pK_{HA} of the base employed in the arylation reaction should be below the pK_{HA} of the amide substrate.



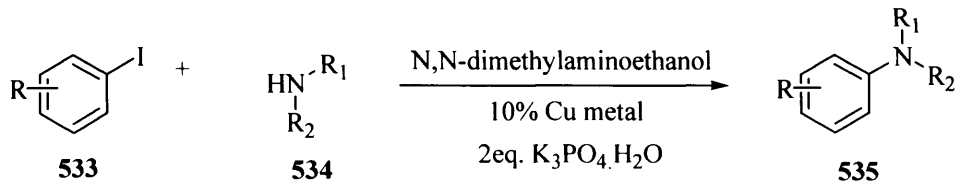
Scheme 5.28

O-Donor ligands can also be used in C-N bond forming reactions. Buchwald reported a mild, practical Cu-catalyzed amination of functionalized aryl iodides (scheme 5.29).[93d] This simple C-N bond-forming protocol used CuI as the catalyst and ethylene glycol as the ligand in 2-propanol. The reactions could be performed without protection from air or moisture. Keto, cyano, nitro, amino, carboxylate, methoxy, bromo and chloro groups were tolerant on the aryl iodide component. No significant electronic effects were observed for *para*- and *meta*-substituted aryl iodides.



Scheme 5.29

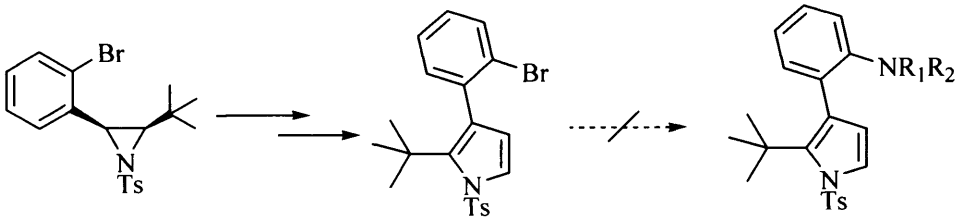
However, more work still needs to be done to find new ligands and to expand the scope of the substrates and reactions that may be catalyzed by copper species. Twieg also reported an alternative solvent, 2-*N,N*-dimethylaminoethanol, and copper metal as a useful catalyst precursors for the amination of aromatic halides.[93e] The combination of metallic copper catalyst with $K_3PO_4.H_2O$ often affords the best results (Scheme 5.30).



533 534 535

Scheme 5.30

Unfortunately, following the application of both the palladium-catalyzed and copper-catalyzed aminations by Buchwald,[93a,c] and the copper-catalyzed amination by Twieg,[93e] we have not been able to convert 3-(*o*-bromophenyl)-pyrrole **523** into the desired 3-(*o*-aniline)-pyrrole **455**. All crude reaction mixtures have been tested by low-resolution MS and showed mainly the starting material **523**. However, the model study discussed in this chapter reaffirms the utility of the aziridination process for the construction of the 3-(*o*-bromophenyl)-2-*t*-butyl-pyrrole **523** frameworks. Due to time constraints, the desired pyrrole **455** could unfortunately not be synthesized (Figure 5.6).

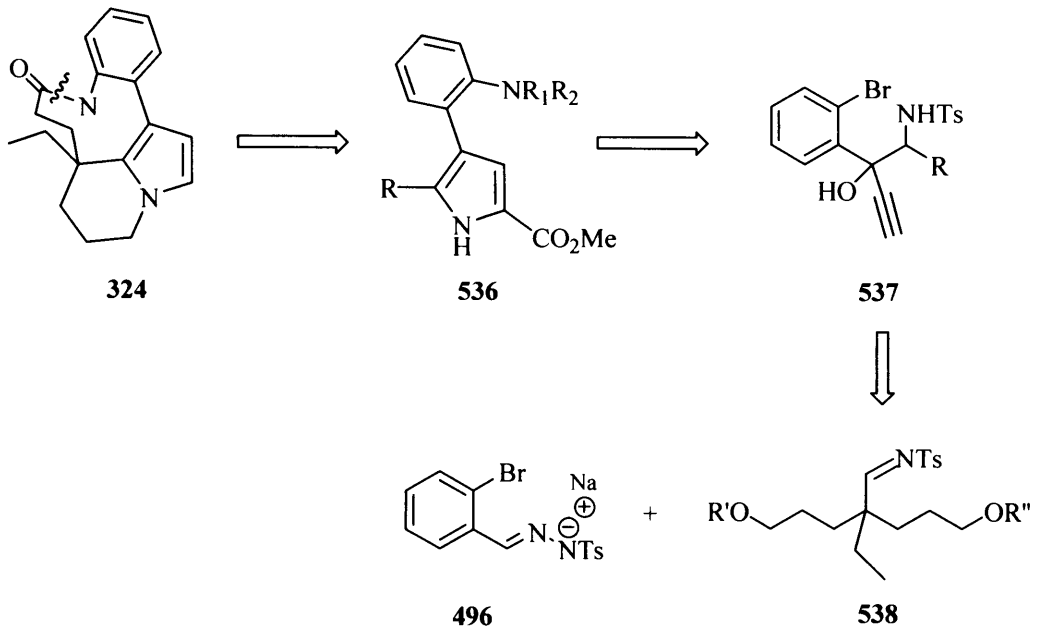


459 523 455

Figure 5.6

5.4 Retrosynthetic Analysis and strategy

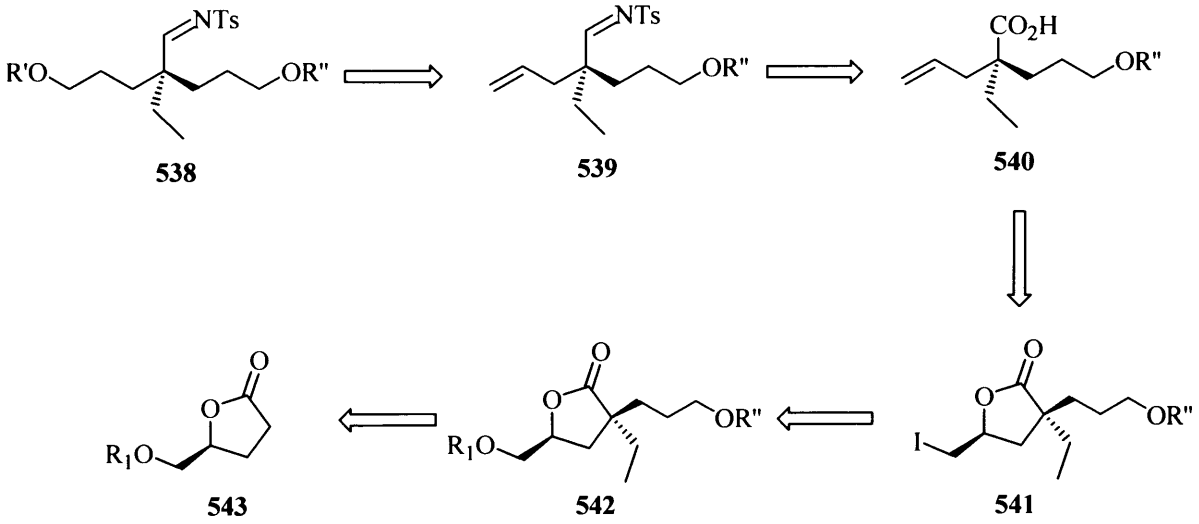
According to the retrosynthetic study of Rhazinilam **324**, disconnection of the amide functionality would lead to the pyrrole **536**. To obtain the pyrrole **536**, silver-mediated cyclization would apply to α-amino alcohol **537**, only if the aziridination could be applied successfully to an imine **538** (Scheme 5.31).



324 536 537 496 538

Scheme 5.31

Since one important objective of the synthetic work was to establish the precise structure of the molecule, it is necessary to design a flexible strategy allowing for the eventual formation of all possible stereoisomers. The logic for our design was based on the retrosynthetic analysis of the imine **538** shown in Scheme 5.32. It was anticipated that C-2 in structure **539** could be stereoselectively introduced in a fragmentation[94] of the lactone **541**, thereby establishing the necessary single stereogenic center and two side chains which could be independently manipulated.



538 539 540 543 542 541

Scheme 5.32

The forward transformation, stereoselective synthesis of lactone **543** from *L*-glutamic acid **545**, is well documented in the literature.[95] A potential advantage of this strategy is that it leads to the establishment of all structural elements of the nine-membered lactam B-ring, the piperidine D-ring and ethyl group in Rhazinilam **324**. We will observe the absolute stereochemistry of the molecules from their specific rotation; the ability of chiral molecules to rotate plane-polarized light. It is a function of structure (chirality), concentration, temperature, path length and wavelength, as shown in the formula below.

$[\alpha]_D = \alpha / lc$

α = observed rotation

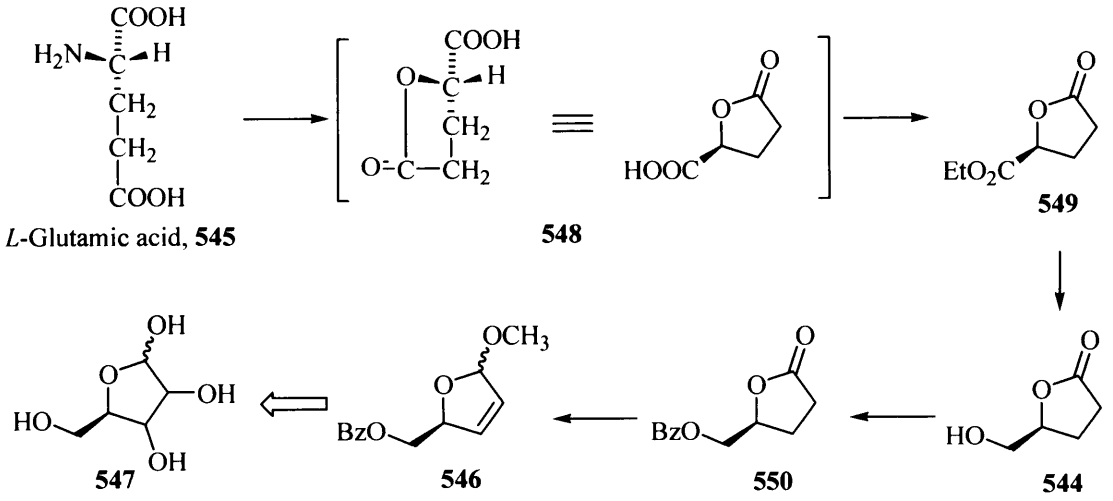
l = cell length

c = concentration (g/100mL)

$_D$ = wavelength, sodium D-line (656 nm)

5.4.1 The synthesis of (S)-γ -hydroxymethyl-γ-butyrolactone 544[95a]

(S)-γ-Hydroxymethyl-γ-butyrolactone **544** has been successfully used as a chiral synthon toward the asymmetric total synthesis ofa number of natural products.[95b] It is highly desirable to use a suitably constructed and optically active compound as a starting material, thereby avoiding a resolution step later in the synthesis. Yamada and co-workers reported a synthesis of the important intermediate **546** of *D*-ribose **547** from *L*-glutamic acid **545** as shown in Scheme 5.33, by making use of the chiral center present in **545**.[95a]

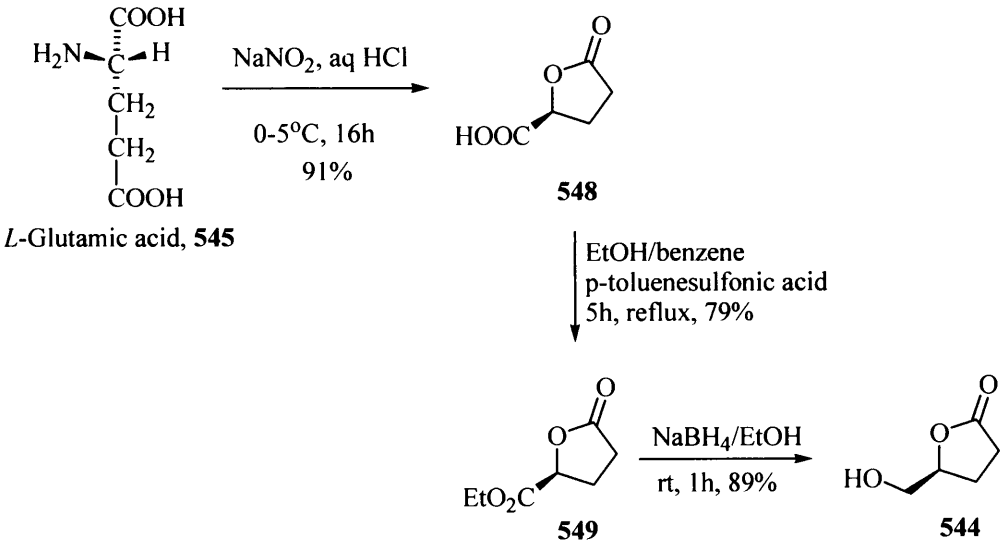


Scheme 5.33

The key feature of the nitrous acid deamination of **545** is that it gives only the substitution product **548**, which proceeds with full retention of configuration due to the participation of the neighbouring α–carboxylate group. Selective reduction of the ester group in (S)-γ-ethoxycarbonyl-γ-butyrolactone **549** to (S)-γ-hydroxymethyl-γ-butyrolactone **544** may be reliably performed using sodium borohydride.[95a]

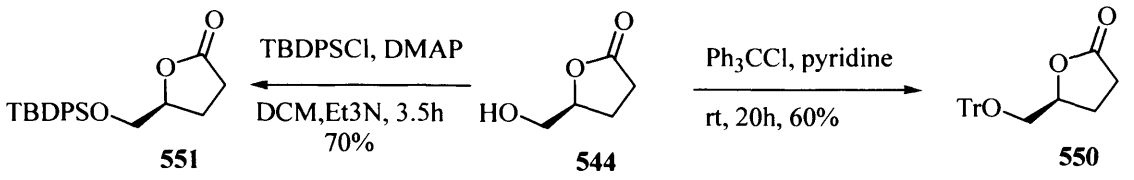
Thus, *L*-glutamic acid **545** was converted into the enantiomerically pure γ-butyrolactone **544** *via* three literature steps (Scheme 5.34).[95a] Nitrous acid deamination of **545** in aqueous solution gave the lactone acid **548**, which was converted into the corresponding lactone ester **549** in 79% yield. Reduction of **549** with sodium borohydride in ethanol at room temperature afforded γ-butyrolactone **544** in 89% yield. IR absorptions at 3384 and 1767 cm^{-1} indicated the presence of the hydroxy and γ-lactone functions respectively.

Any protecting group for the hydroxy function in **544** must be stable under both reduction (reductive opening of the lactone ring with Zn dust) and alkaline (alkylation) conditions. Tanano[19b] and Koga[96a] observed that in the alkylation reaction, the very large trityl group consistently directs the approach of the incoming group to the opposite side; consequently, the stereochemistry of the newly generated chiral center may be arbitrarily controlled merely by changing the alkylation sequence.



Scheme 5.34

Treatment of lactone **544** with triphenylmethyl chloride in pyridine at room temperature gave (*S*)-trityloxymethyl-γ-butyrolactone **550** in 60% yield with $[\alpha]_D$ +26.7° (c 1, $CHCl_3$), which is almost identical to that observed by Takano[97a] {$[\alpha]_D$ +28.6° (Scheme 5.35)}.

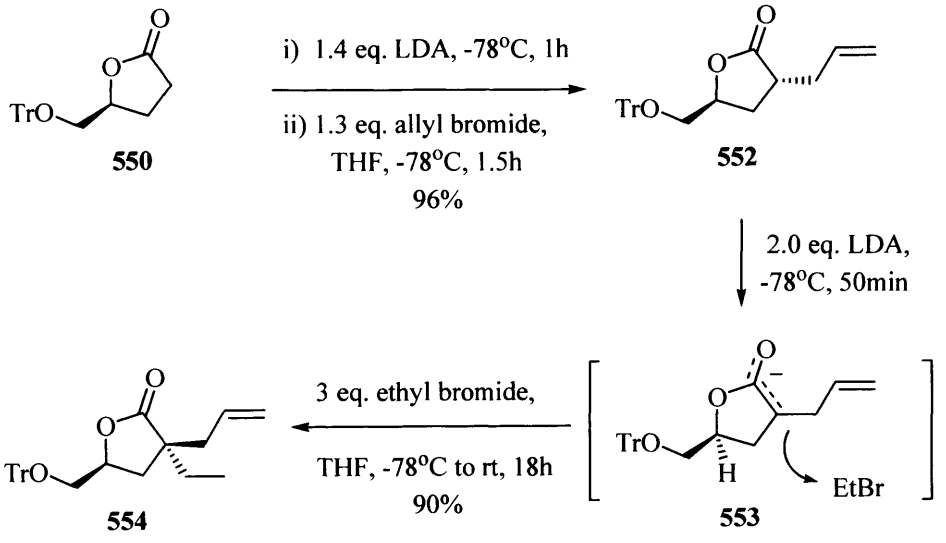


Scheme 5.35

Brückner also reported the similar transformation by using *tert*-butyldiphenylsilyl as the protecting group.[96b] Silylation[97b] of the hydroxy group in **544** with *tert*-butyldiphenylsilyl chloride under standard conditions (triethylamine, 1.1 equiv. of TBDPSCl, and catalytic amount of DMAP in DCM) gave (*S*)-*t*-butyldiphenylsilyl-γ-butyrolactone **551** in 70% yield with $[\alpha]_D$ +24.95° (c 1, $CHCl_3$) (Scheme 5.35).

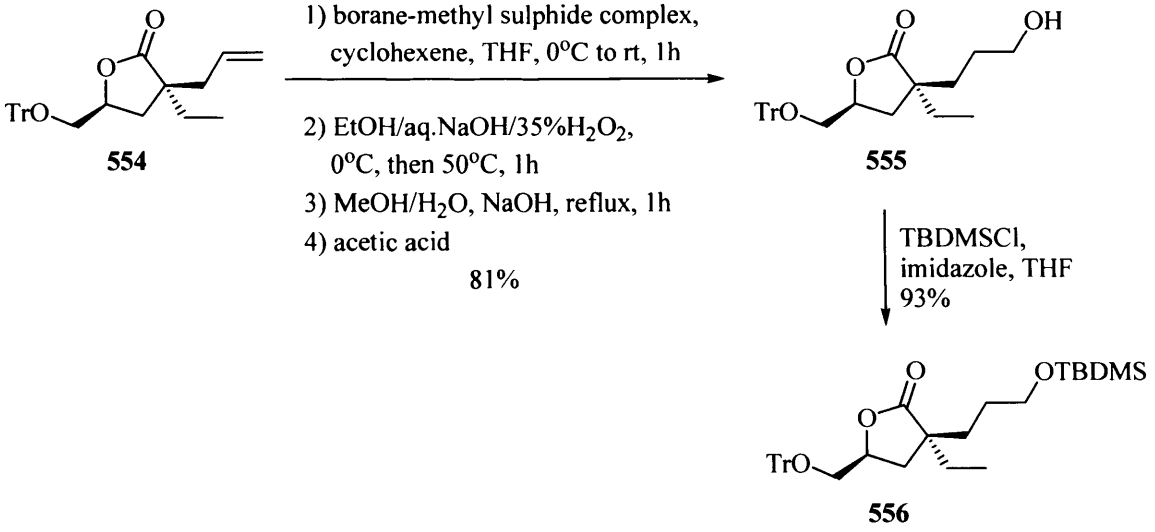
5.4.2 Synthesis of Chiral Quaternary Carbon (C-3)

Following from Takano's work,[95b] treatment of the trityloxymethyl-γ-butyrolactone **550** with LDA and allyl bromide in tetrahydrofuran, affords the allyl-lactone **552** in 96% yield (Scheme 5.36).



Scheme 5.36

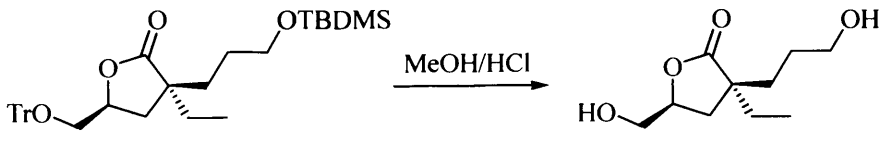
The allyl-lactone **552** was treated again with LDA to generate the enolate **553,** which on alkylation with ethyl bromide *anti* to the trityloxy group regernerated the chiral center to produce the lactone **554** in 90% yield. Hydroboration of the lactone **554** with dicyclohexylborane then selectively generated the primary alcohol **555** in 81% yield (Scheme 5.37). Silylation of the new hydroxy group with *tert*-butyldimethylsilyl chloride under standard condition gives the desired silyl ether **556**.



554 555 556

Scheme 5.37

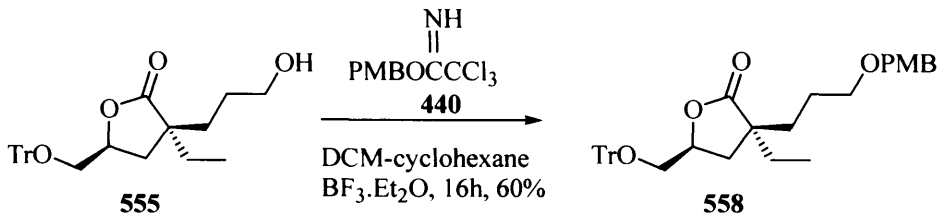
Detritylation of the lactone **556** in methanol containing a trace of hydrochloric acid for 5 hours at room temperature gave an undesired product, the hydroxylactone **557**, caused by loss of the silyl group (Scheme 5.38).



556 557

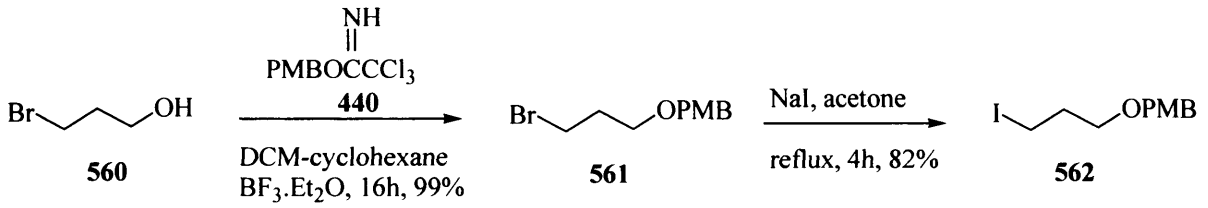
Scheme 5.38

To prevent losing this protecting group on the hydroxypropyl side chain under the detritylation conditions, the primary alcohol **555** was treated with the trichloroacetimidate **440** and boron trifluoride etherate in DCM/cyclohexane to give *p*-methoxybenzyloxy ether **558** in 60% yield (Scheme 5.39).



Scheme 5.39

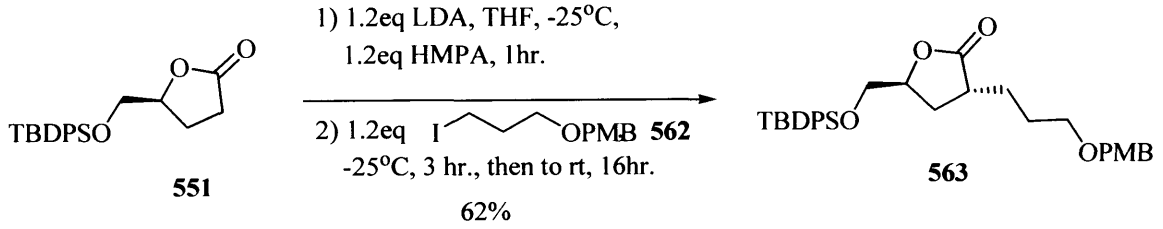
Although this route proceeded in good yield, we attempted to introduce the PMB propanol directly to C-3, which would remove two subsequent steps (hydroboration and protection of the generated hydroxyl). Through some straightforward functional group manipulations, PMB propyl iodide **562** was prepared from 1,3-propanediol **559**[98a] (PMB protection, mesylation, and iodination) or bromopropanol **560**[98b] (PMB protection and iodination).



Scheme 5.40

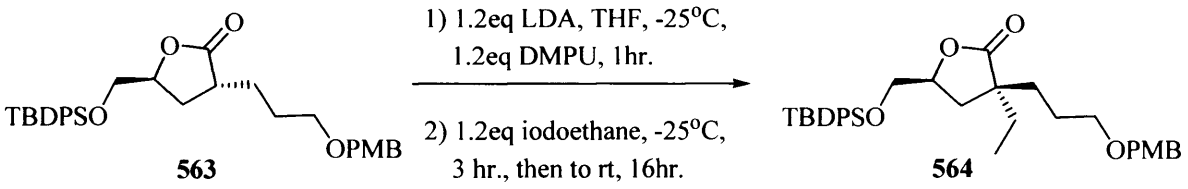
Treatment of readily available bromopropanol 560 with the trichloroacetimidate **440** and a catalytic amount of camphorsulfonic acid in DCM/cyclohexane gave *p*-methoxybenzyloxy propyl bromide **561** in 99% yield (Scheme 5.40). Treatment of the bromide **561** with sodium iodide in refluxing acetone resulted the PMB propyl iodide **562** in 82% yield (Scheme 5.40).

The critical stage of the present synthesis is the alkylation of the lactone **543** with the iodide **562**. Due to facile deprotection of the silyl group, the lactone **551** was tested in this sequential dialkylation. Optimization of the alkylation of **551** makes use of Koga's procedure[95a] giving the desired lactone **563** in a satisfactory yield (62% isolated yield) when the reaction was carried out at -25°C for 3 hours, and then at room temperature for 16 hours (Scheme 5.41).



Scheme 5.41

The ^{1}H NMR spectrum of the lactone **563** shows the characteristic resonance for the proton H-3 at 3.37-3.41 ppm as a multiplet and the proton H-5 at 4.41-4.45 ppm as a double doublet. The structure of **563** was also confirmed by ^{13}C NMR (carbon C-3 and C-5 at 39.4 and 77.8 ppm respectively), IR (strong at 1769 cm^{-1}), low resolution MS (533 $[M+H]^{+}$) and high-resolution MS (533.2723 $[M+H]^{+}$).



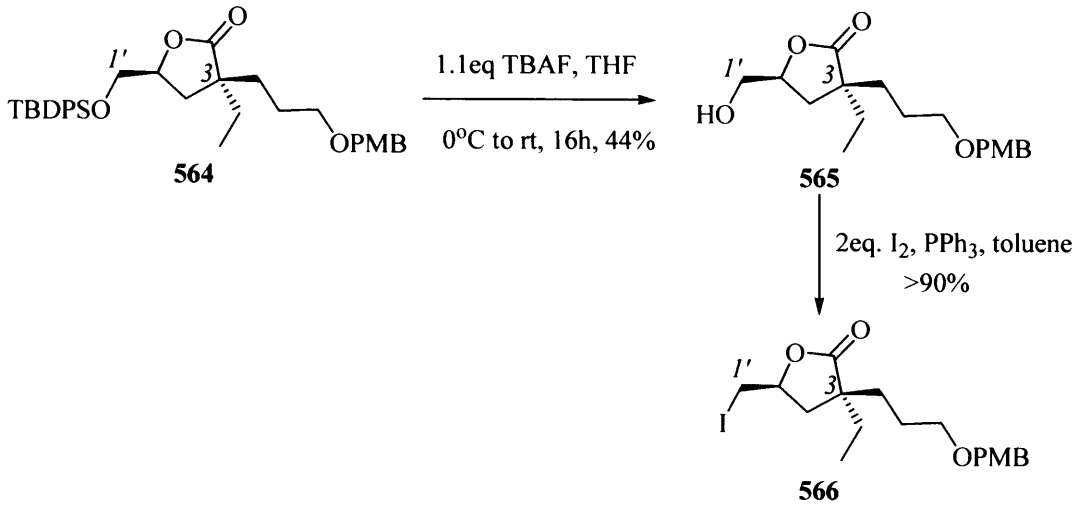
Scheme 5.42

The lactone enolate derived from **563** is treated at –25°C with iodoethane in the presence of DMPU to furnish the lactone **564** having a quanternary carbon at C-3 (Scheme 5.42). In its spectral data, the crude lactone **564** shows the characteristic resonance corresponding to the carbon C-3 at 47.8 ppm, low resolution MS (561 $[M+H]^{+}$), high-resolution MS (561.3031 $[M+H]^{+}$), and $[\alpha]_D$ +14.5° (c 1, $CHCl_3$), which indicates the desired configuration when compared to the lactone **558** with $[\alpha]_D$ +16.1° (c 1, $CHCl_3$).

Further, ^{1}H NMR indicated only very low levels at most of any diastereoisomer. All attempts to carry out both alkylations in one flask failed, however.

5.4.3 Reducetive opening of the lactone ring

The final drive towards the target imine **528** proceeded as follows. The silyl group in **564** was removed using fluoride ions and the resulting hydroxylactone **565** was converted into the corresponding iodide **566** (40% overall yield, Scheme 5.43).



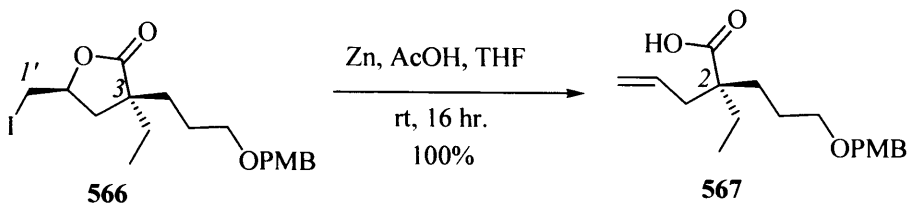
Scheme 5.43

The formation of these three lactones is confirmed by ^{1}H NMR analysis (Table 5.1). The signal corresponding to both CH_2s at position 4 and 1' in lactone **564** are rather complicated, due to their enantiotopic nature. However, after desilylation, both CH_2s of the alcohol **565** appear clearly as four double doublets, likewise in the iodide **566**, but the protons of CH_2-1' in **566** are shifted downfield with a difference of 0.32-0.4 ppm from the alcohol **565**.

Compound	$[\alpha]_D$ (c 1, $CHCl_3$)	CH_2-4, *J* (ppm, Hz)	CH_2-1', *J* (ppm, Hz)	C-3 (ppm)
564	+14.5°	1.78-1.84 (m) 2.01-2.10 (m)	3.55 (dd, 11.4, 4.4) 3.61-3.68 (m)	47.8
565	+15.4°	1.90 (dd, 13.1, 8.3) 1.99 (dd, 13.1, 8.3)	3.46 (dd, 12.5, 4.1) 3.73 (dd, 12.5, 4.1)	47.9
566	-16.8°	1.80 (dd, 13.3, 7.9) 2.20 (dd, 13.3, 7.9)	3.14 (dd, 10.1, 6.2) 3.33 (dd, 10.1, 6.2)	48.8

Table 5.1: data for the lactones 564, 565 and 566

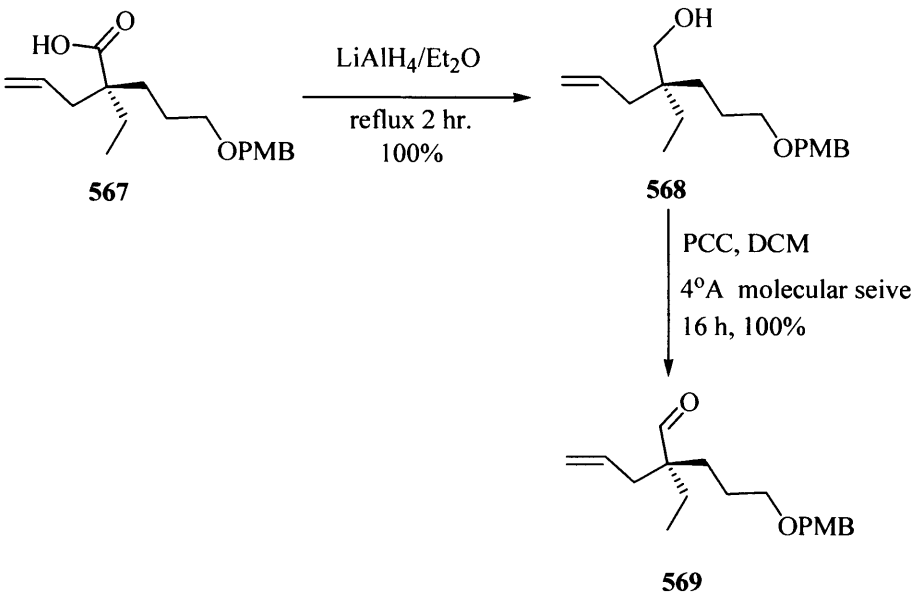
Another critical stage in the synthesis of the imine **539** had been reached. As hoped, application of Florent's procedure[94] to the lactone **566** using non-preactivated zinc in THF/HOAc as solvent afforded the unsaturated carboxylic acid **567** (Scheme 5.44).



566 567

Scheme 5.44

Analysis of the IR spectrum showed the disappearance of the lactone carbonyl absorption at 1750 cm^{-1} and the appearance of acid absorption at 1696 and 3657 cm^{-1}. Specific rotation ($[\alpha]_D$ –3.7°) confirms the *2S*-configuration of the acid **567**.



567 568 569

Scheme 5.45

The completion of the synthesis of the imine **539** then required only a few straightforward functional group manipulations. Thus, reduction of the carboxylic acid in **567** with lithium aluminium hydride provided in quantitative yield a primary alcohol **568** which was oxidized to aldehyde **569** by PCC (Scheme 5.45). The signal for the quaternary carbon (C-2) in **568** was shifted downfield with a difference of 8.9 ppm from that in the acid **567**, and is then shifted back to a higher field with a difference of 11.8 ppm when the aldehyde carbonyl in **569** has formed.

The retrosynthetic analysis outlined in Scheme 5.31 identified imine **539** as a potential synthetic intermediate: the construction of this compound would make the achievement of the synthetic objective, for it would permit an evaluation of the crucial aziridination. Treatment of

the aldehyde **569** with *p*-toluenesulfonamide monohydrate, 4°A molecular sieve and catalytic amount of boron trifluoride etherate in toluene under reflux for 16 hours did not give the desired imine **570** in reasonable yield (10-30 %).[85] It was gratifying to find that imine formation had been conducted smoothly by Trost and Marrs.[99] These authors suggested that the mechanism of this particular reaction involves a cycloaddition to give a four-membered ring **573**, followed by cyclo-reversion to generate the desired product (Figure 5.7).

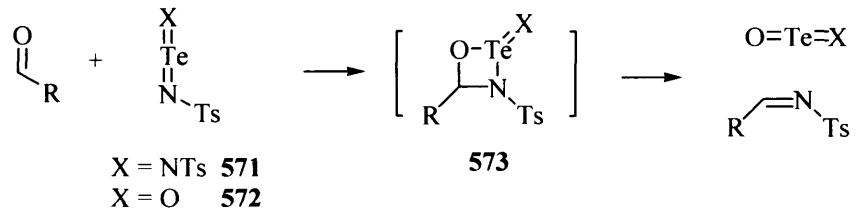
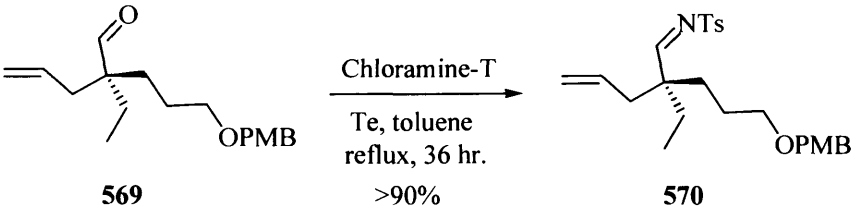


Figure 5.7

Exposure of the aldehyde **569** to the action of chloramine-T in the presence of tellurium powder in refluxing toluene provided the imine **570** in essentially quantitative yield (Scheme 5.46). Analysis of the IR spectrum showed the disappearance of the aldehyde carbonyl absorption at 1722 cm^{-1}. The ^1H NMR spectrum of **570** showed the characteristic resonance for a proton of an imine at 8.33 ppm as a singlet, which was also confirmed by ^{13}C NMR (the carbon of the imine at 185.6 ppm), low resolution MS (444 $[M+H]^+$) and high-resolution MS (444.2202 $[M+H]^+$).



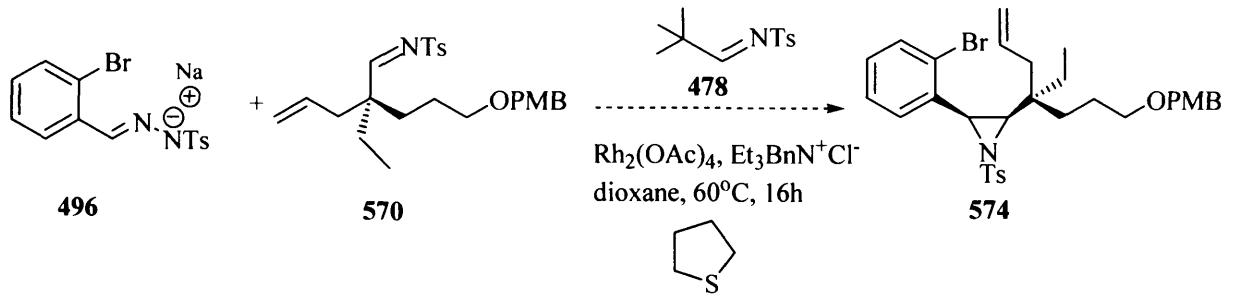
569 >90% **570**

Scheme 5.46

5.5 Aziridination of the imine 570

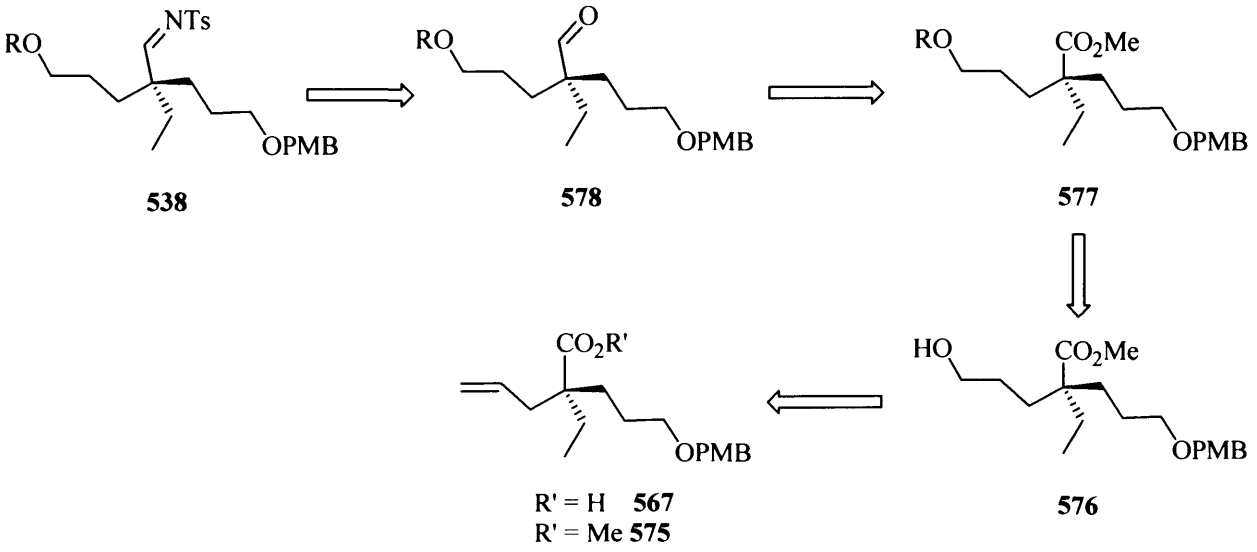
At first glance, the imine **570** might appear to be well suited for the crucial aziridination step;[81b] it possesses an electrophilic moiety. However, reaction of the tosylhydrazone sodium salt **496** with the imine **570** in the presence of a catalytic amount of rhodium acetate, $BnEt_3N^+Cl^-$, and tetrahydrothiophene in dioxane at 60°C provided none of the desired

aziridine **574** (Scheme 5.47). It was deduced that the double bond in **570** should be masked in order to enhance the possibility of this reaction taking place.



Scheme 5.47

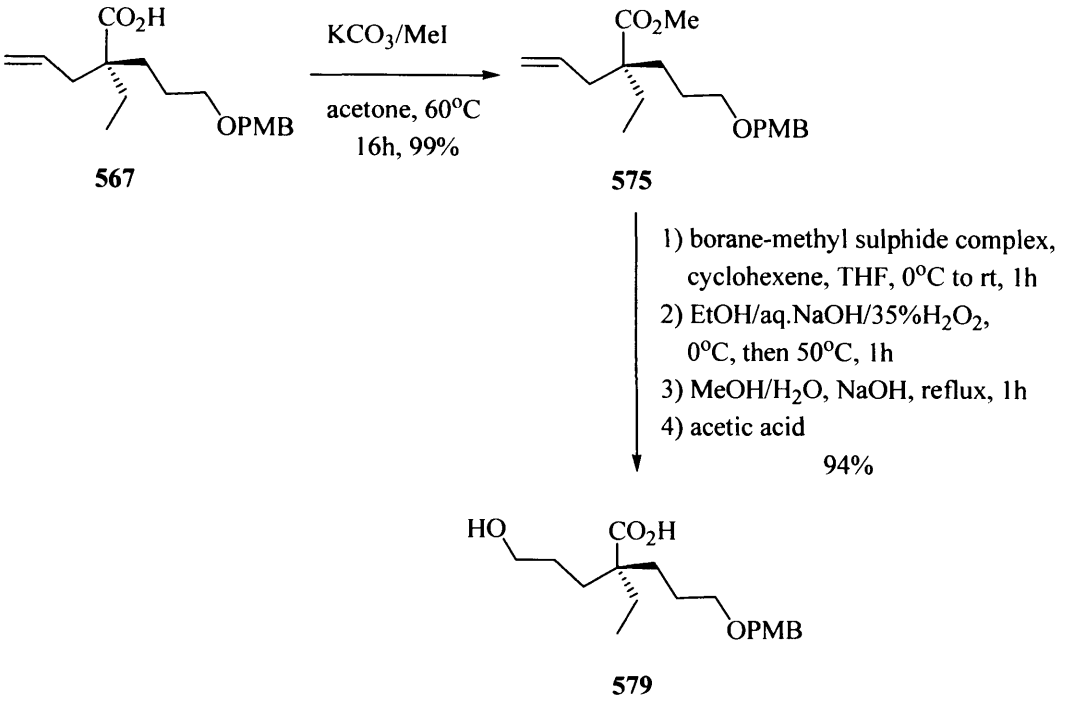
Hydroboration of the double bond appeared reasonable because it would allow construction of the seemingly optimum imine **538**. This could be achieved by protection of the acid **567** as a methyl ester, followed by hydroboration of the existing double bond to give a primary alcohol **576**, and protecting the alcohol in **576** to give the methyl ester **577**, which would be ready to reduce to an aldehyde **578** and form the imine **538** (Scheme 5.48).



Scheme 5.48

Treatment of the acid **567** with potassium carbonate and methyl iodide in acetone resulted in the formation of methyl ester **575** in quantitative yield (Scheme 5.49).[100] The ^{1}H NMR spectrum of **575** showed the characteristic resonance for the three protons of the methoxyl group at 3.57 ppm as a singlet, and this was also confirmed by ^{13}C NMR (the quaternary carbon at 49.4 ppm), low resolution MS (321 $[M+H]^{+}$) and high-resolution MS

(321.2058[M+H]$^+$). Unfortunately, during the hydroboration process, the methoxy group in **575** is also deprotected to give the unwanted acid **579** (Scheme 5.49). Due to time constraints, our research program had to finish at this stage.



567 **575** **579**

Scheme 5.49

5.6 Conclusion

The silver-mediated cyclization emerged as perhaps a useful method for pyrrole formation, allowing the incorporation of highly hindered substituents at positions 2 and 3. Keys steps within our target synthesis were the application of the imine **478** to aziridination reactions and the ring opening of aziridine **459** to form the corresponding β-amino alcohol **458**. Unfortunately, this technology failed to provide the desired pyrrole **455** by amination. Finally, although it was not possible to form the corresponding aziridine, the synthesis of the imine **570** emphasized the difficulties encountered and often overcome in this important area of the total synthesis of (-)-rhazinilam **283**.

Chapter 6

Experimental

6.1 General Details

All non-aqueous reaction, unless otherwise stated, were conducted in oven or flame-dried apparatus under an atmosphere of dry nitrogen with magnetic stirring. Low temperatures were obtained using solid carbon dioxide and an acetone bath (-78°C) or an ice-water bath (0°C). Heated reactions were conducted in a stirred oil bath heated on a magnetically stirred hotplate. All microwave reaction were conducted in a Discover Benchmate, microwave synthesis system.

Solvents were dried and purified prior to use, where necessary. Tetrahydrofuran and diethyl ether was distilled from sodium benzophenone ketyl. *N,N*-Dimethylformamide, triethylamine, dichloromethane and acetonitrile were dried over 4°A molecular sieves. Toluene, pyridine and diisopropylamine were dried over and distilled from potassium hydroxide. Ether was distilled from sodium benzophenone ketyl. All solutions of crude products were dried by brief exposure to anhydrous magnesium sulphate ($MgSO_4$), unless otherwise stated, then filtered and evaporated under reduced pressure (Buchi rotary evaporator under water pump pressure and a warm water bath). Column chromatography was carried out on Merk silica gel 60 (230-400 mesh) as the stationary phase, in association with the R_f values quoted using the solvents stated. All reactions were monitored by tlc using Merck silica gel 60 F_{254} precoated aluminium backed plates that were visualised with ultraviolet light, potassium permanganate or ammonium molybdenate. Retention factor values (R_f) are reported in the appropriate solvent system.

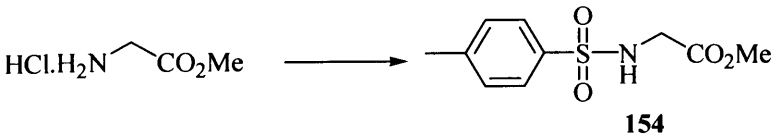
All melting points (mp °C) were determined on a Kofler hot-stage apparatus. All boiling points (bp °C) were determined by bulb-to-bulb distillation using a Buchi GKR-51 kugelrohr distillation apparatus. Melting and boiling points are uncorrected. Infrared spectra were obtained using a Perkin Elmer 1600 series Fourier Transform Infra-red Spectrometer, as liquid films on sodium chloride plates [film], as a solution in dichloromethane [CH_2Cl_2] or as nujol mulls on sodium chloride plates [nujol]. The signals are described by the following abbreviations: strong (s), medium (m) weak (w) and broad (br). Specific rotations $[\alpha]_D$ were determined on a AA-1000 polarimeter with millidegree-auto-ranging observing at room temperature.

Proton (^{1}H) NMR spectra were recorded on a Bruker DPX 400 instrument at 400 MHz, as dilute solutions in deuteriochloroform at 298 K. The abbreviations δ_H and δ_C denote ^{1}H and ^{13}C NMR data respectively. The chemical shifts are recorded relative to residual chloroform (7.27 ppm) as an internal standard. The following abbreviations are used throught: s = singlet, d = doublet, t = triplet, q = quartet, m = unresolved multiplet, dd = doublet of doublets, td = triplet of doublets, br s = broad singlet, app td = apparent triplet of doublets *etc.* All coupling constants (*J*) are recorded in Hertz (Hz). Carbon (^{13}C) NMR spectra were recorded on the same instrument and conditions, but operating at 100.6 MHz. Chemical shifts are reported relative to residual chloroform (77.0 ppm) as an internal standard in a broad band decoupled mode. Assignments were made on the basis of chemical shift and coupling constant data using DEPT-135 and COSY experiments where required.

Low resolution mass spectra were recorded on a Fisons VG Platform Quadrapole Mass Spectrometer using atmospheric pressure chemical ionisation [APcI]. *M/z* values are reported with the percentage abundance in parentheses, only for peaks with intensities of 10% or greater. Accurate high-resolution mass spectrometric data were determined by the EPSRC Mass Spectrometry Service centre at University College Swansea and the molecular formula corresponds to the observed signal using the most abundant isotopes of each element. All molecular formulae are quoted for molecular + hydrogen $[M+H]^+$, molecular + ammonium ion $[M+NH_4]^+$ or molecular + sodium ion $[M+Na]^+$. Microanalytical data were obtained on a Perkin Elmer Elemental 2400 CHN elemental analyser and are quoted as atom percentages. X-ray crystal structures were determined by Dr K. M. A. Malik amd Dr M. P. Coogan, Cardiff University.

6.2 Experimental

Methyl (4-methylphenylsulfonylamino)-acetate 154 [101]

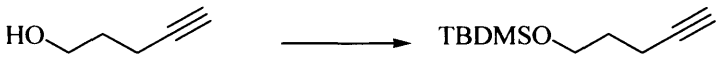


154

Glycine methyl ester hydrochloride (5.0 g, 39.82 mmol) and *p*-toluenesulfonyl chloride (8.35 g, 43.8 mmol) were placed in a dried round bottom flask and partially dissolved in 100 mL of dried dichloromethane. After adding 4-dimethylaminopyridine (0.97 g, 7.96 mmol), the mixture was cooled to 0°C and triethylamine (11.1 mL, 79.64 mmol) was added dropwise.

The resulting mixture was allowed to stir for 30 min at 0°C, then left to stir at room temperature overnight. After 18 h, the mixture was diluted with dichloromethane (25 mL) then washed with 25 mL of 2M HCl. The organic layer was further washed with water (100 mL) and brine (100 mL), then dried and evaporated. When the crude product (10.89 g) was completely dry, it was recrystallized from petroleum ether 40-60°C, diethyl ether and dichloromethane in the water bath (80°C), followed by strorage at 0°C overnight. The precipitate was filtrated and washed with ice-cold diethyl ether. The dried product was a colourless crystalline solid, *N-tosyl glycine ester* **154** (6.46 g, 67%), mp 92-93°C [lit. mp[101] 92-93°C]; ν_{max}/cm^{-1} [nujol] 3276 (s), 1729 (s), 1352 (s), 1162 (s) and 811 (w); δ_H 2.26 (3H, s, $ArCH_3$), 3.47 (3H, s, OCH_3), 3.62 (2H, d, *J* 5.2, 2-CH_2), 4.92 (1H, t, *J* 5.2, NH), 7.15 (2H, d, *J* 8.0, 2 x ArH) and 7.58 (2H, d, *J* 8.0, 2 x ArH); δ_C 22.2 ($ArCH_3$), 44.4 (2-CH_2), 53.0 (OCH_3), 127.7 (2 x ArCH), 129.3 (2 x ArCH), 144.3, 147.2 (2 x ArC) and 170 (C=O); *m/z* [APcI] 244 ($[M+H]^+$, 100), 198 (25), 184 (50), 155 (40), 102 (20); Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.32; H, 5.34; N, 5.75. Found: C, 49.02; H, 5.37; N, 5.68%. *These data are consistent with those recorded in the literature.*[101]

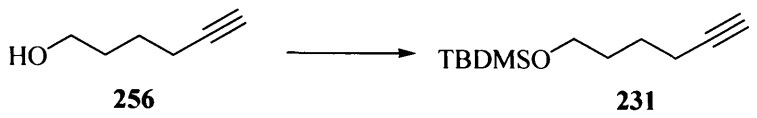
1-(tert-Butyldimethylsilyloxy)-pent-4-yne **229** [102a]



225 **229**

To a stirred solution of 4-pentyn-1-ol **225** (4.40 mL, 48 mmol) in anhydrous tetrahydrofuran (100 mL) was added imidazole (3.92 g, 57 mmol). After a clear solution was obtained, *tert*-butyldimethylsilyl chloride (8.70 g, 57 mmol) was added to give a cloudy white solution. The mixture was allowed to stir for 16 h at room temperature, then quenched with water (100 mL) and diluted with dichloromethane (50 mL). The organic layer was separated and washed with brine (100 mL). The organic layer was then dried and the solution evaporated to give the *ynyloxy-silane* **229** as a light yellow oil (9.40 g, 100%); ν_{max}/cm^{-1} [film] 3313 (m), 2954 (s), 2859 (m), 2112 (w), 1472 (w), 1257 (s), 1103 (s), 835 (s) and 776 (m); δ_H 0.00 (6H, s, 2 x $SiCH_3$), 0.83 (9H, s, 3 x CH_3), 1.67 (2H, pen, *J* 6.5, 2-CH_2), 1.87 (1H, t, *J* 2.7, 5-H), 2.22 (2H, td, *J* 6.5, 2.7, 3-CH_2) and 3.64 (2H, t, *J* 6.5, 1-CH_2); δ_C -5.3 (2 x $SiCH_3$), 14.8 (2-CH_2), 18.3 (SiC), 25.9 (3 x CH_3), 31.5 (3-CH_2), 61.42 (1-CH_2), 68.2 (5-CH) and 84.2 (4-C≡). *These data are consistent with those recorded in the literature.*[102a]

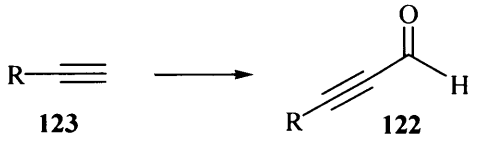
***1-(tert-Butyldimethylsiloxy)-hex-5-yne* 231** [102b]



256 **231**

Starting from 5-hexyn-1-ol **256** (5 g, 50 mmol) and using exactly the same method described in the foregoing experiment, the *ynyloxy-silane* **231** was obtained as a light yellow oil (10.6 g, 100%); ν_{max}/cm^{-1} [film] 3313 (m), 2929 (s), 2875 (m), 2122 (w), 1472 (m), 1255 (s), 1107 (s), 836 (s) and 776 (s); δ_H 0.00 (6H, s, 2 x $SiCH_3$), 0.84 (9H, s, 3 x CH_3), 1.54-1.60 (4H, m, 2- and 3-CH_2), 1.90 (1H, t, *J* 2.6, 6-H), 2.18 (2H, td, *J* 6.7, 2.6, 4-CH_2) and 3.58 (2H, t, *J* 6.0, 1-CH_2); δ_C -5.3 (2 x $SiCH_3$), 18.1 (4-CH_2), 18.3 (SiC), 24.9 (3-CH_2), 25.9 (3 x CH_3), 31.8 (2-CH_2), 62.6 (1-CH_2), 68.2 (6-CH) and 84.5 (5-C≡). *These data are consistent with those recorded in the literature.*[102b]

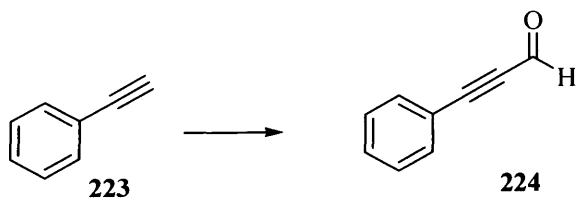
General Procedure of the Preparation of Acetylene Aldehydes [103a]



123 **122**

To a stirred solution of the acetylene **123** (50 mmol, 1 eq.) in anhydrous tetrahydrofuran (50 mL) at –40°C was added *n*-butyl lithium (20 mL of a 2.5M solution in hexanes, 50 mmol, 1 eq.) dropwise and, when this addition was completed, anhydrous dimethylformamide (7.80 mL, 100 mmol, 2 eq.) was added in one portion. The mixture was then warmed to room temperature and stirred for 30 min then poured into a well-stirred mixture of 10% aqueous KH_2PO_4 (200 mL, 160 mmol, 3.2 eq.) and diethyl ether (200 mL) maintained at 5°C and the resulting mixture stirred vigorously for 10 min. The aqueous layer was separated and extracted with ether (2 x 100 mL), The combined organic solutions were then dried and evaporated to give the *aldehyde* **122**, which was usually ready for further use.

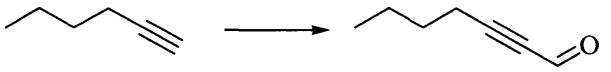
***3-Phenyl-2-propynal* 224** [103a]



223 **224**

Phenylacetylene **223** (5.10 g, 50 mmol) in anhydrous tetrahydrofuran (50 mL) at –40°C was reacted with *n*-butyl lithium (20 mL of a 2.5M solution in hexanes, 50 mmol) dropwise and anhydrous dimethylformamide (7.80 mL, 100 mmol) according to the general procedure. Work-up yielded the *aldehyde* **224** as a yellow oil (6.5 g, ca. 100%); ν_{max}/cm^{-1} [film] 2855 (w), 2182 (s), 1659 (s), 1483 (m), 1438 (m), 1388 (w), 1257 (w), 1022 (w), 946 (m), 755 (w) and 685 (w); δ_H 7.33 (2H, dd, *J* 7.7, 7.4, 2 x ArH), 7.41 (1H, tt, *J* 7.4, 2.3, ArH), 7.54 (2H, dd, *J* 7.7, 2.3, 2 x ArH) and 9.36 (1H, s, CHO); δ_C 88.8, 95.5 (C≡C), 119.8 (ArC), 129.1 (2 x ArCH), 131.7 (ArCH), 133.7 (2 x ArCH) and 177.2 (C=O); *m/z* [APcI] 131 ($[M+H]^+$, 100). *These data are consistent with those recorded in the literature.* [103a]

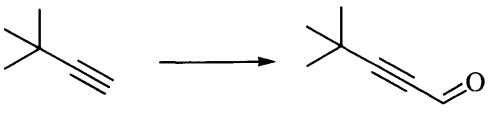
***2-Heptynal* 226** [103b]



225 **226**

1-Hexyne **225** (5.8 ml, 50 mmol) in anhydrous tetrahydrofuran (50 mL) at –40°C was reacted with *n*-butyl lithium (20 mL of a 2.5M solution in hexanes, 50 mmol) dropwise and anhydrous dimethylformamide (7.80 mL, 100 mmol) according to the general procedure. Work-up yielded the *aldehyde* **226** as a light yellow oil (4.90 g, ca. 100%); ν_{max}/cm^{-1} [film] 2959 (s), 2201 (s), 1672 (s), 1466 (m), 1213 (m) and 1137 (m); δ_H 0.82 (3H, t, *J* 7.3, CH_3), 1.35 (2H, hex, *J* 7.3, 6-CH_2), 1.48 (2H, pen, *J* 7.3, 5-CH_2), 2.32 (2H, t, *J* 7.3, 4-CH_2) and 9.07 (1H, s, CHO); δ_C 13.1 (CH_3), 18.4, 21.5, 29.2 (4-, 5- and 6-CH_2), 81.3, 98.7 (C≡C) and 176.7 (C=O); *m/z* [APcI] 111 ($[M+H]^+$, 100). *These data are consistent with those recorded in the literature.*[103b]

***4-Dimethylpent-2-ynal* 228** [103c]

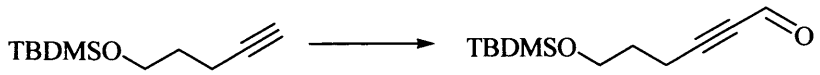


227 **228**

3,3-Dimethyl-1-butyne **227** (5.0 g, 60 mmol) in anhydrous tetrahydrofuran (50 mL) at –40°C was reacted with *n*-butyl lithium (24 mL of a 2.5M solution in hexanes, 60 mmol) dropwise and anhydrous dimethylformamide (9.36 mL, 120 mmol) according to the general procedure. Work-up yielded the *aldehyde* **228** as a light yellow oil (6.60 g, ca. 100%); ν_{max}/cm^{-1} [film]

2862 (s), 2770 (m), 2220 (w), 1685 (s), 1602 (w), 1518 (w), 1456 (m), 1364 (m), 1265 (m), 1067 (br) and 803 (w); δ_H 1.19 (9H, s, 3 x CCH_3) and 9.09 (1H, s, CHO); δ_C 28.0 (C), 30.2 (3 x CCH_3), 71.6, 99.6 (C≡C) and 158.0 (C=O). *These data are consistent with those recorded in the literature.*[103c]

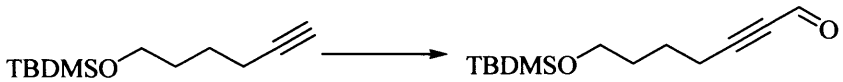
***6-(tert-Butyldimethylsilyloxy)-hex-2-ynal* 2230** [103d]



229 **230**

The ynyloxy-silane **229** (9.00 g, 45.4 mmol,) in anhydrous tetrahydrofuran (45 mL) at –40°C was reacted with *n*-butyl lithium (18 mL of a 2.5M solution in hexanes, 45.8 mmol) dropwise and anhydrous dimethylformamide (7.00 mL, 91 mmol) according to the general procedure. Work-up yielded the *aldehyde* **230** as a brownish oil (8.40 g, 82%); ν_{max}/cm^{-1} [film] 2955 (m), 2929 (s), 2856 (m), 2203 (s), 1671 (s), 1472 (w), 1388 (w), 1256 (m), 1136 (m), 1106 (s), 959 (w), 837 (s) and 776 (m); δ_H 0.00 (6H, s, 2 x $SiCH_3$), 0.84 (9H, s, 3 x CH_3), 1.74 (2H, pen, *J* 6.5, 5-CH_2), 2.46 (2H, t, *J* 6.5, 4-CH_2), 3.58 (2H, t, *J* 6.5, 6-CH_2) and 9.16 (1H, s, CHO); δ_C -5.4 (2 x $SiCH_3$), 15.7 (5-CH_2), 18.3 (SiC), 25.9 (3 x CH_3), 30.6 (4-CH_2), 61.1 (6-CH_2), 81.7, 99.1 (C≡C) and 177.2 (C=O); *m/z* [APcI] 227 ($[M+H]^+$, 100), 211 (50), 95 (28). *These data are consistent with those recorded in the literature.*[103d]

***7-(tert-Butyldimethylsilanyloxy)-hept-2-ynal* 232** [102b]

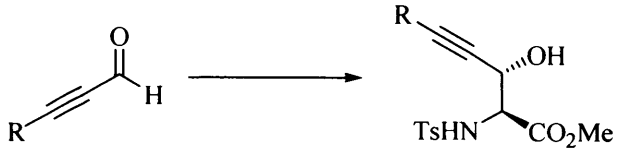


231 **232**

The ynyloxy-silane **231** (6.00 g, 25 mmol) in anhydrous tetrahydrofuran (25 mL) at –40°C was reacted with *n*-butyl lithium (10 mL of a 2.5M solution in hexanes, 25 mmol) dropwise and anhydrous dimethylformamide (3.90 mL, 50 mmol) according to the general procedure. Work-up yielded the *aldehyde* **232** as a brownish oil (4.42 g, 80%); ν_{max}/cm^{-1} [film] 2953 (s), 2857 (m), 2201 (s), 1672 (s), 1102 (s), 1256 (m), 1106 (s), 837 (s) and 776 (s); δ_H 0.00 (6H, s, 2 x $SiCH_3$), 0.84 (9H, s, 3 x CH_3), 1.55-1.62 (4H, m, 5- and 6-CH_2), 2.40 (2H, t, *J* 6.6, 4-CH_2), 3.59 (2H, t, *J* 6.6, 7-CH_2) and 9.13 (1H, s, CHO); δ_C -4.9 (2 x $SiCH_3$), 19.3, 26.0 (5- and 6-CH_2), 24.5 (SiC), 26.3 (3 x CH_3), 32.1 (4-CH_2), 62.7 (7-CH_2), 82.1, 86.5 (2 x C≡) and

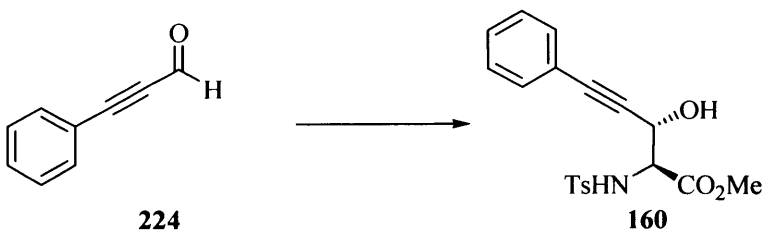
177.7 (C=O); *m/z* [APcI] 241 ([M+H]$^+$, 100), 225 (18), 157 (45), 109 (100). *These data are consistent with those recorded in the literature.*[102b]

General Procedure for the Prepaprtion of β-Hydroxy-α-Amino Ester from Chelated Glycine Enolates [33]



Diisopropylamine (10 mmol, 2.5 eq.) was dissolved in anhydrous tetrahydrofuran (5 mL) at 0°. A solution of *n*-butyl lithium (5 mL of a 2.5M solution in hexanes, 10 mmol, 2.5 eq.) was added dropwise and the solution stirred at 0°C for 30 min. The lithium diisopropylamide solution thus formed was cooled to –78°C. A solution of methyl *N*-tosyl glycinate **154** (1.00 g, 4 mmol, 1 eq.) and tin(II) chloride (1.9 g, 10 mmol, 2.5 eq.) in anhydrous tetrahydrofuran (25 mL) was added dropwise and the resulting mixture stirred at –78°C for 10 min. The ynal **122** (0.53 g, 4.8 mmol, 1.2 eq.) was then added and the reaction stirred at –78°C for 30 min, then quenched by pH 7 buffer solution (5 mL) and diluted with diethyl ether (5 mL). The mixture was allowed to warm to room temperature over 2 h and filtered through celite. The layers were then separated and the aqueous layer extracted with diethyl ether (3 x 5 mL). The combined ether extracts were washed with brine (5 mL) and dried. Removal of the solvent on a rotary evaporator gave the crude product as a yellow solid. Column chromatography gave the *hydroxy ester* **120**.

***Methyl (2SR,3SR)-3-hydroxy-5-phenyl-2- (4-methylphenylsulfonylamino)-pent-4-ynoate* 160**

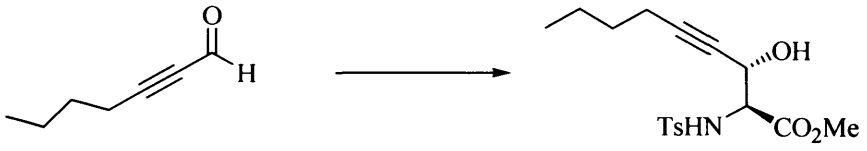


To a solution of lithium diisopropylamine (1.4 mL, 10 mmol) in anhydrous tetrahydrofuran (5 mL) at -78° was added a solution of methyl *N*-tosyl glycinate **154** (1.00 g, 4 mmol), tin(II) chloride (1.9 g, 10 mmol) in anhydrous tetrahydrofuran (25 mL) and 3-phenyl-2-propynal **224** (0.53 g, 4.8 mmol) as described in the general procedure. After the work-up, the product was

purified to give the *hydroxy ester* **160** as a pale yellow solid (1.143g, 76%), mp 133-134°C; R_f 0.2 (40% ethyl acetate in petroleum ether), *anti:syn* = 90:10; ν_{max}/cm^{-1} [nujol] 3328 (br), 2923 (s), 2854 (s), 1750 (w), 1462 (m), 1377 (w), 1234 (w), 1156 (w), 1090 (w) and 762 (w); δ_H (major isomer) 2.36 (3H, s $ArCH_3$), 2.88 (1H, d, *J* 10.2, OH), 3.55 (3H, s, OCH_3), 4.18 (1H, dd, *J* 9.5, 3.4, 2-H), 4.82 (1H, dd, *J* 10.2, 3.4, 3-H), 5.54 (1H, br d, *J* 9.5, NH), 7.20-7.33 (7H, m, ArH) and 7.70 (2H, d, *J* 8.3, 2 x ArH); δ_C 23.0 ($ArCH_3$), 53.5 (OCH_3), 61.0 (2-CH), 64.0 (3-CH), 85.0, 87.3 (C≡C), 121.9 (ArC), 127.8 (2 x ArCH), 128.7 (2 x ArCH), 129.0 (ArCH), 130.2 (2 x ArCH), 132.2 (2 x ArCH), 136.9, 146.0 (2 x ArC) and 168.6 (C=O); *m/z* [APcI] 374 ($[M+H]^+$, 5), 356 (100), 201 (50), 170 (40), 152 (80); Found: $[M+NH_4]^+$, 391.1322. $C_{19}H_{23}N_2O_5S$ requires *M*, 391.1317.

The minor isomer was identified by resonances at δ_H 2.29 (3H, s $ArCH_3$) and 3.60 (3H, s, OCH_3). The ratio was calculated by careful integration of these resonances.

***Methyl (2SR,3SR)-3-hydroxy-2-(4-methylphenylsulfonylamino)-non-4-ynoate* 161**



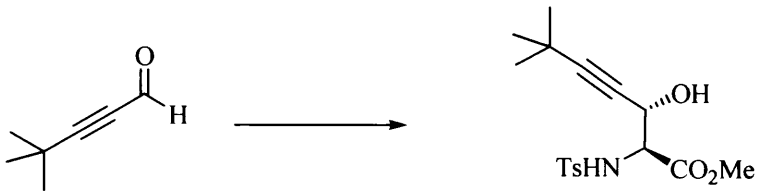
226 **161**

To a solution of lithium diisopropylamine (1.4 mL, 10 mmol) in anhydrous tetrahydrofuran (5 mL) at -78° was added a solution of methyl *N*-tosyl glycinate **154** (1.00 g, 4 mmol) and tin(II) chloride (1.9 g, 10 mmol) in anhydrous tetrahydrofuran (25 mL) and 2-heptynal **226** (0.53 g, 4.8 mmol) as described in the general procedure. After the work-up, the product was purified to give the *hydroxy ester* **161** as a pale yellow solid (1.70 g, 64%), mp 64-65°C, R_f 0.32 (40% ethyl acetate in petroleum ether), *anti:syn* = 96:4; ν_{max}/cm^{-1} [nujol] 3424 (w), 3246 (w), 2930 (s), 2855 (s), 2190 (w), 1750 (w), 1456 (m), 1376 (w), 1159 (w) and 1090 (w); δ_H (major isomer) 0.82 (3H, t, *J* 7.2, 9-CH_3), 1.25-1.31 (2H, m, 8-CH_2), 1.34-1.39 (2H, m, 7-CH_2), 2.09 (2H, td, *J* 7.2, 1.8, 6-CH_2), 2.35 (3H, s, $ArCH_3$), 2.66 (1H, d, *J* 10.5, OH), 3.50 (3H, s, OCH_3), 4.06 (1H, dd, *J* 9.6, 3.6, 2-H), 4.57 (1H, ddt, *J* 10.5, 3.6, 1.8, 3-H), 5.43 (1H, d, *J* 9.6, NH), 7.24 (2H, d, *J* 8.2, 2 x ArH) and 7.68 (2H, d, *J* 8.2, ArH); δ_C 13.6 (9-CH_3), 17.8 (8-CH_2), 21.4 ($ArCH_3$), 24.4, 30.1 (6- and 7-CH_2), 52.3 (OCH_3), 59.8 (2-CH), 63.8 (3-CH), 74.8, 89.5 (C≡C), 127.7, 129.3 (both 2 x ArCH), 135.2, 145.0 (2 x ArC) and 168.2 (C=O); *m/z* [APcI]

354 ([M+H]$^+$, 80), 336 (100), 139 (30); Anal. Calcd for $C_{17}H_{23}NO_5S$: C, 57.79; H, 6.52; N, 3.97. Found: C, 57.87; H, 6.53; N, 4.01%.

The minor isomer was identified by resonance at δ_H 3.57 (3H, s, OCH_3). The ratio was calculated by careful integration of this resonance.

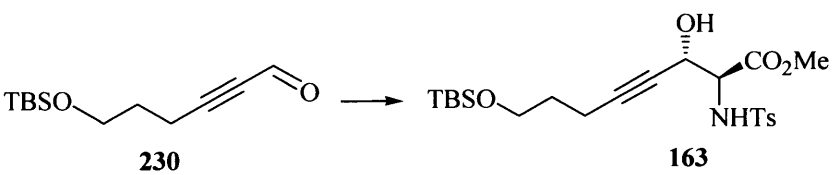
***Methyl (2SR,3SR)-3-hydroxy-6,6-dimethyl-2-(4-methylphenylsulfonylamino)-hept-4-ynoate* 162**



228 **162**

To a solution of lithium diisopropylamine (4.2 mL, 30 mmol) in anhydrous tetrahydrofuran (15 mL) at -78° was added a solution of methyl *N*-tosyl glycinate **154** (3.00 g, 12 mmol) and tin(II) chloride (5.70 g, 30 mmol) in anhydrous tetrahydrofuran (75 mL) and 4,4-dimethyl-2-pentynal **228** (1.58 g, 14.4 mmol) as described in the general procedure. After the work-up, the product was purified to give the *hydroxy ester* **162** as a colourless solid (6.93g, 65%), mp 128-129°C, R_f 0.41 (40% ethyl acetate in petroleum ether), *anti:syn* = 100:0; ν_{max}/cm^{-1} [nujol] 3498 (w), 3267 (w), 2969 (w), 2242 (w), 1743 (m), 1598 (w), 1435 (w), 1342 (m), 1265 (w), 1163 (s), 1092 (m), 815 (w) and 666 (s); δ_H 1.17 (9H, s, 3 x CH_3), 2.43 (3H, s, $ArCH_3$), 2.65 (1H, d, *J* 10.4, OH), 3.57 (3H, s, OCH_3), 4.13 (1H, dd, *J* 9.6, 3.9, 2-H), 4.63 (1H, dd, *J* 10.4, 3.9, 3-H), 5.46 (1H, d, *J* 9.6, NH), 7.31 (2H, d, *J* 8.1, 2 x ArH) and 7.75 (2H, d, *J* 8.1, 2 x ArH); δ_C 21.6 ($ArCH_3$), 27.4 (C), 31.0 (3 x CH_3), 52.7 (OCH_3), 60.6 (2-CH), 62.9 (3-CH), 74.0, 86.8 (C≡C), 127.3, 129.7 (both 2 x ArCH), 136.2, 144.0 (2 x ArC) and 168.7 (C=O); *m/z* [APcI] 354 ([M+H]$^+$, 35), 336 (100), 308 (15), 137 (20); Anal. Calcd for $C_{17}H_{23}NO_5S$: C, 57.79; H, 6.52; N, 3.97. Found: C, 57.88; H, 6.73; N, 4.15%.

***Methyl (2SR,3SR)-8-(tert-butyldimethylsilyloxy)-3-hydroxy-2-(4-methyl phenylsulfonylamino)-oct-4-ynoate* 163**

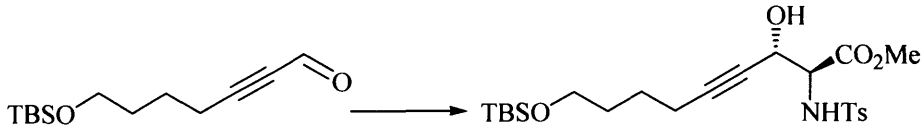


230 **163**

To a solution of lithium diisopropylamine (4.2 mL, 30 mmol) in anhydrous tetrahydrofuran (15 mL) at -78° was added a solution of methyl *N*-tosyl glycinate **154** (3.00 g, 12 mmol) and tin(II) chloride (5.70 g, 30 mmol) in anhydrous tetrahydrofuran (75 mL) and the 6-(silyloxy)-hex-2-ynal **230** (3.25 g, 14.4 mmol) as described in the general procedure. After the work-up, the product was purified to give the *hydroxy ester* **163** as a light yellow solid (3.38 g, 60%), mp 72-73°C, R_f 0.62 (40% ethyl acetate in petroleum ether), *anti:syn* = 92:8; ν_{max}/cm^{-1} [nujol] 3478 (w), 3280 (w), 2954 (m), 2856 (m), 2232 (w), 1744 (m), 1594 (w), 1435 (w), 1342 (m), 1255 (m), 1164 (s), 1094 (s), 836 (s), 776 (m) and 664 (m); δ_H (major isomer) 0.00 (6H, s, 2 x $SiCH_3$), 0.85 (9H, s, 3 x CH_3), 1.61 (2H, pen, *J* 6.1, 7-CH_2), 2.21 (2H, td, *J* 6.1, 2.0, 6-CH_2), 2.38 (3H, s, $ArCH_3$), 2.67 (1H, d, *J* 10.0, OH), 3.57 (3H, s, OCH_3), 3.63 (2H, t, *J* 6.1, 8-CH_2), 4.13(1H, dd, *J* 9.6, 3.7, 2-H), 4.64 (1H, ddt, *J* 10.0, 3.7, 2.0, 3-H), 5.45 (1H, d, *J* 9.6, NH), 7.26 (2H, d, *J* 8.2, 2 x ArH) and 7.7 (2H, d, *J* 8.2, 2 x ArH); δ_C -5.4 (2 x $SiCH_3$), 15.4 (7-CH_2), 18.3 (C), 21.6 ($ArCH_3$), 26.3 (3 x CH_3), 31.8 (6-CH_2), 53.3 (OCH_3), 61.0 (2-CH), 61.7 (8-CH_2), 63.5 (3-CH), 76.0, 89.2 (C≡C), 126.3, 127.7 (both 2 x ArCH), 136.1, 143.2 (2 x ArC) and 168.0 (C=O); *m/z* [APcI] 470 ($[M+H]^+$, 100%), 452 (60), 93 (55); Anal. Calcd for $C_{22}H_{35}NO_6SSi$: C, 56.25; H, 7.46; N, 2.98. Found: C, 56.04; H, 7.49; N, 2.96%.

The minor isomer was identified by resonances at δ_H 2.57 (1H, d, *J* 10.0, OH) and 5.35 (1H, d, *J* 9.6, NH). The ratio was calculated by careful integration of these resonances.

***Methyl (2SR,3SR)-9-(tert-butyldimethylsilyloxy)-3-hydroxy-2-(4-methyl phenylsulfonylamino)-non-4-ynoate* 164**



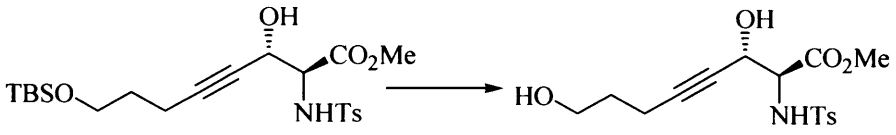
232 **164**

To a solution of lithium diisopropylamine (2.1 mL, 15 mmol) in anhydrous tetrahydrofuran (8 mL) at -78° was added a solution of methyl *N*-tosyl glycine ester **154** (1.50 g, 6 mmol) and tin(II) chloride (2.85 g, 15 mmol) in anhydrous tetrahydrofuran (40 mL) and the 7-(silyloxy)-hept-2-ynal **232** (1.73 g, 7.2 mmol) as described in the general procedure. After the work-up, the product was purified to give the *hydroxy ester* **164** as a light yellow solid (2.90 g, 60%), mp 81-82°C, R_f 0.57 (40% ethyl acetate in petroleum ether), *anti:syn* = 90:10; ν_{max}/cm^{-1} [nujol] 3488 (w), 3288 (w), 2954 (m), 2858 (w), 2232 (w), 1746 (s), 1598 (w), 1436 (m), 1337 (s), 1257 (m), 1163 (s), 1094 (s), 837 (m), 814 (m), 77 (w) and 663 (m); δ_H (major

isomer) 0.04 (6H, s, 2 x $SiCH_3$), 0.89 (9H, s, 3 x CH_3), 1.58-1.65 (4H, m, 7- and 8-CH_2), 2.21 (2H, td, *J* 6.2, 2.0, 6-CH_2), 2.42 (3H, s, $ArCH_3$), 2.74 (1H, d, *J* 10.4, OH), 3.56 (3H, s, OCH_3), 3.60 (2H, t, *J* 6.2, 9-CH_2), 4.13 (1H, dd, *J* 9.5, 3.7, 2-H), 4.64 (1H, br d, *J* 9.5, NH), 5.51 (1H, ddt, *J* 10.4, 3.7, 2.0, 3-H), 7.3 (2H, d, *J* 8.2, 2 x ArH) and 7.75 (2H, d, *J* 8.2, 2 x ArH); δ_C 0.0 (2 x $SiCH_3$), 15.9, 16.2 (7- and 8-CH_2), 18.7 (C), 22.4 ($ArCH_3$), 25.9 (3 x CH_3), 33.1 (6-CH_2), 53.8 (OCH_3), 60.7 (2-CH), 62.6 (9-CH_2), 63.8 (3-CH), 76.6, 89.3 (C≡C), 127.4, 129.8 (both 2 x ArCH), 136.5, 143.9 (2 x ArC) and 168.4 (C=O); *m/z* [APcI] 484 ($[M+H]^+$, 100), 466 (20), 334 (50); Anal. Calcd for $C_{23}H_{37}NO_6SSi$: C, 57.1; H, 7.65; N, 2.90. Found: C, 57.24; H, 7.65; N, 2.80%.

The minor isomer was identified by resonances at δ_H 2.55 (1H, d, *J* 10.0, OH) and 5.54 (1H, d, *J* 9.6, NH). The ratio was calculated by careful integration of these resonances.

***Methyl (2SR,3SR)-3,8-dihydroxy-2-(4'-methylphenylsulfonylamino)-oct-4-ynoate* 240**



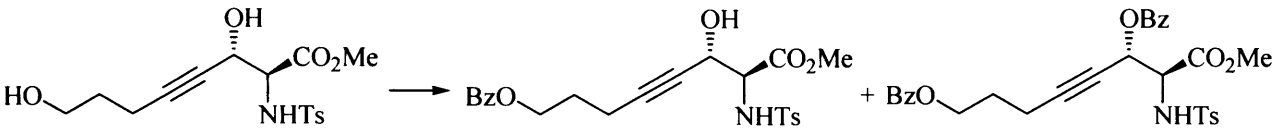
163 **240**

To a stirred solution of the ester **163** (2.0 g, 4.0 mmol) in anhydrous tetrahydrofuran (50 mL) cooled to 0°C was added tetrabutylammonium fluoride (4.2 mL of a 1M solution in THF, 4.2 mmol) dropwise. The mixture was then allowed to stir for 16 h at room temperature. The mixture was then quenched with water (50 mL) and diluted with dichloromethane (25 mL). The separated organic layer was washed with water (2 x 25 mL), dried and evaporated to give light yellow oil. The crude oil was crystallized from hexane and ethyl acetate to give the *alcohol* **240** as a colourless solid (0.61 g, 43%); mp 115-116°C, *anti:syn* = 80:20; R_f 0.07 (50% ethyl acetate in hexane); ν_{max}/cm^{-1} [nujol] 3498 (m), 3290 (m), 2945 (w), 2875 (w), 1728 (m), 1594 (w), 1433 (m), 1336 (m), 1162 (s), 1052 (w), 811 (w) and 650 (m); δ_H (major isomer) 1.68 (2H, pen, *J* 6.1, 7-CH_2), 2.25 (2H, t, *J* 6.1, 6-CH_2), 2.36 (3H, s, $ArCH_3$), 2.74 (1H, d, *J* 9.7, OH), 3.57 (3H, s, OCH_3), 3.70 (2H, t, *J* 6.1, 8-CH_2), 4.11 (1H, dd, *J* 9.8, 3.7, 2-H), 4.58 (1H, br d, *J* 9.8, NH), 5.84 (1H, dd, *J* 9.7, 3.7, 3-H), 7.26 (2H, d, *J* 8.1, 2 x ArH) and 7.70 (2H, d, *J* 8.1, 2 x ArH); δ_C 15.6 (7-CH_2), 21.6 ($ArCH_3$), 31.6 (6-CH_2), 52.9 (OCH_3), 60.8 (2-CH), 61.7 (8-CH_2), 62.8 (3-CH), 78.6, 83.3 (2 x C≡), 127.3, 129.7 (both 2 x ArCH), 136.5, 140.5 (2 x ArC) and 169.1 (C=O); *m/z* [APcI] 356 ($[M+H]^+$, 100), 338 (35), 306 (55); Anal. Calcd for $C_{16}H_{21}NO_6S$: C, 54.02; H, 5.91; N, 3.94. Found: C, 54.21; H, 6.18; N, 4.13%.

The minor isomer was identified by resonance at δ_H 4.64 (1H, d, *J* 9.6, NH). The ratio was calculated by careful integration of this resonance.

Methyl (2SR,3SR)-8-benzoyloxy-3-hydroxy-2-(4'-methyl phenylsulfonylamino)-oct-4-ynoate* 237 *and

***Methyl (2SR,3SR)-3,8-dibenzoyloxy-2-(4'-methyl phenylsulfonylamino)-oct-4-ynoate* 238**



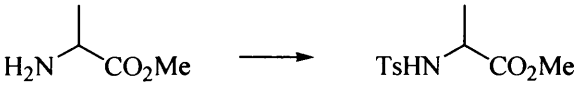
A solution of triethylamine (0.22 mL, 1.54 mmol), DMAP (0.02 g, 0.15 mmol) and benzoyl chloride (0.2 mL, 1.8 mmol) in dichloromethane (5 mL) was cooled to 0°C and to this was slowly added the alcohol **240** (0.528 g, 1.5 mmol) in dichloromethane (5 mL) during 90 min. The mixture was allowed to stir for 16 h at room temperature and then diluted with dichloromethane (25 mL). The separated organic layer was washed with brine (25 mL), saturated aqueous potassium carbonate (25 mL) and 1M HCl (25 mL) at 0°C. Finally, the organic layer was washed again with brine (25 mL), then dried and evaporated to give a light brown oil. Column chromatography then separated the *monobenzoate* **237** as a pale yellow solid (0.30 g, 44%); mp 79-80°C, *anti:syn* = 80:20; R_f 0.68 (40% ethyl acetate in hexane); ν_{max}/cm^{-1} [nujol] 3529 (m), 3278 (m), 2952 (m), 1725 (s), 1599 (w), 1493 (w), 1451 (m), 1340 (m), 1265 (s), 1208 (w), 1162 (s), 1092 (s), 1069 (m), 1026 (m), 982 (w), 815 (w), 714 (m) and 665 (m); δ_H (major isomer) 1.68 (2H, pen, *J* 6.1, 7-CH_2), 2.25 (3H, s, ArCH_3), 2.22-2.29 (2H, m, 6-CH_2), 2.53 (1H, br d, *J* 10.0, OH), 3.57 (3H, s, OCH_3), 4.12 (2H, t, *J* 6.1, 8-CH_2), 4.44 (1H, dd, *J* 10.0, 3.6, 2(3)-H), 5.11 (1H, dd, *J* 10.0, 3.6, 3(2)-H), 5.79 (1H, br d, *J* 10.0, NH), 7.10 (2H, d, *J* 8.2, 2 x ArH), 7.33 (2H, d, *J* 7.4, 2 x ArH), 7.49 (1H, t, *J* 7.4, ArH), 7.64 (2H, d, *J* 8.2, 2 x ArH) and 7.87 (2H, d, *J* 7.4, 2 x ArH); δ_C 16.1 (7-CH_2), 21.9 (ArCH_3), 30.9 (6-CH_2), 53.6 (OCH_3), 59.0 (2(3)-CH), 65.0 (8-CH_2), 65.2 (3(2)-CH), 73.3, 90.3 (2 x C≡), 127.4, 128.9 (both 2 x ArCH), 129.3 (ArC), 130, 130.4 (both 2 x ArCH), 133.9 (ArCH), 137.5, 143.9 (2 x ArC) and 165.6, 168.8 (both C=O); *m/z* [APcI] 460 ($[M+H]^+$, 100), 442 (40), 338 (40), 306 (30), 182 (50); Found: $[M+H]^+$, 460.1432. $C_{23}H_{26}NO_7S$ requires *M*, 460.1424.

The minor isomer was identified by resonances at δ_H 4.34 (1H, dd, *J* 10.0, 3.6, 2(3)-H) and 5.91 (1H, dd, *J* 10.0, 3.6, 3(2)-H). The ratio was calculated by careful integration of these resonances;

Earlier fractions gave the *dibenzoate* **238** as a yellow solid (0.26 g, 37%); mp 66-67°C, *anti:syn* = 80:20; R_f 0.76 (40% ethyl acetate in hexane); ν_{max}/cm^{-1} [nujol] 3264 (w), 3056 (w), 2957 (w), 2242 (w), 1720 (s), 1600 (w), 1492 (w), 1451 (m), 1343 (m), 1272 (s), 1165 (s), 1093 (s), 1026 (m), 814 (w) and 713 (s); δ_H 1.90 (2H, pent, *J* 6.7, 7-CH_2), 3.14-3.46 (5H, m, 6-CH_2 and $ArCH_3$), 3.60 (3H, s, OCH_3), 3.65-3.84 (2H, m, 8-CH_2), 4.47 (1H, dd, *J* 9.9, 3.6, 2(3)-H), 5.78-5.84 (2H, m, NH and 3(2)-H), 7.12 (2H, d, *J* 8.2, 2 x ArH), 7.31-7.36 (4H, m, 2 x ArH and 2 x ArH), 7.53-7.61 (2H, m, 2 x ArH), 7.67 (2H, d, *J* 8.2, 2 x ArH), 7.92 (2H, d, *J* 7.2, 2 x ArH) and 7.97 (2H, d, *J* 7.2, 2 x ArH); δ_C 15.6 (7-CH_2), 21.6 ($ArCH_3$), 27.4 (6-CH_2), 53.2 (OCH_3), 58.5 (2(3)-CH), 63.1 (8-CH_2), 64.7 (3(2)-CH), 73.4, 88.5 (2 x C≡), 127.1, 128.3 (both 2 x ArCH), 129, 129.3 (2 x ArCH), 129.6, 130.0 (both 2 x ArCH), 130.2, 130.5 (both 2 x ArCH), 133.1, 133.4 (2 x ArC), 137.1, 143.6 (2 x ArC) and 165.2, 166.6, 168.1 (3 x C=O); *m/z* [APcI] 564 ($[M+H]^+$, 30), 469 (15), 151 (15), 72 (100).

The minor isomer was identified by resonance at δ_H 3.70 (3H, s, OCH_3). The ratio was calculated by careful integration of this resonance.

***Methyl 2-(4'-methylphenylsulfonylamino)-propanoate* 250**[104]

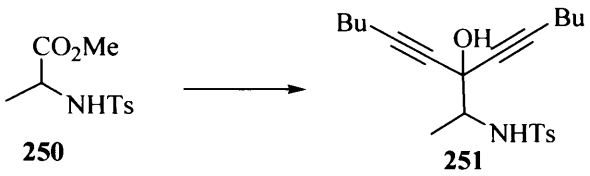


250

Alanine methyl ester (10 g, 71.6 mmol) and *p*-toluenesulfonyl chloride (15 g, 78.8 mmol) were placed in a dry round bottom flask and partially dissolved in 200 mL of anhydrous dichloromethane. After adding DMAP (1.75 g, 17.33 mmol), the reaction mixture was cooled to 0°C and triethylamine (20 mL, 143.3 mmol) added dropwise. The resulting mixture was allowed to stir for 30 min at 0°C, then left to stir at room temperature. After 18 h, the mixture was washed with 50 mL of 2M HCl and then diluted with dichloromethane (100 mL). The mixture was separated and the organic layer washed with water (100 mL) and brine (100 mL) then dried and evaporated. When the crude product (16.3 g) was completely dried, it was recrystallized from petroleum ether 40-60°C and diethyl ether; the mixture was kept in the freezer overnight. The precipitate was filtered and the solid washed with ice-cold diethyl ether.

The dried product was the *N-tosyl ester* **250** (15.3 g, 83%) as colourless crytals, mp 95-96°C [lit. mp[4] 94-95°C]. ν_{max}/cm^{-1} [nujol] 3264 (m), 1734 (m), 1436 (w), 1335 (m), 1209 (w), 1163 (s), 1092 (s), 815 (w) and 650 (m); δ_H 1.38 (3H, d, *J* 6.7, CH_3), 2.40 (3H, s, $ArCH_3$), 3.52 (3H, s, OCH_3), 3.97 (1H, dq, *J* 8.4, 6.7, 2-H), 5.22 (1H, d, *J* 8.4, NH), 7.28 (2H, d, *J* 8.2, 2 x ArH) and 7.73 (2H, d, *J* 8.2, 2 x ArH); δ_C 16.2 (CH_3), 21.2 ($ArCH_3$), 49.6 (2-CH), 50.2 (OCH_3), 125.7 (2 x ArCH), 129.8 (2 x ArCH), 138.4, 146.9 (2 x ArC) and 171.8 (C=O); *m/z* [APcI] 258 ($[M+H]^+$, 55), 198 (100). *These data are consistent with those recorded in the literature.*[104]

***7-Hydroxy-7-[1'-(4-methylphenylsulfonylamino)ethyl]-trideca-5,8-diyne* 251**

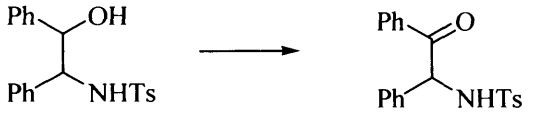


To a solution of 1-hexyne (22.0 mL, 189 mmol) in anhydrous tetrahydrofuran (50 mL) maintained at –40°C was added 2.5 M *n*-butyl lithium (76 mL in hexanes, 189 mmol) dropwise and, when addition was completed, the ester **250** (16.2 g, 63 mmol) was added in one portion. The mixture was then warmed to room temperature and stirred for 30 min, then poured into a mixture of 10% aqueous KH_2PO_4 (600 mL, 480 mmol) and diethyl ether (600 mL) at 5°C and the resulting two-phase mixture stirred for 10 min. The aqueous layer was separated and extracted with ether (2 x 300 mL), The combined organic solutions were then dried and evaporated to leave the *alcohol* **251** (20.9 g, 85%) as a colourless crystalline solid, mp 53-54°C; R_f 0.58 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 3465 (br), 3274 (br), 2956 (s), 2926 (s), 2868 (s), 2233 (m), 1596 (w), 1431 (m), 1379 (w), 1329 (m), 1163 (s), 1092 (m), 1020 (w), 915 (w), 814 (w) and 655 (m); δ_H 0.76-0.81 (6H, m, 2 x CH_3), 1.10 (3H, d, *J* 6.6, CH_3), 1.23-1.38 (2H, m, CH_2), 2.02-2.08 (10H, m, 5 x CH_2), 2.30 (3H, s, $ArCH_3$), 2.72 (1H, s, OH), 3.35 (1H, dq, *J* 9.1, 6.6, 1'-H), 4.55 (1H, d, *J* 9.1, NH), 7.18 (2H, d, *J* 8.1, 2 x ArH) and 7.66 (2H, d, *J* 8.1, 2 x ArH); δ_C 13.6 (2 x CH_3), 17.7 (CH_3), 18.3 (2 x CH_2), 21.5 ($ArCH_3$), 22.0, 30.3 (4 x CH_2), 58.9 (1'-CH), 68.3 (2 x C≡), 78.67 (7-COH), 86.2 (2 x C≡), 127.6 (2 x ArCH), 130.1 (2 x ArCH) and 138.0, 143.9 (2 x ArC); *m/z* [APcI] 372 ($[M-H_2O]^+$, 55), 143 (30), 113 (38), 83 (65), 71 (100); Anal. Calcd for $C_{22}H_{31}NO_3S$: C, 67.87; H, 7.97; N, 3.60. Found: C, 67.79; H, 7.92; N, 3.76%.

General procedure for PCC oxidation of β-hydroxy sulphonamides to tosylamino ketones

To a dried two-necked round bottom flask was added 0.5 g of 4°A molecular sieves, which has been dried in an oven at 110°C for at least 24 h. After the molecular sieves had cooled down to room temperature by using a nitrogen flow, pyridinium chlorochromate (0.44 g, 2.04 mmol, 1.5 eq.) was added. The mixture was suspended in anhydrous dichloromethane (5 mL), then cooled down to 0°C. The alcohol (1.36 mmol, 1 eq.) in dichloromethane (5 mL) was added and the mixture stirred for 15 h at room temperature, then filtered through plug of silica gel using 10-60% diethyl ether in petroleum ether as an eluant. The filtrate was then evaporated and dried under high vacuum to give the crude *ketone*.

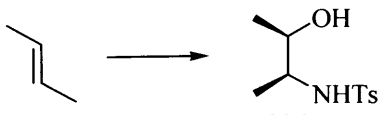
***2-(4-Methylphenylsulfonylamino) -1,2-diphenylethanone* 260** [105]



261 **260**

To a mixture of 4°A molecular sieves (0.5 g) and pyridinium chlorochromate (0.44 g, 2.04 mmol) in anhydrous dichloromethane (5 mL) was added *N*-(2-hydroxy-1,2-diphenyl-ethyl)-4-methylphenylsulfonamide **261** (0.50 g, 1.36 mmol) in dichrolomethane (5 mL) as described in general precedure. Work-up and evaporation gave the *ketone* **260** as a colourless solid (0.40 g, 80%), mp 140-141°C [lit. mp[5] 141-143°C]; R_f 0.78 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 3256 (m), 1680 (m), 1599 (w), 1448 (w), 1329 (m), 1161 (s), 1087 (m) and 700 (s); δ_H 2.23 (3H, s, $ArCH_3$), 5.92 (1H, d, *J* 7.4, 1-CH), 6.14 (1H, d, *J* 7.4, NH), 6.99 (2H, d, *J* 8.1, 2 x ArH), 7.17 (5H, app. s, 5 x ArH), 7.29 (2H, t, *J* 7.6, 2 x ArH), 7.42-7.52 (3H, m, 3 x ArH) and 7.73 (2H, d, *J* 7.6, 2 x ArH); δ_C 20.8 ($ArCH_3$), 63.4 (1-CH), 125.6 (2 x ArCH), 127.1, 127.4, 128.4 (3 x ArCH), 128.5, 128.7 (4 x ArCH), 128.9, 129.3 (4 x ArCH), 131.8 (ArCH), 135.2, 137.5, 134.5, 136.9 (4 x ArC) and 195.6 (C=O); *m/z* [APcI] 366 ($[M+H]^+$, 100), 210 (25), 195 (40). *These data are consistent with those recorded in the literature.*[105]

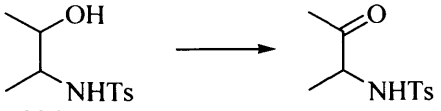
***(2RS,3SR)-3-(4-methylphenylsulfonylamino)-butan-2-ol* 206**



252 **206**

To a solution of $(DHQD)_2AQN$ **253** (0.11 g, 0.125 mmol), chloroamine-T trihydrate (2.11 g, 7.5 mmol) and potassium osmate dihydrate (34 mg, 0.1 mmol) in *t*-butanol (50 mL) and water (50 mL) was added condensed 2-butene **252** (0.14 g, 2.5 mmol). The reaction was immersed in a room temperature water bath and the slurry stirred for 16 h (over the course of the reaction the color changed from brown to deep green and then to yellow). The mixture was evaporated to dryness, the residue treated with ethyl acetate:water (1:1, 50 mL) and the resulting mixture stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic solutions were washed with water (25 mL), brine (25 mL) and dried. Evaporation of the solvent gave the crude hydroxy-sulfonamide mixed with tosylsulfonamide ($TsNH_2$). Column chromatography (10-25% ethyl acetate in petroleum ether) gave the *hydroxy-sulfonamide* **206** as a colourless oil (0.41 g, 66%); ν_{max}/cm^{-1} [film] 3233 (br), 2990 (m), 1492 (w), 1428 (w), 1324 (m), 1158 (s), 1080 (m), 826 (s) and 664 (s); δ_H 0.95 (3H, d, *J* 6.8, CH_3), 1.05 (3H, d, *J* 6.3, CH_3), 1.60 (1H, br, OH), 2.36 (3H, s, $ArCH_3$), 3.07 (1H, ddq, *J* 8.1, 7.2, 6.3, 3-H), 3.54 (1H, dq, *J* 7.2, 6.8, 2-H), 4.68 (1H, d, *J* 8.1, NH), 7.49 (2H, d, *J* 8.1, 2 x ArH) and 7.70 (2H, d, *J* 8.1, 2 x ArH); δ_C 14.6 (CH_3), 17.2 (CH_3), 21.2 ($ArCH_3$), 50.1 (3-CH), 73.8 (2-CH), 125.6, 130.3 (4 x ArCH) and 136.2 140.7 (2 x ArC); *m/z* [APcI] 244 ($[M+H]^+$, 100).

3-(4-Methylphenylsulfonylamino)-butanone 205

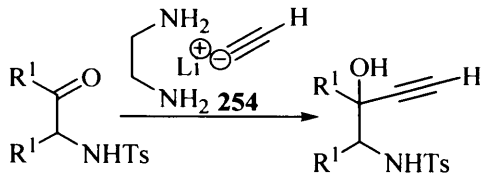


206 **205**

To a mixture of 4°A molecular sieves (3.0 g) and pyridinium chlorochromate (2.66 g, 12.4 mmol) in anhydrous dichloromethane (30 mL) was added the hydroxy-sulfonamide **206** (2.00 g, 8.23 mmol) in anhydrous dichloromethane (30 mL) as described in the general precedure for PCC oxidation. After work-up, flash chromatography (20-40% ethyl acetate in petroleum ether) gave the *ketone* **205** as a colourless oil (1.80 g, 91%); R_f 0.39 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 3258 (b), 2985 (w), 1682 (s), 1496 (w), 1434 (w), 1328 (s), 1160 (s), 1089 (s), 820 (s) and 665 (s); δ_H 1.28 (3H, d, *J* 7.1, 4-CH_3), 2.11 (3H, s, 1-CH_3), 2.35 (3H, s, $ArCH_3$), 3.86 (1H, dq, *J* 9.2, 7.1, 3-H), 5.44 (1H, d, *J* 9.2, NH), 7.22 (2H, d, *J* 8.1, 2 x ArH) and 7.64 (2H, d, *J* 8.1, 2 x ArH); δ_C 16.2 (4-CH_3), 20.8 (1-CH_3), 21.3 ($ArCH_3$), 58.6 (3-CH), 126.9, 130.1 (4 x ArCH), 136.7, 142.9 (2 x ArC) and 206.4 (C=O); *m/z* [APcI] 242 ($[M+H]^+$, 100).

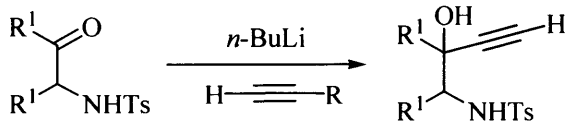
General procedures for the preparation of β–amino-α-hydroxy alkynes by addition of acetylene to α–aminocarbonyls

Method 1



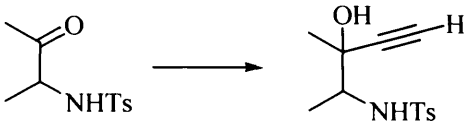
To a solution of lithium acetylide-ethylenediamine **254** (0.12 g, 1.2 mmol, 3 eq.) in anhydrous dimethyl sulfoxide (1 mL) at room temperature were added a solution of the amino-ketone (0.4 mmol, 1 eq.) in anhydrous dimethyl sulfoxide (2 mL) dropwise. The reaction mixture was then stirred at room temperature for 16 h. Water (5 mL) and diethyl ether (5 mL) were added and stirring continued for 10 min. The aqueous layer was separated and extracted with ether (2 x 5 mL). The combined ether solutions were then dried and evaporated to give a crude product. After flash chromatography (40% ethyl acetate in petroleum ether), the *acetylene* was isolated as a mixture of diastereomers.

Method 2



To a stirred solution of the acetylene (0.42 mmol, 1.05 eq.) in anhydrous tetrahydrofuran (1 mL) at –40°C was added 2.5 M *n*-butyl lithium (0.17 mL in hexanes, 0.42 mmol, 1.05 eq.) dropwise and, when this addition was completed, the ketone (0.4 mmol, 1 eq.) was added in one portion. The reaction mixture was then warmed to room temperature and stirred for 30 min, then poured into a well-stirred mixture of 10% aqueous KH_2PO_4 (1 mL, 0.8 mmol) and diethyl ether (1 mL) maintained at 5°C and the resulting mixture stirred vigorously for 10 min. The aqueous layer was separated and extracted with ether (2 x 2 mL). The combined organic layers were then dried and evaporated. The dried product gave the *acetylene* as a mixture of diasteromers.

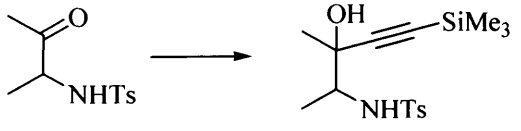
3-Methyl-4-(4'-methylphenylsulfonylamino)- pent-1-yn-3-ol 255



205 **255**

To a solution of lithium acetylide-ethylenediamine (0.12 g, 1.2 mmol) in anhydrous dimethyl sulfoxide (1mL) at room temperature were added a solution of ketone **205** (0.10 g, 0.4 mmol) in anhydrous dimethyl sulfoxide (2 mL) as described in general precedure method 1. After the work-up, flash chromatography (40% ethyl acetate in petroleum ether) gave the *acetylene* **255** (0.10 g, 85%) as a mixture of diastereomers (48:52), mp 102-103°C: R_f 0.45 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 3263 (br), 2983 (w), 2362 (w), 1598 (w), 1495 (w), 1433 (m), 1331 (s), 1163 (s), 1092 (s), 816 (s) and 667 (s); δ_H 0.95 (1.4H, d, *J* 6.7, 5-CH_{3a}), 0.98 (1.6H, d, *J* 6.7, 5-CH_{3b}), 1.35 (1.4H, s, CH_{3a}), 1.37 (1.6H, s, CH_{3b}), 2.33-2.45 (4H, m, 1-CH≡ and $ArCH_3$), 3.19 (0.5H, dq, *J* 9.1, 6.7, 4-H_a), 3.28 (0.5H, dq, *J* 9.1, 6.7, 4-H_b), 5.13 (0.5H, d, *J* 9.1, NH_a), 5.18 (0.5H, d, *J* 9.1, NH_b), 7.22 (2H, m, 2 x ArH) and 7.73 (2H, m, 2 x ArH); δ_C 16.3, 16.9, 21.1, 21.6 (2 x $CH_{3a\&b}$), 26.0, 26.4 ($ArCH_{3\ a\&b}$), 57.5, 58.5 (4-$CH_{a\&b}$), 70.4 (3-C), 73.3, 73.7 and 84.4, 84.9 (2 x $C\equiv_{a\&b}$), 126.4, 127.1 and 129.8, 129.9 (4 x $ArCH_{a\&b}$) and 137.4, 137.5, 143.4, 143.7 (2 x $ArC_{a\&b}$); *m/z* [APcI] 268 ($[M+H]^+$, 10), 250 ($[M-OH]^+$, 100).

3-Methyl-4-(4'-methylphenylsulfonylamino)-1-trimethylsilylpent-1-yn-3-ol 257

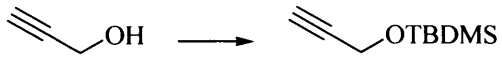


205 **257**

To a stirred solution of trimethylsilylacetylene **297** (0.06 mL, 0.42 mmol) in anhydrous tetrahydrofuran (1 mL) at –40°C was added 2.5 M *n*-butyl lithium (0.17 mL in hexanes, 0.42 mmol) and the ketone **205** (0.21 g, 0.4 mmol) as described in general procedure method 2. After work-up, flash chromatography (20-40% ethyl acetate in petroleum ether) gave the *acethylene* **257** as a colourless solid (50 mg, 34%), as a mixture of diastereomers (61:39), mp 117-118°C: R_f 0.57 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 3440 (br), 3263 (br), 2956 (w), 2170 (w), 1598 (w), 1430 (w), 1331 (m), 1250 (m), 1163 (s), 1092 (s), 945 (s), 816 (m), 760 (m) and 670 (s); δ_H 0.00 (9H, s, 3 x $SiCH_3$), 0.90 (2H, d, *J* 6.9, 5-CH_{3a}), 0.94

(1H, d, *J* 6.9, 5-CH_{3b}), 1.25 (2H, s, $OCCH_{3a}$), 1.26 (1H, s, $OCCH_{3b}$), 2.28 (3H, s, $ArCH_3$), 3.10-3.23 (1H, m, 4-H), 4.57 (0.3H, d, *J* 9.4, NH), 4.60 (0.7H, d, *J* 9.4, NH), 7.17 (2H, d, *J* 8.4, 2 x ArH) and 7.63 (2H, dd, *J* 8.4, 2.0, 2 x ArH); δ_C 0.00 (3 x $SiCH_3$), 16.7 (5-CH_3), 21.7 ($ArCH_3$), 28.0 (CH_3), 58.5 (4-CH), 70.8 (3-C), 90.3, 105.8 (2 x C≡), 127.3, 129.9 (both 2 x ArCH) and 137.7, 143.9 (2 x ArC); *m/z* [APcI] 340 ($[M+H]^+$, 20), 173 (100); Anal. Calcd for $C_{16}H_{25}NO_3SSi$: C, 56.60; H, 7.37; N, 4.13. Found: C, 56.71; H, 7.42; N, 4.35%.

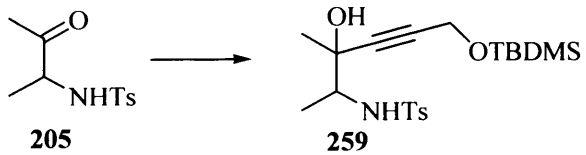
***tert-Butyldimethyl-prop-2-ynyloxy-silane* 258** [106]



258

To a stirred solution of propargyl alcohol (2.00 g, 38 mmol) in tetrahydrofuran (40 mL) was added imidazole (3.20 g, 46 mmol). After a clear solution was obtained, *tert*-butyldimethylsilyl chloride (7.00 g, 46 mmol) was added to give a cloudy solution. The mixture was allowed to stir for 16 h at room temperature, then quenched with water (30 mL) and diluted with dichloromethane (20 mL). The organic layer was separated and washed with brine (30 mL), then dried and evaporated to give the *ynyloxy-silane* **258** as a light yellow oil (6.45 g, 99%); ν_{max}/cm^{-1} [film] 3314 (m), 2953 (s), 2933 (s), 2858 (s), 2118(w), 1472 (w), 1256 (m), 1107 (s), 836 (s) and 776 (s); δ_H 0.00 (6H, s, 2 x $SiCH_3$), 0.78 (9H, s, 3 x CH_3), 2.27 (1H, t, *J* 2.4, CH≡) and 4.13 (2H, d, *J* 2.4, 1-CH_2); δ_C -5.2 (2 x $SiCH_3$), 18.2 (SiC), 25.7 (3 x CH_3), 51.5 (1-CH_2) and 72.9, 82.4 (C≡C). *These data are consistent with those recorded in the literature.*[106]

***1-O-tert-Butyldimethylsilyl-4-methyl-(4-methylphenylsulfonylamino)-hex-2-yne-1,4-diol* 259**

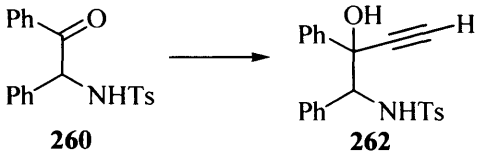


205 **259**

To a stirred solution of the acetylene **258** (80 mg, 0.46 mmol) in anhydrous tetrahydrofuran (1 mL) at –40°C was added 2.5 M *n*-butyl lithium (0.2 mL in haxanes, 0.46 mmol) and the ketone **205** (50 mg, 0.21 mmol) as described in general procedure method 2. After work-up, flash chromatography gave the *acetylene* **259** as a colourless solid (50 mg, 59%) and as a

mixture of diastereomers (55:45), mp 131-132°C; R_f 0.61 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 3346 (b), 3266 (b), 2930 (m), 2857 (m), 1598 (w), 1463 (w), 1331 (m), 1256 (m), 1163 (s), 1092 (s), 837 (s), 752 (m) and 666 (s); δ_H 0.00 (6H, s, 2 x $SiCH_3$), 0.80 (9H, s, 3 x CH_3), 0.93 (1.65H, d, *J* 6.7, 6-CH_{3a}), 0.98 (1.35H, d, *J* 6.7, 6-CH_{3b}), 1.31 (1.65H, s, CH_{3a}), 1.33 (1.35H, s, CH_{3b}), 2.30 (3H, s, $ArCH_3$), 3.18-3.22 (1H, m, 5-H), 4.17 (1.1H, s, 1-CH_{2a}), 4.21 (0.9H, s, 1-CH_{2b}), 4.94 (0.55H, d, *J* 9.9, NH_a), 5.06 (0.45H, d, *J* 9.9, NH_b), 7.21-7.23 (2H, m, 2 x ArH) and 7.62-7.65 (2H, m, 2 x ArH); δ_C –5.1 (2 x $SiCH_3$), 16.6 (CH_3), 18.3 (SiC), 21.6 ($ArCH_3$), 25.8 (3 x CH_3), 26.4 (CH_3), 51.6 (1-CH_2), 58.5 (5-CH), 70.5 (4-C), 84.0, 85.0 (C≡C), 127.1, 129.9 (4 x ArCH) and 137.6, 143.7 (2 x ArC); *m/z* [APcI] 412 ($[M+H]^+$, 25), 394 (100); Found: $[M+H]^+$, 412.1976. $C_{20}H_{34}NO_4SSi$ requires *M*, 412.1972.

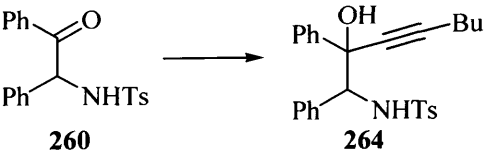
1,2-Diphenyl-1-(4-methylphenylsulfonylamino)-but-3-yn-2-ol 262



260 **262**

To a solution of lithium acetylide-ethylenediamine (0.05 g, 0.45 mmol) in anhydrous dimethyl sulfoxide (1mL) at room temperature were added a solution of the ketone **260** (60 mg, 0.15 mmol) in anhydrous dimethyl sulfoxide (2 mL) as described in general precedure method 1. After work-up, flash chromatography (40% ethyl acetate in petroleum ether) gave the *acetylene* **262** as a colourless solid (40 mg, 67%) and as a single diastereomer, mp 161-162°C; R_f 0.55 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 3278 (m), 2363 (w), 1448 (w), 1325 (m), 1159 (s), 1090 (m) and 698 (s); δ_H 2.23 (3H, s, $ArCH_3$), 2.54 (1H, s, CH≡), 4.51 (1H, d, *J* 8.6, 1-H), 5.34 (1H, d, *J* 8.6, NH), 6.89-6.92 (4H, m, 4 x ArH), 7.02 (2H, t, *J* 7.7, 2 x ArH), 7.15-7.19 (4H, m, 4 x ArH), 7.26 (2H, d, *J* 8.2, 2 x ArH) and 7.32 (2H, dd, *J* 7.7, 1.5, 2 x ArH); δ_C 20.1 ($ArCH_3$), 60.7 (1-CH), 71.2 (C≡), 81.4 (2-C), 84.2 (C≡), 125.3, 125.8 (4 x ArCH), 126.1 (2 x ArCH), 126.5, 127.1 (2 x ArCH), 128.4, 128.8 (4 x ArCH), 128.9, (2 x ArCH) and 136.2, 139.2, 140.1, 143.0 (4 x ArC); *m/z* [APcI] 374 ($[M-OH]^+$, 100), 260 (30), 218 (70); Found $[M+NH_4]^+$, 409.1582. $C_{23}H_{25}N_2O_3S$ requires M, 409.1580.

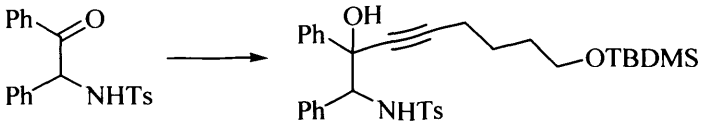
1,2-Diphenyl-1-(4-methylphenylsulfonyl)-2-oct-3-yn-2ol 263



260 **264**

To a stirred solution of hexyne **225** (0.03 g, 0.54 mmol) in anhydrous tetrahydrofuran (1 mL) at –40°C was added 2.5 M *n*-butyl lithium (0.22 mL in hexanes, 0.54 mmol) and the ketone **260** (0.10 g, 0.27 mmol) as described in general procedure method 2. After work-up, flash chromatography (40% ethyl acetate in petroleum ether) gave the *acetylene* **264** as a yellow solid (70 mg, 58%) and as a single diastereomer, mp 168-169°C; R_f 0.44 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 3274 (b), 3046 (m), 3334 (m), 2873 (w), 1692 (s), 1598 (m), 1450 (s), 1416 (m), 1320 (s), 1289 (s), 1161 (s), 1091 (m), 1026 (m), 812 (m), 701 (s) and 671 (s); δ_H 0.84 (3H, t, *J* 7.3, CH_3), 1.19 (2H, pent, *J* 7.3, 7-CH_2), 1.33 (2H, hex, *J* 7.3, 6-CH_2), 1.45 (2H, t, *J* 7.3, 5-CH_2), 2.23 (3H, s, $ArCH_3$), 4.43 (1H, d, *J* 8.1, 1-CH), 5.36 (1H, d, *J* 8.1, NH), 6.89 (2H, t, *J* 8.1, 2 x ArH), 6.97-7.03 (4H, m, 4 x ArH), 7.05-7.15 (4H, m, 4 x ArH), 7.22 (2H, d, *J* 8.2, ArH) and 7.33 (2H, dd, *J* 8.1, 1.8, ArH); δ_C 14.7 (CH_3), 19.1 (CH_2), 22.0 ($ArCH_3$), 22.7, 31.0 (2 x CH_2), 67.4 (1-CH), 75.9 (2-C), 79.9, 91.1 (2 x C≡), 127.4, 127.5, 128.1, 128.7 (8 x ArCH), 129.3 (ArCH), 129.5, 129.8 (4 x ArCH), 130.3 (ArCH) and 134.6, 136.6, 141.5, 143.3 (4 x ArC); *m/z* [APcI] 430 ($[M-OH]^+$, 100), 366 (10), 274 (15).

***8-tert-Butyldimethylsilyloxy-1,2-diphenyl-1-(4-methyl-phenylsulfonyl)-oct-3-yn-2-ol* 264**

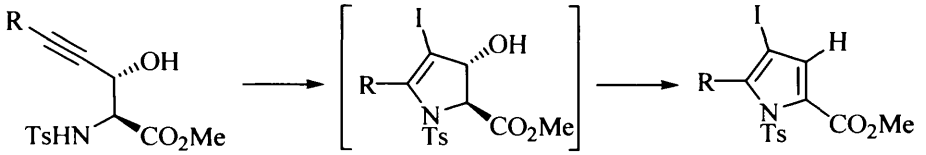


260 **264**

To a stirred solution of the acetylene **231** (0.11 g, 0.55 mmol) in anhydrous tetrahydrofuran (1 mL) at –40°C was added 2.5 M *n*-butyl lithium (0.22 mL in hexanes, 0.55 mmol) and the ketone **260** (0.10 g, 0.27 mmol) as described in general procedure method 2. After work-up, flash chromatography (40% ethyl acetate in petroleum ether) gave the *acetylene* **264** as a yellow solid (38 mg, 25%), as a mixture of diastereomers (80:20), mp 148-149°C; R_f 0.42 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 3257 (b), 2928 (m), 2845 (m), 1450 (m), 1329 (m), 1286 (m), 1161 (s), 1091 (s), 1026 (m), 835 (m) and 699 (s); δ_H 0.00 (6H, s, 2 x $SiCH_3$), 0.85 (9H, s, 3 x CH_3), 1.53-1.56 (4H, m, 6- and 7-CH_2), 2.22-2.26 (5H, m, 5-CH_2 and $ArCH_3$), 3.58 (2H, br, 8-CH_2), 4.45 (0.8H, d, *J* 8.2, 1-H_a), 4.47 (0.2H, d, *J* 8.2, 1-H_b), 5.42 (0.8H, d, *J* 8.2, NH_a), 5.45 (0.2H, d, *J* 8.2, NH_b), 6.78-6.90 (2H, m, 2 x ArH), 6.92-6.98 (2H, m, 2 x ArH), 7.00-7.11 (4H, m, 4 x ArH), 7.15-7.26 (4H, m, 4 x ArH) and 7.34-7.36 (2H, m, 2 x ArH); δ_C -5.0 (2 x $SiCH_3$), 18.2 (SiC), 19.1 (CH_2), 22.0 ($ArCH_3$), 25.7 (3 x CH_3), 25.1, 31.8 (2 x CH_2), 60.5 (1-CH), 64.6 (CH_2), 76.1 (2-C), 80.2, 92.3 (2 x C≡), 125.6, 127.8, 128.3,

128.9 (8 x ArCH), 129.4 (ArCH), 129.6, 130.4 (4 x ArCH), 130.6 (ArCH) and 138.2, 139.6, 140.1, 143.8 (4 x ArC); *m/z* [APcI] 560 ([M-OH]$^+$, 25), 317 (50), 186 (100).

General Procedure for 5-*Endo-Dig* Iodocyclization Reactions.



121 **130** **131**

The tosylamide **121** (1.3 mmol, 1 eq.) was stirred in anhydrous acetonitrile (5 mL) containing potassium carbonate (3.9 mmol, 3 eq.) and cooled in an ice bath. Iodine (3.9 mmol, 3 eq.) was added over 10 min and the resulting suspension stirred for 16 h at room temperature. Saturated aqueous sodium thiosulfate was then added until excess iodine was decolourized and the organic layer separated. The aqueous layer was extracted with dichloromethane (2 x 5 mL) and the combined organic solutions dried and evaporated to give a crude *hydroxy-dihydropyrrole* **130**, which was ready for elimination step.

Elimination Method 1

To a solution of the crude dihydropyrrole **130** (1.3 mmol, 1 eq.) in dichloromethane (5 mL) was added methanesulfonyl chloride (1.4 mmol, 1.1 eq.) dropwise at 0 °C, followed by triethylamine (1.56 mmol, 1.2 eq.) dropwise, and the resulting mixture stirred for 16 h. To the mixture was then added water (5 mL) and the organic layer separated and dried. After evaporation, the crude iodopyrrole was purified by column chromatography (25% EtOAc in petroleum ether) to give the *iodopyrrole* **131**.

Elimination Method 2

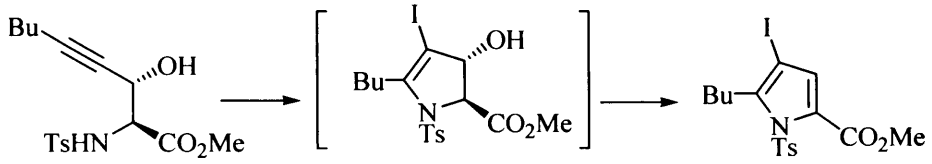
To a solution of the crude dihydropyrrole **130** (1.3 mmol, 1 eq.) in toluene (10 mL) was added a catalytic amount of pyridinium *p*-toluenesulfonate (45 mg) and the mixture refluxed for 16 h. The mixture then was diluted with diethyl ether (10 mL) and washed with water (2 x 10 mL). The organic layer was dried and concentrated to give a crude iodopyrrole. Column chromatography (25% EtOAc in petroleum ether) gave the *iodopyrrole* **131**.

Elimination Method 3

To a solution of the crude dihydropyrrole **130** (0.76 mmol, 1 eq.) in refluxing dichloromethane (5 mL) was carefully added triethylamine (0.33 mmol, 0.5 eq.), followed by methanesulfonyl chloride (0.22 mmol, 0.5 eq.). After 5 minutes, the resulting mixture was allowed to cool to room temperature and then quenched with water (5 mL). The organic layer was separated, washed with water, dried and evaporated to give the crude iodopyrrole, which was then purified by column chromatography (25% EtOAc in petroleum ether) gave the pure *iodopyrrole* **131**.

***Methyl (2SR,3RS)-5-butyl-3-hydroxy-4-iodo-1-(4'-methylphenylsulfonyl)-2,3-dihydro-pyrrole-2-carboxylate* 267**

***And Methyl 5-butyl-4-iodo-1-(4-methylphenylsulfonyl)-pyrrole-2-carboxylate* 268**



161 **267** **268**

The tosylamide **161** (1.1 g, 3.0 mmol) in anhydrous acetonitrile (5 mL) containing potassium carbonate (0.54 g, 3.9 mmol) was added iodine (1.0 g, 3.9 mmol) as described in the general procedure. After the work-up and evaporation, a crude *hydroxy-dihydropyrrole* **267** was obtained as brown oil (1.30 g, 96%); δ_H 0.83 (3H, t, *J* 7.3, CH_3), 1.20-1.26 (2H, m, CH_2), 1.39-1.44 (1H, m, CH_{2a}), 1.50-1.53 (1H, m, CH_{2b}), 1.74 (1H, br, OH), 2.36 (3H, s, $ArCH_3$), 2.41-2.46 (1H, m, pyr-CH_{2a}), 2.64-2.68 (1H, m, pyr-CH_{2b}), 3.75 (3H, s, OCH_3), 4.39 (1H, d, *J* 1.4, 2-H), 4.58 (1H, d, *J* 1.4, 3-H), 7.29 (2H, d, *J* 8.2, 2 x ArH) and 7.71 (2H, d, *J* 8.2, 2 x ArH); δ_C 14.2 (CH_3), 22.0 (CH_2), 22.5 ($ArCH_3$), 29.8, 30.0 (2 x CH_2), 53.4 (OCH_3), 70.1 (2(3)-CH), 78.4 (4-CI), 80.6 (3(2)-CH), 128.0 (2 x ArCH), 130.3 (2 x ArCH), 134.5 (5-C), 145.2, 149.7 (2 x ArC) and 169.7 (C=O);

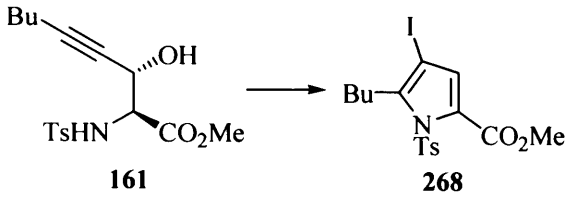
Method A

A solution of the crude dihydropyrrole **267** (1.30 g, 3 mmol) in dichloromethane (5 mL) was added methanesulfonyl chloride (0.26 mL, 3.3 mmol) and triethylamine (0.5 mL, 3.6 mmol) as described in the general elimination method 1. After the work-up, the crude pyrrole was purified to give the *iodopyrrole* **268** as a light brown solid (1.0 g, 73%).

Method B

A solution of the crude dihydropyrrole **267** (0.5 g, 1.4 mmol) in dichloromethane (5 mL) in toluene (5 mL) was added pyridinium *p*-toluenesulfonate (0.04 g, 0.14 mmol) as described in the general elimination method 2. After the work-up, the crude pyrrole was purified to give the *iodopyrrole* **268** as a light brown solid (0.52 g, 81%).

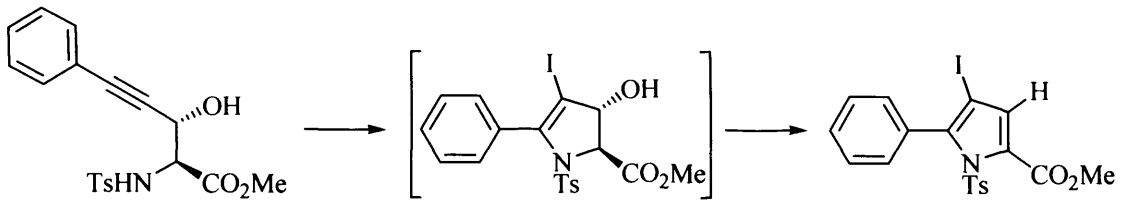
Method C



161 **268**

The tosylamide **161** (0.50 g, 1.40 mmol) was stirred in anhydrous acetonitrile (5 mL) containing sodium hydrogen carbonate (0.40 g, 4.25 mmol) and cooled in an ice bath. Iodine monobromide (0.88 g, 4.25 mmol) was added over 10 min and the resulting suspension stirred for 16 h at room temperature. Saturated aqueous sodium thiosulfate was then added until the mixture was decolourized and the organic layer separated. The aqueous layer was extracted with dichloromethane (2 x 5 mL) and the combined organic solutions dried and evaporated. The crude pyrrole was purified by column chromatography to give *pyrrole* **268** as a light brown solid (0.54 g, 84%); mp 70-71°C, R_f 0.63 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 2915 (w), 2855 (w), 1728 (s), 1589 (w), 1525 (s), 1467 (m), 1347 (m), 1178 (s), 758 (m), 700 (m) and 661 (s); δ_H 0.83 (3H, t, *J* 7.2, CH_3), 1.28 (2H, hex, *J* 7.2, CH_2), 1.37 (2H, pen, *J* 7.2, CH_2), 2.37 (3H, s, $ArCH_3$), 2.78 (2H, t, *J* 7.2, pyr-CH_2), 3.75 (3H, s, OCH_3), 6.80 (1H, s, 3-H), 7.27 (2H, d, *J* 8.3, 2 x ArH) and 7.86 (2H, d, *J* 8.3, 2 x ArH); δ_C 12.6 (CH_3), 20.6 (CH_2), 21.6 ($ArCH_3$), 27.9, 30.6 (2 x CH_2), 51.4 (OCH_3), 68.9 (4-CI), 125.6 (3-CH), 126.5 (2 x ArCH), 127.3 (2(5)-C) 128.8, (2 x ArCH), 135.2, 142.1, 144.3 (5(2)-C and 2 x ArC) and 159.4 (C=O); *m/z* [APcI] 462 ($[M+H]^+$, 20), 430.1 (100), 416 (70); Found: $[M+H]^+$, 462.0226. $C_{17}H_{21}INO_4S$ requires *M*, 462.0230. Anal. Calcd for $C_{17}H_{20}INO_4S$: C, 44.26; H, 4.34; N, 3.04. Found: C, 44.00; H, 4.53; N, 2.89%.

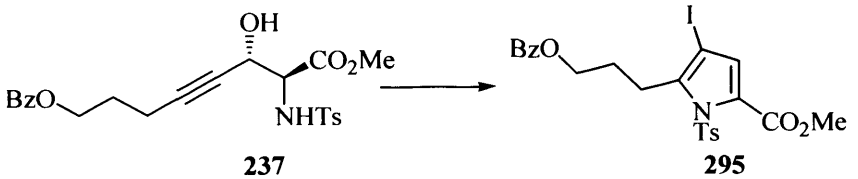
***Methyl 4-iodo-1-(4-methylphenylsulfonyl)- 5-phenyl-pyrrole-2-carboxylate* 275**



160 **274** **275**

The tosylamide **160** (0.485 g, 1.34 mmol) in anhydrous acetonitrile (5 mL) containing potassium carbonate (0.54 g, 3.9 mmol) was added iodine (1.0 g, 3.9 mmol) as described in the general procedure. After work-up, a crude *hydroxy-dihydropyrrole* **274** (0.60 g, 98%) was obtained as brownish oil; δ_H 1.70 (1H, d, *J* 8.4, OH), 2.36 (3H, s, $ArCH_3$), 3.82 (3H, s, OCH_3), 4.57 (1H, dd, *J* 8.4, 1.6, 3-H), 4.84 (1H, d, *J* 1.6, 2-H), 7.08-7.39 (9H, m, 9 x ArCH). To a solution of the crude dihydropyrrole **274** in dichloromethane (5 mL) was added methanesulfonyl chloride (0.26 mL, 3.3 mmol) and triethylamine (0.5 mL, 3.6 mmol) as described in the general procedure 1. After the work-up, the product was purified to give the *iododpyrrole* **275** as a light brown solid (0.52 g, 83%): mp 126-127°C, R_f 0.80 (40% ethyl acetate in petroleum ether): ν_{max}/cm^{-1} [nujol] 2956 (s), 2855 (m), 1734 (s), 1594 (w), 1374 (m), 1178 (s), 1091 (s), 810 (m) and 668 (s); δ_H 2.34 (3H, s, $ArCH_3$), 3.87 (3H, s, OCH_3), 6.92 (1H, s, 3-H), 7.03 (2H, d, *J* 7.9, 2 x ArH), 7.11 (2H, d, *J* 8.2, 2 x ArH), 7.27 (2H, t, *J* 7.9, 2 x ArH) and 7.34-7.39 (3H, m, 3 x ArH); δ_C 22.1 ($ArCH_3$), 53.1 (OCH_3), 71.8 (4-CI), 126.1 (ArC), 127.3 (3-CH), 128.1 (2 x ArCH), 128.5 (2 x ArCH), 129.0 (ArCH), 129.7 (2 x ArCH), 130.8 (2(5)-C), 131.9 (2 x ArCH), 135.6, 142.2, 145.8 (5(2)-C and 2 x ArC) and 161.8 (C=O); *m/z* [APcI] 482 ($[M+H]^+$, 15), 450.0 (100), Anal. Calcd for $C_{19}H_{16}INSO_4$: C, 47.40; H, 3.30; N, 2.90. Found: C, 47.62; H, 3.41; N, 2.71%.

***Methyl 5-(3-benzyloxypropyl)-4-iodo-1-(4'-methylphenylsulfonyl)-pyrrole-2-carboxylate* 295**

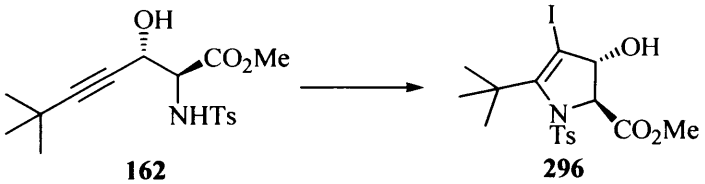


237 **295**

The tosylamide **237** (100 mg, 0.22 mmol) in anhydrous acetonitrile (5 mL) containing potassium carbonate (91 mg, 0.66 mmol) was added iodine (0.17 g, 0.66 mmol) as described

in the general procedure. After the work-up and evaporation, column chromatography (25% ethyl acetate in petroleum ether) gave the *iodopyrrole* **295** (83 mg, 66%) as a colourless solid; mp 109-110°C, R_f 0.30 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 2952 (m), 2925 (m), 1732 (s), 1714 (s), 1598 (w), 1488 (w), 1452 (m), 1373 (m), 1328 (m), 1313 (m), 1276 (s), 1172 (s), 1162 (s), 1112 (m), 1091 (s), 1070 (m), 1027 (m), 813 (w), 714 (m) and 668 (m); δ_H 1.98 (2H, pen, *J* 6.3, CH_2), 2.35 (3H, s, $ArCH_3$), 2.98 (2H, t, *J* 6.3, Pyr-CH_2), 3.76 (3H, s, OCH_3), 4.30 (2H, t, *J* 6.3, OCH_2), 6.81 (1H, s, 3-H), 7.22 (2H, d, *J* 8.4, 2 x ArH), 7.38 (2H, t, *J* 7.4, 2 x ArH), 7.50 (1H, t, *J* 7.4, ArH), 7.85 (2H, d, *J* 8.4, 2 x ArH) and 8.03 (2H, d, *J* 7.4, 2 x ArH); δ_C 21.8 ($ArCH_3$), 26.7, 28.2 (2 x CH_2), 52.4 (OCH_3), 64.2 (OCH_2), 70.5 (4-CI), 127.6 (2 x ArCH), 128.2 (3-CH), 128.4 (2 x ArCH), 128.8, 130.5, 136.3, 142.4, 145.9 (2(5)-C, ArCH and 3 x ArC), 129.7, 129.9, (4 x ArCH), 131.8 (5(2)-C) and 161.7, 167.9 (both C=O); *m/z* [APcI] 568 ($[M+H]^+$, 100), 441 (15), 318 (20), 291 (20); Found: $[M+H]^+$, 568.0286. $C_{23}H_{23}INO_6S$ requires *M*, 568.0285.

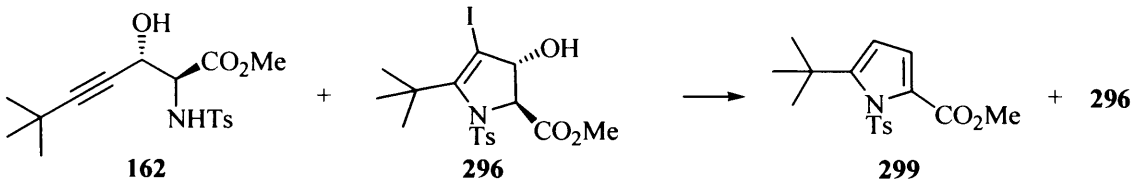
***Methyl (2SR,3RS)-5-t-butyl-3-hydroxy-4-iodo-1-(4'-methylphenylsulfonyl)-2,3-dihydro-pyrrole-2-carboxylate* 296**



162 **296**

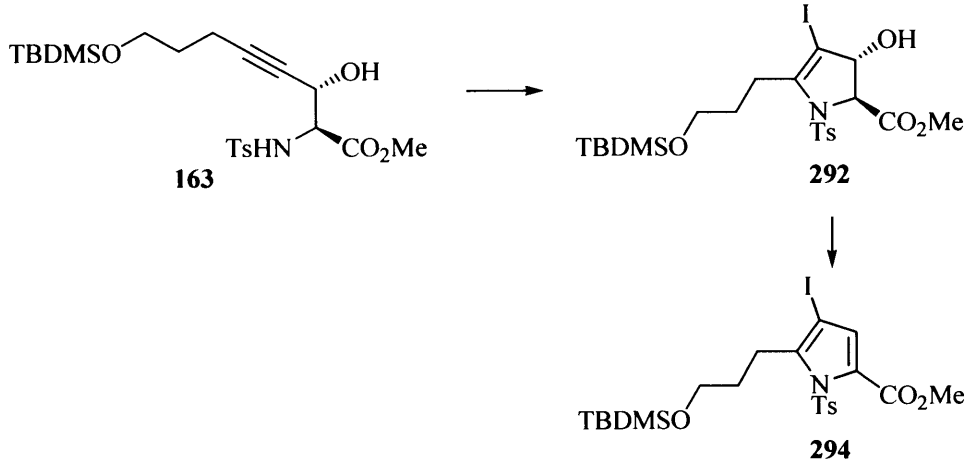
The tosylamide **162** (0.50 g, 1.4 mmol) was stirred in aqueous sodium hydrogen carbonate (5 mL) and cooled in an ice bath. A solution of iodine (1.06 g, 4.2 mmol) in dichloromethane was added over 10 min and the mixture stirred for 16 h at room temperature. Saturated aqueous sodium thiosulfate was then added until excess iodine was decolourized and organic layer separated. The aqueous layer was extracted with dichloromethane (2 x 5 mL) and the combined organic solutions were dried and evaporated. Column chromatography gave the starting tosylamide **162** (0.15 g, 25%) and the *hydroxy-dihydropyrrole* **296** as a colourless solid (0.34 g, 51%), mp 122-123°C, R_f 0.54 (30% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 3478 (s), 2956 (m), 2915 (m), 1749 (m), 1443 (w), 1323 (m), 1156 (s), 1087 (m), 941 (w), 811 (w) and 705 (m); δ_H 1.58 (9H, s, 3 x CH_3), 2.48 (3H, s, $ArCH_3$), 3.67 (3H, s, OCH_3), 4.30 (1H, app. s, 2(3)-H), 4.39 (1H, app. s, 3(2)-H), 7.38 (2H, d, *J* 8.2, 2 x ArH) and 7.88 (2H, d, *J* 8.2, 2 x ArH); δ_C 22.0 ($ArCH_3$), 29.6 (3 x CH_3), 36.2 (C), 53.2 (OCH_3), 68.5. 85.2 (2- and 3-CH), 89.1 (4-CI), 128.7, 130.4 (both 2 x ArCH), 138.9, 145.6, 154.4 (5-C and 2 x ArC) and 168.1 (C=O); *m/z* [APcI] 462 ($[M-H_2O]^+$, 80), 406 (100), 276 (60).

***Methyl 5-tert-butyl-1-(4'-methylphenylsulfonyl)-pyrrole-2-carboxylate* 299**



To a solution of the crude **296** (2:1, dihydropyrrole **296** mixed with the tosylamide **162**) in toluene (5 mL) was added pyridinium *p*-toluenesulfonate (10 mg) as decribed in general elimination method 2. After work-up, column chromatography gave the dihydropyrrole **296**, (51%), and the *pyrrole* **299** as a brownish oil (47 mg, 10%), R_f 0.67 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2924 (s), 2856 (s), 1732 (m), 1597 (w), 1494 (w), 1462 (s), 1376 (m), 1313 (m), 1263 (w), 1154 (w) and 666 (w); δ_H 1.29 (9H, s, 3 x CH_3), 2.34 (3H, s, $ArCH_3$), 3.69 (3H, s, OCH_3), 6.13 (1H, d, *J* 3.7, 4-H), 6.65 (1H, d, *J* 3.7, 3-H), 7.20 (2H, d, *J* 8.2, 2 x ArH) and 7.60 (2H, d, *J* 8.2, 2 x ArH); δ_C 24.4 ($ArCH_3$), 31.3 (3 x CH_3), 38.2 (C), 55.5 (OCH_3), 116.4 (3(4)-CH), 117.8 (4(3)-CH), 119.5 (2(5)-C), 131.0, 132.7 (both 2 x ArCH), 136.4 (5(2)-C), 148.0, 153.9 (2 x ArC) and 172.1 (C=O); *m/z* [APcI] 336 ($[M+H]^+$, 100), 244 (25); Found: $[M+H]^+$, 336.1266. $C_{17}H_{22}NO_4S$ requires *M*, 336.1264

***Methyl (2SR,3RS)-5-(t-butyldimethylsilyloxypropyl)-3-hydroxy-4-iodo-1-(4'-methylphenylsulfonyl)-2,3-dihydro-pyrrole-2-carboxylate* 292**
And *Methyl 5-(t-butyldimethylsilyloxypropyl)-4-iodo-1-(4'-methylphenylsulfonyl)-pyrrole-2-carboxylate* 294

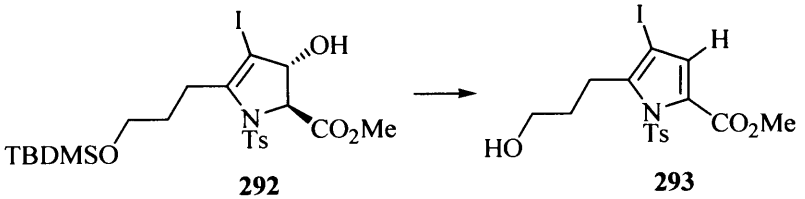


The tosylamide **163** (0.44 g, 0.94 mmol) in anhydrous acetonitrile (5 mL) containing potassium carbonate (0.39 g, 2.82 mmol) was added iodine (0.72 g, 2.82 mmol) as described

in the general procedure. After work-up, a crude *hydroxy-dihydropyrrole* **292** was obtained as brownish oil (0.51g, 91%); ν_{max}/cm^{-1} [film] 3518 (br), 2952 (s), 2856 (s), 1731 (s), 1591 (w), 1471 (m), 1378 (s), 1324 (m), 1252 (s), 1179 (s), 1159 (s), 1090 (s), 836 (s), 770 (m) and 667 (s); δ_H 0.00 (6H, s, 2 x $SiCH_3$), 0.83 (9H, s, 3 x CH_3), 1.52 (1H, d, *J* 7.9, OH), 1.60-1.65 (1H, m, CH_{2a}), 1.80-1.84 (1H, m, CH_{2b}), 2.36 (3H, s, $ArCH_3$), 2.58-2.66 (2H, m, pyr-CH_2), 3.50-3.61 (2H, m, OCH_2), 3.75 (3H, s, OCH_3), 4.38 (1H, dd, *J* 7.9, 1.5, 3-H), 4.56 (1H, d, *J* 1.5, 2-H), 7.27 (2H, d, *J* 8.3, ArH) and 7.65 (2H, d, *J* 8.3, ArH); δ_C -5.1 (2 x $SiCH_3$), 18.3 (C), 21.5 ($ArCH_3$), 26.0 (3 x CH_3), 26.8, 44.0 (2 x CH_2), 53.0 (OCH_3), 62.1 (OCH_2), 69.7 (2(3)-CH), 78.2 (4-CI), 80.3 (3(2)-CH), 127.2, 129.7 (both 2 x ArCH), 133.9 (5-C), 144.8, 149.3 (2 x ArC) and 169.2 (C=O); *m/z* [APcI] 596 ($[M+H]^+$, 5), 578 ($[M-H_2O]^+$, 35), 422 (100); Found: $[M+H]^+$, 596.0997. $C_{22}H_{35}INO_6SSi$ requires *M*, 596.0994.

To a solution of dihydropyrrole **292** (0.45 g, 0.76 mmol) in refluxing dichloromethane (5 mL) was added triethylamine (0.2 mL, 0.33 mmol) and methanesulfonyl chloride (0.35 mL, 0.35 mmol) as decribed in general elimination method 3. After work-up, column chromatography gave the *iodopyrrole* **294** as pale yellow solid (0.22 g, 50%); mp 74-75°C; R_f 0.62 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 2953 (s), 2857 (s), 1732 (s), 1597 (w), 1472 (m), 1434 (m), 1379 (s), 1329 (m), 1300 (m), 1257 (s), 1180 (s), 1159 (s), 1092 (s), 958 (w), 837 (s), 771 (m) and 668 (s); δ_H 0.00 (6H, s, 2 x $SiCH_3$), 0.84 (9H, s, 3 x CH_3), 1.63-1.67 (2H, m, CH_2), 2.34 (3H, s, $ArCH_3$), 2.86-2.90 (2H, m, pyr-CH_2), 3.59 (2H, t, *J* 6.0, OCH_2), 3.74 (3H, s, OCH_3), 6.79 (1H, s, 3-H), 7.26 (2H, d, *J* 8.2, 2 x ArH) and 7.91 (2H, d, *J* 8.2, 2 x ArH; δ_C -4.9 (2 x $SiCH_3$), 18.3 (C), 21.7 ($ArCH_3$), 26.0 (3 x CH_3), 26.3, 32.6 (2 x CH_2), 52.4 (OCH_3), 62.6 (OCH_2), 70.0 (4-CI), 126.5 (3-CH), 127.4 (2 x ArCH), 127.7 (2(5)-C), 130.9 (2 x ArCH), 136.0, 142.5, 145.3 (5(2)-C and 2 x ArC) and 160.4 (C=O); *m/z* [APcI] 578 ($[M+H]^+$, 100), 422 (25); Found: $[M+H]^+$, 578.0885. $C_{22}H_{33}INO_5SSi$ requires *M*, 578.0888.

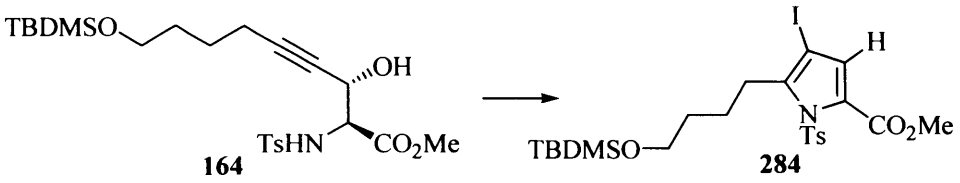
***Methyl 5-(3'-hydroxypropyl)-4-iodo-1-(4-methylphenylsulfonyl)-pyrrole-2-carboxylate* 293**



To a solution of the crude **292** (0.22 g, 0.37 mmol) in toluene (2 mL) was added pyridinium *p*-toluenesulfonate (10 mg) as decribed in general elimination method 2. After work-up, column chromatography (10-30% ethyl acetate in petroleum ether) gave the *pyrrole* **293** as a

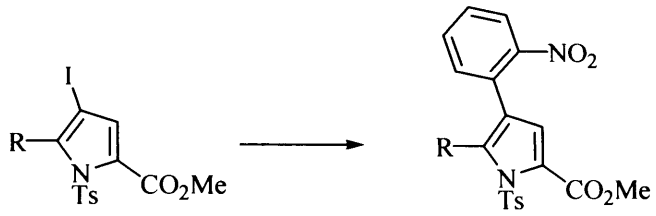
colourless solid (37 mg, 8%); mp 125-126°C, R_f 0.27 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 3355 (br), 2945 (w), 1729.9(s), 1596 (w), 1434 (m), 1368 (m), 1329 (m), 1178 (s), 1090 (s), 813 (m), 756 (w) and 666 (s); δ_H 1.77 (2H, pen, *J* 7.1, CH_2), 2.37 (3H, s, $ArCH_3$), 2.91 (2H, t, *J* 7.1, Pyr-CH_2), 3.64 (2H, t, *J* 7.1, OCH_2), 3.75 (3H, s, OCH_3), 6.81 (1H, s, 3-H), 7.27 (2H, d, *J* 8.2, 2 x ArH) and 7.85 (2H, d, *J* 8.2, 2 x ArH); δ_C 22.1 ($ArCH_3$), 26.2, 32.8 (2 x CH_2), 52.9 (OCH_3), 62.5 (OCH_2), 70.7 (4-CI), 127.0 (2 x ArCH), 127.9 (3-CH), 128.8 (2(5)-C), 130.2 (2 x ArCH), 136.3, 142.4, 145.9 (5(2)-C and 2 x ArC) and 160.7 (C=O); *m/z* [APcI] 464 ($[M+H]^+$, 100), 308 (50); Found: $[M+H]^+$, 464.0024. $C_{16}H_{19}INO_5S$ requires *M*, 464.0023.

***Methyl 5-(t-butyldimethylsilyloxybutyl)-4-iodo-1-(4'-methylphenylsulfonyl)-pyrrole-2-carboxylate* 284**



The tosylamide **164** (0.50 g, 1.0 mmol) in anhydrous acetonitrile (5 mL) containing potassium carbonate (0.41 g, 3.0 mmol) was added iodine (0.77 g, 3.0 mmol) as described in the general procedure. After work-up, a crude *hydroxy-dihydropyrrole* was obtained as a brownish oil (0.55g, 92%). To a solution of the dihydropyrrole (0.45 g, 0.76 mmol) in refluxing dichloromethane (5 mL) was added triethylamine (0.2 mL, 0.33 mmol) and methanesulfonyl chloride (0.35 mL, 0.35 mmol) as decribed in general elimination method 3. After work-up, column chromatography gave the *iodopyrrole* **284** (0.38 g, 65%) as a colourless solid, mp 70-71°C; R_f 0.57 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 2953 (s), 2855 (s), 1737 (s), 1597 (w), 1472 (m), 1434 (m), 1378 (s), 1324 (m), 1249 (m), 1179 (s), 1093 (s), 1006 (w), 836 (s), 776 (m) and 668 (s); δ_H 0.02 (6H, s, 2 x $SiCH_3$), 0.84 (9H, s, 3 x CH_3), 1.50-1.52 (4H, m, 2 x CH_2), 2.39 (3H, s, $ArCH_3$), 2.84 (2H, t, *J* 6.6, Pyr-CH_2), 3.55 (2H, t, *J* 6.6, OCH_2), 3.77 (3H, s, OCH_3), 6.83 (1H, s, 3-H), 7.29 (2H, d, *J* 8.3, 2 x ArH) and 7.89 (2H, d, *J* 8.3, 2 x ArH); δ_C -5.2 (2 x $SiCH_3$), 18.3 (C), 21.7 ($ArCH_3$), 26.0 (3 x CH_3), 26.1, 29.1, 32.7 (3 x CH_2), 52.4 (OCH_3), 62.8 (OCH_2), 70.1 (4-CI), 126.6 (3-CH), 127.5, 129.8 (both 2 x ArCH), 128.3, 136.1, 142.9, 145.3 (2-, 5-C and 2 x ArC) and 160.4 (C=O); *m/z* [APcI] 592 ($[M+H]^+$, 60), 436 (100), 252 (60); Found: $[M+NH_4]^+$, 609.1306. $C_{23}H_{38}IN_2O_5SSi$ requires *M*, 609.1310.

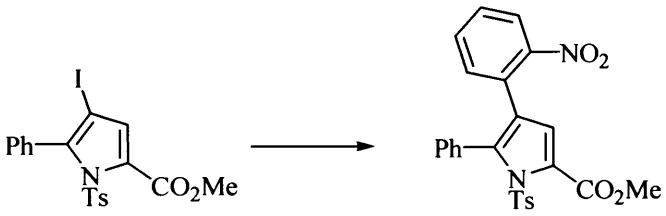
General Precedure for Suzuki Reactions. [45]



118 **280**

A mixture of deoxygenated dimethylformamide and water (4:1, 2 mL) was added to the iodopyrrole **118** (0.40 mmol, 1 eq.), *o*-nitrophenylboronic acid (0.1 g, 0.60 mmol, 1.5 eq.), sodium carbonate (0.16 g) and [1,1'-*bis*-(diphenylphosphino)ferrocene] dichloropalladium(II) (60 mg, 0.08 mmol, 0.2 eq.). The mixture was heated for 2 h in an oil bath maintained at 80°C and then allowed to cool to room temperature. Ethyl acetate (2 mL) and water (2 mL) were added before filtration through celite. The separated organic phase was successively washed with water (5 mL) and brine (5 mL) and dried. After evaporation of the solvent, the residue was purified by flash chromatography using 25% ethyl acetate in petroleum ether to give the *pyrrole* **280**.

***Methyl 4-(2'-nitrophenyl)-5-phenyl-1-(4'-methylphenylsulfonyl)-pyrrole-2-carboxylate* 281**

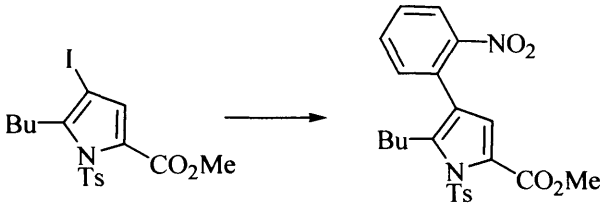


275 **281**

A mixture of deoxygenated dimethylformamide and water (4:1, 2 mL) was added to the iodopyrrole **275** (0.20 g, 0.40 mmol), *o*-nitrophenylboronic acid (0.1 g, 0.60 mmol), sodium carbonate (0.16 g) and [1,1'-*bis*-(diphenylphosphino)-ferrocene] dichloropalladium(II) (60 mg, 0.08 mmol) as decribed in the general procedure. After work-up, flash chromatography (20-40% ethyl acetate in petroleum ether) gave the *pyrrole* **281** as a brownish oil (116 mg, 61%), which crystallised to give colourless crystals; mp 151-152°C: R_f 0.80 (40% ethyl acetate in petroleum ether): ν_{max}/cm^{-1} [nujol] 3063 (w), 2952 (w), 1729 (s), 1596 (w), 1526 (s), 1444 (w), 1373 (m), 1348 (m), 1275 (m), 1179 (s), 1125 (m), 1090 (w), 1046 (w), 854 (w) and 750 (m); δ_H 2.31 (3H, s, $ArCH_3$), 3.88 (3H, s, OCH_3), 6.82 (1H, s, 3-H), 6.85 (2H, d, *J* 8.4, 2 x ArH), 6.92 (1H, dd, *J* 9.2, 1.8, ArH), 7.03-7.08 (4H, m, 4 x ArH), 7.17-7.19 (1H, m, ArH), 7.25-7.29 (4H, m, 4 x ArH) and 7.68 (1H, dd, *J* 9.2, 1.8, ArCH); δ_C 22.1 ($ArCH_3$), 53.1

(OCH_3), 122.2 (3-CH), 122.3 (ArCH), 123.7 (ArC), 124.6 (ArCH), 128.0, 128.3 (ArCH and 2 x ArCH), 128.8, 128.9 (2 x ArC), 129.3 (2 x ArCH), 129.7 (2 x ArCH), 130.4 (4-C), 131.7 (2 x ArCH), 132.9, 133.0 (2 x ArCH), 136.1, 139.5, 142.7, 149.7 (2-, 5-C and 2 x ArC) and 162.1 (C=O); *m/z* [APcI] 445 ($[M-OCH_3]^+$, 100); Anal. Calcd for $C_{25}H_{20}N_2O_6S$: C, 63.00; H, 4.20; N, 5.88. Found: C, 63.03; H, 4.37; N, 5.57%.

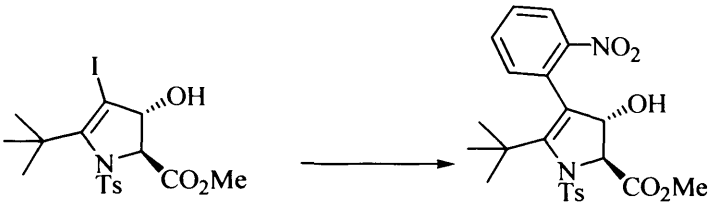
***Methyl 4-(2-nitro-phenyl)-5-butyl-1-(4-methylphenylsulfonyl)-pyrrole-2-carboxylate* 282**



268 **282**

A mixture of deoxygenated dimethylformamide and water (4:1, 5 mL) was added to the iodopyrrole **268** (0.48 g, 1 mmol), *o*-nitrophenylboronic acid (0.25 g, 1.5 mmol), sodium carbonate (0.40 g) and [1,1'-*bis*-(diphenylphosphino)-ferrocene] dichloropalladium(II) (1.5 g, 0.2 mmol) as decribed in the general procedure. After work-up, flash chromatography gave the *pyrrole* **282** (0.33 g, 70%) as a colourless solid; R_f 0.57 (25% ethyl acetate in petroleum ether), mp 111-112°C: R_f 0.63 (25% ethyl acetate in petroleum ether): ν_{max}/cm^{-1} [nujol] 2956 (m), 2871 (w), 1731 (s), 1597 (w), 1527 (s), 1434 (w), 1347 (s), 1228 (m), 1178 (s), 1154 (m), 1089 (m), 854 (w), 813 (w), 757 (w) and 667 (m); δ_H 0.52 (3H, t, *J* 7.3, CH_3), 0.945 (2H, q, *J* 7.3, CH_2), 1.15-1.18 (2H, m, CH_2), 2.27 (3H, s, $ArCH_3$), 2.49 (2H, t, *J* 7.3, Pyr-CH_2), 3.64 (3H, s, OCH_3), 6.60 (1H, s, 3-H), 7.14 (1H, d, *J* 7.6, ArH), 7.18 (2H, d, *J* 8.2, 2 x ArH), 7.34 (1H, t, *J* 7.6, ArH), 7.44 (1H, t, *J* 7.6, ArH), 7.67 (2H, d, *J* 8.2, 2 x ArH) and 7.75 (1H, d, *J* 7.6, ArH); δ_C 13.8 (CH_3), 22.1 ($ArCH_3$), 22.9, 27.0, 32.9 (3 x CH_2), 52.7 (OCH_3), 122.3 (3-CH), 122.4 (ArC), 124.7 (ArCH), 127.4 (2 x ArCH), 127.9 (ArC), 129.2 (4-C), 129.3 (ArCH), 130.2 (2 x ArCH), 132.9, 133.2 (2 x ArCH), 137.1, 141.2, 145.39, 149.97 (2-, 5-C and 2 x ArC) and 161.29 (C=O); *m/z* [ApcI] 457 (15), 426 (100), 144 (25); Anal. Calcd for $C_{23}H_{24}N_2O_6S$: C, 57.97; H, 5.04; N, 5.88. Found: C, 57.71; H, 5.30; N, 6.06%.

***Methyl (2SR,3SR)-5-tert-butyl-3-hydroxy-4-(2'-nitrophenyl)-1-(4'-methylphenylsulfonyl)-2,3-dihydropyrrole-2-carboxylate* 303**

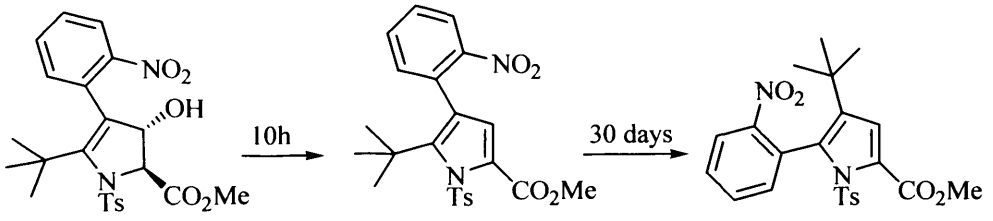


296 **303**

A mixture of deoxygenated dimethylformamide and water (4:1, 5 mL) was added to the *tert*-butyl dihydro-iodopyrrole **296** (105 mg, 0.20 mmol), *o*-nitrophenylboronic acid (0.25 g, 1.5 mmol), and [1,1'-*bis*(diphenylphosphino)ferrocene]dichloropalladium(II) (1.5 g, 0.2 mmol) in the presence of sodium carbonate (74 mg, 0.39 mmol) in place of sodium carbonate decahydrate as decribed in general procedure. After work-up, flash chromatography gave the *hydroxy dihydropyrrole* **303** (15 mg, 15%) as a bright yellow oil, R_f 0.35 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 3332 (br), 2960 (s), 2927 (s), 1732 (s), 1614 (w), 1594 (w), 1526 (m), 1455 (w), 1344 (m), 1318 (w), 1260 (m), 1150 (m), 1094 (w), 813 (w) and 672 (w); δ_H 1.18 (9H, s, 3 x CH_3), 2.39 (3H, s, $ArCH_3$), 3.11 (1H, d, *J* 11.8, OH), 3.72 (3H, s, OCH_3), 4.23 (1H, d, *J* 1.2, 2-H), 4.53 (1H, dd, *J* 11.8, 1.2, 3-H), 7.31 (2H, d, *J* 7.6, 2 x ArH), 7.38 (1H, d, *J* 7.8, ArH), 7.49 (1H, t, *J* 7.8, ArH), 7.62 (1H, t, *J* 7.8, ArH), 7.88 (2H, d, *J* 7.6, 2 x ArH) and 8.15 (1H, d, *J* 7.8, ArCH);

***Methyl 5-tert-butyl-4-(2'-nitrophenyl)-1-(4'-methylphenylsulfonyl)-pyrrole-2-carboxylate* 304**

***And Methyl 4-tert-butyl-5-(2'-nitrophenyl)-1-(4'-methylphenylsulfonyl)-pyrrole-2-carboxylate* 305**



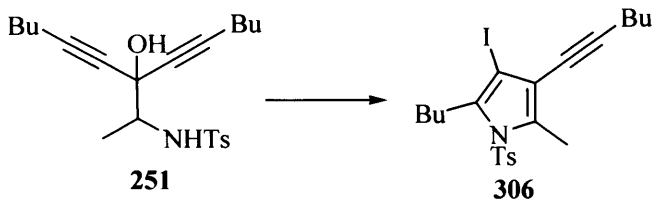
303 **304** **305**

The *dihydropyrrole* **303** (15 mg) underwent dehydration upon standing in deuteriochroloform over 10 h to give the *pyrrole* **304** (14 mg, 99%) as a yellow oil; ν_{max}/cm^{-1} [film] 3498 (w), 2956 (w), 1758 (m), 1594 (w), 1525 (s), 1433 (w), 1343 (s), 1284 (w), 1207 (w), 1164 (s), 1057 (w), 1016 (w), 811 (w) and 665 (m); δ_H 1.16 (9H, s, 3 x CH_3), 2.39 (3H, $ArCH_3$), 3.69 (3H, s, OCH_3), 6.52 (1H, s, 3-H), 7.19-7.26 (3H, m, 3 x ArH), 7.46 (1H, t, *J* 7.7, ArH), 7.51

(1H, t, *J* 7.7, ArH), 7.77 (2H, d, *J* 8.3, 2 x ArH) and 7.93 (1H, d, *J* 7.7, ArH); *m/z* [APcI] 457 (M^++H, 15), 391 (100), 279 (15), 261 (15), 149 (15), 137 (20), 113 (30).

Rearrangement occurred during crystallization (in ethyl acetate/hexane for 30 days) to give the *pyrrole* **305** as a colorless solid, mp 135°C; ν_{max}/cm^{-1} [nujol] 3327 (b), 2976 (s), 2915 (s), 1734 (s), 1524 (s), 1453 (w), 1343 (w), 1318 (w), 1253 (w), 1197 (w), 1147 (m), 1092 (w), 1052 (w) and 665 (m); δ_H 1.18 (9H, s, 3 x CH_3), 2.35 (3H, $ArCH_3$), 3.75 (3H, s, OCH_3), 7.18 (2H, d, *J* 8.0, 2 x ArH), 7.41 (1H, d, *J* 7.5, ArH), 7.52 (1H, t, *J* 7.5, ArH), 7.60 (1H, t, *J* 7.5, ArH), 7.68 (2H, d, *J* 8.0, 2 x ArH), 8.14 (1H, d, *J* 7.5, ArH) and 9.22 (1H, br, 3-H); *m/z* [APcI] 457 (M^++H, 100), 79 (45).

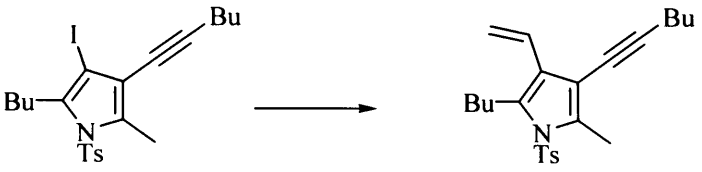
***2-Butyl-4-hexynyl-3-iodo-5-methyl-1-(4'-methylphenylsulfonyl)-pyrrole* 306**



251 **306**

To the tosylamide **251** (20.75 g, 53.3 mmol) in anhydrous acetonitrile (100 mL) containing potassium carbonate (22.08 g, 160 mmol) was added iodine (40.60 g, 160 mmol) as described in the general procedure. The work-up and evaporation gave the *pyrrole* **306** as a brownish oil (17.70 g, 65%); R_f 0.86 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2953 (s), 2856 (m), 1597 (w), 1453 (m), 1365 (s), 1252 (m), 1189 (s), 1089 (s), 1006 (w), 811 (m) and 705 (m); δ_H 0.83-0.91 (6H, m, 2 x CH_3), 1.30-1.51 (8H, m, 4 x CH_2), 2.14 (3H, s, 5-CH_3), 2.32-2.37 (2H, m, $CH_2C\equiv$), 2.40 (3H, s, $ArCH_3$), 2.77-2.84 (2H, m, pyr-CH_2), 7.19-7.22 (2H, m, 2 x ArH) and 7.43-7.53 (2H, m, 2 x ArH); δ_C 14.3 (2 x CH_3), 15.4 (5-CH_3), 19.6 (CH_2), 21.5 ($ArCH_3$), 22.3, 23.0, 30.0, 31.2, 32.7 (5 x CH_2), 69.8 (CI), 74.4, 96.1 (2 x C≡), 113.6, 114.5 (2 x C), 126.6 (2 x ArCH), 130.5 (2 x ArCH) and 135.7, 137.0, 137.3, 145.4 (2 x C and 2 x ArC); *m/z* [APcI] 498 ($[M+H]^+$, 100), 371 (30), 343 (35), 113 (65), 75 (100); Found $[M+H]^+$, 498.0969. $C_{22}H_{29}INO_2S$ requires M, 498.0964.

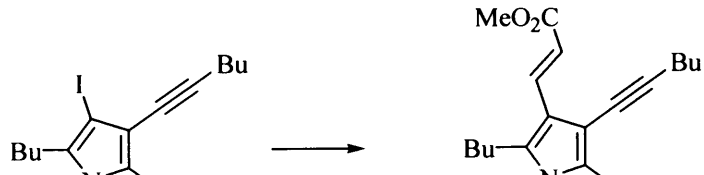
***2-Butyl-4-hexynyl-5-methyl-1-(4'-methylphenylsulfonyl)-3-vinyl-pyrrole* 308**



306 **308**

A mixture of the pyrrole **306** (0.90 g, 1.81 mmol), vinyltributyltin (1.06 mL, 3.62 mmol) and *bis*-(triphenylphosphine)palladium(II) chloride (38.1 mg, 0.05 mmol) in toluene (18 mL) was refluxed for 2 h. The mixture (color changed from yellow to black) was cooled to room temperature, diluted with dichloromethane (80 mL) and the resulting solution washed with brine (80 mL) and water (80 mL). The organic layer was separated, dried and evaporated. Column chromatography (0-10% ethyl acetate in petroleum ether) gave the *pyrrole* **308** as a yellow oil (74 mg, 10%); R_f 0.86 (10% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2958 (s), 2930 (s), 2854 (m), 1597 (w), 1455 (m), 1365 (s), 1256 (m), 1179 (s), 1089 (s), 1008 (m), 810 (m), 705 (m) and 655 (s); δ_H 0.80-0.87 (6H, m, 2 x CH_3), 1.27-1.58 (10H, m, $CH_2C\equiv$ and 4 x CH_2), 2.31 (3H, s, pyr-CH_3), 2.40 (3H, s, $ArCH_3$), 2.74-2.81 (2H, m, pyr-CH_2), 5.14 (1H, dd, *J* 11.2, 1.6, CH_{2a}=), 6.05 (1H, dd, *J* 17.6, 1.6, CH_{2b}=), 6.47 (1H, dd, *J* 17.6, 11.2, CH=), 7.17-7.22 (2H, m, 2 x ArH) and 7.44-7.46 (2H, m, 2 x ArH); δ_C 12.6, 12.8, 13.9 (3 x CH_3), 18.3 (CH_2), 20.6 ($ArCH_3$), 21.0, 21.5, 28.6, 29.8, 31.3 (5 x CH_2), 73.0, 94.7 (2 x C≡), 106.2, 113.1 (2 x C), 113.8 (CH_2=), 120.9 (C), 125.2 (2 x ArCH), 126.4 (CH=), 129.1 (2 x ArCH) and 134.2, 135.9, 144.0 (C and 2 x ArC); *m/z* [APcI] 398 ($[M+H]^+$, 100), 230 (15); Found $[M+H]^+$, 398.2150. $C_{24}H_{32}NO_2S$ requires M, 398.2148.

***Methyl 3-[2'-butyl-4'-hexynyl-5'-methyl-1'-(4''-methylphenylsulfonyl)-pyrrol-3-yl]-acrylate* 310**

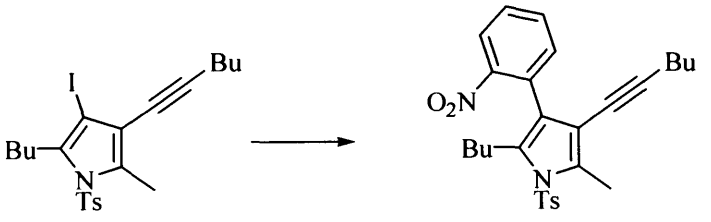


306 **310**

A flask was charged with palladium(II) acetate (0.02 g, 0.08 mmol) and triphenylphosphine (0.13 g, 0.48 mmol), degassed overnight and flushed with nitrogen. Sodium acetate (0.07 g, 0.8 mmol), the pyrrole **306** (0.20 g, 0.4 mmol) and methyl acrylate **309** (0.05 mL, 0.5 mmol) were added. Following the addition of dimethylformamide (2 mL), the flask was closed and,

the mixture stirred for 30 min at 120°C and then for 12 h at 150°C. The mixture was then allowed to cool to room temperature. Ethyl acetate (2 mL) and water (2 mL) were added before filtration through celite. The separated organic phase was successively washed with water and brine and dried. After evaporation of the solvent, the residue was purified by flash chromatography using 10% ethyl acetate in petroleum ether to give the *pyrrole* **310** as a brownish oil (50 mg, 30%); R_f 0.45 (10% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2970 (s), 2925 (s), 2855 (m), 1628 (w), 1433 (w), 1372 (m), 1283 (m), 1261 (m), 1171 (s), 1091 (s), 1017 (m), 809 (m) and 655 (m); δ_H 0.81-0.89 (6H, m, 2 x CH_3), 1.18-1.53 (10H, m, $CH_2C\equiv$ and 4 x CH_2), 2.29 (3H, s, pyr-CH_3), 2.41 (3H, s, $ArCH_3$), 2.85 (2H, t, *J* 7.9, pyr-CH_2), 3.70 (3H, s, OCH_3), 6.38 (1H, d, *J* 16.0, CH=), 6.91 (1H, d, *J* 16.0, CH=), 7.21-7.28 (2H, m, 2 x ArH) and 7.44-7.47 (2H, m, 2 x ArH); δ_C 13.7, 13.8, 14.0 (3 x CH_3), 19.4 (CH_2), 21.7 ($ArCH_3$), 22.1, 22.6, 26.7, 30.7, 33.7 (5 x CH_2), 51.5 (OCH_3), 72.8, 95.8 (2 x C≡), 105.8, 115.8 (2 x C), 118.3 (CH=), 125.0 (2 x ArCH), 127.9 (C), 128.9 (2 x ArCH), 134.0 (CH=), 135.6, 137.6, 143.9 (C and 2 x ArC) and 167.2 (C=O); *m/z* [APcI] 456 ($[M+H]^+$, 30), 390 (15), 227 (15), 137 (100); Found $[M+H]^+$, 456.2204. $C_{26}H_{34}NO_4S$ requires M, 456.2203.

***2-Butyl-4-hexynyl-5-methyl-3-(2'-nitro-phenyl)-1-(4'-methylphenylsulfonyl)-pyrrole* 311**

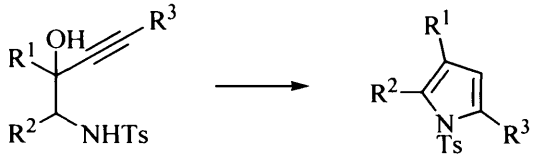


306 **311**

A mixture of degassed dimethylfomamide and water (4:1, 5 mL) was added to the iodopyrrole **306** (0.50 g, 1 mmol), *o*-nitrophenyl boronic acid (0.2 g, 1.1 mmol), sodium carbonate decahydrate (0.26 g, 2.5 mmol) and [1.1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (73 mg, 0.1 mmol) as decribed in the general procedure for the Suzuki reaction. After work-up, flash chromatography (0-10% ethyl acetate in petroleum ether) gave the *pyrrole* **311** as a brownish oil (0.30 g, 61%); R_f 0.90 (10% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2968 (s), 2929 (s), 2865 (w), 1625 (w), 1523 (m), 1436 (w), 1370 (m), 1281 (m), 1260 (m), 1174 (s), 1092 (s), 1021 (m), 811 (m) and 668 (m); δ_H 0.83-0.88 (6H, m, 2 x CH_3), 1.08-1.53 (10H, m, $CH_2C\equiv$ and 4 x CH_2), 2.34 (3H, s, pyr-CH_3), 2.43 (3H, s, $ArCH_3$), 2.80 (2H, t, *J* 7.6, pyr-CH_2), 7.20-7.29 (3H, m, 3 x ArH), 7.43-7.51 (3H, m, 3 x ArH), 7.65 (1H, t, *J* 8.6, ArH) and 8.17 (1H, d, *J* 8.6, ArCH); δ_C 13.7, 13.8, 15.0 (3 x CH_3),

19.3 (CH_2), 21.7 ($ArCH_3$), 22.0, 22.6, 29.6, 30.9, 32.3 (5 x CH_2), 74.0, 95.7 (2 x C≡), 106.1, 114.3 (2 x C), 123.5 (ArCH), 124.7 (C), 126.3 (2 x ArCH), 128.4 (C), 129.3 (2 x ArCH), 130.1 (2 x ArCH), 134.6 (ArCH) and 135.3, 136.7, 136.9, 145.0 (C and 3 x ArC); *m/z* [APcI] 493 ($[M+H]^+$, 35), 477 (20), 338 (25), 176 (100). The pyrrole was unstable as indicated by changing of the brown color to black over a few days at room temperature; the resulting sample showed no ^1H NMR data corresponding to the pyrrole **311**. Keeping at low temperature is required!

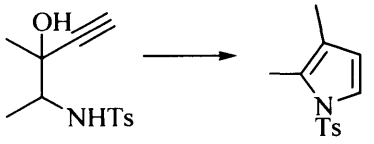
General procedure for silver-mediated cyclizations.



314 **315**

To a stirred solution of the tosylamide **314** (0.34 mmol, 1 eq.) in dichloromethane (2 mL) was added 10%w/w silver nitrate on silica gel (290 mg, 0.17 mmol, 0.5 eq.) in the absence of light. After 16 hr, the mixture was filtered through a short plug of silica gel and the filtrate was evaporated to give the *pyrrole* **315**.

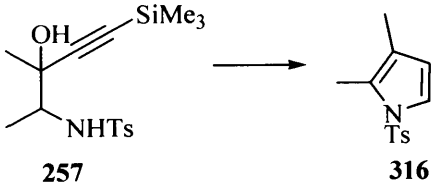
***2,3-Dimethyl-1-(4'-methylphenylsulfonyl)-pyrrole* 316**



255 **316**

Method A

To a stirred solution of the tosylamide **255** (90 mg, 0.34 mmol) in dichloromethane (2 mL) was added 10%wt/wt silver nitrate on silica gel (290 mg, 0.17 mmol) as described in general procedure. The work-up gave the *pyrrole* **49** as a colourless solid (63 mg, 75%), mp 59-60°C.



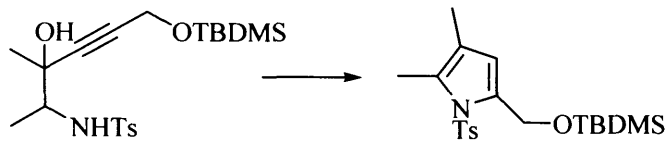
257 **316**

Method B

To a stirred solution of the tosylamide **257** (51 mg, 0.15 mmol) in dichloromethane (10 mL) was added 10%wt/wt silver nitrate on silica gel (1.24 g, 0.73 mmol) as described in general

procedure. The work-up gave the *pyrrole* **316** as a colourless solid (27 mg, 72%) mp 60°C; R_f 0.94 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 2925 (m), 1728 (w), 1596 (w), 1362 (m), 1250 (m), 1183 (s), 1163 (s), 1092 (s), 1026 (m), 813 (m) and 685 (s); δ_H 1.82 (3H, s, CH_3), 2.10 (3H, s, CH_3), 2.32 (3H, s, $ArCH_3$), 5.99 (1H, d, *J* 3.3, 4-H), 7.13 (1H, d, *J* 3.3, 5-H), 7.21 (2H, d, *J* 8.3, 2 x ArH) and 7.57 (2H, d, *J* 8.3, 2 x ArH); δ_C 10.8, 11.2 (2 x CH_3), 21.6 ($ArCH_3$), 113.9, 120.6 (4- and 5-CH), 127.1 (2 x ArCH), 129.9 (2 x ArCH) and 136.4, 139.1, 143.5, 144.5 (all C); *m/z* [APcI] 250 ($[M+H]^+$, 100).

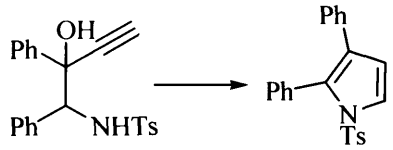
***5-(tert-Butyldimethylsilyloxymethyl)-2,3-dimethyl-1-(4'-methylphenylsulfonyl)-pyrrole* 317**



259 **317**

To a stirred solution of the tosylamide **259** (9 mg, 0.022 mmol) in dichloromethane (1 mL) was added 10%wt/wt silver nitrate on silica gel (20 mg, 0.012 mmol) as described in general procedure. The work-up gave the *pyrrole* **317** as a colorless liquid (8 mg, 93%); R_f 0.88 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2932 (m), 1728 (w), 1360 (m), 1182 (s), 1093 (m), 1057 (m), 837 (m), 779 (m) and 682 (s); δ_H 0.00 (6H, s, 2 x $SiCH_3$), 0.84 (9H, s, 3 x CH_3), 1.80, 2.10 (6H, s, 2- and 3-CH_3), 2.46 (3H, s, $ArCH_3$), 4.79 (2H, s, OCH_2), 5.98 (1H, s, 4-H), 7.16 (2H, d, *J* 8.2, ArCH) and 7.6 (2H, d, *J* 8.2, ArCH); δ_C -0.5 (2 x $SiCH_{32}$), 9.9, 10.6 (2- and 3-CH_3), 20.3 ($ArCH_3$), 24.4 (3 x CH_3), 29.6 (SiC), 56.7 (OCH_2), 113.6 (4-CH), 118.3 (5-C), 125.6 (2 x ArCH), 126.4 (2(3)-C), 128.4 (2 x ArCH), 133.6, 135.9 and 142.9 (3(2)-C and 2 x ArC); *m/z* [APcI] 392 ($[M+H]^+$, 10), 277 (10), 262 (100).

***2,3-Diphenyl-1-(4-methylphenylsulfonyl)-pyrrole* 318**

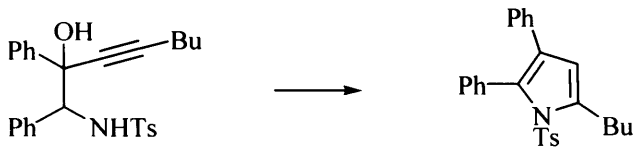


262 **318**

To a stirred solution of the tosylamide **262** (31 mg, 0.08 mmol) in dichloromethane (1.5 mL) was added 10%wt/wt silver nitrate on silica gel (80 mg, 0.04 mmol) as described in general procedure. The work-up gave the *pyrrole* **318** as a colourless solid (29.6 mg, 100%): mp 110-

111°C; R_f 0.72 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 2925 (w), 1597 (w), 1494 (w), 1447 (w), 1370 (m), 1174 (s), 1139 (s), 769 (m) and 686 (s); δ_H 2.28 (3H, s, $ArCH_3$), 6.48 (1H, d, *J* 3.4, 4-H), 6.95-6.98 (4H, m, both 2 x ArH), 7.00-7.04 (4H, m, 4 x ArCH), 7.13-7.18 (4H, m, 4 x ArH), 7.25 (2H, d, *J* 8.3, 2 x ArH) and 7.47 (1H, d, *J* 3.4, 5-H); δ_C 19.1 ($ArCH_3$), 109.54, 120.2 (4-, 5-CH), 123.9 (2 x ArC), 124.9, 125.4, 125.5, 125.6 (8 x ArCH), 126.0 (2 x ArCH), 126.6 (2 x ArCH), 127.8 (2(3)-C), 130.1 (2 x ArCH), 131.8, 133.2, 142.0 (3(2)-C and both Ar-C); *m/z* [APcI] 374 ($[M+H]^+$, 100).

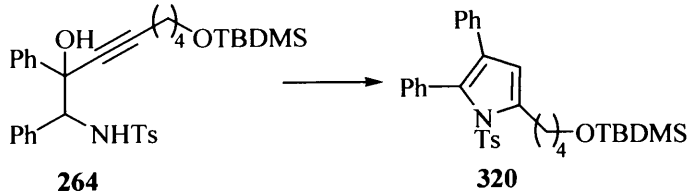
***5-Butyl-2,3-diphenyl-1-(4'-methylphenylsulfonyl)-pyrrole* 319**



263 **319**

To a stirred solution of the tosylamide **263** (55 mg, 0.12 mmol) in dichloromethane (10 mL) was added 10%wt/wt silver nitrate on silica gel (1.2 g, 0.06 mmol) as described in general procedure. The work-up gave the *pyrrole* **319** as a colourless solid (53 mg, 100%); mp 104-105°C; R_f 0.68 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 2956 (m), 2860 (m), 1598 (m), 1536 (w), 1494 (w), 1451 (m), 1368 (s), 1305 (m), 1172 (s), 1094 (m), 1027 (m), 813 (m), 765 (m) and 698 (s); δ_H 0.90 (3H, t, *J* 7.3, CH_3), 1.40 (2H, hex, *J* 7.3, CH_2), 1.68 (2H, pen, *J* 7.3, CH_2), 2.28 (3H, s, $ArCH_3$), 2.92 (2H, t, *J* 7.3, pyr-CH_2), 6.20 (1H, s, 4-H), 6.89 (2H, d, *J* 7.8, 2 x ArH) 6.98-7.06 (6H, m, 6 x ArH) and 7.12-7.24 (6H, m, 6 x ArH); δ_C 14.1 (CH_3), 21.6 ($ArCH_3$), 22.6, 29.2, 31.6 (3 x CH_2), 113.1 (4-CH), 126.6 (2 x ArCH), 127.0 (ArC), 127.4, 127.9, 128.1, 129.4, 129.6 (10 x ArCH), 131.8, 132.0 (2 x C), 132.5 (2 x ArCH), 134.5, 136.9, 138.7 and 144.3 (4 x C); *m/z* [APcI] 430 ($[M+H]^+$, 100).

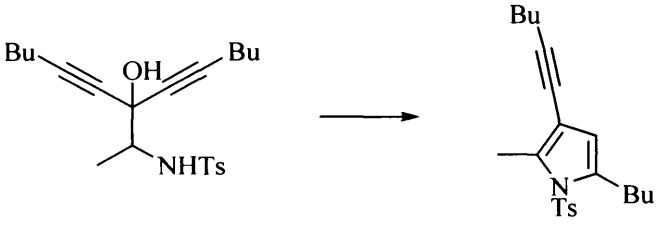
***5-[4'-(tert-Butyldimethylsilyloxy)butyl]-2,3-diphenyl-1-(4'-methylphenylsulfonyl)-pyrrole* 320**



264 **320**

To a stirred solution of the tosylamide **264** (32 mg, 0.06 mmol) in dichloromethane (10 mL) was added 10%wt/wt silver nitrate on silica gel (0.06 g, 0.03 mmol) as described in general procedure. The work-up gave the *pyrrole* **320** as a white solid (18 mg, 58%): mp 60-61°C; R_f 0.62 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 2924 (s), 2860 (m), 2854 (s), 1654 (w), 1604 (w), 1448 (m), 1378 (w), 1323 (w), 1263 (m), 1161 (m), 1092 (m), 735 (m), 695 (m) and 660 (m); δ_H 0.0 (6H, s, 2 x $SiCH_3$), 0.84 (9H, s, 3 x CH_3), 1.60 (2H, pen, *J* 6.7, CH_2), 1.75 (2H, pen, *J* 6.7, CH_2), 2.29 (3H, s, $ArCH_3$), 2.95 (2H, t, *J* 6.7, pyr-CH_2), 3.62 (2H, t, *J* 6.7, OCH_2), 6.22 (1H, s, 4-H), 6.90 (2H, dd, *J* 8.0, 1.8, 2 x ArH), 7.01-7.05 (8H, m, 8 x ArH) and 7.17-7.22 (4H, m, x ArH); δ_H 0.0 (2 x $SiCH_3$), 17.4 (CH_2), 20.6 ($ArCH_3$), 24.5 (SiC), 24.8 (3 x CH_3), 28.2, 31.6 (2 x CH_2), 62.0 (OCH_2), 112.1 (4-CH), 125.2 (2 x ArC), 125.9, 126.1, 126.9, 127.1, 127.9, 128.0 (12 x ArCH), 130.8 (2(3)-C), 131.5 (2 x ArCH), and 133.4, 135.8, 137.3, 143.2 (2(3)-, 5-C and 2 x ArC); *m/z* [APcI] 560 ($[M+H]^+$, 3), 444 (25), 406 (100).

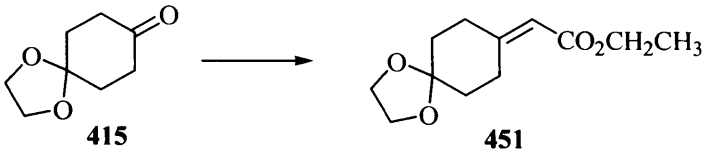
***5-Butyl-3-hex-1-ynyl-2-methyl-1-(4-methylphenylsulfonyl)-pyrrole* 321**



251 **321**

To a stirred solution of the tosylamide **251** (44 mg, 0.11 mmol) in dichloromethane (10 mL) was added 10%wt/wt silver nitrate on silica gel (0.12 g, 0.06 mmol) as described in general procedure. The work-up gave the *pyrrole* **321** as a colourless solid (42 mg, 100%): mp 108-109°C; R_f 0.88 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 2959 (s), 2330 (s), 2871 (m), 1725 (w), 1597 (m), 1457 (m), 1365 (s), 1257 (m), 1191 (s), 1166 (s), 1093 (s), 812 (m) and 686 (s); δ_H 0.83 (6H, m, 2 x CH_3), 1.28 (2H, hex, *J* 7.4, CH_2), 1.37 (2H, hex, *J* 7.4, CH_2), 1.46-1.51 (4H, m, 2 x CH_2), 2.29 (2H, t, *J* 7.4, C≡CCH_2), 2.32, 2.36 (6H, s, $ArCH_3$ and pyr-CH_3), 2.66 (2H, t, *J* 7.4, pyr-CH_2), 5.87 (1H, s, 4-H), 7.23 (2H, d, *J* 8.1, 2 x ArH) and 7.45 (2H, d, *J* 8.1, 2 x ArH); δ_C 13.6, 13.9, 14.1 (3 x CH_3), 19.0, 19.2 (2 x CH_2), 21.6 ($ArCH_3$), 22.0, 22.4, 28.3, 31.0 (4 x CH_2), 73.9, 93.0 (both C≡), 108 (2(3)-C), 113.0 (4-CH), 126.2 (2 x ArCH), 129.9 (2 x ArCH) and 135.3, 136.6, 137.1, 144.6 (3(2)-, 5-C and 2 x ArC); *m/z* [APcI] 372.0 ($[M+H]^+$, 100).

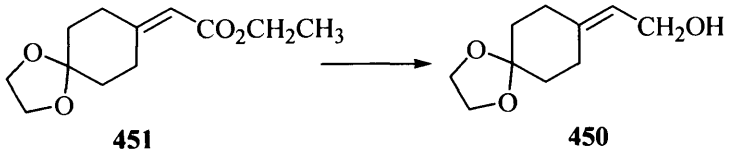
***Ethyl (1,4-dioxa-spiro[4.5]dec-8-ylidene)-acetate* 415**[76a]



415 **451**

To a stirred suspension of sodium hydride (0.40 g, 9.6 mmol, washed with 2 mL of anhydrous tetrahydrofuran), in anhydrous tetrahydrofuran (5 mL) was added dropwise a solution of triethyl phophonoacetate (1.90 mL, 9.6 mmol) in anhydrous tetrahydrofuran (5 mL) at room temperature and the resulting mixture stirred for 30 min. To the mixture, a solution of 1,4-cyclohexanedione monoethylene ketal **415** (1.00 g, 6.4 mmol) in tetrahydrofuran (1 mL) was added dropwise and the mixture then stirred under reflux for 16 h. The cooled mixture was poured into cold water (15 mL) and extracted with hexane (2 x 10 mL). The combined hexane extracts were washed with brine, dried and evaporated to give a crude product as a light yellow oil. The concentrated crude was purified by flash chromatography (25% ethyl acetate in petroleum ether) to give the *ester* **451** as a colourless oil (1.30 g, 90%): R_f 0.54 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2954 (s), 2858 (s), 1712 (s), 1648 (s), 1446 (m), 1364 (m), 1303 (m), 1274 (s), 1200 (s), 1168 (s), 1122 (s), 1088 (s), 1035 (s), 944 (m), 907 (s), 864 (w) and 690 (m); δ_H 1.20 (3H, t, *J* 7.2, CH_3), 1.70 (4H, q, *J* 6.4, 2 x CH_2), 2.31 (2H, app. t, *J* 6.4, CH_2), 2.93 (2H, app. t, *J* 6.4, CH_2), 3.91 (4H, s, 2 x OCH_2), 4.10 (2H, q, *J* 7.2, CO_2CH_2) and 5.60 (1H, s, CH=); δ_C 14.7 (CH_3), 26.4, 35.0, 35.3, 36.1 (4 x CH_2), 60.0 (OCH_2), 64.8 (2 x OCH_2), 108.4 (CH=), 114.7 (C), 160.6 (C=) and 167.0 (C=O); *m/z* [APcI] 227 ($[M+H]^+$, 25), 181 (100). *These data are consistent with those recorded in the literature.*[76a]

***2-(1',4'-Dioxa-spiro[4.5]dec-8'-ylidene)-ethanol* 450** [76a]

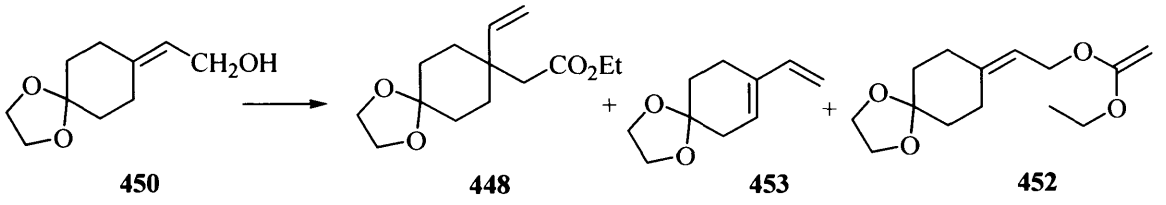


451 **450**

To a solution of the ester **451** (1.00 g, 4.4 mmol) in dry toluene (10 mL) cooled to –78°C was added Dibal-H (13.2 mL, 13.2 mmol) over a period of 20 minutes. After stirring for an additional 2 h, excess reagent was decomposed by the careful addition of 2M HCl (20 mL). The mixture was allowed to warm slowly to 0°C and the organic layer separated. The aqueous

layer was extracted with ethyl acetate (2 x 20 mL) and the combined organic fractions dried and evaporated to give the crude alcohol. The concentrated crude was purified by flash chromatography (25% ethyl acetate in petroleum ether) to give the *alcohol* **450** as a colourless oil (0.50 g, 62%): R_f 0.11 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 3522 (br), 2944 (s), 2868 (s), 1671 (m), 1436 (m), 1364 (m), 1272 (m), 1122 (s), 1096 (s), 1068 (s), 1034 (s), 944 (m), 904 (s) and 683 (m); δ_H 1.63 (4H, app. pen, *J* 6.3, 2 x CH_2), 2.21 (2H, app. t, *J* 6.3, CH_2), 2.27 (2H, app. t, *J* 6.3, CH_2), 3.90 (4H, s, 2 x OCH_2), 4.09 (2H, d, *J* 7.0, 1-CH_2) and 5.37 (1H, t, *J* 7.0, CH=); δ_C 22.7, 23.2, 25.6, 28.4 (4 x CH_2), 41.5 (1-CH_2), 60.5 (2 x OCH_2), 113.5 (C), 124.7 (CH=) and 134.4 (C=); *m/z* [APcI] 167 ($[M-OH]^+$, 30), 122 (100), 104 (95), 71 (50). *These data are consistent with those recorded in the literature.*[76a]

***Ethyl (8'-vinyl-1',4'-dioxa-spiro[4.5]dec-8'-yl)-acetate* 448,**
***8-Vinyl-1,4-dioxa-spiro[4.5]dec-7-ene* 453,**[76b]
***and 8-[2'-(1'-Ethoxy-vinyloxy)-ethylidene]-1,4-dioxa-spiro[4.5]decane* 452** [76c]



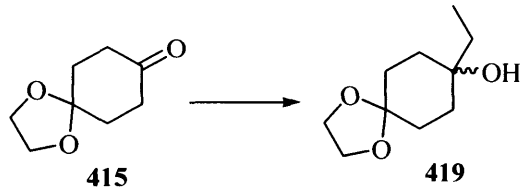
450 **448** **453** **452**

A stirred solution of the alcohol **450** (0.28 g, 1.5 mmol), triethyl orthoacetate (1.50 mL, 8.25 mmol) and propanoic acid (0.10 mL, 1.5 mmol) in dry dimethylformamide (5 mL) was placed in a microwave and irradiated, using power 30W, 100°C, pressure 250 psi, for 10 min. After irradiation, the reaction mixture was cooled, diluted with ether (5 mL), washed with 1M HCl (5 mL), followed by brine (5 mL) and dried. The concentrated crude was purified by flash chromatography (25% ethyl acetate in petroleum ether) to give the *ester* **448** as a colourless oil (0.13 g, 51%): R_f 0.58 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2953 (s), 2848 (s), 1735 (s), 1445 (m), 1370 (m), 1270 (w), 1109 (m), 1035 (m), 910 (w) and 689 (w); δ_H 1.24 (3H, t, *J* 7.1, CH_3), 1.63-1.74 (6H, m, 3 x CH_2), 1.86 (2H, app. dd, *J* 6.4, 2.4, CH_2), 2.33 (2H, s, 2-CH_2), 3.95 (4H, s, 2 x OCH_2), 4.10 (2H, q, *J* 7.1, CH_2O), 5.01 (1H, dd, *J* 17.6, 0.7, CH_{2a}=), 5.17 (1H, dd, *J* 11.0, 0.7, CH_{2b}=) and 5.81 (1H, dd, *J* 17.6, 11.0, CH=); δ_C 12.3 (CH_3), 28.9, 30.8 (4 x CH_2), 33.8 (8'-C), 36.4 (2-CH_2), 58.0 (CH_2O), 62.2 (2 x OCH_2), 106.7 (CH_2=), 112.1 (5'-C), 140.9 (CH=) and 169.3 (C=O); *m/z* [APcI] 255 ($[M+H]^+$, 100), 209 (15), 165 (45), 123 (45), 119 (45). Found $[M+H]^+$, 255.1593. $C_{14}H_{23}O_4$ requires *M*, 255.1596.

Column chromatography also gave the *vinylcyclohexene* **453** as a colourless oil (44 mg, 18%): R_f 0.66 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2929 (s), 2884 (m), 1737 (w), 1643 (w), 1605 (w), 1420 (w), 1362 (m), 1250 (m), 1118 (s), 1060 (s), 1002 (m), 948 (m) and 869 (w); δ_H 1.76 (2H, app. t, *J* 6.7, CH_2), 2.32 (4H, br res., 2 x CH_2), 3.92 (4H, s, 2 x OCH_2), 4.89 (1H, d, *J* 10.7, CH_{2a}=), 5.02 (1H, d, *J* 17.5, CH_{2b}=), 5.58 (1H, br res., 7-H) and 6.28 (1H, dd, *J* 17.5, 10.7, CH=); δ_C 23.4, 31.1, 36.4 (3 x CH_2), 64.8 (2 x OCH_2), 108.5 (5-C), 111.5 (CH_2=), 126.6 (7-CH), 135.9 (8-C) and 139.2 (CH=); *m/z* [APcI] 167 ($[M+H]^+$, 5), 151 (10), 89 (100). *These data are consistent with those recorded in the literature.*[76b]

Column chromatography also gave the *ether* **452** as a colourless oil (63 mg, 20%): R_f 0.76 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2956 (s), 2885 (s), 1674 (m), 1443 (m), 1363 (m), 1258 (m), 1117 (s), 1032 (s), 941 (w) and 796 (w); δ_H 1.14 (3H, t, *J* 7.1, CH_3), 1.63 (4H, pen, *J* 6.6, 2 x CH_2), 2.22 (2H, t, *J* 6.6, CH_2), 2.26 (2H, t, *J* 6.6, CH_2), 3.49 (2H, d, *J* 2.1, CH_2=), 3.90 (4H, s, 2 x OCH_2), 3.98 (2H, q, *J* 7.1, OCH_2), 4.64 (2H, d, *J* 7.0, CH_2=) and 5.30 (1H, t, *J* 7.0, CH=); δ_C 15.1 (CH_3), 22.1, 28.3, 40.0 (4 x CH_2), 47.8 (CH_2=), 58.2, 60.9 (CH_2= and OCH_2), 72.4 (2 x OCH_2), 115.6 (5-C), 119.8 (CH=), 148.9 (8-C) and 181.2 (C=); *m/z* [APcI] 255 ($[M+H]^+$, 15), 211 (15), 167 (15), 123 (8), 89 (50), 61 (100). *These data are consistent with those recorded in the literature.*[76c]

***8-Ethyl-1,4-dioxa-spiro[4.5]decan-8-ol* 419**

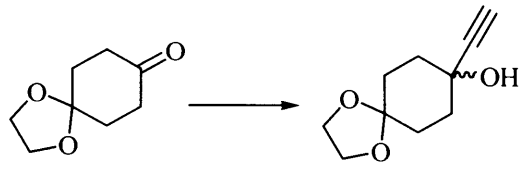


415 **419**

To a stirred solution of the ethylmagnesium bromide (0.84 mL in diethyl ether, 6.4 mmol) in anhydrous diethyl ether (10 mL) was adding first half of the ketone (2.5 g, 1.6 mmol) solution in anhydrous diethyl ether (20 mL). The mixture was allowed to stir for 3 h and then the second half of the ketone **415** (2.5 g, 1.6 mmol) solution was added. The mixture was allowed to stir 2 h further, before heating at to reflux for 16 h. The resulting solution was allowed to cool to room temperature and poured into saturated aqueous ammonium chloride (25 mL). The organic layer was then separated, dried and evaporated to give the crude product as a yellow oil. Column chromatography gave the *alcohol* **419** as a colourless oil (142 mg, 30%): R_f 0.34 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 3456 (br), 2930 (s), 2872 (m), 1438 (w), 1369 (m), 1276 (m), 1238 (m), 1093 (s), 1035 (m), 942 (s) and 650 (m); δ_H 0.89

(3H, t, *J* 7.5, CH_3), 1.48 (2H, q, *J* 7.5, CH_2), 1.55-1.63 (6H, m, 3 x CH_2), 1.83-2.18 (2H, m, CH_2) and 3.88-3.95 (4H, m, 2 x OCH_2); δ_C 7.9 (CH_3), 30.9, 34.6 (4 x CH_2), 38.6 (CH_2), 64.6 (2 x OCH_2), 65.0 (8-C) and 109.3 (5-C); *m/z* [APcI] 169 ($[M-H_2O]^+$, 55), 125 (100), 107 (68), 89 (80), 73 (78).

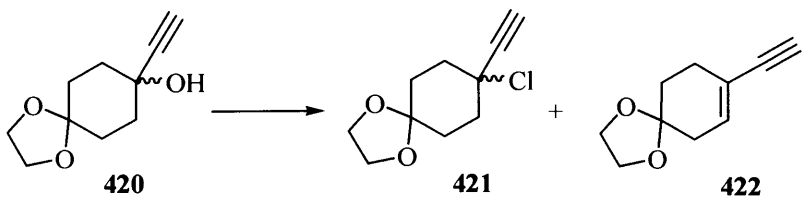
***8-Ethynyl-1,4-dioxa-spiro[4.5]decan-8-ol* 420**[107]



415 **420**

To a stirred solution of lithium acetylide-ethylenediamine **254** (0.52 g, 5 mmol) in anhydrous tetrahydrofuran (10 mL) at 0°C was added a solution of the ketone (0.45 g, 2.8 mmol) in tetrahydrofuran (5 mL) slowly over 30 min. The mixture was then stirred at room temperature for 16 h. Saturated aqueous ammonium chloride (5 mL) and diethyl ether (5 mL) were added to the mixture, which was then stirred for 10 min. The aqueous layer was separated and extracted with ether (2 x 10 mL). The combined extracts were washed with water (3 x 10 mL), dried and evaporated to give an orange oil. The oil was distilled under reduced pressure to give the *alkynol* **420** as a colourless oil (0.31 g, 61%), bp 99-100°C at 0.03 mmHg [lit. bp[107] 97-105°C at 0.03 mmHg]; R_f 0.49 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 3404 (br), 2958 (s), 2890 (m), 2353 (w), 1443 (m), 1367 (m), 1334 (w), 1251 (m), 1162 (s), 1106 (s), 1033 (s), 999 (m), 964 (s), 882 (w) and 733 (w); δ_H 1.62-1.65 (4H, m, 2 x CH_2), 1.68-1.77 (4H, m, 2 x CH_2), 2.33 (1H, s, CH≡) and 3.79 (4H, m, 2 x OCH_2); δ_C 31.67 37.4 (4 x CH_2), 64.7 (2 x OCH_2), 66.3 (8-C), 66.3, 88.7 (both C≡C) and 108.2 (5-C); *m/z* [APcI] 183 ($[M+H]^+$, 15), 165 (60), 125 (100), 121 (40), 79 (25). *These data are consistent with those recorded in the literature.*[107]

***8-Chloro-8-ethynyl-1,4-dioxa-spiro[4.5]decane* 421,**
***and 8-Ethynyl-1,4-dioxa-spiro[4.5]dec-7-ene* 422**

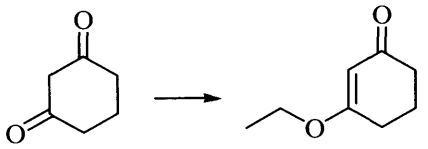


420 **421** **422**

The alcohol **420** (0.30 g, 1.6 mmol) was added to a stirred solution of thionyl chloride in 5 mL of dimethylformamide at room temperature. After the mixture was stirred for 3 h, it was treated with saturated aqueous ammonium chloride (50 mL) and diluted with ether (25 mL). The organic layer was separated and dried. Removal of the solvent *in vacuo* gave a yellow oil. Column chromatography (10% ethyl acetate in petroleum ether) gave the *chloro-acetylene* **421** as a light yellow oil (113 mg, 34%): R_f 0.38 (10% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2958 (m), 2875 (w), 2359 (w), 1438 (w), 1367 (w), 1251 (m), 1163 (m), 1104 (s), 1033 (m) and 963 (m); δ_H 1.51-1.75 (4H, m, 2 x CH_2), 2.14-2.17 (4H, m, 2 x CH_2), 2.62 (1H, s, CH≡) and 3.89 (4H, m, 2 x OCH_2); δ_C 25.2, 31.8 (4 x CH_2), 55.7 (8-CCl), 66.3 (2 x OCH_2), 69.1, 86.1 (2 x C≡) and 112.0 (5-C).

Column chromatography (10% ethyl acetate in petroleum ether) also gave the *enyne* **422** as a colourless oil (102 mg, 40%): R_f 0.57 (10% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2961 (m), 2885 (m), 2367 (w), 1433 (m), 1367 (m), 1260 (m), 1115 (s), 1060 (s), 1042 (s), 948 (m), 868 (m), 798 (w) and 735 (m); δ_H 2.03 (2H, app. t, *J* 6.5, CH_2), 2.51-2.66 (4H, m, 2 x CH_2), 3.07 (1H, s, CH≡), 4.23 (4H, m, 2 x OCH_2) and 6.31-6.33 (1H, m, CH=); δ_C 20.5 (CH_2), 38.2 (2 x CH_2), 67.1 (2 x OCH_2), 79.8, 83.1 (2 x C≡), 117.1 (5-C), 132.7 (8-C) and 136.9 (CH=); *m/z* [APcI] 165 ($[M+H]^+$, 15), 137 (15), 109 (8), 89 (100), 73 (15).

***3-Ethoxy-2-cyclohexen-1-one* 426**[69c]

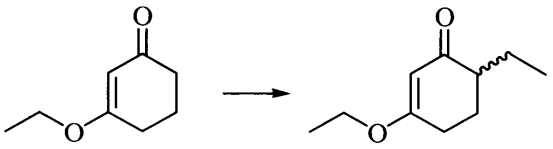


412 **426**

In a three-necked, round-bottomed flask was placed a solution of 1,3-cyclohexanedione **412** (10.00 g, 89 mmol), *p*-toluenesulfonic acid monohydrate (0.30 g, 1.56 mmol) and absolute ethanol (50 mL) in 200 mL of benzene. The mixture was heated to boiling and the azeotrope composed of benzene, alcohol and water was removed at the rate of 20 mL per hour. When the temperature of the distilling vapour reached 78°C (6 h), the distillation was stopped and the residual solution was washed with 10% aqueous sodium hydroxide (4 x 20 mL), which had been saturated with sodium chloride. The resulting organic solution was washed with successive 10 mL portions of water until the aqueous washings were neutral, and then concentrated. The residual liquid was distilled under reduced pressure (98-100°C at 0.5 mbar)[69c] to give the *ethoxy cyclohexenone* **426** as a light brown liquid (6.54 g, 52%); ν_{max}/cm^{-1} [film] 2982 (m), 2947 (s), 2893 (m), 1651 (s), 1602 (s), 1475 (w), 1457 (m), 1429 (m), 1378

(s), 1349 (m), 1328 (s), 1221 (s), 1183 (w), 1136 (s), 1031 (m), 930 (m), 869 (m), 815 (s), 759 (w) and 658 (w); δ_H 1.44 (3H, t, *J* 7.0, CH_3), 2.07 (2H, app. pen, *J* 6.4, 5-CH_2), 2.42 (2H, app. t, *J* 6.4, 4(6)-CH_2), 2.48 (2H, app. t, *J* 6.4, 6(4)-CH_2), 3.98 (2H, q, *J* 7.0, OCH_2) and 5.43 (1H, s, 2-H); δ_C 14.5 (CH_3), 21.6, 29.4, 37.1 (3 x CH_2), 64.5 (OCH_2), 103.0 (2-CH), 178.3(3-C) and 200.1 (C=O); *m/z* [APcI] 141 ($[M+H]^+$, 100). *These data are consistent with those recorded in the literature.*[69c]

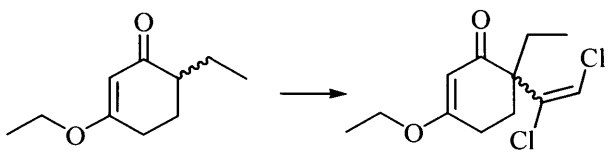
***3-Ethoxy-6-ethyl-cyclohex-2-enone* 427**[69c]



426 **427**

A dry, round-bottomed flask was charged with 40 mL of anhydrous tetrahydrofuran and anhydrous diisopropylamine (6.37 mL, 47 mmol). The flask was cooled to 0°C with an ice bath. A 2.5 M hexane solution of n-butyl lithium (18.8 mL, 47 mmol) was added dropwise with stirring over a 30-min period. The resulting solution of lithium diisopropylamide (LDA) was cooled to –78°C. A solution of 3-ethoxy-2-cyclohexen-1-one **426** (5.00 g, 36 mmol) in 25 mL of anhydrous tetrahydrofuran was added dropwise over a 1h period. The solution was stirred at –78°C for 1 h followed by the rapid addition of zinc chloride (4.90 g, 36 mmol) under a nitrogen flow. The addition of iodoethane (8.7 mL, 107 mmol) and DMPU (9.23 g, 72 mmol) followed. The resulting mixture was stirred at –78°C for 2 h and then at room temperature for 16 h. The mixture was quenched with water (50 mL) and extracted with ether (2 x 50 mL). The combined extracts were dried and evaporated to give a red-brown liquid. The concentrated crude was purified by flash chromatography to give the *3-ethoxy-6-ethyl-cyclohexenone* **427** as a colourless oil (3.49 g, 57%); R_f 0.56 (30% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2974 (m), 2939 (m), 2885 (m), 1655 (s), 1610 (s), 1453 (w), 1423 (w), 1378 (s), 1354 (m), 1302 (w), 1217 (m), 1192 (s), 1107 (w), 1047 (w), 1022 (w), 901 (w), 841 (w) and 816 (m); δ_H 0.88 (3H, t, *J* 7.5, CH_3), 1.29 (3H, t, *J* 7.1, CH_3), 1.37 (1H, hep, *J* 6.9, 6-CH), 1.62-1.71 (1H, m, 5-CH_{2a}), 1.74-1.86 (1H, m, 5-CH_{2b}), 2.00-2.06 (2H, m, CH_2), 2.35 (2H, app. t, *J* 6.2, 4-CH_2), 3.81 (2H, q, *J* 7.1, OCH_2) and 5.23 (1H, s, 2-H); δ_C 11.9, 14.6 (2 x CH_3), 22.8, 26.0, 28.3 (3 x CH_2), 46.9 (6-CH), 64.5 (7-OCH_2), 102.6 (2-CH), 177.1 (3-C) and 202.1 (C= O); *m/z* [APcI] 169 ($[M+H]^+$, 100), 71 (40). *These data are consistent with those recorded in the literature.*[69c]

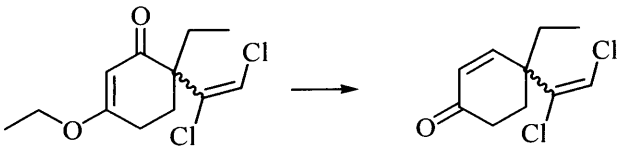
***6-(1,2-Dichloro-vinyl)-3-ethoxy-6-ethyl-cyclohex-2-enone* 428**



427 **428**

Lithium diisopropylamide (LDA) was prepared from anhydrous diisopropylamine (2.70 mL, 19.7 mmol) and a 2.5 M hexane solution of *n*-butyl lithium (7.90 mL, 19.7 mmol) in tetrahydrofuran (20 mL) by using exactly the same method described in the foregoing experiment. The resulting solution of LDA was cooled to –78°C. A solution of the cyclohexenone **427** (3.00 g, 17.9 mmol) in tetrahydrofuran (20 mL) was added dropwise over 1-h period, followed immediately by the addition of hexamethylphosphorus triamide (3.25 mL, 17.9 mmol) over a 5-min period. The resulting solution was stirred at –78°C for 45 min, followed by the dropwise addition of trichloroethylene (1.80 mL, 19.7 mmol). The mixture was allowed to warm to room temperature slowly over 3 h. As the mixture warmed, the color changed from pale yellow to olive green, to pale red and finally to black. The mixture was then quenched with water (50 mL) and organic layer was separated. The aqueous layer was extracted with diethyl ether (4 x 15 mL). The combined organic layers were washed with water (4 x 45 mL) and twice with brine (40 mL) then dried and evaporated. The concentrated crude was purified by flash chromatography (20-40% ethyl acetate in petroleum ether) to give the *6-dichlorovinyl-6-ethyl-cyclohexenone* **428** as a yellow oil (2.50 g, 53%); R_f 0.80 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2938 (w), 1670 (m), 1611 (s), 1449 (w), 1379 (m), 1240 (w), 1189 (s), 1028 (w) and 805 (w); δ_H 1.02 (3H, t, *J* 7.3, CH_3), 1.38 (3H, t, *J* 7.0, CH_3), 1.86-1.97 (3H, m, 5-H_a and CH_2), 2.38 (1H, dt, *J* 17.6, 5.3, 5-H_b), 2.46-2.52 (2H, m, 4-CH_2), 3.92 (2H, q, *J* 7.0, OCH_2), 5.39 (1H, s, 2-H) and 6.39 (1H, s, CClH); δ_C 9.8, 14.6 (2 x CH_3), 26.9, 28.2, 31.1 (3 x CH_2), 54.8 (6-C), 64.8 (OCH_2), 103.1 (2-CH), 116.7 (CClH), 136.9 (CCl), 175.6 (3-C) and 197.4 (C= O); *m/z* [APcI] 265 ($[M+H]^+$, 80), 263 (95), 109 (25), 89 (100), 73 (50); Found $[M(Cl^{35})+H]^+$, 263.0602. $C_{12}H_{17}Cl_2O_2$ requires *M*, 263.0605.

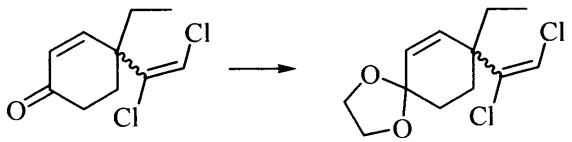
***4-(1',2'-Dichloro-vinyl)-4-ethyl-cyclohex-2-enone* 429**



428 **429**

To a stirred solution of the cyclohexenone **428** (0.50 g, 1.9 mmol) in anhydrous toluene (5 mL) cooled to 0°C, was added Dibal-H (2.3 mL, 2.3 mmol) during 1 h. After stirring for an additional 2 h at 0°C, excess reagent was decomposed by the careful addition of methanol (5 mL), followed by water (10 mL) and then 10% aqueous sulfuric acid (15 mL). The mixture was allowed to stir vigorously for 5 min and the organic layer separated. The aqueous layer was extracted with diethyl ether (4 x 10 mL) and the combined organic fractions were washed with saturated sodium bicarbonate solution (2 x 10 mL), water (2 x 10 mL) and brine (2 x 10 mL). The organic layers were then dried and evaporated. The concentrated crude was purified by distillation at 68-71°C (0.6 mbar) to give the *enone* **429** as a colourless oil (0.16 g, 42%); ν_{max}/cm^{-1} [film] 3068 (w), 2968 (m), 2925 (w), 2875 (w), 1687 (s), 1614 (w), 1459 (w), 1381 (w), 1254 (w), 1219 (w), 1113 (w), 874 (w), 824 (w) and 809 (m); δ_H 0.98 (3H, t, *J* 7.5, CH_3), 1.61-1.68 (2H, m, CH_2), 1.88-1.97 (2H, m, CH_2), 2.42-2.58 (2H, m, CH_2), 5.91 (1H, d, *J* 10.0, 2(3)-H), 6.54 (1H, s, CClH) and 7.19 (1H, d, *J* 10.0, 3(2)-H); δ_C 9.3 (CH_3), 24.4, 25.2 (2 x CH_2), 33.9 (4-C), 38.2 (CH_2), 112.7 (CClH), 127.3 (2(3)-CH), 143.6 (7-CCl), 147.1 (3(2)-CH) and 197.9 (C= O); *m/z* [APcI] 221 ($[M+H]^+$, 20), 219 (45), 183 (100), 153 (35), 61 (40); Found $[M(Cl^{35})+NH_4]^+$, 236.0608. $C_{10}H_{16}Cl_2NO$ requires *M*, 236.0609.

***8-(1',2'-Dichloro-vinyl)-8-ethyl-1,4-dioxa-spiro[4.5]dec-6-ene* 425**

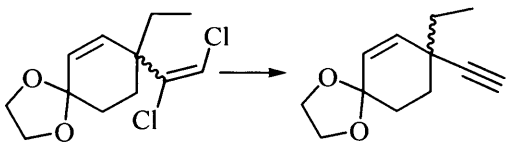


429 **425**

A flask was charged with toluene (10 mL), the cyclohexenone **429** (0.16 g, 0.73 mmol), ethylene glycol (0.23 mL, 2.19 mmol) and *p*-toluenesulfonic acid (catalytic amount). After the mixture was refluxed for 16 h, it was poured into saturated sodium bicarbonate solution (5 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (4 x 10 mL). The organic phases were combined and washed with water (2 x 10 mL) and brine (10 mL) then dried and evaporated to give the *dioxolane* **425** as a brownish oil (0.18 g, 100%); ν_{max}/cm^{-1} [film] 3473 (br), 3066 (w), 2964 (s), 2922 (s), 2880 (s), 1684 (s), 1609 (w), 1453 (m), 1378 (m), 1217 (m), 1107 (s), 1032 (m), 941 (m), 911 (m), 876 (w) and 806 (s); δ_H 0.86 (3H, t, *J* 7.4, CH_3), 1.46-1.53 (2H, m, CH_2), 1.75-1.81 (2H, m, CH_2), 2.18-2.46 (2H, m, CH_2), 3.82-3.95 (4H, m, 2 x OCH_2), 5.55 (1H, d, *J* 10.4, 6(7)-H), 6.18 (1H, d, *J* 10.4, 7(6)-H) and 6.30 (1H, s, CHCl); δ_C 8.7 (CH_3), 31.2, 32.0, 32.6 (3 x CH_2), 34.3 (8-C), 64.8 (2 x OCH_2),

116.0 (5-C), 125.7 (CHCl), 127.7 (6(7)-CH), 135.9 (7(6)-CH) and 143.1 (CCl); *m/z* [APcI] 265 ($[M+H]^+$, 25), 263 (40), 229 (35), 227 (100), 219 (20); Found $[M(Cl^{35})+H]^+$, 263.0607 for $C_{12}H_{17}Cl_2O_2$, calc. 263.0605.

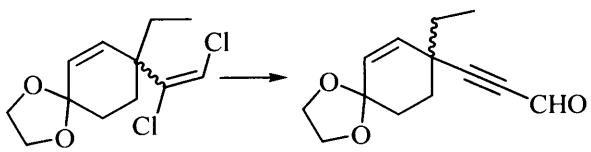
***8-Ethyl-8-ethynyl-1,4-dioxa-spiro[4.5]dec-6-ene* 430** [69b]



425 **430**

A stirred solution of the dichloro-decene **425** (0.16 g, 0.61 mmol) in tetrahydrofuran was cooled to –78°C under nitrogen. A 2.5 M hexane solution of *n*-butyl lithium (0.50 mL, 1.22 mmol) was added dropwise over a 30-min period. The mixture was allowed to stir at –78°C for 2 h, the cold bath removed and stirring continued for 90 min. The mixture was poured into water (10 mL) and the organic layer separated. The aqueous layer was extracted with diethyl ether (4 x 10 mL). The combined organic layers were washed with water (2 x 10 mL), brine (2 x 10 mL) and dried. The concentrated crude was purified by flash chromatography (10% ethyl acetate in petroleum ether) to give the *ethynyl-decene* **430** as a colourless oil (60 mg, 40%); R_f 0.50 (10% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 3490 (br), 3296 (s), 3030 (m), 2962 (s), 2879 (s), 2105 (w), 1673 (m), 1461 (m), 1394 (s), 1348 (m), 1218 (s), 1156 (s), 1108 (s), 1022 (s), 946 (s), 884 (m) and 756 (s); δ_H 0.87-0.92 (3H, m, CH_3), 1.41-1.51 (2H, m, CH_2), 1.58-1.63 (1H, m, CH_{2a}), 1.68-1.78 (1H, m, CH_{2b}), 1.82-2.04 (3H, m, CH≡ and CH_2), 3.86-3.91 (4H, m, 2 x OCH_2), 5.44 (1H, d, *J* 9.9, 6(7)-H) and 5.66 (1H, d, *J* 9.9, 7(6)-H); δ_C 9.1 (CH_3), 31.1, 32.9, 34.2 (3 x CH_2), 36.6 (8-C), 64.8, 65.1 (2 x OCH_2), 70.1, 87.7 (2 x C≡), 105.6 (5-C), 127.3 (6(7)-CH) and 136.5 (7(6)-CH); *m/z* [APcI] 193 ($[M+H]^+$, 100), 137 (25), 73 (35). *These data are consistent with those recorded in the literature.*[69b]

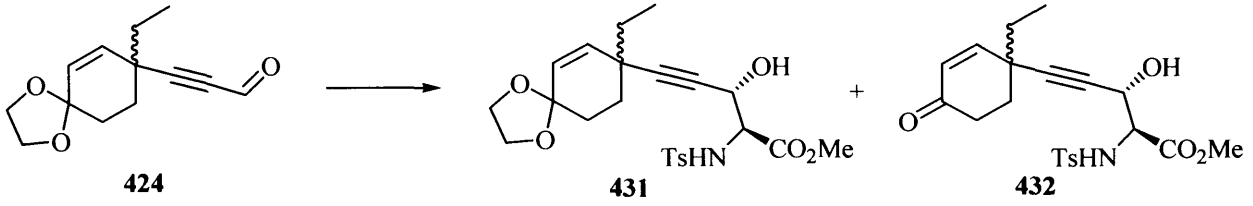
***(8'-Ethyl-1',4'-dioxa-spiro[4.5]dec-6'-en-8'-yl)-propynal* 424**



425 **424**

To a stirred solution of the dichloro-decene **425** (0.16 g, 0.61 mmol) in anhydrous tetrahydrofuran (2 mL) at –78°C was added 2.5M *n*-butyl lithium (0.5 mL in hexane, 1.22 mmol) dropwise and then the mixture was allowed to stir at –78°C for 2 h. To the mixture was added anhydrous dimethylformamide (0.1 mL, 1.22 mmol) in one portion. The reaction mixture was then warmed to room temperature and stirred for 1 h, then poured into a well-stirred mixture of 10% aqueous KH_2PO_4 (3 mL, 2.5 mmol) and diethyl ether (3 mL) at 5°C and this resulting mixture stirred vigorously for 10 min. The aqueous layer was separated and extracted by ether (2 x 5 mL). The combined ether solutions were then dried and evaporated to give the *aldehyde* **424** as a yellow oil (0.12 g, 100%); R_f 0.15 (10% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 3454 (br), 2956 (m), 2930 (m), 2867 (m), 2201 (m), 1666 (s), 1461 (w), 1383 (w), 1121 (m), 1098 (m), 1042 (w), 946 (w) and 758 (w); δ_H 0.93-0.99 (3H, m, CH_3), 1.44-1.67 (2H, m, CH_2), 1.70-1.83 (2H, m, CH_2), 1.91-2.02 (2H, m, CH_2), 3.80-3.97 (4H, m, 2 x OCH_2), 5.59 (1H, d, *J* 10.0, 6'(7')-H), 5.69 (1H, d, *J* 10.0, 7'(6')-H) and 7.79 (1H, s, CHO); δ_C 9.2 (CH_3), 31.2, 32.2, 33.8 (3 x CH_2), 38.5 (8'-C), 64.9, 65.2 (2 x OCH_2), 71.5, 82.8 (2 x C≡), 115.1 (5'-C), 129.2 (6'(7')-CH), 134.0 (7'(6')-CH) and 176.9 (C=O); *m/z* [APcI] 221 ($[M+H]^+$, 100), 217 (20), 72 (35); Found $[M+H]^+$, 221.1173. $C_{13}H_{17}O_3$ requires *M*, 221.1172.

***Methyl (2SR,3SR)-5-(8'-ethyl-1',4'-dioxa-spiro[4.5]dec-6'-en-8'-yl)-3-hydroxy-2-(4-methylphenylsulfonylamino)-pent-4-ynoate* 431**
***and Methyl (2SR,3SR)-5-(1'-Ethyl-4'-oxo-cyclohex-2'-enyl)-3-hydroxy-2-(4-methylphenylsulfonylamino)-pent-4-ynoate* 432**



424 431 432

Diisopropylamine (0.15 mL, 1.13 mmol) was suspended in anhydrous tetrahydrofuran (2 mL) at 0°C. A solution of 2.5M *n*-butyllithium (1.12 mL in hexane, 1.13 mmol) was added dropwise and the mixture stirred at 0°C for 30 min. The solution of lithium diisopropylamide thus formed was cooled to -78°C and added a solution mixture of methyl *N*-tosyl glycine ester **1** (0.11 g, 0.45 mmol) and tin(II) chloride (0.21 g, 1.13 mmol) in anhydrous tetrahydrofuran (5 mL) as described in the general procedure. After the work-up, the product was purified to give the *hydroxy ester* **431** as a pale yellow oil (20 mg, 10%), *anti:syn* = 76:24; R_f 0.1 (40%

ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 3464 (b), 3256 (b), 2956 (m), 2865 (m), 2232 (s), 1745 (s), 1668 (s), 1437 (s), 1342 (s), 1163 (s), 1092 (s), 816 (s) and 668 (s); *m/z* [APcI] 464 ($[M+H]^+$, 100); Found: $[M+NH_4]^+$, 481.2005. $C_{23}H_{33}N_2O_7S$ requires *M*, 481.2003.

Major Isomer:

δ_H 0.89 (3H, t, *J* 7.4, CH_3), 1.29-1.60 (2H, m, CH_2), 1.63-1.98 (4H, m, 2 x CH_2), 2.35 (3H, s, $ArCH_3$), 3.50 (3H, s, OCH_3), 3.82-4.15 (5H, m, 2 x CH_2 and 2-H), 4.57 (1H, d, *J* 5.1, 3-H), 5.43-5.54 (2H, m, 6'(7')-H and NH), 5.62 (1H, dd, *J* 10.0, 2.7, 7'(6')-H), 7.23 (2H, d, *J* 8.1, ArH) and 7.67 (2H, d, *J* 8.1, ArH); δ_C 9.1 (CH_3), 21.9 ($ArCH_3$), 31.1, 32.6, 33.9 (3 x CH_2), 36.7 (5'-C), 53.3 (OCH_3), 60.8 (2-CH), 63.4 (3-CH), 64.8, 65.1 (2 x CH_2), 77.4, 88.9 (2 x C≡), 105.0 (8'-C), 127.5 (6'(7')-CH=), 127.7 (2 x ArCH), 130.2 (2 x ArCH), 135.9 (7'(6')-CH=), 136.9, 144.1 (2 x ArC) and 168.7 (C=O).

Minor Isomer:

The minor isomer was identified by resonances at δ_H 0.85 (3H, t, *J* 7.4, CH_3), 3.52 (3H, s, OCH_3); δ_C 21.7 ($ArCH_3$), 31.0, 32.3, 33.7 (3 x CH_2), 53.1 (OCH_3), 126.1 (6'(7')-CH=) and 135.3 (7'(6')-CH=). The ratio was calculated by careful integration of the resonance at δ_H 3.52 (3H, s, OCH_3).

Column chromatography of the previous crude product also gave the *hydroxy ester* **432** as a pale yellow oil (30 mg, 14%), *anti:syn* = 83:17; R_f 0.45 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 3343 (br), 2958 (m), 2860 (m), 2230 (m), 1744 (s), 1662 (s), 1597 (w), 1437 (m), 1338 (s), 1162 (s), 1092 (s), 813 (m) and 657 (s); *m/z* [APcI] 420 ($[M+H]^+$, 20), 79 (100); Found: $[M+H]^+$, 420.1478. $C_{21}H_{26}NO_6S$ requires *M*, 420.1481.

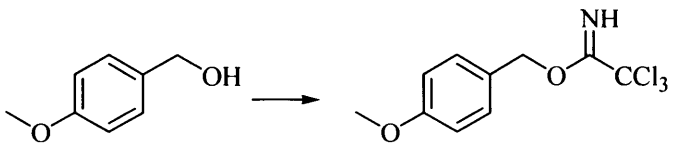
Major Isomer:

δ_H 0.85 (3H, t, *J* 7.4, CH_3), 1.51-1.64 (2H, m, 10'-CH_2), 1.72-2.12 (4H, m, 2 x CH_2), 2.36 (3H, s, $ArCH_3$), 3.16-3.22 (1H, br, OH), 3.40 (3H, s, OCH_3), 3.90-3.94 (1H, m, 2(3)-H), 4.58-4.70 (1H, br, 3(2)-H), 5.58-5.62 (1H, m, NH), 5.85 (1H, d, *J* 10.0, 2'-H), 6.60 (1H, d, *J* 10.0, 3'-H), 7.24 (2H, d, *J* 8.0, 2 x ArH) and 7.67 (2H, d, *J* 8.0, 2 x ArH); δ_C 9.2 (CH_3), 22.0 ($ArCH_3$), 33.5, 33.8, 35.1 (3 x CH_2), 37.1 (1'-C), 53.3 (OCH_3), 60.8, 63.5 (2- and 3-CH), 79.3, 88.7 (2 x C≡), 127.7 (2 x ArCH), 128.6 (CH=), 130.2 (2 x ArCH), 136.4, 144.6 (2 x ArC), 152.3 (CH=), 168.9 (C=O) and 199.2 (4'-C=O).

Minor Isomer:

The minor isomer was identified by resonances at δ_H 0.84 (3H, t, *J* 7.4, CH_3), 6.79 (1H, d, *J* 10.0, 3'-H); δ_C 37.0 (1'-C), 55.6 (OCH_3). The ratio was calculated by careful integration of the resonance at δ_H 6.79 (1H, d, *J* 10.0, 3'-H).

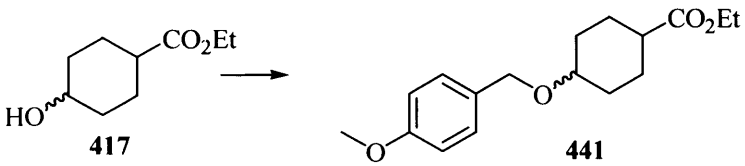
***4'-Methoxybenzyl-2,2,2-trichloroacetimidate* 440**[108]



440

To a suspension of sodium hydride (0.58 g, 14.5 mmol, prewashed by a minimum amount of diethyl ether) in diethyl ether (100 mL) was added a solution of *p*-methoxybenzyl alcohol (20.0 g, 145 mmol) in diethyl ether (100 mL) at room temperature and stirring continued for 1 h. The mixture was cooled to 0°C and then trichloroacetonitrile (16 mL, 30 mmol) was added over 80 min. The mixture was then concentrated with the water bath temperature maintained below 40°C. The residue was treated with a mixture of pentane (200 mL) and methanol (5 mL), stirred at room temperature for 30 min and filtered through a short plug of celite. Concentration gave the trichloroimidate **440** as a yellow oil (20.0 g, 50%), which was suitable for further use.

***Ethyl 4-(4'-methoxybenzyloxy)-cyclohexanecarboxylate* 441**



417 **441**

Method A

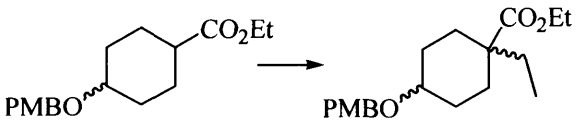
To a solution of sodium hydride (1.40 g, 34.8 mmol, prewashed by minimum amount of tetrahydrofuran) in dimethylformamide (50 mL) was added *p*-methoxybenzyl chloride **417** (4.72 mL, 34.8 mmol) at 0°C and stirring continued for 1 h. The resulting mixture was added to a solution of ethyl hydroxycyclohexane **417** (5.00 g, 30 mmol) in tetrahydrofuran (50 mL) and allowed to stir at room temperature for 16 h. The mixture was then poured into cold water (100 mL) and extracted with diethyl ether (2 x 80 mL). The combined organic layers were

washed with brine (100 mL), dried and evaporated. The concentrated crude was purified by distillation at 200°C (0.1 mbar) to give the *4-(4-methoxy-benzyloxy)-cyclohexanecarboxylate* **441** as a light yellow oil (1.02 g, 12%).

Method B

A solution of the ethyl hydroxycyclohexane **417** (5.00 g, 30 mmol) in dichloromethane/cyclohexane (1:2, 50 mL) was cooled to 0°C and treated with the crude trichloroimidate **440** (10.00 g, 35 mmol) and pyridinium *p*-toluenesulfonate (0.38 g, 1.5 mmol) over 30 min. After 3 h, the mixture was warmed to room temperature, stirred over 48 h and concentrated. Filtration of the crude residue through a short plug of silica (using 20% ethyl acetate in petroleum ether) afforded the corresponding *p-methoxybenzyloxy ether* **441** as a pale yellow oil (7.55 g, 91%); ν_{max}/cm^{-1} [film] 2933 (s), 2862 (m), 1730 (s), 1612 (m), 1586 (w), 1513 (s), 1454 (m), 1366 (w), 1248 (s), 1174 (s), 1086 (m), 1038 (m) and 821 (w); δ_H 1.25–1.29 (3H, m, CH_3), 1.31-1.68 (4H, m, 2 x CH_2), 1.76-2.14 (4H, m, 2 x CH_2), 2.23-2.32 (0.5H, m, 1-H_a), 2.34-2.43 (0.5H, m, 1-H_b), 3.53 (1H, pen, *J* 7.0, 4-H), 3.82 (3H, s, OCH_3), 4.10-4.16 (2H, m, OCH_2), 4.46-4.49 (2H, m, OCH_2Ar), 6.86-6.89 (2H, m, 2 x ArH) and 7.28-7.34 (2H, m, 2 x ArH); δ_C 14.6 (CH_3), 24.3, 37.6, 29.5, 31.7 (4 x CH_2), 43.2 (1-CH), 55.7 (OCH_3), 61.8 (OCH_2), 70.4 (OCH_2Ar), 74.8 (4-CH), 114.2 (2 x ArCH), 129.5 (2 x ArCH), 132.1, 164.2 (both x ArC) and 177.8 (C=O); *m/z* [APcI] 276 ($[M+H]^+$, 100).

***Ethyl 1-ethyl-4-(4'-methoxybenzyloxy)-cyclohexanecarboxylate* 439**

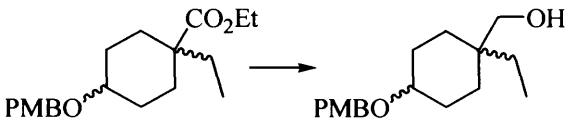


441 **439**

Diisopropylamine (0.20 mL, 1.43 mmol) was dissolved in anhydrous tetrahydrofuran (2 mL) at 0°C under nitrogen. A solution of 2.5M *n*-butyl lithium (1.43 mL in hexane, 1.43 mmol) was added dropwise and the solution stirred at 0°C for 30 min. The solution of lithium diisopropylamide thus formed was cooled to -78°C. To the resulting solution was added a solution of cyclohexanecarboxylate **441** (0.33 g, 1.19 mmol) in tetrahydrofuran (3 mL). After stirring at -78°C for 10 min, ethyl bromide (0.2 mL, 3.39 mmol) was added dropwise over a 10 min period. The mixture was stirred at -78°C for 1 h, then quenched by the addition of saturated aqueous ammonium chloride (5 mL) and extracted with diethyl ether (2 x 5 mL). The combined organic layers were washed with brine (5 mL), dried and evaporated to give the

1-ethyl cyclohexanecarboxylate **439** as a yellow oil (0.34 g, 94%); ν_{max}/cm^{-1} [film] 2936 (s), 2858 (m), 1724 (s), 1613 (m), 1586 (w), 1513 (s), 1462 (m), 1368 (m), 1301 (m), 1248 (s), 1202 (s), 1172 (m), 1094 (s), 1036 (s), 926 (w), 821 (m) and 749 (w); δ_H 0.74 (3H, t, *J* 7.4, CH_3), 1.18 (3H, t, *J* 7.1, CH_3), 1.23-1.46 (2H, m, CH_2), 1.48-1.56 (2H, m, CH_2), 1.48-1.56 (2H, m, CH_2), 1.82-1.91 (2H, m, CH_2), 2.14-2.23 (2H, m, CH_2), 3.16-3.28 (1H, m, 4-H), 3.73 (3H, s, OCH_3), 4.08 (2H, q, *J* 7.1, CH_2), 4.35-4.42 (2H, m, OCH_2Ar), 6.78-6.84 (2H, m, 2 x ArH) and 7.18-7.22 (2H, m, 2 x ArH); δ_C 9.2 , 14.7 (2 x CH_3), 27.7, 29.0, 29.9, 32.3, 34.2 (5 x CH_2), 47.3 (1-C), 55.6 (OCH_3), 60.5 (CH_2), 69.8 (OCH_2Ar), 72.8 (4-CH), 114.1 (2 x ArCH), 129.5 (2 x ArCH), 131.5, 159.4 (both x ArC) and 176.3 (C=O); *m/z* [APcI] 321 ($[M+H]^+$, 20), 184 (85), 137 (100).

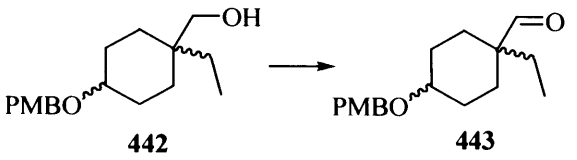
***[1'-Ethyl-4'-(4-methoxy-benzyloxy)-cyclohexyl]-methanol* 442**



439 **442**

To a stirred solution of lithium aluminium hydride (3.00 g, 75 mmol) in anhydrous diethyl ether (20 mL) cooled to -78°C, was added dropwise a solution of the cyclohexanecarboxylate **439** (8.00 g, 25 mmol) in anhydrous diethyl ether (20 mL). After stirring for an additional 2 h at -78°C, the mixture was slowly brought to room temperature over 30 min. The excess lithium aluminium hydride was decomposed by careful addition of ethyl acetate (2 mL) followed by water (20 mL) and 10% sulfuric acid (20 mL). The mixture was extracted with diethyl ether (3 x 40 mL). The combined organic fractions were dried and evaporated to give the crude alcohol. The concentrated crude was purified by flash chromatography (30-50% ethyl acetate in petroleum ether) to give the *alcohol* **442** as a colourless oil (0.50 g, 62%); R_f 0.30 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 3414 (br), 2930 (s), 2855 (s), 1612 (s), 1586 (w), 1513 (s), 1460 (m), 1367 (w), 1301 (m), 1248 (s), 1172 (m), 1085 (m), 1037 (s) and 822 (m); δ_H 0.75 (3H, t, *J* 7.5, CH_3), 1.06-1.27 (5H, m, CH_{2a} and 2 x CH_2), 1.35-1.47 (2H, m, CH_2), 1.49-1.57 (1H, m, CH_{2b}), 1.67-1.74 (2H, m, CH_2), 3.28-3.33 (1H, m, 4-H), 3.45 (2H, s, CH_2OH), 3.73 (3H, s, OCH_3), 4.37-4.41 (2H, m, OCH_2Ar), 6.79-6.84 (2H, m, 2 x ArH) and 7.19-7.22 (2H, m, 2 x ArH); δ_C 8.1 (CH_3), 27.3 (CH_2), 27.4, 29.5, (4 x CH_2), 36.6 (1-C), 55.7 (OCH_3), 65.8 (CH_2OH), 69.8 (OCH_2Ar), 75.6 (4-CH), 114.1, 129.5 (4 x ArCH) and 131.6, 159.4 (2 x ArC); *m/z* [APcI] 279 ($[M+H]^+$, 10), 121 (100), 79 (60); Found: $[M+NH_4]^+$, 296.2228 $C_{17}H_{30}NO_3$ requires *M*, 296.2226.

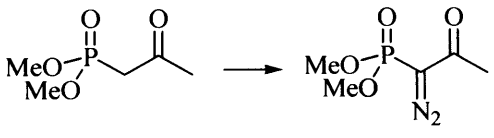
1-Ethyl-4-(4'-methoxy-benzyloxy)-cyclohexanecarbaldehyde 443



442 443

To a dried two-necked round bottom flask was added 0.5 g of 4°A molecular sieve, which had been dried at 110°C for 24 h. After the molecular sieves cooled down to room temperature under a nitrogen flow, pyridinium chlorochromate (0.43 g, 2.0 mmol) was added. The mixture was suspended in anhydrous dichloromethane (4 mL), then cooled to 0°C. The alcohol **442** (0.37 g, 1.33 mmol) in anhydrous dichloromethane (4 mL) was added and the mixture was stirred for 16 h at room temperature, then filtered through a short plug of silica gel by using 10-60% diethyl ether in petroleum ether as eluant. The filtrate was then evaporated and dried *in vacuo* to dryness to give the *aldehyde* **443** as a light brown oil (0.33 g, 92%); R_f 0.76 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2936 (s), 2856 (m), 1722 (s), 1612 (m), 1586 (w), 1513 (s), 1463 (m), 1366 (w), 1301 (m), 1247 (s), 1173 (m), 1085 (s), 1036 (s) and 823 (m); δ_H 0.69 (3H, t, *J* 7.6, CH_3), 1.14-1.26 (4H, m, 2 x CH_2), 1.37 (2H, q, *J* 7.6, CH_2), 1.84-1.89 (2H, m, CH_2), 2.01-2.05 (2H, m, CH_2), 3.19-3.26 (1H, m, 4-H), 3.73 (3H, s, OCH_3), 4.39 (2H, s, OCH_2Ar), 6.79 (2H, d, *J* 8.6, 2 x ArH), 7.18 (2H, d, *J* 8.6, 2 x ArH) and 9.34 (1H, s, CHO); δ_C 8.6 (CH_3), 26.0, 27.1, 28.9, 29.0, 29.7 (5 x CH_2), 50.0 (1-C), 55.7 (OCH_3), 69.8 (OCH_2Ar), 76.6 (4-CH), 114.1, 129.5 (4 x ArCH), 131.4, 159.4 (2 x ArC) and 212.3 (CHO); *m/z* [APcI] 277 ($[M+H]^+$, 15), 140 (100), 121 (10).

Dimethyl (1'-diazo-2'-oxo-propyl)-phosphonate 436[72]

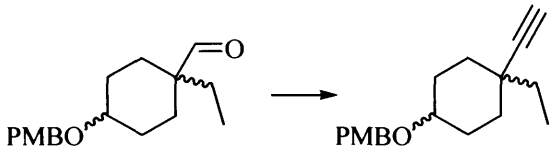


436

To a stirred suspension of sodium hydride (0.29 g, 12 mmol) in anhydrous benzene (100 mL) and tetrahydrofuran (20 mL) cooled to 0-5°C, was added dropwise a solution of dimethyl (2-oxopropyl)-phosphonate (2.0 g, 12 mmol) in anhydrous benzene (40 mL). After stirring for 1 h at 0-5°C, a solution of tosyl azide (2.37 g, 12 mmol) in anhydrous benzene (20 mL) was added. The resulting mixture was warmed to room temperature and stirred for an additional 2

h. The mixture was filtered through a short plug of silica. The filtrate was concentrated and the residue purified by flash chromatography (20-50% ethyl acetate in petroleum ether) to give the *diazo ester* **436** as a colourless oil (1.92 g, 84%), which was suitable for further use; R_f 0.09 (40% ethyl acetate in petroleum ether); δ_H 2.20 (3H, s, CH_3), 3.77 (6H, s, 2 x OCH_3); *m/z* [APcI] 193 ($[M+H]^+$, 75), 165 (100), 133 (60), 109 (55). *These data are consistent with those recorded in the literature.*[72]

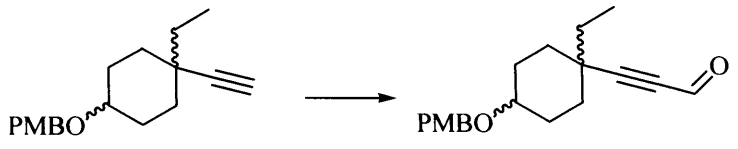
***1-Ethyl-1-ethynyl- 4-(4'-methoxyphenyloxy)-cyclohexane* 444**



443 **444**

To a stirred mixture of the aldehyde **443** (0.33 g, 1.2 mmol) and potassium carbonate (0.33 g, 2.4 mmol) in dry methanol (30 mL) was added the phosphonate **444** (0.69 g, 3.6 mmol) and stirring was continued until the reaction was complete as indicated by TLC. After 24 h, the mixture was diluted with diethyl ether (50 mL), washed with aqueous sodium bicarbonate solution (5%) and dried. Evaporation of the solvent yielded the *ethynyl-cyclohexyloxy ether* **444** as a light yellow oil (0.31 g, 95%); R_f 0.79 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 3295 (m), 2934 (s), 2852 (m), 2105 (w), 1612 (w), 1513 (s), 1462 (m), 1364 (w), 1301 (w), 1247 (s), 1172 (w), 1090 (m), 1036 (m) and 823 (w); δ_H 0.93 (3H, t, *J* 7.4, CH_3), 1.00-1.11 (2H, m, CH_2), 1.32-1.41 (2H, m, CH_2), 1.62-1.81 (4H, m, 2 x CH_2), 1.87-1.93 (2H, m, CH_2), 2.08 (1H, s, CH≡), 3.16-3.21 (1H, m, 4-H), 3.73 (3H, s, OCH_3), 4.43 (2H, s, OCH_2Ar), 6.80 (2H, d, *J* 8.5, 2 x ArH) and 7.25 (2H, d, *J* 8.5, 2 x ArH); δ_C 9.4 (CH_3), 27.2, 29.3, 32.0, 35.8, 35.8 (5 x CH_2), 36.9 (1-C), 55.7 (OCH_3), 69.3 (C≡), 69.9 (OCH_2Ar), 71.3 (4-CH), 88.7 (C≡), 114.1, 129.5 (4 x ArCH) and 132.5, 158.1 (2 x ArC); *m/z* [APcI] 273 ($[M+H]^+$, 100), 243 (20), 137 (90).

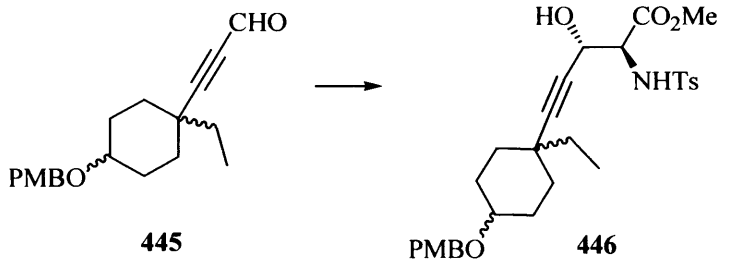
***[1'-Ethyl-4'-(4-methoxy-benzyloxy)-cyclohexyl]-propynal* 445**



444 445

The acetylene **444** (0.3 g, 1.1 mmol) in anhydrous tetrahydrofuran (3 mL) at –40°C was reacted *n*-butyl lithium (4.4 mL of a 2.5M solution in hexane, 1.1 mmol) dropwise anhydrous dimethylfomamide (0.2 mL, 2.2 mmol) according to the general procedure of the preparation of acetylene aldehydes (page 150). Work-up yielded the *propynal* **445** as a brownish oil (0.33 g, 100%), bp 210°C at 0.09 mbar; ν_{max}/cm^{-1} [film] 2936 (s), 2858 (s), 2202 (s), 1665 (s), 1612 (s), 1513 (s), 1462 (s), 1365 (s), 1248 (s), 1172 (s), 1072 (m), 1035 (s) and 821 (s); δ_H 0.93 (3H, t, *J* 7.4, CH_3), 1.15-1.20 (2H, m, CH_2), 1.41-1.47 (2H, m, CH_2), 1.57-1.61 (3H, m, CH_2), 1.89-1.95 (3H, m, CH_2), 3.20-3.23 (1H, m, CH), 3.73 (3H, s, OCH_3), 4.42 (2H, s, OCH_2), 6.81 (2H, d, *J* 8.0, 2 x ArH), 7.12 (2H, d, *J* 8.0, 2 x ArH) and 9.32 (1H, s, 1-H); δ_C 9.1 (CH_3), 26.9, 29.1, 31.0, 34.5, 34.8 (5 x CH_2), 37.5 (1'-C), 55.3 (OCH_3), 69.6 (OCH_2), 76.5 (4'-CH), 84.2, 103.2 (2 x C≡), 113.7, 129.1 (4 x ArCH), 130.8, 159.1 (2 x ArC) and 177.2 (C=O); *m/z* [APcI] 301 ($[M+H]^+$, 8), 121 (100); Found: $[M+NH_4]^+$, 318.2065. $C_{19}H_{28}NO_3$ requires *M*, 318.2069.

***(2SR,3SR)-Methyl 5-[1'-ethyl-4'-(4'-methoxy-benzyloxy)-cyclohexyl]-3-hydroxy-2-(4-methylphenylsulfonylamino)-pent-4-ynolate* 446**



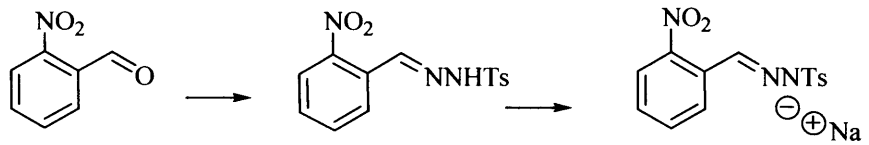
445 446

To a solution of lithium diisopropylamine (2.04 mL, 15.0 mmol) in anhydrous tetrahydrofuran (15 mL) at -78°C was added a solution of methyl *N*-tosyl glycinate **154** (1.46 g, 6.0 mmol) and tin(II) chloride (2.84 g, 15.0 mmol) in anhydrous tetrahydrofuran (15 mL) and the ynal **445** (1.80 g, 6.0 mmol) as described in the general procedure. After the work-up, the product was purified by column chromatography (20-50% ethyl acetate in petroleum ether) to give the *hydroxy ester* **446** (mixed with *N*-tosyl glycinate, 12% by NMR) as a pale yellow oil (110 mg, 3%), *anti:syn* = 75:25; R_f 0.10 (40% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 3286 (br), 2933 (m), 2855 (w), 2232 (w), 1745 (m), 1612 (w), 1514 (s), 1443 (m), 1337 (m), 1248 (s), 1164 (s), 1092 (s), 1035 (w) and 816 (m); δ_H 0.87 (3H, t, *J* 7.8, CH_3), 1.00-1.87 (10H, m, 5

x CH_2), 2.36 (3H, s, $ArCH_3$), 2.67 (1H, d, *J* 10.5, OH), 3.10-3.16 (1H, m, 4'-H), 3.49 (3H, s, OCH_3), 3.72 (3H, s, $ArOCH_3$), 4.06 (1H, dd, *J* 9.3, 3.6, 2-H), 4.3-4.41 (2H, m, OCH_2), 4.61 (1H, dd, *J* 10.5, 3.6, 3-H), 5.45 (1H, d, *J* 9.3, NH), 6.79 (2H, d, *J* 8.4, 2 x ArH), 7.18-7.26 (4H, m, 4 x ArH) and 7.67 (2H, d, *J* 8.2, 2 x ArH); δ_C 6.6 (CH_3), 12.8 ($ArCH_3$), 26.4, 26.6, 29.1, 32.4, 32.7 (5 x CH_2), 34.2 (1'-C), 50.4 (OCH_3), 52.8 (2(3)-CH), 58.1 ($ArOCH_3$), 60.6 (3(2)-CH), 69.9 (OCH_2), 74.3 (4'-CH), 76.2, 90.1 (2 x C≡), 111.2 , 126.7, 127.1, 127.3 (8 x ArCH), 128.5, 133.6, 141.5, 156.5 (4 x ArC) and 167.0 (C=O); *m/z* [APcI] 544 ($[M+H]^+$, 15), 391 (15), 338 (50), 104 (78), 89 (100); Found: $[M+H]^+$, 544.2370. $C_{29}H_{38}NO_7S$ requires *M*, 544.2363.

The minor isomer was identified by resonances at δ_H 4.03 (1H, dd, *J* 9.3, 3.6, 2-H), 4.57 (1H, dd, *J* 10.5, 3.6, 3-H) and 5.35 (1H, d, *J* 9.3, NH). The ratio was calculated by careful integration of the resonance at δ_H 5.35 (1H, d, *J* 9.3, NH).

***2-Nitrobenzaldehyde tosylhydrazone sodium salt* 495** [109]

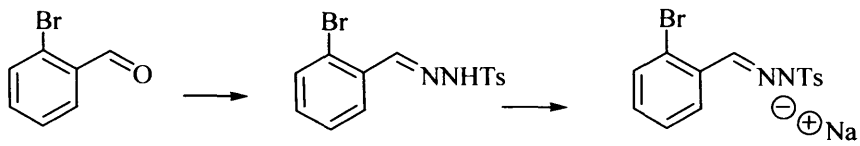


493 **491** **495**

To a stirred solution of *p*-toluenesulfonyl hydrazide (0.93 g, 5.0 mmol) in methanol (5 mL) was added *o*-nitrobenzaldehyde **493** (0.76 g, 5.0 mmol) rapidly. A mild exothermic reaction ensued and the hydrazide dissolved. Within a few minutes, the hydrazone began to crystallize. After 15 min, the mixture was cooled in an ice bath. The product was collected on a Büchner funnel, washed with a small amount of cold methanol and dried *in vacuo*. After 6 h, the dry *tosylhydrazone* **491** was left as a colourless solid (1.30 g, 76%), mp 153-154°C [lit. mp[109] 154°C]; ν_{max}/cm^{-1} [nujol] 3192 (m), 2921 (s), 2853 (s), 1596 (w), 1524 (m), 1462 (s), 1376 (m), 1345 (m), 1171 (m), 1087 (w), 1065 (w), 948 (w), 932 (w), 809 (w), 746 (w) and 664 (w); δ_H 2.37 (3H, s, $ArCH_3$), 7.43 (2H, d, *J* 8.1, 2 x ArH), 7.64 (1H, t, *J* 7.7, ArH), 7.74-7.78 (3H, m, 3 x ArH), 7.82 (1H, d, *J* 7.7, ArH), 8.03 (1H, d, *J* 7.7, ArH), 8.28 (1H, s, CH) and 10.25 (1H, s, NH); δ_C 21.4 ($ArCH_3$), 125.0 (ArCH), 127.5 (2 x ArCH), 128.2 (ArCH), 128.3 (ArC), 130.2 (2 x ArCH), 131.1, 134.1 (2 x ArCH), 136.4, 142.7, 144.0 (3 x ArC) and 148.7 (CH=); *m/z* [APcI], 320 ($[M+H]^+$, 55), 137 (30), 114 (55), 76 (100). To a solution of the tosylhydrazone **491** (0.5 g, 1.6 mmol) in methanol (2 mL) was added a 25% solution of sodium methoxide in methanol (0.34 mL, 1.6 mmol) and the mixture was stirred for 30 min.

The methanol was then evaporated and the last traces removed *in vacuo* for 6 h to give the *tosylhydrazone sodium salt* **495** as a red-brown solid, which was suitable for further use.

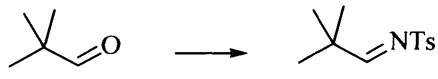
2-Bromobenzaldehyde tosylhydrazone sodium salt 496 [86]



494 **492** **496**

To a stirred solution of *p*-toluenesulfonyl hydrazide (1.10 g, 5.91 mmol) in methanol (5 mL) was added *2*-bromobenzaldehyde **494** (1.09 g, 5.91 mmol) and using exactly the same method described in the foregoing experiment, column chromatography gave the *tosylhydrazone* **492** as a colourless solid (1.2 g, 55%), mp 152-153°C [lit. mp[86] 151-152°C]; ν_{max}/cm^{-1} [nujol] 3169 (m), 2916 (s), 2853 (s), 1458 (s), 1378 (m), 1323 (w), 1162 (m), 1062 (w), 951 (w), 926 (w), 816 (w), 760 (w) and 660 (w); δ_H 2.27 (3H, s, $ArCH_3$), 7.23 (1H, td, *J* 7.8, 1.8, ArH), 7.32-7.34 (3H, m, 3 x ArH), 7.55 (1H, d, *J* 7.8, ArH), 7.62 (1H, dd, *J* 7.8, 1.8, ArH), 7.67 (2H, d, *J* 8.3, 2 x ArH), 8.11 (1H, s, CH) and 11.65 (1H, s, NH); δ_C 21.0 ($ArCH_3$), 123.1 (ArC), 126.8 (ArCH), 127.1 (2 x ArCH), 128.1 (ArCH), 129.8 (2 x ArCH), 131.8 (ArCH), 132.2 (ArC), 133.1 (ArCH), 135.8, 143.9 (2 x ArC) and 144.9 (CH=); *m/z* [APcI], 355 ($[M(^{81}Br)+H]^+$, 35), 353 (40), 169 (15), 113 (100), 73 (95). To a solution of the tosylhydrazone **57** (1.0 g, 2.83 mmol) in methanol (3 mL) was added a solution of 25% sodium methoxide in methanol (0.62 mL, 2.87 mmol) as described in the forgoing experiment. The work-up and evacuation gave the *tosylhydrazone sodium salt* **496** as a pale pink solid, which was suitable for further use.

N-(2,2-Dimethyl-propylidene)-4-methyl-benzenesulfonamide 478 [85]

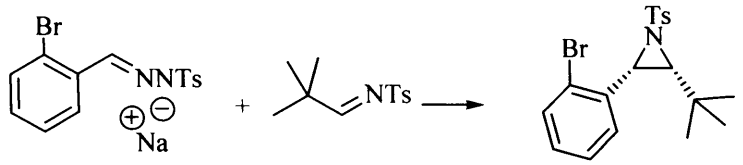


478

To a stirred solution of pivalaldehyde (0.86 g, 10 mmol) and toluene-*p*-sulfonamide (1.70 g, 10 mmol) in anhydrous benzene (70 mL) under reflux containing 4°A molecular sieves (1.00 g), was added a catalytic amount of BF_3-Et_2O. Reflux was continued for 16 h and the mixture was then cooled, filtered and washed with 2M aqueous sodium hydroxide (20 mL). The organic layer was separated, dried and evaporated to give the crude *imine* **478** as a colourless

solid (1.21 g, 50%), which was ready for further use; mp 57-59°C [lit. mp[85] 58°C]; R_f 0.76 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 2970 (w), 1782 (w), 1752 (w), 1715 (w), 1630 (m), 1320 (s), 1158 (s), 1091 (m), 755 (m) and 670 (s); δ_H 1.07 (9H, s, 3 x CH_3), 2.34 (3H, s, $ArCH_3$), 7.27 (2H, d, *J* 7.6, 2 x ArH), 7.74 (2H, d, *J* 7.6, 2 x ArH) and 8.38 (1H, s, CH=); δ_C 22.7 ($ArCH_3$), 27.2 (3 x CH_3), 128.4 (2 x ArCH), 130.2 (2 x ArCH), 134.1, 144.2 (2 x ArC) and 171.0 (CH=); *m/z* [APcI], 340 ($[M+H]^+$, 100), 155 (15). *These data are consistent with those recorded in the literature.*[85]

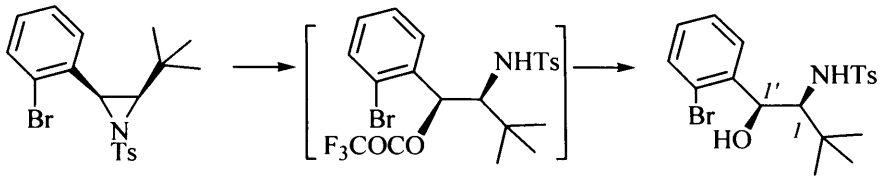
***2-(2'-Bromo-phenyl)-3-t-butyl-1-(4'-methylphenylsulfonyl)-aziridine* 459**



496 **478** **459**

To a round-bottomed flask containing the tosylhydrazone sodium salt **496** (1.88 g 5.01 mmol) were added sequentially: rhodium acetate (14.8 mg, 0.03 mmol), triethylbenzylammonium chloride (152 mg 0.67 mmol), a solution of imine **478** (0.80 g, 3.34 mmol) in dioxane (10 mL) and tetrahydrothiophene (0.3 mL, 3.34 mmol). The mixture was stirred vigorously at room temperature for 10 min, then at 40°C for 16 h. The reaction was diluted with dichloromethane (10 mL) and filtered through a short plug of silica. The filtrate was washed with water (2 x 10 mL) and dried. The concentrated crude product was purified by flash column chromatography to give the *aziridine* **459** as a yellow solid (0.75g, 60%), mp 88-89°C: R_f 0.57 (10% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 2954 (s), 1597 (m), 1478 (m), 1439 (m), 1410 (m), 1364 (m), 1328 (s), 1292 (m), 1160 (s), 1091 (m), 1025 (m), 962 (m), 889 (m), 775 (s), 754 (m) and 679 (m); δ_H 0.62 (9H, s, 3 x CH_3), 2.37 (3H, s, $ArCH_3$), 2.84 (1H, d, *J* 7.4, 3-H), 3.81 (1H, d, *J* 7.4, 2-H), 7.02-7.05 (2H, m, 2 x ArH), 7.23 (1H, dd, *J* 7.7, 1.7, ArH), 7.28 (2H, d, *J* 8.2, 2 x ArH), 7.42 (1H, dd, *J* 7.7, 1.7, ArH) and 7.84 (2H, d, *J* 8.2, 2 x ArH); δ_C 21.7 ($ArCH_3$), 27.99 (3 x CH_3), 32.2 (C), 47.4, 55.2 (2- and 3-CH), 123.0 (ArCBr), 127.0 (ArCH), 128.3 (2 x ArCH), 129.3 (ArCH), 129.7 (2 x ArCH), 130.3, 132.3 (2 x ArCH) and 131.6, 133.8, 134.7 (3 x ArC); *m/z* [APcI], 410 ($[M(^{81}Br)+H]^+$, 100), 408 (92), Found $[M(^{79}Br)+H]^+$, 408.0631. $C_{19}H_{23}{}^{79}BrNO_2S$ requires *M*, 408.0627.

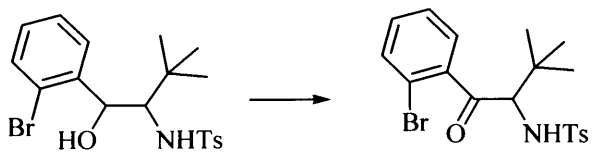
***(1'SR,1RS)-N-{1-[(2''-Bromo-phenyl)-1'-hydroxymethyl]-2,2-dimethyl-propyl}-4'-methyl-phenylsulfonamide* 458**



459 517 458

The aziridine **459** (2.10 g, 5.15 mmol) was dissolved in trifluoroacetic acid (17 mL) at room temperature and the solution stirred for 15 h. Concentration under reduced pressure gave a crude *trifluoroacetate* **517**; ν_{max}/cm^{-1} [film] 2969 (m), 2926 (m), 1787 (m), 1598 (w), 1470 (m), 1440 (m), 1337 (m), 1224 (m), 1158 (s), 1091 (m), 1026 (m), 914 (w), 813 (w), 752 (m) and 657 (m); δ_H 0.92 (9H, s, 3 x CH_3), 2.31 (3H, s, $ArCH_3$), 3.72 (1H, dd, *J* 10.4, 1.0, 1-H), 4.73 (1H, d, *J* 10.4, 1'-H) and 6.96-7.85 (8H, m, 8 x ArH); *m/z* [APcI] 525 ($[M+H]^+$, 10), 524 (50), 522 (100), 407 (55), 409 (60), 354 (50), 352 (20). The trifluoroacetate was dissolved in methanol (20 mL) and saturated aqueous potassium carbonate (20 mL) was added. The mixture was stirred for 2 h at room temperature and then concentrated. The residue was extracted with dichloromethane (2 x 20 mL) and the extracts dried, diluted with ether (5 mL), filtered through a short plug of silica gel and evaporated to give the *alcohol* **458** as a brownish oil (1.75 g, 80%): ν_{max}/cm^{-1} [film] 3504 (br), 2946 (m), 2906 (s), 1761 (w), 1598 (w), 1469 (m), 1415 (m), 1327 (m), 1223 (s), 1155 (s), 1093 (m), 1068 (m), 1028 (m), 910 (w), 813 (w), 752 (m) and 657 (m); δ_H 0.95 (9H, s, 3 x CH_3), 2.29 (3H, s, $ArCH_3$), 3.46 (1H, d, *J* 9.6, 1.1, 1-H), 5.04 (1H, d, *J* 9.6, 1'-H), 5.33 (1H, s, NH), 7.00-7.09 (2H, m, 2 x ArH) and 7.29-7.41 (6H, m, 6 x ArH); δ_C 21.4 ($ArCH_3$), 28.0 (3 x -CH_3), 36.5 (C), 64.9, 71.2 (1- and 2-CH), 121.3 (ArCBr), 126.4, 127.2 (2 x ArCH), 127.6, 127.9 (4 x ArCH), 132.4, 129.3 (2 x ArCH) and 139.4, 141.2, 142.2 (3 x ArC); *m/z* [APcI] 409 ($[M(^{81}Br) -H_2O]^+$, 100), 407 (^{79}Br, 98), 352 (50), Found $[M+NH_4]^+$, 443.1004. $C_{19}H_{28}{}^{79}BrN_2O_3S$ requires *M*, 443.0999.

***1-(2'-Bromobenzoyl)-3,3-dimethyl-2-(4-Methyl-phenylsulfonamino)-butan-1-one* 457**

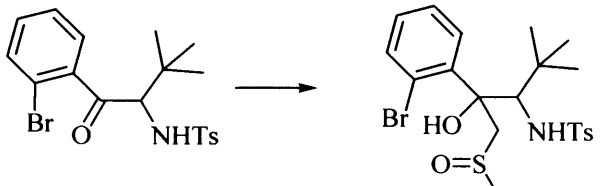


458 457

To a mixture of 4°A molecular sieves (1.5 g) and pyridinium chlorochromate (1.03 g, 4.77 mmol) in anhydrous dichloromethane (15 mL) was added *N*-(2-hydroxy-1,2-diphenyl-ethyl)-4-methylphenylsulfonamide **458** (1.35 g, 3.18 mmol) in dichrolomethane (15 mL) as

described in general precedure for PCC oxidation. Work-up gave the *ketone* ***457*** as a light brown solid (1.24 g, 92%), mp 123-124°C; ν_{max}/cm^{-1} [nujol] 3496 (br), 2964 (s), 2918 (s), 1697 (m), 1598 (w), 1466 (m), 1429 (m), 1336 (s), 1222 (m), 1164 (s), 1090 (m), 1029 (m), 980 (w), 932 (w), 814 (m), 768 (m), 728 (m) and 667 (m); δ_H 0.81 (9H, s, 3 x CH_3), 2.24 (3H, s, $ArCH_3$), 4.33 (1H, d, *J* 10.0, 2-H), 5.72 (1H, d, *J* 10.0, NH), 6.92 (1H, dd, *J* 7.3, 1.7, ArH), 7.13-7.25 (4H, m, 4 x ArH), 7.53 (1H, dd, *J* 7.3, 1.7, ArH) and 7.67 (2H, d, *J* 8.3, 2 x ArH); δ_C 21.5 ($ArCH_3$), 27.0 (3 x CH_3), 36.5 (C), 70.0 (2-CH), 120.2 (ArCBr), 126.9, 129.2 (4 x ArCH), 132.7, 134.9 (2 x ArCH), 127.5, 129.7 (2 x ArCH), 136.7, 139.3, 143.8 (3 x ArC) and 201.1 (C=O); *m/z* [APcI] 425 ([M(^{81}Br)+H]$^+$, 52), 424 (^{79}Br, 50), 426 (12), 88 (40), 72 (100), Found [M+H]$^+$, 424.0576. $C_{19}H_{23}{}^{79}BrNO_3S$ requires *M*, 424.0577.

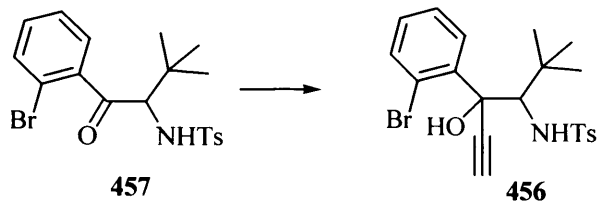
***1-(2'-Bromobenzoyl)-3,3-dimethyl-2-(4-methylphenylesulfonamino)-1-methylsulphinylmethyl-butan-1-ol* 522**



457 **522**

To a solution of lithium acetylide-ethylenediamine **254** (73 mg, 0.71 mmol) in anhydrous dimethylsulfoxide (1mL) at room temperature were added a solution of ketone **457** (50 mg, 0.12 mmol) in anhydrous dimethylsulfoxide (1 mL) as described in general precedure method 1. After the work-up and the combined ether solutions were then dried and evaporated to give a white solid. After flash chromatography (25% ethyl acetate in petroleum ether), the *alcohol* **522** (0.1 g, 85%) was isolated, mp 234-235°C: R_f 0.12 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 3318 (br), 3267 (br), 2935 (w), 1594 (w), 1426 (m), 1329 (m), 1212 (w), 1156 (s), 1073 (m), 1018 (s), 908 (m), 816 (w), 760 (w), 734 (m) and 660 (m); δ_H 0.52 (9H, s, 3 x CH_3), 2.35 (3H, s, CH_3), 2.37 (3H, s, CH_3), 3.21 (1H, d, *J* 13.4, SCH_a), 4.09 (1H, d, *J* 13.4, SCH_b), 4.53 (1H, dd, *J* 9.8, 1.8, 2-CH), 5.31 (1H, d, *J* 9.8, NH), 5.47 (1H, d, *J* 1.8, OH), 7.14 (1H, td, *J* 7.8, 1.5, ArH), 7.25 (2H, d, *J* 8.2, 2 x ArH), 7.36 (1H, td, *J* 7.8, 1.5, ArH), 7.51 (1H, dd, *J* 7.8, 1.5, ArH), 7.75 (2H, d, *J* 8.2, 2 x ArH) and 7.97 (1H, td, *J* 7.8, 1.5, ArH); δ_C 21.5 ($ArCH_3$), 28.8 (3 x CH_3), 37.8 (C), 39.0 (SCH_3), 60.2 (SCH_2), 65.1 (2-CH), 81.8 (1-C), 120.9 (ArCBr), 126.9 (2 x ArCH), 128.1 (ArCH), 129.6 (2 x ArCH), 130.0, 130.6, 134.9 (3 x ArCH) and 139.5, 141.6, 143.1 (3 x ArC); *m/z* [APcI] 505 ([M(^{81}Br)+H]$^+$, 100), 502 (^{79}Br, 98), Found [M+H]$^+$, 502.0719. $C_{21}H_{29}{}^{79}BrNO_4S_2$ requires *M*, 502.0716.

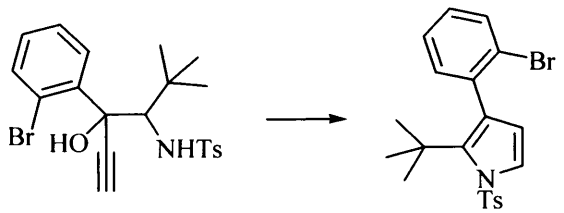
3-(2'-Bromobenzoyl)-5,5-dimethyl-4-(4-methylphenylesulfonamino)-hex-1-yn-3-ol 456



457 456

To a stirred solution of 0.5 M ethynylmagnesium bromide (12.74 mL in THF, 6.4 mmol) in anhydrous tetrahydrofuran (5 mL) was adding the ketone **457** (0.9 g, 2.12 mmol) in anhydrous tetrahydrofuran (5 mL) at 0°C. The mixture was allowed to stir at room temperature for 16 h and then poured into saturated aqueous ammonium chloride (25 mL). The organic layer was separated, dried and evaporated to give the crude product as a yellow oil. Column chromatography (25% ethyl acetate in petroleum ether) gave the *ynol* **456** as a colourless solid (0.5 g, 52%), mp 175-176°C; R_f 0.30 (25% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [nujol] 3486 (br), 2955 (s), 2212 (w), 1594 (w), 1463 (m), 1432 (m), 1328 (m), 1155 (s), 1083 (m), 1028 (m), 901 (w), 813 (w), 755 (w), 690 (w) and 661 (s); δ_H 0.74 (9H, s, 3 x CH_3), 2.31 (3H, s, $ArCH_3$), 3.09 (1H, s, 1-CH), 4.64 (1H, d, *J* 9.8, 4-CH), 5.18 (1H, d, *J* 9.8, NH), 7.06 (1H, td, *J* 7.8, 1.6, ArH), 7.10-7.15 (3H, m, 3 x ArH), 7.51 (1H, dd, *J* 7.8, 1.6, ArH), 7.58 (2H, d, *J* 8.0, 2 x ArH) and 7.76 (1H, td, *J* 7.8, 1.6, ArH); δ_C 21.5 ($ArCH_3$), 28.9 (3 x CH_3), 37.6 (5-C), 65.0 (4-CH), 76.5, 77.8 (C≡ and 3-C), 84.6 (CH≡), 121.5 (ArCBr), 126.9 (2 x ArCH), 127.4 (ArCH), 128.9 (2 x ArCH), 129.2, 129.7, 135.0 (3 x ArCH) and 139.9, 140.5, 142.3 (3 x ArC); *m/z* [APcI] 434 ($[M(^{81}Br)\text{-}OH]^+$, 30), 432 (^{79}Br, 28), 378 (100), 376 (85), Found $[M+NH_4]^+$, 467.1004. $C_{21}H_{28}{}^{79}BrN_2O_4S$ requires *M*, 467.0999.

3-(2'-Bromophenyl)-2-tert-butyl-1-(4'-methylphenylsulfonyl)-pyrrole 523

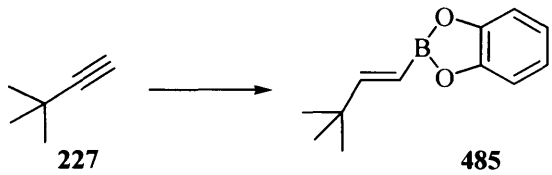


456 523

To a stirred solution of acetylene **456** (0.20 g, 0.44 mmol) in dichloromethane (5 mL) was added 10%w/w silver nitrate on silica gel (0.75 g, 0.44 mmol) as described in the general procedure for silver-mediated cyclization. Work-up gave the *pyrrole* **523** as a yellow oil (125 mg, 65%); ν_{max}/cm^{-1} [nujol] 2925 (s), 1594 (w), 1499 (w), 1453 (w), 1368 (m), 1354 (m),

1258 (w), 1172 (m), 1082 (m), 1021 (m), 811 (w) and 676 (m); δ_H 1.13 (9H, s, 3 x CH_3), 2.34 (3H, s, $ArCH_3$), 5.95 (1H, d, *J* 3.5, 4-H), 7.06-7.10 (1H, m, ArH), 7.16-7.21 (4H, m, 2 x ArH), 7.37 (2H, d, *J* 8.2, 2 x ArH), 7.40 (1H, d, *J* 3.5, 5-H) and 7.49 (1H, d, *J* 8.2, ArH); δ_C 21.6 ($ArCH_3$), 31.8 (3 x CH_3), 36.1 (C), 114.7 (CH), 124.9 (ArCBr), 125.7 (2 x ArCH), 126.7, 126.7 (2 x CH), 128.2 (C), 128.7 (CH), 129.7 (2 x ArCH), 131.8, 132.2 (2 x CH) and 138.9, 140.2, 140.9, 144.2 (4 x C); *m/z* [APcI] 434 ($[M(^{81}Br)+H]^+$, 100), 432 (^{79}Br, 98), 322 (30), 320 (38), Found $[M+H]^+$, 432.0629. $C_{21}H_{26}{}^{79}BrNO_2S$ requires *M*, 432.0627.

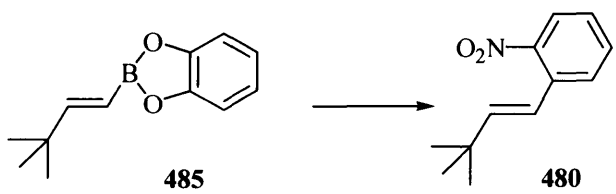
***2-(3',3'-Dimethyl-but-1'-enyl)-benzo[1,3,2]dioxaborole* 485**[110]



227 **485**

A mixture of 3,3-dimethylbut-1-yne **227** (2.05 g, 25 mmol) and catecholborane **484** (3.00 g, 25 mmol) was stirred at 70-100°C under nitrogen for 2 h. Distillation yielded the *dioxaborole* **485** as a colorless liquid (2.68 g, 61%) at 70°C (1.8 mbar);[110] ν_{max}/cm^{-1} [film] 2960 (s), 2868 (m), 1633 (s), 1474 (s), 1398 (s), 1370 (s), 1329 (s), 1266 (s), 1236 (s), 1127 (m), 998 (m), 915 (m), 875 (w), 809 (m) and 740 (w); δ_H 1.03 (9H, s, 3 x CH_3), 5.68 (1H, d, *J* 20.0, CH=), 7.09 (1H, d, *J* 20.0, CH=), 6.97-7.00 (2H, m, 2 x ArH), 7.11-7.16 (2H, m, 2 x ArH); δ_C 29.0 (3 x CH_3), 35.9 (C), 112.6 (2 x ArC), 122.8, 122.9 (4x ArCH) and 148.7, 168.0 (2 x CH=); *m/z* [APcI] 202 ($[M+H]^+$, 10), 89 (100). *These data are consistent with those recorded in the literature.*[110]

***(E)-1-(3',3'-Dimethyl-but-1'-en-1-yl)-2-nitrobenzene* 480**

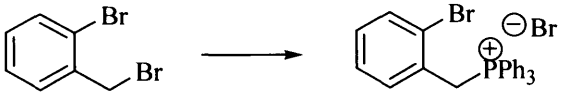


485 **480**

A round bottom flask was charged with $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol), powdered sodium hydroxide (0.60 g, 15 mmol) and tetrahydrofuran (15mL). To this mixture was added 2-iodonitrobenzene **483** (1.25 g, 5 mmol) and the borole **485** (1.04 g, 5.9 mmol) at room temperature and the mixture heated to reflux for 4 h. The mixture was then cooled to room

temperature and 3N NaOH (5 mL) and 30% hydrogen peroxide (1 mL) were added to decomposed unreacted borole. The resulting mixture was extracted with hexane (200 mL) and the extract washed with brine (150 mL) and dried. After evaporation, the crude product was purified by column chromatography (10% ethyl acetate in petroleum ether) to give the *nitro-benzene* **480** as a pale brown oil (0.70 g, 68%): R_f 0.61 (10% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 3532 (br), 2958 (s), 2855 (m), 1735 (m), 1634 (m), 1606 (m), 1524 (s), 1468 (m), 1347 (s), 1261 (m), 969 (w), 783 (w) and 737 (m); δ_H 1.07 (9H, s, 3 x CH_3), 6.15 (1H, d, *J* 16.0, CH=), 6.71 (1H, d, *J* 16.0, CH=), 7.27 (1H, td, *J* 7.4, 1.5, ArH), 7.46 (2H, td, *J* 7.4, 1.5, ArH), 7.51 (1H, dd, *J* 7.4, 1.5, ArH) and 7.98 (1H, dd, *J* 7.4, 1.5, ArH); δ_C 29.7 (3 x CH_3), 31.7 (C), 121.8 (CH=), 124.8, 127.7, 128.9 (3 x ArCH), 130.4 (ArC), 133.2 (ArCH), 139.6 (CH=) and 147.6 (ArC); *m/z* [APcI] 206 ($[M+H]^+$, 100), 146 (18); Found: $[M+NH_4]^+$, 223.1447. $C_{12}H_{19}N_2O_2$ requires *M*, 223.1447.

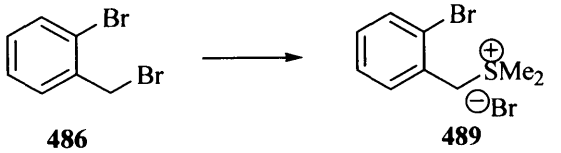
***(2-Bromo-benzyl)-triphenyl-phosphonium bromide salt* 487** [111]



486 **487**

A stirred solution of 2-bromobenzyl bromide **486** (1.00 g, 4 mmol) and triphenylphosphine (1.36 g, 5.2 mmol) in anhydrous chloroform (15 mL) was refluxed for 2 h. The mixture was then poured into anhydrous ether (80 mL) and the precipitate was filtered and dried to give the *salt* **487**, as a colourless solid (2.00 g, 98%), mp 138-140°C [lit. mp[111] 137-138°C]; δ_H (DMSO) 5.17 (2H, d, *J* 14.8, CH_2), 7.14-7.20 (1H, m, ArH), 7.28-7.36 (2H, m, 2 x ArH), 7.55-7.68 (7H, m, 7 x ArH), 7.71-7.79 (6H, m, 6 x ArH) and 7.92-7.97 (3H, m, 3 x ArH). *These data are consistent with those recorded in the literature.*[111]

***(2'-Bromo-benzyl)-dimethylsulfonium bromide* 489**[112a]

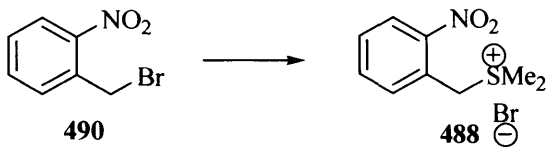


486 **489**

To a stirred solution of 2-bromobenzyl bromide **486** (2.00 g, 8 mmol) in chloroform (15 mL) was added dimethyl sulfide (0.92 mL, 12.8 mmol) dropwise. After stirring for 24 h at 50°C, the *sulfonium salt* **489** was filtered and rinsed with chloroform (2 x 5 mL). A white solid was

obtained (2.00 g, 80%), mp 126-127°C [lit. mp[112a] 126°C]; ν_{max}/cm^{-1} [nujol] 2922 (s), 2855 (s), 1568 (m), 1467 (s), 1442 (s), 1377 (m), 1330 (m), 1276 (m), 1224 (m), 1204 (m), 1047 (m), 1021 (s), 1007 (m), 755 (s), 722 (m) and 658 (m); δ_H (D_2O) 2.76 (6H, s, 2 x CH_3), 4.65 (2H, s, CH_2), 7.28 (1H, td, *J* 7.7, 1.5, ArH), 7.34 (1H, td, *J* 7.7, 1.5, ArH), 7.40 (1H, dd, *J* 7.7, 1.5, ArH) and 7.65 (1H, dd, *J* 7.7, 1.5, ArH). *These data are consistent with those recorded in the literature.*[112a]

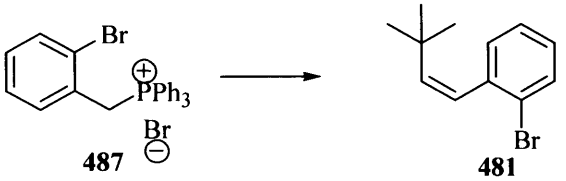
***Dimethyl-(2'-nitrobenzyl)-sulfonium bromide* 488** [112b]



490 **488**

Starting from 2-nitrobenzyl bromide **490** (1.90 g, 8.8 mmol) and using exactly the same method described in the foregoing experiment, the work-up to dryness gave the *sulfonium salt* **488** as a pale purple solid (2.00 g, 82%), mp 128-129°C [lit. mp[112b] 127-128°C]; ν_{max}/cm^{-1} [nujol] 3448 (s), 3392 (s), 2925 (s), 2855 (s), 1610 (w), 1577 (w), 1526 (s), 1463 (s), 1377 (m), 1346 (s), 1308 (m), 1264 (w), 1172 (w), 1047 (w), 1008 (w), 860 (w), 793 (w), 793 (w) and 710 (w); δ_H (D_2O) 2.88 (6H, s, 2 x CH_3), 4.74 (2H, s, CH_2), 7.32 (1H, dd, *J* 7.8, 1.2, ArH), 7.33 (1H, td, *J* 7.8, 1.2, ArH), 7.50 (1H, td, *J* 7.8, 1.2, ArH) and 8.66 (1H, dd, *J* 7.8, 1.2, ArH). *These data are consistent with those recorded in the literature.*[112b]

***(Z)-1-Bromo-2-(3',3'-dimethyl-but-1'-enyl)-benzene* 481**

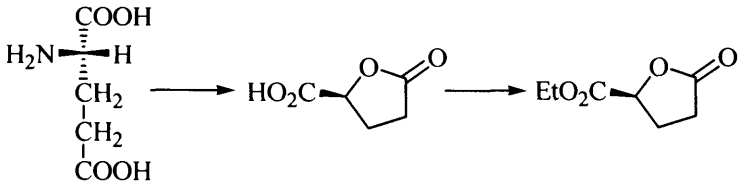


487 **481**

To a suspension of the phosphonium salt **487** (1.00 g, 1.95 mmol) in anhydrous tetrahydrofuran (10 mL) was added 2.5M n-butyl lithium (0.58 mL in hexanes, 1.45 mmol) at –30°C dropwise. After 10 min, pivalaldehyde (0.17 mL, 1.61 mmol) was added in one portion. The mixture was slowly warmed to room temperature and stirred for 16 h. The mixture was then evaporated to give a slurry, which was suspended in pentene (10 mL) and filtered through a short plug of celite. The flitrate was evaporated and the residue dissolved in a minimum of ether. The mixture was then filtered through a short plug of silica gel to

give a solution, when evaporated, gave the *styrene* **481** (0.28 g, 60%) as a light yellow oil; R_f 0.63 (10% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2958 (s), 2855 (m), 1634 (m), 1606 (m), 1524 (s), 1468 (m), 1347 (s), 1261 (m), 969 (w), 783 (w) and 737 (m); δ_H 0.88 (9H, s, 3 x CH_3), 5.58 (1H, d, *J* 12.5, CH=), 6.13 (1H, d, *J* 12.5, CH=), 6.99-7.02 (1H, m, ArH), 7.15 (1H, t, *J* 8.0, ArH), 7.23-7.26 (1H, m, ArH) and 7.46 (1H, d, *J* 8.0, ArH); δ_C 30.7 (3 x CH_3), 34.5 (C), 123.5 (ArCBr), 125.9, 126.4, 128.1, 131.3, 132.0 (all CH), 140.0 (ArC) and 143.0 (CH); *m/z* [APcI] 239 ($[M+H]^+$, 100). This styrene **481** was unstable as indicated by changing of the light yellow color to dark orange over few days at room temperature. Keeping at low temperature is required!

***(S)-(+)-γ-Ethoxycarbonyl-γ-butyrolactone* 549**[95a]

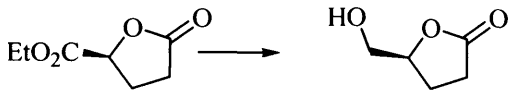


545 **548** **549**

To a suspension of L-glutamic acid **545** (90.00 g, 0.612 mol) in water (240 mL) and concentrated hydrochloric acid (126 mL) was added a solution of sodium nitrite (63.00 g, 0.912 mol) in water (135 mL) during 4 h under vigorous stirring at –5-0°C; the resulting clear solution was allowed to stand at room temperature for 16 h. The solvent was evaporated in *vacuo* below 50°C to give a residue, which was shaken with ethyl acetate (300 mL). The insoluble material was filtered off and washed with ethyl acetate. The filtrate and washings were combined and dried. Evaporation of the solvent afforded the *(S)-γ-carboxy-γ-butyrolactone* **548** as a pale yellow syrup (72.30 g, 91%). A solution of the (S)-γ-carboxy-γ-butyrolactone **548** (72.30 g, 0.556 mol) and *p*-toluenesulfonic acid monohydrate (2.50 g, 0.013 mol) in ethanol (130 mL) and benzene (300 mL) was refluxed for 5 h and the solvent then was distilled off under atmospheric pressure until the head temperature was raised to 79°C. The residue was cooled to room temperature and toluene (1 L) was added. The resulting solution was washed with water (2 x 500 mL), 10% aqueous sodium carbonate (2 x 500 mL) and dried. Evaporation of the solvent and distillation of the residue gave the *ethoxycarbonyl-γ-butyrolactone* **549** as a light yellow liquid (69.00 g, 79%) of bp 123-128°/8 mm [Lit.[95a] bp 135-140°/10mm]; ν_{max}/cm^{-1} [film] 2984 (m), 1789 (s), 1746 (s), 1378 (m), 1276 (s), 1216 (s), 1146 (s), 1069 (s), 1027 (s) and 854 (m); δ_H 1.25 (3H, t, *J* 7.1, CH_3), 2.28-2.54 (4H, m, 2 x CH_2), 4.21 (2H, q, *J* 7.1, OCH_2) and 4.65-4.87 (1H, m, CH); δ_C 14.1 (CH_3),

25.9, 26.8, 62.1 (3 x CH_2), 75.8 (CH) and 169.9, 176.1 (2 x C=O); *m/z* [APcI] 159 ($[M+H]^+$, 100), 79 (15), 71 (20 *These data are consistent with those recorded in the literature.*[95a]

***(S)-(+)-γ-Hydroxymethyl-γ-butyrolactone* 544**[95a]



549 **544**

To a suspension of sodium borohydride (8.40 g, 0.221 mol) in ethanol (180 mL) was added a solution of ethoxycarbonyl-γ-butyrolactone **549** (35.00 g, 0.221 mol) in ethanol (300 mL) at 20-25°C and the resulting mixture stirred at room temperature for 1 h. The mixture was adjusted to pH 3 with 10% aqueous HCl, the resulting white solid was filtered off and the filtrate was evaporated. The process of methanol addition and evaporation was repeated 4 times and then the residue was purified by column chromatography on silica gel (250 g) with 7% ethanol-chloroform as eluting solvent to give a yellow oil. Distillation of this oil gave *hydroxymethyl-γ-butyrolactone* **544** as a light yellow liquid (22.82 g, 89%) of bp 120-122°C/5mm [Lit.[95a] bp 131-147°/7mm]; ν_{max}/cm^{-1} [film] 3384 (b), 2930 (m), 2875 (w), 1767 (s), 1357 (m), 1192 (s), 1062 (s) and 854 (m); δ_H 2.17-2.29 (2H, m, CH_2), 2.54-2.71 (2H, m, CH_2), 3.64-3.75 (2H, m, CH_2) and 4.65-4.67 (1H, m, CH); δ_C 23.2, 28.7, 64.1 (3 x CH_2), 80.8 (CH) and 177.8 (C=O); *m/z* [APcI] 117 ($[M+H]^+$, 100), 99 (65), 71 (20). *These data are consistent with those recorded in the literature.*[95a]

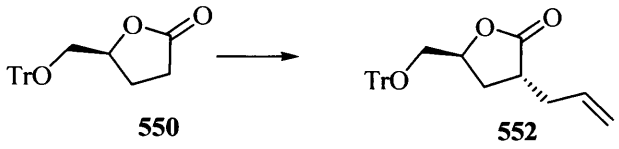
***(S)-(+)-γ-trityloxymethyl-γ-butyrolactone* 550** [95a]

544 **550**

To a stirred solution of hydroxymethyl-γ-butyrolactone **544** (4.0 g, 34.48 mmol) in pyridine (35 mL) was added triphenylmethyl chloride (9.61 g, 34.48 mmol) at room temperature and stirring was continued for 20 h. Most of the pyridine was then distilled off at 50-60°C under vacuum. The residue was dissolved in dichloromethane (70 mL) and the resulting solution washed thoroughly with brine (5 x 20 mL) then dried and evaporated. The residue was purified by column chromatography with 25% ethyl acetate in petroleum ether as eluting solvent to give a colorless crystalline solid which was recrystallised twice from boiling

methanol to give *γ -trityloxymethyl-γ-butyrolactone* **550** as white needles (7.50 g, 60%), mp 148-149°C [Lit.[95a] mp 148-149°C]; $[\alpha]_D$ +26.7° (c 1, $CHCl_3$) [lit.[17b] $[\alpha]_D$ +28.6° (c 1, $CHCl_3$)]; ν_{max}/cm^{-1} [nujol] 2931 (m), 2860 (m), 1767 (s), 1474 (w), 1426 (w), 1362 (w), 1180 (m), 1110 (s), 997 (m), 944 (m), 826 (m) and 700 (m); δ_H 1.90-2.03 (1H, m, CH_{2a}), 2.12-2.23 (1H, m, CH_{2b}), 2.45 (1H, ddd, *J* 17.2, 10.9, 6.6, CH_{2a}), 2.61 (1H, ddd, *J* 17.2, 10.9, 6.6, CH_{2b}), 3.08 (1H, dd, *J* 10.4, 4.3, OCH_{2a}), 3.35 (1H, dd, *J* 10.4, 4.3, OCH_{2b}), 4.57-4.61 (1H, m, CH), 7.16-7.20 (3H, m, 3 x ArH), 7.23-7.26 (6H, m, 6 x ArH) and 7.36-7.38 (6H, m, 6 x ArH); δ_C 24.2, 28.5, 65.2 (3 x CH_2), 79.1 (CH), 96.7 (C), 127.2 (3 x ArCH), 128.0 (6 x ArCH), 128.6 (6 x ArCH), 143.5 (3 x ArC) and 172.3 (C=O); *m/z* [APcI] 359 ($[M+H]^+$, 100). *These data are consistent with those recorded in the literature.*[95a]

(+)-(3R,5S)-3-Allyl-5-trityloxymethyl-γ-butyrolactone **552**[95b]

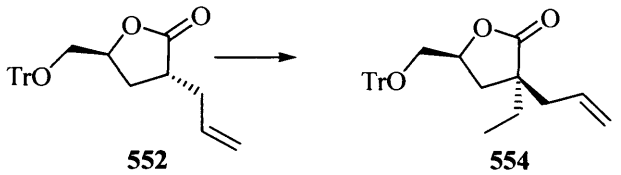


550 **552**

Diisopropylamine (2.4 mL, 17.44 mmol) was dissolved in anhydrous tetrahydrofuran (5 mL) at 0°C under nitrogen. A solution of 2.5M *n*-butyl lithium (6.98 mL in hexane, 17.44 mmol) was added dropwise and the solution stirred at 0°C for 30 min. The lithium diisopropylamide thus formed was cooled to –78°C. A solution of the lactone **550** (4.60 g, 12.8 mmol) in anhydrous tetrahydrofuran (50 mL) was added dropwise during 25 min and the resulting mixture stirred at –78°C for 1 h. Allyl bromide (1.45 mL, 16.74 mmol) was added and the reaction stirred at –78°C for 1.5 h, then quenched by aqueous sodium sulphate solution (25 mL) and diluted with diethyl ether (25 mL). The layers were then separated and the organic layer was washed twice with brine and dried. Removal of the solvent gave the *3-allyl-γ-butyrolactone* **552** as a light yellow oil (4.90 g, 96%); $[\alpha]_D$ +15.7° (c 1, $CHCl_3$) [Lit.[95b] $[\alpha]_D$ +24.8° (c 1.96, $CHCl_3$)]; ν_{max}/cm^{-1} [film] 2925 (w), 2865 (w), 1755 (s), 1644 (m), 1490 (m), 1448 (m), 1265 (w), 1220 (w), 1154 (w), 1071 (m), 1032 (m), 899 (m), 745 (s) and 706 (s); δ_H 1.92-1.97 (1H, m, 4-CH_{2a}), 2.06-2.09 (1H, m, 4-CH_{2b}), 2.18-2.22 (1H, m, CH_{2a}), 2.42-2.58 (1H, m, CH_{2b}), 2.82-2.86 (1H, m, 3-CH), 3.05 (1H, dd, *J* 10.4, 3.8, OCH_{2a}), 3.36 (1H, dd, *J* 10.4, 3.8, OCH_{2b}), 4.47-4.52 (1H, m, CH), 5.00-5.07 (2H, m, CH_2=), 5.66-5.73 (1H, m, CH=), 7.15-7.19 (3H, m, 3 x ArH), 7.22-7.26 (6H, m, 6 x ArH) and 7.34-7.39 (6H, m, 6 x ArH); δ_C 29.6, 35.2 (2 x CH_2), 39.0 (3-CH), 65.3 (OCH_2), 77.1 (5-CH), 87.1 (C), 117.8 (CH_2=), 127.2 (3 x ArCH), 127.9 (6 x ArCH), 128.0 (6 x ArCH), 134.5 (CH), 143.4 (3 x ArC) and 179.0

(C=O); *m/z* [APcI] 359 ([M+H]$^+$, 40), 243 (100). *These data are consistent with those recorded in the literature.*[95b]

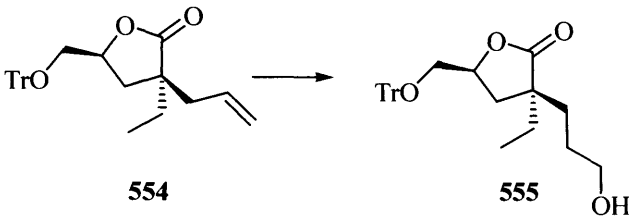
***(+)-(3S,5S)-3-Allyl-3-ethyl-5-trityloxymethyl-γ-butyrolactone* 554**[95b]



552 **554**

To a solution of lithium diisopropylamide prepared as above from diisopropylamine (0.44 mL, 3.2 mmol) and 2.5M *n*-butyl lithium (1.28 mL, 3.2 mmol) in anhydrous tetrahydrofuran (3 mL) was added a solution of the lactone **552** (0.64 g, 1.6 mmol) in anhydrous tetrahydrofuran (2 mL) during 10 min at –78°C. After stirred at –78°C for 40 min, ethyl bromide (0.36 mL, 4.8 mmol) was added to the mixture and stirring continued for 18 h without further cooling. The reaction was quenched by aqueous sodium sulphate (5 mL) and diluted with diethyl ether (25 mL). The layers were then separated and the organic layer was washed twice with brine and dried. Evaporation of the solvent gave the *3-allyl-3-ethyl-γ-butyrolactone* **554** as a light yellow oil (0.62 g, 90%); $[\alpha]_D$ +29.7° (c 1, $CHCl_3$) [lit.[95b] $[\alpha]_D$ +30.8° (c 2, CH_2Cl_2)]; ν_{max}/cm^{-1} [film] 2965 (m), 2966 (m), 2875 (w), 1767 (s), 1640 (w), 1597 (w), 1490 (w), 1448 (m), 1413 (w), 1192 (m), 11152 (w), 1077 (m), 1033 (w), 1002 (w), 747 (w) and 707 (s); δ_H 0.89 (3H, t, *J* 7.4, CH_3), 1.58 (2H, q, *J* 7.4, CH_2), 1.84 (1H, dd, *J* 13.2, 7.1, 4-CH_a), 2.01 (1H, dd, *J* 13.2, 7.1, 4-CH_b), 2.22 (2H, d, *J* 8.4, CH_2), 3.05 (2H, dd, *J* 13.2, 6.0, OCH_2), 4.44-4.48 (1H, m, CH), 5.00 (1H, app. s, CH_a=), 5.02 (1H, d, *J* 6.0, CH_b=), 5.52 (1H, td, *J* 8.4, 6.0, CH=), 7.17-7.23 (3H, m, 3 x ArH), 7.24-7.26 (6H, m, 6 x ArH) and 7.33-7.37 (6H, m, 6 x ArH); δ_C 8.8 (CH_3), 30.0, 33.3, 40.3 (3 x CH_2), 47.8 (3-C), 65.1 (OCH_2), 76.2 (5-CH), 86.8 (C), 119.3 (CH_2=), 127.1 (3 x ArCH), 127.9 (6 x ArCH), 128.7 (6 x ArCH), 133.3 (CH), 143.6 (3 x ArC) and 180.4 (C=O); *m/z* [APcI] 427 ([M+H]$^+$, 10), 243 (100). *These data are consistent with those recorded in the literature.*[95b]

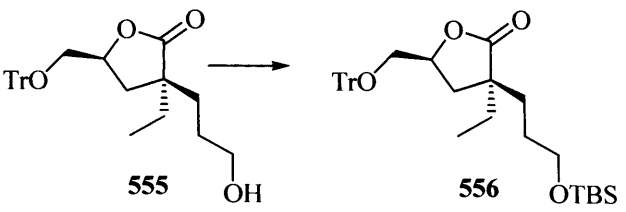
***(+)-(3S,5S)-3-Ethyl -3-(3-hydroxypropyl) -5-trityloxymethyl-γ-butyrolactone* 555**



554 555

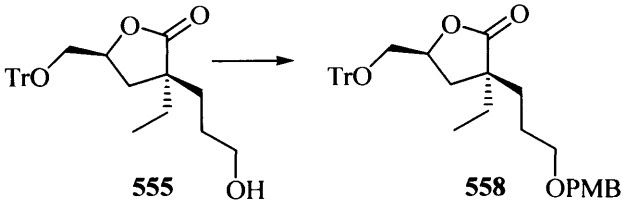
To a stirred solution of cyclohexene (1.00 mL, 9.81 mmol) in tetrahydrofuran (2 mL) was added borane-methyl sulphide complex (0.46 mL, 4.9 mmol) at 0°C with stirring. After 1 h, the dialkyl-γ-butyrolactone **554** (1.30 g, 3.27 mmol) in tetrahydrofuran (5 mL) was added to the mixture at 0°C and stirring was continued for 1 h at room temperature. The mixture was then treated with ethanol (2 mL), followed by 3N aqueous sodium hydroxide (1.5 mL) and 35% aqueous hydrogen peroxide (2 mL, 17.98 mmol) at 0°C and the resulting mixture warmed to 50°C for 1 h. Cold water (8 mL) was then added, the mixture was extracted with ether (2 x 10 mL) and the combined extracts were washed with brine (20 mL), dried and evaporated to leave a colourless oil. The oil was dissolved in aqueous methanol ($MeOH/H_2O$, 10:1, 5 mL) and the solution refluxed with sodium hydroxide (0.45 g) for 1 h. After evaporation of the solvent, the residue was dissolved in water (5 mL) and the resulting solution washed with ether, acidified with acetic acid and extracted with dichloromethane. The organic extracts were washed with brine, dried and evaporated to give the crude *alcohol* **555** as a colourless oil (1.09 g, 81%); $[\alpha]_D$ +18.7° (c 1, $CHCl_3$); ν_{max}/cm^{-1} [film] 3396 (br), 2930 (s), 2865 (m), 1760 (s), 1448 (m), 1190 (m), 1070 (m), 748 (w) and 701 (m); δ_H 0.86 (3H, t, *J* 7.4, CH_3), 1.29-1.61 (6H, m, 3 x CH_2), 1.87-1.96 (2H, m, CH_2), 2.96-3.01 (2H, m, CH_2OH), 3.49 (1H, dd, *J* 12.3, 2.8, OCH_{2a}), 3.74 (1H, dd, *J* 12.3, 2.8, OCH_{2b}), 4.40-4.47 (1H, m, 5-CH), 7.11-7.18 (3H, m, 3 x ArCH), 7.20-7.24 (6H, m, 6 x ArH) and 7.33-7.38 (6H, m, 6 x ArH); δ_C 8.8 (CH_3), 25.0, 29.7, 29.9, 33.1 (4 x CH_2), 48.0 (3-C), 60.5, 63.6 (2 x OCH_2), 77.7 (5-CH), 86.5 (C), 126.9 (3 x ArCH), 127.8 (6 x ArCH), 128.7 (6 x ArCH), 144.3 (3 x ArC) and 181.0 (C=O); *m/z* [APcI] 427 ($[M-OH]^+$, 40), 243 (100).

***(+)-(3S,5S)-3-Ethyl -3-(3-(tert-butyldimethylsilyloxy)-propyl) -5-trityloxymethyl-γ-butyrolactone* 556**



To a stirred solution of the 3-ethyl-3-hydroxypropyl-lactone **555** (1.20 g, 2.7 mmol) in tetrahydrofuran (20 mL) was added imidazole (0.24 g, 3.456 mmol). After a clear solution was obtained, *tert*-butyldimethylsilyl chloride (0.52 g, 3.456 mmol) was added to give a cloudy white solution. The mixture was allowed to stir for 16 h at room temperature, then quenched with water (20 mL) and diluted with dichloromethane (20 mL). The organic layer was separated and washed with brine (20 mL), then dried and evaporated to give the *3-silylated-propyl-γ-butyrolactone* **556** as a light yellow oil (1.4 g, 93%); $[\alpha]_D$ +14.7° (c 1, $CHCl_3$); ν_{max}/cm^{-1} [film] 3421 (br), 3064 (m), 2929 (s), 2856 (s), 1754 (s), 1596 (w), 1490 (m), 1449 (s), 1254 (m), 1192 (m), 1089 (s), 836 (m), 767 (m) and 707 (s); δ_H 0.00 (6H, s, 2 x $SiCH_3$), 0.79-0.88 (12H, m, 3 x $SiCCH_3$and CH_3), 1.52-1.62 (6H, m, 3 x CH_2), 1.87-1.95 (2H, m, CH_2), 3.10 (1H, dd, *J* 10.3, 3.6, OCH_{2a}), 3.22 (1H, dd, *J* 10.3, 3.6, OCH_{2b}), 3.57-3.67 (2H, m, CH_2O), 4.40-4.52 (1H, m, 5-CH), 7.13-7.16 (3H, m, 3 x ArH), 7.18-7.23 (6H, m, 6 x ArH) and 7.30-7.35 (6H, m, 6 x ArH); δ_C –5.6 (2 x $SiCH_3$), 8.9 (CH_3), 15.4 (C), 20.6 (3 x $SiCCH_3$), 25.8, 29.0, 29.8, 30.1 (4 x CH_2), 47.6 (3-C), 66.5, 68.8 (2 x OCH_2), 78.6 (5-CH), 88.6 (C), 126.5 (3 x ArCH), 128.3 (6 x ArCH), 128.9 (6 x ArCH), 143.2 (3 x ArC) and 178.1 (C=O); *m/z* [APcI] 559 ($[M+H]^+$, 5), 427 (10), 243 (100); Found $[M+H]^+$, 559.3238. $C_{35}H_{47}O_4Si$ requires *M*, 559.3238.

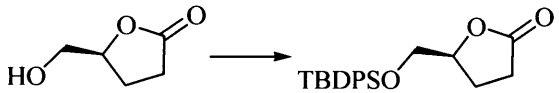
***(+)-(3S,5S)-3-Ethyl -3-(3'-(4-methoxybenzyloxy)-propyl) -5-trityloxymethyl-γ-butyrolactone* 558**



A stirred solution of the 3-ethyl-3-hydroxypropyl-lactone **555** (90 mg, 0.20 mmol) in dichloromethane/cyclohexane (1:2, 1.5 mL) was cooled to 0°C and treated sequentially with crude trichloroimidate **440** (86 mg, 0.30 mmol) and boron trifluoride etherate (one drop, catalytic amount). The mixture was warmed to room temperature and stirred for 16 h, then filtered through celite. The solid was washed with dichloromethane/cyclohexane (1:2, 2 x 2 mL). The combined filtrates were washed with saturated aqueous sodium bicarbonate (2 mL),

then dried and concentrated. The crude residue was purified by flash chromatography (40% ethyl acetate in petroleum ether) to give the *p-methoxybenzyloxypropyl-γ-butyrolactone* **558** as a pale yellow oil (68 mg, 60%); R_f 0.76 (40% ethyl acetate in petroleum ether); $[\alpha]_D$ +16.1° (c 1, $CHCl_3$); ν_{max}/cm^{-1} [film] 3412 (br), 2945 (s), 2855 (s), 1730 (s), 1649 (m), 1613 (s), 1513 (s), 1447 (m), 1353 (w), 1298 (w), 1248 (s), 1175 (m), 1092 (w), 1034 (m), 823 (m), 764 (m) and 702 (s); δ_H 0.86 (3H, t, *J* 7.4, CH_3), 1.52-1.64 (6H, m, 3 x CH_2), 1.86-1.92 (2H, m, CH_2), 3.13 (1H, dd, *J* 10.4, 5.0, OCH_{2a}), 3.20 (1H, dd, *J* 10.4, 5.0, OCH_{2b}), 3.33 (2H, td, *J* 6.2, 2.5, CH_2O), 3.71 (3H, s OCH_3), 4.31 (2H, s, Ar-CH_2O), 4.32-4.51 (1H, m, CH), 6.78 (2H, d, *J* 6.8, 2 x ArH), 7.13-7.17 (5H, m, 5 x ArH), 7.21-7.24 (6H, m, 6 x ArCH) and 7.37 (6H, d, *J* 7.4, 6 x ArCH); δ_C 8.8 (CH_3), 25.0, 29.7, 32.4, 34.1 (4 x CH_2), 47.7 (3-C), 55.3 (Ar-OCH_3), 63.6, 71.4, 73.3 (3 x OCH_2), 76.2 (5-CH), 86.5 (C), 113.9 (2 x ArCH), 127.0 (3 x ArCH), 127.8 (6 x ArCH), 128.6 (6 x ArCH), 130.5 (2 x ArCH), 144.3 (3 x ArC), 159.3, 163.7 (2 x ArC) and 180.7 (C=O); *m/z* [APcI] 565 ($[M+H]^+$, 5), 243 (100).

***(S)-(O)-tert-Butyldiphenylsilyl-γ-hydroxymethyl-γ-butyrolactone* 551**[97b]

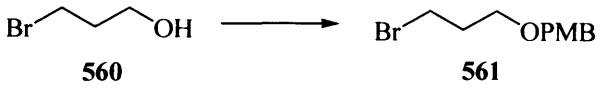


544 **551**

To a stirred solution of the hydroxymethyl-γ-butyrolactone **544** (4.77 g, 41.12 mmol) in dichloromethane (45 mL) was added triethylamine (8.6 mL, 61.68 mmol) at 0°C. After stirring for 10 min, *t*-butyldiphenylsilyl chloride (11.76 mL, 45.23 mmol) and 4-dimethylaminopyridine (catalytic amount) were added and the resulting solution stirred at room temperature for 3.5 h. The mixture containing crystalline triethylamine hydrochloride was diluted with ether (170 mL) and water (90 mL). The separated ether solution was washed with water, 1N HCl, aqueous sodium bicarbonate, brine and water, then dried and evaporated to leave a syrup, which was dissolved in warm hexane (90 mL). Upon cooling, the product crystallized. Filtration and washing with hexane (25 mL) gave crystalline *t-butyldiphenylsilyl-γ-hydroxymethyl-γ-butyrolactone* **551** (10.20 g, 70%), mp 74-76°C [Lit.[97b] mp 75-79°C]; $[\alpha]_D$ +24.95° (c 1, $CHCl_3$) [Lit.[18] $[\alpha]_D$ +28.95° (c 2, $CHCl_3$)]; ν_{max}/cm^{-1} [nujol] 2933 (m), 2857 (m), 1777 (s), 1472 (w), 1428 (w), 1361 (w), 1175 (m), 1113 (s), 996 (m), 942 (m), 823 (m), 743 (m) and 703 (s); δ_H 1.07 (9H, s, 3 x $SiCCH_3$), 2.25-2.33 (2H, m, CH_2), 2.54 (1H, ddd, *J* 17.1, 10.0, 6.6, CH_{2a}), 2.71 (1H, ddd, *J* 17.5, 10.2, 6.6, CH_{2b}), 3.70 (1H, dd, *J* 11.4, 3.2, OCH_{2a}), 3.91 (1H, dd, *J* 11.4, 3.2, OCH_{2b}), 4.43 (1H, dddd, *J* 6.6, 5.2, 5.2, 3.2, CH), 7.40-7.49

(6H, m, 6 x ArCH) and 7.67-7.69 (4H, m, 6 x ArCH); δ_C 19.2 (C), 23.7 (CH_2), 26.7 (3 x CH_3), 28.6, 65.5 (2 x CH_2), 80.0 (CH), 127.9 (4 x ArCH), 129.9 (2 x ArCH), 132.5 (2 x ArC), 135.6, 135.7 (4 x ArCH) and 178.0 (C=O); *m/z* [APcI] 355 ($[M+H]^+$, 10), 167 (5), 158 (5), 83 (15), 71 (100). *These data are consistent with those recorded in the literature.*[97b]

1-(3'-Bromo-propoxymethyl)-4-methoxybenzene **561**[98]



560 **561**

A solution of 3-bromo-1-propanol (3.20 mL, 35 mmol) in dichloromethane/cyclohexane (1:2, 90 mL) was cooled to 0°C and treated with crude trichloroimidate **440** (10.62 g, 37.6 mmol) and camphorsulfonic acid (0.40 g, catalytic amount) over 30 min. After 3 h, the mixture was warmed to room temperature, stirred over 48 h and concentrated. Filtration of the crude residue through a short plug of silica (using 20% ethyl acetate in petroleum ether) afforded the corresponding *p-methoxybenzyloxy ether* **561** as a pale yellow oil (8.95 g, 99%); ν_{max}/cm^{-1} [film] 3000 (m), 2934 (s), 2858 (s), 1732 (m), 1612 (s), 1586 (m), 1513 (s), 1464 (m), 1442 (m), 1362 (m), 1247 (s), 1173 (s), 1099 (s), 1035 (s) and 821 (s); δ_H 2.14 (2H, pen, *J* 6.2, 2'-CH_2), 3.54 (2H, t, *J* 6.2, CH_2), 3.60 (2H, t, *J* 6.2, CH_2), 3.83 (3H, s, OCH_3), 4.47 (2H, s, OCH_2), 6.90 (2H, d, *J* 8.6, 2 x ArH) and 7.28 (2H, d, *J* 8.6, 2 x ArH); δ_C 30.8, 32.9 (2 x CH_2), 55.3 (OCH_3), 67.4, 72.8 (2 x OCH_2), 113.8, 129.3 (4 x ArCH) and 130.3, 159.2 (2 x ArC); *m/z* [APcI] 259 (^{79}Br; $[M+H]^+$, 80), 257 (100), 228 (25), 192 (25). *These data are consistent with those recorded in the literature.*[98]

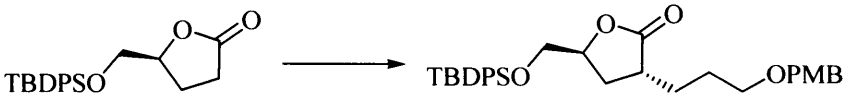
1-(3'-Iodo-propoxymethyl)-4-methoxy-benzene **562**[98]

561 **562**

To a stirred solution of sodium iodide (25.20 g, 0.168 mol) in a minimum amount of anhydrous acetone was added the bromopropoxy ether **561** (8.70 g, 0.034 mol). The mixture was refluxed for 4 h and then cooled to room temperature. Water (30 mL) was added and the mixture was extracted with pentane (2 x 30 mL). The combined extracts were washed with water (30 mL), dried and concentrated. The concentrated crude was purified by flash chromatography (20% ethyl acetate in petroleum ether) to give the *iodopropoxy ether* **562** as a yellow syrup (8.50 g, 82%); ν_{max}/cm^{-1} [film] 2949 (m), 2858 (m), 1612 (m), 1585 (w), 1513

(s), 1463 (w), 1302 (w), 1247 (s), 1174 (m), 1098 (m), 1035 (m) and 820 (w); δ_H 2.00 (2H, pen, *J* 6.2, 2'-CH_2), 3.22 (2H, t, *J* 6.2, CH_2), 3.44 (2H, t, *J* 6.2, CH_2), 3.74 (3H, s, OCH_3), 4.38 (2H, s, OCH_2), 6.82 (2H, d, *J* 8.6, 2 x ArH) and 7.19 (2H, d, *J* 8.6, 2 x ArH); δ_C 3.7, 33.5 (2 x CH_2), 55.3 (OCH_3), 69.3, 72.8 (2 x OCH_2), 113.8, 129.3 (4 x ArCH) and 130.3, 159.2 (2 x ArC); *m/z* [APcI] 259 (^{79}Br; $[M+H]^+$, 80), 257 (100), 228 (25), 192 (25). *These data are consistent with those recorded in the literature.*[98]

***(+)-(3R,5S)-5-(tert-Butyldiphenylsilanyloxymethyl)-3-[3'-(4-methoxy-benzyloxy)-propyl]-γ-butyrolactone* 563**

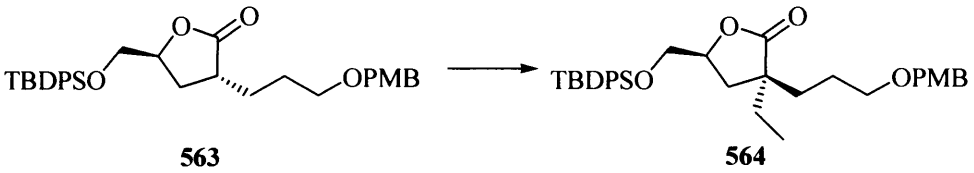


551 563

Diisopropylamine (1.34 mL, 9.88 mmol) was dissolved in anhydrous tetrahydrofuran (5 mL) at 0°C under nitrogen. A solution of 1.6M *n*-butyl lithium (6.2 mL in hexane, 9.88 mmol) was added dropwise and the solution stirred at 0°C for 30 min. The lithium diisopropylamide thus formed was cooled to –25°C. The solution of the lactone **551** (2.92 g, 8.23 mmol) in anhydrous tetrahydrofuran (30 mL) was added dropwise, followed by hexamethylphosphoramide (1.7 mL, 9.87 mmol,) and the resulting solution stirred at –25°C for 1 h. Iodopropyl PMB ether **562** (2.77 g, 9.05 mmol) was added and the reaction stirring at –25°C for 3 h, then warmed to room temperature slowly and stirred for 16 h. The reaction was quenched by saturated aqueous ammonium chloride (10 mL) and diluted with diethyl ether (20 mL). The layers were then separated and the organic layer washed with water (4 x 30 mL), twice with brine and dried. Removal of the solvent on a rotary evaporator gave a crude product as a light yellow syrup. The concentrated crude was purified by flash chromatography (60% ethyl acetate in petroleum ether) to give the *lactone* **563** as a yellow syrup (2.70 g, 62%); R_f 0.65 (60% ethyl acetate in petroleum ether); $[\alpha]_D$ +16.4° (c 1, $CHCl_3$); ν_{max}/cm^{-1} [film] 2929 (m), 2856 (m), 1769 (s), 1667 (w), 1612 (w), 1513 (m), 1472 (w), 1428 (m), 1360 (w), 1248 (s), 1171 (m), 1113 (s), 1031 (m), 823 (m) and 703 (s); δ_H 0.94 (9H, s, 3 x CH_3), 1.46-1.53 (1H, m, 2'$_a$-CH_2), 1.59-1.67 (1H, m, 2'$_b$-CH_2), 1.84-1.98 (2H, m, 1'-CH_2), 2.21-2.27 (1H, m, 4$_a$-CH_2), 2.94-2.99 (1H, m, 4$_b$-CH_2), 3.37-3.41 (3H, m, 3-CH and OCH_2), 3.55 (1H, dd, *J* 11.4, 3.2, 3'-OCH_{2a}), 3.71 (3H, s, OCH_3), 3.75 (1H, dd, *J* 11.4 and 3.2, 3'-OCH_{2b}), 4.33 (2H, s, OCH_2), 4.41-4.45 (1H, m, 5-CH), 6.78 (2H, d, *J* 8.6, 2 x ArH), 7.16 (2H, m, 2 x ArH), 7.27-3.34 (6H, m, 6 x ArH) and 7.54-7.63 (4H, m, 4 x ArH); δ_C 19.2 (C), 26.7 (3 x

CH_3), 27.8, 28.2, 30.0 (3 x CH_2), 39.4 (3-CH), 55.29 (OCH_3), 65.2, 69.5, 72.7 (3 x OCH_2), 77.8 (5-CH), 113.8 (2 x ArCH), 127.8 (4 x ArCH), 129.3 (2 x ArCH), 129.9 (4 x ArCH), 130.3 (ArC), 133.0 (2 x ArC), 135.6, 135.7 (4 x ArCH), 159.0 (ArC) and 179.9 (C=O); *m/z* [APcI] 533 ($[M+H]^+$, 32), 532 (100), 412 (15), 395 (25), 268 (25), 242 (70). Found $[M+H]^+$, 533.2723. $C_{32}H_{41}O_5Si$ requires *M*, 533.2718.

***(+)-(3R,5S)-5-(tert-Butyldiphenylsilanyloxymethyl)-3-ethyl-3-[3-(4-methoxy-benzyloxy)-propyl]-γ-butyrolactone* 564**

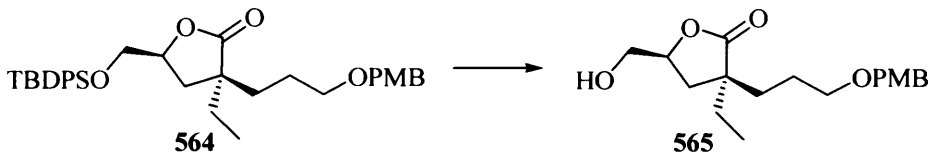


563 **564**

Diisopropylamine (0.41 mL, 3.0 mmol) was dissolved in anhydrous tetrahydrofuran (2 mL) at 0°C under nitrogen. A solution of 2.5M *n*-butyllithium (1.2 mL in hexane, 3 mmol) was added dropwise and the solution stirred at 0°C for 30 min. The lithium diisopropylamide thus formed was cooled to –25°C. A solution of the lactone **564** (1.33 g, 2.5 mmol,) in anhydrous tetrahydrofuran (15 mL) was added dropwise, followed by 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (0.38 g, 3 mmol,) and the resulting solution stirred at –25°C for 1 h. Iodoethane (0.28 mL, 3.5 mmol) was added and the mixture stirred at –25°C for 3 h. The reaction mixture was then warmed to room temperature slowly and stirred for 16 h, then quenched by saturated aqueous ammonium chloride (15 mL) and diluted with diethyl ether (20 mL). The layers were separated and the organic layer washed with water (3 x 20 mL), once with brine and dried. Removal of the solvent on a rotary evaporater gave a crude product, the *lactone* **564** as a brownish yellow oil (1.50 g, crude yield of 120%); $[\alpha]_D$ +14.5° (c 1, $CHCl_3$); ν_{max}/cm^{-1} [film] 2934 (s), 2857 (s), 1767 (s), 1612 (w), 1513 (w), 1462 (w), 1428 (m), 1358 (w), 1313 (w), 1248 (m), 1192 (m), 1113 (s), 1032 (m), 823 (m) and 703 (s); δ_H 0.87 (3H, t, *J* 7.4, 10-CH_3), 0.92 (9H, s, 3 x $SiCCH_3$), 1.51-1.65 (4H, m, 2 x CH_2), 1.78-1.84 (3H, m, 7-CH_2 and 4-CH_{2a}), 2.01-2.10 (1H, m, 4-CH_{2b}), 3.28 (2H, td, *J* 5.9, 2.3, OCH_2), 3.55 (1H, dd, *J* 11.4, 4.4, $SiOCH_{2a}$), 3.61-3.68 (4H, m, OCH_3 and $SiOCH_{2b}$), 4.28-4.35 (3H, m, 5-H and OCH_2Ar), 6.74 (2H, d, *J* 8.6, 2 x ArCH), 7.09 (2H, d, *J* 8.6, 2 x ArCH), 7.22-7.32 (6H, m, 6 x ArH) and 7.50-7.59 (4H, m, 4 x ArCH); δ 8.8 (CH_3), 19.2 (C), 24.8, 25.6 (2 x CH_2), 26.7 (3 x CH_3), 29.8, 32.3 (2 x CH_2), 47.8 (3-C), 55.3 (OCH_3), 68.0, 70.0, 72.6 (3 x OCH_2), 77.2 (5-CH), 113.7 (2 x ArCH), 127.8 (4 x ArCH), 129.3 (2 x ArCH), 129.9 (2 x ArCH), 130.5 (ArC), 132.8, 133.0 (2 x ArC), 135.6, 135.7 (4 x ArCH), 159.1 (ArC) and

180.8 (C=O); *m/z* [APcI] 561 ([M+H]$^+$, 8), 278 (10), 218 (25), 130 (100), 122 (70), Found [M+H]$^+$, 561.3032. $C_{34}H_{45}O_5Si$ requires *M*,. 561.3031.

***(+)-(3R,5S)-3-Ethyl-5-hydroxymethyl-3-[3-(4-methoxy-benzyloxy)-propyl]-γ-butyrolactone* 565**



564 565

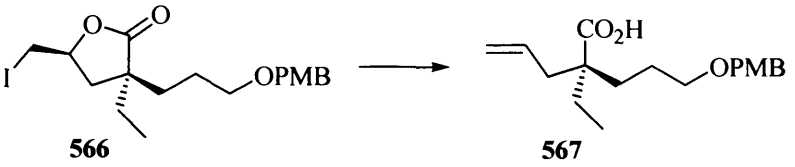
To a solution of the crude silylated lactone **564** (1.40 g, 2.5 mmol) in anhydrous tetrahydrofuran (25 mL) was added tetrabutylammonium fluoride (2.75 mLof 1M solution in THF, 2.75 mmol) dropwise at 0°C. The mixture was allowed to stir for 16 h without further cooling, then quenched with water (25 mL) and diluted with diethyl ether (50 mL). The separated organic layer was washed with water (3 x 20 mL) and dried. The concentrated crude was purified by flash chromatography (30-60% ethyl acetate in petroleum ether) to give the *hydroxymethyl-lactone* **565** as a colourless oil (0.27 g, 33%); R_f 0.25 (60% ethyl acetate in petroleum ether); $[\alpha]_D$ +15.4° (c 1, $CHCl_3$); ν_{max}/cm^{-1} [film] 3470 (br), 2917 (s), 2876 (s), 1761 (s), 1613 (m), 1513 (s), 1454 (m), 1358 (m), 1303 (m), 1248 (s), 1194 (s), 1098 (s), 1032 (s) and 819 (w); δ_H 0.87 (3H, t, *J* 7.5, CH_3), 1.35-1.72 (6H, m, 3 x CH_2), 1.90 (1H, dd, *J* 13.1, 8.3, 4_a -CH_2), 1.99 (1H, dd, *J* 13.1, 8.3, 4_b -CH_2), 3.36 (2H, td, *J* 6.1, 1.4, 3'-OCH_2), 3.46 (1H, dd, *J* 12.5, 4.1, OCH_{2a}), 3.72 (3H, s, $ArOCH_3$), 3.73 (1H, dd, *J* 12.5, 4.1, OCH_{2b}), 4.33 (2H, s, OCH_2Ar), 4.40-4.46 (1H, m, 5-H), 6.8 (2H, d, *J* 8.5, 2 x ArH) and 7.17 (2H, d, *J* 8.5, 2 x ArH); δ_C 8.7 (CH_3), 24.7, 29.9, 32.2, 32.7 (2 x CH_2), 47.9 (3-C), 55.3 (OCH_3), 64.0, 70.0, 72.6 (3 x OCH_2), 77.7 (5-CH), 113.7 (2 x ArCH), 129.4 (2 x ArCH), 130.4 159.1 (2 x ArC) and 180.9 (C=O); *m/z* [APcI] 323 ([M+H]$^+$, 10), 241.6 (15), 191 (15), 121 (100), Found [M+H]$^+$, 323.1857. $C_{18}H_{27}O_5$ requires *M*, 323.1853.

***(+)-(3R,5S)-3-Ethyl-5-iodomethyl-3-[3'-(4-methoxy-benzyloxy)-propyl]-]-γ-butyrolactone* 566**

565 566

The hydroxymethyl lactone **565** (0.20 g, 0.62 mmol) was dissolved in toluene (4 mL). After the addition of imidazole (0.15 g, 1.5 mmol) and triphenylphosphine (0.20 g, 0.74 mmol), the solution was heated to 70°C. At this temperature, iodine (0.19 g, 0.74 mmol) was added and stirring continued for 2 h. The brown precipitate which formed was separated by decantation and the solution was evaporated to dryness. The residue was extracted with diethyl ether (3 x 2 mL) and the solvent was evaporated and filtrated through a short plug of silica gel. The solvent was then evaporated to afford the *iodolactone* **566** as a yellow oil (0.27 g, 99%): R_f 0.50 (25% ethyl acetate in petroleum ether); $[\alpha]_D$ –16.8° (c 1, $CHCl_3$); ν_{max}/cm^{-1} [film] 2936 (s), 2875 (m), 1750 (s), 1611 (w), 1513 (s), 1459 (w), 1248 (s), 1173 (w), 1097 (m), 1036 (m), 919 (w) and 819 (m); δ_H 0.89 (3H, t, *J* 7.5, CH_3), 1.55-1.66 (6H, m, 3 x CH_2), 1.80 (1H, dd, *J* 13.3, 7.9, 4_a-CH_2), 2.20 (1H, dd, *J* 13.3, 7.9, 4_b-CH_2), 3.14 (1H, dd, *J* 10.1, 6.2, ICH_{2a}), 3.33 (1H, dd, *J* 10.1, 6.2, ICH_{2b}), 3.38 (2H, m, 3'-OCH_2), 3.74 (3H, s, $ArOCH_3$), 4.34-4.39 (3H, m, 5-H and OCH_2), 6.8 (2H, dt, *J* 8.6, 2.3, 2 x ArH) and 7.18 (2H, d, *J* 8.6, ArH); δ_C 7.8 (ICH_2), 8.9 (CH_3), 24.9, 29.9, 32.1, 32.7 (4 x CH_2), 48.8 (3-C), 55.3 (OCH_3), 69.9, 72.6 (2 x OCH_2), 75.5 (5-CH), 113.8, 129.3 (4 x ArCH), 130.4 159.2 (2 x ArC) and 179.9 (C=O); *m/z* [APcI] 433 ($[M+H]^+$, 30), 242 (18), 122 (100), Found $[M+NH_4]^+$, 450.1141. $C_{18}H_{29}INO_4$ requires *M*, 450.1136.

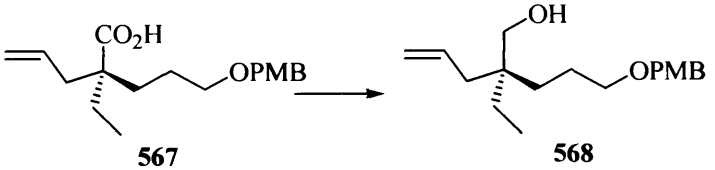
***(-)-(2S)-2-Ethyl-2-[3'-(4-methoxy-benzyloxy)-propyl]-pent-4-enoic acid* 567**



566 **567**

To a stirred solution of the iodolactone **566** (0.20 g, 0.46 mmol) in tetrahydrofuran (2 mL), water (0.5 mL) and acetic acid (0.5 mL) at 0°C was added zinc powder (52 mg, 0.8 mmol). The mixture was stirred vigorously at room temperature for 16 h. The resulting mixture was diluted with diethyl ether (2 mL) and filtered through a pad of celite. The filtrate was concentrated and diluted with water (5 mL) neutralized with aqueous NaOH (1N) and then extracted with dichloromethane (2 x 5 mL). The combined organic layers were then dried and concentrated to afford the *acid* **567** as a light yellow oil (0.135 g, 98%); $[\alpha]_D$ –3.7° (c 1, $CHCl_3$); ν_{max}/cm^{-1} [film] 3657 (br), 2937 (s), 2871 (m), 1696 (m), 1611 (w), 1523 (s), 1456 (w), 1244 (s), 1172 (w), 1099 (m), 1036 (m), 917 (w) and 818 (m); δ_H 0.73 (3H, t, *J* 7.5, CH_3), 1.36-1.51 (6H, m, 3 x CH_2), 2.19 (2H, d, *J* 7.4, 3-CH_2), 3.34 (2H, t, *J* 6.1, OCH_2), 3.73 (3H, s, $ArCH_3$), 4.29 (2H, s, OCH_2Ar), 4.99 (1H, d, *J* 10.0, 5-CH_{2a}), 5.02 (1H, d, *J* 17.0, 5-CH_{2b}), 5.58 (1H, ddt, *J* 17.0, 10.0, 7.4, 4-H), 6.81 (2H, d, *J* 8.5, ArH) and 7.18 (2H, d, *J* 8.5, ArH); δ_C 8.4 (CH_3), 23.4, 27.4, 30.7, 39.1 (4 x CH_2), 49.1 (2-C), 55.3 (OCH_3), 70.3, 72.5 (2 x OCH_2), 113.8 (2 x ArCH), 118.3 (5-CH_2=), 129.3 (2 x ArCH), 130.5 (ArC), 133.6 (4-CH=), 159.1 (ArC) and 182.9 (C=O); *m/z* [APcI] 307 ($[M+H]^+$, 15), 279 (5), 191 (25), 146 (75), 117 (60). Found $[M+NH_4]^+$, 307.1901. $C_{18}H_{27}O_4$ requires *M*, 307.1904.

***(+)-(2S)-2-Ethyl-2-[3'-(4'-methoxy-benzyloxy)-propyl]-pent-4-en-1-ol* 568**

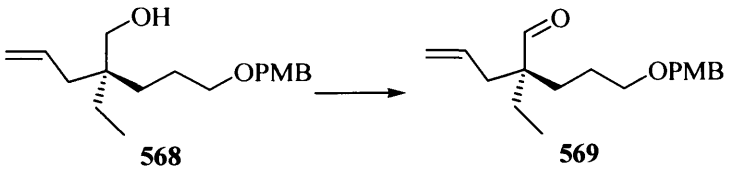


567 **568**

A stirred solution of the acid **567** (1.40 g, 4.57 mmol) in anhydrous diethyl ether (5 mL) was slowly treated with lithium aluminium hydride (5.30 mL of a 1M solution in ether, 5.3 mmol) and the resulting mixture was refluxed for 1 h. After cooling to room temperature, the mixture was diluted with dichloromethane (5 mL) and hydrolysed with saturated aqueous sodium sulfate until a mobile suspension was formed. The mixture was filtered though celite and the filtrate concentrated to give the *alcohol* **568** as a colourless oil (1.33 g, 100%); R_f 0.26 (10%

ethyl acetate in petroleum ether); $[\alpha]_D$ +2.9° (c 1, $CHCl_3$); ν_{max}/cm^{-1} [film] 3405 (br), 2936 (s), 2855 (m), 1613 (m), 1513 (s), 1462 (m), 1438 (m), 1360 (w), 1302 (m), 1248 (s), 1174 (m), 1096 (s), 1036 (s), 913 (w), 820 (m), 746 (w), 723 (m) and 696 (m); δ_H 0.76 (3H, t, *J* 7.8, CH_3), 1.16-1.22 (4H, m, 2 x CH_2), 1.49 (2H, pen, *J* 6.4, CH_2), 1.86-1.93 (2H, m, CH_2), 3.28 (2H, s, 1-CH_2O), 3.34 (2H, t, *J* 6.4, 3'-OCH_2), 3.73 (3H, s, Ar-OCH_3), 4.36 (2H, s, OCH_2Ar), 4.98 (2H, dd, *J* 17.0, 10.0, 5-CH_2), 5.75 (1H, ddt, *J* 17.0, 10.0, 7.5, 4-H), 6.80 (2H, d, *J* 8.5, 2 x ArH) and 7.18 (2H, d, *J* 8.5, 2 x ArH); δ_C 7.5 (CH_3), 23.2, 25.7, 29.4, 38.5 (4 x CH_2), 40.2 (2-C), 55.3 (OCH_3), 66.4, 70.8, 72.7 (2 x OCH_2), 113.8 (2 x ArCH), 117.2 (5-CH_2=), 129.3 (2 x ArCH), 130.4 (ArC), 135.0 (4-CH=) and 159.1 (ArC); *m/z* [APcI] 293 ($[M+H]^+$, 5), 241 (5), 191 (30), 121 (100), 117 (75). Found $[M+H]^+$, 293.2108. $C_{18}H_{29}O_3$ requires *M*, 293.2111.

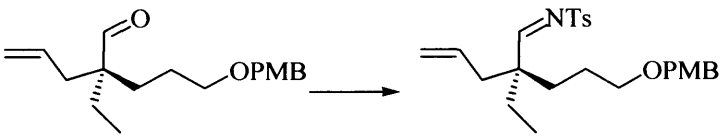
***(-)-(2S)-2-Ethyl-2-[3'-(4-methoxy-benzyloxy)-propyl]-pent-4-enal* 569**



568 **569**

To a dried two-necked round bottom flask was added 1.5 g of celite, which has been dried in a oven for at least 24 h. After the celite had cooled to room temperature by using nitrogen flow, pyridinium chlorochromate (1.45 g, 6.72 mmol) was added. The mixture was suspended in anhydrous dichloromethane (20 mL), then cooled to 0°C. The alcohol **568** (1.30 g, 4.48 mmol) in dichrolomethane (20 mL) was added as described in the general procedure for PCC oxidation. Work-up gave the *aldehyde* **569** as a colourless oil (0.93 g, 72%); $[\alpha]_D$ -0.24° (c 1, $CHCl_3$); R_f 0.75 (10% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2940 (m), 2862 (m), 1722 (s), 1612 (w), 1513 (s), 1458 (w), 1360 (w), 1302 (w), 1248 (s), 1173 (m), 1098 (m), 1035 (m), 918 (w) and 819 (w); δ_H 0.73 (3H, t, *J* 7.5, CH_3), 1.36-1.51 (6H, m, 3 x CCH_2), 2.19 (2H, d, *J* 7.4, 3-CH_2), 3.37 (2H, t, *J* 6.4, CH_2O), 3.73 (3H, s, OCH_3), 4.29 (2H, s, OCH_2), 5.00 (2H, dd, *J* 17.4, 10.3, 5-CH_2), 5.59 (1H, ddt, *J* 17.4, 10.3, 7.4, 4-H), 6.81 (2H, d, *J* 8.6, ArH), 7.18 (2H, d, *J* 8.6, ArH) and 9.34 (1H, s, CHO); δ_C 7.9 (CH_3), 23.8, 24.9, 28.3, 35.6 (4 x CH_2), 52.0 (2-C), 55.3 (OCH_3), 70.1, 72.5 (2 x OCH_2), 113.8 (2 x ArCH), 118.3 (5-CH_2=), 129.2 (2 x ArCH), 130.5 (ArC), 133.0 (4-CH=), 159.1 (ArC) and 206.6 (C=O); *m/z* [APcI] 291 ($[M+H]^+$, 15), 273 (45), 241 (25), 153 (10), 121 (80). Found $[M+NH_4]^+$, 308.2220. $C_{18}H_{30}NO_3$ requires *M*, 308.2220.

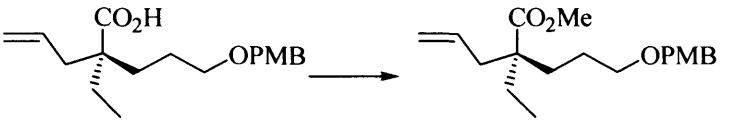
***(-)-(2S)-N-{2-Ethyl-2-[3-(4-methoxy-benzyloxy)-propyl]-pent-4-enylidene}-4-methyl-phenylsulfonamide* 570**



569 **570**

A suspension of tellurium powder (0.22 g, 1.74 mmol) and chloramine-T (0.54 g, 1.91 mmol) in toluene (5 mL) was heated at reflux for 1 h, at which time the suspension become gray. The aldehyde **569** (0.50 g, 1.74 mmol) in toluene (2 mL) was added and heating continued for 48 h. Dichloromethane (5 mL) was added and the mixture filtered through celite. Removal of solvent *in vacuo* gave the *N-tosylimine* **570** as a yellow oil (0.77g, 100%), which was suitable for further use; $[\alpha]_D$ –3.7° (c 1, $CHCl_3$); R_f 0.22 (10% ethyl acetate in petroleum ether); ν_{max}/cm^{-1} [film] 2938 (m), 2855 (w), 1614 (m), 1513 (m), 1453 (w), 1325 (m), 1303 (w), 1247 (m), 1160 (s), 1091 (m), 1034 (w), 916 (w), 775 (w) and 676 (m); δ_H 0.68 (3H, t, *J* 7.5, CH_3), 1.33-1.39 (2H, m, CH_2), 1.46-1.54 (4H, m, 2 x CH_2), 2.21 (2H, d, *J* 7.5, 3'-CH_2), 3.29 (2H, t, *J* 6.3, CH_2O), 3.74 (3H, s, OCH_3), 4.31 (2H, s, OCH_2Ar), 4.95 (2H, dd, *J* 17.4, 12.0, 5'-CH_{2b}), 5.52 (1H, ddt, *J* 17.4, 12.0, 7.5, 4-H), 6.81 (2H, dd, *J* 8.6, 1.8, 2 x ArH), 7.18 (2H, dd, *J* 8.6, 1.8, 2 x ArH), 7.25 (2H, d, *J* 8.2, 2 x ArH), 7.72 (2H, d, *J* 8.2, 2 x ArH) and 8.33 (1H, s, CHN); δ_C 7.2 (CH_3), 21.6 (Ar-CH_3), 27.6, 28.8, 30.3, 35.4 (4 x CH_2), 39.0 (2-C), 55.3 (OCH_3), 64.4, 65.7 (2 x OCH_2), 113.7 (2 x ArCH), 118.2 (5'-CH_2=), 127.1 (2 x ArCH), 127.7 (ArC), 129.3 (2 x ArCH), 129.9 (4'-CH=), 134.3 (2 x ArCH), 138.9, 143.2, 159.1 (3 x ArC) and 185.6 (CHN); *m/z* [APcI] 444 ($[M+H]^+$, 30), 324 (25), 273 (25), 153 (100), 121 (85). Found $[M+H]^+$, 444.2202. $C_{25}H_{34}NO_4S$ requires *M*, 444.2203.

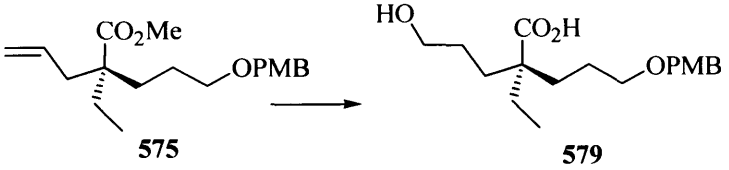
***(+)-(2S)-Methyl 2-ethyl-2-[3'-(4-methoxy-benzyloxy)-propyl]-pent-4-enolate* 575**



567 **575**

To a stirred solution of the acid **567** (100 mg, 0.33 mmol) in acetone (1 mL) was added potassium carbonate (68 mg, 0.5 mmol) followed by methyl iodide (0.03 mL), added dropwise at room temperature. The mixture was allowed to stir at 60°C for 16 h. After cooling the mixture to room temperature, it was evaporated to dryness. The residue was diluted with ether (2 mL), washed with water and dried. Evaporation of the solvent gave the *ester* **575** as a colourless oil (100 mg, 100%); $[\alpha]_D$ +4.0° (c 1, $CHCl_3$); ν_{max}/cm^{-1} [film] 2957 (s), 2856 (s), 1730 (s), 1614 (m), 1513 (s), 1462 (m), 1428 (m), 1360 (w), 1302 (w), 1247 (s), 1113 (s), 1036 (m), 821 (s), 743 (m) and 703 (s); δ_H 0.71 (3H, t, *J* 7.5, CH_3), 1.42-1.54 (6H, m, 3 x CH_2), 2.26 (2H, d, *J* 7.4, 3-CH_2), 3.33 (2H, t, *J* 6.5, CH_2O), 3.57 (3H, s, OCH_3), 3.72 (3H, s, Ar-OCH_3), 4.34 (2H, s, OCH_2Ar), 4.95-5.03 (2H, m, 5-CH_2), 5.76 (1H, ddt, *J* 15.0, 10.1, 7.5, 4-H), 6.80 (2H, dd, *J* 8.6, 2 x ArH) and 7.16-7.19 (2H, m, 2 x ArH); δ_C 8.5 (CH_3), 24.4, 27.5, 30.7, 38.0 (4 x CH_2), 49.4 (2-C), 51.6, 55.3 (2 x OCH_3), 70.3, 72.5 (2 x OCH_2), 113.7 (2 x ArCH), 117.9 (5-CH_2=), 129.6 (2 x ArCH), 130.6 (ArC), 133.8 (4-CH=), 135.3 (ArC) and 177.1 (C=O); *m/z* [APcI] 321 ($[M+H]^+$, 15%), 279 (5), 149 (5), 121 (100). Found $[M+H]^+$, 321.2058. $C_{19}H_{28}O_4$ requires *M*, 321.2060.

***(+)-(2R)-2-Ethyl-2-(3'-hydroxy-propyl)-5-(4-methoxy-benzyloxy)-pentanoic acid* 579**



575 **579**

To a solution of cyclohexene (0.10 mL, 0.94 mmol) in tetrahydrofuran (1 mL) was added borane-methyl sulphide complex (0.05 mL, 0.47 mmol) at 0°C with stirring. After 1 h, the ester **575** (100 mg, 0.31 mmol) in tetrahydrofuran (1 mL) was added to the mixture at 0°C and stirring was continued for 1 h at room temperature. The mixture was then treated with ethanol (0.2 mL), followed by 3N aqueous sodium hydroxide (0.1 mL) and 35% aqueous hydrogen peroxide (0.2 mL, 1.72 mmol) at 0°C. The mixture was then warmed to 50°C for 1 h. Cold water (1 mL) was then added and the mixture extracted with ether (2 x 1 mL). The combined

extracts were washed with brine (2 mL), dried and evaporated to leave a colourless oil. The oil was dissolved in aqueous methanol ($MeOH/H_2O$, 10:1, 0.5 mL) and the solution refluxed with sodium hydroxide (0.05 g) for 1 h. After evaporation of the solvent, the residue was extracted with water (0.5 mL) and the aqueous extract washed with ether, acidified with acetic acid and extracted with dichloromethane (2 x 0.3 mL). The organic extracts were washed with brine, dried and evaporated to give the crude *hydroxy-acid* **579** as a yellow oil (100 mg, 94%); $[\alpha]_D$ +13.5° (c 1, $CHCl_3$); ν_{max}/cm^{-1} [film] 3399 (b), 2933 (s), 2856 (s), 1698 (s), 1613 (m), 1586 (w), 1514 (s), 1454 (m), 1362 (w), 1302 (m), 1248 (s), 1174 (m), 1092 (m), 1065 (m), 1036 (m), 968 (w), 821 (m), 744 (w) and 705 (m); δ_H 0.74 (3H, t, *J* 7.4, CH_3), 1.17-1.20 (2H, m, CH_2), 1.44-1.55 (4H, m, 4 x CH_2), 1.64-1.66 (2H, m, CH_2), 1.81-1.85 (2H, m, CH_2), 3.36 (2H, t, *J* 6.5, 5-CH_2O), 3.51-3.57 (2H, m, 3'-CH_2O), 3.72 (3H, s, OCH_3), 4.34 (2H, s, OCH_2Ar), 6.80 (2H, d, *J* 8.6, 2 x ArH) and 7.18 (2H, d, *J* 8.6, 2 x ArH); δ_C 8.3 (CH_3), 24.2, 25.4, 27.1, 29.9, 35.3 (5 x CH_2), 48.6 (2-C), 55.3 (OCH_3), 62.9, 70.3, 72.5 (3 x OCH_2), 113.8, 129.3 (4 x ArCH), 130.4, 159.1 (2 x ArC) and 176.9 (C=O); *m/z* [APcI] 307 ($[M-OH]^+$, 15%), 191 (15), 121 (100).

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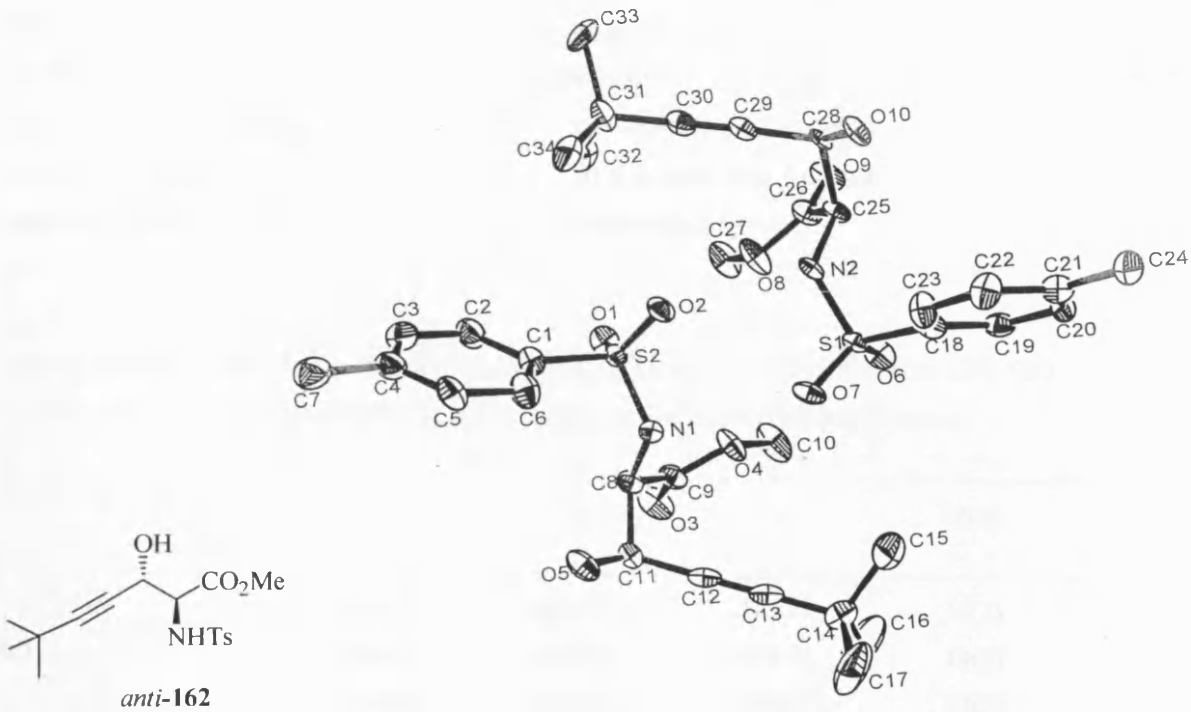
APPENDICES

X-RAY CRYSTAL DATA



anti-**162**

Appendix 7.1: Methyl (2SR,3SR)-3-hydroxy-6,6-dimethyl-2-(4-methylphenylsulfonylamino)-hept-4-ynoate **162**

Table 1. Crystal data and structure refinement for 01DWK04.

Identification code	01DWK04	
Empirical formula	C17 H23 N O5 S	
Formula weight	353.42	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 21.5587(9) Å	α= 90°.
	b = 6.7392(2) Å	β= 90.020(10)°.
	c = 25.2084(11) Å	γ = 90°.
Volume	3662.5(2) $Å^3$	
Z	8	
Density (calculated)	1.282 Mg/m^3	
Absorption coefficient	0.202 mm^{-1}	
F(000)	1504	
Crystal size	? x ? x ? mm^3	
Theta range for data collection	2.95 to 27.55°.	
Index ranges	-27<=h<=27, -8<=k<=8, -32<=l<=32	
Reflections collected	21764	
Independent reflections	6151 [R(int) = 0.0694]	
Completeness to theta = 27.55°	72.8 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	6151 / 0 / 443
Goodness-of-fit on F^2	1.004
Final R indices [I>2sigma(I)]	R1 = 0.0988, wR2 = 0.2659
R indices (all data)	R1 = 0.1614, wR2 = 0.2914
Largest diff. peak and hole	0.628 and -0.589 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for 01DWK04. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	1703(1)	4864(2)	743(1)	19(1)
S(2)	3283(1)	5021(2)	-448(1)	19(1)
O(1)	3335(2)	7088(7)	-614(2)	31(1)
O(2)	2688(2)	4105(7)	-458(2)	27(1)
O(3)	4173(2)	9490(7)	575(3)	40(2)
O(4)	3235(2)	8040(7)	661(2)	32(1)
O(5)	4744(2)	3303(7)	529(2)	34(1)
O(6)	1669(2)	6836(6)	946(2)	28(1)
O(7)	2285(2)	3801(7)	777(2)	30(1)
O(8)	1857(2)	8205(7)	-272(2)	38(2)
O(9)	888(2)	9474(7)	-337(2)	32(1)
O(10)	359(2)	3329(6)	-370(2)	25(1)
N(1)	3539(2)	4753(7)	157(2)	17(1)
N(2)	1515(2)	4746(8)	116(3)	22(1)
C(1)	3785(3)	3636(10)	-845(3)	25(2)
C(2)	4012(3)	4441(12)	-1319(4)	35(2)
C(3)	4399(3)	3269(12)	-1637(3)	37(2)
C(4)	4554(3)	1327(11)	-1494(4)	35(2)
C(5)	4317(3)	541(12)	-1026(4)	38(2)
C(6)	3928(3)	1704(11)	-691(4)	38(2)
C(7)	5003(4)	102(12)	-1829(4)	44(2)
C(8)	4051(3)	6048(10)	320(3)	22(2)
C(9)	3825(3)	8063(11)	519(3)	26(2)
C(10)	3003(3)	9851(11)	887(4)	46(3)
C(11)	4471(3)	5050(11)	730(3)	27(2)
C(12)	4134(3)	4734(10)	1231(3)	26(2)
C(13)	3848(3)	4622(10)	1652(3)	27(2)
C(14)	3506(3)	4533(11)	2152(3)	31(2)
C(15)	2806(4)	4427(16)	2055(4)	67(3)

C(16)	3615(6)	6477(15)	2460(4)	81(4)
C(17)	3690(5)	2739(15)	2474(4)	77(3)
C(18)	1107(3)	3468(10)	1048(3)	25(2)
C(19)	704(3)	4423(10)	1396(3)	24(2)
C(20)	220(3)	3290(11)	1617(3)	27(2)
C(21)	123(3)	1307(10)	1468(3)	28(2)
C(22)	542(3)	413(11)	1121(3)	33(2)
C(23)	1031(3)	1471(10)	910(3)	30(2)
C(24)	-411(3)	130(12)	1687(4)	41(2)
C(25)	1017(3)	6071(9)	-66(3)	20(2)
C(26)	1240(3)	8116(10)	-237(3)	26(2)
C(27)	2117(3)	10093(10)	-438(4)	41(2)
C(28)	647(3)	5103(9)	-531(3)	14(1)
C(29)	1057(3)	4871(10)	-996(3)	22(2)
C(30)	1410(3)	4731(10)	-1357(3)	27(2)
C(31)	1841(3)	4666(11)	-1812(4)	32(2)
C(32)	2268(4)	6465(13)	-1764(4)	50(2)
C(33)	1477(4)	4664(13)	-2332(3)	47(2)
C(34)	2260(4)	2826(13)	-1749(4)	49(2)

Table 3. Bond lengths [Å] and angles [°] for 01DWK04.

S(1)-O(6)	1.426(5)
S(1)-O(7)	1.448(4)
S(1)-N(2)	1.634(6)
S(1)-C(18)	1.769(7)
S(2)-O(2)	1.424(4)
S(2)-O(1)	1.459(5)
S(2)-N(1)	1.630(6)
S(2)-C(1)	1.745(7)
O(3)-C(9)	1.228(8)
O(4)-C(9)	1.322(8)
O(4)-C(10)	1.437(8)
O(5)-C(11)	1.411(8)
O(8)-C(26)	1.334(8)
O(8)-C(27)	1.452(8)
O(9)-C(26)	1.215(8)
O(10)-C(28)	1.408(7)
N(1)-C(8)	1.467(8)
N(2)-C(25)	1.470(8)
C(1)-C(6)	1.393(10)
C(1)-C(2)	1.401(11)
C(2)-C(3)	1.402(11)
C(3)-C(4)	1.398(10)
C(4)-C(5)	1.391(11)
C(4)-C(7)	1.527(11)
C(5)-C(6)	1.424(11)
C(8)-C(9)	1.527(10)
C(8)-C(11)	1.528(10)
C(11)-C(12)	1.474(11)
C(12)-C(13)	1.230(11)
C(13)-C(14)	1.460(11)
C(14)-C(17)	1.509(11)
C(14)-C(15)	1.531(11)
C(14)-C(16)	1.542(11)
C(18)-C(19)	1.393(10)
C(18)-C(23)	1.400(9)
C(19)-C(20)	1.407(9)
C(20)-C(21)	1.404(10)
C(21)-C(22)	1.394(10)
C(21)-C(24)	1.503(10)
C(22)-C(23)	1.379(10)
C(25)-C(26)	1.522(9)
C(25)-C(28)	1.560(9)
C(28)-C(29)	1.476(10)
C(29)-C(30)	1.191(10)
C(30)-C(31)	1.476(11)
C(31)-C(32)	1.527(10)
C(31)-C(33)	1.529(11)
C(31)-C(34)	1.541(10)
O(6)-S(1)-O(7)	119.0(3)
O(6)-S(1)-N(2)	112.3(3)
O(7)-S(1)-N(2)	104.3(3)
O(6)-S(1)-C(18)	107.6(3)
O(7)-S(1)-C(18)	110.0(3)
N(2)-S(1)-C(18)	102.4(3)
O(2)-S(2)-O(1)	118.5(3)
O(2)-S(2)-N(1)	105.8(3)
O(1)-S(2)-N(1)	110.4(3)
O(2)-S(2)-C(1)	108.4(3)
O(1)-S(2)-C(1)	107.4(3)
N(1)-S(2)-C(1)	105.5(3)
C(9)-O(4)-C(10)	115.6(5)
C(26)-O(8)-C(27)	116.3(5)
C(8)-N(1)-S(2)	116.8(4)
C(25)-N(2)-S(1)	116.9(5)
C(6)-C(1)-C(2)	121.5(7)
C(6)-C(1)-S(2)	118.5(6)
C(2)-C(1)-S(2)	119.9(5)
C(1)-C(2)-C(3)	118.5(7)
C(4)-C(3)-C(2)	121.5(8)
C(5)-C(4)-C(3)	119.2(8)
C(5)-C(4)-C(7)	119.7(7)
C(3)-C(4)-C(7)	121.0(8)
C(4)-C(5)-C(6)	120.6(7)
C(1)-C(6)-C(5)	118.7(8)
N(1)-C(8)-C(9)	112.4(5)
N(1)-C(8)-C(11)	111.9(5)

C(9)-C(8)-C(11)	111.0(6)	C(22)-C(21)-C(24)	119.9(7)
O(3)-C(9)-O(4)	124.5(7)	C(20)-C(21)-C(24)	121.2(7)
O(3)-C(9)-C(8)	122.6(6)	C(23)-C(22)-C(21)	121.0(7)
O(4)-C(9)-C(8)	112.7(6)	C(22)-C(23)-C(18)	119.3(7)
O(5)-C(11)-C(12)	113.2(6)	N(2)-C(25)-C(26)	114.0(5)
O(5)-C(11)-C(8)	111.8(6)	N(2)-C(25)-C(28)	110.6(5)
C(12)-C(11)-C(8)	110.6(5)	C(26)-C(25)-C(28)	109.1(6)
C(13)-C(12)-C(11)	175.2(7)	O(9)-C(26)-O(8)	125.0(6)
C(12)-C(13)-C(14)	178.8(8)	O(9)-C(26)-C(25)	122.9(6)
C(13)-C(14)-C(17)	111.4(7)	O(8)-C(26)-C(25)	112.0(6)
C(13)-C(14)-C(15)	111.2(7)	O(10)-C(28)-C(29)	113.8(5)
C(17)-C(14)-C(15)	107.9(8)	O(10)-C(28)-C(25)	111.3(5)
C(13)-C(14)-C(16)	108.9(7)	C(29)-C(28)-C(25)	109.6(5)
C(17)-C(14)-C(16)	111.7(8)	C(30)-C(29)-C(28)	176.7(7)
C(15)-C(14)-C(16)	105.6(7)	C(29)-C(30)-C(31)	177.0(8)
C(19)-C(18)-C(23)	121.9(7)	C(30)-C(31)-C(32)	107.2(7)
C(19)-C(18)-S(1)	118.8(5)	C(30)-C(31)-C(33)	110.1(6)
C(23)-C(18)-S(1)	119.2(6)	C(32)-C(31)-C(33)	112.2(7)
C(18)-C(19)-C(20)	117.4(6)	C(30)-C(31)-C(34)	108.2(7)
C(21)-C(20)-C(19)	121.5(7)	C(32)-C(31)-C(34)	106.1(6)
C(22)-C(21)-C(20)	118.8(7)	C(33)-C(31)-C(34)	112.9(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for 01DWK04. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

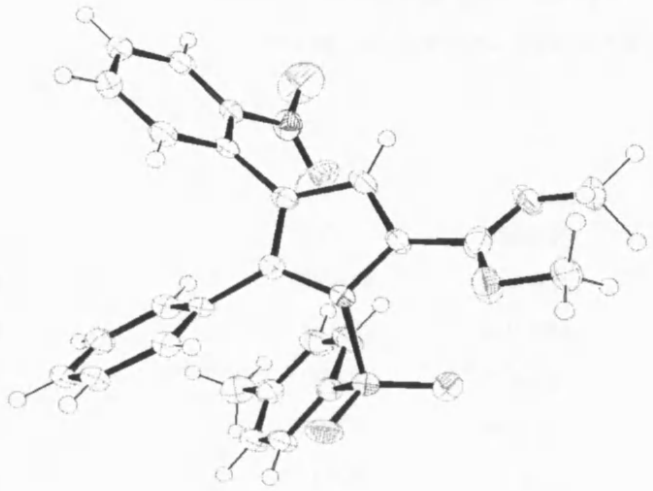
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	14(1)	16(1)	27(1)	-3(1)	-5(1)	1(1)
S(2)	16(1)	17(1)	23(1)	-1(1)	2(1)	-1(1)
O(1)	33(3)	18(3)	41(4)	3(2)	2(2)	4(2)
O(2)	14(2)	31(3)	36(4)	-3(2)	-1(2)	-5(2)
O(3)	30(3)	21(3)	71(5)	0(3)	-2(3)	-9(2)
O(4)	14(3)	18(3)	64(4)	-13(3)	2(2)	-2(2)
O(5)	23(3)	19(3)	59(4)	0(3)	0(2)	7(2)
O(6)	28(3)	12(3)	44(4)	-5(2)	1(2)	0(2)
O(7)	20(3)	28(3)	40(4)	-1(2)	-11(2)	10(2)
O(8)	19(3)	16(3)	77(5)	6(3)	7(3)	-1(2)
O(9)	25(3)	13(3)	56(4)	3(2)	-10(2)	0(2)
O(10)	15(2)	18(3)	42(4)	-1(2)	1(2)	-1(2)
N(1)	20(3)	10(3)	22(3)	2(2)	-5(2)	-4(2)
N(2)	11(3)	21(3)	34(4)	2(3)	-4(2)	3(2)
C(1)	24(4)	12(4)	38(5)	-2(3)	5(3)	0(3)
C(2)	24(4)	36(5)	45(6)	7(4)	3(4)	3(4)
C(3)	38(5)	38(5)	35(6)	3(4)	-1(4)	-9(4)
C(4)	30(4)	31(5)	44(6)	-1(4)	-7(4)	10(4)
C(5)	27(4)	32(5)	55(7)	4(4)	10(4)	9(4)
C(6)	36(5)	26(5)	51(6)	-1(4)	7(4)	5(4)
C(7)	47(5)	42(5)	42(6)	-11(4)	-6(4)	3(4)
C(8)	12(3)	25(4)	29(5)	2(3)	0(3)	-7(3)
C(9)	22(4)	24(5)	33(5)	3(3)	-3(3)	-3(3)
C(10)	32(5)	21(5)	84(8)	-23(4)	9(4)	12(4)
C(11)	18(4)	32(5)	31(5)	0(4)	1(3)	1(3)
C(12)	28(4)	18(4)	34(5)	1(3)	-15(4)	3(3)
C(13)	27(4)	23(4)	32(5)	1(3)	-15(3)	0(3)
C(14)	37(4)	32(5)	24(5)	0(3)	-2(3)	1(4)
C(15)	52(6)	107(9)	43(7)	-16(6)	5(5)	-1(6)
C(16)	147(10)	57(7)	39(7)	-21(5)	19(7)	-30(7)
C(17)	119(9)	69(8)	43(8)	28(6)	24(6)	13(7)
C(18)	19(4)	22(4)	33(5)	-3(3)	-6(3)	-1(3)
C(19)	27(4)	20(4)	25(5)	-6(3)	-7(3)	1(3)
C(20)	20(4)	38(5)	21(5)	0(3)	0(3)	9(3)
C(21)	30(4)	22(4)	31(5)	2(3)	-4(3)	-3(3)

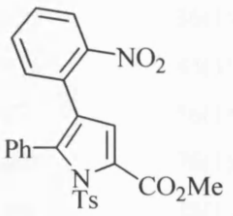
C(22)	42(5)	22(4)	33(5)	-8(3)	8(4)	-6(4)
C(23)	30(4)	22(5)	38(6)	-9(3)	11(4)	1(3)
C(24)	34(4)	55(6)	36(6)	0(4)	4(4)	-9(4)
C(25)	16(3)	7(4)	35(5)	-2(3)	-5(3)	3(3)
C(26)	22(4)	16(4)	41(5)	0(3)	-1(3)	1(3)
C(27)	24(4)	18(4)	80(8)	14(4)	5(4)	-7(3)
C(28)	5(3)	7(3)	30(4)	2(3)	0(3)	-2(3)
C(29)	16(4)	16(4)	33(5)	-1(3)	-3(3)	-1(3)
C(30)	25(4)	16(4)	41(6)	-3(3)	-10(3)	6(3)
C(31)	18(4)	33(5)	45(6)	3(4)	4(3)	2(3)
C(32)	48(5)	56(6)	46(7)	14(5)	8(4)	-12(5)
C(33)	60(6)	60(6)	23(5)	-3(4)	3(4)	4(5)
C(34)	50(5)	63(6)	33(6)	-6(5)	12(4)	10(5)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 01DWK04.

	x	y	z	U(eq)
H(2)	3907	5725	-1421	42
H(3)	4557	3796	-1950	45
H(5)	4413	-756	-930	45
H(6)	3772	1183	-377	45
H(7A)	5387	-59	-1639	66
H(7B)	5080	773	-2158	66
H(7C)	4825	-1177	-1899	66
H(8)	4305	6296	4	26
H(10A)	3220	10128	1211	69
H(10B)	2568	9714	959	69
H(10C)	3066	10922	642	69
H(11)	4809	5978	806	33
H(15A)	2681	5521	1836	101
H(15B)	2592	4491	2388	101
H(15C)	2707	3202	1880	101
H(16A)	4048	6605	2543	121
H(16B)	3378	6454	2783	121
H(16C)	3486	7583	2247	121
H(17A)	3622	1559	2268	115

H(17B)	3444	2686	2791	115
H(17C)	4121	2831	2567	115
H(19)	752	5758	1480	29
H(20)	-40	3866	1867	32
H(22)	492	-916	1031	39
H(23)	1307	864	677	36
H(24A)	-278	-1205	1756	62
H(24B)	-743	115	1433	62
H(24C)	-552	729	2010	62
H(25)	729	6254	231	23
H(27A)	1927	10502	-764	61
H(27B)	2556	9951	-490	61
H(27C)	2041	11073	-169	61
H(28)	318	6032	-631	17
H(32A)	2029	7657	-1805	75
H(32B)	2579	6407	-2036	75
H(32C)	2464	6461	-1422	75
H(33A)	1214	3515	-2345	71
H(33B)	1760	4636	-2625	71
H(33C)	1227	5841	-2352	71
H(34A)	2454	2851	-1406	73
H(34B)	2573	2836	-2019	73
H(34C)	2013	1646	-1782	73





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Appendices 7.2: Methyl 4-(2'-nitrophenyl)-5-phenyl-1-(4'-methylphenylsulfonyl)-pyrrole-2- carboxylate **281**

Table 1. Crystal data and structure refinement for 01DWK01.

Identification code	01DWK01	
Empirical formula	C25 H20 N2 O6 S	
Formula weight	476.49	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 8.7396(13) Å	α= 90°.
	b = 22.831(5) Å	β= 95.407(14)°.
	c = 11.115(2) Å	γ = 90°.
Volume	2207.9(7) $Å^3$	
Z	4	
Density (calculated)	1.433 Mg/m^3	
Absorption coefficient	0.193 mm^{-1}	
F(000)	992	
Crystal size	0.45 x 0.20 x 0.20 mm^3	
Theta range for data collection	2.34 to 25.34°.	
Index ranges	-10<=h<=0, -27<=k<=9, -13<=l<=13	
Reflections collected	4330	
Independent reflections	3989 [R(int) = 0.0357]	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3989 / 0 / 317	
Goodness-of-fit on F^2	1.071	
Final R indices [I>2sigma(I)]	R1 = 0.0462, wR2 = 0.1317	
R indices (all data)	R1 = 0.0591, wR2 = 0.1376	
Largest diff. peak and hole	0.429 and -0.677 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 01DWK01. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	1397(1)	4006(1)	2561(1)	29(1)
O(1)	2559(2)	4443(1)	2661(2)	36(1)
O(2)	511(2)	3917(1)	1440(2)	43(1)
O(3)	-1500(3)	2706(1)	5342(2)	56(1)
O(4)	-3089(3)	2427(1)	6554(2)	76(1)
O(5)	-1818(2)	4746(1)	1668(2)	38(1)
O(6)	-3671(2)	4093(1)	1895(2)	41(1)
N(1)	100(2)	4175(1)	3577(2)	24(1)
N(2)	-2138(2)	2771(1)	6251(2)	34(1)
C(1)	-1491(2)	4080(1)	3293(2)	24(1)
C(2)	-2101(2)	3909(1)	4309(2)	26(1)
C(3)	-905(2)	3884(1)	5274(2)	23(1)
C(4)	436(2)	4046(1)	4819(2)	24(1)
C(5)	2155(2)	3337(1)	3130(2)	27(1)
C(6)	1160(3)	2889(1)	3388(2)	34(1)
C(7)	1757(3)	2385(1)	3923(2)	38(1)
C(8)	3342(3)	2317(1)	4210(2)	33(1)
C(9)	3956(3)	1776(1)	4856(3)	45(1)
C(10)	4300(3)	2764(1)	3894(2)	35(1)
C(11)	3734(2)	3277(1)	3366(2)	31(1)
C(12)	1985(2)	4082(1)	5464(2)	24(1)
C(13)	2579(2)	3603(1)	6136(2)	29(1)
C(14)	4003(3)	3643(1)	6785(2)	33(1)
C(15)	4826(2)	4160(1)	6800(2)	33(1)
C(16)	4240(2)	4637(1)	6147(2)	31(1)
C(17)	2833(2)	4598(1)	5463(2)	27(1)
C(18)	-1097(2)	3780(1)	6566(2)	22(1)
C(19)	-675(2)	4222(1)	7403(2)	27(1)
C(20)	-910(3)	4166(1)	8609(2)	32(1)
C(21)	-1606(2)	3673(1)	9023(2)	31(1)
C(22)	-2028(2)	3225(1)	8221(2)	29(1)
C(23)	-1758(2)	3281(1)	7024(2)	24(1)
C(24)	-2388(3)	4300(1)	2189(2)	34(1)
C(25)	-2871(4)	5015(2)	729(3)	36(1)
C(26)	-4491(9)	4488(4)	1043(7)	36(2)

Table 3. Bond lengths [Å] and angles [°] for 01DWK01.

S(1)-O(2)	1.4181(18)	O(2)-S(1)-O(1)	119.74(11)
S(1)-O(1)	1.4207(17)	O(2)-S(1)-N(1)	105.72(9)
S(1)-N(1)	1.7177(18)	O(1)-S(1)-N(1)	107.61(9)
S(1)-C(5)	1.7594(23)	O(2)-S(1)-C(5)	110.33(11)
O(3)-N(2)	1.2089(27)	O(1)-S(1)-C(5)	109.84(10)
O(4)-N(2)	1.2126(27)	N(1)-S(1)-C(5)	101.99(10)
O(5)-C(24)	1.2937(30)	C(24)-O(5)-C(25)	114.1(2)
O(5)-C(25)	1.4596(36)	C(24)-O(6)-C(26)	108.4(4)
O(6)-C(24)	1.2325(29)	C(1)-N(1)-C(4)	107.19(16)
O(6)-C(26)	1.4489(79)	C(1)-N(1)-S(1)	121.00(14)
N(1)-C(1)	1.4130(26)	C(4)-N(1)-S(1)	120.39(14)
N(1)-C(4)	1.4148(27)	O(3)-N(2)-O(4)	122.4(2)
N(2)-C(23)	1.4668(28)	O(3)-N(2)-C(23)	119.28(19)
C(1)-C(2)	1.3508(31)	O(4)-N(2)-C(23)	118.3(2)
C(1)-C(24)	1.4802(31)	C(2)-C(1)-N(1)	108.32(18)
C(2)-C(3)	1.4263(30)	C(2)-C(1)-C(24)	124.9(2)
C(3)-C(4)	1.3695(29)	N(1)-C(1)-C(24)	124.51(19)
C(3)-C(18)	1.4800(29)	C(1)-C(2)-C(3)	108.76(18)
C(4)-C(12)	1.4733(28)	C(4)-C(3)-C(2)	107.64(19)
C(5)-C(11)	1.3864(31)	C(4)-C(3)-C(18)	125.49(19)
C(5)-C(6)	1.3900(32)	C(2)-C(3)-C(18)	126.43(18)
C(6)-C(7)	1.3748(36)	C(3)-C(4)-N(1)	108.08(18)
C(7)-C(8)	1.4003(33)	C(3)-C(4)-C(12)	127.88(19)
C(8)-C(10)	1.3846(33)	N(1)-C(4)-C(12)	124.04(18)
C(8)-C(9)	1.5022(36)	C(11)-C(5)-C(6)	121.3(2)
C(10)-C(11)	1.3808(34)	C(11)-C(5)-S(1)	119.26(17)
C(12)-C(17)	1.3925(30)	C(6)-C(5)-S(1)	119.41(17)
C(12)-C(13)	1.3963(31)	C(7)-C(6)-C(5)	119.0(2)
C(13)-C(14)	1.3820(31)	C(6)-C(7)-C(8)	121.2(2)
C(14)-C(15)	1.3822(34)	C(10)-C(8)-C(7)	118.0(2)
C(15)-C(16)	1.3808(34)	C(10)-C(8)-C(9)	121.9(2)
C(16)-C(17)	1.3867(31)	C(7)-C(8)-C(9)	120.1(2)
C(18)-C(23)	1.3955(30)	C(11)-C(10)-C(8)	122.0(2)
C(18)-C(19)	1.3984(30)	C(10)-C(11)-C(5)	118.4(2)
C(19)-C(20)	1.3810(33)	C(17)-C(12)-C(13)	119.50(19)
C(20)-C(21)	1.3789(34)	C(17)-C(12)-C(4)	120.77(19)
C(21)-C(22)	1.3835(33)		
C(22)-C(23)	1.3786(31)		
C(25)-C(26)	1.9147(89)		

C(13)-C(12)-C(4)	119.65(19)	C(20)-C(21)-C(22)	119.2(2)
C(14)-C(13)-C(12)	119.9(2)	C(23)-C(22)-C(21)	119.6(2)
C(13)-C(14)-C(15)	120.3(2)	C(22)-C(23)-C(18)	122.8(2)
C(16)-C(15)-C(14)	120.1(2)	C(22)-C(23)-N(2)	116.23(19)
C(15)-C(16)-C(17)	120.2(2)	C(18)-C(23)-N(2)	120.86(19)
C(16)-C(17)-C(12)	119.9(2)	O(6)-C(24)-O(5)	124.2(2)
C(23)-C(18)-C(19)	115.98(19)	O(6)-C(24)-C(1)	119.1(2)
C(23)-C(18)-C(3)	125.07(19)	O(5)-C(24)-C(1)	116.2(2)
C(19)-C(18)-C(3)	118.84(19)	O(5)-C(25)-C(26)	91.9(3)
C(20)-C(19)-C(18)	121.7(2)	O(6)-C(26)-C(25)	100.4(4)
C(21)-C(20)-C(19)	120.7(2)		

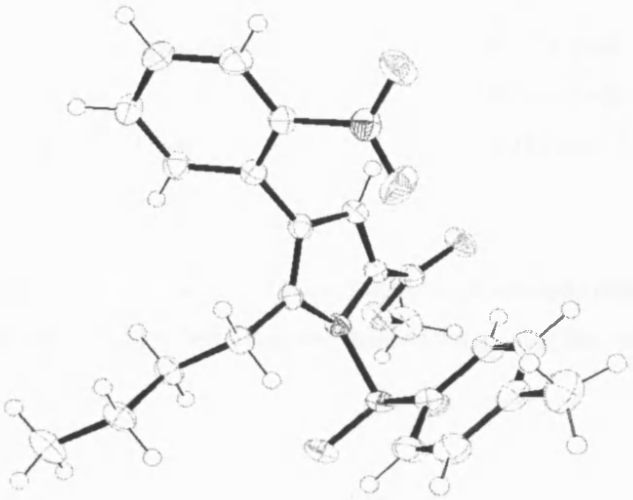
Symmetry transformations used to generate equivalent atoms:

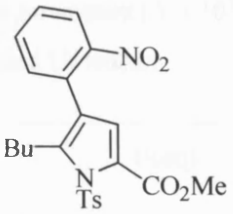
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for 01DWK01. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	21(1)	41(1)	25(1)	-1(1)	5(1)	-2(1)
O(1)	27(1)	43(1)	40(1)	7(1)	12(1)	-6(1)
O(2)	32(1)	69(1)	28(1)	-4(1)	3(1)	5(1)
O(3)	88(2)	40(1)	45(1)	-15(1)	29(1)	-16(1)
O(4)	94(2)	63(1)	76(2)	-15(1)	30(1)	-53(1)
O(5)	34(1)	42(1)	36(1)	9(1)	-9(1)	-7(1)
O(6)	19(1)	64(1)	38(1)	10(1)	-5(1)	-6(1)
N(1)	16(1)	34(1)	24(1)	-1(1)	2(1)	-3(1)
N(2)	38(1)	30(1)	34(1)	0(1)	0(1)	-7(1)
C(1)	16(1)	29(1)	27(1)	-4(1)	-2(1)	-1(1)
C(2)	15(1)	30(1)	33(1)	-2(1)	0(1)	-3(1)
C(3)	19(1)	24(1)	27(1)	-1(1)	3(1)	-1(1)
C(4)	21(1)	26(1)	25(1)	-1(1)	2(1)	-2(1)
C(5)	22(1)	34(1)	27(1)	-8(1)	5(1)	-2(1)
C(6)	19(1)	40(1)	44(1)	-7(1)	4(1)	-6(1)
C(7)	29(1)	36(1)	50(2)	-7(1)	10(1)	-9(1)
C(8)	29(1)	38(1)	33(1)	-8(1)	7(1)	1(1)
C(9)	45(2)	45(2)	46(2)	-2(1)	12(1)	2(1)
C(10)	20(1)	45(1)	39(1)	-7(1)	6(1)	1(1)
C(11)	18(1)	40(1)	35(1)	-5(1)	7(1)	-4(1)
C(12)	15(1)	34(1)	23(1)	-2(1)	5(1)	0(1)
C(13)	23(1)	34(1)	30(1)	0(1)	4(1)	-1(1)
C(14)	24(1)	43(1)	30(1)	3(1)	3(1)	7(1)
C(15)	15(1)	56(2)	28(1)	-3(1)	2(1)	0(1)
C(16)	20(1)	41(1)	32(1)	-3(1)	5(1)	-6(1)
C(17)	22(1)	33(1)	26(1)	1(1)	4(1)	0(1)
C(18)	12(1)	30(1)	25(1)	1(1)	1(1)	2(1)
C(19)	21(1)	31(1)	31(1)	-2(1)	2(1)	-3(1)
C(20)	24(1)	42(1)	29(1)	-8(1)	0(1)	-1(1)
C(21)	21(1)	49(1)	24(1)	2(1)	2(1)	3(1)
C(22)	17(1)	37(1)	33(1)	7(1)	2(1)	0(1)
C(23)	16(1)	30(1)	27(1)	1(1)	-1(1)	1(1)
C(24)	34(1)	42(1)	24(1)	-6(1)	-2(1)	11(1)
C(25)	28(2)	45(2)	34(2)	9(2)	-2(1)	10(2)
C(26)	28(4)	52(5)	24(4)	5(3)	-7(3)	-3(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 01DWK01.

	x	y	z	U(eq)
H(2)	-3152	3820	4371	31
H(6)	83	2930	3199	41
H(7)	1083	2077	4100	45
H(9A)	4890	1647	4510	68
H(9B)	3181	1465	4763	68
H(9C)	4198	1864	5716	68
H(10)	5381	2715	4046	42
H(11)	4409	3581	3169	37
H(13)	2004	3250	6146	34
H(14)	4419	3313	7223	39
H(15)	5796	4187	7260	40
H(16)	4803	4994	6167	37
H(17)	2447	4923	4994	32
H(19)	-215	4569	7135	33
H(20)	-588	4470	9159	38
H(21)	-1795	3642	9848	38
H(22)	-2500	2881	8494	35
H(25A)	-2284	5364	464	50
H(25B)	-3105	4736	97	50
H(25C)	-3817	5204	1006	50
H(26A)	-4154	4413	94	50
H(26B)	-5647	4281	827	50
H(26C)	-4364	4897	1116	50





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Appendix 7.3: Methyl 4-(2-nitro-phenyl)-5-butyl-1-(4-methylphenylsulfonyl)-pyrrole-2-carboxylate **282**

Table 1. Crystal data and structure refinement for 01DWK03.

Identification code	01DWK03	
Empirical formula	C23 H24 N2 O6 S	
Formula weight	456.50	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	?	
Space group	?	
Unit cell dimensions	a = 10.5251(2) Å	α= 90°.
	b = 18.4199(3) Å	β= 94.724(9)°.
	c = 11.5026(2) Å	γ = 90°.
Volume	2222.45(7) $Å^3$	
Z	4	
Density (calculated)	1.364 Mg/m^3	
Absorption coefficient	0.188 mm^{-1}	
F(000)	960	
Crystal size	0.25 x 0.20 x 0.20 mm^3	
Theta range for data collection	5.87 to 27.41°.	
Index ranges	-13<=h<=12, -23<=k<=23, -14<=l<=14	
Reflections collected	16184	
Independent reflections	4835 [R(int) = 0.0274]	
Completeness to theta = 27.41°	95.4 %	
Absorption correction	None	
Max. and min. transmission	0.9633 and 0.9545	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4835 / 0 / 292	

Goodness-of-fit on F^2	1.041
Final R indices [I>2sigma(I)]	R1 = 0.0364, wR2 = 0.0929
R indices (all data)	R1 = 0.0408, wR2 = 0.0961
Largest diff. peak and hole	0.288 and -0.299 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for 01DWK03. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	1950(1)	4485(1)	3444(1)	23(1)
O(1)	2814(1)	3887(1)	3534(1)	30(1)
O(2)	651(1)	4385(1)	3676(1)	32(1)
O(3)	4736(1)	3911(1)	1064(1)	36(1)
O(4)	2794(1)	3431(1)	1243(1)	30(1)
O(5)	4504(1)	7542(1)	737(1)	43(1)
O(6)	3688(1)	6797(1)	1916(1)	52(1)
N(1)	1934(1)	4789(1)	2052(1)	22(1)
N(2)	3668(1)	7123(1)	984(1)	30(1)
C(1)	3007(1)	4684(1)	1406(1)	22(1)
C(2)	3119(1)	5269(1)	706(1)	23(1)
C(3)	2102(1)	5758(1)	893(1)	22(1)
C(4)	1399(1)	5475(1)	1728(1)	22(1)
C(5)	3633(1)	3975(1)	1253(1)	24(1)
C(6)	3295(2)	2708(1)	1100(2)	41(1)
C(7)	1783(1)	6411(1)	175(1)	23(1)
C(8)	2553(1)	7028(1)	141(1)	24(1)
C(9)	2294(1)	7585(1)	-653(1)	30(1)
C(10)	1227(1)	7539(1)	-1437(1)	33(1)
C(11)	417(1)	6947(1)	-1406(1)	32(1)
C(12)	699(1)	6391(1)	-614(1)	27(1)
C(13)	284(1)	5810(1)	2254(1)	25(1)
C(14)	-1018(1)	5475(1)	1887(1)	28(1)
C(15)	-2068(1)	5857(1)	2497(1)	30(1)
C(16)	-3397(1)	5568(1)	2147(2)	40(1)
C(17)	2596(1)	5214(1)	4284(1)	24(1)
C(18)	3825(1)	5448(1)	4131(1)	29(1)
C(19)	4321(1)	6023(1)	4799(1)	33(1)
C(20)	3617(1)	6364(1)	5614(1)	31(1)
C(21)	2396(2)	6113(1)	5757(1)	35(1)

C(22)	1874(1)	5541(1)	5095(1)	31(1)
C(23)	4170(2)	6999(1)	6310(2)	44(1)

Table 3. Bond lengths [Å] and angles [°] for 01DWK03.

S(1)-O(2)	1.4262(10)
S(1)-O(1)	1.4269(10)
S(1)-N(1)	1.6952(10)
S(1)-C(17)	1.7577(13)
O(3)-C(5)	1.2040(16)
O(4)-C(5)	1.3351(15)
O(4)-C(6)	1.4460(16)
O(5)-N(2)	1.2221(15)
O(6)-N(2)	1.2271(16)
N(1)-C(1)	1.4163(15)
N(1)-C(4)	1.4200(15)
N(2)-C(8)	1.4703(17)
C(1)-C(2)	1.3573(17)
C(1)-C(5)	1.4792(17)
C(2)-C(3)	1.4284(17)
C(3)-C(4)	1.3638(17)
C(3)-C(7)	1.4811(16)
C(4)-C(13)	1.4969(16)
C(7)-C(8)	1.3982(17)
C(7)-C(12)	1.3986(18)
C(8)-C(9)	1.3862(18)
C(9)-C(10)	1.383(2)
C(10)-C(11)	1.387(2)
C(11)-C(12)	1.3869(19)
C(13)-C(14)	1.5303(18)
C(14)-C(15)	1.5278(17)
C(15)-C(16)	1.520(2)
C(17)-C(22)	1.3884(18)
C(17)-C(18)	1.3889(18)
C(18)-C(19)	1.3849(19)
C(19)-C(20)	1.393(2)
C(20)-C(21)	1.388(2)
C(20)-C(23)	1.507(2)
C(21)-C(22)	1.386(2)

O(2)-S(1)-O(1)	120.08(6)
O(2)-S(1)-N(1)	106.53(6)
O(1)-S(1)-N(1)	106.30(5)
O(2)-S(1)-C(17)	109.25(6)
O(1)-S(1)-C(17)	109.50(6)
N(1)-S(1)-C(17)	103.90(5)
C(5)-O(4)-C(6)	116.45(10)
C(1)-N(1)-C(4)	107.51(9)
C(1)-N(1)-S(1)	120.26(8)
C(4)-N(1)-S(1)	120.98(8)
O(5)-N(2)-O(6)	123.50(12)
O(5)-N(2)-C(8)	118.18(11)
O(6)-N(2)-C(8)	118.26(11)
C(2)-C(1)-N(1)	108.28(10)
C(2)-C(1)-C(5)	124.75(11)
N(1)-C(1)-C(5)	124.50(10)
C(1)-C(2)-C(3)	108.02(11)
C(4)-C(3)-C(2)	108.78(10)
C(4)-C(3)-C(7)	126.27(11)
C(2)-C(3)-C(7)	124.48(11)
C(3)-C(4)-N(1)	107.38(10)
C(3)-C(4)-C(13)	128.03(11)
N(1)-C(4)-C(13)	124.58(10)
O(3)-C(5)-O(4)	124.90(11)
O(3)-C(5)-C(1)	123.54(11)
O(4)-C(5)-C(1)	111.28(10)
C(8)-C(7)-C(12)	116.51(11)
C(8)-C(7)-C(3)	124.76(11)
C(12)-C(7)-C(3)	118.42(11)
C(9)-C(8)-C(7)	122.54(12)
C(9)-C(8)-N(2)	116.73(11)
C(7)-C(8)-N(2)	120.71(11)
C(10)-C(9)-C(8)	119.27(12)
C(9)-C(10)-C(11)	119.96(12)
C(10)-C(11)-C(12)	119.93(13)
C(11)-C(12)-C(7)	121.74(12)
C(4)-C(13)-C(14)	115.87(10)
C(15)-C(14)-C(13)	110.66(10)
C(16)-C(15)-C(14)	113.70(11)
C(22)-C(17)-C(18)	121.15(12)
C(22)-C(17)-S(1)	119.50(10)

C(18)-C(17)-S(1)	119.34(10)
C(19)-C(18)-C(17)	118.67(12)
C(18)-C(19)-C(20)	121.42(13)
C(21)-C(20)-C(19)	118.63(12)
C(21)-C(20)-C(23)	121.10(13)
C(19)-C(20)-C(23)	120.26(14)
C(22)-C(21)-C(20)	121.09(13)
C(21)-C(22)-C(17)	119.04(13)

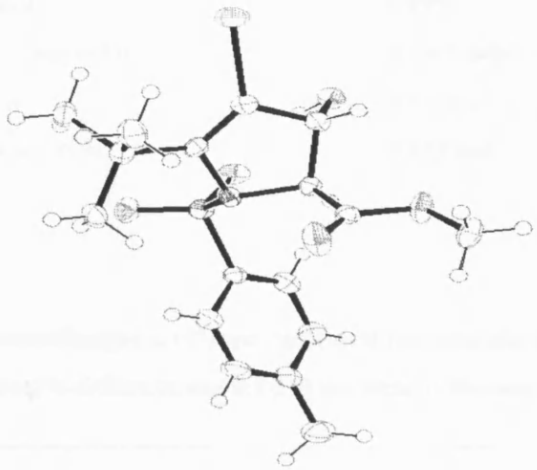
Symmetry transformations used to generate equivalent atoms:

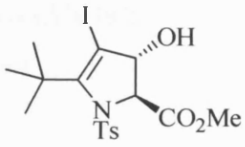
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for 01DWK03. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	24(1)	21(1)	25(1)	2(1)	7(1)	-2(1)
O(1)	36(1)	24(1)	32(1)	5(1)	6(1)	4(1)
O(2)	28(1)	33(1)	36(1)	-1(1)	13(1)	-8(1)
O(3)	25(1)	29(1)	56(1)	2(1)	12(1)	5(1)
O(4)	28(1)	23(1)	42(1)	-7(1)	7(1)	-2(1)
O(5)	33(1)	50(1)	46(1)	-6(1)	3(1)	-15(1)
O(6)	63(1)	46(1)	42(1)	12(1)	-25(1)	-19(1)
N(1)	20(1)	21(1)	24(1)	0(1)	5(1)	1(1)
N(2)	31(1)	27(1)	33(1)	-4(1)	-3(1)	-2(1)
C(1)	18(1)	24(1)	24(1)	-1(1)	3(1)	0(1)
C(2)	21(1)	24(1)	25(1)	0(1)	4(1)	-1(1)
C(3)	21(1)	21(1)	24(1)	-1(1)	-1(1)	-1(1)
C(4)	20(1)	21(1)	25(1)	-2(1)	1(1)	1(1)
C(5)	24(1)	24(1)	25(1)	0(1)	3(1)	1(1)
C(6)	43(1)	22(1)	59(1)	-10(1)	6(1)	-1(1)
C(7)	23(1)	22(1)	23(1)	-1(1)	3(1)	2(1)
C(8)	25(1)	24(1)	24(1)	-3(1)	0(1)	0(1)
C(9)	34(1)	24(1)	32(1)	2(1)	3(1)	-3(1)
C(10)	39(1)	28(1)	31(1)	7(1)	0(1)	4(1)
C(11)	30(1)	32(1)	31(1)	2(1)	-5(1)	3(1)
C(12)	25(1)	25(1)	31(1)	0(1)	-2(1)	-1(1)
C(13)	24(1)	23(1)	29(1)	-4(1)	4(1)	3(1)
C(14)	23(1)	29(1)	33(1)	-7(1)	6(1)	2(1)
C(15)	27(1)	29(1)	37(1)	-5(1)	11(1)	1(1)
C(16)	26(1)	42(1)	54(1)	-11(1)	15(1)	-1(1)
C(17)	26(1)	23(1)	22(1)	2(1)	4(1)	-1(1)
C(18)	26(1)	31(1)	31(1)	-2(1)	7(1)	-2(1)
C(19)	29(1)	33(1)	36(1)	0(1)	2(1)	-6(1)
C(20)	39(1)	26(1)	26(1)	2(1)	-4(1)	1(1)
C(21)	40(1)	37(1)	28(1)	-5(1)	8(1)	3(1)
C(22)	30(1)	36(1)	28(1)	-1(1)	9(1)	-3(1)
C(23)	53(1)	37(1)	42(1)	-10(1)	-7(1)	-2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 01DWK03.

	x	y	z	U(eq)
H(2)	3760	5341	183	28
H(6A)	3553	2652	306	62
H(6B)	2636	2349	1236	62
H(6C)	4035	2632	1662	62
H(9)	2843	7994	-660	36
H(10)	1049	7913	-1995	39
H(11)	-331	6923	-1926	38
H(12)	142	5985	-608	33
H(13A)	253	6332	2047	30
H(13B)	432	5777	3114	30
H(14A)	-1197	5519	1031	33
H(14B)	-1007	4953	2089	33
H(15A)	-1888	5801	3351	36
H(15B)	-2046	6382	2316	36
H(16A)	-3622	5670	1320	60
H(16B)	-4012	5804	2619	60
H(16C)	-3413	5042	2278	60
H(18)	4316	5219	3579	35
H(19)	5160	6189	4698	39
H(21)	1909	6337	6318	41
H(22)	1036	5375	5195	37
H(23A)	5101	6990	6318	66
H(23B)	3923	6968	7112	66
H(23C)	3845	7453	5954	66





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Appendix 7.4: Methyl (2SR,3RS)-5-t-butyl-3-hydroxy-4-iodo-1-(4'-methylphenylsulfonyl)-2,3-dihydro-pyrrole-2-carboxylate **296**

Table 1. Crystal data and structure refinement for 02DWK8

Identification code	02DWK8	
Empirical formula	C17 H22 I N O5 S	
Formula weight	479.32	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 9.4745(2) Å	α= 90°.
	b = 24.9490(5) Å	β= 115.2031(7)°.
	c = 9.0708(3) Å	γ = 90°.
Volume	1940.03(9) $Å^3$	
Z	4	
Density (calculated)	1.641 Mg/m^3	
Absorption coefficient	1.784 mm^{-1}	
F(000)	960	
Crystal size	0.25 x 0.25 x 0.22 mm^3	
Theta range for data collection	2.97 to 27.48°.	
Index ranges	-12<=h<=12, -32<=k<=31, -11<=l<=10	
Reflections collected	14793	
Independent reflections	4417 [R(int) = 0.0957]	
Completeness to theta = 27.48°	99.4 %	
Absorption correction	None	
Max. and min. transmission	0.6949 and 0.6640	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4417 / 1 / 235	

Goodness-of-fit on F^2	0.972
Final R indices [I>2sigma(I)]	R1 = 0.0409, wR2 = 0.0783
R indices (all data)	R1 = 0.0711, wR2 = 0.0866
Largest diff. peak and hole	0.673 and -1.256 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for 02DWK8. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
I(1)	3687(1)	4872(1)	-2748(1)	36(1)
S(1)	2889(1)	3937(1)	2094(1)	24(1)
O(1)	4323(3)	3644(1)	2723(3)	32(1)
O(2)	2969(3)	4498(1)	2507(3)	29(1)
O(3)	1647(3)	5164(1)	-399(3)	27(1)
O(4)	-575(3)	3485(1)	-2549(3)	43(1)
O(5)	-1887(3)	4241(1)	-2659(3)	32(1)
N(1)	2032(3)	3847(1)	46(3)	20(1)
C(1)	1506(4)	3627(1)	2612(4)	21(1)
C(2)	652(5)	3926(1)	3239(4)	28(1)
C(3)	-463(5)	3670(1)	3601(4)	31(1)
C(4)	-714(4)	3120(1)	3374(4)	28(1)
C(5)	164(5)	2835(1)	2759(4)	32(1)
C(6)	1267(5)	3076(1)	2374(4)	30(1)
C(7)	-1962(5)	2842(2)	3729(4)	41(1)
C(8)	3033(4)	3955(1)	-793(4)	21(1)
C(9)	2657(4)	4434(1)	-1507(4)	24(1)
C(10)	1293(4)	4693(1)	-1357(4)	23(1)
C(11)	686(4)	4217(1)	-702(4)	20(1)
C(12)	-635(4)	3923(1)	-2065(4)	21(1)
C(13)	-3253(4)	4022(1)	-3997(4)	32(1)
C(14)	4094(4)	3511(1)	-931(4)	26(1)
C(15)	3884(5)	2978(1)	-213(4)	32(1)
C(16)	3599(5)	3406(2)	-2765(4)	34(1)
C(17)	5810(4)	3682(1)	-111(4)	32(1)

Table 3. Bond lengths [Å] and angles [°] for 02DWK8.

I(1)-C(9)	2.086(3)
S(1)-O(1)	1.431(3)
S(1)-O(2)	1.442(2)
S(1)-N(1)	1.696(2)
S(1)-C(1)	1.750(3)
O(3)-C(10)	1.414(4)
O(4)-C(12)	1.188(4)
O(5)-C(12)	1.336(4)
O(5)-C(13)	1.452(4)
N(1)-C(8)	1.472(4)
N(1)-C(11)	1.484(4)
C(1)-C(2)	1.387(5)
C(1)-C(6)	1.395(4)
C(2)-C(3)	1.389(5)
C(3)-C(4)	1.392(5)
C(4)-C(5)	1.380(5)
C(4)-C(7)	1.519(5)
C(5)-C(6)	1.374(5)
C(8)-C(9)	1.334(4)
C(8)-C(14)	1.535(5)
C(9)-C(10)	1.502(5)
C(10)-C(11)	1.544(4)
C(11)-C(12)	1.521(4)
C(14)-C(15)	1.531(4)
C(14)-C(17)	1.532(5)
C(14)-C(16)	1.547(4)
O(1)-S(1)-O(2)	117.20(16)
O(1)-S(1)-N(1)	107.41(14)
O(2)-S(1)-N(1)	111.14(13)
O(1)-S(1)-C(1)	111.04(15)
O(2)-S(1)-C(1)	108.80(16)
N(1)-S(1)-C(1)	99.88(15)
C(12)-O(5)-C(13)	115.8(3)
C(8)-N(1)-C(11)	105.5(2)
C(8)-N(1)-S(1)	115.4(2)
C(11)-N(1)-S(1)	109.63(19)
C(2)-C(1)-C(6)	120.6(3)
C(2)-C(1)-S(1)	120.4(3)
C(6)-C(1)-S(1)	119.0(3)
C(1)-C(2)-C(3)	119.0(3)
C(2)-C(3)-C(4)	121.1(4)
C(5)-C(4)-C(3)	118.3(4)
C(5)-C(4)-C(7)	120.5(3)
C(3)-C(4)-C(7)	121.2(4)
C(6)-C(5)-C(4)	122.2(3)
C(5)-C(6)-C(1)	118.8(4)
C(9)-C(8)-N(1)	108.4(3)
C(9)-C(8)-C(14)	131.0(3)
N(1)-C(8)-C(14)	120.0(3)
C(8)-C(9)-C(10)	113.9(3)
C(8)-C(9)-I(1)	129.9(3)
C(10)-C(9)-I(1)	116.2(2)
O(3)-C(10)-C(9)	115.2(3)
O(3)-C(10)-C(11)	115.6(3)
C(9)-C(10)-C(11)	100.3(2)
N(1)-C(11)-C(12)	108.7(2)
N(1)-C(11)-C(10)	105.4(3)
C(12)-C(11)-C(10)	111.7(2)
O(4)-C(12)-O(5)	124.9(3)
O(4)-C(12)-C(11)	126.3(3)
O(5)-C(12)-C(11)	108.9(3)
C(15)-C(14)-C(17)	109.8(3)
C(15)-C(14)-C(8)	112.5(3)
C(17)-C(14)-C(8)	110.9(3)
C(15)-C(14)-C(16)	106.0(3)
C(17)-C(14)-C(16)	110.0(3)
C(8)-C(14)-C(16)	107.5(3)

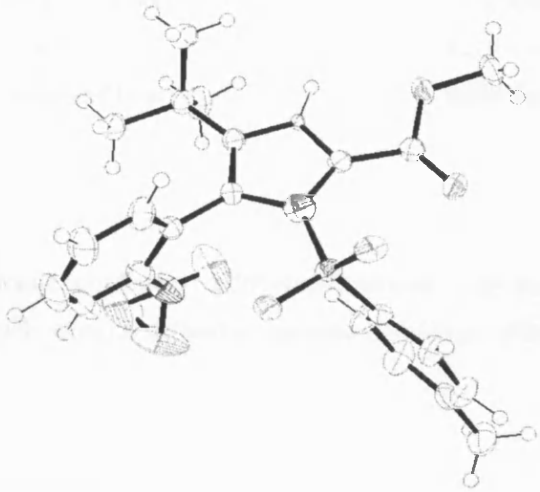
Symmetry transformations used to generate equivalent atoms:

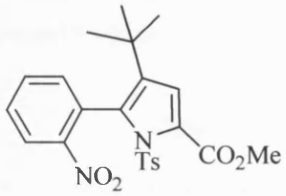
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for 02DWK8. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
I(1)	45(1)	27(1)	47(1)	4(1)	30(1)	-1(1)
S(1)	22(1)	26(1)	19(1)	0(1)	3(1)	-4(1)
O(1)	22(2)	42(2)	24(1)	2(1)	2(1)	3(1)
O(2)	34(2)	27(1)	22(1)	-8(1)	8(1)	-11(1)
O(3)	30(2)	17(1)	34(2)	-6(1)	13(1)	-1(1)
O(4)	33(2)	26(1)	48(2)	-11(1)	-4(1)	4(1)
O(5)	20(2)	35(1)	30(1)	-11(1)	-1(1)	6(1)
N(1)	17(2)	20(1)	17(1)	-1(1)	2(1)	0(1)
C(1)	20(2)	23(2)	17(2)	4(1)	4(2)	-3(1)
C(2)	34(3)	24(2)	22(2)	0(2)	8(2)	0(2)
C(3)	33(3)	33(2)	29(2)	0(2)	15(2)	1(2)
C(4)	25(2)	31(2)	17(2)	6(2)	-1(2)	-2(2)
C(5)	38(3)	19(2)	37(2)	0(2)	12(2)	-6(2)
C(6)	32(3)	24(2)	36(2)	4(2)	16(2)	2(2)
C(7)	39(3)	46(2)	35(2)	9(2)	12(2)	-8(2)
C(8)	13(2)	24(2)	20(2)	-2(1)	2(2)	-4(1)
C(9)	26(2)	23(2)	24(2)	-3(2)	13(2)	-2(2)
C(10)	22(2)	19(2)	22(2)	-2(1)	4(2)	-2(2)
C(11)	18(2)	22(2)	17(2)	0(1)	6(2)	0(1)
C(12)	23(2)	22(2)	18(2)	4(2)	8(2)	0(2)
C(13)	18(2)	47(2)	23(2)	-8(2)	0(2)	0(2)
C(14)	22(2)	23(2)	29(2)	-5(2)	9(2)	-1(2)
C(15)	31(3)	19(2)	42(2)	-1(2)	13(2)	4(2)
C(16)	36(3)	29(2)	34(2)	-5(2)	12(2)	5(2)
C(17)	22(2)	29(2)	44(2)	1(2)	11(2)	4(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 02DWK8.

	x	y	z	U(eq)
H(3A)	2250(50)	5073(14)	708(15)	57(14)
H(2)	828	4300	3417	34
H(3)	-1065	3873	4011	37
H(5)	-1	2460	2596	39
H(6)	1858	2871	1953	36
H(7A)	-1745	2457	3864	62
H(7B)	-2986	2902	2820	62
H(7C)	-1962	2989	4731	62
H(10)	491	4783	-2475	28
H(11)	338	4344	136	24
H(13A)	-3020	3964	-4939	49
H(13B)	-4124	4274	-4292	49
H(13C)	-3536	3680	-3663	49
H(15A)	4343	3004	978	47
H(15B)	4406	2692	-534	47
H(15C)	2770	2896	-624	47
H(16A)	4257	3124	-2895	51
H(16B)	3720	3736	-3287	51
H(16C)	2505	3292	-3276	51
H(17A)	6107	3756	1044	48
H(17B)	5956	4006	-642	48
H(17C)	6465	3393	-211	48





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Appendix 7.5: Methyl 4-tert-butyl-5-(2'-nitrophenyl)-1-(4'-methylphenylsulfonyl)-pyrrole-2-carboxylate **305**

Table 1. Crystal data and structure refinement for 02DWK03.

Identification code	02DWK03	
Empirical formula	C23 H24 N2 O6 S	
Formula weight	456.50	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 11.8359(4) Å	α= 90°.
	b = 13.5348(5) Å	β= 102.043(2)°.
	c = 14.5414(5) Å	γ = 90°.
Volume	2278.21(14) $Å^3$	
Z	4	
Density (calculated)	1.331 Mg/m^3	
Absorption coefficient	0.184 mm^{-1}	
F(000)	960	
Crystal size	0.28 x 0.20 x 0.18 mm^3	
Theta range for data collection	3.01 to 27.49°.	
Index ranges	-15<=h<=15, -17<=k<=17, -18<=l<=18	
Reflections collected	14148	
Independent reflections	5180 [R(int) = 0.0629]	
Completeness to theta = 27.49°	99.2 %	
Max. and min. transmission	0.9677 and 0.9504	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5180 / 0 / 303	
Goodness-of-fit on F^2	0.969	

Final R indices [I>2sigma(I)]	R1 = 0.0602, wR2 = 0.1591
R indices (all data)	R1 = 0.1009, wR2 = 0.1773
Largest diff. peak and hole	0.646 and -0.588 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for 02DWK03. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	1117(1)	3476(1)	3192(1)	25(1)
O(1)	-118(2)	3459(1)	3033(1)	34(1)
O(2)	1755(2)	3179(1)	4113(1)	34(1)
O(3)	-18(2)	4126(1)	1044(1)	36(1)
O(4)	-12(2)	2913(2)	-15(1)	38(1)
O(5)	4459(2)	2822(2)	3003(2)	92(1)
O(6)	5792(4)	2261(5)	4056(4)	89(2)
O(6')	5372(7)	3014(7)	4293(5)	87(3)
N(1)	1603(2)	2711(2)	2390(2)	40(1)
N(2)	4725(2)	2445(2)	3726(2)	51(1)
C(1)	1567(2)	4690(2)	3014(2)	25(1)
C(2)	2605(2)	4876(2)	2756(2)	41(1)
C(3)	2991(2)	5830(2)	2748(2)	48(1)
C(4)	2380(2)	6615(2)	3026(2)	34(1)
C(5)	1334(3)	6407(2)	3255(2)	40(1)
C(6)	920(2)	5462(2)	3248(2)	35(1)
C(7)	2806(3)	7669(2)	3030(3)	55(1)
C(8)	1213(2)	2731(2)	1417(2)	24(1)
C(9)	342(2)	3355(2)	817(2)	27(1)
C(10)	-903(3)	3417(3)	-693(2)	46(1)
C(11)	1732(2)	1971(2)	1065(1)	12(1)
C(12)	2441(2)	1450(2)	1759(2)	24(1)
C(13)	2374(2)	1891(2)	2610(2)	24(1)
C(14)	2872(2)	1530(2)	3576(2)	27(1)
C(15)	3943(2)	1785(2)	4110(2)	35(1)
C(16)	4365(3)	1433(3)	5008(2)	50(1)
C(17)	3669(3)	818(3)	5411(2)	58(1)
C(18)	2597(3)	545(3)	4908(2)	50(1)
C(19)	2211(3)	891(2)	4001(2)	37(1)
C(20)	3114(2)	575(2)	1491(2)	28(1)

C(21)	3933(2)	954(2)	869(2)	42(1)
C(22)	2263(3)	-178(2)	939(2)	41(1)
C(23)	3835(2)	58(2)	2347(2)	33(1)

Table 3. Bond lengths [Å] and angles [°] for 02DWK03.

S(1)-O(1)	1.4321(18)
S(1)-O(2)	1.4494(18)
S(1)-N(1)	1.744(2)
S(1)-C(1)	1.763(3)
O(3)-C(9)	1.199(3)
O(4)-C(9)	1.336(3)
O(4)-C(10)	1.455(3)
O(5)-N(2)	1.152(3)
O(6)-O(6')	1.215(9)
O(6)-N(2)	1.278(5)
O(6')-N(2)	1.263(7)
N(1)-C(8)	1.394(3)
N(1)-C(13)	1.431(3)
N(2)-C(15)	1.477(4)
C(1)-C(6)	1.379(4)
C(1)-C(2)	1.380(4)
C(2)-C(3)	1.370(4)
C(2)-H(2)	0.9500
C(3)-C(4)	1.392(4)
C(3)-H(3)	0.9500
C(4)-C(5)	1.377(4)
C(4)-C(7)	1.513(4)
C(5)-C(6)	1.368(4)
C(5)-H(5)	0.9500
C(6)-H(6)	0.9500
C(7)-H(7A)	0.9800
C(7)-H(7B)	0.9800
C(7)-H(7C)	0.9800
C(8)-C(11)	1.352(3)
C(8)-C(9)	1.471(4)
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-C(12)	1.366(3)
C(11)-H(11)	0.9500
C(12)-C(13)	1.392(3)
C(12)-C(20)	1.523(3)
C(13)-C(14)	1.487(3)
C(14)-C(15)	1.385(4)
C(14)-C(19)	1.395(4)
C(15)-C(16)	1.382(4)
C(16)-C(17)	1.384(5)
C(16)-H(16)	0.9500
C(17)-C(18)	1.377(5)
C(17)-H(17)	0.9500
C(18)-C(19)	1.383(4)
C(18)-H(18)	0.9500
C(19)-H(19)	0.9500
C(20)-C(23)	1.524(4)
C(20)-C(22)	1.536(4)
C(20)-C(21)	1.545(4)
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
O(1)-S(1)-O(2)	117.52(11)
O(1)-S(1)-N(1)	110.48(11)
O(2)-S(1)-N(1)	105.82(12)
O(1)-S(1)-C(1)	108.72(11)
O(2)-S(1)-C(1)	106.19(12)
N(1)-S(1)-C(1)	107.64(11)
C(9)-O(4)-C(10)	116.7(2)
O(6')-O(6)-N(2)	60.8(4)
O(6)-O(6')-N(2)	62.1(5)
C(8)-N(1)-C(13)	107.6(2)
C(8)-N(1)-S(1)	125.59(19)
C(13)-N(1)-S(1)	126.50(18)
O(5)-N(2)-O(6')	109.8(5)
O(5)-N(2)-O(6)	119.3(4)
O(6')-N(2)-O(6)	57.1(4)
O(5)-N(2)-C(15)	122.7(3)

O(6')-N(2)-C(15)	117.6(4)	C(12)-C(11)-H(11)	124.1
O(6)-N(2)-C(15)	112.9(3)	C(11)-C(12)-C(13)	107.1(2)
C(6)-C(1)-C(2)	120.0(3)	C(11)-C(12)-C(20)	119.1(2)
C(6)-C(1)-S(1)	118.00(19)	C(13)-C(12)-C(20)	133.7(2)
C(2)-C(1)-S(1)	121.5(2)	C(12)-C(13)-N(1)	106.6(2)
C(3)-C(2)-C(1)	119.4(3)	C(12)-C(13)-C(14)	127.9(2)
C(3)-C(2)-H(2)	120.3	N(1)-C(13)-C(14)	125.1(2)
C(1)-C(2)-H(2)	120.3	C(15)-C(14)-C(19)	116.0(2)
C(2)-C(3)-C(4)	121.5(3)	C(15)-C(14)-C(13)	125.7(2)
C(2)-C(3)-H(3)	119.3	C(19)-C(14)-C(13)	118.3(2)
C(4)-C(3)-H(3)	119.3	C(16)-C(15)-C(14)	123.5(3)
C(5)-C(4)-C(3)	117.5(3)	C(16)-C(15)-N(2)	115.8(3)
C(5)-C(4)-C(7)	120.5(3)	C(14)-C(15)-N(2)	120.7(2)
C(3)-C(4)-C(7)	121.9(3)	C(15)-C(16)-C(17)	118.5(3)
C(6)-C(5)-C(4)	121.9(3)	C(15)-C(16)-H(16)	120.7
C(6)-C(5)-H(5)	119.1	C(17)-C(16)-H(16)	120.7
C(4)-C(5)-H(5)	119.1	C(18)-C(17)-C(16)	120.0(3)
C(5)-C(6)-C(1)	119.5(3)	C(18)-C(17)-H(17)	120.0
C(5)-C(6)-H(6)	120.2	C(16)-C(17)-H(17)	120.0
C(1)-C(6)-H(6)	120.2	C(17)-C(18)-C(19)	120.0(3)
C(4)-C(7)-H(7A)	109.5	C(17)-C(18)-H(18)	120.0
C(4)-C(7)-H(7B)	109.5	C(19)-C(18)-H(18)	120.0
H(7A)-C(7)-H(7B)	109.5	C(18)-C(19)-C(14)	121.9(3)
C(4)-C(7)-H(7C)	109.5	C(18)-C(19)-H(19)	119.0
H(7A)-C(7)-H(7C)	109.5	C(14)-C(19)-H(19)	119.0
H(7B)-C(7)-H(7C)	109.5	C(12)-C(20)-C(23)	112.4(2)
C(11)-C(8)-N(1)	106.8(2)	C(12)-C(20)-C(22)	109.2(2)
C(11)-C(8)-C(9)	122.0(2)	C(23)-C(20)-C(22)	108.5(2)
N(1)-C(8)-C(9)	131.0(2)	C(12)-C(20)-C(21)	108.5(2)
O(3)-C(9)-O(4)	125.2(2)	C(23)-C(20)-C(21)	108.5(2)
O(3)-C(9)-C(8)	125.6(2)	C(22)-C(20)-C(21)	109.7(2)
O(4)-C(9)-C(8)	109.2(2)	C(20)-C(21)-H(21A)	109.5
O(4)-C(10)-H(10A)	109.5	C(20)-C(21)-H(21B)	109.5
O(4)-C(10)-H(10B)	109.5	H(21A)-C(21)-H(21B)	109.5
H(10A)-C(10)-H(10B)	109.5	C(20)-C(21)-H(21C)	109.5
O(4)-C(10)-H(10C)	109.5	H(21A)-C(21)-H(21C)	109.5
H(10A)-C(10)-H(10C)	109.5	H(21B)-C(21)-H(21C)	109.5
H(10B)-C(10)-H(10C)	109.5	C(20)-C(22)-H(22A)	109.5
C(8)-C(11)-C(12)	111.8(2)	C(20)-C(22)-H(22B)	109.5
C(8)-C(11)-H(11)	124.1	H(22A)-C(22)-H(22B)	109.5

C(20)-C(22)-H(22C)	109.5	H(23A)-C(23)-H(23B)	109.5
H(22A)-C(22)-H(22C)	109.5	C(20)-C(23)-H(23C)	109.5
H(22B)-C(22)-H(22C)	109.5	H(23A)-C(23)-H(23C)	109.5
C(20)-C(23)-H(23A)	109.5	H(23B)-C(23)-H(23C)	109.5
C(20)-C(23)-H(23B)	109.5		

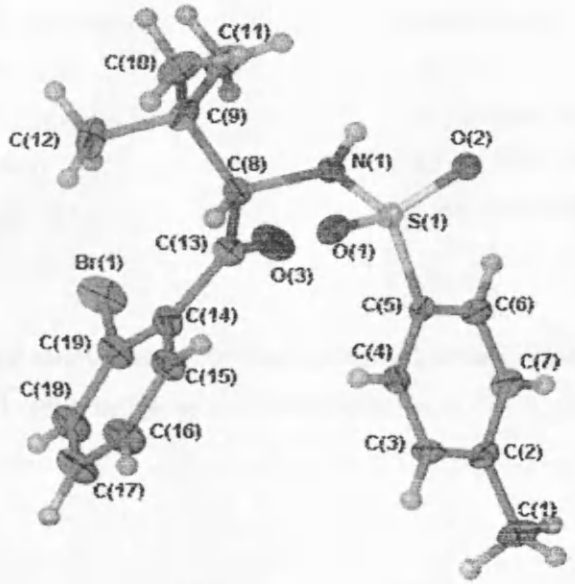
Symmetry transformations used to generate equivalent atoms:

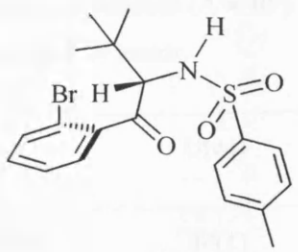
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for 02DWK03. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	31(1)	26(1)	21(1)	-1(1)	10(1)	-1(1)
O(1)	29(1)	35(1)	40(1)	-5(1)	15(1)	-4(1)
O(2)	50(1)	34(1)	18(1)	2(1)	9(1)	0(1)
O(3)	45(1)	31(1)	32(1)	-1(1)	5(1)	13(1)
O(4)	47(1)	42(1)	21(1)	-2(1)	-3(1)	20(1)
O(5)	52(2)	111(3)	100(2)	61(2)	-9(2)	-36(2)
O(6)	27(2)	122(5)	107(4)	30(4)	-7(2)	-13(3)
O(6')	66(5)	123(7)	68(5)	-31(5)	8(4)	-66(5)
N(1)	45(1)	41(2)	36(1)	1(1)	13(1)	-2(1)
N(2)	36(2)	68(2)	48(2)	1(2)	3(1)	-19(1)
C(1)	27(1)	26(1)	20(1)	-2(1)	5(1)	1(1)
C(2)	35(2)	31(2)	63(2)	-3(2)	22(2)	3(1)
C(3)	30(2)	36(2)	80(2)	6(2)	16(2)	-3(1)
C(4)	28(1)	31(2)	38(2)	4(1)	-7(1)	-2(1)
C(5)	47(2)	28(2)	48(2)	0(1)	15(2)	11(1)
C(6)	36(2)	31(2)	43(2)	6(1)	16(1)	5(1)
C(7)	43(2)	32(2)	81(3)	3(2)	-8(2)	-7(1)
C(8)	29(1)	24(1)	21(1)	2(1)	7(1)	0(1)
C(9)	30(1)	30(2)	22(1)	2(1)	8(1)	1(1)
C(10)	51(2)	55(2)	27(2)	0(1)	-7(1)	25(2)
C(11)	18(1)	13(1)	6(1)	1(1)	3(1)	5(1)
C(12)	25(1)	25(1)	22(1)	2(1)	6(1)	0(1)
C(13)	22(1)	24(1)	25(1)	3(1)	5(1)	1(1)
C(14)	30(1)	26(1)	24(1)	1(1)	5(1)	3(1)
C(15)	33(1)	40(2)	30(1)	-3(1)	2(1)	1(1)
C(16)	44(2)	70(3)	30(2)	-2(2)	-6(1)	7(2)
C(17)	73(2)	70(3)	30(2)	19(2)	10(2)	17(2)
C(18)	61(2)	51(2)	41(2)	21(2)	16(2)	4(2)
C(19)	38(2)	33(2)	43(2)	13(1)	13(1)	0(1)
C(20)	30(1)	29(2)	27(1)	0(1)	8(1)	6(1)
C(21)	40(2)	46(2)	46(2)	7(2)	19(1)	16(1)
C(22)	44(2)	33(2)	45(2)	-10(1)	3(1)	10(1)
C(23)	35(2)	30(2)	35(2)	3(1)	9(1)	9(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 02DWK03.

	x	y	z	U(eq)
H(2)	3048	4347	2586	49
H(3)	3691	5958	2548	58
H(5)	888	6934	3424	48
H(6)	192	5339	3402	42
H(7A)	2192	8088	2673	82
H(7B)	3482	7696	2740	82
H(7C)	3020	7908	3679	82
H(10A)	-1621	3435	-457	70
H(10B)	-1037	3062	-1293	70
H(10C)	-653	4094	-785	70
H(11)	1617	1819	415	15
H(16)	5116	1609	5341	60
H(17)	3932	584	6035	69
H(18)	2121	120	5183	60
H(19)	1474	688	3659	44
H(21A)	3475	1212	277	63
H(21B)	4421	410	735	63
H(21C)	4422	1482	1200	63
H(22A)	1745	-417	1336	62
H(22B)	2693	-736	753	62
H(22C)	1807	138	376	62
H(23A)	4391	527	2701	50
H(23B)	4250	-498	2140	50
H(23C)	3326	-186	2749	50





457

Appendix 7.6: 1-(2'-Bromobenzoyl)-3,3-dimethyl-2-(4-Methyl-phenylsulfonamino)-butan-1-one **457**

Table 1. Crystal data and structure refinement for dwk0302.

Identification code	dwk0302	
Empirical formula	C19 H22 Br1 N1 O3 S1	
Formula weight	424.35	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.1302(2) Å	α= 103.252(1)°.
	b = 9.4741(3) Å	β= 95.192(1)°.
	c = 12.9808(4) Å	γ = 92.679(1)°.
Volume	966.89(5) $Å^3$	
Z	2	
Density (calculated)	1.458 Mg/m^3	
Absorption coefficient	2.251 mm^{-1}	
F(000)	436	
Crystal size	0.23 x 0.20 x 0.08 mm^3	
Theta range for data collection	3.04 to 27.42°.	
Index ranges	-10<=h<=10, -12<=k<=11, -16<=l<=16	
Reflections collected	15273	
Independent reflections	4347 [R(int) = 0.0748]	
Completeness to theta = 27.42°	98.5 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.835 and 0.673
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4347 / 0 / 230
Goodness-of-fit on F^2	1.023
Final R indices [I>2sigma(I)]	R1 = 0.0526, wR2 = 0.1087
R indices (all data)	R1 = 0.0882, wR2 = 0.1228
Largest diff. peak and hole	0.806 and -0.909 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for dwk0302. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8923(5)	-978(4)	8370(4)	40(1)
C(2)	7524(4)	-7(4)	8628(3)	26(1)
C(3)	5904(4)	-591(4)	8547(3)	27(1)
C(4)	4621(4)	291(4)	8786(3)	24(1)
C(5)	4951(4)	1792(3)	9103(3)	21(1)
C(6)	6558(4)	2395(4)	9171(3)	28(1)
C(7)	7830(4)	1495(4)	8943(3)	31(1)
C(8)	2280(4)	3576(4)	7639(3)	24(1)
C(9)	1201(4)	4797(4)	7397(3)	29(1)
C(10)	-218(5)	4930(5)	8115(3)	40(1)
C(11)	2210(5)	6261(4)	7607(3)	38(1)
C(13)	3498(5)	3114(4)	6815(3)	30(1)
C(12)	467(5)	4381(5)	6231(3)	48(1)
C(14)	3058(5)	1754(4)	5957(3)	31(1)
C(15)	2439(5)	508(4)	6236(3)	33(1)
C(16)	2239(5)	-829(4)	5518(3)	43(1)
C(17)	2630(6)	-945(4)	4494(3)	45(1)
C(18)	3180(5)	269(4)	4177(3)	42(1)
C(19)	3382(5)	1605(4)	4900(3)	36(1)
N(1)	3162(3)	4047(3)	8713(2)	22(1)
O(1)	1855(3)	2060(2)	9348(2)	26(1)
O(2)	3930(3)	3850(2)	10528(2)	24(1)
O(3)	4807(3)	3822(3)	6874(2)	42(1)
S(1)	3371(1)	2945(1)	9493(1)	20(1)
Br(1)	4082(1)	3235(1)	4382(1)	51(1)

Table 3. Bond lengths [Å] and angles [°] for dwk0302.

C(1)-C(2)	1.508(5)
C(2)-C(3)	1.390(5)
C(2)-C(7)	1.391(5)
C(3)-C(4)	1.380(5)
C(4)-C(5)	1.393(5)
C(5)-C(6)	1.388(5)
C(5)-S(1)	1.760(3)
C(6)-C(7)	1.381(5)
C(8)-N(1)	1.470(4)
C(8)-C(13)	1.527(5)
C(8)-C(9)	1.555(5)
C(9)-C(12)	1.530(5)
C(9)-C(11)	1.533(5)
C(9)-C(10)	1.540(5)
C(13)-O(3)	1.218(4)
C(13)-C(14)	1.502(5)
C(14)-C(15)	1.397(5)
C(14)-C(19)	1.397(5)
C(15)-C(16)	1.383(5)
C(16)-C(17)	1.375(6)
C(17)-C(18)	1.377(6)
C(18)-C(19)	1.385(5)
C(19)-Br(1)	1.904(4)
N(1)-S(1)	1.617(3)
O(1)-S(1)	1.431(2)
O(2)-S(1)	1.439(2)
C(3)-C(2)-C(7)	118.6(3)
C(3)-C(2)-C(1)	120.9(3)
C(7)-C(2)-C(1)	120.6(3)
C(4)-C(3)-C(2)	121.1(3)
C(3)-C(4)-C(5)	119.5(3)
C(6)-C(5)-C(4)	120.2(3)
C(6)-C(5)-S(1)	118.9(2)
C(4)-C(5)-S(1)	120.8(3)
C(7)-C(6)-C(5)	119.5(3)
C(6)-C(7)-C(2)	121.1(3)
N(1)-C(8)-C(13)	110.6(3)
N(1)-C(8)-C(9)	109.9(3)
C(13)-C(8)-C(9)	112.7(3)
C(12)-C(9)-C(11)	109.0(3)
C(12)-C(9)-C(10)	109.1(3)
C(11)-C(9)-C(10)	109.6(3)
C(12)-C(9)-C(8)	109.5(3)
C(11)-C(9)-C(8)	111.8(3)
C(10)-C(9)-C(8)	107.9(3)
O(3)-C(13)-C(14)	121.3(3)
O(3)-C(13)-C(8)	120.3(3)
C(14)-C(13)-C(8)	118.4(3)
C(15)-C(14)-C(19)	116.9(3)
C(15)-C(14)-C(13)	118.9(3)
C(19)-C(14)-C(13)	123.9(3)
C(16)-C(15)-C(14)	121.8(4)
C(17)-C(16)-C(15)	119.7(4)
C(16)-C(17)-C(18)	120.2(4)
C(17)-C(18)-C(19)	119.8(4)
C(18)-C(19)-C(14)	121.5(3)
C(18)-C(19)-Br(1)	117.0(3)
C(14)-C(19)-Br(1)	121.5(3)
C(8)-N(1)-S(1)	121.5(2)
O(1)-S(1)-O(2)	119.43(14)
O(1)-S(1)-N(1)	107.31(14)
O(2)-S(1)-N(1)	105.40(14)
O(1)-S(1)-C(5)	107.65(15)
O(2)-S(1)-C(5)	107.49(14)
N(1)-S(1)-C(5)	109.28(1

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for dwk0302. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	34(2)	35(2)	53(3)	11(2)	14(2)	16(2)
C(2)	27(2)	30(2)	26(2)	12(2)	6(2)	9(2)
C(3)	35(2)	18(2)	28(2)	5(1)	4(2)	3(2)
C(4)	24(2)	24(2)	23(2)	5(1)	-1(1)	-2(1)
C(5)	19(2)	22(2)	22(2)	8(1)	0(1)	2(1)
C(6)	22(2)	21(2)	40(2)	5(2)	-1(2)	-1(1)
C(7)	19(2)	30(2)	44(2)	9(2)	2(2)	0(2)
C(8)	26(2)	24(2)	23(2)	6(1)	2(1)	0(1)
C(9)	26(2)	35(2)	31(2)	17(2)	2(2)	7(2)
C(10)	31(2)	44(2)	55(3)	25(2)	16(2)	14(2)
C(11)	36(2)	33(2)	49(2)	20(2)	6(2)	8(2)
C(13)	31(2)	29(2)	28(2)	5(2)	4(2)	0(2)
C(12)	43(3)	63(3)	39(2)	20(2)	-9(2)	7(2)
C(14)	32(2)	35(2)	24(2)	5(2)	1(2)	1(2)
C(15)	41(2)	31(2)	26(2)	5(2)	5(2)	-2(2)
C(16)	53(3)	33(2)	40(2)	5(2)	10(2)	-9(2)
C(17)	59(3)	32(2)	37(2)	-2(2)	4(2)	-10(2)
C(18)	56(3)	42(2)	25(2)	3(2)	7(2)	-4(2)
C(19)	44(2)	33(2)	29(2)	7(2)	7(2)	-6(2)
N(1)	26(2)	17(1)	23(1)	6(1)	-1(1)	0(1)
O(1)	18(1)	27(1)	36(1)	12(1)	2(1)	0(1)
O(2)	26(1)	25(1)	22(1)	6(1)	3(1)	3(1)
O(3)	37(2)	42(2)	41(2)	-4(1)	14(1)	-7(1)
S(1)	18(1)	21(1)	23(1)	7(1)	1(1)	1(1)
Br(1)	77(1)	39(1)	42(1)	12(1)	23(1)	-6(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for dwk0302.

	x	y	z	U(eq)
H(1A)	9951	-378	8406	60
H(1B)	8673	-1599	7652	60
H(1C)	9053	-1586	8886	60
H(3)	5677	-1614	8324	32
H(4)	3521	-123	8736	29
H(6)	6781	3420	9374	34
H(7)	8932	1908	9001	37
H(8)	1521	2709	7625	29
H(10A)	-901	5712	7991	60
H(10B)	245	5152	8863	60
H(10C)	-901	4011	7950	60
H(11A)	3148	6160	7178	56
H(11B)	2621	6568	8363	56
H(11C)	1505	6991	7414	56
H(12A)	-368	5056	6111	72
H(12B)	-51	3389	6065	72
H(12C)	1349	4431	5771	72
H(15)	2148	582	6938	40
H(16)	1832	-1663	5730	51
H(17)	2520	-1867	4004	54
H(18)	3421	191	3464	50
H(1)	3586	4949	8937	26

COMMUNICATION

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A stereoselective synthesis of *anti*-γ,δ-alkynyl- and -alkenyl-β-hydroxy-α-amino esters from tin(II) enolates of glycinate†

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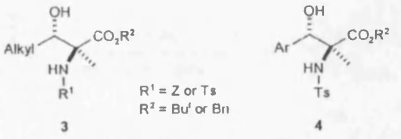
Received (in Cambridge, UK) 3rd June 2003, Accepted 18th July 2003
First published as an Advance Article on the web 17th September 2003

Condensations between the tin(II) enolate 11 of ethyl *N*-tosylglycinate and conjugated ynals 12 and ynones 14 are highly diastereoselective, in favour of the *anti*-isomers 13 and 15; similar reactions of enals and enones 17 show lower but still useful levels of *anti*-stereoselectivity.

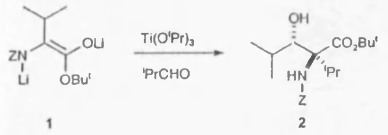
Despite a plethora of recent advances in the synthesis of non-natural and more highly functionalised α-amino acid derivatives,[1] there remains a need for the definition of practical and general approaches to such compounds. Not only are these of considerable importance as components of novel pharmaceuticals, but such densely functionalised compounds can find many applications in general synthesis. Doubtless with these ideas in mind, the Kazmaier group have carried out extensive studies of condensations between aldehydes and dianionic species derived from simple *N*-protected α-amino esters. Variations in both the amine protecting group and the counter cations, unsurprisingly, were found to have profound effects on both the efficiency and stereoselectivity of such condensations. In general, these favour formation of an *anti* arrangement between the amino group and the new hydroxyl group. Of a number of alternatives, one of the best turned out to be a combination of the dilithio dianion **1** of *N*-Z-valine *tert*-butyl ester with 2 equiv. of $TiCl(OPr^i)_3$ which provided, almost exclusively, the *anti*-diastereoisomer **2** when isobutanal was the electrophile, in 60% isolated yield (Scheme 1).[2] These conditions were less successful with similar alanine derivatives but it was subsequently discovered that replacement of the titanium alkoxides with 2.5 equiv. tin(II) chloride restored this excellent level of stereoselection, as well as giving improved yields.[3] In addition, both *N*-tosyl and benzyl esters of alanine could be used to obtain the *anti*-diastereoisomers **3**, but this generality was restricted to condensations with aliphatic aldehydes.



3 **4**

To achieve similarly high levels of stereoselection (98 : 2) with aromatic aldehydes, it was found essential to use a combination of $SnCl_2$ and *N*-tosyl protection to obtain the *anti*-isomers **4**. The more easily removed *N*-SES group could be used equally effectively.

A combination of the tin(II) enolate derived from *N*-tosyl alanine *tert*-butyl ester and a chiral α-hydroxyaldehyde derivative resulted in excellent levels of asymmetric induction,

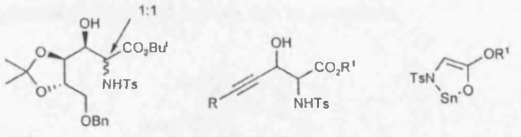


1 **2**

Scheme 1

† Electronic supplementary information (ESI) available: crystal data. See http://www.rsc.org/suppdata/cc/b3/b306291k/

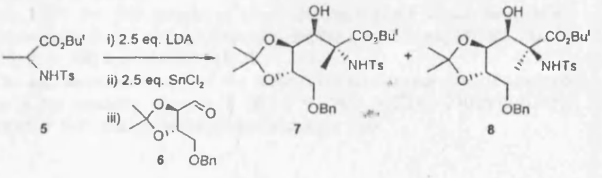
especially at the new β-hydroxyl centre. For example, such a reaction between *N*-tosyl alaninate **5** and aldehyde **6** gave essentially only the expected products **7** and **8**, in an 80 : 20 ratio (Scheme 2). Unfortunately, similar condensations involving glycinates gave products [*e.g.* **9**] which were epimeric at the α-centre. This was explained by post-condensation epimerisation, rather than a lack of stereocontrol during the condensation, or its reversibility.[4]



9 **10** **11**

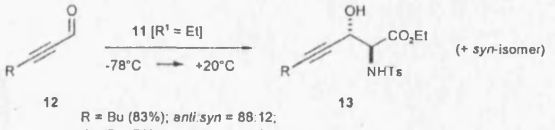
The structures provided by this methodology were ideal for projected developments of our 5-*endo* cyclisation methodology aimed at the construction of pyrrolidines and pyrroles,[5] given that it could be applied successfully to conjugated ynals and enals, types of electrophiles not examined by Kazmaier. Herein, we report that such condensations are indeed successful and also show synthetically very useful levels of stereoselection.

Our initial requirements were for a series of alkynyl-β-hydroxy-α-amino ester derivatives **10**. In view of the foregoing chemistry, it seemed possible that these could be obtained from the corresponding ynals and the tin(II) enolate of a glycinate. Such an intermediate has been formulated as structure **11**; the requirement of a second equivalent of $SnCl_2$ is ascribed to a role in electrophile activation.[2–4] The required ynals **12** were obtained using the excellent method developed by Journet *et al.* by 1-alkyne formylation (BuLi, THF; DMF; inverse quench) in around 90% yields.[6] We were pleased to find that the desired condensations proceeded smoothly in THF, following mixing the reactants at −70 °C and warming to ambient temperature.[2–4] Isolated yields of the hoped-for adducts **13** were between 60 and 83%. Further, these were isolated as largely the *anti*-isomers, as shown (Scheme 3). This was a surprise, in view of the results



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

Scheme 2



12 **13**

R = Bu (83%); *anti*:*syn* = 88:12;
R = Ph (76%); *anti*:*syn* = 94:6;
R = 2-propenyl (63%); *anti*:*syn* = 93:7;
R = But (65%); *anti*:*syn* = 99:1;
$TBSO(CH_2)_3$ (60%); *anti*:*syn* = 92:8;
$TBSO(CH_2)_4$ (62%); *anti*:*syn* = 90:10;
2-(cyclohexyl)ethyl (77%); *anti*:*syn* = 100:0 (after recrystallisation)

Scheme 3

DOI: 10.1039/b306291k

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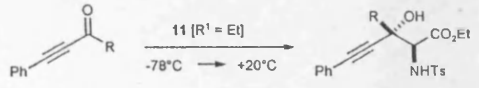
obtained from previous condensations with glycinates **11** (*cf.* **9**).[4] The *anti* : *syn* ratios were determined by integration of the ^{1}H NMR spectra of the crude products. These data also revealed that the remaining material balance from the condensations was largely *N*-tosyl glycinate, probably formed in most cases by competing deprotonation of the ynals **12**. In many cases, the major *anti*-isomers **13** could be separated by fractional crystallisation in 60–70% yields. Subsequent chemistry revealed that the adducts **13** were relatively prone to α-epimerization and so we were somewhat nervous about structural determination by, for example, manipulation through to a cyclic structure. Fortunately, the *anti*-phenyl derivative [**13**; R = Ph] provided crystals suitable for X-ray analysis,[7] which revealed the *anti*-stereoselection.

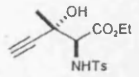
Thus encouraged, we carried out similar condensations using conjugated ynones **14** as the electrophiles. These too were successful and showed very useful levels of, again, *anti*-stereoselectivity (Scheme 4). 3-Butyn-2-one also condensed well with enolate **11**, without the need to protect the potentially labile alkynyl proton, to give adduct **16** in similar yield and selectivity. Again, the pure *anti*-isomers could be separated by careful crystallization in 60–70% yields and the relative stereochemistry confirmed by X-ray analysis [**15**; R = Pr^i].[7]



14 **15**

R = Me (79%); *anti*:*syn* = 92:8;
R = C_7H_{15} (80%); *anti*:*syn* = 90:10;
R = Pr^i (76%); *anti*:*syn* = 84:7;
R = Bu^t (65%); *anti*:*syn* = 99:1.

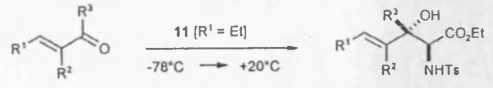
Scheme 4



16 (81%); *anti*:*syn* = 88:12

Finally, we briefly examined the outcome of such condensations when applied to enals and enones **17**. In general, these showed lower, but still useful, levels of *anti*-stereoselection in the expected products **18**. These results are collected in Scheme 5.[8]

The high *anti*-stereoselectivity of the condensations between the glycinate enolate **11** and ynals **12** (Scheme 3) certainly fits



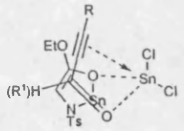
17 **18**

R¹ = Ph, R² = R³ = H (67%); *anti*:*syn* = 80:20;
R¹ = Me, R² = R³ = H (69%); *anti*:*syn* = 63:37;
R¹ = Bu, R³ = H, R³ = Me (79%); *anti*:*syn* = 79:21;
R¹ = R² = R³ = Me (91%); *anti*:*syn* = 70:30;

Scheme 5

well with Kazmaier's results and with his explanation based on a Felkin–Anh model.[2–4] However, these results are not consistent with his conclusion that the mixture of adducts **9**, obtained from glycinate **11**, was due to epimerization.

Uncertainties regarding the true nature of glycinate enolate **11** preclude much speculation. Indeed, the picture appears more complicated, because the condensations with ynones **14** gave adducts **15** with the *same anti*-selection, despite the larger substituent now being the "R" group rather than the alkyne residue, in contrast to the related ynals **12**, especially when "R" is branched [**14**; R = Pr^i]. Currently, one suggestion is that, if structure **11** is correct, the *anti*-stereoselection requires the alkyne group to be positioned axially, in a typical chair-like transition state **19**. Could this be due to donation from the alkyne bond into vacant tin orbitals? The same effect could be responsible for the similar but lower *anti*-stereoselection of condensations with enals and enones **17**. Of relevance is our observation, consistent with Kazmaier's, that condensations between enolate **11** and saturated aldehydes show almost no stereoselection. Hence, lack of complexation and not later epimerization may be responsible for this. Further studies aimed at shedding light on this along with synthetic applications of the various products reported herein are in progress.



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We are grateful to the Government of Thailand, Millennium Pharmaceuticals and the EPSRC for financial support and the EPSRC Mass Spectrometry Service, University College, Swansea for high resolution mass spectrometric data

Notes and references

1 For recent contributions, see A. E. Taggi, A. M. Hafez and T. Lectka, *Acc. Chem. Res.*, 2003, **36**, 10; V. A. Soloshonok, *Curr. Org. Chem.*, 2002, **6**, 341.
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7 See ESI† for full details of these determinations which have been deposited at the Cambridge Crystallographic Data Centre, CCDC 210386 [**13**; R = Ph] and 210604 [**15**; R = Pr^i].
8 The *anti*-stereochemistry of the major diastereoisomer was determined by X-ray analysis of *anti*-**18** [R$^{1-3}$ = Me] [CCDC 210387, ESI†], together with comparisons of spectroscopic data.

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