# New Stereoselective Approaches to Highly Substituted Pyrrolidines

**A thesis submitted to Cardiff University**

**By**

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In candidature of

**Doctor of Philosophy**

September 2005

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# Abstract

In studies towards the synthesis of substituted pyrroles, the Knight group have adapted an aldol reaction, originally developed by Kazmaier, as a highly diastereoselective method for the synthesis of the cyclisation precursors. Both acetylenic and α,β-unsaturated aldehydes have been successfully utilised in this reaction to afford a variety of β-hydroxy-α-amino ester precursors. This project centred around establishing the optimum conditions for the iodocyclisations of these precursors, and highly substituted pyrrolidines were obtained in the majority of cases. Also it was noted that these aldol adducts were structurally similar to Sphingosine, and *via* a series of selective reductions, a formal diastereoselective synthesis of Sphingosine was accomplished.

In addition, silver-nitrate catalysed 5-*endo*-dig cyclisations were also applied towards the total synthesis of both Preussin and Codonopsinine.

Finally, studies were conducted to establish the selectivity of 5-*exo*-trig cyclisations in the synthesis of iodo-lactones, and using this methodology, the piperidine core of Pseudodistomin was successfully synthesised.

## Acknowledgements

Firstly, I would like to thank Dave Knight for all his support during my time in Cardiff. Also huge thanks to my parents and Rhiannon for their encouragement throughout my Degree and PhD and to Paul for tolerating all the mess, whinging and stresses over the last four years.

Thanks to all members of lab 1.107D, especially Tai and Charlie for their help in my first year and also to Em, Mel, Chris, Nick, Amjad, Xu, Charlie-boy, Wen Fei, Ying-Fa, Simon, Tony, Stu and Ian.

Thanks to Rob Jenkins for taking the time to run numerous NMR experiments and help with interpretating the results, it was really appreciated and also to Robin for the mass spec data of several of my key compounds. Thanks also to Abdul Malik and Dr. Liling Ooi for the X-ray crystal structures and the EPSRC mass spec centre at Swansea for the high resolution data.

Also thanks to Millennium Pharmaceuticals for funding the research.

# Abbreviations

| | |
|---|---|
| Ac | Acetyl |
| APCI | Atmospheric pressure chemical ionisation |
| Ar | Aryl |
| Boc | Tertiarybutyloxycarbonyl |
| BOP-Cl | Bis(2-oxo-3-oxazolidinyl)phosphinic chloride |
| Bu | Butyl |
| DABCO | 1,4-Diazabicyclo[2.2.2]octane |
| DCC | 1,3 dicyclohexylcarbodiimide |
| DCM | Dichloromethane |
| DEAD | Diethyl azodicarboxylate |
| DIAD | Diisopropyl azodicarboxylate |
| Dibal-H | Diisobutylaluminium hydride |
| DMAP | 4-(dimethylamino)pyridine |
| DME | ethylene glycol dimethyl ether |
| DMF | *N, N*-dimethylformamide |
| DMSO | dimethyl sulphoxide |
| e.g. | *exempli gratia* |
| eq. | Equivalents |
| ES | Electrospray |
| Et | Ethyl |
| Ether | diethyl ether |
| GOESY | Gradient 1D difference Nuclear Overhauser effect |
| Hunigs Base | N,N'-diisopropylethylamine |
| *i.e.* | *id est* |
| *J* | coupling constant |
| LDA | Lithium diisopropylamide |
| $LiAlH_4$/LAH | Lithium aluminium hydride |
| Lindlars Catalyst | $Pd/CaCO_3$ poisoned with lead acetate |
| L-selectride | Lithium tri-sec-butyl borohydride |
| m.p. | Melting point |
| Me | Methyl |

| | |
|---|---|
| MS | Mass spectrometry |
| $NaBH_4$ | Sodium borohydride |
| NMR | Nuclear magnetic resonance |
| NOE | Nuclear Overhauser effect |
| *P* | para |
| Ph | phenyl |
| R | aryl or alkyl group |
| Red-al | bis(2-methoxyethoxy)aluminium hydride |
| SES | 2-trimethylsilylethanesulfonyl |
| Superhydride | Lithium triethyl borohydride |
| *t* | tertiary |
| TBS | Dimethyl Tertiary butyl silyl |
| Tf | Triflate |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| THP | Tetrahydropyran |
| TIPS | Triisopropylsilyl |
| Tlc | thin layer chromatography |
| Ts/ tosyl | *para*-toluenesulfonyl group |
| TsCl | Tosyl chloride |

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**Chapter Six: Experimental Chapter**

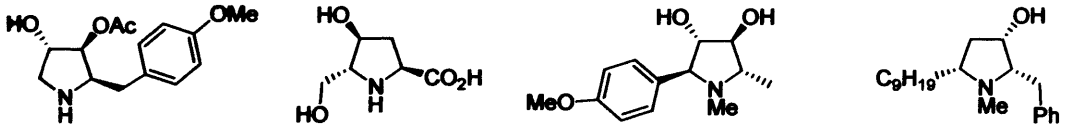


**Appendix**

# Chapter One

# Introduction

With a variety of natural products containing a heterocycle core, such as anisomycin[1] **1**, bulgecinine[2] **2**, (-)-codonopsine[3] **3** and (+)-preussin[4] **4** there is an obvious need to synthesise such compounds highly selectively (Figure 1.10). This project centres around the synthesis of pyrrolidines *via* 5-*endo*-trig cyclisations of amino alcohol derivatives.




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

**Figure 1.10**

## 1.10. Baldwin's Rules

The synthesis of various heterocycles is frequently *via* an electrophilic cyclisation of unsaturated molecules containing an internal nucleophile. In these cyclisations, the ring formation can occur in either an *exo* or *endo* manner (Figure 1.11).

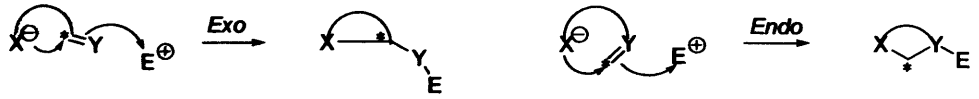



**Figure 1.11**

*Exo* describes the cyclisation when the bond that is broken is exocyclic to the smallest ring formed, while *endo* is when the bond that is broken is endocyclic to the smallest ring formed. The description of ring closure is subdivided further into three types of atoms; tetrahedral (Tet.) for $sp^3$, trigonal (Trig.) for $sp^2$ and digonal (Dig.) for sp systems. In 1976, J. E. Baldwin[5] developed a series of rules that predicts whether a cyclisation proceeds *via* an *exo* or *endo* pathway. These rules predict whether a reaction is favoured or disfavoured by taking into account the geometry of the transition state and also the balance

of electronic and steric factors. The rules for ring closures of 3- to 7-membered rings are as follows: -

1. Tetrahedral systems
    a) 3 to 7-*Exo-Tet* are all favoured processes
    b) 5 to 6-*Endo-Tet* are disfavoured

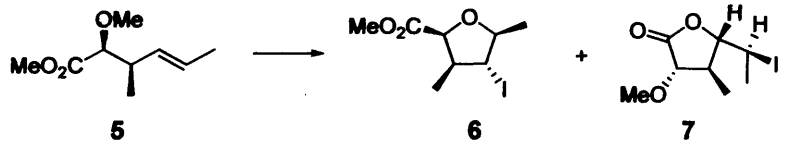
2. Trigonal systems
    a) 3 to 7-*Exo-Trig* are all favoured
    b) 3 to 5-*Endo-Trig* are disfavoured
    c) 6 and 7-*Endo-Trig* are favoured

3. Digonal systems
    a) 3 to 4-*Exo-Dig* are disfavoured
    b) 5 to 7-*Exo-Dig* are favoured
    c) 3 to 7-*Endo-Dig* are favoured

Favoured cyclisations are those in which the atoms can achieve the correct geometries, while disfavoured cyclisations require severe distortions of both the bond angles and distances. However, it is noteworthy that just because a cyclisation is labelled "disfavoured", does not necessarily mean it cannot occur, it is just more difficult than a favoured case.

## 1.20. 5-*endo*-trig Cyclisations in the Synthesis of Tetrahydrofurans

Barlett and Myerson[6] first recorded the use of 5-*endo*-trig cyclisations in the synthesis of tetrahydrofurans in 1978. They conducted an iodolactonisation on methyl ester **5**, which furnished a 2:1 mixture of the desired lactone **7** and an iodotetrahydrofuran **6**, *via* a competing iodoetherification reaction (Scheme 1.10).

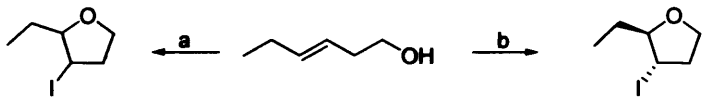



**5** **6** **7**

**Scheme 1.10.** *Reagents:* $I_2$, MeCN, 0°C.

In addition to the iodotetrahydrofuran **6** being the result of a disfavoured 5-*endo*-trig cyclisation, the reaction also involved the cleavage of the methyl ether moiety, hence it was the minor product. When the corresponding free alcohol was treated with the same reagents, the cyclisation afforded exclusively the iodotetrahydrofuran **6**.

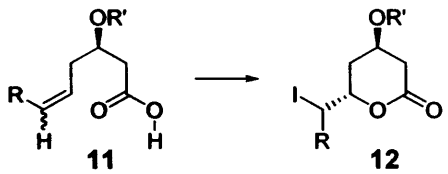
Other approaches utilising novel iodonium ion sources have also afforded iodotetrahydrofurans. In 1984, Mechoulam and Srebnik[7] cyclised (*E*)-hex-3-en-1-ol **8** using a mixture of sodium iodide and *m*-chloroperbenzoic acid (mCPBA), while Schauble[8] cyclised the same homoallylic alcohol **8** with bis(*sym*-collidine)iodine(I)perchlorate (Scheme 1.11).




**9** **8** **10**

**Scheme 1.11.** *Reagents:* a) NaI, mCPBA, 18-crown-6, $CH_2Cl_2$, 20 °C-0 °C; b) $I(collidine)_2^+ClO_4^-$, $CH_2Cl_2$, 20 °C.

It was during the early 1990s that the Knight[9,10] group commenced research in this field. In model studies towards the valerolactone moiety of Mevinic acids, the Knight group discovered that iodolactonisations of 3-hydroxyalk-5-enoic acid derivatives **11**, gave predominately the *trans*-3,5-disubstituted lactones **12** (Scheme 1.12)[11,12]. This result was unexpected since normally, such cyclisations give the 3,5-*cis* diastereoisomers *via* a chair-like transition state[13]. This divergence from the trend was presumed to be due to intramolecular hydrogen bonding between the 3-oxygen function and the carboxylic acid.




**11** **12**

**Scheme 1.12.** *Reagents:* $I_2$, $NaHCO_3$, MeCN-$H_2O$.

A trace of by-product (≤5%) was also observed and when R was alkyl, these by-products were determined to be single diastereoisomers of β-iodo-tetrahydrofurans **13** (Figure 1.12).

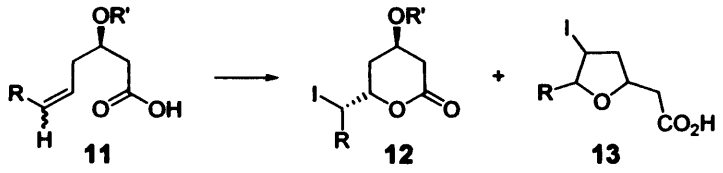
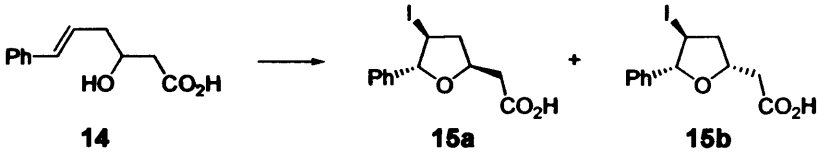



**Figure 1.12**

These β-iodo-tetrahydrofurans **13** were believed to arise from a 5-*endo-trig* cyclisation of the precursor with a loss of either a proton or a silyl group, which appeared to contravene Baldwin's rules. However, a literature search suggested that such cyclisations were viable and so further investigations were conducted.

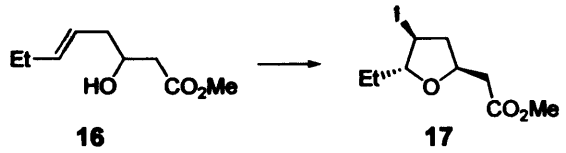
The (*E*)-hydroxy-acid **14** was thus subjected to the kinetic iodolactonization conditions developed by Bartlett[6], three equivalents of iodine and sodium hydrogen carbonate in aqueous acetonitrile. The tetrahydrofuranacetic acids **15** were isolated in a 7:1 (a:b) ratio in approximately 80% yield (Scheme 1.13).[14]




**Scheme 1.13.** *Reagents:* $I_2$, $NaHCO_3$, MeCN-$H_2O$, 80%.

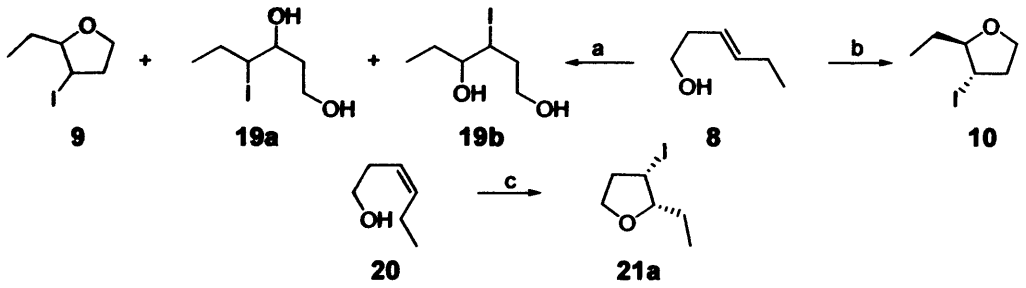
However, when the phenyl group was substituted with alkyl groups, the cyclisation yielded valerolactones with only traces of iodotetrahydrofurans evident. Hence this initial cyclisation was a special case arising because the phenyl group was able to stabilize the electron deficient benzylic centre and consequently favour the overall 5-*endo*-cyclisation at the expense of the 6-*exo* lactonization.

To prevent this unwanted 6-*exo* cyclisation, the corresponding methyl ester **16** was cyclised, again using Bartlett's[6] conditions, largely a single isomer of the iodotetrahydrofuran **17** was obtained (Scheme 1.14).



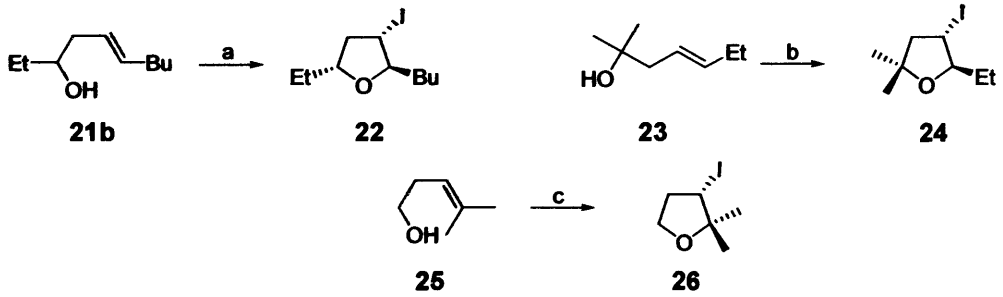

**Scheme 1.14.** *Reagents:* $I_2$, $NaHCO_3$, MeCN, 10% $H_2O$, 67%.

Once again this was a special case since exposure of (*E*)-hex-3-en-1-ol **8** to Bartlett's standard conditions afforded 5% of iodotetrahydrofuran **9**, in addition to iodohydrins **19**, formed by intermolecular attack by water (Scheme 1.15; a). However, in anhydrous solvents, the cyclisation rapidly proceeded to give virtually quantitative yield of the *trans*-iodotetrahydrofuran **10** (Scheme 1.15; b), while the corresponding (*Z*)-hex-3-en-1-ol **20** cyclised at a much slower rate (72 h), to afford the product **21a** in 60% yield (Scheme 1.15; c).



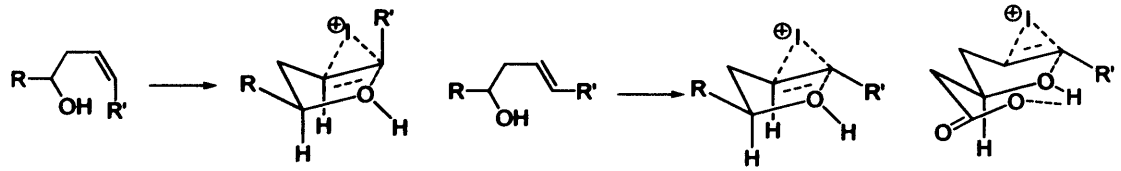

**Scheme 1.15.** *Reagents:* a) $I_2$, $NaHCO_3$, MeCN-$H_2O$, 5%, **9**; b) $I_2$, $NaHCO_3$, *anh* MeCN, 5 mins, 0°C, 95%, **10**; c) $I_2$, $NaHCO_3$, *anh* MeCN, 72 h, 0°C, 60%, **21a**.

These 5-*endo*-trig cyclisations were also successful for a variety of substrates including secondary homoallylic alcohols (**21b**), tertiary alcohols (**23**) and trisubstituted olefins (**25**) (Scheme 1.16).




**Scheme 1.16.** *Reagents:* a) $I_2$, $NaHCO_3$, *anh* MeCN, 3 h, 0°C, 90% **22**; b) $I_2$, $NaHCO_3$, *anh* MeCN, 1 h, 0°C, 90% **24**; c) $I_2$, $NaHCO_3$, *anh* MeCN, 1 h, 0°C, 85% **26**.

To explain the difference in rates of the cyclisations of the (*E*)- and (Z)-olefins **27**, chair-like transition state diagrams **28** can be drawn, arising from the addition of iodine across the double bond followed by the rearside attack of the oxygen (Figure 1.13).



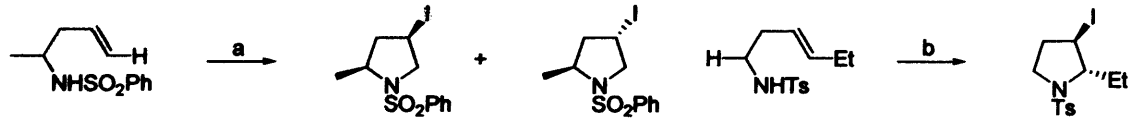
**27a** **28a** **27b** **28b** **29**

**Figure 1.13**

The high stereoselectivity obtained resulted because 5-*endo*-trig cyclisations are unfavourable and, as such, the process will be more demanding in terms of transition state geometry, since the favoured 5-*exo*-trig cyclisations are frequently non-stereoselective.[14] In the proposed transition states, substituent $R^1$ can be positioned pseudo-equatorially or in the less favourable pseudo-axial position, depending on the geometry of the olefin. Presumably this unfavourable position of the substituent $R^1$ is why cyclisations of (*Z*)-olefins **27a** are generally slower than the (*E*)-olefins **27b**. With a (Z)-olefin **27a**, this substituent is in the axial position which presumably permits the intermolecular attack by small amounts of water (arising from the neutralisation of hydrogen iodide by the base), to compete. In addition, due to the strain involved in forming such a transition state in these 5-*endo*-trig ring closures, this explains why water frequently competes to give iodohydrins (Scheme 1.15). It is presumed that in cyclisations of β-hydroxy esters, hydrogen bonding between the ester and hydroxyl group, may assist the O-H cleavage as depicted by transition state **29**, which inevitably means that this cyclisation can then compete with the intermolecular attack by water.[15]

## 1.30. 5-*Endo*-Trig Cyclisations in Pyrrolidine Synthesis

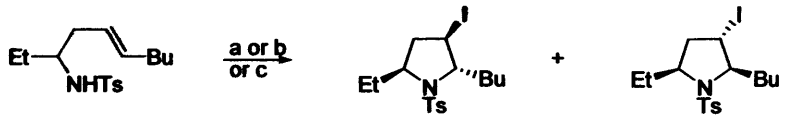
The success of 5-*endo*-trig cyclisations of both (*E*)- and (*Z*)-homoallylic alcohols led the Knight group to apply this methodology to homoallylic amines to afford pyrrolidines. Naturally, the conditions that were previously successful for the corresponding homoallylic alcohols, three equivalents of iodine, sodium hydrogen carbonate in anhydrous acetonitrile, were tested. However, precursor **30** cyclised, but with little stereocontrol to afford a 60:40 (a:b) mixture of diastereoisomers **31** (Scheme 1.17; a).[16] A more substituted derivative **32**, however encouragingly cyclised to furnish exclusively the *trans*-2,3-iodopyrrolidine **33** (Scheme 1.17; b).




**30** **31a** **31b** **32** **33**

**Scheme 1.17.** *Reagents:* a) $NaHCO_3$, $I_2$, *anh.* MeCN, 1 h, 42%; b) $NaHCO_3$, $I_2$, *anh.* MeCN, 10 mins, 84%.

Unlike the related alcohol derivatives, less stereoselectivity was observed in the synthesis of trisubstituted pyrrolidines. Improvements were not observed despite lowering the temperature from 0°C to -78°C, or by changing the solvent to ether or dichloromethane. It was discovered that by changing the base to slightly stronger potassium carbonate, this selectivity was greatly increased to afford predominately the 2,5-*trans* isomer **35a** (Scheme 1.18; b).




**34** **35a** **35b**

**Scheme 1.18.** *Reagents:* a) $NaHCO_3$, $I_2$, MeCN, 0.25 h, 76%, 74:26 (**a**:**b**); b) $K_2CO_3$, $I_2$, MeCN, 0.5 h, 74%, 94:6 (**a**:**b**); c) $I_2$, MeCN, 3 mins, 78%, 0:100 (**a**:**b**).

Interestingly, the addition of small amounts of water to the reaction mixture improved the yields, which was in contrast to the results observed in tetrahydrofuran synthesis. The group assumed that under these conditions, the hydrogen iodide formed is more quickly

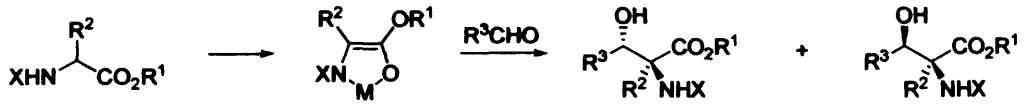
neutralised by the base and consequently cannot isomerise the initial products. Thus in theory, in the absence of base, complete isomerisation of the initial products should occur and thus sulfonamide **34** was treated with iodine in acetonitrile to afford the 2,5-*cis* isomer **35b** (Scheme 1.18; c). This isomerisation was not observed with the methanesulfonamide derivatives.

The cyclisations of the (*Z*)-sulfonamides unfortunately gave lower yields and selectivities than the related (*E*)-derivatives, despite the use of different conditions, which can be again reasoned by considering the transition states. Again, as observed with the (*E*)-homoallylic alcohols, the disfavoured ring closure of the sulfonamides requires a more demanding transition state, and as such the cyclisation occurs selectively. With the corresponding (Z)-derivatives, a substituent will be in the unfavourable axial position again allowing for competing reactions to occur.

## 1.40. Synthesis of Cyclisation Precursors: Introduction to the Kazmaier aldol Reaction

Throughout the previous research conducted by Sharland[17] and the present research, an aldol reaction developed by Kazmaier[18] had been used extensively in the synthesis of amino alcohol derivatives used in cyclisation studies. Accordingly, the methodology developed by Kazmaier is described below, in addition to the modifications of the procedure conducted by Sharland.

Research by Kazmaier, Grandel and Nuber showed that deprotonation of the *N*-protected ester of various amino acids **36** using LDA followed by addition of a metal salt resulted in the formation of probably a chelated metal enolate **37** (Figure 1.14). Subsequent aldol reactions involving this enolate **37** and aldehydes were found to be highly diastereoselective, yielding *anti* isomers **38a** of α-amino-β-hydroxy acids (Figure 1.14; b). The synthesis of such compounds is synthetically useful since they are sub-structures of biologically active molecules such as myricoin[19], lactacysin[20] and sphinogofungins E and F.



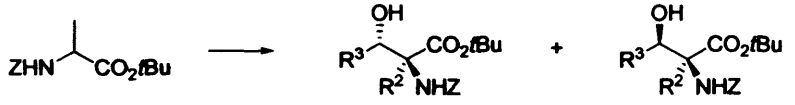

**36** **37** **38a** *anti* **38b** *syn*

**Figure 1.14**

Kazmaier reported that the relative configuration of the aldol product depends on the configuration of the enolate. It was also found that the configuration of the double bond in a lithium ester enolate was related to the polarity of the medium.[21]

## 1.41. Optimisation Studies: Metal Salt Employed (MXn)

Various optimisation studies were undertaken by Kazmaier[18] to determine how to increase the selectivity of the reaction. In the initial studies, *N*-(benzyloxylcarbonyl)alanine *tert*-butyl ester **39** was condensed with either pivalaldehyde **42** or isobutyraldehyde **43** in the presence of a variety of metal salts (Table 1.10).




**39** **40-41a** **40-41b**

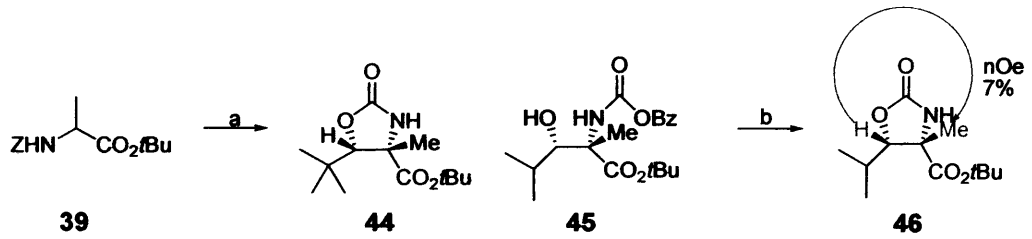
| | Aldehyde | ($MX_n$) | Eq | Product | Crude *anti:syn* ratio (%) | Isolated yield | |
|---|---|---|---|---|---|---|---|
| | | | | | | *Anti* (%) | Total (%) |
| 1 | *t*-BuCHO **42** | Li | / | **40** | 79:21 | 30 | / |
| 2 | *t*-BuCHO **42** | $MgCl_2$ | 1 | **40** | 76:24 | 48 | / |
| 3 | *t*-BuCHO **42** | $MgCl_2$ | 2 | **40** | 77:23 | 40 | / |
| 4 | *t*BuCHO **42** | $Al(OiPr)_3$ | 1 | **40** | 76:24 | 58 | / |
| 5 | *t*-BuCHO **42** | $Al(OiPr)_3$ | 2 | **40** | 78:22 | 51 | / |
| 6 | *t*-BuCHO **42** | $ZnCl_2$ | 1 | **40** | 81:19 | 49 | / |
| 7 | *t*-BuCHO **42** | $ZnCl_2$ | 2 | **40** | 90:10 | 60 | / |
| 8 | *t*-BuCHO **42** | $TiCl(OiPr)_3$ | 1 | **40** | 83.17 | 40 | / |
| 9 | *t*-BuCHO **42** | $TiCl(OiPr)_3$ | 2 | **40** | 97:3 | 70 | / |
| 10 | *i*-PrCHO **43** | Li | / | **41** | 60:40 | / | 60 |
| 11 | *i*-PrCHO **43** | $TiCl(OiPr)_3$ | 1 | **41** | 72:28 | / | 76 |
| 12 | *i*-PrCHO **43** | $TiCl(OiPr)_3$ | 2 | **41** | 92:8 | / | 87 |
| 13 | *i*-PrCHO **43** | $TiCl(OiPr)_3$ | 3 | **41** | 92:8 | / | 84 |
| 14 | *i*-PrCHO **43** | $TiCl(OiPr)_3$ | 4 | **41** | 93:7 | / | 55 |

**Table 1.10**

From Table 1.10 it is clear that the metal salt and the number of equivalents used effects greatly the observed diastereoselectivity. When lithium was employed, the reaction was low yielding and low diastereoselectivity was obtained, while the use of magnesium or aluminium failed to increase this selectivity. However, both zinc and titanium showed an increase in diastereoselectivity. With regards to the yield, Kazmaier and co-workers reported that the yield greatly increased when two equivalents of the metal salt was employed (Table 1.10 entries 9 and 12), while no significant improvement was observed when three equivalents was employed and the use of four equivalents led to a lower yield. The optimum conditions however were found to be two equivalents of $TiCl(O\textit{i}Pr)_3$.
The explanation given by Kazmaier to account for the need for two equivalents of the metal salt (MXn) was that one metal atom is required to form the chelated enolate, while the other coordinates and activates the aldehyde. This has yet to be proven and the precise structure of the enolate is unknown.

### 1.42. Optimisation Studies: Reaction Time and Temperature

The standard conditions used were stirring the reaction mixture for half and hour at -78°C before quenching the reaction with aqueous hydrochloric acid, but what would be the affect on the selectivity and yield by raising the temperature? When the reaction time was increased and the mixture was warmed to 0°C, the yield and the selectivity was not affected. However, when the reaction time was increased to one day and the mixture was warmed to room temperature an oxazolidinone **44** side product was formed
(Scheme 1.19; a).




**39** **44** **45** **46**

**Scheme 1.19.** *Reagents:* a) LDA, $TiCl(O\textit{i}\text{-}Pr)_3$, *t*-BuCHO, -78-RT°C; b) $TiCl(O\textit{i}\text{-}Pr)_3$, Toluene, 70°C

Interestingly, this occurrence was only observed with α-alkyl, β-hydroxy-α amino acids. nOe and X-Ray diffraction data was collected for **46** which confirmed that the

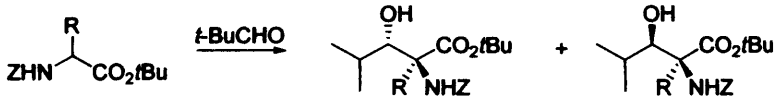
stereochemistry of the major isomer of the aldol reaction was the *anti* diastereoisomer **45** (Scheme 1.19; b).

### 1.43. Optimisation Studies: Nature of the Substituent (R), Aliphatic or Aromatic

Next, experiments were conducted to determine if the substituent (R) on the aldehyde influenced the reaction in any way. Kazmaier determined that when the aldol reaction involves aliphatic aldehydes, the reaction proceeds irreversibly. Also it became apparent that the nature of the substituent (R) influenced the diastereoselectivity, in that aromatic aldehydes showed no significant diastereoselectivity unlike the alkyl ones with *N*-(benzyloxylcarbonyl)alanine *tert*-butyl ester **39**.

### 1.44. Optimisation Studies: Size of the substituent ($R^1$) on the amino acid

Aldol reactions were conducted using the more bulkier amino acids including the tertiary-butyl esters of ethyl glycine **47**, valine **48** and phenylalanine **49**, using two equivalents of $TiCl(O\textit{i}Pr)_3$ and with *iso*-butyraldehyde **43**, to determine whether the aldol reaction was limited to small amino acids such as alanine. These experiments using more hindered amino acid substrates showed that the diastereoselectivity increases with the size of the $\alpha$ alkyl substituent (Table 1.11).




**39, 47-49** **40a, 50-51a** **40a, 50-51b**

| R | $TiCl(OiPr)_3$ (eq) | Product | Ratio *Anti:syn* | Yield (%) | |
|---|---|---|---|---|---|
| | | | | Mixture | *Anti* isomer |
| Ethyl **47** | 0 | **50** | 69:31 | 75 | / |
| Ethyl **47** | 1 | **50** | 84:16 | 73 | / |
| Ethyl **47** | 2 | **50** | 95:5 | 85 | / |
| *i*-Pr **48** | 0 | **51** | 84:16 | 40 | / |
| *i*-Pr **48** | 1 | **51** | 95:5 | 60 | / |
| *i*-Pr **48** | 2 | **51** | 98:2 | 60 | / |
| Bzl **49** | 0 | **52** | 72:28 | / | 60 |
| Bzl **49** | 1 | **52** | 75:25 | / | 65 |
| Bzl **49** | 2 | **52** | 90:10 | / | 78 |
| Me **39** | 2 | **40** | 92:8 | 87 | |

**Table 1.11**

## 1.45. Proposed Mechanism

The mechanism proposed by Kazmaier to account for the diastereoselectivity observed in this aldol reaction is illustrated in Figure 1.15.

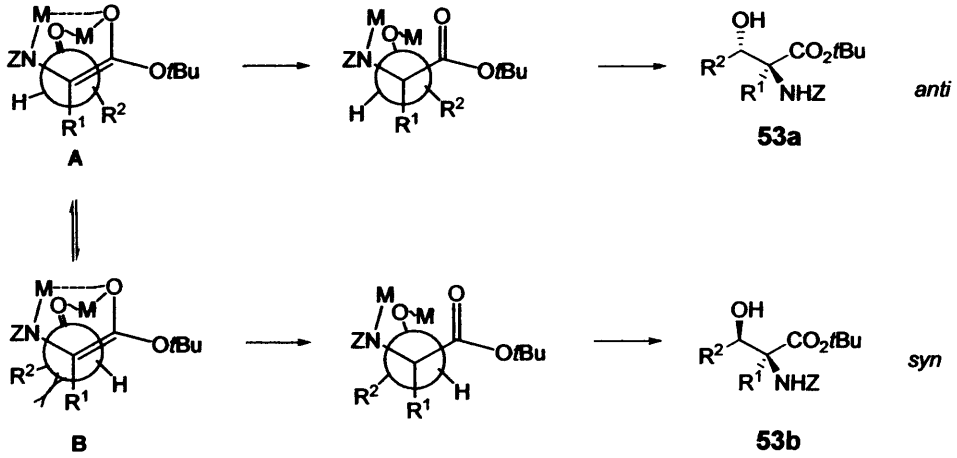


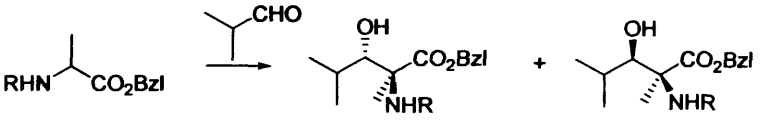

**Figure 1.15**

In α-amino acid ester enolates, the chelation with lithium leads predominately to the *Z* configuration of the enolate. Since transmetalation reactions occur usually with retention

of this configuration, the enolate geometry resulting from the initial deprotection would determine the configuration of the metal enolate formed. Kazmaier proposed that transition state A is favoured over transition state B due to the interactions between $R^1$ and $R^2$ in transition state B (Figure 1.14). The results obtained proved that these interactions are stronger in the reaction involving pivalaldehyde **42** than isobutyraldehyde **43** because $R^2$ exerts a more stronger steric influence. This was deduced by the higher selectivity observed in the aldol condensation utilising pivalaldehyde **42** than isobutyraldehyde **43** (Table 1.10). In addition, from the results Kazmaier proposed that the interactions between $R^2$ and the ester moiety in transition state A appear not be so crucial as those between $R^1$ and $R^2$ in transition state B. This was deduced by comparison of the reactions of the amino acids ethylglycine **47** and valine **48** with the aldol reaction involving alanine, since as $R^1$ increases, the interactions between $R^1$ and $R^2$ disfavour transition state B, and thus the amount of *anti* diastereoisomer formed increases (Table 1.11).

## 1.46. Influence of Nitrogen-Protecting Group

The highest reported selectivity was 92% when using Z-alanine butyl ester **39**, isobutyraldehyde **43** and 2.5 equivalents of $TiCl(O\textit{i}\text{-}Pr)_3$.[22] However, this was limited to alkyl substituted aldehydes. Further experiments were conducted to determine the influence of the nitrogen protecting group (Table 1.12).[23]




Where R= Z = **54**
R=Ts = **55**

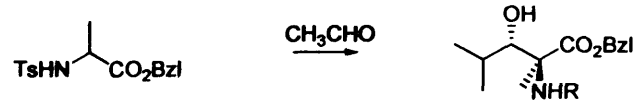
**56a**
**57a**

**56b**
**57b**

| R | MXn (eq) | Product | *Anti: Syn* ratio | Total Yield (%) |
|---|---|---|---|---|
| Z **54** | 1.2 eq. $TiCl(O\textit{i}\text{-}Pr)_3$ | **56** | 72:28 | 76 |
| Z **54** | 2.5 eq.$TiCl(O\textit{i}\text{-}Pr)_3$ | **56** | 92:8 | 87 |
| Ts **55** | 1.2 eq.$TiCl(O\textit{i}\text{-}Pr)_3$ | **57** | 63:35 | 86 |
| Ts **55** | 2.5 eq $TiCl(O\textit{i}\text{-}Pr)_3$ | **57** | 65:35 | 90 |
| Ts **55** | 1.2 eq $TiCl(O\textit{i}\text{-}Pr)_3$ | **57** | 60:40 | 70 |
| Ts **55** | 2.5 eq $SnCl_2$ | **57** | 98:2 | 80 |

**Table 1.12**

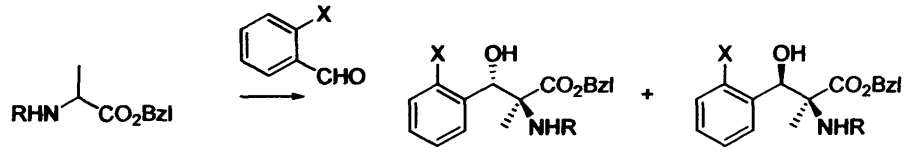
Table 1.12 shows that the nature of the protecting group is also a factor that contributes to the diastereoselectivity. For example, when the protecting group was Z **54**, 92% diastereoselectivity was observed using $TiCl(O\textit{i}\text{-}Pr)_3$, however, no significant diastereoselectivity was observed for the corresponding tosyl derivative **55**. All the various chelating metals tested including $ZnCl_2$, $MgCl_2$, $NiCl_2$, $CoCl_2$ and $Al(O\textit{i}\text{-}Pr)_3$, gave similar results. However, when 2.5 equivalents of $SnCl_2$ (entry 6) was used, this resulted in an excellent 98% diastereoselectivity. One further experiment was conducted using acetaldehyde **55** where the product **59** was obtained in 82% yield with a diastereoselectivity of 95%.




**55** **59**

**Scheme 1.20.** *Reagents*: LDA, $SnCl_2$, THF, 82%.

To widen the scope of the aldol reaction, the problem of high diastereoselectivities involving the use of aromatic aldehydes had to be solved. As previously described when the nitrogen protection group was Z, the aldol reactions conducted with aromatic aldehydes displayed no significant diastereoselectivity, irrespective of the metal salt used.




**54-55** **62-64a** **62-64b**

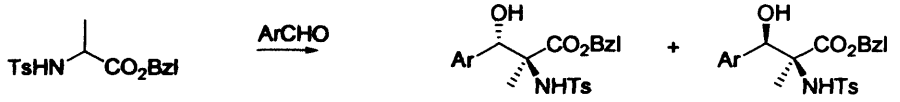
| R | X eq. MXn | Aldehyde X= | Product | *Anti: Syn* ratio | Total Yield (%) |
|---|---|---|---|---|---|
| Z **54** | 2.5eq. $TiCl(O\textit{i}\text{-}Pr)_3$ | H **60** | **62** | 51:49 | 54 |
| Z **54** | 1.2 eq. $TiCl(O\textit{i}\text{-}Pr)_3$ | $NO_2$ **61** | **63** | 48:52 | 61 |
| Z **54** | 2.5 eq.$TiCl(O\textit{i}\text{-}Pr)_3$ | $NO_2$ **61** | **63** | 49:51 | 69 |
| Z **54** | 2.5 eq $SnCl_2$ | $NO_2$ **61** | **63** | 58:42 | 74 |
| Ts **54** | 2.5eq $TiCl(O\textit{i}\text{-}Pr)_3$ | $NO_2$ **61** | **64** | 70:30 | 58 |
| Ts **54** | 2.5 eq $SnCl_2$ | $NO_2$ **61** | **64** | 99:1 | 60 |

**Table 1.13**

However, experiments conducted on the same substrate but with a tosyl protecting group displayed 99% diastereoselectivity with $SnCl_2$, but only 70% ds was recorded for $TiCl(O\textit{i}\text{-}Pr)_3$ (Table 1.13). Kazmaier proposed that the lower diastereoselectivities observed in the presence of other metal salts (e.g. $TiCl(O\textit{i}\text{-}Pr)_3$) may be the result of retroaldol reaction.

## 1.47. Substituents on the Aromatic ring of the Aldehyde

With this excellent result, further reactions were conducted with a tosyl nitrogen protecting group. Next, it was decided to test the diastereoselectivity of the reaction by altering the substituents on the aromatic side chain of the aldehyde (Table 1.14).




**55** **77-89a** **77-89b**

| | RCHO | Product | *Anti: Syn* ratio | Total Yield (%) |
|---|---|---|---|---|
| 1 | Benzaldehyde **60** | **77** | 98:2 | 91 |
| 2 | 4-methylbenzaldehyde **65** | **78** | 97:3 | 66 |
| 3 | 4-methoxybenzaldehyde **66** | **79** | 98:2 | 70 |
| 4 | 4-bromobenzaldehyde **67** | **80** | 98:2 | 70 |
| 5 | 4-chlorobenzaldehyde **68** | **81** | 98:2 | 87 |
| 6 | 4-nitrobenzaldehyde **69** | **82** | 98:2 | 60 |
| 7 | 2-nitrobenzaldehyde **70** | **83** | 99:1 | 60 |
| 8 | 3,4-dichlorobenzaldehyde **71** | **84** | 98:2 | 65 |
| 9 | 2,6-dichlorobenzaldehyde **72** | **85** | 99:1 | 70 |
| 10 | 3,4,5-trimethoxybenzaldehyde **73** | **86** | 90:10 | 75 |
| 11 | 2,4,6-trimethoxybenzaldehyde **74** | **87** | 85:15 (crude) | 77 |
| 12 | 9-anthranyl carbaldehyde **75** | **88** | 99:1 | 87 |
| 13 | 3-(*N*-Boc-indol)carbaldehyde **76** | **89** | 96:4 | 84 |

**Table 1.14**

These results suggest that neither the different substituents nor their position on the aromatic ring has any effect on the diastereoselectivity originally observed (Table 1.14, entry 1). The only notable difference was observed with the trimethoxy-substituted aldehydes (entries 10 and 11), which showed a marginal decrease in diastereoselectivity.

## 1.48. Detosylation Problem: the Search for Alternative Protecting Groups

Early indications showed that the best nitrogen protecting group for the aldol reaction was the tosyl group (Table 1.14). However, despite numerous literature methods for removal of this protecting group, such transformations are often problematic. So an alternative protecting group, which is easier to remove, but still gives the high diastereoselectivity and yields was necessary. Numerous sulphonyl groups were tested including 2-nitrobenzenesulfonyl, which did not survive the reaction conditions, presumably deprotection occurred during the reaction. The protecting group of choice was found to be the SES (2-trimethylsilylethanesulfonyl) group, developed by Weinreb[24] *et. al.* (Scheme 1.21).

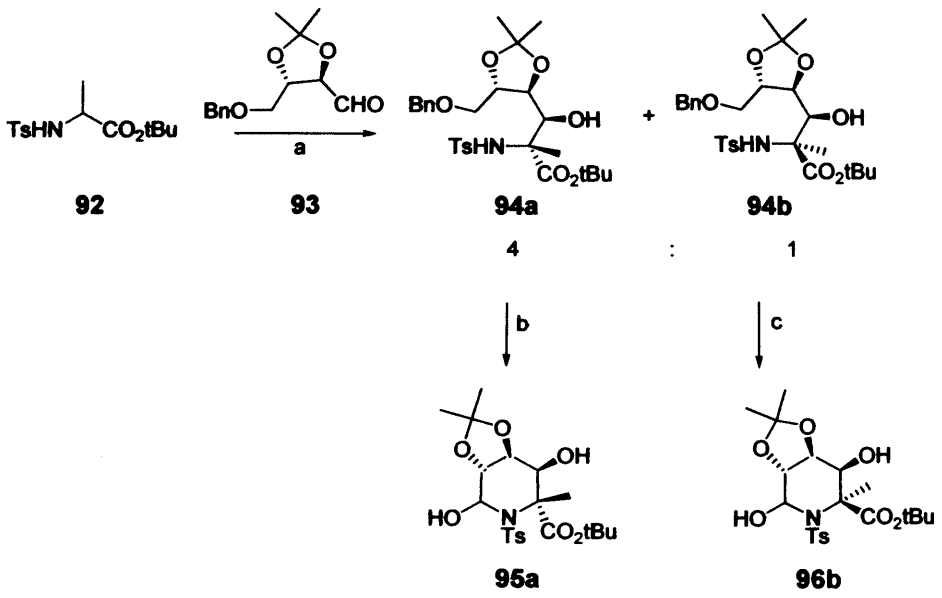

**90** **91**

**Scheme 1.21.** *Reagents:*LDA, THF, -78°C, 88%, 99% de.

Highly basic conditions are necessary to cleave the SES group, so to prevent a retroaldol reaction, the β-hydroxy substituent was protected as the corresponding THP ether, before cleaving the SES group using TBAF and refluxing in THF. Thus the problem of detosylation was solved by substituting the tosyl group for a SES group, which gave the same desired high yield and diastereoselectivity.[23]

## 1.49. Desymmetrising the Aldol Reaction: the Use of Chiral Aldehydes

With the optimum conditions established for the aldol reaction, Kazmaier naturally felt it was desirable for the reaction to be enantioselective. Hence, in studies towards the synthesis of α-unsubstituted pipecolinic acids, the enolate of alanine ester was condensed with the chiral aldehyde **93**, using the standard conditions previously established, to form the polyhydroxylated amino acids **94** in a 4:1 ratio (Scheme 1.22; a).[25]




**Scheme 1.22.** *Reagents:* a) LDA, THF, -78°C, 90%; b) i) $H_2$, Pd/C, MeOH, ii) $PPh_3$, DEAD, THF, RT, 92%; c) i) $H_2$, Pd/C, MeOH, ii) $PPh_3$, DEAD, THF, RT, 75%.

The major isomer **94a** was recrystallised from the mixture while the minor isomer **94b** was obtained from the residue by flash chromatography. In both cases the α-methylated pipecolinic acid derivatives **95a** and **95b** were synthesised in high yields (Scheme 1.22). These cyclic derivatives were subjected to nOe experiments to confirm the configuration of the two stereogenic centres formed in the aldol reaction.

The same reaction was carried out this time using glycine ester **96**. The induced diastereoselectivity (β-C) was greater than 95%, but unfortunately epimerisation occurred at the α-centre, producing a 1:1 mixture, believed to be due to the labile nature of this proton. However, the aldol product was used successfully for the azasugar synthesis (Figure 1.16).

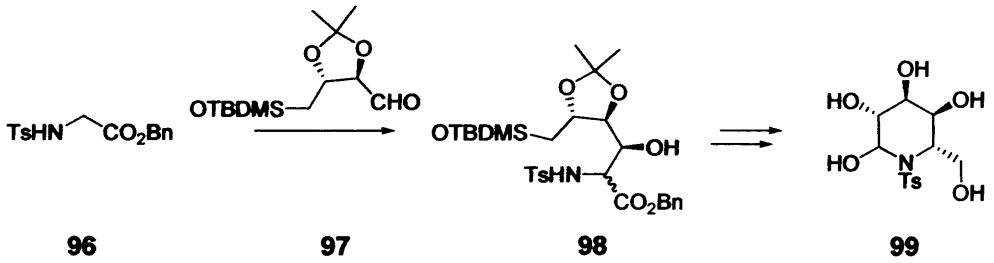



**Figure 1.16**

In an attempt to synthesise optically active polyhydroxylated amino acids, Kazmaier, Grandel and Rominger used the aldehydes shown in Figure 1.17, the results of which are shown in Table 1.15.[26]

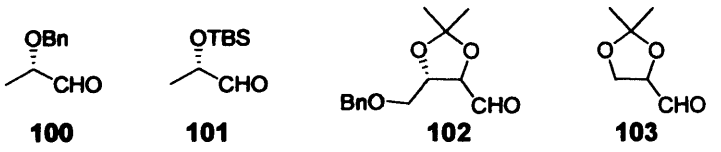
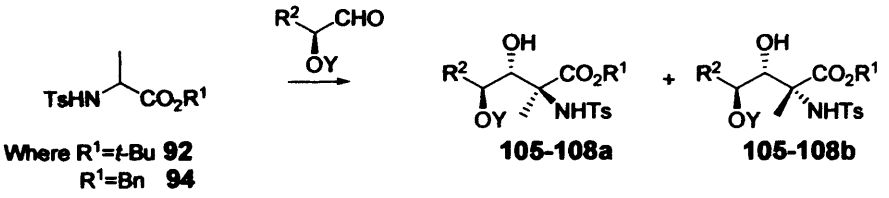



**Figure 1.17**




| Aldehyde | Ester (R) | MXn | Product | *anti:syn* | Yield % |
|---|---|---|---|---|---|
| OBn CHO **100** | *t*-Bu **92** | 2.5 eq $ZnCl_2$ | **105** | 55:45 | / |
| OBn CHO **100** | *t*-Bu **92** | 1.2 eq $SnCl_2$ | **105** | 59:41 | / |
| OBn CHO **100** | *t*-Bu **92** | 2.5 eq $SnCl_2$ | **105** | 81:19 | 88 |
| OTBS CHO **101** | Bn **94** | 2.5 eq $SnCl_2$ | **106** | 89:11 | 85 |
| BnO CHO **102** | *t*-Bu **92** | 1.2 eq $SnCl_2$ | **107** | 67:33 | / |
| BnO CHO **102** | *t*-Bu **92** | 2.5 eq $SnCl_2$ | **107** | 78:22 | 90 |
| CHO **103** | Bn **94** | 2.5 eq $SnCl_2$ | **108** | 80:20 | 87 |

**Table 1.15**

From the Table, it is clear that the simple diastereoselectivities shown were nearly independent of the aldehyde used. However, the highly oxygenated aldehydes **102** and **103** displayed exceptional induced selectivities. Hence this method can be used as a simple and highly selective route to α-alkylated polyhydroxylated amino acids, provided alanine esters are used instead of the glycine derivatives, which undergo epimerisation.

## 1.50. Application of the Kazmaier Aldol Reaction to the Synthesis of Pyrroles

Sharland's[17] research centred around the synthesis of pyrroles, however problems arose with the synthesis of the starting materials in some of the original strategies. A new route was envisaged utilising the Kazmaier[18] aldol reaction, previously described, provided that the condensation of a tin(II) enolate of ethyl *N*-tosyl glycinate would be successful with a variety of acetylenic aldehydes and ketones (Figure 1.18).

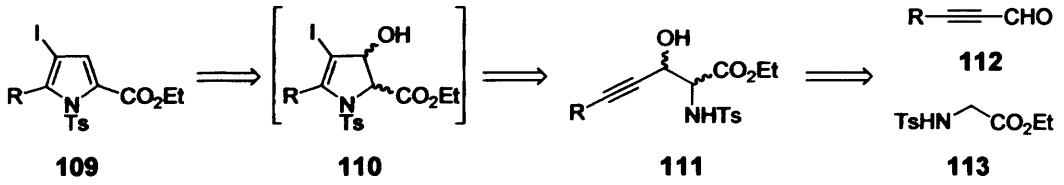
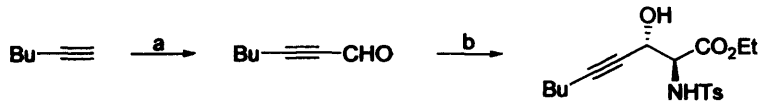



**Figure 1.18**

Kazmaier reported that the use of a glycine ester **96** in such a tin(II) mediated aldol reaction resulted in epimerisation of the α-position due to the presence of the ester functionality, while the level of control at the new β-position was excellent (Figure 1.16).[25] At this stage, it was not clear whether any diastereoselectivity would be obtained in the proposed condensation (Figure 1.18), since Kazmaier did not conduct experiments with any acetylenic aldehydes. However, the selectivity was not important since, inevitably, to form the corresponding pyrroles **109**, both stereogenic centres would be destroyed (Figure 1.18).

To prepare the acetylenic aldehydes **112**, the corresponding terminal acetylenes were formylated using *N*,*N*-dimethylformamide following a procedure devised by Journet[27] and co-workers (Scheme 1.23; a). Excellent yields were obtained provided a reverse quench into a biphasic solution of 10% aqueous potassium dihydrogen phosphate was utilised. For example, hept-2-yn-1-al **115** was obtained in 81% yield following purification (Scheme 1.23; a). Next, this was reacted with the tin enolate of ethyl *N*-tosyl glycinate at -78°C

which following the work-up, afforded the crude β-hydroxy-α-amino ester **116** in a yield of 83% (Scheme 1.23; b). Surprisingly, the reaction was quite diastereoselective, affording a 7.5:1 mixture of diastereoisomers, which following recrystallisation, afforded the product **116** in 54% yield.




**114** **115** **116**

**Scheme 1.23.** *Reagents:* a) n-BuLi, DMF, THF, 1 h, 81%; b) **113**, LDA, $SnCl_2$, THF, -78°C, 16 h, 83%.

From Kazmaier's[18] research, the major product was believed to be the *anti* diastereoisomer **116**. This was confirmed when the product **119** resulting from the condensation of phenyl substituted aldehyde **117** with the enolate of ethyl *N*-tosylglycinate, was subjected to X-ray diffraction. The results obtained are summarised in Table 1.16.[28]

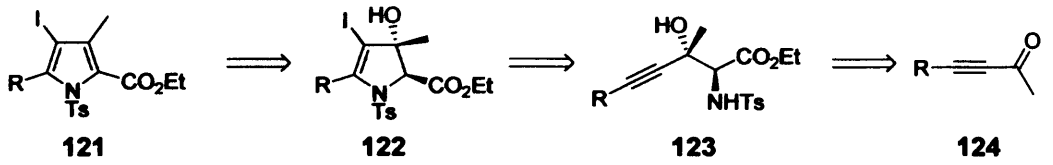

**115-116** **111a**

| Aldehyde (R) | Product | Ratio (*anti:syn*) | *anti* diastereoisomer (%) |
|---|---|---|---|
| Bu **115** | **116** | 88:2 | 54 |
| Ph **117** | **119** | 93:7 | 58 |
|  **118** | **120** | 94:6 | 63 |

**Table 1.16**

## 1.51. Extending the tin(II)-mediated aldol reaction methodology to ketones

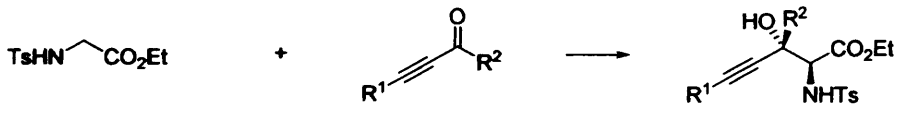
With the success of this aldol reaction with a range of acetylenic aldehydes, the next logical step was to test if the same high diastereoselectivity would be obtained with the corresponding ketones **124**, and if the resulting products **123** could be used in the synthesis of more highly substituted pyrroles **121** (Figure 1.19).




**121** **122** **123** **124**

**Figure 1.19**

However, Kazmaier[18] had not conducted studies with ketones, so no examples were available for comparison. A variety of ketones were thus subjected to the tin(II)-mediated aldol reaction when the effect of the size of the substituent in the β-position on the diastereoselectivity of the reaction could be deduced. The results are shown in Table 1.17.




**113** **125-9** **130-134**

| $R^1$ | $R^2$ | Starting Material | Product | Ratio (*anti:syn*) | Yield *anti* diastereoisomer (%) |
|---|---|---|---|---|---|
| Ph | Me | **125** | **130** | 92:8 | 79 |
| Ph | $C_7H_{15}$ | **126** | **131** | 90:10 | 80 |
| Ph | *i*-Pr | **127** | **132** | 84:16 | 76 |
| H | Me | **128** | **133** | 88:12 | 81 |
| Bu |  | **129** | **134** | / | / |

**Table 1.17**

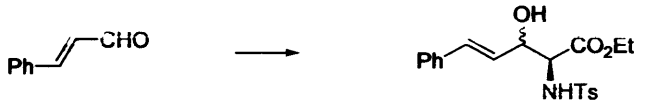
Delightfully, the selectivity of the reaction was still high when the aldehydes were substituted by acetylenic ketones and clarification that the major products formed were the

*anti* diastereoisomers was once again obtained by conducting X-ray diffraction on the products. Also, it can be seen that as the size of the group in the β position increases, the stereoselectivity decreases marginally. This observation can be explained by taking into account the transition state models proposed by Kazmaier,[18] since the difference in the stability between transition state A and B becomes less distinct, and thus the diastereoselectivity falls (Figure 1.14). In addition, it was noteworthy that the same *anti* diastereoselectivity was observed with the ketones as the aldehydes, regardless of the fact that the substituent ($R^2$) is now larger than the alkyne functionality.

The findings from Sharland's study were in agreement with Kazmaier's results, with regards to the fact that the major isomer obtained was the *anti* diastereoisomer. However, the success with the glycine enolate was not consistent with Kazmaier's previous study where epimerisation was observed. Accordingly, the structure of the tin enolate needs to be verified.

### 1.52. Expanding the methodology to α,β-unsaturated Aldehydes and Ketones

With the high selectivity obtained in the tin(II)-mediated aldol condensation, between acetylenic aldehyde and ketones, it was desirable to test the selectivity with a variety of α,β-unsaturated aldehydes and ketones. Thus, in the latter stages of his research, Sharland conducted a brief study with aldehydes and ketones of this type to use the products in the synthesis of highly substituted pyrrolidines.[29] The initial substrate tested was (*E*)-cinnamaldehyde **135** which gave the desired β-hydroxy-α-amino ester **136**, but as a mixture of diastereoisomers in the ratio of 4:1 which could not be separated completely (Scheme 1.24).




**135** **136**

**Scheme 1.24.** *Reagents:* **113**, LDA, THF, $SnCl_2$, -78°C-0°C, 66%.

By analogy with the products of the previous reactions, the major diastereoisomer should be the *anti* diastereoisomer. This was confirmed by the coupling constants. This lower diastereoselectivity was disappointing and believed to be due to either an increase in the

steric hindrance between the phenyl group and the ester or a reduced steric hindrance between the phenyl group and the ester moiety, since either of these factors would lower the selectivity. With this successful addition, the reaction was repeated with various commercially available (*E*)-α-β-unsaturated aldehydes and ketones (Table 1.18).

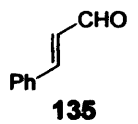
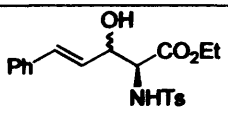
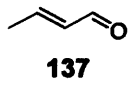
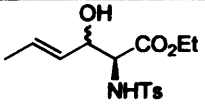
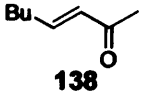
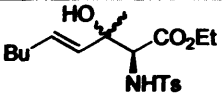
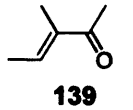
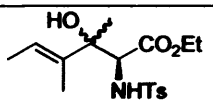
| Aldehyde or ketone | Product | % *Anti* | % *Syn* | Combined Yield (%) |
|---|---|---|---|---|
|  **135** |  **136** | 80 | 20 | 67 |
|  **137** |  **140** | 63 | 37 | 69 |
|  **138** |  **141** | 71 | 29 | 79 |
|  **139** |  **142** | 53 | 47 | 91 |

**Table 1.18**

It can be seen from Table 1.18 that as the two groups on the alkene become equal in size, the selectivity of the reaction approaches zero. Overall, the results show that the selectivity decreased from 9:1 when acetylenic aldehydes and ketones were used to approximately 4:1 when (*E*)-α,β-unsaturated aldehydes and ketones were utilised. However, this ratio was still synthetically useful for the synthesis of a variety of cyclisation precursors.

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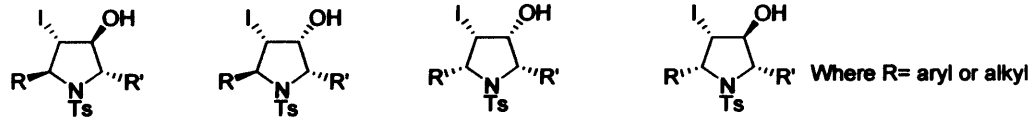
# Chapter Two

# Synthesis of Cyclisation Precursors

## 2.10. Introduction

The aim of the present research was to synthesise a range of pyrrolidines both aryl and alkyl, with different stereochemistries (Figure 2.10).

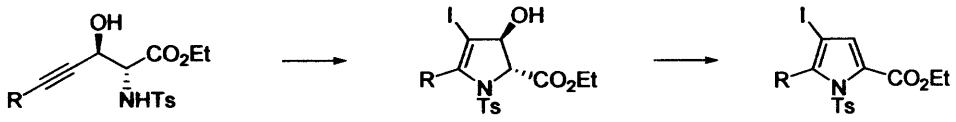



**143a** **143b** **143c** **143d**

**2,5-*trans*** **3,4-*cis*** **all *cis*** **2,5-*cis***

**Figure 2.10**

Previously in the Knight group, Sharland[1] utilised a tin(II) mediated aldol condensation of the enolate of ethyl *N*-tosyl glycinate with various acetylenic aldehydes and ketones to furnish the *anti* amino alcohol precursors highly diastereoselectively. These *anti* diastereoisomers **111** were reacted with iodine and following elimination, the corresponding pyrrole **109** was isolated (Scheme 2.10a).



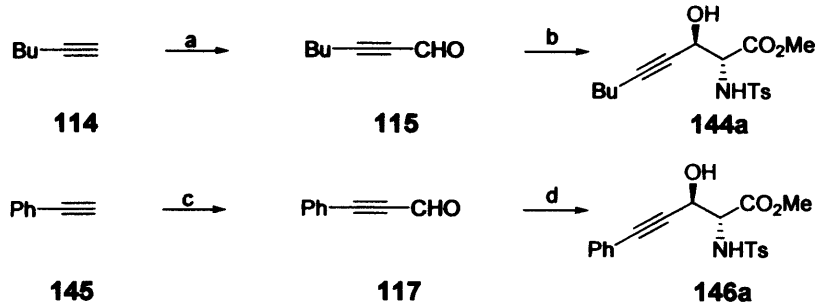
**111** **110** **109**

**Scheme 2.10a**

Following reduction of the alkyne moiety of these aldol precursors **111**, a (*Z*)-amino alcohol derivative would be obtained which following a 5-*endo*-trig cyclisation should afford a pyrrolidine. Hence, this previously developed methodology was utilised in the quest for cyclisation precursors, but in the aldol condensation the methyl ester glycine derivative was used in preference to the previously used ethyl ester **113**, to prevent any of the ethyl ester protons obscuring the pyrrolidine ring protons.

## 2.20. Kazmaier aldol reaction[2]

The acetylenic aldehydes hep-2-ynal **115** and phenyl-propynal **117** and were prepared in excellent yields by formylation of the corresponding lithium acetylides with DMF followed by a reverse quench procedure in the work-up (Scheme 2.10b).[3] Formation of these aldehydes was evident by the new singlets at around 9.0 ppm in the $^1$H NMR spectrum.



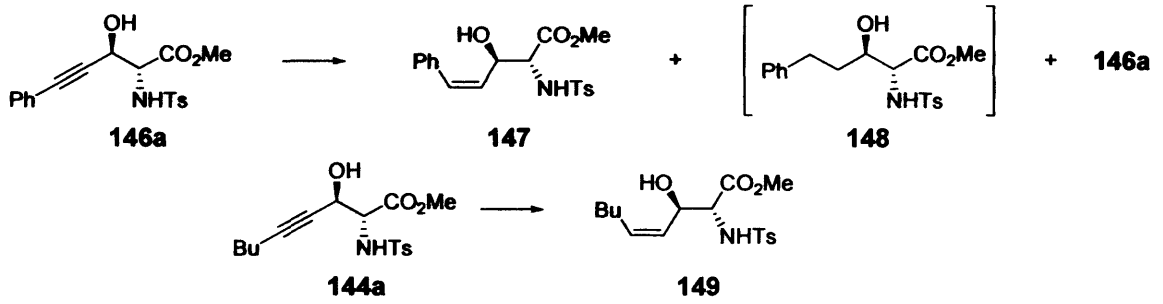

**Scheme 2.10b.** *Reagents:* a) THF, -40°C, n-BuLi, 89%; b) **152**, $SnCl_2$, LDA, THF, -78°C, 41%; c) THF, -40°C, n-BuLi, 98%; d) **152**, $SnCl_2$, LDA, THF, -78°C, 45%.

Condensation of phenyl propynal **117** with the enolate of methyl *N*-tosylglycinate in the presence of tin(II) chloride afforded a 9:1 mixture of diastereoisomers, and following chromatography and recrystallisation, the major *anti* isomer **146a** was obtained in 45% yield, as apparent from a molecular ion of 376 ($M^+$ + Na) and the new C*H*OH and C*H*N protons in the range 4.10 to 4.60 ppm, with a coupling constant of 3.9 Hz (the *syn* isomer was not isolated). When the reaction was repeated using hept-2-ynal **115**, following chromatography and recrystallisation, the *anti* diastereoisomer **144a** was isolated in 41% yield, as apparent from the new C*H*OH and C*H*N protons in the range 4.15 to 4.90 ppm, also with a coupling constant of 3.9 Hz. In both cases, following chromatography, the aldol adducts were isolated in approximately 60% yield, which was lowered to approximately 40% following recrystallisation to remove the methyl *N*-tosyl glycinate starting material. Numerous recrystallisations were necessary to obtain pure material for use in the subsequent Lindlar reductions, to prevent the impurities poisoning the catalyst further.

In the initial Lindlar[4] reduction of the phenyl aldol adduct **146a**, the catalyst (5% palladium on calcium carbonate) was poisoned by the addition of quinoline. However, over-

poisoning of the catalyst frequently occurred. So, in later experiments, commercially available Lindlar's catalyst (5% palladium on calcium carbonate poisoned with lead acetate) was purchased to obviate this problem. Unfortunately, despite this the Lindlar reduction of the phenyl substrate **146a** was capricious and so complete reduction was not achieved (Scheme 2.11). Despite the poisoning of the catalyst, some (*Z*)-olefin **147** was reduced to the alkane **148**, before all the alkyne **146a** had been reduced, hence various mixtures of the alkyne **146a**, (*Z*)-olefin **147** and alkane **148** were used "crude" in the subsequent cyclisations (Section 3.21a, Chapter 3). Formation of the (*Z*)-olefin **147** was confirmed by the new olefin peaks at 5.55 and 6.60 ppm, with a *cis* coupling of 11.7 Hz.

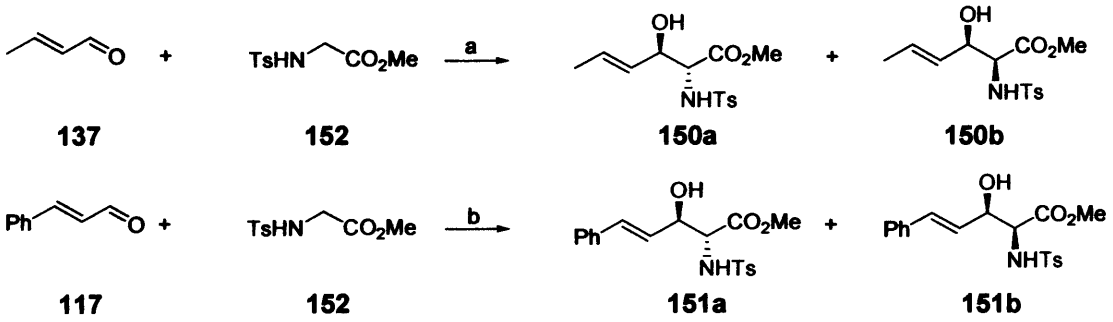
Fortunately, in the case of the butyl derivative **144a**, after a few teething problems, complete reduction was achieved to afford the *cis*-olefin **149** in quantitative yield, as confirmed by the new olefin resonances in the range 5.25-5.60 ppm, with a typical *cis* coupling of 10.9 Hz (Scheme 2.11).




**Scheme 2.11.** *Reagents*: Lindlar's catalyst, EtOAc, $H_2$.

With the (*Z*)-precursors synthesised, next the corresponding (*E*)-precursors were required. Obviously, reduction of the alkyne to the (*E*)-olefin would also reduce the ester so another approach was necessary. In the latter stages of Sharland's[5] PhD, condensations were conducted with the enolate of *N*-tosyl glycine ethyl ester and various α,β-unsaturated aldehydes and ketones to afford β-hydroxy-α-amino esters but with reduced diastereoselectivity (Section 1.52). Separation of the diastereoisomers was not conducted in most cases. Accordingly, the enolate derived methyl *N*-tosylglycinate by deprotonation using LDA was condensed with (*E*)-crotonaldehyde **137** to afford a 5:1 mixture of diastereoisomers in the crude product, according to $^1$H NMR integration of the C*H*N protons. Based on the previous results, the major isomer **150** was presumed to be the *anti* diastereoisomer **150**. Following chromatography and recrystallisation, this major

diastereoisomer was isolated in 36% yield while the minor diastereoisomer **253** together with methyl *N*-tosyl glycinate **152** starting material was in the mother liquors. The proposed *anti* diastereoisomer **150** was characterised by a new C*H*N proton at 4.00 ppm with a coupling of 9.2 Hz to the NH and a 4.2 Hz coupling to the C*H*OH proton. Despite numerous recrystallisations to remove the starting material **152**, the minor isomer **253** could not be isolated cleanly and hence, alternatives methods were used to synthesise this precursor. A later route afforded the minor isomer **253** (Scheme 2.47) and the coupling between the C*H*OH and C*H*N protons was revealed to be 3.5 Hz.




**Scheme 2.12.** *Reagents:* a) $SnCl_2$, **137**, LDA, THF, -78°C, **150a** 36%; b) $SnCl_2$, **117**, LDA, THF, -78°C, 57%.

By considering the Newman projections illustrated in Figure 2.12, when the dihedral angle is 180°, that is when the OH and NH groups are in an *anti* relationship, from the Karplus equation it can be seen that the coupling constant is at its largest since the orbitals are overlapping most efficiently, while when these two groups have a *syn* relationship, this dihedral angle is reduced to 60° resulting in a smaller coupling constant. However, with a dihedral angle of 180°, one would expect the coupling constant to be greater than the 4.2 Hz observed. With only about 1 ppm difference in the J values of the diastereoisomers, X-ray diffraction studies previously conducted by Sharland[6] confirmed the stereochemistry of the major isomer was in fact the *anti* diastereoisomer as proposed. It is possible that due to hydrogen bonding, the dihedral angle is closer to 60°, explaining the small magnitude of the coupling constant, but this is purely speculation.

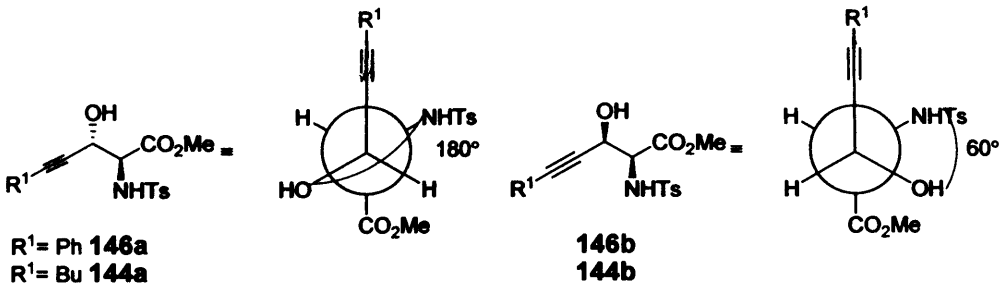
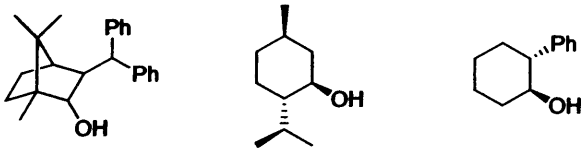



**Figure 2.12**

When the enolate of methyl *N*-tosyl glycinate was treated with (*E*)-cinnamaldehyde **135** the NMR spectrum of the crude product, displayed a 4:1 mixture of diastereoisomers **151**, based on the integration of the methyl ester signals. The major isomer **151a** showed a coupling between the C*H*OH and C*H*N protons of 4.2 Hz while for the minor isomer **151b**, slightly smaller coupling of 3.3 Hz was recorded. So, since *anti* couplings are larger than *syn* couplings, as expected, the major isomer was the *anti* diastereoisomer **151a**. Complete separation of the diastereoisomers could not be achieved, but the quantity of the *anti* diastereoisomer could be increased by repeated recrystallisations.

## 2.21. Desymmetrising the Aldol Reaction Using Chiral Auxiliaries

This aldol reaction was proving to be a very useful synthetic method for synthesising a range of cyclisation precursors, but could it be made enantioselective? The use of chiral aldehydes was not an option, unlike in Kazmaier's[7] research, but as an alternative, it was hoped to introduce chirality by using an auxiliary as the ester on the *N*-protected amine. Numerous auxiliaries were tested which are shown in Figure 2.13.



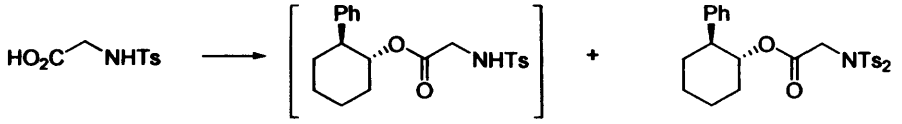

**153** **154** **155**

**Figure 2.13**

The initial auxiliary[8] **153** was synthesised from D-camphor, but recrystallisation failed due to its sticky gum-like consistency, despite the use of numerous solvent systems.

Chromatography was also unsuccessful and consequently, an alternative auxiliary was employed, as complete purification was never completely acheived.

The next auxiliary tested was *trans* 2-phenylcyclohexanol **155**, which though expensive was commercially available. Accordingly, *N*-tosyl glycine **156** and *trans*-2-phenyl-cyclohexanol **155** were reacted with dicyclohexylcarbodiimide **157** (DCC) in the presence of catalytic DMAP in tetrahydrofuran (Scheme 2.13; a). The resonances in the NMR spectrum of the crude product were broad and as such coupling constants could not be deduced accurately. Following chromatography, an 8:1 mixture of the alcohol **155** and the bis-sulfonamide **159** was obtained as deduced from the downfield shift of the AB system of doublets at 3.25 and 3.45 ppm corresponding to the $CH_2$ group adjacent to the nitrogen. No mono-sulfonamide **158** was identified in any of the fractions and the yield of **159** was not determined.




**156** **158** **159**

**Scheme 2.13.** *Reagents:* a) DCC, DMAP, THF, 15 h; b) BOPCl, *anh.* py, 0.5 h, 0°C, DMAP, 24 h, R.T.; c) DMAP, DCC, $CH_2Cl_2$, -20°C, 17.5 h, R.T.; d) DMAP, DCC, $CH_2Cl_2$, HOBt, -20°C, 17.5 h, R.T.

Next the coupling reaction was repeated but using BOP-Cl as the coupling agent in pyridine, but frustratingly only starting material **155** was recovered (Scheme 2.13; b). DCC **157** was once again used as the coupling agent but in dichloromethane, following a procedure by Steglich,[10] but only a small degree of coupling was observed (Scheme 2.13; c).

1-Hydroxybenzotriazole hydrate (HOBt) **160** is often used as an additive in reactions where an activated ester of an amino acid (*i.e.* one containing a good $RO^-$ leaving group) is coupled with the free amino group of another. Usually, the activated ester **161** is formed using a coupling reagent such as DCC **157**. However, when this activated ester **161** is attacked directly with the amino group of the second amino acid, racemization often occurs (Figure 2.14, red scheme). To prevent this, HOBt **160** is added to react with the activated

ester first (Figure 2.14, blue scheme). This new intermediate does not racemize because the reaction is highly accelerated due to the addition of HOBt[11] **160**.

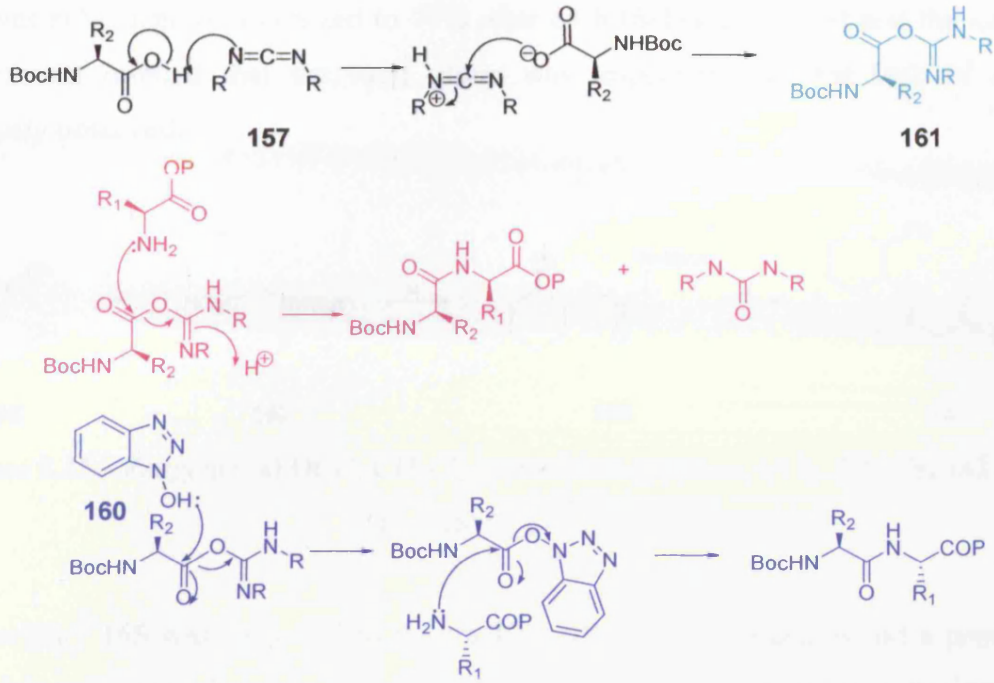
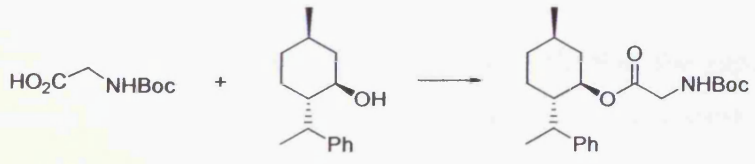


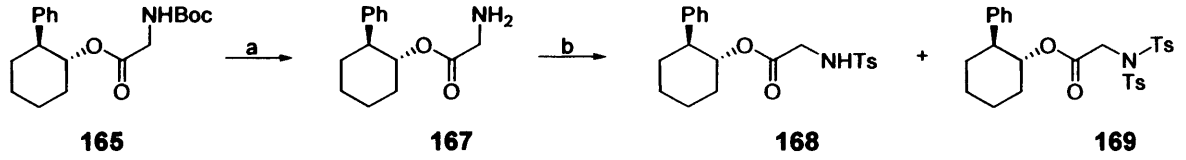

**Figure 2.14**

Despite the addition of one equivalent of HOBt **160** to the reaction mixture, no increase in the level of coupling was observed. Since no significant coupling was observed, despite the use of different coupling agents, an alternative catalyst, 4-pyrrolidino-pyridine, was tested. Regrettably, sufficient quantity of mono-tosylate **158** was not isolated to allow continuation of the sequence on realistic scale. This lack of coupling was believed to be due to the tosyl group, presumably due to the lability of the NH in the sulfonamide given that Hamon[12] *et al.,* successfully coupled 8-phenylmenthol **163** with *N*-Boc-glycine **162a** in 93% using DCC **157** and DMAP (Scheme 2.14).




**Scheme 2.14.** *Reagents:* DCC, DMAP, 93%.

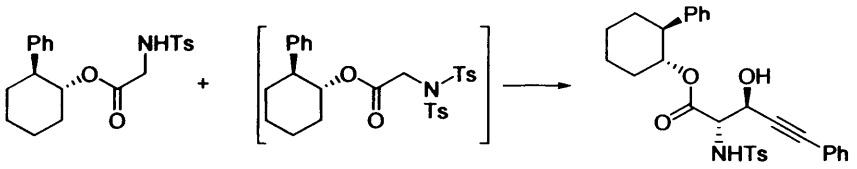
Regrettably, following chromatography of the crude product, a 3.6:1 mixture of bis-sulfonamide **169** and mono-sulfonamide **168**, was obtained, which due to similar $R_f$'s, were only partially separated. Clearly optimisation was required, but at this time it was desirable to test **168** to verify if a mixture of diastereoisomers would be obtained, as the previous reaction of the Boc derivative **165** suggested (Scheme 2.15; b).




**165** **167** **168** **169**

**Scheme 2.16.** *Reagents:* a) TFA, $CH_2Cl_2$, 1 h, 81%; b) TsCl, DMAP, $CH_2Cl_2$, 16 h.

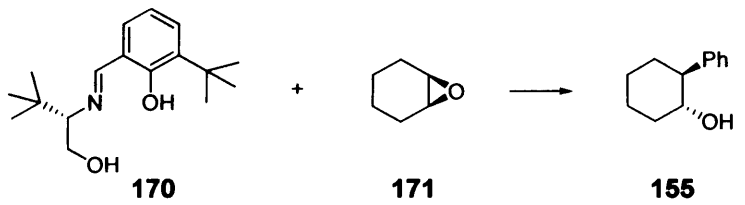
So a 4:1 mixture of the bis-sulfonamide **169** and mono-sulfonamide **168** was reacted with phenyl propynal **117** in the presence of tin(II) chloride (Scheme 2.17). Following chromatography and the recovery of the bis-sulfonamide **169**, the methanol fraction appeared to contain the desired product **170** as a single diastereoisomer, as apparent from the two new broad resonances at 3.40 and 4.10 corresponding to the C*H*OH and C*H*N protons respectively, and disappearance of the doublets of the ABX system. The yield of **170** was not obtained.




**168** **169** **170**

**Scheme 2.17.** *Reagents:* $SnCl_2$, LDA, -78°C, THF, **117**, 0.5 h.

Despite these promising results, the expense of the auxiliary precursor **155** was evidently a problem. The Oguni[13] group reported the synthesis of *trans* 2-phenyl-cyclohexanol **155** in 90% enantiomeric excess from epoxide **172** using phenyllithium in the presence of a chiral Schiff reagent **171** (Scheme 2.18).

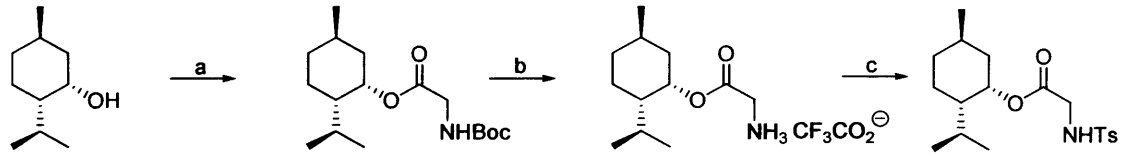



**170** **171** **155**

**Scheme 2.18.** *Reagents:* PhLi, 5 mol% chiral Schiff Base, 100% yield, 90% ee.

However this Schiff base **171** was not commercially available and as such the Oguni group prepared it from relatively expensive (*L*)-*tert*-leucinol. Due to the uncertainty regarding the aldol reaction with this auxiliary **168**, it would have been prudent to purchase (*L*)-*tert*-leucinol at this stage. Instead, being keen to reduce the number of steps in the sequence, L-menthol **154** was employed as a cost effective alternative, since both the racemate and the single enantiomers are inexpensive.

L-Menthol **154** and *N*-Boc glycine **162a** were coupled together in the presence of DCC **157** and 4-pyrrolidino-pyridine to afford the ester **173** in 75% yield, consistent with the appearance of two carbonyl signals at $\delta_C$ 155.6 and 170.0 ppm (Scheme 2.19; a). Condensation with phenyl propynal **117** in the presence of tin(II) chloride failed, but would the reaction be successful with the tosyl derivative **175**? Subsequent deprotection of the carbamate **173** with a 20% solution of trifluoroacetic acid in dichloromethane afforded **174**, as apparent from the loss of the *t*-Bu singlet. Treatment of **174** with triethylamine and *p*-tosyl chloride in dichloromethane furnished the sulfonamide **175** in 60% yield after chromatography, as apparent from the new doublets at 7.20 and 7.85 (AA'BB' system) with a typical *ortho* coupling of 8.4 Hz (Scheme 2.19; c).



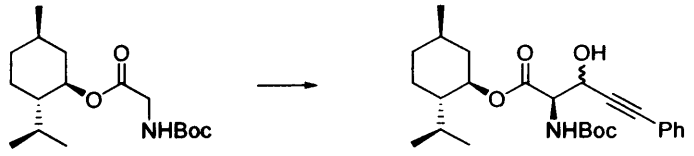

**154** **173** **174** **175**

**Scheme 2.19.** *Reagents:* a) DCC, 4-pyrrolidino pyridine, $CH_2Cl_2$, 16 h, 75%; b) TFA, $CH_2Cl_2$, 3 h, 84 h; c) $Et_3N$, $CH_2Cl_2$, DMAP, TsCl, 16 h, 51%.

Following treatment of **175** with phenyl propynal **117** in the presence of tin(II) chloride and base, only starting material was isolated. So unlike the *trans*-2-phenyl-cyclohexanol

derivative **168**, this aldol reaction under these conditions was not successful with the menthol ester **175**, irrespective of the nitrogen-protecting group employed. Presumably, the isopropyl group of the menthol ester **175** exerted a greater steric influence than the phenyl group of the cyclohexanol auxiliary **168** and so, seemingly, sterically hindered 8-phenyl menthol **163** would also not have been suitable as a chiral auxiliary. Clearly, a number of options would need to be examined to prove this.

Finally, the menthol auxiliary **173** was treated with phenyl propynal **117** in the absence of tin(II) chloride, but although condensation occurred, as expected low selectivity was obtained to furnish the product **176** as a 1:1 mixture of diastereoisomers, as judged from the integrations of the broad C*H*N signals at 4.50 and 4.60 ppm (Scheme 2.20). Following chromatography, the product was isolated in 45% yield, but once again, the presence of the Boc protecting group resulted in unresolved resonances. Consequently, differentiation between the *syn* and *anti* diastereoisomers was not achieved.




**173** **176**

**Scheme 2.20.** *Reagents:* LDA, THF, -78°C, **117**, 0.5 h, 45%.

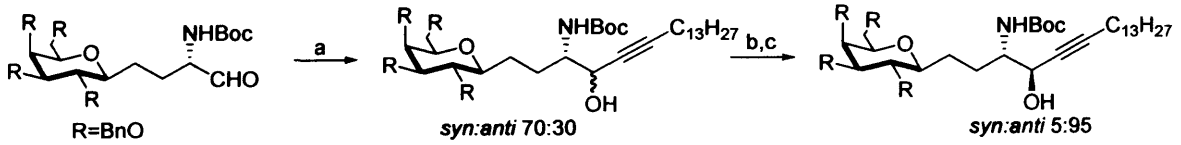
## 2.22. Conclusion

Under these conditions therefore, this aldol reaction was not be made enantioselective using menthol as a chiral auxiliary. However, the promising results obtained from the use of the *trans*-2-phenyl-cyclohexanol based auxiliary **168** should be further studied and hopefully in the future, by following Oguni's research, the *trans*-2-phenyl based auxiliary **168** should successfully furnish the aldol products as single diastereoisomers.

## 2.30. Introduction: Alternative Route to Cyclisation Precursors

The aldol reaction was limited since no (*Z*)-*syn* precursors could be synthesised, and the (*E*)-*syn* precursors were only obtainable in low yields, due to the diastereoselectivity of the reaction. Hence, alternative strategies to the cyclisation precursors were required. Ideally,

these routes would afford the desired cyclisation precursors as single enantiomers, and with the disappointing results obtained for the asymmetric aldol reaction (Section 2.21), routes to single enantiomers of all precursors were necessary. In addition, a route was required that did not incorporate an ester moiety, which would also be reduced in the conversion of the alkyne into the (*E*)-olefin. The second route tested was based on research conducted by the Dondoni[14] group in their synthesis of β-D-galactosyl ceramide methylene isostere; a portion of the route is illustrated in Scheme 2.21.




**177** **178a** **178b**

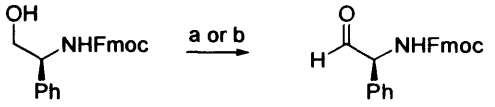
**Scheme 2.21.** *Reagents:* a) 1-pentadecynyllithium, THF, 65%; b) oxalyl chloride, DMSO, *i*-$Pr_2EtN$, $CH_2Cl_2$, -78°C, 90%; c) THF, -78°C, L-Selectride, 0.5 h, 90%.

Due to the single protection of the amino group, addition of the organometal to the aldehyde **177** should give the undesired *syn* stereochemistry. To obtain the *anti* diastereoisomer **178b**, their previously developed oxidation-reduction sequence was used (Scheme 2.21; b and c). The optimum reagent for the reduction of the aldehyde was established to be L-selectride, which afforded predominately the *anti* diastereoisomer (Table 2.10).

| **Conditions** | **Solvent** | **Temperature (°C)** | **Yield (%)** | ***Anti:syn* ratio in crude product** |
|---|---|---|---|---|
| 5 eq $NaBH_4$ | THF/MeOH 4:1 | -60 | 60 | 60:40 |
| 5 eq $NaBH_4$, +1 eq $CeCl_3$ | EtOH | -60 | 90 | 73:27 |
| 1 eq Red-Al | THF | -78 | 60 | 70:30 |
| 1 eq LABOH | THF | -78 | 24 | 48:52 |
| 3 eq DIBAH | THF | -78 | 43 | 78:22 |
| 2 eq L-Selectride | THF | -78 | 90 | 95:5 |
| 2 eq L-Selectride with 1 eq $ZnBr_2$ | THF | -78 | 65 | 85:15 |

**Table 2.10**

*N*-Protected α-amino alcohols are prone to racemization if they contain epimerisation enhancing features such as an α-aryl group or a strongly electron-withdrawing *N*-protecting group. Research by Myers[15] has shown that Swern[16] oxidation of the sensitive precursor **179** afforded the aldehyde **180** in only 50% ee, compared to the excellent 99% ee recorded for the Dess-Martin periodinane[17] (Scheme 2.22).




**179** **180**

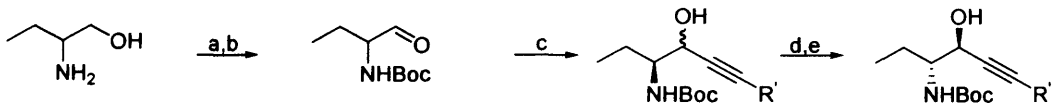
**Scheme 2.22.** *Reagents*: a) Swern Oxidation, (*i*-$Pr_2NEt$), 50% ee; b) Dess-Martin periodinane, 99% ee.

In light of these discoveries the route devised by Dondoni was adapted to include a Dess-Martin oxidation in place of the Swern oxidation, to lessen the chance of epimerisation. In addition to the high enantioselectivity, the Dess-Martin oxidation is more suitable for use in larger scale reactions, due to the unpleasant odour of dimethyl sulfide generated in Swern oxidations.

## 2.31. Results and Discussion

2-Amino-1-butanol **181** was treated with triethylamine and Boc anhydride in dichloromethane for 16 h to afford the carbamate **182** in 56% yield, as confirmed by the new visible carbonyl stretch at 1692 $cm^{-1}$ in the infra red spectrum in addition to appearance of a *t*-butyl singlet at $\delta_H$ 1.35 ppm and also a molecular ion of 190 ($M^+$ + H), consistent with carbamate formation was apparent. Treatment with the Dess-Martin periodinane in dichloromethane furnished the aldehyde **183** in 68% yield, as apparent from a resonance at 9.50 ppm (Scheme 2.23; a and b). Reaction of the aldehyde **183** with 1-hexynyllithium furnished the amino alcohol **184**. In the NMR spectrum of the crude product, all significant protons appeared as broad resonances and there were too many to be purely due to a mixture of diastereoisomers. The remaining peaks must have been due to the presence of rotamers, hence the selectivity of the reaction was not determined. Instead, the crude product **184** was immediately subjected to a Swern oxidation to afford the ketone **185**, as confirmed by the new carbonyl signal at $\delta_C$ 185.0 ppm. The crude

ketone **185** was then reacted with L-selectride to afford the amino alcohol **186** in a disappointing 10% yield, following chromatography (Scheme 2.23; d and e). According to Dondoni's research, this amino alcohol should be the *anti* diastereoisomer **186**, but both the C*H*OH and C*H*N protons were broad resonances, hence coupling constants could not be calculated, to confirm this.

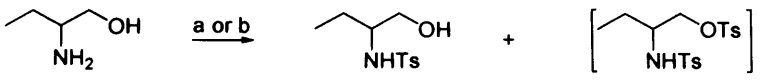



**181** **183** **184** **186**

**Scheme 2.23.** *Reagents:* a) $Et_3N$, $CH_2Cl_2$, cat DMAP, $Boc_2O$, 16 h, 56%; b) $CH_2Cl_2$, Dess- Martin periodinane, 2 h; c) **114**, n-BuLi, THF, -78°C, 2 h; d) oxalyl chloride, DMSO, $CH_2Cl_2$, Hünigs base; e) L-Selectride, -100°C, THF, 0.5 h, 10% over 4 steps.

Due to the acid sensitivity of the Boc group, problems were encountered in the removal of the L-selectride residues and so the quantity of material obtained was low. All previous cyclisations in the Knight group had been conducted on tosylated precursors, so for continuity, the Boc group needed to be replaced with a tosyl group. With the limited amount of material from the L-selectride step (Scheme 2.23; e), test reactions were conducted on readily available 2-amino-1-butanol **181** to determine the optimum conditions for tosylation of a free amine in the presence of a hydroxyl group (Scheme 2.24).

Treatment of the amino alcohol **181** with triethylamine and *p*-tosyl chloride furnished the monotosylate **187** in a moderate 43% yield, following recrystallisation as apparent from the two AA'BB' doublets at 7.20 and 7.70 ppm and the presence of an OH signal at 2.55 ppm (Scheme 2.24; a). When the reaction was repeated, using pyridine as the base, a 1.5:1 mixture of mono-sulfonamide **187** and tosylate **188** was obtained. Formation of the tosylate **188** was apparent from the two aryl methyl singlets at 2.30 and 2.35 ppm and the NH signal at 5.30 ppm (Scheme 2.23). Disappointingly, following deprotection of substrate **186** and treatment with triethylamine and *p*-tosyl chloride, no product was isolated, presumably due to the small scale, thus alternative routes were researched.




**181** **187** **188**

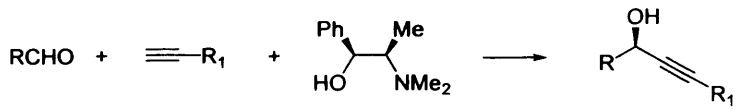
**Scheme 2.24.** *Reagents:* a) $Et_3N$, $CH_2Cl_2$, DMAP, TsCl, 43%; b) Pyridine, $CH_2Cl_2$, DMAP, TsCl.

## 2.40. Route 3

## 2.41. Introduction

Previous methods for the asymmetric synthesis of optically active propargylic alcohols involved either nucleophilic addition of metallated acetylenes to aldehydes, or ynone reduction.[18-22] However, only some of the catalysts and reagents are commercially available and as such, the known methods require the synthesis of one of the starting materials since neither metallated terminal alkynes (stannyl, boryl or zinc for example) nor ynones are accessible commercially. Aldehyde addition procedures are advantageous over ynone reduction methods since they result in the formation of a new carbon-carbon bond and stereogenic centre in one step.[23,24]

In initial studies, the Carreira[25] group observed that terminal alkynes undergo addition to aldehydes in excellent yields in the presence of zinc triflate and an amine base at ambient temperature (Scheme 2.25). This reaction was made asymmetric by adding *N*-methylephedrine, the results of which are shown in Table 2.11.




**189a-e** **190a-e** **191** **192a-n**

**Scheme 2.25.** *Reagents:* 1.1 eq. $Zn(OTf)_2$, 1.2 eq. $Et_3N$, 1.2 eq *N*-methylephedrine, 23°C, Toluene, 2-20 h.

Excellent enantiomeric excesses were obtained with both aromatic and aliphatic aldehydes and in addition, either enantiomer could be accessed depending on which enantiomer of the chiral additive was utilized. Changing the solvent to dichloromethane or tetrahydrofuran resulted in a slight decrease in enantioselectivity and crucially, unlike conventional methods employing pyrophoric organozinc reagents ($Me_2Zn$, for example) anhydrous

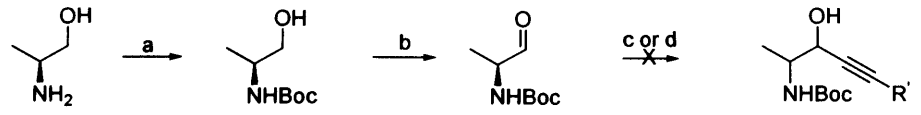
conditions were not essential in this procedure. A plethora of alkynes and aldehydes were tested (Table 2.11).

| Aldehyde (R) | 189 | Alkyne ($R^1$) | 190 | Time (h) | Product 192 | Yield (%) | Enantiomeric excess (%) |
|---|---|---|---|---|---|---|---|
| *c*-$C_6H_{11}$ | **a** | Ph | **a** | 1 | **a** | 99 | 96 |
| *c*-$C_6H_{11}$ | **a** | $Ph(CH_2)_2$ | **b** | 4 | **b** | 98 | 99 |
| *i*-Pr | **b** | $Ph(CH_2)_2$ | **b** | 2 | **c** | 90 | 99 |
| *i*-Pr | **b** | Ph | **a** | 2 | **d** | 95 | 90 |
| PhCH=CH | **c** | $Ph(CH_2)_2$ | **b** | 20 | **e** | 39 | 80 |
| *t*-Bu | **d** | $Ph(CH_2)_2$ | **b** | 2 | **f** | 84 | 99 |
| *t*-Bu | **d** | Ph | **a** | 2 | **g** | 99 | 94 |
| Ph | **e** | $Ph(CH_2)_2$ | **b** | 20 | **h** | 52 | 96 |
| Ph | **e** | Ph | **a** | 20 | **i** | 53 | 94 |
| *c*-$C_6H_{11}$ | **a** | $Me_3Si$ | **c** | 2 | **j** | 93 | 98 |
| $Me_3CCH_2$ | **f** | $Ph(CH_2)_2$ | **b** | 2 | **k** | 72 | 99 |
| $Me_3CCH_2$ | **f** | Ph | **a** | 2 | **l** | 90 | 97 |
| *c*-$C_6H_{11}$ | **a** | $Me_3SiCH_2$ | **d** | 4 | **m** | 84 | 98 |
| *c*-$C_6H_{11}$ | **a** | $TBSOCH_2$ | **e** | 5 | **n** | 83 | 98 |

**Table 2.11**

## 2.42. Results and Discussion

(*S*)-2-Aminopropan-1-ol **193** was reacted with Boc anhydride to afford the carbamate **194** as apparent from the *t*-butyl singlet at 1.35 ppm and carbonyl signal at 1730 $cm^{-1}$ (Scheme 2.26; a). The crude carbamate **194** was then treated with Dess-Martin periodinane in dichloromethane for 3.45 h to afford the aldehyde **195** as confirmed by the signal at 9.50 ppm in the proton NMR spectrum in addition to a molecular ion of 174 ($M^+$ + H), consistent with oxidation, in a disappointing 18% yield, due to the problems with the work-up (Scheme 2.26; b). Unfortunately, treatment of this aldehyde **195** with 1-hexyne **114** in the presence of (*1R,2S*)-*N*-methylephedrine failed, even after 48 h (Scheme 2.26; c and d). This was presumably due to the *N*HBoc moiety of the aldehyde, since the Carreira group's research did not include aldehydes of this type (Table 2.11).

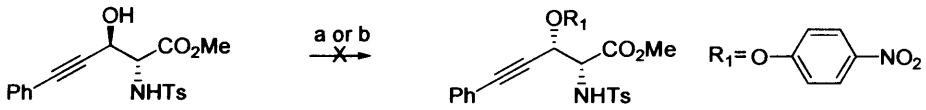



**193** **194** **195** **196**

**Scheme 2.26.** *Reagents:* a) $Boc_2O$, $CH_2Cl_2$, DMAP, 24 h, 100% crude; b) Dess-Martin oxidation, 3.45 h, 18%; c) $Zn(OTf)_2$, $Et_3N$, (*1R,2S*)-*N*-methylephedrine, 1-hexyne, toluene, 0.25 h, 0°C; d) $Zn(OTf)_2$, $Et_3N$, (*1R,2S*)-*N*-methylephedrine, 1-hexyne, toluene, RT, 48 h.

## 2.50. Route 4: Use of the Mitsunobu Reaction

With the problems experienced previously in the quest for the *syn* cyclisation precursor, an obvious answer to the problem was the Mitsunobu[26] reaction. If the *anti* precursors from the aldol reaction (Section 2.10) were subjected to this classic inversion of stereochemistry reaction, the desired *syn* precursor would be obtained, ready for cyclisation studies. Hence, the readily available phenyl aldol adduct **146a** was treated with *p*-nitrobenzoic acid, DIAD (diisopropyl azodicarboxylate) and triphenylphosphine, but no product or starting material was recovered (Scheme 2.27; a).




**146a** **197**

**Scheme 2.27.** *Reagents:* a) *p*-$NO_2C_6H_4CO_2H$, $Ph_3P$, DIAD, THF, 16 h, 0%; b) *p*-$NO_2C_6H_4CO_2H$, $Ph_3P$, THF, 24 h, DEAD, 0%.

A scan of the literature revealed a procedure using DEAD (diethyl azodicarboxylate) on a substrate **198** also bearing an ester moiety (Scheme 2.28).[27]


**198** **199**

**Scheme 2.28.** *Reagents:* *p*-$NO_2C_6H_4CO_2H$, $Ph_3P$, DEAD b) NaOH, EtOH, 70%.

This method was applied to substrate **146a**, but, the NMR spectrum of the crude product revealed only starting material among the DEAD residues (Scheme 2.27; b).

## 2.51. Conclusion

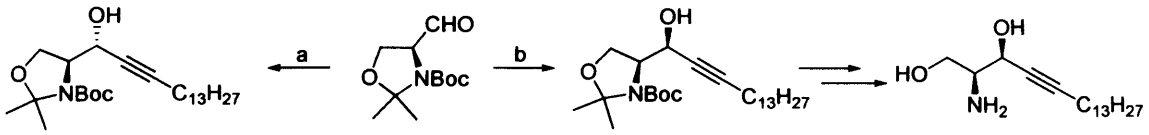
The Mitsunobu reaction has been proven to be sensitive to the steric environment of the alcohol. Frequently, hindered alcohols give low yields of the adduct or starting material is recovered. Zbiral[28] reported that in these instances, changing the solvent from THF to benzene gave higher yields of the products for steroid-derived compounds. However, when Martin and Dodge[29] applied this to their substrates, the Mitsunobu products were only formed in 27% yield. They discovered that on replacing benzoic acid with *p*-nitro benzoic acid, dramatically increased yields were obtained. However, despite using *p*-nitro benzoic acid in the Mitsunobu reaction of substrate **146a**, no reaction was observed with either DIAD or DEAD. No reactions were conducted however in anhydrous benzene, so it is possible that by trying alternative solvents, the reaction may have afforded the desired product, so further study is necessary.

## 2.60. Route 5: Synthesis of *Syn* Cyclisation Precursors Using Garner's Aldehyde

## 2.61. Introduction

Due to the disappointing enantioselectively and diastereoselectivity observed with the aldol reaction using the menthol based auxiliary **175** (Section 2.21), it was decided to use conventional auxiliaries, in the hope that this would afford single enantiomers of the cyclisation precursors and ultimately the pyrrolidines.

Herold[30] used Garner's aldehyde[31] **201** in his enantioselective synthesis of L-*threo* sphingosine **202b**. The key acetylide attack on the aldehyde **201** showed that the stereochemistry of the product obtained could be controlled by the conditions employed in the condensation. With zinc dibromide, chelation occurs between the *N*-Boc group and the aldehyde **201**, which favours addition from the *si*-face, to give predominantly the *syn* isomer **200b** (95:5) while in its absence, predominately the *anti* isomer **200a** is isolated (95:5), by addition from the *re*-face (Scheme 2.29).

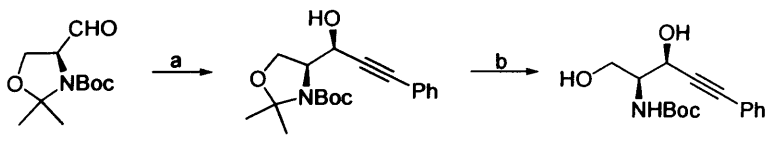



**200a** **201** **200b** **202b**

**Scheme 2.29.** *Reagents:* a) 1-pentadecynyllithium, $Et_2O$, -78°C-R.T., 71%; b)1-pentadecynyllithium, $ZnBr_2$, $Et_2O$, -78°C-R.T., 87%;

## 2.62. Results and Discussion

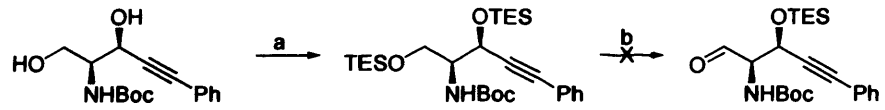
Garner's aldehyde **201** was synthesised according to literature precedent, but unfortunately could not be purified by distillation, as reported in the literature.[31] Purification using a Kügelrohr was also attempted, but disappointingly, the products obtained were only marginally purer than the crude product. Separation of the precursor ester from the aldehyde **201** could be achieved using careful chromatography, despite similar $R_f$ values. However, in practise, the alkylation was usually carried out on the crude aldehyde **201** and chromatography was conducted following deprotection, since the separation was easier. The formation of the propargylic alcohol **204** from Garner's aldehyde **201** was conducted according to literature precedent[32] (Scheme 2.30). Crude Garner's aldehyde **201** was thus treated with lithiophenyl acetylide in the presence of zinc dibromide to afford the desired product **203**, as confirmed by the disappearance of the aldehyde singlet, a new CH signal and a molecular ion of 332 ($M^+$ + H), consistent with alkylation. The crude product was then treated with Amberlyst 15 resin for 64 h to afford the propargylic diol **204** in 53% yield, as confirmed by the loss of the two acetyl methyls and molecular ion of 292 ($M^+$ + H), consistent with deprotection (Scheme 2.30; b). Comparison of the optical rotation recorded {$[\alpha]_D$ -15.74 (*c* 3.39, $CHCl_3$}, with the literature[32] value {$[\alpha]_D$ -19.36 (*c* 1.1, $CHCl_3$)} suggested that the product was indeed the *syn* diastereoisomer **204**.




**201** **203** **204**

**Scheme 2.30.** *Reagents:* a) Ph-≡-CHO **117**, $Et_2O$, BuLi, -20°C, 1 h, 0°C, $ZnBr_2$, 1 h, 0°C-R.T., -78°C, **201**, -78°C- R.T., 8 h, 77%; b) Amberlyst 15, MeOH, 41 h, 53%.

With the *syn* stereochemistry established, the next step was to convert the primary alcohol into an ester, to prevent the possibility of precursor **204** cyclising through the oxygen (Figure 3.27, Chapter 3). This functional group interchange was problematic and test reactions were conduced on crude material. Protection strategies were not an option, as the primary alcohol would be protected in preference to the secondary alcohol. However, Rodriguez[33] *et. al.,* reported a Swern oxidation in which the primary triethylsilyl protected alcohol was oxidised to the aldehyde in the presence of a protected secondary alcohol. Accordingly, the crude amino alcohol **204** was treated with triethylsilyl triflate for 2 h to afford the bis-triethylsilyl ether **205** in 34% yield over 4 steps, as apparent from the new ethyl resonances in the $^1$H NMR spectrum (Scheme 2.31; a). Exposure of the silyl ether **205** to standard Swern oxidation conditions, unfortunately furnished at least four aldehydes (Scheme 2.31; b).



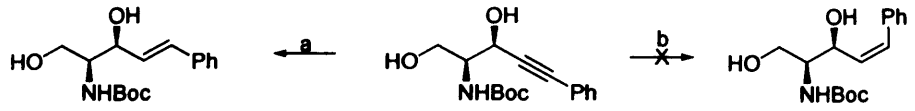

**204** **205** **206**

**Scheme 2.31.** *Reagents:* a) THF, $Et_3N$, TESOTf, 2 h, 34%, over 4 steps; b) $CH_2Cl_2$, oxalyl chloride, DMSO, -75°C, 0.25 h, **205** in $CH_2Cl_2$, 20 mins, -40°C, 20 mins, -70°C, $Et_3N$, -70°C-R.T., 0.5 h.

Once again, the precursor **204** bore the undesirable Boc protecting group, so it was treated with a solution of trifluoroacetic acid in dichloromethane, but no product was isolated. This is hardly surprising considering the product would be a water-soluble amino diol. Despite the fact that precursor **204** contained a Boc protecting group and a primary alcohol, which could both influence the type of cyclisation observed, reductions of the alkyne moiety were conducted, so that at a later stage the manner in which the precursors **207** and **208** cyclised upon treatment with iodine could be determined.

Exposure of the amino alcohol **204** to Red-Al in diethyl ether, successfully afforded the (*E*)-olefin **207**, as confirmed by the new olefin signals at 6.10 and 6.55 ppm, with a *trans* coupling of 15.9 Hz (Scheme 2.32; a). However, when the amino alcohol **204** in ethyl acetate was stirred under an atmosphere of hydrogen, despite numerous attempts, sufficient

quantity of the (*Z*)-olefin **208** was not isolated and no further attempts were conducted (Scheme 2.32; b).



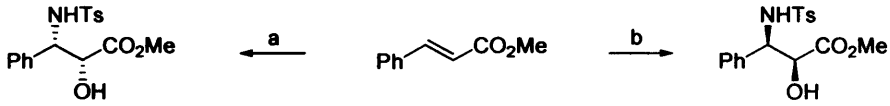

**207** **204** **208**

**Scheme 2.32.** *Reagents:* a) Red-Al, $Et_2O$, 24 h, 70%; b) Lindlar's catalyst, EtOAc, $H_2$, 0%.

## 2.70. Route 6: Asymmetric Aminohydroxylations (AA) of Dienes

## 2.71. Introduction

Sharpless[34] reported that the β-hydroxyamino group frequently found in biologically active molecules, can be synthesised directly from alkenes to give amino alcohols in enantiomerically enriched form. The use of different ligands in this asymmetric process can lead to different enantiomers **209** (Scheme 2.33).




**210a** **209** **210b**

**Scheme 2.33.** *Reagents:* a) 4% $K_2OsO_2(OH)_4$, 5% $(DHQD)_2PHAL$ , 3 eq Chloramine-T-trihydrate, 1:1 $MeCN/H_2O$, 71% ee; b) 4% $K_2OsO_2(OH)_4$, 5% $(DHQ)_2PHAL$ , 3eq Chloramine-T-trihydrate, 1:1 $MeCN/H_2O$, 66%, 81% ee.

For *trans* disubstitued olefins, the same face selection rule for the related asymmetric dihydroxylations (AD)[35] applies. That is, $(DHQD)_2PHAL$ directs addition to the β-face, while $(DHQ)_2PHAL$ directs addition to the α-face. From the initial mechanistic studies conducted, evidence suggests that there is more than one catalytic cycle involved. Four key points have been established:

1. The asymmetric aminohydroxylation reaction is an asymmetric version of the catalytic aminohydroxylation process reported by Sharpless in 1976[36];

2. The ligand not only leads to enantioselectivity, but in some cases accelerates catalytic turnover, a process termed ligand-accelerated catalysis[37] (LAC);
3. The ligand suppresses the formation of the diol by-product.
4. The ligand influences the regioselectivity.

Some further examples are illustrated in Table 2.12. In many cases the enantiomeric excess can be greatly enhanced following recrystallisation.

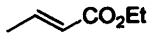
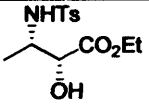
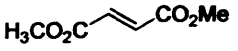
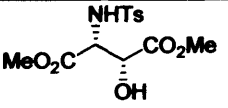
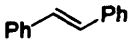
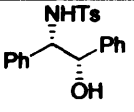
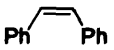
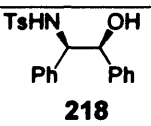
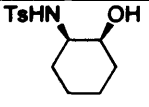
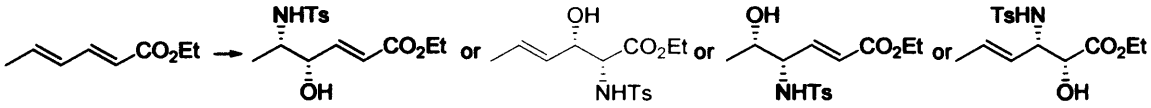
| | Olefin | Product | *ee* Values (%) prior to recrystallisation | | Yield (%) |
|---|---|---|---|---|---|
| | | | $(DHQ)_2PHAL$ | $(DHQD)_2PHAL$ | |
| 1 |  **211** |  **212** | 74 | 60 | 52 |
| 2 |  **213** |  **214** | 77 | 53 | 65 |
| 3 |  **215** |  **216** | 62 | 50 | 52 |
| 4 |  **217** |  **218** | 33 | 48 | 48 |
| 5 |  **219** |  **220** | 45 | 64 | 64 |

**Table 2.12**

In entry one, the ligand steers the nitrogen centre to the β-carbon atom, that is, in electronically unsymmetrical olefins, the nitrogen becomes attached to the carbon atom distal to the strongest electron-withdrawing group (Table 2.12). Interestingly, generally the DHQ series gives higher enantiomeric excesses, which is the reverse of the trend in the AD reaction. One downside of the reaction is that it can be difficult to separate the *p*-toluenesulfonamide by-product from the desired product by chromatography.

## 2.72. Results and Discussion

Surprisingly, there was no literature precedent for the asymmetric aminohydroxylation reactions on dienes. Depending on the regioselectivity, the AA reaction would provide a rapid route to the required cyclisation precursors, perhaps as single enantiomers. The study commenced with commercially available ethyl sorbate **221**. Four isomers were possible and to be a suitable route for the synthesis of cyclisation precursors, it was desirable for isomer **223** to be the sole product (Scheme 2.34).




**211** **222** **223** **224** **225**

**Scheme 2.34.** *Reagents:* $(DHQD)_2AQN$, Chloramine-T-hydrate, $K_2OsO_2(OH)_4$, 1:1 $MeCN/H_2O$, 8%.

Frustratingly, the NMR spectrum of the crude product revealed that the product was either **222** or **224** since the olefin resonances at 5.70 and 6.60 ppm were a doublet and double doublet respectively. If the product was **223** or **225**, one of the olefin resonances would be a quartet of doublets (Scheme 2.34). Unfortunately further speculation about the product was not possible since the C*H*NH and C*H*OH resonances were coincidental. According to Sharpless's research, the amino alcohols are formed with a *syn* relationship between the two new groups, but formation of the enantiomers shown in Scheme 2.34 is purely speculative. Difficulities were experienced with separating the Chloramine-T by-product, $TsNH_2$, from the product and so the yield obtained was very low. In an attempt to separate these coincidental resonances, a mixture of the product and by-product was treated with acetic anhydride in pyridine (Scheme 2.35). As expected, a shift of *ca* 1 ppm for the C*H*O proton was observed, and since this signal was a quartet of doublets (qd), the product of the aminohydroxylation reaction had to be **224** since the quartet splitting is caused by the adjacent methyl group (Scheme 2.34).


**224** **226**

**Scheme 2.35.** *Reagents:* Acetic anhydride, pyridine, 16 h.

The aminohydroxylation reaction was repeated on ethyl sorbate **221** but using $(DHQ)_2PHAL$ as the ligand, but the yield was only 6%, and complete separation of the by-product ($TsNH_2$) from the product was not achieved (Scheme 2.36). According to Sharpless's research, substituting a $(DHQD)_2$ ligand for a (DHQ) ligand results in the formation of the other enantiomer (Scheme 2.33), thus the other enantiomer should have been formed in this reaction, as Scheme 2.36 suggests.


**221** **227**

**Scheme 2.36.** *Reagents:* $(DHQ)_2PHAL$, Chloramine-T-hydrate, $K_2OsO_2(OH)_4$, 1:1 $MeCN/H_2O$.

Despite the undesired regioselectivity of the asymmetric amino hydroxylation reactions, it would have been interesting to clarify if different enantiomers were afforded by the use of different ligands, *via* the use of optical rotations. Disappointingly, due to the impure nature of the products, determination of the enantiomeric excess of the reaction or measurement of the optical rotation was not attempted.

Although poor results were recorded for the alkyl derivative, it was important to determine if the amino hydroxylation reaction was successful with other substrates, in particular one bearing an aryl group adjacent to the olefin. The corresponding phenyl derivative **229** was not commercially available. Subsequently, the corresponding carboxylic acid **228** was treated with acetyl chloride in methanol at reflux to afford the methyl ester **229**, as confirmed by the ester singlet at 3.70 ppm, in 78% yield (Scheme 2.37).


**228** **229**

**Scheme 2.37.** *Reagents:* 0°C, Acetyl chloride, MeOH, 0.5h, reflux, 8 h, 78%.

The methyl ester **229** was then subjected to the standard asymmetric aminohydroxylation conditions using both $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ ligands, but the NMR spectrum of the crude products showed mainly starting material, by-product and only a trace of product, even though the same colour changes were observed as the previous example. Unfortunately, sufficient quantity of the product could not be isolated to ascertain the regioselectively of the reaction.

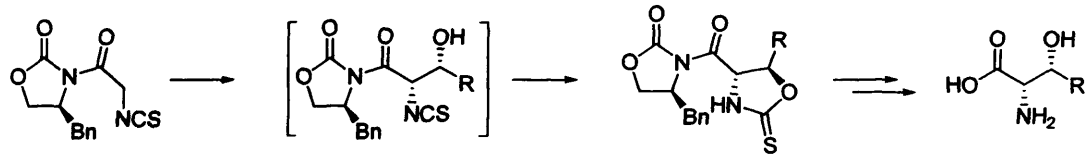
## 2.73. Conclusion

The lack of literature precedent, suggested that the asymmetric aminohydroxylation reaction cannot be applied to dienes. So once again, alternative routes were researched.

## 2.80. Route 7: Use of The Evans Auxiliary in the Synthesis of Cyclisation Precursors

## 2.81. Introduction

Evans[38] and co-workers created an isothiocyanate **230** that can be used as a chiral glycine equivalent in the synthesis of β-hydroxy-α-amino acids. They reported that when a stannous enolate mediated aldol reaction was conducted with a variety of aldehydes, predominately the *syn* diastereoisomer **232** (>90:10) was formed in excellent yields (Table 2.13).[39]




**230** **232** **233a-f** **234a-f**

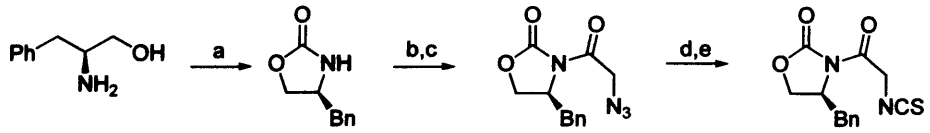
| R-CHO | Ratio 233 | Yield (%) | R-CHO | Ratio | Yield (%) |
|---|---|---|---|---|---|
| R= **231a** | 94:6 | 73 | R= **231d** | 99:1 | 92 |
| R= **231b** | 97:3 | 71 | R= **231e** | 91:9 | 75 |
| R= **231c** | 93:7 | 81 | R= Ph **231f** | 99:1 | 91 |

**Table 2.13**

A literature search revealed that (*E*)-crotonaldehyde **137** and phenyl propynal **117** had not been used in this aldol reaction. Nevertheless, it was evident that the α,β-unsaturated aldehydes utilised by Evans (Table 2.14) were similar to (*E*)-crotonaldehyde **137**, and as such, similar results were expected to solve the problems associated with synthesising the *syn* precursors.

## 2.82. Results and Discussion

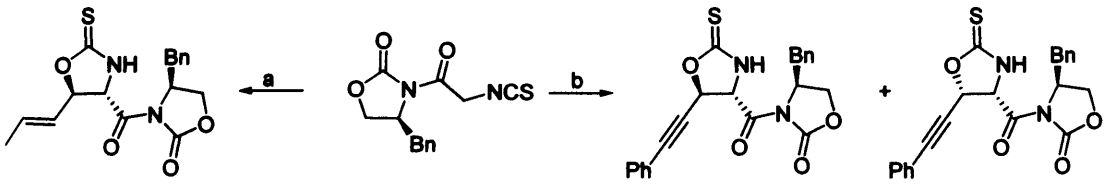
The chiral glycine synthon **231** was prepared from commercially available (*S*)-phenyl alaninol **235** in 53% overall yield, according to the procedure outlined by Evans (Scheme 2.38).




**235** **236** **237** **231**

**Scheme 2.38.** *Reagents:* $K_2CO_3$, diethyl carbonate, 135°C, 2 h, 76%; b) n-BuLi, THF, -78°C, chloroacetyl chloride, 0.25 h, -78°C, 0.25, 0°C; c) $CH_2Cl_2$, $NaN_3$, $H_2O$, $[\{CH_3(CH_2)_3\}_4N]_2SO_4$, 1 h, 84%; d) 10% Pd/C, MeOH, perchloric acid, $H_2$; e) thiophosgene, $H_2O$, $CHCl_3$, $NaHSO_4$, 10 mins, 83%.

In Evans' research, the aldehydes used were not commercially available and were not used in stoichiometric amounts. However, in order to afford the aldol products in high yields, it was decided to use one equivalent of the aldehydes, which were easier to obtain than the isothiocyanate **231**. Accordingly, the isothiocyanate **231** was treated with tin(II) triflate, *N*-ethyl piperidine and 1.1 equivalents of (*E*)-crotonaldehyde **137**, to afford the assumed *syn* diastereoisomer **238** in 33% yield, as confirmed by the loss of the C*H*$_2$NCS singlet, and in addition to the appearance of new C*H*O and C*H*N protons at 4.85 and 5.65 ppm. Further clarification was obtained from the molecular ion of 374 ($M^+$ + H), which was consistent with the proposed structure (Scheme 2.39).



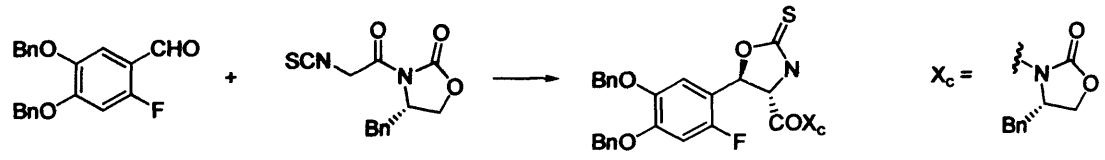

**238** **231** **239a** **239b**

**Scheme 2.39**. *Reagents:* a) *N*-ethyl piperidine, THF, $Sn(OTf)_2$, 33%; b) *N*-ethyl piperidine, THF, $Sn(OTf)_2$, 29%.

The reaction was repeated using phenyl propynal **117** as the aldehyde, but unfortunately, although the reaction was successful, the desired product **239** was isolated as a 7:3 mixture of diastereoisomers in a low 29% yield, as apparent from the loss of the C*H*$_2$NCS singlet and a molecular ion of 407 ($M^+$ + H), consistent with a successful aldol reaction was apparent. According to Evans, the reaction should afford predominately the *syn* diastereoisomer **239a**, however, the coupling constant between the C*H*O and C*H*N of the new ring of the major isomer was 9.7 Hz, while for the minor isomer, this value was 4.2 Hz. This suggested that the minor isomer was the *syn* diastereoisomer **239a**, which contradicts what Evans reported. However, the Evans group did not conduct condensations with acetylenic aldehydes (Table 2.14). In addition, the coupling in the product **238** from the condensation with (*E*)-crotonaldehyde **137**, was 4.4 Hz between the C*H*O and C*H*N protons, indicating that this was the *syn* diastereoisomer **238**, which was in agreement with Evans' findings. Since the major isomer formed in the condensation with phenyl propynal **117** with isothiocyanate **230** was the *anti* diastereoisomer **239a**, it is possible that acetylenic aldehydes do not follow the same trends as alkenyl aldehydes. Evans reported that the diastereoselectively could be reduced by the quality of the stannous triflate, which could explain the surprising lack of diastereoselectivity from the condensation with phenyl propynal **117** with the enolate of the isothiocyanate. The Evans group prepared the reagent from anhydrous stannous chloride and trifluoromethanesulfonic acid, using a modified literature procedure[40], involving prolonged heating. Since stannous triflate was extremely sensitive to moisture, the reagent was purchased, and due to its expense, the reactions were conducted on a small scale. In initial experiments, the stannous triflate was weighed out under a stream of nitrogen, but despite extreme care during handling, the reagent rapidly degraded, which could explain the low yields experienced. Consequently, due to these low yields, in later experiments, the stannous triflate was used in 1 gram quantities, to eliminate exposure to moisture during weighing.

Also it became apparent that careful control of the cold bath temperature was mandatory to achieve high selectivity.

From the general procedure outlined by Evans, the quantities of reagents varied, and as such to determine the optimum conditions, numerous conditions would have to be tested and with the expense of the stannous triflate this was not fully investigated. A search of the literature revealed that Herbert[41] also experienced disappointing yields and selectivity when applying the Evans methodology to his substrates, despite various optimisation reactions, but by changing the base to LHMDS, the aldol product **241** was obtained in good yield and highly selectively (Table 2.14).

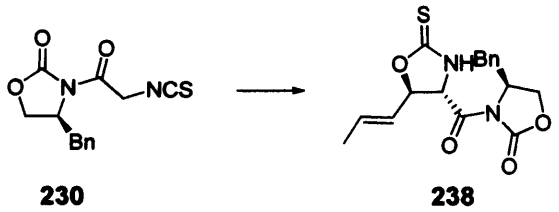



**240** **230** **241**

| Base | Lewis Acid (eqs) | NCS (eqs) | Temp (°C) | Diastereoisomer ratio of Crude Product | Yield (%) |
|---|---|---|---|---|---|
| 1.5 eq *N*-ethyl piperidine | 1.1 | 1.3 | -78 | Not reported | |
| 1.5 eq *N*-ethyl piperidine | 1.2 | 1.2 | -78 to -50 to 0 | Not reported | |
| 1.4 eq LHMDS | | 1.4 | -78 | 4:1 | 52 |
| 1 eq LHMDS | 1.0 | 1.0 | -78 | Not reported | 34 |
| 1.3 eq LHMDS | 1.3 | 1.3 | -78 | 10:1 | 50 |
| 2.0 eq LHMDS | 2.0 | 2.0 | -78 | 20:1 | 81 |

**Table 2.14**

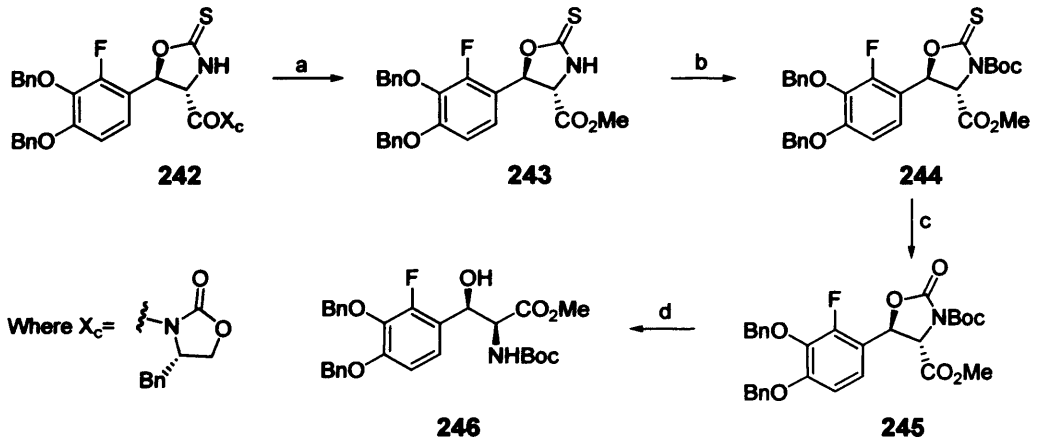
When the isothiocyanate **230** was treated with (*E*)-crotonaldehyde **137**, in the presence of tin triflate and LHMDS, the aldol adduct **238** was isolated in a modest yield of 35% (Scheme 2.40). This yield was calculated by taking into account the recovered starting material. The NMR spectrum of the crude product displayed only starting material and product. Subsequently, in future experiments, the aldol product **238** was used crude in the cleavage reaction.



**230** **238**

**Scheme 2.40.** *Reagents:* a) LHMDS, THF, -78°C, **137**, 35%.

The Herbert group also reported a sequence to the amino alcohol **246**, which hopefully could be adapted for use in the present research to give the desired cyclisation precursor (Scheme 2.41).



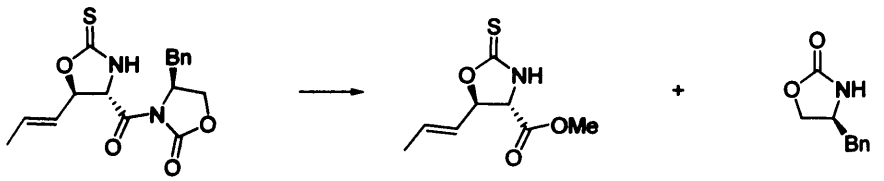
**242** **243** **244** **245** **246**

**Scheme 2.41.** *Reagents:* a) MeOMgBr, THF, MeOH, 0°C, 20 mins, 88%; b) $Boc_2O$, DMAP, $CH_2Cl_2$, 40 mins, 86%; c) $Hg(OAc)_2$, $CH_2Cl_2$, 0°C, 1 h, R.T. 2.5 h, 96%; d) $Cs_2CO_3$, MeOH, 3.5 h, 83%.

As explained previously, the precursor would have to contain a tosyl group, not a Boc group as in Herbert's route. The only foreseeable problem with this change in protecting group, was the mercury acetate step (Scheme 2.41; c), but it was believed that the tosyl sulfur would not be targeted in preference to the sulfur of the thiocarbamate.

The auxiliary cleavage reaction proceeded cleanly and following chromatography, the ester **247** was obtained in a moderate yield of 52%, as deduced from the appearance of a new methyl ester singlet at 3.75 ppm, the loss of the auxiliary peaks in the $^1H$ NMR spectrum and a molecular ion of 202 ($M^+$ + H), consistent with the proposed structure (Scheme 2.42). The auxiliary **236** was recovered in a marginally greater 65% yield, but was not clearly visualised on the tlc plate by UV or various stains. Consequently, complete

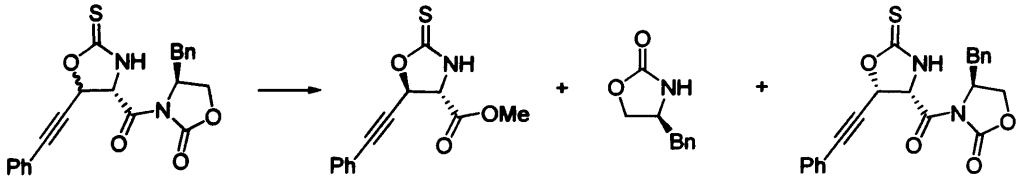
separation of the two entities was problematic. However an important property of a chiral auxiliary is recovery, so in future work, this issue should be addressed.



**238** **247** **236**

**Scheme 2.42.** *Reagents:* MeMgBr, MeOH, THF, 20 mins, 52% **247** and 65% **236**.

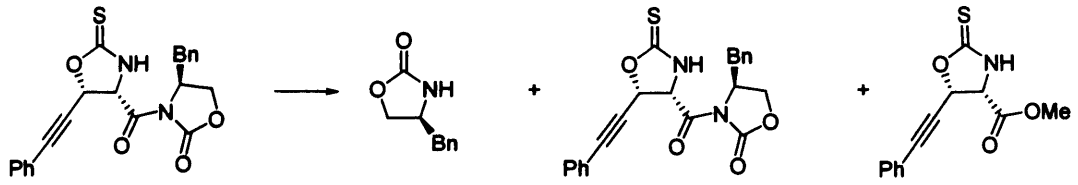
In an attempt to increase the yield of the aldol reaction, as previously mentioned, the crude aldol product **238** was cleaved using identical conditions and following chromatography, the thiocarbamate **247** was obtained in an overall 46% yield over two steps and the oxazolidine auxiliary **236** in 84% yield. When these two reactions were conducted on clean material, the overall yield of the methyl ester **247** over two steps was 18% (Scheme 2.42). This was considerably lower than the 46% yield recorded when the crude aldol product was used in the cleavage reaction. Hence, as suspected, the aldol product **238** was unstable to chromatography.



**239** **248a** **236** **239b**

**Scheme 2.43.** *Reagents:*MeOH, MeMgBr, THF, 0°C, 20 mins, 62% **248a** and 22% **236**.

The auxiliary was substituted by a methoxy group using magnesium methoxide, prepared from methylmagnesium bromide and methanol. Interestingly, on treatment of a 7:3 (*anti:syn*) mixture of diastereoisomers **239** from the condensation of the enolate of isothiocyanate with phenyl propynal **117** with freshly prepared magnesium methoxide, it was apparent that only the minor *syn* isomer had reacted, to give the methyl ester **248b** and auxiliary **236** in 62% and 22% yield respectively (Scheme 2.44). The auxiliary **236** was only recovered in low yield, due to the problems previously described.

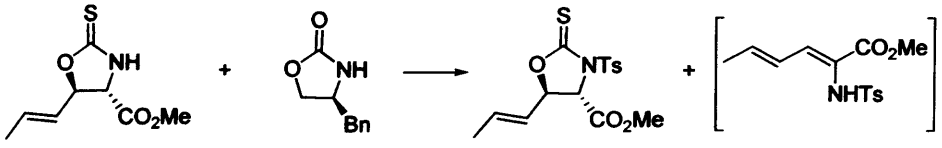


**239b** **236** **239b** **248b**

**Scheme 2.44.** *Reagents*: MeMgBr, MeOH, THF, 20 mins, 62% **248a** and 22% **236**.

However, when the recovered *anti* diastereoisomer **239b**, was treated with magnesium methoxide even after 3.5 h, the reaction had not gone to completion. Hence, the stereochemistry of the thiocarbamate influences the speed of the cleavage reaction. Optimisation of the aldol reaction (Scheme 2.44) is required, but since a sample of the *syn* precursor **249** from an alternative route (Scheme 3.35, Chapter 3) did not cyclise, this route was not continued.

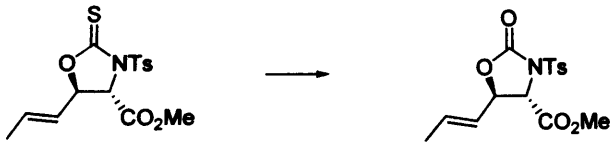
With the separation problems previously described, a 1.9:1 mixture of the methyl ester **247** and auxiliary **236** were treated with tosyl chloride in the presence of triethylamine to afford the desired sulfonamide **250**, characterised by new doublets at 7.30 and 7.95 ppm and a molecular ion of 356 ($M^+$ + H), consistent with formation of the tosylate in 61% yield. A diene **251** was also isolated in 2% yield as confirmed by the new olefin signal at 7.10 ppm, with a *cis* coupling of 11.3 Hz to 4-H and a molecular ion of 296 ($M^+$ + H), consistent with ring opening and elimination (Scheme 2.45).



**247** **236** **250** **251**

**Scheme 2.45.** *Reagents*: $CH_2Cl_2$, $Et_3N$, DMAP, TsCl, 61% **250** and 2% **251**.

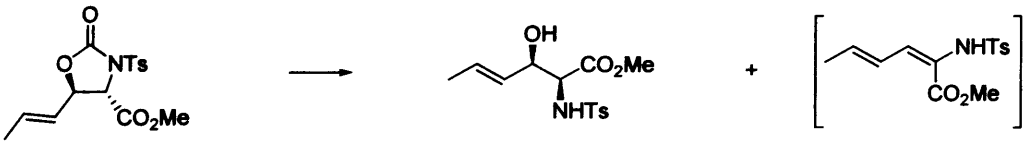
Next, the thiocarbamate **250** was treated with mercury(II) acetate in dichloromethane to afford the carbamate **252**, in quantitative yield (Scheme 2.46). Both the thiocarbamate **250** and carbamate **252** had identical $^1H$ NMR spectra. However, the disappearance of the C=S resonance and two C=O peaks at 150.8 and 168.5 ppm in addition to a molecular ion of 340 ($M^+$ +H), consistent with carbamate formation, confirmed that the reaction had been successful.



**250** **252**

**Scheme 2.46.** *Reagents:* $Hg(OAc)_2$, $CH_2Cl_2$, 0°C, 1 h, R.T. 2.5 h, 100%.

The final step was to ring open the carbamate **252** using cesium carbonate in methanol. Herbert reported that the ring opening sequence was complete in 3.5 h at ambient temperature, but when substrate **252** was subjected to these conditions, only starting material was recovered. After an additional 21 h, the *syn* amino alcohol **253** was obtained in a disappointing 9% yield, in addition to the diene **251** in 43% yield (Scheme 2.47). Formation of the *syn* amino alcohol **253** was apparent by the loss of one of the C=O signals in the $^{13}C$ NMR spectrum and a molecular ion of 314 ($M^+$ + H), consistent with a successful reaction. The *syn* stereochemistry was confirmed by a coupling of 3.5 Hz, between the C*H*O and C*H*N protons. In an attempt to decrease the level of elimination, the reaction was cooled to -10°C using a methanol bath for two days, but no reaction was observed. Optimisation was again required, but due to the length of the entire reaction sequence and low yields experienced, shorter alternative approaches were investigated.



**252** **253** **251**

**Scheme 2.47.** *Reagents:* $Cs_2CO_3$, MeOH, 24 h, 9% **253** and 43% **251**.

Determination of the enantiomeric excess of the precursor **253** was attempted, but a suitable solvent system was not discovered and the results obtained were inconclusive. Also the product obtained was not pure enough to warrant an optical rotation, hence this data is not present in the experimental section.

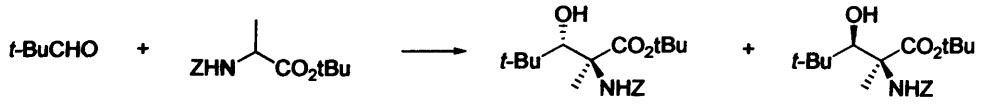
## 2.83. Conclusion

Although the desired *syn* precursor **253** was isolated, the quantity of material was low. This together with the length of the route once again lead to the exploration of alternative sequences.

## 2.90a. Route 8: Lowering the Selectivity of the Aldol Reaction

## 2.91a. Introduction

The Kazmaier[2] aldol reaction utilising acetylenic aldehydes and ketones provided an excellent route to *anti* precursors (Section 1.50). When this reaction was applied to α,β-unsaturated aldehydes, the selectivity was reduced from 9:1 to around 5:1 but still sufficient quantity of the *syn* precursors was not obtained and so alternative routes were explored, but with limited success. Due to this it was decided to repeat the aldol reaction but to make it less selective and then separate the resultant two isomers. In order to make this reaction less selective, Kazmaier's initial research was studied. He revealed that the selectivity varied depending on the Lewis acid used. However, Kazmaier's studies did not include acetylenic aldehydes or α,β-unsaturated aldehydes, and so experiments were conducted to establish the effect on the stereoselectivity of the reaction. In Kazmaier's initial studies, it was discovered that in the absence of a Lewis acid, the product **40** was isolated as a 79:21 mixture of diastereoisomers, but only in 30% yield (Chapter 1, Table 1.10). However, when two equivalents of zinc chloride was used, the selectivity was reduced from 100:1 to 9:1 and furnished the *anti* diastereoisomer **40a** in 60% yield (Scheme 2.48). These results suggested that the 9:1 selectivity obtained previously from the condensation of acetylenic aldehydes with the enolate of methyl *N*-tosyl glycinate (Section 2.10) could be lowered. Accordingly, zinc chloride, being readily available in the laboratory, was used in the initial studies.



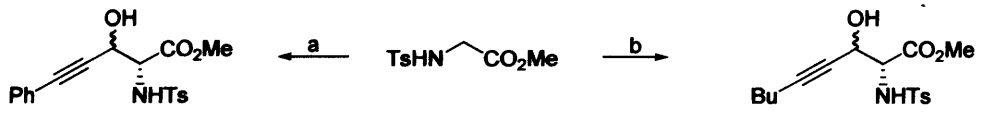

**42** **39** **40a** **40b**

**Scheme 2.48.** *Reagents:* LDA, *anh.* $ZnCl_2$, THF, 60%.

**2.92a. Results and Discussion**

When phenyl propynal **117** and hept-2-ynal **115** were treated with the enolate of methyl *N*-tosyl glycinate in the presence of anhydrous zinc chloride, in both cases, the NMR spectrum of the crude product revealed only a hint of product among starting material residues.

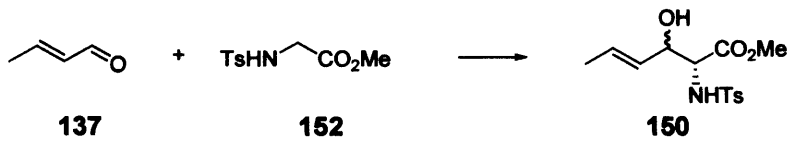
It was hoped that in the absence of any Lewis acid, two diastereoisomers would be isolated in sufficient yield to perform the key cyclisation. However, when phenyl propynal **117**, was treated with the enolate of methyl *N*-tosyl glycinate in the absence of a Lewis acid, a 1:1 mixture of diastereoisomers **146** was obtained in 15% yield, as determined from the ratio of the methyl ester singlets (Scheme 2.49; a).




**146** **152** **144**

**Scheme 2.49.** *Reagents:* a) LDA, THF, -78°C, **117**, 0.5 h, 15%; b) LDA, THF, -78°C, **115**, 0.5 h, 25%.

When hept-2-ynal **115** was treated with the enolate of methyl *N*-tosyl glycinate, a 1:1 mixture of diastereoisomers **144** in a slightly higher 25% yield, was isolated following chromatography (Scheme 2.49; b). Complete separation of diastereoisomers was not achieved in either case. So, interestingly, in the absence of a Lewis acid the selectivity decreased substantially from 9:1 to 1:1. With the low yield obtained of the *syn* precursor **253** and lengthy sequence from route 7 (Scheme 2.47), it was decided to repeated the aldol reaction of the enolate of methyl *N*-tosyl glycinate with (*E*)-crotonaldehyde **137** in the absence of a Lewis acid, in an attempt to isolate sufficient material for cyclisation. The NMR spectrum of the crude product revealed a 1:1.3 (*anti:syn*) ratio of diastereoisomers **150** in a crude yield of 19%. Following chromatography, partial separation of the diastereoisomers was achieved and the product was isolated in 10% yield (Scheme 2.50). Accordingly, in the presence of tin(II) chloride, the *anti* diastereoisomer **150a** is the predominant isomer (4:1), but in the absence of a Lewis acid, the selectivity is lowered to 1:1.3, in favour of the *syn* diastereoisomer.



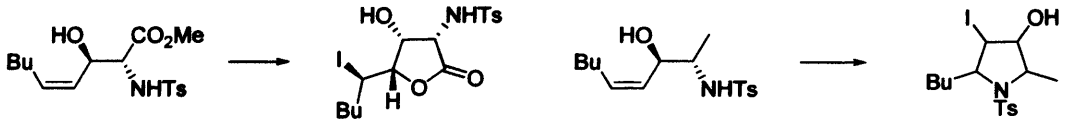

**137** **152** **150**

**Scheme 2.50.** *Reagents:* LDA, THF, -78°C, 0.5 h, 10%.

## 2.90b. Route 9: Preparation of Amino alcohols Devoid of the Ester Moiety

## 2.91b. Introduction

Cyclisation of the amino alcohols bearing an ester functionality revealed that in certain cases, lactones were formed in preference to and also in addition to the desired pyrrolidines (Figure 2.15). In the absence of an ester group, would pyrrolidines be isolated and what level of selectivity would be observed?




**149** **254** **255** **256**

**Figure 2.15**

## 2.92b. Results and Discussion

The study commenced with aldehyde **195** synthesised in a previous route (Scheme 2.26; b). Before this aldehyde **195** was alkylated, experiments were conducted to optimise the oxidation of the precursor **195**. This oxidation had previously been conducted with Dess-Martin periodinane (Scheme 2.26; b), but due to the work-up the yield recorded was low, but this was subsequently optimised. Despite the straightforward preparation of this reagent, large quantities were necessary for oxidation, as such the reaction could not be conducted on large scales. Literature precedent indicated that both TEMPO[42] and Swern[43] oxidations on this substrate were high yielding. Accordingly, the alcohol **194** was exposed to a mixture of the TEMPO free radical, sodium bromide and NaOCl in a biphasic mixture of toluene, water and ethyl acetate, but the NMR spectrum of the crude product revealed only a trace of aldehyde **195** among starting material resonances. Rapid stirring of the biphasic mixture is mandatory for TEMPO oxidations, so it is possible that this may have caused the lack of reaction or the quality of the reagents. Accordingly, the amino alcohol

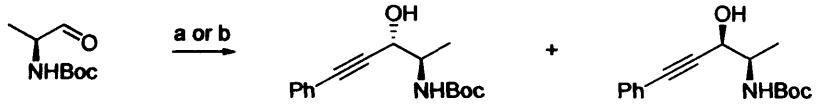
**194** was subjected to standard Swern oxidation conditions to afford the aldehyde **195** in a crude yield of 80% as an alternative method. Pyridinium chlorochromate oxidations are used extensively in organic synthesis and despite no literature precedent, substrate **194** was treated with pyridinium chlorochromate (PCC) in dichloromethane. The only drawback with this oxidation is the tedious chromatography required to removed the chromium residues. Disappointingly, despite careful chromatography, some polymerised PCC was evident in the NMR spectrum of the product, hence alternative oxidation procedures were investigated.


**194** **195**

**Scheme 2.51.** *Reagents*: a) TEMPO, NaBr, EtOAc, $H_2O$, Toluene, $NaHCO_3$, NaOCl, KI; 0%; b) Swern Oxidation, 80%; c) PCC, $CH_2Cl_2$, NaOAc, 2 h, 55%; d) IBX, DMSO, 16 h, 0%; e) Dess-Martin periodinance, 16 h. $CH_2Cl_2$, 16 h, 57%.

IBX[44] (1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide) is the precursor to Dess-Martin periodinane, and being neither moisture or air sensitive, it does not have to be used under anhydrous conditions. The disadvantage of this mild chemoselective oxidant is that it is insoluble in most conventional organic solvents, and consequently oxidations are usually conducted in dimethyl sulfoxide (DMSO), which requires the use of copious quantities of water in the work-up to remove the solvent[45]. The carbamate **194** in dimethyl sulfoxide was treated with 1.1 equivalents of IBX for 16 h, but disappointingly, no reaction was observed. The rate of oxidation has been reported to be accelerated by the use of excess IBX, typically 5-10 equivalents. However, such a large excess would again limit the amount of material used in the oxidation and so would not solve the original problem. However, it has been reported that alcohols can be oxidised in the presence of amines in excellent yields, when 1-1.5 equivalents of trifluoroacetic acid is added to protonate the amine, which speeds up the oxidation. But to make use of this, the oxidation would have to be carried out prior to the Boc protection. So ultimately, in light of the problems discussed, it was decided that the best conditions for oxidation was the Dess-Martin periodinane (Scheme 2.26; b), since it was discovered that by increasing the reaction time, the yield of the aldehyde **195** had been increased from 18% to 57% (Scheme 2.51; e).

Next, the aldehyde **195** was treated with lithio phenylacetylide to furnish the propargylic alcohol **257** as a 3:1 (X:Y) mixture of diastereoisomers, in 68% yield, as apparent from the loss of the aldehyde singlet, in addition to a molecular ion of 276 ($M^+$ + H), which correlated with alkylation. Again due to the presence of the Boc protecting group, determination of the stereochemistry was not established, but from Dondoni's research, the major isomer was likely to be the *syn* isomer (Scheme 2.21). Herold reported that in the synthesis of D-threo-sphingosine **202b**, when Garner's aldehyde **201** was alkylated with 1-pentadecynyllithium, in the presence of anhydrous zinc dibromide, predominantly the *syn* diastereoisomer **200b** was obtained (Scheme 2.29). Accordingly, to increase this quantity of the *syn* diastereoisomer **257a**, the aldehyde **195** was treated with lithio phenylacetylide, in the presence of zinc dibromide. The NMR spectrum of the crude product revealed a 1:1.2 (X:Y) mixture of diastereoisomers **257** in a crude yield of 85%. The selectivity this time was reversed, again broad resonances were observed in both spectra.

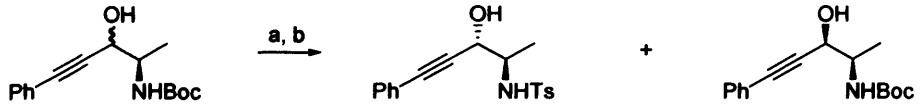



**195** **257a** **257b**

**Scheme 2.52.** *Reagents:* a) Phenylacetylene **145**, THF, n-BuLi, -20°C, 0.5 h, 78°C, **195**, 2 h, 68%; b) Phenylacetylene **145**, -20°C, $Et_2O$, n-BuLi, 1 h, 0°C, ZnBr, 1 h, R.T. 1 h, -78°C, **195**, R.T., 16 h, 85%.

For comparison with the initial studies, a tosyl *N*-protecting group was required, hence the carbamate **257** was treated with 20% solution of trifluoroacetic acid in dichloromethane for 1.5 h. Following the work-up, the crude amine was immediately treated with triethylamine and *p*-tosyl chloride in dichloromethane, but unfortunately, very little sulfonamide **258** was isolated. Tests on a model substrate revealed that in the tosylation of amino alcohols, triethylamine generated the desired compound, while pyridine furnished a mixture of sulfonamide **187** and tosylate **188** (Scheme 2.24). Fortunately, when 2,4,6-collidine was employed as the base, the sulfonamide **258** was isolated as a 1.8:1 mixture of diastereoisomers in 23% yield (over three steps), as confirmed by the two new aryl methyl singlets at 2.25 and 2.30 ppm and a molecular ion at 330 ($M^+$ + H), consistent with tosylation. Although the C*H*N protons were coincidental, the C*H*O protons were adequately separated and consequently from coupling constants, the predominant isomer

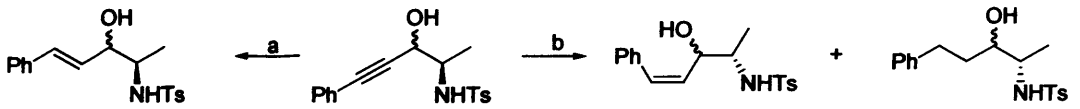
was established to be the *syn* diastereoisomer **258b**. This confirmed that alkylation in the presence of zinc dibromide, did afford the *syn* diastereoisomer as the major isomer, but in a poorer selectivity than reported in the literature. Hence, excellent selectivities were only obtained using Garner's aldehyde **201** which has a more rigid conformation than aldehyde **195**. Further optimisation was not attempted due to lack of time. Separation of the *anti* diastereoisomer **258a** was possible by careful chromatography, but typically, only small amounts were isolated, thus reduction was carried out on mixtures.




**257** **258a** **258b**

**Scheme 2.53.** *Reagents:* a) TFA, $CH_2Cl_2$, 1.5 h, 83%; b) $CH_2Cl_2$, 2,4,6-collidine, DMAP, *p*-TsCl, 16 h, 23%.

Next, reduction of the alkyne moeity was required and with the lack of an ester group, no problems were envisaged. Accordingly, a 1.8:1 (*syn*:*anti*) mixture of diastereoisomers of the propargylic alcohol **258** was treated with Red-Al in diethyl ether for 24 h to afford the (*E*)-olefin as a 1.6:1 (*syn*:*anti*) mixture of diastereoisomers **259**, in an excellent 83% yield as confirmed by the new olefin signals in the 5.92-6.45 ppm region of the $^1$H NMR spectrum, (Scheme 2.54; a).



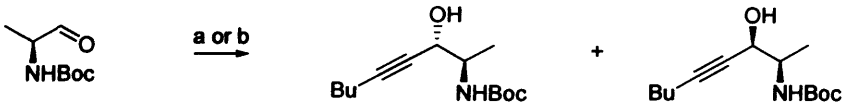

**259** **258** **260** **261**

**Scheme 2.54.** *Reagents:* a) Red-Al, $Et_2O$, R.T., 86%; b) Lindlar's catalyst, EtOAc, $H_2$.

The transformation of alkyne **258** to the (*Z*)-olefin **160** was more tedious. When a 1:1 mixture of diastereoisomers of the propargylic alcohol **258** and Pd/C catalyst in ethyl acetate was stirred under an atmosphere of hydrogen, although the catalyst absorbed the required volume of hydrogen, reduction to the (*Z*)-olefin **260** had not occurred. The reaction was repeated numerous times, without success and so instead to generate the (*Z*)-olefin, the reaction was purposely left until approximately double the required volume of hydrogen had been absorbed by the catalyst, which ultimately produced some alkane **261**.

Formation of the (*Z*)-olefins **260** was confirmed by the olefin signals at 5.55-6.55, all with a *cis* coupling of 11.7 Hz, but due to the impurities an accurate yield was not recorded.

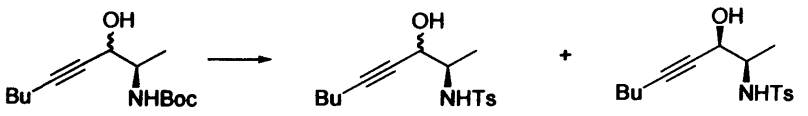
For the cyclisation studies, an alkyl derivative was also required. Thus, the aldehyde **195** was treated with 1-hexynyllithium in tetrahydrofuran to afford the propargylic alcohol **262**, as a 3.5:1 mixture of diastereoisomers in 70% yield, as deduced from an observed molecular ion of 256 ($M^+$ + H), which was consistent with alkylation in addition to the loss of the aldehyde singlet (Scheme 2.55; a). In the presence of anhydrous zinc dibromide, the selectivity was reduced to 3:1, in a crude yield of 85% and again due to the ill-defined resonances, determination of the stereochemistry of the major isomers could not easily be established at this stage (Scheme 2.55; b).




**195** **262a** **262b**

**Scheme 2.55.** *Reagents:* a) **115**, THF, n-BuLi, -20°C, 0.5 h, -78°C, **262**, 2 h, 70%; b) **115**, -20°C, $Et_2O$, n-BuLi, 1 h, 0°C, ZnBr, 1 h, R.T. 1 h, - 78°C, **262**, R.T., 16 h, crude 85%.

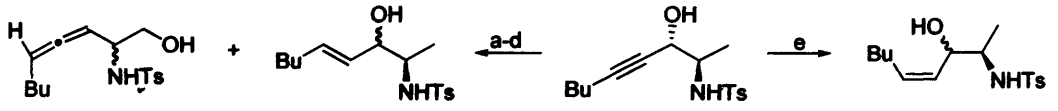
Again a tosyl *N*-protecting group was necessary for comparison with the initial substrates. So the a 2:1 mixture of diastereoisomers of the carbamate **262** was treated with 20% solution of trifluoroacetic acid in dichloromethane to afford the amine in 62% yield (Scheme 2.56; a), as confirmed by the loss of the *t*-butyl singlet. With the previous problems of tosylation of the amino alcohol **257** using triethylamine as the base (Scheme 2.24), instead the amine was treated with 2,4,6-collidine and *p*-tosyl chloride to afford the sulfonamide **263** as a 2.7:1 mixture of diastereoisomers (*anti*:*syn*), in a much greater yield of 46% as confirmed by two new aryl methyl singlets and a molecular ion of 310 ($M^+$ + H), which was consistent with tosylation (Scheme 2.56; b).




**262** **263a** **263b**

**Scheme 2.56.** *Reagents:* i) TFA, $CH_2Cl_2$, 1.5 h, 62%; ii) $CH_2Cl_2$, 2,4,6-collidine, DMAP, *p*-TsCl, 16 h, 46%.

The next step was to reduce the alkyne moiety to both (*E*)- and (*Z*)-olefins. From experience, when the alkyne moiety bears an alkyl substituent in these systems, elimination occurs during reduction to form an allene (Scheme 5.14; b, Chapter 5). As expected, when a 6:2 (*anti:syn*) mixture of diastereoisomers **263** was treated with Red-Al, an allene **265** was isolated as a 7:1 mixture of diastereoisomers in 11% yield. The formation of the allene **265** was determined by the characteristic absorbance at 1965 $cm^{-1}$ in the infrared spectrum and a resonance at $\delta_C$ 201.8 ppm (=·=). In addition, a 3:1 mixture of starting material **263** and (*E*)-olefin **264** was also isolated, but only in 12% yield, as apparent by the molecular ion of 334 ($M^+$ + Na), and olefin signals at 5.20, 5.25 and 5.60 ppm in the $^1H$ NMR spectrum (Scheme 2.57; a).




**265** **264** **263** **266**

**Scheme 2.57.** *Reagents:* a) Red-Al, $Et_2O$, 24 h, 11% **265** and 12% **264**; b) LAH, THF, 17.25 h, R.T. 0%; c) Red-Al, THF, reflux, 22.25 h; 20% **264**; d) 3 eq LAH, 20 h, 52% **264** and 16% **265**; e) Lindlar's catalyst, EtOAc, $H_2$.

The lack of (*E*)-olefin **264** isolated led to the use of alternative reducing agents. Treatment of the alkyne **263** with LAH in tetrahydrofuran for 17.25 h at ambient temperature, afforded only starting material. In a bid to increase the amount of (*E*)-olefin **264** isolated, the reduction with Red-Al was repeated, but at an elevated temperature. When a 1.2:1 mixture of diastereoisomers (*anti:syn*) of the sulfonamide **263** in tetrahydrofuran was treated with Red-Al and the reaction mixture refluxed for 19.25 h followed by chromatography, the (*E*)-olefin was obtained as a 5:1 mixture of diastereoisomers **264** (*anti:syn*), in 20% yield, together with the allene as 3:1 mixture of diastereoisomers **265**, in 15% yield. In light of these results, once again LAH was used as the reducing agent, but elevated temperatures, were employed in a bid to initiate the reaction. When a 5:4.5 mixture of diastereoisomers (*anti:syn*) of the sulfonamide **263** was treated with lithium aluminium hydride in tetrahydrofuran and refluxed for 20 h, the (*E*)-olefin was isolated as a 1.3:1 (*anti:syn*) mixture of diastereoisomers **264**, in an improved 52% yield. Again, some allene **265** was isolated in the same ratio of diastereoisomers, but in 16% yield. No further optimisation experiments were conducted at this stage. Next, reduction to the *cis*-olefin **265** was conducted but, as expected, the reduction was capricious. When the *anti*-

amino-alcohol **263** in ethyl acetate was treated with catalytic Pd/C, and stirred under an atmosphere of hydrogen, after numerous attempts, partial reduction had occurred to furnish a 3:1 mixture of the *cis-olefin* **265** and starting material **263**. Formation of an olefin was confirmed by the molecular ion of 294 ($M^+$ - $H_2O$) and two new multiplets in the olefin region. Although no coupling constant data could be obtained, due to overlapping resonances, since Lindlar reductions afford (*Z*)-olefins, this was presumed to be the case here.

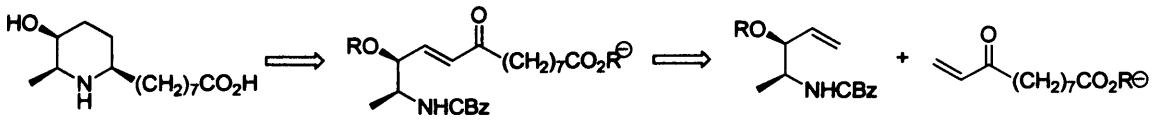
### 2.93b. Conclusion and Future Work

Despite numerous routes being undertaken, the required *syn* precursors were never satisfactorily synthesised as single diastereoisomers. However the synthesis of similar olefin containing *syn* precursors has been extensively reported in the literature. In particular, the synthesis of α-vinyl-β-aminoalcohols *via* the addition of vinyl anions to *N*-protected α-alaninals has been intensively studies, but unfortunately the diastereoselectivities observed were low.[50] Yamamoto[51] reported that following DIBAL reduction of *N*-Boc-alanine methyl ester **267** and *in situ* addition of vinylmangnesium chloride to the intermediate, the product was obtained in 52% yield as an 8:1 (*syn:anti*) mixture of diastereoisomers **268** (Scheme 2.58). Separation was achieved following conversion to the corresponding TBS ethers.


**267** **268**

**Scheme 2.58.** *Reagents*: i) DIBAL, $CH_2Cl_2$, -78°C; ii) $C_2H_3MgCl$, THF, -78°C-R.T., 52%.

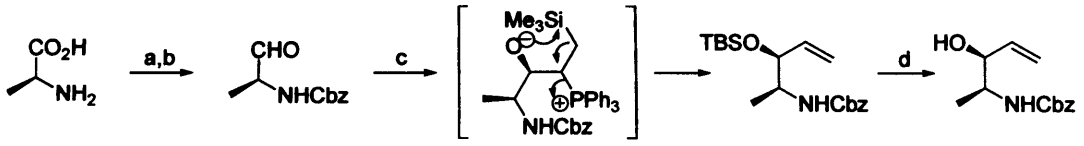
In their proposed synthesis of (+)-carpamic acid **268**, Randl and Blechert[52] aimed to synthesise amino alcohol **271** from (L)-alanine utilising Yamamoto's research (Figure 2.16) but the additional deprotection of the Boc and reprotection steps lead them to research conducted by Taddei[53] and co-workers.




**269** **270** **271** **272**

**Figure 2.16**

The Taddei group synthesised various α-vinyl-β-aminoalcohols with excellent *syn* selectivities (20:1) from the reaction of *N*-Boc-protected amino aldehydes with the Seyferth-Fleming ylide[54], $Ph_3P{=}CHCH_2TMS$ and subsequent desilylation of the resultant TMS ether. When Randl and Blechert applied this methodology to *N*-Cbz protected alaninal **275**, they isolated the required precursor **276** in a disappointing 15% yield, presumably due to the enhanced lability of the Cbz group compared to the Boc group. Luckily, by slightly altering step c, by stirring the reaction mixture at 0°C for only 1 h, the precursor **276** was isolated as a 12:1 mixture of diastereoisomers in a more satisfactory 64% yield (Scheme 2.59).




**273** **274** **275** **276** **277**

**Scheme 2.59.** *Reagents:* ai) MeOH, $SOCl_2$; ii) CbzCl, $NaHCO_3$, 71%; b) DIBAL, toluene, -78°C, 68%; c) $Ph_3P{=}CHCH_2TMS$, THF, -78°C to 0°C, $NH_4Cl$, 64%; d) TBAF, THF, 90%.

Unfortunately, only vinyl precursors were synthesised by the Taddei group. Hopefully this research could be adapted to include the use of different ylides which would then incorporate the desired R groups *i.e.* phenyl and methyl, into the *syn* precursors ready for cyclisation. The route could not be adapted to include *N*-tosyl amino aldehydes since they have previously been proven difficult to handle within the Knight group.

## 2.90c. References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# Chapter Three

# Iodocyclisations of Amino Alcohol Derivatives

## 3.10. Introduction: Background to Previous Work

Previously, the Knight group showed that (*E*)-homoallylic alcohols **8** undergo 5-*endo* trig cyclisations to afford tetrahydrofurans **10** in excellent yields and selectivities, while the corresponding (*Z*)-homoallyclic alcohols **20** cyclised in the same manner, but in lower yields (Figure 3.11).[1] However, when an additional hydroxyl moiety, beta to $R^2$, was present, β-hydroxytetrahydrofurans were isolated (Figure 3.10). Interestingly, the (*Z*)-*anti* alkene diols **284** underwent 5-*endo* trig cyclisations with the highest degree of selectivity (Section 1.20, Chapter 1 and Figure 3.10).[2]

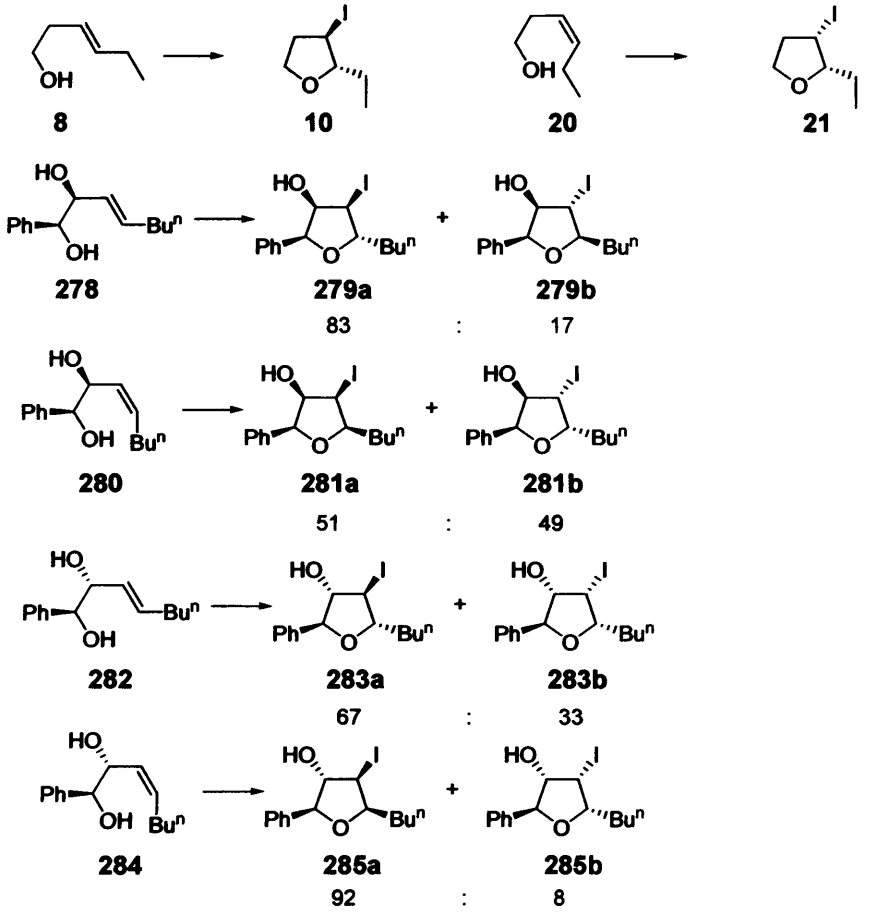



**Figure 3.10**

In the cyclisations of (*E*)-homoallylic sulfonamides, high selectivities were observed (Figure 3.11), while the corresponding (*Z*)-homoallylic sulfonamides, cyclised to afford pyrrolidines in moderate yields and disappointing selectivities.[3] These observations have led to work being undertaken using amino-alcohols to investigate if with an additional β hydroxyl group present, this would lead to improved yields and selectivities as previously observed with the tetrahydrofuran derivatives (Figure 3.11).

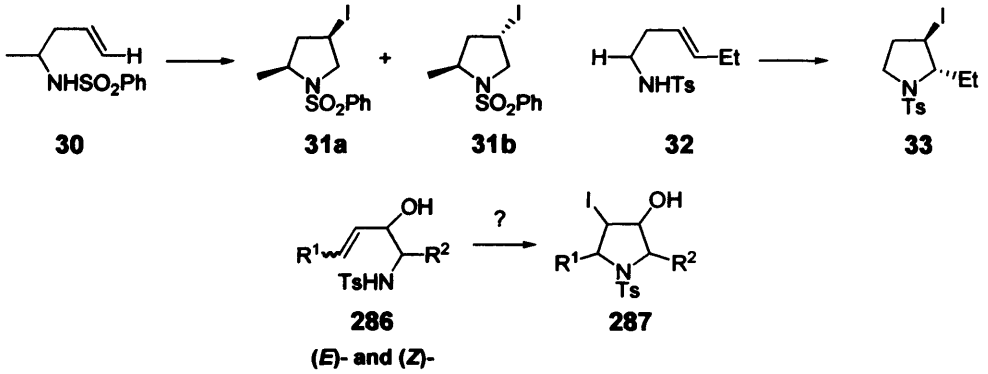



**Figure 3.11**

The introduction of an additional hydroxyl group could affect the stability of the products. Elimination of hydrogen iodide and water could occur to furnish pyrroles and, in addition, the centre adjacent to the ester may epimerise, thus affecting the stereoselectivity observed (Figure 3.12).

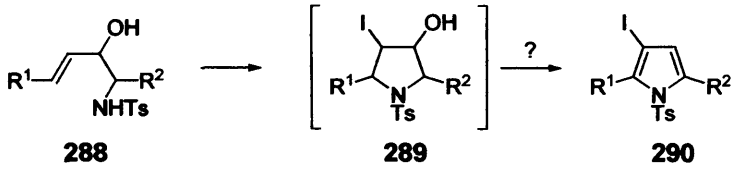
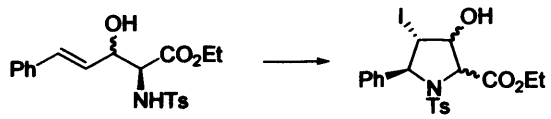



**Figure 3.12**

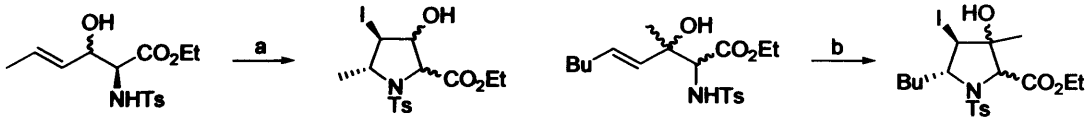
In the later stages of Sharland's[4] PhD, a limited study was conducted on readily available diastereoisomeric mixtures of β-hydroxy-α-amino esters obtained from the Kazmaier[5] aldol reaction. When a 4:1 mixture of diastereoisomers of the amino alcohol **136** was treated with a set of standard conditions used by the Knight group, iodine monobromide, sodium hydrogen carbonate in dichloromethane at -20°C for 4 h, a 19:13:7:5 mixture of diastereoisomers **291** was obtained (Scheme 3.10).




**136** **291**

**Scheme 3.10.** *Reagents:* IBr, $NaHCO_3$, *anh* $CH_2Cl_2$, 4 h, -20°C, crude 83%.

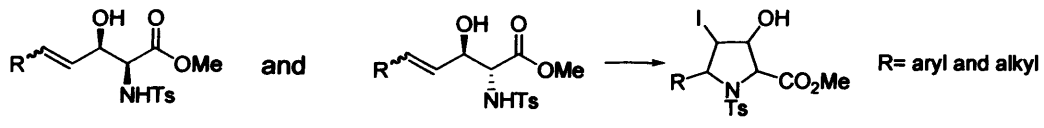
Separation of the isomers was not attempted. Confirmation of the cyclisation was apparent from the loss of the olefin signals, a molecular ion of 515 Daltons and the appearance of new richly detailed resonances in the region 3.90-5.20 ppm, consistent with previously synthesised pyrrolidines. The selectivity of the cyclisation was not ascertained, but the principle that such cyclisations could be viable had been established. The next two experiments conducted by Sharland were again on mixture of diastereoisomers but, aspects of the stereochemistry were ignored. Cyclisation of both **140** and **141** was successful utilizing iodine and potassium carbonate in acetonitrile at room temperature (Scheme 3.11).




**140** **292** **141** **293**

**Scheme 3.11.** *Reagents:* a) $I_2$, $K_2CO_3$, MeCN, 16 h, 86%; b) $I_2$, $K_2CO_3$, MeCN, 16 h, 87%.

These promising results warranted further study and this was the starting point of the present research. Thus, the original concept was to synthesis highly substituted pyrrolidines **143a-e** with various stereochemistries from precursors containing both *E* and *Z* double bonds, with an *anti* and *syn* relationship between the hydroxyl and ester functionalities (Figure 3.13 and Figure 2.10, Chapter 2). Methyl esters were used in preference to the ethyl esters previously studied, to prevent overlap of the pyrrolidine resonances by some of the ethyl ester peaks.




**294** **295** **143a-d**

(*E*)- and (*Z*)-

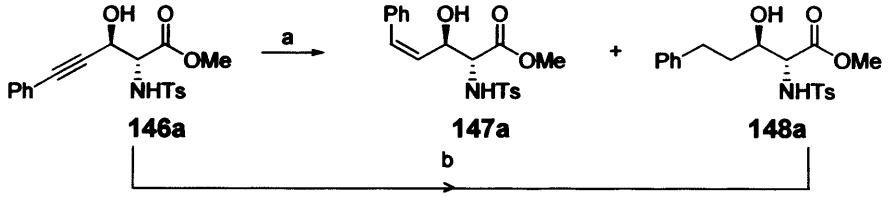
**Figure 3.13**

## 3.20. Results and Discussion: Cyclisations of Amino Ester Derivatives

### 3.21a. Cyclisation of an aryl, *cis,anti* Precursor

The study commenced with the phenyl *anti* diastereoisomer **146a** obtained from the Kazmaier aldol reaction (Scheme 2.10, Chapter 2). To obtain the (Z)-olefin **147a**, the aldol product **146a** was reduced with 5% palladium on calcium carbonate poisoned with quinoline (modified Lindlar's catalyst[6]), but unfortunately, the reaction was capricious and despite numerous attempts, complete reduction was never achieved.

An initial reduction afforded an in inseparable 8:3:1.5 mixture of *cis*-alkene **147a**: alkyne **147b**: alkane **147c** (Scheme 3.12). New olefin signals were apparent in the $^1$H NMR spectrum at 5.55 and 6.60 ppm, with a coupling constant of 11.7 Hz, indicating a (*Z*)-alkene.



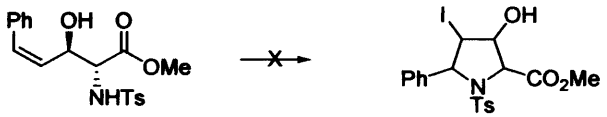

**Scheme 3.12.** *Reagents:* a) cat 5% Pd/ $CaCO_3$, 0.3 eq quinoline, $H_2$, EtOAc; b) cat 5% Pd/ $CaCO_3$, quinoline, $H_2$, EtOAc, 16 h, 80%.

To identify the relevant resonances in the $^1$H NMR spectrum, the alkyne **146a** was deliberately reduced to the alkane **148a** in 80% yield, as confirmed by the absence of olefin protons and two new $CH_2$ resonances in the 1.75-3.00 ppm region of the spectra (Scheme 3.12).

Being a new substrate **147a**, obviously there were numerous conditions to be tested to determine the optimum conditions for yield and selectivity. A plethora of iodonium sources[7] including iodine itself, iodine monochloride, iodine monobromide, NIS and $Py_2IBF_4$ can be used in various solvents including dichloromethane, acetonitrile, methanol and ethers. A wide range of temperatures have been successful, ranging from -78°C to ambient temperature and in addition, a choice of carbonate bases have been utilised. Based

on the previous successful 5-*endo*-trig cyclisations conducted in the Knight group[1,3], the conditions tested were narrowed down to either dichloromethane or acetonitrile as the solvent, iodine or iodine monobromide as the iodonium source and potassium carbonate as the base. When iodine was used the temperature was maintained at 0°C, while the temperature was lowered to -20°C when iodine monobromide was employed. Finally, due to the problems experienced with Boc protection in previous cyclisations[3], the use of the tosyl group was continued despite problems associated with its removal.

The initial substrate **147a** tested, in retrospect, was probably not the easiest since (*Z*)-olefins are known to isomerise in the presence of iodine. In addition, with the adjacent phenyl group, there was the possibility of forming a stable benzylic carbocation, so this position was significantly activated and hence more reactive than an alkyl chain, for example. The resultant weak C-I bond could also affect the selectivity of the cyclisation, and hence, these theories had to be clarified. Surprisingly, treatment of the crude *cis*-olefin **147a** with iodine and potassium carbonate in acetonitrile, had failed to induce reaction and purely starting material was obtained (Scheme 3.13).




**147a** **296**

**Scheme 3.13.** *Reagents:* $I_2$, $K_2CO_3$, *anh* MeCN, 2 h, 0°C, 0%.

Consequently, the 8:3:1.5 mixture of *cis*-alkene **147a**: alkyne **146a**: alkane **148** was treated with the more reactive iodine monobromide and potassium carbonate in dichloromethane, at -20°C for 4 h (Scheme 3.14). Following chromatography, a 9:1 mixture of diastereoisomers was isolated, in addition to the recovered alkane **148a** thereby overcoming the foregoing, rather worrying result. The 9:1 ratio was tentatively determined from the integrals of the methyl ester singlets. The alkyne **146a** starting material would also have given rise to a dihydropyrrole, which was removed during chromatography.

### 3.22a. Structure Elucidation

The disappearance of the olefin signals was convincing evidence that cyclisation had occurred to afford either a pyrrolidine **296** *via* a 5-*endo*-trig cyclisation, or an azetidine **297** *via* a 4-*exo*-trig ring closure. Also, addition of iodine to the double bond could have occurred, or if water was present, iodohydrins **298a** and **298b** could have been formed, so confirmation of the iodopyrrolidine structure **296** was first pursued (Figure 3.14).

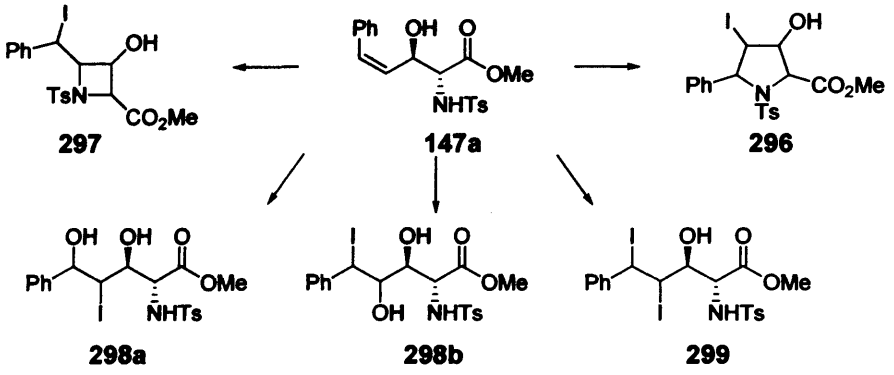
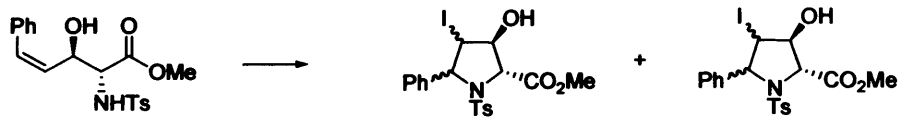



**Figure 3.14**

The infrared spectrum showed the presence of an ester by the carbonyl stretch at 1747 $cm^{-1}$ and an O-H stretch at 3488 $cm^{-1}$. LRMS using a very mild ionisation technique, APcI, perhaps surprisingly gave a molecular ion at 502 ($M^+$ +H, 100%), with no loss of HI. Therefore, the major product could not be iodohydrin **298a** or **298b** or the diiodide **299**. In the $^{13}C$ NMR spectrum, four methine groups were evident. One might expect all to be at around 70 ppm, but due to the heavy atom effect[8] one is at around 30 ppm. For the major product, the C*H*I resonance was at 35.5 ppm which correlated to the apparent triplet at 4.20 ppm in the $^1H$ NMR spectrum. In the azetidene **297**, the C*H*I proton would be a doublet, hence the evidence suggested that the product was indeed an iodo-pyrrolidine **296**. $^1H$-$^1H$ correlation spectrum revealed that the C*H*I proton was coupled to two others protons, a doublet at 4.90 ppm and a rounded, ill-defined resonance at 4.65 ppm. This clarified that the product was not the azetidine **297** since the C*H*I proton could only couple to one other resonance in that structure. The C*H*I proton in the pyrrolidine **296** would be coupled to the C*H*OH and the C*H*Ph protons. The doublet at 4.90 ppm was therefore the C*H*Ph proton and the ill-defined resonance at 4.65 ppm was the C*H*OH proton. By elimination, the remaining doublet at 4.30 ppm had to correspond to the C*H*$CO_2$Me proton.




**Scheme 3.14.** *Reagents:* IBr, $K_2CO_3$, $CH_2Cl_2$, -20°C, 4 h, 63%.

### 3.23a. Determination of Stereochemistry of the Pyrrolidine 296a

All the products should be formed by *anti* addition of the iodine and the nitrogen to the olefin, according to the proposed mechanism. Since the original mixture was exclusively *anti* with respect to the ester and hydroxyl groups, the stereochemistry of the 2- and 3-positions should theoretically remain *trans* in the product. In addition, epimerisation of the acidic proton adjacent to the ester moiety was unlikely since the adjacent hydroxyl group was *trans* to the ester. Finally, provided no isomerisation of the (*Z*)-olefin **147a** occurred in the reaction, the phenyl and iodide moieties should remain *cis* in the product. Thus, the two possible isomers are shown in Figure 3.15.

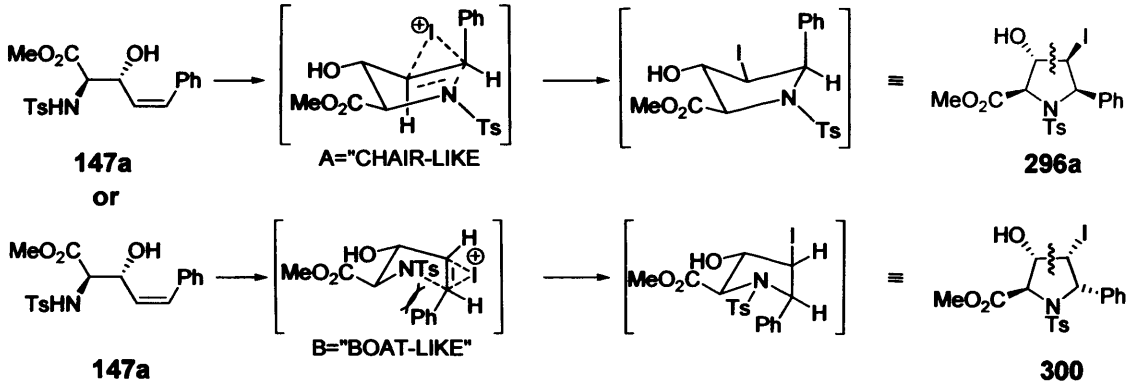



**Figure 3.15**

Unlike, 6-membered rings, the coupling constants of 5-membered rings cannot be used with confidence to determine the stereochemistry[9]. In addition, due to the close proximity of the C*H*I and C*H*$CO_2$Me resonances, nOe experiments could not be conducted to ascertain the stereochemistry. Another approach was necessary, was it possible to establish the stereochemistry by chemical correlation.

### 3.24a. Establishing the Stereochemistry *via* Epoxide Formation

Previously in the Knight group, when iodotetrahydrofuran **301** was treated with aqueous sodium hydroxide in dichloromethane, an epoxide **302** was formed, provided there was a *trans* relationship between the iodine and hydroxyl moieties (Scheme 3.15).[2]


**301** **302**

**Scheme 3.15.** *Reagents:* $CH_2Cl_2$, aq. NaOH, 95%.

With this *trans* relationship, an $S_N2$ displacement of the iodine with the oxygen from the hydroxyl group could occur (Figure 3.16). With the corresponding *cis* stereochemistry the nucleophile cannot attack from the front face by the same mechanism because it is not in the correct orientation, thus a ketone is formed (Figure 3.16).

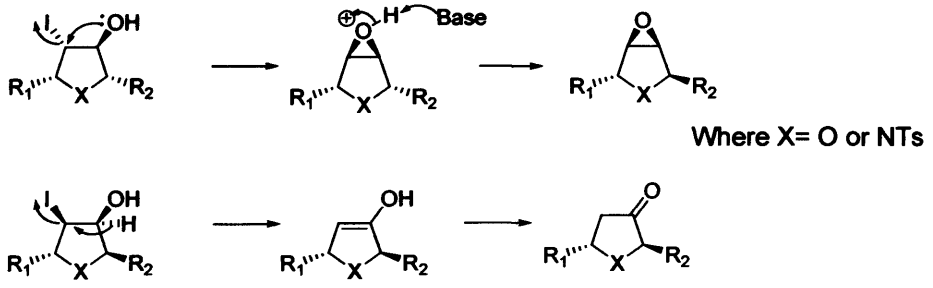
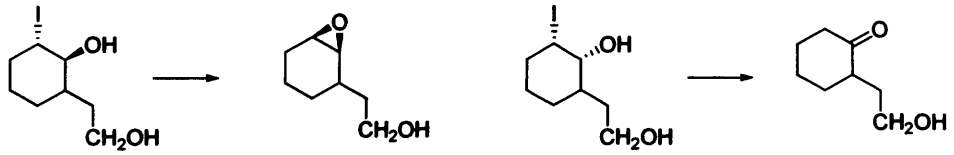



**Figure 3.16**

Being very different systems to tetrahydrofurans, there was no guarantee that this methodology could be applied to iodo-pyrrolidines to afford epoxy-pyrrolidines. Treatment of the 9:1 mixture of pyrrolidines **296a** and **296b** with aqueous sodium hydroxide in dichloromethane for 24 h, failed to induce any reaction (Scheme 3.17; a). Hence, the reaction was repeated but using a stronger base, sodium hydride but complete degradation of the precursor pyrrolidines **296** occurred (Scheme 3.17; b). Fetizon[10] *et. al.* reported that silver carbonate on celite yields epoxides from halohydrins, provided there is a *trans* relationship between the halide and the hydroxyl moiety. If the relationship is *cis*, then a ketone is formed in virtually quantitative yield (Scheme 3.16). This "reverse" tactic succeeds by the initial removal of the iodide by silver (I) in contrast to its displacement by

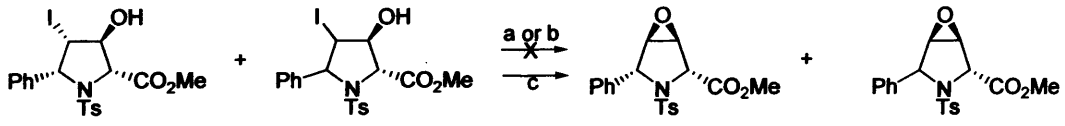
an adjacent alkoxide. Despite this apparent change to an $S_N1$ mechanism, it is evident from Scheme 3.16 that stereochemistry is retained, presumably the alcohol begins to attack the CI carbon as the iodine begins to leave.




**303** **304** **305** **306**

**Scheme 3.16.** *Reagents:* 6 eq 50% by weight silver carbonate on celite, *anh* $CH_2Cl_2$, 24 h.

The 9:1 mixture of iodopyrrolidines **296a** and **296b** was therefore treated with 50% silver carbonate on celite, to yield a 9:1 mixture of diastereoisomers **307a** and **307a** in 97% yield (Scheme 3.17; c). The NMR spectrum of the major isomer **307a** revealed the loss of the C*H*I signal at 4.25 ppm, the absence of new $CH_aCH_b$ resonances, expected α to the new carbonyl and no protons in the olefin region; thus elimination had not occurred. In addition, no ketone resonance was evident in either the $^{13}C$ NMR spectrum or infrared spectrum and LRMS detected a molecular ion at 374 ($M^+$ + H), which was consistent with epoxide formation. All this evidence indicated that the product was an epoxide **307a**, not a ketone and so this implied that there was a *trans* relationship between the 3- and 4-positions of the major iodopyrrolidine **296** (Scheme 3.13). The epoxide **307a** was characterised by two new apparent singlets at 4.65 and 4.95 ppm corresponding to the new C*H*O protons. The remaining ring protons were both doublets, but the coupling constants were very small, 2.8 Hz, indicative perhaps of a relatively symmetrical structure **307a**.

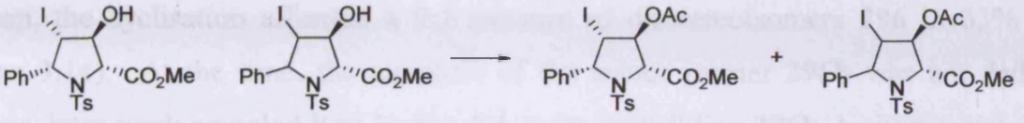



**296a** **296b** **307a** **307b**

**Scheme 3.17.** *Reagents:* a) $CH_2Cl_2$, aq. NaOH, 24 h, 0% b) NaH, THF, 16 h, 0°C; c) 6 eq 50% wt/ wt $Ag_2CO_3$ on celite, $CH_2Cl_2$, 24 h, 97 %.

In order to sharpen and separate the overlapping resonances in the NMR spectrum of the iodopyrrolidines **296a** and **296b**, an 8:1 mixture of diastereoisomers **308a** and **308b** from another cyclisation was treated with pyridine and acetic anhydride (Scheme 3.18). It was

anticipated that a shift in the C*H*OH proton would be observed of *ca* 1 ppm, without significantly affecting the other signals. The formation of the acetate **308a** was confirmed by the disappearance of the O-H stretch in the infrared spectrum, a new methyl group at 1.95 ppm and the expected shift in the 3-H signal, from 4.65 to 5.70 ppm, was observed. Following recrystallisation *via* vapour diffusion, a pure sample of the major isomer **308a** was obtained, but disappointingly, the C*H*$CO_2$Me and C*H*I signals were still too close together for unambiguous analysis of the stereochemistry by nOe experiments.




**Scheme 3.18.** *Reagents:* acetic anhydride, pyridine, 24 h, R.T, 72%.

Fortuitously, the acetate **308a** was crystalline, thus the structure of the major isomer **308a** was confirmed by the X-ray diffraction (Figure 3.17). The structure obtained was in agreement with the structure deduced from epoxide formation (Scheme 3.17; c). All observed bond angles and lengths were consistent with the literature and the structure adopted is dependent on the stereochemistry of the various groups in the precursor.

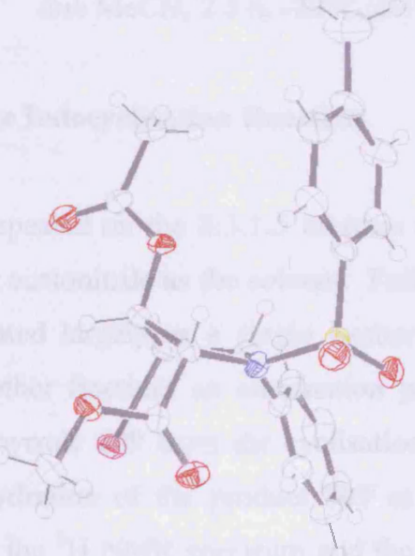
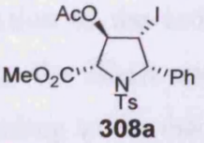


**Figure 3.17:** Crystal Structure of the 2,5-*cis* iodo-pyrrolidine **308**

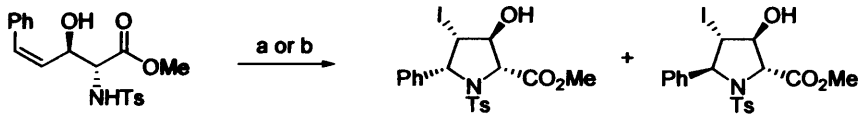



**308a**

### 3.25a. Explanation of the Observed Stereochemistry

The most stable transition state will be chair-like, with the majority of the (largest) groups equatorial. The "boat-like" transition state in Figure 3.15 is severely crowded, particularly when one considers the phenyl and tosyl substituents, thus transition state A is more likely to be adopted and hence, the predominant isomer should be the 2,5-*cis* diastereoisomer **296a**.

To recap, the cyclisation afforded a 9:1 mixture of diastereoisomers **296** in 63% yield (Scheme 3.14). At the time, the structure of the minor isomer **296b** was not deduced. However, later work revealed it to be the 2,5-*trans* pyrrolidine **296b**, by comparison with an authentic sample (Figure 3.22). Therefore, unsurprisingly, slight isomerisation of the olefin **147a** to the more stable *trans* geometry had occurred, prior to cyclisation.



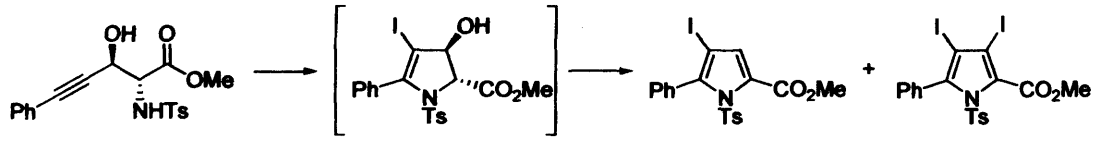

**147a** **296a** **296b**

**Scheme 3.19.** *Reagents:* a) IBr, $K_2CO_3$, *anh* $CH_2Cl_2$, -20°C, 4 h, 63 %; b) IBr, $K_2CO_3$, *anh* MeCN, 2.5 h, -20°C, 19 %.

### 3.26a. Optimisation of the Iodocyclisation Reaction

The iodocyclisation was repeated on the 8:3:1.5 mixture of (*Z*)-olefin **147a**, alkyne **146a** and alkane **148a**, but using acetonitrile as the solvent. Following chromatography, the 2,5-*cis* isomer **296a** was isolated largely as a single isomer, in a disappointing 19% yield (Scheme 3.19; b). In another fraction, an elimination product was evident, which was determined to be the iodopyrrole **109** from the cyclisation of the alkyne starting material **146a** and subsequent dehydration of the product **309** as deduced from the lack of any pyrrolidine ring protons in the $^1H$ NMR spectrum and the characteristic resonance at 6.92 ppm, corresponding to the β pyrrole proton (Figure 3.18). [11a] In addition, two methyl ester singlets were apparent and so in addition to the iodopyrrole **109**, the other product was believed to be the diiodide **310**, since the NMR spectrum revealed only protons in the aromatic region and protons corresponding to the ester. However, this theory would have

been confirmed by LRMS but no further study was necessary since both these products were from the cyclisation of residual starting material **146a**, which was covered in the research conducted by Singkhonrat. [11a]




**146a** **309** **109** **310**

**Figure 3.18a**

### 3.27a. Summary of Results

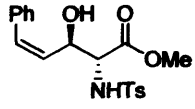
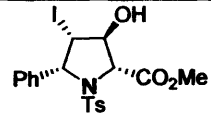
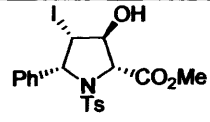
| | Conditions | Time (h) | Yield (%) | Major Product |
|---|---|---|---|---|
|  **147a** | $I_2$, MeCN, $K_2CO_3$, 0°C | 2 | 0 | No cyclisation |
| | IBr, $CH_2Cl_2$, $K_2CO_3$, -20°C | 4 | 63 |  **296a** |
| | IBr, MeCN, $K_2CO_3$, -20°C | 1.5 | 19 |  **296a** |

**Table 3.10**

### 3.28a. Conclusion

From this initial study, the (*Z*)-phenyl *anti* amino alcohol **147a** cyclised highly selectively in good yield, but only under one set of conditions, iodine monobromide and potassium carbonate in anhydrous dichloromethane at -20°C. Surprisingly, when the (*Z*)-olefin **147a** was treated with iodine and potassium carbonate in anhydrous acetonitrile after 2 h at 0°C, only starting material was recovered (Table 3.10). It is plausible that leaving the reaction for longer would yield the desired product **296a**, but further optimisation of the reaction was not conducted during this study, but these results were encouraging and warranted further study with a variety of substituents (R).

### 3.21b. Cyclisation of an alkyl, *cis, anti* Precursor

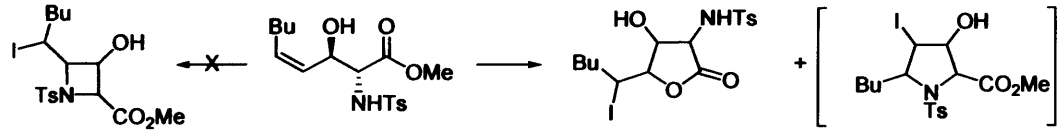
Cyclisation studies were conducted on the alkyl, *cis, anti*-derivative **147a**, to determine if the substituent (R) affects the cyclisation. The precursor **144a** obtained from the aldol condensation of hept-2-ynal **115** with the enolate of *N*-tosyl glycinate (Scheme 2.10; a, Chapter 2) was treated with Lindlar's catalyst, but like the aryl precursor **146a**, the Lindlar reduction was capricious, but eventually the *cis*-alkene **149** was obtained cleanly in quantitative yield, as apparent from the two new olefin resonances in the range 5.25 to 5.50 ppm with a coupling constant of 10.9 Hz, corresponding to a *cis* double bond (Scheme 3.20).


**144a** **149a**

**Scheme 3.20.** *Reagents:* Lindlar's Catalyst, EtOAc, $H_2$, 1 h, 100%.

An initial reaction revealed that, like the previous example, use of iodine monobromide was necessary to effect reaction. When dichloromethane was employed as the solvent, numerous products were evident in the NMR spectrum of the crude product, together with some starting material, so further investigation was not conducted. However, with acetonitrile as the solvent, after some optimisation, followed by NMR spectroscopy and purification by chromatography, it became apparent that the major product was not a

pyrrolidine. The NMR spectrum revealed the loss of the olefin resonances and the methyl ester. In addition, a molecular ion of 468 and the retention of the NH signal indicated that cyclisation through the nitrogen to yield a pyrrolidine **312** had not occurred. A characteristic carbonyl stretch of 1767cm$^{-1}$ in the infrared spectrum, together with the loss of the methyl ester singlet suggested the product was a butyrolactone **254**. The C*H*I signal at 30.1 ppm in the $^{13}$C NMR spectrum correlated to the resonance at 4.20 ppm in the $^{1}$H NMR spectrum. $^{1}$H-$^{1}$H correlation showed that this C*H*I proton was coupled to the C*H*O proton at 4.45 ppm and also a methylene in the butyl side chain. This C*H*O proton in addition was coupled to the C*H*OH proton at 4.62 ppm, which was also coupled to the C*H*N proton at 3.80 ppm. Once again because the C*H*I proton coupled to two different protons, the product was not the azetidine **311** and the data obtained indicated the presence of a lactone **254** (Scheme 3.21).




**Scheme 3.21.** *Reagents:* IBr, $K_2CO_3$, MeCN, -20°C-R.T., 29.25 h, 14%.

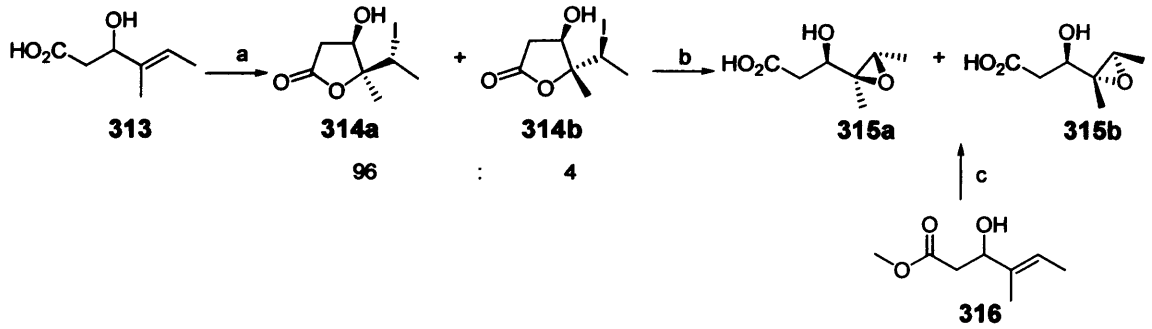
Therefore, a 5-*exo*-trig cyclisation gave rise to a 5-ring lactone **254**, largely as a single diastereoisomer, but in only 14% yield (Scheme 3.21). Further inspection of the NMR spectrum of the crude product revealed the presence of two sulfonamide groups. In addition to the lactone **254** resonances, a singlet at 3.70 ppm together with numerous resonances characteristic of pyrrolidine ring protons in the region 3.50-4.30 ppm of the spectra were present. This suggests that pyrrolidines **312** were formed in the reaction, but were not isolated after chromatography at this time.

### 3.22b. Determination of Stereochemistry

Due to the suitably separated ring protons, this lactone **254** was a perfect candidate for determination of stereochemistry by nOe. A relatively new technique in Cardiff, GOESY[11b-d] was used which revealed that on irradiation of the C*H*OH resonance enhancement of both the C*H*N, and C*H*O signals was observed, with no enhancement of the C*H*I resonance. This suggested that the C*H*OH, C*H*N, and C*H*O protons were *cis* to

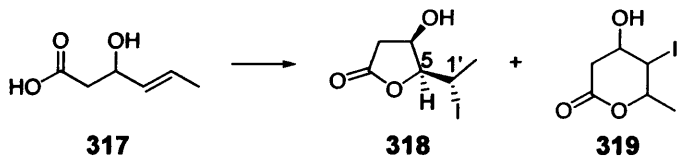
each other (Figure 3.18). The data obtained from this technique is contained in the appendix. However, the stereochemistry of the C*H*I proton is dependent on the conformation of the lactone and since it was not in a ring, nOe experiments could not confirm the stereochemistry.

However, the Chamberlin[12] group conducted a plethora of iodocyclisations of 3-hydroxyl-4-alkenoic acids **313** to form the butyrolactones **314**, and deduced the stereochemistry of the major products by subjecting these to methanolysis to furnish epoxides **315**, which were then compared with an authentic sample produced from an epoxidation reaction on the corresponding allylic alcohol esters **316** (Scheme 3.22).




**Scheme 3.22.** *Reagents:* a) $I_2$, 0°C, $Et_2O$/THF/aq bicarbonate, 96:4 (a:b); b) $K_2CO_3$, MeOH, 96:4 (a:b); c) *t*-BuOOH, $VO(acac)_2$, (3:97) a:b.

The iodolactonisation of substrate **317**, conducted by the Chamberlin group, proceeded with retention of the *trans* geometry, *J* (5*H*-1'*H* = 10.8 Hz) to yield the iodolactone **318** in a 95:5 ratio in 49% yield, in addition to some δ-lactone **319** (Scheme 3.23).




**Scheme 3.23.** *Reagents:* $I_2$, 0°C, $Et_2O$/THF/aq bicarbonate.

This lactone **318** was similar in structure to lactone **254** arising from the iodocyclisation of the butyl *anti*-amino alcohol **149a** (Scheme 3.21), and thus was used for comparison. Lactone **254** displayed a coupling constant of 10.1 Hz between the C*H*I and C*H*O protons,

which being of similar magnitude to Chamberlin's example (Scheme 3.23), implied a *trans* relationship (Figure 3.18b).

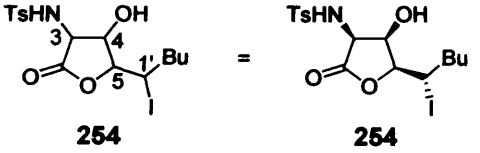



**Figure 3.18b**

This *trans* relationship between the C*H*I and the C*H*O protons suggests that prior to cyclisation, isomerisation of the *cis* olefin occurred and the *trans* olefin **320** then underwent a 5-*exo* cyclisation to afford the lactone **254** (Figure 3.19).

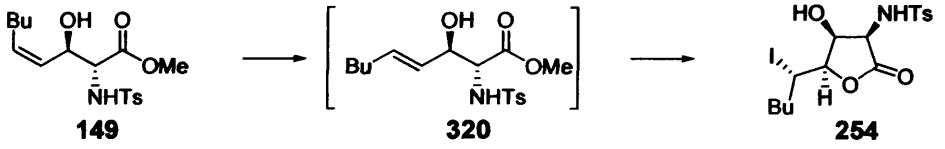



**Figure 3.19**

### 3.23b. Summary Table

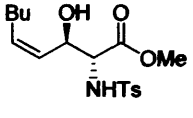
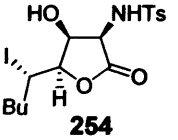
| | Conditions | Time (h) | Yield (%) | Product |
|---|---|---|---|---|
|  **149** | $I_2$, $CH_2Cl_2$, $K_2CO_3$, 0°C | 16 | / | Mixture of products |
| | $I_2$, MeCN, $K_2CO_3$, 0°C | / | 0 | No cyclisation |
| | IBr, $CH_2Cl_2$, $K_2CO_3$, -20°C | / | 0 | No cyclisation |
| | IBr, MeCN, $K_2CO_3$, -20°C | 29.25 | 14 |  **254** |

**Table 3.11**

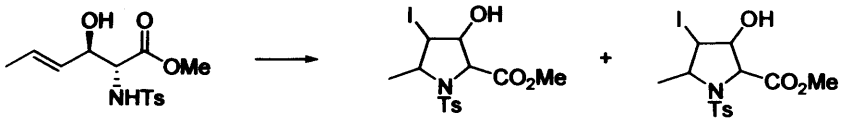
### 3.24b. Conclusion

The study showed that the nature of the alkene substituent (R) was instrumental to the success of the iodocyclisation, with the phenyl derivative **147a** afforded a pyrrolidine **296a** in good yield and high selectivity, while the butyl derivative **149**, gave a lactone **254** in low yield in addition to a mixture of pyrrolidines. However, some similarities were apparent between the two. For example, neither substrate cyclised upon treatment with iodine, only in the presence of the more reactive iodine monobromide. For the butyl *cis, anti* precursor **149**, only one set of conditions was successful, IBr, MeCN, $K_2CO_3$, at -20°C, which yielded predominately a lactone **254**, as a single diastereoisomer in only 14% yield. Initially, the lactone result appeared to be a special case, however when the phenyl *cis, anti* precursor **147a** was subjected to identical conditions (Table 3.10), the pyrrolidine **296a** was isolated in only 19% yield. So it is plausible that the remaining material was a lactone, which at the time was not isolated. Also, when Sharland[4] conducted his iodocyclisations on the butyl *trans, anti* precursor **141**, preliminary findings suggested that the product was a pyrrolidine **293** not a lactone (Scheme 3.11; b). Hence, it is feasible that in addition to forming the lactone **254** *via* the 5-*exo* cyclisation, a competing 5-*endo* trig cyclisation of the isomerised olefin **149** yielded a pyrrolidine **312** where the phenyl and iodine had a *trans* relationship. Due to other unknown impurities in the NMR spectrum of the crude product, the quantity of the assumed pyrrolidine **312** was not determined. Further optimisation of the iodocyclisations is required. Later, optimisation of the lactone **254** formation was achieved by cyclising the corresponding carboxylic acid **370** (Section 3.44).

### 3.21c. Cyclisation of an alkyl, *trans, anti* Precursor

When the precursor **150a** derived from the aldol reaction of (*E*)-crotonaldehyde **137** with the enolate of methyl *N*-tosyl glycinate (Scheme 2.12, Chapter 2), was treated with iodine and potassium carbonate in dichloromethane for 24 h, a 6:1 mixture of diastereoisomers **321** and **322** was obtained (Scheme 3.24). Again, confirmation that cyclisation had occurred was apparent by the disappearance of the alkene resonances, and new characteristic ring protons in the range 3.60-4.45 ppm. In addition, the methyl ester was intact and a molecular ion at 462 ($M^+$ + Na, 100%), was observed, which was consistent

with an iodo-pyrrolidine and thus confirming that the product was not a lactone, iodohydrin or diidodide. The C*H*I signal at 33.4 ppm in the $^{13}C$ NMR spectrum correlated to a double doublet at 3.65 ppm in the proton NMR spectrum. This indicated that the major isomer **321** was indeed a pyrrolidine, not an azetidine, where the C*H*I signal would be a double quartet. The C*H*$CO_2Me$ was instantly recognisable as the only doublet at 4.40 ppm, and so the remaining doublet doublet at 4.45 ppm was the C*H*OH. Thus the cyclisation afforded the iodopyrrolidines in 80% yield (Scheme 3.24).




**150a** **321** : **322**

6 : 1

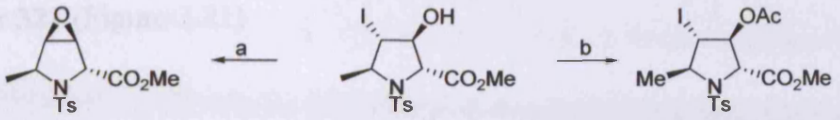
**Scheme 3.24.** *Reagents:* $I_2$, $K_2CO_3$, $CH_2Cl_2$, 0°C, 24 h, 80%.

### 3.22c. Determination of Stereochemistry

The issue of stereochemistry between the 3- and 4- positions had to be addressed, hence Fetizon's[10] previously successful methodology was applied to substrate **321**. The major isomer **321** was treated with silver carbonate on celite, to afford the epoxide **323** cleanly in quantitative yield, as confirmed by the loss of the C*H*I resonance and also a molecular ion of 312 ($M^+$ + H) which was consistent with epoxide formation. Also the lack of new $CH_aCH_b$ protons expected α to the carbonyl and the absence of a ketone signal in either the infrared or $^{13}C$ NMR spectrum confirmed the formation of the epoxide **323**. Once again the epoxide **323** exhibited very small couplings, with both the C*H*O protons appearing as apparent singlets at 3.55 and 4.65 ppm (Scheme 3.25; a).

The formation of the epoxide **323** suggested the stereochemistry in the precursor **321** between the 3- and 4- positions was *trans*. The results of nOe experiments conducted on the iodopyrrolidine **321** were inconclusive. However, previously when iodopyrrolidine **296a** was an oil, fortuitously the corresponding acetate derivative **308a** (Scheme 3.18) was crystalline and as such, X-ray diffraction could be used to determine the stereochemistry. The major iodopyrrolidine **321** was thus treated with acetic anhydride and pyridine, to afford the acetate **324**, in an excellent 88% yield as confirmed by the shift in the 3-H signal from 4.45 to 5.40 ppm, the new methyl singlet at 2.05 ppm and a molecular ion of 482

(Scheme 3.25; b). While the new carbonyl stretch in the infrared spectrum was masked by the carbonyl stretch of the ester, the presence of two carbonyls was apparent in the $^{13}C$ NMR spectrum at 169.9 and 170.5 ppm.




**323** **321** **324**

**Scheme 3.25.** *Reagents:* a) $Ag_2CO_3$ 50% by wt on celite, $CH_2Cl_2$, 24 h, 100%; b) $Ac_2O$, py, 24 h, 88 %.

Despite the evidence obtained proposing the stereochemistry of the major isomer **321** from the cyclisation of the (*E*)-methyl *anti* precursor **150a** (Scheme 3.24), the fact that the acetate derivative **324** was crystalline, allowed the use of X-ray diffraction to further clarify the stereochemistry (Figure 3.20). As expected, the data obtained was in agreement with the structure proposed by the epoxide forming reaction (Scheme 3.25; a). From Figure 3.20 it can be seen that as expected the *trans* geometry is retained in the product.

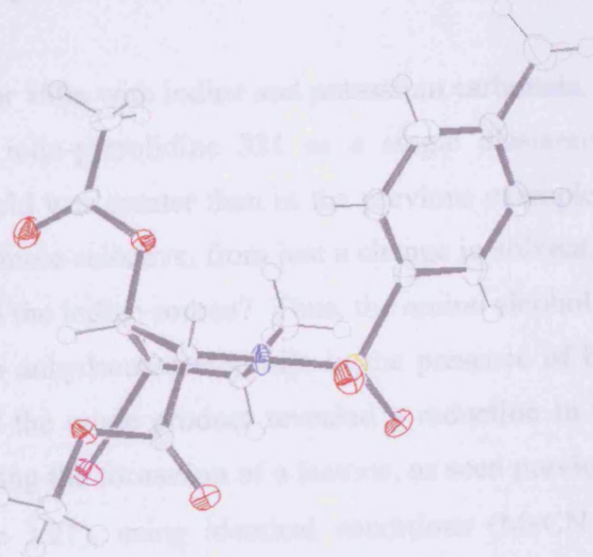
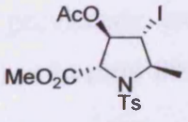


**Figure 3.20**: Crystal Structure of the 2,5-*trans* iodo-pyrrolidine **324**




**324**

### 3.23c. Transition States

The most stable chair-like transition state will be achieved where all the large substituents are in the equatorial position as in transition state A, hence the major isomer should be the 2,5-*trans* isomer **321** (Figure 3.21)

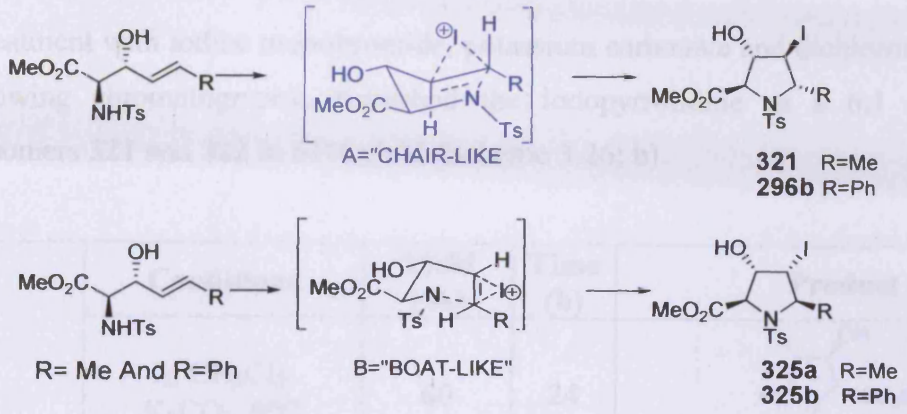
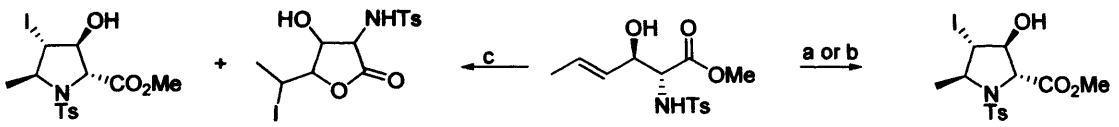



**Figure 3.21**

### 3.24c. Optimisation Experiments

Reaction of the precursor **150a** with iodine and potassium carbonate, in acetonitrile for 1.5 h, gave the same iodo-pyrrolidine **321** as a single diastereoisomer in 86% yield (Scheme 3.26). The yield was greater than in the previous example, and the reaction was considerably faster and more selective, from just a change in solvent. So what would be the influence of a change in the iodine source? Thus, the amino alcohol **150a** was treated with iodine monobromide in anhydrous acetonitrile in the presence of base (Scheme 3.26; c). The NMR spectrum of the crude product revealed a reduction in the size of the methyl ester resonance, indicating the formation of a lactone, as seen previously with the (*Z*)-butyl example **266**, (Scheme 3.21), using identical conditions (MeCN, IBr, $K_2CO_3$, -20°C). Following chromatography, the desired iodopyrrolidine **325** was isolated, but in a 15:1.5:1.5 ratio, as judged from the methyl doublets, in an overall low yield of 27%. The major isomer **321** was the same as previously isolated (Scheme 3.24), while a minor fraction also contained a lactone **326**, but in only 8% yield, whose stereochemistry was not determined.




**321** **326** **150a** **321**

**Scheme 3.26.** *Reagents:* a) $I_2$, $K_2CO_3$, MeCN, 0°C, 1.5 h, 86%; b) IBr, $K_2CO_3$, $CH_2Cl_2$, -20°C, 2 h, 61%; c) *anh* MeCN, IBr, $K_2CO_3$, -20°C, 27% **321** and 8% **326**.

Finally, treatment with iodine monobromide, potassium carbonate and dichloromethane for 2 h, following chromatography, furnished the iodopyrrolidine as a 6:1 mixture of diastereoisomers **321** and **322** in 61% yield (Scheme 3.26; b).

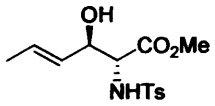
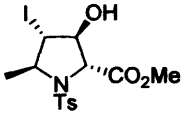
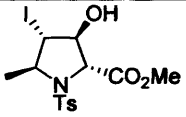
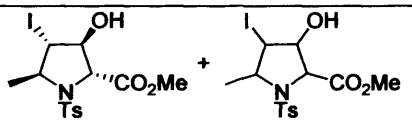
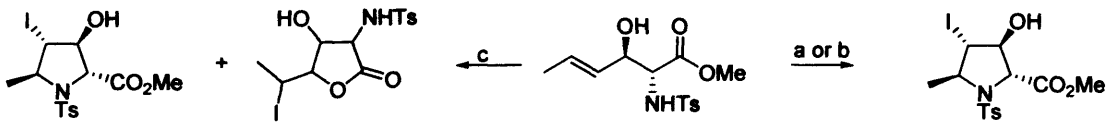
| | Conditions | Yield (%) | Time (h) | Product |
|---|---|---|---|---|
|  **150a** | $I_2$, $CH_2Cl_2$, $K_2CO_3$, 0°C | 80 | 24 |  **321** |
| | $I_2$, MeCN, $K_2CO_3$, 0°C | 86 | 1 |  **321** |
| | IBr, $CH_2Cl_2$, $K_2CO_3$, -20°C | 61 | 2 |  **321** **322** |
| | IBr, MeCN, $K_2CO_3$, -20°C | (**326**) 8 and (**321**) 27 | 3.25 |  **321** **326** |

**Table 3.12**

## 3.25. Conclusion

Once again, the conditions employed in the cyclisations were not trivial; they affected the yield, selectivity and the product isolated. Early indications suggested that the geometry of the double bond was instrumental to the success of these cyclisations, with the (*E*)-amino alcohols yielding pyrrolidines in higher yields than the corresponding (*Z*)-derivatives. One set of conditions, iodine monobromide and potassium carbonate in acetonitrile, again furnished a mixture of pyrrolidine **321** and lactone **326** (Scheme 3.26; c).




**321** **326** **150a** **321**

**Scheme 3.26.** *Reagents:* a) $I_2$, $K_2CO_3$, MeCN, 0°C, 1.5 h, 86%; b) IBr, $K_2CO_3$, $CH_2Cl_2$, -20°C, 2 h, 61%; c) *anh* MeCN, IBr, $K_2CO_3$, -20°C, 27% **321** and 8% **326**.

Finally, treatment with iodine monobromide, potassium carbonate and dichloromethane for 2 h, following chromatography, furnished the iodopyrrolidine as a 6:1 mixture of diastereoisomers **321** and **322** in 61% yield (Scheme 3.26; b).

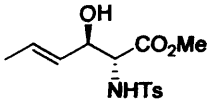
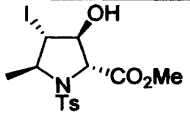
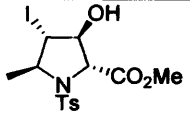
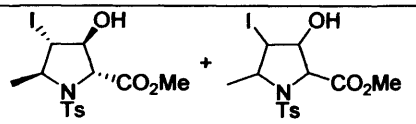
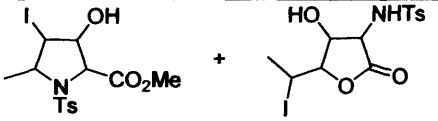
| | Conditions | Yield (%) | Time (h) | Product |
|---|---|---|---|---|
|  **150a** | $I_2$, $CH_2Cl_2$, $K_2CO_3$, 0°C | 80 | 24 |  **321** |
| | $I_2$, MeCN, $K_2CO_3$, 0°C | 86 | 1 |  **321** |
| | IBr, $CH_2Cl_2$, $K_2CO_3$, -20°C | 61 | 2 |  **321** **322** |
| | IBr, MeCN, $K_2CO_3$, -20°C | (**326**) 8 and (**321**) 27 | 3.25 |  **321** **326** |

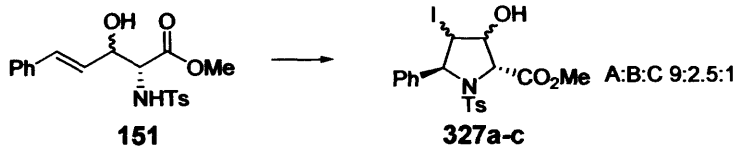
**Table 3.12**

## 3.25. Conclusion

Once again, the conditions employed in the cyclisations were not trivial; they affected the yield, selectivity and the product isolated. Early indications suggested that the geometry of the double bond was instrumental to the success of these cyclisations, with the (*E*)-amino alcohols yielding pyrrolidines in higher yields than the corresponding (*Z*)-derivatives. One set of conditions, iodine monobromide and potassium carbonate in acetonitrile, again furnished a mixture of pyrrolidine **321** and lactone **326** (Scheme 3.26; c).

### 3.21d. Cyclisation of aryl, *trans*, *anti* Precursor

Separation of the diastereoisomers **151a** and **151b** from the aldol condensation of (*E*)-cinnamaldehyde **137** with the enolate of *N*-tosyl glycine could not be achieved (Scheme 2.12, Chapter 2). The cyclisations were therefore conducted on various mixtures, with the aim of separating these isomers later. With two diastereoisomers in the cyclisation, a minimum of two iodopyrrolidines would likely be produced. A 5.8:1 (*anti:syn*) mixture of diastereoisomers **151** was treated with iodine and potassium carbonate in dichloromethane for 3.5 h at 0°C to afford a 9:2.5:1 (A:B:C) mixture of diastereoisomers **327** (Scheme 3.27). Following chromatography, isomer A **327a** and B **327b** were isolated in a combined yield of 39%, but no trace of the minor isomer was evident in any of the fractions. Again confirmation of cyclisation was evident from the loss of the olefin signals. Major isomer A **327a** was characterised by a C*H*I resonance at 33.1 ppm, a molecular ion of 524 ($M^+$ + Na) and new pyrrolidine resonances in the range 4.00-5.10 ppm. Identification of the individual protons was achieved by the use of coupling constants. However, despite all the evidence suggesting that the product was a pyrrolidine, since no $^1H$-$^{13}C$ correlation data was obtained, the possibility that the product was an azetidine could not be eliminated, but was believed to be unlikely since none of the other precursors afforded an azetidine.




**151** **327a-c**

**Scheme 3.27.** *Reagents:* $I_2$, $K_2CO_3$, $CH_2Cl_2$, 0°C, 3.5 h.

### 3.22d. Determination of Stereochemistry of Isomer A 296b

Frustratingly, the results obtained from nOe experiments conducted on the major isomer A **327b** were unambiguous, thus it was treated with silver carbonate on celite as a means to determine if the product was a pyrrolidine, and if so, to ascertain the stereochemistry between the 3- and 4- positions. Treatment of major isomer A **327b** with silver carbonate on celite afforded the epoxide **307b** in quantitative yield, as indicated from the loss of the C*H*I signal, the new apparent singlets corresponding to the C*H*O protons at 4.80 and 5.00 ppm, a molecular ion at 374 and the absence of any ketone signals in either the $^{13}C$ NMR

spectrum or infrared spectrum (Scheme 3.28). All this evidence suggested that isomer A **327b** could not be an azetidine, but a 3,4-*trans* iodo-pyrrolidine **296b**.


**296b** **307b**

**Scheme 3.28.** *Reagents:* 6 eq $Ag_2CO_3$ on celite, $CH_2Cl_2$, 24 h, 100 %.

This predicted stereochemistry of isomer A **296b** was in agreement with the structure deduced by X-ray diffraction (Figure 3.22). From Figure 3.22, it can clearly be seen that the *trans* geometry has been retained in the product and also that the structure exhibits π-stacking of the two phenyl rings. The data obtained indicates a centroid-centroid distance of 3.66 Å, consistent with π-stacking.[13]

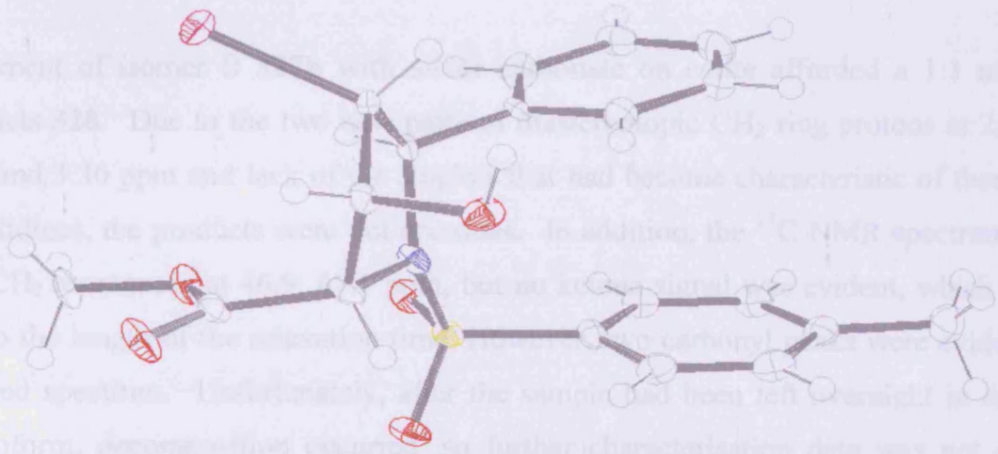
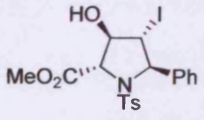


**Figure 3.22: Crystal Structure of the 2,5-*trans* iodo-pyrrolidine 296b**




**296b**

So isomer A **296b** was the cyclisation product from the *anti* diastereoisomer **151a** (Scheme 3.27). By taking into account the quantity of the *anti* diastereoisomer **151a** in the starting material, the yield of the major (2,5-*trans*) isomer **296b** was determined to be 39%, suggesting that the reaction was not very selective (Scheme 3.27).

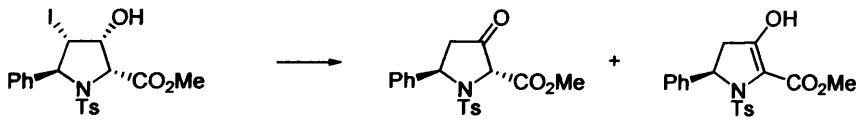
### 3.23d. Explanation of the Observed Stereochemistry

Once again, the most stable chair-like transition state is one where the largest groups are in the equatorial positions (transition state A, Figure 3.21), thus the predominant isomer from the cyclisation of the *anti* diastereoisomer **151a** should be the 2,5-*trans* pyrrolidine **296b**, which is in accordance with the structure deduced by X-ray diffraction (Figure 3.22).

### 3.24d. Determination of the Structure of Isomer B 327b

Isomer B **327b** was characterised by the appearance of new C*H*I resonance at 38.2 ppm, new pyrrolidine resonances in the 4.25-5.15 ppm region of the NMR spectrum and a molecular ion of 502. This time, the coupling constants were too similar to differentiate between the various ring proton signals in the NMR, and hence correlation experiments were employed to confirm that isomer B **327b** was a pyrrolidine, not an azetidine *via* the same methods as used previously.

Treatment of isomer B **327b** with silver carbonate on celite afforded a 1:1 mixture of products **328**. Due to the two new pairs of diastereotopic $CH_2$ ring protons at 2.55, 2.65, 3.05 and 3.30 ppm and lack of the singlets that had become characteristic of these epoxy-pyrrolidines, the products were not epoxides. In addition, the $^{13}C$ NMR spectrum showed two $CH_2$ resonances at 46.9, 47.1 ppm, but no ketone signal was evident, which could be due to the length of the relaxation time. However, two carbonyl peaks were evident in the infrared spectrum. Unfortunately, after the sample had been left overnight in deuterated chloroform, decomposition occurred, so further characterisation data was not obtained. From this limited data, it was apparent that the product was a 1:1 mixture of keto **328a** and enol **328b** tautomers (Scheme 3.29).




**327b** **328a** **328b**

**Scheme 3.29.** *Reagents:* 6 eq 50 % wt/wt $Ag_2CO_3$ on celite, $CH_2Cl_2$, 24 h, 72%.

### 3.25d. Explanation of the Observed Stereochemistry of Isomer B 327b

The most stable transition state adopted will be chair-like transition state A to afford the 3,4-*cis* isomer **327b** as the predominant isomer (Figure 3.23). These findings are in agreement with the stereochemistry deduced from the silver carbonate reaction (Scheme 3.29).

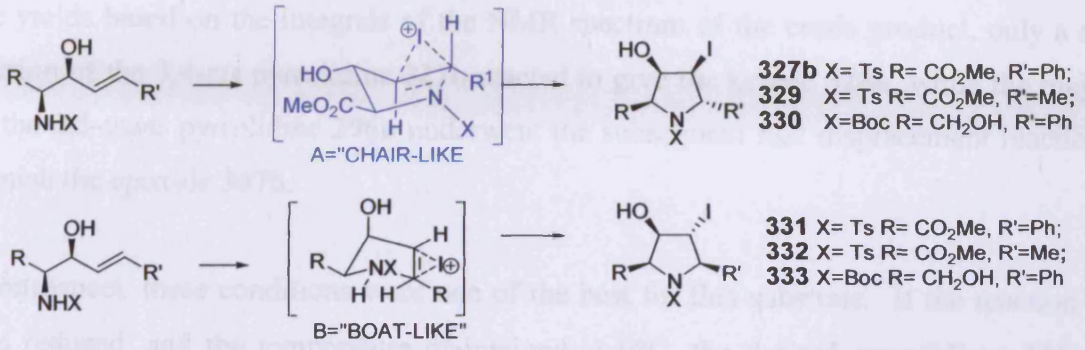



**Figure 3.23**

Thus, isomer B (3,4-*cis* isomer) **327b** from the initial cyclisation was the product from the cyclisation of the *syn* diastereoisomer **151b**, and by taking into account the quantity of *syn* isomer **151b** in the starting material, the yield of the 3,4-*cis* isomer **327b** was determined to be 40% (Scheme 3.27). Therefore, in the course of the reaction, the original 5.8:1 ratio had been reduced to 9:2.5:1, so, optimisation of the iodocyclisations was conducted.

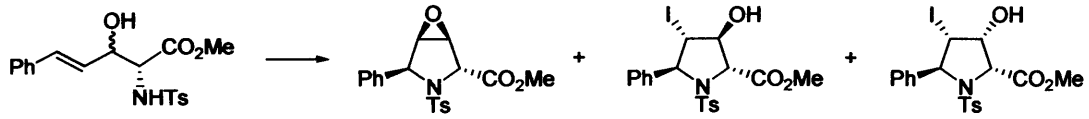
### 3.26d. Optimisation Experiments

An 8:1.5 (*anti*:*syn*) mixture of diastereoisomers **151** was treated with iodine and potassium carbonate in acetonitrile at 0°C and was then gradually allowed to warm to room temperature over 21 h to give 3 distinct products in a ratio of 5:1.4:1 (X:Y:Z) (Scheme 3.30). Complete separation of these three components was not achieved. The major product X **307b** was not a pyrrolidine, due to the absence of a C*H*I signal. Comparison with genuine samples from a previous experiment revealed product Y to be the 2,5-*trans* pyrrolidine **296b** and product Z, the 3,4-*cis* pyrrolidine **327b**.

This odd result was initially dismissed, but later the major product X **307b** was determined to be the 2,5-*trans* epoxide **307b** (Scheme 3.28). So, why were these the only conditions

for any substrate that resulted in the formation of the epoxide *in situ*? It is plausible that the cyclisation was complete after a few hours, and once the reaction vessel had reached ambient temperature, $S_N2$ displacement of the iodine occurred to afford the epoxide **307b**. Closer inspection of the NMR spectrum of the crude product revealed small double doublets in the region 2.00-3.00 ppm, which corresponded to the diastereotopic $CH_2$ protons on the pyrrolidinone ring. No trace was observed in any of the column fractions, because this ketone **328a** had previously been proved to be unstable (Scheme 3.29). From the yields based on the integrals of the NMR spectrum of the crude product, only a small portion of the 3,4-*cis* pyrrolidine **327b** reacted to give the ketone **328a**, while the majority of the 2,5-*trans* pyrrolidine **296b** underwent the subsequent $S_N2$ displacement reaction, to furnish the epoxide **307b**.

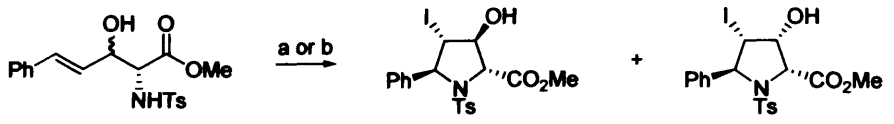
In retrospect, these conditions were one of the best for this substrate. If the reaction time was reduced, and the temperature maintained at 0°C, the desired pyrrolidines **296a** and **327b** would probably have been isolated as single diastereoisomers. The fact that the iodocyclisation and epoxide formation reactions can be carried out in "one pot" is very encouraging and further investigation is warranted, for all substrates. Potassium carbonate being considerably cheaper than silver carbonate, also makes this "one pot" method more viable financially, on a large scale.




**151** **307b** **296b** **327b**

**Scheme 3.30**. *Reagents:* $I_2$, $K_2CO_3$, MeCN, 21 h, 0-21°C, 72% **307b**, 20% **296b** and 79% **327b**.

A 2.3:1 mixture of diastereoisomers **151** (*anti:syn*) was treated with iodine monobromide and potassium carbonate in acetonitrile for 2.5 h to give a 3:1 mixture of iodopyrrolidines. Following chromatography, the 2,5-*trans* pyrrolidines **296b** and 3,4-*cis* pyrrolidines **327b** were isolated in 83% and 75% yield respectively (Scheme 3.31; a).




**151** **296b** **327b**

**Scheme 3.31.** *Reagents:* a) IBr, $K_2CO_3$, MeCN, 2.5 h, -20°C, 83% **296b**, 75% **327b**; b) IBr, $K_2CO_3$, $CH_2Cl_2$, 2.5 h, -20°C, 67% **296b**, 78% **327b**.

Finally, a 2.3:1 mixture of diastereoisomers **151** (*anti:syn*) was treated with iodine monobromide and potassium carbonate in dichloromethane for 2.5 h to furnish a 4:1.8:1 (2,5-*trans* **296b**:3,4-*cis* **327b**:minor) mixture of iodopyrrolidines in 84% yield (Scheme 3.31; b). Following chromatography, the 2,5-*trans* pyrrolidine **296b** was isolated in 67% yield and the 3,4-*cis* pyrrolidine **327b** in 78% yield. Sufficient quantity of the minor isomer was not obtained for characterisation.

### 3.27d. Summary Table

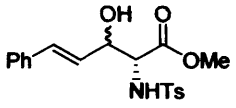
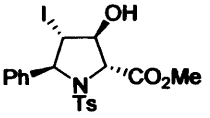
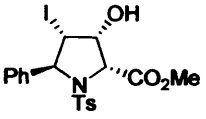
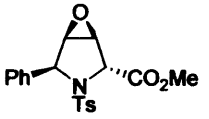
|  **151** | **Conditions** | **Yield (%)**  **296b** | **Yield (%)**  **327b** | **Yield (%)**  **307b** |
|---|---|---|---|---|
| | $I_2$, $CH_2Cl_2$, $K_2CO_3$, 3.5 h, 0°C | 39 | 40 | / |
| | $I_2$, MeCN, $K_2CO_3$, 21 h, 0°C | 20 | 79 | 72 |
| | IBr, $CH_2Cl_2$, $K_2CO_3$, 2.5 h, -20°C | 67 | 78 | / |
| | IBr, MeCN, $K_2CO_3$, 2.5 h, -20°C | 83 | 75 | / |

**Table 3.13**

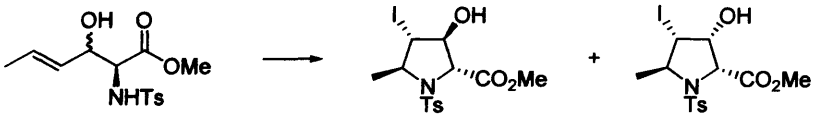
### 3.28d. Conclusion

The results obtained for the (*E*)-phenyl amino alcohols **151** mirror the results obtained for the corresponding (*E*)-methyl *anti* amino alcohols **150**, since in both cases the selectivity and yield is dependent on the reaction conditions. Unlike the methyl derivative **150**, iodine monobromide and potassium carbonate in acetonitrile afforded the pyrrolidines in excellent yields, without any observed lactone formation.

### 3.21e. Cyclisation of an alkyl, *trans, syn* Precursor 150b

A 1:1.2 *anti*:*syn* mixture of diastereoisomers, obtained from the aldol reaction in the absence of tin(II) chloride (Scheme 2.12, Chapter 2), was treated with iodine and potassium carbonate in acetonitrile, *i.e.* the optimum conditions for the *anti* diastereoisomer **150a** (Table 3.12). Following optimisation of the reaction time using tlc and NMR, a 1.6:1 (A:B) mixture of iodopyrrolidines was obtained. The isomers were separated by chromatography to give 2,5-*trans* pyrrolidine **321** in 42% yield.

Unfortunately, in the NMR spectrum of the major isomer A **329** two protons were coincidental. The C*H*I resonance was identified at 38.1 ppm but was coincidental with another resonance. The C*H*$CO_2$Me signal at 4.80 ppm was easily identifiable as the only doublet, while $^1$H-$^1$H correlation identified the C*H*OH proton as the multiplet at 4.25-4.30 ppm and revealed that one of the coincidental resonances was coupled to the C*H*OH proton. In the azetidine, the C*H*OH proton would not show coupling to either the C*H*Me or C*H*I protons, therefore the product was a pyrrolidine **329**, not an azetidine.



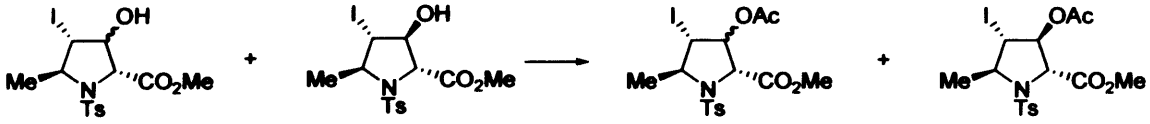

**150** **321** **329**

**Scheme 3.32.** *Reagents:* $I_2$, $K_2CO_3$, MeCN, 0°C 2,5-*trans* 42% **321** and 3,4-*cis* 57% **329**.

### 3.22e. Determination of Stereochemistry

Isomer A was believed to be the 3,4-*cis* iodopyrrolidine **329**, since the same transition state should apply for both (*E*)-*syn* precursors **150b** and **151b** (Figure 3.23).

To hopefully separate the coincident signals, a 7:1 mixture of iodopyrrolidines **329** and **321** (A:B) was treated with acetic anhydride in pyridine to furnish a 7:1 mixture of acetates **334** and **324** in 50% yield (Scheme 3.33). Following repeated recrystallisations, a sample of the major acetate **334** was isolated. The acetate was characterised by new carbonyl signals at 168.7 and 169.4 ppm, a molecular ion at 482 ppm and a shift in the C*H*OH signal by approximately 1 ppm.




**Scheme 3.33.** *Reagents:* $Ac_2O$, py, 16 h, 50%.

Disappointingly, separation of the coincidental protons was not achieved. nOe experiments were again conducted on pyrrolidine **334**, but using a new program. On irradiating the C*H*OAc signal, enhancement of the C*H*$CO_2$Me resonance was apparent, indicating that these groups were *cis* to each other. When the methyl resonance was irradiated, no enhancement was evident in either the C*H*OAc or C*H*$CO_2$Me signal, while enhancement was evident in the coincidental resonance. This indicated that neither the C*H*OAc or C*H*$CO_2$Me groups were *cis* to the methyl. Since the methyl and iodine groups would have been *trans* to each other due to the cyclisation being of a *trans* olefin, the structure was deduced to be the 3,4-*cis* isomer **334** (Figure 3.24), as expected.

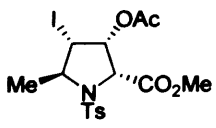
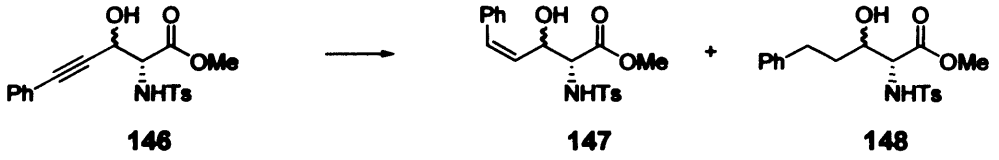



**Figure 3.24**

### 3.21f. Cyclisation of Aryl, *cis, syn* Precursor 151b

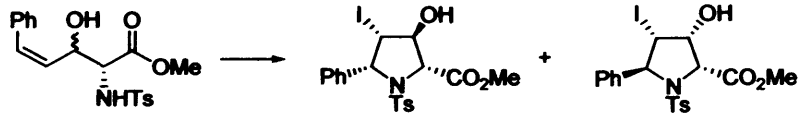
The final pyrrolidines to be synthesised were those from (*Z*)-*syn* precursors. A 1:1 mixture of diastereoisomers **146** arising from the aldol reaction in the absence of tin(II) chloride (Scheme 2.49; a, Chapter 2), were subjected to Lindlar reduction, to give the *cis*-olefin as a 1:1 mixture of diastereoisomers **147** as confirmed by the four olefin double doublets between 5.55 and 6.55 ppm, which all exhibited a typical *cis* coupling of 11.7 Hz (Scheme 3.34). A small amount of alkanes **148** was also evident.




**146** **147** **148**

**Scheme 3.34.** *Reagents*: Lindlar's catalyst, EtOAc.

The crude product was treated with iodine monobromide and potassium carbonate in dichloromethane, to give a vast array of isomers. Following chromatography, as expected, one of the fractions contained predominately the 2,5-*cis*-iodopyrrolidine **296a** in approximately 45% yield. In two of the more polar fractions, the major iodopyrrolidine was determined to be 3,4-*cis* iodopyrrolidine **327b** in approximately 25% yield, based on the integrals in the NMR spectra (Scheme 3.35). The stereochemistry of the remaining isomers was not determined.




**147** **296a** **327b**

**Scheme 3.35.** *Reagents*: IBr, $K_2CO_3$, $CH_2Cl_2$, 45% **296a**, 25% **327b**.

Thus, the cyclisation of the *cis, syn* **147b** precursor was not selective and some isomerisation to the *trans* derivative occurred prior to cyclisation. Fortunately, authentic samples of the 2,5-*cis* iodopyrrolidine **296a** and 3,4-*cis* iodopyrrolidine **327b** were available from previous experiments for comparison and were essential in determining the selectivity of the *syn* diastereoisomer. Cyclisation of the butyl derivative was not carried

out due to the difficulties perceived in interpreting the spectra with a lack of pyrrolidines for comparison.

### 3.22f. Conclusions and Trends

The cyclisations of the (*E*)-phenyl *trans* amino alcohols **151** were successful to a certain degree with a range of conditions, while the (*Z*)-analogues only cyclised on exposure to the more reactive iodine monobromide (Tables 3.13 and 3.10). Thus, the geometry of the double bond is critical to the success of the cyclisations. Due to the problems encountered with the Lindlar reductions, direct comparisons were difficult. The poor results obtained for the (Z)-phenyl, *anti* amino alcohol **146a** cyclisations were presumably due to the large phenyl group being in the unfavourable axial position in the transition state (Figure 3.15), while for the *trans* derivatives, all the large groups are in equatorial positions (Figure 3.21).

It is noteworthy that in all cases, the conditions employed in the reaction are critical to its success in terms of yield, selectivity and in some cases the product formed. For example, only iodine monobromide and potassium carbonate in acetonitrile, furnished a lactone by a competing 5-*exo* cyclisation when the substituent (R) was alkyl.

Finally, this additional β-hydroxyl group does not seem to have had an adverse or beneficial affect on the yield or selectivity of the cyclisations of the (*E*)-amino alcohols, unlike the corresponding (*E*)-homoallylic alcohols (Chapter 1). However, previous cyclisations of (*Z*)-homoallylic sulphonamides afforded pyrrolidines with poor selectivity[3], while from this limited study involving the (*Z*)-phenyl *anti* amino alcohol **146a**, an improved selectivity (7:1) and yield was obtained, with the minor isomer **296b** resulting from isomerisation of the precursor, prior to cyclisation. However, the (*Z*)-butyl *anti* amino alcohol **149a** gave an apparent mixture of products. The pyrrolidine coupling constants are summarised in Table 3.13, but unfortunately, any difference between *cis* and *trans* couplings was marginal.

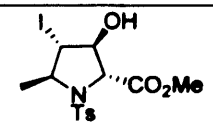
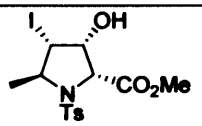
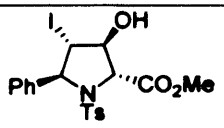
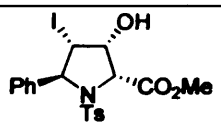
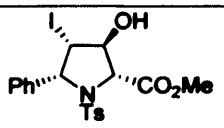
| **Pyrrolidine** | ***J*4-5H (Hz)** | ***J*4-3H (Hz)** | ***J*3-2H (Hz)** | **Pyrrolidine** | ***J*4-5H (Hz)** | ***J*4-3H (Hz)** | ***J*3-2H (Hz)** |
|---|---|---|---|---|---|---|---|
|  **321** | 8.9 | 7.3 | 5.1 |  **329** | / | / | 6.2 |
| **Relationship** | *Trans* | *Trans* | *Trans* | **Relationship** | *Trans* | *Cis* | *Cis* |
|  **296b** | 6.7 | Av. 6.7 | Av. 6.3 |  **327b** | 8.0 | 5.7 | 4.0 |
| **Relationship** | *Trans* | *Trans* | *Trans* | **Relationship** | *Trans* | *Cis* | *Cis* |
|  **296a** | 8.2 | Av. 7.8 | 5.8 | | | | |
| **Relationship** | *Cis* | *Trans* | *Trans* | | | | |

**Table 3.14**

# 3.30. 5-*endo*-trig Cyclisations of Amino Alcohol Derivatives Devoid of an Ester Moiety

## 3.31. Introduction

Previously, 5-*endo*-trig cyclisations were conducted on substrates bearing an ester moiety (Section 3.20). In the case of the (*Z*)-butyl, *anti* precursor **149**, treatment with iodine monobromide and potassium carbonate in acetonitrile yielded a lactone **254** in addition to numerous other resonances. In the absence of this ester group, lactone formation would be eliminated. Therefore, a limited number of cyclisations were conducted on substrates that lacked the ester moiety. With the absence of such a group, this would determine if these precursors that previously gave lactones, formed iodopyrrolidines and also to ascertain the selectivity of such cyclisations (Figure 3.25). The results obtained should also indicate if the ester group is essential for high selectivity in these reactions, by hydrogen bonding for example. Once again the same conditions were tested as in the previous cyclisations, that is iodine or iodine monobromide in acetonitrile or dichloromethane (Table 3.10). The starting materials were synthesised from the condensation of aldehyde **195** with either 1-hexyne **114** or phenylacetylene **145** (Schemes 2.52 and 2.55, Chapter 2).

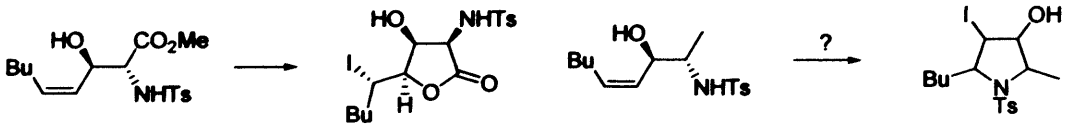



**Figure 3.25**

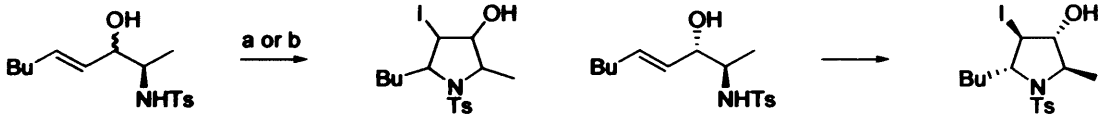
Due to the problems previously discussed (Chapter 2) regarding the synthesis of the starting materials, cyclisations were conducted on various mixtures of diastereoisomers and so the results reported are the basis for future work.

## 3.32. Results and Discussion

### 3.33a. Cyclisation of an Alkyl *trans* Derivative

In the previous cyclisations of (*E*)-methyl *anti* amino alcohol **150a** lactone formation was only observed when iodine monobromide in acetonitrile was used (Table 3.12). In the cyclisations of the (*Z*)-ester derivative **149**, iodine failed to induce cyclisation (Scheme 3.10), this was also found to be the case with the (*E*)-methyl substituted derivative **337** (Scheme 3.26; a). In order to afford a sample of the desired pyrrolidine **338**, conditions were used which had previously proved successful with the (*E*)-ester derivative **150a**, iodine monobromide in dichloromethane (Table 3.12). This would then be useful for comparisons.

Thus, a 5:1 mixture of diastereoisomers **337a** and **337b** of the amino alcohol was treated with iodine monobromide and potassium carbonate in dichloromethane for 2.5 h, to furnish the product **338**, largely as a single diastereoisomer (Scheme 3.26; b). Confirmation of the cyclisation was evident from the loss of the olefin resonances, the appearance of new pyrrolidine resonances in the 3.65-4.40 ppm region and a new C*H*I signal at 36.4 ppm. $^{1}H$-$^{13}C$ correlation identified the double doublet at 4.40 ppm as the C*H*I proton, hence the product could not be an azetidine, where the C*H*I would have been a double triplet. Thus the cyclisation afforded the pyrrolidine **338** in a yield of 50% (Scheme 3.26; b).




**337** **338** **337a** **339**

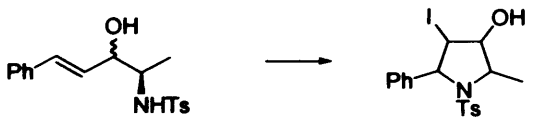
**Scheme 3.36.** *Reagents*: a) $I_2$, $CH_2Cl_2$, $K_2CO_3$, 0°C, 2 h, 0%; b) IBr, $CH_2Cl_2$, $K_2CO_3$, -20°C, 2.5 h, 50%.

Since the starting material was largely the (*E*)-*anti* diastereoisomer **337a**, it is reasonable to assume that these *trans* relationships were retained in the product. nOe experiments were not conducted to ascertain the stereochemistry due to the close proximity of the resonances. From the previous constructed transition states (Figure 3.21), the predominant isomer was believed to be the 2,5-*trans* 3,4-*trans* isomer **339** (Scheme 3.36), however,

confirmation is necessary. Since coupling constants cannot be relied upon to determine the stereochemistry of pyrrolidines, comparisons with the original series of pyrrolidines (Table 3.14) were not be used to confirm the suggested stereochemistry.

### 3.33b. Cyclisation of an Aryl *trans* Derivative

Again as in the previous study with the corresponding esters, it was important to test different substituents on the olefin. In the cyclisation of the corresponding ester derivatives **151**, no lactone was isolated under any conditions (Table 3.13), so no problems were perceived in isolating pyrrolidines **341** from the cyclisations of the corresponding methyl substituted derivatives **340.** Thus, a 2.9:1 (*anti*: *syn*) mixture of diastereoisomers **340** of the amino alcohol was treated with iodine monobromide and potassium carbonate in dichloromethane, to furnish a 3.8:1 (A:B) mixture of diastereoisomers **341** (Scheme 3.37a). Cyclisation was once again confirmed by the loss of the olefin signals in addition to the appearance of new (pyrrolidine) resonances at $\delta_H$ 3.70-5.25 ppm region of the spectrum. Also a molecular ion of 458 ($M^+$ + H) consistant with cyclisation was apparent, further clarifying that the reaction was indeed successful, however, once again it was important to confirm the structures of the cyclised products. The C*H*I signal of the major isomer was an apparent triplet, hence the major product was a pyrrolidine, not an azetidine. The pyrrolidines **341** were isolated in a yield of 21%. These conditions were deemed too harsh, hence milder conditions were explored in subsequent reactions.




**340** **341**

**Scheme 3.37a.** *Reagents:* a) IBr, $CH_2Cl_2$, $K_2CO_3$, 2 h, 21%; b) $I_2$, $CH_2Cl_2$, $K_2CO_3$, 10 h, 70%.

Again due to the closeness of resonances, nOe experiments were not conducted. By considering the most stable chair-like transition state, the predominant isomer from the cyclisation of the *anti* diastereoisomer **340a** should be the 3,4-*trans* isomer **341a** (Figure 3.21), while the *syn* diastereoisomer **340b** should afford the 3,4-*cis* isomer **341b** (Figure 3.23).


**340a** **341a** **340b** **341b**

**Scheme 3.37b**

Since the previous conditions were deemed too harsh (Scheme 3.38; a), accordingly, the reaction was repeated, but using iodine. After some optimisation by NMR and tlc to determine formation of the product, a 1.6:1 (*syn:anti*) mixture of diastereoisomers **340** afforded an inseparable 4.6:1:6.7 (A:B:C) mixture of diastereoisomers **341** of the iodopyrrolidine in an excellent 70% yield. Unfortunately, separation of these three isomers was not achieved and so determination of stereochemistry was not accomplished. Interestingly, major isomer (C) was not isolated in the preceding reaction, instead isomer A was the major isomer in that example. Therefore, it is plausible that isomer C is the result of the cyclisation of the *syn* diastereoisomer **340b** and hence as explained previously should be the 3,4-*cis* isomer **341b**, not isomer B as previously suggested (Figure 3.23), however clarification is necessary.

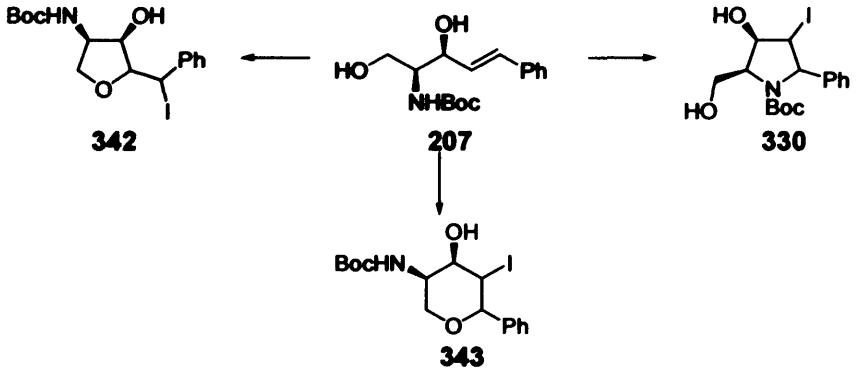
### 3.33c. Conclusion

When the corresponding *cis* olefins were subjected to iodocyclisation conditions (iodine monobromide and potassium carbonate in dichloromethane, -20°C), the results obtained were inconclusive, and pyrrolidine formation could not be ascertained. However, once the problems associated with synthesising the starting materials have been resolved, a more thorough study can be conducted.

However, the corresponding *trans* derivatives **337** and **340** did afford the desired pyrrolidines. A more thorough study is however necessary, in particular the conditions which had previously gave lactones needed to be tested, to determine if pyrrolidines could be isolated.

### 3.34a. Introduction: Substrates Bearing an Alcohol side chain

From the previous chapter, it can be seen that various routes were attempted in order to synthesise amino alcohol derivatives for cyclisation. The route involving the use of Garner's aldehyde **201** as a chiral auxiliary furnished an amino alcohol derivative with a primary alcohol side-chain (Scheme 2.30, Chapter 2). This substrate **207** could cyclise either *via* 5-*endo*-trig, as desired, through the nitrogen, or through the oxygen of the secondary alcohol, either *via* a 5-*exo*-trig or a 6-*endo*-trig cyclisation (Scheme 3.37c). Despite being a deviation from the original theme, the material **207** was cyclised.




**Scheme 3.37c**

### 3.34b. Results and Discussion

Since 5-*endo*-trig cyclisations are disfavoured, the substrate **207** should preferentially undergo a 6-*exo* cyclisation to form cyclic carbamates, *via* loss of the *t*-butyl group, as previously observed in the Knight[3] group (Figure 3.26). Consequently, in all our iodocyclisations a tosyl group was employed.

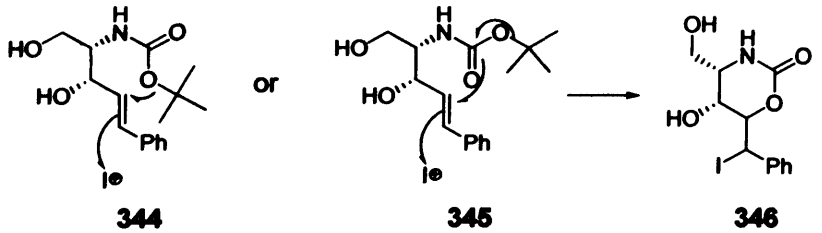
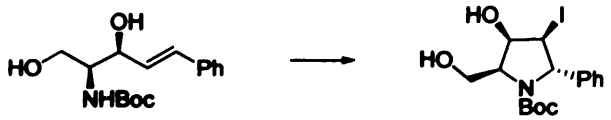



**Figure 3.26**

Following treatment with iodine in dichloromethane, the product **330** was isolated largely as a single diastereoisomer, with the Boc group intact. Again loss of the olefin resonances indicated that cyclisation had occurred, but unfortunately the new ring protons were coincidental with only the C*H*Ph doublet being distinguishable. The lack of $CH_aCH_b$ resonances in the 2-3 ppm region, strongly suggested that the cyclic structure did not consist of a $CH_2$ group in the ring, ruling out both the tetrahydrofuran **342** and tetrahydropyran **343** (Figure 3.27). So surprisingly, it appeared that precursor **207** had cyclised through the nitrogen to give rise to the desired pyrrolidine **330** in 84% yield (Scheme 3.40). Once again, since the precursor was an (*E*)-*syn* diastereoisomer **307**, the most stable chair-like transition state with all large groups equatorial (Figure 3.23) should afford the 3,4-*cis*-pyrrolidine **330** (Scheme 3.38).



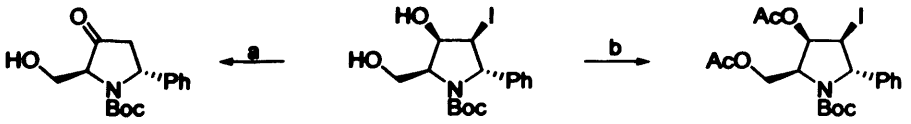

**207** **330**

**Scheme 3.38.** *Reagents*: $I_2$, $K_2CO_3$, $CH_2Cl_2$, 84%.

To further clarify the gross structure of the cyclisation product, the proposed pyrrolidine **330** was treated with silver carbonate on celite (Scheme 3.39; a). If one assumed the product to be the 3,4-*cis* pyrrolidine **330**, a ketone should form. If the cyclisation product was the tetrahydrofuran **342**, by the proposed mechanisms in Figure 3.16, no displacement of the iodine would occur. However, depending on the stereochemistry of the tetrahydropyran **343**, treatment with silver carbonate on celite should afford either the corresponding ketone or epoxide. Treatment with silver carbonate on celite afforded a ketone **347** in an excellent 68% yield (Scheme 3.39; a) as confirmed by the new C=O signal at 210.5 ppm, new $CH_2$ resonance at 46.2 ppm, new $CH_aCH_b$ resonances adjacent to the new carbonyl group and a molecular ion of 292 ($M^+$ + H), consistent with loss of HI. In addition an absorbance at 1761 $cm^{-1}$ was apparent in the infrared and retention of the broad resonance at 3444 $cm^{-1}$ was observed.

Slight separation of the resonances was observed in the $^1H$ NMR spectrum, but due to the hindered rotation around the C-N bond of the Boc protecting group, the resonances were

still broad. $^1$H-$^1$H correlation revealed that the C*H*Ph proton was coupled to the new diastereotopic $CH_2$ protons in the ring, confirming that the cyclisation product could not be the tetrahydropyran **343** where the C*H*Ph proton is not adjacent to a diastereotopic $CH_2$ group (Figure 3.27). Further confirmation was apparent from the present of an exchangeable OH signal at 3.60 ppm because the only structure that retained such a group after treatment with silver carbonate would again be the pyrrolidinone **347**. This time the ketone **347** was stable, and its formation confirmed the predicted 3,4-*cis* stereochemistry of the pyrrolidine **330**.




**347** **330** **349**

**Scheme 3.39.** *Reagents:* a) $Ag_2CO_3$, $CH_2Cl_2$, 24 h, 68 %; b) $Ac_2O$, pyridine, 20 h, 71%.

Previously, acetates were prepared to hopefully separate any overlapping resonances (Scheme 3.18). Thus, iodopyrrolidine **330** was treated with acetic anhydride in pyridine for 20 h, to afford the diacetate **349** in 71% yield (Scheme 3.39; b). Despite the separation of the resonances, no coupling data was obtained, due to broad resonances. High temperature NMR spectroscopy also failed to sharpen the signals. Confirmation of the structure was obtained by the lack of an O-H stretch, an addition carbonyl stretch at 1748cm$^{-1}$ and two new carbonyls signals at 169.4 and 170.5 ppm.

## 3.40. Hydrogenolysis

### 3.41. Introduction

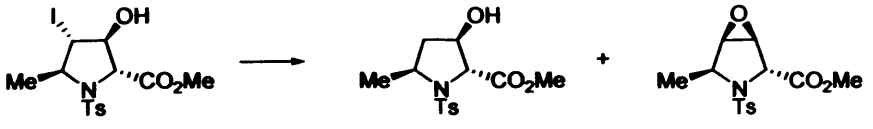
Removal of an iodide group from tetrahydrofurans can be achieved using tri-n-butyl stannane with catalytic AIBN (Scheme 3.42).[14] However, is often more desirable due to the toxicity of tin hydride and problems with removal of the tin residues, to use hydrogenolysis.


**349** **350**

**Scheme 3.40.** *Reagents:* Tri-n-butylstannane (3 eq), AIBN (cat), benzene, reflux 4 h.

### 3.42. Results and Discussion

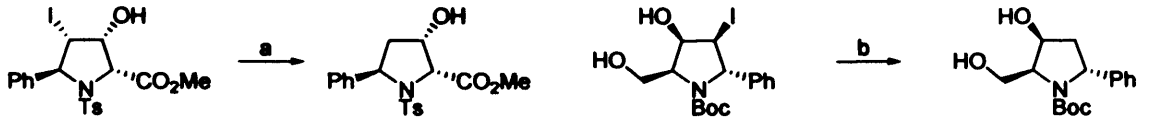
When the 2,5-*trans* pyrrolidine **321** was subjected to standard hydrogenolysis[15] conditions, (Pd/C, triethylamine and methanol as the solvent) a separable mixture of hydroxy pyrrolidine **351** and epoxide **323**, were isolated (Scheme 3.41). The formation of the hydroxy pyrrolidine **351** was evident by the loss of the C*H*I resonance, new $CH_aCH_b$ resonances at 1.65 and 2.40 ppm and a molecular ion of 314. The formation of the epoxide **323** was not completely unexpected since treatment of 3,4 *trans*-iodopyrrolidines with base yields epoxides as previously illustrated (Scheme 3.25; a).




**321** **351** **323**

**Scheme 3.41.** *Reagents:* Pd/C, $Et_3N$, MeOH, 16 h, 36% **351** and 57% **323**.

The hydrogenolysis of 3,4-*cis* iodopyrrolidine **327b** was considerably slower, proceeding only after 64 h, to afford the hydroxy pyrrolidine **352** as the sole product in 63% yield (Scheme 3.42). Once again, loss of the C*H*I resonance was apparent in both the $^1H$ and $^{13}C$ NMR spectra.




**327b** **352** **330** **353**

**Scheme 3.42.** *Reagents:* a) Pd/C, $Et_3N$, MeOH, 64 h, 63%; b) Pd/C, $Et_3N$, MeOH, 46 h, 48%.

Finally hydrogenolysis of the 3,4-*cis* iodopyrrolidine **330** for 46 h, following chromatography, afforded the hydroxy pyrrolidine **353** in a moderate 48% yield, as confirmed by the loss of the C*H*I signal, two new $CH_aCH_b$ resonances and a molecular ion of 294.

### 3.43. Conclusion

Predictably, the stereochemistry of the pyrrolidine of the 3- and 4- positions affected the rate, and also the product formed in the hydrogenolysis reaction. When this stereochemistry was *trans* the reaction was considerably faster than the corresponding *cis* derivatives (Table 3.15). This difference in rates correlates with what was observed in the Lindlar reductions, the *anti* species were reduced rapidly, while for the *syn* substrates complete reduction was rarely achieved. The results are summarised in Table 3.15.

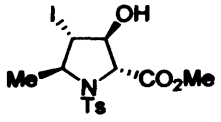
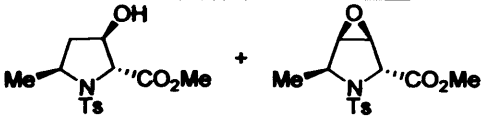
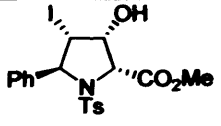
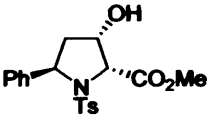
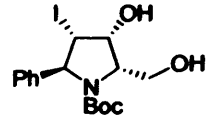
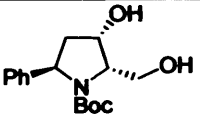
| Precursor | Time (h) | Product(s) | Yield (%) |
|---|---|---|---|
|  **321** | 16 |  **351** **323** | 36 (**351**)<br>57 (**323**) |
|  **327b** | 64 |  **352** | 63 |
|  **352** | 46 |  **353** | 48 |

**Table 3.15**

## 3.50. Nucleophilic Attack on the Epoxides

### 3.51. Introduction

With a variety of epoxy pyrrolidines formed, it was desirable to test the regioselectivity of opening these epoxides with various nucleophiles. Studies were conducted using epoxy-pyrrolidine **323**, being the easiest to synthesis in large quantities (Scheme 3.25; a).

### 3.52. Results and Discussion

### 3.53. Nucleophilic attack by Azide

There are numerous examples for the use of azide in the regioselective opening of epoxides[16-21]. However, many require elevated temperatures and long reaction times. Wang and Jimenez[22] reported that epoxides could be opened using mild conditions; sodium azide in a 1:1 mixture of acetone and water at room temperature (Scheme 3.43).


**354** **355**

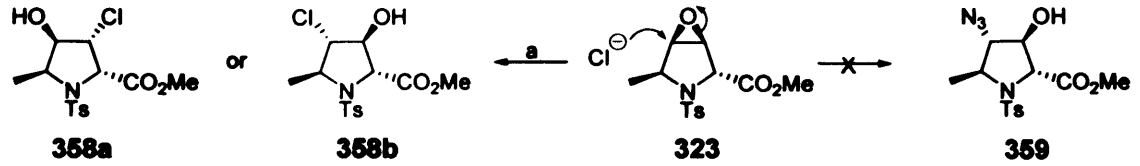
**Scheme 3.43.** *Reagents:* $NaN_3$, Acetone and water (1:1), 12 h, R.T., 78 %.

Unfortunately, when this method was applied to substrate **323**, no reaction was observed. To avoid the use of harsh conditions, an attractive method proposed by Kobayashi[23], involving the use of trimethylsilylazide and zinc chloride in refluxing 1,2-dichloroethane, was employed (Scheme 3.44).


**356** **357**

**Scheme 3.44.** *Reagents:* a) $TMSN_3$, $ZnCl_2$, $C_2H_2Cl_2$, reflux, 1.5 h; b) cat. HCl/MeOH, 99%.

Exposure of the epoxide **323** to $TMSN_3$ in the presence of zinc chloride in refluxing dichloroethane afforded predominately a single diastereoisomer, which decomposed on exposure to silica. A non-polar fraction, however, contained the product with only traces of decomposition products (Scheme 3.45).



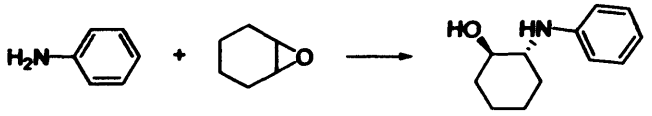

**358a** **358b** **323** **359**

**Scheme 3.45.** *Reagents:* $TMSN_3$, $ZnCl_2$, $ClCH_2CH_2Cl$, reflux, 16h, cat. HCl/MeOH, 80%.

Confirmation of the opening of epoxide **323** was obtained by the disappearance of both C*H*O signals and the appearance of an OH stretch in the infrared spectrum. The $^{13}C$ NMR spectrum also showed four methine resonances in the region 62.8 to 79.9 ppm. The gross structure was confirmed by mass spectrometry, where a 3:1 ratio of molecular ions was observed which was characteristic of a monochloride. Thus from the HRMS the product was deduced to be a chlorohydrin **358b**. Attack of the chloride ion from the back face is more likely to occur on the side of the methyl since the methyl ester shields the back face, so one can assume that the product is chlorohydrin **358b**. Coupling constant data was unfortunately not available, due to broadened resonances, to compare with the corresponding 2,5-*trans*-iodopyrrolidine **321** (Table 3.12). Interestingly, comparisons of the NMR spectrum with that of the corresponding 2,5-*trans*-iodopyrrolidine **321** revealed a similar pattern of resonances but, the positions of specific protons was different. Unfortunately, as this was one of the reactions conducted in the latter stages of the research, lack of material meant that no further experiments were conducted, with different azide sources.

### 3.54. Nucleophilic Attack by Amines

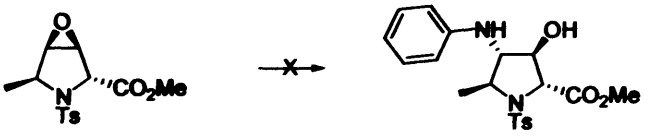
Conventional methods for synthesising β-amino alcohols from epoxides involve harsh conditions; often an excess of amine and elevated temperatures are mandatory. Due to sensitivity of some functional groups to high temperatures, often expensive or corrosive catalysts are required. To combat this, Ollevier[24] *et. al*, reported that *meso*-epoxides could be regioselectively opened with anilines using catalytic bismuth (III), at ambient temperature (Scheme 3.46).




**360** **361** **362**

**Scheme 3.46.** *Reagents:* cat. $BiCl_3$, $CH_2Cl_2$, 7-11 h, 78%.

Bismuth compounds are generally thought of as being relatively environmentally friendly, and with the drive towards so-called "green chemistry this research was applied to substrate **323**, but, unfortunately, no reaction was observed under any conditions.




**323** **363**

**Scheme 3.47.** *Reagents*: cat. $BiCl_3$, $CH_2Cl_2$, 24 h, 0%.

### 3.55. Nucleophilic Opening of Epoxides with Water

In the synthesis of codonopsine **3**, Wang[25] and Calabrese treated an epoxide **457** with a mixture of concentration sulphuric acid, water and dioxane, in a ratio of 9.8:1:14.7 to yield a diol **458** (Figure 4.15, Chapter 4). When this method was applied to substrate **323**, unfortunately the reaction was not regioselective and a 1.6:1 mixture of diastereoisomers was formed in a low 16% yield, due to isolation problems (Scheme 3.48). Formation of the diol **366** was confirmed by the disappearance of the C*H*O signals, a molecular ion of 352 ($M^+$ + Na, 100%) and the presence of a new O-H stretch in the infrared spectrum.


**323** **366**

**Scheme 3.48.** *Reagents:* dioxane, concentrated. $H_2SO_4$, water, 90°C, 6 h, 16%.

## 3.56. Conclusion

Frustratingly, opening of the epoxide **323** was not very successful in terms of yield and regioselectivity. In particular, the use of azide nucleophiles failed to afford the desired azido pyrrolidine **359**, instead an unstable chlorohydrin **358b** was isolated (Scheme 3.45). Therefore, further study with different azide nucleophiles is necessary. In addition, the use of water as a nucleophile did not afford the diol **366** selectively. In Wang's synthesis of Codonopsine **3**, the epoxidation reaction was conducted on a mixture of olefins, and the mixture of epoxides **457** were not separated prior to treatment with the nucleophile (Figure 4.15, Chapter 4), thus the regioselectivity of this reaction (Scheme 3.48) could not be compared with Wang's example.

# 3.60. Iodolactonisations

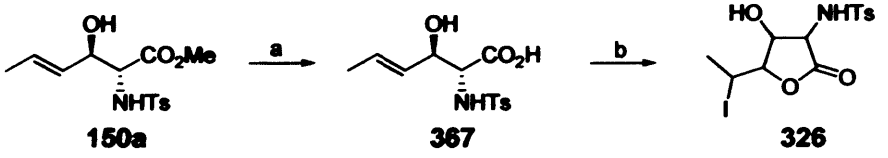
## 3.61. Introduction

During the previous iodocyclisations on amino alcohols, two of these compounds gave rise to a lactone, *via* a 5-*exo*-trig cyclisation, but only when the substituent (R) was alkyl (Tables 3.11 and 3.12). To optimise the lactone formation, iodolactonisation was encouraged by converting the ester into a carboxylic acid. Thus, during the cyclisation, the unfavourable loss of the methyl moiety will be omitted.

## 3.62. Results and Discussion

### 3.63a. Cyclisation of an alkyl, *trans*, *anti* Precursor

The ester **150a** derived from the aldol condensation of the enolate of *N*-tosyl glycinate with croton aldehyde **137** (Scheme 2.12, Chapter 2), was converted into the corresponding acid **367** in 81% yield as apparent by the loss of the methyl ester singlet and a molecular weight of 317 ($M^+ + NH_4$) (Scheme 3.49; a).




**150a** **367** **326**

**Scheme 3.49.** *Reagents:* a) 2M KOH, MeOH, 16 h, 81%; b) IBr, $K_2CO_3$, MeCN, 2 h, 70%.

Treatment of the acid **367** with iodine monobromide, potassium carbonate in acetonitrile furnished a 6.4:1:2.4 mixture of diastereoisomers **326**, in 70% yield, Fortuitously, on addition of chloroform to the crude product, the major isomer A **326a**, precipitated from solution. Major isomer A **326a** exhibited a carbonyl stretch at 1811 $cm^{-1}$ in the infrared, and a molecular ion at 426 ($M^+ + H$), which suggested the reaction was successful. The $^{13}C$ NMR spectrum contained four methine groups with the C*H*I signal at 19.0 ppm, corresponding to the double quartet at 4.15 ppm in the $^1H$ NMR spectrum. Thus, the product could not be a pyrrolidine, where the C*H*I signal would be a double doublet.

### 3.64a. Determination of Stereochemistry

For major isomer A **326a**, a *trans* coupling constant of 10.8 Hz between the C*H*I and C*H*O protons was apparent. Further information regarding the stereochemistry of the remaining ring protons was not attempted by nOe since all the ring protons were in close proximity to each other. However after recrystallisation of isomer A **326a** from ethyl acetate and pentane *via* vapour diffusion, X-ray diffraction of the crystal obtained confirmed the predicted *trans* relationship between the C*H*I and C*H*O protons in the lactone **326a** (Figure 3.27).

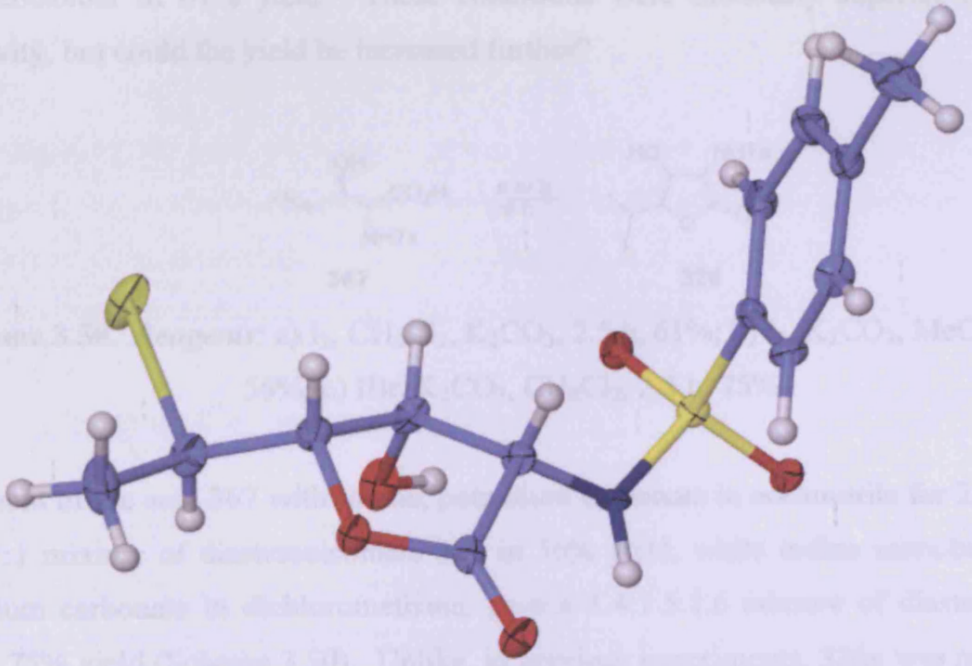
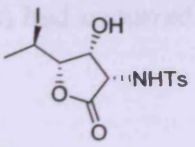


**Figure 3.27: Crystal Structure of the isomer A 326a**




**326a**

The proposed mechanism is shown in Figure 3.28.

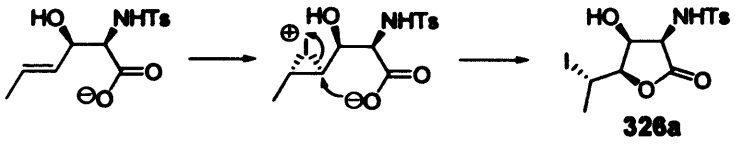
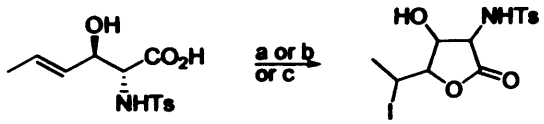



**Figure 3.28**

### 3.65a. Optimisation Studies

Based on the ratio in the NMR spectrum of the crude product, isomer A **326a** was obtained in 46% overall yield (Scheme 3.51). Treatment of the (*E*)-acid **367** with iodine and dichloromethane in the presence of base afforded lactone A **326a**, largely as a single diastereoisomer in 61% yield. These conditions were obviously superior in terms of selectivity, but could the yield be increased further?




**367** **326**

**Scheme 3.50.** *Reagents:* a) $I_2$, $CH_2Cl_2$, $K_2CO_3$, 2.5 h, 61%; b) $I_2$, $K_2CO_3$, MeCN, 2.5 h, 56%; c) IBr, $K_2CO_3$, $CH_2Cl_2$, 2.5 h, 75%.

Treatment of the acid **367** with iodine, potassium carbonate in acetonitrile for 2.5 h gave a 5.4:2.4:1 mixture of diastereoisomers **326** in 56% yield, while iodine monobromide and potassium carbonate in dichloromethane, gave a 1.4:1.5:1.6 mixture of diastereoisomers **326** in 75% yield (Scheme 3.50). Unlike, in previous experiments, **326a** was not the most abundant isomer, but interestingly, following recrystallisation, **326a** was isolated in 35% yield, despite the NMR spectrum of the crude product revealing the yield to be 23%. Therefore, at some stage isomerisation had occurred. The results are summarised in Table 3.16.

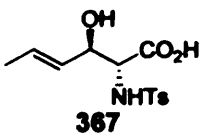
| | Conditions | Time (h) | Ratio in crude product | CrudeYield of lactone 326a (%) | Combined yield (%) |
|---|---|---|---|---|---|
|  367 | IBr, $K_2CO_3$, MeCN, -20°C | 2 | 6.4:1:2.4 | 46 | 70 |
| | $I_2$, $K_2CO_3$, $CH_2Cl_2$, 0°C | 2.5 | 1 | 61 | 61 |
| | $I_2$, $K_2CO_3$, MeCN, 0°C | 2.5 | 5.4:2.4:1 | 35 | 56 |
| | IBr, $K_2CO_3$, $CH_2Cl_2$, -20°C | 2.5 | 1.4:1.5:1.6 | 23 | 75 |

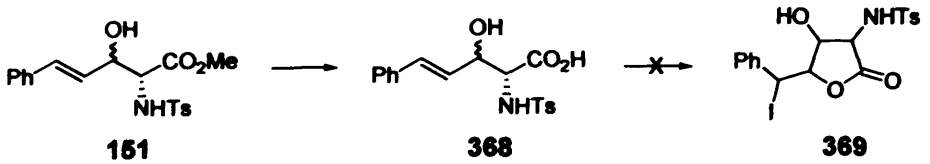
**Table 3.16**

### 3.66a. Conclusion

So by changing the ester for an acid group, formation of the lactone **326** was increased. Once again, the conditions employed were crucial to the selectivity of the reaction. In the cases where three diastereoisomers were obtained, it is possible that the minor isomers could have been the iodopyrrolidines, but this was not investigated (Table 3.16).

### 3.63b. Cyclisation of an aryl, *trans*, Precursor

The next precursor tested was the phenyl *trans* acid **368**. In the cyclisations of the corresponding ester **151**, no lactone was isolated under any of the conditions employed, accordingly, it was unlikely that any lactone would be formed by the cyclisation of the (*E*)-acid **368**. A 17:4 mixture of diastereoisomers of the ester **151**, obtained from the aldol reaction of cinnamaldehyde **135** with the LDA derived enolate of *N*-tosyl glycinate (Scheme 2.12, Chapter 2), was treated with a 2M solution of potassium hydroxide in methanol, to afford the carboxylic acid **368** in excellent yield as confirmed by the loss of the methyl ester singlet and HRMS (Scheme 3.51).




**Scheme 3.51.** *Reagents:* 2M KOH in MeOH, 16 h, 88%.

The acid **368** was then reacted with a range of conditions previously utilised in the cyclisations of the ester derivative **151** (Table 3.13), however, the yields were low and no conclusive evidence was obtained for lactone **369** formation. As a result, no further experiments were conducted.

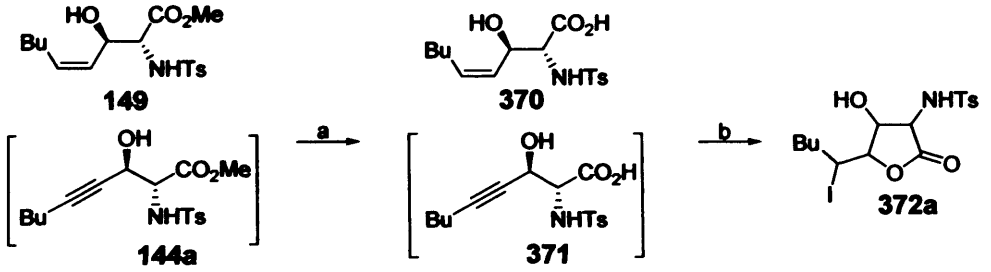
### 3.64b. Conclusion

These results mirror what was previously observed with the corresponding ester derivatives (Table 3.13). It is possible that lactone formation failed due to the activated benzylic position causing the degradation of the cyclisation product, or that a suitable transition state could not be adopted to afford the desired lactone **369**.

### 3.63c. Cyclisation of an alkyl, *cis*, *anti* Precursor

Unlike the *trans* precursors, the corresponding *cis* derivatives were difficult to synthesise cleanly. The Lindlar reduction was capricious and, hence, an accurate comparison of conditions could not be established. In the case of the butyl derivative **370**, only two cyclisation conditions were directly compared, iodine and potassium carbonate in dichloromethane and iodine monobromide and potassium carbonate in acetonitrile. This was because these were the only two conditions in which the previous Lindlar reduction successfully afforded predominately the (*Z*)-olefin **370** with no unknown contaminants.

A 7:1 mixture of *cis*-alkene **149** and alkyne **144a** obtained from a Lindlar reduction of the butyl aldol product **144a** (Scheme 3.20) was treated with a 2M solution of potassium hydroxide to give the corresponding carboxylic acids **370** and **371** (Scheme 3.52; b). Once again the loss of the methyl ester was apparent and an accurate mass of 359.1635, which corresponded to the expected value, was obtained by HRMS. Treatment of the crude acid with iodine and potassium carbonate in dichloromethane gave what was presumed to be the lactone, in quantitative yield. Following recrystallisation, it was clear that the product was a different isomer to that obtained from the previous cyclisation of the (*Z*)-ester **149** (Figure 3.19) which gave **254**.



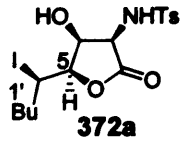

**Scheme 3.54.** *Reagents:* a) Lindlar's catalyst, EtOAc, $H_2$; b) 2M KOH, MeOH, 16 h; c) $I_2$, $CH_2Cl_2$, 3 h, 100%.

The product was established to be a lactone **372a** by the characteristic carbonyl absorption at 1784 $cm^{-1}$ and a molecular ion at 468. The C*H*I proton was a ddd and so the product could not have been a pyrrolidine and a coupling constant of 5.0 Hz was recorded between the C*H*I and C*H*O protons. This value was approximately half the magnitude of that

recorded for the previous lactone **254** with *trans* geometry between the C*H*I and C*H*O protons, suggesting a *cis* relationship (Figure 3.19).

### 3.64c. Explanation of the Proposed Stereochemistry

In the cyclisations of the methyl ester **149**, only iodine monobromide in acetonitrile furnished the lactone **254**, but only after a lengthy reaction time. Obviously, cyclisation of the ester involves the loss of the methyl group of the ester at some stage, while for the carboxylic acid proton abstraction occurs readily so cyclisation should progress at a faster rate. Thus cyclisation of the acid **370** should occur with retention of the double bond geometry. However, due to the close proximity of the ring protons in the NMR spectrum, nOe experiments could not confirm the stereochemistry, but the *J* (5H-1'H) value of 5.0 Hz, suggested a *cis* relationship between the C*H*I and C*H*O protons (Figure 3.29). The proposed structure of the lactone is thus:




**372a**

**Figure 3.29**

### 3.65c. Optimisation Experiments

Interestingly the corresponding (*Z*)-methyl ester **149** cyclised only on treatment with the more reactive iodine monobromide. Accordingly, the conditions that previously afforded the lactone **254** from the cyclisation of the (*Z*)-methyl ester **149** were used to test which lactone would be formed (Scheme 3.21). When the carboxylic acid **370** was treated with iodine monobromide and potassium chloride in acetonitrile, a vast mixture of isomers was obtained in a disappointing 14% yield. Interestingly, the major product was the lactone **254** from the initial cyclisation on the corresponding (*Z*)-methyl ester **149** (Figure 3.18). So one set of conditions, iodine monobromide in acetonitrile, seemed to have given rise to the same product in the cyclisation of the ester **149** and acid **370**. In both cases, the products were grubby, which could have been due to incomplete isomerisation during the reaction or δ-lactone formation.

As explained previously, when the Lindlar reduction was repeated, incomplete reduction occurred and another substance was also apparent in the NMR spectrum. This mixture was treated with a 2M solution of potassium hydroxide in methanol to give the corresponding carboxylic acid **370** which was treated with iodine monobromide, potassium carbonate in dichloromethane to furnish the lactone as a 6:1.5 mixture of diastereoisomers, in 85% yield. No purification was conducted, but it was tangible from the NMR spectrum of the crude product, that the major isomer was lactone **372a** (Figure 3.29).


**371** **372**

**Scheme 3.53.** *Reagents*: a) IBr, $CH_2Cl_2$, $K_2CO_3$, 1.75 h, 85%; b) $I_2$, MeCN, 2.75 h, 74%.

Finally, iodine and potassium carbonate in acetonitrile gave a 4.5:1.5 mixture of diastereoisomers in 74% yield, the major isomer of which was lactone **372a**. Once again, the conditions employed in the cyclisations, greatly affect the yield and diastereoselectivity. The results are summarised in Table 3.17.

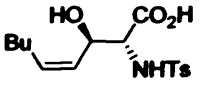
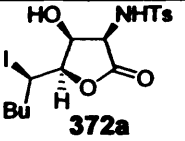
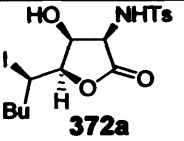
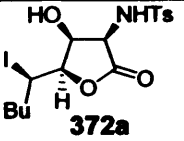
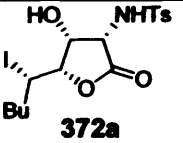
| | Conditions | Time (h) | Ratio in crude NMR | Major Product | Crude Yield (%) |
|---|---|---|---|---|---|
|  **370** | IBr, $K_2CO_3$, MeCN, -20°C | 2 | Mixture |  **372a** | 14 |
| | $I_2$, $K_2CO_3$, $CH_2Cl_2$, 0°C | 3 | 1 |  **372a** | 100 |
| | $I_2$, $K_2CO_3$, MeCN, 0°C | 2.75 | 4.5:1.5 |  **372a** | 74 |
| | IBr, $K_2CO_3$, $CH_2Cl_2$, -20°C | 1.75 | 6:1.5 |  **372a** | 85 |

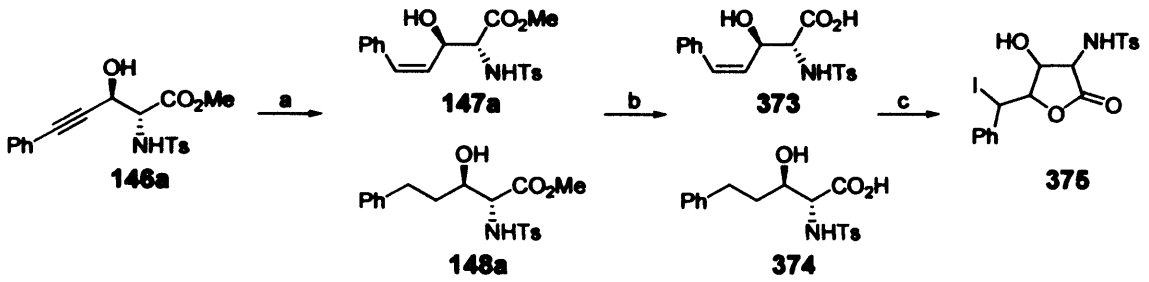
**Table 3.17**

### 3.66c. Conclusion

From Table 3.17 it is apparent that these results were very different to what was observed with the corresponding (*Z*)-methyl ester derivative **144a**, since iodine failed to initiate cyclisation to the pyrrolidine (Table 3.10). In addition, only one set of conditions furnished any product, while the corresponding acid derivative **370** cyclised to lactones with all the conditions tested. Interestingly, the conditions that afforded a lactone **254** with *trans* relationship between the C*H*I and C*H*O protons, iodine monobromide in acetonitrile, from the cyclisation of the methyl ester **149** also gave the same lactone **254** with the corresponding acid **370**, but in addition to other isomers. The major isomer isolated in these cyclisations however was the lactone **372a** with a *cis* relationship between the C*H*I and C*H*O protons, which was not previously isolated in the cyclisations of the methyl ester (Table 3.11).

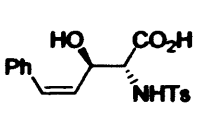
### 3.63d. Cyclisation of aryl, *trans*, *anti* Precursor

The alkyne **146a** from the aldol condensation of the enolate of *N*-tosyl glycine with phenylpropynal **117** (Scheme 2.10, Chapter 2) was exposure to Lindlar's catalyst in ethyl acetate to give a 3:1 mixture of the *cis*-alkene **147a** and saturated product **148a** (Scheme 3.54; a). The crude product was treated with a 2M solution of potassium hydroxide in methanol to form the corresponding carboxylic acids **373** and **374** in a 10:3 ratio, with retention of the (*Z*)-geometry of the olefin (*J* 11.7 Hz) (Scheme 3.54; b). The product was reacted crude with iodine monobromide, potassium carbonate in acetonitrile (Scheme 3.54; c). Formation of a lactone **375** was suggested by the classic carbonyl signal at 1790 $cm^{-1}$ in the infrared spectrum, a molecular ion of 488 together with the C*H*I signal at 28.5 ppm and carbonyl signal at 171.8 ppm. The NMR spectrum of the proposed lactone **374** displayed a series of doublets and lacked the expected two double doublets. Presumably, the second coupling value was very close to zero. A coupling of 5.4 Hz was observed between the C*H*I and C*H*O protons, suggesting a *cis* relationship. nOe experiments were attempted, but unfortunately, decomposition of the lactone **375** occurred, prior to analysis.




**Scheme 3.54.** *Reagents:* a) $H_2$, Lindlar's catalyst, EtOAc, 75% **147a** and 25% **148a** b) 2M KOH, MeOH, R.T., 16 h, 57% **373** and 50% **374**; c) IBr, MeCN, $K_2CO_3$, 20%.

Despite being a single diastereoisomer, following the workup, the lactone **375** was isolated in only 20% yield (Scheme 3.54; c). No other material was isolated and due to the problems highlighted by the corresponding *trans* derivative **369**, it was unclear if this reaction could be optimised. Sufficient quantity of the carboxylic acid **373** was synthesised and was divided into three batches, with each batch subjected to different conditions. When iodine or iodine monobromide in dichloromethane was used, the NMR data was inconclusive. However, iodine and potassium carbonate in acetonitrile delivered the lactone **375** in 69% yield, as the sole product.




| Conditions | Timescale (h) | Crude Yield (%) |
|---|---|---|
| IBr, $K_2CO_3$, MeCN, -20°C | 2 | 20 |
| $I_2$, $K_2CO_3$, $CH_2Cl_2$, 0°C | 19 | 0 |
| $I_2$, $K_2CO_3$, MeCN, 0°C | 3 | 69 |
| IBr, $K_2CO_3$, $CH_2Cl_2$, -20°C | 2.75 | 11 |

**Table 3.18**

With regards to the stereochemistry, it was assumed that the *cis* relationship in the olefin was retained in the lactone **375**. Previously, to deduce the stereochemistry between the C*H*O and C*H*I protons, coupling constants were used. In this example **375**, this coupling constant was found to be 5.4 Hz. In the case of the lactone **326a**, where there was a *trans* relationship between these two groups, the coupling constant was 10.8 Hz, while a much smaller value of 5.0 Hz was observed with the *cis* substituted latone **372a**. Thus, it can be assumed that there was a *cis* relationship between the C*H*O and C*H*I protons in lactone

**375**. To confirm this, nOe experiments were conducted, but unfortunately, the sample degraded prior to analysis.

### 5.64d. Conclusion

Interestingly, the best conditions for the pyrrolidine **296a** formation, iodine monobromide and potassium carbonate in dichloromethane only afforded the lactone **375** in 11% yield, the optimum conditions being iodine in acetonitrile, which failed to give the pyrrolidine **296a** in the previous series of cyclisations (Table 3.10). In addition, the geometry of the olefin appears to be crucial in these cyclisations with the (Z)-phenyl acid **373** affording a lactone **375** while the corresponding (*E*)-phenyl acid **368** did not. This is a stark contrast to what was observed previously with the cyclisations of the methyl esters (Tables 3.10 and 3.13). Generally, in comparison with the iodopyrrolidines, the yields were lower and the cyclisations less selective.

## 3.70. Methodology towards the core of Pseudodistomin

### 3.71. Introduction

Pseudodistomins A **376** and B **377** isolated from the Okinawan tunicate *Pseudodistoma kanoko* are potent antineoplastic piperidine alkaloids which exhibit calmodulin antagonistic activity, the proposed structures of which are shown in Figure 3.26.[26]

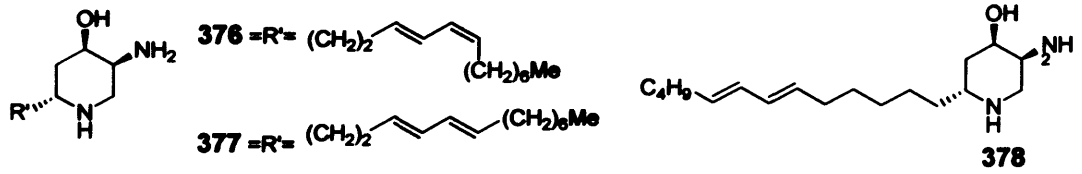
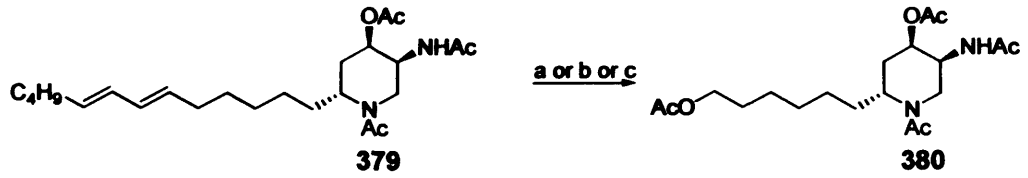


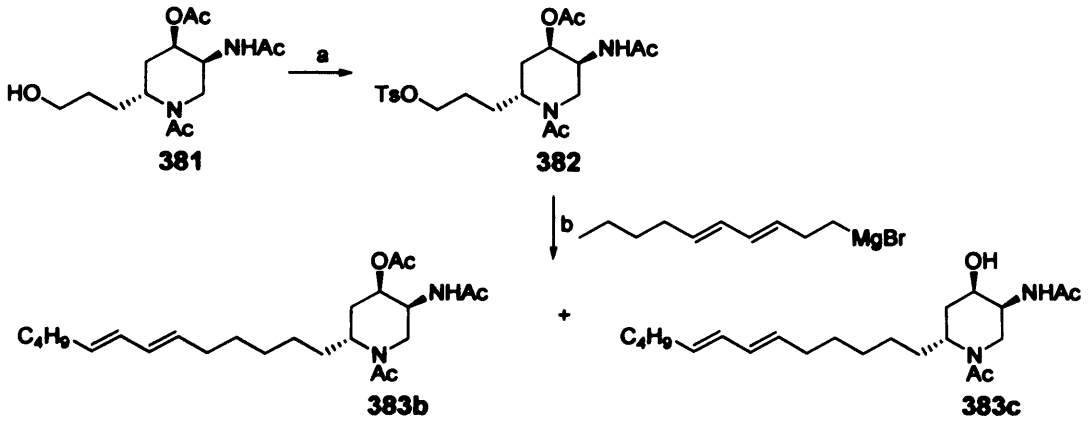

**Figure 3.32**

However, further work by the Naito[27] group revealed these structures were inaccurate. Pseudodistomin B acetate **379**, prepared from a natural sample was subjected to ozonolysis, followed by reduction and acetylation to furnish the tetraacetate **380**. FABS mass spectroscopy of **378** revealed the side chain was 6',8'-tridecadiene, not 3'-5'-tridecadiene as originally believed (Scheme 3.55).



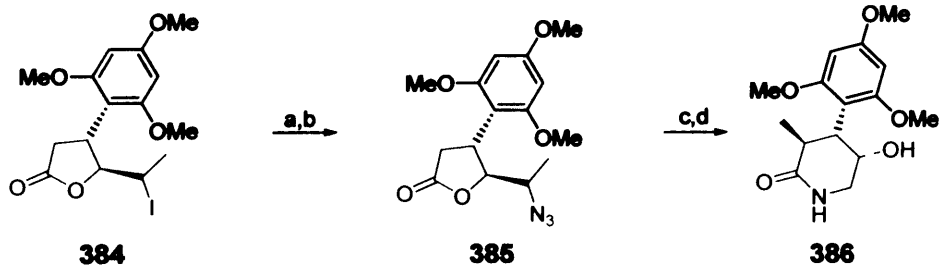

**Scheme 3.55.** *Reagents*: a) $O_3$; b) $NaBH_4$; c) $Ac_2O$, py.

The structure of pseudodistomin B was revised to **378** (Figure 3.32) following the total synthesis of its acetate **383b** (Scheme 3.56). Tosylation of the known alcohol **381**, following by a coupling reaction gave a 2:1 mixture of **383b** and **383c**. Acylation of **383c** gave the acetate **383b** the data obtained for which was identical with natural pseudodistomin B acetate **383b** (Scheme 3.56).




**Scheme 3.56.** *Reagents*: a) TsCl, DMAP, $Et_3N$, 70%; b) $Li_2CuCl_4$, -20°C, 61%.

Gross[28] *et. al.*, reported that lactones bearing a secondary iodide can be converted into piperidones **386**, after treatment with sodium azide, hydrogenation and rearrangement of the amine in the presence of catalytic sodium methoxide (Scheme 3.57).




**Scheme 3.57.** *Reagents:* a) $NaN_3$, DMF, 100°C, 3 h, 95%; b) LiHMDS, THF, MeI, 60%, c) $H_2$, Pd/C, 60 psi, EtOH, 100 %; d) NaOMe (cat), MeOH, 65°C, 2 h, 75%.

The developed lactone methodology was to be used to synthesise the pseudodistomin core, involving a rearrangement of the amino lactone **II** to lactam **I**, as the key step (Figure 3.33).

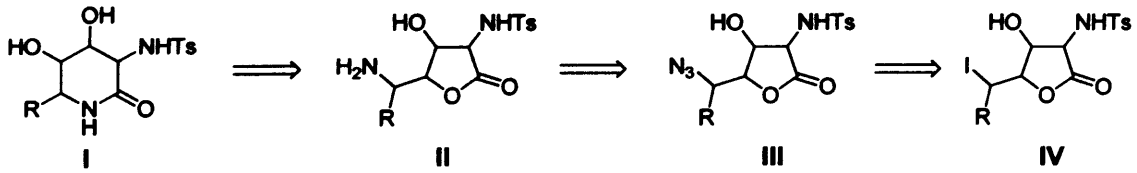
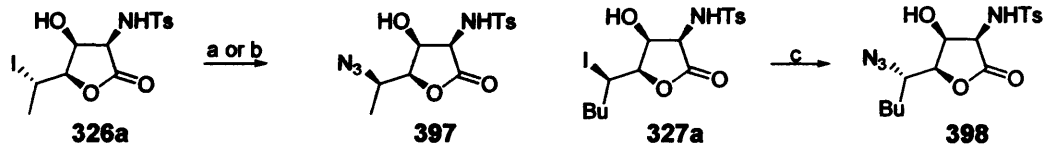



**Figure 3.33**

## 3.72. Results and Discussion

Problems arose early on in the synthesis with the azide displacement. When the methyl lactone **326a** derived from the iodolactonisation of the (*E*)-methyl *anti* acid **367** (Scheme 3.58; a) was treated with sodium azide according to the conditions reported by Gross, detosylation occurred (p 117). Accordingly, milder conditions were necessary. With the destruction of the starting material the next test reaction was conducted on the available butyl lactone **327a** (Scheme 3.58; c). The temperature was lowered to 60°C for 2 h to give a mixture of products. Following chromatography, the azide **398** was isolated as a single diastereoisomer, but in very low yield, 6% as apparent from the characteristic azide absorbance in the infrared spectrum at 2106 $cm^{-1}$, the loss of the C*H*I signal and HRMS (Scheme 3.58; b). The mechanism of azide displacement is $S_N2$, therefore inversion of the C*H*I proton should occur, but due to coincidental resonances, verification of the new *trans* relationship between the C*H*N and C*H*O protons was not determined. Olefin resonances due to elimination were also apparent in the NMR spectrum of the crude product, but confirmation was not ascertained.



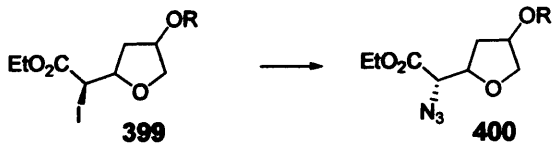

**326a** **397** **327a** **398**

**Scheme 3.58.** *Reagents*: a) $NaN_3$, DMF, 100°C, 3h, 0%; b) $NaN_3$, DMF, 60°C, 3 h, 8%; c) $NaN_3$, DMF, 60°C, 2 h, 6%.

Further optimisation reactions were conducted on the methyl substituted lactone **326a**, being easier to synthesise. When lactone **326a** was treated with sodium azide in DMF at 60°C for 3 h the crude product contained an elimination product. Following purification, the azide **397** was formed in 8% yield, together with some tosyl impurity, as confirmed by HRMS, the distinctive azide peak at 2094 $cm^{-1}$ in the infrared spectrum and loss of the C*H*I signal (Scheme 3.58; b). This time the new C*H*$N_3$ signal was easily identifiable and a coupling of 9.1 Hz between the C*H*$N_3$ and C*H*O protons, which was only slightly smaller than the 10.8 Hz *trans* coupling for the iodolactone **326a**.

The iodolactone **326a** precipitated out of chloroform, but the azide **397** was soluble so this gave an early indication that the reaction was successful, but made comparison of the

NMR spectra more difficult. The abysmal yield meant that an alternative strategy was required. Labelle[29] *et. al.,* reported that tetrahydrofurans containing a secondary iodide, gave an azide on treatment with sodium azide in DMSO (Scheme 3.59), but since lactones are different systems, the methodology might not be successful.




**Scheme 3.59.** *Reagents:* DMSO, 45°C, 4 h, $NaN_3$.

When the temperature was lowered to 45°C using DMSO as the solvent, numerous products were formed; accordingly, the reaction using DMF as the solvent continued to be optimised in view of this. Since the reaction proceeded at 45°C, this suggested that the temperature could be lowered further from 60°C and hopefully reduce the amount of elimination observed.

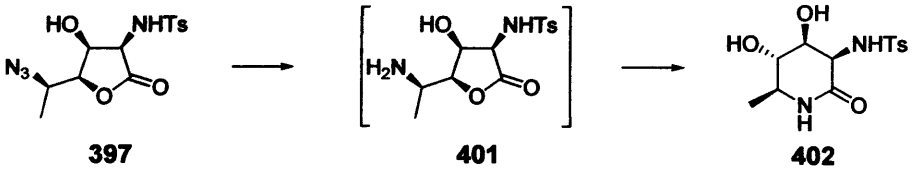
Subsequently, the azide displacement step was repeated using 15-crown-5 initially at 45°C for 16 h, but unfortunately no reaction was observed, suggesting that the ideal temperature range was 45-60°C. The optimum temperature range was discovered to be 60°C, but the yield was still very poor, 8%. The low crude yields obtained in the reaction, were believed to be due to ring opening of the lactone. To test this theory, after the initial ether extraction, the combined aqueous phases were acidified to pH 1 to hopefully re-close the lactone, and re-extracted with ether, but no product was isolated.

When the reaction time was lengthened from 3 h to 16 h, a marginal increase in the yield was observed (Scheme 3.60). Disappointingly, reduction in the level of elimination observed was not achieved in any of the conditions employed.


**Scheme 3.60.** *Reagents*: a) $NaN_3$, DMF, 100°C, 16 h, 12%.

The azide displacement was repeated at 60°C for 5.5 h, but starting material remained. So, complete reaction could not have occurred in the previous 3 h experiments. Following optimisation, the azide **397** was obtained in 12% yield. As this was only a sideline, no significant time was spent on further optimisation.

When the azide **397** and impurity apparently containing a tosyl group was subjected to hydrogenation for 16 h, only starting material was isolated (Scheme 3.61; a). This was not unexpected, since Bernsmann conducted the experiment under pressure (60 psi). The reaction was repeated but for 64 h, and, fortuitously, when deuterated chloroform was added to the residue, a fine white precipitate was formed. This precipitate was too fine to collect by normal filtration, so instead, the product dissolved in chloroform was filtered through a plug of cotton wool and the remaining solid was washed with more chloroform. The solid was then dissolved in methanol and filtered through the plug. The two fractions were evaporated separately and following NMR analysis, the methanol fraction contained the product **402** as a single diastereoisomer, while the chloroform fraction contained the impurity (Scheme 3.64; b).




**Scheme 3.61.** *Reagents:* a) $H_2$, Pd/C, MeOH, 16 h, 0%; b) $H_2$, Pd/C, MeOH, 64 h, 83%.

The NMR spectrum of the product **402** in deuterated acetone showed two NH resonances at 5.80 and 6.40 ppm and two OH resonances at 4.55 and 4.65 ppm, all of which exchanged with $D_2O$. The ring protons were unresolved; hence the sample was rerun in deuterated methanol to determine the coupling constants. In addition, to the loss of the

azide peak at 2106 $cm^{-1}$, a carbonyl resonance at 1658 $cm^{-1}$ was apparent in the infrared spectrum, corresponding to a 6-ring lactam. All this evidence indicated that the amine **401** underwent rearrangment to afford the desired lactam **402**, highly selectively (Scheme 3.61; b). By taking into account the amount of tosyl impurity recovered, it was discovered that the hydrogenation and subsequent rearrangement had occurred in an excellent 83% yield, despite being on such a small scale (Scheme 3.61; b).

The coupling constants for 6-membered rings, unlike the 5-membered rings can be used to define the stereochemistry. From Table 3.19, it is apparent that the couplings are in the range 3-5 Hz, that is axial-equatorial couplings and/or equatorial-equatorial couplings.

| **Coupling** | ***J* value** |
|---|---|
| *J*(3-4-H) | 3.2 |
| *J*(4-5-H) | 4.4 |
| *J*(5-6-H) | 3.1 |

**Table 3.19**

### 3.73. Conclusion

Despite the high yield and excellent selectivity for the key step, optimisation of the cyclisation and azide displacement is required (Scheme 3.50 and 3.60). However, the fact that sodium methoxide was not necessary to induce the rearrangement, was advantageous since it shortens the synthetic route. Also the stereochemistry of the lactam **402** needs to be verified and once optimisation of the azide displacement step is achieved, these results could be applied to the synthesis of pseudodistomins.

## 3.80. References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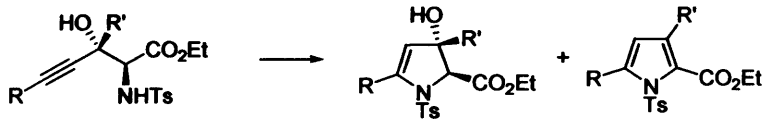
# Chapter Four

# Silver Catalysed Cyclisations and Natural Product Synthesis

## 4.10. Introduction: Alternatives to Iodine in 5-*Endo*-dig Cyclisations

## 4.11. Copper(I) Mediated Cyclisations

Previous work in the Knight group by Sharland[1] involved 5-*endo*-dig cyclisations using acids and transition metal salts as alternatives to iodocyclisations for pyrrole syntheses.[1] Treatment of the amino alcohols **403** derived from the aldol condensation of the enolate of ethyl *N*-tosyl glycinate with various aldehydes or ketones (Section 1.40, Chapter 1) with copper(I) acetate in a refluxing mixture of pyridine and diethyl ether gave dihydropyrroles **404a-e** in high yields, with only traces of pyrroles **405a-e** (Table 4.10).




**403** **404a-e** **405a-e**

**Scheme 4.10.** *Reagents*: 1.0 eq Cu(I)OAc, 1:1 pyridine/ether, 90°C.

| | R | R' | 403 | Timescale (h) | Dihydropyrrole | | Pyrrole | |
|---|---|---|---|---|---|---|---|---|
| | | | | | (%) | 404 | (%) | 405 |
| 1 | Butyl | H | **116** | 6 | 86 | **a** | 14 | **a** |
| 2 |  | H | **120** | 4.5 | 71 | **b** | 29 | **b** |
| 3 | Ph | H | **119** | 1 | 95 | **c** | 5 | **c** |
| 4 | Ph | Me | **130** | 16 | 100 | **d** | 0 | **d** |
| 5 | Ph | *i*-Pr | **132** | 16 | 100 | **e** | 0 | **e** |

**Table 4.10**

The rates varied considerably; in particular when there was conjugation of the acetylene to the R group, the rate of the reaction is greatly increased provided there are no steric constraints. It was surprising that the dihydropyrroles **404** could be isolated especially when one considers that in the iodocyclisations of alkyne diols **406**, conversion to the iodofurans **407** was observed, but the intermediate could not be isolated (Figure 4.10).[2,3] However, when the related alkyne sulfonamides **408**, dihydroxypyrroles **409** were isolable,

sometimes as the sole product, which following an elimination reaction afforded the corresponding pyrroles **410** (Figure 4.10)[1].

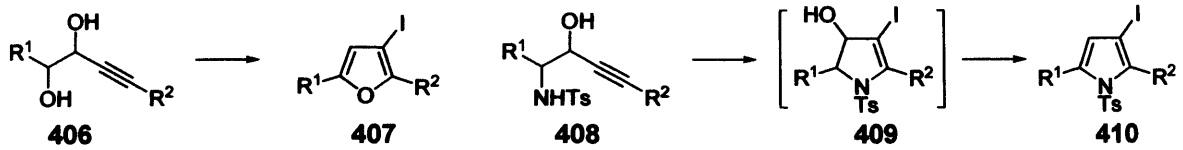



**Figure 4.10**

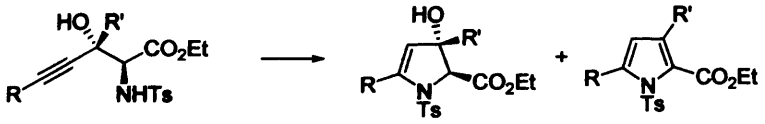
## 4.12. Palladium Catalysts

This success led Sharland to test various other metal salts in these cyclisations using identical conditions used in the copper(I) cyclisation, in a sealed tube at 90°C with one equivalent of the metal salt. Tetrakis(triphenylphosphine)palladium(0), dichloro-*bis*-(triphenylphosphine)-palladium(II) and palladium(II) acetate were all tested. No reaction occurred with the Pd(0) species, while dichloro-*bis*-(triphenylphosphine)-palladium(II) gave the dihydropyrrole **404a**, together with large amounts of triphenylphosphine residues. Palladium(II) acetate and chloride both gave the desired product after extended reaction times. However, the reactions of these palladium(II) salts were not as clean as those of copper(I) acetate and traces of *N*-tosyl glyine ethyl ester **113**, presumably due to palladium-catalysed side reactions and subsequent decomposition, were evident in the NMR spectrum of the crude product. These factors, coupled with the high cost of palladium salts made these reactions less than attractive.

## 4.13. Mercury(II) Acetate

Mercury(II) acetate has been used for 5-*endo* dig cyclisations in the synthesis of (+)-preussin **4** (Figure 4.36).[4] However, when a variety of substrates **403** were subjected to the same conditions as used for the cyclisations with copper(I) acetate, all the reactions were successful, yielding mixtures of dihydropyrroles **404a-e** and pyrroles **405a-e**, but again not as cleanly as when using copper(I) acetate (Table 4.10). Also, more decomposition of the precursor to ethyl *N*-tosyl glycinate **113** was observed. With the demand for green chemistry, the toxicity of mercury(II) acetate was clearly a highly negative factor. In

addition nickel(II) acetate, tin(IV) chloride and zinc(II) bromide, all failed to induce cyclisation, while lead(IV) acetate gave similar results to mercury acetate, (Table 4.11).

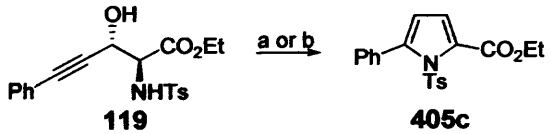



| | R | R' | 403 | $M(L)_n$ | Timescale (h) | Dihydropyrrole (%) | 404 | Pyrrole (%) | 405 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Butyl | H | **116** | $Pd(OAc)_2$<br>$Hg(OAc)_2$ | 6 | 74<br>77 | **a** | 26<br>23 | **a** |
| 2 |  | H | **120** | $Pd(OAc)_2$<br>$Hg(OAc)_2$ | 5 | 54<br>61 | **b** | 49<br>39 | **b** |
| 3 | Ph | H | **119** | $Pd(OAc)_2$<br>$Hg(OAc)_2$ | 2 | 66<br>72 | **c** | 34<br>28 | **c** |
| 4 | Ph | Me | **130** | $Pd(OAc)_2$<br>$Hg(OAc)_2$ | 16 | >95<br>>95 | **d** | >5<br>>5 | **d** |
| 5 | Ph | *i*-Pr | **132** | $Pd(OAc)_2$<br>$Hg(OAc)_2$ | 16 | >95<br>>95 | **e** | >5<br>>5 | **e** |

**Table 4.11**

## 4.14. Mineral Acids

With the success of the previous cyclisations, Sharland conducted cyclisation studies with both 4-toluenesulfinic acid and 4-toluenesulfonic acids. Precursor **119** in benzene was refluxed with half an equivalent of 4-toluenesulfonic acid for 6 h, to give the pyrrole **405c** in 86% yield (Scheme 4.11; a). When the reaction was repeated using 4-toluenesulfinic acid, again the pyrrole **405c** was isolated, but in 72% yield (Scheme 4.11; b)




**Scheme 4.11.** *Reagents:* a) 0.5 eq 4-toluenesulfinic acid, toluene, 110°C, 6 h, 86%; b) 0.5 eq 4-toluenesulfonic acid, toluene, 110°C, 6 h, 72%.

The reaction was repeated with the same variety of substrates **403a-e** previously used in the cyclisation studies, but in all cases, the pyrroles **405a-e** were isolated, with no trace of

the desired dihydropyrroles **404a-e** (Figure 4.11). This result was not totally unexpected, since these acids had previously been investigated in the dehydration of iodo-dihydropyrroles (Figure 4.10), but although the reaction was deemed successful, some degradation of the product led to the use of methansulfonyl chloride and pyridine as an alternative.

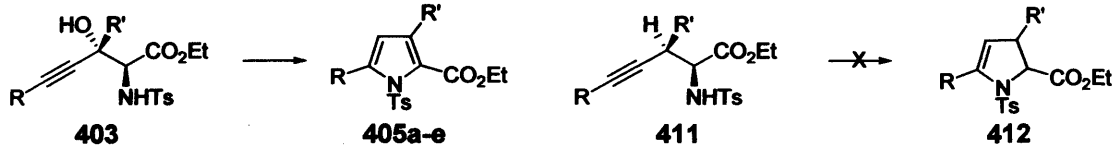
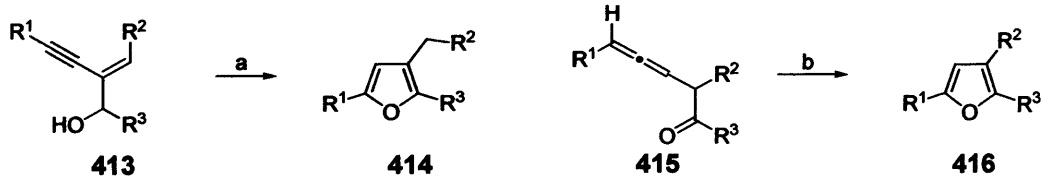



**Figure 4.11**

The presence of the 3-hydroxyl group appears to be crucial in these reactions. The related homopropargylic sulfonamides **411** did not cyclise under identical conditions to form the corresponding dihydropyrroles **412** (Figure 4.11). The process is believed to be in equilibrium and hence the irreversible dehydration of the dihydropyrroles could be responsible for driving the reaction to completion.

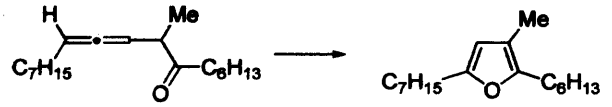
## 4.15. Background: Silver(I) Nitrate-Induced Cyclisations

In studies towards the synthesis of 2,3,5-trisubstituted furans, Marshall and Sehon[5] discovered that a base-catalysed isomerisation of α- and β-alkynyl allylic alcohols **413** occurred to form furans **414** in yields ranging from 65-95% (Scheme 4.12; a). Clearly, this method would be inappropriate in the synthesis of furans containing base sensitive groups. Fortunately, related research[6] revealed that 10 mol% of silver nitrate in anhydrous acetone successfully catalysed the isomerisation of allenones **415** to furans **416**, but in variable yields (10-80%) (Scheme 4.12; b).




**Scheme 4.12.** *Reagents:* a) KO-*t*-Bu, 18-crown-6, *t*-BuOH, 3-6 h, 65-95%; b) $AgNO_3$, Acetone-water, $CaCO_3$.

Marshall and Bartley[7] conducted further experiments to determine if the presence of water and calcium carbonate was mandatory for the silver catalysed cyclisation to occur. Accordingly, substrate **417** was treated with 0.2 equivalents of 10% silver nitrate on silica gel, but using various ratios of acetone to water and also in anhydrous solvents (Table 4.13, entries 4 and 5). Research revealed that the reactions proceeded more efficiently in the absence of calcium carbonate, and also that accelerated rates of reaction were achieved by decreasing the water content (Table 4.13).




**417** **418**

| | Conditions | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | $Me_2CO$-$H_2O$ (60:40)/$CaCO_3$, (0.2 eq) $AgNO_3$ | 72 | 73 |
| 2 | $Me_2CO$-$H_2O$ (75:25)/$CaCO_3$, (0.2 eq) $AgNO_3$ | 36 | 84 |
| 3 | $Me_2CO$-$H_2O$ (90:10)/$CaCO_3$, (0.2 eq) $AgNO_3$ | 4.5 | 84 |
| 4 | Acetone, (0.2 eq) $AgNO_3$ | <1 | 90 |
| 5 | Tetrahydrofuran, (0.2 eq) $AgNO_3$ | 3 | 84 |

**Table 4.13**

With the success of these silver nitrate-catalysed cyclisations, experiments were conducted on a more readily accessible substrate **419** (Table 4.14). However, unlike the cyclisations of the allenes[7], the reaction time scale was much greater and so in a bid to decrease this, alternative sources of the Ag(I) ion were tested[5] (Table 4.14).

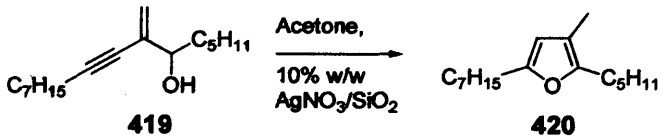

**419** **420**

| | Catalyst (eq) | Timescale (h) | Yield (%) |
|---|---|---|---|
| 1 | $AgNO_3$ (0.2) | 12 | 86 |
| 2 | AgOTf (0.2) | 12 | 91 |
| 3 | $AgBF_4$ (0.2) | 2 | 97 |
| 4 | $AgOCOCF_3$ (0.2) | 2 | 93 |
| 5 | $AgNO_3$/silica gel (0.1) | 12 | 92 |

**Table 4.14**

From Table 4.13, it can be seen that the best catalysts were silver tetrafluoroborate and trifluoroacetate, both in terms of timescale and yield and, in addition, commercially available 10% $AgNO_3$/silica gel yielded the desired furan **420** in 92% over a 12 h period.

These reactions were proving to be virtually quantitative, but was it possible to reduce the reaction time? Consequently, Marshall and Sehon conducted further experiments utilising commercially available 10% $AgNO_3$/silica gel, in a variety of solvents (Table 4.15). It was discovered that the rate was significantly slower using diethyl ether, acetonitrile or tetrahydrofuran. Marshall believed that a non-polar solvent would increase the affinity of the polar alcohol towards the surface of the silica gel, hence, hexane was tested.




**419** **420**

| | Solvent | Timescale (h) | Eq of catalyst | Yield (%) |
|---|---|---|---|---|
| 1 | $Me_2CO$ | 12 | 0.2 | 92 |
| 2 | MeOH | 12 | 0.2 | 96 |
| 3 | $CH_2Cl_2$ | 12 | 0.2 | 87 |
| 4 | Hexane | 1 | 0.1 | 96 |
| 5 | Hexane | 2* | 0.1 | 91 |

**Table 4.15**

Marshall's hypothesis proved correct but in addition the catalyst could be reused (entry 5, Table 4.15). A flow system was developed where this cyclisation was performed repeatedly by passing the alcohol in hexane through a stainless steel column packed with the catalyst. To date, no work has been published using this methodology to form nitrogen-containing heterocycles.

The final set of experiments conducted by Sharland on the 5-*endo* dig cyclisations of the amino alcohol derivatives **403** exploited Marshall's silver catalysed cyclisation methodology.[5,6,7] If 10% w/w silver nitrate on silica gel could give the desired dihydropyrroles **404a-e**, then hopefully the use of pyridine and heating would not be necessary. Hence the same precursors **403**, used in the previous studies (Section 4.10) were treated with one equivalent of 10% w/w silver nitrate on silica gel in anhydrous ether and delightfully, the dihydropyrroles **404a-e** were isolated cleanly and in virtually quantitative yield (Table 4.16). Hence, 10% w/w silver nitrate on silica gel could be used as an alternative to sealed tube reactions in 5-*endo*-dig cyclisations on these substrates **403**. These dihydropyrroles **404a-e** were sensitive to elimination and dehydration to the corresponding pyrroles **405a-e** was observed when these dihydropyrroles **404a-e** were left standing in deuteriochloroform overnight. The reaction times again depended upon the

nature of the R group, less reactive bulky precursors required extended reaction times (Table 4.16).


**403** **404a-e**

| | R | R' | 403 | Timescale (h) | Yield (%) | 404 |
|---|---|---|---|---|---|---|
| 1 | Butyl | H | 116 | 3 | 98 | a |
| 2 |  | H | 120 | 3 | 96 | b |
| 3 | Ph | H | 119 | 2 | 87 | c |
| 4 | Ph | Me | 130 | 48 | 91 | d |
| 5 | Ph | *i*-Pr | 132 | 48 | 94 | e |

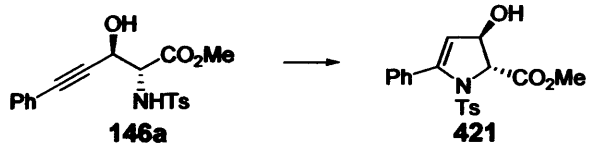
**Table 4.16**

Based on Sharland's results, 10% silver nitrate on silica gel appeared to be an excellent choice of reagent for the cyclisations of amino alcohol derivatives **403**, affording the products cleanly without the need for any purification, which is in contrast to several of the previously tested reagents. However, it was unclear whether due to the instability of the dihydropyrroles **404**, this methodology be further exploited in the synthesis of pyrrolidines.

# 4.20. Results and Discussion: Silver(I) Nitrate Cyclisations in the Synthesis of Pyrrolidines

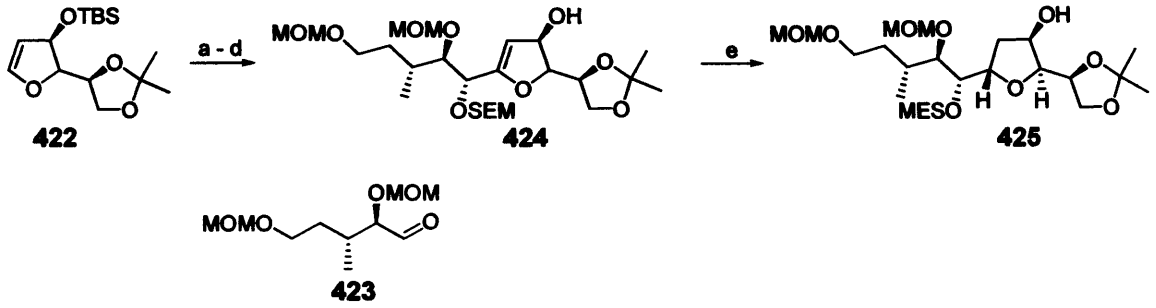
## 4.21. Cyclisation of an Aryl Substituted Amino Alcohol

Previously, in the silver-catalysed cyclisations of the amino alcohols, Sharland had used one equivalent of 10% silver nitrate on silica gel in anhydrous ether (Table 4.16), but could the reactions proceed using a catalytic amount of 10% w/w silver nitrate on silica gel? Accordingly, **146a** was treated with 0.5 equivalents of 10% silver nitrate on silica gel for 1 h to afford the dihydropyrrole **421** in 93% yield, as apparent from the loss of the alkyne signals in the $^{13}C$ NMR spectrum and the appearance of a new olefin doublet at 5.40 ppm (Scheme 4.13). This suggested that a stoichiometric amount of the silver reagent was not necessary for complete reaction. Presumably, the amount of silver reagent could be lowered further, but experiments were not conducted at this stage. For convenience, the products are drawn in enantiomeric form to those drawn in the introduction.




**Scheme 4.13.** *Reagents:* 0.5 eq $AgNO_3/SiO_2$, $CH_2Cl_2$, 1 h, 93%.

The reality that these dihydropyrroles were isolated is less surprising when one considers that Paquette[8] synthesised a dihydrofuran **424** from D-mannose and manipulated this to form the corresponding hydroxy tetrahydrofuran **425**, by stereo-directed catalytic hydrogenation (Scheme 4.14).



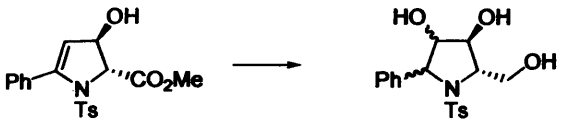

**Scheme 4.14.** *Reagents:* a) *t*-BuLi, THF, -78°C; b) **423**, THF, -78°C, 52%; c) SEMCl, (*i*-Pr)$_2$NEt, $CH_2Cl_2$, 85%; d) TBAF, THF, 0°C, 66%; e) [Rh(NBD)(DIPHOS-4)]$BF_4$, $H_2$, (800 psi), NaH, THF, 68%.

A hydroxyl-directed hydrogenation procedure was used to establish the third stereogenic centre of the tetrahydrofuran ring and since the dihydrofuran **424** had a tendency to eliminate water, a considerable amount of pressure was mandatory (800 psi).

In order to synthesise the desired pyrrolidines from the dihydropyrroles using this methodology, it was necessary to perform an addition reaction to the double bond to discourage elimination to the corresponding pyrrole. It was decided to exposure the dihydropyrrole to hydroboration conditions, using borane-tetrahydrofuran complex. The dihydropyrrole **421** contained an ester group, which under normal circumstances would not be reduced by borane. However, the presence of a hydroxyl group β to this ester meant that reduction of the methyl ester might occur. This is because an intermediate is formed which following electron donation, results in nucleophilic activation of the B-H bond, which ultimately makes this intermediate a stronger reducing agent than borane, hence reduction of the ester moiety can occur. This reduction would overtly be advantageous since this would reduce the likelihood of elimination to the corresponding pyrrole and thus increase the stability of the product.

When the dihydropyrrole **421** was treated with a 1M solution of borane-tetrahydrofuran complex in tetrahydrofuran for 16 h, followed by oxidation using sodium hydroxide and hydrogen peroxide, the $^1$H NMR spectrum of the crude product revealed that absence of the alkene resonance at 5.5 ppm and also that incomplete reduction of the methyl ester had occurred (Scheme 4.15). There were at least three signals in the methyl ester region of the spectrum indicating that either a mixture of diastereoisomers had formed or that the

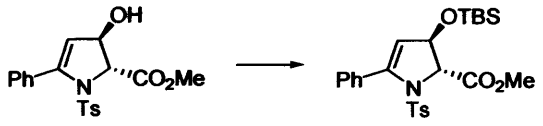
reaction gave a mixture of products. At this stage no purification was attempted. However if the product was a mixture of diastereoisomers, the selectivity of the reaction could in theory be improved by sterically shielding the top face of the olefin to encourage attack of the electrophile from the back face of the olefin. Hence to shield the top face of the olefin, it was decided to protect the hydroxyl group as a sterically hindered silyl ether, in an attempt to obtain the desired product **426**.




**421** **426**

**Scheme 4.15.** *Reagents*: a) 4 eq. $BH_3$-THF, THF, $H_2O_2$, NaOH.

The dihydropyrrole **421** was treated with triethylamine and TBS triflate in tetrahydrofuran to afford the TBS ether **427** in 86% yield, as deduced by the new *t*-butyl singlet at 0.75 ppm in addition to the two SiMe singlets at -0.0 and 0.0 ppm and the slight shift of the C*H*O and C*H*$CO_2$Me protons (Scheme 4.16). It was hoped that this protection of the hydroxy group would reduce the likelihood of elimination occurring, but it was decided not to purify the crude product.

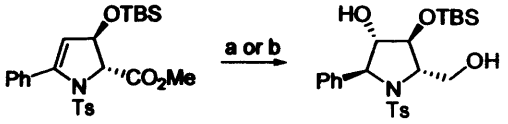



**421** **427**

**Scheme 4.16.** *Reagents*: TBSOTf, $Et_3N$, THF, 2 h, 86%.

The TBS ether **427** was then subjected to hydroboration using four equivalents of borane-tetrahydrofuran complex and following oxidative workup and chromatography, the product was obtained as a single diastereoisomer **428a** (Scheme 4.17). Other than the obvious loss of the olefin signal and methyl ester singlet, the $^1$H NMR spectrum was unfortunately not very informative, while the $^{13}$C NMR spectrum revealed four methine resonances at 71.9, 75.3, 83.0 and 84.1 ppm, characteristic of a pyrrolidine ring. An observed molecular ion of 478 ($M^+$ + H), further clarified the formation of the desired pyrrolidinol. Unfortunately, the pyrrolidine ring protons in the region 3.95-4.95 ppm were all apparent singlets, and as such no coupling data could be obtained, to differentiate between the ring protons. Also

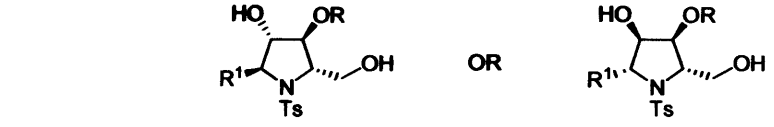
their close proximity meant that nOe experiments could not be conducted to deduce the stereochemistry and being an oil, X-ray diffraction was also not an option.




**427** **428a**

**Scheme 4.17.** *Reagents*: a) 4 eq. $BH_3$-THF, THF, $H_2O_2$, NaOH, 44%; b) 2 eq. $BH_3$-THF, THF, $H_2O_2$, NaOH, 23%.

Despite being unable to determine the stereochemistry, the structure of the product could be determined by considering the mechanism of the reaction. Hydroboration is regioselective and so the boron always adds to carbon of the alkene that is less substituted. Following a controlled oxidation, to convert the C-B bond into a C-O bond, overall it can be seen that *cis* addition of water to the olefin occurs, with the new hydroxyl group attached to the less substituted end of the alkene. So there are two possible isomers, depending on the face of the alkene to which addition occurs (Figure 4.12).




Where $R^1$= Ph, R=H **426a** Where $R^1$= Ph, R=H **426b**
Where $R^1$= Ph, R=OTBS **428a** Where $R^1$= Ph, R=OTBS **428b**

**Figure 4.12**

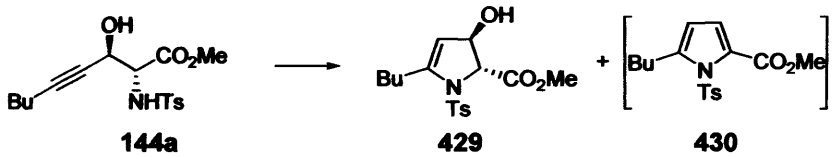
In addition, borane-tetrahydrofuran complex is a relatively small electrophile, so high selectivity was not necessarily expected to occur. When substituent ($R^1$) was hydrogen, a mixture of products was formed, while when the substituent ($R^1$) was a much larger TBS group, a single diastereoisomer was obtained (Figure 4.12). So it seems logical to assume that in the presence of the sterically hindered TBS group, the front face of the alkene is shielded and so addition to the boron occurs from the back face of the alkene and following a controlled oxidation using alkaline hydrogen peroxide, the 3,4-*trans* isomer **428a** had been obtained. In the absence of this large protecting group, either face of the alkene can add to the electrophile, to give a mixture of isomers, as observed.

With a view to eliminating the use of excess reagents, the hydroboration of the dihydropyrrole **421** was repeated with two equivalents of the borane-tetrahydrofuran complex, but the NMR spectrum of the crude product revealed only partial reduction of the

methyl ester and following chromatography, the pyrrolidinol **428a** was obtained in a reduced 23% yield, confirming that four equivalents of the borane reagent was necessary to reduce the ester in addition to the hydroboration of the olefin (Scheme 4.17; b).

## 4.22. Cyclisation of an Alkyl Substituted Amino Alcohol 144a

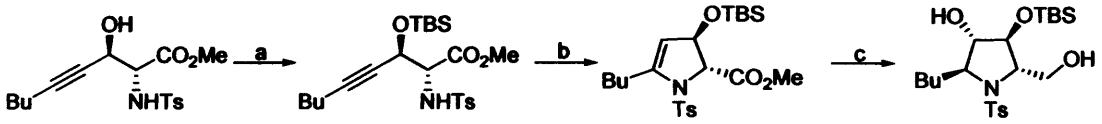
To be a useful synthetic method for the synthesis of pyrrolidines, the reaction must be compatible with a variety of R groups, so would the same success be achieved when the phenyl substituent was replaced with a butyl group? With the analogous phenyl derivative **146a**, the number of equivalents utilised in the silver catalysed cyclisation were halved, without impairing the yield (Scheme 4.13). Accordingly, the butyl *anti* amino alcohol **144a** derived from the tin(II) mediated condensation of the enolate of methyl *N*-tosyl glycinate with hept-2-ynal **115** (Scheme 2.10;a , Chapter 2) was treated with 0.5 equivalents of 10% silver nitrate on silica gel for 1.5 h, to give a 5:1 mixture of the dihydropyrrole **429** and pyrrole **430** (Scheme 4.18). The pyrrole **430** was characterised by the new olefin doublets at 5.95 and 6.75 ppm and a molecular ion of 336 ($M^+$ + H), consistent with cyclisation and elimination, was observed. Confirmation of the formation of the dihydropyrrole **429** was apparent from the OH stretch in the infrared spectrum and a new olefin resonance at 134.7 ppm in the $^{13}C$ NMR spectrum. From the ratio in the NMR spectrum of the crude product, the dihydropyrrole **429** was formed in approximately 79% yield.




**Scheme 4.18.** *Reagents:* a) $CH_2Cl_2$, 0.5 eq 10% w/w $AgNO_3/SiO_2$, 1.5 h, R.T., 79% **429** and 16% **430**.

No purification was attempted to prevent further dehydration of the dihydropyrrole **429**. In an attempt to reduce the level of elimination observed, the precursor **144a** was protected as the TBS ether **431**, prior to cyclisation. Subsequent treatment of the aldol product **144a** with triethylamine and TBS triflate in tetrahydrofuran for 2 h afforded a 3:1 mixture of diastereoisomers of the TBS ether **431** in 70% yield. The appearance of a new *t*-butyl

singlet at 0.75 ppm, new SiMe singlets at -0.05 and 0.00 ppm and a molecular ion of 468 ($M^+ + H$), all indicated the presence of a TBS ether (Scheme 4.19; a). No purification was performed to avoid any epimerisation of the sensitive centre, and so the TBS ether **431** was immediately exposed to 10% silver nitrate on silica gel for 1 h. Following filtration through celite and evaporation of the solvent, the dihydropyrrole **432** was obtained as the sole product in 43% yield (Scheme 4.19; b). Formation of the dihydropyrrole **432** was apparent from the loss of the alkyne signals in the $^{13}C$ NMR spectrum and new olefin signal at $\delta_C$ 110.9 ppm. Again, since the product had an identical molecular weight to the starting material, mass spectrometry data was not informative.




**Scheme 4.19.** *Reagents:* a) TBSOTf, $Et_3N$, THF, 100%; b) 0.5 eq $AgNO_3$/ $SiO_2$, 4 h, 43%; c) 4 eq $BH_3$-THF, THF, 16 h, NaOH, $H_2O_2$, 1 h, 24%.

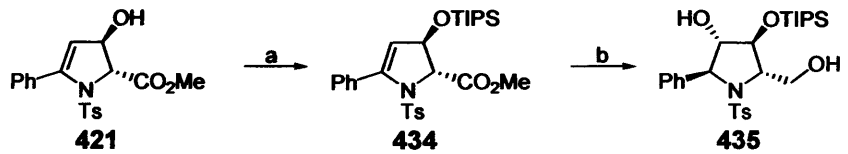
The silyl ether was then treated with four equivalents of a 1M solution of borane-tetrahydrofuran complex for 16 h, followed by addition of alkaline hydrogen peroxide. Despite careful chromatography, the pyrrolidinol **433** was obtained in only 24% yield, deduced from a molecular ion of 458 ($M^+ + H$), consistent with the proposed structure in addition to the loss of both the olefin and methyl ester signals (Scheme 4.19; c). This time the C*H*$CH_2OH$ and C*H*OTBS protons showed some degree of coupling, but both the C*H*OH and C*H*Bu protons were apparent singlets. Again, the ring protons were in close proximity to each other and so nOe experiments could not be conducted to ascertain the stereochemistry, but it was assumed that due to the large TBS group, as previously observed with the phenyl derivative **428a**, the product would be the 3,4 *trans* isomer (Figure 4.12).

However, this limited study showed that there was a significant difference in the yield of the hydroboration reaction depending on the nature of the substituent. In addition, this substituent does affect the degree of β-elimination observed in the silver catalysed

cyclisation, with the butyl dihydropyrrole **432** being more susceptible than the phenyl derivative **427**.

### 4.23. Hydroboration: Optimisation Studies

Before this methodology could be applied to natural product targets, optimisation of the hydroboration reaction was required. Clearly, protection of the hydroxyl group was necessary for the reaction to be diastereoselective as previously determined, but could the yield be increased by using alternative protecting groups? Optimisation studies were conducted on the phenyl substituted dihydropyrrole **421**, being similar to the natural product (-)-codonopsinine **3** (Figure 4.13). The dihydropyrrole **421** was treated with TIPS triflate and 2,6-lutidine in dichloromethane for 16.5 h and following chromatography, the TIPS ether **424** was isolated in 64%, as illustrated by the isopropyl multiplet in the $^1$H NMR spectrum (Scheme 4.20; a). Thankfully, upon treatment of the TIPS ether **424** with a 1M solution of borane-tetrahydrofuran complex in tetrahydrofuran followed by addition of alkaline hydrogen peroxide afforded the desired pyrrolidinol **435** as a single diastereoisomer in an improved 64% yield, without the need for purification. Formation of the pyrrolidinol **435** was confirmed by the expected disappearance of both the olefin signal and methyl ester singlet and also a molecular ion of 520 ($M^+$ + H), consistent with the proposed structure (Scheme 4.20; b). As observed previously with the TBS derivative **427**, all the ring protons were apparent singlets and due to their close proximity, nOe experiments were not conducted. However, it was believed that the product was the 3,4-*trans* isomer **435** (Scheme 4.20; b).




**421** **434** **435**

**Scheme 4.20.** *Reagents*: a) 2,6-lutidine, TIPSOTf, $CH_2Cl_2$, 16.5 h, 64%; b) $BH_3$-THF, THF, 16 h, NaOH, $H_2O_2$, 1 h, 72%.

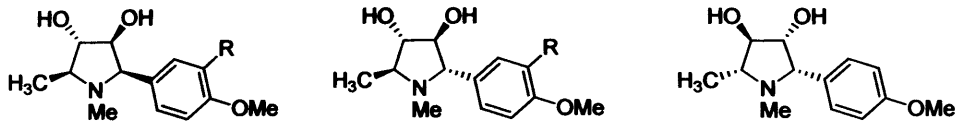
## 4.24. Conclusion

So the silver catalysed cyclisation successfully afforded the dihydropyrroles which following protection as the silyl ether, were sufficiently stable to undergo the hydroboration reaction to form the desired pyrrolidines. With the hydroboration reaction optimised, the results could be applied to the natural product, but would the additional methoxy group on the benzene ring influence the chemistry? Also, the stereochemistry of the pyrrolidinol **435** needed to be established and to be a viable synthetic route to the natural product, it was essential that the product from the hydroboration reaction was the 3,4-*trans* isomer (Figure 4.12).

## 4.30. Studies Towards the Total synthesis of Codonopsinine

### 4.31. Introduction: Isolation and Biological Activity

(-)-codonopsine **436b** and (-)-codonopsinine **3b** are members of a class of pentasubstituted pyrrolidine alkaloids isolated from *Codonopsis clematidea* (Figure 4.13).[9] (-)-codonopsinine **3b** possesses antibiotic and hypotensive pharmacological activity and does not affect the central nervous system.[10]




**436a** R=OMe
**3a** R=H

**436b** R=OMe
**3b** R=H

**3c**

**Figure 4.13**

In 1972, Matkhalikova[11] originally assigned the stereochemistry to be 2R, 3S, 4S, 5S **3a**, an assumption based on analyses of $^1$H NMR coupling constants using the Karplus equation. However, vicinal coupling constants can be unreliable when assigning the configuration of substituted pyrrolidines, as apparent from Table 3.14 (Chapter 3).[12]

### 4.32. Previous Synthetic Approaches

Iida[13], Yamazaki and Kibayashi conducted the first attempted synthesis of the natural product **3b** in 1985. Their route commenced from L-tartaric acid which was converted into aldehyde **437** over 4 steps. Following treatment of aldehyde **437** with *p*-methoxy-phenylmagnesium bromide, a 3.3:1 mixture of diastereoisomers was obtained. This mixture was then subjected to a Mitsunobu reaction using phthalimide and DEAD to afford a separable 1:1 mixture of epimers **438**. What was believed to be the *syn* diastereoisomer **438a** following various deprotection, oxidation, alkylation and protection steps was converted into the mesylate **439**. Upon exposure of the mesylate **439** to catalytic hydrogenolysis *in situ* cyclisation occurred to afford **440**. Finally, *N*-methylation and deprotection of the resultant substrate afforded what was assumed to be the natural isomer of (-)-codonopsinine **3a**. It was only upon comparison of the optical rotation of the

synthetic material with that of the natural product that the group established that they had synthesised the enantiomer of the apparent naturally occurring isomer **3c** (Figure 4.14).

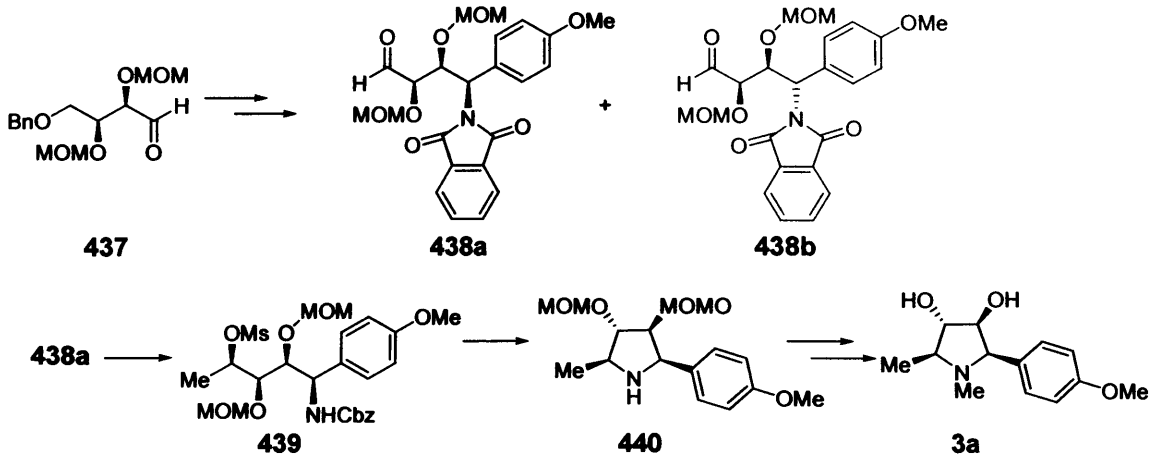



**Figure 4.14a**

However, later in 1986, work by Iida[14], Yamazaki and Kibayashi revealed that what was previously believed to be the *syn, syn* isomer in the initial synthesis (Figure 4.14a) was in fact the *syn, anti* diastereoisomer **438b** (Figure 4.14b). Hence their previously deduced relative configuration of the natural product was incorrect. Accordingly, the structure of natural (-)-codonopsinine was revised from **3a** to **3b** (Figure 4.13).

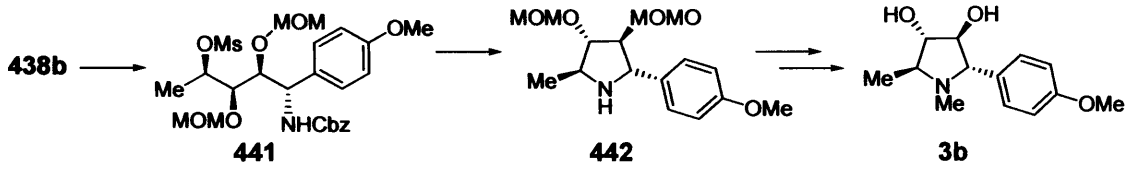



**Figure 4.14b**

Later in 1991, Wang[15] and Calabrese reported the first total synthesis of (-)-codonopsine **436b**, (Figure 4.15). The sequence commenced with *trans*-3,4-dimethoxycinnamic acid **443**, which was converted into (*E*)-vinyl bromide. The vinyl anion of the bromide was subsequently reacted with the dianion generated from the treatment of *N*-(ethoxycarbonyl)-D-alanine with n-BuLi to afford the enone **444**. Reduction, followed by cyclisation using sodium hydride afforded the cyclic carbamate **445** as a 2:1 mixture (*cis*:*trans*). Next decarboxylative cyclisation with boron trifluoride etherate, followed by addition of $ClCO_2Me$ gave the product **446** as a 1.3:1 mixture (*trans*:*cis*). Epoxidation using *m*-CPBA afforded a mixture of epoxides **447** which upon hydrolysation with concentrated sulphuric

acid in a mixture of dioxane and water at 95°C gave the desired product **436a** in 30% yield in addition to other isomers (23%) (Figure 4.15).

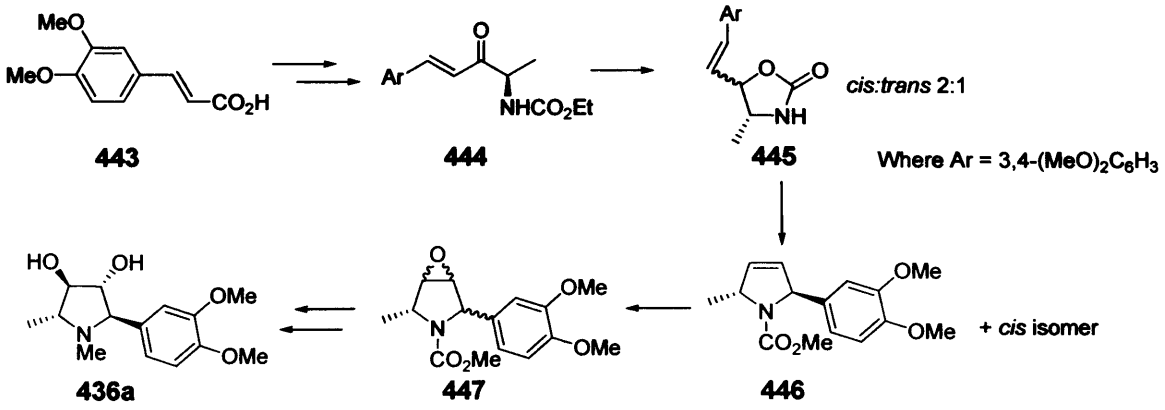



**Figure 4.15**

In 1996, Yoda[16] and Takabe reported a 9-step synthesis of (-)-codonopsinine **3b** from D-tartaric acid in 33% overall yield. The sequence involved the formation of a quaternary α-hydroxylactam intermediate **450**, which was subjected to reduction deoxygenation to afford a single stereoisomer of a homochiral lactam. Following protecting group exchange and addition of *p*-methoxyphenylmagnesium bromide the labile quaternary α-hydroxypyrrolidine **450** was formed. Sodium borohydride reduction using SmCl3 as the additive gave alcohol **451** as virtually a single diastereoisomer. Mesylation of the *syn* diastereoisomer **451**, followed by cyclisation using *t*-BuOk gave the pentasubstituted pyrrolidine **452**. Finally, lithium aluminium hydride reduction of **452**, in refluxing tetrahydrofuran gave the natural product **3b** (Figure 4.16).

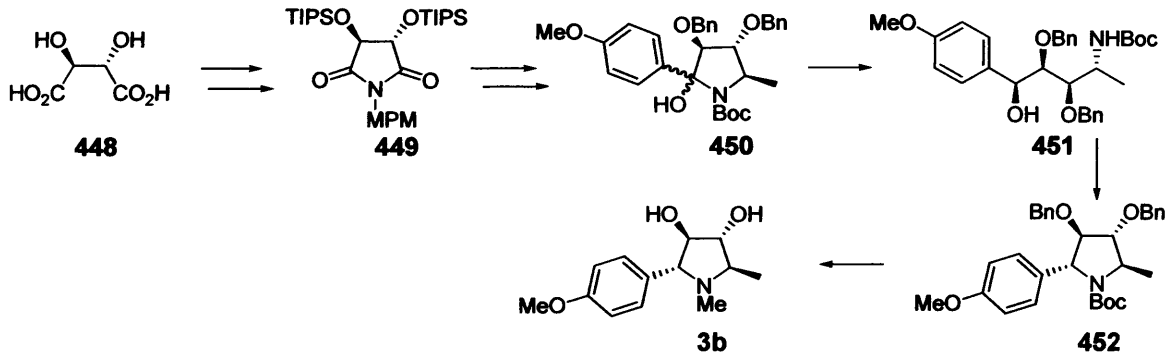



**Figure 4.16**

In 1999 the Correia[17] group conducted studies towards the synthesis of the pyrrolidine alkaloids (-)-codonopsine **436b** and (-)-codonopsinine **3b** utilising a Heck reaction of endocyclic enecarbamates with diazonium salts. When endocyclic enecarbamate **453** was treated with the diazonium salt **454**, the product **455** was formed largely as a single diastereoisomer. After deprotection of the trityl group and mesylation of the alcohol, the substrate was deoxygenated using sodium borohydride to afford the C-5 methyl pyrrolidine **446**. This substrate was identical to the intermediate previously synthesised by Wang and Calabrese (Figure 4.15), hence a formal synthesis of (-)-codonopsinine **436b** had been accomplished. Accordingly, the group theorized that substrate **456** could be converted into (-)-codonopsinine **3b** using the same sequence as Wang[15] and Calabrese.

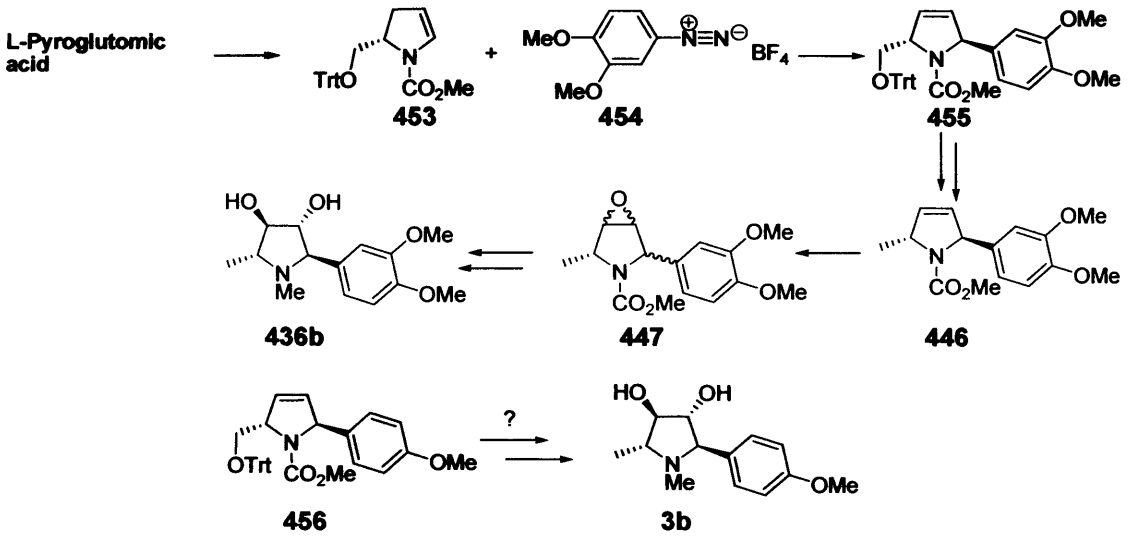



**Figure 4.17**

However, optimisation was necessary since Heck arylation of the enencarbamates using traditional conditions (*i.e.* aryl triflates and or aryl iodides in the presence of phosphine ligands) afforded the desired pyrrolidines in typically 10-20% yield, together with recovered starting material. Accordingly, the group deduced that benzene-diazonium tetrafluoroborates could act as suitable arylating agents for enecarbamates to successfully afford the desired products highly selectively in yields ranging from 90-95% (Figure 4.18a).[18]

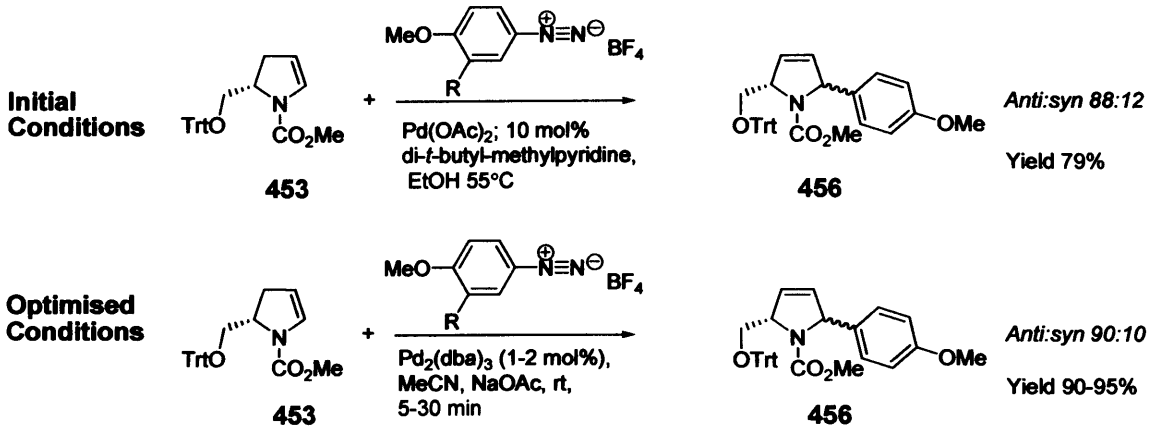



**Figure 4.18a**

With the optimisation complete the group used the previously developed methodology of the Wang and Calabrese group and applied it to substrate **456** to afford (-)-codonopsinine **3b** in 16% overall yield from enecarbamate **453** (Scheme 4.18b).

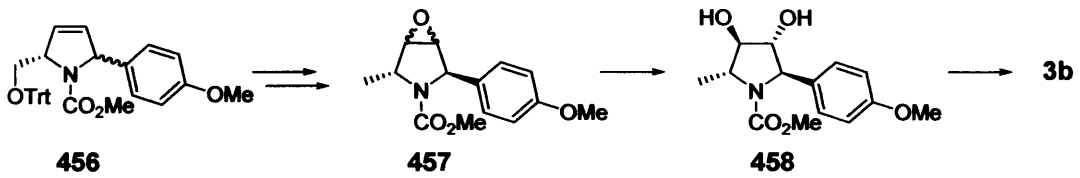



**Figure 4.18b**

In 2002, Ishibashi[19] and co-workers completed the most recent synthesis of (-)-codonopsinine **3b** in thirteen steps from lactol **460** in 41% overall yield (Figure 4.19). The sequence commenced with lactal **459** which was treated with trichloroethanol and catalytic TsOH to afford a 3:1 mixture of α- and β-anomers. The product was then protected as its MOM ether and following reductive cleavage of the trichloroethyl group, lactol **460** was obtained. Exposure of lactol **460** to $NH_2OTBDPS$ and mesyl chloride furnished mesyloxyoxime **461**, which then underwent desilyative nitrone formation to generate the key cyclic nitrone **462**. Treatment of nitrone **462** with 4-methyoxyphenylmagnesium bromide gave the hydroxylamine **463** as a single diastereoisomer. Next reduction followed by protection of the secondary amine afforded the corresponding carbamate, which was subsequently hydrolysed and the resulting alcohol protected as the tosylate **464**. Finally by refluxing the tosylate **464** in THF in the presence of lithium aluminium hydride and deprotection of the MOM group the natural product **3b** was obtained (Figure 4.19).

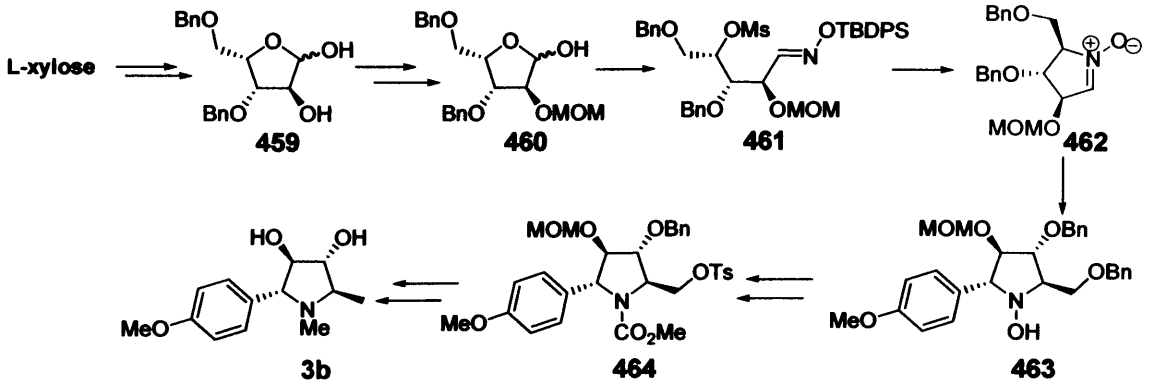



**Figure 4.19**

In addition the group also used the key nitrone intermediate **462** to synthesise the novel pyrrolizidine alkaloids Hyacinthacines $A_1$ **465** and $A_2$ **466** (Figure 4.20).[20]

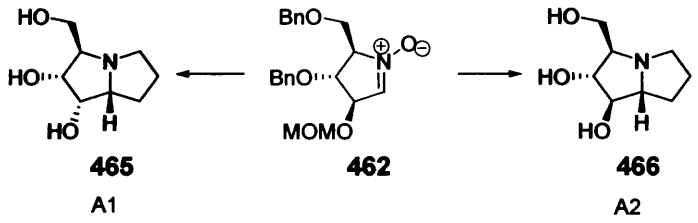
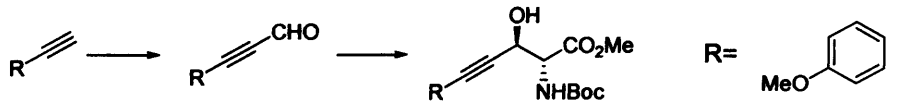



**Figure 4.20**

## 4.33. Results and Discussion

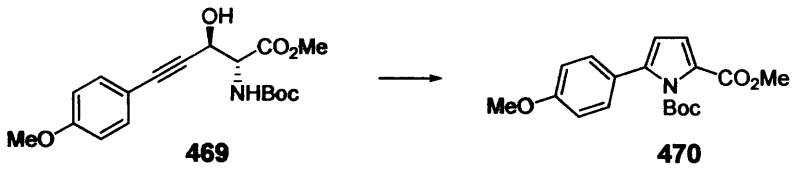
The optimum conditions for the silver cyclisation and hydroboration steps had been established for the model (Scheme 4.20) and these were applied to the synthesis of (-)-codonopsinine **3b**. However, the model substrate **435** contained a tosyl protecting group and later in the synthesis this would have to be replaced with a methyl group. Tosyl groups are notoriously difficult to remove, despite various literature procedures, and frequently harsh conditions are required.[21] To obviate this problem, it was decided to use a Boc group as an alternative, since this can be easily converted into a methyl group upon treatment with lithium aluminium hydride. First the carbamate **469** needed to be synthesised. 1-Ethynyl-4-methoxybenzene **467** was treated with n-BuLi and *N,N*-dimethylformamide to afford the acetylenic aldehyde **468** in an excellent 96% yield, as confirmed by the appearance of a new aldehyde singlet at 9.65 ppm in addition to a carbonyl stretch at 1650 $cm^{-1}$ in the infrared spectrum (Scheme 4.21; a). Also a melting point of 43-45°C, consistent with the literature value (lit[22] m.p. 47-48.5°C) was observed.




**467** **468** **469**

**Scheme 4.21.** *Reagents:* n-BuLi, DMF, THF, -40°C, 96%; b) **162b**, LDA, $SnCl_2$, **468**, THF, 21%.

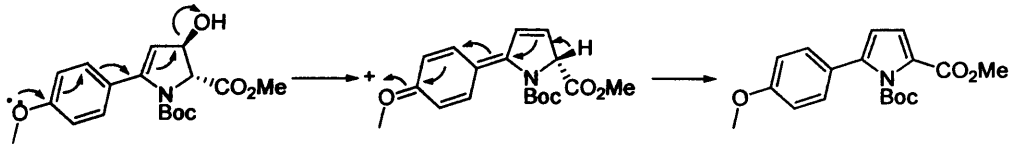
Next, this aldehyde **468** was reacted with the enolate of methyl *N*-Boc glycine in the presence of tin(II) chloride to give the desired amino alcohol **469**, but in a disappointing 21% yield, together with some recovered aldehyde **468** (Scheme 4.21; b). Formation of the desired carbamate **469** was tangible by the loss of the aldehyde singlet in the proton NMR spectrum, in addition to the appearance of new C*H*N and C*H*O protons as multiplets in the range $\delta_H$ 4.55-4.95 ppm. Interestingly, in subsequent reactions, if the scale of this aldol reaction was relatively small *e.g.* 1.25 mmol of aldehyde **468**, no reaction was observed. Now that the required carbamate **469** had been synthesised, the crucial silver-catalysed cyclisation could be attempted. Treatment of the amino alcohol **469** with 0.5 equivalents of 10% silver nitrate on silica gel for 2 h, afforded the pyrrole **470**, with no trace of the desired dihydropyrrole. Confirmation of cyclisation to the pyrrole **470** was deduced from the disappearance of the alkyne resonances in the $^{13}C$ NMR spectrum and the emergence of new olefin signals at $\delta_H$ 6.00-7.00 ppm. In addition, a molecular ion of 332 ($M^+$ + H) was observed by APcI, which correlated with the proposed structure (Scheme 4.22a).




**469** **470**

**Scheme 4.22a.** *Reagents:* 0.5 eq 10% w/w $AgNO_3/SiO_2$, $CH_2Cl_2$, 2 h, 100%.

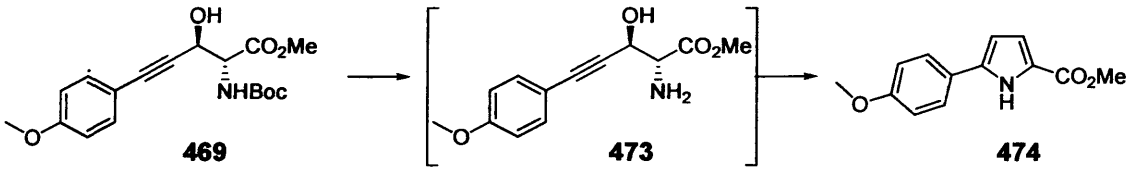
This result was not totally unexpected, due to the electron donating *p*-methoxy group on the benzene ring perfectly setting up the compound for elimination (Scheme 4.22b).




**Scheme 4.22b**

This result is very useful in pyrrole syntheses since this obviates the need for an extra β-elimination step. In the parallel synthesis of (+)-preussin **4**, the key silver-catalysed cyclisation of the carbamate **471** also gave the pyrrole **472** (Scheme 4.34). This result suggested that the Boc protecting group caused the observed β-elimination, hence alternative *N*-protecting groups were investigated. An obvious choice was the *p*-nitrobenzenesulfonyl protecting group (nosyl), due to the pioneering work conducted by Fukuyama.[23] However, when the aldol reaction was repeated using the enolate of methyl *N*-nosyl glycinate and aldehyde **468** in the presence of tin(II) chloride, only starting material was recovered. Accordingly, the previously successful tosyl group was tested and the detosylation issue would be addressed at a later stage.

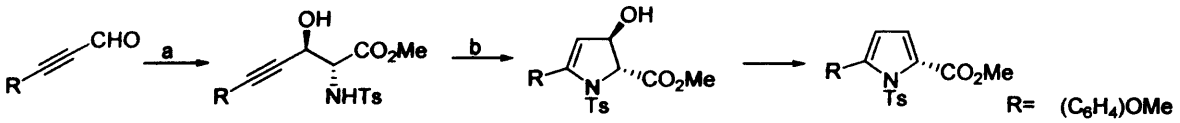
To conserve the expensive aldehyde **468**, rather than repeat the tin(II) chloride-mediated aldol reaction with the enolate of methyl *N*-tosyl glycinate to obtain the tosylate, it was decided to first deprotect the *N*-Boc amino alcohol **469** and then tosylate the free amine **473**. When the carbamate **469** was treated with a 20% solution of trifluoroacetic acid in dichloromethane, from the $^1$H NMR of the crude product, it was visible that, in addition to deprotection, cyclisation to the pyrrole **474** had occurred *in situ*, in quantitative yield, as deduced from the loss of the *t*-butyl singlet and the appearance of an additional olefin signal at $\delta_H$ 6.40-6.90 ppm. A molecular ion of 231 ($M^+$ + H) which was consistent with the pyrrole **474** was observed in addition to a new NH stretch in the infrared spectrum at 3324 cm$^{-1}$, both providing further clarification for the proposed structure (Scheme 4.23).




**Scheme 4.23.** *Reagents:* TFA, $CH_2Cl_2$, 16 h, 100%.

Sharland previously conducted cyclisations on similar substrates using acids, but not using trifluoroacetic acid (Scheme 4.11). This result was indeed a special case since in the parallel synthesis of (+)-preussin **4**, no pyrrole was isolated, following the deprotection of the carbamate **471** (Scheme 4.35). So to obtain the desired sulfonamide **475** to test the key cyclisation, the aldol reaction was repeated using the enolate of methyl *N*-tosyl glycinate and aldehyde **468**, to afford the sulfonamide **475** in 59% yield, as illustrated by an

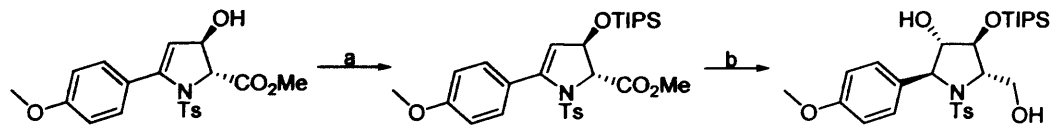
observed molecular ion of 404 ($M^+$ + H), consistent with the structure and the emergence of new C*H*OH and C*H*N signals at 4.20 and 4.80 ppm (Scheme 4.24; a). Now the key cyclisation could be conducted, and treatment of the sulfonamide **475** with 0.2 equivalents of 10% silver nitrate on silica gel for 1.5 h, afforded the dihydropyrrole **476** in 98% yield, as evident from only one olefin doublet at $\delta_H$ 5.30 ppm and also the loss of the alkyne resonances in the $\delta_C$ NMR spectrum (Scheme 4.24; b). Consequently, the accelerated rate of β-elimination observed in the previous cyclisation of the *t*-butyloxycarbonyl derivative **469** was due to the *N*-Boc protecting group, not the *p*-methoxyl benzene functionality as expected (Scheme 4.22a).




**468** **475** **476** **476b**

**Scheme 4.24.** *Reagents*: a) LDA, $SnCl_2$, THF, -78°C, 0.5 h, 59%; b) $AgNO_3$, $CH_2Cl_2$, 1.5 h, 98%.

This dihydropyrrole **476** was very unstable, due to the *p*-methoxy moeity and dehydrated to the corresponding pyrrole **476b** in a few hours at room temperature. To be a viable route to the natural product **3b**, it was mandatory that the hydroxyl group could be protected as the TIPS ether **477**, before complete dehydration happened. Thankfully, rapid treatment of the dihydropyrrole **476** with TIPS triflate and 2,6-lutidine in dichloromethane successfully afforded the TIPS ether **477** (Scheme 4.25; a). Confirmation of the successful protection was obtained by the new *iso*-propyl resonances in the NMR spectrum of the crude product and also the loss of the O-H stretch in the infrared spectrum.




**476** **477** **478**

**Scheme 4.25.** *Reagents*: a) TIPSOTf, THF, 2,6-lutidine, 18.5 h; b) $BH_3$-THF, THF, 16 h, $NaOH/H_2O_2$, 1 h, 30%.

Due to the perceived instability of the product **477**, limited characterisation data was obtained. Around two thirds of the crude material **477** was chromatographed, to test the

compound's stability to silica. Unsurprisingly, slight isomerisation occurred to give a 7:1 mixture of diastereoisomers and on leaving the product in deuteriochloroform overnight, complete isomerisation to **479** was observed (Figure 4.22). This was deduced since all the ring protons had become apparent singlets. This same sample was analysed by $^{1}H$ NMR spectroscopy after the weekend, after which time the pyrrole **480**, with the OTIPS group intact had formed (Figure 4.22). This was deduced since the $^{1}H$ NMR spectrum showed retention of the *i*-propyl signals of the protecting group, and that the spectrum was very different to that of the disubstitued pyrrole **476b**, suggesting that the presence of the *i*-propyl signals was not due to presence of excess reagent. In addition the $^{13}C$ NMR spectrum showed only one olefin CH signal at 117.7 ppm and seven quaternary carbons, confirming that the product was not the disubstituted pyrrole, but the TIPS protected pyrrole **480** (Figure 4.21).

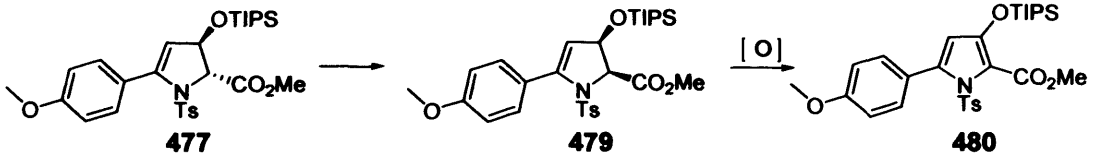
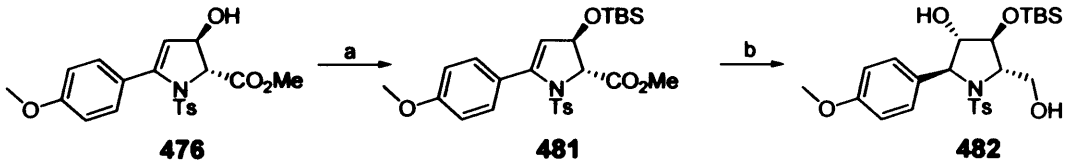



**Figure 4.21**

With the instability of the TIPS ether **477** established, the TIPS protection of the dihydropyrrole **476** was repeated, but the silyl ether **477** was immediately treated with a 1M solution of borane-tetrahydrofuran complex, followed by alkaline hydrogen peroxide after 16 h at room temperature. The crude product was chromatographed to afford the desired pyrrolidine **478**, in only 30% yield, but as a single diastereoisomer (Scheme 4.25; b). Once again formation of this product was apparent from the loss of both the olefin and methyl ester resonances and this pyrrolidinol **478** displayed many of the characteristic traits previously seem with these systems, with all the new ring protons at $\delta_H$ 3.90-4.75 ppm, being apparent singlets. This yield was lower than that obtained on the model substrate **465**, (Scheme 4.20; b), just with an additional methoxy group on the benzene ring. It was hoped that by using a slightly smaller silicon protecting group, the yield of the hydroboration reaction would be increased and since a TBS group had proven to be successful in the model, (Scheme 4.17; b) it was tested here. Consequently, the dihydropyrrole **476** was treated with triethylamine and TBS triflate in tetrahydrofuran, to afford the TBS ether **481** in 92%, as evident from the new *t*-butyl singlet and SiMe singlets

in the $^1$H NMR spectrum, with both corresponding to the new TBS protecting group (Scheme 4.26). The crude product **481** was immediately treated with a 1M solution of borane-tetrahydrofuran complex and stirred for 16 h, prior to the addition of alkaline hydrogen peroxide. Following chromatography, the pyrrolidinol **482** was isolated as a single diastereoisomer in an improved yield of 47% over two steps (Scheme 4.26). Again the success of the reaction was evident due to the loss of the olefin and methyl ester resonances. Further confirmation for the proposed structure was obtained by LRMS where a molecular ion of 530 ($M^+$ + Na), corresponding to the sodium adduct, was observed and again the new pyrrolidine ring protons were visible as apparent singlets. Due to the close proximity of these resonances. nOe experiments were not conducted to ascertain the stereochemistry, but it was believed that due to the large TBS group, the back face of the alkene attacked the electrophile, thus the product formed should be the 3,4-*trans* isomer **482** (Figure 4.12). It was essential that this was the stereochemistry to enable the synthesis of the nature isomer, (-)-codonopsinine **3b**.




**476** **481** **482**

**Scheme 4.26.** *Reagents*: a) TBSOTf, THF, $Et_3N$, 2 h, 92%; b) $BH_3$-THF, THF, 16 h, $NaOH/H_2O_2$, 1 h, 47%.

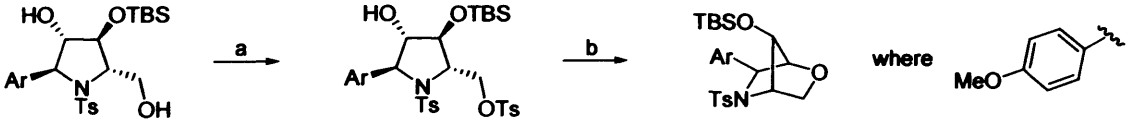
Further optimisation was attempted, but unfortunately both the protection and hydroboration reactions were dreadfully capricious. In addition, the stability of the dihydropyrrole **476** meant that cyclisation and protection had to be conducted on the same day to prevent dehydration to the pyrrole **476b**, which left very little room for error where purity of reagents was concerned.

### 4.18. Functional Group interchange: Primary Alcohol to Methyl

The next step was to convert the primary alcohol into a methyl group, for which there are many ways documented in the literature. With a view to minimising the number of synthetic steps, first it was decided to selectively derivatise the primary alcohol as the tosylate **483** and then using a hydride source to displace it to generate the desired methyl

substituted pyrrolidine **484**. To tosylate an alcohol, pyridine is often used as the base. However, following treatment of the pyrrolidinol **482** for 4 h at 0°C, only starting material was recovered, even with the addition of catalytic DMAP. However, by increasing the reaction time to 16 h and conducted the reaction at room temperature, partial protection occurred. Following chromatography, the mono-tosylate **483** was isolated in 20% yield. The reaction was deemed successful due to the observation of a molecular ion of 662 ($M^+$ + H) by LRMS, which was in agreement with the structure. The retention of an O-H stretch in the infrared spectrum in addition to one extra methyl singlet at $\delta_H$ 2.35 ppm strongly implied that only the primary alcohol had been protected. This low conversion was due to the presence of the large TBS group, shielding the primary alcohol. So in retrospect, the use of the larger TIPS group would have reduced this yield further still. This reaction needed optimisation, but first it was desirable to see if the super hydride reaction would successfully furnish the methyl substituted pyrrolidine **484**. Also, in the absence of the silicon protecting group, there was the possibility that all three alcohol groups would be protected, hence protection of the secondary alcohol was mandatory.

When the monotosylate **483** was reacted with superhydride in tetrahydrofuran, early indications were encouraging due to the disappearance of one of the tosyl groups. However, the lack of a new methyl doublet at around $\delta_H$ 1-2 ppm indicated that the product formed was not the desired methyl substituted pyrrolidine **484**. Instead it became apparent that displacement of the OTs group had occurred, but by the secondary alcohol to form a bicyclic species **485**, as determined by a molecular ion of 490 ($M^+$ + H), which was in agreement with this structure, in addition to the retention of the $CH_2$ group at 69.4 ppm and also the lack of an O-H stretch in the infrared spectrum (Scheme 4.27).




**482** **483** **485**

**Scheme 4.27.** *Reagents:* a) Py, TsCl, DMAP, 16 h, 20%; b) Superhydride, THF, 2 h, 100%.

With these types of pyrrolidines, the interpretation of the NMR spectrums was onerous, most of the resonances corresponding to the ring protons were apparent singlets;

consequently, coupling data was unavailable. nOe measurements on the precursors **482** and **478** were not attempted due to the close proximity of the ring protons, but the formation of this bicyclic compound **485**, confirmed that the stereochemistry of the hydroboration product **482** was indeed the 3,4-*trans* isomer, as predicted (Figure 4.12), since this is the only stereochemistry where the hydroxyl group is in the correct orientation for such a displacement reaction to occur (Figure 4.22).

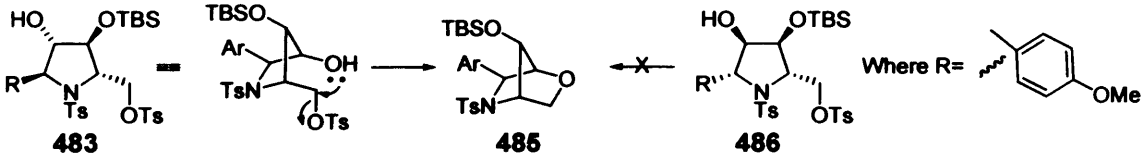


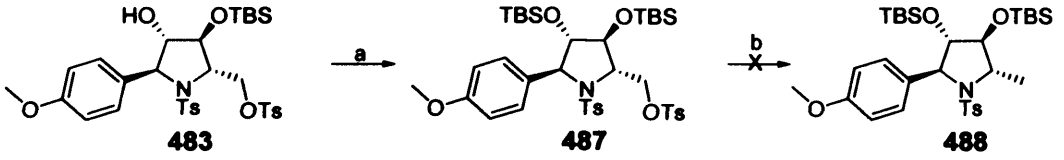

**Figure 4.22**

This result led to the use of a new strategy to form the desired product **484**. Several alternative routes were feasible: -

- Protect the secondary alcohol and thus prevent the displacement reaction;
- Use triphenylphosphine to convert the primary alcohol directly into the iodide;
- Displace the tosylate with iodide and then perform a hydrogenolysis reaction on the resultant iodide;
- Barton McCombie[24], deoxygenation procedure using tin hydride and catalytic AIBN.

Next, it was decided to protect the secondary alcohol as the TBS ether and then treat the product with superhydride to hopefully access the desired product, since both steps seemed plausible and would involve minimum purification. When the mono-tosylate **483** was treated with triethylamine and TBS triflate in tetrahydrofuran for 20 h, the *bis*-TBS ether **487** was obtained in 60% yield, as determined from the extra methyl singlets and *t*-butyl singlet observed and also the loss of the O-H stretch in the infrared spectrum (Scheme 4.28; a). Despite the protection of all of the hydroxyl groups, the pyrrolidine ring protons remained as apparent singlets. The lengthy reaction time was required due to the hindered nature of the substrate, but would this affect the subsequent superhydride™ reaction? When the *bis*-TBS ether **487** was treated with superhydride™ in tetrahydrofuran, even after 16 h, only starting material was recovered, so as expected, the hindered nature of the substrate was preventing the hydride nucleophile from displacing the OTs group. Finally,

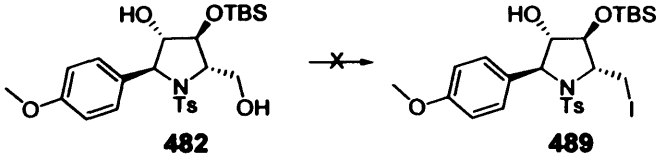
the reaction mixture was refluxed for 3 h, but only mild degradation of the starting material **487** was observed (Scheme 4.28; b) and so an alternative approach was undertaken.




**483** **487** **488**

**Scheme 4.28.** *Reagents:* a) TBSOTf, $Et_3N$, THF, 20 h, 60%; b) Super-hydride™, 16 h, NaOH, $H_2O_2$, 0%; c) Superhydride™, 3 h reflux, NaOH, $H_2O_2$, 0%.

Garegg[25] and Samuelsson reported that primary alcohols could be converted into iodides using triphenylphosphine and iodine in the presence of imidazole. Accordingly, the hydroboration product **482** was treated with triphenylphospine and iodine, but even after 16 h, only starting material was isolated (Scheme 4.29).

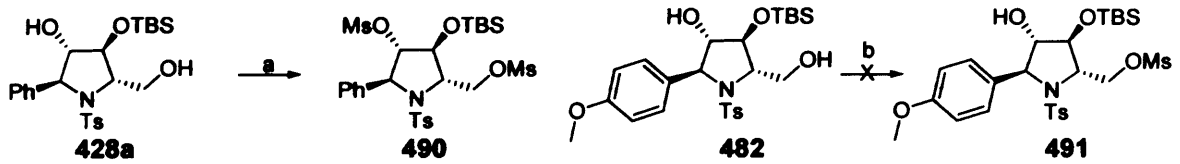



**482** **489**

**Scheme 4.29.** *Reagents:* Imidazole, $PPh_3$, $I_2$, $CH_2Cl_2$, 1 h, 0°C, 1.5 h R.T., 0%.

An exceptionally useful protocol for the removal of a (primary) alcohol group is known as the Barton-McCombie deoxygenation method and consists of derivatisation to give the corresponding xanthate and radical-mediated reduction using a tin hydride. However, a signification drawback of this procedure is the difficulty in complete removal of the inevitable tin residues. A much cleaner procedure features hydrogenolysis of the derived halides, especially iodides, which would be applicable in this case, given that cleavage of the benzylic C-N bond did not occur. However, first more of the monotosylate **483** had to be synthesised. Problems were experienced previously with the tosylation of the primary alcohol due to the hindered nature of the substrate. Instead of reducing the size of the silicon protecting group, would an increase in the yield of the product be observed by using a smaller oxygen derivatising group? Hence, experiments were conducted, but using mesyl chloride. There was a concern however, that being such a small protecting group, protection of the secondary alcohol may also occur and so the reaction was tested on the model substrate **428a** from the original hydroboration studies (Scheme 4.17). Paquette[26]

*et. al.*, reported the selective protection of a primary alcohol in the presence of another species bearing a secondary alcohol. Treatment of the diol **428a** with mesyl chloride with Hünigs base in dichloromethane, afforded the dimesylate **490** in 78% yield. This was confirmed by the appearance of two new singlets at 3.00 and 3.05, corresponding to the new mesyl methyl groups, in addition to the lack of an O-H stretch in the infrared spectrum. Further evidence for this structure was obtained from mass spectrometry using electrospray where a molecular ion of 656 ($M^+$ + Na), consistent with the protection of both the alcohols was observed (Scheme 4.30). Due to the small scale (0.083 mmol) it was plausible that excess mesyl chloride had been added, resulting in the protection of both alcohol functionalities.

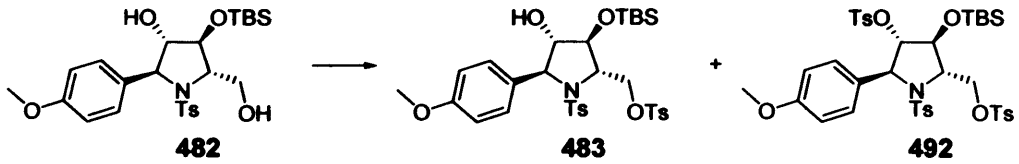



**Scheme 4.30.** *Reagents:* MsCl, Hünigs Base, $CH_2Cl_2$, -78°C, 3 h, 16 h, R.T.

It was believed that by dissolving both the mesyl chloride and Hünigs base separately in dichloromethane in known concentrations, that one equivalent of each reagent could accurately be administered. Accordingly, the reaction was repeated on the natural product derivative **482**, but from the NMR spectrum of the crude product it was apparent that a mixture of products had been formed and although the chemistry was compatible with the model substrate **428a**, incorporation of the *p*-methoxy group on the benzene ring clearly had a detrimental influence on the reaction (Scheme 4.31; b). Due to these results, it was decided to optimise the tosylation reaction, which had previously been selective, but only partial protection had been observed. Literature precedent[27] has shown that DABCO can be used as a substitute to pyridine in the tosylation of alcohols. In particular, where tosylation using pyridine had failed to afford the tosylate in sufficient yield, it was found that the use of two equivalents of DABCO in place of the pyridine gave the desired product in greater yield. However, this research was only conducted on substrates bearing only one hydroxyl group, and so in substrate **482** it was decided to reduce the number of equivalents of the base to hopefully prevent over-tosylation. Subsequent treatment of the diol **482** with 1.3 equivalents of DABCO and *p*-tosyl chloride in dichloromethane for 48 h at ambient temperature, following purification by chromatography, furnished a 9:2 mixture of mono-

tosylate **483**: *bis*-tosylate **492**, in addition to the recovery of 40% of the starting material **482**. Formation of the *bis*-tosylate **492** was deduced from an observed molecular ion of 816 ($M^+$ + H) which was in accordance with protection of both alcohols, in addition to three aryl methyl singlets at $\delta_H$ 2.45, 2.55 and 2.60 ppm and the lack of an O-H stretch in the infrared spectrum. From the integrals of the $^1$H NMR spectrum, the approximate quantity of the mono-tosylate **483** was 20% and the *bis*-tosylate **492** 6%. So no increase was apparent in the yield, but the selectivity of the reaction had been lowered considerably.

To reduce the level of protection of the secondary alcohol witnessed, the temperature was lowered to 0°C, but to achieve an increased, yield longer reaction times would be mandatory. Hence, following numerous experiments, after 24 h at -20°C and 96 h at 0°C, the desired mono-tosylate **483** was eventually obtained in an excellent 67% yield, following chromatography, together with only trace quantities of the *bis*-tosylate **492** (4%) and starting material (3%), this was found to be the optimum conditions for the reaction (Scheme 4.31; b).

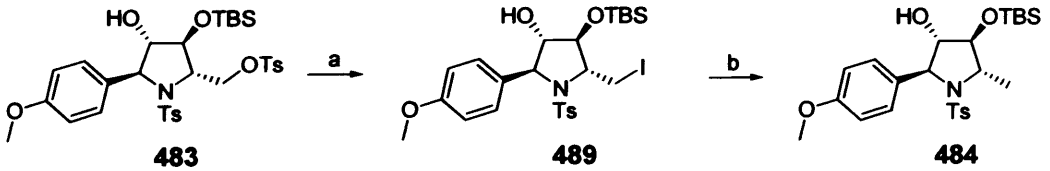



**Scheme 4.31.** *Reagents*: a) DABCO, $CH_2Cl_2$, TsCl, 48 h, 20% **483** and 6% **492**; b) DABCO, $CH_2Cl_2$, TsCl, -20°C, 24 h, 64 h, 0°C, 67% **483** and 4% **492**.

With the tosylation step optimised, displacement of this OTs group with iodide was examined. Literature[28] precedent suggested the use of 1.5 equivalents of iodide, but tests on substrate **482** were unsuccessful. Ultimately it was found that the use of four equivalents of sodium iodide in distilled acetone was necessary to obtain the iodide **489** but in quantitative yield. The reaction was proven successful due to an observed molecular ion of 618 ($M^+$ + H) consistent with displacement of the tosylate with iodine and the loss of the OTs methyl singlet in the $^1$H NMR spectrum. In addition, a shift in the position of the $CH_2$ to 7.1 ppm in the $^{13}$ C NMR spectrum, further indicated that the reaction had been successful (Scheme 4.32; a). In early experiments, the iodide **489** was purified by chromatography, but was found to be unstable. Later, it was determined that the

*anhydrous* quality of the sodium iodide rapidly degraded, hence greater quantities were ultimately used.

The next step in this sequence was to use hydrogenolysis to cleave the C-I bond using catalytic 10% palladium on carbon in the presence of triethylamine. However, when this method was applied to the iodide **489**, the NMR spectrum of the crude product was not very informative due to overlapping resonances and so it was difficult to determine if the reaction had been successful. Following purification using chromatography, the methyl-substituted pyrrolidine **484** was obtained in only 27% yield (Scheme 4.33; b). Formation of the desired product **484** was instantly recognizable from the appearance of a new methyl doublet at 1.50 ppm and the loss of the $CH_2$ resonance, in addition to a molecular ion of 492 ($M^+$ + H) which correlated with the substitution of a hydrogen for an iodine atom. Due to the small scale, the NMR spectra of the remaining column fractions were too weak to determine the structures of the additional products. Previously, during hydrogenolysis of iodopyrrolidines using identical conditions, some epoxide **323** was formed (Table 3.15, Chapter 3). Thus it was plausible that the presence of base resulted in the formation of some of the previously obtained bicyclic product **485** (Scheme 4.27; b). However, due to the similar positions of the resonances of the ring protons of both the product **484**, bicyclic **485** and the iodide **489** it was not possible to determine if any bicyclic product **485** had been formed in the reaction from the NMR spectrum of the crude product. However, in a bid to reduce the possibility of this alternative pathway to the bicyclic **485**, Hünigs base was used instead, which being sufficiently hindered should not abstract the proton of the secondary alcohol. This time only a small amount of product **484** was isolated (15%), and on scaling up the reactions problems were again experienced with the iodide displacement due to the quality of sodium iodide, and also the hydrogenolysis step.




**483** **489** **484**

**Scheme 4.32.** *Reagents*: a) *anh* NaI, $Me_2CO$, reflux, 100%, 20 h; b) $H_2$, Pd/C, MeOH, EtOH, 20 h, 27%.

Despite the synthesis of the methyl substituted pyrrolidine **484** as a single diastereoisomer, the low yield obtained meant that optimisation was required, but due to lack of material and time, no further studies were conducted. To complete the total synthesis, detosylation of the nitrogen followed by *N*-methylation is required in addition to the removal of the TBS protecting group at some stage. Ultimately, the presence of this tosyl group is disadvantageous in this synthetic route and so new routes need to be explored using alternative nitrogen protection groups that can easily be replaced with a methyl substituent. However, the present research shows that to isolate the dihydropyrrole intermediate **482** in the silver catalysed cyclisation, a tosyl protecting group was essential. Hence a new approach is necessary to eliminate the problems highlighted in this research.

# 4.40. Silver Cyclisations: Studies towards the total Synthesis of (+)-Preussin

## 4.41. Discovery and Biological Activity

The antifungal antibiotic (+)-preussin (L-657, 398) **4** was first isolated in 1988 from fermentation broths of *Aspergillus ochraceus*[29] ATTCC 22947 and *Preussia sp*[30] which inhibits the growth of the bacteria, *Candida* and filamentous fungi such as *Microsporum canis* and *Trichophyton menta.* (+)-preussin **4** and its acetate ester **493** exhibit a wider spectrum of antifungal activity against both yeasts and filamentous fungi than structurally similar anisomycin **1**. In addition, (+)-preussin **4** has recently been shown to be a potent inhibitor of cyclin E kinase in human tumour cell lines[31] as well as an inhibitor of cell growth in yeast mutants with defective *cdc* 2 regulatory genes.[32] The absolute configuration of (+)-preussin **4** was determined by Johnson[30] *et. al.*, to be 2*S*, 3*S*, 5*R*.


**Figure 4.23**

## 4.42. Previous Miscellaneous Synthetic Approaches to (+)-Preussin 4

These biological properties and structural features have resulted in numerous total syntheses. Summaries of the key steps in each synthesis are outlined. Pak[33] and Lee accomplished the first synthesis in 1991, over 17 steps starting from D-glucose to give (+)-preussin **4** in 31% yield from **494** (Figure 4.24). Despite the lengthy sequence, the majority of the steps gave virtually quantitative yields with the key steps involving sequential reduction and cyclisation of the azidotriflate **496** to establish the pyrrolidine ring. Epoxyfuranose **494** obtained from D-glucose *via* known literature procedures was then subjected to a copper catalysed Grignard reaction. Tosylation of the resultant secondary alcohol followed by displacement with sodium azide afforded azide **495** in addition to a small quantity of the corresponding elimination product. Exposure of **495** to a solution of methanolic hydrogen chloride furnished a separable mixture of anomers **496**

(β/α = 5.3:1). After separation, each anomer was subjected to the same sequence of reactions, hence the lack of stereochemistry illustrated in Figure 4.24. Next the corresponding triflates were synthesised and following hydrogenation it became apparent that cyclisation had occurred to afford a mixture of *exo* and *endo* bicyclic amines **497**. Following carbomethoxylation and demethylation, identical mixtures of equilibrated hemiacetal-aldehyde **498** were obtained, irrespective of which anomer **496** had been utilised in the previous steps. Next a Wittig reaction on the isomeric mixture gave a mixture of *Z*:*E* (81:9) **499** isomers. Finally the unseparated olefins were subjected to hydrogenation and following reduction using lithium aluminium hydride, (+)-preussin **4** was obtained (Figure 4.24).

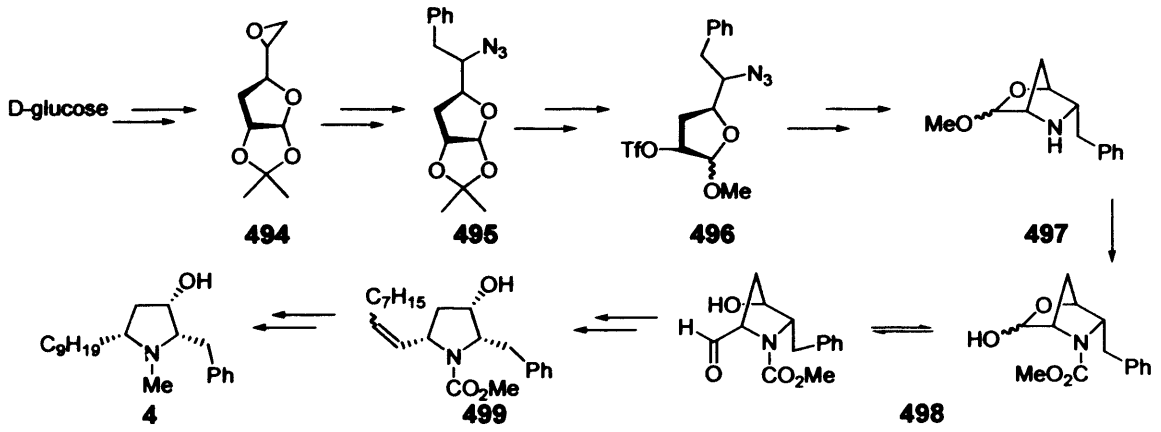



**Figure 4.24**

In 1996 the Yoda[34] group reported a 13 step asymmetric synthesis employing 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose **500** as the starting material, with no separation of stereoisomers, to give (+)-preussin **4** in 18% overall yield. Their approach involved formation of *N*-Boc lactam **501** *via* protecting group exchange. After removal of the benzyl groups, the substrate underwent a highly regioselective acylation reaction, followed by radical deoxygenation with tin hydride to afford **502**. Silylation and subsequent addition of nonylmagnesium bromide afforded the labile quaternary α-hydroxy *N*-Boc intermediate, which upon exposure to reductive deoxygenation afforded **503**. Finally reduction using lithium aluminium hydride afforded the natural product **4** (Figure 4.25).

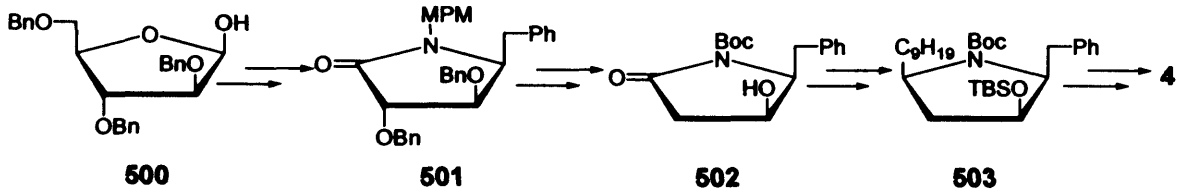



**Figure 4.25**

Two years later, Dong[35] and Lin synthesised the natural product **4** utilising the Sharpless asymmetric epoxidation and oxidative cyclisation as key steps. This route involved separation of isomers to give (+)-preussin **4** in 10 steps in overall 14% yield from epoxide **505** (Figure 4.26). The route commenced with the Sharpless[36] asymmetric epoxidation of divinylcarbinol **504**, followed by benzyl protection to afford epoxide **505**. The epoxide was ring-opened with phenylmagnesium bromide and the resultant product **506** was mesylated prior to exposure to sodium azide in *N,N*-dimethylformamide. The azide was reduced and the amino group Boc protected using standard conditions. The carbamate was then hydroborated to give **507**, which upon treatment with PDC cyclised to generate pyrrolidine **508**. Next **508** was reacted with *n*-$C_9H_{19}MgBr$ to afford **509**, which when treated with $LiAl(OBu^t)_3H$ gave a separable 3.3:1 mixture of diastereoisomers **510**. Mesylation of **510a** followed by the addition $KOBu^t$ afforded pyrrolidine **511**. Finally deprotection then lithium aluminium hydride reduction furnished the desired product **4** (Figure 4.26).

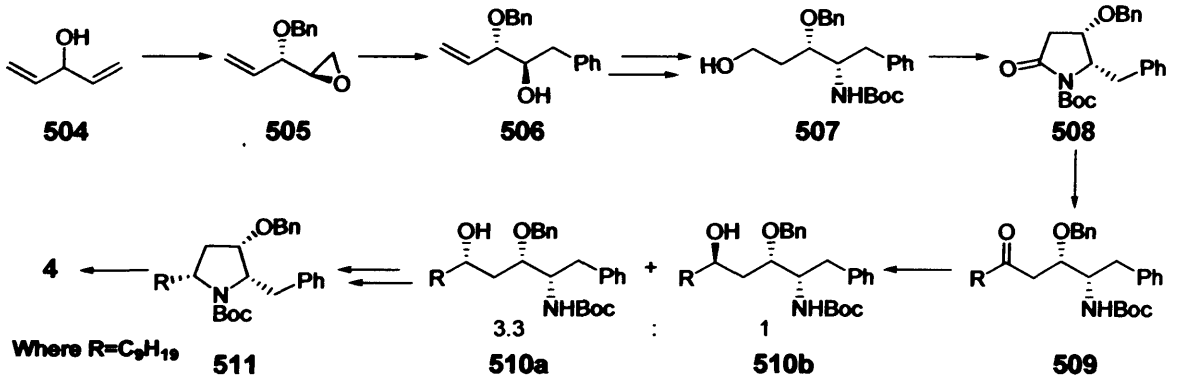



**Figure 4.26**

Also in 1997, Yamamato[37] and co-workers reported the synthesis of (+)-preussin **4** from L-aspartic acid in 16 steps, in 2% overall yield (Figure 4.27). Their route involved Boc protection of **512** followed by treatment with HOSu/DCC then sodium borohydride reduction to furnish the corresponding alcohol. This was converted into the acetonide, the

ester group of which was reduced with lithium aluminium hydride and then the alcohol moiety, silyl protected to afford **513**. Selective hydrolysis with $PdCl_2(CH_3CH)_2$ furnished the alcohol with was then tosylated prior to alkylation with $C_8H_{17}Li$ to give **514**. Next allylation of the amino group and deprotection of the silyl group gave **515**. The anion of which was trapped with *n*-$Bu_3SnCl$ to afford **516** together with recovered starting material. Next oxidation with $SO_3$.py/DMSO/$Et_3N$ followed by thermal cyclisation gave an inseparable 1:1 diastereoisomer mixture of pyrrolidines, which were separable when they were converted into their TBS ethers **517**. Ozonolysis of **517a** afforded the aldehyde with was subsequently reacted with PhMgBr. Then treatment with thiocarbonyldiimidazole gave the corresponding imidazole which was then deoxygenated. Finally deprotection of the TBDMS group and reduction with lithium aluminium hydride furnished **4** (Figure 4.27).

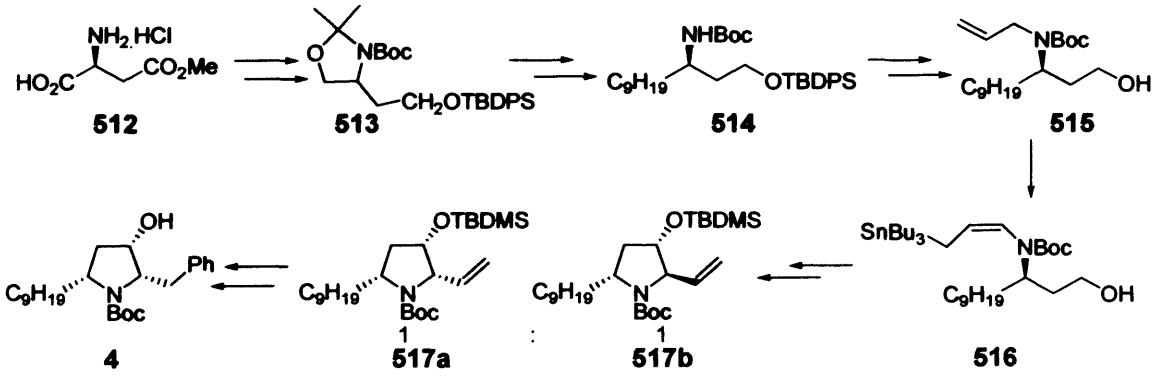



**Figure 4.27**

Greene's[38] approach in 1998 involved a novel dichloroketene chiral enol ether cycloaddition and a Beckman ring expansion to form the pyrrolidinone **521**. Thus (+)-preussin **4** was synthesised in 15% overall yield, in 10 steps (Figure 4.28). The synthesis commenced with the conversion of **518** into the benzylated ynol ether, followed by partial reduction with hydrogen to give the (*Z*)-enol ether **519**. Addition of dichloroketene to **519**, gave dichlorocyclobutanone **520** largely as a single diastereoisomer. Next the group used Tamura's Beckmann reagent[39], *O*-(mesitylenesulfonyl)hydroxyl-amine (MSH), to convert this cyclobutanone **520** into the pyrrolidinone **521**. Boc protection followed by addition of nonyl-magnesium bromide generated the all-*cis* pyrrolidine **522**, which following treatment with trifluoroacetic acid and subsequent *N*-methylation afforded (+)-preussin **4** (Figure 4.28).

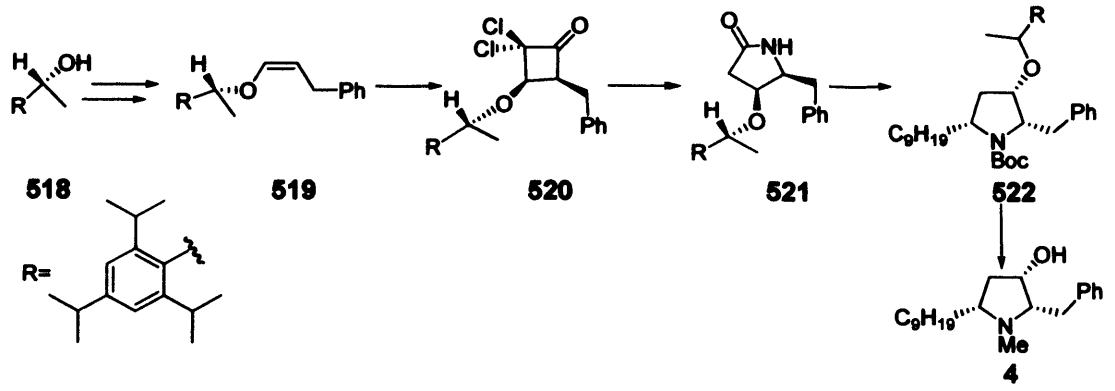



**Figure 4.28**

Also in 1998, Bach[40] and Brummerhop published a 9 step synthesis of (+)-preussin **4** from (*S*)-pyroglutaminol **523**. There approach utilised a Paternò-Büchi reaction[41] between benzaldehyde **60** and a dihydropyrrole **526** and thus the natural product was obtained in 10% overall yield (Figure 4.29). Commercially available (*S*)-pyroglutaminol **523** was tosylated and then nucleophilic addition of $Li_2Cu(n\text{-}C_8H_{17})_2CN$ led to the incorporation of the desired side chain. The product was acylated, and then reduced to the hemiaminal with $LiBEt_3H$, which was subsequently converted into the *N,O*-acetal **525** using dimethoxypropane. Next, elimination using $Ni Pr_2Et$/TMSOTf gave the dihydropyrrole **526** which underwent the Paternò-Büchi reaction, to give three products, an unstable 2-aminooxetane in addition to two diastereoisomers of 3-aminooxetane **527**. The major isomer **527a** was hydrogenated to afford pyrrolidinol **528**, which following treatment with lithium aluminium hydride, gave **4** (Figure 4.29).

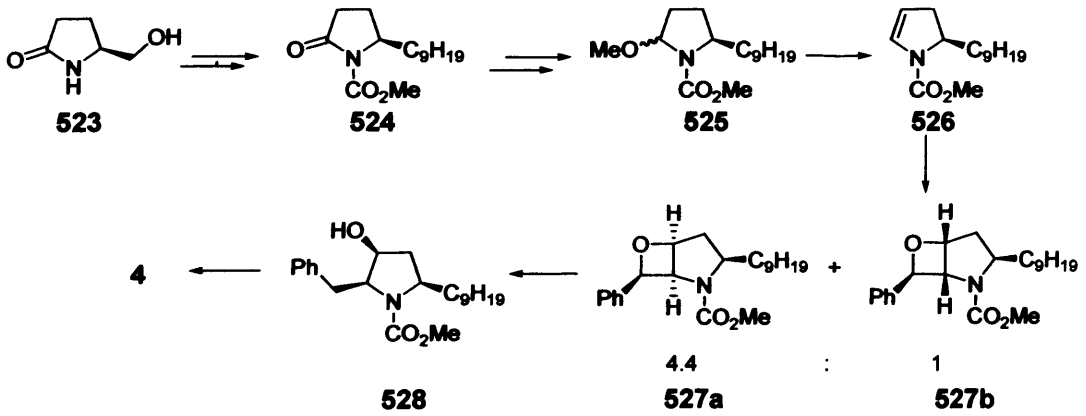



**Figure 4.29**

Verma and Ghosh[42] reported a 19 step synthesis of (+)-preussin **4** from 3-hydroxyglutaric anhydride **528**, in 1997. From the homochiral half ester **531** the overall yield was 17%

(Figure 4.30). The sequence commenced with the opening of anhydride **528** with the lithium anion of Evans' oxazolidinone to give a mixture of diastereoisomers **529** which were separated on conversion to their corresponding *tert*-butyl esters. Next the oxazolidone group was removed and following hydrogenolysis and esterification, the methyl ester was obtained. The *tert*-butyl moiety was removed and the product **530** was converted into the corresponding acid chloride and reacted with nonylmagnesium bromide to give the keto ester. This keto ester was then protected as the corresponding acetal **531** which was alkylated and the product hydrolysed and converted into the primary amide **533**. The resultant product was treated with lead tetraacetate and benzyl alcohol and following removal of the acetyl group, the ketone **534** was obtained. Following hydrogenolysis, cyclisation occurred to give the pyrrolidine. Next the NH functionality was protected to give the ethoxycarbonyl derivative, and the silyl group was converted into a hydroxyl group which was subsequently protected as an acetate **536**. Finally lithium aluminium hydride reduction afforded **4** (Figure 4.30).

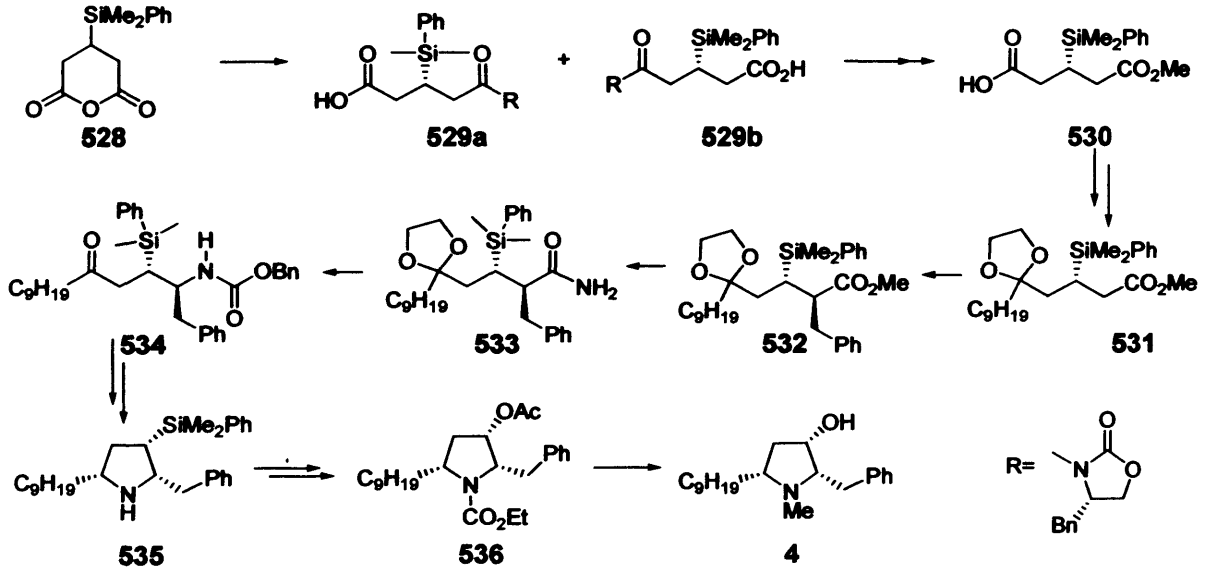
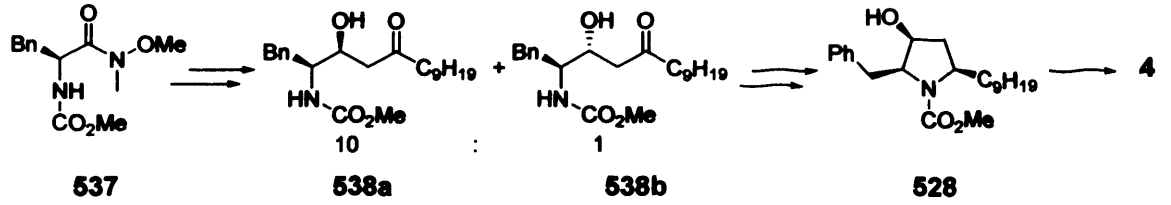



**Figure 4.30**

Later, in 2001, the Kitahara[43] group accomplished a short stereoselective synthesis of (+)-preussin **4** in 5 steps in an overall yield of 16%, where the key step was a stereoselective aldol reaction utilising zinc chloride to give predominately the *syn* adduct **538** (10:1) (Figure 4.31). The sequence commenced with the lithium aluminium hydride reduction of Weinreb amide **537** to the aldehyde which was then used in a chelation controlled aldol reaction using zinc chloride to afford predominately the *syn*

diastereoisomer **538a**. TBS protection followed by treatment with $Et_3GeH$ in the presence of $BF_3.OEt_2$ caused reductive cyclisation and desilylation to occur to form the pyrrolidine **528**. Finally, reduction with lithium aluminium hydride afforded **4** (Figure 4.31).




**537** **538a** **538b** **528**

**Figure 4.31**

Finally in 2003 Raghaven[44] and Rasheed synthesised (+)-preussin **4** in an overall yield of 7% over 12 steps utilising regio- and stereospecific bromohydration of the olefin **539** and a Pummerer reaction[45] (Figure 4.32). Alcohol **539** was protected as the TBS ether prior to treatment with *N*-bromosuccinimide in toluene to afford a bromohydrin. Reaction of the bromohydrin with methyl isocyanate afforded the carbamate **540**, which was treated with NaHMDS to give oxazolidinone **541**. Oxazolidinone **541** was then subjected to the Pummerer reaction to give intermediate **542**, which was then reduced to the alcohol **543**. Hydrolysis afforded the corresponding aldehyde that was condensed with a dithane derived anion to give **544** as a mixture of epimers. The dithane moiety was deprotected and the resultant keto alcohol was acetylated to give the ketoacetate, which upon treated with Na-Hg under buffered conditions gave **545**. Finally, exposure of **545b** to $Pd(OH)_2$ under a hydrogen atmosphere afforded the TBS protected pyrrolidine, that was reacted with TBAF to furnish the desired product **4** (Figure 4.32).

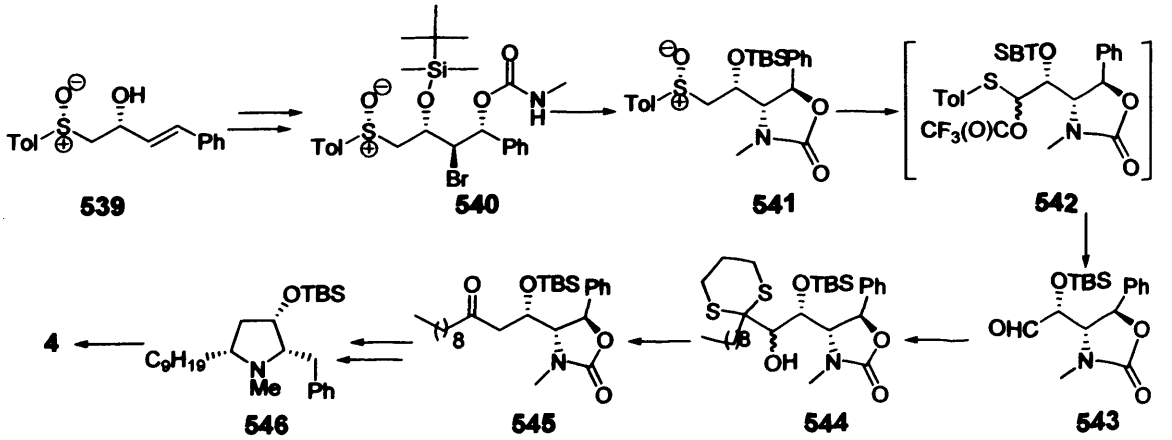
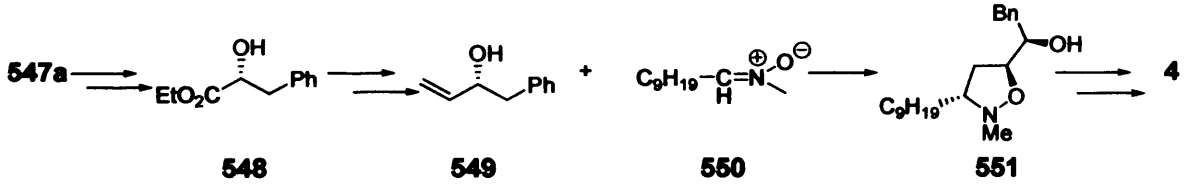



**Figure 4.32**

### 4.43. (+)-Preussin 4 Synthesis from Phenylalanine 547

One of the first syntheses of (+)-preussin **4** from D-phenylalanine **547a** was conducted by Shimazaki[46] and co-workers in 1993. Their synthetic sequence utilised an asymmetric 1,3-dipolar-cycloaddition reaction as the key step, but involved separation of stereoisomers. Thus (+)-preussin **4** was obtained in 3% yield from **548** in 9 steps (Figure 4.33). D-phenyl alanine **547** was converted into **548** according to literature precedent[47], following TBS protection and DIBAL reduction the corresponding aldehyde was obtained. This was reacted with methyltriphenylphosphonium bromide to give the alkene which was deprotected to afford **549**. Next the key cycloaddition reaction was performed between **549** and *N*-methylhydroxylamine hydrochloride **550** to give a mixture of four cycloadducts, which were separable by chromatography. The desired adduct **551** was then mesylated and the product hydrogenolysed to afford the natural product **4** (Figure 4.33).




**548** **549** **550** **551**

**Figure 4.33**

Also in 1993, Livinghouse[48] and McGrane synthesised (+)-preussin **4** in 19% overall yield over 10 steps *via* an imidotitanium-alkyne [2+2] cycloaddition (Figure 4.34). The synthesis commenced with the addition of a 1:1 mixture of *i*-$Bu_2AlH$ and *i*-$Bu_3Al$ to methyl *N*-(diphenylmethylene)-L-phenylalaninate **552** to give a separable 3.2:1 mixture of isomers **553**. Next **553a** was O-benzylated and the imino ether produced hydrolysed to afford **554**. Reaction with $CpTi(CH_3)_2Cl$ followed by treatment with octanoyl cyanide *in situ*, afforded an α,β-unsaturated nitrile **555**. *N*-methylation of **555** followed by reduction gave pyrrolidine **556** and subsequent reduction of the olefin using Mg in methanol gave a mixture of pyrrolidines **557**. Finally, reductive cleavage of the cyano group, reductive O-benzylation and hydrogenation of the resultant crude product gave the natural product **4** (Figure 4.34).

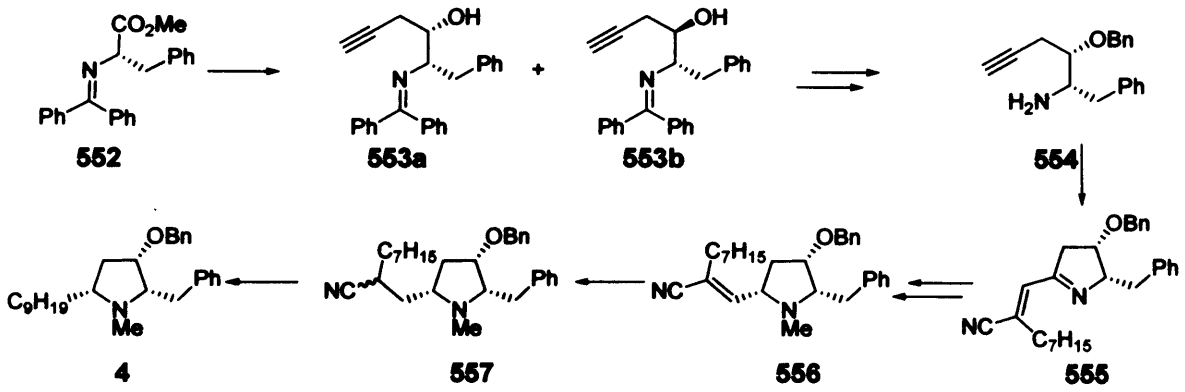



**Figure 4.34**

A year later, Overman[49] and Deng published a synthesis of (+)-preussin **4** again from a (*S*)-phenylalanine derivative **558**. Overall the natural product was obtained in 11% yield in 6 steps from the readily available ketone **559**. *N*-Cbz-(S)-Phe **558** was converted into ketone **559** *via* a Weinreb amide intermediate. Treatment of the ketone with vinylmagneisum bromide gave 6:1 separable mixture of diastereoisomers. Hydrolysis of the *syn* diastereoisomer afforded the primary alcohol **560** which, following treatment with decanal using an Aza-Cope-Mannich reaction[50] gave oxazolidine **561**. When this was treated with CSA in $CF_3CH_2OH$, the all *cis*-pyrrolidine **562** was obtained, which was then treated with ethyl chloroformate to give the corresponding carbamate. To complete the synthesis a Baeyer-Villiger oxidation[51] was utilised to give **563** which when reduced gave the natural product **4** (Figure 4.35).

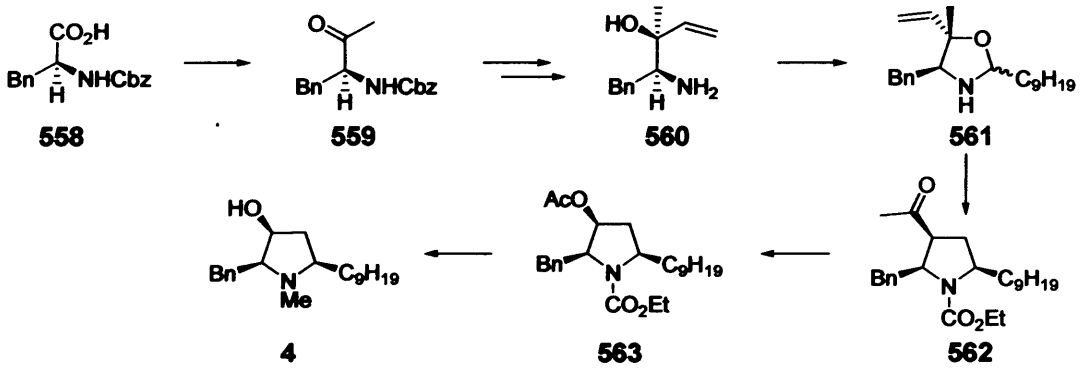



**Figure 4.35**

In the same year, Hecht[4] and Overhand synthesised (+)-preussin **4** from *t*-Boc (*S*)-phenylalanine **564** in 5 steps, the key step being a Hg(II) mediated 5-*endo* dig ring closure of the ynone **565** to form an 8:1 mixture of pyrrolidinones **566** in excellent yield. The

synthesis commence with conversion of *t*-Boc (*S*)-phenylalanine **564** into the corresponding Weinreb amide using DCC and *N,O*-dimethylhydroxylamine. The Weinreb amide was then reacted with undecynyllithium to afford the ynone **565** which upon exposure to mercury acetate underwent a 5-*endo*-dig cyclisation to give an 8:1 mixture of pyrrolidines **566** (a:b). This mixture was reduced using sodium borohydride, to afford the pyrrolidinol as the sole product which was subsequently upon exposure to lithium aluminium hydride gave the natural product **4** (Figure 4.36).

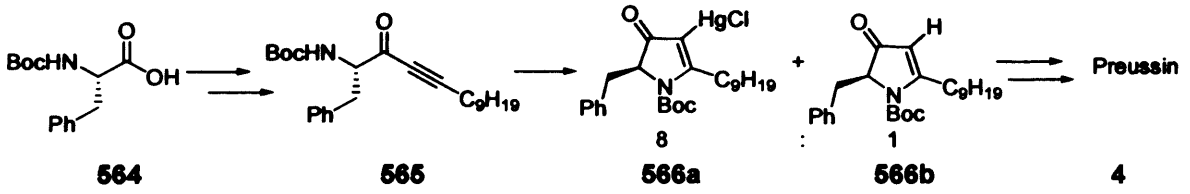
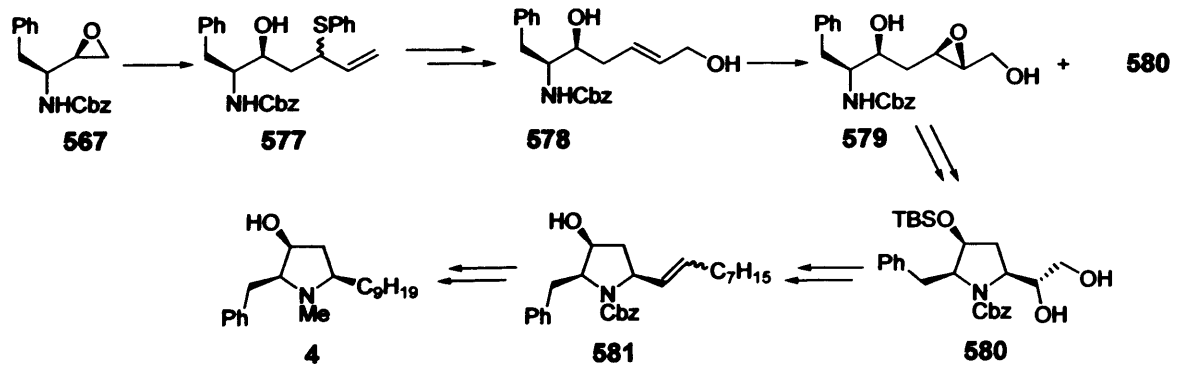



**Figure 4.36**

Schaumann[50] and Beier reported the synthesis of (+)-preussin **4** in 28% overall yield in 12 steps from epoxide **567**, in 1997. In their approach epoxide **567** derived from (*S*)-phenylalanine was ring opened to afford a 1:1 mixture of diastereoisomers **577**. Following TBS protection of the alcohol and oxidation, the corresponding *S*-oxide was obtained. This was subjected to a [2,3]-sigmatropic rearrangement to generate **578** which was subjected to a Sharpless epoxidation reaction gave a mixture of the epoxide **579** and pyrrolidine **580**. To afford additional pyrrolidine **580**, the epoxide **579** was subjected to hydrogenolysis and the product was immediately re-protected. Next, the diol unit was cleaved using periodate to give the aldehyde which was the used in a Wittig olefination. The silyl group was deprotected and the following lithium aluminium hydride reduction, pyrrolidine **581** was obtained. Finally, hydrogenation of **581** gave **4** (Figure 4.37).




**Scheme 4.37**

In 1998, Veeresa[51] and Datta reported a 10 step synthesis of (+)-preussin **4** in 9% overall yield from L-Phenylalanine **547b**. The synthetic sequence commenced with the reduction of L-phenylalanine **547b** with lithium aluminium hydride followed by a Swern oxidation to give the corresponding aldehyde which when reacted *in situ* with allylmagnesium bromide afforded the homoallylic alcohol **582** as a 6:1 mixture of diastereoisomers (*syn*:*anti*). The separated *syn* diastereoisomer **582a** was converted into the oxazolidine derivative and following oxidative cleavage, the aldehyde **583** was obtained. Reaction of the aldehyde **583b** with the Grignard reagent derived from 1-bromononane gave an inseparable 7:3 mixture of isomers which were oxidised to the ketone **584**. The stereoselective reduction of **584** using L-Selectride gave a primary alcohol moiety that was mesylated to give a separable 9:1 mixture of diastereoisomers **585**. Finally, deprotection of the acetonide group generated the pyrrolidine derivative **586** which was readily converted into the natural product **4** (Figure 4.38).

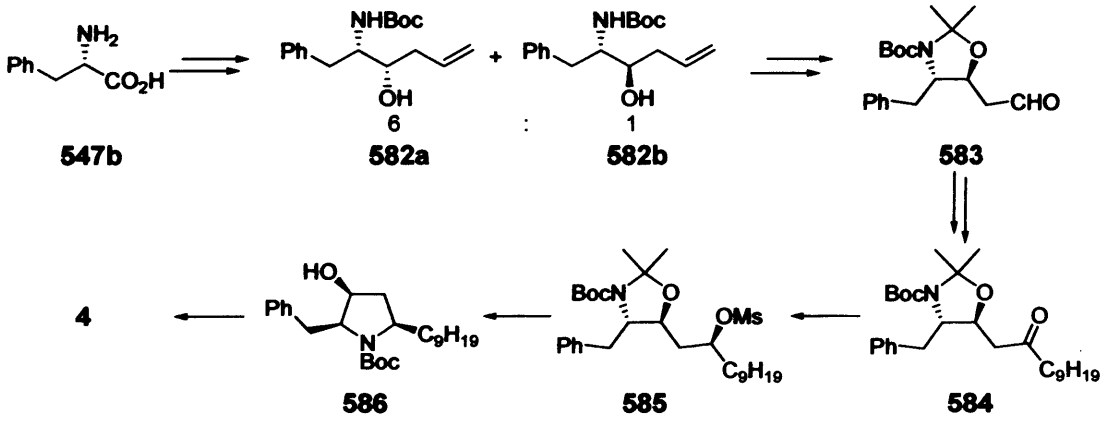



**Figure 4.38**

In the same year, the De Armas group[52] reported the diastereoselective formal synthesis of (+)-preussin **4** in 13 steps, (9% overall yield) from commercially available 1,2:3,5-di-O-isopropylidene-α-D-mannofuranose. The sequence commenced with the ring opening of epoxide **587** with PhMgCl to give a secondary alcohol that was converted into the corresponding trifluoromethanesulphonate ester, prior to treatment with sodium azide. Following reduction of the azide moiety and benzyloxy-carbonylation, the carbamate **588** was obtained. The anomeric protecting group was removed and following ionic cyclisation promoted by $PhIO/I_2$, **589** was isolated. Next, the bicyclic ketal **589** was reacted with allyltrimethylsilane in the presence of $BF_3OEt_2$ to give a 95:5 (*anti*:*syn*) ratio of

diastereoisomers of **590**. Finally, oxidative cleavage of the alkene followed by a Wittig reaction and hydrogenation gave **4** (Scheme 4.39).

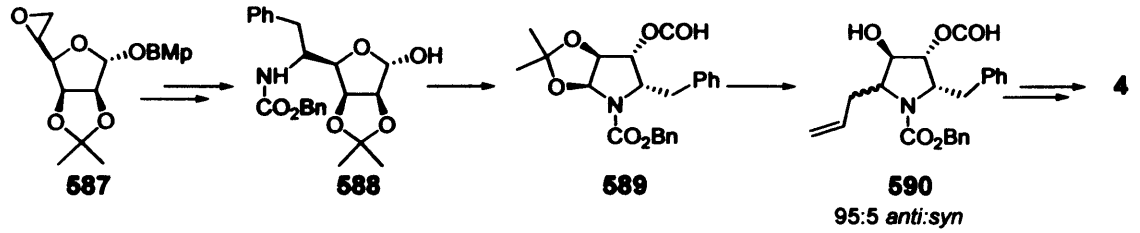



**Figure 4.39**

Finally, in 2000[53], Lee and co-workers reported an enantioselective synthesis of (+)-preussin **4**, in 13% overall yield, over 10 steps (Scheme 4.10). The synthesis commenced with the Dess-Martin oxidation of **591** followed by the addition of vinylmagnesium bromide to the resultant aldehyde to give a 1.1:1 (*syn:anti*) mixture of diastereoisomers. Following acetate protection of the hydroxyl group and a standard oxazoline ring forming reaction, the *trans*-oxazoline **592** was obtained. The alkene was then oxidised to the alcohol with 9-BBN which was then further oxidised to the carboxylic acid using ruthenium chloride. Conversion to the Weinreb amide followed by treatment with nonylmagnesium bromide gave the ketone **593**. Hydrogenolysis under 70 psi pressure led to hydrogenolysis of the oxazolidine in addition to cyclisation to give pyrrolidine **594**, which following methylation afforded (+)-preussin **4** (Figure 4.40).

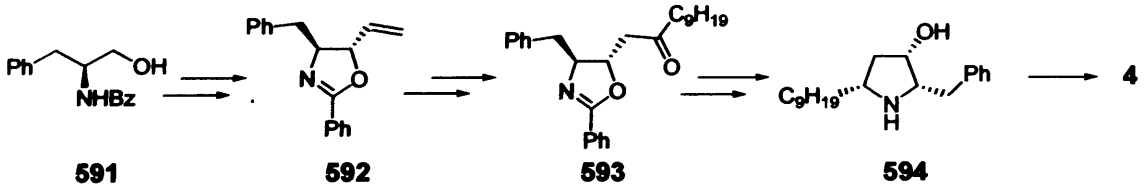
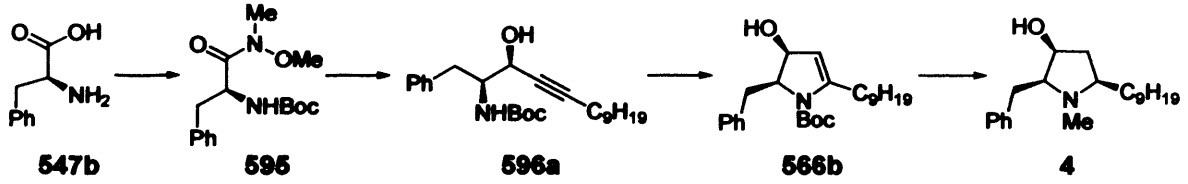



**Figure 4.40**

## 4.44. Results and Discussion: Silver Nitrate Cyclisations

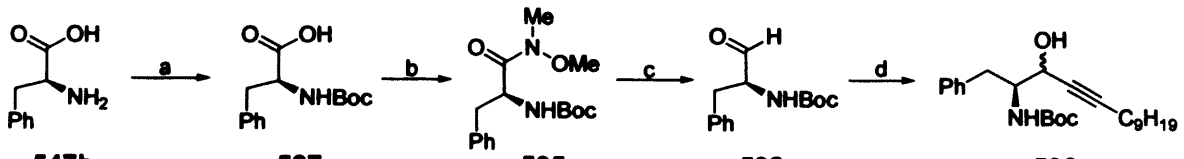
The stability of the dihydropyrroles, from the silver induced cyclisation of the aldol products, suggested that it may be possible to synthesise (+)-preussin **4** from (*S*)-phenylalanine **547b**, in a route analogous to that of Hecht[4] and Overhand (Figure 4.36), utilising the novel silver nitrate-cyclisation as the key step (Figure 4.41).




**547b** **595** **596a** **566b** **4**

**Figure 4.41**

The sequence commenced with commercially available (*S*)-phenylalanine **547b**, which was treated with Boc anhydride and triethylamine in an biphasic mixture of 1M sodium hydroxide solution and 1,4-dioxane to afford the carbamate **597** as a rotameric mixture, in 92% yield, as apparent from the *t*-butyl singlets at 1.15 and 1.35 ppm and the new carbonyl signal at $\delta_C$ 155.7 ppm (Scheme 4.33; a). The crude product was then reacted with *N,O*-dimethylhydroxylamine using DCC as the coupling agent. Following chromatography, the Weinreb amide **595** was isolated in a disappointing 33% yield, together with some starting material (Scheme 4.33; b). Formation of the Weinreb amide **595** was confirmed by the new methyl singlets at 3.10 and 3.60 ppm and the observed optical rotation (+ 22.7 [$CH_2Cl_2$, c 10.75]), was comparable with the literature[4] data (+ 28.7 [$CH_2Cl_2$, c 1.0]).. Next, an ice-cold solution of the Weinreb amide **595** in diethyl ether was treated with lithium aluminium hydride for 10 minutes, to afford the desired aldehyde **598**, in 68% yield. The successful reaction was confirmed by the presence of a new aldehyde singlet at 9.50 ppm and a melting point of 86-87°C, which was consistent with the literature[54] value (m.p. 86-88°C) (Scheme 4.32; c).




**547b** **597** **595** **598** **596**

**Scheme 4.33.** *Reagents:* a) $Boc_2O$, 1,4-dioxane, NaOH, 4.25 h, 92% **597**; b) DCC, *N,O*-dimethylhydroxylamine, $CH_2Cl_2$, 33% **595**; c) LAH, 10 mins, $Et_2O$, 68%; d) 1-undecynyllithium, $Et_2O$, $ZnBr_2$, 0%.

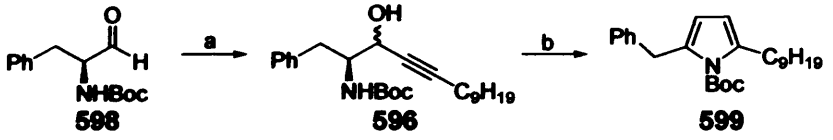
The next stage was to alkylate the aldehyde **598**, to afford the *syn* diastereoisomer **596a**, ready for the key cyclisation. In the synthesis of L-*threo* Sphingosine **203b** Herold[55] had alkylated Garner's aldehyde **201** with 1-pentadecynyllithium, in the presence of anhydrous zinc dibromide, to afford predominately the *syn* diastereoisomer **200b** (Scheme 2.29, Chapter 2). Hence, the aldehyde **598** was treated with 1-undecynyllithium in diethyl ether in the presence of anhydrous zinc bromide, but disappointingly, only starting material was recovered (Scheme 4.33; d). It is possible that the zinc dibromide had degraded over time, explaining the lack of reaction. With the expense of *N,O*-dimethylhydrochloride and low yield obtained in the Weinreb amide formation (Scheme 4.33; b), it was more practical and financially viable to use the commercially available aldehyde **598**, to test if the proposed chemistry would successfully afford the desired dihydropyrrole **566b** (Figure 4.41).

With the failure of the alkylation under chelation control, it was decided to alkylate the aldehyde **598** directly with a large excess of the 1-undecynyllithium and then separate the resultant diastereoisomers. Treatment of the aldehyde **598** with 1-undecynyllithium in tetrahydrofuran, afforded a 1.4:1 mixture of diastereoisomers **596**, in 61% yield as confirmed by the loss of the aldehyde singlet, and the appearance of new CH protons in the range 3.85-4.30 ppm. In addition, a molecular ion of 402 ($M^+$ + H) was observed by ApCI which was consistent with alkylation. As previously experienced, the presence of the Boc protecting group meant that the relevant resonances in the NMR spectrum were unresolved and hence determination of the stereochemistry of the major isomer could not be achieved. At a later stage this selectivity would be addressed, but first it was important to establish if the key silver catalysed cyclisation was successful.

The previous study had involved an adjacent ester moiety together with a tosyl nitrogen-protecting group (Scheme 4.13), so would a change in the electronic properties of the

protecting group affect the isolation of the dihydropyrrole **566b**? It was believed that the absence of an ester functionality would be advantageous in that the β-elimination would occur to a lesser extent. Also with the difficulties foreseen in tosyl group removal, alternative protecting groups were essential and the advantage of the *N*-Boc group was that it could be easily converted into a methyl upon treatment with lithium aluminium hydride in refluxing tetrahydrofuran.

The precursor **596** was treated with silver nitrate (0.2 equivalents) for 2 h to give the pyrrole **599** in quantitative yield, as apparent from the observed molecular ion of 384 ($M^+$ + H), which was consistent with the proposed structure (Scheme 4.44; b). In addition, new characteristic olefin doublets at 5.60 and 5.75 ppm were evident and a shift in the C*H*-Ph proton from 2.90 to 4.05 ppm was apparent as well as change in the multiplicity of the C*H*-Ph proton from a multiplet to singlet, further clarifying that the product was indeed the 2,5-disubstituted pyrrole **599**.




**Scheme 4.34.** *Reagents:* a) 1-undecynyllithium, THF, -20°C, 2 h, 61%; b) 0.1 eq 10% w/w $AgNO_3/SiO_2$, 2 h, 100%.

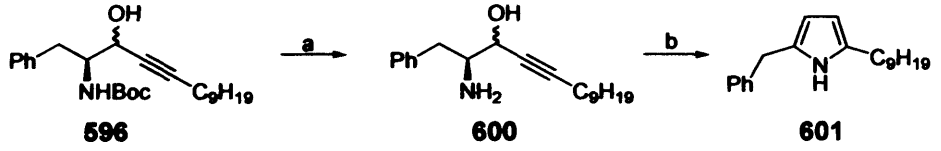
It was originally believed that this rapid elimination was due to the *N*-Boc protecting group, and so alternative nitrogen protecting groups were tested. This sequence was carried out prior to the codonopsinine methodology (Section 4.33) and so the findings previously reported regarding the nitrogen protecting group were not applied here.

### 4.45. The Influence of Protecting Group on the Silver Cyclisation.

A plethora of nitrogen protecting groups were contemplated, but was a *N*- protecting group necessary? The absence of a protecting group would be advantageous in terms of atom efficiency. Accordingly, a mixture of diastereoisomers of the amino alcohol **596** was treated with a 20% solution of trifluoroacetic acid in dichloromethane, to afford the amine in 86% yield, as deduced from the loss of the *t*-butyl singlet in the $^1$H NMR spectrum, and a molecular ion of 302 ($M^+$ + H), in agreement with deprotection. In studies towards the

synthesis of (-)-codonopsinine **3b**, when the *N*-Boc amino alcohol **469** was deprotected using trifluoroacetic acid in dichloromethane, cyclisation had occurred *in situ*, to generate the pyrrole **474** (Scheme 4.23). The results found here, suggested that this result was a special case, perhaps due to the presence of the ester moiety.

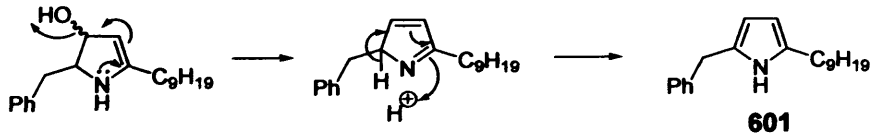
The free amine **600** was then treated immediately with 0.2 equivalents of silver nitrate on silica gel, and cyclisation occurred (Scheme 4.35; b). After filtration through a plug of silica, the pyrrole **601** was obtained in 43% yield, as apparent from an absorbance at 3380cm$^{-1}$ in the infrared spectrum corresponding to the NH and the change in multiplicity and shift in the C$H_2$-Ph signal. Also new olefin signals at 5.60 and 5.70 ppm were observed and further clarification was obtained from LRMS where a molecular ion of 284 ($M^+$ + H) consistent with cyclisation and elimination was witnessed.




**596** **600** **601**

**Scheme 4.35a.** *Reagents:* a) TFA, $CH_2Cl_2$, 16 h, 86%; b) 0.2 eq $AgNO_3/SiO_2$, $CH_2Cl_2$, 2 h, 43%.

With the presence of a free amine, the lone pair is much more available and so it is plausible that with the desire to establish an aromatic system elimination takes place (Figure 4.42).

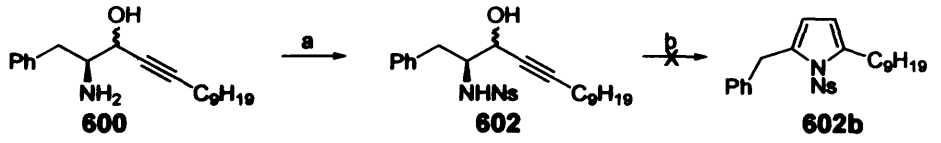



**601**

**Figure 4.42**

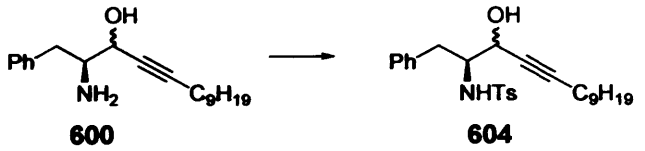
With the problems associated with tosyl removal, the nosyl protecting group was tested which can be removed with the use of mercaptoacetic acid in *N*, *N*-dimethylformamide. Treatment of the amine **600** with *p*-nitrobenzenesulfonyl chloride, DMAP and dichloromethane, disappointingly furnished the nosylate **602** in only 24% yield, mirroring the problems previously experienced with tosylation of an amine in the presence of a

hydroxy functionality (Scheme 2.24, Chapter 2). The major isomer was characterised by new doublets at 7.60 and 8.05 ppm, which a typical *ortho* coupling of 8.8 Hz. Despite the yield, sufficient material was obtained to carry out the crucial cyclisation. However, on treatment of the precursor with 10% silver nitrate on silica gel, the NMR spectrum of the crude product revealed a mixture of products (Scheme 4.36), hence it was decided to test the previously successful tosyl group.




**Scheme 4.36.** *Reagents:* a) NsCl, DMAP, $CH_2Cl_2$, 16 h, 24%; b) $AgNO_3$, $CH_2Cl_2$, 0%.

A mixture of the diastereoisomers of the amine **600** was treated with *p*-tosyl chloride, triethylamine and DMAP in dichloromethane. Following chromatography of the crude material, the sulfonamide **604** was obtained as a 4:1.5 mixture of diastereoisomers, in 62% yield, as deduced from the molecular ion of 302 ($M^+$ + H), consistent with tosylation and the appearance of new aryl methyl singlets at 2.25 ppm (Scheme 4.37). Due to the overlapping multiplets in the proton NMR spectrum, differentiation between the *syn* and *anti* isomers could not be achieved.




**Scheme 4.37.** *Reagents:* a) *p*-TsCl, DMAP, $CH_2Cl_2$, 16 h, 62%.

When this sulfonamide **604** was treated with 0.5 equivalents of 10% silver nitrate on silica for 2 h, the NMR spectrum of the crude product revealed that interestingly, one diastereoisomer appeared to have cyclised faster than the other isomer. Also, the cyclisation product **601** was deduced to be the deprotected pyrrole **601**, on comparison with a genuine sample (Scheme 4.35). The remaining resonances in the spectrum suggested a single diastereoisomer of the starting material, as deduced from the two distinct double doublets at 2.60 and 2.80 ppm. By considering Figure 4.43, it can be seen that in the case of the *anti* diastereoisomer **604a**, the two largest groups are positioned equatorially in the transition state while for the corresponding *syn* diastereoisomer, one of

these groups is in the unfavoured axial position. This suggests that since the diequatorial transition state is more favourable, this will lead to a faster rate of reaction (Figure 4.43).

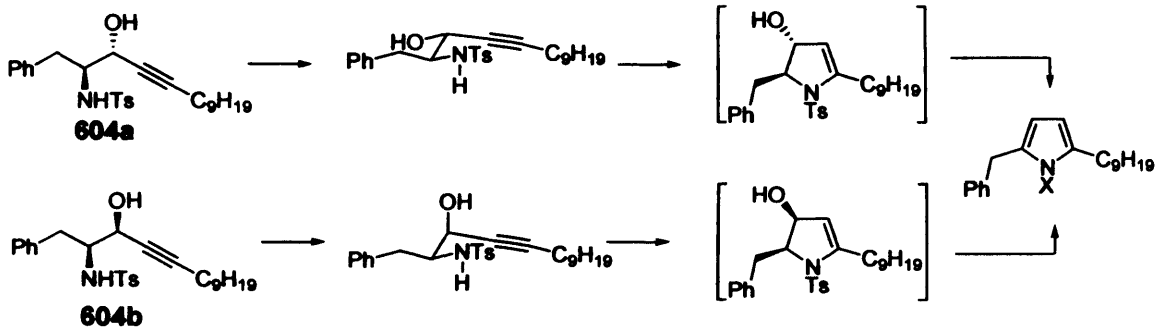



**Figure 4.43**

Hence, this suggests that the *anti* diastereoisomer **604a** had cyclised faster than the *syn* diastereoisomer **604b**. Accordingly, in a bid to encourage cyclisation of the *syn* diastereoisomer **604b**, the crude reaction mixture was treated with a further 0.3 equivalents of 10% silver nitrate on silica gel for 2 h, but no further reaction was observed. At this stage chromatography was conducted to afford the deprotected pyrrole **601**, in 37% yield, together with the recovered *syn* diastereoisomer **604b**. In order to synthesise (+)-preussin **4**, it was fundamental that the *syn* diastereoisomer **604b** cyclised and that the resulting dihydropyrrole **566b** was isolatable. Accordingly, the recovered *syn* diastereoisomer **604b** was treated with the same equivalents of the silver reagent for a further 16 h where partial cyclisation (15%) and elimination was observed, but with the protecting group intact, as apparent from the characteristic pyrrole doublets at 5.60 and 5.80 ppm and the retention of the aryl methyl singlet at 2.35 ppm, corresponding to the tosyl group. With the failure of the cyclisation, optimisation of the tosylation was not conducted.

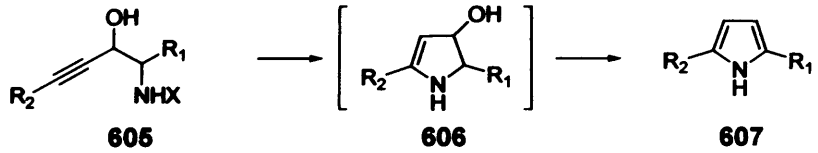
## 4.46. Conclusion

Despite the use of a variety of nitrogen protecting groups, the desired *syn* intermediate dihydropyrrole was not isolated after the silver-catalysted cyclisation, elimination always occurred to afford the corresponding pyrroles, even with the previously successful tosyl group. Interestingly, with this tosyl protecting group the rate of cyclisation of the two diastereoisomers **604** was different, but cyclisation of the required *syn* diastereoisomer **604b** was very slow and could not be stopped at the dihydropyrrole stage (Figure 4.42). In the absence of an ester group, it was believed that the elimination previously experienced with the dihydropyrroles from the cyclisation of the aldol adducts (Scheme 4.13), would occur to a lesser extent. So the fact that in the absence of the ester group, elimination occurred very rapidly, was startling and consequently the promising silver catalysed cyclisation could not be used to synthesise the core pyrrolidine ring of (+) preussin **4**. Ultimately, a new approach is required. However, these findings are useful for pyrrole synthesis since elimination occurs rapidly, obviating the need for the extra elimination step.

# 4.50. Miscellaneous Silver Cyclisations

## 4.51. Introduction

Various amino alcohol derivatives were synthesised in the quest for cyclisation precursors. A thorough study was not conducted but any available amino alcohol derivative were treated with 10% silver nitrate on silica gel, to hopefully afford dihydropyrroles **606** or pyrroles **607**, so as to determine the scope and limitations of these cyclisations, as the basis for future work (Figure 4.44). In the studies towards the synthesis of (-)-codonopsinine **3b** and (+)-preussin **4**, it was discovered that the nitrogen protecting group was fundamental to the success of the reaction and the presence of an ester in the 2-position allowed the dihydropyrrole intermediate to be isolated. The lack of this ester group, lead to rapid elimination *in situ* to afford the corresponding pyrroles **607**.

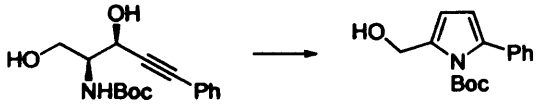



**605** **606** **607**

**Figure 4.44**

## 4.52. Results and Discussion

The initial substrate tested was derived from the condensation of Garner's aldehyde **201** with lithio phenylacetylide (Scheme 2.30, Chapter 2). This amino alcohol **204** bore a primary alcohol side chain in place of the ester moiety and so, there was a possibility that on treatment with silver nitrate on silica gel, a 5-*exo*-dig cyclisation could occur. When this substrate **204** was treated with 0.2 equivalents of 10% silver nitrate on silica gel for 1 h, delightfully, the pyrrole **608** was obtained in quantitative yield, with no trace of the product from a 5-*exo*-dig cyclisation. This was verified by the loss of the alkyne signals and also the new but familiar olefin doublets at $\delta_H$ 6.05 and 6.15 ppm.




**Scheme 4.38.** *Reagents:* 0.2 eq $AgNO_3$, $CH_2Cl_2$, 1 h, 100%.

In a later route to the required cyclisation precursors, substrates were synthesised that bore a methyl side chain in place of the methyl ester from the alkylation of aldehyde **195** with either lithiophenylacetylide or 1-hexynyllithium (Scheme 2.52 and 2.55, Chapter 2). Bearing a Boc protecting group, it was assumed from the previous research that these precursors **258** and **262** would afford pyrroles. When this phenyl derivative **258** was treated with 10% silver nitrate on silica gel, the cyclisation was expectedly very slow and proceeded to completion after 64 h. Following purification using chromatography, the pyrrole **609** was isolated in 48% yield, as deduced from the molecular ion of 258 ($M^+ + H$), consistent with cyclisation and dehydration of the intermediate together with two new olefin signals at $\delta_C$ 110.3 and 112.2 ppm (Scheme 4.39; a).

The corresponding butyl derivative **262** also cyclised slowly and after 64 h, the pyrrole **610** was isolated as the only isolated product (Scheme 4.39; b). Confirmation of this structure was again obtained from the loss of the alkyne signals in addition to the appearance of new olefin resonances at 109.0 and 110.1 ppm in the $^{13}C$ NMR spectrum. However, this time, mass spectrometry failed to produce a molecular ion that corresponded to this pyrrole **610**, but sufficient evidence for this structure had nevertheless been obtained.


**Scheme 4.39.** *Reagents:* a) 0.5 eq $AgNO_3$, $CH_2Cl_2$, 64 h, 48%; b) 0.5 eq $AgNO_3$, $CH_2Cl_2$, 64 h, 50%.

So, from these two reactions, whereas cyclisation with a substrate bearing a methyl ester proceeded on average after two hours, if this ester is substituted with a methyl side chain, the cyclisation takes considerably longer and the yields obtained are lower (Scheme 4.39).

## 4.23. Summary of Silver Cyclisations

To summarise, all the substrates exposed to 10% silver nitrate on silica gel are illustrated in Table 4.16

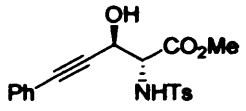
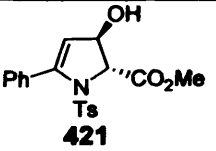
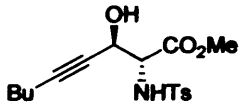
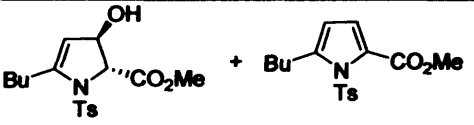
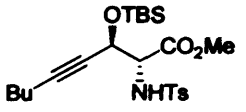
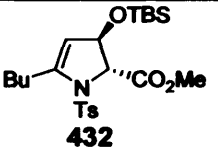
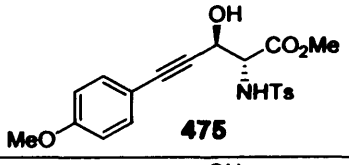
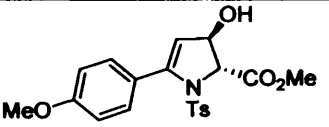
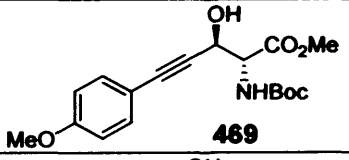
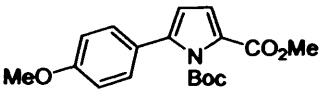
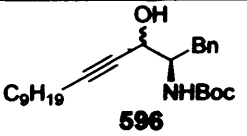
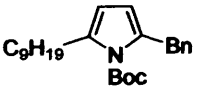
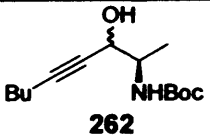
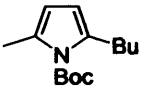
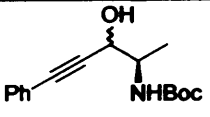
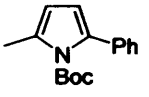
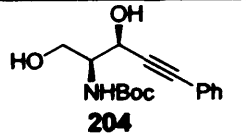
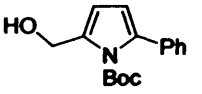
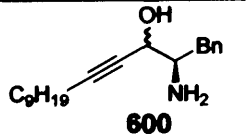
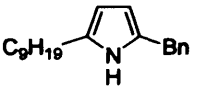
| | Precursor | Cyclisation conditions | Product(s) | Yield (%) |
|---|---|---|---|---|
| 1 |  **146a** | 0.5 eq $AgNO_3$, $CH_2Cl_2$, 1 h |  **421** | 93 |
| 2 |  **144a** | 0.5 eq $AgNO_3$, $CH_2Cl_2$, 1.5 h |  **429** **430** | 79 (**429**) and 16 (**430**) |
| 3 |  **431** | 0.5 eq $AgNO_3$, $CH_2Cl_2$, 1.5 h |  **432** | 43 |
| 4 |  **475** | 0.2 eq $AgNO_3$, $CH_2Cl_2$, 1.5 h |  **476** | 98 |
| 5 |  **469** | 0.5 eq $AgNO_3$, $CH_2Cl_2$, 1.5 h |  **470** | 92 |
| 6 |  **596** | 0.1 eq $AgNO_3$, $CH_2Cl_2$, 2 h |  **599** | 100 |
| 7 |  **262** | 0.5 eq $AgNO_3$, $CH_2Cl_2$, 64 h |  **610** | 50 |
| 8 |  **258** | 0.5 eq $AgNO_3$, $CH_2Cl_2$, 64 h |  **609** | 48 |
| 9 |  **204** | 0.2 eq $AgNO_3$, $CH_2Cl_2$, 1 h |  **608** | 100 |
| 10 |  **600** | 0.2 eq $AgNO_3$, $CH_2Cl_2$, 2 h |  **601** | 43 |

**Table 4.16**

## 4.54. Conclusion

Interestingly, the presence of an ester group adjacent to the nitrogen is essential for successful isolation of the dihydropyrroles, provided that the nitrogen-protecting group is a tosyl group. In the absence of the ester, regardless of the nitrogen-protecting group, the product of the silver-catalysed cyclisation was the pyrrole. Thus, despite the excellent yields obtained, the restrictions regarding the nitrogen protection group mean that the silver-catalysed cyclisation is not a synthetically viable means of synthesising pyrrolidines, due to the problems associated with the removal of tosyl protecting groups. However, the present research has shown that when a Boc protecting group is implemented, the silver catalysed cyclisation provides an excellent route to 2,5-pyrroles since it obviates the need for an additional elimination step in the synthetic sequence. However, it can be seen from Table 4.16 that the length of the side-chain adjacent to the NHBoc moiety influences the timescale of the reaction considerably, with longer chains leading to a rapid reaction.

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# Chapter Five

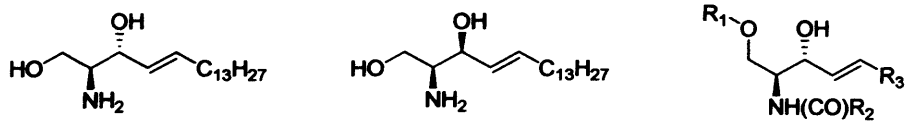
# Studies Towards the Total Diastereoselective Synthesis of Sphingosine

## 5.10. Introduction

## 5.11. Discovery and Structure Elucidation

In 1882, Thudichum isolated sphingosine **202a** as a waxy substance from the hydrolysis of a lipid fraction of brain tissue.[1] In the early nineteen hundreds, various investigators[2-4] identified sphingosine **202a** as a dihydroxyaminooctadecene, but it was not until 1947 that the position of the three functional groups was proven by Carter and co-workers.[5-6] Several researchers[7-11] confirmed the (*2S,3R*) relationship between carbons 2 and 3, while Mislow[12], Marinetti and Stotz[13] verified that the geometry of the double bond to be *trans*. Thus, the structure of sphingosine was deduced to be *trans*-D-*erythro*-1,3-dihydroxy-2-amino-4-octadecene **202a** (Figure 5.10).

Sphingosines are a group of related long-chain aliphatic 2-amino 1,3-diols. The most abundant of which in animal glycosphingolipids, ceramides or glycosides of *N*-acylsphingosines is (*2S,3R*)-*erythro*-sphingosine **202a** (Figure 5.10).[14]




**202a** D-erythro-sphingosine

**202b** L-threo-sphingosine

**611**

**Figure 5.10**

## 5.12. Biological Activity

Glycosphingolipids consist of carbohydrate and ceramide structural units and are found in all the cell membranes of animal and plant cells. The ceramide unit comprises of a sphingoid base and an amide-linked fatty acyl chain such as stearoyl or palmitoyl.[15] Subsequently, due to the structural variation of sphingosines, carbohydrates and the *N*-acyl moiety of fatty acids there is a vast number of chemically distinct glycosphingolipids[14].

In these cell membranes, glycosphingolipids regulate cellular recognition, development and growth, in addition to acting as identifying markers. They are believed to act by anchoring the hydrophobic ceramide constituent in the plasma membrane, thereby exposing the hydrophilic carbohydrate functionality to the surrounding area, which specifies the proposed biological function.[15] Sphingolipids are involved in virtually all aspects of cell regulation and consequently, defects in sphingolipid metabolism leads to numerous inherited human diseases.[16]

The numerous biological roles of glycosphingolipids include: -

- HIV binding to galactosyl ceramide receptor sides in cells devoid of the principal CD4 cellular receptor;
- A link between specific sphingolipids and malignant tumours, allows them to be used as 'biological markers' for the possible early detection of cancer[15];
- Transfer of information between developing cells in vertebrates[14];
- Various cell growth processes including, differentiation, neuronal repair and adhesion[15];
- Reversible inhibition of protein kinase C *via* their breakdown products, sphingosine, sphinganine and lysosphingolipids and since protein kinase C mediates cell responses for hormones, growth factor and tumour promoters, its reversible inhibition is significant.

It is due to these biological properties, that there is an ongoing interest in this field of research[14].

## 5.13. Synthetic Approaches

There are a large number of known sphingolipids **611** where $R^1$, $R^2$ and $R^3$ can vary, and as such, isolation of homogeneous material is problematic (Figure 5.10).[16] In addition, the allylic alcohol moiety undergoes epimerisation readily and, consequently, synthetic approaches are an attractive alternative. In these synthetic strategies, it is important to control the geometry of the olefin, since the *trans* derivatives exhibit the desired activity.

Following the first synthesis of sphingosine in 1954 by Shapiro and Segal[17], there have been numerous approaches to this natural product.[18] In 1970, Reist[19] was the first chemist to synthesise sphingosine **202a** utilising a carbohydrate building block. Sphingosine synthesis from chiral sources of this type has become commonplace for both the natural *erythro* and *threo* isomer and, later in 1973, Newman[20] became the first to synthesise the natural isomer **202a** from L-serine. Since then, there have been numerous approaches to sphingosines from L-serine, in particular, Polt's[21] approach afforded L-*threo*-sphingosine **202b** in five steps in an excellent 60% overall yield. However, there are numerous novel approaches to the natural isomer, for example in 1983, Vasella[22,23] synthesised sphingosine in 6 steps in an overall yield of 50%, by utilising a Katsuki-Sharpless asymmetric epoxidation reaction as the key step.

## 5.20. Results and Discussion

## 5.21. Initial Studies: Sphingosine Model

Much of the present research has utilised the tin(II) mediated aldol reaction[24] to afford the desired cyclisation precursors. These aldol adducts clearly resemble sphingosine **202a**, and as a side-line, research was conducted to ascertain if, following reduction of both the methyl ester and alkyne and then detosylation, this would provide a rapid route to the natural product (Figure 5.11). If these reductions could be conducted in one step this would overtly be advantageous. The retrosynthesis is shown in Figure 5.11.

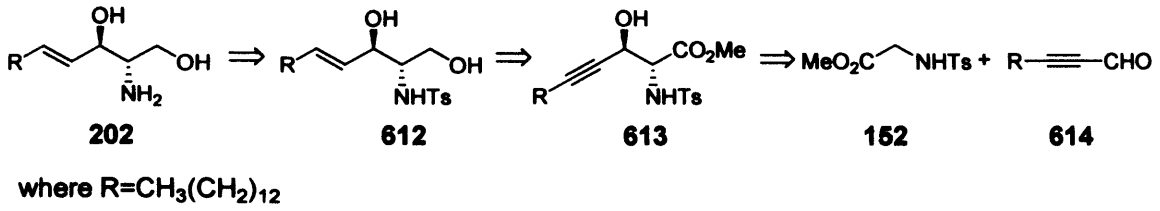
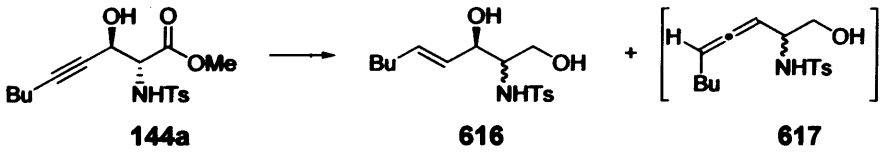



**Figure 5.11**

With the expense of 1-Pentadecyne **615**, it was more viable to conduct experiments to determine the optimum reduction conditions using a readily available substrate **144a** from the condensation of the enolate of methyl *N*-tosyl glycinate with hept-2ynal **115** (Scheme 2.10; a, Chapter 2).

## 5.22. Red-Al Reduction

In Herold's[25] synthesis of sphingosine, Red-Al was used to reduce the alkyne moiety and hence, this was an obvious first choice of reagent (Scheme 2.29, Chapter 2). Treatment with Red-Al afforded a 1:1 mixture of diastereoisomers of the (*E*)-amino alcohol **616** in 85% yield, together with a trace of what was assumed to be an allene **617** on comparisons with products from later experiments (Scheme 5.13). Reductions of both the ester and alkyne moieties were evident from the loss of the methyl ester singlet and the appearance of four new olefin signals at $\delta_H$ 5.0-6.0 ppm. Therefore, due to the observed epimerisation, the reductions could not be conducted in "one pot" as desired.




**Scheme 5.11**. *Reagents:* Red-Al, $Et_2O$, 24 h, 85%.

Adversely, the acidic nature of the proton adjacent to the carbonyl compound caused racemisation, hence in subsequent reactions, the ester was reduced, prior to the alkyne reduction, to eliminate this possibility. Again various reducing agents were employed, and to conserve pure substrate **144a**, the remaining test reactions were carried out on a mixture of the heptynal aldol product **144a** and methyl *N*-tosyl glycinate **152** (Scheme 2.10; a, Chapter 2).

## 5.23. DIBAL Reduction

Treatment of a 1.75:1 mixture of the heptynal aldol product **144a** and methyl *N*-tosyl glycinate **152** with 3 equivalents of DIBAL for 2 h at -78°C, only gave a minor trace of aldehyde, but after 16 h, all the methyl *N*-tosyl glycinate ester had been reduced, and the resulting alcohol subsequently removed *via* aqueous work-up. Next, a further 4 equivalents of DIBAL was added to the crude product and the mixture was refluxed for 4 h. Following chromatography, it was apparent that transesterification had occurred to form the *iso*-butyl ester **618** in 25% yield over 3 steps. This structure **618** was deduced from the loss of the methyl ester singlet at 3.50 ppm, in addition to the appearance of two new resonances representing the new $CH_aCH_b$ protons of the new ester group at 3.65 and 3.75 ppm and a doublet at 0.75 ppm, integrating for 6 protons corresponding to the two methyl groups of the *iso*-butyl ester (Scheme 5.12).

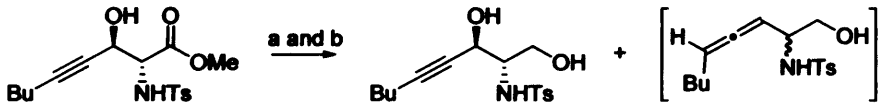

**Scheme 5.12.** *Reagents:* i) DIBAL, 2 h, -78°C, toluene; ii) DIBAL, 16 h, R.T.; iii) DIBAL, 4 h, reflux, 25%.

## 5.24. Lithium Aluminium Hydride (LAH) Reduction

Exposure of the 1.75:1 mixture of the heptynal aldol product **144a** and methyl *N*-tosyl glycinate **152** to LAH in THF for 3 h, followed by quenching with a 1 M sodium hydroxide solution and standard aqueous work-up, gave the amino diol **619** as the only isolated product in 30% yield. The NMR spectrum of the product **619** showed the absence of the methyl ester singlet at 3.50 ppm and the appearance of two new double doublets at 3.50 and 3.95 ppm, corresponding to new $CH_aCH_b$ protons of the new alkyl chain and APcI confirmed a molecular ion of 326 ($M^+$ + H), which was in agreement with the proposed structure (Scheme 5.13; a).

The reduction of the ester **144a** was repeated but after 3 h, an extra equivalent of LAH was added, to hopefully reduce the alkyne moeity, and the reaction mixture was stirred for a

further 16 h. Alternatively, the excess reagent was decomposed with ethyl acetate, followed by water and finally 10% sulphuric acid, in an attempt to optimise the yield. Following optimisation using NMR spectroscopy to determine product formation and chromatography of the crude product, the diol **619** was isolated in an improved 62% yield over 2 steps, in addition to 10% allene **617.** The presence of the allene **617** was deduced from the characteristic absorption at 1965 $cm^{-1}$ in the infrared spectrum, together with a resonance at 202.3 ppm, corresponding to the new carbon (C=*C*=C).

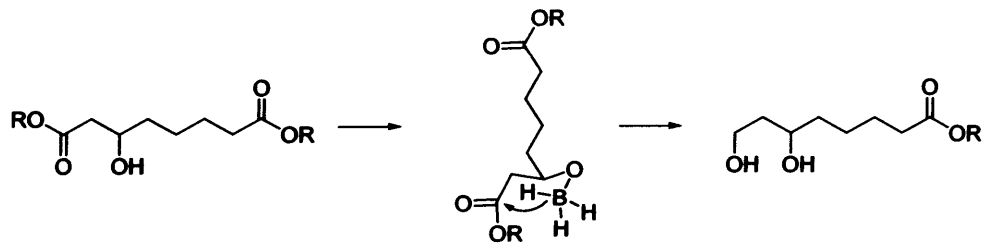



**144a** **619** **617**

**Scheme 5.13.** *Reagents:* a) LAH, THF, 3 h, 30%; b) LAH, THF, 62% **619** and 10% **617.**

## 5.25. Sodium Borohydride Reduction

Since complete reduction to the alcohol was very slow and variable, one final reagent sodium borohydride, was tested. Sodium borohydride being a mild reducing agent does not usually reduce less reactive carbonyl compounds like esters. However, when a hydroxy ester reacts with sodium borohydride, an alkoxy borohydride intermediate **621** is formed (Figure 5.12). The electron donation by this alkoxy group results in a nucleophilic activation of the B-H bond, which makes the alkoxy borohydride a stronger reducing agent than uncoordinated sodium borohydride. Hence sodium borohydride can be an effective reducing agent of hydroxy esters.[26]

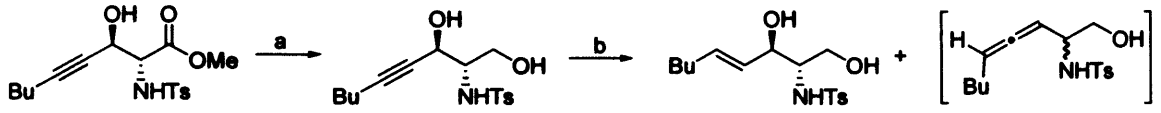



**620** **621** **622**

**Figure 5.12**

Treatment of a pure sample of the heptynal hydroxy-ester **144a** with sodium borohydride in ethanol, gave a single diastereoisomer of the diol **616a** in an excellent 74% yield

(Scheme 5.14; a), and therefore some optimum conditions for the reduction were established.




**144a** **619** **616a** **617**

**Scheme 5.14.** *Reagents:* a) $NaBH_4$, EtOH, 16 h, 74%; b) Red-Al, $Et_2O$, 24 h, 72% **616a** and 25% **617**.

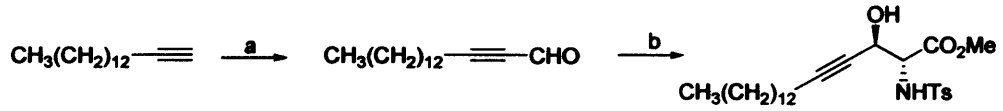
With the ester functionality reduced, the diol **619** was treated with a solution of Red-Al in diethyl ether, and in the absence of the ester, no epimerisation occurred to afford the (*E*)-olefin **616a** cleanly in 72% yield, together with 25% allene **617** (Scheme 5.14; b). The (*E*)-olefin **616a** displayed a molecular ion of 328 ($M^+$ + H), consistent with reduction of the alkyne and two new olefin resonances at 5.25 and 5.65 ppm with a typical *trans* coupling of 15.4 Hz.

## 5.26. Conclusion

The optimum strategy therefore involved two separate reductions, the first employing sodium borohydride to reduce the ester, followed by Red al to reduce the alkyne. With optimisation complete, the reductions were carried out on the target substrate **613** (Section 5.30).

## 5.30. Initial Route to sphingosine: Results and Discussion

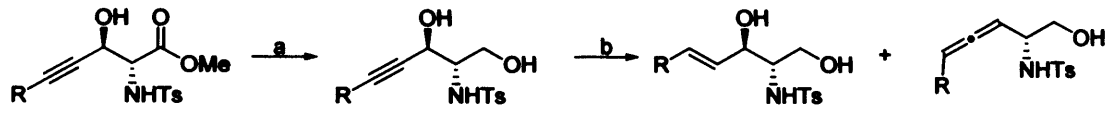
1-Pentadecyne **615** was formylated according to Journet's[27] method to furnish the acetylenic aldehyde **614** which was isolated in 99% yield, as apparent from the singlet at 9.10 ppm (Scheme 5.15; a). The aldehyde **614** was reacted with the enolate of methyl *N*-tosyl glycinate in the presence of tin(II) chloride to give the amino alcohol **613** in 47% yield, following chromatography and recrystallisation, as deduced by a molecular weight of 480 ($M^+$ +H) corresponding to the desired structure and the new C*H*OH and C*H*$CO_2$Me protons in the range $\delta_H$ 4.05-4.60 ppm.




**615** **614** **613**

**Scheme 5.15.** *Reagents:* a) n-BuLi, DMF, THF, -40°C, 99%; b) **152**, $SnCl_2$, LDA, THF, -78°C, 0.5 h, then add **614**, 47%.

Treatment of the aldol product **613** with sodium borohydride in ethanol furnished the desired alcohol **623**, as a single diastereoisomer in exemplary 77% yield as confirmed by the loss of the methyl ester singlet in the proton NMR spectrum in addition to the presence of new $CH_aCH_b$ protons at $\delta_H$ 3.50 and 3.95 ppm (Scheme 5.16; a). Finally, LRMS using APcI generated a molecular ion of 452 ($M^+$ + H), corresponding to the specified structure. Subsequent treatment of the diol **623** with a solution of Red-Al in toluene for 24 h afforded the (*E*)-amino alcohol **624**, together with a small quantity of allene **625** in 51% and 8% respectively (Scheme 5.16; b). The presence of the (*E*)-olefin **624** was evident by the new olefin signals at 5.25 and 5.60 ppm in the proton NMR spectrum with a *trans* coupling of 15.4 Hz. Formation of the allene **625** was deduced by the distinctive absorbance at 1965$cm^{-1}$ in the infrared spectrum in addition to the characteristic new quaternary carbon (C=*C*=C) at $\delta_C$ 202.6 ppm. It is possible that by lowering the temperature, the degree of allene formation would have been deduced, but no studies were conducted.



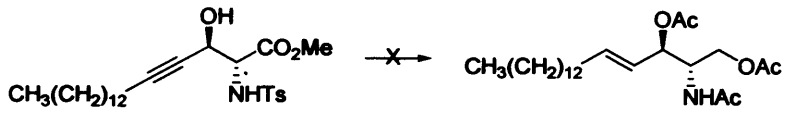

**613** **623** **624** **625**

Where R= $CH_3(CH_2)_{12}$-

**Scheme 5.16.** *Reagents:* a) $NaBH_4$, EtOH, 16 h, 77%; b) Red-Al, $Et_2O$, 24 h, 51%.

## 5.31. The Detosylation Predicament

Detosylation is a common problem for synthetic chemists, despite literature precedent.[28] The conditions employed are often harsh, commonly involving dissolving metal reductions. With the removal of the tosyl group, a water-soluble amino-diol **202a** would have to be isolated, and with the isolation problems previously experienced, could this be achieved? Since dissolving metal reductions are commonly used to remove tosyl groups, a "one pot" reaction using sodium in liquid ammonia was tested, to carry out the two reductions and detosylation. It was hoped that the speed of the reaction would lower the risk of epimerisation of the centre adjacent to the ester. No aqueous workup was conducted, due to the perceived problems with isolation. Instead, following the quenching of the reaction by ammonium chloride, the salt was immediately treated with acetic anhydride in pyridine (Scheme 5.17).

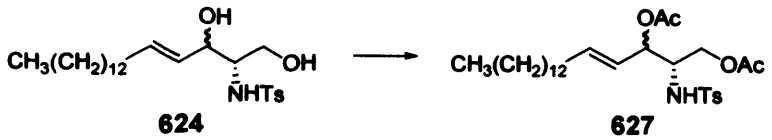



**613** **626**

**Scheme 5.17**

Regrettably, following the workup and purification by chromatography, the desired product **626** was not isolated in any of the fractions, thus alternative reagents were sought. Another commonly used procedure is the use of sodium naphthalenide in DME. An 8:1 (*anti*:*syn*) mixture of diastereoisomers of the (*E*)-amino diol **624** was therefore treated with freshly prepared sodium naphthalenide and the crude product was immediately exposed to excess acetic anhydride in pyridine for 88 h. Following chromatography, the diacetate **627** was isolated as an 8:1 mixture of diasteroisomers (*anti*:*syn*) in 57% yield, but with the tosyl group intact (Scheme 5.18). The major isomer was characterised by the new acetate

methyl singlets at 1.75 and 1.80 ppm and the two tosyl doublets at 7.25 and 7.65 ppm in the $^1$H NMR spectrum.




**Scheme 5.18.** *Reagents:* i) Sodium Naphthalenide, DME, -78°C; ii) $Ac_2O$, py, 88 h, 57%.

## 5.27. Conclusion

Unfortunately, despite the success of the aldol condensation and the reductions, the detosylation issue was still a problem, and was not successfully achieved. Obviously there was still reagents left to try, but instead it was decided to explore the possibility of different protection groups to obviate this hurdle.

## 5.40. Alternative Nitrogen Protecting Groups: Formal Synthesis of Sphingosine

## 5.41. Introduction

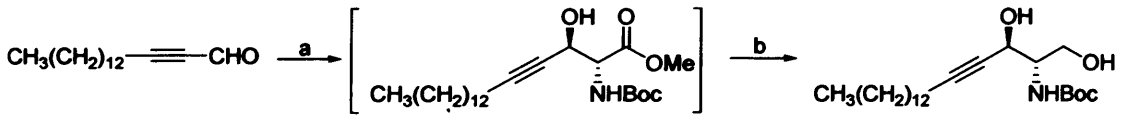
At this stage the possibility of alternative nitrogen protecting groups was explored. An obvious choice would have been the 4-nitro benzene sulfonyl group, since these are easier to remove that the tosyl group.[29] However, Kazmaier reported that this group did not survive the tin(II) mediated aldol condensation, and so turned to the SEM group as an alternative.[30] Unfortunately, the synthesis of the SEM group involves the use of carbon tetrachloride and due to the new restrictions regarding its use, this protecting group was not an option.

## 5.42. Results and Discussion

In the previous Chapter, the *N*-Boc group survived the aldol reaction and so was used as an alternative to the tosyl group, in this second route to sphingosine **223a**. In the aldol condensation of the enolate of methyl *N*-Boc glycinate with hexadec-2-ynal **614**, the NMR spectrum of the crude product showed a single diastereoisomer of the product **628** together with starting material (Scheme 5.19; a). Chromatography failed to separate the methyl *N*-

Boc glycinate **162b** from the desired product **628** and since both compounds were oils, recrystallisation was not an option. Consequently, the yields were calculated from the ratio in the $^1$H NMR spectrum to give the product **628** in 41%, taking into account the recovered starting material. Formation of the desired aldol product **628** was tangible from the molecular ion of 426 ($M^+$ + H), visible in the mass spectrum which was consistent with the product as well as the appearance of new C*H*$CO_2$Me and C*H*OH protons at $\delta_H$ 4.50 and 4.70 ppm.

The same strategy that was successful for the initial route was adopted here. Accordingly, a 1:1.15 mixture of methyl *N*-Boc glycinate **162b** and amino alcohol **628** was treated with sodium borohydride in ethanol. After chromatography of the crude product, the diol **629** was isolated as a single diastereoisomer in 50% yield (Scheme 5.19; b). Formation of the desired product was apparent from the observed molecular ion of 398 ($M^+$ + H), which was consistent with the product, in addition, a new $CH_2$ signal at 63.0 ppm was observed in the $^{13}$C NMR spectrum and together with the disappearance of the methyl ester singlet, this was strong evidence for structure **629**. This diol **629** was an intermediate in the synthesis of sphingosine **203a** by Herold.[25] Hence, a concise, diastereoselective formal synthesis of sphingosine **203a** in an overall yield of 16% was achieved.



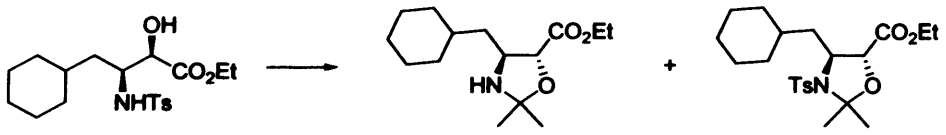

**614** **628** **629**

**Scheme 5.19.** *Reagents:* a) $SnCl_2$, LDA, THF, -78°C; b) $NaBH_4$, EtOH, 16 h, 50%.

## 5.50. Route 3

## 5.51. Introduction

A literature search of detosylation methods revealed an interesting observation by the Chandrasekhar group.[31] They reported that when a sulfonamide **630** with an adjacent ester group was treated with 2,2-dimethoxypropane in refluxing toluene with catalytic PPTS, detosylation occurred simultaneously, with only 10% of the undesired product **632** obtained (Scheme 5.20).



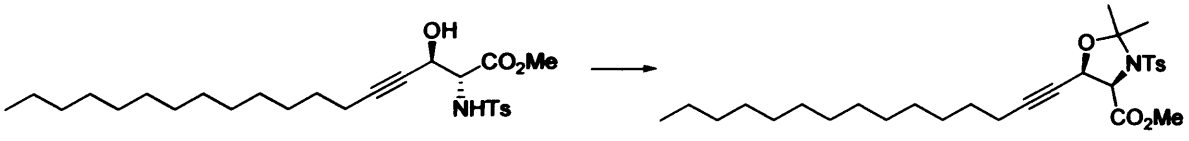

**630** **631** **632**

**Scheme 5.20**. *Reagents:* 2,2-Dimethylpropane, PPTS, Toluene, 70°C, 4 h.

If this reaction proved successful when applied to the aldol adduct (Scheme 5.15), then this would solve the detosylation problem.

## 5.52. Results and Discussion

When the aldol adduct **613** was treated with a mixture of 2,2-dimethoxypropane and catalytic PPTS in refluxing toluene for 6 h, no reaction was observed. In fact, prolonged heated was necessary to initiate reaction, but even after 24 h at reflux, only 44% conversion had occurred, to furnish the acetal **633** in 85% yield, but unfortunately with the tosyl group still intact, which was confirmed by the retention of the tosyl doublets at $\delta_H$ 7.20 and 7.65 ppm along with two aryl methyl singlets at 1.55 and 1.75 ppm (Scheme 5.21). Again the yield was calculated based on the amount of starting material recovered.




**613** **633**

**Scheme 5.21**. *Reagents:* 2,2-Dimethylpropane, PPTS, Toluene, 70°C, 24 h, **633** 85%.

## 5.53. Conclusion

In summary, the sphingosine backbone was successfully formed using the tin(II) mediated aldol reaction as the key step (Scheme 5.15; b). However, the detosylation issue still needs to be addressed. In addition, a *N*-Boc protecting group was suitable for use with this aldol reaction, but unfortunately, separation of the methyl *N*-Boc glycinate **162b** starting material from the amino alcohol product **628** could not satisfactorily be achieved. Reduction of this adduct **628** gave the alcohol **629** previously reported by Herold[25], and thus, a formal diastereoselective synthesis of sphingosine **202a** was achieved in 16% overall yield.

## 5.60. References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# Chapter Six

# Experimental Section

## General Procedures

All non-aqueous reactions (unless stated otherwise) were carried out in flame or oven-dried glassware under a dry nitrogen atmosphere with magnetic stirring. To obtain low temperatures solid carbon dioxide and an acetone bath (-78°C), an ice-water bath (0°C) or solid carbon dioxide and an acetonitrile bath (-40°C) were employed. Elevated temperatures were achieved using a stirred oil bath (either paraffin or silicon oil) on a magnetically stirred hotplate.

Solvents and reagents were dried and purified according to standard procedures[1] Tetrahydrofuran was distilled from sodium benzophenone ketal. Dichloromethane was distilled from calcium hydride. Diisopropylamine, *N*-ethyl-piperidine and pyridine were dried over and distilled from potassium hydroxide. Acetonitrile and *N,N*-dimethylformamide were dried over 4Å molecular sieves. Methanol was dried over and distilled from potassium carbonate. All solutions of crude products were dried by brief exposure to dried magnesium sulfate ($MgSO_4$), unless stated otherwise, then filtered and evaporated under reduced pressure using a Büchi rotary evaporator under water pump pressure and a warm water bath. Column chromatography was conducted using Fisher silica gel 60A (35-70 micron) as the stationary phase, (using gradient elution with the solvent system used to elute the product indicated in brackets). Reactions were monitored by tlc using Merck silica gel 60 $F_{254}$ precoated aluminium backed plates that were visualised using either ultraviolet light, ammonium molybdenate, potassium permanganate or vanillin stains. Retention factor values ($R_f$) are reported in the appropriate solvent system.

Melting points (m.p.°C) were measured using an Electrothermal 9100 melting point apparatus and are uncorrected. Infrared spectra were recorded using a Perkin Elmer 1600 series Fourier Transform Infra-red Spectrometer as either liquid films on sodium chloride

plates [Film] or as a solution in dichloromethane [$CH_2Cl_2$]. The signals are described with the following abbreviations: strong (s), medium (m), weak (w) or broad (br).

Proton ($\delta_H$) NMR spectra were recorded on a Bruker DPK 400 instrument at 400 MHz as dilute solution in deuteriochloroform, unless otherwise stated, at 298 K. The chemical shifts are recorded relative to residual chloroform (7.27ppm) as the internal standard. The multiplicity symbols used throughout are s (singlet), d (doublet), t (triplet), q (quartet) quin (quintet), br. (broad), m (unresolved multiplet), app. (apparent) or dd (double doublet etc). All coupling constants (*J*) are measured in Hertz (Hz). Carbon ($\delta_C$) NMR spectra were recorded on the same instrument and conditions, but operating at 100.6 MHz and the chemical shifts are recorded relative to residual chloroform (77.0 ppm) as the internal standard in a broad band decoupled mode. The assignments made were on the bases of chemical shift and coupling constant data using DEPT-135, COSY and HMQC experiments where necessary.

Mass spectra were recorded on a Fisons VG Platform Quadrapole Mass Spectrometer using atmospheric pressure chemical ionisation [ApcI] at Cardiff University. *m/z* Values are reported with the percentage abundance in parentheses, only for peaks with intensities of 10% or more. Electrospray [ES] and accurate high resolution data were recorded by the EPRSC Mass Spectrometry Service Centre at University of Wales Swansea and the molecular formula corresponds to the observed signal using the most abundant isotopes of each element. All the molecular formulae given for the value are quoted either as molecular + hydrogen ($M^+ + H$), molecular + sodium ($M^+ + Na$) or molecular + ammonium ion ($M^+ + NH_4$). Microanalysis data was recorded on a Perkin Elmer Elemental analyser and are quoted as atom percentages.

Optical rotations ($\alpha_D$) were measured using an Optical Activity Limited AA 1000 Polarimeter using a path length of 0.5 cm at 294 K. The solvent employed and concentration of the solutions are shown in brackets. UV/VIS data ($\lambda_{MAX}$) was recorded using a Perkin Elmer UV/VIS lambda 20 Spectrometer.

High performance liquid chromatography (HPLC) was carried out on a HPLC Agilent 1100 Series using a Chiralcel OD column.

**General Procedure A: Lithium diisopropylamide / Lithium hexamethyldisilazane Preparation**

In a flame-dried flask, freshly distilled diisopropylamine (2.5 equivalents) was dissolved in anhydrous tetrahydrofuran (2 ml $mmol^{-1}$ of amine). The solution was stirred and cooled in an ice bath before adding dropwise a 2.5 M solution of BuLi in hexanes (2.5 equivalents). The resulting mixture was stirred for 0.5 h at this temperature and then cooled to -78°C prior to use.

Lithium hexamethyldisilazane was also prepared by the same procedure but using 1,1,1,3,3,3-hexamethyldisilazane in place of diisopropylamine

**General Procedure B: Preparation of pH 7 Phosphate Buffer**

The phosphate buffer was prepared by dissolving potassium dihydrogen phosphate (1.75 g) in 0.1 M potassium hydroxide (73.75 ml) and then adding water to achieve a total volume of 250 ml.

**General Procedure C: Kazmaier Aldol Reaction[2]**

The *N*-protected glycinate (1 equivalent) was added to a suspension of anhydrous tin(II) chloride (2.5 equivalents) in dry tetrahydrofuran (12 ml $g^{-1}$ of tin(II) chloride) maintained at -78°C before adding dropwise freshly prepared LDA (2.5 equivalents) in tetrahydrofuran (2 ml $mmol^{-1}$) *via* cannula. After 10 minutes, a solution of the aldehyde (1.2 equivalents) in dry tetrahydrofuran (10 ml $g^{-1}$) was added slowly *via* syringe. After stirring the resulting mixture for 0.5 h, the reaction was quenched with pH 7 phosphate buffer and diluted with ether (10 ml $g^{-1}$ of glycinate). The solution was allowed to warm to room temperature before being filtered through a pad of celite. The layers were separated, the aqueous layer was extracted twice with ether (20 ml $g^{-1}$ of glycinate) and the combined organic solutions were washed with brine (50 ml $g^{-1}$ of glycinate), then dried and evaporated to yield the aldol product which was purified by column chromatography or recrystallisation.

**General Procedure D: Hydrogenation**

To the acetylenic aldol product (1 equivalent) in ethyl acetate (5 ml $g^{-1}$) was added Lindlar's catalyst (palladium on calcium carbonate, poisoned with lead acetate) (1.2 mg per ml of $H_2$) and the mixture was stirred vigorously under a hydrogen atmosphere until hydrogen (22.5 ml $mmol^{-1}$ of acetylene) was absorbed. The suspension was then filtered through a pad of celite, the solid washed with diethyl ether and the filtrate and washings evaporated to yield the *cis* product, which was used without further purification.

**General Procedure E: Dicyclohexylcarbodiimide Coupling Procedure[3]**

To a stirred solution of the alcohol (1 equivalent) and 4-pyrrolidino-pyridine (0.09 equivalents) in anhydrous dichloromethane (10 ml $g^{-1}$ of alcohol) was added dicyclohexylcarbodiimide (1.1 equivalents) in dichloromethane (10 ml $g^{-1}$). The resulting solution was cooled to -20°C, the acid (1 equivalent) in dichloromethane (10 ml $g^{-1}$) was added and immediately a white precipitate formed. The reaction was stirred overnight at room temperature and the precipitate was filtered off, washed with dichloromethane and the filtrate washed with water (3 x 40 ml $g^{-1}$ of alcohol), 5% acetic acid solution (3 x 40 ml $g^{-1}$ of alcohol) and water (3 x 40 ml $g^{-1}$ of alcohol). The organic layer was then dried and evaporated to yield the ester.

**General Procedure F: Boc Deprotection Using Trifluoroacetic acid**

To an ice-cold solution of the *N*-Boc protected amine in dichloromethane (8 ml $g^{-1}$) was added trifluoroacetic acid (2 ml $g^{-1}$) dropwise. When the reaction was judged to be complete by tlc (1-2 h), the solvent was evaporated. The residue was partitioned between saturated aqueous sodium carbonate and dichloromethane (20 ml $g^{-1}$). The separated organic phase was washed with saturated aqueous sodium carbonate (2 x 10 ml $g^{-1}$) then dried and evaporated to yield the amine.

**General Procedure G: Tosylation of Secondary Amines**

To an ice-cold solution of the crude amine (1 equivalent) in dichloromethane (10 ml $g^{-1}$) was added the base (either triethylamine, pyridine or 2,4,6-collidine) (various equivalents) as specified in the individual experiment. After 0.25 h DMAP (catalytic) was added followed by a solution of tosyl chloride (various equivalents) indichloromethane (10 ml $g^{-1}$). The ice bath was removed and the reaction mixture was stirred for 16 h. 2M hydrochloric acid (10 ml $g^{-1}$ of amine) was added, the resultant two layers were separated and the aqueous phase was extracted with dichloromethane (3 x 10 ml $g^{-1}$ of amine). The combined organic phases were dried and evaporated to furnish the crude sulfonamide.

**General Procedure H: Reduction of Alkynes using a 65% w/w solution of Red-al[4]**

A solution of the alkyne (1 equivalent) in anhydrous ether (10 ml $g^{-1}$) was added dropwise to a 65% w/w solution of Red-al (5 equivalents) in anhydrous ether (3 mmol $ml^{-1}$ of Red-al) cooled in an ice-bath. The colourless solution was then stirred at room temperature for 24 h before adding methanol (0.14 ml $mmol^{-1}$ of Red-al) dropwise at 0°C. The solution was diluted with ether (8 ml $mmol^{-1}$ of alkyne), saturated aqueous potassium sodium tartrate (8 ml $mmol^{-1}$ of alkyne) was added and the mixture was stirred vigorously for 3 h at room temperature. The separated aqueous layer was extracted with ether (2 x 8 ml $mmol^{-1}$ of alkyne) and the combined organic solutions were washed with saturated aqueous potassium sodium tartrate (20 ml $mmol^{-1}$ of alkyne), saturated brine (20 ml $mmol^{-1}$ of alkyne) and were then dried and evaporated to yield the (*E*)-alkene, which was purified using column chromatography.

**General Procedure I: Iodocyclisation Using Iodine Monobromide**

Potassium carbonate (3 equivalents) was added to a stirred solution of the alkene (1 equivalent) in acetonitrile or dichloromethane (10 ml $g^{-1}$ of alkene) maintained at -10°C. After stirring the mixture for 0.25 h, iodine monobromide (3 equivalents) was added, and the mixture was maintained at this temperature until tlc showed the reaction to be complete. Saturated aqueous sodium thiosulfate (10 ml $g^{-1}$ of alkene) was added and after separating the layers, the aqueous layer was extracted with dichloromethane (3 x 10 ml $g^{-1}$

of alkene). The combined organic layers were dried and evaporated to yield the crude product.

**General Procedure J: Epoxide Forming Reaction Using Silver Carbonate (50% w/w on celite)[5]**

Silver carbonate on celite (50% by weight, 6 equivalents) was added to a stirred solution of the iodopyrrolidine (1 equivalent) in freshly distilled dichloromethane (30 ml $g^{-1}$). The reaction was stirred for 24 h at room temperature before filtering the mixture through a plug of celite. The solid was washed with dichloromethane and the combined filtrate and washings evaporated to yield the epoxide.

**General Procedure K: Acetate Formation**

The pyrrolidine (1.0 equivalent) was dissolved in anhydrous pyridine (10 ml $g^{-1}$), acetic anhydride (1.0 equivalent) was added and the reaction was stirred at room temperature for 24 h. The reaction mixture was then diluted with water (50 ml $g^{-1}$ of pyrrolidine), the aqueous layer extracted with ether (2 x 50 ml $g^{-1}$ of pyrrolidine) and the combined ether extracts were washed with saturated aqueous copper(II) sulfate solution (3 x 50 ml $g^{-1}$ of pyrrolidine). The ether layers were then dried and concentrated to give the acetate.

**General Procedure L: Iodocyclisation using Iodine**

Potassium carbonate (3 equivalents) was added to a stirred solution of the alkene (1 equivalent) in anhydrous acetonitrile or dichloromethane (10 ml $g^{-1}$ of alkene) cooled in an ice bath. After stirring the mixture for 0.25 h, iodine (3 equivalents) was added. The reaction was maintained at this temperature until tlc showed the reaction to be complete. Saturated aqueous sodium thiosulfate (10 ml $g^{-1}$ of alkene) was added and after separating the layers, the aqueous layer was extracted with dichloromethane (3 x 10 ml $g^{-1}$ of alkene). The combined organic layers were dried and evaporated to yield the crude product.

**General Procedure M: Hydrogenolysis to remove Iodine**

To a solution of the iodopyrrolidine (1 equivalent) in methanol (0.2 g $ml^{-1}$) was added triethylamine (1 equivalent) and 10% palladium on carbon (1.2 g per ml of hydrogen) and the mixture was stirred vigorously under an atmosphere of hydrogen for the specified time. The suspension was then filtered through a pad of celite and the solid was washed with diethyl ether. The filtrate was washed with an equal volume of 1 M hydrochloric acid and the organic layer was dried and evaporated.

**General Procedure N: Saponification**

The ester (1 equivalent) was dissolved in an ice-cold solution of 2 M potassium hydroxide in methanol (64 ml $g^{-1}$) and the solution stirred overnight. The bulk of the solvent was evaporated and the residue was acidified using 2M hydrochloric acid to pH 1. An equal volume of dichloromethane was added, the layers were separated and the aqueous phase was extracted with dichloromethane (x 4). The combined organic phases were dried and evaporated.

**General Procedure O: Silver Cyclisation using 10% w/w Silver Nitrate on Silica Gel[6]**

In a flame dried flask containing the alkyne in anhydrous dichloromethane (30 ml $g^{-1}$) was added 10% by weight silver nitrate on silica (various equivalents), as specified in the individual experiment. After the specified time at room temperature, the mixture was filtered through a plug of celite, the solid washed with dichloromethane and the combined filtrate and washings were evaporated to yield the cyclised product.

**General Procedure P: TBS protection of secondary alcohols**

The alcohol (1 equivalent) in tetrahydrofuran (10 ml $g^{-1}$) was cooled in an ice bath prior to the addition of triethylamine (1.1 equivalent) and TBS triflate (1.1 equivalent), the ice bath was removed and the reaction mixture stirred for the specified time. Water (5 ml $g^{-1}$ of alcohol) was added, followed by diethyl ether (5 ml $g^{-1}$ of alcohol) and the resulting two layers were separated. The aqueous phase was extracted with diethyl ether (3 x 5 ml $g^{-1}$ of

alcohol) and the combined ether layers were washed with saturated aqueous sodium bicarbonate (2 x 15 ml $g^{-1}$ of alcohol), then dried and evaporated.

**General Procedure Q: Hydroboration**

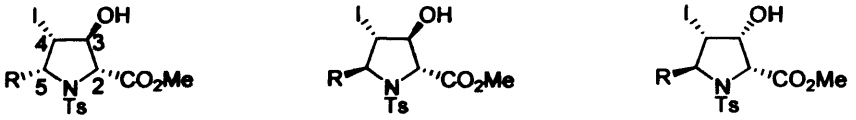
To an ice-cold solution of the dihydropyrrole (1 equivalent) in tetrahydrofuran (10 ml $g^{-1}$) was added a 1M solution of borane-tetrahydrofuran complex in tetrahydrofuran (4 equivalents). The ice-bath was removed and the solution was stirred for 16 h. The reaction mixture was re-cooled in an ice bath prior to the addition of a 10% aqueous solution of sodium hydroxide (equal volume to borane-THF complex) followed by a 30% by weight aqueous solution of hydrogen peroxide (equal volume to borane-THF complex) and the resulting solution stirred vigorously for a further 1 h. The solvent was evaporated then water (5 ml $g^{-1}$) was added followed by dichloromethane (5 ml $g^{-1}$). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml $g^{-1}$). The combined organic layers were dried and evaporated.

**General Method R: Synthesis of Acetylenic Aldehydes**[7]

The terminal acetylene (1 equivalent) was dissolved in anhydrous tetrahydrofuran (10 ml $g^{-1}$) and the stirred solution cooled to -40°C. To this, a 2.5 M solution of BuLi in hexanes (1.1 equivalent) was added dropwise over a period of 5 minutes. Next, anhydrous *N,N* dimethylformamide (2 equivalents) was added, the cooling bath removed and the solution stirred for 0.5 h. This mixture was then poured into a rapidly stirred biphasic solution of 10% aqueous potassium dihydrogen phosphate (4.4 equivalents) and diethyl ether (11 ml $g^{-1}$) at 5°C. The two layers were separated, the organic layer washed twice with water (15 ml $g^{-1}$ of acetylene) and then the combined aqueous layers were back extracted with diethyl ether (2 x 20 ml $g^{-1}$). The combined organic layers were dried and evaporated to yield the α,β acetylenic aldehyde which was purified using column chromatography.

**Pyrrolidine Nomeclature.**

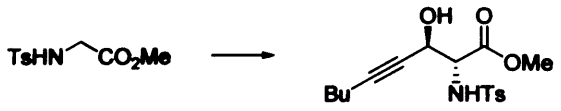
For ease of differentiation, and to avoid confusion, each pyrrolidine has a name and number which is used throughout the text (Figure 6.10).




2,5-*cis* isomer 2,5-*trans* isomer 3,4-*cis* isomer

**Figure 6.10**

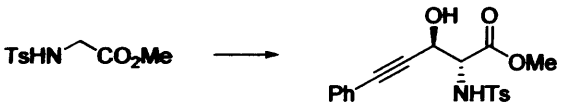
**(*2RS,3RS*)-Methyl 3-hydroxy-2-(tosylamino)-non-4-ynoate 144a**




**152** **144a**

Methyl *N*-tosyl glycinate **152** (5.52 g, 22.70 mmol) and hept-2-ynal **115** (3.0 g, 27.23 mmol) were reacted together according to general procedure C. The residue, following chromatography (40% ethyl acetate/petroleum ether) and recrystallisation (10% ethyl acetate/petroleum ether), gave the *aldol product* **144a** (3.30 g, 41%) as a colourless solid. The data obtained was in accordance with that previously reported in the literature: m.p. 68-69°C [lit[8] m.p. 64-65°C]; $R_f$ 0.47 (50% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3468 (br), 2925 (s), 2825 (s), 2863 (s), 1745 (m), 1456 (s), 1342 (m); $\delta_H$ 0.75 (3H, t, *J* 7.3, Me), 1.20-1.40 (4H, m, 2 x $CH_2$), 2.10 (2H, app. dt, *J* 7.0 and 2.0, 6-$CH_2$), 2.35 (3H, s, Ar-Me), 2.70 (1H, d, *J* 10.5, OH), 3.50 (3H, s, $CO_2Me$), 4.10 (1H, dd, *J* 9.6 and 3.9, 2-H), 4.50-4.60 (1H, m, 3-H), 5.45 (1H, d, *J* 9.6, NH), 7.20 (2H, d, *J* 8.2, 2 x Ar-H) and 7.65 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ 13.9 (9-Me), 18.6 ($CH_2$), 22.0 (Ar-Me), 22.19, 30.1 (both $CH_2$), 53.2 ($CO_2Me$), 61.2, 63.5 (both CH), 75.9, 89.2 (C≡C), 127.6, 130.1 (both ArCH), 136.8, 144.3 (both ArC) and 169.0 (C=O); *m/z* [ES] 376 ($M^+$ + Na, 90%) and 336 (100).

**(*2RS,3RS*)-Methyl 3-hydroxy-5-phenyl-2-(tosylamino)-pent-4-ynoate 146a**

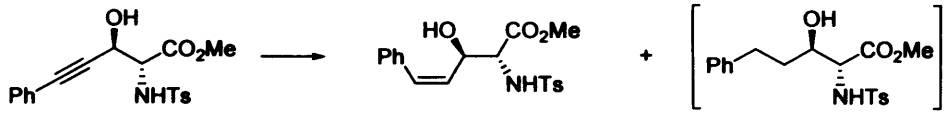



**152** **146a**

The *N*-protected glycinate **152** (5.52 g, 21.4 mmol, 1.0 eq) and phenylpropynal **117** (3.35 g, 25.7 mmol) were reacted together according to general procedure C. The residue following chromatography (40% ethyl acetate/petroleum ether) and recrystallisation (10% ethyl acetate/petroleum ether) gave the *anti-aldol diastereoisomer* **146a** (3.37 g, 45%), as cream crystals: m.p. 135-138°C [lit[9] m.p. 133-134°C]; $R_f$ 0.58 (40% ethyl

acetate/petroleum ether), $\nu_{max}/cm^{-1}$ 3269 (br), 1742 (s), 1598 (m), 1490 (m), 1339 (s) and 1163 (s); $\delta_H$ 2.35 (3H, s, Ar-Me), 2.90 (1H, d, *J* 10.2, OH), 3.55 (3H, s, $CO_2Me$), 4.15 (1H, dd, *J* 9.5 and 3.9, 2-H), 4.90 (1H, dd, *J* 10.2 and 3.9, 3-H), 5.6 0 (1H, d, *J* 9.5, NH), 7.20-7.30 (7H, m, Ph and 2 x Ar-H) and 7.70 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ 22.0 (Ar-Me), 53.5 ($CH_3$), 61.1, 64.0 (both CH), 84.6, 88.0 (both C≡C), 121.9 (ArC), 127.8, 128.8, 129.5, 130.2, 132.3 (all ArCH), 136.5, 144.6 (both ArC) and 168.9 (C=O); *m/z* [ES] 396 ($M^+$ + Na, 80%) and 356 (100). [Found: C, 61.16; H, 5.44, N, 3.67. $C_{19}H_{19}NO_5S$ requires C, 61.11; H, 5.13; N, 3.75%].

**(*E,2S,3R*)-Methyl 3-hydroxy-5-phenyl-2-(tosylamino)pent-4-enoate 147 and (*2S,3R*)-Methyl 3-hydroxy-5-phenyl-2-(tosylamino)pentanoate 148**




**146a** **147** **148**

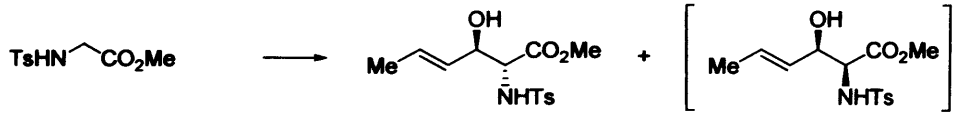
The alkyne **146** (500 mg, 1.34 mmol) was reduced using Lindlars' catalyst as described in general procedure D to give an inseparable 8:3:1.5 mixture of i) *cis*-alkene **147** ii) alkane **148** and starting material **146a**. The (*Z*)-alkene was characterised by characterised by: $R_f$ 0.27 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3474 (br), 2957 (s), 1738 (s), 1598 (s), 1494 (s), 1435 (s), 1339 (s), 1162 (s), 815 (s) and 763 (m); $\delta_H$ 2.35 (3H, s, Ar-Me), 2.75 (1H, d, *J* 7.7, OH), 3.30 (3H, s, $CO_2Me$), 4.00 (1H, dd, *J* 8.8 and 4.0, 2-H), 4.70-4.80 (1H, m, 3-H), 5.55 (1H, dd, *J* 11.7 and 9.6, 4-H), 5.60 (1H, d, *J* 8.8, NH), 6.60 (1H, d, *J* 11.7, 5-H), 7.15-7.30 (7H, m, Ph and 2 x Ar-H) and 7.65 (2H, d, *J* 8.1, 2 x Ar-H); $\delta_C$ 21.6 (Ar-Me), 52.6 ($CO_2Me$), 60.7, 68.7 (both CH), 127.7 (ArCH), 127.7, 127.9 (both CH), 128.5, 128.7, 129.7 (all ArCH), 134.0 (CH), 135.8, 136.4, 143.9 (All ArC) and 169.3 (C=O); *m/z* [APcI] 358 ($M^+$ - $H_2O$, 100%). The data obtained for the alkane **148** is reported later (p 247).

**(*4Z,2RS, 3RS*)-Methyl 3-hydroxy-2-(tosylamino)-non-4-enoate 144a**


**144a** **149**

The alkyne **144a** (100 mg, 0.28 mmol) was subjected to Lindlar reduction according to general procedure D to give the *cis-alkene* **149**, (100 mg, 100%) as a brown oil: $R_f$ 0.2 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [Film] 3508 (br), 2955 (s) 1742 (s), 1434 (m), 1341 (m), 1163 (s) and 1092 (m); $\delta_H$ 0.80 (3H, br. res., 9-Me), 1.20-1.25 (4H, br. res, 2 x $CH_2$), 1.80-2.00 (2H, br. res., $CH_2$), 2.35 (3H, s, Ar-Me), 3.45 (3H, s, $CO_2Me$), 3.9 (1H, dd, *J* 8.8 and 3.9, 2-H), 4.70 (1H, dd, *J* 9.1 and 3.9, 3-H), 5.25 (1H, dd, *J* 10.9 and 9.1, 4-H), 5.45-5.50 (1H, m, 5-H), 5.60 (1H, d, *J* 8.8, NH), 7.20 (2H, d, *J* 8.1, 2 x Ar-H) and 7.80 (2H, d, *J* 8.1, 2 x Ar-H); $\delta_C$ 12.9 (9-Me), 20.6 (Ar-Me), 21.3, 26.5, 30.5 (all $CH_2$), 51.6 ($CO_2Me$), 59.5, 67.4 (both CH) 125.0 (=CH), 126.3 128.7 (both ArCH), 134.5 (=CH), 135.3, 142.9 (both ArC) and 168.6 (C=O); *m/z* [ES] 378 ($M^+$ + Na, 100%), 338 (60). [Found $M^+ + NH_4$: 373.1809. $C_{17}H_{29}N_2O_5S$ requires *M*, 373.1797].

**(*4E,2RS,3RS*)- and (*4E,2SR,3RS*)-Methyl 3-hydroxy-2-(tosylamino)-hex-4-enoate 150a and 150b**

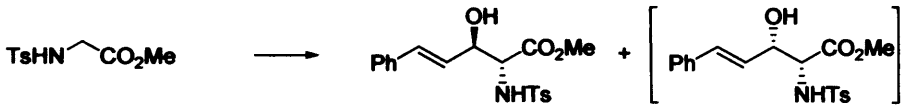



**152** **150a** **150b**

*N*-tosyl glycinate **152** (5.0 g, 20.55 mmol) and (*E*)-croton aldehyde **137** (1.73 g, 2.0 ml, 24.68 mmol) were reacted together according to general procedure C. The residue was purified by column chromatography (40% ethyl acetate/ petroleum ether) and recrystallisation (10% ethyl acetate/petroleum ether) to give the *anti-diastereoisomer* **150a** (1.88 g, 36%), as a white solid. The *syn* isomer **150b** together with impurities was isolated from the mother liquors (1.08 g) as a yellow oil. The *anti* diastereoisomer **150a** showed: m.p. 108-109.5°C; $R_f$ 0.2 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3274

(br), 1739 (s), 1599 (s), 1337 (s), 1162 (s) and 969 (s); $\delta_H$ 1.70 (3H, d, *J* 6.5, 6-Me), 2.45 (1H, s, Ar-Me), 2.60 (1H, d, *J* 8.1, OH), 3.50 (3H, s, $CO_2CH_3$), 4.00 (1H, dd, *J* 9.2 and 4.2, 2-H), 4.35-4.40 (1H, m, 3-H), 5.25-5.30 (1H, m, 4-H), 5.50 (1H, d, *J* 9.2, NH), 5.80 (1H, dq, *J* 15.2 and 6.5, 5-H), 7.30 (2H, d, *J* 8.3, 2 x Ar-H), and 7.80 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ 18.2 (6-Me), 22.0 (ArMe), 53.0 ($CO_2CH_3$), 60.8, 73.2 (both CH), 127.8 (ArCH), 128.0 (C=C), 130.1 (ArCH), 130.6 (C=C), 136.6, 144.4 (both ArC) and 170.0 (C=O); *m/z* [APcI] 378 ($M^+$ + H, 10%), 296 (100) and 236 (55). [Found: C, 53.74; H, 6.36, N, 4.49. $C_{14}H_{19}NO_5S$ requires C, 53.66; H, 6.11; N, 4.47%].

## (*4E,2RS,3RS*)- and (*4E,2RS,3SR*)-Methyl 3-Hydroxy-5-phenyl-2-(tosylamino)-pent-4-enoate 151a and 151b

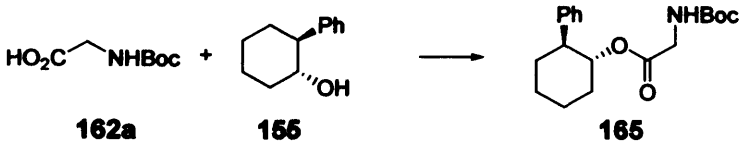



**152** **151a** **151b**

The *N*-tosyl glycinate **152** (5.0 g, 20.55 mmol) was reacted with (*E*)-cinnamaldehyde **117** (3.26 g, 24.6 mmol, 3.1 ml) according to general procedure C. The residue was chromatographed (30% ethyl acetate / petroleum) and recrystallised (10% ethyl acetate / hexane) to give the *amino alcohol adduct* **151** (4.43 g, 57%), as a mixture of diastereoisomers in a ratio of 9:5:1, as colourless crystals, (the *syn* diastereoisomer is the minor isomer): m.p. 119-120°C; $R_f$ 0.11 (40% ethyl acetate / petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3490 (br), 3270 (br), 1738 (s), 1598 (m), 1494 (m), 1338 (s), 1162 (s) and 969 (s); $\delta_H$ (400 MHz) 2.30 (3H, s, *syn*, Ar-Me), 2.35 (3H, s, *anti*, Ar-Me), 2.40 (1H, d, *J* 4.9, *syn* , OH), 2.75 (1H, d, *J* 7.9, *anti*, OH), 3.45 (3H, s, *anti*, $CO_2Me$), 3.50 (3H, s, *syn*, $CO_2Me$), 3.95 (1H, dd, *J* 9.5 and 3.3, *syn*, 2-H), 4.05 (1H, dd, *J* 9.1 and 4.2, *anti*, 2-H), 4.55–4.60 (1H, m, both, 3-H), 5.55 (1H, d, *J* 9.0, both, NH), 6.0 (1H, dd, *J* 15.9 and 6.1, *anti*, 4-H), 6.10 (1H, dd, *J* 15.9 and 6.8, *syn*, 4-H), 6.55 (1H, d, *J* 15.9, both, 5-H), 7.10-7.25 (7H, m, both, Ph and 2 x Ar-H) and 7.65 (2H, d, *J* 8.3, both, 2 x Ar-H); ); $\delta_C$ 22.0 (Ar-Me), 53.2 ($CO_2Me$), 60.8, 73.4 (both CH), 126.0, 127.1, 127.8, 128.6, 129.0, 130.2, 133.5 (all CH), 136.3, 136.5, 144.5 (all ArC) and 169.9 (C=O); *m/z* [ES] 398 ($M^+$ + Na, 80%),

358 (100) and 298 (30). [Found: C, 61.07; H, 5.58, N, 3.76. $C_{19}H_{21}NO_5S$ requires C, 60.78; H, 5.64; N, 3.73%].

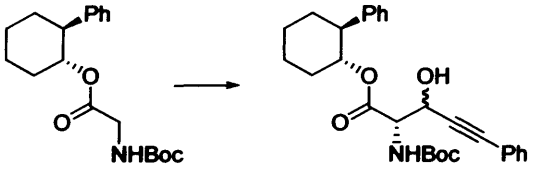
### *(1RS,2SR)*-2-Phenylcyclohexyl *N*-(*t*-butoxycarbonylamino)acetate 165




**162a** **155** **165**

The alcohol **155** (231 mg, 1.31 mmol) was reacted with the *N*-Boc glycine **162a** (192 mg, 1.19 mmol, Lancaster) according to the method outlined in general procedure E, for 64 h, to furnish the *ester* **165** (324 mg, 74%), as a colourless oil: $R_f$ 0.69 (60% ethyl acetate/petroleum ether); $\delta_H$ 1.30 (9H, s, *t*-Bu), 1.15-2.05 (8H, m, cyclohexane resonances), 2.60 (1H, td, *J* 12.3 and 3.6, 2-H), 3.35 (1H, dd, *J* 18.3 and 4.9, $C\underline{H}_aCH_bN$), 3.65 (1H, d, *J* 18.3 and 5.9, $CH_aC\underline{H}_bN$), 4.70 (1H, br. res., NH), 4.95-5.00 (1H, m, 1-H), 7.05-7.20 (5H, m, Ph); $\delta_C$ 24.7, 25.7 (both $CH_2$), 28.3 (*t*-Bu), 32.2, 33.4 (both $CH_2$), 42.3 ($CH_2$-N), 49.7, 77.3 (both CH), 126.6, 127.5, 128.4 (both ArCH), 142.7 (ArC), 155.5 (N-C=O) and 169.5 (C=O); *m/z* [APcI] 279 ($M^+$ - ⅄, 12%), 226 (55), 160 (100), 121 (72) and 108 (40).

### Tin(II) Chloride Aldol Reaction of *(1RS,2SR)*-2-Phenylcyclohexyl *N*-(*t*-butoxycarbonylamino)acetate 165

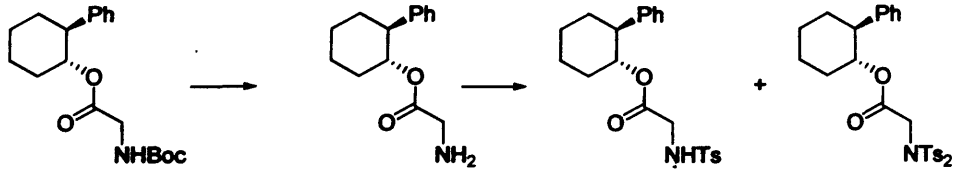



**165** **166**

The ester **165** (56 mg, 0.17 mmol) was condensed with phenyl propynal **117** (26 mg, 0.20 mmol) according to general procedure C. The residue was chromatographed (10% ethyl acetate/petroleum ether) to give the *aldol adduct* **166** (21 mg, 28%), in a 5:2 ratio, as a yellow oil (product A is the major product): $R_f$ 0.58 (40% ethyl acetate/petroleum ether);

$\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2936 (s), 2858 (s), 1738 (s), 1716 (s), 1600 (s), 1509 (s), 1450 (m) and 1368 (s); $\delta_H$ 1.35 (9H, s, *t*-Bu), 1.15-2.15 (8H, m, cyclohexane residues), 2.65 (2H, app. td, *J* 11.8 and 3.4, 2-H, both products), 3.20 (1H, br. d, *J* 8.6, OH, exchanges with $D_2O$, product A), 3.55 (1H, br. res., OH, exchanges with $D_2O$, product B), 4.25-4.35 (1H, m, CHN, product A), 4.40 (1H, br. d, *J* 5.9, CHN, product B), 4.65 (1H, br. res., *J* 4.2, CHO, product B), 4.80 (1H, br. d, *J* 5.3, CHO, product A), 4.90-5.15 (2H, m, 1-H, both products), 5.25 (1H, br. d, *J* 6.7, NH, product B), 5.35 (1H, br. d, *J* 7.7, NH, product A) and 7.05-7.30 (20H, m, 2 x Ph, both products); $\delta_C$ (two products) 24.7, 25.7 (both $CH_2$), 28.3 (*t*-Bu), 32.2, 34.1 (both $CH_2$), 49.5, 49.7, 58.0, 58.5, 59.3, 64.4, 65.0, 77.3 (all CH, both products), 78.4 (C-$(CH_3)_3$), 126.8, 126.9, 127.3, 127.4, 127.5, 128.2, 128.3, 128.5, 131.8, 131.8 (all ArCH, both products), 142.5 (N-C=O, both products) and 167.9 (C=O, both products), (All ArC and acetylene resonances missing); *m/z* [APcI] 464 ($M^+$ H, 22%), 463 (100 ), 408 (17) and 390 (29). [Found $M^+$ + H: 464.2433. $C_{28}H_{34}NO_5$ requires *M*, 464.2431].

**Tosylation of *(1RS,2SR)*-2-Phenylcyclohexyl *N*-(*t*-butoxycarbonylamino)acetate 167**




*i) Deprotection using TFA*

The crude ester **165** (324 mg, 0.97 mmol) was deprotected using trifluoroacetic acid (0.7 ml) according to general procedure F, for 1 h to give the *amine* **167** (183 mg, 81%) as a brown oil.

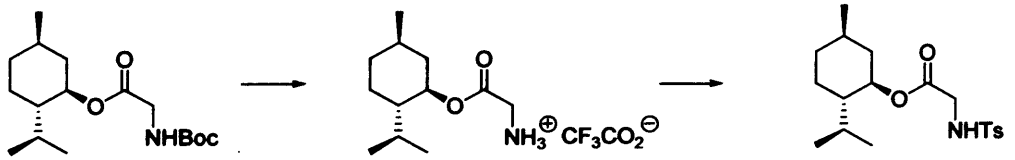
*ii) N-Tosylation*

The crude amine **167** (183 mg, 0.78 mmol) was tosylated using triethylamine (79 mg, 0.11 ml, 0.78 mmol, 1.0 eq) and *p*-tosyl chloride (150 mg, 0.78 mmol, 1.0 eq) according to general procedure G. Following chromatography (20% ethyl acetate/petroleum ether) a 3.6:1 mixture of i) the *bis-sulfonamide* **169** and ii) the *mono-sulfonamide* **168**, (64 mg),

were obtained as a pale yellow oil. The bis-sulfonamide **169** was characterised by: $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3366 (br), 2930 (s), 2857 (s), 1740 (s), 1600 (s), 1494 (m), 1450 (s), 1340 (s), 1163 (s), 815 (m), 737 (s) and 701 (s); $\delta_H$ 0.65-2.20 (8H, m, cyclohexane resonances), 2.40 (3H, s, Ar-Me), 2.50-2.65 (1H, m, CH-Ph), 3.90 (1H, d, *J* 18.5, $C\underline{H}_aCH_b$-N), 4.10 (1H, d, *J* 18.5, $CH_aC\underline{H}_b$-N), 4.85 (1H, td, *J* 10.6 and 4.4, CHO), 7.05-7.25 (9H, m, Ph and 2 x Ar-H) and 7.70 (4H, d, *J* 8.4, 4 x Ar-H); $\delta_C$ 21.8 (Me), 24.7, 25.7, 31.0, 33.7 (all $CH_2$), 48.2 ($CH_2$-N), 49.4, 77.8 (both CH), 126.6, 127.5, 128.4, 128.7, 129.5 (all ArCH), 136.1, 142.6, 145.0 (all ArC) and 166.8 (C=O) (only one set of tosyl peaks evident).

The mono-sulfonamide **168** was characterised by: $\delta_H$ 1.20-2.10 (8H, m, cyclohexane resonances), 2.35 (3H, s, Ar-Me), 2.50-2.60 (1H, m, 2-H), 3.30 (1H, dd, *J* 17.8 and 4.8, $C\underline{H}_aCH_b$-N), 3.50 (1H, d, *J* 17.8 and 5.8, $CH_aC\underline{H}_b$-N), 4.65-4.70 (1H, m, NH), 4.80 (1H, td, *J* 10.7 and 4.4, 1-H), 7.00-7.30 (7H, m, Ph and 2 x Ar-H) and 7.55 (2H, d, *J* 8.3, 2 x Ar-H).

**(*1R,2S,5R*)-2-isopropyl-5-methylcyclohexyl 2-(tosylamino)acetate 175**




**154** **174** **175**

*i) Deprotection Using Trifluoroacetic acid*

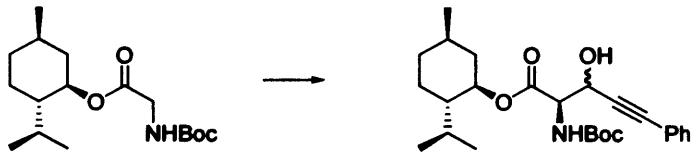
The menthol ester **154** (1.00 g, 3.19 mmol, 1.0 eq) was deprotected using trifluoroacetic acid (2 ml) according to general procedure F, for 3 h to furnish the *trifluoroacetate* **174** (575 mg, 55%) as a brown oil: $\delta_H$ 0.70 (3H, d, *J* 7.0, 5-Me), 0.80 (6H, app. t, $J_{approx}$ 7.2, *i*-Pr), 1.85-2.00 (10H, m, cyclohexane protons and $C\underline{H}(Me)_2$), 3.20-3.35 (2H, m, $CH_2$-N) and 4.65 (1H, td, *J* 10.8 and 4.20, 1-H).

*ii) Tosylation*

The crude trifluoroacetate **174** (288 mg, 0.88 mmol, 1.0 eq) was tosylated using triethylamine (163 mg, 0.23 ml, 1.60 mmol, 1.8 eq) as the base and *p*-tosyl chloride (308 mg, 1.60 mmol, 1.8 eq) according to general procedure G. The residue was chromatographed (20% ethyl acetate/petroleum ether) to give the *sulfonamide* **175** (297 mg, 51%, over two steps), as a pale yellow oil: $R_f$ 0.58 (40% ethyl acetate/petroleum ether); $\delta_H$ 0.65 (3H, d, *J* 6.9, 5-Me), 0.70-1.90 (15 H, m, cyclohexane protons and

C<u>H</u>(Me)$_2$), 2.35 (3H, s, Ar-Me), 4.25 (1H, d, *J* 18.4, C<u>H$_a$</u>CH$_b$-N) 4.35 (1H, d, *J* 18.4, CH$_a$CH$_b$-N), 4.55 (1H, td, *J* 10.9 and 4.4, 1-H), 7.20 (2H, d, *J* 8.4, 2 x Ar-H) and 7.85 (2H, d, *J* 8.4, 2 x Ar-H).

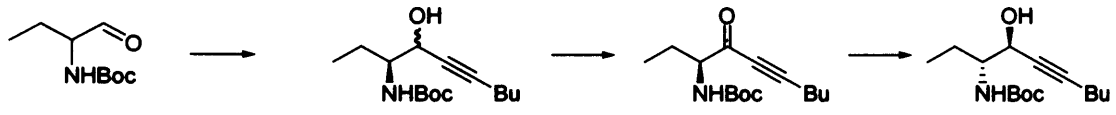
**(*1RS,2SR,5RS*) *tert*-butyl 1-[{-2-isopropyl-5-methylcyclohexyloxy}carbonyl]-2-hydroxy-4-phenylbut-3-ynylcarbamate 176**




**154** **176**

Phenyl propynal **117** (897 mg, 6.89 mmol) was reacted with the menthol auxiliary **173** (1.80 g, 5.74 mmol) according to general procedure C, except in the absence of tin(II) chloride. The residue was chromatographed (10% ethyl acetate/petroleum ether) to give aldol product **176** (1.136 g, 45%), as a 6:4 mixture of diastereoisomers. The major diastereoisomer was characterised by: $R_f$ 0.68 (40% ethyl acetate/petroleum ether); $\nu_{max}$/cm$^{-1}$ [$CH_2Cl_2$] 2960 (s), 2868 (s), 1721 (s), 1491 (m), 1454 (m), 1368 (s) and 757 (m); $\delta_H$ 0.55-1.95 (19H, complex, cyclohexane resonances and 3 x Me), 1.35 (9H, s, *t*-Bu), 3.50 (1H, br. res., OH), 4.50 (1H, br. dd, *J* 9.0 and 2.9, CHN), 4.65-4.75 (1H, m, 1-H), 4.85 (1H, br. res, CHO), 5.40 (1H, d, *J* 9.0, NH), 7.10-7.20 (3H, m, 3 x Ar-H) and 7.25-7.30 (2H, m, 2 x Ar-H); $\delta_C$ (certain signals rotameric*) 16.2*, 16.3, 20.7*, 20.9, 21.9*, 22.3 (all Me), 23.1*, 23.3 ($CH_2$), 26.0, 26.1 (both CH), 28.3 (*t*-Bu), 31.3, 31.4 (CH), 34.1*, 34.5, 40.8*, 40.8 ($CH_2$), 46.8, 58.4*, 58.5, 63.9*, 64.0, 76.3*, 76.3, (CH), 80.3 (<u>C</u>-$(CH_3)_3$), 86.1, 86.4 (C≡C), 122.0 (ArC), 128.3, 128.8, 131.9 (all ArCH), 155.6 (N-C=O), 169.4* and 169.6* (both C=O); *m/z* [APcI] 444 ($M^+$ + H, 35%), 388 (28), 326 (21), 232 (60) and 74 (100). [Found $M^+$ + H: 444.2744. $C_{26}H_{38}NO_5$ requires *M*, 444.2746].

**(*3SR,4RS*)-*tert*-(butoxycarbonylamino)-dec-5-yn-1-ol 186**




**183** **184** **185** **186**

*i) Alkylation of ±-2-(t-butoxycarbonylamino)butanal* **183**

To a -20°C solution of 1-hexyne **114** (2.19 g, 3.1 ml, 26.66 mmol, 3.33 eq) in tetrahydrofuran (20 ml) was added a 2.5 M solution of n-BuLi (11.75 ml, 29.38 mmol, 3.67 eq) and the resultant solution stirred for 0.5 h. The reaction mixture was cooled to -78°C and then the crude aldehyde **183** (1.50 g, 8.01 mmol, 1.0 eq) in tetrahydrofuran (15 ml) was added dropwise to the solution and which was then stirred for 2 h. The reaction was quenched with phosphate buffer (5 ml), filtered through a pad of celite and the solid was washed with ethyl acetate. The resulting filtrate was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 ml). The combined organic solutions were dried and evaporated to give the *alcohol* **185** (1.82 g), as a yellow oil, which was used crude in the next step: $R_f$ 0.69 and 0.54 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3356 (br), 2965 (s), 2875 (s), 1688 (s), 1455 (s), 1392 (s) and 1366 (s); $\delta_C$ 10.9, 14.0 (both Me), 18.8, 22.3, 24.0 (all $CH_2$), 28.7 (*t*-Bu), 31.0 ($CH_2$), 57.3, 65.3 (both CH), 82.4 (C-$(CH_3)_3$), 86.8, 102.8 (both C≡C) and 156.9 (C=O); *m/z* [APcI] 214 ($M^+$ -  , 100%).

*ii) Swern Oxidation*

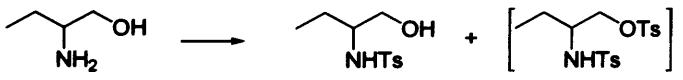
A solution of oxalyl chloride (569 mg, 0.39 ml, 4.48 mmol, 1.51 eq) in anhydrous dichloromethane (11.4 ml) was cooled to -78°C prior to the addition of anhydrous dimethylsulfoxide (698 mg, 0.63 ml, 8.94 mmol, 3.0 eq) in anhydrous dichloromethane (5.36 ml). The resultant solution was stirred for 0.5 h and then the crude alcohol **184** (800 mg, 3.0 mmol, 1 eq) in dichloromethane (3.2 ml) was added and the reaction mixture stirred for an addition hour. *N,N*-Diisopropylethylamine (2.34 g, 3.2 ml, 18.1 mmol, 6.1 eq) was added and the reaction was allowed to warm to 0°C over a 1 h period, then an ice-cold 1M solution of hydrochloric acid (3.2 ml) was added. The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 10 ml). The combined organic solutions were washed with pH 7 phosphate buffer (30 ml) then dried and evaporated to yield the *ynone* **185** (697 mg) as a yellow oil: $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3356 (br), 2969 (s), 1713 (br), 1461 (s) and 1367 (s); $\delta_H$ 0.85 (6H, t, *J* 7.3, 1-Me and 10-Me), 1.05-1.55 (4H, m, 2 x

$CH_2$), 1.40 (9H, s, *t*-Bu), 1.55-1.70 (1H, m, $C\underline{H}_aCH_b$), 1.90-2.00 (1H, m, $CH_aC\underline{H}_b$), 2.30 (3H, t, *J* 7.0, 5-$CH_2$), 4.25-4.35 (1H, m, 3-H) and 5.15 (1H, br. d, *J* 7.1, NH); $\delta_C$ 7.4, 17.6 (both Me), 16.9, 18.3, 23.0 (all $CH_2$), 26.5 (*t*-Bu), 27.7 ($CH_2$), 60.3 (CH), 77.9 (C≡C), 81.0 ($\underline{C}$-$(CH_3)_3$), 96.12 (C≡C), 153.5 (N-C=O) and 185.0 (C=O)

*iii) Reduction*

To a solution of the crude ketone **185** (547 mg, 2.00 mmol, 1.0 eq) in anhydrous tetrahydrofuran (12 ml) at -100°C was added a 1 M solution of L-selectride in tetrahydrofuran (4.1 ml, 4.01 mmol, 2.0 eq). The reaction was stirred for 0.5 h and was then quenched with methanol (2 ml). The cold bath was removed and the reaction vessel was allowed to warm up to room temperature. The product was extracted into diethyl ether (3 x 15 ml) and the combined ether solutions were washed with saturated brine (20 ml). The organic layers were dried and evaporated. The residue was purified (10% ethyl acetate/petroleum) to furnish the *alcohol* **186** (91 mg, 10%, over 4 steps) as a yellow oil. $R_f$ 0.6 (40% ethyl acetate/petroleum ether; $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3390 (br), 2966 (s), 2874 (s), 1692 (s), 1458 (s) and 1366 (s); $\delta_H$ 0.90 (6H, t, *J* 7.4, 1-Me and 10-Me), 1.35 (9H, s, *t*-Bu), 1.50-1.65 (1H, m, $C\underline{H}_aCH_b$), 1.65-1.80 (1H, m, $CH_aC\underline{H}_b$), 3.95 (1H, br. d, *J* 5.1, OH), 4.00-4.10 (1H, m, 4-H), 4.55 (1H, br. d, *J* 5.2, 3-H) and 4.95 (1H, br. d, *J* 8.0, NH); $\delta_C$ 11.1, 14.0 (both Me), 18.8, 22.3, 24.7 (all $CH_2$), 28.8 (*t*-Bu), 31.1 ($CH_2$), 57.6, 62.2 (both CH), 78.1 (C≡C), 80.2 ($\underline{C}$-$(CH_3)_3$), 87.5 (C≡C) and 157.3 (C=O); *m/z* [APcI] 196 ($M^+$ CO-*t*-Bu, 20%), 170 (22) and 152 (100).

## 2-(Tosylamino)butan-1-ol 187




**181** **187** **188**

*i) Method A*

2-amino-1-butanol **181** (500 mg, 5.61 mmol) was tosylated using *p*-tosyl chloride (1.07 g, 5.61 mmol) and triethylamine (680 mg, 6.73 mmolaccording to general procedure G. Following recrystallisation (10% ethyl acetate/petroleum ether) of the residue the *sulfonamide* **187** was obtained (585 mg, 43%, first recrystallisation), as an off-white solid. The data obtained was in accordance with that reported in the literature for (*S*)-2-

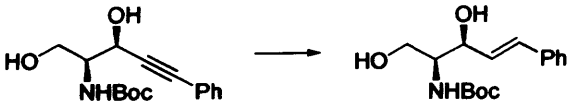
(tosylamino)butan-1-ol, with the exception of the chemical shifts for the $^1$H NMR. $R_f$ 0.13 (40% ethyl acetate/petroleum ether); m.p. 65-67°C [lit[10] m.p. 73°C]; $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3473 (br), 2950 (s), 2950 (s), 1598 (s), 1431 (s), 1313 (s), 1157 (s) and 810 (s); $\delta_H$ 0.60 (3H, t, *J* 7.5, 4-Me), 1.25-1.45 (4H, m, 3-$CH_2$), 2.35 (3H, s, Ar-Me), 2.55 (1H, br. res, OH), 3.00-3.10 (1H, m, 2-CH), 3.40 (1H, dd, *J* 11.3 and 5.2, 1-C$\underline{H_a}CH_b$), 3.50 (1H, dd, *J* 11.3 and 3.8, 1-$CH_aC\underline{H_b}$), 5.30 (1H, br. res., NH), 7.20 (2H, d, *J* 8.1, 2 x Ar-H), and 7.70 (2H, d, *J* 8.1, 2 x Ar-H); $\delta_C$ 10.6 (4-Me), 22.0 (Ar-Me), 25.0 (3-$CH_2$), 57.6 (CH), 64.7 (1-$CH_2OH$), 127.5, 130.1 (both ArCH), 138.0 and 143.87 (both ArC); *m/z* [APcI] 244 ($M^+$ + H, 100%), 226 (35), 184 (25) and 155 (22). [Found: C, 54.25; H, 7.09, N, 5.94 $C_{11}H_{17}NO_3S$ requires C, 54.30; H, 7.04; N, 5.76%].

*ii) Method B*

The amino alcohol **181** (500 mg, 5.61 mmol) was tosylated using an identical procedure to that above except utilising pyridine (530mg, 6.73 mmol) as the base to give a 1.5:1 mixture of i) the *sulfonamide* **187** and ii) the *tosylate* **188** (1.37 g). The sulfonamide **188** was characterised by: $\delta_H$ 0.55-0.65 (3H, m, 4-Me), 1.20-1.45 (2H, m, 3-$CH_2$), 2.30 (3H, s, Ar-Me), 2.35 (3H, s, Ar-Me), 3.15-3.25 (1H, m, 2-CH), 3.75 (1H, dd, *J* 10.0 and 5.1, 1-C$\underline{H_a}CH_b$), 3.85 (1H, dd, *J* 10.0 and 3.8, 1-$CH_aC\underline{H_b}$), 5.30 (1H, d, *J* 8.3, NH), 7.15-7.25 (4H, m, 4 x Ar-H) and 7.55-7.65 (4H, m, 4 x Ar-H).

The data obtained for the sulfonamide **187** was in aggrement with that reported above.

### (*4E,2S,3S*)-2-(*t*-butoxycarbonylamino)-5-phenylpent-4-en-1,3-diol 207

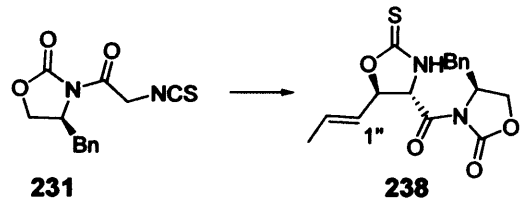



**204** **207**

The amino alcohol **204** (222 mg, 0.76 mmol) was reduced using a 35% Red-al in toluene according to general procedure H. The residue was purified by chromatography (50% ethyl acetate/petroleum ether) to furnish the *(E)-olefin* **207** (157 mg, 70%), as a colourless oil: $R_f$ 0.11 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3396 (br), 2977 (s), 1692 (s), 1504 (s), 1451 (s), 1392 (s), 1367 (s), 967 (s), 755 (s) and 694 (s); $\delta_H$ 1.30 (9H, s, *t*-Bu), 2.70 (1H, br. res, OH), 3.00 (1H, br. res, OH), 3.65 (1H, br. res, 2-H), 3.80 (2H, br.

res., $CH_2$), 4.50 (1H, br. res, 3-H), 5.25 (1H, d, *J* 8.2, NH), 6.10 (1H, dd, *J* 15.9 and 5.8, 4-H), 6.55 (1H, d, *J* 15.9, 5-H) and 7.10-7.25 (5H, m, Ph); $\delta_C$ 28.3 (*t*-Bu), 55.5 (CH), 63.9 ($CH_2$), 73.0 (CH), 80.0 ($\underline{C}(CH_3)_3$), 126.6 (ArCH), 127.8 (=CH), 128.6, 128.7 (both ArCH), 131.4 (=CH), 136.5 (ArC) an 156.6 (C=O). The data obtained was in agreement with the literature[14] (except that the literature proton data was reported in $d_6$-DMSO).

**(*4S*), (*1''E,4'S,5'R*)-4-Benzyl-3-(5-propenyl-2-thioxo-oxazolidine-4-carbonyl)-oxazolidin-2-one 238**




**231** **238**

*i) Method A*

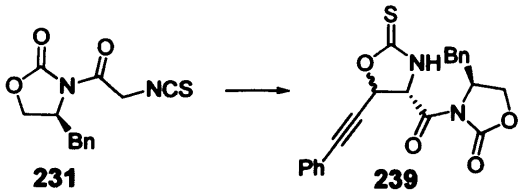
To a flame dried flask purged with nitrogen was added tin triflate (1.0 g, 2.40 mmol, 1.0 eq), which was dissolved in anhydrous tetrahydrofuran (12.6 ml), which on cooling to -78°C gave a cloudy solution. Next *N*-ethylpiperidine (407 mg, 0.49 ml, 3.60 mmol, 1.5 eq) was added and the solution was stirred for 5 minutes prior to the addition of a -78°C solution of the isothiocyanate **231** (729 mg, 2.64 mmol, 1.1 eq) in tetrahydrofuran (10 ml), to give a yellow solution which was stirred for a further 1.5 h at this temperature. Freshly distilled (*E*)-croton aldehyde (185 mg, 0.22 ml, 2.64 mmol, 1.0 eq) was added slowly and the mixture was stirred for an additional 4 h. The reaction was quenched with pH 7 phosphate buffer (8 ml) and the resultant white suspension was then filtered through celite, and the solid was washed with dichloromethane. The filtrate and washings were diluted with dichloromethane and washed with 1M $NaHSO_3$ (2 x 20 ml). The organic phase was dried over sodium sulfate and the solvent was evaporated. The residue was purified by chromatography (30% ethyl acetate/petroleum ether) to yield the *aldol product* **238** (223 mg, 33%) as a yellow oil, together with some recovered *isothiocyanate* **231** (182 mg): $R_f$ 0.23 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}[CH_2Cl_2]$ 3327 (br), 2921 (s), 1778 (s), 1706 (s), 1604 (m), 1494 (s), 1392 (s), 1178 (s), 975 (s), 735 (s) and 703 (s); $\delta_H$ 1.65 (3H, d, *J* 6.6, Me), 2.80 (1H, dd, *J* 13.6 and 8.9, $C\underline{H}_aCH_b$-Ph), 3.15 (1H, dd, *J* 13.6 and 3.3,

$CH_aC\underline{H}_b$-Ph), 4.20-4.45 (2H, m, $OCH_2$), 4.60-4.70 (1H, m, CHN), 4.85 (1H, d, *J* 4.4, CHN), 5.55 (1H, dd, *J* 14.9 and 7.5, =CH), 5.65 (1H, dd, *J* 7.5 and 4.4, CHO), 5.95 (1H, dq, *J* 14.9 and 6.6, =CHMe), 7.10-7.35 (5H, m, Ph) and 7.70 (1H, br. res., NH, exchanges with $D_2O$); $\delta_C$ 17.8 (Me), 37.5 ($CH_2$-Ph), 55.3, 63.2 (both CH), 67.7 ($CH_2$-CH), 84.1, 121.3 (both CH), 129.2, 129.5 (both ArCH), 133.5 (=CH), 134.2 (ArC), 153.7, 166.3 (both C=O) and 188.9 (C=S); *m/z* [APcI] 347 ($M^+$ + H, 100%), 178 (93), 117 (38) and 110 (43). [Found $M^+$+H: 347.1060. $C_{17}H_{19}N_2O_4S$ requires *M*, 347.1060].

*ii) Method B*

To a flame dried flask purged with nitrogen was added tin triflate (1.0 g, 2.40 mmol, 2.2 eq), isothiocyanate **231** (624 mg, 2.26 mmol, 1.9 eq) followed by anhydrous tetrahydrofuran (10 ml) and the resulting solution was cooled to -78°C. Next a -78°C solution of freshly prepared Lithium hexamethyldisilazane (425 mg, 2.64 mmol, 0.56 ml, 2.2 eq) was added *via* canula and the solution was stirred for 0.5 h. Freshly distilled (*E*)-croton aldehyde (84 mg, 0.1 ml, 1.20 mmol, 1.0 eq) was added slowly and the mixture was stirred for a further 1.5 h. The reaction was quenched with a 1:1 solution of pH 7 phosphate buffer / saturated aqueous ammonium chloride solution (10 ml) and the white suspension produced was filtered through celite. The filtrate and washings were poured onto dichloromethane and the resultant two layers were separated. The organic solutions were washed with 1M $NaHSO_3$ (2 x 10 ml). The combined organic solutions were dried, and evaporated. The residue was purified by chromatography (30% ethyl/petroleum ether) and the mixed fractions recolumned using the same solvent system to furnish the *aldol adduct* **238** (145 mg, 35%) together with some recovered isothiocyanate **231** (232 mg). The data obtained was in accordance with that reported previously.

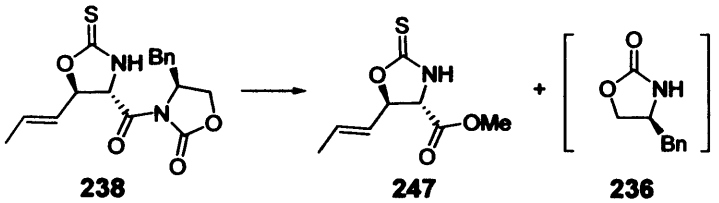
**(*4S*), (*4'S*)-4-Benzyl-3-(5-phenylethynyl-2-thioxo-oxazolidine-4-carbonyl)-oxazolidin-2-one 239**




A solution of tin triflate (333 mg, 0.80 mmol, 1.30 eq) dissolved in tetrahydrofuran (4.16 ml) was cooled to -78°C, to give a cloudy solution. Next distilled *N*-ethylpiperidine (104 mg, 0.13 ml, 0.92 mmol, 1.5 eq) was added and the solution was stirred for 5 minutes before adding a -78°C solution of the isothiocyanate **231** (187 mg, 0.68 mmol, 1.1 eq) in tetrahydrofuran 1.35 ml), to give a yellow solution which was stirred for 1.5 h at this temperature. The acetylenic aldehyde **117** (104 mg, 0.80 mmol, 1.3 eq) dissolved in tetrahydrofuran (2 ml) was added slowly and the mixture was stirred for a further 4 h. The reaction was quenched with pH 7 phosphate buffer (3 ml) and the white suspension produced was then filtered through celite. The filtrate was diluted with dichloromethane and washed with 1M sodium bisulfate solution (2 x 10 ml). The organic phase was dried over sodium sulfate and the solvent was evaporated. The residue was purified using column chromatography (30% ethyl acetate/petroleum ether) to yield the *aldol product* **239** (80 mg, 29%) as a 7:3 mixture of diastereoisomers, (B is the minor isomer) as yellow oil: $R_f$ 0.29 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$[$CH_2Cl_2$] 3390 (br), 1779 (s), 1709 (s), 1490 (s), 1393 (s), 1117 (s) and 759 (s); $\delta_H$ 2.75 (1H, dd, *J* 13.5 and 9.6, C$\underline{H}_a$C$H_b$-Ph, major isomer), 2.90 (1H, dd, *J* 13.6 and 8.6, C$\underline{H}_a$C$H_b$-Ph, minor isomer), 3.15 (1H, dd, 13.6 and 3.4, C$H_a$C$\underline{H}_b$-Ph, minor isomer), 3.25 (1H, dd, *J* 13.5 and 3.2, C$H_a$C$\underline{H}_b$-Ph, major isomer), 3.75 (1H, app t, *J* 8.6, C$\underline{H}_a$C$H_b$O, major isomer), 4.05 (1H, dd, *J* 9.4 and 3.0, C$H_a$C$\underline{H}_b$O, major isomer), 4.25 (1H, dd, *J* 9.1 and 3.3, C$\underline{H}_a$C$H_b$O, minor isomer), 4.35 (1H, app t, *J* 9.1 and 8.6, C$H_a$C$\underline{H}_b$O, minor isomer), 4.45-4.55 (1H, m, CHN, major), 4.70-4.75 (1H, m, CHN, minor), 5.25 (1H, d, *J* 4.2, CHN minor), 5.80 (1H, d, *J* 9.7, CHN, major), 6.0 (1H, d, *J* 9.7, CHO, major), 6.25 (1H, d, *J* 4.2, CHO, minor), 7.05-7.40 (10H, m, 2 x Ph), 7.95 (1H, br. res., NH, min) and 8.15 (1H, br. res, NH, maj); $\delta_C$ (major isomer) 37.8, ($CH_2$), 55.4, 62.7 (both CH), 67.5 ($CH_2$), 73.6 (CH), 80.0, 90.7 (both C≡C), 127.7, 128.7, 129.1, 129.4, 130.0, 131.8 (all ArCH), 134.4, 153.6 (both ArC), 166.5 (C=O) and 188.8

(C=S); *m/z* [APcI] 407 ($M^+ + H$, 100%). [Found $M^+ + H$: 407.1061. $C_{22}H_{19}N_2O_4S$ requires *M*, 407.1060].

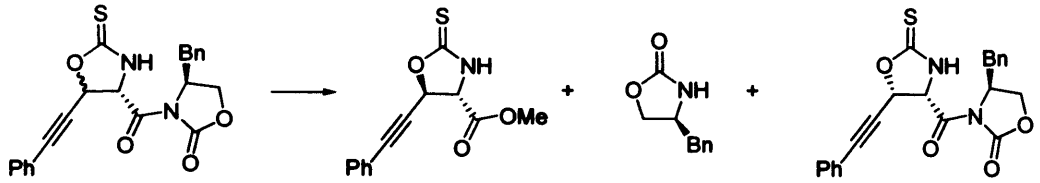
**Cleavage of Auxiliary from (*4S*), (*1''E,4'S,5'R*)-4-Benzyl-3-(5-propenyl-2-thioxo-oxazolidine-4-carbonyl)-oxazolidin-2-one 238**




**238** **247** **236**

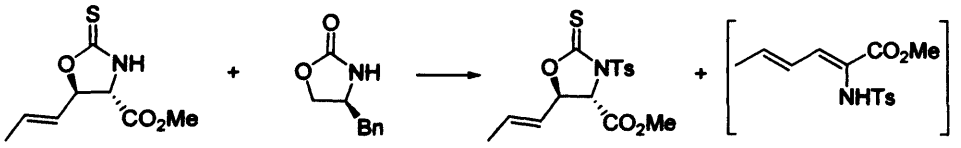
To an ice-cold solution of 3M methyl magnesium bromide in diethyl ether (0.07 ml, 0.22 mmol, 1.5 eq) was added anhydrous tetrahydrofuran (0.69 ml), followed by anhydrous methanol (1.38 ml) dropwise. The resultant solution was stirred for 5 minutes before adding the aldol product **238** (50 mg, 0.14 mmol, 1.0 eq) in tetrahydrofuran (2 ml). The yellow solution was stirred for a further 20 mins at this temperature. The reaction was quenched by the addition of a 1M solution of $KHSO_4$ and then the solvent was evaporated. The aqueous solution was diluted with water (1 ml) and the product was extracted into dichloromethane (3 x 2 ml) and the combined organic solutions were dried and evaporated. The residue was purified by column chromatography (30% ethyl acetate/petroleum ether) to yield i) the *ester* **247** (15 mg, 52%) as a pale yellow oil and ii) the *auxiliary* **236** (17 mg, 65%). The ester **247** was characterised by: $R_f$ 0.23 (40% ethyl acetate/petroleum ether); $\delta_H$ 1.70 (3H, app dd, *J* 6.6 and 1.4, Me), 3.75 (3H, s, $CO_2Me$), 4.25 (1H, d, *J* 6.2, CHN), 5.25 (1H, app t, *J* 7.4 and 6.2, CHO), 5.55 (1H, app ddd, *J* 15.2, 7.4 and 1.6, =CH), 5.90 (1H, dq, *J* 15.2 and 6.6, =CH-Me); $\delta_C$ 17.8 (Me), 53.4 ($CO_2Me$), 62.5, 85.6 (both CH), 125.6, 134.3 (both =CH), 168.5 (C=O) and 189.0 (C=S); *m/z* [APcI] 202 ($M^+ + H$, 100%). The data obtained for the auxilary **236** was identical to that reported in the literature.[12]

**Cleavage of Auxiliary from (4*S*),(*4'S*)-4-Benzyl-3-(5-phenylethynyl-2-thioxo-oxazolidine-4-carbonyl)-oxazolidin-2-one 239**



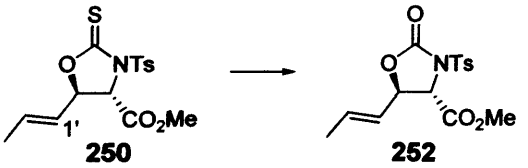

A 3M solution of methylmagnesium bromide in diethyl ether (0.08 ml, 0.24 mmol, 1.5 eq) in tetrahydrofuran (0.8 ml) was cooled in an ice-bath, prior to the careful addition of distilled methanol (1.53 ml). The solution was stirred for 5 mins and a 7:3 mixture of diastereoisomers of the aldol product **239** (66 mg, 0.16 mmol, 1 eq) was added dropwise as a solution in tetrahydrofuran (1 ml). The reaction mixture was stirred for 20 mins and was then quenched with a 1M solution of sodium hydrogen sulfate. The solvent was evaporated, the aqueous solution was diluted with water (0.5 ml) and the aqueous phase was extracted with dichloromethane (3 x 2 ml). The combined organic solutions were dried and evaporated. The residue was chromatographed (20% ethyl acetate/petroleum ether) to give i) *thiocarbamate* **248a** (8 mg, 62%), as an orange oil: $R_f$ 0.21 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$[$CH_2Cl_2$] 3320 (s), 2954 (s), 2233 (s), 1748 (s), 1491 (s), 1442 (s), 1216 (s), 758 (s) and 736 (s); $\delta_H$ 3.80 (3H, s, $CO_2Me$), 4.60 (1H, d, *J* 5.1, CHN), 5.80 (1H, d, *J* 5.1, CHO), 7.15-7.55 (5H, m, Ph) and 7.65 (1H, br. res., NH); $\delta_C$ 53.7 (Me), 63.4, 74.2 (both CH), 82.0, 90.1 (both C≡C), 120.9 (ArC), 128.5, 129.7, 132.0 (all ArCH), 167.5 (C=O) and 188.3 (C=S); *m/z* [APcI] 262 ($M^+$ + H, 19%), 230 (20), 202 (38), 170 (78), 167 (28) and 149 (100). [Found $M^+$ +H: 260.0532. $C_{13}H_{12}NO_3S$ requires *M*, 262.0532]. ii) Evans' Auxiliary **236** (2 mg, 22%) the data obtained for which is in accordance with the liteature[12] and iii) the recovered major isomer **239b** (35 mg).

**Tosylation of (*1'E,4S,5R*)-methyl 5-(prop-1-enyl)-2-thiooxazolidine-4-carboxylate 5-propenyl-2-thioxo-oxazolidine-4-carboxylate 247**




A 1.9:1 mixture of the methyl ester **247** and auxiliary **236** (60 mg) was tosylated according to general procedure G with *p*-tosyl chloride (63 mg, 0.33 mmol, 1.1 eq) and triethylamine (33 mg, 0.045 ml, 0.33 mmol, 1.1 eq). The residue was purified using chromatography (20% ethyl acetate/petroleum ether) to give i) *sulfonamide* **250** (44 mg, 61%) as a colourless oil and ii) the *diene* **251** (1 mg, 2%). The sulfonamide **250** was characterised by: $R_f$ 0.25 (40% ethyl acetate/petroleum ether); $[\alpha]_D$ +30.53 ($CH_2Cl_2$, c 0.76); $R_f$ 0.25 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}[CH_2Cl_2]$ 2955 (m), 1757 (s), 1595 (m), 1375 (s), 1171 (s), 1087 (m) and 813 (m); $\delta_H$ 1.70 (3H, app. dd, *J* 6.6 and 1.3, Me), 2.40 (3H, s, Ar-Me), 3.80 (3H, s, $CO_2Me$), 4.85 (1H, d, *J* 5.1, CHN), 4.95 (1H, dd, *J* 7.5 and 5.1, CHO), 5.45 (1H, app ddd, *J* 15.2, 7.5 and 1.5, =CH), 5.85 (1H, dq, *J* 15.2 and 6.6, =CH-Me), 7.30 (2H, d, *J* 8.4, 2 x Ar-H) and 7.95 (2H, d, *J* 8.4, 2 x Ar-H); $\delta_C$ 17.8 (Me), 21.8 (Ar-Me), 53.6 ($CO_2Me$), 66.2, 82.8 (both CH), 124.6 (=CH), 129.3, 130.3 (both ArCH), 133.1 (ArC), 135.0 (=CH), 146.2 (ArC), 168.3 (C=O) and 182.6 (C=S); *m/z* [APcI] 356 ($M^+ + H$, 100%). [Found $M^+$+H: 356.0623. $C_{15}H_{18}NO_5S$ requires *M*, 356.0621]. The data obtained for the diene **251** is reported later (p 237).

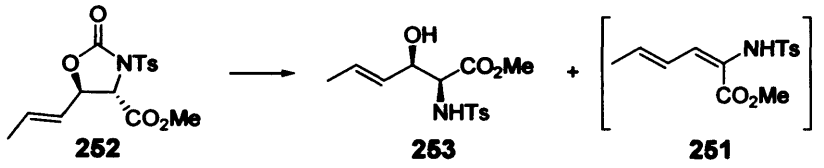
**(*1'E,4S,5S*) Methyl 2-oxo-5-(prop-1-enyl)-3-tosyloxazolidine-4-carboxylate 252**




To an ice-cold solution of the thiocarbamate **250** (18 mg, 0.050 mmol, 1.0 eq) in dichloromethane (0.5 ml) was added mercury acetate (24 mg, 0.076 mmol, 1.5 eq) in one portion. The reaction was stirred at this temperature for 1 h, and then was allowed to warm

to room temperature and stirred for an additional 2.5 h. The white suspension was recooled in an ice-bath and quenched with a 1 M solution of potassium carbonate (1 ml). The resultant layers were separated and the aqueous phase was extracted with dichloromethane (3 x 2 ml). The combined organic layers were washed with saturated brine (5 ml), dried and evaporated. The residue was purified by chromatography (20% ethyl acetate/petroleum ether) to give the *carbamate* **252** (17 mg, 100%): $[\alpha]_D$ +22.69 ($CH_2Cl_2$, c 0.52); $R_f$ 0.39 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2956 (m), 1790 (s), 1758 (s), 1674 (w), 1597 (m), 1494 (w), 1439 (m), 1365 (s), 1309 (m), 1173 (s), 1090 (m), 966 (m) and 816 (m); $\delta_H$ 1.70 (3H, app dd, *J* 6.6 and 1.4, Me), 2.40 (3H, s, Ar-Me), 3.75 (3H, s, $CO_2Me$), 4.60 (1H, d, *J* 5.0, CHN), 4.70 (1H, dd, *J* 7.4 and 5.0, CHO); 5.45 (1H, app ddd, *J* 15.2, 7.4 and 1.6, =CH), 5.85 (1H, dq, *J* 15.2 and 6.6, =CH-Me), 7.30 (2H, d, *J* 8.4, 2 x Ar-H) and 7.90 (2H, d, *J* 8.4, 2 x Ar-H); $\delta_C$ 17.8 (Me), 21.8 (Ar-Me), 53.4 ($CO_2Me$), 62.6, 77.8 (both CH), 125.1 (=CH), 129.1, 129.6 (both ArCH), 134.1 (=CH), 134.3, 146.0 (both ArC), 150.8 and 168.5 (both C=O); *m/z* [APcI] 340 ($M^+$ + H, 100%) and 296 (20). [Found $M^+$ +$NH_4$: 357.1115. $C_{15}H_{21}N_2O_6S$ requires *M*, 357.1115].

**Ring Opening of (*1'E,4S,5R*) Methyl 2-oxo-5-(prop-1-enyl)-3-tosyloxazolidine-4-carboxylate 252**

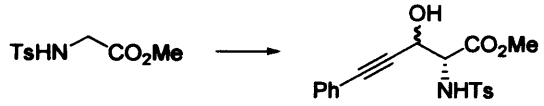



**252** **253** **251**

Cesium carbonate (5 mg, 0.015 mmol, 1.0 eq) was added to a solution of the cyclic carbamate **252** (24 mg, 0.071 mmol, 4.75 eq) in distilled methanol (1 ml) and the reaction mixture was stirred for 3.5 h. Next, the reaction mixture was cooled in an ice-bath and 1 M hydrochloric acid (2 ml) was added. The solvent was evaporated and the product was taken up in dichloromethane. The two layers were separated and the aqueous phase was extracted with dichloromethane (2 x 3 ml). The combined organic solutions were dried and evaporated. The NMR of the crude product revealed that the reaction was incomplete, so the residue was treated with the same quantities of reagents for an additional 21 h at room temperature. The residue was purified by chromatography (40% ethyl acetate/petroleum ether) to furnish i) the (*E*)-*alkene* **253** (2 mg, 9%) and ii) the *diene* **251** (9 mg, 43%). The (*E*)-alkene **253** was characterised by: $R_f$ 0.13 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$[$CH_2Cl_2$] 3499 (br), 3280 (br), 2923 (m), 1738 (s), 1598 (s), 1495 (m), 1435 (m), 1337 (s), 1162 (s), 1040 (s), 968 (s) and 816 (s); $\delta_H$ 1.60 (3H, app. dd, *J* 6.6 and 1.3, 6-Me), 2.10 (1H, br. res., OH, exchanges with $D_2O$), 2.35 (3H, s, Ar-Me), 3.45 (3H, s, $CO_2Me$), 3.85 (1H, dd, *J* 9.7 and 3.5, 2-H), 4.30 (1H, br. res., 3-H), 5.35 (1H, d, *J* 9.7, NH), 5.40 (1H, ddd, *J* 15.2, 7.3 and 1.6, 4-H), 5.70 (1H, dq, *J* 15.2 and 6.6, 5-H), 7.20 (2H, d, *J* 8.2, 2 x Ar-H) and 7.65 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ 17.8 (6-Me), 21.6 (Ar-Me), 52.7 ($CO_2Me$), 60.2, 73.4 (both CH), 127.3 (ArCH), 128.4 (=CH), 129.6 (ArCH), 130.9 (=CH), 136.7, 143.7 (both ArC) and 170.3 (C=O); *m/z* [APcI] 314 ($M^+$ + H, 18%), 296 (100) and 236 (48). [Found $M^+$+$NH_4$: 331.1326. $C_{14}H_{23}N_2O_5S$ requires *M*, 331.1322]. The *diene* **251** was characterised by: $R_f$ 0.37 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3278 (br), 2927 (m), 2854 (m), 1736 (s), 1598 (m), 1494 (w), 1338 (m), 1166 (s), and 814 (m); $\delta_H$ 1.85 (3H, app dd, *J* 6.9 and 1.5, 6-Me), 2.35 (3H, s, Ar-Me), 3.35 (3H, s, $CO_2Me$), 6.10 (1H, s, NH), 6.15 (1H, qd, *J* 15.1 and 6.9, 5-H), 6.65 (1H, app ddd, *J* 15.1, 11.3 and 1.7, 4-H), 7.10 (1H, d, *J* 11.3, 3-H), 7.20 (2H, d, *J* 8.2, 2 x Ar-H); and 7.60 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ 19.2, 21.6 (both Me), 52.3 ($CO_2Me$), 120.1, (=CH), 127.3 (C),

127.6, 129.4 (both ArCH), 136.0 (ArC), 139.8, 141.9 (both =CH), 143.9 (ArC) and 165.1 (C=O); *m/z* [APcI] 296 ($M^+ + H$, 100%), 291 (47) and 276 (37).

**(*2RS*)-Methyl 3-hydroxy-5-phenyl-2-(tosylamino)pent-4-ynoate 146**




**152** **146**

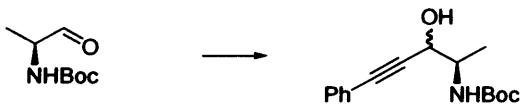
*N*-tosyl glycine **152** (6.35 g, 26.1 mmol) was reacted with phenyl propynal **117** (4.08 g, 31.3 mmol) according to general procedure C except in the absence of tin(II) chloride. The residue was purified by chromatography (30% ethyl acetate/petroleum ether) to yield the *aldol adduct* **146** (1.45 g, 15%) as a 1:1 mixture of diastereoisomers, as a brown oil: $R_f$ 0.58 (40% ethyl acetate/petroleum ether), $\nu_{max}/cm^{-1}$ 3298 (br), 2930 (m), 1715 (s), 1598 (m), 1491 (s), 1443 (m), 1383 (m), 1335 (s), 1164 (s), 848 (m), 814 (m), 758 (s) and 691 (s); $\delta_C$ (both diastereoisomers) 21.5, 21.6 (Ar-Me), 53.1, 53.1 ($CO_2Me$), 60.6, 60.7 (CH), 63.5, 64.3 (CH), 84.3, 85.2, 87.2, 87.6 (all C≡C), 121.5, 121.7 (ArC), 127.2, 127.4, 128.3, 128.3, 128.9, 129.0, 129.6, 129.8, 131.9, 132.0 (all ArCH), 136.1, 136.9, 143.7, 144.1 (all ArC), 168.6 and 169.5 (both C=O); *m/z* [APcI] 356 ($M^+ - H_2O$, 100%). The *syn* diastereoisomer **146b** was characterised by: $\delta_H$ 2.25 (3H, s, Ar-Me), 3.45 (3H, s, $CO_2Me$), 4.15-4.25 (2H, m, 2-H), 4.90 (1H, d, *J* 3.5, 3-H), 5.85 (2H, br. res., NH), 7.05-7.35 (7H, m, Ph and 2 x Ar-H) and 7.70 (2H, d, *J* 8.3, 2 x Ar-H). The data obtained for the *anti* diastereoisomer **146a** is identical with that previously reported (p 219).

**(*4E,2RS*)-Methyl 3-hydroxy-2-(tosylamino)hex-4-enoate 150**


**137** **152** **150**

*N*-tosyl glycinate **152** (1.0 g, 4.11 mmol) and (*E*)-croton aldehyde **137** (0.41 g, 0.48 ml, 5.85 mmol) were reacted together according to general procedure C, except for the absence of tin(II) chloride. The residue was purified by column chromatography (40% ethyl acetate/ petroleum ether) to give the *amino alcohol* **150** (132 mg, 10%) as an inseparable mixture of *anti* and *syn* diastereoisomers in the ratio of 1:1.6 respectively, as a pale yellow oil, together with a trace of impurities. The data obtained for the both the diastereoisomers was identical to that previously reported (p 221).

**(*2R*)-*tert*-butyl-3-hydroxy-5-phenylpent-4-yn-2-ylcarbamate 257**




**195** **257**

*i) Method A- Alkylation using lithioalkyne*

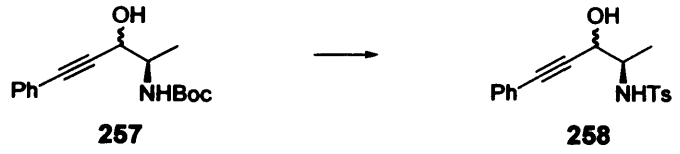
Phenylacetylene **145** (391 mg, 0.42 ml, 1.53 mmol, 2.5 eq) was dissolved in distilled tetrahydrofuran (6 ml) and the resulting solution was cooled to -20°C. A 2.5 M solution of n-BuLi in hexanes (1.68 ml, 4.21 mmol, 2.75 eq) was added drop-wise and the solution was stirred at this temperature for 0.5 h. The reaction mixture was cooled to -78°C for 10 mins prior to the dropwise addition of the aldehyde **195** (265 mg, 1.53 mmol, 1.0 eq), in tetrahydrofuran (3 ml). The reaction mixture was stirred for 2 h at -78°C and was then quenched with pH 7 phosphate buffer (3 ml). The solution was filtered through celite and the solid was washed with ethyl acetate. The aqueous layer was extracted ethyl acetate (2 x 10 ml). The combined ethyl acetate solutions were dried, filtered and evaporated. The residue was purified by column chromatography (20% ethyl acetate/petroleum ether) to give the *alkyne* **257** (286 mg, 68%), as a 3:1 mixture of diastereoisomers, as a yellow oil:

$R_f$ 0.31 (40% ethyl acetate/ petroleum ether); $\nu_{max}$ /cm$^{-1}$ [Film] 3355 (br), 2977 (s), 1694 (s), 1505 (s) and 1470 (s); $\delta_H$ 1.15-1.20 (3H, m, 2-Me, major isomer), 1.25 (3H, d, *J* 6.8, 2-Me, minor isomer), 1.40 (18H, s, 2 x *t*-Bu, both isomers), 3.05 (1H, br. res., OH, major isomer), 3.40 (1H, br. res., OH, minor isomer), 3.85-3.95 (1H, br. res., 2-H, major isomer), 3.95 (1H, br. res., 2-H, minor isomer), 4.50 (1H, d, *J* 5.4, 3-H, major isomer), 4.60 (1H, br. res., 3-H, minor isomer), 4.70 (1H, d, *J* 8.5, NH, major isomer), 4.75 (1H, br. res., NH, minor isomer), 7.20-7.30 (6H, m, 6 x Ar-H, both isomers) and 7.30-7.40 (4H, m, 4 x Ar-H, both isomers); $\delta_C$ 16.2 (Me), 28.4 (*t*-Bu), 50.9, 51.3, 66.2, 66.5 (all CH), 79.8, 79.9 (both $\underline{C}$-$(CH_3)_3$), 85.7, 86.1, 87.1, 87.6 (all C≡C), 112.4, 112.5 (both ArC), 128.2, 128.3, 128.5, 128.5, 131.8, 131.8 (all ArCH), 156.0 and 156.3 (both C=O); *m/z* [APcI] 276 ($M^+$ + H, 100%), 260 (18), 220 (15), 202 (17) and 53 (32).

*ii) Method B- Alkylation in the presence of zinc bromide.*

A solution of the alkyne **145** (1.24 g, 12.14 mmol, 1.3 eq) in distilled diethyl ether (12 ml) was cooled to -20°C in a salt-ice bath. A 2.5 M solution of n-BuLi (5.24 ml, 13.1 mmol, 1.4 eq) was added and the resultant solution was stirred for 1 h. The solution was warmed to 0°C and anhydrous zinc bromide (2.95 g, 13.1 mmol, 1.4 eq) was added and the reaction mixture was stirred for an additional hour at this temperature and then an hour at room temperature. The reaction mixture was cooled to -78°C and then the racemic aldehyde **195** (1.62 g, 9.35 mmol, 1.0 eq) was added as a solution in diethyl ether (16 ml). The cold bath was removed and the reaction mixture was stirred for 16 h. The solution was cooled to -20°C and the reaction was quenched by the addition of saturated aqueous ammonium chloride (6 ml). Water (10 ml) was added, the two layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 ml). The combined ether layers were dried and evaporated to furnish the *amino alcohol* **257** (approx. 2.60 g), as a 1.2:1 mixture of diastereoisomers together with some phenyl acetylene as a yellow oil. The data obtained was in accordance with that previously reported.

**(*4RS*)-1-phenyl-4-(tosylamino)pent-1-yn-3-ol 258**




**257** **258**

*i) Deprotection with trifluoroacetic acid*

The crude mixture of *N*-Boc protected amine **257** and phenylacetylene **145** (2.60 g, *ca* 9.44 mmol) was deprotected using trifluoroacetic acid (5.2 ml) according to general procedure F, for 1.5 h to furnish the crude *amine* (1.16 g), as a brown oil which was used without further purification.

*ii) Tosylation*

The crude amine (1.16 g, 6.61 mmol) was tosylated using a mixture of 2,4,6 collidine (1.38 g, 11.39 mmol) and *p*-toluene sulphonyl chloride (2.16 g, 11.3 mmol) according to general procedure H. The residue was purified by column chromatography (20% ethyl acetate/petroleum ether) to yield the *sulfonamine* **258** (698 mg, 23%, over 3 steps), as a mixture of diastereoisomers in the ratio 1.8:1 (*syn* **258b**: *anti* **258a**) as a brown oil: $R_f$ 0.33 and 0.25 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3500 (br), 3273 (s), 2926 (m), 1598 (m), 1491 (s), 1442 (s), 1382 (m), 1334 (s), 1164 (s), 814 (m), 758 (s) and 691 (s); $\delta_H$ 1.05 (3H, d, *J* 6.7, 2-Me, *syn* isomer), 1.10 (3H, d, *J* 6.7, 2-Me, *anti* isomer), 2.25 (3H, s, Ar-Me, *anti* isomer), 2.30 (3H, s, Ar-Me, *syn* isomer), 3.10-3.25 (2H, m, 2 x OH, exchanges with $D_2O$), 3.35-3.55 (2H, m, 2-H, both isomers), 4.40 (1H, d, *J* 5.5, 3-H, *anti* isomer), 4.45 (1H, br. d, *J* 2.1, 3-H, *syn* isomer), 5.35 (1H, d, *J* 8.2, NH, exchanges with $D_2O$, *anti* isomer), 5.40 (1H, d, *J* 8.9, NH, exchanges with $D_2O$, *syn* isomer), 7.05-7.30 (14H, m, 2 x Ph and 4 x Ar-H, both isomers) and 7.65-7.70 (4H, m, 4 x Ar-H); *m/z* [APcI] 330 ($M^+$ + H, 10%) and 312 (100). [Found $M^+ + NH_4$: 347.1423. $C_{18}H_{23}N_2O_3S$ requires *M*, 347.1424].

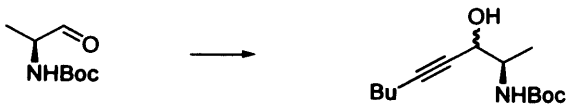
The *anti* diastereoisomer **258a** was isolated as a single diastereoisomer from a previous experiment and was characterised by: $[\alpha]_D$ -31.43 ($CHCl_3$, c 1.26 ); $\delta_C$ 17.0 (2-Me), 21.5 (Ar-Me), 54.1, 66.2 (both CH), 88.5 (C≡C, only one evident), 122.0 (ArC), 127.1, 128.3, 128.5, 129.8, 131.7 (all ArCH), 137.5 and 143.5 (both ArC).

**(*E,4RS*)-1-phenyl-4-(tosylamino)pent-1-en-3-ol 259**


**258** **259**

A 1.8:1 (*syn*:*anti*) mixture of diastereoisomers of the alkyne **258** (406 mg, 1.23 mmol) was reduced using a 70% solution of Red-al in toluene (1.85 ml, 6.16 mmol, 5.0 eq) according to general procedure H to give the *alkene* **259** (0.283 mg, 86%) as a yellow oil, as a mixture of diastereoisomers in the ratio 1.6:1 (*syn*:*anti*) which was used without purification: $R_f$ 0.36 and 0.31 (40% ethyl acetate/petroleum ether); $\nu_{max}$ /cm$^{-1}$ [$CH_2Cl_2$] 3500 (br), 3277 (s), 2976 (s), 2930 (s), 1598 (s), 1494 (s), 1449 (s), 1327 (s), 1160 (s), 967 (s), 814 (s), 751 (s) and 694 (s); $\delta_H$ 0.90 (3H, d, *J*, 6.9, 2-Me, *syn* isomer), 1.00 (3H, d, *J*, 6.7, 2-Me, *anti* isomer), 2.25 (3H, s, Ar-Me, *anti* isomer), 2.30 (3H, s, Ar-Me, *syn* isomer), 3.25 (1H, qd, *J* 6.1 and 5.1, 2-H, *anti* isomer), 3.40 (1H, qd, *J* 6.9 and 2.6, 2-H, *syn* isomer), 4.00-4.05 (1H, m, 3-H, *anti* isomer), 4.15-4.25 (1H, m, 2-H, *syn* isomer), 5.92 (1H, dd, *J* 16.0 and 6.9, 4-H, *anti* isomer), 6.00 (1H, dd, *J* 16.0 and 6.2, 4-H, *syn* isomer), 6.45 (2H, app t, *J* 16.0, 5-H, both isomers), 7.15-7.30 (14H, m, 14 x Ar-H, both isomers), 7.65 (2H, d, *J* 8.2, 2 x Ar-H, *anti* isomer) and 7.70 (2H, d, *J* 8.2, 2 x Ar-H, *anti* isomer); $\delta_C$ 14.5 (Me, *syn* isomer), 17.1 (Me, *anti* isomer), 20.4 (Ar-Me both isomers), 53.1 (CH, both isomers), 73.8 (CH, *syn* isomer), 74.3 (CH, *anti* isomer), 125.5, 125.6, 126.0, 126.7, 126.8, 127.3, 127.4, 127.5, 128.6, 128.7 (all ArCH, both isomers), 130.9, 131.3 (both =CH, both isomers), 135.3, 135.4, 136.6, 136.7, 142.2 and 142.3 (all ArC, both isomers); *m/z* [APcI] 314 ($M^+$ - $H_2O$, 100%). [Found $M^+$ +$NH_4$ 349.1576. $C_{18}H_{25}N_2O_3S$ requires *M*, 349.1580].

**(*2R*)-*tert*-butyl 3-hydroxynon-4-yn-2-ylcarbamate 262**




**195** **262**

*i) Method A*

1-hexyne **114** (314 mg, 0.44 ml, 3.82 mmol, 2.5 eq) was dissolved in distilled tetrahydrofuran (6 ml) and the solution was cooled to -20°C. A 2.5 M solution of n-BuLi in hexanes (1.68 ml, 1.53 mmol, 2.75 eq) was added drop-wise and the solution was stirred for 0.5 h. The solution was cooled to -78°C for 10 mins before the aldehyde **195**, in tetrahydrofuran (3 ml) was added slowly. The reaction mixture was stirred for 2 h at -78°C and was then quenched with pH 7 phosphate buffer (3 ml). The solution was filtered through celite and the aqueous phase was extracted ethyl acetate (2 x 10 ml). The combined ethyl acetate solutions were dried, filtered and evaporated. The residue was purified by column chromatography (20% ethyl acetate/petroleum ether) to give the *alkyne* **262** (272 mg, 70%), as a 3.5:1 mixture of diastereoisomers, as a yellow oil: $R_f$ 0.54 (40% ethyl acetate/ petroleum ether); $\nu_{max}/cm^{-1}$ [Film] 3388 (br), 2974 (s), 2932 (s), 1694 (s), 1455 (s), 1392 (s) and 1367 (s); $\delta_H$ 0.85 (6H, t, *J* 7.2, 9-Me, both isomers), 1.15 (1H, d, *J* 7.2, 1'-Me, minor isomer), 1.18 (1H, d, *J* 7.2, 1'-Me, major isomer), 1.30-1.45 (26H, m, *t*-Bu and 2 x $CH_2$, both isomers), 2.15 (6H, 2 x t, *J* 7.1 and 7.1, 6-$CH_2$, both isomers), 3.30 (1H, br. res., OH, major isomer), 3.40 (1, br. res., OH, minor isomer), 3.40 (1H, br. res, 2-H, major isomer), 3.85 (1H, br. res., 2-H, minor isomer), 4.30 (1H, br. res., 3-H, major isomer), 4.35 (1H, br. res, 3-H, minor isomer), 4.75 (1H, d, *J* 8.7, NH, major isomer) and 4.85 (1H, br. res., NH, minor isomer); $\delta_C$ 13.5 (9-Me, both isomers), 15.9, 16.1 (both 1'-Me), 18.3 ($CH_2$, minor isomer), 18.3 (CH2, major isomer), 21.9 ($CH_2$, both isomers), 28.2 (*t*-Bu, both isomers), 30.6, 30.6 ($CH_2$ both isomers), 50.8, 51.1, 65.7, 66.0 (both isomers), 77.9, 78.4 (both $\underline{C}$-$(CH_3)_3$, both isomers), 79.5, 80.0, 86.4, 86.8 (all C≡C, both isomers), 155.5 and 155.8 (C=O, both isomers); *m/z* [APcI] 256 ($M^+$ +H, 15%), 200 (35), 185 (43), 182 (100) and 138 (78). [Found $M^+$+$NH_4$: 327.1737. $C_{16}H_{27}N_2O_3S$ requires *M*, 327.1737].

*ii) Method B*

To a -20°C solution of the alkyne **262** (998 mg, 1.40 ml, 12.14 mmol, 1.3 eq) in distilled diethyl ether (12 ml) was added a 2.5 M solution of n-BuLi (5.24 ml, 13.1 mmol, 1.4 eq) and the resultant solution was stirred for 1 h. The solution was warmed to 0°C and

anhydrous zinc bromide (2.95 g, 13.1 mmol, 1.4 eq) was added, the reaction mixture was stirred for 1 h at this temperature and then a further h at ambient temperature. The reaction vessel was cooled to -78°C and then the racemic aldehyde **195** (1.62 g, 9.35 mmol, 1.0 eq) was added in diethyl ether (16 ml). The cold bath was removed and the reaction mixture was stirred for 16 h. The solution was re-cooled to -20°C, saturated aqueous ammonium chloride (6 ml) was added followed by water (10 ml). The resultant two layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 ml). The combined ether layers were dried and evaporated to furnish the *amino alcohol* **262** (2.08 g, 87%), as a 3:1 mixture of diastereoisomers. as a yellow oil. The data obtained was in accordance with that previously reported.

**(*2R*)-2-(tosylamino)non-4-yn-3-ol 263**


**262** **263**

*i) Deprotection using Trifluoroacetic acid*

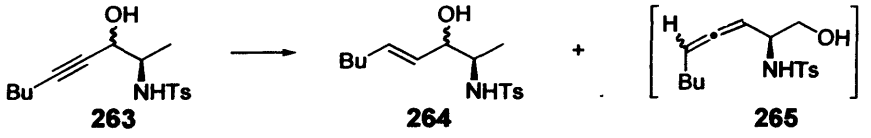
A 2:1 mixture of diastereoisomers of the *N*-Boc protected amine **262** (1.08 g, 4.21 mmol, 1.0 eq) was deprotected using trifluoroacetic acid (2.0 ml) according to general procedure F to yield the *amine* (407 mg, 62%), as a mixture of diastereoisomers in the approximate ratio 2:1, as a brown oil which was used without further purification and showed: $\nu_{max}/cm^{-1}$ [Film] 3400-3000 (br), 2874 (s), 1460 (s) and 1391 (m); $\delta_H$ 0.80 (6H, t, *J* 9-Me, both isomers), 1.15-1.45 (10H, m, 2-Me and 2 x $CH_2$, both isomers), 2.05-2.15 (4H, m, 6-$CH_2$, both isomers), 3.10 (1H, br. t, *J* 6.5, 2-H, major isomer), 3.20 (1H, br. res., 2-H, minor isomer), 4.15 (1H, d, *J* 7.8, 3-H, major isomer) and 4.40 (1H, br. res, 3-H, minor isomer); $\delta_C$ (major isomer only) 13.5 (9-Me), 16.2 (2-Me), 18.3, 21.9, 30.5, (all $CH_2$), 52.9, 64.7 (both CH), 87.6 and 88.5 (both C≡C).

*ii) Tosylation of (S)-2-aminonon-4yn-3-ol* **263**

The crude amine (407 mg, 2.62 mmol, 1.0 eq) was tosylated according to general procedure G. The residue was purified by column chromatography (10% ethyl acetate/petroleum ether) and the mixed fractions re-columned to yield the *sulfonamide* **263**

(371 mg, 29% over 2 steps), as a mixture of diastereoisomers in the ratio of 2.7:1 (*anti:syn*) as an orange oil: $R_f$ 0.43 (40% ethyl acetate/petroleum ether); $\nu_{max}$ /cm$^{-1}$ [$CH_2Cl_2$] 3490 (br), 3282 (br), 2932 (s), 2872 (s), 1598 (m), 1495 (m), 1428 (s), 1328 (s), 1161 (s) and 815 (s); $\delta_H$ 0.85 (6H, 2 x t, *J* 7.2 and 7.1, 9-Me, both isomers), 1.00 (3H, d, *J* 6.8, 2-Me, *syn* isomer), 1.05 (3H, d, *J* 6.6, 2-Me, *anti* isomer), 2.05-2.15 (4H, m, 2 x 6-$CH_2$, both isomers), 2.35 (6H, s, Ar-Me, both isomers), 3.35 (1H, m, 2-H, *anti* diastereoisomer), 3.35-3.45 (1H, m, 2-H, *syn* diastereoisomer), 4.15-4.20 (2H, m, 3-H, both isomers), 4.55 (1H, d, *J* 8.1, NH, exchanges with $D_2O$), 4.65 (1H, d, *J* 9.3, NH, exchanges with $D_2O$), 7.30-7.35 (4H, m, 4 x Ar-H, both isomers) and 7.70 (4H, 2 x d, *J* 8.3 and 8.3, 4 x Ar-H, both isomers); $\delta_C$ 13.6 (9-Me, both isomers), 16.6, 16.6 (2-Me both isomers), 18.3 ($CH_2$, both isomers), 21.6 (Ar-Me, both isomers), 22.0 ($CH_2$, both isomers), 30.5, 30.5 ($CH_2$, both isomers), 53.9, 54.2, 65.6, 65.9 (all CH, both isomers), 77.2, 87.9, 88.2 (all C≡C, both isomers), 127.1, 127.1, 129.7, 129.8 (all ArCH, both isomers), 137.6, 143.5, 143.6 (all ArC, both isomers); *m/z* [APcI] 310 ($M^+$ + H, 23%) and 292 ($M^+$ - $H_2O$, 100%). [Found $M^+$ + $NH_4$] 327.1737. $C_{16}H_{27}N_2O_3S$ requires *M*, 327.1737].

**Reduction of 2-(tosylamino)non-4-yn-3-ol 263**




*i) Method A*

A 1.2:1 mixture of diastereoisomers **263** (*anti:syn*) of the amino alcohol (116 mg, 0.38 mmol) was reduced using a 35% by weight solution of Red-al in toluene according to general procedure H, except that the reaction mixture was refluxed for 19.25 h in tetrahydrofuran. The residue was chromatographed (10% ethyl acetate/petroleum ether) to furnish i) the allene **265** (17 mg, 15%) as a 3:1 mixture of diastereoisomers and ii) (*E*)-*alkene* **264** (23 mg, 20%) as a 5:1 mixture of diastereoisomers (*anti:syn*). The allene **265** was characterised by: $R_f$ 0.63 (40% ethyl acetate/petroleum ether); $\nu_{max}$ /cm$^{-1}$ [$CH_2Cl_2$] 3269 (br), 2926 (s), 1965 (s), 1599 (s), 1495 (s), 1454 (s), 1377 (s), 1328 (s), 1162 (s) and 815 (s); $\delta_H$ 0.75-0.95 (6H, m, 9-Me, both isomers), 1.15 (6H, d, *J* 6.6, 2-Me, both isomers), 1.15-1.35 (12H, m, 3 x $CH_2$, both isomers), 1.80-1.95 (4H, m, 6-$CH_2$, both isomers), 2.35

(6H, s, Ar-Me, both isomers), 3.75-3.85 (2H, m, 2-H, both isomers), 4.45 (2H, d, *J* 7.7, NH, exchanges with $D_2O$, both isomers), 4.95-5.00 (1H, m, 3-H, both isomers), 5.05 (1H, app. qd, *J* 6.6 and 3.0, 5-H, major isomer), 5.15 (1H, app. qd, *J* 6.7 and 3.3, 5-H, minor isomer), 7.20 (4H, d, *J* 8.5, 4 x Ar-H, both isomers) and 7.65 (4H, d, *J* 8.5, 4 x Ar-H, both isomers); $\delta_C$ 13.9 (9-Me, both isomers), 21.6 (Ar-Me, both isomers), 22.2 ($CH_2$, both isomers), 22.3 (2-Me, both isomers), 28.3 ($CH_2$, both isomers), 29.7 ($CH_2$, minor isomer), 31.1 ($CH_2$, major isomer), 48.0 (CH, major isomer), 48.1 (CH, minor isomer), 94.4 (=CH, both isomers), 95.6 (=CH, minor isomer), 95.8 (=CH, major isomer), 127.1, 129.6 (ArCH, both isomers), 137.9, 143.3 (ArC, both isomers) and 201.8 (=C=, both isomers).

The (*E*)-alkene **264** was characterised by: $R_f$ 0.39 (40% ethyl acetate/petroleum ether); $\nu_{max}$ /$cm^{-1}$ [$CH_2Cl_2$] 3500 (br), 3278 (br), 2926 (s), 1598 (m), 1495 (m), 1434 (m), 1328 (s), 1161 (s) and 815 (m); $\delta_H$ 0.75-0.85 (6H, m, 9-Me, both isomers), 0.90 (3H, d, *J* 6.8, 2-Me, *syn* diastereoisomer), 1.00 (3H, d, *J* 6.8, 2-Me, major isomer), 1.10-1.30 (6H, m, 2 x $CH_2$, both isomers), 1.80-1.20 (4H, m, 4-$CH_2$, both isomers), 2.35 (6H, s, Ar-Me, both isomers), 3.10 (1H, app sext, *J* 6.8, 2-H, *anti* diastereoisomer), 3.25-3.35 (1H, m, 2-H, *syn* diastereoisomer), 3.75 (1H, app. t, $J_{approx.}$ 6.5, 3-H, *anti* diastereoisomer), 3.95 (1H, br. res., 3-H, *syn* diastereoisomer), 4.60-4.65 (1H, m, NH, *syn* diastereoisomer), 4.65 (1H, d, *J* 7.6, NH, exchanges with $D_2O$, *anti* diastereoisomer), 5.20 (1H, dd, *J* 15.4 and 7.6, 4-H, *anti* diastereoisomer), 5.25 (1H, dd, *J* 15.4 and 6.6, 4-H, *syn* diastereoisomer), 5.60 (2H, dt, *J* 15.4 and 7.6, 5-H, both diastereoisomers), 7.20 (4H, *J* 8.2, 4 x Ar-H, both diastereoisomers) and 7.70 (4H, *J* 8.2, 4 x Ar-H, both diastereoisomers); *m/z* [ES] 334 ($M^+$ + Na, 100%), 294 (65), 198 (25) and 155 (65). [Found $M^+ + NH_4$ 329.1892. $C_{16}H_{29}O_3N_2S$ requires *M*, 329.1893].

*iii) Method B*

To an ice-cold solution of a 5:4.5 mixture of diastereoisomers (*anti:syn*) of the alkyne **263** (99 mg, 0.32 mmol, 1.0 eq) in tetrahydrofuran was added lithium aluminium hydride (36 mg, 0.96 mmol, 3.0 eq) slowly. The grey suspension was then refluxed for 20 h. The solution was then cooled in an ice bath and the reaction was quenched by the slow addition of ethyl acetate (7 ml), followed by water (7 ml) and a 10% solution of sulphuric acid (10 ml). Diethyl ether (10 ml) was added, the resultant layers were separated and the aqueous phase was extracted with diethyl ether (3 x 20 ml). The combined organic layers were dried and evaporated and the residue was purified by chromatography (10% ethyl acetate/petroleum ether) to furnish i) the *(E)-alkene* **264** (51 mg, 52%), as a mixture of

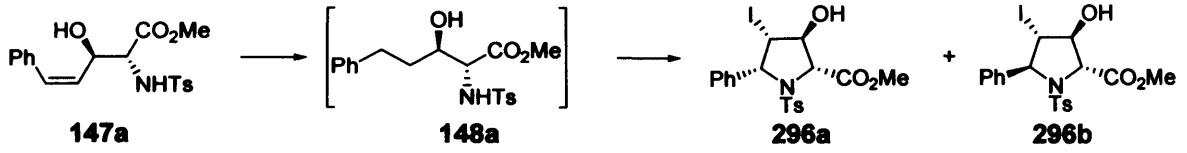
diastereoisomers in the ratio1.3:1 (*anti*:*syn*), as a brown oil and ii) the allene **265** (15 mg, 16%), as a mixture of diastereoisomers in the ratio 3:1 as a brown oil. The data obtained for both is in accordance with that previously reported.

### (*2RS, 3RS*)-Methyl 3-hydroxy-5-phenyl-2-(tosylamino)pentanoate 148a


**146a** **148a**

To the alkyne **146a** (200 mg, 54 mmol, 1.0 eq) in methanol (0.2 ml) was added 5% palladium on calcium carbonate (13 mg) poisoned with quinoline (20 mg, 0.02 ml, 0.16 mmol, 0.3 eq) and the reaction mixture was stirred under a hydrogen atmosphere for 16 h. The reaction mixture was filtered through celite, and the solid was washed with diethyl ether. The combined filtrates were washed with 0.5 M hydrochloric acid (5 ml) and the aqueous phase was extracted with ether (2 x 10 ml). The combined organic phases were dried and evaporated to give the *alkane* **148a** (180 mg, 80%), as a white solid: m.p. 102-103°C; $R_f$ 0.40 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3281 (br), 2954 (s), 1738 (s), 1599 (m), 1496 (m), 1454 (s), 1337 (s) and 1162 (s); $\delta_H$ 1.75-1.85 (2H, m, 4-$CH_2$), 1.95 (1H, br. res, OH), 2.50 (3H, s, Ar-Me), 2.60-2.70 (1H, m, 5-C$\underline{H_a}$CH$_b$), 2.80-3.0 (1H, m, 5-CH$_a$C$\underline{H_b}$), 3.50 (3H, s, $CO_2Me$), 3.90 (1H, app. quint, *J* 4.3, 3-H), 4.0-4.01 (1H, br. res, 2-H), 5.60 (1H, br. res, NH), 7.10-7.35 (7H, m, Ph and 2 x Ar-H) and 7.90 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ 22.0 (Ar-Me), 32.2, 35.2 (both $CH_2$), 53.1 ($CO_2Me$), 60.4, 72.4 (both CH), 126.5, 127.7, 128.9, 128.9, 130.2 (all ArCH), 135.0, 141.5, 144.4 (all ArC) and 170.5 (C=O); *m/z* [ES] 400 ($M^+$ + Na, 100%), 378 (90), 318 (10) and 300 (10). [Found: C, 59.97; H, 6.09, N, 3.72. $C_{19}H_{23}NO_5S$ requires C, 60.46; H, 6.14; N, 3.71%].

**(2RS,3SR,4SR,5RS) and (2RS,3SR,4SR,5SR)Methyl 3-hydroxy-4-iodo-5-phenyl-1-tosylpyrrolidine-2-carboxylate 296a and 296b**




**147a** **148a** **296a** **296b**

*a) Iodocyclisation*

The crude 8:3:1.5 mixture of the *cis*-alkene **147a**, alkane **148a** and alkyne **146a** (200 mg, 0.53 mmol) prepared according to page 220 was reacted with iodine monobromide (330 mg, 1.60 mmol) in dichloromethane for 4 h according to general procedure I. The residue was purified (30% ethyl acetate/petroleum ether) to yield a 7:1 mixture of the *2,5-cis pyrrolidine* **296a** and *2,5-trans pyrrolidine* **296b** (108 mg, 16%) as an orange oil together with some recovered alkane and iodopyrrole (88 mg). The *iodopyrrolidines* **296** were characterised by: $R_f$ 0.35 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ (both isomers) [Film] 3489 (br), 2955 (m), 1747 (s), 1598 (m), 1495 (m), 1343 (m) and 1159 (s); *m/z* [APcI] 502 ($M^+$ + H, 100%) and 374 (25). [Found $M^+$ + H: 502.0190. $C_{19}H_{20}INSO_5$ requires *M*, 502.0185].

The *2,5-cis iodopyrrolidine* **296a** was characterised by: $\delta_H$ 2.50 (3H, s, Ar-Me), 3.10 (1H, s, OH), 3.80 (3H, s, $CO_2Me$), 4.20 (1H, app. t, *J* 7.8, 4-H), 4.30 (1H, d, *J* 5.8, 2-H), 4.60-4.70 (1H, br. res, 3-H), 4.90 (1H, d, *J* 8.2, 5-H), 6.85-7.45 (7H, m, both diastereoisomers, Ph and 2 x Ar-H) and 7.50 (2H, d, *J* 8.30, 2 x Ar-H). $\delta_C$ 22.0 (Ar-Me), 35.5 (4-CH-I), 53.5 ($CO_2Me$), 65.9 (5-H), 66.61 (2-H), 80.17 (3-H), 128.2, 128.5, 128.6, 128.8, 129.8 (all ArCH), 134.5, 139.8, 144.6 (all ArC) and 171.1 (C=O).

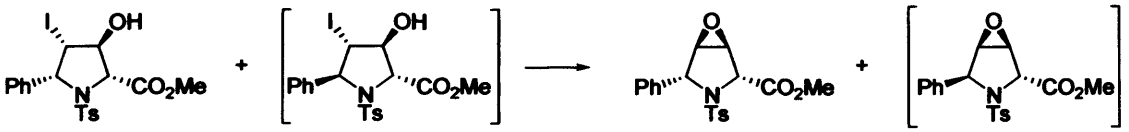
The *2,5-trans iodopyrrolidine* **296b** was characterised by: $\delta_H$ 2.50 (3H, s, Ar-Me), 3.80 (3H, s, $CO_2Me$), 3.90-4.10 (1H, m, 4-H), 4.55 (1H, d, *J* 3.9, 2-H), 4.60-4.70 (1H, br. res, 3-H), 5.05 (1H, d, *J* 8.0, 5-H) 6.85-7.45 (7H, m, Ph and 2 x Ar-H) and 7.50 (2H, d, *J* 8.30, 2 x Ar-H). The data obtained for the alkane **148a** was identical with that previously reported.

*b) Iodocyclisation*

An 8:3:1.5 mixture of the *cis*-alkene **147a**, alkane **148a** and alkyne **146a** (300 mg, *ca* 0.80 mmol) were reacted with iodine monobromide (330 mg, 1.60 mmol) in acetonitrile for 2.5 h, after which time the reaction was judged to be complete by tlc, according to general

procedure I. The residue was purified (30% ethyl acetate/petroleum ether) to yield the 2,5-*cis* pyrrolidine **296a** (48 mg, 19%), largely as a single diastereoisomer, as an orange oil. The data for the iodo-pyrrolidine **296a** was identical to that previously reported.

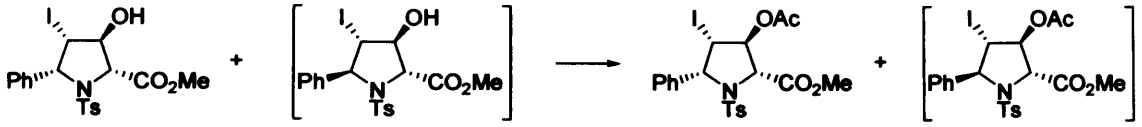
### (*1SR,2RS,4RS,5RS*) and (*1SR,2RS,4SR,5RS*)-Methyl 4-phenyl-3-tosyl-6-oxa-3-aza-bicyclo[3.1.0]hexane-2-carboxylate 307a and 307b




**296a** **296b** **307a** **307b**

Following general procedure J, a 9:1 mixture of 2,5-*cis* and 2,5-*trans* iodo-pyrrolidine **296a** and **296b** (51 mg, 0.10 mmol) was reacted with 50% w/w of silver carbonate on celite (448 mg, 0.81 mmol, 8.0 eq) to give the *epoxide* as a 91:9 mixture of diastereoisomers **307a** and **307b**, (37 mg, 97%) as a brown oil. The major product **307a** was characterised by: $R_f$ 0.34 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3058 (br), 2955 (s), 1757 (s), 1598 (s), 1495 (s), 1342 (s), 1166 (s), 1038 (s), 738 (s) and 700 (s); $\delta_H$ 2.30 (3H, s, Ar-Me), 3.55 (1H, d, *J* 2.8, 5(1)-CH), 3.70 (3H, s, $CO_2Me$), 3.80 (1H, d, *J* 2.8, 1(5)-CH), 4.65 (1H, app. s, 2-H), 4.95 (1H, app. s, 4-H), 7.15-7.25 (5H, m, Ph) and 7.40 (2H, d, *J* 7.3, 2 x Ar-H) and 7.55 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ 20.6 (Ar-Me), 51.8 ($CO_2Me$), 56.6, 59.0, 61.5, 63.6 (all CH), 126.2, 126.8, 127.2, 127.6, 128.5 (all ArCH), 133.9, 135.2, 143.0 (all ArC) and 167.9 (C=O); *m/z* [APcI] 374 ($M^+$ + H, 100%), 324 (85) and 314 (30), 202. (48), 170 (56). [Found $M^+$ + H: 374.1059. $C_{19}H_{20}NO_5S$ requires *M*, 374.1057]. The 2,5-*trans* epoxide **307b** data is reported later.

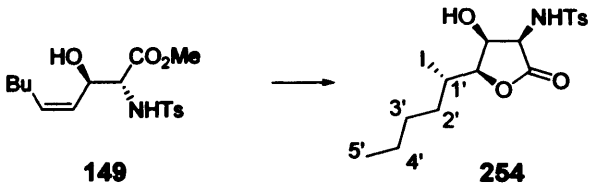
**(*2RS,3SR,4SR,5RS*)-Methyl-3-acetoxy-4-iodo-5-phenyl-1-tosylpyrrolidine-2-carboxylate 308a**




**296a** **296b** **308a** **308b**

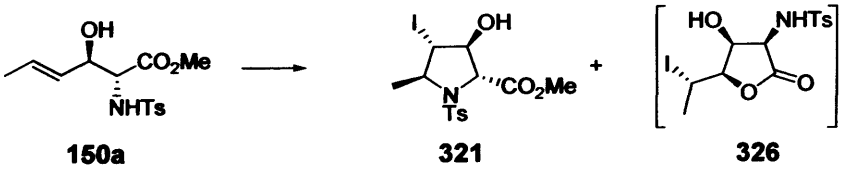
A 9:1 mixture of 2,5-*cis* and 2,5-*trans* iodo-pyrrolidines **296** (50 mg, 0.1 mmol) was protected using acetic anhydride (0.02 ml, 0.1 mmol) as described in general procedure K to yield the *acetate* **308** (39 mg, 72%) as a mixture of diastereoisomers in the ratio 5.7: 1 (4,5-*cis*: 4,5-*trans*), as a colourless solid. An analytical sample was prepared by recrystallisation using vapour diffusion (10% ethyl acetate/pentane) to give the 2,5-*cis* pyrrolidine **308a** as a single diastereoisomer: m.p. 132-133°C; $R_f$ 0.78 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2950 (w), 1749 (s), 1598 (m), 1359 (s), 1220 (s) and 1164 (s); $\delta_H$ (major diastereoisomer) 1.95 (3H, s, OAc), 2.30 (3H, s, Ar-Me), 3.80 (3H, s, $CO_2CH_3$), 4.40 (1H, dd, *J* 7.1 and 4.5, 4-H), 4.55 (1H, d, *J* 3.4, 2-H), 4.85 (1H, d, *J* 7.1, 5-H), 5.65 (1H, dd, *J* 4.5 and 3.4, 3-H), 7.05-7.25 (7H, m, Ph and 2 x Ar-H) and 7.50 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ 21.0, 21.9 (both Me), 32.1 (4-CHI), 53.5 ($CO_2CH_3$), 65.4, 66.4, 80.7 (all CH), 127.8, 128.2, 128.3, 128.3, 129.3 (all ArCH), 135.0, 139.4, 144.5 (all ArC) 169.7 and 169.8 (both C=O); *m/z* [ES] 566 ($M^+$ + Na, 100%) and 484 (60).

**(*3RS,4SR,5RS*)-(*1SR'*)-dihydro-4-hydroxy-(1-iodopentyl)-3-(tosylamino)furan-2(3*H*)-one 254**




The (*Z*)-alkene **149** (100 mg, 0.28 mmol) was treated with iodine monobromide (175 mg, 0.84 mmol) in acetonitrile according to general procedure I, for 29.25 h. The residue was purified by chromatography (20% ethyl acetate/petroleum ether) to give the *lactone* **254** (18 mg, 14%): m.p. 144-145°C; $R_f$ 0.52 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [KBr] 3515 (br), 2924 (s), 1767 (s), 1458 (s), 1340 (s), 1161 (s) and 813 (s); $\delta_H$ 0.85 (3H, t, *J* 7.2, 5'-Me), 1.20-1.80 (6H, m, 3 x $CH_2$), 2.35 (3H, s, Ar-Me), 2.55 (1H, br. res., OH), 3.80 (1H, app. t, *J* 3.9, 3-H), 4.20 (1H, app. td, *J* 10.1 and 2.9, CHI), 4.45 (1H, dd, *J* 10.1 and 3.0, 5-H), 4.62 (1H, dd, *J* 3.9 and 3.0, 4-H), 5.14 (1H, d, *J* 3.3, NH), 7.30 (2H, d, *J* 8.2, 2 x Ar-H) and 7.70 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ 14.2 (5'-Me), 21.7 (Ar-Me), 21.7 ($CH_2$), 30.1 (CHI), 31.6, 33.7 (both $CH_2$) 59.1, 69.5, 86.1 ( all CH), 127.4 (ArCH), 130.3 (ArCH and ArC), 134.2 (ArC) and 170.3 (C=O); *m/z* [APcI] 468 ($M^+$ + H, 63%), 422 (20), 107 (100). [Found $M^+$ + H: 468.0341. $C_{16}H_{23}INO_5S$ requires *M*, 468.0349].

**Iodocyclisation of (*4E,2RS,3RS*)-Methyl 3–hydroxy-2-(tosylamino)hex-4-enoate 150a**




*i) Method A*

The alkene **150a** (50 mg, 0.16 mmol) in anhydrous dichloromethane was cyclised using iodine (121 g, 0.48 mmol) for 24 h, as described in general procedure L. The crude product was purified by chromatography (30% ethyl acetate/petroleum ether) to furnish the *iodopyrrolidine* (46 mg, 80%), as a 6:1 mixture of diastereoisomers (**321**:**352**), as a pale yellow oil. The major isomer **321** was characterised by: $R_f$ 0.44 (40% ethyl acetate/

petroleum ether); $\nu_{max}/cm^{-1}$ [Film] 3475 (br), 2956 (br), 1745 (s), 1598 (m), 1335 (s), 1155 (s), 1091 (s) and 816 (m); $\delta_H$ 1.30 (3H, d, *J* 6.4, Me), 2.35 (3H, s, Ar-Me), 3.65 (1H, dd, *J* 8.9 and 7.3, 4-H), 3.75 (3H, s, $CO_2Me$), 3.95 (1H, dq, *J* 8.9 and 6.4, 5-H), 4.40 (1H, d, *J* 5.1, 2-H), 4.45 (1H, dd, *J* 7.3 and 5.1, 3-H), 7.25 (2H, d *J* 8.3, 2 x Ar-H) and 7.70 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ 17.8, 22.0 (both Me), 33.4 (4-CHI), 53.4 ($CO_2Me$), 64.1 (5-CH), 68.3 (2-CH), 81.9 (3-CH), 127.8, 130.1 (both ArCH), 138.8, 144.3 (both ArC) and 172.0 (C=O); *m/z* [ES] 462 ($M^+$ + Na, 100%), 440 (80), 334 (50) and 312 (30). [Found $M^+$ +H: 440.0031. $C_{14}H_{19}INSO_5$ requires *M*, 440.0028].

*ii) Method B*

The alkene **150a** (516 mg, 1.65 mmol) dissolved in anhydrous acetonitrile was cyclised using iodine (1.25 g, 4.94 mmol) for 1 h, as described in general procedure L. The residue was purified by column chromatography (30% ethyl acetate/petroleum ether) to give the *iodopyrrolidine* **321** (619 mg, 86%) as a yellow oil. The data obtained was identical with that reported previously.

*iii) Method C*

The alkene **150a** (100 mg, 0.32 mmol) dissolved in anhydrous acetonitrile was cyclised using iodine monobromide (197 mg, 0.96 mmol) for 3.25 h, as described in general procedure I. The residue was purified (30% ethyl acetate/petroleum ether) to furnish i) the *lactone* **326** (10 mg, 8%) and ii) the *iodopyrrolidine* **321** (38 mg, 27%) as a mixture of diastereoisomers in the ratio 15:1.5:1.5. The data obtained for the pyrrolidine was in agreement with that previously reported. The data for the lactone is reported later (p 268).

*iv) Method D*

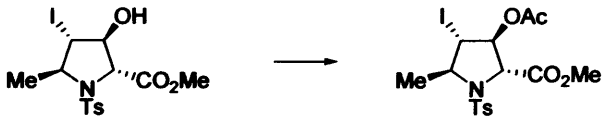
The alkene **150a** (100 mg, 0.32 mmol) dissolved in anhydrous dichloromethane was cyclised using iodine monobromide (198 mg, 0.96 mmol) for 2 h, as described in general procedure I. The residue was purified by chromatography (30% ethyl acetate /petroleum ether) to yield the *iodopyrrolidine* **321** (85 mg, 61%), as a 6:1 mixture of diastereoisomers, as a yellow oil. The data obtained was in agreement with that previously reported.

**(*1SR,2RS,4SR,5RS*)-methyl-4-methyl-3-tosyl-6-oxa-3-aza-bicyclo[3.1.0]hexane-2-carboxylate 323**


**321** **323**

Following general procedure J, the iodo-pyrrolidine **321** (55 mg, 0.13 mmol) was reacted with 50% w/w $Ag_2CO_3$ on celite (414 mg, 0.75 mmol) to give the *epoxide* **323** (48 mg, 100%), as a yellow oil: $\nu_{max}/cm^{-1}$ [Film] 2955 (s), 1755 (s), 1598 (s), 1495 (s), 1334 (s), 1265 (s), 1156 (s), 916 (s) and 856 (s); $\delta_H$ 1.20 (3H, d, *J* 6.4, Me), 2.35 (3H, s, Ar-Me), 3.55 (1H, app. s, 5-H), 3.65 (1H, app. d, *J* 3.0, 1-H), 3.80 (3H, s, $CO_2Me$), 4.15 (1H, app. quart, *J* 6.4, 4-H), 4.65 (1H, app. s, 2-H), 7.20 (2H, d, *J* 8.3, 2 x Ar-H) and 7.60 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ 14.7, 21.6, 52.9 (all Me), 55.1, 55.9, 59.5, 64.2 (all CH) 126.6, 129.6 (both ArCH), 139.3, 143.4 (both ArC) and 170.0 (C=O); *m/z* [APcI] 312 ($M^+$ + H, 50%), 249 (45) and 71 (100). [Found M + H: 312.0900. $C_{14}H_{18}NO_5S$ requires *M*, 312.0899].

**(*2RS,3SR,4SR,5SR*) Methyl-3-acetoxy-4-iodo-5-methyl-1-tosyl -pyrrolidine-2-carboxylate 324**

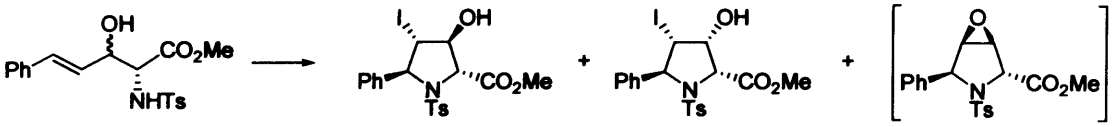



**321** **324**

The pyrrolidine **321** (131 mg, 0.30 mmol) was protected using acetic anhydride (0.03 ml, 0.30 mmol) according to general procedure K, to yield the *acetate* **324** (124 mg, 88%) as a yellow solid: m.p. 94-95°C; $R_f$ 0.51 (40% ethyl acetate/petroleum ether) $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2953 (br), 1748 (s), 1598 (m), 1496 (m), 1343 (m), 1159 (s) and 816 (m); $\delta_H$ 1.30 (3H, d, *J* 6.5, Me), 2.05 (3H, s, OAc), 2.30 (3H, s, Ar-Me), 3.70 (3H, s, $CO_2CH_3$), 3.75 (1H, dd, *J* 7.2 and 5.4, 4-H), 4.00 (1H, app. quin, *J* 6.5, 5-H), 4.45 (1H, d, *J* 3.5, 2-H), 5.40 (1H, dd, *J* 5.4 and 3.5, 3-H), 7.25 (2H, d, *J* 8.3, 2 x Ar-H) and 7.75 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ 18.7, 21.0, 22.0 (all Me), 27.2 (4-C*H*I), 53.3 ($OCH_3$), 65.0 (5-CH), 66.8 (2-CH),

81.6 (3-CH), 127.9, 130.5 (both ArCH), 138.1, 144.3 (both ArC) 169.9 and 170.5 (both C=O); *m/z* [APcI] 482 ($M^+$ + H, 100%) and 422 (18).

**Cyclisation of (*2RS,E*)-methyl 3-hydroxy-5-phenyl-2-(tosylamino)pent-4-enoate 151**




**151** **296b** **327b** **307b**

*i) Method A*

A 5.8:1 (*anti:syn*) mixture of diastereoisomers of the alkene **151** (100 mg, 0.27 mmol) were cyclised with iodine (202 mg, 0.80 mmol) in dichloromethane for 3.5 h according to general procedure L to give three diastereoisomers in the ratio 9:2.5:1 (*3,4-trans:3,4-cis:min*). The residue was purified (30% ethyl acetate/petroleum ether) to give i) *2,5-trans pyrrolidine* **296b** (44 mg, 39%) and ii) *3,4-cis pyrrolidine* **327b** (8 mg, 40%). The minor isomer was not isolated. The *2,5-trans pyrrolidine* **296b** was characterised by: m.p. 140-147°C; $R_f$ 0.50 (40% ethyl acetate/petroleum ether); $\nu_{max}$ /$cm^{-1}$ [$CH_2Cl_2$] 3468 (br), 2950 (m), 1747 (s), 1596 (s), 1495 (m), 1329 (s), 1153 (s) and 1049 (s); $\delta_H$ 2.25 (3H, s, Ar-Me), 3.80 (3H, s, $CO_2Me$), 4.00 (1H, dd, *J* 8.0 and 5.7, 4-H), 4.55 (1H, d, *J* 4.0, 2-H), 4.65 (1H, dd, *J* 5.7 and 4.0, 3-H), 5.10 (1H, d, *J* 8.0, 5-H) and 6.70-7.20 (9H, m, Ph and 2 x Ar-H); $\delta_C$ 21.9 (Ar-Me), 33.1 (CH-I), 53.5 ($CO_2Me$), 66.9, 73.1, 82.1 (all CH), 127.5, 128.6, 128.9, 129.3, 129.6 (all ArCH), 135.0, 138.5, 143.3 (all ArC) and 171.8 (C=O); *m/z* [ES] 524 ($M^+$ + Na, 90%) and 502 (100).

The *3,4-cis pyrrolidine* **327b** was characterised by: m.p. 153-154°C; $R_f$ 0.33 (40% ethyl acetate/petroleum ether); $\nu_{max}$/$cm^{-1}$ [$CH_2Cl_2$] 3469 (m), 1743 (m), 1337 (m), 1153 (m) and 1044 (w); $\delta_H$ 2.30 (3H, s, Ar-Me), 3.80 (3H, s, $CO_2Me$), 4.25 (1H, app. t, *J* 6.3, 2-H), 4.40 (1H, app. t, *J* 6.1, 4-H), 4.85 (1H, app. d, *J* 6.7, 3-H), 5.15 (1H, d, *J* 6.7, 5-H) and 6.85-7.20 (9H, m, Ph and 2 x Ar-H); $\delta_C$ 21.9 (Ar-Me), 38.2 (CH-I), 53.3 ($CO_2Me$), 65.4 (3-CH), 69.8 (2-CH), 71.7 (5-CH), 127.8, 128.8, 128.8, 129.0, 129.4 (all ArCH), 135.9, 137.9, 143.6 (all ArC) and 170.3 (C=O); *m/z* [APcI] 502 ($M^+$ + H, 100%). [Found $M^+$ + H: 502.0182. $C_{19}H_{20}INSO_5$ requires *M*, 502.0185].

ii) *Method B*

An 8:1.5 (*anti:syn*) mixture of diastereoisomers of the alkene **151** (156 mg, 0.42 mmol) was cyclised using iodine (316 mg, 1.28 mmol) in anhydrous acetonitrile according to general procedure L for 21 h to give an inseparable 5:1.4:1 mixture of i) the epoxide **307b** ii) *2,5-trans pyrrolidine* **296b** and iii) 3,4-*cis pyrrolidine* **327b** (155 mg). The data corresponding to the epoxide **307b** is reported later, and the data obtained for the pyrrolidines **296b** and **327b** is in accordance with that previously reported.

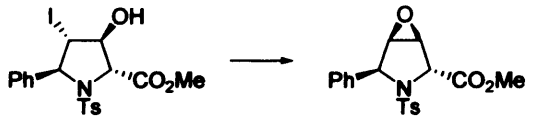
*iii) Method C*

A 2.3:1 (*anti:syn*) mixture of diastereoisomers of the alkene **151** (100 mg, 0.27 mmol) was cyclised using iodine monobromide (165 mg, 0.80 mmol) and anhydrous acetonitrile as described in general procedure I for 2.5 h. The residue was purified using chromatography (30% ethyl acetate/petroleum ether) to give i) the *2,5-trans pyrrolidine* **296b** (77 mg, 83%) and ii) the *3,4-cis pyrrolidine* **327b** (30 mg, 75%). The data obtained is in agreement with that previously reported.

*iv) Method D*

A 2.3:1 (*anti: syn*) mixture of diastereoisomers of the amino alcohol **151** (100 mg, 0.27 mmol) was cyclised using iodine monobromide (165 mg, 0.80 mmol) and anhydrous dichloromethane as described in general procedure I for 2.5 h to give the iodopyrrolidines as a mixture of diastereoisomers in the ratio 4:1.8:1 (*2,5-trans: 3,4-cis:min*). The residue was purified using chromatography (30% ethyl acetate/petroleum ether) to give i) the *2,5-trans pyrrolidine* **296b** (60 mg, 67%) ii) the *3,4-cis pyrrolidine* **327b** (31 mg, 78%). The data obtained is in agreement with that previously reported for the 2,5-*trans* **296b** and 3,4-*cis* **327b** pyrrolidines, no data was obtained for the minor isomer.

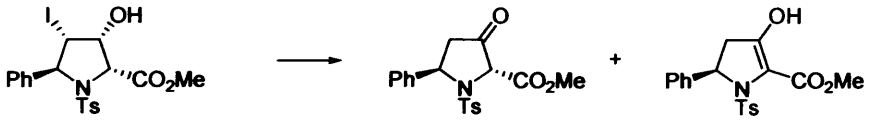
**(*1SR,2RS,4SR,5RS*)-Methyl 4-Phenyl-3-tosyl-6-oxa-3-aza-bicyclo[3.1.0]hexane-2-carboxylate 307b**




**296b** **307b**

Following general procedure J, the 2,5-*trans* pyrrolidine **296b** (50 mg, 0.10 mmol) was reacted with 50% w/w of silver carbonate on celite (330 mg, 0.59 mmol) to give the *epoxide* **307b**, (41 mg, 100%) as a brown solid: m.p. 140-144°C; $R_f$ 0.37 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3057 (m), 2964 (s), 2368 (m), 1747 (m), 1599 (m), 1495 (m), 1344 (m), 1264 (s) and 1159 (s); $\delta_H$ 2.25 (3H, s, Ar-Me), 3.70-3.80 (2H, m, 3-H and 4-H), 3.85 (3H, s, $CO_2Me$), 4.80 (1H, app. s, (5)1-H), 5.00 (1H, app. s, (1)5-H), 6.90 (2H, d, *J* 8.1, 2 x Ar-H) and 6.9-7.2 (7H, m, Ph and 2 x Ar-H); $\delta_C$ 21.4 (Ar-Me), 53.0 ($CO_2Me$), 55.2, 59.8, 62.8, 64.3 (all CH), 126.8, 127.8, 128.5, 128.8, 129.8 (all ArCH), 133.2, 138.4, 142.8 (all ArC) and 170.4 (C=O); *m/z* [APcI] 374 ($M^+$ + H, 100%). [Found $M^+$ +H: 374.1061. $C_{19}H_{20}NO_5S$ requires *M*, 374.1062].

**(*2RS,5RS*)-Methyl 3-oxo-5-phenyl-1-tosylpyrrolidine-2-carboxylate 328a and (*5RS*)-methyl 4,5-dihydro-3-hydroxy-5-phenyl-1-tosyl-1*H*-pyrrole-2-carboxylate 328b**

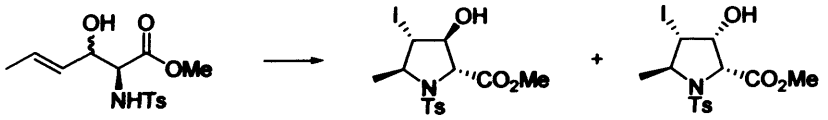



**327b** **328a** **328b**

A 10:1 mixture of iodo-pyrrolidines **327b** (38 mg, 0.075 mmol) was reacted with 50% w/w $Ag_2CO_3$ on celite (250 mg, 0.45 mmol) as described in general procedure J to yield a 1:1 mixture of keto and enol tautomers **328** (28 mg, 72%), as a brown oil: $\delta_H$ 2.20-2.30 (3H, m, Ar-Me, both isomers), 2.55 (1H, dd, *J* 18.5 and 3.6, $C\underline{H}_aCH_b$, isomer A), 2.65 (1H, dd, *J* 18.8 and 7.5, $C\underline{H}_aCH_b$, isomer B), 3.05 (1H, dd, *J* 18.8 and 8.8, $CH_aC\underline{H}_b$, isomer B), 3.30 (1H, dd, *J* 18.8 and 8.8, $CH_aC\underline{H}_b$, isomer A), 3.70-3.90 (3H, m, $CO_2Me$, both isomers), 4.50 (1H, s, 2-H, keto tautomer), 5.00-5.05 (1H, m, 5-H isomer B), 5.40 (1H, dd, *J* 9.3 and

3.6, 5-H isomer A) and 6.85-7.40 (9H, m, Ph and 4 x Ar-H, both isomers); $\delta_C$ 21.5, 21.6 (both Ar-Me), 46.9, 47.1 (both $CH_2$), 53.4, 53.6 ($CO_2Me$), 59.7, 60.2, 67.2, 67.3 (all CH), 127.1, 127.3, 127.9, 128.0, 128.1, 128.3, 128.7, 128.7, 129.0, 129.1 (all ArCH), 136.0, 138.7 and 143.4 (all ArC). Limited characterisation was obtained due to decomposition of the product.

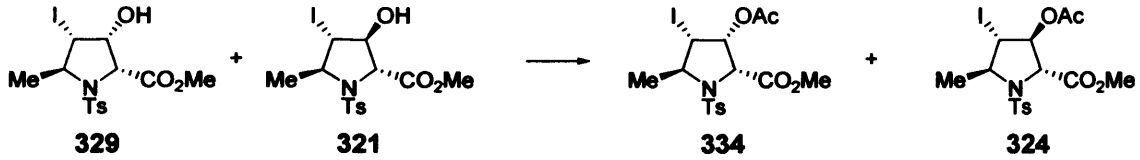
**(*2RS,3SR,4SR,5SR*) and (*2RS,3RS,4SR,5SR*)-Methyl 3-hydroxy-4-iodo-5-methyl-1-tosyl-pyrrolidine-2-carboxylate 321 and 329**




**150** **321** **329**

A 1:1.2 mixture diastereoisomers (*anti*:*syn*) of the amino alcohol **150** (86 mg, 0.27 mmol) was treated with iodine (209 mg, 0.82 mmol) in anhydrous acetonitrile (1 ml) for 2.25 h, according to general procedure L, after which time the reaction was judged to be approximately 50% complete. The residue was treated with the same quantities of reagents for a further 4.25 h. The residue was purified by chromatography (30% ethyl acetate/petroleum ether) to give i) the *3,4-cis pyrrolidine* **329** (27 mg, 50%) and ii) the *2,5-trans pyrrolidine* **321** (30 mg, 46%), both as pale yellow oils. The data obtained for the *2,5 trans pyrrolidine* **321** was identical to that previously reported. The *3,4 cis pyrrolidine* **329** was characterised by: $R_f$ 0.51 (40% ethyl acetate/ petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3500 (br), 2952 (s), 1745 (s), 1598 (m), 1437 (m), 1335 (s), 1158 (s) and 816 (m); $\delta_H$ (500 MHz) 1.30 (3H, d, *J* 6.2, 5-Me), 2.35 (3H, s, Ar-Me), 2.50 (1H, d, *J* 5.2, OH, exchanges with $D_2O$), 3.75 (3H, s, $CO_2Me$), 3.85-3.90 (2H, m, 4-H and 5-H), 4.25-4.30 (1H, m, 3-H), 4.80 (1H, d, *J* 6.2, 2-H), 7.25 (2H, d *J* 8.2, 2 x Ar-H) and 7.70 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ 17.5 (5-Me), 22.0 (Ar-Me), 38.1 (4-C*H*I), 53.0 ($CO_2CH_3$), 62.1, 64.6, 70.3 (all CH) 128.2, 130.1 (both ArCH), 138.3, 144.3 (both ArC) and 169.9 (C=O); *m/z* [APcI] 440 ($M^+$ + H, 100%), 296 (20), 287 (15), 243 (15) and 107 (12). [Found $M^+$ +H: 440.0020. $C_{14}H_{19}INSO_5$ requires *M*, 440.0028].

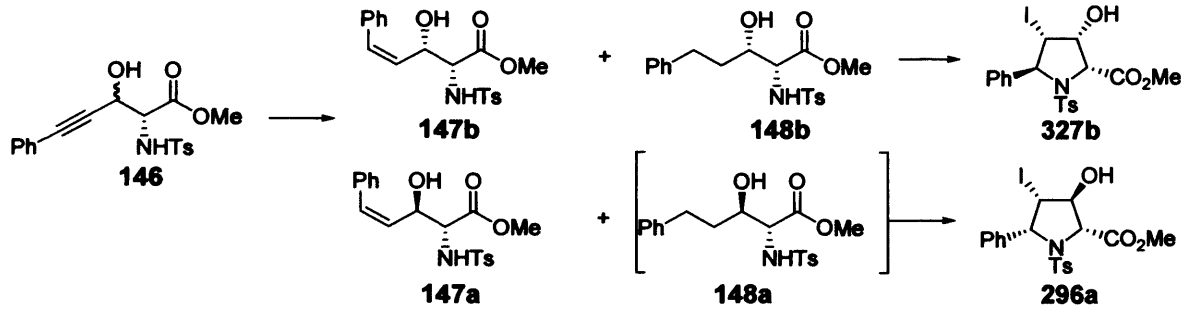
**(*2RS,3RS,4SR,5SR*)-Methyl-3-acetoxy-4-iodo-5-methyl-1-tosylpyrrolidine-2-carboxylate 334**




**329** **321** **334** **324**

A 7:1 ratio of *3,4-cis pyrrolidine* **329** and *2,5-trans pyrrolidine* **321** (20 mg, 0.046 mmol) were treated with acetic anhydride (1 drop) as described in general procedure K. The residue was purified using column chromatography (25% ethyl acetate/petroleum ether) to give the a 7:1 mixture of *acetates* **334** and **324** (11 mg, 50%) as a pale yellow solid. An analytical sample of **334** was prepared by recrystallisation from 10% ethyl acetate/petroleum ether: m.p. 135-137°C; $R_f$ 0.58 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 1757 (s), 1338 (m), 1220 (m), 1159 (s) and 1071 (s); $\delta_H$ 1.35 (3H, d, *J* 6.1, Me), 2.05 (3H, s, $CO_2Me$), 2.35 (3H, s, Ar-Me), 3.70 (3H, s, $CO_2Me$), 3.85-3.95 (2H, m, 4-H and 5-H), 4.90 (1H, d, *J* 6.8, 2-H), 5.55 (1H, d, *J* 6.8 and 4.6, 3-H), 7.25 (2H, d, *J* 8.1, 2 x Ar-H) and 7.80 (2H, d, *J* 8.1, 2 x Ar-H); $\delta_C$ 17.5, 21.3, 22.0 (All Me), 30.8 (4-C*H*I), 52.9 (Me), 63.2, 63.9, 70.1 (all CH), 128.1, 130.1 (both ArCH), 138.3, 144.4 (both ArC), 168.7 and 169.4 (both C=O); *m/z* [APcI] 482 ($M^+$ + H, 100%) and 287 (35). [Found $M^+$ +H: 482.0132. $C_{16}H_{21}INSO_6$ requires *M*, 482.0134].

**(*2RS,3SR,4SR,5RS*) and (*2RS,3RS,4SR,5SR*)-Methyl 3-hydroxy-4-iodo-5-phenyl-1-tosylpyrrolidine-2-carboxylate 296a and 327b**



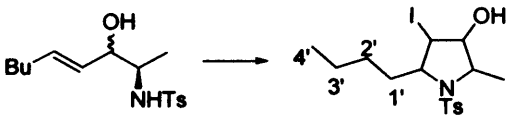

*i) Lindlar Reduction*

A 1:1 mixture of diastereoisomers of the aldol adduct **146** (103 mg, 0.28 mmol) was stirred under an atmosphere of hydrogen in the presence of Lindlar's catalyst according to general procedure D, until complete reduction of the double bond had occurred as determined by $^1$H NMR, to furnish a mixture of the *cis* alkenes **147** and the alkanes **148** as an orange oil. The (*Z*)-*syn* alkene **147b** was characterised by: $\delta_H$ 2.25 (3H, s, Ar-Me), 2.95 (1H, br. res., OH, exchanges with $D_2O$), 3.30 (3H, s, Ar-Me), 3.90 (1H, dd, *J* 9.9 and 2.9, 2-H), 4.70-4.85 (2H, m, 3-H), 5.75 (1H, dd, *J* 11.7 and 9.3), 5.90 (1H, d, *J* 9.8, NH), 6.50 (1H, d, *J* 11.7, 5-H), 7.05-7.25 (7H, m, Ph and 2 x Ar-H) and 7.55-7.70 (2H, m, 2 x Ar-H).

*ii) Cyclisation*

The crude product (100 mg, 0.27 mmol) was reacted with iodine monobromide (165 mg, 0.80 mmol) according to general procedure I. The residue was purified by chromatography (30% ethyl acetate/petroleum ether) to furnish the iodopyrrolidine (68 mg, 51%) as an inseparable mixture of isomers. The two major isomers were i) the *2,5-cis pyrrolidine* **296a** (approx. 30 mg, 45%) and ii) the *2,5-trans pyrrolidine* **327b** (approx. 17 mg, 25%). The data obtained for both was in accordance with that previously reported.

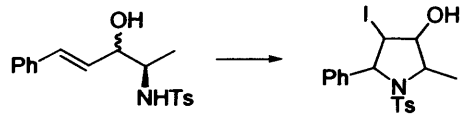
**5-Butyl-4-iodo-2-methyl-1-tosyl-pyrrolidin-3-ol 338**




**337** **338**

The a 5:1 (*anti*:*syn*) mixture of diastereoisomers of the amino alcohol **337** (16 mg, 0.051 mmol) was cyclised with iodine monobromide in dichloromethane according to general procedure I, for 2.5 h to furnish the *iodopyrrolidine* **338** (11 mg, 50%), largely as a single diastereoisomer, as a brown oil: $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3488 (br), 2926 (s), 2860 (s), 1598 (m), 1495 (m), 1454 (s), 1379 (s), 1330 (s), 1161 (s) and 813 (s); $\delta_H$ 0.75-0.85 (3H, m, 4'-Me), 1.15-1.30 (5H, m, 3'-$CH_2$ and 2-Me), 1.45-1.55 (2H, m, 2'-$CH_2$), 1.90-2.05 (2H, m, 1'-$CH_2$), 2.30 (3H, s, Ar-Me), 3.65 (1H, br. res., 3-H), 3.95 (1H, app. quin, $J_{approx.}$ 6.8, 2-H), 4.20 (1H, dt, *J* 9.7 and 3.0, 5-H), 4.40 (1H, dd, *J* 5.1 and 2.9, 4-H), 7.20 (2H, d, *J* 8.3, 2 x Ar-H) and 7.65 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ 14.0, 14.7 (both Me), 21.6 (Ar-Me), 22.6, 27.9, 35.1 (all $CH_2$), 36.4 (CH-I), 57.6, 69.7, 71.3 (all CH), 127.2, 129.5 (both ArCH), 139.2 and 143.3 (both ArC); *m/z* [ES] 460 ($M^+$ + Na, 55%), 455 (30), 438 (100). [Found $M^+$ + H: 438.0600. $C_{16}H_{25}INO_3S$ requires *M*, 438.0594].

**4-Iodo-2-methyl -5-phenyl-1-tosylpyrrolidin-3-ol 341**




**340** **341**

*i) Method A*

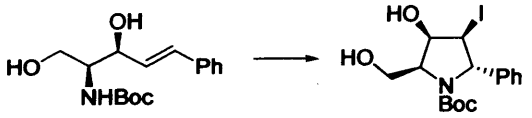
A 2.9:1 (*anti*:*syn*) mixture of diastereoisomers of the amino alcohol **340** (35 mg, 0.11 mmol) was cyclised using iodine monobromide (65 mg, 0.32 mmol) in dichloromethane, according to general procedure I, for 1.5 h. The residue was chromatographed (20% ethyl acetate/petroleum ether) to furnish the *iodopyrrolidine* **341a** (10 mg, 21%), largely as a single diastereoisomer (7.5:1, A:B) as a pale orange oil: $R_f$ 0.34 (40% ethyl acetate/petroleum ether). The major isomer was characterised by: $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3334 (br), 2922 (s), 1600 (m), 1463 (s), 1264 (s), 1159 (s), 964 (s), 849 (s) and 815 (s); $\delta_H$ 1.45

(3H, d, *J* 6.9, 2-Me), 2.05 (1H, d, *J* 8.1, OH), 2.30 (3H, s, Ar-Me), 3.70-3.80 (1H, m, 3-H), 4.25 (1H, app. quin, *J* 6.7, 2-H), 4.35 (1H, app. t, *J* 4.5, 4-H), 5.25 (1H, d, *J* 4.2, 5-H), 7.05-7.25 (7H, m, Ph and 2 x Ar-H) and 7.45 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ 15.1 (Me), 21.6 (Ar-Me), 39.6 (CH-I), 59.2, 71.3, 72.7 (all CH), 126.4, 127.2, 128.4, 128.7, 129.3 (all ArCH), 138.8, 140.2 and 143.1 (all ArC); *m/z* [APcI] 458 ($M^+$ +H, 100%), 440 (12), 330 (25). [Found $M^+ + NH_4$: 475.0543. $C_{18}H_{24}IN_2O_3S$ requires *M*, 475.0547].

*ii) Method B*

A 1.6:1 (*syn*: *anti*) mixture of diastereoisomers of the amino alcohol **340** (283 mg, 0.85 mmol) was cyclised using iodine (650 mg, 2.56 mmol) in dichloromethane, according to general procedure L, for 5 h. A trace of starting material was evident in the NMR of the crude product and hence the crude product was treated with the same quantities of reagents for a further 5 h. The residue was chromatographed (20% ethyl acetate/petroleum ether) to furnish the *iodopyrrolidine* **341** (272 mg, 70%) as a 4.6:1.0:6.7 (A:B:C) mixture of diastereoisomers. The data obtained for isomer A **341a** was in accordance with that previously reported. $\delta_H$ (isomers B and C) 1.45 (3H, d, *J* 6.8, 2-Me, isomer B), 1.55 (3H, d, *J* 6.6, 2-Me, isomer C), 2.25 (3H, s, Ar-Me, isomer C), 2.32 (3H, s, Ar-Me, isomer B), 2.35 (1H, d, *J* 8.7, OH, isomer B), 3.00 (1H, br. res, OH, isomer C), 3.50 (1H, br. res., 3-H, isomer B), 3.80-3.90 (2H, m, 3-H and 4-H, isomer C), 3.95 (1H, qd, *J* 6.7 and 2.7, 2-Me, isomer B), 4.15 (1H, dd, *J* 7.8 and 3.5, 4-H, isomer B), 4.70 (1H, d, *J* 7.8, 5-H, isomer B), 5.00 (1H, d, *J* 6.7, 5-H, isomer C) and 6.95-7.25 (18H, m, 2 x Ph, 8 x Ar-H).

**(*2S,3R,4S,5S*)-*tert*-butyl-3-hydroxy-2-(hydroxymethyl)-4-iodo-5-phenyl-pyrrolidine-1-carboxylate 330**



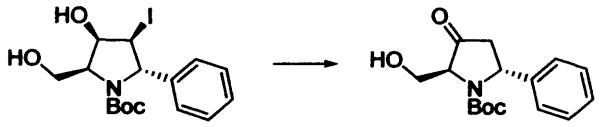

**207** **330**

The alkene **207** (150 mg, 0.51 mmol) was cyclised using iodine (389 mg, 1.53 mmol) according to general procedure L for 3 h. The residue was purified using column chromatography (30% ethyl acetate/petroleum ether) to give the *iodo-pyyrolidine* **330** (180 mg, 84%) as a yellow oil which showed: $[\alpha]_D$ +2.35 ($CHCl_3$, c 0.34); $R_f$ 0.27 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3444 (br), 2977 (m), 1761 (s), 1693 (s), 1456

(m), 1392 (s) and 772 (m); $\delta_H$ 0.95 (9H, s, *t*-Bu), 3.95-4.15 (3H, m, $CH_2$ and 4-H), 4.15-4.20 (2H, m, 2-H and 3-H), 4.90 (1H, d, *J* 8.5, 5-H), 7.10-7.30 (5H, m, 5 x Ar-H); $\delta_C$ 27.8 (*t*-Bu), 38.5 (4-CHI), 63.1 ($CH_2$), 65.0, 70.4, 73.7 (all CH), 81.0 (C-$(CH_3)_3$), 126.1, 127.8, 128.6 (all ArCH), 141.5 (ArC) and 154.9 (C=O); *m/z* [APcI] 420 ($M^+$ + H, 28%), 364 (100) and 346 (32). [Found $M^+$ + H: 420.0674. $C_{16}H_{23}INO_4$ requires *M*, 420.0666].

**(*2S,5R*)-tert-butyl-2-(hydroxymethyl)-3-oxo-5-phenylpyrrolidine-1-carboxylate**

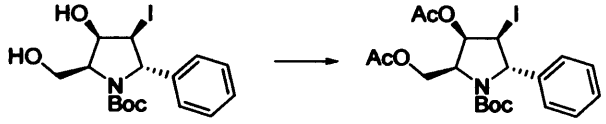
**347**




**330** **347**

The iodopyrrolidine **330** (32 mg, 0.076 mmol) was reacted with 50% w/w silver carbonate on celite (337mg, 0.62 mmol, 8.0 eq) according to general procedure J to give the *ketone* **347** (15 mg, 68%) as a pale oil: $[\alpha]_D$ + 10.42 ($CHCl_3$, c 0.47); $R_f$ 0.51 (40% ethyl acetate/ petroleum ether), $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3444 (br), 2977 (m), 1761 (s), 1693 (s), 1456 (m), 1392 (s) and 772 (m); $\delta_H$ 1.20 (9H, s, *t*-Bu), 2.45 (1H, d, *J* 18.5, 4-C$\underline{H}_a$C$H_b$), 3.00 (1H, dd, *J* 18.5 and 10.0, 4-C$H_a$C$\underline{H}_b$), 3.60 (1H, br. res., OH, exchanges with $D_2O$), 3.75-3.90 (1H, m, 2-C$\underline{H}_a$C$H_b$OH), 4.10-4.15 (1H, m, 2-C$H_a$C$\underline{H}_b$OH), 4.20 (1H, br. res., 2-H), 5.15 (1H, d, *J* 9.5, 5-H), 7.05 (2H, d, *J* 8.2, 2 x Ar-H) and 7.15-7.30 (3H, m, 3 x Ar-H); $\delta_H$ ($D_2O$ shake) 1.15 (9H, s, *t*-Bu), 2.45 (1H, d, *J* 18.5, 4-C$\underline{H}_a$C$H_b$), 3.00 (1H, dd, *J* 18.5 and 10.0, 4-C$H_a$C$\underline{H}_b$), 3.75-3.90 (1H, m, 2-C$\underline{H}_a$C$H_b$OH,), 4.10 (1H, dd, *J* 11.4 and 2.1, 2-C$H_a$C$\underline{H}_b$OH), 4.20 (1H, br. res., 2-H), 5.15 (1H, br. d, *J* 9.0, 5-H), 7.05 (2H, d, *J* 7.4, 2 x Ar-H) and 7.15-7.30 (3H, m, 3 x Ar-H); $\delta_H$ (50°C) 1.25 (9H, s, *t*-Bu), 2.50 (1H, d, *J* 18.5, 4-C$\underline{H}_a$C$H_b$), 3.05 (1H, dd, *J* 18.5 and 10.0, 4-C$H_a$C$\underline{H}_b$), 3.85-3.95 (1H, m, 2-C$\underline{H}_a$C$H_b$OH), 4.20 (2H, br. res., 2-C$H_a$C$\underline{H}_b$OH and 2-H), 5.15 (1H, br. d, *J* 9.0, 5-H), 7.05 (2H, d, *J* 7.4, 2 x Ar-H) and 7.15-7.30 (3H, m, 3 x Ar-H); $\delta_C$ 28.0 (*t*-Bu), 46.2 (4-$CH_2$), 60.8 (CH), 58.3 (CH), 63.8 ($CH_2$), 66.6 (CH), 81.4 (C-$(CH_3)_3$), 125.3, 127.6, 128.9 (all ArCH), 143.6 (ArC), 155.4 (N-C=O) and 210.5 (3-C=O); *m/z* [APcI] 292 ($M^+$ + H, 22%), 236 (100) and 218 (39). [Found $M^+$+H: 292.1539. $C_{16}H_{22}NO_4$ requires *M*, 292.1543].

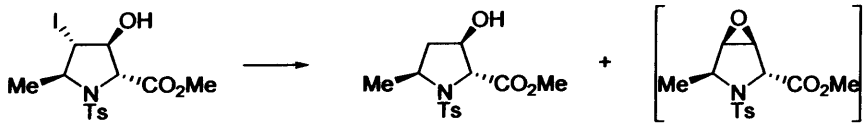
**(*2S,3R,4S,5R*)-*tert*-butyl -3-acetoxy-2-(acetoxymethyl)-4-iodo-5-phenyl-pyrrolidine-1-carboxylate 349**




**330** **349**

The iodo-pyrrolidine **330** (24 mg, 0.06 mmol) was reacted with acetic anhydride (0.01ml, 0.12 mmol, 2.0 eq) for 20 h according to general procedure K. The residue was purified by flash chromatography (20% ethyl acetate/petroleum ether) to give the *diacetate* **349** (20 mg, 71%): $[\alpha]_D$ +3.82 ($CHCl_3$, c 1.0); $R_f$ 0.53 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2978 (s), 2930 (s), 1748 (s), 1695 (s), 1455 (s), 1368 (s), 767 (m) and 737 (m); $\delta_H$ 0.95 (9H, s, *t*-Bu), 1.95 (3H, s, OAc), 2.10 (3H, s, OAc), 4.25 (1H, br. res., 4-H), 4.40 (1H, br. res., C$\underline{H}_a$C$H_b$), 4.55 (1H, br. res., 2-H), 4.80 (1H, br. res., C$\underline{H}_a$C$H_b$), 4.95 (1H, br. res., 5-H), 5.35 (1H, br. res., 3-H), 7.05 (2H, d, *J* 6.9, 2 x Ar-H) and 7.20-7.30 (3H, m, 3 x Ar-H); $\delta_C$ 20.9, 21.0 (both Me), 27.7 (*t*-Bu), 31.2 (4-CHI), 58.4 (2-CH), 61.7 ($CH_2$), 71.3 (3-CH and 5-CH), 80.7 ($\underline{C}$-$(CH_3)_3$), 125.8, 128.0, 128.8 (all ArCH), 141.3 (ArC), 153.2 (N-C=O), 169.4 and 170.5 (both O-C=O); *m/z* [APcI] 504 ($M^+$ + H, 45%), 448 (97) and 91 (100). [Found $M^+$ + H: 504.0875. $C_{20}H_{27}INO_6$ requires *M*, 504.0878].

**Hydrogenolysis of (*2RS,3SR,4SR,5SR*)-Methyl 3-hydroxy-4-iodo-5-methyl-1-(tosylamino)-pyrrolidine-2-carboxylate 321**




**321** **351** **323**

The 2,5-*trans* iodopyrrolidine **321** (39 mg, 0.089 mmol) was subjected hydrogenolysis as described in general procedure M for 16 h. The residue was chromatographed (20% ethyl acetate/petroleum ether) to give i) *hydroxy pyrrolidine* **351** (10 mg, 36%) and ii) the *epoxide* **323** (16 mg, 57%), both as yellow oils. The *hydroxy pyrrolidine* **351** was characterised by: $R_f$ 0.11 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3500

(br), 2953 (s), 1743 (s), 1598 (m) and 1495 (m); $\delta_H$ 1.25 (3H, d, *J* 6.5, 5-Me), 1.65 (1H, d, *J* 13.7, C$\underline{H}_a$CH$_b$), 2.25 (1H, br. res., OH), 2.35 (3H, s, Ar-Me), 2.40 (1H, ddd, *J* 13.7, 9.1 and 5.0, CH$_a$C$\underline{H}_b$), 3.65 (3H, s, $CO_2Me$), 4.10-4.20 (1H, m, 5-H), 4.30 (1H, br. res., 3-H), 4.40 (1H, app. s, 2-H), 7.20 (2H, d, *J* 8.3, 2 Ar-H) and 7.70 (2H, d, *J* 8.3, 2 Ar-H); $\delta_C$ 21.6, 22.3 (both Me), 40.8 ($CH_2$), 52.6 ($CO_2Me$), 56.1, 71.2, 74.6 (all CH), 127.2, 129.5 (both ArCH) and 171.1 (C=O); *m/z* [APcI] 314 ($M^+$ + H, 88%), 254 (100), 158 (48) and 156 (68). [Found $M^+$ + H: 314.1059. $C_{14}H_{20}NSO_5$ requires *M*, 314.1057]. The data obtained for the epoxide **323** was in agreement with that previously reported.

### (*2RS,3SR,5RS*)-Methyl 3-hydroxy-5-phenyl-1-tosylpyrrolidine-2-carboxylate 352


**327b** **352**

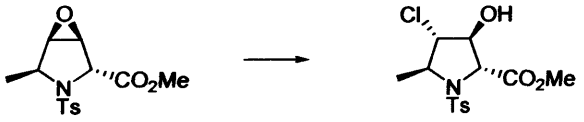
The iodopyrrolidine **327b** (26 mg, 0.052 mmol) was subjected to hydrogenolysis according to general procedure M for 64 h. Following chromatography (60% ethyl acetate/petroleum ether) the *hydroxy pyrrolidine* **352** (12 mg, 63%) was obtained, as a yellow oil: m.p. 148.5-151.3°C; $R_f$ 0.47 (70% ethyl acetate /petroleum ether); $\nu_{max}$/cm$^{-1}$ [$CH_2Cl_2$] 3499 (br), 1716 (s), 1337 (s), 1263 (s), 1156 (s) and 808 (s); $\delta_H$ 2.00-2.15 (2H, m, C$\underline{H}_a$CH$_b$ and OH), 2.30 (3H, s, Ar-Me), 2.55-2.70 (1H, m, CH$_a$C$\underline{H}_b$), 3.70 (3H, s, $CO_2Me$), 4.60 (1H, d, *J* 7.7, 2-H), 4.75-4.90 (1H, m, 3-H), 5.20 (1H, d, *J* 8.8, 5-H) and 6.90-7.25 (9H, m, 9 x Ar-H); $\delta_C$ 21.5 (Ar-Me), 41.2 ($CH_2$), 52.5 ($CO_2Me$), 62.1, 64.9, 70.2 (all CH), 126.7, 127.1, 127.4, 128.4, 129.0 (all ArCH), 137.2, 141.5, 143.1 (all ArC) and 170.8 (C=O); *m/z* [APcI] 376 ($M^+$ + H, 100%) and 358 (35). [Found $M^+$ + H: 376.1210. $C_{19}H_{22}NSO_5$ requires *M*, 376.1213].

**(*2S,3S,5R*)-*tert*-Butyl 3-hydroxy-2-(hydroxymethyl)-5-phenyl-pyrrolidine-1-carboxylate 353**


**330** **353**

The iodopyrrolidine **330** (69 mg, mmol) in methanol (0.5 ml) was exposed to standard hydrogenolysis conditions (General procedure M) for 46 h. The residue was chromatographed (40% ethyl acetate/petroleum ether) to give the *hydroxy pyrrolidine* **353** (23 mg, 48%): m.p. 104-105°C; $R_f$ 0.28 (60% ethyl acetate/petroleum ether), $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3399 (s), 2976 (s), 1667 (s), 1454 (s), 1402 (s), 1264 (s), 1149 (s) and 737 (s); $\delta_H$ 1.05 (9H, s, *t*-Bu), 1.85-2.00 (1H, m, $C\underline{H}_aCH_b$), 2.20-2.35 (1H, m, $CH_aC\underline{H}_b$), 2.90 (1H, br. res., OH, exchanges with $D_2O$), 3.75 (1H, br. res., OH, exchanges with $D_2O$), 3.90 (1H, br. res., $C\underline{H}_aCH_bOH$), 4.05 (2H, br. res., $CH_aC\underline{H}_bOH$ and 2-H), 4.50 (1H, br. res., 3-H), 4.85 (1H, dd, *J* 8.1 and 4.9, 5-H), 7.00 (2H, d, *J* 8.1, 2 x Ar-H) and 7.10-7.25 (3H, m, 3 x ArCH); $\delta_C$ 27.9 (*t*-Bu), 42.6 ($CH_2$), 60.8 (CH), 62.0 ($CH_2OH$), 63.2, 71.1 (both CH), 80.3 ($\underline{C}$-$(CH_3)_3$), 125.2, 126.8, 128.4 (all ArCH), 145.0 (ArC) and 155.4 (C=O); *m/z* [APcI] 294 ($M^+$ + H, 48) and 238 (100%). [Found $M^+$ +H: 294.1701. $C_{16}H_{23}NO_4$ requires *M*, 294.1700].

**(*2RS,3SR,4SR,5SR*)-Methyl 4-chloro-3-hydroxy-5-methyl-1-tosylpyrrolidine-2-carboxylate 358b**




**323** **358b**

To a stirred solution of the epoxide **323** (130 mg, 0.47 mmol, 2.88 eq) in anhydrous 1,2-dichloroethane (1.2 ml) was added trimethylsilyl azide (58 mg, 0.07 ml, 0.50 mmol, 2.86 eq) followed by a 1M solution of zinc chloride in diethyl ether (0.18 ml, 0.18 mmol, 1.0 eq). The reaction mixture was then refluxed for 21.5 h. The solution was poured onto

saturated brine (2 ml), the resultant two layers were separated and the aqueous phase was extracted with dichloromethane (3 x 2 ml). The combined organic phases were washed with water (5 ml) and saturated brine (5 ml). The organic phases were dried and evaporated and then the residue was dissolved in methanol (1 ml) and to this solution was added 6 M hydrochloric acid (1 drop). The solution was stirred for 10 mins at ambient temperature, and then the solvent was evaporated. The residue was chromatographed (20% ethyl acetate/petroleum ether) to yield the *epichlorohydrin* **358b** (28 mg, 19%), as a brown oil: $R_f$ 0.44 (50% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3480 (br), 2954 (s), 1749 (s), 1598 (s), 1496 (s), 1437 (s), 1339 (s), 863 (s), 816 (s) and 740 (s); $\delta_H$ 1.30 (3H, d, *J* 6.6, 5-Me), 2.35 (3H, s, Ar-Me), 3.25 (1H, br. res, OH), 3.60-3.65 (1H, m, 4-H), 3.70 (3H, s, $CO_2Me$), 3.80 (1H, app. q, *J* 6.6, 5-H), 4.35 (1H, br. res., 3-H), 4.40 (1H, d, *J* 4.0, 2-H), 7.20 (2H, d, *J* 8.2, 2 x Ar-H) and 7.70 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ 17.7 (5-Me), 21.6 (Ar-Me), 52.9 ($CO_2Me$), 62.8, 66.6 (both CH), 67.9 (2-CH), 79.9 (3-CH), 127.4, 129.7 (both ArCH), 138.3, 143.8 (both ArC) and 171.2 (C=O); *m/z* [APcI] 370 ($M^+$ + Na, 100%) and 348 (73). [Found M + $NH_4$: 365.0925 (±5 ppm). $C_{14}ClH_{22}N_2O_5S$ requires *M*, 365.0938].

**(*2RS,5SR*)-Methyl 3,4-dihydroxy-5-methyl-1-tosylpyrrolidine-2-carboxylate 366**


**323** **366**

The epoxide **323** (96 mg, 0.31 mmol) was dissolved in a mixture of dioxane (0.98 ml), water (0.66 ml) and concentrated sulphuric acid (0.07 ml). The reaction mixture was heated at 95°C for 6 h. The oil bath was removed and the reaction vessel was allowed to reach room temperature. A 10% aqueous solution of sodium hydroxide (0.8 ml) was added, followed by toluene (1 ml) and the solvent was evaporated. The residue was purified by chromatography (50% ethyl acetate/petroleum ether) to furnish the *pyrrolidine* **366** (16 mg, 16%) as a mixture of diastereoisomers in the ratio 1.6:1, with a trace of starting material, as a yellow oil: $R_f$ 0.31 (70% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3477 (br), 2931 (s), 1732 (s), 1598 (s), 1496 (m), 1454 (s), 1329 (s), 1153 (s) and

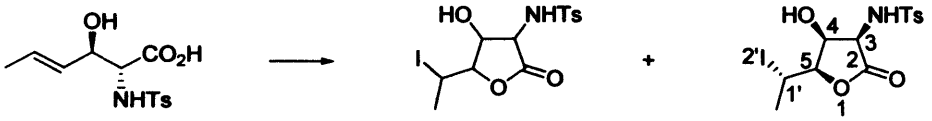
815 (s); $\delta_H$ 1.05 (3H, d, *J* 6.6, 5-Me, minor isomer), 1.15-1.20 (3H, m, 5-Me, major isomer), 2.30-2.35 (6H, m, 2 x Ar-Me, both isomers), 3.70 (6H, s, 2 x $CO_2Me$, both isomers), 3.75 (1H, app. s, CH, major isomer), 3.80-3.90 (3H, m, 2 x 5-H and CH minor isomer), 4.20 (1H, app. s, CH, major isomer), 4.35-4.40 (2H, m, CH, both isomers), 4.45 (1H, app. s, CH, minor isomer), 7.15-7.25 (4H, m, 4 x Ar-H, both isomers) and 7.65 (4H, d, *J* 8.3, 4 x Ar-H, both isomers); $\delta_C$ 17.6 (5-Me, minor isomer) 18.2 (5-Me, minor isomer), 21.6, 21.6 (Ar-Me, both isomers), 53.3 ($CO_2Me$, both isomers), 637 (CH, minor isomer), 64.2, 68.7 (both CH, major isomer), 69.4, 79.1 (CH, minor isomer), 79.2 (CH, major isomer), 82.1 (CH, minor isomer), 82.6 (CH, major isomer), 127.2 (ArCH, minor isomer), 127.3, 129.7 (both ArCH, major isomer), 129.8 (ArCH, minor isomer), 137.9 (ArC, major isomer), 138.4 (ArC, minor isomer), 143.7 (ArC, major isomer), 143.8 (ArC, minor isomer) and 173.2 (C=O, both isomers); *m/z* [APcI] 352 ($M^+$ + Na, 100%), 330 (10), 270 (85) and 155 (48). [Found $M^+ + NH_4$: 347.1271. $C_{14}H_{23}IN_2O_6S$ requires *M*, 347.1271].

**(*4E,2RS,3RS*)-3-hydroxy-2-(tosylamino)hex-4-enoic acid 367**


**150a** **367**

The amino alcohol **150a** (1.00 g, 3.19 mmol) was treated with potassium hydroxide (7.18 g, 128.0 mmol) according to general procedure N to give the *carboxylic acid* **367** (770 mg, 81%) as a white solid: m.p. 150-152°C; $\nu_{max}/cm^{-1}$ [KBr] 3321 (br), 2962 (s), 1728 (s), 1597 (s), 1496 (s), 1456 (s), 1345 (s), 1168 (s), 1046 (s), 974 (s), 845 (s) and 812 (s); $\delta_H$ (MeOD) 1.55 (3H, d, *J* 6.4, 6-Me), 2.35 (3H, s, Ar-Me), 3.70 (1H, d, *J* 6.3, 2-H), 4.05 (1H, app. t, *J* 6.3, 3-H), 5.25 (1H, dd, *J* 15.2 and 7.2, 4-H), 5.60 (1H, qd, *J* 15.2 and 6.4, 5-H), 7.30 (2H, d, *J* 8.1, 2 x Ar-H) and 7.60 (2H, d, *J* 8.1, 2 x Ar-H); $\delta_C$ (MeOD) 18.8 (6-Me), 22.2 (Ar-Me), 62.4, 73.0 (both CH), 127.8 (ArCH), 128.3 (=CH), 130.5 (ArCH), 132.3 (=CH), 139.7, 143.6 (both ArC) and 172.6 (C=O); *m/z* [CI] 317 ($M^+ + NH_4$, 100%) and 299 (15). [Found $M^+ + NH_4$: 317.1164. $C_{13}H_{21}N_2O_5S$ requires *M*, 317.1166].

**(*3RS,4SR,5RS*), (*1'SR*)-dihydro-4-hydroxy-5-(1-iodoethyl)-3-(tosylamino)furan-2(3*H*)-one 326a**




**367** **326** **326a**

*i) Method A*

The carboxylic acid **367** (80 mg, 0.27 mmol) in anhydrous acetonitrile (20 ml) was cyclised using iodine monobromide (166 mg, 0.80 mmol) for 2 h, according to general procedure I to give the *lactone* **326** (80 mg, 70%) as a 6.4:1.0:2.4 mixture of diastereoisomers. The crude mixture was recrystallised from hot chloroform to give the *lactone* **326a** (35 mg, 31%) as a white solid: m.p. 182.4-184.4°C; $R_f$ 0.49 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [KBr] 3556 (br), 3229 (s), 2950 (m), 2924 (m), 1811 (s), 1654 (w), 1596 (m), 1494 (m), 1448 (m), 1406 (m), 1379 (m), 1358 (m), 1323 (s), 1189 (s), 1157 (s), 1055 (m) and 819 (s); $\delta_H$ (MeOD) 1.90 (3H, d, *J* 6.8, 2'-Me), 2.30 (3H, s, Ar-Me), 4.15 (1H, dq, *J* 10.8 and 6.8, CHI), 4.30 (1H, dd, *J* 4.5 and 2.7, 4-H), 4.41 (1H, dd, *J* 10.8 and 2.7, 5-H), 4.45 (1H, d, *J* 4.5, 3-H), 7.25 (2H, d, *J* 8.3, 2 x Ar-H) and 7.75 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ (MeOD) 19.0 (CHI), 20.1, 23.6 (both Me), 58.1, 70.5, 85.1 (all CH), 126.8, 129.2 (both ArCH), 138.3, 143.3 (both ArC) and 174.53 (C=O); *m/z* [APcI] 426 ($M^+$ + H, 100%), 380 (30) and 107 (42). [Found $M^+ + NH_4$: 358.1180. $C_{13}H_{20}N_5O_5S$ requires *M*, 358.1180]. [Found: C, 36.12; H, 3.70, I, 29.5, N, 3.10. S, 7.26. $C_{13}H_{16}INO_5S$ requires C, 36.72; H, 3.79; I, 29.84, N, 3.29, S, 7.54%].

*ii) Method B*

The carboxylic acid **367** (100 mg, 0.33 mmol) in distilled dichloromethane (10 ml) was treated with iodine (251 mg, 0.10 mmol) for 2.5 h according to general procedure L. Following the workup, the *lactone* **326a** (87 mg, 61%) was isolated largely as a single diastereoisomer. The residue was recrystallised (hot chloroform) to furnish the lactone **326a** (65 mg, 46%). The data obtained was in accordance with that previously reported.

*iii) Method C*

A solution of the carboxylic acid **367** (100 mg, 0.33 mmol) in acetonitrile (20 ml) was treated with iodine (251 mg, 0.10 mmol) for 2.5 h according to general procedure L, to furnish the *lactone* **326** (80 mg, 56%) as a mixture of diastereoisomers in the ratio

5.4:2.4:1. The mixture was recrystallised (hot chloroform) to give the *lactone* **326a** (29 mg, 30%). The data obtained is in accordance with that previously reported.

*iv) Method D*

The carboxylic acid **367** (100 mg, 0.33 mmol) in distilled dichloromethane (10 ml) was reacted with iodine monobromide (207 mg, 0.10 mmol) according to general procedure I, for 2.5 h, to give the *lactone* **326** as a mixture of diastereoisomers in the ratio 1.4:1.5:1.6. The residue was recrystallised (hot chloroform) to furnish the *lactone* **326a** (50 mg, 35%).

### *(Z,2RS)*-3-hydroxy-5-phenyl-2-(tosylamino)pent-4-enoic acid 368

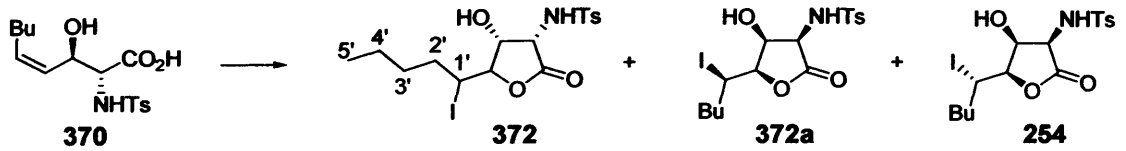

To a 17:4 mixture of diastereoisomers of the ester **151** (802 mg, 2.14 mmol) was treated with potassium hydroxide (7.18 g, 0.13 mol) according to general procedure N to yield the *carboxylic acid* **368** (772 mg, 88%), as a mixture of diastereoisomers in the ratio 17:4, as a cream solid: m.p. 130-132°C; $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3252 (br), 1729 (s), 1332 (s), 1160 (s) and 814 (m); $\delta_H$ (MeOD) 2.20 (3H, s, Ar-Me, minor), 2.25 (3H, s, Ar-Me, major), 3.75 (1H, app. d, *J* 6.7, 2-H, major) 3.85 (1H, app. d, *J* 3.0, 2-H, minor), 4.25 (1H, app. t, *J* 6.7, 3-H, major) 4.50 (1H, br. res., 3-H, minor), 6.00 (1H, dd, *J* 15.9 and 7.0, 4-H, both), 6.50 (1H, d, *J* 15.9, 5-H, both), 7.15-7.25 (8H, m, 7 x Ar-H and NH) and 7.60 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ (MeOD) 20.2 (Ar-Me), 61.2, 72.8 (both CH), 126.3, 126.8 (both ArCH), 127.5 (=CH), 128.2, 129.2 (both ArCH), 131.5 (ArC), 132.4 (=CH), 136.6, 137.5 and 143.4 (all ArC), no C=O evident; *m/z* [APcI] 344 ($M^+$ - $H_2O$, 48%), 133 (40) and 107 (100%). [Found $M^+ + NH_4$: 379.1320. $C_{18}H_{23}N_2O_5S$ requires M, 379.1322].

**(*EZ,2RS,3RS*)-3-Hydroxy-2-(tosylamino)non-4-enoic acid 370**


**149** **144a** **370** **371**

To a solution of a 7:1 mixture of the *cis*-amino alcohol **149** and alkyne **144a** (118 mg, 0.33 mmol) in methanol (5 ml) was added potassium hydroxide (529 mg, 9.42 mmol) and the solution was stirred for 16 h, according to general procedure N to furnish the *carboxylic acid* **370** (101 mg) as a brown oil: $\nu_{max}/cm^{-1}$ [$CH_3OH$] 3964 (br), 3917 (br), 2956 (s), 1729 (s), 1598 (m), 1331 (s), 1161 (s), 814 (s) and 668 (s); $\delta_H$ (MeOD) 0.80 (3H, app. s, 9-Me), 1.15-1.30 (4H, m, 2 x $CH_2$), 1.85-2.05 (2H, m, $CH_2$), 2.30 (3H, s, Ar-Me), 3.75 (1H, br. res., 2-H), 4.55 (1H, br. res., 3-H), 5.30 (1H, br. t, *J* 9.5, 4-H), 5.35-5.50 (1H, m, 5-H), 7.20 (2H, d, *J* 8.1, 2 x Ar-H) and 7.65 (2H, d, *J* 8.1, 2 x Ar-H); $\delta_C$ (MeOD) 13.0 (9-Me), 20.2 (Ar-Me), 22.0, 27.1, 31.5 (all $CH_2$), 67.8 (CH, only one evident), 126.9, (ArCH), 127.6 (=CH), 129.2 (ArCH), 133.8 (ArC), 137.8 (=CH) and 143.3 (ArC), no C=O evident; *m/z* [APcI] 325 ($M^+$ - $H_2O$, 100%) and 278 (25). [Found $M^+ + NH_4$: 359.1635. $C_{16}H_{27}N_2O_5S$ requires *M*, 359.1637].

**(*3RS,4SR,5RS*), (*1'RS*)-dihydro-4-hydroxy-5-(1-iodopentyl)-3-(tosylamino)furan-2(*3H*)-one 372**




**370** **372** **372a** **254**

*i) Method A*

To an ice-cold solution of the carboxylic acid **370** (40 mg, 0.12 mmol) in distilled dichloromethane (2 ml) was added iodine (89 mg, 0.35 mmol) according to general procedure L, for 3 h to furnish the *lactone* **372a** (55 mg, 100%): m.p. 129-128°C; $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3275 (br), 2958 (s), 2930 (s), 2872 (m), 1784 (s), 1599 (s), 1494 (m), 1331 (s), 1162 (s) and 814 (s); $\delta_H$ 0.80 (3H, t, *J* 7.1, 5'-Me), 1.15-1.35 (2H, m, $CH_2$), 1.60-1.70 (1H,

m, C$\underline{H}_a$CH$_b$), 1.80-1.90 (1H, m, CH$_a$C$\underline{H}_b$), 2.35 (3H, s, Ar-Me), 3.20 (1H, d, *J* 2.2, OH, exchanges with $D_2O$), 4.10-4.15 (1H, ddd, *J* 9.4, 5.0, 2.9, CHI), 4.30 (1H, dd, *J* 6.1 and 2.2, 4-H), 4.37 (1H, d, *J* 2.6, 3-H), 4.40 (1H, app. t, *J* 6.1 and 5.0, 5-H), 5.25 (1H, d, *J* 4.7, NH, exchanges with $D_2O$), 7.30 (2H, d, *J* 8.3, 2 x Ar-H) and 7.75 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ 13.9 (5'-Me), 21.7 (Ar-Me), 31.6 ($CH_2$), 34.3 (CHI), 36.9 ($CH_2$), 55.5, 71.3, 88.7 (all CH), 127.6, 130.2 (both ArCH), 134.4, 144.9 (both ArC) and 172.1 (C=O) (only 2 $CH_2$ apparent); *m/z* [APcI] 468 ($M^+$ + H, 100%), 155 (22), 107 (85) and 83 (71). [Found $M^+$ + H: 468.0339. $C_{16}H_{23}INO_5S$ requires *M*, 468.0336].

*ii) Method B*

To an ice-cold solution of the carboxylic acid **370** (80 mg, 0.23 mmol) in anhydrous acetonitrile (3 ml) was added iodine monobromide (145 mg, 0.70 mmol) according to general procedure I, for 2 h to yield the *lactone* **372** (15 mg, 14%), as a vast mixture of diastereoisomers. Further investigation was not conducted.

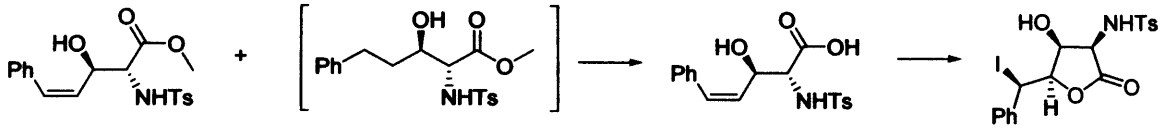
*iii) Method C*

A 7:2 mixture of the carboxylic acid **370** and saturated product **371** (94 mg, 0.28 mmol) in dichloromethane (3 ml) was cooled to -10°C prior to the addition of iodine monobromide (171 mg, 0.83 mmol) according to general procedure I for 1.75 h, to give the *lactone* **372** (85 mg, 85%), as a 6:1.5 mixture of diastereoisomers, as a cream solid. The data obtained for the major isomer **254** was in accordance with that previously reported.

*iv) Method D*

To an ice-cold solution of a 7:2 mixture of the carboxylic acid **370** and saturated product **371** (160 mg, 0.47 mmol) in acetonitrile (5 ml) was added iodine (290 mg, 1.41 mmol) according to general procedure L for 2.75 h, to give the *lactone* **372** (126 mg, 74%), as a 4.5:1.5 mixture of diastereoisomers, as a cream solid. The data obtained for the major isomer **372a** was in accordance with that previously reported.

**(*3RS,4SR,5RS*),(*1'SR*)-dihydro-4-hydroxyl-5-(iodo(phenyl)methyl)-3-(tosylamino)furan-2(3*H*)-one 375**




**147a** **148a** **373** **375**

*i) Saponification*

To an ice-cold solution of a 3:1 mixture of the *cis*-alkene **147a** and alkane **148a** (101 mg), in methanol (8 ml) was added solid potassium hydroxide (900 mg, 16 mmol) according to general procedure N to give predominatley the *acid* **373**, as an orange oil (53 mg). The acid **373** was characterised by: $\delta_H$ (MeOD) 2.25 (3H, s, ArMe), 3.85 (1H, d, *J* 5.5, 2-H), 4.60 (1H, dd, *J* 9.7 and 5.5, 3-H), 5.65 (1H, dd, *J* 11.7 and 9.7, 4-H), 6.55 (1H, d, *J* 11.7, 5-H), 7.10-7.30 (7H, m, 7 x Ar-H) and 7.60 (2H, d, *J* 8.3, 2 x Ar-H).

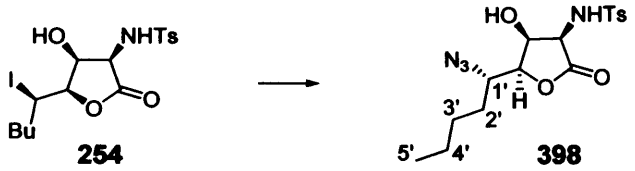
*ii) Iodolactonisation-Method A*

A solution of the crude acid **373** (53 mg) at -10°C in anhydrous acetonitrile (5 ml) was cyclised using iodine monobromide (91 mg, 0.44 mmol) for 2 h according to general procedure I to yield the *lactone* **375** (11 mg, 20%, over 3 steps) as an orange oil: $R_f$ 0.12 (20% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3272 (s), 2962 (s), 1790 (s), 1598 (s), 1494 (s), 1453 (s), 1334 (s), 1160 (s) and 814 (s); $\delta_H$ 2.40 (3H, s, Ar-Me), 3.10 (1H, br. res., OH), 3.30 (1H, app. t, *J* 4.3, 4(3)-H), 4.35 (1H, app. d, *J* 5.6, CHOH), 4.80 (1H, d, *J* 5.4, 3(4)-H), 5.05 (1H, br. res, NH), 5.10 (1H, d, *J* 5.4, CH-I), 7.15-7.35 (7H, m, 7 x Ar-H) and 7.55 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ 21.7 (Ar-Me), 28.5 (CH-I), 55.3, 69.2, 89.4 (all CH), 127.4, 128.8, 129.2, 130.1 (all ArCH), 134.5, 137.1, 144.8 (all ArC) and 171.8 (C=O); *m/z* [APcI] 488 ($M^+$ + H, 100%). [Found $M^+$ + H: 488.0019. $C_{18}H_{19}INO_5S$ requires *M*, 488.0023].

*iii) Iodolactonisation-Method B*

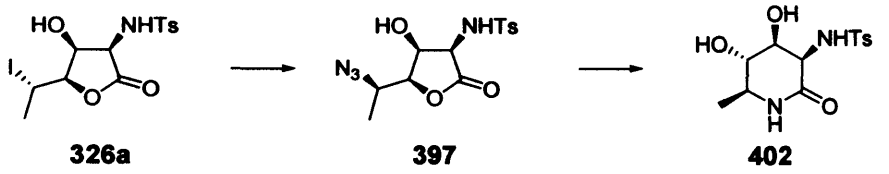
An ice-cold solution of the crude acid **373** (89 mg) in anhydrous acetonitrile (5 ml) was treated with iodine (188 mg, 0.74 mmol) for 3 h according to general procedure L, to yield the *lactone* **375** (58 mg, 69%, over 3 steps), as an orange oil. The data obtained was in accordance with that previously reported.

**(*3RS,4SR,5SR*) (*1'SR*)-(1-azidopentyl)-dihydro-4-hydroxy-3-(tosylamino)furan-2(3*H*)-one 398**




To a solution of the iodolactone **254** (102 mg, 0.22 mmol, 1.0 eq) in anhydrous dimethylformamide (1 ml) was added sodium azide (21 mg, 0.33 mmol 1.5 eq) and the solution was then heated to 60°C for 2 h. The oil bath was removed, the solution was allowed to cool and saturated aqueous sodium thiosulfate (2.5 ml) was added. Diethyl ether (2.5 ml) was added and the resultant two layers were separated. The aqueous phase was extracted with diethyl ether (3 x 2.5 ml) and the combined organic phases were washed with water (3 x 8 ml). The residue was purified (10% ethyl acetate/petroleum ether) to furnish the *azide* **398** (5 mg, 6%) as a pale green solid: m.p. 133-134°C; $R_f$ 0.55 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3270 (s), 2925 (s), 2106 (s), 1789 (s), 1598 (m), 1454 (s), 1336 (s), 1161 (s) and 814 (s); $\delta_H$ 0.90 (3H, d, *J* 7.1, 5'Me), 1.10-1.65 (6H, m, 3 x $CH_2$), 2.40 (3H, s, Ar-Me), 3.70-3.80 (2H, m, 1'-H and 3-H), 4.25 (1H, dd, *J* 7.7 and 3.2, 4(5)-H), 4.55 (1H, app. t, *J* 7.7, 5(4)-H), 5.25 (1H, d, *J* 6.2, NH, exchanges with $D_2O$), 7.30 (2H, d, *J* 8.2, 2 x Ar-H) and 7.75 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ (Acetone) 13.3 (5'-Me), 20.5 (Ar-Me), 22.1, 28.6, 29.0 (all $CH_2$), 60.5, 63.0, 72.5, 82.0 (all CH), 127.0, 129.3, (both ArCH), 139.3, 143.0 (both ArC) and 170.3 (C=O); *m/z* [APcI] 355 ($M^+$ - $N_2$, 32%), 113 (48) and 65 (100). [Found $M^+ + NH_4$: 400.1651. $C_{16}H_{26}N_5O_5S$ requires *M*, 400.1649].

**(*3RS,4SR,5SR,6SR*)-4,5-dihydroxy-6-methyl-3-(tosylamino)-piperidin-2-one 402**




**326a** **397** **402**

*i) Azide displacement*

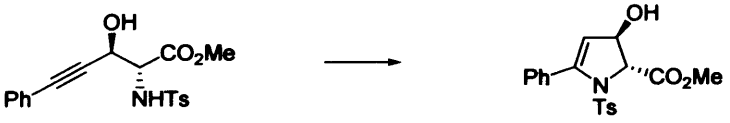
To the iodo-lactone **326a** (135 mg, 0.32 mmol, 1.0 eq) in anhydrous *N,N*-dimethylformamide (5 ml) was added sodium azide (41 mg, 0.63 mmol, 2.0 eq) and 15-crown-5 (1 drop). The mixture was heated to 60°C for 11.5 h. The reaction mixture was allowed to cool to ambient temperature, saturated aqueous sodium thiosulfate (2 ml) was added, the resulting two layers were separated, the aqueous phase was extracted with diethyl ether (4 x 2 ml) and the combined organic layers were washed with water (2 x 10 ml) and saturated brine (10 ml). The organic layers were dried and evaporated. The residue was chromatographed (30% ethyl acetate/petroleum ether) to give i) the *azide* **397** (13 mg, 12%) together with some inseparable tosyl impurity. The azide **397** was characterised by: $R_f$ 0.18 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3266 (br), 2926 (m), 2094 (s), 1789 (s), 1598 (m), 1454 (m), 1331 (s), 1160 (s) and 814 (m); $\delta_H$ 1.25 (3H, d, *J* 6.6, 2'-Me), 2.35 (3H, s, Ar-Me), 3.05 (1H, br. res., OH), 3.85 (1H, d, *J* 4.1, 3-H), 3.95 (1H, dq, *J* 9.1 and 6.6, 1'-H), 4.10 (1H, dd, *J* 9.1 and 3.0, 5-H), 4.45 (1H, dd, *J* 4.1 and 3.0, 4-H), 5.35 (1H, br. res., NH), 7.25 (2H, d, *J* 8.2, 2 x Ar-H) and 7.75 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ 15.1 (2'-Me), 21.7 (Ar-Me), 56.8, 57.9, 69.0, 84.4 (all CH), 127.4, 130.2 (both ArCH), 139.0, 144.9 (both ArC) and 171.5 (C=O); *m/z* [ES] 363 ($M^+$ + Na, 100%), 358 (75), 341 (20). [Found $M^+ + NH_4$: 358.1180. $C_{13}H_{20}N_5O_5S$ requires *M*, 358.1180].

*i) Hydrogenation*

To the azide **397** (13 mg, 0.038 mmol,) in methanol (0.5 ml) was added 10% palladium on carbon (5 mg) and the suspension was stirred under an atmosphere of hydrogen for 64 h. The suspension was filtered through a plug of celite, the solid was washed with ether (10 ml) and the combined filtrates were evaporated. Chloroform was added and the precipitate was filtered off to give the *piperidinone* **402** (10 mg, 83%, over 3 steps) as a white solid: m.p. 166.3-170°C; $\nu_{max}/cm^{-1}$ [KBr] 3328 (br), 2935 (s), 1658 (s), 1438 (br), 1384 (s), 1324 (s), 1165 (s) and 818 (s); $\delta_H$ (MeOD) 1.00 (3H, d, *J* 6.8, 6-Me), 2.30 (3H, s, Ar-Me), 3.60 (1H, dd, *J* 4.4 and 3.1, 5-H), 3.66 (1H, qd, *J* 6.8 and 3.1, 6-H), 3.95 (1H, app. t, *J* 4.4 and

3.2, 4-H), 3.99 (1H, d, *J* 3.2, 3-H), 7.25 (2H, d, *J* 8.3, 2 x Ar-H) and 7.70 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_H$ (Acetone) 1.05 (3H,d, *J* 6.7, Me), 2.25 (3H, s, Ar-Me), 3.70-3.80 (2H, m, 6-H and 5(4)-H), 3.85 (1H, br. t, *J* 3.1, 4(5)-H), 4.15 (1H, br. q, *J* 3.5, 3-H), 4.55 (1H, d, *J* 5.0, OH, exchanges with $D_2O$), 4.65 (1H, d, *J* 3.6, OH, exchanges with $D_2O$), 5.80 (1H, br. res., NH, exchanges with $D_2O$), 6.40 (1H, br. res., NH, exchanges with $D_2O$), 7.25 (2H, *J* 8.3, 2 x Ar-H) and 7.65 (2H, *J* 8.3, 2 x Ar-H); $\delta_H$ (Acetone, $D_2O$ shake) 1.00 (3H, d, *J* 6.8, 6-Me), 2.25 (3H, s, Ar-Me), 3.65-3.70 (1H, m, 6-H), 3.70 (1H, app. t, *J* 4.5 and 3.1, 5-H), 3.85 (1H, d, *J* 2.9, 3-H), 4.10 (1H, dd, *J* 4.4 and 3.1, 4-H), 7.25 (2H, d, *J* 8.1, 2 x Ar-H) and 7.65 (2H, d, *J* 8.1, 2 x Ar-H); $\delta_C$ (MeOD) 16.5, 21.5 (both Me), 49.4, 54.7, 70.7, 72.7 (all CH), 128.5, 130.6 (both ArCH), 138.8, 144.7 (both ArC) and 171.1 (C=O); *m/z* [ES] 337 ($M^+$ + Na, 100%) and 315 (40). [Found $M^+$ + H: 315.0998. $C_{13}H_{19}N_2O_5S$ requires *M*, 315.1009].

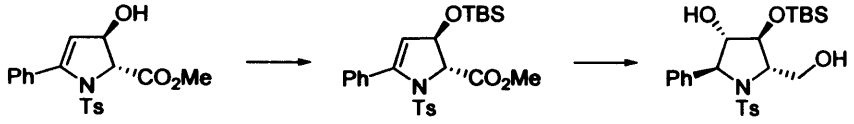
**(*2RS,3RS*)-Methyl-2,3-dihydro-3-hydroxy-5-phenyl-1-tosyl-1*H*-pyrrole-2-carboxylate 421**




**146a** **421**

The alkyne **146a** (200 mg, 0.54 mmol) was cyclised using 10% by weight $AgNO_3$ on $SiO_2$ (456 mg, 0.27 mmol, 0.5 eq) for 1 h according to general procedure O to yield the *dihydropyrrole* **421** (185 mg, 93%), as a colourless solid: m.p. 97.5-98.6°C; $R_f$ 0.18 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2955 (m), 1754 (s), 1638 (m), 1597 (m), 1492 (s), 1447 (m), 1358 (s), 1167 (s), 1090 (s), 815 (m) and 761 (s); $\delta_H$ 0.95 (1H, dd, *J* 9.3, OH, exchanges with $D_2O$), 2.35 (3H, s, Ar-Me), 3.75 (3H, s, $CO_2Me$), 4.55 (1H, dd, *J* 9.3 and 3.1, 3-H), 4.65 (1H, app. s, 2-H), 5.40 (1H, d, *J* 3.1, 4-H) and 7.15-7.50 (9H, m, Ph and 4 x Ar-H); $\delta_C$ 21.7, 53.1 (both Me), 71.8, 74.2 (both CH), 115.0 (4-CH), 127.9, 128.2, 128.6, 129.6, 129.8 (all ArCH), 131.3, 131.9, 144.7, 149.2 (all C) and 169.6 (C=O); *m/z* [APcI] 356 ($M^+$ - $H_2O$, 100%), 324 (20). [Found $M^+$ + $NH_4$: 391.1323. $C_{19}H_{23}N_2SO_5$ requires *M*, 391.1322].

**(*1SR,2SR,3SR,4SR,5SR*)-4-(*tert*-butyldimethyl-silyloxy)-5-hydroxymethyl-2-phenyl-1-(tosyl)-pyrrolidine-3-ol 428a**



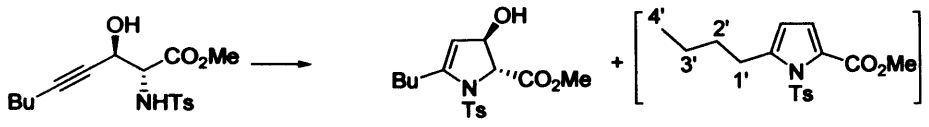

i) *TBS protection*

The dihydropyrrole **421** (180 mg, 0.48 mmol) was protected using TBSTriflate according to general procedure P to yield the *TBS ether* **427** (204 mg, 86%) together with some silicon residues as a cream solid which was used without further purification: m.p. 95-97°C; $R_f$ 0.65 (40% ethyl acetate /petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2952 (s), 2854 (s), 1760 (s), 1599 (s), 1471 (s), 1360 (s), 1169 (s), 1091 (s), 839 (s) and 778 (s); $\delta_H$ -0.05 (3H, s, SiMe), 0.00 (3H, s, Si-Me), 0.75 (9H, s, *t*-Bu), 2.35 (3H, s, Ar-Me), 3.80 (3H, s, $CO_2Me$), 4.55-4.60 (2H, m, 2-H and 3-H) 5.20 (1H, d, *J* 3.0, 4-H) and 7.20-7.60 (9H, m, Ph and 4 x Ar-H); $\delta_C$ -3.5, -3.4 (both SiMe), 17.9 ($\underline{C}(CH_3)_3$), 21.6 (Ar-Me), 25.6 (*t*-Bu), 52.8 ($CO_2Me$), 72.2, 74.5 (both CH), 115.2 (=CH), 127.7, 128.2, 128.8, 129.4, 129.5, (all ArCH), 131.6, 133.4, 143.9, 147.5 (all C) and 170.3 (C=O); *m/z* [APcI] 356 ($M^+$ - HOTBS, 100%) and 488 (5%).

*ii) Hydroboration*

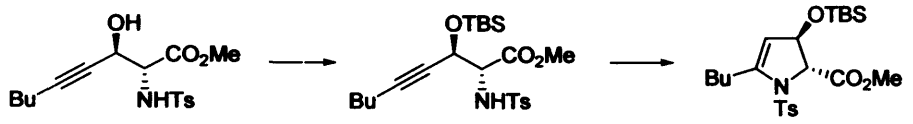
The crude silyl ether **427** (200 mg, 0.41 mmol) was hydroborated according to general procedure Q to yield the *pyrrolidine* **428a** (87 mg, 40%, over two steps) as a white solid: mp 127-130°C; $R_f$ 0.56 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3624 (br), 2928 (s), 2856 (s), 1599 (m), 1496 (m), 1462 (s), 1336 (s), 1158 (s), 1104 (s), 838 (m), 780 (m) and 701 (m); $\delta_H$ 0.00 (3H, s, Si-Me), 0.10 (3H, s, Si-Me), 0.85 (9H, s, *t*-Bu), 2.35 (3H, s, Ar-Me), 2.30 (3H, s, Ar-Me), 3.85 (1H, app. d, *J* 12.3, $C\underline{H}_aCH_b$), 3.95 (1H app. s, 4-H), 4.00 (1H, app. s, 5-H), 4.25 (1H, app. s, 3-H), 4.50 (1H, dd, *J* 12.3 and 3.2, $CH_aC\underline{H}_b$), 4.95 (1H, app. s, 2-H), 7.00-7.20 (5H, m, 5 x Ar-H), 7.25 (2H, d, *J* 8.4, 2 x Ar-H) and 7.30 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ -5.0, -5.0 (both SiMe), 17.8 ($\underline{C}$-$(CH_3)_3$), 21.5 (Ar-Me), 25.5 (*t*-Bu), 63.4 ($CH_2$), 71.9, 75.3, 83.0, 84.1 (all CH), 127.0, 127.1, 127.7, 128.7, 129.0 (all ArCH), 137.6, 138.6 and 143.0 (all ArC); *m/z* [APcI] 478 ($M^+$ + H, 100%) and 460 (10). [Found $M^+$ + H: 478.2082. $C_{24}H_{36}NO_5SSi$ requires *M*, 478.2078].

**Silver Cyclisation of (*2RS,3RS*)-Methyl 3-hydroxy-2-(tosylamino)non-4-ynoate 144a**




The alkyne **144a** (33 mg, 0.093 mmol) was cyclised using 10% silver nitrate on silica gel (79 mg, 0.047 mmol, 0.5 eq) for 1.5 h according to general procedure O to give a 5:1 mixture of i) the *dihydropyrrole* **429** and ii) the *pyrrole* **430** both as a colourless oils (31 mg). The dihydropyrrole **429** was characterised by: $R_f$ 0.35 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$[$CH_2Cl_2$] 3514 (br), 2957 (m), 2872 (m), 1736 (s), 1598 (m), 1495 (m), 1437 (m), 1356 (s), 1166 (s), 814 (m) and 666 (s); $\delta_H$ 0.85 (3H, t, *J* 7.3, 4'-Me), 1.15-1.55 (4H, m, 2 x $CH_2$), 2.20-2.40 (4H, m, $C\underline{H}_aCH_b$ and Ar-Me), 2.40-2.50 (1H, m, $CH_aC\underline{H}_b$), 3.70 (3H, s, Ar-Me), 4.40-4.50 (2H, m, 2-H and 3-H), 5.0 (1H, app. s, 4-H), 7.20-7.30 (2H, m, 2 x Ar-H) and 7.65-7.75 (2H, m, 2 x Ar-H); $\delta_C$ 13.8 (Me), 21.6 (Ar-Me), 22.2, 28.7, 29.4 (all $CH_2$), 52.8 ($CO_2Me$), 71.6, 74.4 (2-CH and 3-CH), 110.7 (4-CH), 127.6, 129.9 (both ArCH), 134.7 (=C), 144.4, 149.8 (both ArC) and 169.9 (C=O). The *pyrrole* **430** was characterised by: m.p. 76-78.7°C; $R_f$ 0.69 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2956 (s), 1729 (s), 1491 (s), 1369 (s), 1324 (s), 1176 (s), 114 (s) and 802 (m); $\delta_H$ 0.85 (3H, t, *J* 7.3, 4'-Me), 1.25-1.40 (2H, m, $CH_2$), 1.50-1.60 (2H, m, $CH_2$), 2.35 (3H, s, Ar-Me), 2.75 (2H, t, *J* 7.8, 1'-$CH_2$), 3.75 (3H, s, $CO_2Me$), 5.95 (1H, d, *J* 3.5, 4-H), 6.75 (1H, d, *J* 3.5, 3-H), 7.25 (1H, d, *J* 8.3, 2 x Ar-H) and 7.85 (1H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ 13.9 (Me), 21.7 (Ar-Me), 22.5, 28.3, 30.9 (all $CH_2$), 52.2 ($CO_2Me$), 110.9, 120.8, 127.4, 129.7, (all ArCH), 136.8, 144.2, 144.8 and 161.2 (all ArC); *m/z* [APcI] 336 ($M^+$ + H, 100%), and 304 (93).

**(*2RS,3RS*) Methyl 5-butyl –3-(*tert*-butyldimethyl-silyloxy)-1-tosyl-2,3-dihydro-1*H*-pyrrole-2-carboxylate 432**




*i) TBS protection*

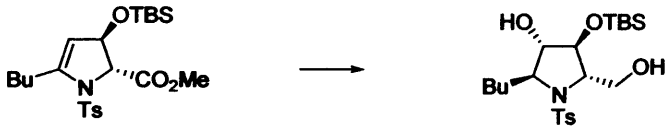
The amino alcohol **144a** (300 mg, 0.85 mmol) was protected using TBS-triflate according to general procedure P, for 2 h to furnish the *TBS ether* **431** (397 mg, 100%) as a 3:1 mixture of diastereoisomers. The product was not suitable for chromatography and so was used without further purification. The *TBS ether* **431** was characterised by: $R_f$ 0.74 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2948 (s), 2242 (m), 1747 (s), 1599 (m), 1434 (s), 1350 (s), 1114 (s) and 839 (s); $\delta_H$ -0.05 (3H, s, SiMe, both isomers), 0.00 (3H, s, SiMe, both isomers), 0.75 (9H, s, *t*-Bu, both isomers), 1.25-1.40 (4H, m, 2 x $CH_2$, both isomers), 1.95-2.05 (1H, m, 6-$CH_2$, minor isomer), 2.10 (2H, app. td, *J* 6.9 and 1.9, 6-$CH_2$, major isomer), 2.35 (3H, s, Ar-Me, both isomers), 3.30 (3H, s, $CO_2Me$, minor isomer), 3.45 (3H, s, $CO_2Me$, major isomer), 3.95 (1H, d, *J* 4.6, 2-H, major isomer), 4.00 (1H, br. res., 2-H, minor isomer), 4.50-4.55 (1H, m, 3-H, major isomer), 4.65-4.70 (1H, m, 3-H, minor isomer), 5.20 (1H, br. res., NH), 7.20 (2H, d, *J* 8.0, 2 x Ar-H) and 7.60-7.70 (2H, m, 2 x Ar-H); $\delta_C$ (Major isomer only) -4.5, -4.7 (both $SiMe_2$), 13.6 (Me), 17.9 ($CH_2$), 18.0 (C-*t*-Bu), 21.5 (Ar-Me), 21.8 ($CH_2$), 25.6 (*t*-Bu), 27.1 ($CH_2$), 52.5 ($CO_2Me$), 61.4, 64.5 (both CH), 87.8, 88.2 (C≡C), 127.3, 129.6 (both ArCH), 137.0, 143.5 (both ArC) and 169.1 (C=O); *m/z* [APcI] 468 ($M^+$ + H, 18%) and 337 (100).

*ii) Silver Cyclisation*

To the crude silyl ether **431** (397 mg, 0.85 mmol) in dichloromethane (4 ml) was added 10% silver nitrate on silica gel (720 mg, 0.42 mmol, 0.5 eq) and the reaction was stirred for 1.5 h, according to general procedure O. Following chromatography (20% ethyl acetate /petroleum ether) the *dihydropyrrole* **432** (171 mg, 43%), was isolated as a yellow oil: $R_f$ 0.74 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2957 (s), 2864 (s), 1764 (m), 1599 (s), 1462 (m), 1360 (s), 1168 (m), 1067 (m) and 840 (m); $\delta_H$ -0.05 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.75 (9H, s, *t*-Bu), 0.90 (3H, t, *J* 7.2, Me), 1.20-1.60 (4H, m, 2 x $CH_2$), 2.25-2.35 (1H, m, $C\underline{H}_aCH_b$), 2.40 (3H, s, Ar-Me), 2.55-2.65 (1H, m, $CH_aC\underline{H}_b$), 3.80 (3H, s, $CO_2Me$), 4.45 (1H, d, *J* 1.6, 2-H), 4.55 (1H, app. s, 3-H), 4.89-4.92 (1H, m, 4-H), 7.25

(2H, d, *J* 8.4, 2 x Ar-H) and 7.70 (2H, d, *J* 8.4, 2 x Ar-H); $\delta_C$ -4.6, -4.5 (both SiMe), 13.9 (Me), 17.8 (C-$(CH)_3)_3$), 21.6 (Ar-Me), 22.2 ($CH_2$), 25.6 (*t*-Bu), 28.7, 29.4 (both $CH_2$), 52.7 ($CO_2Me$), 71.9, 74.8 (both CH), 110.9 (=CH), 127.5, 129.6 (both ArCH), 135.1, 143.8, 148.0 (all C) and 170.4 (C=O); *m/z* [APcI] 468 ($M^+$ + H, 100%) and 336 (53). [Found $M^+$ + H: 468.2235. $C_{23}H_{37}NO_5SSi$ requires *M*, 468.2234].

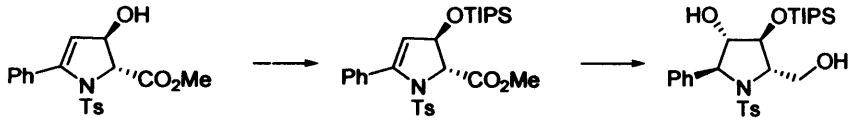
**(*2SR,3SR,4SR,5SR*)-2-Butyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5-hydroxymethyl-1-(tosyl)-pyrrolidine-3-ol 433**




**432** **433**

The TBS ether **432** (150 mg, 0.32 mmol) was treated with a 1M solution of borane-tetrahydrofuran complex in tetrahydrofuran according to general procedure Q to give the *pyrrolidine* **433** (35 mg, 24%), as a yellow oil: $R_f$ 0.45 (40% ethyl acetate/ petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2955 (s), 2863 (s), 1471 (m), 1331 (m), 1157 (s), 1103 (s), 839 (m) and 814 (m); $\delta_H$ -0.05 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.75 (9H, s, *t*-Bu), 0.80 (3H, t, *J* 6.9, Me), 1.15-1.35 (4H, m, 2 x $CH_2$), 1.60-1.70 (1H, m, C$H_a$C$H_b$), 1.85-2.00 (1H, m, C$H_a$C$H_b$), 2.35 (3H, s, Ar-Me), 3.40 (1H, app. d, *J* 3.1, 4-H), 3.55 (1H, app. d, *J* 12.3, C$H_a$C$H_b$O), 3.75 (1H, app. s, 2(3)-H), 3.90 (1H, app. dd, *J* 11.7 and 3.6, 5-H), 4.05 (1H, app. s, 3(2)-H), 4.15 (1H, dd, *J* 12.3 and 3.6, C$H_a$C$H_b$O), 7.20 (2H, d, *J* 8.1, 2 x Ar-H) and 7.70 (2H, d, *J* 8.1, 2 x Ar-H); $\delta_C$ -5.1, -4.9 (both SiMe), 14.0 (Me), 17.7 (C-$(CH_3)_3$), 21.5 (Ar-Me), 22.6 ($CH_2$), 25.5 (*t*-Bu), 28.5, 31.5 (both $CH_2$), 62.5 ($CH_2OH$), 69.9, 72.2, 77.5, 83.3 (all CH), 127.0, 129.7 (both ArCH), 137.9 and 143.4 (both ArC); *m/z* [APcI] 458 ($M^+$ + H, 100%) and 440 (19). [Found $M^+$ + H: 458.2390. $C_{22}H_{40}NO_5SSi$ requires *M*, 458.2391].

**(*2SR,3SR,4SR,4SR,5SR*)-5-Hydroxymethyl-2-phenyl-1-tosyl-4-triisopropylsilanyloxy-pyrrolidin-3-ol 435**




**421** **434** **435**

*i) TIPS protection*

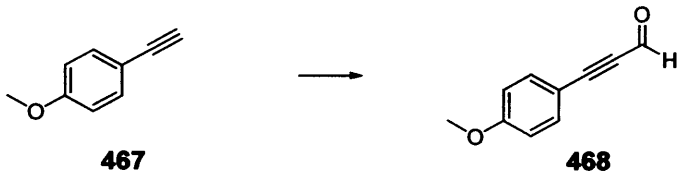
To an ice-cold solution of the dihydropyrrole **421** (489 mg, 1.31 mmol, 1.0 eq) in anhydrous dichloromethane (5 ml) was added 2,6-lutidine (351 mg, 0.38 ml, 3.27 mmol, 2.5 eq) followed by triisopropylsilyltriflate (522 mg, 0.46 ml, 1.70 mmol, 1.3 eq) and the solution was stirred for 16.5 h at room temperature. The solvent was evaporated, water (2 ml) was added and the product was extracted into dichloromethane (3 x 5 ml). The dichloromethane solutions were washed with saturated aqueous sodium bicarbonate solution (20 ml) and the solutions were dried and evaporated. The residue was purified by chromatography (10% ethyl acetate/ petroleum ether) to give the TIPS ether **434** (446 mg, 64%) as a pale yellow oil: $R_f$ 0.53 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2948 (s), 2867 (s), 1761 (s), 1599 (s), 1464 (s), 1366 (s), 1170 (s) and 813 (s); $\delta_H$ 0.95-1.00 (21H, m, 3 x *i*-Pr), 2.30 (3H, s, Ar-Me), 3.75 (3H, s, $CO_2Me$), 4.60-4.63 (1H, m, 2-H), 4.65-4.70 (1H, m, 3-H) and 5.20 (1H, d, *J* 3.2, 4-H), 7.10 (2H, d, *J* 8.2, 2 x Ar-H) and 7.25-7.45 (7H, m, Ph and 2 x Ar-H); $\delta_C$ 12.1 ($C\underline{H}Me_3$), 17.7 (*i*-Pr), 21.5 (Ar-Me), 52.9 ($CO_2Me$), 72.6, 74.5 (both CH), 115.1 (=CH), 127.7, 128.1, 128.8, 129.4, 129.5 (all ArCH), 131.6, 133.6, 143.9, 147.5 (all C) and 170.4 (C=O); *m/z* [APcI] 356 ($M^+$ -OTIPS, 100%). [Found $M^+ + NH_4$: 547.2663. $C_{28}H_{43}N_2O_5SSi$ requires *M*, 547.2656].

*ii) Hydroboration*

The silyl ether **434** (440 mg, 0.83 mmol) was treated with a 1M solution of borane-tetrahydrofuran complex in tetrahydrofuran (3.32 ml, 3.32 mmol) according to general procedure Q, to furnish the *pyrrolidine-2-methanol* **435** (309 mg, 72%), as a pale white oil: $R_f$ 0.37 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2942 (s), 2860 (s), 1599 (m), 1495 (m), 1462 (m), 1330 (s), 1159 (s), 1068 (s) and 811 (m); $\delta_H$ 0.85-1.00 (21H, m, *i*-Pr), 2.20 (3H, s, Ar-Me), 3.70 (1H, app. d, *J* 11.9, $C\underline{H}_aCH_b$), 3.85 (1H, app. s, 3(4)-H), 4.05 (1H, app. s, 5-H), 4.15 (1H, app. s, 4(3)-H), 4.35 (1H, dd, *J* 11.9 and 5.0, $CH_aC\underline{H}_b$), 4.75 (1H, app. s, 2-H) and 6.80-7.10 (9H, m, 4 x Ar-H and Ph); $\delta_C$ 11.8 ($C\underline{H}Me_2$), 17.8 (*i*-Pr),

21.5 (Ar-Me), 63.8 ($CH_2$), 73.0, 75.3, 83.1, 85.0 (all CH), 126.8, 127.0, 127.5, 128.8, 129.0 (all ArCH), 138.2, 138.3 and 142.3 (all ArC); *m/z* [APcI] 520 ($M^+$ +H, 100%). [Found $M^+$ + H: 520.2548. $C_{27}H_{42}NO_5SSi$ requires *M*, 520.2547].

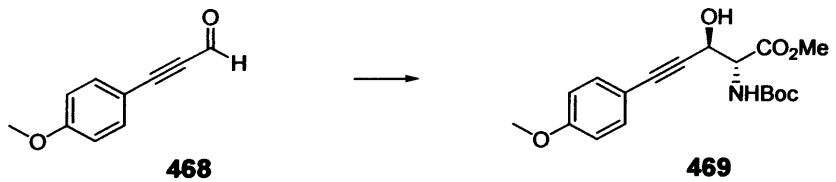
**(4-Methoxy-phenyl)-propynal 468**



**467** **468**

1-Ethynyl-4-methoxy-benzene **467** (1.00 g., 7.57 mmol, Maybridge) was condensed with *N, N*-dimethylformamide according to general procedure R, to give the *aldehyde* **468** (1.16 g, 96%), as an orange solid which was used without further purification. The data obtained was in accordance with that previously reported in the literature: m.p. 43-45°C (lit[13] m.p. 47-48.5°C); $R_f$ 0.41 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2180 (s), 1650 (s), 1599 (s) and 1509 (s); $\delta_H$ 3.80 (3H, s, OMe), 6.85 (2H, d, *J* 8.9, 2 x Ar-H), 7.45 (2H, d, *J* 8.9, 2 x Ar-H) and 9.65 (1H, s, CHO); $\delta_C$ 55.5 (Me), 88.8, 96.6 (both ArCH), 162.1 (ArC) and 176.8 (C=O).

**(*1RS,2RS*)-Methyl 2-*tert*-Butoxycarbonylamino-3-hydroxy-5-(4-methoxy-phenyl)-pent-4-ynoate 469**

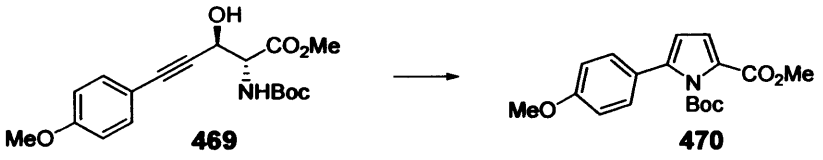


**468** **469**

*N*-Boc glycine methyl ester **162b** (2.60 mmol, 492 mg, 2.60 mmol) and (4-methoxy-phenyl)propynal **468** (500 mg, 3.12 mmol) were reacted together according to general procedure C. The residue was purified by flash chromatography (30% ethyl acetate/

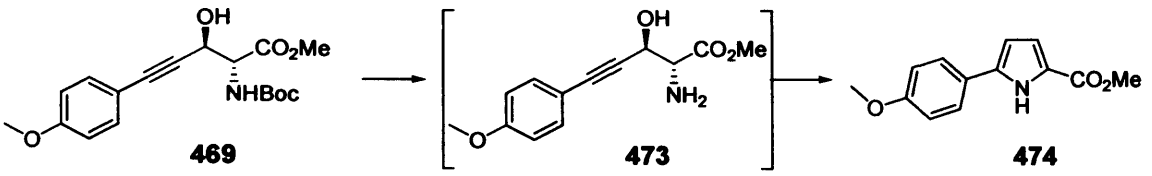
petroleum ether) to yield the *amino alcohol* **469** (158 mg, 21%), as a brown oil together with some aldehyde **468** (95 mg, 19% recovered). The aldol adduct **469** was characterised by: $R_f$ 0.30 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ 2976 (s), 1720 (s), 1606 (s), 1510 (s), 1438 (s) and 1368 (s); $\delta_H$ 1.35 (9H, s, *t*-Bu), 3.70 (6H, s, $CO_2Me$ and OMe), 4.55-4.65 (1H, br. m, 2-H), 4.90-4.95 (1H, br. m, 3-H), 5.50 (1H, br. d, *J* 7.8, NH), 6.75 (2H, d, *J* 8.8, 2 x Ar-H) and 7.25 (2H, d, *J* 8.8, 2 x Ar-H); $\delta_C$ (rotameric) 28.0 (*t*-Bu), 52.8 and 52.9, 55.3 and 55.3 (all OMe), 58.4 and 58.9, 64.1 and 64.5 (all CH), 80.3 and 80.9 (C-$(CH_3)_3$), 83.6 (C≡C), 86.5 and 87.0 (C≡C), 113.9, 133.4 (both ArCH), 156.4 and 160.0 (N-C=O), 169.7 and 170.4 (C=O), no ArC evident; *m/z* [APcI] 332 ($M^+$ - $H_2O$, 17%), 277 (20), 251 (65) and 233 (100).

**Methyl 1-(*t*-butoxycarbonyl)-5-(4-methoxyphenyl)-pyrrole-2-carboxylate 470**



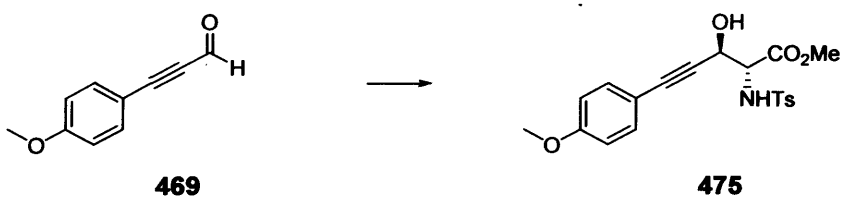

The amino alcohol **469** (82 mg, 0.24 mmol) was subjected to silver catalysed cyclisation (0.5 eq, 2 h), according to general procedure O. The residue was chromatographed (10% ethyl acetate/petroleum ether) to yield the *pyrrole* **470** (72 mg, 92%), as a yellow oil which showed: $R_f$ 0.51 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2930 (m), 2854 (m), 1766 (s), 1713 (s), 1614 (m), 1552 (m), 1511 (m), 1395 (m), 1371 (s) and 835 (m); $\delta_H$ 1.35 (9H, s, *t*-Bu), 3.76 (3H, s, OMe), 3.78 (3H, s, OMe), 6.10 (1H, d, *J* 3.6, 4-H), 6.80-6.85 (3H, m, 2 x Ar-H and 3-H) and 7.30 (2H, d, *J* 8.7, 2 x Ar-H); $\delta_C$ 27.3 (*t*-Bu), 51.7, 55.3 (both OMe), 85.3 (C$(CH_3)_3$), 110.0 (4-CH), 113.6 (2 x Ar-H), 118.2 (3-CH), 123.9, 124.1 (both C), 130.2 (2 x Ar-H), 139.5, 149.8 (both ArC), 159.8 and 160.8 (both C=O); *m/z* [APcI] 332 ($M^+$ +H, 62%), 276 (100%) and 232 (18%). [Found $M^+$ + H: 332.1488. $C_{18}H_{22}NO_5$ requires *M*, 332.1492].

**Methyl 5-(4-methoxyphenyl)-pyrrole-2-carboxylate 474**




The aldol product **469** (136 mg, 0.34 mmol) was treated with trifluoroacetic acid in dichloromethane for 16 h, as described in general procedure F to yield the *pyrrole* **474** (90 mg, 100%), as a yellow crystalline solid: m.p. 147-149°C; $R_f$ 0.30 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3324 (s), 1694 (s), 1478 (m), 1277 (s), 1191 (s), 1149 (s) and 796 (m); $\delta_H$ 3.76 (3H, s, OMe), 3.79 (3H, s, OMe), 6.40 (1H, app. dd, *J* 3.6 and 2.9, 4-CH), 6.80-6.90 (3H, m, 3-CH and 2 x Ar-H), 7.45 (2H, d, *J* 8.8, ArCH) and 9.40 (1H, br. res., NH); $\delta_C$ 51.5, 55.4 (both OMe), 107.1 (4-CH), 114.5 (2 x Ar-H), 117.0 (3-CH), 122.7, 124.2 (both C), 126.2 (2 x Ar-H), 137.0, 159.4 (both C) and 161.70 (C=O); *m/z* [APcI] 231 ($M^+$ + H, 100%). [Found $M^+$ + H: 232.0968. $C_{13}H_{14}NO_3$ requires *M*, 232.0968].

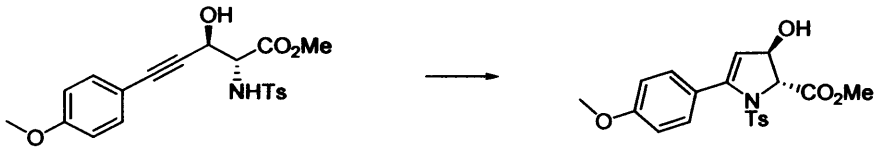
**(*2RS,3RS*)-Methyl 3-hydroxy-5-(4-methoxyphenyl)-2-(tosylamino)pent-4-ynoate 475**




Methyl *N*-tosyl glycinate **156** (1.58 g, 6.49 mmol) and (4-methoxy-phenyl)propynal **468** (1.25 g, 7.82 mmol) were condensed together according to general procedure C. The residue was purified by column chromatography (40% ethyl acetate/petroleum ether) and recrystallisation (10% ethyl acetate/petroleum ether) to give the *amino alcohol* **475** (2.53 g, 59%), as an orange solid: m.p. 126-129°C; $R_f$ 0.23 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3638 (s), 2964 (s), 1746 (m), 1606 (s), 1511 (s), 1434 (m), 1341 (s), 1163 (s) and 832 (m); $\delta_H$ 2.40 (3H, s, Ar-Me), 2.80 (1H, d, *J* 10.5, OH, exchanges with $D_2O$), 3.55 (3H, s, OMe), 3.75 (3H, s, OMe), 4.20 (1H, dd, *J* 9.5 and 3.9, 2-H), 4.80 (1H,

dd, *J* 10.5 and 3.9, 3-H), 5.50 (1H, d, *J* 9.5, NH, exchanges with $D_2O$), 6.80 (2H, d, *J* 8.6, 2 x Ar-H), 7.20-7.30 (4H, m, 4 x Ar-H) and 7.70 (2H, d, *J* 8.6, 2 x Ar-H); $\delta_C$ 21.6, 53.1, 55.3 (all Me), 60.7, 63.6 (both CH), 82.8, 87.8 (both C≡C), 113.5 (ArC), 114.0, 127.4, 129.8, 133.4 (all ArCH), 136.2, 144.1, 160.1 (all ArC) and 168.5 (C=O); *m/z* [APcI] 404 ($M^+$ +H, 18%), 386 (100) and 333 (25). [Found $M^+$ + $NH_4$: 421.1427. $C_{20}H_{25}NO_6S$ requires *M*, 421.1427].

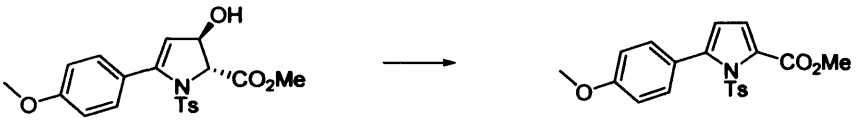
**(*2RS,3RS*)-Methyl 2,3-dihydro-3-hydroxyl-5-(4-methoxyphenyl)-1-tosyl-1*H*-pyrrole-2-carboxylate 476**




**475** **476**

The amino alcohol **475** (1.22 g, 3.01 mmol) was cyclised using 10% silver nitrate on silica gel (1.02 g, 0.60 mmol, 0.2 eq) for 1.5 h according to general procedure O, to give the *dihydropyrrole* **476** (1.20 g, 98%), as an orange solid which showed: m.p. 46-48°C; $R_f$ 0.17 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3500 (br), 2956 (m), 1754 (s), 1607 (s), 1511 (s), 1357 (s), 1169 (s) and 814 (m); $\delta_H$ 2.35 (3H, s, Ar-Me), 3.76 (3H, s, OMe), 3.79 (3H, s, OMe), 4.50 (1H, br. res, 3-H), 4.65 (1H, app. s, 2-H), 5.30 (1H, d, *J* 3.3, 4-H), 6.80 (2H, d, *J* 8.8, 2 x Ar-H), 7.25 (2H, d, *J* 8.2, 2 x Ar-H) and 7.45 (4H, 2 x d, *J* 8.8 and 8.2, 4 x Ar-H); $\delta_C$ 20.6 (Ar-Me), 51.9, 54.5 (both OMe), 71.4, 73.0 (both CH), 112.2 (ArCH), 112.5 (CH), 122.6 (ArC) 127.1, 128.5, 129.1 (all ArCH), 132.0, 143.6, 147.7, 167.4 (all ArC) and 168.7 (C=O); *m/z* [APcI] 386 ($M^+$ -$H_2O$, 100%).

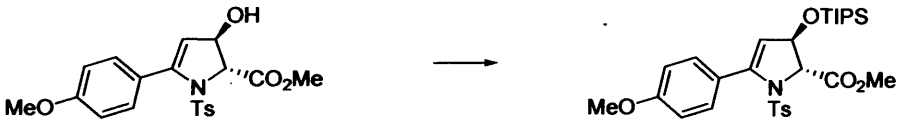
**Methyl 5-(4-methoxyphenyl)-1-tosyl-1*H*-pyrrole-2-carboxylate 476b**




**476** **476b**

At room temperature overnight, the dihydropyrrole **476** as a solution in deuteriochloroform dehydrated to form the corresponding *pyrrole* **476a** as an orange oil: $R_f$ 0.56 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2957 (s), 1730 (s), 1607 (s), 1511 (s), 1481 (s), 1354 (s), 1167 (s) and 814 (s); $\delta_H$ 2.30 (3H, s, Ar-Me), 3.75 (3H, s, OMe), 3.85 (3H, s, OMe), 5.95 (1H, d, *J* 3.5, 4-H), 6.75 (2H, d, *J* 8.7, 2 x Ar-H), 6.85 (1H, d, *J* 3.5, 3-H), 7.00-7.05 (4H, m, 4 x Ar-H) and 7.25 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ 21.7 (Ar-Me), 52.5, 55.4 (both OMe), 113.1 (ArCH), 113.9, 122.3 (both =CH), 123.7 (C), 127.5, 129.1 (both ArCH), 130.3 (C), 131.5 (ArCH), 135.4, 143.9, 144.9, 160.2 (all ArC) and 162.0 (C=O); *m/z* [APcI] 386 ($M^+$ + H, 100%).

***(2RS,3RS)* Methyl 5-(4-methoxy-phenyl)-1-tosyl-3-triisopropylsilanyloxy-2,3-dihydro-1H-pyrrole-2-carboxylate 477**

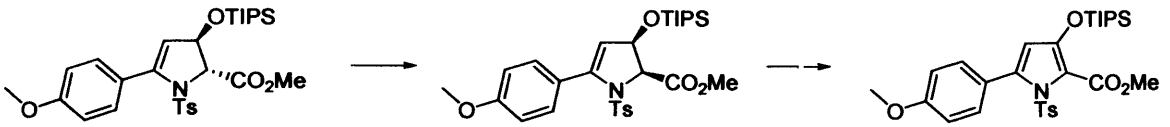



**476** **477**

*i) TIPS protection*

To an ice-cold solution of the dihydropyrrole **476** (206 mg, 0.51 mmol, 1.0 eq) in dichloromethane (2 ml) was added 2,6-lutidine (136 mg, 0.15 ml, 1.28 mmol, 2.5 eq) followed by TIPS triflate (203 mg, 0.18 ml, 0.66 mmol, 1.3 eq). The ice-bath was removed and the reaction mixture was stirred for 18.5 h. The solvent was evaporated, water (1 ml) was added and the product was extracted into dichloromethane (3 x 5 ml). The combined dichloromethane layers were washed with saturated aqueous sodium bicarbonate solution (20 ml) and the layers were dried and evaporated to furnish the TIPS ether **477** (336 mg, > 100%), as an orange oil: $R_f$ 0.63 (20% ethyl acetate/petroleum ether);

$\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2944 (s), 2867 (s), 1738 (s), 1639 (m), 1607 (s), 1573 (m), 1511 (s), 1463 (s), 1362 (s), 1170 (s), 831 (s) and 813 (s); $\delta_H$ 0.95-1.00 (21H, m, 3 x *i*-Pr), 2.45 (3H, s, Ar-Me), 3.75 (6H, s, 2 x OMe), 4.55-4.65 (2H, m, 2-H and 3-H), 5.10 (1H, d, *J* 3.1, 4-H), 6.75 (2H, d, *J* 8.8, 2 x Ar-H), 6.85 (2H, d, *J* 7.6, 2 x Ar-H), 7.30-7.40 (4H, m, 4 x Ar-H); *m/z* [APcI] 386 ($M^+$ -OTIPS, 100%).




**477** **479** **480**

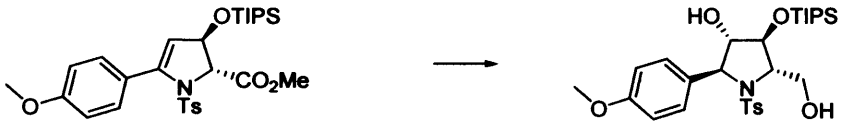
*ii) Isomerisation*

Approximately two thirds of the crude reaction mixture **477** was purified by chromatography (20% ethyl acetate/petroleum ether). The NMR of the product revealed that isomerisation had occurred to give the *silyl ether* as a mixture of diastereoisomers in the ratio 7:1. To obtain further NMR data this sample was left as a solution in deuterated chloroform overnight, during which time complete isomerisation to **479** had occurred: $\delta_H$ 0.85-1.00 (21H, m, 3 x *i*-Pr), 2.30 (3H, s, Ar-Me), 3.70 (3H, s, OMe), 3.75 (3H, s, OMe), 4.60 (1H, app. s, 3-H), 4.90 (1H, app. s, 2-H), 5.15 (1H, app. s, 4-H), 6.75 (2H, d, *J* 8.1, 2 x Ar-H), 7.15 (2H, d, *J* 8.1, 2 x Ar-H), 7.55 (2H, d, *J* 8.3, 2 x Ar-H), and 7.75 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ 11.9 (C<u>H</u>-*i*-Pr), 17.7 (*i*-Pr-<u>Me</u>), 21.6 (Ar-Me), 52.6, 55.4 (both OMe), 77.0, 80.1, 83.6 (all CH), 113.6 (=CH), 125.5 (C), 129.3, 129:4, 131.0 (all ArCH), 134.9, 145.4, 162.1, 165.1 (all C) and 169.6 (C=O).

*iii) Elimination of Isomerised Product* **480**

The isomerised product **479** was left over the weekend, as a solution in deuterated chloroform and elimination occurred to generate the *pyrrole* **480**: $\delta_H$ 0.95-1.00 (21H, m, 3 x *i*-Pr), 2.25 (3H, s, Ar-Me), 3.70 (3H, s, OMe), 3.75 (3H, s, OMe), 6.80 (2H, d, *J* 8.2, 2 x Ar-H), 7.05 (2H, d, *J* 8.2, 2 x Ar-H), 7.25 (1H, d, *J* 2.8, 4-H), and 7.45-7.55 (4H, m, 2 x Ar-H); $\delta_C$ 12.3 (C<u>H</u>-*i*-Pr), 17.9 (*i*-Pr-<u>Me</u>), 21.5 (Ar-Me), 55.1, 55.4 (both OMe), 113.7 (ArCH), 117.7 (=CH), 121.4, 121.4, 123.6 (all C), 127.0, 129.3, 131.0 (all ArCH), 138.5, 139.7, 143.4, 160.7 (all C) and 161.3 (C=O); *m/z* [APcI] 386 ($M^+$ -HOTIPS, 100%).

**(2SR,3SR,4SR,5SR)-5-Hydroxymethyl-2-(4-methoxy-phenyl)-1-tosyl-4-triisopropylsilanyloxy-pyrrolidin-3-ol 478**

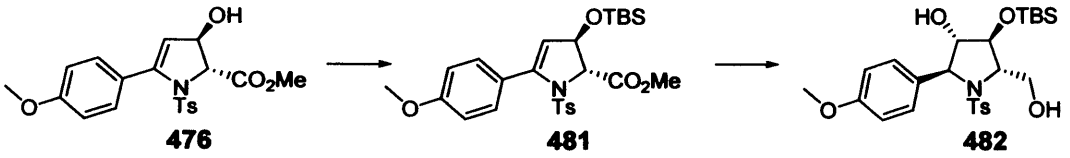



**477** **478**

*ii) Hydroboration*

The crude silyl ether **477** (629 mg, 1.12 mmol, 1.0 eq) was reacted with a 1 M solution of borane-THF complex in tetrahydrofuran according to general procedure Q to furnish the pyrrolidine **478** (158 mg, 30%, over 2 steps), as a pale yellow oil: $R_f$ 0.40 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [Film] 3461 (br), 2956 (s), 2866 (s), 1612 (m), 1514 (s), 1463 (s), 1333 (s), 1178 (s), 1179 (s), 1103 (s), 827 (s), 810 (s), 734 (s) and 704 (m); $\delta_H$ 0.90-1.10 (21H, m, OTIPS), 2.20 (3H, s, Ar-Me), 3.70 (3H, s, OMe), 3.75 (1H, app. d, *J* 11.6, $C\underline{H}_aCH_b$), 3.90 (1H, app. s, 3-H), 4.00 (1H, app. s, 5-H), 4.15 (1H, app. s, 4-H), 4.40 (1H, dd, *J* 11.7 and 2.1, $CH_aC\underline{H}_b$), 4.75 (1H, app. s, 2-H), 6.45 (2H, d, *J* 7.9, 2 x Ar-H), 6.90 (2H, d, *J* 7.9, 2 x Ar-H), 7.05 (2H, d, *J* 8.1, 2 x Ar-H) and 7.15 (2H, d, *J* 7.9, 2 x Ar-H); $\delta_C$ 11.9 (CH-Si), 17.8 (*i*-Pr), 21.4 (Ar-Me), 55.2 (OMe), 64.2 ($CH_2OH$), 72.7, 74.8, 83.1, 85.0 (all CH), 112.9, 126.9, 128.9, 130.4 (all ArCH), 130.6, 138.2, 142.5 (all ArC) and 158.7 (C=O); *m/z* [APcI] 549 ($M^+$, 100%). Sample decomposed prior to HRMS measurement.

**(2RS,3SR,4SR,5SR)-4-(*t*-Butyldimethylsilanyloxy)-5-Hydroxymethyl-2-(4-methoxy-phenyl)-1-tosyl-pyrrolidin-3-ol 482**




*i) TBS protection*

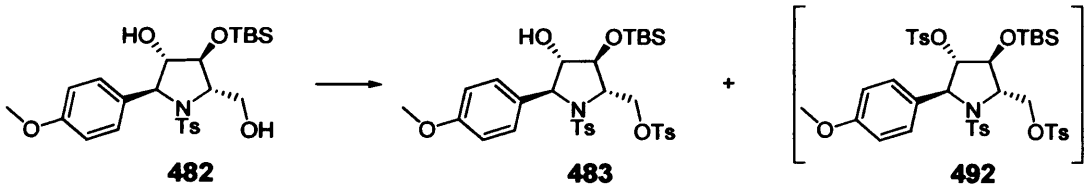
To the dihydropyrrole **476** (155 mg, 0.38 mmol) was protected as the TBS ether according to general procedure P to yield the *TBS ether* **481** (183 mg, 92%), as an orange oil, which was used immediately without further purification and showed: m.p.106-107.3°C; $R_f$ 0.55 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2956 (s), 2855 (s), 1758 (s), 1643 (s), 1607 (s), 1511 (s), 1472 (s), 1360 (s), 1166 (s), 1087 (s), 837 (s) and 783; $\delta_H$ -0.10 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.75 (9H, s, *t*-Bu), 2.35 (3H, s, Ar-Me), 3.80 (3H, s, OMe), 4.60 (1H, dd, *J* 3.2 and 1.3, 3-H), 4.62 (1H, d, *J* 1.3, 2-H), 5.10 (1H, d, *J* 3.2, 4-H), 6.85 (2H, d, *J* 8.8, 2 x Ar-H), 7.18 (2H, d, *J* 8.2, 2 x Ar-H), 7.40 (2H, d, *J* 8.2, 2 x Ar-H) and 7.55 (2H, d, *J* 8.8, 2 x Ar-H); $\delta_C$ -3.6, -2.9, (both SiMe), 17.9 ($\underline{C}(CH_3)_3$), 21.6 (Ar-Me), 25.6 (*t*-Bu), 52.8, 55.4 (both OMe), 113.2 (ArCH), 113.7 (=CH), 128.2, 129.3, 130.3 (all ArCH), 133.6, 144.9, 147.3, 160.6 (all ArC) and 170.4 (C=O).

*ii) Hydroboration*

The crude TBS ether **481** (180 mg, 0.38 mmol, 1.0 eq) was hydroborated according to general procedure Q. The residue was purified by column chromatography (20% ethyl acetate/petroleum ether) to yield the *pyrrolidine* **482** (92 mg, 47%, over 2 steps) as a white solid: $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3398 (br), 2929 (s), 2857 (s), 1612 (s), 1514 (s), 1496 (s), 1464 (s), 1332 (s), 1252 (s), 1156 (s), 1103 (s), 1037 (s) and 837 (s); $R_f$ 0.30 (40% ethyl acetate/petroleum ether); $\delta_H$ 0.00 (3H, s, SiMe), 0.10 (3H, s, SiMe), 0.80 (9H, s, *t*-Bu), 2.30 (3H, s, Ar-Me), 3.70 (3H, s, OMe), 3.80-3.85 (1H, m, $C\underline{H}_aH_b$), 3.90 (1H, app. s, CH), 4.00 (1H, app. s, CH), 4.20 (1H, app. s, CH), 4.45 (1H, dd, *J* 11.8 and 3.3, $CH_aC\underline{H}_b$), 4.80 (1H, app. s, 4-H) 6.50 (2H, d, *J* 8.7, 2 x Ar-H), 7.00 (2H, d, *J* 8.3, 2 x Ar-H), 7.10 (2H, d, *J* 8.7, 2 x Ar-H) and 7.20 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ -5.0, -4.9, (both SiMe), 17.9 ($\underline{C}(CH_3)_3$), 21.4 (Ar-Me), 25.6 (*t*-Bu), 55.3 (OMe), 63.7 ($CH_2$), 72.2, 74.6, 82.5, 84.4 (all CH), 113.0, 128.8, 130.3, 130.5 (all ArCH), 131.0, 138.1, 142.6 and 158.8 (all ArC); *m/z*

[ES] 530 ($M^+$ + Na, 100%), 525 (52) and 508 (88). [Found $M^+$ + $NH_4$: 525.2444. $C_{25}H_{41}N_2O_6SSi$ requires *M*, 525.2449].

**(2SR,3SR,4SR,5SR)-Toluene-4-sulfonic acid 3-(*t*-Butyldimethylsilyloxy)4-Hydroxy-5-(4-methoxyphenyl)-1-tosyl-pyrrolidin-2-ylmethyl ester 483**




*i) Method A*

To an ice-cold solution of the diol **482** (83 mg, 0.16 mmol, 1.0 eq) in anhydrous pyridine (1 ml) was added DMAP (2 mg) and the mixture was stirred for 0.25 h. Next *p*-tosyl chloride (31 mg, 0.16 mmol, 1.0 eq) was added and the reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was poured into ice-cold water (0.5 ml), ether was added (2 ml) and the resulting two layers were separated. The aqueous phase was extracted with ether (4 x 2 ml) and the combined ether layers were washed with saturated aqueous copper sulfate solution (3 x 8 ml). The ether layers were dried and evaporated. The residue was chromatographed (25% ethyl acetate/petroleum ether) to furnish the *tosylate* **483** (22 mg, 20%) as a colourless oil, together with some recovered starting material (45 mg, 54% recovered). The tosylate **483** was characterised by: $R_f$ 0.34 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3498 (br), 2929 (s), 2858 (s), 1613 (m), 1599 (m), 1515 (s), 1464 (s), 1343 (s), 1252 (s), 1158 (s), 1097 (s), 1064 (s) and 839 (s); $\delta_H$ 0.00 (3H, s, SiMe), 0.10 (3H, s, SiMe), 0.75 (9H, s, *t*-Bu), 2.25 (3H, s, OTs-Me), 2.40 (3H, s, NTs-Me), 3.70 (3H, s, OMe), 4.05 (1H, app. s, 4-H), 4.10 (1H, dd, *J* 10.1 and 4.4, 2-H), 4.30 (1H, app. s, 3-H), 4.45 (1H, app. t, *J* 9.8, $C\underline{H}_aCH_b$), 4.50 (1H, dd, *J* 9.8 and 4.4 $CH_aC\underline{H}_b$), 4.65 (1H, app. s, 5-H), 6.40 (2H, d, *J* 8.7, 2 x Ar-H), 6.85 (2H, d, *J* 8.2, 2 x Ar-H), 7.0 (2H, d, *J* 8.3, 2 x Ar-H), 7.05 (2H, d, *J* 8.7, 2 x Ar-H), 7.30 (2H, d, *J* 8.2, 2 x Ar-H), 7.80 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_C$ -5.1, -4.9 (both Si-Me), 17.8 ($\underline{C}$-$(CH_3)_3$), 21.4, 21.7 (both Ar-Me), 25.6 (*t*-Bu), 55.3 (OMe), 68.9 ($CH_2$), 69.0, 73.3, 78.7, 85.3 (all CH), 112.9, 126.7, 128.2, 128.7 (all ArCH), 128.7 (ArC), 130.0, 131.0 (both ArCH), 132.5, 138.2, 142.5, 145.2 and 159.1 (all ArC); *m/z* [APcI] 662 ($M^+$ + H, 19%) and 435 (100).

*ii) Method B*

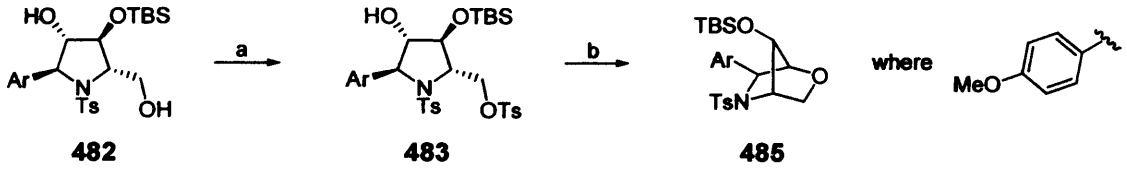
To an ice-cold solution of the diol **482** (146 mg, 0.29mmol, 1.0 eq) and DABCO (42 mg, 0.37 mmol, 1.3 eq) in anhydrous dichloromethane (2 ml) was added *p*-tosyl chloride (54 mg, 0.29 mmol, 1.0 eq) gradually over 15 minutes. The reaction was stirred for a further h at 0°C, the ice-bath was removed and the solution was stirred for 48 h. The solution was filtered through a pad of celite and solid was washed with dichloromethane. The combined filtrates and washings were evaporated. The residue was purified by column chromatography (20% ethyl acetate/petroleum ether) to yield a 9:2 mixture of i) the *tosylate* **483** and ii) *bis-tosylate* **492** as a colourless oil, together with some starting material (58 mg, 40% recovered). The data obtained for the tosylate **483** was identical to that previously reported. The data corresponding to the tritosylate will be reported later.

*iii) Method C*

To a -20°C solution of DABCO (157 mg, 1.40 mmol, 1.3 eq) and the diol **482** (545 mg, 1.07 mmol, 1.0 eq) in distilled dichloromethane (8 ml) was added *p*-tosyl chloride (205 mg, 1.07 mmol, 1.0 eq) gradually over 15 minutes. The reaction was stirred for 24 h at -20°C, and the solution was then warmed to 0°C and the reaction mixture was stirred for a further 96 h. Following an identical work-up to that described above and purification by column chromatography (20% ethyl acetate/petroleum ether) a mixture of i) the *tosylate* **483** (459 mg, 67%) as a colourless oil, ii) *bis-tosylate* **492** (33 mg, 4%) as a pale yellow oil and some starting material **482** (approx. 19 mg, 3% recovered) was obtained. The data obtained for the tosylate **483** was identical to that previously reported. The *bis*-tosylate **492** was characterised by: $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2928 (s), 2856 (m), 1598 (m), 1514 (s), 1463 (m), 1369 (m), 1190 (s), 1178 (s), 1159 (s), 1096 (m), 838 (m) and 814 (m); $\delta_H$ 0.00 (3H, s, SiMe), 0.15 (3H, s, SiMe), 0.85 (9H, s, *t*-Bu), 2.45 (3H, s, Ar-Me), 2.55 (3H, s, Ar-Me), 2.60 (3H, s, Ar-Me), 3.85 (3H, s, OMe), 4.20 (1H, app. t, *J* 11.2 and 9.5, $C\underline{H}_aCH_b$), 4.25 (1H, dd, *J* 11.2 and 3.7, $CH_aC\underline{H}_b$), 4.50 (1H, app. s, 3(4)-H), 4.60 (1H, app. s, 4(3)-H), 4.85 (1H, dd, *J* 9.5 and 3.7, 2-H), 4.95 (1H, app. s, 5-H), 6.55 (2H, d, *J* 8.7, 2 x Ar-H), 6.95 (2H, d, *J* 8.7, 2 x Ar-H), 7.05 (2H, d, *J* 8.2, 2 x Ar-H), 7.15 (2H, d, *J* 8.3, 2 x Ar-H), 7.40 (2H, d, *J* 8.2, 2 x Ar-H), 7.50 (2H, d, *J* 8.2, 2 x Ar-H), 7.75 (2H, d, *J* 8.3, 2 x Ar-H) and 7.95 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ -5.4, -5.3 (both SiMe), 17.7 (Si-$\underline{C}(CH_3)_3$), 21.4, 21.7, 21.8 (all Ar-Me), 25.4 (*t*-Bu), 55.3 (OMe), 68.1 ($CH_2$), 68.6, 70.7, 77.0, 90.5 (all CH), 113.0 (ArCH), 126.7 (ArC), 127.2, 128.1, 128.2, 128.8, 130.1, 130.1, 130.6 (all ArCH) 132.3, 132.6,

137.9, 142.9, 145.3, 145.5 and 159.2 (all ArC); *m/z* [APcI] 816 ($M^+$ + H, 31%), 358 (22), 340 (24), 287 (65), 186 (31), 157 (84) and 139 (100).

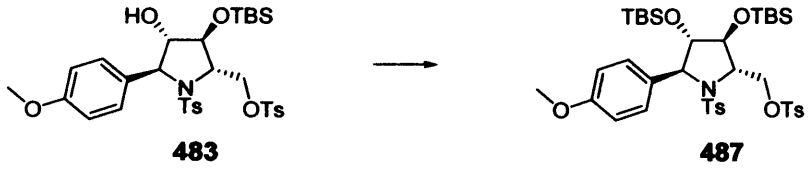
**(*1SR,4SR,6SR,7SR*)-7-(*tert*-Butyl-dimethyl-silanyloxy)-6-(4-methoxy-phenyl)-5-tosyl-2-oxa-5-aza-bicyclo [2.2.1]heptane 485**




**482** **483** **485**

The mono-O-tosylate **483** (22 mg, 0.033 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 ml) and the solution was purged with nitrogen while a 1.0 M solution of lithium triethylborohydride in tetrahydrofuran (0.10 ml, 0.10 mmol, 3.1 eq) was added dropwise. After 2 h, methanol (0.3 ml) was added dropwise. The solution was then cooled in an ice-bath and rapidly stirred as a 27% aqueous solution of hydrogen peroxide (0.11 ml) was added slowly. The mixture was transferred to a separating funnel and then was vigorously shaken with chloroform (2 ml) and the resulting layers were separated. The aqueous phase was extracted with chloroform (3 x 2 ml), and the combined organic solutions were dried and evaporated to give the *bicyclic product* **485** (16 mg, 100%), as a white solid: m.p. 129.5-131°C; $R_f$ 0.58 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2956 (s), 2929 (s), 2857 (s), 1613 (m), 1514 (s), 1391 (s), 1346 (m), 1179 (s), 1154 (s), 829 (s) and 805 (m); $\delta_H$ -0.15 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.75 (9H, s, *t*-Bu), 2.40 (3H, s, NTs-Me), 3.75 (3H, s, OMe), 3.85 (1H, dd, *J* 8.6 and 1.4, $C\underline{H}_aCH_b$), 3.90-4.00 (2H, m, $C\underline{H}_aCH_b$ and 7-H), 4.25-4.30 (2H, m, 1(4)-H), 4.85 (1H, app. s, 6-H), 6.65 (2H, d, *J* 8.6, 2 x Ar-H), 7.20 (4H, 2 x d, *J* 8.6 and 8.4, 4 x Ar-H), 7.60 (2H, d, *J* 8.4, 2 x Ar-H); $\delta_C$ -6.3, -6.1 ($SiMe_2$), 17.1 ($\underline{C}$-$(CH_3)_3$), 20.5 (Ar-Me), 24.5 (*t*-Bu), 54.2 (OMe), 63.8, 68.5 (both CH), 69.4 ($CH_2$), 75.0, 82.0 (both CH), 112.0, 126.6 (both ArCH), 127.4 (ArC), 128.3, 128.4 (both ArCH), 136.4, 142.5 and 157.4 (all ArCH); *m/z* [APcI] 490 ($M^+$ + H, 100). [Found $M^+$ + H: 490.2079. $C_{25}H_{36}NO_5SSi$ requires *M*, 490.2078].

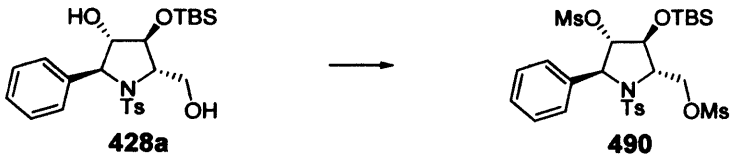
**(2SR,2SR,4SR,5SR)-Toluene-4-sulfonic acid 3,4-bis-(*tert*butyldimethylsilyloxy)-5-(4-methoxyphenyl)-1-tosyl-pyrrolidin-2-ylmethyl ester 487**




**483** **487**

The alcohol **483** (13 mg, 0.020 mmol) was protected using TBS Triflate (1 drop) according to general procedure P for 20 h. The residue was purified using column chromatography (30% ethyl acetate/petroleum ether) to furnish the *silyl ether* **487** (9 mg, 60%) as a pale yellow oil: $R_f$ 0.31 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2927 (s), 2857 (s), 1613 (s), 1599 (s), 1514 (s), 1470(s), 1348 (s), 1252 (s), 1178 (s), 1159 (s) and 836 (s); $\delta_H$ -0.10, (3H, s, SiMe), -0.05 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.10 (3H, s, SiMe), 0.75 (9H, s, *t*-Bu), 0.80 (9H, s, *t*-Bu), 2.25 (3H, s, Ar-Me), 2.40 (3H, s, Ar-Me), 3.70 (3H, s, OMe), 3.90 (1H, app. s, 4(3)-H), 4.05 (1H, dd, *J* 11.2 and 4.3, $C\underline{H}_aCH_b$), 4.20 (1H, app. s, 3(4)-H), 4.30 (1H, dd, *J* 11.2 and 9.6, $CH_aC\underline{H}_b$), 4.55 (1H, app. s, 5-H), 4.60 ( 1H, dd, *J* 9.6 and 4.3, 2-H), 6.45 (2H, d, *J* 8.8, 2 x Ar-H), 6.90 (2H, d, *J* 8.2, 2 x Ar-H), 7.00 (2H, d, *J* 8.2, 2 x Ar-H), 7.05 (2H, d, *J* 8.8, 2 x Ar-H), 7.30 (2H, d, *J* 8.2, 2 x Ar-H) and 7.80 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ -5.0, -5.0, -4.9, -4.7 (all SiMe), 17.8, 17.8 (both $\underline{C}$-$(CH_3)_3$), 21.4, 21.7 (Ar-Me), 25.4, 25.6 (both *t*-Bu), 55.2 (OMe) 69.0 ($CH_2$), 69.0, 74.3, 79.3, 86.2 (all CH), 112.9, 126.7, 128.2, 128.7 (all ArCH), 129.0 (ArC), 130.0, 130.9 (both ArCH), 138.4, 142.4 and 158.9 (all ArC), one ArC not evident in spectrum.

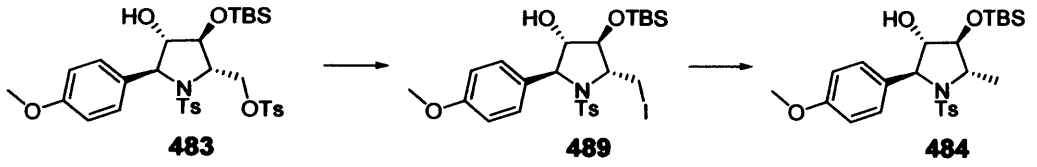
**Mesylation of (*2SR,3SR,4SR,5SR*)-4-(*tert*butyldimethyl-silyloxy)-5-hydroxymethyl-2-phenyl-1-tosyl-pyrrolidine-3-ol 428a**




**428a** **490**

To a mixture of the diol **428a** and unknown impurity (44 mg, 0.083 mmol, 1.0 eq) in anhydrous dichloromethane (2 ml) at -78°C was added Hünigs base (22 mg, 0.03 ml, 0.17 mmol, 2.0 eq) dropwise followed by mesyl chloride (1 drop). The reaction mixture was stirred for 3 h at -78°C and then allowed to warm to room temperature over 16 h. The solution was poured into saturated aqueous ammonium chloride solution (3 ml), the two layers were separated and the aqueous layer was extracted with diethyl ether (3 x 6 ml). The combined organic layers were dried and evaporated. The residue was chromatographed (30% ethyl acetate/petroleum ether) to yield the *mesylate* **490** (approx. 40 mg, 78%) as an orange oil, together with some in separable impurities. The mesylate **490** was characterised by: $R_f$ 0.41 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2931 (s), 2857 (s), 1598 (m), 1495 (m), 1470 (s), 1347 (s), 1177 (s), 838 (s), 815 (s) and 737 (s); $\delta_H$ 0.00 (3H, s, SiMe), 0.10 (3H, s, SiMe), 0.75 (9H, s, *t*-Bu), 2.25 (3H, s, Ar-Me), 3.00 (3H, s, $SO_2Me$), 3.05 (3H, s, $SO_2Me$), 4.20 (1H, dd, *J* 10.2 and 4.3, 2-H), 4.40 (1H, app. t, *J* 10.0, $C\underline{H}_aCH_b$), 4.55 (1H, app. s, 3(4)-H), 4.80 (1H, app. s, 4(3)-H), 4.85 (1H, dd, *J* 10.0 and 4.3, $CH_aC\underline{H}_b$), 5.00 (1H, app. s, 5-H), 6.85-7.10 (9H, m, Ph and 4 x Ar-H); $\delta_C$ -5.2, -5.1 (both SiMe), 17.7 (Si-$\underline{C}(CH)_3)_3$), 21.5 (Ar-Me), 25.5 (*t*-Bu), 37.4, 38.6 (both $SO_2Me$), 67.6 ($CH_2$), 68.6, 71.0, 77.2, 88.9 (all CH), 126.8, 128.0, 128.1, 129.0, 129.4 (all ArCH), 135.0, 137.7 and 143.2 (all ArC); *m/z* [ES] 656 ($M^+$ + Na, 80%), 651 (78), 634 (12) and 538 (100). [Found $M^+$ +H: 634.1636. $C_{26}H_{40}NO_9S_3Si$ requires *M*, 634.1629].

**(2SR,3SR,4SR,5SR)-4-(*tert*-butyl-dimethyl-silanyloxy)-2-(4-methoxypheny)-5-methyl-1-tosyl-pyrrolidin-3-ol 484**




*i) Displacement with Sodium Iodide.*

A mixture of the mono-O-tosylate **483** (28 mg, 0.042 mmol, 1.0 eq) and sodium iodide (25 mg, 0.17 mmol, 4.0 eq) in distilled acetone (2.5 ml) was refluxed for 20 h, then cooled to room temperature. Water (0.5 ml) was added and the product was extracted into diethyl ether (3 x 3 ml). The combined organic layers were washed with sodium thiosulfate solution (2 x 9 ml), saturated brine (9 ml) and dried to give the *iodide* **489** (26 mg, 100%) as an orange oil: $R_f$ 0.60 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3496 (br), 2953 (s), 2928 (s), 2856 (s), 1613 (m), 1514 (s), 1463 (s), 1338 (s), 1178 (s), 1094 (s), 840 (s), 811 (s) and 779 (s); $\delta_H$ 0.00 (3H, s, SiMe), 0.10 (3H, s, SiMe), 0.75 (9H, s, *t*-Bu), 2.20 (3H, s, Ar-Me), 3.60 (3H, s, OMe), 3.60-3.70 (1H, m, $C\underline{H}_aCH_b$), 3.85 (1H, dd, *J* 9.4 and 3.7, $CH_aC\underline{H}_b$), 4.00 (1H, app s, 3(5)-H), 4.15 (1H, dd, *J* 12.1 and 3.1, 4-H), 4.35 (1H, app s, 5(3)-H), 4.60 (1H, d, *J* 1.1, 2-H), 6.35 (2H, d, *J* 8.7, 2 x Ar-H), 6.80 (1H, d, *J* 8.2, 2 x Ar-H), 7.0 (4H, 2 x d, *J* 8.7 and 8.2, 4 x ArCH); $\delta_C$ -4.6, -4.2 (both SiMe), 7.1 ($CH_2I$), 17.9 ($\underline{C}$-$(CH_3)_3$), 21.4 (Ar-Me), 25.7 (*t*-Bu), 55.3 (OMe), 72.0, 72.8, 80.6, 85.8 (all CH), 113.0, 126.7, 128.7 (all ArCH), 128.9 (ArC), 131.0 (ArCH), 138.9, 142.3 and 159.0 (all ArC); *m/z* [APcI] 618 ($M^+$ + H, 100%), 600 (28), 490 (18), 486 (55), 358 (80), 187 (82). [Found $M^+$ + H: 618.1208. $C_{25}H_{37}INO_5SSi$ requires *M*, 618.1201].

*ii) Hydrogenolysis of Iodide*

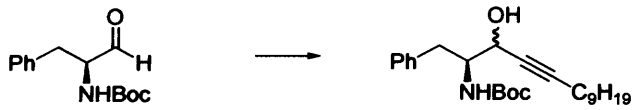
The crude iodide **489** (26 mg, 0.042 mmol) in methanol was subjected to standard hydrogenolysis conditions according to general procedure M for 19.5 h. Following purification of the residue by chromatography (15% ethyl acetate/petroleum ether) the *methyl pyrrolidine* **484** (6 mg, 27%) was obtained as a cream solid: m.p. 140-142°C; $R_f$ 0.55 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3430 (s), 2954 (s), 2930 (s), 2856 (s), 1613 (m), 1514 (s), 1463 (s), 1368 (m), 1178 (s), 856 (s), 838 (s) and 822 (s); $\delta_H$ 0.00 (3H, s, SiMe), 0.05 (3H, s, SiMe), 0.80 (9H, s, *t*-Bu), 1.50 (3H, d, *J* 6.8, Me), 2.30 (3H, s, Ar-Me), 3.70 (3H, s, OMe), 3.70-3.75 (1H, m, 4-H), 3.80 (1H, app. t, *J* 2.0, 3-H),

4.00-4.10 (1H, m, 2-H), 4.60 (1H, d, *J* 2.7, 5-CH), 6.50 (2H, d, *J* 8.8, 2 x Ar-H), 6.95 (2H, d, *J* 8.2, 2 x Ar-H), 7.05 (2H, d, *J* 8.8, 2 x Ar-H) and 7.10 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ -4.8 ($SiMe_2$), 17.9 (C-$(CH_3)_3$), 18.8 (5-Me) 21.4 (Ar-Me), 25.6 (*t*-Bu), 55.3 (OMe), 63.2, 71.4, 82.9, 86.1 (all CH), 113.1, 126.9, 128.1, 130.2 (all ArCH), 130.3, 139.2, 142.1 and 159.0 (all ArC); *m/z* [APcI] 492 ($M^+$ + H, 100%). [Found $M^+$ + H: 490.2237. $C_{25}H_{38}NO_5SSi$ requires *M*, 490.2234].

*ii) Hydrogenolysis of Iodide Method B*

To the crude iodide **489** (30 mg, 0.049 mmol, 1.0 eq) in methanol (0.3 ml) was subjected to standard hydrogenolysis conditions according to general procedure M for 19.5 h, except using Hünigs base. The residue was chromatographed (20% ethyl acetate/petroleum ether) to give the *methyl pyrrolidine* **484** (8 mg, 15%, over 2 steps) as a cream solid. The data obtained was in accordance with that previously reported.

### *(2SR)-tert*-butyl-3-hydroxy-1-phenyltetradec-4-yn-2-ylcarbamate 596




**598** **596**

*i) Method A*

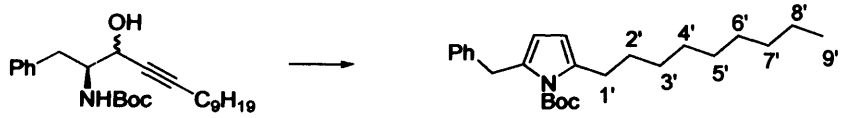
To a -20°C solution of 1-undecyne (79 mg, 0.10 ml, 0.52 mmol, 1.3 eq) in distilled diethyl ether (2 ml) was added a 2.5 M solution of n-BuLi dropwise (0.21 ml, 0.52 mmol, 1.3 eq). The resulting white suspension was stirred for 1 h at -20°C and was warmed to 0°C prior to the addition of a 1M solution of zinc chloride (0.56 ml, 0.56 mmol, 1.4 eq). The suspension was stirred for an additional hour at this temperature and then for an hour at room temperature. The suspension was re-cooled to -78°C and a solution of the aldehyde **598** (100mg, 0.04 mmol, 1.0 eq) in diethyl ether (1 ml) was added dropwise. The reaction mixture was allowed to warm to room temperature over 16 h, re-cooled to -20°C and quenched by the addition of saturated aqueous ammonium chloride (1.1 ml). Water (1.6 ml) was added, the two layers were separated and the aqueous phase was extracted with diethyl ether (3 x 5 ml). The combined organic solutions were dried and evaporated. The residue was purified by chromatography (10% ethyl acetate/ petroleum ether) to furnish the

*amino alcohol* **596** (12 mg, 7%) as a mixture of diastereoisomers in the ratio 3:1, as a pale yellow oil: $R_f$ 0.50 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [Film] 2921 (s), 2855 (s), 1693 (s), 1501 (s), 1454 (s), 1392 (s) and 1367 (s); $\delta_H$ 0.80 (3H, 2 x t, *J* 7.0 and 7.4, 14-Me, both isomers), 1.10-1.35 (19H, m, *t*-Bu and 5 x $CH_2$ both isomers), 1.40-1.50 (2H, m, 7-$CH_2$, both isomers), 2.10 (2H, app. td, *J* 7.1 and 1.6, 6-$CH_2$, major isomer), 2.15 (2H, app. td, *J* 7.1 and 1.6, 6-$CH_2$, minor isomer), 2.70-2.90 (2H, m, $CH_2$-Ph, major isomer), 2.90-3.05 (2H, m, $CH_2$-Ph, minor isomer), 3.85 (1H, br. res., 2-H, major isomer), 3.90-3.40 (1H, m, 2-H, minor isomer), 4.25 (1H, br. res., 3-H, major isomer), 4.30 (1H, br. res., 3-H, minor isomer), 4.65-4.80 (1H, m, NH, both isomers) and 7.10-7.25 (5H, m, Ph, both isomers); $\delta_C$ 14.2 (14-Me, both isomers), 18.7, 22.7 (both $CH_2$, both isomers), 28.3 (*t*-Bu, both isomers), 28.6, 28.7, 29.0, 29.2, 29.3, 29.5, 29.6, 31.9, 36.8, 37.6 (all $CH_2$, both isomers), 56.5, 56.8, 64.0, 64.9 (all CH, both isomers), 78.7 ($\underline{C}(CH_3)_3$, both isomers), 79.6, 79.9, 87.0, 87.9 (all -C≡C-, both isomers), 126.4, 126.6, 128.5, 128.5, 129.2, 129.4 (all ArCH, both isomers), 137.6, 138.0 (both ArC, both isomers), 156.1 and 156.3 (both C=O, both isomers); *m/z* [APcI] 402 ($M^+$ + H, 68%), 346 (100), 328 (38) and 117 (62); [Found $M^+$ + H: 402.3004. $C_{25}H_{40}NO_3$ requires *M*, 402.3003].

*ii) Method B*

To a -20°C suspension of 1-undecyne (916 mg, 1.20 ml, 6.01 mmol, 5 eq) and powdered molecular sieves (approx 200 mg) in tetrahydrofuran (10 ml) was slowly added a 2.5 M solution of n-BuLi (2.41 ml, 6.01 mmol, 5 eq). The suspension was stirred for a further 0.5 h and then the reaction mixture was cooled to -50°C over a period of 10 mins. A solution of the aldehyde **598** (300 mg, 1.20 mmol, 1.0 eq) in tetrahydrofuran (3 ml) was added and the solution was stirred for 2 h. The reaction was quenched by the addition of pH 7 phosphate buffer (10 ml) and the cold bath was removed. The suspension was filtered through a plug of celite and the solid was washed with ethyl acetate. The two layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 10 ml). The combined organic solutions were dried and evaporated. The residue was purified by chromatography (20% ethyl acetate/ petroleum ether) to give the *amino alcohol* **596** (294 mg, 61%). The data obtained was in accordance with that previously reported.

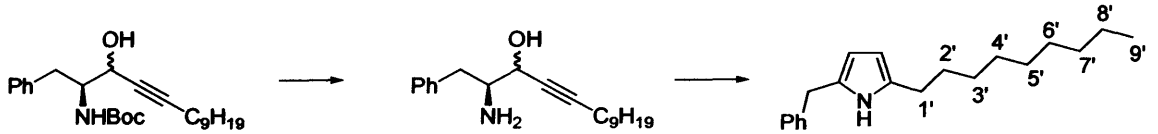
**_tert_-butyl 2-benzyl-5-nonyl-1*H*-pyrrole-1-carboxylate 599**




**596** **599**

To a solution of the amino alcohol **596** (50 mg, 0.12 mmol) in dichloromethane (1 ml) was added 10% w/w silver nitrate on silica gel (21 mg, 0.012 mmol, 0.1 eq), according to general procedure O. The solution was stirred for 2 h and following the workup, furnished the *pyrrole* **599** (48 mg, 100%): $R_f$ 0.80 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [Film] 2962 (s), 2925 (s), 2852 (s), 2362 (m), 1739 (s), 1392 (m), 1370 (m) and 799 (s); $\delta_H$ 0.80 (3H, t, *J* 6.7, 9'-Me), 1.10-1.30 (12H, m, 6 x $CH_2$), 1.35 (9H, s, *t*-Bu), 1.40-1.55 (2H, m, 2'-$CH_2$), 2.70 (2H, t, *J* 7.7, 1'-$CH_2$), 4.05 (2H, s, $CH_2$-Ph), 5.60 (1H, d, *J* 3.2, 4-H), 5.75 (1H, d, *J* 3.2, 3-H), 7.03 (2H, d, *J* 7.3, 2 x Ar-H), 7.10 (2H, app. t, *J* 7.3, Ar-H) and 7.22 (2H, app. t, *J* 7.5, 2 x Ar-H); $\delta_C$ 14.2 (9'-Me), 22.7 ($CH_2$), 27.8 (*t*-Bu), 29.2, 29.4, 29.6, 29.6, 32.0, 35.8 (all $CH_2$) only 8 evident, 83.4 (C-($CH_3$)$_3$), 108.9, 111.6 (both =CH), 126.0, 128.3, 128.6 (all ArCH), 133.5, 137.0, 140.3 (all C) and 150.3 (C=O); *m/z* [APcI] 384 ($M^+$ + H, 8%), 328 (13), 285 (20), 110 (42) and 108 (100). [Found $M^+$ + H: 384.2895. $C_{25}H_{38}NO_2$ requires *M*, 384.2897].

**2-Benzyl-5-nonyl-1H-pyrrole 601**




**596** **600** **601**

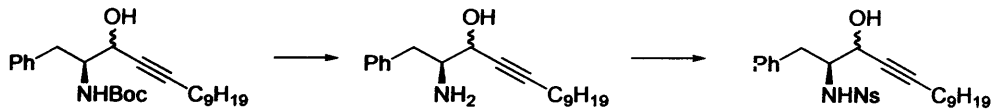
*i) Deprotection*

To the *N*-Boc protected amino alcohol **596** (47mg, 0.12 mmol) in dichloromethane (0.4 ml) was added trifluoroacetic acid (0.1 ml) following the method outlined in general procedure F to yield the *amine* **600** (30 mg, 86%) which was used instantaneously without purification.

*ii) Silver Catalysed Cyclisation*

To the amine **600** (30 mg, 0.1 mmol, 1.0 eq) in anhydrous dichloromethane (1 ml) was added 10% silver nitrate on silica gel (34 mg, 0.21 mmol, 0.2 eq). The reaction was stirred at room temperature for 2 h in the absence of light. Following the work up described in general procedure O, the residue was purified using flash chromatography (30% ethyl acetate/petroleum ether) to yield predominantly the *pyrrole* **601** (12 mg, 43%) as a pale yellow oil. $R_f$ 0.83 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [Film] 3380 (br), 2924 (s), 2835 (s), 1591 (m), 1494 (m), 1454 (s) and 764 (s); $\delta_H$ 0.80 (3H, t, *J* 6.8, Me), 1.20 (12H, br. s., $CH_2$ x 6), 1.40-1.55 (2H, m, 2'-$CH_2$), 2.40 (2H, t, *J* 7.7, -1'-$CH_2$), 3.85 (2H, s, $CH_2$-Ph), 5.60 (1H, app. t, *J* 2.7, CH=), 5.70 (1H, app. t, *J* 2.7, CH=), 7.10-7.25 (5H, m, Ph) and 7.40 (1H, br. res., NH); $\delta_C$ 14.2 (Me), 22.7, 27.8, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 34.2 (all $CH_2$), 104.6, 106.3 (both =CH), 126.3, 128.6, 128.7 (all ArCH), 132.4 and 139.9 (both C, one ArC missing); *m/z* [APcI] 284 ($M^+$ + H, 100%). [Found $M^+$ + H: 284.2376. $C_{20}H_{30}N$ requires *M*, 284.2373].

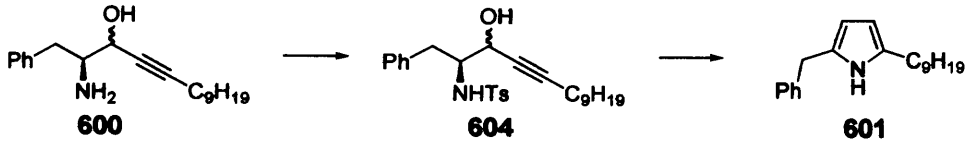
### *(1SR)* 1-Phenyl-2-(nosylamino)tetradec-4-yn-3-ol 602




To an ice-cold solution of the crude amine **600** (101 mg, 0.33 mmol, 1.0 eq) in dichloromethane (2 ml) was carefully added triethylamine (37 mg, 0.05 ml, 0.37 mmol, 1.1 eq) and the solution was stirred for 0.25 h. DMAP (5 mg) was added followed by a solution of 4-nitrobenzene sulfonyl chloride (75 mg, 0.34 mmol, 1.1 eq) in dichloromethane (1 ml). The ice-bath was removed and the reaction mixture was stirred for 19 h. A 2M hydrochloric acid solution (4 ml) was added and the resultant two layers were separated. The aqueous phase was extracted with dichloromethane (3 x 4 ml) and the combined dichloromethane solutions were dried and evaporated. The residue was purified (20% ethyl acetate/petroleum ether) to give the *nosylate* **602** (40 mg, 24%), as a yellow oil: $R_f$ 0.58 (40% ethyl acetate/petroleum ether); $\delta_H$ (major isomer) 0.80 (3H, t, *J* 6.8, Me), 1.10-60 (23H, m, *t*-Bu and 7-$CH_2$), 2.05 (2H, app. td, *J* 7.2 and 1.7, 6-$CH_2$), 2.60 (1H, dd, *J*

14.0 and 7.2, C$\underline{H}_a$C$H_b$), 3.05 (1H, dd, *J* 14.0 and 5.1, C$H_a$C$\underline{H}_b$), 3.50 (1H, app septet, *J* 8.9 and 5.1, 1-H), 4.45 (1H, app. s, 3-H), 4.80 (1H, d, *J* 8.9, NH), 6.90 (2H, d, *J* 8.1, 2 x Ar-H), 7.0-7.30 (3H, m, 3 x Ar-H), 7.60 (2H, d, *J* 8.8, 2 x Ar-H) and 8.05 (2H, d, *J* 8.8, 2 x Ar-H); $\delta_C$ 14.2 (Me), 18.7, 22.7, 28.5, 29.0, 29.1, 29.3, 29.5, 31.9, 37.0 (all $CH_2$), 60.8, 65.0 (both CH), 76.9, 89.5 (both C≡C), 124.0, 126.8, 128.0, 128.6, 129.1 (all ArCH), 136.9, and 145.7 (both ArC, only two ArC evident).

**2-benzyl-5-nonyl-1*H*-pyrrole 601**




*i) Tosylation*

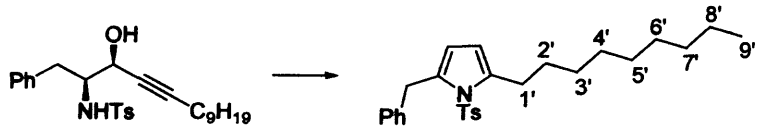
The crude amine **600** (190 mg, 0.63 mmol) was tosylated using triethylamine and *p*-tosyl chloride according to general procedure G. The residue was purified by chromatography which failed to elute the product. The sulfonamide **604** was isolated in the methanol fraction (178 mg, 62%), together with some impurities in an approximate ratio of 4:1.5, which was used without further purification: $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2930 (s), 2854 (s), 1606 (m), 1496 (m), 1455 (m), 1174 (s), 815 (s), 749 (m) and 702 (s); $\delta_H$ 0.70-0.85 (6H, m, Me, both isomers), 1.10-1.25 (24H, m, 12 x $CH_2$, both isomers), 1.25-1.1.35 (2H, m, 7-$CH_2$, major isomer), 1.35-1.50 (2H, m, 7-$CH_2$, minor isomer), 1.95-2.05 (4H, m, 6-$CH_2$, both isomers), 2.25 (6H, m, s, Ar-Me, both isomers), 2.75-2.95 (4H, m, $C\underline{H}_aCH_b$-Ph, both isomers), 3.00-3.10 (4H, m, $CH_aC\underline{H}_b$-Ph), both isomers), 3.40 (1H, app. q, *J* 7.0, 2-H, major isomer), 3.65 (1H, br. res, 2-H, minor isomer), 4.35 (2H, d, *J* 8.1, 3-H, both isomers), 7.00-7.25 (14H, m, Ph and 2 x Ar-H, both isomers) and 7.60 (2H, d, *J* 8.0, 2 x Ar-H, both isomers); $\delta_C$ (major isomer) 14.2 (14-Me), 18.7 ($CH_2$), 21.4 (Ar-Me), 22.7, 28.5, 29.2, 29.2, 29.3, 29.4, 29.4, 29.5, 35.3 (all $CH_2$), 58.4, 61.6 (both CH), 126.2, 127.0, 128.7, 128.8, 129.7 (all ArCH), 135.3, 140.4 and 141.2 (all ArC); *m/z* [APcI] 302 ($M^+$ + H, 58%), 284 (32) and 82 (100).

*ii) Silver cyclisation*

The impure sulfonamide **604** (80 mg, 0.18 mmol, 1.0 eq) in dichloromethane (1 ml) was added 10% w/w silver nitrate on silica gel (149 mg, 0.088 mmol, 0.5 eq) and the suspension was stirred for 2 h, according to the procedure outlined in general method O. The NMR revealed cyclisation of the major diastereoisomer to furnish the deprotected *pyrrole* **601**, together with the minor diastereoisomer in a ratio of 2:1 (54 mg). The reaction was repeated using a further 0.3 equivalents of reagent for 2 h, but no further cyclisation was observed. The residue was purified (20% ethyl acetate/petroleum ether) to give i) the *pyrrole* **601** (13 mg, 37%) and i) the *sulfonamide* **604b** (19 mg). The data obtained for the *pyrrole* **601** was in agreement with that previously reported. The

sulfonamide **604b** was characterised by: $R_f$ 0.69 (40% ethyl acetate/petroleum ether); $\delta_H$ 0.80 (3H, t, *J* 6.8, Me), 1.10-1.40 (12H, m, 6 x $CH_2$), 1.45-1.50 (2H, m, 7-$CH_2$), 2.20 (1H, app. td, *J* 7.1 and 1.9, 6-$CH_2$), 2.30 (3H, s, Ar-Me), 2.60 (1H, dd, *J* 13.9 and 7.7, $C\underline{H}_aCH_b$-Ph), 2.80 (1H, dd, *J* 13.9 and 7.2, $CH_aC\underline{H}_b$-Ph), 3.47 (1H, app. td, *J* 7.5 and 2.9, 2-H), 4.30 (1H, br. d, *J* 1.9, 3-H), 4.80 (1H,d, *J* 8.8, NH), 6.85-6.95 (2H, m, 2 x Ar-H), 7.05-7.30 (5H, m, 5 x Ar-H) and 7.50 (2H, d, *J* 8.3, 2 x Ar-H).

**2-Benzyl-5-nonyl-1-tosyl-1*H*-pyrrole 603**




**604b** **603**

The *syn* diastereoisomer **604b** (14 mg, 0.031 mmol, 1.0 eq) was treated with 10% by weight silver nitrate on silica gel (26 mg, 0.015 mmol, 0.5 eq) for 16 h according to general procedure O to yield a 4:1 mixture of *pyrrole* **603** and starting material. The pyrrole **xx** was characterised by: $\delta_H$ 0.80 (3H, t, *J* 6.7, Me), 1.10-1.30 (12H, m, 6 x $CH_2$), 1.45-1.55 (2H, m, 2'-$CH_2$), 2.35 (3H, s, Ar-Me), 2.65 (2H, t, *J* 7.7, 1'-$CH_2$), 4.05 (2H, s, $CH_2$-Ph), 5.60 (1H, d, *J* 3.2, =CH), 5.80 (1H, d, *J* 3.2, =CH), 7.05-7.20 (7H, m, 7 x Ar-H) and 7.30 (2H, d, *J* 8.2, 2 x Ar-H).

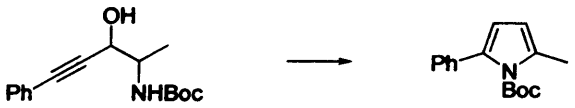
***tert*-butyl 2-(hydroxymethyl)-5-phenyl-pyrrole-1*H*-1-carboxylate 608**


**204** **608**

The acetylenic diol **204** (20 mg, 0.069 mmol) was subjected to silver cyclisation according to general procedure O for 1 h using 10% w/w silver nitrate on silica gel (23 mg, 0.14 mmol, 0.2 eq) to give the *pyrrole* **608** (21 mg, 100%), as an orange oil. An analytical sample was prepared by filtering the residue through a plug of silica which showed: $R_f$

0.58 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3368 (s), 2978 (s), 1746 (s), 1605 (s) 1450 (s), 1370 (s), 759 (s) and 699 (s); $\delta_H$ 1.10 (9H, s, *t*-Bu), 3.65 (1H, t, *J* 7.2, OH, exchanges with $D_2O$), 4.55 (2H, d, *J* 7.2, $CH_2$), 6.05 (1H, d, *J* 3.4, 3-H), 6.15 (1H, d, *J* 3.4, 4-H) and 7.15-7.30 (5H, m, Ph); $\delta_C$ 27.2 (*t*-Bu), 58.2 ($CH_2$), 84.7 (C-$CH_3)_3$), 112.3, 112.8 (both =CH), 127.1, 127.8, 128.7 (all ArCH), 131.8, 135.1, 136.3 (all C) and 151.0 (C=O); *m/z* [APcI] 256 ($M^+$ - $H_2O$, 39%), 200 (100) and 156 (39). [Found $M^+$ +$NH_4$: 291.1706. $C_{16}H_{23}N_2O_3$ requires *M*, 291.1703].

### *tert*-butyl 2-Methyl -5-phenyl-1*H*-pyrrole-1-carboxylate 609




**258** **609**

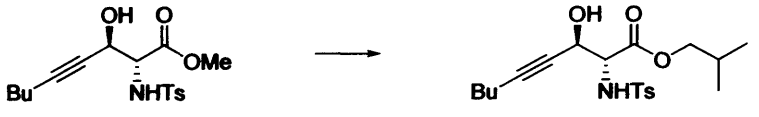
The alkyne **258** (62 mg, 0.23 mmol) was cyclised using 10% silver nitrate on silica gel (191 mg, 0.11 mmol, 0.5 eq) in anhydrous dichloromethane for 64 h as described in general procedure O. The residue was purified using columned chromatography (10% ethyl acetate/petroleum ether) to give the *pyrrole* **609**, (27 mg, 48%) as a pale yellow oil: $R_f$ 0.68 (20% ethyl acetate/ petroleum ether); $\nu_{max}$ /$cm^{-1}$ [Film] 2979 (s), 2927 (s), 1741 (s), 1616 (m), 1445 (s), 1393 (s), 1367 (s), 787 (s), 758 (s) and 699 (s); $\delta_H$ 1.20 (9H, s, *t*-Bu), 2.40 (3H, s, $CH_3$), 5.90 (1H, app. dd, *J* 3.2 and 0.8, 3-H), 6.0 (1H, d, *J* 3.2, 4-H) and 7.15-7.20 (5H, m, Ph); $\delta_C$ 15.4 (Me), 27.4 (*t*-Bu), 83.4 (C-$(CH_3)_3$), 110.3, 112.2 (both =CH), 126.6, 127.8 and 128.4 (all ArCH), 133.1, 134.8 and 135.5 (all C) and 150.3 (C=O); *m/z* [APcI] 258 ($M^+$ + H, 72%), 202 (100) and 158 (63). [Found $M^+$ + H: 258.1490. $C_{16}H_{20}O_2N$ requires *M*, 258.1489].

**tert-butyl 2-butyl-5-methyl-1*H*-pyrrole-1-carboxylate 610**


**262** **610**

The alkyne **262** (41 mg, 0.16 mmol) was cyclised using silver nitrate on silica gel (136 mg, 0.08 mmol, 0.5 eq) in anhydrous dichloromethane for 64 h as described in general procedure O. The residue was purified using columned chromatography (petroleum ether) to give the *pyrrole* **610** (18 mg, 50%) as a pale yellow oil: $R_f$ 0.73 (40% ethyl acetate/ petroleum ether); $\nu_{max}$ /cm$^{-1}$ [Film] 3456 (br), 2928 (s), 2850 (s), 1738 (s), 1455 (s), 1369 (s) and 825 (s); $\delta_H$ 0.85 (3H, t, *J* 7.3, 4'Me), 1.25-1.40 (2H, m, 3'-$CH_2$), 1.4-1.55 (11H, m, *t*-Bu and 2'-$CH_2$) 2.30 (3H, s, 5-Me), 2.70 (2H, t, *J* 7.7, 1'-$CH_2$) and 5.70 (2H, app. s, 3-H and 4-H); $\delta_C$ 14.1, 16.5 (both Me), 22.6 ($CH_2$), 28.1 (*t*-Bu), 29.4 and 31.4 (both $CH_2$), 83.2 (C-$(CH_3)_3$), 109.0, 110.1 (both =CH), 131.2 and 136.2 (both C) and 150.5 (C=O); *m/z* [APcI] 182 ($M^+$ -55, 100%) and 236 (12). Accurate HRMS data could not be obtained.

**Reduction of (2*RS*,3*RS*)-Methyl 3-hydroxy-2-(tosylamino)non-4-ynoate 144A**



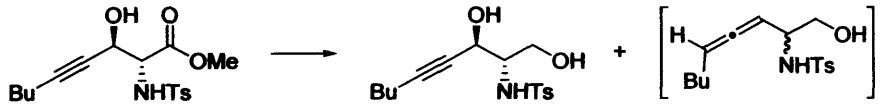

**144a** **618**

*i) Method A*

To a 1.75:1 mixture of the aldol product **144a** and *N*-tosyl glycine **156** (100 mg, 0.28 mmol, 1.0 eq) in dry tetrahydrofuran (5 ml) at -78°C was added a 1.0 M solution of DIBAL in toluene (0.85 ml, 0.85 mmol, 3.0 eq) over a period of 20 min. The solution was stirred for a further 2h and then the excess reagent was quenched by the slow addition of 2 M hydrochloric acid. The reaction mixture was allowed to warm to 0°C the two layers were separated and the aqueous phase was extracted with diethyl ether (3 x 10 ml). The combined organic phases were dried and evaporated. The NMR of the crude product

revealed no reaction had occurred so the reaction was repeated with the same equivalents but stirred for 16 h at room temperature. The NMR of the crude product showed partial reduction of the methyl ester so the reaction was repeated using another 4 equivalents of Dibal and refluxing the mixture for 4 hours and quenched as previously described. The residue was purified (40% ethyl acetate/ petroleum ether) to give the *iso-butyl ester* **618** (20 mg, 25%, over 3 steps), as a pale yellow oil: $R_f$ 0.42 (40% ethyl acetate/petroleum ether); $\delta_H$ 0.75 (6H, d, *J* 6.8, 2 x Me), 0.85 (3H, t, *J* 7.2, 9-Me), 1.25-1.40 (4H, m, 2 x $CH_2$), 1.65-1.70 (1H, m, C<u>H</u>$(Me)_2$), 2.00-2.10 (2H, m, $CH_2$), 2.35 (3H, s, Ar-Me), 2.70 (1H, br. d, *J* 10.7, OH), 3.65 (1H, dd, *J* 10.5 and 6.6, C<u>H</u>$_a$CH$_b$O), 3.72 (1H, dd, *J* 10.5 and 6.6, CH$_a$C<u>H</u>$_b$O), 4.05 (1H, dd, *J* 9.5 and 3.7, 2-H), 4.60 (1H, br. res., 3-H), 5.45 (1H, d, *J* 9.5, NH), 7.20 (2H, d, *J* 8.4, 2 x Ar-H) and 7.70 (2H, d, *J* 8.4, 2 x Ar-H).

**Reduction of (*2RS,3RS*)-Methyl 3-hydroxy-2-(tosylamino)non-4-ynoate 144a**




*i) Method B*

To a solution of Lithium aluminium hydride (21 mg, 0.57 mmol, 2.0 eq) in tetrahydrofuran (2 ml) was cautiously added a 1.75:1 mixture of the aldol product **144a** and methyl *N*-tosyl glycine **152** (100 mg, 0.28 mmol, 1.0 eq) in tetrahydrofuran (2 ml). The reaction was monitored by tlc and was judged to be complete after 4 h. The reaction was quenched by the addition of a 1 M solution of sodium hydroxide (2 ml), the solid was removed by filtration and was washed with dichloromethane. The layers were separated, and the aqueous phase was extracted with dichloromethane (3 x 5 ml). The combined organic phases were dried and evaporated to yield the *alcohol* **619** (19 mg, 30%), as a pale yellow oil: $R_f$ 0.11 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3862 (br), 2937 (s), 1331 (m), 1158 (s), 1092 (s) and 815 (s); $\delta_H$ 0.80 (3H, t, *J* 7.2, 9-Me), 1.20-1.40 (4H, m, 2 x $CH_2$), 2.10 (2H, app. td, *J* 7.1 and 1.8, 6-$CH_2$), 2.30 (3H, s, Ar-Me), 3.25 (1H, br. res., 2-H), 3.50 (1H, dd, *J* 11.6 and 4.1, C<u>H</u>$_a$H$_b$), 3.95 (1H, dd, *J* 11.6 and 3.7, CH$_a$<u>H</u>$_b$), 4.40 (1H, br, res., 3-H), 5.80 (1H, br, res., NH), 7.20 (2H, d, *J* 8.2, 2 x Ar-H), and 7.70 (2H, d, *J* 8.2,

2 x Ar-H); $\delta_C$ 13.6 (Me), 18.4 ($CH_2$), 21.6 (Ar-Me), 22.0, 30.5 (both $CH_2$), 58.0 (CH), 62.2 ($CH_2OH$), 64.7 (CH), 77.0, 88.8 (both C≡C), 127.1, 129.8 (both ArCH), 137.3 and 143.7 (both ArC); *m/z* [APcI] 326 ($M^+$ + H, 33%), 308 (76) and 278 (100). [Found $M^+$ + $NH_4$: 343.1686. $C_{16}H_{27}N_2O_4S$ requires *M*, 343.1686].

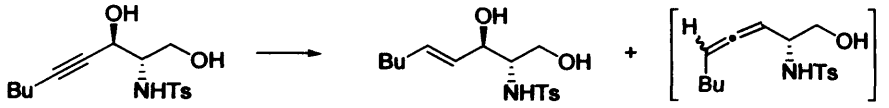
*ii) Method C*

Lithium aluminium hydride (21 mg, 0.57 mmol, 2 eq) was dissolved in tetrahydrofuran (2 ml) and to the resultant solution was cautiously added a solution of 1.75:1 mixture of the aldol product **144a** and methyl *N*-tosyl glycinate **152** (100 mg, 0.28 mmol, 1.0 eq) in tetrahydrofuran (2 ml). The solution was stirred for 4 h after which time Lithium aluminium hydride (11 mg, 0.29 mmol, 1.0 eq) was added and the solution was stirred for 16 h. Ethyl acetate (1 ml) was added, followed by water (1 ml) and 10% sulphuric acid (1 ml). The aqueous phase was extracted with diethyl ether (3 x 5 ml) and the combined organic phases were dried and evaporated. The NMR of the crude product revealed a 1:1 mixture of product and starting material. The substrate was treated with a further two equivalents of Lithium aluminium hydride (21 mg) and stirred for 16 h and quenched as previously described. The residue was purified (20% ethyl acetate/petroleum ether) to give i) the *allene* **617** (6 mg, 10%) and ii) the *alcohol* **619** (40 mg, 62%). The data obtained the allene **617** is reported later.

*iii) Method D*

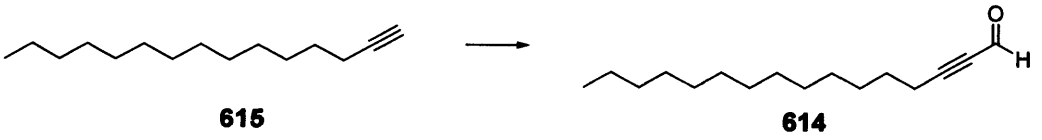
To a solution of the ester **144a** (100 mg, 0.28 mmol, 1.0 eq) in absolute ethanol (5 ml) was added sodium borohydride (32 mg, 0.84 mmol, 3.0 eq) in one portion. The reaction mixture was stirred for 16.5 h at room temperature and then the solvent was evaporated, water (2 ml) was added and the product was extracted into diethyl ether (3 x 2 ml). The organic solutions were dried and evaporated to yield the *alcohol* **619** (68 mg, 74%) as a pale yellow oil. The data obtained was identical to that previously reported.

**Reduction of (*2SR,3RS*)-2-(tosylamino)non-4-yne-1,3-diol 619**




The alkyne **619** (51 mg, 0.16 mmol) was reduced using a 65% w/w solution of Red-Al in toluene (0.24 ml, 0.78 mmol) as described in general procedure H. The residue was purified using column chromatography (30% ethyl acetate/petroleum ether) to give i) the *allene* **617** (12 mg, 25%) and ii) the (*E*)-*olefin* **616a** (36 mg, 72%), both as yellow oils. The allene **617** was characterised by: $R_f$ 0.32 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3373 (br), 2926 (s), 1967 (m), 1599 (s), 1454 (s), 1328 (m), 1160 (s) and 814 (s); $\delta_H$ 0.80-0.90 (3H, m, 9-Me), 1.10-1.30 (4H, m, 2 x $CH_2$), 1.85-1.95 (2H, m, 6-$CH_2$), 2.00 (1H, br. res., OH), 2.35 (3H, s, Ar-Me), 3.40-3.60 (2H, m, 1-$CH_2$), 3.70-3.80 (1H, m, 2-H), 4.70 (1H, d, *J* 7.7, NH), 4.85-4.95 (1H, m, 3-H), 5.10 (1H, app. qd, *J* 6.7 and 3.1, 5-H), 7.20 (2H, d, *J* 8.2, 2 x Ar-H) and 7.65 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ 13.6, 21.6 (both Me), 22.2, 28.2, 31.1 (all $CH_2$), 53.8. (CH), 65.5 ($CH_2OH$), 89.7, 96.4 (both =C), 127.3, 129.7 (both ArCH), 137.1, 143.7 (both ArC) and 202.3 (=˙=); *m/z* [APcI] 310 ($M^+$ + H, 70%), 292 (65), 278 (10), 172 (57), 155 (32), 139 (82) and 121 (100). The (*E*)-*olefin* **616a** was characterised by: $R_f$ 0.16 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3516 (br), 2926 (s), 1328 (s), 1158 (s) and 815 (s); $\delta_H$ 0.80 (3H, t, *J* 7.1, 9-Me), 1.15-1.30 (4H, m, 2 x $CH_2$), 2.35 (3H, s, Ar-Me), 2.40-2.60 (2H, m, 2 x OH, exchanges with $D_2O$), 3.05-3.15 (1H, m, 2-H) 3.40 (1H, dd, *J* 11.6 and 3.5, $C\underline{H_a}H_b$), 3.75 (1H, dd, *J* 11.6 and 3.5, $CH_a\underline{H_b}$), 4.10 (1H, br. res., 3-H), 5.25 (1H, dd, *J* 15.5 and 6.3, 4-H), 5.45 (1H, d, *J* 7.8, NH, exchanges with $D_2O$), 5.65 (1H, dt, *J* 15.4 and 6.6, 5-H) 7.25 (2H, d, *J* 8.2, 2 x Ar-H), and 7.70 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ 13.9, (Me), 21.2 ($CH_2$), 21.6 (Ar-Me), 31.1, 31.9 (both $CH_2$), 57.8 (CH), 62.0 ($CH_2OH$), 74.6 (CH), 127.1, (ArCH), 128.1 (=CH), 129.8 (ArCH), 134.6 (=CH), 136.3 and 142.6 (both ArC); *m/z* [APcI] 328 ($M^+$ + H, 70%) and 117 (100). [Found $M^+$ + H: 328.1585. $C_{16}H_{26}NO_4S$ requires *M*, 343.1582].

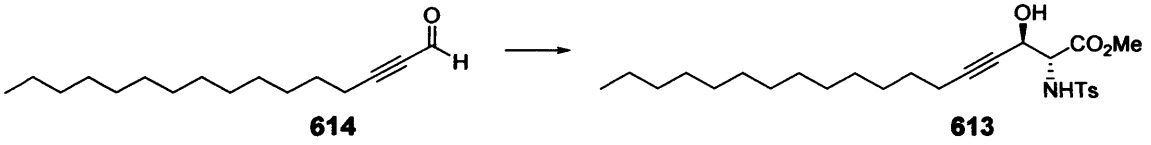
**Hexadec-2-ynal 614**




**615** **614**

1-pentadecyne **615** (10.0 g, 48.0 mmol) was condensed with *N*, *N*-dimethylformamide (7.00 g, 7.4 ml, 96.0 mmol) according to general procedure R to give the *aldehyde* **614** (11 34 g, 100%), as an orange oil: $R_f$ 0.68 (25% ethyl acetate in petroleum ether); $\nu_{max}/cm^{-1}$ [Film] 2928 (s), 2854 (s), 2278 (m), 2201 (s), 1674 (s), 1467 (m), 1388 (w) and 721 (w); $\delta_H$ 0.80 (3H, t, *J* 6.8, Me), 1.10-1.40 (22H, m, 10 x $CH_2$), 1.50 (2H, app quin, $J_{approx}$ 7.3, 4-$CH_2$), 2.30 (2H, t, *J* 7.2, 3-$CH_2$) and 9.10 (1H, s, CHO); $\delta_C$ 14.1 (Me), 19.0, 22.7, 27.5, 28.8, 29.0, 29.4, 29.4, 29.6, 29.6, 29.7, 31.9 (all $CH_2$, only 11 visible), 81.6, 99.0 (both C≡C) and 176.9 (CH). No data was reported in the literature[14]

***(2RS,3RS)*-Methyl-3-Hydroxyl-2-(tosylamino)octadec-4-ynoate 613**

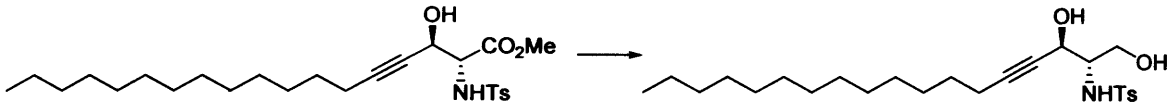



**614** **613**

Methyl *N*-tosyl glycinate **152** (1.72 g, 7.07 mmol) was reacted with hexadec-2-ynal **614** (2.00 g, 7.46 mmol) according to general procedure C. The residue was chromatographed (20% ethyl acetate/petroleum ether) to furnish the *amino alcohol* **613** (1.61 g, 47%), as an orange solid: m.p. 77-78°C; $R_f$ 0.39 (40% ethyl acetate in petroleum ether); $\nu_{max}/cm^{-1}$ 2922 (s), 2853 (m), 1744 (m), 1436 (m), 1340 (m), 1164 (s) and 815 (w); $\delta_H$ 0.80 (3H, t, *J* 6.8, 18-Me), 1.10-1.30 (20H, m, 10 x $CH_2$), 1.35 (2H, app. quin, $J_{approx.}$ 7.0, 7-$CH_2$), 2.05 (2H, td, *J* 7.0 and 1.9, 6-$CH_2$), 2.35 (3H, s, Ar-Me), 2.65 (1H, d *J* 10.5, OH, exchanges with $D_2O$), 3.50 (3H, s, $CO_2Me$), 4.05 (1H, dd, *J* 9.6, 3.7, 2-H), 4.55-4.60 (1H, m, 3-H), 5.45 (1H, d, *J* 9.6, NH, exchanges with $D_2O$), 7.20 (2H, d, *J* 8.2, 2 x ArCH), 7.65 (2H, d, *J* 8.2, 2 x ArCH); $\delta_C$ 14.1 (18-Me), 18.6 ($CH_2$), 21.6 (Ar-Me), 22.7, 28.3, 28.8, 29.1, 29.4, 29.5, 29.7, 29.7, 31.9 (all $CH_2$, only 9 visible), 52.9 ($CO_2Me$), 60.7, 63.1 (both CH), 75.4, 89.1 (both C≡C), 127.4, 129.8 (both ArCH), 136.3, 144.0 (both ArC) and 168.5 (C=O); *m/z*

[APcI] 480 ($M^+$ + H, 44%), 462 (35), 291 (30), 244 (100), 184 (93) and 155 (30). [Found $M^+$ + H: 480.2277. $C_{26}H_{42}NO_5S$ requires *M*, 480.2777].

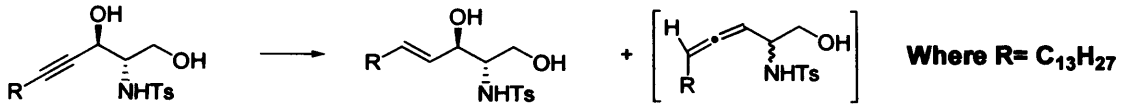
***(2SR, 3RS)-2-*(tosylamino)octadec-4-yne-1,3-diol 623**




**613** **623**

To an ice-cold solution of the ester **613** (84 mg, 0.18 mmol, 1.0 eq) in absolute ethanol (1 ml) was added sodium borohydride (13 mg, 0.35 mmol, 2.0 eq) in one portion. The ice-bath was removed and the reaction mixture was stirred for 16 h. The solvent was evaporated, and to the residue was added water (2 ml) and diethyl ether (2 ml). The resultant two layers were separated, and the aqueous phase was extracted with diethyl ether (3 x 2 ml). The combined organic layers were dried and evaporated to yield the *diol* **623** (61 mg, 77%) as a pale yellow oil: $R_f$ 0.35 (40% ethyl acetate in petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3476 (br), 2236 (m), 1598 (m), 1462 (s), 1332 (s), 1160 (s), 1050 (s) and 815 (m); $\delta_H$ 0.80 (3H, t, *J* 6.6, 18-Me), 1.10-1.30 (20H, m, 10 x $CH_2$), 1.35-1.45 (2H, m, 7-$CH_2$), 2.10 (2H, t, *J* 7.1, 6-$CH_2$), 2.35 (3H, s, Ar-Me), 3.25 (1H, app. quart, $J_{approx}$ 3.5, 2-H), 3.50 (1H, dd, *J* 11.6 and 4.2, $C\underline{H}_aCH_b$), 3.95 (1H, dd, *J* 11.6 and 3.5, $CH_aC\underline{H}_b$), 4.35 (1H, br. res., 3-H), 5.90 (1H, d, *J* 8.03, NH), 7.20 (2H, d, *J* 8.0, 2 x Ar-H), 7.70 (2H, d, *J* 8.0, 2 x Ar-H); $\delta_C$ 14.2 (18-Me), 18.7 ($CH_2$), 21.6 (Ar-Me), 22.7, 28.462, 28.5, 29.0, 29.1, 29.4, 29.5, 29.7, 29.7, 31.9 (all $CH_2$, only 10 visible), 57.9 (CH), 62.3 ($CH_2$), 64.8 (CH), 77.2, 88.9 (both C≡C), 127.1, 129.9 (both ArCH), 137.3 and 143.8 (both ArC); *m/z* [APcI] 452 ($M^+$ + H, 100%), 434 (33) and 404 (21). [Found $M^+$ + H: 452.2834. $C_{25}H_{42}NO_4S$ requires *M*, 452.2829].

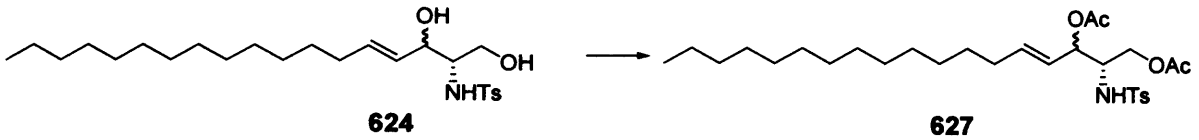
**Reduction of amino alcohol 623**




The alcohol **623** (61 mg, 0.14 mmol) was reduced using Red-Al (0.68 mmol, 0.21 ml) as described in general procedure H to give i) the *alkene* **624** (31 mg, 51%) as a colourless oil and ii) the *allene* **625** (5mg, 8%) as a pale yellow oil. The *E-olefin* **624** was characterised by: $R_f$ 0.16 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3334 (br), 2922 (s), 1600 (m), 1463 (s), 1264 (s), 1159 (s), 964 (s), 849 (m) and 815 (s); $\delta_H$ 0.80 (3H, t, *J* 6.8, 18-Me), 1.10-1.30 (22H, m, 11 x $CH_2$), 1.85-1.95 (1H, m, 6-$CH_2$), 2.35 (3H, s, Ar-Me), 3.10 (1H, app. quart, $J_{approx.}$ 3.7, 2-H), 3.45 (1H, dd, *J* 11.6 and 3.7, C$\underline{H_a}CH_b$), 3.45 (1H, dd, *J* 11.6 and 3.4, $CH_aC\underline{H_b}$), 4.10 (1H, br. t, $J_{approx.}$ 5.0, 3-H), 5.25 (1H, dd, *J* 15.4 and 6.2, 4-H), 5.60 (1H, td, *J* 15.4 and 6.8, 5-H), 7.20 (2H, d, *J* 8.2, 2 x Ar-H) and 7.70 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ 14.2 (18-Me), 21.6 (Ar-Me), 22.7, 29.0, 29.3, 29.4, 29.5, 29.6, 29.7, 29.7, 31.9, 32.3 (all $CH_2$, only 10 visible), 57.8 (CH), 62.0 (1-$CH_2$), 74.6 (CH), 127.1 (ArCH), 128.0 (=CH), 129.8 (ArCH), 134.7 (=CH), 137.3 and 143.7 (both ArC). LRMS failed to produce a molecular ion. No literature data was recorded for the alkene **624**.

The allene **625** was characterised by: $R_f$ 0.38 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3500 (br), 3280 (br) 2924 (s), 2853 (s), 1965 (m) 1599 (m), 1466 (s), 1329 (s), 1161 (s) and 814 (m); $\delta_H$ 0.80 (3H, t, *J* 6.8, 18-Me), 1.20 (1H, app. s, 11 x $CH_2$), 1.80-1.90 (2H, m, 6-$CH_2$), 2.20 (1H, br. res., OH, exchanges with $D_2O$), 2.35 (3H, s, Ar-Me), 3.45-3.55 (1H, m, C$\underline{H_a}CH_b$), 3.55-3.65 (1H, m, $CH_aC\underline{H_b}$), 3.70-3.80 (1H, m, 2-H), 4.75-4.95 (2H, m, 3-H and NH), 5.10 (1H, app. qd, *J* 6.7 and 3.1, 5-H), 7.20 (2H, d, *J* 8.3, 2 x Ar-H) and 7.70 (2H, d, *J* 8.3, 2 x Ar-H); $\delta_H$ ($D_2O$ shake) 0.80 (3H, t, *J* 6.8, 18-Me), 1.10-1.25 (1H, app. s, 11 x $CH_2$), 1.80-1.90 (2H, m, 6-$CH_2$), 2.35 (3H, s, Ar-Me), 3.55 (1H, dd, *J* 11.4 and 6.5, C$\underline{H_a}CH_b$), 3.55 (1H, dd, *J* 11.4 and 4.1, $CH_aC\underline{H_b}$), 3.75-3.80 (1H, m, 2-H), 4.80-4.90 (1H, m, 3-H), 4.95-5.05 (1H, qd, *J* 6.0 and 2.9, 5-H), 7.20 (2H, d, *J* 8.2, 2 x Ar-H) and 7.70 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ 14.2 (18-Me), 21.6 (Ar-Me), 22.7, 28.5, 29.1, 29.2, 29.4, 29.5, 29.6 29.7, 29.7, 31.9 (all $CH_2$, only 10 visible), 54.2 (2-CH), 65.4 ($CH_2$), 89.5, 95.6 (both =CH), 127.3, 129.6 (both ArCH), 137.4, 143.5 (both ArC) and 202.6 (=˙=). LRMS failed to produce a molecular ion.

**Detosylation of *(E,2SR,3RS)*-2-(tosylamino)octadec-4-ene-1,3-diol 624**




**624** **627**

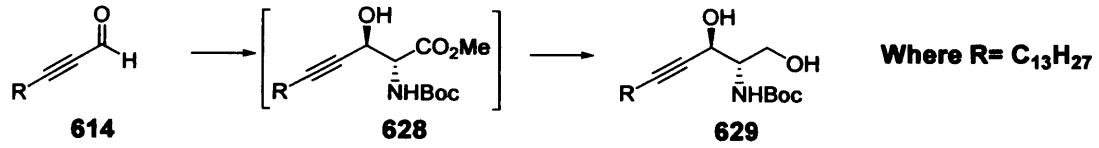
*i) Reduction Using Sodium Napthalenide*

Sodium (100 mg, 4.35 mmol, 39.5 eq) was added in small pieces to a solution of napthalene (700 mg, 5.46 mmol, 49.5 eq) in anhydrous DME (2.9 ml) and the solution was stirred for 3 h at ambient temperature to generate a dark green solution. In a separate flask an 8:1 mixture of diastereoisomers (*anti:syn*) of *N*-tosyl sphingosine **624** (50 mg, 0.11 mmol, 1.0 eq) in anhydrous DME (1.46 ml) was cooled to -78°C and to this was added the sodium naphthalenide solution *via* cannula, until the green colour persisted. The solution was stirred for an additional 0.5 h, and then the cold bath was removed. Saturated aqueous sodium bicarbonate (6 ml) was added, the product was extracted into chloroform (3 x 5 ml) and the combined organic solutions were dried and evaporated.

*ii) Acetate Formation*

The crude product was reacted with acetic anhydride (3 drops) in pyridine for 88 h according to general procedure K. The residue was purified by chromatography (petroleum ether) to elute the naphthalene and then the polarity was increased (20% ethyl acetate/petroleum ether) to yield the *diacetate* **627** (34 mg, 57%), as a 8:1 mixture of diastereoisomers, as a pink oil: $R_f$ 0.44 (40% ethyl acetate/petroleum ether); $\delta_H$ (*anti* diastereoisomer) 0.80 (3H, t, *J* 6.8, Me), 1.10-1.25 (24H, m, 12 x $CH_2$), 1.75 (3H, s, OAc), 1.80 (3H, s, OAc), 2.35 (3H, s, Ar-Me), 3.55-3.65 (1H, m, CHN), 3.85 (1H, dd, *J* 11.6 and 4.9, $C\underline{H}_aCH_b$), 4.05 (1H, dd, *J* 11.6 and 6.4, $CH_aC\underline{H}_b$), 4.90 (1H, d, *J* 8.8, NH), 5.05 (1H, dd, *J* 7.3 and 4.8, CHO), 5.15 (1H, dd, *J* 15.2 and 7.3, =CH), 5.65 (1H, dt, *J* 15.2 and 6.7, =CH), 7.25 (2H, d, *J* 8.2, 2 x Ar-H) and 7.65 (2H, d, *J* 8.2, 2 x Ar-H); $\delta_C$ 14.2 (Me), 20.6, 21.0, 21.5 (Ar-Me and 2 x $COCH_3$), 22.7, 28.7, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 32.4 (all $CH_2$, only 9 visible), 54.9 (CH), 62.6 ($CH_2$), 73.5 (CH), 122.8 (=CH), 127.2, 129.7 (both ArCH), 137.9 (=CH), 169.9 and 170.7 (both C=O), no ArC evident.

**(2SR,3RS)-*tert*-butyl-1,3-dihydroxyoctadec-4-yn-2-ylcarbamate 629**



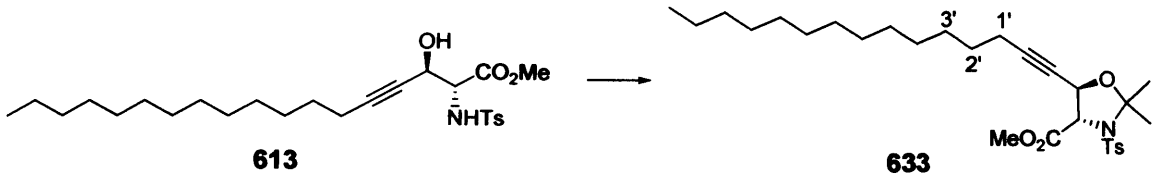

*i) Aldol reaction*

Hexadec-2-ynal **614** (1.0 g, 4.23 mmol) was condensed with Methyl *N*-Boc glycinate **162b** (667 mg, 3.53 mmol) according to general procedure C to give an inseparable mixture of the amino alcohol **628** and methyl *N*-Boc glycinate **162b.** The amino alcohol **628** was characterised by: $R_f$ 0.54 (40% ethyl acetate/petroleum ether); $\delta_H$ 0.80 (3H, t, *J* 6.9, 18-Me), 1.20 (22H, s, 11 x $CH_2$), 1.40 (9H, s, *t*-Bu), 2.10 (2H, app. td, *J* 7.0 and 1.8, 6-$CH_2$), 3.40 (1H, br. d, *J* 6.7, OH, exchanges with $D_2O$), 3.70 (3H, s, $CO_2Me$), 4.50 (1H, br. res., 2-H), 4.70 (1H, br. res., 3-H), 5.40 (1H, br. d, *J* 8.2, NH); $\delta_C$ 14.1 (18-Me), 18.6, 22.7, 28.2, 28.3, 28.4, 28.8, 29.1, 29.3, 29.5, 29.6, 29.7, 31.9 (all $CH_2$), 52.6 ($CO_2Me$), 58.8, 63.6 (both CH), 76.1 (C≡C), 80.6 ($(CH_3)_3$-C), 88.0 (C≡C), 156.2, 169.8 (both C=O); *m/z* [APcI] 426 ($M^+$ + H, 39%), 370 (80), 352 (39), 259 (30) and 134 (100).

*ii) Sodium borohydride reduction*

To a 1:1.15 mixture of methyl *N*-Boc glycinate **162b** and the ester **628** (148 mg, 0.35 mmol, 1.0 eq) in absolute ethanol (5 ml) was added sodium borohydride slowly (26 mg, 0.70 mmol, 2.0 eq) and the reaction was stirred for 16 h. The solvent was evaporated and the residue was partitioned between water (2 ml) and ether (2 ml). The two phases were separated and the aqueous phase was extracted with ether (3 x 2 ml) to give the *amino alcohol* **629** (52 mg, 50%); $R_f$ 0.22 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 3420 (br), 2925 (s), 2853 (s), 1694 (s), 1466 (m), and 1367 (s); $\delta_H$ 0.80 (3H, t, *J* 6.8, 18-Me), 1.20 (22H, br s, 10 x $CH_2$), 1.35-1.50 (11H, m, *t*-Bu and $CH_2$), 2.15 (1H, td, *J* 7.2 and 1.9, 6-$CH_2$), 2.45 (1H, br. res., OH, exchanges with $D_2O$), 2.90 (1H, br. res., OH, exchanges with $D_2O$), 3.70 (2H, br. res., $CH_2OH$), 4.05 (1H, br. res., 2-H), 4.50 (1H, br. res., 3-H) and 5.25 (1H, br. d, *J* 6.23, NH); $\delta_C$ 14.2 (18-Me), 18.7, 22.7, 28.4, 28.5, 28.9, 29.1, 29.4, 29.5, 29.7, 29.7, 31.9 (all $CH_2$), 55.5 (CH), 63.0 ($CH_2$), 64.9 (CH), 77.8 ($(CH_3)_3$-C), 80.1, 88.4 (both C≡C); *m/z* [APcI] 398 ($M^+$ + H, 100%).

**(*4SR,5RS*)-Methyl 2,2-Dimethyl-5-(pentadec-1-ynyl)-3-tosyloxazolidine-4-carboxylate 633**




**613** **633**

To a 6:2 mixture of the amino alcohol **613** and Methyl *N*-tosyl glycine **156** (100 mg, 0.21 mmol, 1.0 eq) in anhydrous toluene (2 ml) was added 2,2-dimethoxypropane (0.51 ml, 4.17 mmol, 20 eq) and catalytic PPTS. The reaction mixture was then stirred at 70°C for 24 h. The solvent was evaporated and the residue was chromatographed (10% ethyl acetate/ petroleum ether) to give the *acetyl* **633** (41 mg, 85%, 44% conversion) as a pale yellow oil together with some starting material **613** (42 mg, 49% recovered). The acetyl **633** was characterised by: $R_f$ 0.64 (40% ethyl acetate/petroleum ether); $\nu_{max}/cm^{-1}$ [$CH_2Cl_2$] 2925 (s), 2854 (s), 1761 (s), 1598 (m), 1495 (m), 1457 (s), 1436 (s), 1348 (s), 1165 (s), and 815 (s); $\delta_H$ 0.80 (3H, t, *J* 6.8, Me), 1.10-1.30 (20H, m, 10 x $CH_2$), 1.35-1.45 (2H, m, $CH_2$), 1.55 (3H, s, 2-Me), 1.75 (3H, s, 2-Me), 2.05-2.15 (2, m, 1'-$CH_2$), 2.35 (3H, s, Ar-Me), 3.45 (3H, s, $CO_2Me$), 4.30 (1H, d, *J* 6.5, 4-H), 4.80 (1H, app. dt, *J* 6.5 and 1.9, 5-H), 7.20 (2H, d, *J* 8.0, 2 x Ar-H) and 7.65 (2H, d, *J* 8.0, 2 x Ar-H); $\delta_C$ 14.1 (Me), 18.7 ($CH_2$), 21.5 (Me), 22.4 ($CH_2$), 26.2, 27.2 (both Me), 27.7, 28.2, 28.6, 28.8, 29.1, 29.4, 29.6, 29.6, 29.7, 31.9 (all $CH_2$), 52.1 ($CO_2Me$), 63.5, 67.3 (both CH), 71.6, 90.8, 98.8 (all C), 129.6, 127.7 (both ArCH), 137.1, 143.9 (both ArC) and 168.7 (C=O).

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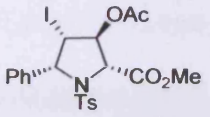
# Appendix

## X-ray data




**308a**

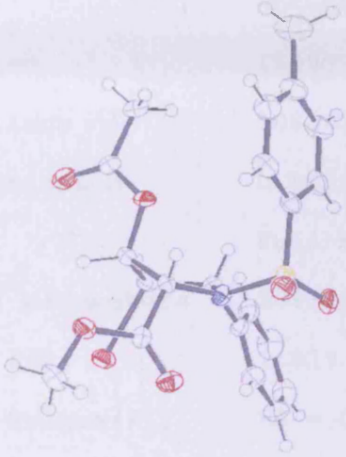


Table 1. Crystal data and structure refinement for 02DWK7.

| | |
|---|---|
| Identification code | s92 |
| Empirical formula | C21 H22 I N O6 S |
| Formula weight | 543.36 |
| Temperature | 150(2) K |
| Wavelength | 0.71073 A |
| Crystal system | Monoclinic |
| Space group | P2(1)/n |
| Unit cell dimensions | a = 6.8409(2) A alpha = 90 deg.<br>b = 15.1448(5) A beta = 92.6436(16) deg.<br>c = 21.7405(6) A gamma = 90 deg. |
| Volume | 2250.01(12) A^3 |

| | |
|---|---|
| Z | 4 |
| Density (calculated) | 1.604 Mg/m^3 |
| Absorption coefficient | 1.552 mm^-1 |
| F(000) | 1088 |
| Crystal size | 0.25 x 0.15 x 0.12 mm |
| Theta range for data collection | 3.08 to 27.47 deg. |
| Index ranges | -8<=h<=8, -19<=k<=19, -28<=l<=28 |
| Reflections collected | 15095 |
| Independent reflections | 5083 [R(int) = 0.1275] |
| Max. and min. transmission | 0.8356 and 0.6976 |
| Refinement method | Full-matrix least-squares on F^2 |
| Data / restraints / parameters | 5083 / 0 / 274 |
| Goodness-of-fit on F^2 | 1.019 |
| Final R indices [I>2sigma(I)] | R1 = 0.0552, wR2 = 0.1263 |
| R indices (all data) | R1 = 0.0865, wR2 = 0.1428 |
| Largest diff. peak and hole | 1.191 and -1.303 e.A^-3 |

À

Table 2. Atomic coordinates ( x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 02DWK7. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| I(1) | -768(1) | -1859(1) | 2676(1) | 29(1) |
| S(1) | 3272(2) | 1037(1) | 3058(1) | 25(1) |
| O(1) | 3129(5) | 1387(2) | 2449(2) | 34(1) |
| O(2) | 5137(5) | 797(2) | 3332(2) | 30(1) |
| O(3) | -544(4) | 105(2) | 4104(1) | 24(1) |
| O(4) | -3189(5) | -628(2) | 4413(2) | 35(1) |
| O(5) | 3228(5) | -1853(2) | 3900(2) | 26(1) |
| O(6) | 4402(4) | -1334(2) | 3021(1) | 29(1) |
| N(1) | 1953(5) | 131(3) | 3045(2) | 22(1) |
| C(1) | 2163(7) | 1793(3) | 3550(2) | 25(1) |
| C(2) | 2585(8) | 1739(3) | 4182(2) | 32(1) |
| C(3) | 1657(8) | 2306(4) | 4574(2) | 37(1) |
| C(4) | 304(8) | 2916(4) | 4347(2) | 34(1) |
| C(5) | -71(8) | 2971(4) | 3715(3) | 38(1) |
| C(6) | 836(7) | 2412(3) | 3314(2) | 32(1) |
| C(7) | -710(10) | 3508(5) | 4792(3) | 58(2) |
| C(8) | -129(6) | 188(3) | 2798(2) | 22(1) |
| C(9) | -1101(6) | -597(3) | 3118(2) | 23(1) |

| | | | | |
|---|---|---|---|---|
| C(10) | 5(6) | -646(3) | 3737(2) | 23(1) |
| C(11) | 2132(6) | -458(3) | 3583(2) | 20(1) |
| C(12) | -365(7) | 191(3) | 2099(2) | 27(1) |
| C(13) | 1023(8) | -156(4) | 1725(2) | 37(1) |
| C(14) | 682(10) | -140(4) | 1091(2) | 47(2) |
| C(15) | -1042(10) | 208(4) | 832(3) | 51(2) |
| C(16) | -2430(9) | 543(4) | 1213(3) | 48(2) |
| C(17) | -2086(8) | 537(4) | 1842(2) | 37(1) |
| C(18) | -2209(6) | 34(3) | 4409(2) | 24(1) |
| C(19) | -2614(7) | 883(3) | 4736(2) | 28(1) |
| C(20) | 3367(6) | -1262(3) | 3451(2) | 22(1) |
| C(21) | 4433(8) | -2634(3) | 3849(3) | 37(1) |

Å

Table 3. Bond lengths [A] and angles [deg] for 02DWK7.

| | |
|---|---|
| I(1)-C(9) | 2.156(4) |
| S(1)-O(1) | 1.425(3) |
| S(1)-O(2) | 1.430(3) |
| S(1)-N(1) | 1.641(4) |
| S(1)-C(1) | 1.764(5) |
| O(3)-C(18) | 1.348(5) |
| O(3)-C(10) | 1.450(5) |
| O(4)-C(18) | 1.206(6) |
| O(5)-C(20) | 1.332(5) |
| O(5)-C(21) | 1.449(6) |
| O(6)-C(20) | 1.204(5) |
| N(1)-C(11) | 1.471(5) |
| N(1)-C(8) | 1.501(6) |
| C(1)-C(6) | 1.387(7) |
| C(1)-C(2) | 1.392(7) |
| C(2)-C(3) | 1.384(7) |
| C(2)-H(2) | 0.9500 |
| C(3)-C(4) | 1.382(8) |
| C(3)-H(3) | 0.9500 |
| C(4)-C(5) | 1.389(7) |
| C(4)-C(7) | 1.510(8) |
| C(5)-C(6) | 1.383(7) |
| 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(12) | 1.521(6) |
| C(8)-C(9) | 1.544(6) |
| C(8)-H(8) | 1.0000 |
| C(9)-C(10) | 1.516(6) |
| C(9)-H(9) | 1.0000 |
| C(10)-C(11) | 1.535(6) |
| C(10)-H(10) | 1.0000 |
| C(11)-C(20) | 1.517(6) |
| C(11)-H(11) | 1.0000 |
| C(12)-C(13) | 1.381(7) |
| C(12)-C(17) | 1.383(7) |
| C(13)-C(14) | 1.388(8) |
| C(13)-H(13) | 0.9500 |
| C(14)-C(15) | 1.388(9) |

| | |
|---|---|
| C(14)-H(14) | 0.9500 |
| C(15)-C(16) | 1.386(9) |
| C(15)-H(15) | 0.9500 |
| C(16)-C(17) | 1.376(7) |
| C(16)-H(16) | 0.9500 |
| C(17)-H(17) | 0.9500 |
| C(18)-C(19) | 1.501(7) |
| C(19)-H(19A) | 0.9800 |
| C(19)-H(19B) | 0.9800 |
| C(19)-H(19C) | 0.9800 |
| C(21)-H(21A) | 0.9800 |
| C(21)-H(21B) | 0.9800 |
| C(21)-H(21C) | 0.9800 |
| O(1)-S(1)-O(2) | 120.3(2) |
| O(1)-S(1)-N(1) | 106.3(2) |
| O(2)-S(1)-N(1) | 105.9(2) |
| O(1)-S(1)-C(1) | 108.1(2) |
| O(2)-S(1)-C(1) | 108.2(2) |
| N(1)-S(1)-C(1) | 107.5(2) |
| C(18)-O(3)-C(10) | 117.0(4) |
| C(20)-O(5)-C(21) | 115.6(4) |
| C(11)-N(1)-C(8) | 111.2(3) |
| C(11)-N(1)-S(1) | 117.9(3) |
| C(8)-N(1)-S(1) | 118.0(3) |
| C(6)-C(1)-C(2) | 120.5(5) |
| C(6)-C(1)-S(1) | 120.4(4) |
| C(2)-C(1)-S(1) | 119.0(4) |
| C(3)-C(2)-C(1) | 119.3(5) |
| C(3)-C(2)-H(2) | 120.3 |
| C(1)-C(2)-H(2) | 120.3 |
| C(4)-C(3)-C(2) | 121.0(5) |
| C(4)-C(3)-H(3) | 119.5 |
| C(2)-C(3)-H(3) | 119.5 |
| C(3)-C(4)-C(5) | 118.8(5) |
| C(3)-C(4)-C(7) | 119.3(5) |
| C(5)-C(4)-C(7) | 121.9(5) |
| C(6)-C(5)-C(4) | 121.4(5) |
| C(6)-C(5)-H(5) | 119.3 |
| C(4)-C(5)-H(5) | 119.3 |
| C(5)-C(6)-C(1) | 119.0(5) |
| C(5)-C(6)-H(6) | 120.5 |
| C(1)-C(6)-H(6) | 120.5 |
| C(4)-C(7)-H(7A) | 109.5 |
| C(4)-C(7)-H(7B) | 109.5 |
| H(7A)-C(7)-H(7B) | 109.5 |
| C(4)-C(7)-H(7C) | 109.5 |
| H(7A)-C(7)-H(7C) | 109.5 |
| H(7B)-C(7)-H(7C) | 109.5 |
| N(1)-C(8)-C(12) | 114.4(4) |
| N(1)-C(8)-C(9) | 102.5(3) |
| C(12)-C(8)-C(9) | 115.1(4) |
| N(1)-C(8)-H(8) | 108.2 |
| C(12)-C(8)-H(8) | 108.2 |
| C(9)-C(8)-H(8) | 108.2 |
| C(10)-C(9)-C(8) | 103.2(4) |
| C(10)-C(9)-I(1) | 107.1(3) |
| C(8)-C(9)-I(1) | 115.2(3) |
| C(10)-C(9)-H(9) | 110.3 |
| C(8)-C(9)-H(9) | 110.3 |
| I(1)-C(9)-H(9) | 110.3 |
| O(3)-C(10)-C(9) | 108.6(4) |

| | |
|---|---|
| O(3)-C(10)-C(11) | 104.3(3) |
| C(9)-C(10)-C(11) | 103.7(3) |
| O(3)-C(10)-H(10) | 113.1 |
| C(9)-C(10)-H(10) | 113.1 |
| C(11)-C(10)-H(10) | 113.1 |
| N(1)-C(11)-C(20) | 111.3(3) |
| N(1)-C(11)-C(10) | 104.0(3) |
| C(20)-C(11)-C(10) | 115.7(4) |
| N(1)-C(11)-H(11) | 108.5 |
| C(20)-C(11)-H(11) | 108.5 |
| C(10)-C(11)-H(11) | 108.5 |
| C(13)-C(12)-C(17) | 120.1(4) |
| C(13)-C(12)-C(8) | 122.9(5) |
| C(17)-C(12)-C(8) | 117.0(4) |
| C(12)-C(13)-C(14) | 119.3(5) |
| C(12)-C(13)-H(13) | 120.3 |
| C(14)-C(13)-H(13) | 120.3 |
| C(15)-C(14)-C(13) | 120.7(6) |
| C(15)-C(14)-H(14) | 119.7 |
| C(13)-C(14)-H(14) | 119.7 |
| C(16)-C(15)-C(14) | 119.3(5) |
| C(16)-C(15)-H(15) | 120.3 |
| C(14)-C(15)-H(15) | 120.3 |
| C(17)-C(16)-C(15) | 120.1(6) |
| C(17)-C(16)-H(16) | 120.0 |
| C(15)-C(16)-H(16) | 120.0 |
| C(16)-C(17)-C(12) | 120.5(5) |
| C(16)-C(17)-H(17) | 119.7 |
| C(12)-C(17)-H(17) | 119.7 |
| O(4)-C(18)-O(3) | 123.5(4) |
| O(4)-C(18)-C(19) | 126.5(4) |
| O(3)-C(18)-C(19) | 110.0(4) |
| C(18)-C(19)-H(19A) | 109.5 |
| C(18)-C(19)-H(19B) | 109.5 |
| H(19A)-C(19)-H(19B) | 109.5 |
| C(18)-C(19)-H(19C) | 109.5 |
| H(19A)-C(19)-H(19C) | 109.5 |
| H(19B)-C(19)-H(19C) | 109.5 |
| O(6)-C(20)-O(5) | 125.0(4) |
| O(6)-C(20)-C(11) | 124.9(4) |
| O(5)-C(20)-C(11) | 110.0(3) |
| O(5)-C(21)-H(21A) | 109.5 |
| O(5)-C(21)-H(21B) | 109.5 |
| H(21A)-C(21)-H(21B) | 109.5 |
| O(5)-C(21)-H(21C) | 109.5 |
| H(21A)-C(21)-H(21C) | 109.5 |
| H(21B)-C(21)-H(21C) | 109.5 |

Symmetry transformations used to generate equivalent atoms:

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Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 02DWK7.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [ h^2 a*^2 U11 + ... + 2 h k a* b* U12 ]

| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| I(1) | 30(1) | 25(1) | 32(1) | -7(1) | 2(1) | -1(1) |
| S(1) | 26(1) | 23(1) | 26(1) | 2(1) | 3(1) | -3(1) |
| O(1) | 48(2) | 28(2) | 27(2) | 7(2) | 5(2) | -6(2) |
| O(2) | 25(2) | 32(2) | 35(2) | -1(2) | 5(2) | -1(1) |
| O(3) | 29(2) | 23(2) | 20(2) | -7(1) | 4(1) | -1(1) |
| O(4) | 35(2) | 38(2) | 32(2) | -3(2) | 10(2) | -3(2) |
| O(5) | 31(2) | 22(2) | 27(2) | 0(1) | 2(1) | 3(1) |
| O(6) | 24(2) | 35(2) | 29(2) | -5(2) | 3(1) | 0(2) |
| N(1) | 18(2) | 27(2) | 21(2) | 2(2) | 0(2) | -3(2) |
| C(1) | 28(2) | 22(2) | 26(2) | -2(2) | -5(2) | -3(2) |
| C(2) | 32(3) | 29(3) | 33(3) | -2(2) | -9(2) | 1(2) |
| C(3) | 42(3) | 39(3) | 29(3) | -2(2) | -7(2) | -5(3) |
| C(4) | 38(3) | 29(3) | 34(3) | -5(2) | -8(2) | 8(2) |
| C(5) | 40(3) | 32(3) | 41(3) | -3(2) | -10(3) | 14(2) |
| C(6) | 42(3) | 23(3) | 30(2) | 7(2) | -7(2) | -1(2) |
| C(7) | 67(4) | 61(4) | 44(3) | -8(3) | -9(3) | 27(4) |
| C(8) | 21(2) | 27(3) | 19(2) | 1(2) | -1(2) | 1(2) |
| C(9) | 23(2) | 19(2) | 26(2) | -5(2) | 2(2) | -1(2) |
| C(10) | 26(2) | 17(2) | 27(2) | -1(2) | 3(2) | 1(2) |
| C(11) | 21(2) | 17(2) | 21(2) | 1(2) | -1(2) | 0(2) |
| C(12) | 36(3) | 24(3) | 20(2) | 1(2) | 2(2) | -5(2) |
| C(13) | 47(3) | 35(3) | 30(3) | 0(2) | 1(2) | 0(3) |
| C(14) | 69(4) | 44(4) | 30(3) | -10(3) | 16(3) | -8(3) |
| C(15) | 79(5) | 49(4) | 24(3) | 2(3) | -11(3) | -22(3) |
| C(16) | 52(4) | 56(4) | 33(3) | 12(3) | -19(3) | -5(3) |
| C(17) | 44(3) | 36(3) | 29(2) | 6(2) | -2(2) | -6(2) |
| C(18) | 23(2) | 31(3) | 16(2) | 0(2) | -3(2) | 1(2) |
| C(19) | 28(2) | 34(3) | 22(2) | -5(2) | 2(2) | 5(2) |
| C(20) | 21(2) | 23(2) | 20(2) | 3(2) | -2(2) | -4(2) |
| C(21) | 43(3) | 22(3) | 45(3) | 1(2) | -1(3) | 4(2) |

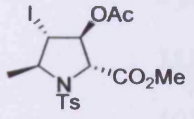
Å

Table 5. Hydrogen coordinates ( x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 02DWK7.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2) | 3500 | 1317 | 4342 | 38 |
| H(3) | 1954 | 2276 | 5004 | 44 |
| H(5) | -969 | 3401 | 3555 | 45 |
| H(6) | 554 | 2451 | 2883 | 38 |
| H(7A) | -541 | 3267 | 5209 | 86 |
| H(7B) | -2108 | 3540 | 4673 | 86 |
| H(7C) | -139 | 4101 | 4781 | 86 |
| H(8) | -710 | 746 | 2955 | 27 |
| H(9) | -2517 | -471 | 3174 | 27 |
| H(10) | -160 | -1224 | 3951 | 28 |

| | | | | |
|---|---|---|---|---|
| H(11) | 2779 | -125 | 3933 | 24 |
| H(13) | 2198 | -402 | 1900 | 45 |
| H(14) | 1640 | -370 | 832 | 57 |
| H(15) | -1269 | 216 | 397 | 61 |
| H(16) | -3621 | 778 | 1041 | 57 |
| H(17) | -3038 | 772 | 2101 | 44 |
| H(19A) | -2918 | 1347 | 4432 | 42 |
| H(19B) | -1458 | 1054 | 4992 | 42 |
| H(19C) | -3729 | 802 | 4998 | 42 |
| H(21A) | 3979 | -2976 | 3487 | 55 |
| H(21B) | 4339 | -2996 | 4220 | 55 |
| H(21C) | 5798 | -2457 | 3804 | 55 |

Å

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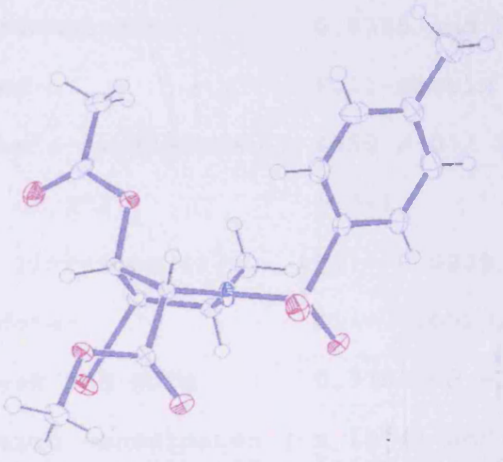

Table 1. Crystal data and structure refinement for S92.

| | |
|---|---|
| Identification code | s92 |
| Empirical formula | C16 H20 I N O6 S |
| Formula weight | 481.29 |
| Temperature | 150(2) K |
| Wavelength | 0.71073 A |
| Crystal system | Monoclinic |
| Space group | P2(1)/c |
| Unit cell dimensions | a = 7.15670(10) A alpha = 90 deg. |
| | b = 36.1816(7) A beta = 95.8708(6) deg. |

| | |
|---|---|
| | c = 7.22260(10) A gamma = 90 deg. |
| Volume | 1860.42(5) A^3 |
| Z | 4 |
| Density (calculated) | 1.718 Mg/m^3 |
| Absorption coefficient | 1.865 mm^-1 |
| F(000) | 960 |
| Crystal size | 0.15 x 0.12 x 0.10 mm |
| Theta range for data collection | 2.92 to 27.41 deg. |
| Index ranges | -9<=h<=9, -46<=k<=46, -9<=l<=9 |
| Reflections collected | 11586 |
| Independent reflections | 4050 [R(int) = 0.0568] |
| Max. and min. transmission | 0.8355 and 0.7673 |
| Refinement method | Full-matrix least-squares on F^2 |
| Data / restraints / parameters | 4050 / 0 / 230 |
| Goodness-of-fit on F^2 | 1.041 |
| Final R indices [I>2sigma(I)] | R1 = 0.0339, wR2 = 0.0843 |
| R indices (all data) | R1 = 0.0523, wR2 = 0.1131 |
| Largest diff. peak and hole | 0.778 and -0.807 e.A^-3 |

Å

Table 2. Atomic coordinates ( x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for S92. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| I(1) | 4899(1) | 2064(1) | 3242(1) | 26(1) |
| S(1) | 939(1) | 974(1) | 5826(2) | 18(1) |
| O(1) | -553(4) | 1145(1) | 6697(4) | 23(1) |
| O(2) | 615(4) | 834(1) | 3970(4) | 26(1) |
| O(3) | 188(4) | 1834(1) | 4573(4) | 23(1) |
| O(4) | 1401(3) | 2226(1) | 6820(4) | 17(1) |
| O(5) | 5582(3) | 1511(1) | 8572(4) | 18(1) |
| O(6) | 8062(4) | 1896(1) | 8609(4) | 27(1) |
| N(1) | 2633(4) | 1275(1) | 5917(5) | 18(1) |
| C(1) | 2576(5) | 1619(1) | 6937(6) | 15(1) |
| C(2) | 1233(5) | 1905(1) | 5934(6) | 16(1) |
| C(3) | 136(5) | 2514(1) | 6040(6) | 23(1) |
| C(4) | 4651(5) | 1737(1) | 7082(6) | 16(1) |
| C(5) | 7333(5) | 1630(1) | 9228(6) | 21(1) |

| | | | | |
|---|---|---|---|---|
| C(6) | 8200(6) | 1388(1) | 10749(6) | 26(1) |
| C(7) | 5308(5) | 1611(1) | 5234(6) | 17(1) |
| C(8) | 4134(5) | 1268(1) | 4626(6) | 18(1) |
| C(9) | 5296(5) | 913(1) | 4846(6) | 24(1) |
| C(10) | 1717(5) | 600(1) | 7292(6) | 18(1) |
| C(11) | 2066(6) | 660(1) | 9195(6) | 24(1) |
| C(12) | 2446(6) | 361(1) | 10371(7) | 29(1) |
| C(13) | 2492(5) | 1(1) | 9704(7) | 26(1) |
| C(14) | 2167(6) | -49(1) | 7784(7) | 28(1) |
| C(15) | 1776(6) | 245(1) | 6579(6) | 24(1) |
| C(16) | 2858(6) | -315(1) | 11036(7) | 37(1) |

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Table 3. Bond lengths [A] and angles [deg] for S92.

| | |
|---|---|
| I(1)-C(7) | 2.182(4) |
| S(1)-O(2) | 1.429(3) |
| S(1)-O(1) | 1.434(3) |
| S(1)-N(1) | 1.626(3) |
| S(1)-C(10) | 1.772(4) |
| O(3)-C(2) | 1.201(5) |
| O(4)-C(2) | 1.325(5) |
| O(4)-C(3) | 1.456(4) |
| O(5)-C(5) | 1.364(5) |
| O(5)-C(4) | 1.457(5) |
| O(6)-C(5) | 1.202(5) |
| N(1)-C(1) | 1.451(5) |
| N(1)-C(8) | 1.492(4) |
| C(1)-C(4) | 1.538(5) |
| C(1)-C(2) | 1.542(5) |
| C(1)-H(1) | 1.0000 |
| C(3)-H(3A) | 0.9800 |
| C(3)-H(3B) | 0.9800 |
| C(3)-H(3C) | 0.9800 |
| C(4)-C(7) | 1.529(5) |
| C(4)-H(4) | 1.0000 |
| C(5)-C(6) | 1.490(6) |
| C(6)-H(6A) | 0.9800 |
| C(6)-H(6B) | 0.9800 |
| C(6)-H(6C) | 0.9800 |
| C(7)-C(8) | 1.538(5) |
| C(7)-H(7) | 1.0000 |
| C(8)-C(9) | 1.528(5) |
| C(8)-H(8) | 1.0000 |
| C(9)-H(9A) | 0.9800 |
| C(9)-H(9B) | 0.9800 |
| C(9)-H(9C) | 0.9800 |
| C(10)-C(15) | 1.385(6) |
| C(10)-C(11) | 1.388(6) |
| C(11)-C(12) | 1.383(6) |
| C(11)-H(11) | 0.9500 |
| C(12)-C(13) | 1.390(6) |
| C(12)-H(12) | 0.9500 |
| C(13)-C(14) | 1.394(7) |
| C(13)-C(16) | 1.501(6) |
| C(14)-C(15) | 1.386(6) |
| C(14)-H(14) | 0.9500 |

| | |
|---|---|
| C(15)-H(15) | 0.9500 |
| C(16)-H(16A) | 0.9800 |
| C(16)-H(16B) | 0.9800 |
| C(16)-H(16C) | 0.9800 |
| | |
| O(2)-S(1)-O(1) | 120.50(18) |
| O(2)-S(1)-N(1) | 108.88(17) |
| O(1)-S(1)-N(1) | 106.17(16) |
| O(2)-S(1)-C(10) | 107.54(19) |
| O(1)-S(1)-C(10) | 105.67(18) |
| N(1)-S(1)-C(10) | 107.43(18) |
| C(2)-O(4)-C(3) | 114.8(3) |
| C(5)-O(5)-C(4) | 114.4(3) |
| C(1)-N(1)-C(8) | 113.0(3) |
| C(1)-N(1)-S(1) | 122.4(2) |
| C(8)-N(1)-S(1) | 123.0(3) |
| N(1)-C(1)-C(4) | 101.3(3) |
| N(1)-C(1)-C(2) | 112.8(3) |
| C(4)-C(1)-C(2) | 113.4(3) |
| N(1)-C(1)-H(1) | 109.7 |
| C(4)-C(1)-H(1) | 109.7 |
| C(2)-C(1)-H(1) | 109.7 |
| O(3)-C(2)-O(4) | 127.0(4) |
| O(3)-C(2)-C(1) | 123.1(4) |
| O(4)-C(2)-C(1) | 109.9(3) |
| O(4)-C(3)-H(3A) | 109.5 |
| O(4)-C(3)-H(3B) | 109.5 |
| H(3A)-C(3)-H(3B) | 109.5 |
| O(4)-C(3)-H(3C) | 109.5 |
| H(3A)-C(3)-H(3C) | 109.5 |
| H(3B)-C(3)-H(3C) | 109.5 |
| O(5)-C(4)-C(7) | 108.6(3) |
| O(5)-C(4)-C(1) | 105.1(3) |
| C(7)-C(4)-C(1) | 103.8(3) |
| O(5)-C(4)-H(4) | 112.9 |
| C(7)-C(4)-H(4) | 112.9 |
| C(1)-C(4)-H(4) | 112.9 |
| O(6)-C(5)-O(5) | 122.8(4) |
| O(6)-C(5)-C(6) | 125.5(4) |
| O(5)-C(5)-C(6) | 111.6(4) |
| C(5)-C(6)-H(6A) | 109.5 |
| C(5)-C(6)-H(6B) | 109.5 |
| H(6A)-C(6)-H(6B) | 109.5 |
| C(5)-C(6)-H(6C) | 109.5 |
| H(6A)-C(6)-H(6C) | 109.5 |
| H(6B)-C(6)-H(6C) | 109.5 |
| C(4)-C(7)-C(8) | 106.4(3) |
| C(4)-C(7)-I(1) | 108.6(3) |
| C(8)-C(7)-I(1) | 112.7(3) |
| C(4)-C(7)-H(7) | 109.7 |
| C(8)-C(7)-H(7) | 109.7 |
| I(1)-C(7)-H(7) | 109.7 |
| N(1)-C(8)-C(9) | 111.6(3) |
| N(1)-C(8)-C(7) | 102.4(3) |
| C(9)-C(8)-C(7) | 111.8(3) |
| N(1)-C(8)-H(8) | 110.2 |
| C(9)-C(8)-H(8) | 110.2 |
| C(7)-C(8)-H(8) | 110.2 |
| C(8)-C(9)-H(9A) | 109.5 |
| C(8)-C(9)-H(9B) | 109.5 |
| H(9A)-C(9)-H(9B) | 109.5 |

| | |
|---|---|
| C(8)-C(9)-H(9C) | 109.5 |
| H(9A)-C(9)-H(9C) | 109.5 |
| H(9B)-C(9)-H(9C) | 109.5 |
| C(15)-C(10)-C(11) | 120.2(4) |
| C(15)-C(10)-S(1) | 120.3(3) |
| C(11)-C(10)-S(1) | 119.1(3) |
| C(12)-C(11)-C(10) | 119.4(4) |
| C(12)-C(11)-H(11) | 120.3 |
| C(10)-C(11)-H(11) | 120.3 |
| C(11)-C(12)-C(13) | 121.9(4) |
| C(11)-C(12)-H(12) | 119.1 |
| C(13)-C(12)-H(12) | 119.1 |
| C(12)-C(13)-C(14) | 117.4(4) |
| C(12)-C(13)-C(16) | 120.1(5) |
| C(14)-C(13)-C(16) | 122.5(4) |
| C(15)-C(14)-C(13) | 121.8(4) |
| C(15)-C(14)-H(14) | 119.1 |
| C(13)-C(14)-H(14) | 119.1 |
| C(10)-C(15)-C(14) | 119.3(4) |
| C(10)-C(15)-H(15) | 120.3 |
| C(14)-C(15)-H(15) | 120.3 |
| C(13)-C(16)-H(16A) | 109.5 |
| C(13)-C(16)-H(16B) | 109.5 |
| H(16A)-C(16)-H(16B) | 109.5 |
| C(13)-C(16)-H(16C) | 109.5 |
| H(16A)-C(16)-H(16C) | 109.5 |
| H(16B)-C(16)-H(16C) | 109.5 |

Symmetry transformations used to generate equivalent atoms:

Å

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for S92. The anisotropic displacement factor exponent takes the form: -2 pi^2 [ h^2 a*^2 U11 + ... + 2 h k a* b* U12 ]

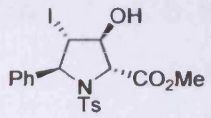
| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| I(1) | 27(1) | 24(1) | 27(1) | 10(1) | 7(1) | 3(1) |
| S(1) | 13(1) | 16(1) | 24(1) | -1(1) | -1(1) | -2(1) |
| O(1) | 14(1) | 21(2) | 36(2) | 2(1) | 6(1) | 1(1) |
| O(2) | 26(1) | 27(2) | 24(2) | -3(1) | -8(1) | -5(1) |
| O(3) | 23(1) | 24(2) | 21(2) | 1(1) | -5(1) | -1(1) |
| O(4) | 19(1) | 14(2) | 18(2) | 2(1) | 1(1) | 2(1) |
| O(5) | 17(1) | 17(2) | 18(2) | 3(1) | -2(1) | -2(1) |
| O(6) | 23(1) | 28(2) | 31(2) | -3(2) | -1(1) | -8(1) |
| N(1) | 12(1) | 13(2) | 28(2) | -4(2) | 6(1) | -3(1) |
| C(1) | 17(2) | 13(2) | 15(2) | 1(2) | 2(2) | -2(2) |
| C(2) | 16(2) | 15(2) | 16(2) | 0(2) | 5(2) | 1(2) |
| C(3) | 28(2) | 15(2) | 25(2) | -4(2) | -2(2) | 13(2) |
| C(4) | 18(2) | 12(2) | 18(2) | 2(2) | 1(2) | -1(2) |
| C(5) | 16(2) | 27(2) | 18(2) | -10(2) | -1(2) | 4(2) |
| C(6) | 26(2) | 30(3) | 19(2) | -1(2) | -3(2) | 5(2) |
| C(7) | 13(2) | 19(2) | 21(2) | 5(2) | 0(2) | 2(2) |
| C(8) | 17(2) | 20(2) | 16(2) | -2(2) | 3(2) | 0(2) |
| C(9) | 20(2) | 20(2) | 34(3) | -6(2) | 9(2) | 3(2) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(10) | 15(2) | 17(2) | 24(2) | -2(2) | 3(2) | -2(2) |
| C(11) | 27(2) | 18(2) | 27(3) | -4(2) | 2(2) | -1(2) |
| C(12) | 28(2) | 38(3) | 22(3) | 4(2) | 2(2) | 1(2) |
| C(13) | 13(2) | 23(2) | 41(3) | 10(2) | 4(2) | 0(2) |
| C(14) | 26(2) | 16(2) | 43(3) | 1(2) | 6(2) | 0(2) |
| C(15) | 25(2) | 19(2) | 28(3) | -6(2) | 5(2) | -2(2) |
| C(16) | 27(2) | 33(3) | 50(3) | 14(2) | 5(2) | -2(2) |

Å

Table 5. Hydrogen coordinates ( x 10^4) and isotropic displacement parameters (A^2 x 10^3) for S92.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1) | 2198 | 1570 | 8209 | 18 |
| H(3A) | 563 | 2604 | 4874 | 35 |
| H(3B) | 132 | 2719 | 6927 | 35 |
| H(3C) | -1137 | 2414 | 5796 | 35 |
| H(4) | 4830 | 2008 | 7307 | 19 |
| H(6A) | 8795 | 1175 | 10208 | 38 |
| H(6B) | 7226 | 1301 | 11505 | 38 |
| H(6C) | 9148 | 1528 | 11533 | 38 |
| H(7) | 6669 | 1543 | 5421 | 21 |
| H(8) | 3569 | 1295 | 3309 | 21 |
| H(9A) | 5874 | 893 | 6132 | 36 |
| H(9B) | 6281 | 920 | 3998 | 36 |
| H(9C) | 4480 | 699 | 4550 | 36 |
| H(11) | 2044 | 903 | 9685 | 29 |
| H(12) | 2683 | 404 | 11672 | 35 |
| H(14) | 2214 | -292 | 7289 | 34 |
| H(15) | 1550 | 204 | 5276 | 29 |
| H(16A) | 3610 | -229 | 12163 | 55 |
| H(16B) | 3543 | -510 | 10447 | 55 |
| H(16C) | 1660 | -413 | 11366 | 55 |




**296b**

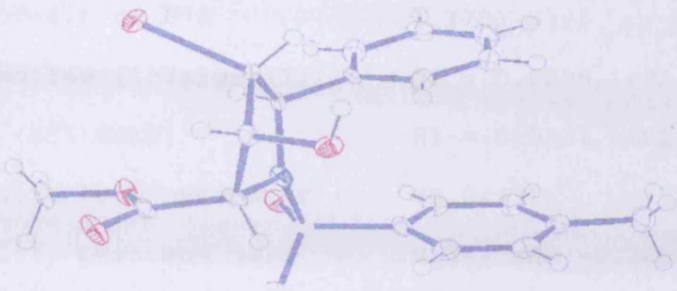


Table 1. Crystal data and structure refinement for 02DWK5.

| | |
|---|---|
| Identification code | s92 |
| Empirical formula | C19 H20 I N O5 S |
| Formula weight | 501.32 |
| Temperature | 150(2) K |
| Wavelength | 0.71073 A |
| Crystal system | Monoclinic |
| Space group | P2(1) |
| Unit cell dimensions | a = 7.3609(2) A alpha = 90 deg.<br>b = 11.7345(4) A beta = 107.3814(12) deg.<br>c = 11.7854(4) A gamma = 90 deg. |
| Volume | 971.50(5) A^3 |
| Z | 2 |
| Density (calculated) | 1.714 Mg/m^3 |
| Absorption coefficient | 1.786 mm^-1 |
| F(000) | 500 |
| Crystal size | 0.12 x 0.10 x 0.10 mm |
| Theta range for data collection | 2.92 to 27.47 deg. |
| Index ranges | -9<=h<=9, -15<=k<=12, -15<=l<=15 |
| Reflections collected | 8296 |
| Independent reflections | 3599 [R(int) = 0.0517] |

| | |
|---|---|
| Max. and min. transmission | 0.8416 and 0.8142 |
| Refinement method | Full-matrix least-squares on F^2 |
| Data / restraints / parameters | 3599 / 1 / 250 |
| Goodness-of-fit on F^2 | 1.170 |
| Final R indices [I>2sigma(I)] | R1 = 0.0295, wR2 = 0.0878 |
| R indices (all data) | R1 = 0.0331, wR2 = 0.1086 |
| Absolute structure parameter | -0.04(3) |
| Largest diff. peak and hole | 0.547 and -0.705 e.A^-3 |

Table 2. Atomic coordinates ( x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 02DWK5. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| I(1) | 1952(1) | 1684(1) | 190(1) | 20(1) |
| S(1) | 5845(2) | 3589(1) | -2553(1) | 15(1) |
| O(1) | 6780(6) | 2503(4) | -2516(4) | 21(1) |
| O(2) | 6977(6) | 4553(4) | -1967(4) | 20(1) |
| O(3) | 5438(7) | 4458(5) | 1130(4) | 27(1) |
| O(4) | 6395(7) | 2982(4) | 233(4) | 21(1) |
| O(5) | 783(6) | 4744(4) | -1931(4) | 19(1) |
| N(1) | 4124(7) | 3494(5) | -1961(4) | 15(1) |
| C(1) | 3985(8) | 4215(6) | -985(5) | 15(1) |
| C(2) | 5350(8) | 3905(6) | 242(5) | 16(1) |
| C(3) | 7543(10) | 2598(7) | 1383(6) | 31(2) |
| C(4) | 1935(8) | 4018(5) | -998(5) | 14(1) |
| C(5) | 1540(8) | 2759(5) | -1368(5) | 14(1) |
| C(6) | 2960(8) | 2423(5) | -2069(5) | 12(1) |
| C(7) | 2042(8) | 2095(5) | -3345(5) | 13(1) |
| C(8) | 2512(9) | 1077(6) | -3765(6) | 20(1) |
| C(9) | 1709(9) | 779(6) | -4962(6) | 22(1) |
| C(10) | 454(9) | 1527(8) | -5730(5) | 24(2) |
| C(11) | -44(9) | 2547(6) | -5296(5) | 21(1) |
| C(12) | 720(9) | 2829(5) | -4122(5) | 17(1) |
| C(13) | 4766(8) | 3946(6) | -4044(5) | 16(1) |
| C(14) | 3740(9) | 4964(6) | -4316(6) | 20(1) |
| C(15) | 2817(9) | 5231(6) | -5488(6) | 21(1) |
| C(16) | 2920(9) | 4509(6) | -6413(5) | 20(1) |
| C(17) | 3984(9) | 3520(6) | -6129(5) | 21(1) |
| C(18) | 4926(9) | 3221(5) | -4934(6) | 19(1) |
| C(19) | 1807(10) | 4802(7) | -7701(6) | 28(2) |

Table 3. Bond lengths [A] and angles [deg] for 02DWK5.

| | |
|---|---|
| I(1)-C(5) | 2.172(5) |
| S(1)-O(1) | 1.443(5) |

| | |
|---|---|
| S(1)-O(2) | 1.451(4) |
| S(1)-N(1) | 1.623(5) |
| S(1)-C(13) | 1.750(6) |
| O(3)-C(2) | 1.216(8) |
| O(4)-C(2) | 1.331(8) |
| O(4)-C(3) | 1.439(7) |
| O(5)-C(4) | 1.448(7) |
| O(5)-H(5) | 0.87(6) |
| N(1)-C(1) | 1.456(7) |
| N(1)-C(6) | 1.505(8) |
| C(1)-C(4) | 1.522(8) |
| C(1)-C(2) | 1.538(8) |
| C(1)-H(1) | 1.0000 |
| C(3)-H(3A) | 0.9800 |
| C(3)-H(3B) | 0.9800 |
| C(3)-H(3C) | 0.9800 |
| C(4)-C(5) | 1.543(9) |
| C(4)-H(4) | 1.0000 |
| C(5)-C(6) | 1.564(8) |
| C(5)-H(5A) | 1.0000 |
| C(6)-C(7) | 1.503(7) |
| C(6)-H(6) | 1.0000 |
| C(7)-C(8) | 1.376(8) |
| C(7)-C(12) | 1.413(8) |
| C(8)-C(9) | 1.401(9) |
| C(8)-H(8) | 0.9500 |
| C(9)-C(10) | 1.394(11) |
| C(9)-H(9) | 0.9500 |
| C(10)-C(11) | 1.392(11) |
| C(10)-H(10) | 0.9500 |
| C(11)-C(12) | 1.370(9) |
| C(11)-H(11) | 0.9500 |
| C(12)-H(12) | 0.9500 |
| C(13)-C(18) | 1.382(8) |
| C(13)-C(14) | 1.398(9) |
| C(14)-C(15) | 1.381(9) |
| C(14)-H(14) | 0.9500 |
| C(15)-C(16) | 1.400(9) |
| C(15)-H(15) | 0.9500 |
| C(16)-C(17) | 1.384(9) |
| C(16)-C(19) | 1.533(9) |
| C(17)-C(18) | 1.416(9) |
| C(17)-H(17) | 0.9500 |
| C(18)-H(18) | 0.9500 |
| C(19)-H(19A) | 0.9800 |
| C(19)-H(19B) | 0.9800 |
| C(19)-H(19C) | 0.9800 |

| | |
|---|---|
| O(1)-S(1)-O(2) | 118.2(3) |
| O(1)-S(1)-N(1) | 110.6(3) |
| O(2)-S(1)-N(1) | 105.0(3) |
| O(1)-S(1)-C(13) | 108.2(3) |
| O(2)-S(1)-C(13) | 108.4(3) |
| N(1)-S(1)-C(13) | 105.7(3) |
| C(2)-O(4)-C(3) | 115.2(5) |
| C(4)-O(5)-H(5) | 108(4) |
| C(1)-N(1)-C(6) | 112.3(4) |
| C(1)-N(1)-S(1) | 123.2(4) |
| C(6)-N(1)-S(1) | 121.3(4) |
| N(1)-C(1)-C(4) | 102.0(5) |
| N(1)-C(1)-C(2) | 115.2(5) |

| | |
|---|---|
| C(4)-C(1)-C(2) | 110.0(5) |
| N(1)-C(1)-H(1) | 109.8 |
| C(4)-C(1)-H(1) | 109.8 |
| C(2)-C(1)-H(1) | 109.8 |
| O(3)-C(2)-O(4) | 124.0(5) |
| O(3)-C(2)-C(1) | 122.4(6) |
| O(4)-C(2)-C(1) | 113.7(5) |
| O(4)-C(3)-H(3A) | 109.5 |
| O(4)-C(3)-H(3B) | 109.5 |
| H(3A)-C(3)-H(3B) | 109.5 |
| O(4)-C(3)-H(3C) | 109.5 |
| H(3A)-C(3)-H(3C) | 109.5 |
| H(3B)-C(3)-H(3C) | 109.5 |
| O(5)-C(4)-C(1) | 105.8(5) |
| O(5)-C(4)-C(5) | 109.3(4) |
| C(1)-C(4)-C(5) | 104.5(5) |
| O(5)-C(4)-H(4) | 112.3 |
| C(1)-C(4)-H(4) | 112.3 |
| C(5)-C(4)-H(4) | 112.3 |
| C(4)-C(5)-C(6) | 106.9(5) |
| C(4)-C(5)-I(1) | 110.5(3) |
| C(6)-C(5)-I(1) | 110.7(4) |
| C(4)-C(5)-H(5A) | 109.6 |
| C(6)-C(5)-H(5A) | 109.6 |
| I(1)-C(5)-H(5A) | 109.6 |
| C(7)-C(6)-N(1) | 111.9(5) |
| C(7)-C(6)-C(5) | 114.9(5) |
| N(1)-C(6)-C(5) | 101.5(4) |
| C(7)-C(6)-H(6) | 109.4 |
| N(1)-C(6)-H(6) | 109.4 |
| C(5)-C(6)-H(6) | 109.4 |
| C(8)-C(7)-C(12) | 119.6(5) |
| C(8)-C(7)-C(6) | 119.8(5) |
| C(12)-C(7)-C(6) | 120.6(5) |
| C(7)-C(8)-C(9) | 120.2(6) |
| C(7)-C(8)-H(8) | 119.9 |
| C(9)-C(8)-H(8) | 119.9 |
| C(10)-C(9)-C(8) | 119.6(6) |
| C(10)-C(9)-H(9) | 120.2 |
| C(8)-C(9)-H(9) | 120.2 |
| C(11)-C(10)-C(9) | 119.9(5) |
| C(11)-C(10)-H(10) | 120.0 |
| C(9)-C(10)-H(10) | 120.0 |
| C(12)-C(11)-C(10) | 120.4(6) |
| C(12)-C(11)-H(11) | 119.8 |
| C(10)-C(11)-H(11) | 119.8 |
| C(11)-C(12)-C(7) | 120.2(6) |
| C(11)-C(12)-H(12) | 119.9 |
| C(7)-C(12)-H(12) | 119.9 |
| C(18)-C(13)-C(14) | 121.0(5) |
| C(18)-C(13)-S(1) | 119.9(5) |
| C(14)-C(13)-S(1) | 119.1(5) |
| C(15)-C(14)-C(13) | 119.6(6) |
| C(15)-C(14)-H(14) | 120.2 |
| C(13)-C(14)-H(14) | 120.2 |
| C(14)-C(15)-C(16) | 121.1(6) |
| C(14)-C(15)-H(15) | 119.4 |
| C(16)-C(15)-H(15) | 119.4 |
| C(17)-C(16)-C(15) | 118.5(6) |
| C(17)-C(16)-C(19) | 121.6(6) |
| C(15)-C(16)-C(19) | 119.9(6) |

| | |
|---|---|
| C(16)-C(17)-C(18) | 121.4(6) |
| C(16)-C(17)-H(17) | 119.3 |
| C(18)-C(17)-H(17) | 119.3 |
| C(13)-C(18)-C(17) | 118.4(6) |
| C(13)-C(18)-H(18) | 120.8 |
| C(17)-C(18)-H(18) | 120.8 |
| C(16)-C(19)-H(19A) | 109.5 |
| C(16)-C(19)-H(19B) | 109.5 |
| H(19A)-C(19)-H(19B) | 109.5 |
| C(16)-C(19)-H(19C) | 109.5 |
| H(19A)-C(19)-H(19C) | 109.5 |
| H(19B)-C(19)-H(19C) | 109.5 |

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 02DWK5.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [ h^2 a*^2 U11 + ... + 2 h k a* b* U12 ]

| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| I(1) | 24(1) | 21(1) | 17(1) | 5(1) | 9(1) | -1(1) |
| S(1) | 9(1) | 20(1) | 15(1) | -2(1) | 4(1) | -2(1) |
| O(1) | 15(2) | 24(2) | 23(2) | -3(2) | 6(2) | 3(2) |
| O(2) | 14(2) | 24(2) | 22(2) | -8(2) | 7(2) | -7(2) |
| O(3) | 24(3) | 37(3) | 16(2) | -10(2) | -2(2) | -3(2) |
| O(4) | 16(2) | 29(3) | 15(2) | 0(2) | 0(2) | 5(2) |
| O(5) | 15(2) | 18(2) | 24(2) | 3(2) | 9(2) | 1(2) |
| N(1) | 11(2) | 23(3) | 11(2) | -6(2) | 5(2) | -2(2) |
| C(1) | 13(3) | 18(3) | 15(3) | -8(2) | 4(2) | -3(2) |
| C(2) | 10(3) | 21(3) | 15(3) | 0(2) | 0(2) | -1(2) |
| C(3) | 20(3) | 45(5) | 16(3) | 7(3) | -11(2) | -5(3) |
| C(4) | 8(2) | 18(3) | 14(3) | 3(2) | 1(2) | 4(2) |
| C(5) | 13(3) | 17(3) | 9(2) | 4(2) | 0(2) | -3(2) |
| C(6) | 12(3) | 16(3) | 7(2) | 0(2) | 0(2) | 0(2) |
| C(7) | 9(3) | 15(3) | 12(3) | -3(2) | 0(2) | -3(2) |
| C(8) | 17(3) | 24(4) | 22(3) | 3(3) | 9(2) | 8(3) |
| C(9) | 27(3) | 21(3) | 21(3) | -12(3) | 11(3) | -7(3) |
| C(10) | 25(3) | 33(5) | 14(2) | -9(3) | 7(2) | -8(3) |
| C(11) | 20(3) | 23(3) | 18(3) | 4(3) | 4(2) | -1(3) |
| C(12) | 15(3) | 18(3) | 19(3) | 2(2) | 6(2) | 3(2) |
| C(13) | 10(3) | 24(3) | 14(3) | 0(2) | 4(2) | -1(2) |
| C(14) | 24(3) | 16(3) | 22(3) | -3(2) | 10(3) | -1(2) |
| C(15) | 22(3) | 16(3) | 26(3) | -2(3) | 12(2) | -1(2) |
| C(16) | 22(3) | 24(3) | 15(3) | -1(2) | 9(2) | -5(3) |
| C(17) | 27(3) | 21(3) | 17(3) | -8(2) | 11(2) | -3(3) |
| C(18) | 19(3) | 17(3) | 22(3) | -2(2) | 8(2) | 1(2) |
| C(19) | 30(4) | 34(4) | 19(3) | 4(3) | 7(3) | -2(3) |

Table 5. Hydrogen coordinates ( x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 02DWK5.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(5) | -400(90) | 4610(50) | -2010(50) | 0(13) |
| H(1) | 4166 | 5031 | -1170 | 18 |
| H(3A) | 8529 | 3166 | 1730 | 46 |
| H(3B) | 8145 | 1871 | 1298 | 46 |
| H(3C) | 6737 | 2495 | 1903 | 46 |
| H(4) | 1740 | 4182 | -210 | 17 |
| H(5A) | 203 | 2678 | -1897 | 16 |
| H(6) | 3794 | 1786 | -1646 | 15 |
| H(8) | 3383 | 575 | -3242 | 25 |
| H(9) | 2018 | 70 | -5249 | 27 |
| H(10) | -60 | 1342 | -6548 | 29 |
| H(11) | -918 | 3049 | -5817 | 25 |
| H(12) | 359 | 3521 | -3830 | 21 |
| H(14) | 3678 | 5469 | -3699 | 24 |
| H(15) | 2099 | 5915 | -5670 | 25 |
| H(17) | 4085 | 3031 | -6750 | 25 |
| H(18) | 5650 | 2539 | -4748 | 22 |
| H(19A) | 544 | 5090 | -7731 | 41 |
| H(19B) | 1670 | 4117 | -8195 | 41 |
| H(19C) | 2496 | 5387 | -8001 | 41 |

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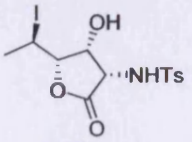
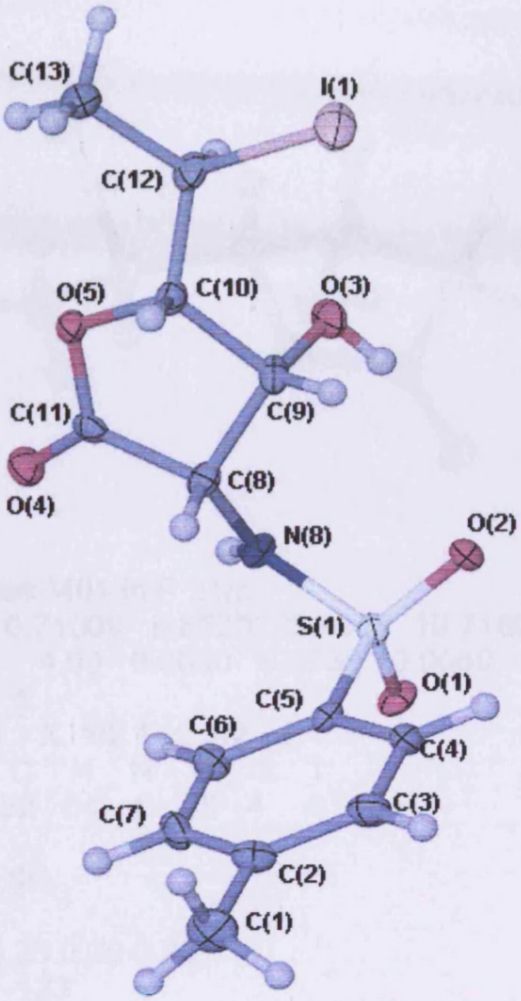
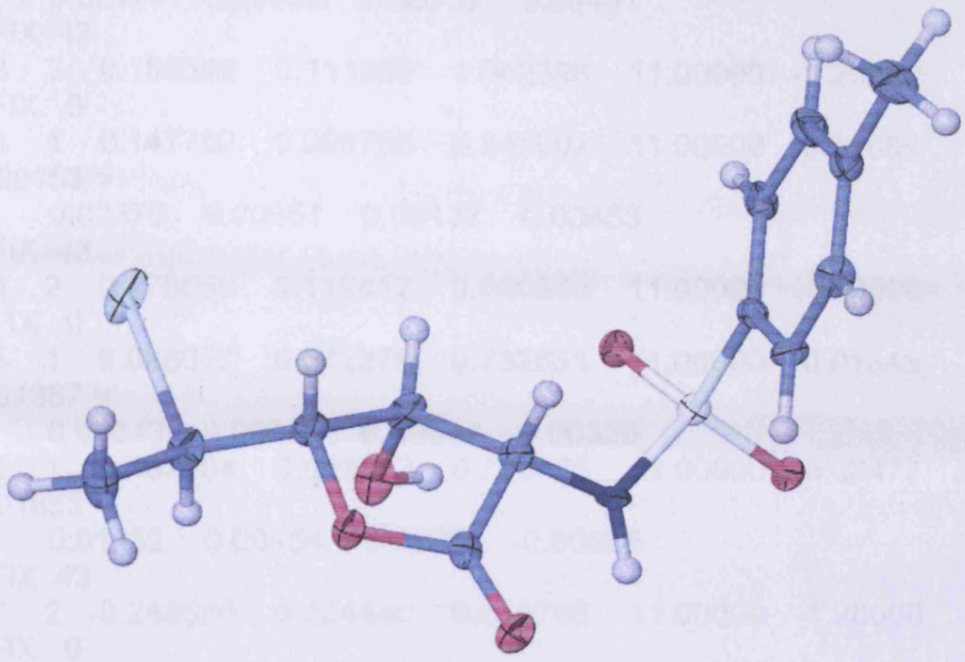

OH
NHTs
O
O

**326a**


C(13)
I(1)
C(12)
O(5)
C(10)
O(3)
C(11)
C(9)
O(4)
C(8)
N(8)
O(2)
S(1)
O(1)
C(5)
C(6)
C(4)
C(7)
C(3)
C(2)
C(1)



```
TITL dwk0401 in P 21/c
CELL  0.71069   5.8520  26.4610  10.2180   90.000  104.118   90.000
ZERR    4.00   0.0050   0.0050   0.0050    0.005    0.005    0.005
LATT  1
SYMM  - X, 1/2 + Y, 1/2 - Z
SFAC  C   H   N   O   S   I
UNIT  52  64  4   20  4   4
CONF
BOND $H
ACTA
SIZE 0.20 0.20 0.23
TEMP -123
REM colourless block
L.S.  4
WGHT    0.037100
FVAR      0.10493
C1    1  -0.206148    0.062280    1.098499    11.00000    0.03895
0.04544 =
      0.02351    0.00215    0.01557    0.00201
AFIX 137
H1A   2  -0.312564    0.090651    1.101159    11.00000   -1.50000
H1B   2  -0.071036    0.063990    1.176934    11.00000   -1.50000
H1C   2  -0.290375    0.030378    1.100337    11.00000   -1.50000
AFIX   0
C2    1  -0.120097    0.065101    0.969987    11.00000    0.03065
0.02105 =
      0.01959    0.00250    0.00844    0.00277
C3    1   0.073441    0.094487    0.964168    11.00000    0.03036
0.02833 =
```

```
     0.02127   0.00538   0.00757   0.00161
AFIX 43
H3   2   0.156648   0.111950   1.042598   11.00000  -1.20000
AFIX  0
C4   1   0.147702   0.098785   0.845002   11.00000   0.02089
0.02153 =
     0.02376   0.00551   0.00137  -0.00453
AFIX 43
H4   2   0.278668   0.119412   0.840945   11.00000  -1.20000
AFIX  0
C5   1   0.026077   0.072279   0.732651   11.00000   0.01345
0.01887 =
     0.01643   0.00002   0.00034   0.00325
C6   1  -0.167504   0.042572   0.736485   11.00000   0.02477
0.01853 =
     0.01952  -0.00454   0.00593  -0.00305
AFIX 43
H6   2  -0.248686   0.024440   0.658765   11.00000  -1.20000
AFIX  0
C7   1  -0.240588   0.039764   0.855465   11.00000   0.01826
0.02519 =
     0.03092   0.00237   0.01129  -0.00378
AFIX 43
H7   2  -0.375270   0.020172   0.858425   11.00000  -1.20000
AFIX  0
C8   1  -0.290497   0.117440   0.458470   11.00000   0.01555
0.02105 =
     0.02203  -0.00118   0.00331   0.00397
AFIX 13
H8   2  -0.333491   0.117792   0.547368   11.00000  -1.20000
AFIX  0
C9   1  -0.225354   0.170597   0.423907   11.00000   0.01403
0.01752 =
     0.03202  -0.00379   0.00432  -0.00119
AFIX 13
H9   2  -0.134452   0.189144   0.505321   11.00000  -1.20000
AFIX  0
C10  1  -0.470954   0.193598   0.368260   11.00000   0.01694
0.01804 =
     0.02556  -0.00113  -0.00078  -0.00137
AFIX 13
H10  2  -0.534182   0.205880   0.445060   11.00000  -1.20000
AFIX  0
C11  1  -0.508461   0.106792   0.346503   11.00000   0.02019
0.01983 =
     0.02032   0.00527   0.01120  -0.00033
C12  1  -0.491710   0.234982   0.265358   11.00000   0.01524
0.02445 =
     0.03531   0.00132   0.00351   0.00457
AFIX 13
```

```
H12  2  -0.419163   0.223149   0.191736   11.00000  -1.20000
AFIX  0
C13  1  -0.744397   0.251668   0.202847   11.00000   0.02532
0.03418 =
     0.04716   0.01731   0.00052   0.00042
AFIX 137
H13A 2  -0.832467   0.223553   0.151751   11.00000  -1.50000
H13B 2  -0.743312   0.280294   0.142147   11.00000  -1.50000
H13C 2  -0.819683   0.261873   0.274498   11.00000  -1.50000
AFIX  0
N8   3  -0.116506   0.077975   0.458772   11.00000   0.01625
0.01953 =
     0.01198  -0.00597  -0.00015   0.00186
AFIX 43
H8A  2  -0.139199   0.055498   0.393390   11.00000  -1.20000
AFIX  0
O1   4   0.240123   0.030318   0.562790   11.00000   0.01798
0.01892 =
     0.02361  -0.00227   0.00252   0.00887
O2   4   0.241423   0.123370   0.580437   11.00000   0.02047
0.01720 =
     0.02408   0.00311   0.00552  -0.00318
O3   4  -0.109197   0.171339   0.317924   11.00000   0.01609
0.02704 =
     0.04464   0.00778   0.01294   0.00367
AFIX 147
H3A  2   0.021251   0.156562   0.342806   11.00000  -1.50000
AFIX  0
O4   4  -0.583245   0.066851   0.299919   11.00000   0.02326
0.01842 =
     0.03381  -0.00101   0.00726  -0.00151
O5   4  -0.614524   0.151251   0.302220   11.00000   0.01392
0.01765 =
     0.02844   0.00256   0.00408   0.00118
S1   5   0.119889   0.076030   0.581421   11.00000   0.01565
0.01637 =
     0.02070  -0.00040   0.00495  -0.00067
I1   6  -0.293084   0.299638   0.364947   11.00000   0.02760
0.02057 =
     0.06649   0.00050   0.00311   0.00038
HKLF  4

REM  dwk0401 in P 21/c
REM R1 =  0.0482 for   1907 Fo > 4sig(Fo)  and  0.1297 for all   3450 data
REM    193 parameters refined using      0 restraints

END

WGHT     0.0366     0.0000
REM Highest difference peak  0.747,  deepest hole -1.046,  1-sigma level
```

0.175 Q1 1 -0.4350 0.0582 1.0903 11.00000 0.05 0.75 Q2 1
-0.1029 0.1981 0.4403 11.00000 0.05 0.64 Q3 1 -0.4371 0.1483
1.1127 11.00000 0.05 0.61 Q4 1 0.4501 0.0700 0.7030 11.00000
0.05 0.60 Q5 1 -0.1435 0.0375 0.4579 11.00000 0.05 0.59 Q6
1 -0.3240 0.3216 0.4357 11.00000 0.05 0.59 Q7 1 -0.2229
0.0538 0.7397 11.00000 0.05 0.59 Q8 1 -0.4667 0.0307 0.2409
11.00000 0.05 0.59 Q9 1 -0.8725 0.2988 -0.0029 11.00000 0.05
0.58 Q10 1 -0.3854 0.1208 1.1385 11.00000 0.05 0.57 Q11 1
-0.0440 0.0570 0.7548 11.00000 0.05 0.57 Q12 1 -0.6638 0.0231
0.3393 11.00000 0.05 0.56 Q13 1 0.1501 0.1889 0.3873 11.00000
0.05 0.56 Q14 1 0.3559 0.1246 0.8093 11.00000 0.05 0.56 Q15
1 -0.7084 0.1623 0.2589 11.00000 0.05 0.54 Q16 1 -0.3320
0.1298 0.2522 11.00000 0.05 0.54 Q17 1 -0.4545 0.2465 0.1378
11.00000 0.05 0.54 Q18 1 0.2437 0.0592 0.7958 11.00000 0.05
0.53 Q19 1 -1.0955 0.3012 0.2047 11.00000 0.05 0.53 Q20 1
-0.0270 0.0573 1.2571 11.00000 0.05 0.53