Novel Approaches Towards Pyrrolidines and Piperidines

by

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This thesis is dedicated to

Mum and Dad

Declaration

The research described in this thesis is, to the best of my knowledge, original except where due reference is made to other authors. The work described has not been submitted in any part or form for a degree at this or any other university.

Acknowledgements

I should like to express my sincere thanks to my supervisor Prof. Keith Jones for giving me the opportunity to work in his research group; for his enthusiasm, advice, endless patience and encouragement throughout the years.

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To each of the above, I extend my deepest appreciation.

Abstract

During recent years, there has been considerable interest in the synthesis of pyrrolidines and piperidines as they occur in a variety of natural products ranging from simple monocyclic alkaloids to complex polycyclic molecules. This thesis begins with a selective review of various approaches towards the syntheses of 5- and 6-membered nitrogen containing heterocycles.

The first approach investigated utilises a tandem Michael-Dieckmann reaction towards pyrrolidines, starting with α-amino acids. The aim was to investigate the stereochemical outcome of the Michael-Dieckmann sequence, as this would provide a valuable and efficient approach to the synthesis of highly functionalised pyrrolidines in high enantiomeric excess. In order to gain insight into the stereochemical integrity of the pyrrolidinone, a related compound with known optical rotation was synthesised. The Michael-Dieckmann cyclisation sequence gave pyrrolidines in good yields with encouraging enantiomeric excess. This chemistry was extended towards a formal total synthesis of (-)-anisomycin.

A potential route to the synthesis of a portion of the alkaloid germine is presented. This utilises an aza-annulation reaction of a nitroenamine to create a bicyclic quinolizidine.

Finally, a titanium-mediated radical cyclisation has been developed for the synthesis of pyrrolidines. This reaction uses the titanium-mediated opening of an epoxide to generate a carbon-centered radical, which adds to an alkyne. Various *N*-protecting groups are explored.

Full experimental and spectroscopy data is given for all new and key intermediary compounds.

Abbreviations

Ac	acetyl
ADDP	1,1'-(azodicarbonyl)dipiperidine
AIBN	azoisobutyronitrile
Ar	aryl
Bn	benzyl
^{t}BOC	*tert*-butyloxycarbonyl
Bu^{t}	*tert*-butyl
Bu	butyl
CBZ	benzyloxycarbonyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarization transfer
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyl dioxirane
DMSO	dimethylsulfoxide
DMF	*N,N*-dimethylformamide
DMP	2,2-dimethoxypropane
Et	ethyl
EtOAc	ethyl acetate
GC-MS	gas chromatography-mass spectrometry
HPLC	high performance liquid chromatography
IR	infra red
LAH	lithium aluminium hydride
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MOM-Cl	4-methoxybenzyl magnesium chloride
mp	melting point
Ms	methanesulfonyl

MSH	*ortho*-methylenesulfonylhydroxylamine
m/z	mass to charge ratio
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Nuc	nucleophile
Ph	phenyl
PPTS	pyridinium *p*-toluenesulfonate
PTSA	toluene-*p*-sulfonic acid
R_f	retention factor
rt	room temperature
TBDMS	*tert*-butyldimethylsilyl
TBP	*tri*-butylphosphine
TBTH	tributyltin hydride
THF	tetrahydrofuran
TLC	thin layer chromatography
Tol	*p*-tolyl
UV	ultra violet

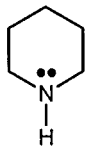
Contents

CHAPTER I

Pyrrolidines and Piperidines

1.1 Introduction.

The pyrrolidine and piperidine ring systems (Figure 1.1) are the nitrogen-containing equivalents of cyclopentane and cyclohexane. Nitrogen-containing heterocycles can also be referred to as azacycles. During recent years, there has been considerable interest in the synthesis of molecules containing these subunits as they occur in a variety of natural products ranging from simple monocyclic alkaloids to complex polycyclic molecules of chemical and biological interest. Analogues of these naturally occurring compounds would be expected to possess modified biochemical properties, and hence potential pharmacological value.



pKa 11.29

Piperidine

pKa 11.27

Pyrrolidine

Figure 1.1.

Pyrrolidines are of considerable pharmaceutical and biological importance because of their antibiotic, antibacterial, antifungal and cytotoxic effects, e.g pramanicin, preussin, anisomycin and the kanoids. Owing to their presence in alkaloids and other bioactive compounds, homochiral pyrrolidines are starting materials for natural,[1] as well as nonnatural compounds.[2,3] Molecules containing an (*S*)-proline derived pyrrolidine ring have been used as chiral auxiliaries.[4] Functionalised piperidines are among the most ubiquitous heterocyclic subunits in natural products and synthetic compounds with important biological activities. With respect to biologically active target molecules, there is an increasing interest in the diastereo- and enantioselective synthesis of piperidines.

The related pyrrolizidine, indolizidine and quinolizidine alkaloids are also of importance from an agricultural and medicinal viewpoint. The pyrrolidine and piperidine skeletons (Figure 1.2) can be seen in numerous natural products such as hygroline (**1**), coniine (**2**)[5], through more complex pyrrolidines such as the neurotoxin kainic acid (**3**) to more complex pyrrolidine-containing oxindole alkaloids such as elacomine (**4**) or the piperidine-containing natural product germine (**5**).

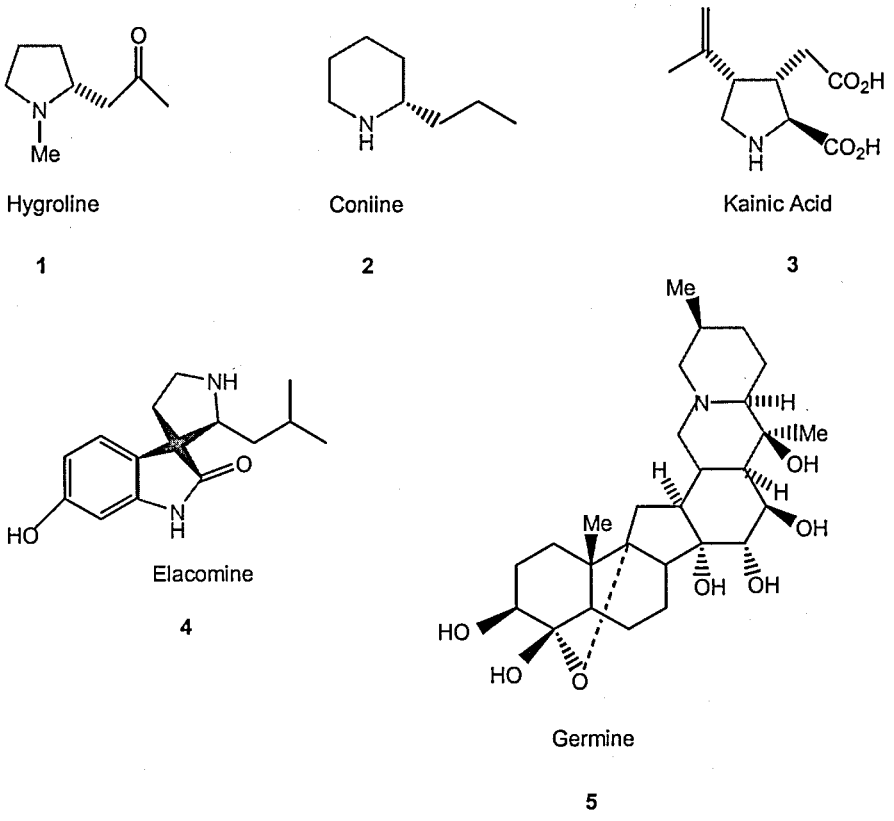


Figure 1.2.

Pyrrolidine and piperidine are examples of non-aromatic heterocyclic amines and have basicities that are approximately the same as those of acyclic amines. The nitrogen atom of both these amines is very similar to that of ammonia, as they are sp^3-hybridised. The three substituents occupy corners of a tetrahedron; the sp^3-orbital containing the unshared electron pair is directed toward the other corner. Owing to this conformation, the geometry of these amines by location of its atoms is described as trigonal pyramidal. The pKa values of pyrrolidine and piperidine are 11.27 and 11.29 respectively, typical of amine bases and are slightly stronger than open-chain bases such as diethylamine (10.98). This means that in aqueous solution at pH 11.27 pyrrolidine is 50% protonated. These values will vary according to solvent and other factors. To what extent the properties of both

pyrrolidine and piperidine heterocycles differ from those of analogous open-chain compounds will be discussed.

1.2 The stability of cyclic molecules.

We can recognise that the size of the ring system and the overall shape of the molecule are the most important factors that will distinguish the cyclic and the acyclic compounds. The existence of a ring system imposes constraints on the molecule, which may be absent in the acyclic model. The greater these constraints, the more likely there will be differences in properties between the cyclic and the acyclic systems. Flexible molecules preferentially adopt conformations in which the bonding interactions are maximised and repulsive non-bonding interactions are minimised. If the presence of a ring system compels the molecule to adopt a structure in which these preferred features cannot be attained, the molecule can be regarded as *strained*.[6] Strain introduced in a molecule in any fashion tends to be minimised by becoming distributed among several modes, such as bond strain, angle strain, torsional strain and van der Waals compression. The division is an arbitrary one because the components of strain are interdependent and changes in any one component affect the others. Owing to the fact that the strain in cyclanes is actually not purely angle strain, it becomes desirable to define strain in an entirely different manner, in terms of energy. The chair conformation adopted by cyclohexane and its derivatives is also the preferred one for six-membered heterocycles (Figure 1.3). The conformational energy barrier to ring inversion in piperidine is very similar to that in cyclohexane, as are those in other simple six-membered heterocycles.[7]

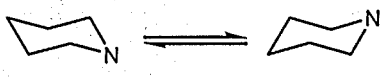


Figure 1.3. Ring inversion in six-membered heterocycles.

Piperidine undergoes a complicated set of conformational changes because two different types of change occur: tetrahedral inversion of the nitrogen substituents, and ring inversion. These conformational changes are shown for piperidine in Figure 1.4. Tetrahedral inversion at nitrogen is the lower energy process. The

invertomer in which the NH group is equatorial is more stable both in the gas phase and in solution.[8] Alkyl groups attached to nitrogen also preferentially occupy equatorial positions: for *N*-methylpiperidine the energy difference between conformers having axial and equatorial methyl is 2.7 kcal mol $^{-1}$ (11.3 kJ mol^{-1}).

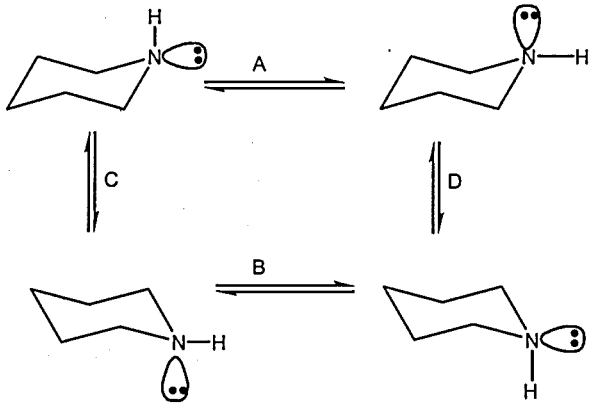


Figure 1.4.

Processes A and B involve pyramidal inversion at nitrogen; processes C and D are ring inversions. The strong preference is for conformations with an axial lone pair and an equatorial alkyl substituent at nitrogen. The conformations adopted by substituted piperidines are governed by the same principles as substituted cyclohexanes, for example, bulky substituents on carbon preferentially adopt an equatorial orientation.

There are two reasons why the axial conformer is higher in energy than the equatorial conformer. The first is that the axial conformer is destabilised by the repulsion between the axial group R and the two axial hydrogen atoms on the same side of the ring. This interaction is known as the 1,3-diaxial interaction, (Figure 1.5). As the R group gets larger, this interaction becomes more severe and there is less of the conformer with the R group axial. The second reason is that in the equatorial conformer the C-R bond is anti-periplanar to two C-C bonds, while, for the axial conformer, the C-R bond is syn-clinal to two C-C bonds.

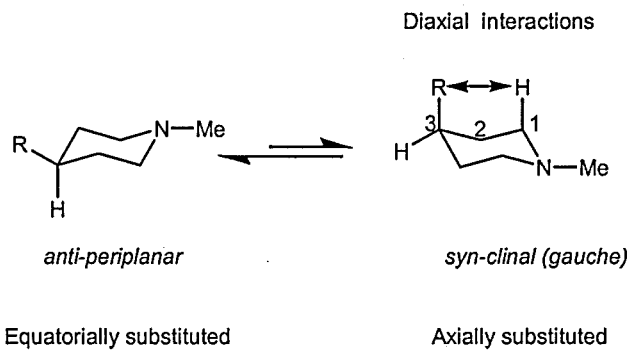


Figure 1.5.

The strong preference for conformations with an axial lone pair and an equatorial alkyl substituent at nitrogen is also seen in the bicyclic system, for which the *transoid* conformation (**6**) is more stable than the *cisoid* conformation (**7**).[9]

6 **7**

The conformation of five-membered ring systems is more complicated. Cyclopentane might be expected to be planar, since the angles of a regular pentagon are 108°, but it is not so, also because of eclipsing effects. There are two puckered conformations, the *envelope* (**8**) and the *half-chair* (**9**) (Figure 1.6). There is little energy difference between these two forms and many five-membered ring systems have conformations somewhere between them.[10] Although in the envelope conformation one carbon is shown above the others, ring motions cause each of the carbons in rapid succession to assume this position. The puckering rotates around the ring in what may be called a *pseudorotation.*[11] In substituted cyclopentanes and five-membered rings in which at least one atom does not contain two substituents (such as cyclopentanone) one conformer may be more stable than the other. Conformations of saturated heterocycles are qualitatively similar to those of analogous carbocycles but with modifications resulting from different torsional barriers. Consequently, the conformation of pyrrolidines is not easy to analyse.

8 9

Figure 1.6.

1.3 Ring synthesis.

For many of the common ring systems, there is a wide range of practical synthetic routes. These can vary in complexity from one-step syntheses using a single reaction component to multi-component procedures with a large number of steps. Some useful heterocyclic syntheses involve the conversion of one ring system into another by heat, by irradiation, or by the use of additional reagents. The method of choice in a particular case usually depends upon the pattern of substituents required in the product.

The types of ring-forming reactions available are not usually limited to a particular heterocycle but apply to a range of structures. The precursor components are varied to incorporate the appropriate heteroatoms and substituents, but the nature of the ring-closure reaction is usually more dependent upon the size of the ring being formed and its degree of unsaturation than upon the types of heteroatom present. It is therefore appropriate that we treat these ring-forming reactions as general methods.

The types of ring-forming reaction available can be divided into two broad groups. Reactions, in which a single ring bond is formed in the ring-closure process, are called *cyclisation* reactions, whereas those in which two ring bonds are formed, and in which no small molecules are eliminated in the process, are called *cycloaddition* reactions. This classification will be used although it is over-simplified. In practice, there is not always a clear-cut distinction between the two groups and in many heterocyclic syntheses, the timing of the steps is uncertain. It is also important to appreciate that the ring-closure step in a multi-step reaction sequence may not be the most difficult one; indeed, many such ring-closures are fast relative to the other steps in the sequence and so the 'cyclisation precursor' may not be detectable. A "ring-closure" reaction is one in which a new covalent bond is formed in the cyclisation process. The stereochemical demands on an equilibrium ring closure reaction can be more severe than simple proximity of the

reactants attached to the chain termini. The angular relationship between the reactants must correspond to the bond angle of the appropriate atoms in the product or reaction transition state. Thus, it is necessary to distinguish this term from the more general term "cyclisation" reaction.[12]

In designing a synthesis of a particular heterocycle, we need to consider (a) which bonds are most conveniently made in the ring-forming step, (b) what degree of unsaturation is required in the heterocycle, and whether or not the oxidation state can easily be altered after the formation of the ring, and (c) what functional groups are required, and whether they are best introduced before, during, or after the ring-closure step. Regarding the first point, we will consider the major ring-forming reactions and some of their limitations. As for the second point, we can recognise that further unsaturation can often be introduced after the formation of the ring, especially when the target compound is aromatic in character and that double bonds can often be reduced without causing ring cleavage. Thus, it is not always necessary to arrive at the correct oxidation state in the ring-forming step. In order to deal with the final point we need to know more about the properties of the particular heterocycle in question, but some useful generalisations will be illustrated.

1.4 Principles of cyclisation reactions.

Effect of Ring Size:

In order to decide whether a particular ring system can be prepared efficiently by one of these cyclisation processes, it is necessary to take into consideration the size of the ring being formed and the nature of the transition state leading to its formation. The free energy of activation $\Delta G^{\ddagger}$ for the cyclisation process is made up of enthalpy of activation ($\Delta H^{\ddagger}$) and entropy of activation ($T\Delta S^{\ddagger}$) (T being the absolute temperature).

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$

The entropy of activation for the intramolecular process is related to the probability of the two ends of the chain approaching each other. This probability decreases (and $\Delta S^{\ddagger}$ has a larger negative value) as the chain length increases. The

enthalpy of activation reflects the strain in the transition state leading to the product. This is generally lowest for the formation of five- and six- membered rings and somewhat higher for the formation of the more strained three- and four-membered rings. The $\Delta H^{\ddagger}$ values are also high for the formation of rings of medium size (of eight to eleven members) because of non-bonded interactions in these rings. The free energies of activation for medium sized rings are also high and it is therefore often difficult to form these rings efficiently by cyclisation processes. When comparing five- and six-membered rings exclusively, the activation energy is less for the formation of the five-membered ring, hence this ring is formed faster (i.e., it is the product of kinetic control: $k_5 > k_6$). However, the reaction is reversible and the six-membered ring is slightly more stable, so after some time it will become the major product (product of thermodynamic control).

The relative thermodynamic instability of medium size rings has made their derivatives relatively difficult to obtain, the first successful general synthesis (acyloin reaction) having been described only in the 1940s[13] although, since then, numerous preparations have been developed. Large rings, despite their low strain, present synthetic difficulties also. It was recognised many years ago[14] that a complicating factor is the difficulty of getting the ends of a long chain to approach each other: the conformational entropy of a chain compound is greater than that of a ring. A competing reaction in ring closure tends to be dimerisation or oligomerisation, since, if in $X(-CH_2-)_n-Y$ the functional groups X and Y are capable of interacting to form a ring, there is also the possibility of similar interaction between two molecules to form a dimer. These competing reactions are not much of a problem in small and common ring compounds where the loss of translational entropy in a dimerisation or oligomerisation reaction tends to be much more severe than the loss of conformational entropy in cyclisation. This situation is reversed in medium and especially in large rings, where the possibility of rotation about a large number of bonds leads to a high conformational entropy in the open-chain precursor as well as the linear dimer or oligomer, which is largely lost in the cyclic product. Cyclisation leading to such rings must frequently be carried out under high dilution, where bimolecular reactions tend to be suppressed (but, unfortunately, operating conditions make for long reaction times).[15]

Although a great deal of synthetic and qualitative information on medium and large rings is available, quantitative data on ring closure is more limited. For example, the entropies of formation of cyclanes are available only up to C_8; from data, the following entropies of ring closure can be computed (Table 1.1).[16]

Cycloalkane	Cal mol^{-1} K^{-1}	J mol^{-1} K^{-1}
Cyclopropane	-7.7	-32.2
Cyclobutane	-10.9	-45.6
Cyclopentane	-13.3	-55.6
Cyclohexane	-21.2	-88.7
Cycloheptane	-19.8	-82.8
Cyclooctane	-19.0	-79.5

Table 1.1. Entropy changes accompanying cyclisation.

The sharp drop for cyclohexane formation reflects the stiffness (or deep energy well) of this ring system compared to the flexibility of cyclopentane, cycloheptane and cyclooctane rings, but it is not clear from the data if the negative entropy of cyclisation has come to a plateau with the eight-membered ring or whether it drops further for larger rings.

Rates of ring-closure and corresponding activation enthalpies and entropies for closure of three- to five-membered rings are shown in (Table 1.2).[17] These values refer to the cyclisation rates of anions derived from ω-halodisulfones. The specific rate is very high for three- and five-membered rings and much lower for four-membered ones. However, the high rate of ring-closure in the five-membered ring is due to a relatively low activation enthalpy (reflecting the low amount of strain in the five-membered ring), whereas the high rate for the three-membered ring (which is quite strained) is due to a very favourable activation

entropy. The two ends of the ring are always favourably disposed for ring formation, but, of course, the C-C-C bond angle needs to be deformed, which causes the unfavourable activation enthalpy. The four-membered ring loses out on both grounds (the ends are apart in the more stable anti conformation of the open-chain precursor, hence unfavourable enthalpy). It is perhaps somewhat surprising that the enthalpy of activation for its formation is higher than that for the three-membered ring, but the difference is small.

Ease of ring closure is usually in the order three-, five-membered greater than four- or six-membered rings, in part for the reasons just discussed. Since the high rate of ring closure of three- and five-membered rings is based on different factors, predictions as to which closure will occur more rapidly in a given case are unsafe. Six-membered rings usually cyclise less rapidly than five-membered rings, but a firm prediction on this point is risky since the strain in the six-membered ring is appreciably less; however, this is usually more than out-weighed by the much greater loss of entropy in the formation of the six-membered ring. A factor that must be considered is thermodynamic versus kinetic control; since six-membered rings tend to be more stable than five-membered rings, their formation may be favoured thermodynamically, even if not kinetically.

	3	4	5
$K(s^{-1})$	9.05×10^{-1}	6.05×10^{-6}	1.49×10^{-2}
$\Delta H^{\ddagger a}$	20.5 (85.7)	21.8 (91.2)	16.3 (68.2)
$\Delta S^{\ddagger b}$	+10.0 (+42)	-9.3 (-39)	-12.2 (-51)

Table 1.2. Rates of Ring Closure of $(C_6H_5SO_2)_2C(CH_{2)n-1}Cl$

[a] In kilocalories per mole (kcal mol^{-1}); data in parentheses are in kilojoules per mole (kJ mol^{-1}).

[b] In calories per mole kelvin (cal $mol^{-1}K^{-1}$); data in parentheses are in joules per mole kelvin (J $mol^{-1}K^{-1}$).

1.5 Rules for cyclisation reactions.

When synthesising cyclic compounds two different approaches may be generally employed. They may be prepared from acyclic precursors, or alternatively a readily available cyclic molecule may be used as a template upon which to build further rings, this is known as an annulation procedure. Cyclisation reactions can involve any intramolecular versions of the common σ-bond-forming processes. By far the most common are those in which a nucleophilic atom interacts with an electrophile. Baldwin studied many nucleophilic, radical and cationic ring closure reactions and developed a set of guidelines that can be used to successfully predict the outcome of such cyclisation reactions. The physical basis of the guidelines lie in the stereochemical requirements and the angles of approach for bringing together two reactive centres when they are connected together by a chain of atoms. If the length and nature of the chain linking terminal atoms X and Y allows the attainment of a certain geometry, then ring formation is favoured. If not then ring formation is disfavoured and generally, alternative or competitive processes dominate. This classification is based on three features of the reaction and is known as Baldwin's rules (Figure 1.7).[14]

The ring size, being the number of atoms constituting the skeleton of the cycle is represented using a numerical prefix.

Whether the bond that breaks as the ring forms is inside (*endo*) or outside (*exo*) the new ring.

Whether the atom to which the ring forms is an sp (digonal), sp^2 (trigonal), or sp^3 (tetrahedral) atom

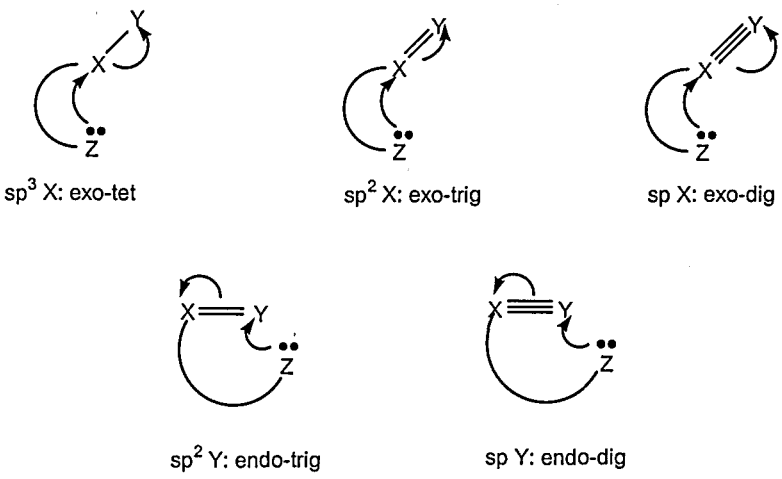
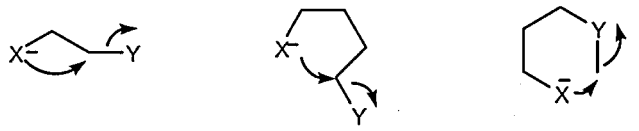


Figure 1.7. Types of nucleophile-electrophile cyclisation.

1.5.1 Baldwin's guidelines are as follows:

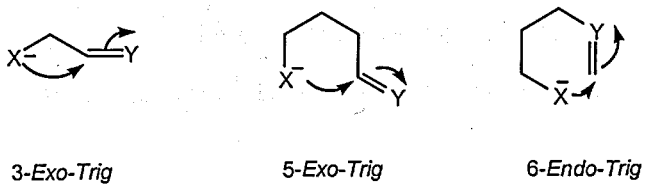
Guideline 1: Tetrahedral Systems:



(a) 3 to 7–*Exo-Tet* are all favoured processes;

(b) 5 to 6-*Endo-Tet* are disfavoured.

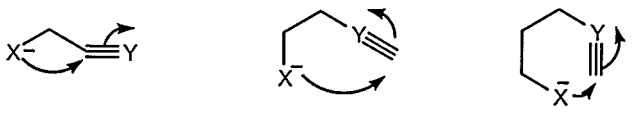
Guideline 2: Trigonal Systems:



(a) 3 to 7-*Exo-Trig* are all favoured processes;

(b) 3 to 5-*Endo-Trig* are disfavoured, 6 to 7-*Endo-Trig* are favoured.

Guideline 3: Digonal Systems:

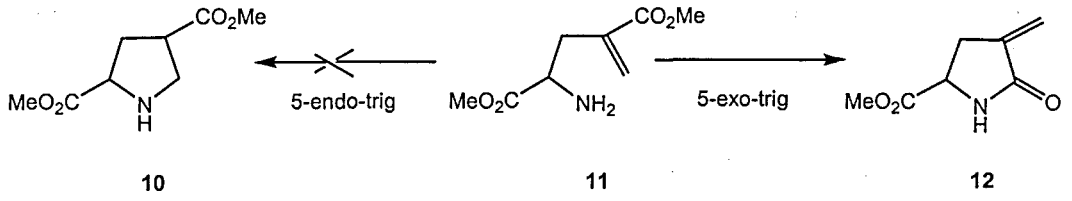


3-*Exo-Dig* 5-*Endo-Dig* 6-*Endo-Dig*

(a) 3 to 4-*Exo-Dig* are disfavoured processes; 5 to 7-*Exo-Dig* are favoured;

(b) 3 to 7-*Endo-Dig* are favoured.

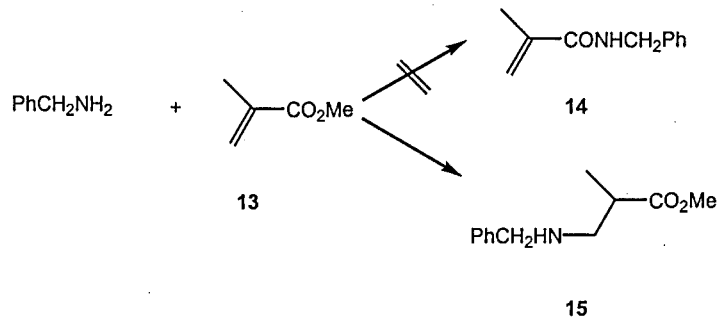
An example of intramolecular addition of a nucleophile to a double bond is illustrated in Scheme 1.1. The amino-diester (**11**), upon release from its stable hydrochloride salt rapidly closed at 25 °C to the lactam (**12**) in 100% yield via the favoured 5-*exo-trig* pathway. The amino-diester (**11**) is not able to obtain the correct angle of appraoch to close by 1,4-Michael additon to give (**10**).



10 **11** **12**

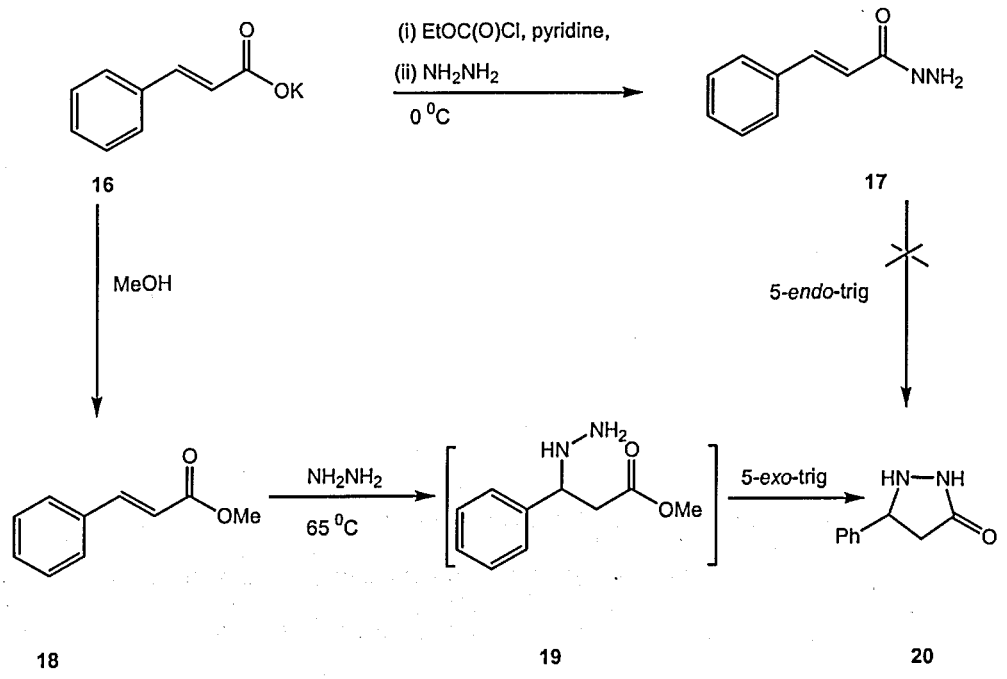
Scheme 1.1 Example of exo-cyclisation onto a trigonal centre.

It is known that primary amines add in a 1,4-manner to α-substituted acrylic esters (**13**) to (**15**) more rapidly than they are transacylated to α-substituted acrylamides, (**13**) to (**14**) (Scheme 1.2).[18] Thus, the conversion of (**11**) into the lactam (**12**) shows that the normally preferred 1,4-addition is disfavoured with respect to 5-*exo-trig* transacylation.



Scheme 1.2

The reactions of cinnamic acid derivatives with hydrazine are also in accord with these ideas. Scheme 1.3 illustrates this situation. The hydrazine (**17**) cannot, even at 200 °C, be converted into the pyrazolone (**20**) (5-*endo-trig* process); however, the ester (**18**) reacts with hydrazine at 65 °C to give cleanly (**20**), by way of the 1,4-adduct (**19**), followed by the favoured 5-*exo-trig* closure.[19]



Scheme 1.3

1.6 Methods for the Synthesis of Reduced Heterocycles:

The importance of nitrogen heterocycles, especially pyrrolidine and piperidine types, as sub-units of bioactive molecules, has stimulated the development of new synthetic methods. The most common methods for constructing reduced heterocycles can be categorised into five main groups, most of which involve a nucleophilic atom interacting with an electrophile. We have briefly mentioned some of these earlier but now we will discuss them in more detail. The predominant reaction types are:

(1) Substitution reactions.

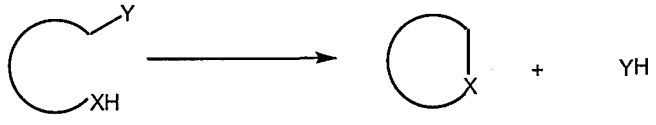
(2) Addition reactions where the heteroatom is directly involved.

(3) Carbanion addition to an unactivated carbon double bond.

(4) Intramolecular radical reactions.

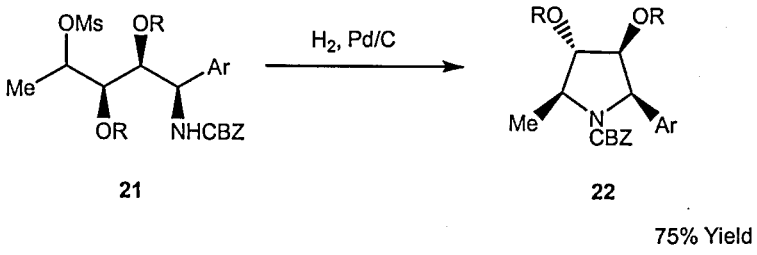
(5) Carbene reactions.

1.7 Cylisation by Nucleophilic Substitution Reactions.



Intramolecular S_N2 reactions are widely used for the construction of saturated heterocyclic compounds. Five-membered rings are generally the easiest to form, as the ring size represents the best balance between enthalpy and entropy terms: the rings are strain-free and the transition states are accessible. This involves the formation of C-X bonds (X = nitrogen heteroatom) by S_N reactions. Substitution reactions in general are defined as the replacement of one atom or functional group for another. Simply, this process can involve dissociation of the leaving group (Y) prior to C-X bond formation (S_N1- type) or concerted displacement of Y (S_N2-type). Both are extremely useful in introducing heteroatoms and carbon functional groups into the carbon skeleton. Many examples of syntheses of functionalised pyrrolidines (**22**) by intramolecular S_N2 nucleophilic substitution

from aminoalcohol derivatives such as (**21**) are described in the literature.[20] The cyclisation is usually stereospecific (Scheme 1.4).[21]

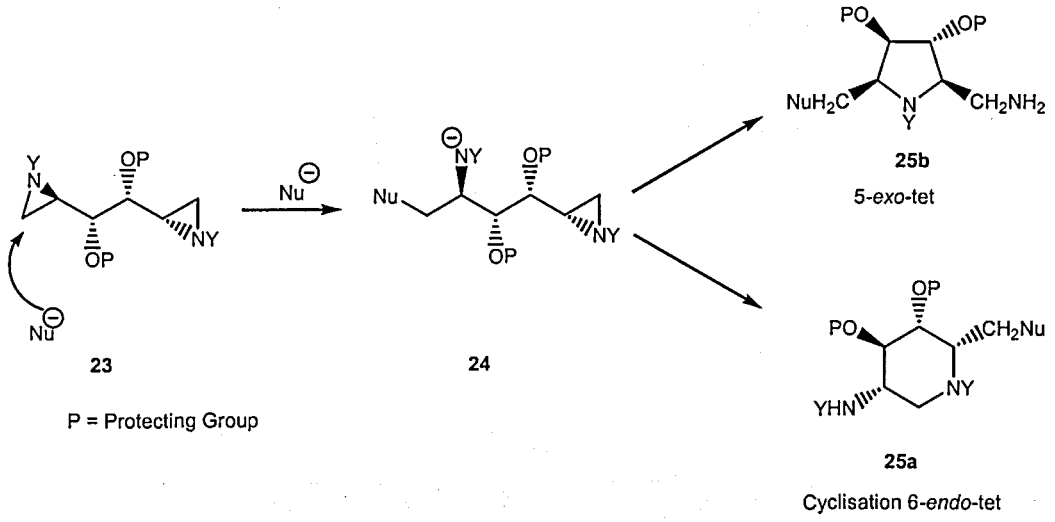


21 **22**

75% Yield

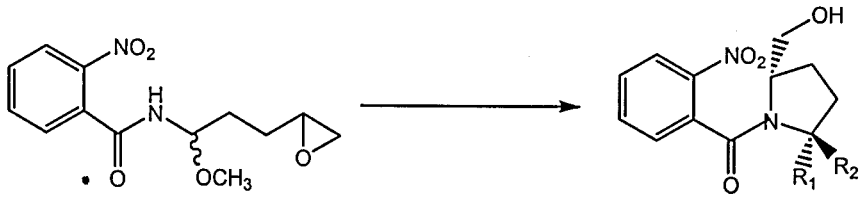
Scheme 1.4

Depezay[22] described the nucleophilic opening of bis-aziridines (**23**) by phenylthiolates ions or azides, followed by cyclisation to pyrrolidines. A mixture of polysubstituted pyrrolidines (**25b**) and piperidines (**25a**) was thus obtained (Scheme 1.5). Usually, pyrrolidines (**25b**) are the major compounds formed (along with 7% of piperidines (**25a**) with chemical yields ranging from 51 to 84%.



Scheme 1.5

Intramolecular cyclisation of γ-amidoepoxides is a very attractive method for the preparation of 2,5-disubstituted pyrrolidines. Langlois[23] used this strategy for the synthesis of neothramycines (Scheme 1.6). Starting with a mixture (**26**), two diastereomers (**27a**) and (**27b**) were obtained in 24 and 46% yield respectively

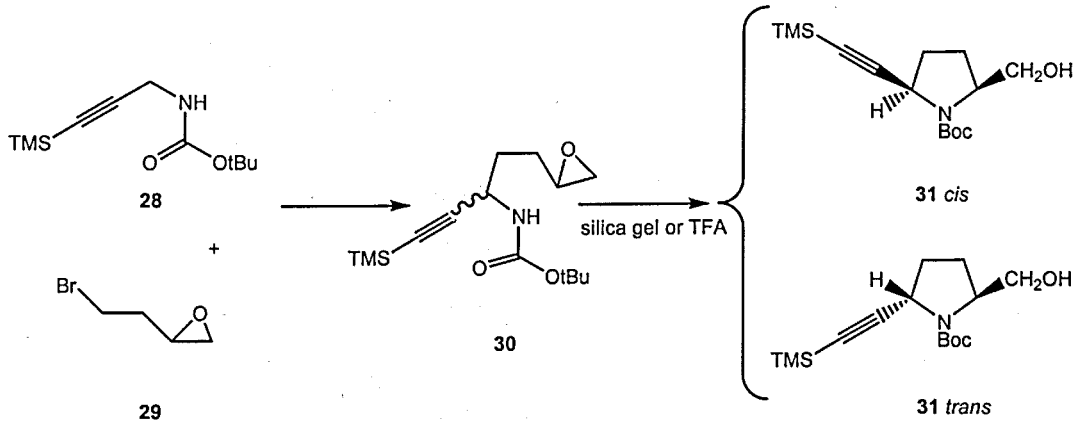


26

27 a: $R^1 = OCH_3$, $R^2 = H$
b: $R^1 = H$, $R^2 = OCH_3$

Scheme 1.6

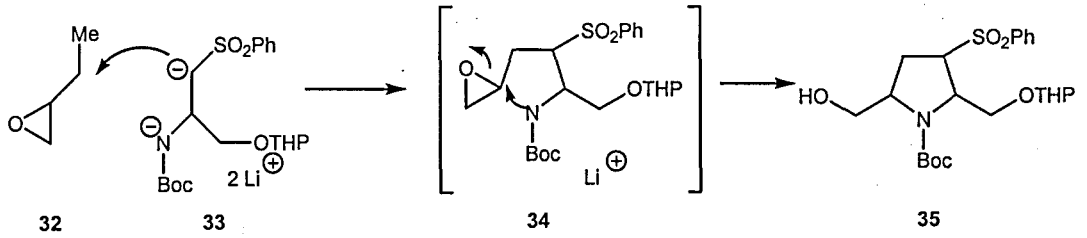
Baldwin[24] synthesised a 1:1 mixture of *cis* and *trans*-2,5-dicarboxylic acid pyrrolidines through an identical method. Biellmann[25] proposed a modification of this strategy: in a stepwise manner, first the C-4/C-5 bond is created with the control of the configuration and then the N/C-2 bond by nucleophilic substitution of the amidoepoxide. The dianion of propynylamine (**28**) (Scheme 1.7) is obtained by treatment with LDA, and reacted with the bromide (**29**) leading to an inseparable mixture (30:70) of amidoepoxides (**30**) with 60% chemical yield. The mixture of (**30**) is then either treated with silica gel at 65 °C giving a mixture of products (**31**) (*cis*:*trans*/1:9), or by trifluoroacetic acid at 0 °C leading to pyrrolidines (**31**) with a 15:85/*cis*:*trans* ratio.



Scheme 1.7

Sasaki[26] described the synthesis of 4 isomers of 2,5-disubstituted pyrrolidines, using this strategy (Scheme 1.8). α-Sulfonyl carbanion (**33**) regioselectively

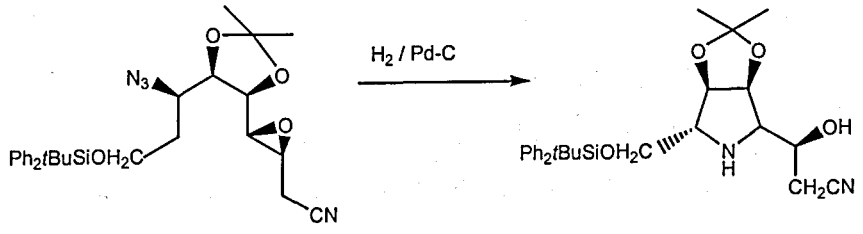
reacted with glycydic triflate (**32**) to give epoxide (**34**) which cyclised onto 2,3,5-trisubstituted pyrrolidines (**35**) via 5-*exo* opening of the epoxide. By using either *R*- or *S*- enantiomer of (**32**) and (**33**), Sasaki prepared all enantiomerically pure stereomers of (**35**) with excellent chemical yields (90%) and e.e's ranging from 84 to 92%. It is noteworthy that the best chemical yields and e.e's are obtained with the triflates rather than with the corresponding tosylates.



32 33 34 35

Scheme 1.8

The "one pot" reduction-cyclisation of the γ-azido-epoxides follows the same process, as shown by Fleet[27] (Scheme 1.9). Hydrogenation in the presence of palladium-on-charcoal of the azido compound led to the corresponding amine which spontaneously cyclised into the pyrrolidine in 82% yield with total stereospecificity.

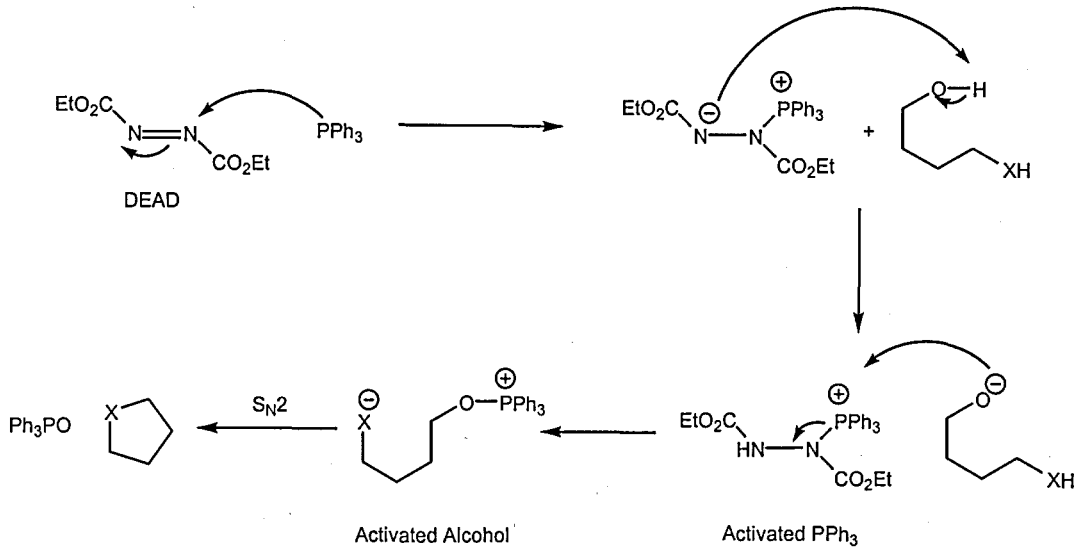


36 37

Scheme 1.9

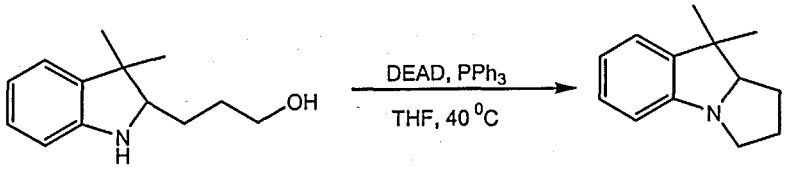
So far we have referred to methods of displacing an OH group by first converting it into something else; a better leaving group such as Br, for example. However, in contrast to this, the Mitsunobu reaction allows the addition of an alcohol into a reaction mixture and obtains an S_N2 product in one operation.[28] The Mitsunobu

reaction is undoubtedly the most popular method for activating an OH group thereby facilitating cyclisation. The mechanism is illustrated in Scheme 1.10.[29]



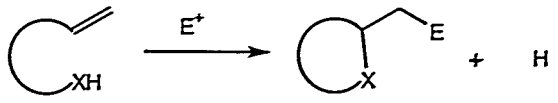
Scheme 1.10

The phosphine adds to the weak N=N π bond to give an anion stabilised by one of the ester groups. The anion produced is basic enough to remove a proton from the alcohol and the new alkoxide ion immediately attacks the positively charged phosphorus atom displacing a second nitrogen anion stabilised the same way as the first. The second basic nitrogen anion removes a proton from the nucleophile. Finally, the anion of the nucleophile attacks the phosphorus derivative of the alcohol in a normal S_N2 reaction at carbon with phosphine oxide as the leaving group. The S_N2 step leads to inversion of configuration. The XH (e.g. amine) must have a pKa < 16, therefore secondary amines react well under these conditions as opposed to primary amines which fail to do the reaction. Use of the Mitsunobu method for the cyclisation of secondary amines (Scheme 1.11) works well (64% yield) to give a strained product.[30]



Scheme 1.11

1.8 Cyclisation by addition reactions.



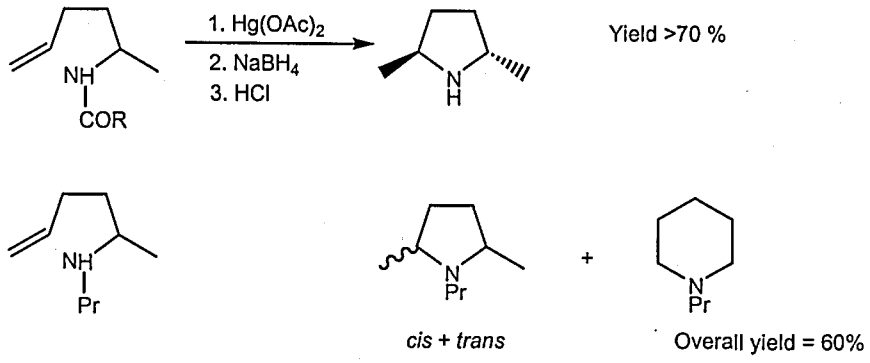
Addition reactions can be divided into three groups.

A). Intramolecular nucleophilic addition to carbonyl groups: this type of process is the most common cyclisation reaction in heterocyclic synthesis. Internal nucleophilic attack at the carbonyl group of esters, acid chlorides, etc. is followed by displacement of the leaving group, and the carbonyl function is retained in the cyclic product.

B). Intramolecular addition of nucleophiles to other double bonds: activated C=N bonds can act as the electrophile. The electrophile can also be an activated C=C bond to which an internal conjugate addition reaction can occur. The great majority of cyclisations take place by reaction at an electrophilic carbon centre but there are a few heterocyclic syntheses, which involve cyclisation onto electrophilic nitrogen. For example, a nitro group can act as the electrophile.

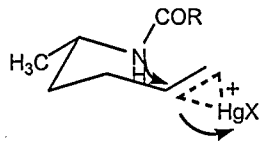
C). Cyclisation onto triple bonds: nucleophilic addition to cyano groups provides an important method of synthesis of C-amino-substituted heterocycles. The *exo* addition to carbon-carbon triple bonds is not so common.

Intramolecular aminomercuration (with $HgCl_2$) of δ-alkenylamines have been studied by Perie (Scheme 1.12).[31] Harding noticed that the regio- and stereoselectivities are better for the amidomercuration than for the aminomercuration and that the *trans*-isomer is always the major one formed (*trans*:*cis*/98:2) (Scheme 1.12).

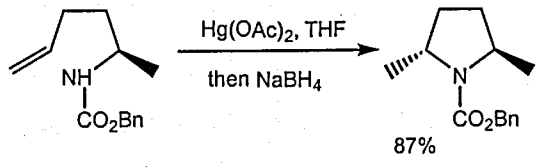


Scheme 1.12

The stereochemistry of the cyclisation may be explained by the preferred chair transition state with the equatorial methyl group.

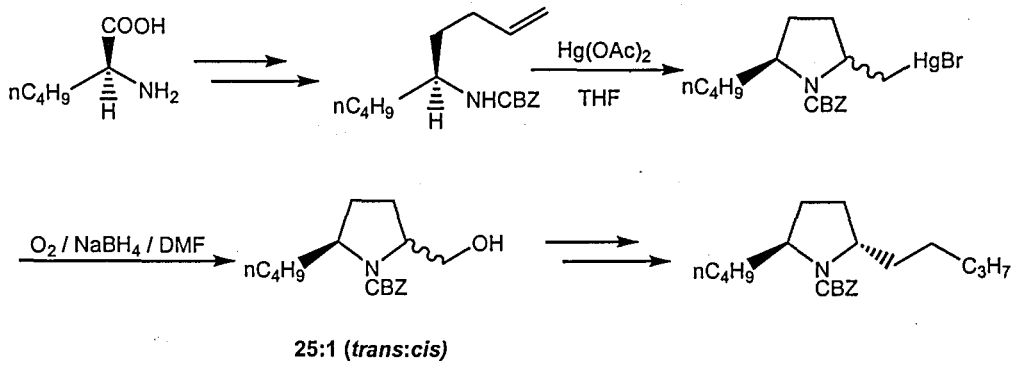


The mechanism involves using metal ions as the electrophile. Here, an intermediate is formed by mercuration of the double bond and then the carbamate is captured. The C-Hg bond formed can be easily replaced by other groups such as C-H by reduction with $NaBH_4$[32] (Scheme 1.13).



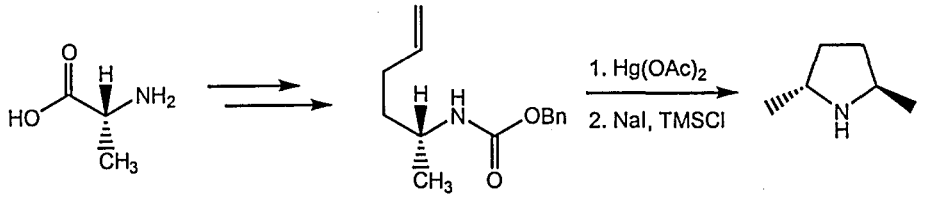
Scheme 1.13

Harding showed that ω-alkenylamines, when treated by $Hg(OAc)_2$ in CH_3CN, led to 2,6-disubstituted piperidines, and observed an equilibrium between *trans*- and *cis*- products. Takahata[33] used this strategy for the synthesis of *trans*-2,5-dialkylpyrrolidines (with d.e *trans*:*cis* = 25:1 and e.e = 98%) from *L*-norleucine (Scheme 1.14).



Scheme 1.14

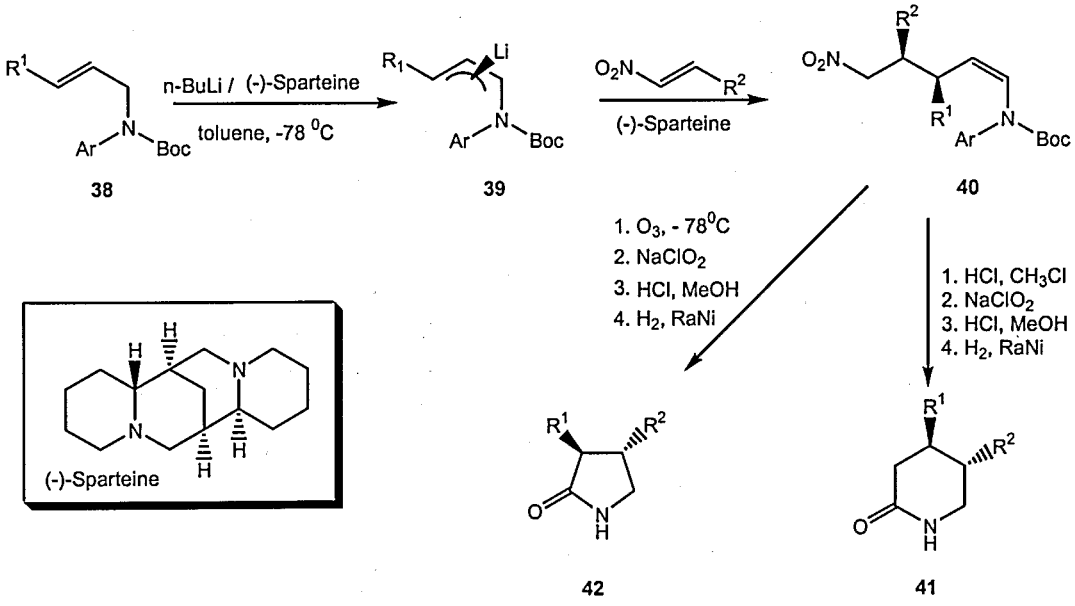
Following this strategy numerous syntheses of 2,5-disubstituted pyrrolidines have been performed such as (+) and (-)-*trans* 2,5-dimethylpyrrolidines from *D* or *L*-alanine, respectively as shown in scheme 1.15.[34,35]



Scheme 1.15

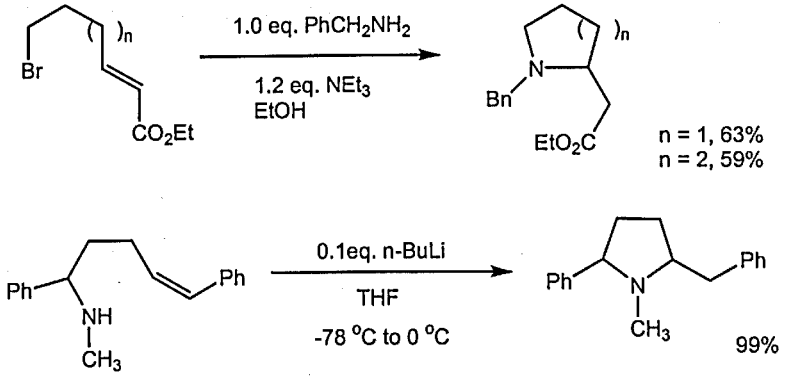
A recent example of a cyclisation addition reaction for the synthesis of substituted piperidines and pyrrolidines involves the conjugate addition of lithiated *N*-Boc-allylic and benzylic amines to nitroalkenes.[36] (-)-Sparteine mediated lithiations of *N*-Boc-allylic and benzylic amines provide configurationally-stable organolithium intermediates (**39**). Conjugate addition of these intermediates to nitroalkenes provide highly enantio-enriched enecarbamate products (**40**) in good yields and with high diastereoselectivities (Scheme 1.16). The enecarbamates derived from these conjugate additions are useful precursors to 3,4-substituted piperidines and pyrrolidines. Hydrolysis of the enecarbamate (**40**) with HCl in CH_3Cl provides the crude nitroaldehyde. Oxidation with $NaClO_2$, esterification, hydrogenation of the nitro group, and concomitant cyclisation provides piperidones, which can be reduced with LAH, providing the piperidine (**41**).

The pyrrolidine ring can be accessed by a sequence, which begins with ozonolysis of the enecarbamate double bond (**40**). This is then followed by a reductive workup with dimethyl sulfide to provide the requisite aldehyde, which is subjected to oxidation, esterification, reduction, and cyclisation to provide the pyrrolidinone. As in the piperidine synthesis, conversion to the pyrrolidine (**42**) is achieved by LAH reduction.



Scheme 1.16

Another example of an addition reaction is the following tandem reaction (Scheme 1.17), which comprises of *N*-alkylation and conjugate addition to an enone.[37] This illustrates a reaction where substitution and addition occur in one synthetic step.

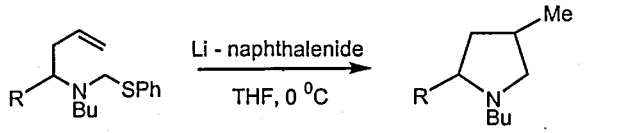


Scheme 1.17

1.9 Cyclisation by carbanion reactions.

An *organometallic* compound is a compound that contains a bond between a carbon atom and a metal atom. Many such compounds are known, and organometallic chemistry is a very large area, occupying a borderline region between organic and inorganic chemistry. Many carbon-metal bonds, e.g., carbon-mercury bonds, are undoubtedly covalent. Whether the position of the electrons in a given bond is close enough to the carbon to justify calling the bond ionic and the carbon moiety a carbanion depends on the metal, on the structure of the carbon moiety, and on the solvent and in some cases, is a matter of speculation.

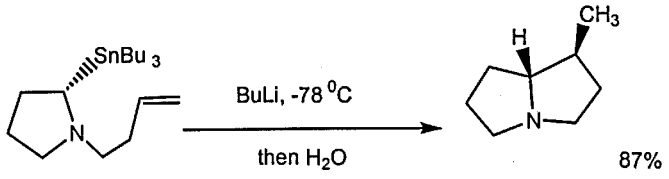
Below are examples where simple carbanions add to unactivated C=C bonds. The first example[38] (Scheme 1.18) shows a reaction with lithium naphthalide, which results in lithium/sulfur exchange followed by subsequent cyclisation to give the pyrrolidine (44) in 60% yield.[39] The reaction proceeds via cleavage of the C-S bond and formation of a C-Li bond. The *cis*-product (44) is the major isomer.



43 44 60%

Scheme 1.18

The second example (Scheme 1.19) proceeds via tin-lithium exchange followed by cyclisation giving (46) in 87% yield. Significantly, tin/lithium exchange occurs with retention of configuration with no racemisation upon cyclisation.

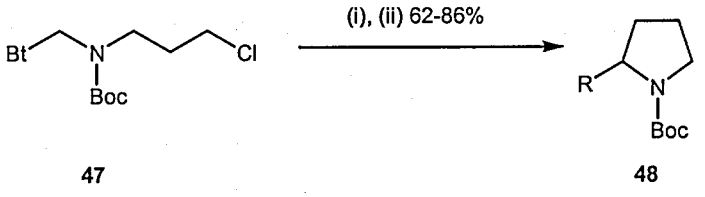


45 46 87%

94% ee 94% ee

Scheme 1.19

A general method using *N*-Boc-*N*-(3-halopropyl)(benzotriazole-1-yl-methyl)amine as a starting material (**47**) was used in the preparation of 2-substituted-*N*-Boc-pyrrolidines in excellent yields. In the cyclisation step, the benzotriazole moiety assists the dipole stabilisation in the formation of a carbanion intermediate to make the lithiation regiospecific. The benzotriazole group is displaced from 2-benzatriazole-*N*-Boc-pyrrolidine with Grignard reagents (Scheme 1.20).[40]



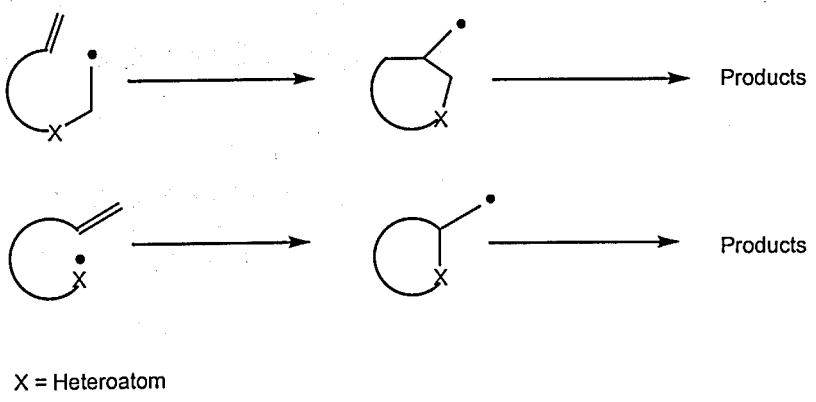
47 **48**

Reagents: (i) ^{n}BuLi, PhMe, -78 ^{0}C; (ii) RMgBr, $ZnCl_2$, THF, reflux.

Scheme 1.20

1.10 Cyclisation by radical reactions.

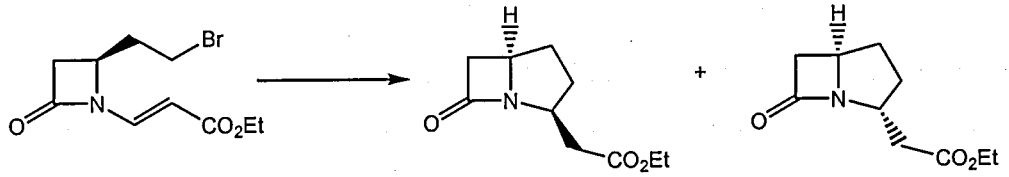
Heterocycles can be generated by the intramolecular addition of a radical to a double bond, a triple bond or an aromatic ring. Most of the useful reactions give five- or six-membered heterocycles. The heteroatom can be the radical centre, or it can be incorporated into the connecting chain. The kinetically favoured cyclisations are illustrated in Scheme 1.21.



Scheme 1.21

The addition to double bonds occurs predominantly in an *exo*-manner in kinetically controlled processes, although this leads to the formation of less stable radical intermediates. This is because, as with nucleophilic addition, the transition state for *exo*-addition is more favourable. Substituents on the double bond can, however, disfavour attack at the substituted position resulting in *endo*-cyclisation and a six-membered transition state.

Tributyltin hydride continues to be the reagent of choice in radical cyclisations yielding products as diverse as indolones, sugar-derived spiro acetals, and bicyclic pyrrolidine derivatives (Scheme 1.22).[41]



49% 3%

49 **50** **51**

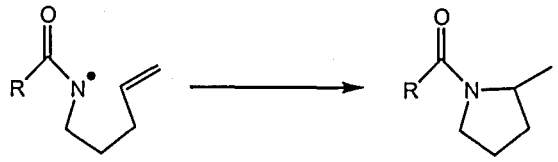
Reagents: (i) Bu_3SnH, AIBN, C_6H_6, reflux, 5 h.

Scheme 1.22

This is an example of a carbon-centered radical cyclisation of (**49**) which, under standard high dilution conditions, led to the formation of the novel bicyclic β-lactam (**50**) in 49% yield. An epimeric product (**51**) was isolated in 3% yield along with the simple reduction product 4-ethyl-azetidin-2-one in 28% yield.

Nitrogen-centered radicals have also been used in the synthesis of pyrrolidines. There are different forms of nitrogen-centered radicals:

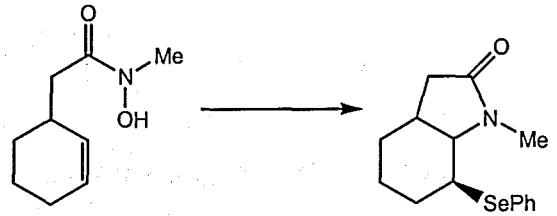
The Amidyl radical:



Amidyl Radical

Figure 1.8.

A typical example of an amidyl radical is illustrated in Figure 1.8, where the nitrogen of an amido group bears a radical. An efficient methodology[42] (Scheme 1.23) was devised to generate and cyclise amidyl radicals formed from a variety of hydroxamic acids (**52**) under mild reaction conditions (-50 °C to room temperature). Treatment of an olefinic hydroxamic acid with tert-butylsulfinyl chloride and Hünig's base in the presence of a radical trap such as diphenyl diselenide afforded the indolizidine (**53**). The procedure leads to cyclisation products which are highly functionalised, and thus more amenable to further manipulation than those produced by the more common tributylstannane-mediated methods.[43] This methodology has also been extended to a formal synthesis of peduncularine, a major alkaloid from the Tasmanian shrub *Aristotelia peduncularis.*



52 **53**

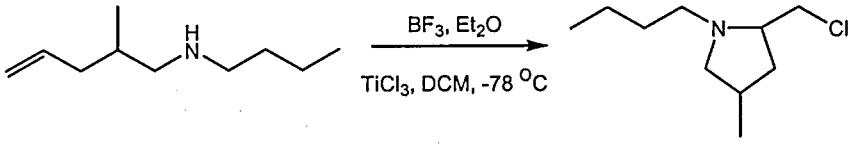
Reagents: (i) ^{t}BuSOCl, DIEA, $(PhSe)_2$, $CHCl_2$, -50 °C to RT.

Scheme 1.23

The Aminyl radical:

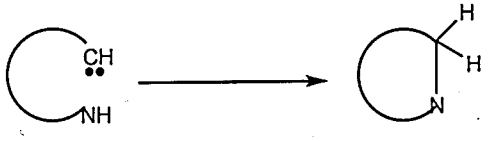
Figure 1.9.

The aminyl radical, illustrated in Figure 1.9, is a nitrogen centred radical bearing an R group. In the example below (Scheme 1.24), the nitrogen firstly becomes chlorinated to form a saturated *N*-chloroalkylamine which then undergoes radical formation.[44]

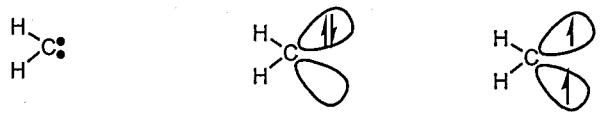


Scheme 1.24.

1.11 Carbene/Nitrene cyclisations.

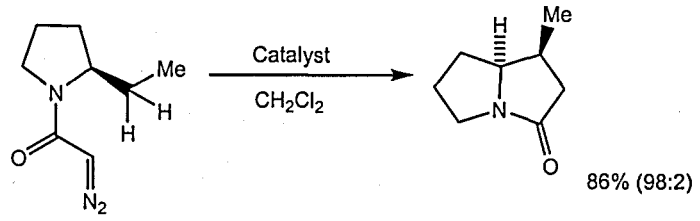


Monovalent nitrogen intermediates (nitrenes) and divalent carbon intermediates (carbenes) are highly reactive species, which can undergo addition reactions with multiple bonds and can insert into unactivated carbon-hydrogen bonds. Carbenes are reactive species, which consist of divalent carbon with a non-bonding pair of electrons (**54**). The two non-bonded electrons can have antiparallel spins in a single orbital (**55**, a singlet carbene) or parallel spins in different orbitals (**56**, a triplet carbene).



54 55 56

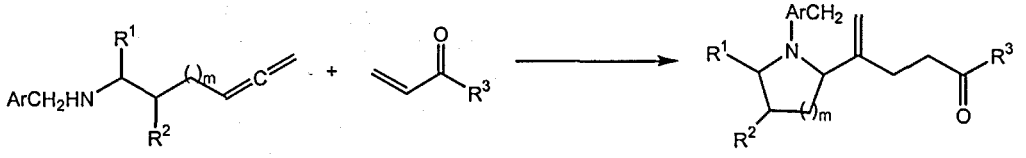
An example of an intramolecular insertion reaction leading to a bicyclic heterocycle is illustrated below (Scheme 1.25).[45]



Scheme 1.25

1.12 Ring-closing metathesis.

Metal-mediated synthesis of five-membered heterocycles has seen some innovative developments in recent years. Alkene metathesis continues to find wide-ranging applications in the synthesis of heterocycles, in particular for stereocontrolled ring-closures and consecutive synthesis of polycyclic compounds.[46] Ruthenium catalysts have been used to synthesise heterocycles, including the cyclisation of amino-allenes and coupling of α,β-unsaturated ketones to afford pyrrolidines and piperidines (Scheme 1.26).[47]. Analogous formation of piperidines under optimised conditions for pyrrolidine formation gave only modest yields.

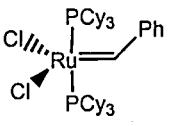


Reagents: (i) $[CpRu(NCCH_3)_3]^+PF6^-$ (10%), $TiCl_4$ or Me_2AlCl, 60 °C or 40 °C, 2 h or 1 h work-up with pyrrolidine.

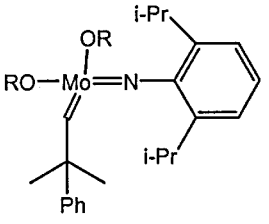
Scheme 1.26

One of the most recent (and currently popular) methods for cyclisation involves metal-carbene complexes in Ring Closing Metathesis (RCM) reactions. RCM has

found many applications. Its efficiency has been proven in the synthesis of various carbo- and heterocycles and especially in the synthesis of natural products.[48] This is largely due to the introduction of the well defined molybdenum and ruthenium catalysts developed by Grubbs[49] and Schrock.[50] This chemistry seems to work best for systems in which the metallobicycle is not too strained e.g. 6-membered and larger rings. For unstrained targets, polymerisation may be avoided by using lower concentrations and alkenes that produce low molecular weight by-products, thus causing entropically favourable equilibrium outcome. It is not useful in forming strained rings due to a competing polymerisation pathway (ROMP, ring-opening metathesis polymerisation).

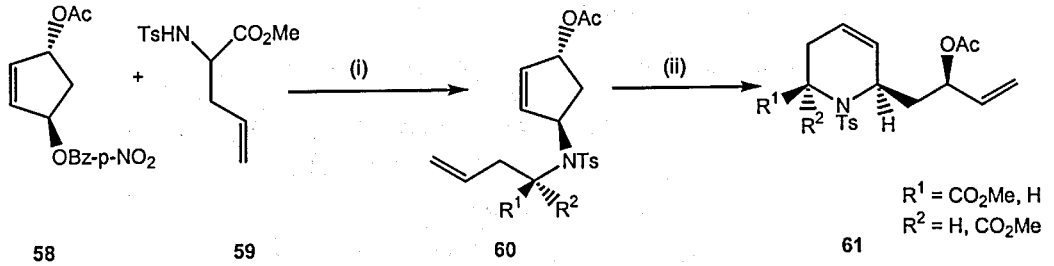


Grubbs' catalyst



Schrock's catalyst

Ring–closing alkene metathesis (RCM) has found applications in the construction of piperidine derivatives. The sequential application of π-allyl palladium chemistry and alkene metathesis leads to the enantioselective synthesis of α, α'-disubstituted piperidines (Scheme 1.27)[51].



58 59 60 61

Reagents: (i) $Pd(OAc)_2$, PPh_3, NaH, DMF, RT to 40 °C; (ii) $Cl_2(PCy_3)_2RuCHPh$ (5 mol%), CH_2Cl_2, RT.

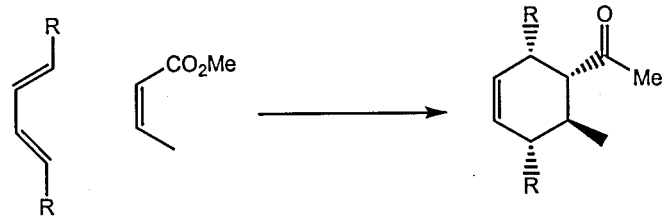
Scheme 1.27

In this reaction, a domino ring-opening, ring-closing metathesis has been reported where termination occurs by methylene transfer. This concept enables the

preparation of enantiomerically pure *cis*- or *trans*- α, α'-disubstituted piperidines, which can be transformed into indolizidines using easily available racemic or enantiomerically-pure starting materials. This reaction involves a palladium catalysed allylation of *rac*-allylglycine ester (**59**) with (**58**), which gives rise to 1:1 mixture of diastereomers (**60**). This mixture was then treated with the ruthenium catalyst where ring rearrangement occurs to form the disubstituted piperidine (**61**).

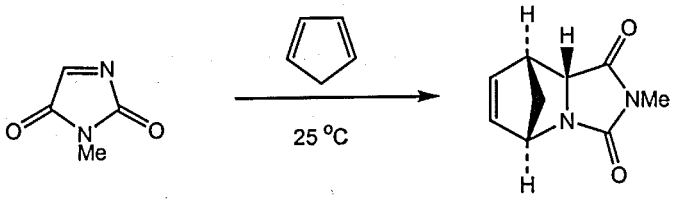
1.13 Cycloaddition reactions.

One of the most widely used reactions for the synthesis of carbocyclic rings is the Diels-Alder reaction in which a 1,3-diene reacts with an alkene to give a cyclohexene. Up to four stereogenic centres are created in the reaction, often with a high degree of stereocontrol. This is illustrated in scheme 1.28.



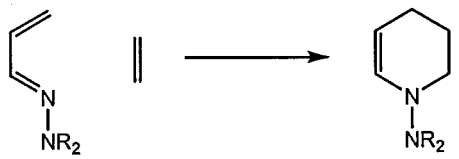
Scheme 1.28

Nitrogen can be introduced into either the diene or dienophile enabling the synthesis of piperidine-derivatives via a [4+2] cycloaddition. An example of a heterodienophile is shown in scheme 1.29.



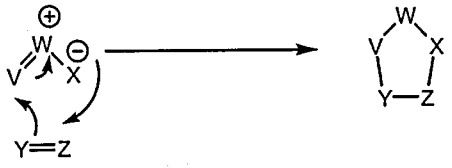
Scheme 1.29

Alternatively, a heterodiene can be used as shown in scheme 1.30. Without the hydrazine moiety, such cycloadditions are not successful.[52]



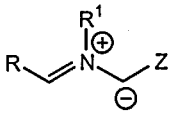
Scheme 1.30

An alternative class of cycloadditions is the [3+2] cycloaddition involving a 1,3-dipole and a dipolarophile as illustrated in scheme 1.31.



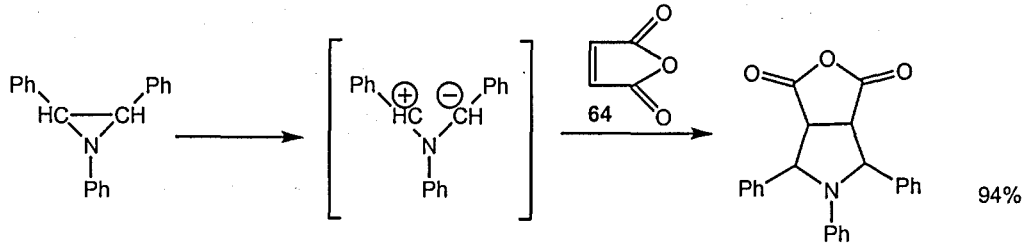
Scheme 1.31

The 1,3-dipole is a three-atom π-electron system with four π-electrons delocalised over three atoms. The dipolarophile has two π-electrons and so the reaction obeys the Woodward-Hoffman rules. An example of such a reaction in the synthesis of pyrrolidines involves the azomethine ylide (**63**).



63

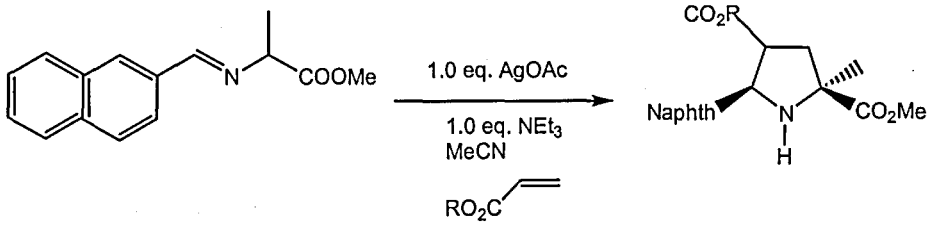
This can be generated *in situ* in a number of ways. Opening of aziridine (**62**) affords the ylide (**63**). The ylide (**63**) can add to the activated double bond (**64**) to give the pyrrolidine in 94% yield (Scheme 1.32).[20]



62 63 65

Scheme 1.32

Another example of 1,3-dipolar cycloaddition involves a "metallo azomethine-ylide" with a homochiral dipolarophile (Scheme 1.33).[35] Imines of α-aminoesters are known for reacting with electron deficient alkenes in the presence of Lewis acids to give polysubstituted pyrrolidines. Kanemasa reported the synthesis of 2,5-*cis* polysubstituted pyrrolidines by cyclisation of azomethine ylides with α,β-unsaturated esters bearing chiral imidazoline. Pyrrolidines are enantiomerically pure, but Kanesama noted a large difference of selectivity for the formation of compounds, depending on the nature of the R and R' substituents. (d.e ranging from 10 to 100%).

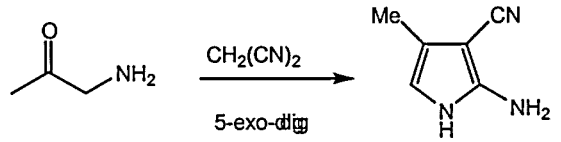


Scheme 1.33

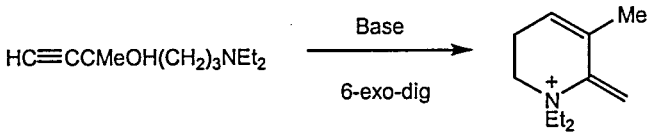
1.14 Ring formation by attack on carbon-carbon triple bonds:

Nucleophilic addition to cyano groups provides an important method of synthesis of amino-substituted heterocycles, as exemplified by equation 1. The *exo*-addition to carbon-carbon triple bonds is not as common, but it has been used to synthesise some five- and six-membered heterocycles, as shown in equation 2. There are also a significant number of examples of heterocyclic syntheses, which involve *endo*-cyclisation onto a triple bond. Although such reactions appear

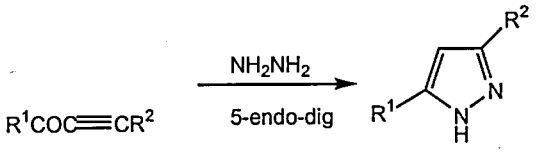
sterically unfavourable because of the linear nature of the triple bond, it is easy to distort the triple bond to achieve the required transition-state geometry.[53] An example of a cyclisation, which can be rationalised as an *endo*-addition to a carbon-carbon triple bond, is shown in equation 3.



(Eq. 1)



(Eq. 2)



(Eq. 3)

1.15 Summary

In this chapter, we have seen many types of reaction, which have allowed the synthesis of 5- and 6-membered heterocycles. However, tandem chemistry has played a very important role in forming these heterocycles in a very efficient, economical and elegant manner. The synthetic potential of tandem chemistry in organic synthesis will be explored in the next chapter.

CHAPTER II

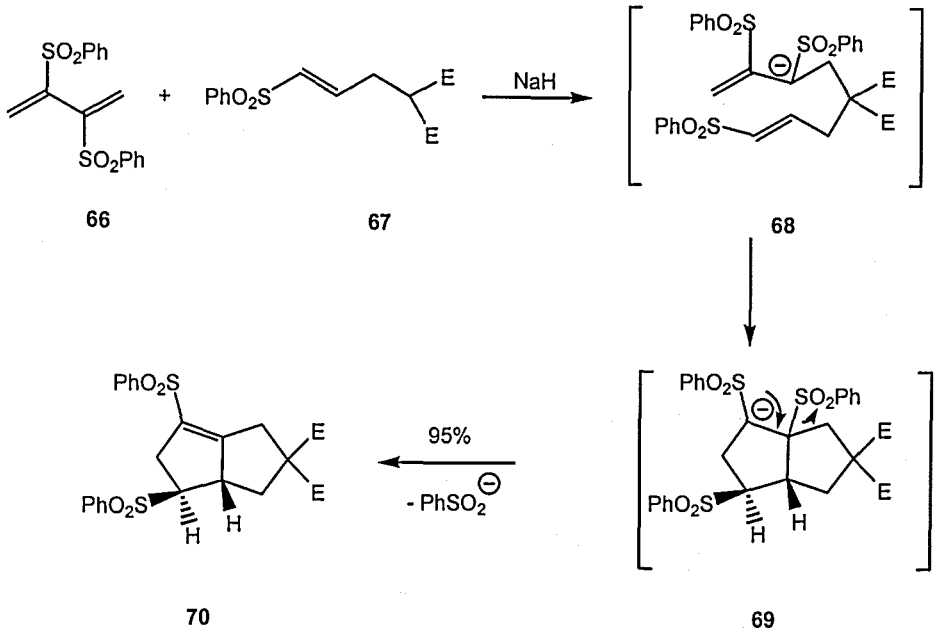
A Tandem Michael-Dieckmann approach towards substituted Pyrrolidines.

2.1 Introduction.

The design of tandem processes for the construction of highly functionalised complex molecules is an important area in organic chemistry. The future of organic synthesis lies in efficient methodology and the discovery of new processes for controlling the formation of homochiral centres as well as building up complex chemical architecture using simple techniques. A cascade sequence can lead to an increase in molecular complexity by combining a series of reactions in one synthetic operation.[54] These reactions offer a convenient and economical method to prepare desired organic molecules.[55] The Michael addition and the aldol reaction are acknowledged as useful tools for constructing complex organic molecules, and combining the two reactions in one pot has attracted much attention in organic synthesis.[56]

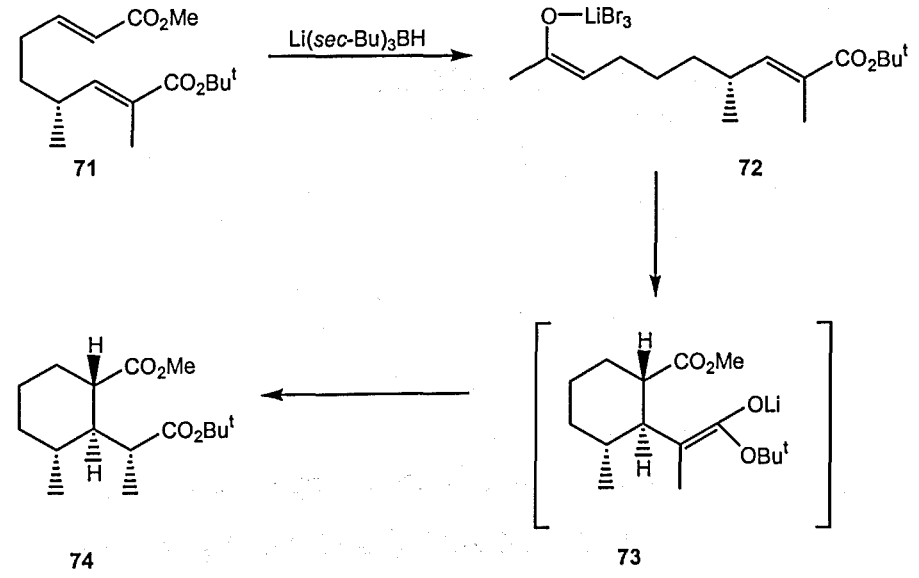
2.2 Tandem anionic reactions.

Padwa[57] reported an elegant use of a tandem Michael sequence for the construction of fused rings (Scheme 2.1). Formation of the malonate anion is followed by Michael addition to a vinylsulfone unit. The intermediate generated (**68**) undergoes a second cyclisation via a double Michael addition. The reaction sequence is terminated by elimination of $PhSO_2^-$ to furnish the fused carbocyclic ring system.



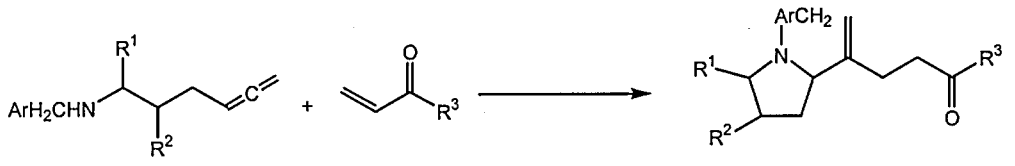
Scheme 2.1

Yoshii[58] demonstrated the use of a sequential Michael addition sequence for the formation of a carbocyclic ring with a high degree of stereocontrol (Scheme 2.2). In this example, reductive annulation of 2,4-dimethyl-2,7-nonadiene diester (**71**) gave cyclohexane diester (**74**) as the only product. This sequence involes regioselective conjugative addition of L-selectride® to the least hindered double bond to generate an enolate intermediate (**72**) followed by an intramolecular Michael addition reaction furnishing (**74**).



Scheme 2.2

Ruthenium catalysts have been used to synthesise heterocycles, including the cyclisation of amino allenes and coupling of α,β-unsaturated ketones to afford pyrrolidines and piperidines (Scheme 2.3).[47] This extends the utility of ruthenium catalyst to include basic amines. Mechanistically, two pathways are possible; the allene and the enone could both coordinate to the ruthenacycle, allowing internal attack of the nitrogen or the reaction might be initiated by a ruthenium catalysed azametalation of the allene resulting in a vinylruthenium species which could then insert into the enone and proceed to form the pyrrolidine. It is of note that the reaction appears to tolerate other functional groups and further elaboration of the products is facilitated by the juxtaposition of the functionality.

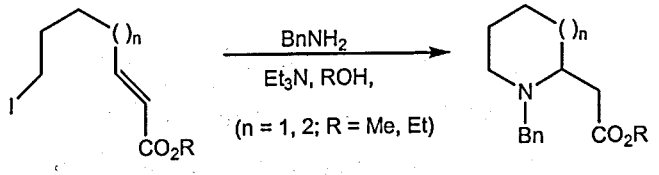


75 76 77

Reagents: (i) $[CpRu(NCCH_3)_3]^+ PF_6^-$ (10 mol%), $TiCl_4$ or Me_2AlCl, 60 ^0C

Scheme 2.3

The S_N2/Michael reaction constitutes an efficient approach to the construction of five- and six-membered ring heterocycle-substituted carboxylic acid derivatives.[59] This one-pot synthesis proceeded by reaction of 6- or 7-halo-2-alkenoate esters (**78**) with benzylamine (Scheme 2.4).

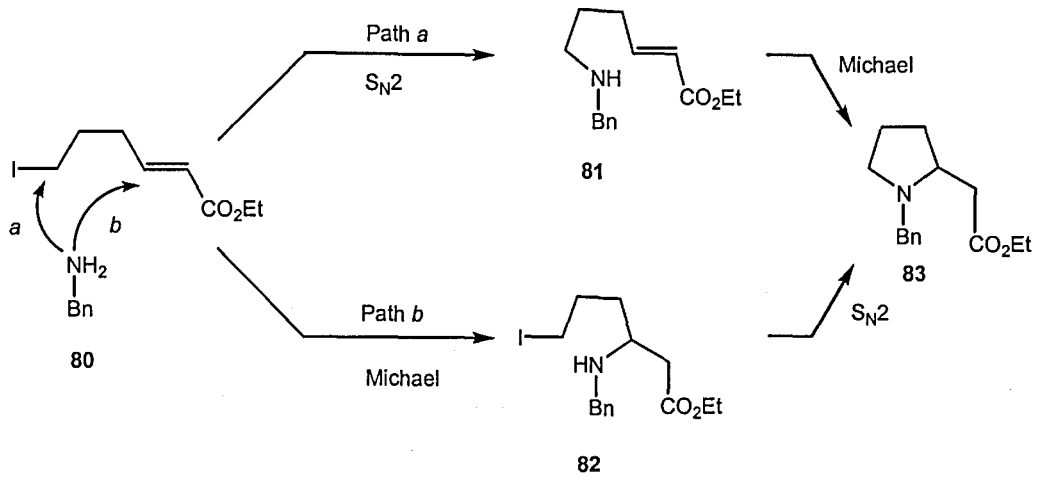


78 79

Scheme 2.4

The ease and efficiency of the process make it a valuable addition to the limited synthetic methodology available for the preparation of these systems. The mechanistic possibilities for the formation of nitrogen heterocycles are illustrated in (Scheme 2.5). In the formation of cyclic amines, it is conceivable that S_N2

reaction occurs first followed by Michael addition (path a) but it is possible that the reverse sequence initiated by Michael addition (path b) is operating.

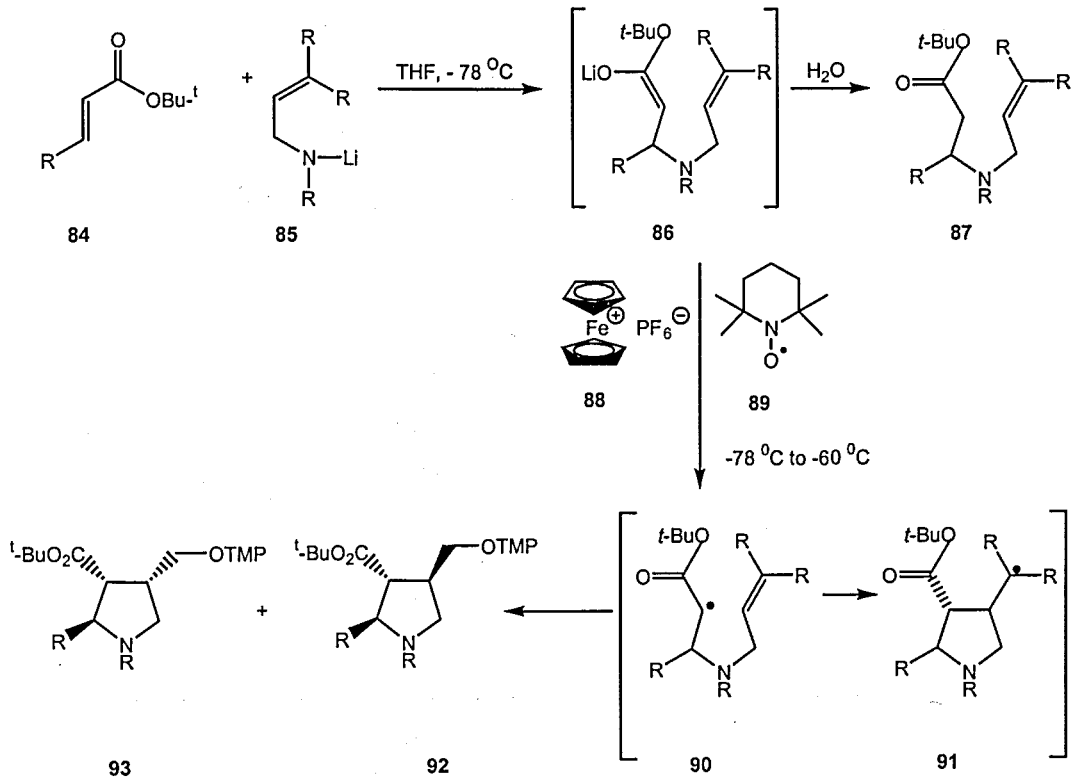


Scheme 2.5

2.3 Tandem radical processes.

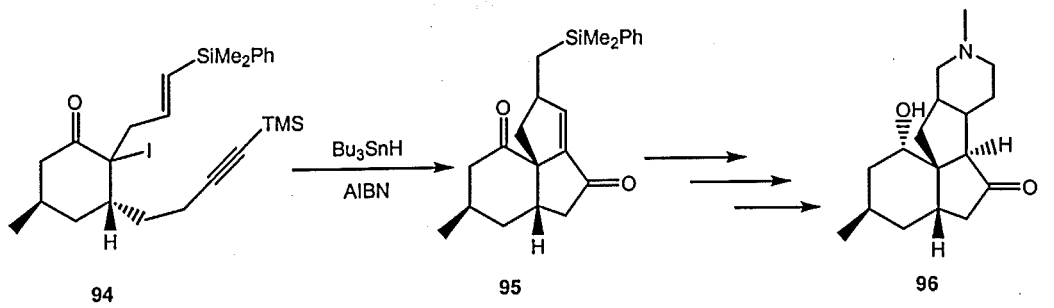
Tandem radical reactions involve two or more radical reactions in a reaction sequence. That is, the initially generated radical undergoes a radical reaction, generating a new radical, which becomes a precursor for the subsequent radical step in a sequence of reactions. Curran[60] defines these reactions as transformations, in which a substrate undergoes two or more subsequent radical reactions, excluding steps that involve the initial radical generation and radical termination.

It was recently reported that tandem lithium amide conjugate addition / radical 5-*exo*-cyclisation reactions can be performed with ferrocenium hexafluorophosphate (**88**) as SET oxidant[61] for the β-amino enolate (**86**). This is an attractive strategy to obtain highly functionalised pyrrolidines in a single operation from very simple precursors.[62] For the termination of the reaction sequence, free radical TEMPO (**89**) was added since it reacts more slowly with α-carbonyl radicals (**90**) than with alkyl radicals (**91**) and oxygenated products are obtained, which provide ample opportunities for further transformations. The study shows that the stereochemical information of enolates can be translated into radical cyclisations as illustrated in scheme 2.6.



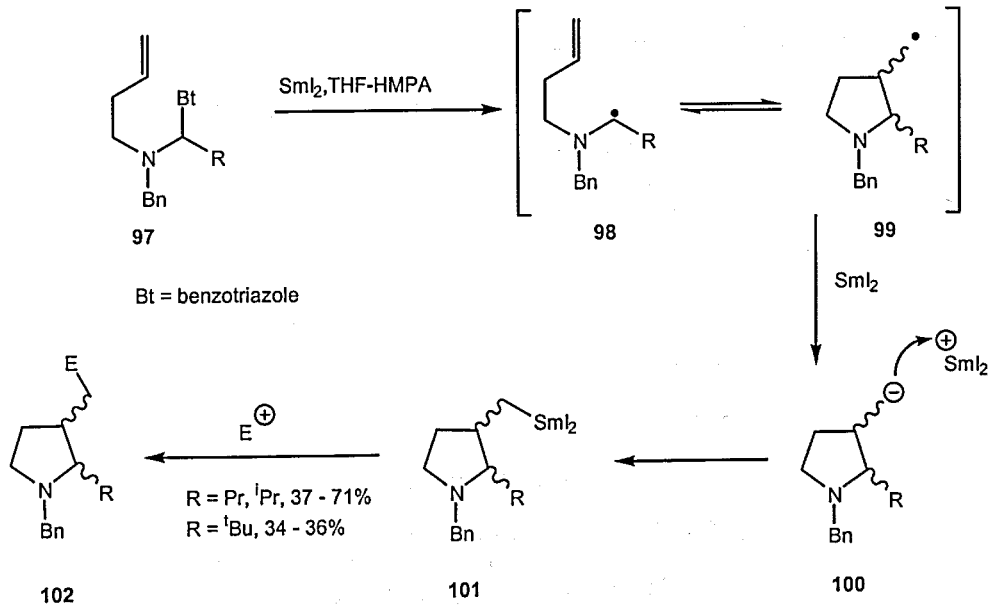
Scheme 2.6

An efficient α-carbonyl radical initiated tandem cyclisation reaction was reported[63] for the synthesis of angularly fused tricyclic ketones. This methodology was applied towards the first total synthesis of (+)-paniculatine (**96**). A radical generated from the iodo ketone (**94**), using tributyl tin hydride and AIBN in benzene undergoes a tandem radical cyclisation reaction to produce the fused tricyclic ketone (**95**). Subsequent modification furnished paniculatine (Scheme 2.7).



Scheme 2.7

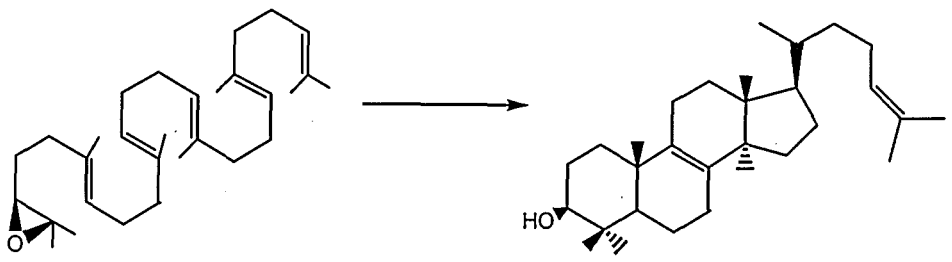
For reductive tandem processes, SmI_2[64] has proven a valuable reagent. On the other hand, oxidative reaction sequences incorporating anionic and radical steps are hardly explored.[65] The use of samarium iodide is a non-toxic method to mediate radical reactions and has been used in two procedures to facilitate pyrrolidine formation by the addition of α-aminoalkyl radicals to alkenes. Radicals (**98**) generated from α-amino-benzotriazoles (**97**) exist in equilibrium with cyclised radicals (**99**) (Scheme 2.8).[66] The equilibrium could be driven towards (**99**) by rapidly reducing the cyclised radicals to organosamarium compounds (**101**), which could finally be trapped by electrophiles yielding products (**102**). Therefore, a synthetic advantage of using this method is its ability to terminate a single or tandem radical reaction with another carbon-carbon bond forming step, instead of the usual hydrogen-atom transfer. The same procedure applied to intramolecular radical addition to electron-deficient alkenes was also reported.[67]



Scheme 2.8

2.4 Tandem cationic processes.

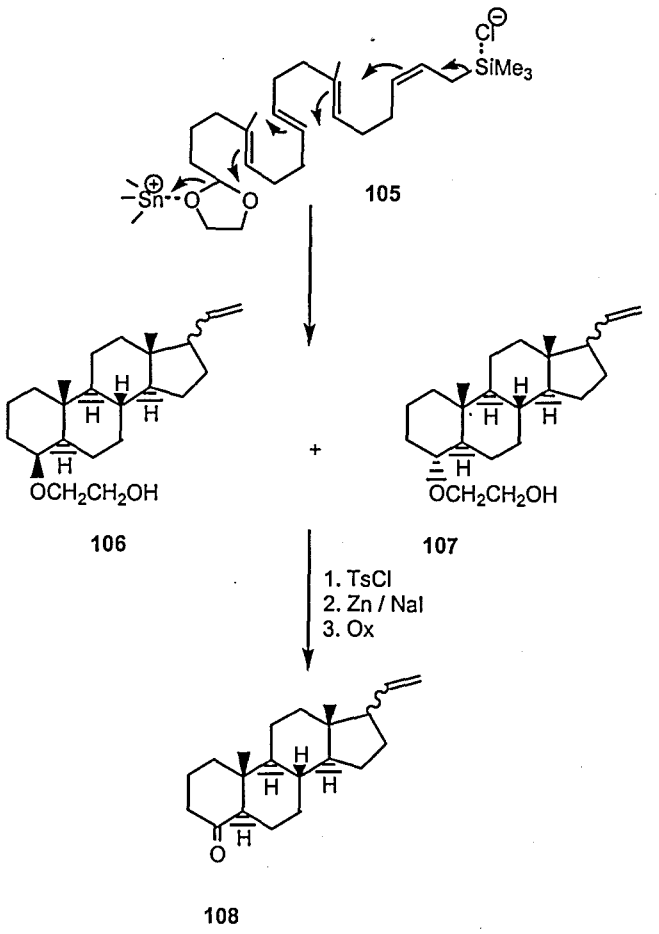
The *in vitro* imitation of the cyclisation of squalene oxide (**103**) to lanosterol (**104**) is regarded as a particulary elegant biomimetic synthesis, developed by W. S. Johnson (Figure 2.1).[68]



103 104

Figure 2.1

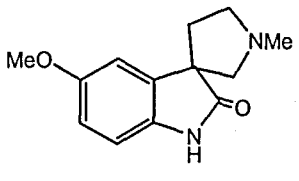
The term "biomimetic" has been adopted for synthetic strategies that attempt to imitate *in vitro* either a proven biosynthesis or a speculative biogenetic pathway.[69] This is an example of a multi-bond-forming reaction, leading to an increase in molecular complexity, and shows the power of such a cascade sequence using a cationic process. This is a dramatic example; as many bonds are formed in one-pot and the stereochemistry is controlled. Since Johnson's pioneering work, many variations of this type of reaction have been applied in diverse steroid syntheses. Synthesis of "regular" steroids (i.e. steroids with a five-membered D ring) is also possible, provided the allylsilane group is used as the terminator for this "zipper" reaction.[70] Thus, tetraene (**105**) affords the isomers (**106**) and (**107**) in 34% yield when treated with $SnCl_4$ as outlined in scheme 2.9. The hydroxyethoxy side chain is subsequently removed to provide, after oxidation, a mixture of epimeric ketones (**108**). Six stereogenic centres are formed stereoselectively in a single step.



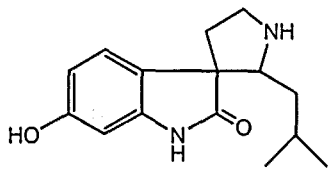
Scheme 2.9

2.5 Pyrrolidines from α-amino acids.

The examples in the previous sections show a selection of tandem reactions, which have been used effectively in the synthesis of carbocyclic and heterocyclic compounds. Previous work in the group has focused on the spiropyrrolidinyl-oxindole alkaloids, horsfiline (**109**) and elacomine (**110**).



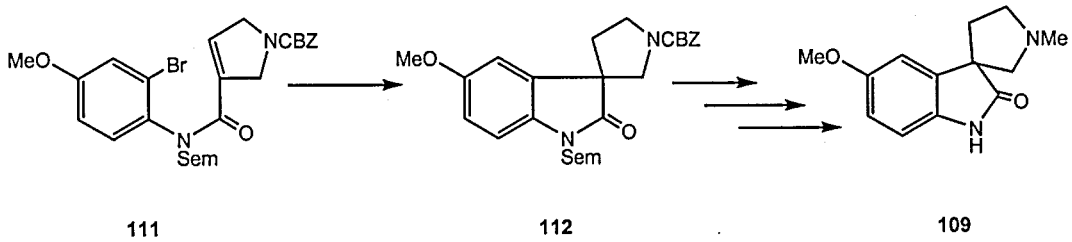
109



110

Wilkinson[71,72] explored the synthesis of horsfiline (**109**) via an aryl radical cyclisation. He utilised the cyclisation of an aryl radical generated from (**111**) onto a 2,5-dihydropyrrole unit to give a spiropyrrolidinyl-oxindole (**112**) as the key step in a total synthesis of horsfiline (**109**) (Scheme 2.10). Horsfiline is an

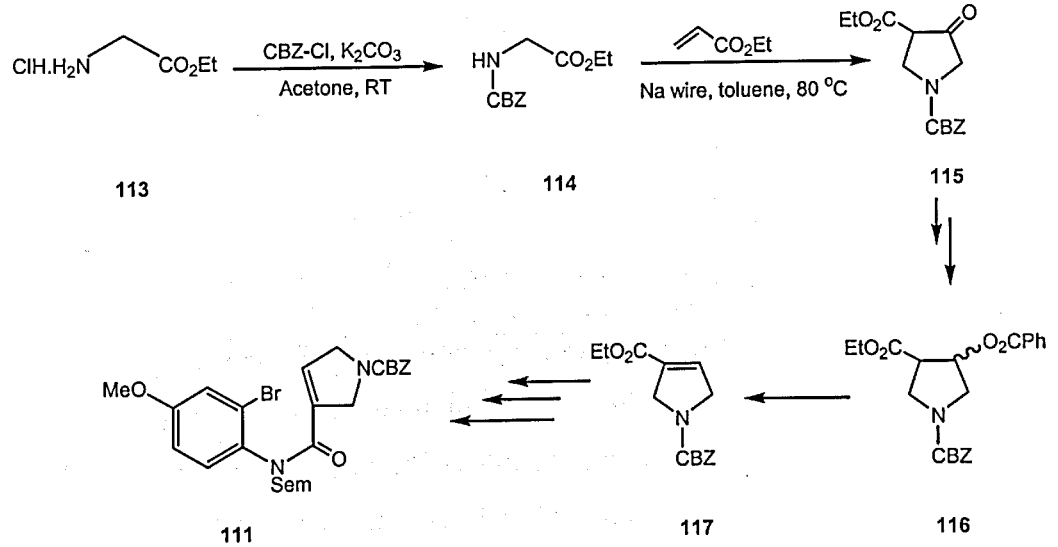
oxindole alkaloid isolated from *Horsfieldia superba*, a Malaysian tree that has some local popularity as a medicinal plant.[73]



111 112 109

Scheme 2.10

The cyclisation precursor (**111**) was prepared based on an approach used by MacDonald[74] starting from a glycine derivative, following the pathway illustrated in scheme 2.11. Glycine ethyl ester hydrochloride (**113**) was protected[75] with the benzyloxycarbonyl (CBZ) group to give (**114**). The protected glycine ester (**114**) was treated with ethyl acrylate in toluene containing sodium wire[76] leading to conjugate addition of the amide anion (Michael addition) followed by a Dieckmann cyclisation of the intermediate carbanion giving rise to a β-keto ester (**115**).

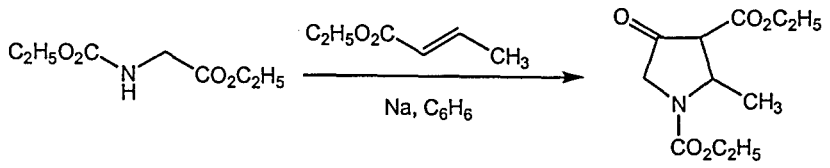


113 114 115 116 117 111

Scheme 2.11

Reduction of the ketone (**115**) using sodium borohydride, followed by benzoylation of the resultant alcohol furnished (**116**). Further transformations furnished the key cyclisation precursor (**111**). Thus, the tandem Michael-Dieckmann sequence was successful in furnishing the desired pyrrolidine (**115**) in

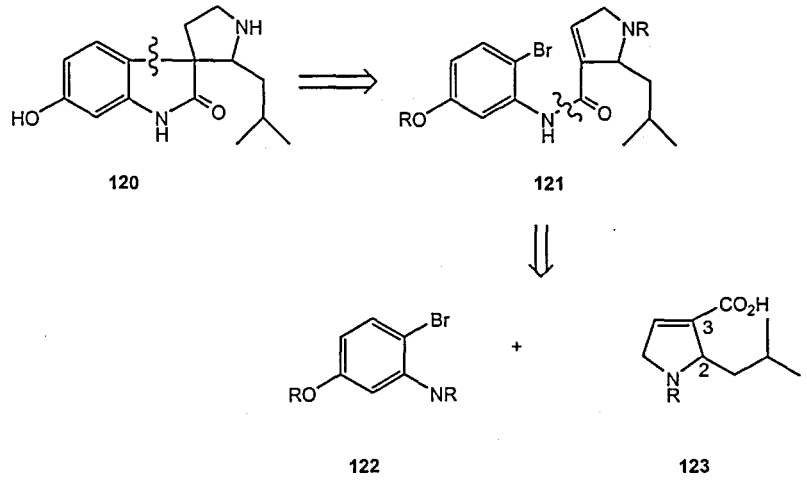
good yields. Kuhn and Oswald[76] first reported this Michael-Dieckmann reaction in 1956, starting from the amino acid glycine (Scheme 2.12).



118 119

Scheme 2.12

Ho extended this research towards the synthesis of elacomine (**120**) as shown in scheme 2.13.[77]

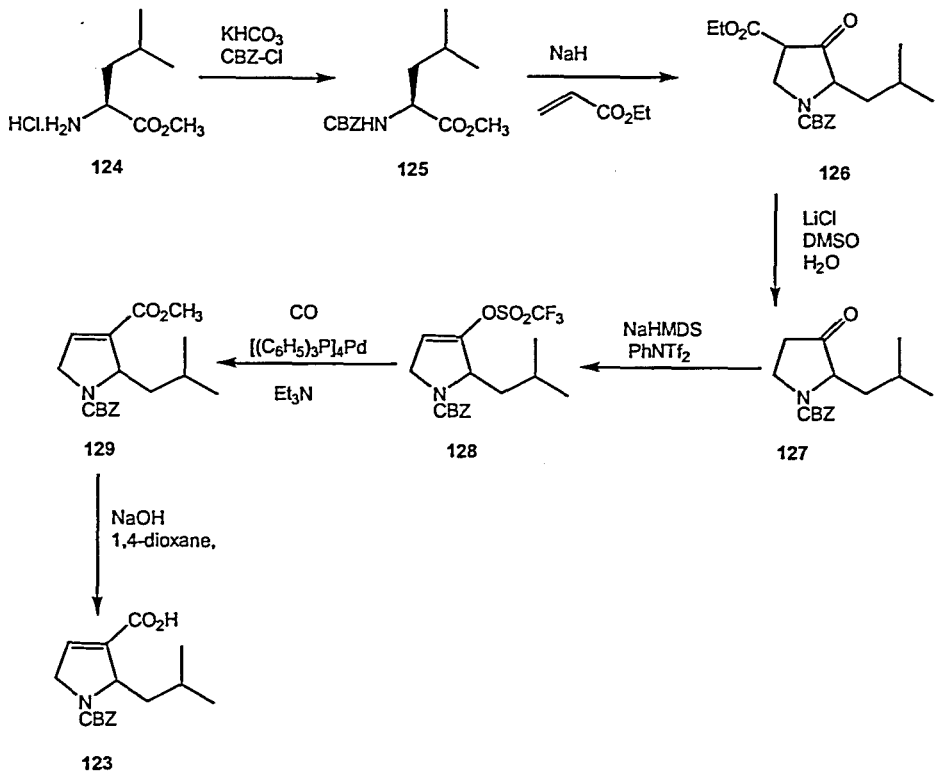


120 121 122 123

Scheme 2.13

The key step involved the formation of the spiropyrrolidinyl oxindole skeleton via an aryl radical cyclisation onto the C-3 position of the 2,4-disubstituted-2,5-dihydropyrrole (**120**). Again, the key intermediate for the synthesis of the desired radical cyclisation precursor was the dihydropyrrole (**123**), now carrying an isobutyl group at the C-2 position. The dihydropyrrole (**123**) was synthesised in six steps starting from (S)-leucine methyl ester hydrochloride (**124**).

The synthesis of the key dihydropyrrole (**123**) is outlined in scheme 2.14 and follows the Mac Donald approach used by Ewin and Ho.[77]

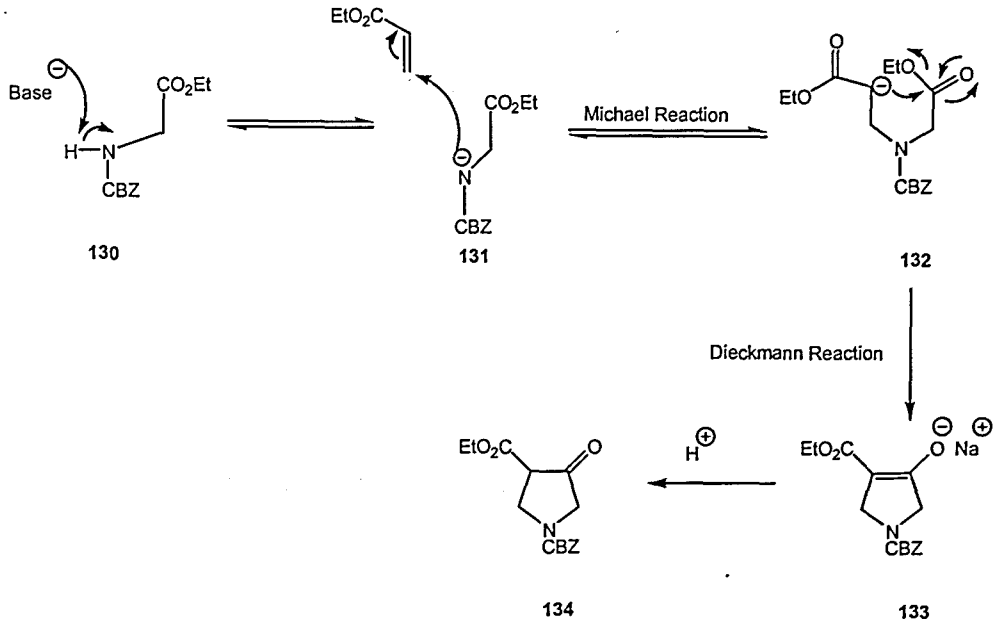


Scheme 2.14

The Michael-Dieckmann sequence afforded β-keto ester (**126**) in 58% yield. Remarkably, this material had a non-zero optical rotation. The possibility of diastereomers complicated the analysis of (**126**) but dealkoxycarbonylation yielded ketone (**127**) which possessed an $[\alpha]_D^{20}$ + 43.1.[77] The non-racemic nature of (**126**) and (**127**) was surprising as the Michael-Dieckmann sequence was carried out under strongly basic conditions which might be expected to lead to racemisation at C-2.

2.6 Aim of project.

The aim of this part of my work was to investigate the stereochemical outcome of the Michael-Dieckmann sequence. If the stereochemical purity of the β-keto ester pyrrolidines such as (**126**) were high, this would provide a valuable and efficient approach to the synthesis of highly functionalised pyrrolidines in high enantiomeric excess. The mechanism for the reaction is illustrated in scheme 2.15.

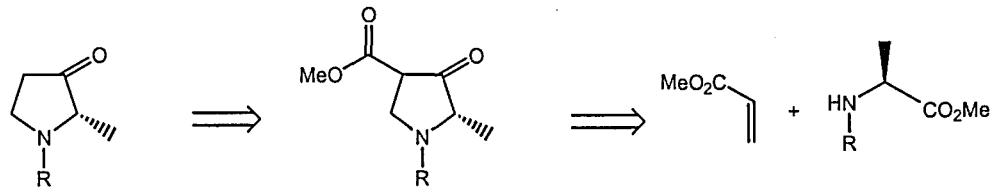


Scheme 2.15

The protected glycine (130) was reacted with ethyl acrylate in the presence of base. Deprotonation of the nitrogen causes it to act as a nucleophile (131) which undergoes a conjugate addition onto the α,β-unsaturated carbonyl compound (ethyl acrylate). In this case, however, the reaction proceeds via a Dieckmann cyclisation where the carbanion formed undergoes an intramolecular addition onto the other ester group (132). This leads to the enolate of a 1,3-dicarbonyl compound (133) rendering the process irreversible. On work-up, (133) is protonated to give the β-keto ester (134).

2.7 Michael-Dieckman reaction sequence with alanine.

In order to investigate the observation by Ho, we chose to explore the Michael-Dieckmann reaction sequence using the simplest chiral amino acid (-) alanine. Our synthetic approach towards the synthesis of *N*-benzyloxycarbonyl-(*2S*)-2-methyl-pyrrolidin-3-one (134) is illustrated in the following retrosynthetic pathway (Scheme 2.17).

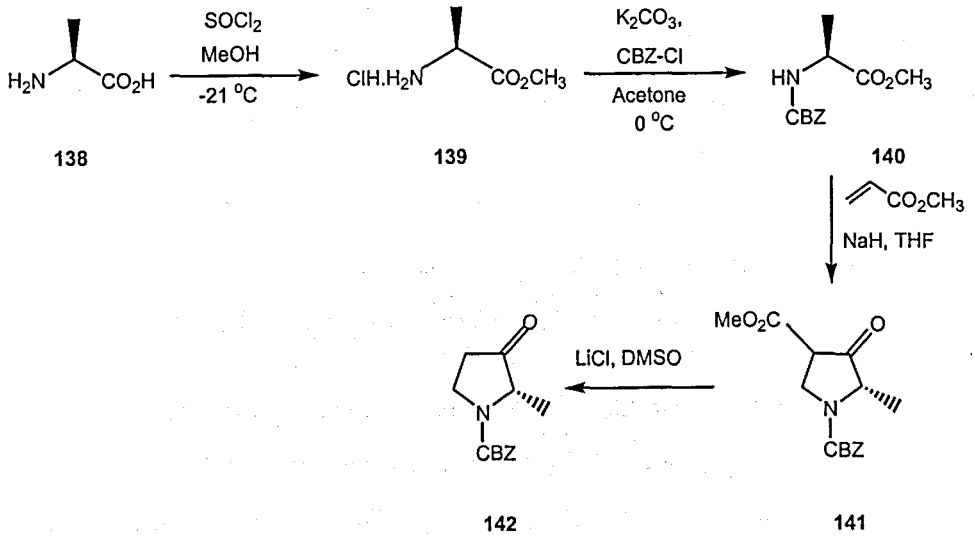


134 135 136 137

Scheme 2.17

Initially, the feasibility of this route was investigated. The β-keto ester (**135**) could be formed by Michael addition of (**137**) onto methyl acrylate (**136**) followed by Dieckmann cyclisation. Dealkoxycarbonylation of the β-keto ester (**135**) could be achieved using the method of Krapcho[78] to give the required ketone (**134**). We initially carried out the Michael-Dieckmann reaction using ethyl acrylate. However, ethyl acrylate was replaced with methyl acrylate to give less complex ^{1}H NMR spectra.

The desired (*2S*)-*N*-benzyloxycarbonyl-2-methyl-pyrrolidin-3-one compound (**142**) was synthesised following the pathway shown in scheme 2.18.



138 139 140 141 142

Scheme 2.18

The conversion of (*S*)-(-)-alanine (**138**) to its methyl ester hydrochloride was achieved in 99% yield using an excess of thionyl chloride in methanol. The optical rotation for (**139**) $[\alpha]_D^{20}$ +6.1 is in accord with the literature[79] value $[\alpha]_D^{20}$

+7.0). In the ^{1}H NMR, a singlet δ 3.71 ppm with an integration of 3 protons was assigned to the ester methyl group. Protection of the amino function (**138**) with the benzyloxycarbonyl group using potassium carbonate in acetone gave (**140**) in 79% yield,[77] after removal of the benzyl alcohol by-product by distillation. This showed an optical rotation of $[\alpha]_D^{20}$ -28.1, which is also in accord with the literature[83] value ($[\alpha]_D^{20}$ -26.8). The protected alanine (**140**) was then treated with methyl acrylate in THF containing sodium hydride to give the β-ketoester (**141**) in 51% yield. This showed an optical rotation of $[\alpha]_D^{20}$ +4.5 which has the opposite sign to its starting material, thus indicating that racemisation has not occurred and the stereochemistry is not due to the presence of any starting material. Analysis of ^{1}H NMR and ^{13}C NMR revealed that some of the product existed in the enol form. An indication of this was observed in the ^{13}C NMR when the expected ketone peak at around δ 200 ppm was not evident. Further evidence of the enol form (OH bond) was observed in the IR spectrum, which showed a peak at 3409cm^{-1}.

Dealkoxycarbonylation, of the β-ketoester (**141**) using the procedure of Krapcho[78] involving lithium chloride in wet dimethylsulfoxide heated to 100 °C gave the ketone (**142**) in 63% yield. This showed an optical rotation of $[\alpha]_D^{20}$ +16.3. Two inferences can be made from this measurement. Firstly, a non-zero value of the optical rotation means that there is some enantiomeric excess, that is, the chiral centre at C-2 is not racemic. Secondly, the optical rotation of (**142**) is substantially greater than that of the starting material (**141**) (+16.3 versus +4.5 respectively), indicating that there is no optical contamination from the starting material. The value of the optical rotation of (**142**) is non-zero for two reasons.

Firstly, in the presence of a base, an anion is generated on the C-4 centre, in preference to the C-2 centre, as it is less sterically hindered and has a lower pka than the C-2 centre, ~11 vs ~17 respectively (Figure 2.2). A dianion would be required to racemise the C-2 centre.

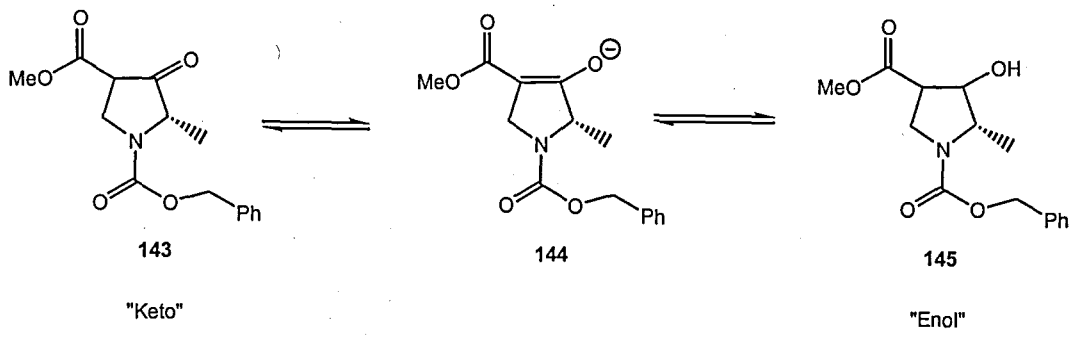


Figure 2.2.

Secondly, it is unlikely that an enolate anion would be generated to racemise the C-2 centre, as this would result in an allylic ($A^{1,3}$) strain between the methyl group on C-2 and the carbonyl group within the benzyloxycarbonyl group (Figure 2.3).

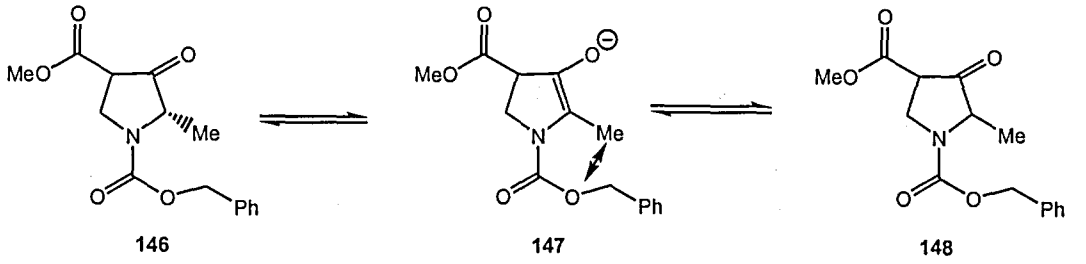
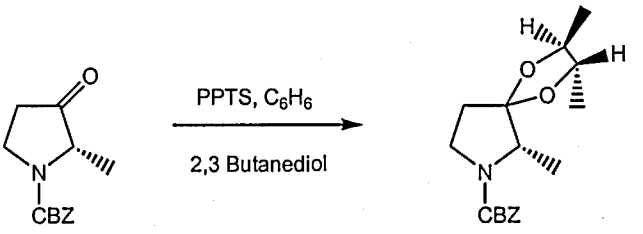


Figure 2.3.

At this stage, we were interested in gaining some insight into the stereochemical integrity at the C-2 of the ketone (**142**). The ^{1}H NMR spectra (**141**) was very broad and complex and thus, it was decided to analyse compound (**142**), as this ^{1}H NMR spectrum was slightly sharper and less complex. Many analytical techniques were employed to establish the extent chirality had been retained at the C-2 centre. The techniques utilised were chiral HPLC, chiral GC and ^{1}H NMR. All techniques failed. Although many chiral HPLC columns were employed, none were successful in separating the enantiomers of compound (**142**) or the diastereomers of compound (**141**). The column used for chiral GC seemed incompatible with these pyrrolidine compounds. Finally, variable temperature ^{1}H NMR was employed to eliminate the restricted rotation but failed to give clearly resolved peaks. The spectra remained broad and complex.

2.8 Ketalisation of carbonyl group.

Owing to the difficulties associated with determining the stereochemical integrity of the C-2 of ketone (**142**), it was decided to synthesise a derivative of (**142**) in order to create diastereoisomers within the compound (Scheme 2.19).



149 **150**

Scheme 2.19

The aim of this reaction was to synthesise a ketal with C_2 symmetry.[80] Ketalization with an enantiopure diol of C_2 symmetry would give distereoisomers, which could be analysed by ^{1}H NMR spectroscopy. The entantiomerically pure diol would be expected to react preferentially with one enantiomer over another and the ratio of the diastereoisomers formed could then be determined by ^{1}H NMR spectra. Standard ketalization conditions were employed [pyridinium *p*-toluenesulfonate (PPTS), refluxing benzene, Dean-Stark apparatus] with (R,R)-2,3-butanediol. However, the procedure failed as the ^{1}H NMR spectra was extremely complex due to the fact that:

A) Restricted rotation within the molecule leads to the formation of rotamers.

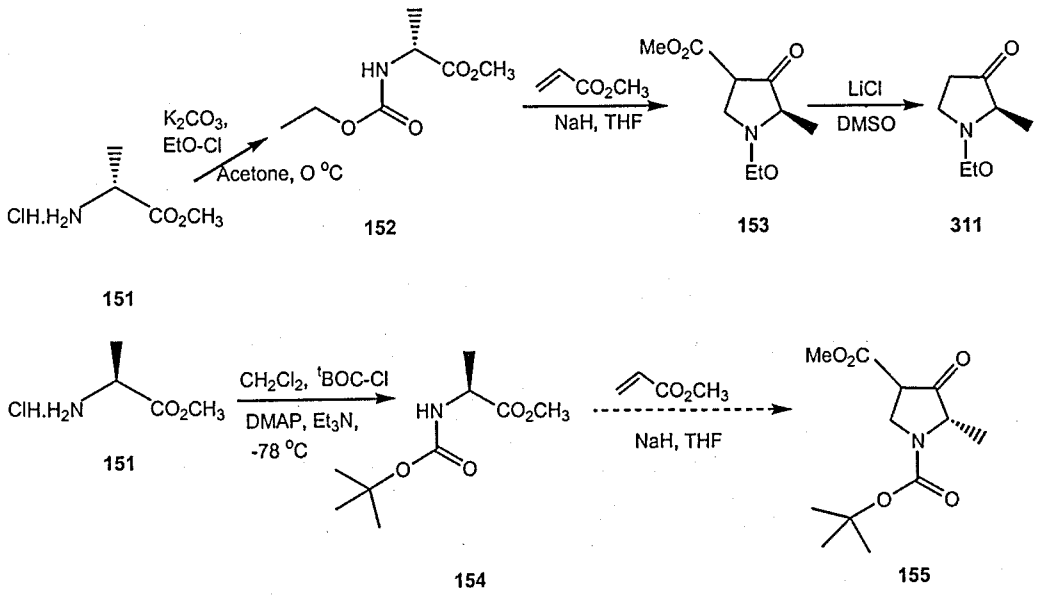
B) The enol form is present within the molecule.

C) Diastereoisomers are formed from ketalisation of the carbonyl group.

In order to clarify this uncertainty, variable temperature ^{1}H NMR was again employed, but failed to give clearly resolved peaks.

2.9 Alternative protecting groups.

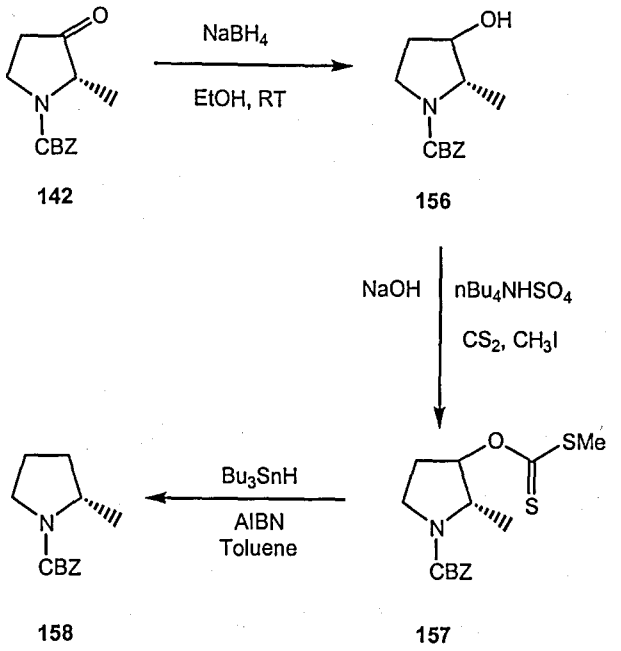
Whilst investigating the tandem Michael-Dieckmann reaction, alanine methyl ester hydrochloride (**151**) was also protected with ethyl chloroformate to afford (**152**) in 59% yield and with di-*tert*-butyl dicarbonate to afford (**154**) in 62% yield as illustrated in scheme 2.20. It was thought that these protecting groups might simplify the ^{1}H NMR spectrum somewhat, perhaps alleviating the restricted rotation. However, this was not the case as it proved more difficult to assign the protons around the pyrrolidine ring as the protons of the protecting group appeared in the same proximity as the protons on the ring.



Scheme 2.20

2.10 Synthesis of (*S*)-CBZ-2-methyl-pyrrolidine (158).

Owing to the fact that the above techniques were unsuccessful, we thought to synthesise a related compound with known optical rotation.[81] This would indicate if compound (**142**) has some enantioselectivity by means of deduction. The synthetic approach towards the desired (*S*)-CBZ-2-methyl-pyrrolidine (**158**) was synthesised following the pathway shown in scheme 2.21.

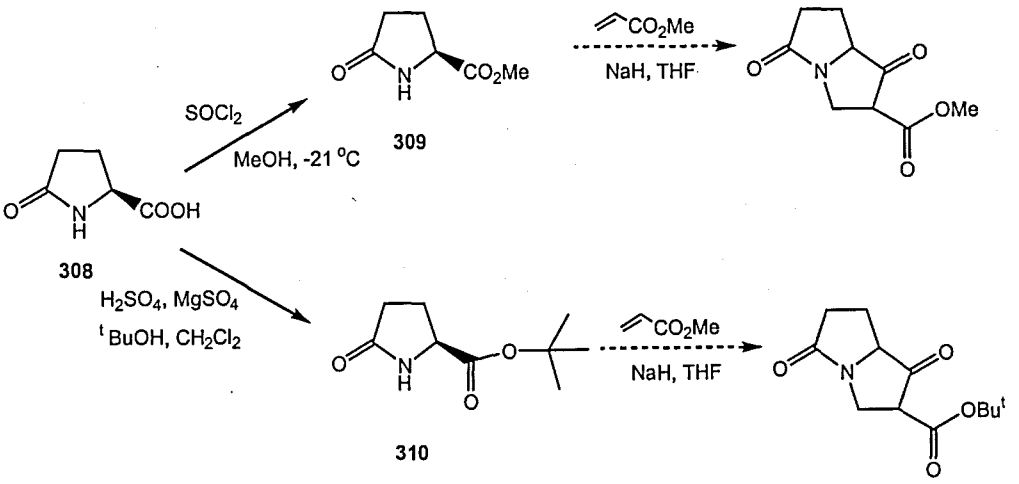


Scheme 2.21

The ketone (**142**) was reduced[82] using sodium borohydride in ethanol to give the corresponding alcohol (**156**) in 87% yield. In the ^{1}H NMR spectrum, the C-2 hydrogen was observed at δ 3.82 ppm as a quintet with a ^3J value of 6.4 Hz and the C-3 hydrogen was observed at δ 4.17 ppm as a broad multiplet. Conversion of the alcohol into the xanthate ester under phase transfer conditions[82] with sodium hydroxide solution, carbon disulfide, methyl iodide and catalytic *tetra*butyl ammonium hydrogen sulfate gave xanthate (**157**)[83] in 48% yield. The ^{1}H NMR spectrum, a singlet appears at δ 2.48 ppm, integrating for the three protons of SCH_3. The C-3 hydrogen is now observed at δ 5.82 ppm as a multiplet. Reaction of (**157**) under typical radial cyclisation conditions [(tributyltin hydride, azobisisobutyronitrile (AIBN) in toluene][84] gave (*S*)-2-methyl-1-pyrrolidine carboxylic acid phenylmethyl ester (**158**) as the target molecule in 27% yield. The four hydrogens of C-3 and C-4 can be seen as a multiplet between δ 1.5 and δ 2.1 ppm in the ^{1}H NMR spectrum. The hydrogen at C-2 is now observed as a broad singlet between δ 3.8 and δ 4.0 ppm. The optical rotation of this molecule is $[\alpha]_D^{20}$ +21.4. This indicates that some chirality has been retained throughout the synthesis. The literature value[84] for this compound is $[\alpha]_D^{20}$ –24.9 for the *R* isomer. Thus, we can deduce that the configuration of our pyrrolidine (**158**) is *S* and the optical purity (ee) is 86%. The molecule has retained its stereochemistry throughout the reaction sequence.

2.11 Future work

The Michael-Dieckmann chemistry could be applied towards the synthesis of indolizidines (Scheme 2.22). We briefly attempted this reaction but did not study it in detail. The cyclic amino acid, pyroglutamic acid (**308**) was converted to the ester (**309**) in 74 % yield. However, application of the tandem Michael-Dieckmann reaction conditions using methyl acrylate did not generate the desired indolizidine. It was thought that changing the ester for a bulkier group such as tertiary butyl would be better suited to the tandem chemistry. Again, conversion of (**308**) to the tertiary butyl ester occurred easily in 76 % yield. However, this also failed to afford the indolizidine. This is an area that could be studied further as it would be a very elegant synthesis of indolizidines and perhaps extendable to quinolizidines.



Scheme 2.22

2.12 Conclusion

The Michael-Dieckmann cyclisation sequence successfully gave pyrrolidines in good yields with encouraging enantiomeric excess (86% ee). As the simplest enantiopure amino acid was chosen to initiate this research, we can assume that other amino acids with bulkier side chains would also retain their stereochemistry at the C-2 position. This will allow the synthesis of pyrrolidines (**141**) with a range of groups at the C-2 position. The ester and ketone group will allow elaboration into complex, heavily substituted pyrrolidines in optically–active form.

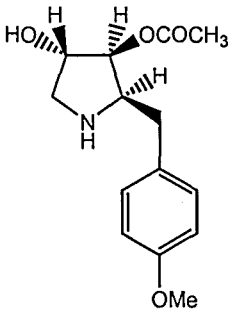
CHAPTER III

A Novel Tandem Michael-Dieckmann Approach towards the Natural Product Anisomycin.

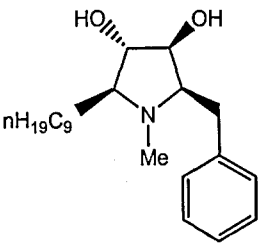
3.1 Introduction.

The Michael-Dieckmann reaction sequence as described in Chapter II has potential applicability towards the synthesis of the natural product (-)-anisomycin.

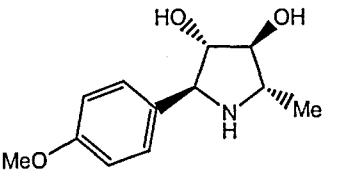
Polysubstituted pyrrolidines represent a class of natural products as exemplified by the antifungal antibiotics (-)-anisomycin, (+)-preussin and (-)codonopsinine.



(-)-Anisomycin



(+)-Preussin



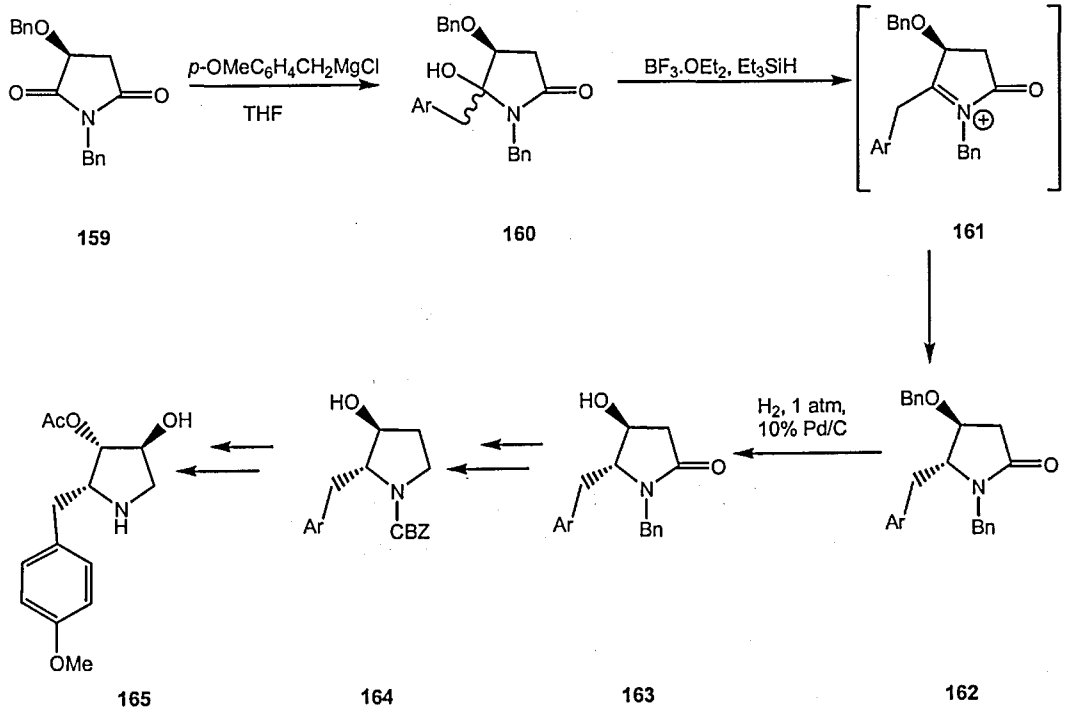
(-)-Codonopsinine

The antibiotic (-)-anisomycin was first isolated from the fermentation broths of *Streptomyces griseolus* and *Streptomyces roseochromogenes* by Pfizer, Inc., in 1954.[84] Some ten years after its initial isolation, its structure and relative stereochemistry were elucidated by chemical and spectroscopic means and confirmed by X-ray crystallography.[85] The absolute stereochemistry of this alkaloid has been firmly established as 2R, 3S, 4S by chemical correlation with *L*-tyrosine.[86] The literature contains many references toward this alkaloid, which will be discussed briefly.

3.2 Previous approaches towards (-)-anisomycin.

There have been a large number of syntheses of anisomycin.[87] These will not be exhaustively reviewed but a selection of syntheses leading to optically pure anisomycin will be discussed briefly, highlighting the key reactions used.

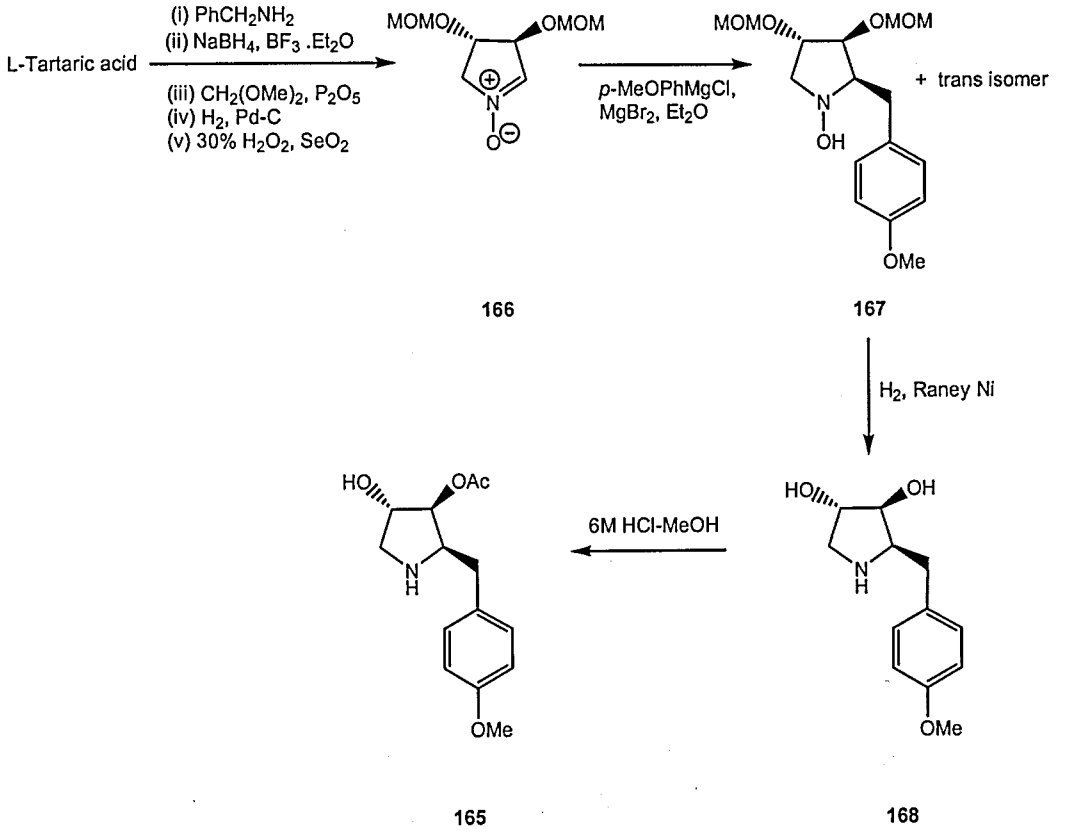
One of the main approaches to single enantiomer synthesis involves using the chiral pool as a starting material, such as L-malic acid, L-tartaric acid, D-glucose, D-ribose, D-galactose, D-mannitol, D-tyrosine, or L-aspartic acid and has often proceeded in modest yield.[88] In this context Huang and Zheng[89] used a malic acid-based methodology to *N*-containing compounds, in particular (-)-anisomycin. In the approach, the key reductive alkylation of (*S*)-*N*, *O*-dibenzylmalimide (**159**) (Scheme 3.1), which was prepared starting from (*S*)-malic acid led to (**163**) in high regio- and stereoselectivity. This was then transformed into the desired compound (**165**).



Scheme 3.1

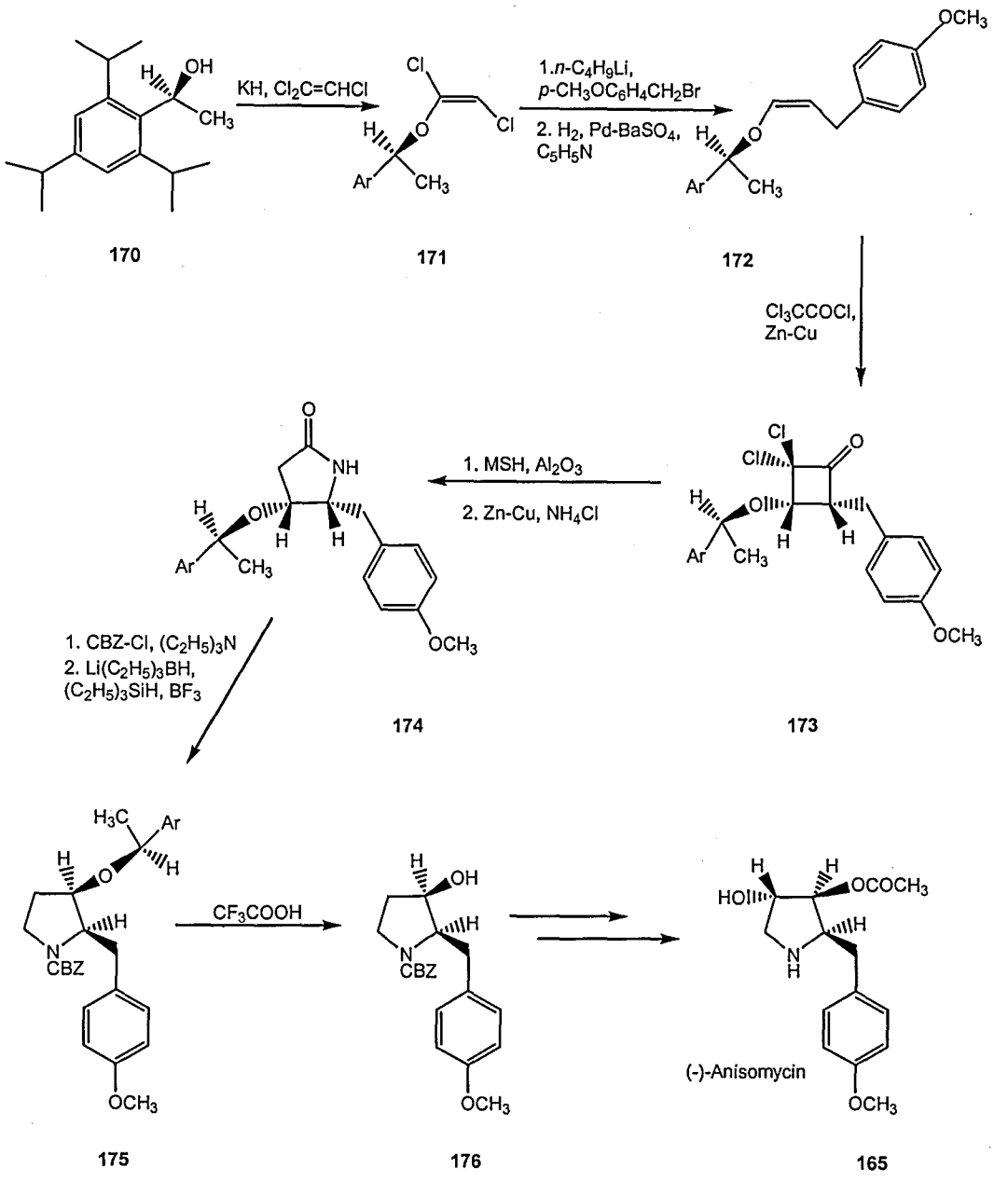
An alternative chiral pool approach towards (-)-anisomycin was reported.[90] Nitrone was utilised in this enantioselective synthesis. The required nitrone (**166**), prepared from L-tartaric acid, on reaction with (4-methoxybenzyl)magnesium

chloride followed by reduction and deprotection gave deacetylanisomycin in 12% overall yield (Scheme 3.2).



Scheme 3.2

A synthesis using a chiral auxiliary to control the stereochemistry was reported by Greene and co-workers.[91] Given the sustained interest in this alkaloid, they used a dichloroketene-chiral *O*-alkylation enol ether cycloaddition methodology[91] for flexible access towards (-)-anisomycin. This is shown in scheme 3.3.



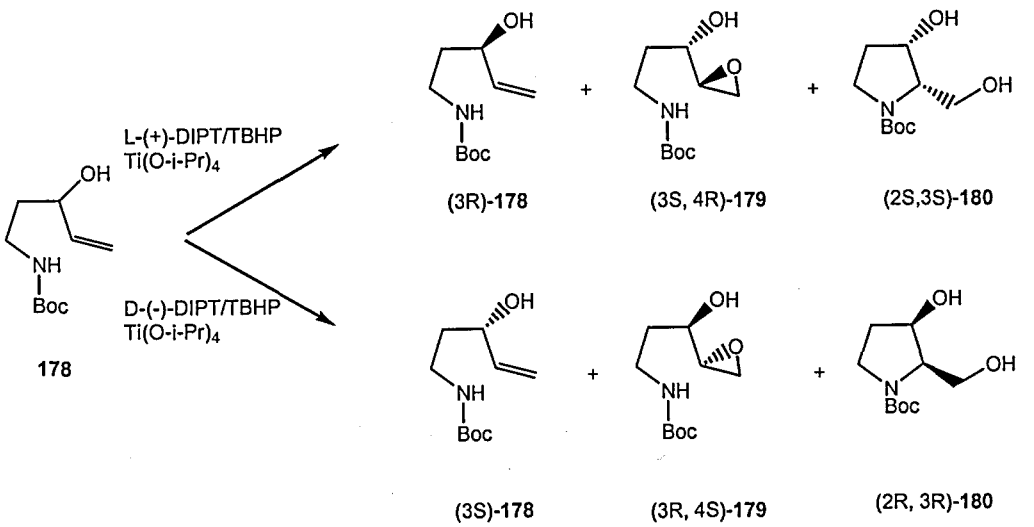
Scheme 3.3

In the presence of dichloroketene (DCK), generated *in situ* from trichloroacetyl chloride and zinc-copper couple, the chiral enol ether (**172**) underwent face-selective cycloaddition to produce the 2+2 cycloadduct, dichlorocyclobutanone (**173**). The pyrrolidinone (**174**) was accessed through Beckmann ring expansion, dechlorination, and *N*-protection of dichlorobutanone (**173**).

The pyrrolidinone derivative (**174**) was converted to anisomycin (**165**) through formal *syn* elimination of water, *trans*-dihydroxylation-monoacetylation, and *N*-deprotection. This highly enantioselective formal total synthesis, based on

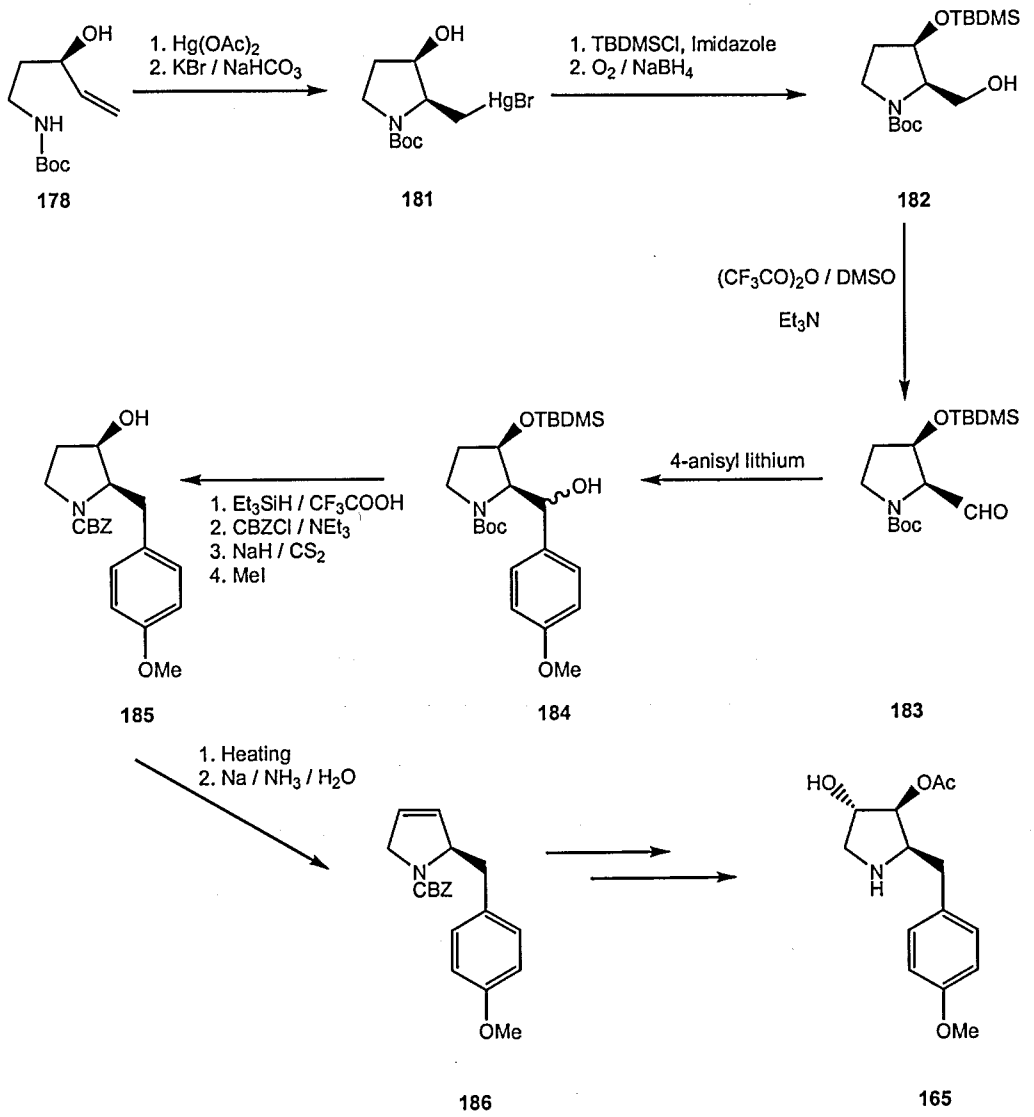
effective asymmetric 2+2 cycloaddition, produces (-)-anisomycin in approximately 8% overall yield.

An approach towards anisomycin was reported by Momose and co-workers,[92] employed the Sharpless asymmetric oxidation[93] of racemic *N*-(*tert*-butoxycarbonyl)-3-hydroxy-4-pentenylamine (**178**) allowing not only kinetic resolution to provide optically active compounds (*3R*-**178**) and (*3S*-**178**). These compounds are used for intramolecular amidomercuration and also promote asymmetric epoxidation (**179**), accompanied by concomitant intramolecular *N*-alkylation to give optically active *cis*-3-hydroxy-2-(hydroxymethyl)pyrrolidine (**180**) (Scheme 3.4).



Scheme 3.4

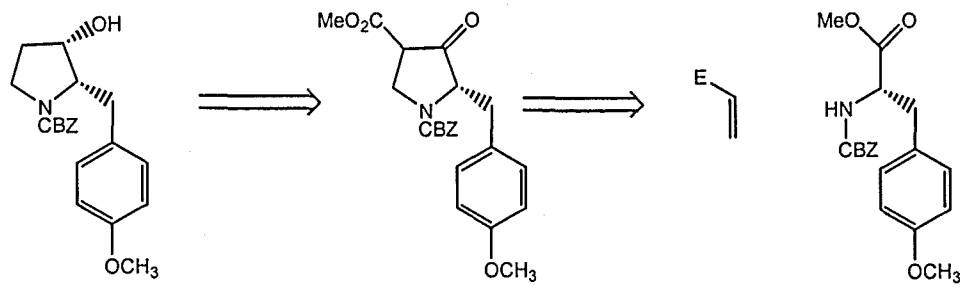
The optically active diols (**180**) have been expediently used as chiral building blocks in the asymmetric synthesis of (-)-anisomycin. The efficient transformation of (*2R*, *3R*) (**183**) into intermediate (**186**) for the construction of (-)-anisomycin, was performed via a short route as shown in Scheme 3.5. Debenzylation of (**186**) with sodium/ammonia furnished a known secondary amine[94], which has been converted into (-)-anisomycin (**165**) by Meyers.[95] This method also provided access to chiral pyrrolidine-related alkaloids and unusual amino acids containing vicinal amino alcohol functionality.



Scheme 3.5

3.3 A Michael-Dieckmann approach towards (+)-anisomycin (165).

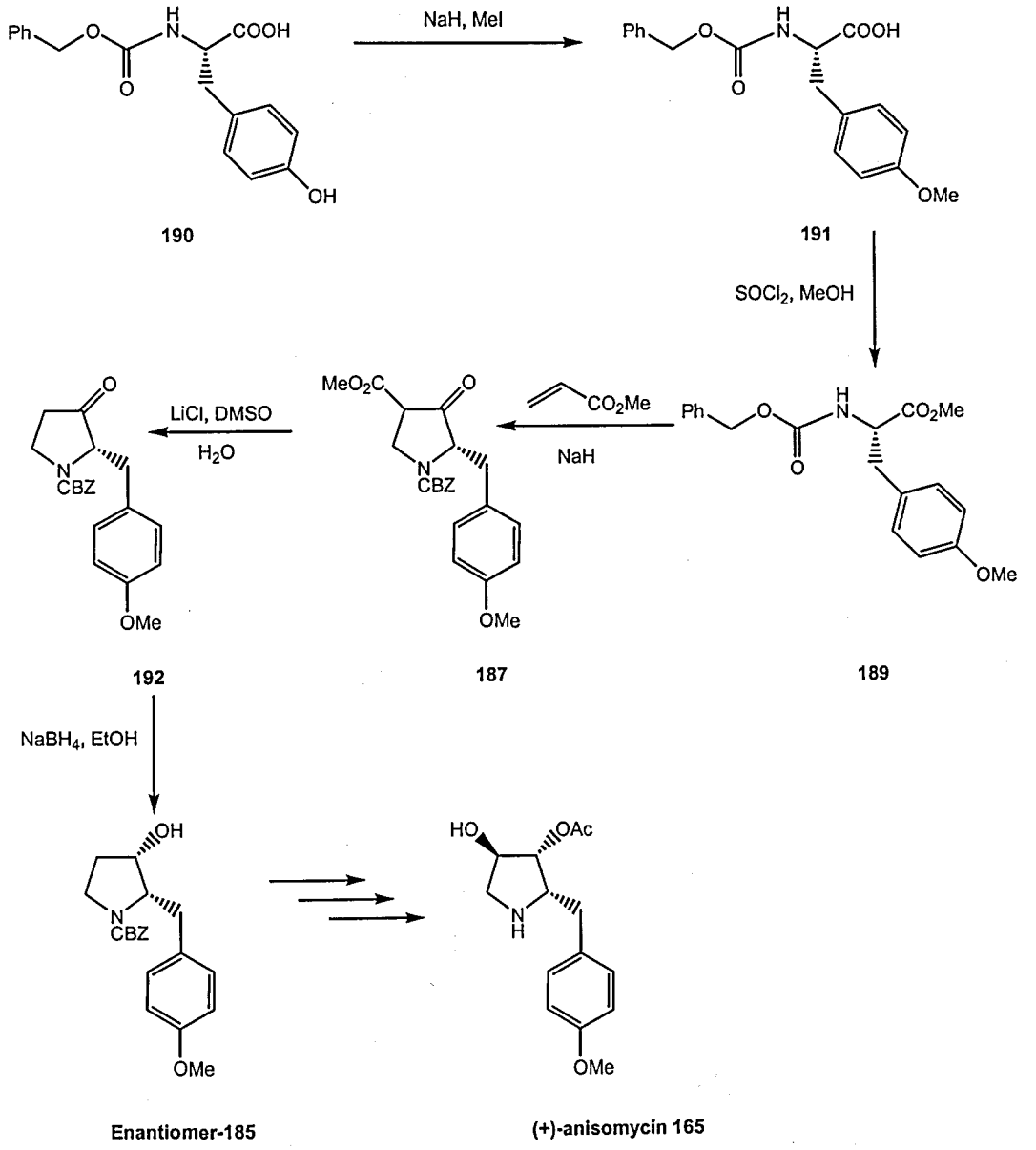
The continued interest in anisomycin (**165**) prompted us to consider using the Michael-Dieckmann chemistry described in the previous chapter as a short approach to the key enantiomer of the precursor (**185**) of Momose (Scheme 3.5). This is described retrosynthetically in scheme 3.6.



Enantiomer-185 187 188 189

Scheme 3.6

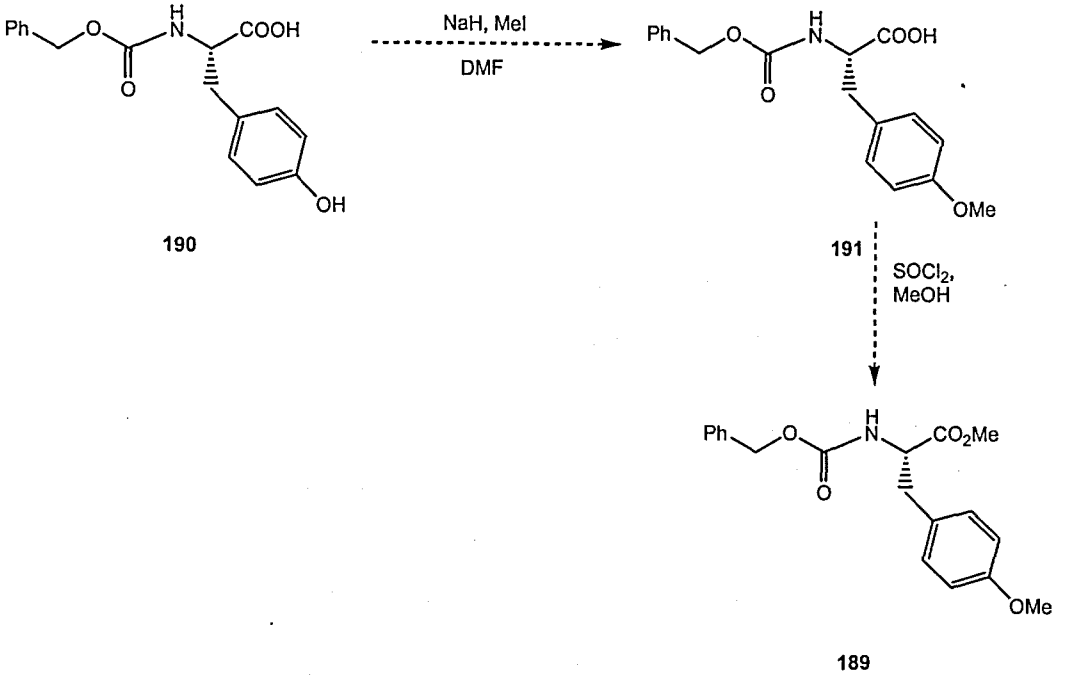
The Michael-Dieckmann reaction using CBZ-(*S*) tyrosine methyl ester (**189**) and methyl acrylate (**188**) should lead to (**187**). Krapcho dealkoxycarbonylation would be expected to give the ketone (**192**), which should undergo reduction from the face opposite substituted benzyl group to give the correct relative stereochemistry. Momose converted (**185**) into (-)-anisomycin in 7 steps. Our proposed synthesis of (+)-anisomycin would lead to a very short synthesis of intermediate (**185**) in just five steps. This intermediate can be easily transformed into the desired product (**165**) as described by Meyers.


NaH, MeI
190
191
SOCl2, MeOH
LiCl, DMSO
H2O
NaH
192
187
189
NaBH4, EtOH
Enantiomer-185
(+)-anisomycin 165

Scheme 3.7

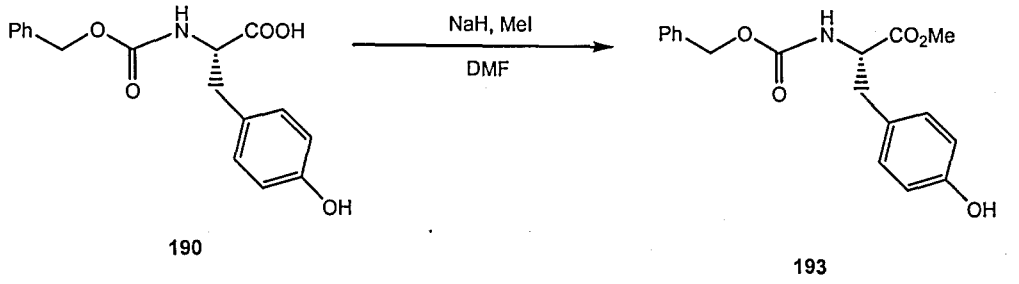
3.4 Preparation of the cyclisation precursor (189).

Preparation of 2-benzyloxycarbonylamino-3-(-4-methoxy-phenyl)-propionic acid methyl ester (**189**) was envisaged to occur in two steps. (Scheme 3.8).



Scheme 3.8

The reaction of (**190**) with sodium hydride and iodomethane afforded a mono-methylated product in 41% yield.[96] The ^{1}H NMR spectrum of this product showed a singlet at δ 3.6 ppm integrating for 3 H assigned to a O-CH_3 group. It is unclear from this whether the phenol or the carboxy group has been methylated. A sharp OH peak was observed at 3354cm^{-1} in the IR spectrum. If the acid was present, a broad OH peak would have been observed. Finally, thin layer chromatography showed a sharp spot when visualised with $KMnO_4$ very unlike a carboxyl acid. The tentative conclusion drawn from this data is that we have converted (**190**) into methyl ester (**193**) (Scheme 3.9).

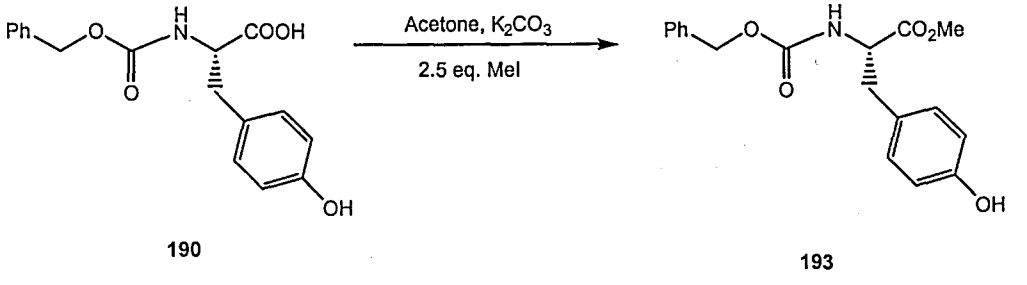


190 193

Scheme 3.9

It was thus decided to change the alkylating conditions. We varied the amount of methyl iodide but this continually yielded the supposed methylated ester.

The alkylating conditions were changed to potassium carbonate in acetone and 2.5 equivalents of methyl iodide (Scheme 3.10). The reaction was monitored by thin layer chromatography but again, only the ester was produced. The reaction was also carried out using dimethyl sulfate but excess reagent proved very difficult to remove from the final product.

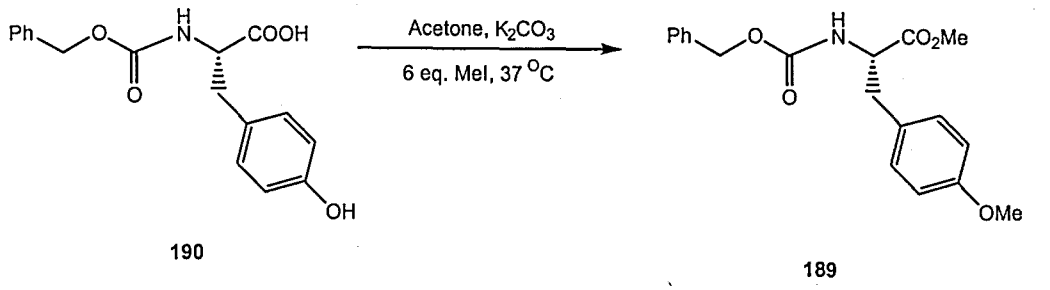


190 193

Scheme 3.10

We altered the reaction conditions to six equivalents of methyl iodide. After 4 hours two spots appeared on the TLC plate. Leaving the reaction for a further 12 hours with gentle heating produced only one spot on the TLC plate. Two singlets were now observed at δ 3.6 ppm and δ 3.65 ppm in the ^{1}H NMR spectrum both integrating for 3 H and which we assigned to two O-CH_3 groups. The peak, which we previously assigned to the ester, again appeared as a singlet at δ 3.6 ppm, while what we suppose to be the ether appeared next to it as a singlet at δ 3.65 ppm (Scheme 3.11). Finally, no peak at 3354cm^{-1} was observed in the IR spectrum indicating that no O-H stretch is present. This product showed an

optical rotation of $[\alpha]_D^{20}$ + 47. The literature value for this compound is $[\alpha]_D^{20}$ + 46.8.[79]



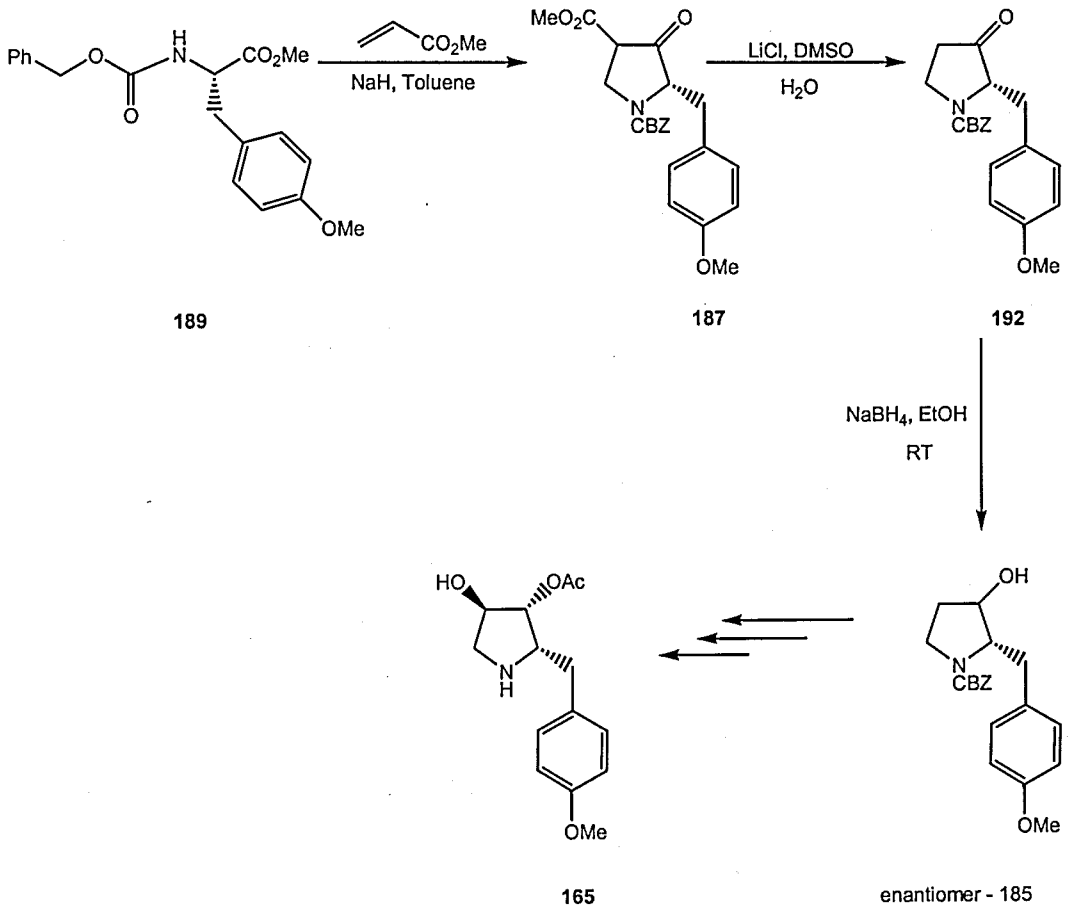
190 189

Scheme 3.11

3.5 Preparation of the anisomycin intermediate (185).

The cyclisation precursor (**189**) was cyclised under the Michael-Dieckmann reaction conditions as shown in scheme 3.12.[76] This involved addition of methyl acrylate to a reaction mixture of 2-benzyloxycarbonylamino-3-(-4-methoxy-phenyl)-propionic acid methyl ester (**189**) and sodium hydride in dry toluene. This afforded the β-ketoester (**187**) in 67% yield. The optical rotation of this compound was recorded as $[\alpha]_D^{20}$ + 17.4. The ^{1}H NMR spectrum revealed the α-proton resonating as a multiplet at δ 4.3 ppm. In the ^{13}C NMR, we observed an additional CH_2 peak resonating at δ 44.8ppm. As before, this spectrum was very complex due to restricted rotation.

Dealkoxycarbonylation of the β-ketoester (**187**) using the procedure of Krapcho[78] involving lithium chloride in wet dimethylsulfoxide heated to 100 °C gave the ketone (**192**) in 68% yield. This showed an optical rotation of $[\alpha]_D^{20}$ + 19.3. This ^{1}H NMR spectrum was sharper than that of the β-ketoester (**187**). Again, additional CH_2 peaks at δ 30.0 ppm, δ 36.2 ppm, δ 42.2 ppm and δ 67.0 ppm were observed in the ^{13}C NMR spectrum.



Scheme 3.13

Reduction of the ketone (**192**) was carried out by dissolving (**192**) in ethanol and adding sodium borohydride in small portions. The reaction was left stirring for 8 hours whereupon reduction occurred affording the alcohol (**185**) in 77% yield. A broad O-H stretch was observed in the IR spectrum at 3430 cm^{-1}. The ^1H NMR spectrum was very similar to the recorded literature values.[91] The OH peak was observed as a broad singlet at δ 1.88 ppm. A multiplet at δ 2.85 ppm was observed in the ^1H NMR integrating for two protons, which were assigned to the tyrosine CH_2. The NCH_2 was observed as a multiplet at δ 3.37-3.48 ppm. A multiplet at δ 3.98 ppm was assigned to the hydrogen next to the OH group.

3.6 Determining the optical purity of anisomycin intermediate (185).

We decided to determine the optical purity of (**185**) by obtaining an optical rotation of compound (**185**). However, whether due to the lack of compound or due to the compound being racemic, we observed a very small optical rotation of compound (**185**). This was inconclusive even when run with greater amounts of compound. The literature contains two different values for the $[\alpha]_D^{20}$ of (**169**). Greene et al[91] reported a value of $[\alpha]_D^{20}$ -6.0 (*c* 1.3, chloroform) while Momose[95] at al reported $[\alpha]_D^{20}$ -4.99. There are three possible explanations for our very low value of $[\alpha]_D^{20}$. Firstly, $[\alpha]_D^{20}$ values can be unreliable and our result is not very different from either literature value. Secondly, the product is racemic. This seems unlikely in light of our findings in chapter 2. In this case as we have a far more sterically hindered molecule than what we had in chapter 2, we would assume that racemisation would be more difficult to occur. Unless, upon reduction of (**192**), the sodium borohydride is acting as a very mild base and racemising the C-2 position. Our final explanation is that diastereomers are formed on the reduction of the ketone (**192**) to the alcohol (**185**).

Clearly, we need a better method to explore the stereochemical integrity of (**185**). Momose et al record analysis of (**185**) using chiral phase HPLC as a method of determining the optical purity of their sample. We used exactly the same conditions (Chiracel OD-H, 5mm, 2-propanol/hexane 15:85, 0.5 mL/min, t_R 20.7 min (vs 24.5 min) indicated an ee of ≥99%) as Momose and obtained retention times of 20.3 mins and 24.9 mins for compound (**185**). However another peak on the HPLC was observed with a retention time of 27.6 mins. Although the retention times we observed were extremely similar to those recorded by Momose we were unable to explain the third peak at 27.6 mins. If we assume the first two peaks to be enantiomers, then we can calculate that compound (**185**) has an e.e of 90%. However, we cannot ignore the ambiguous third peak, which could be a) the *trans*-isomer or b) a UV active impurity in the compound. We did repeat running the chiral HPLC several times but unfortunately were never able to repeat these results. We also tried crystallising compound (**185**) but it remained an oil.

3.7 Possible future work to determine optical purity (185)

A) To run HPLC on an achiral column with diode array detector to observe the U.V spectrum of each peak. That is, if the peak at 27.6 mins is uv active and has the some wavelength as the enantiomers then we could assume this to be a diastereomer. If it has a different wavelength then it could be assumed to be an impurity.

B) To synthesise the racemic compound starting from D, L tyrosine

C) To use alternative reducing agents such as lithium borohydride, L-selectride®, diisobutylaluminiumhydride (Dibal), 9-borobicyclo [3.3.1] (9-BBN) or lithium tri-*tert*-butoxyaluminium hydride.

D) To remove the CBZ protecting group but there is no data on this compound.

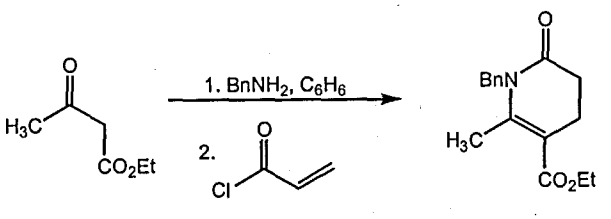
CHAPTER IV

Heterocycle formation through Aza-Annulation.

4.1. Introduction.

Alkaloids that contain saturated 6-membered nitrogen heterocycles, such as piperidine,[97] indolizidine,[98] and quinolizidine[103] natural products, have been very popular synthetic targets due to the array of potent biological activities of these compounds, and the variety of structural challenges that are encountered in their construction. A general approach to the preparation of these ring systems is the aza-annulation with imines and various acrylate derivatives.[99]

Weisner originally described the aza-annulation reaction. In 1968, Weisner and co-workers completed the total synthesis of optically active annotinine[100,101] which involved an aza-annulation reaction of a β-enamino ketone with acrylic acid. In the early 1990's, Stille extended Weisner's work and reported a general aza-annulation reaction leading to tetrahydropyridone rings. This involves the reaction of an ester (**195**) with an acryloyl chloride as shown in scheme 4.1.



195 **196**

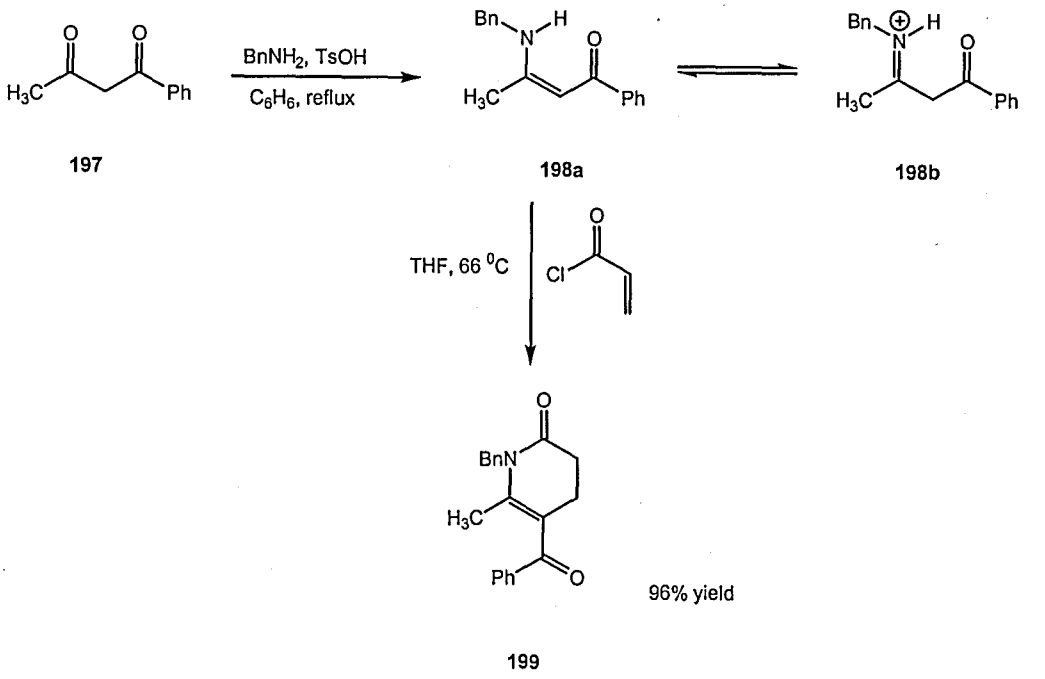
Scheme 4.1

Further investigation of the aza-annulation methodology with acyclic β-enaminoesters has led to development of an efficient method for the regiospecific formation of heterocyclic amines. The condensation of (**195**) with $BnNH_2$, driven to completion by azeotropic removal of H_2O, produced a β-enaminoester (**196**).

Treatment with acryloyl chloride or acrylic acid anhydride gave (**196**) in this two-step condensation / aza-annulation reaction. Compound (**196**), the product of carbon-carbon bond formation by conjugate addition followed by *N*-acylation, was formed to the exclusion of the 4-pyridone, the product of *C*-acylation of the enamine and conjugate addition of the amine.[102]

4.2. Mechanistic studies of the aza-annulaton reaction.

Stille reported in his studies[104] that reaction occurred as a result of imine/enamine tautomerisation, and produced a mixture of products when the imines were treated with α,β-unsaturated acid chlorides. However, by using substrates in which the alkyl imine is in conjugation with a carbonyl group, the amine functionality exists as the enamine tautomer (**198a**), and the annulation process was more facile. The electron-withdrawing group shifts the tautomeric equilibrium from the ketimine (**198b**) form to that of the β-enamino functionality (**198a**), thus significantly increasing both reaction yield and the selectivity under aza-annulation conditions. (Scheme 4.2).[103]

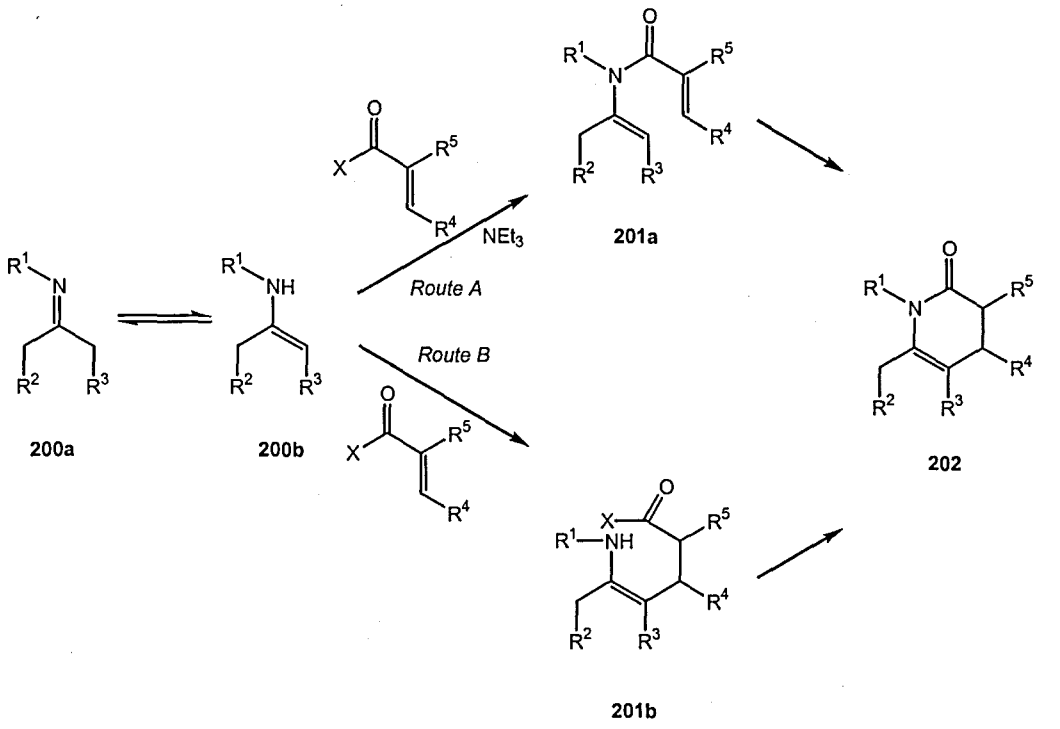


197 198a 198b 199

Scheme 4.2

Generation of 6-membered ring systems through the aza-annulation reaction of enamino ester substrates with acrylate derivatives, such as esters,[104] acid chlorides,[108] and acid anhydridess,[105]has predominated, and the use of anhydride and ester acrylate annulation has led to elegant syntheses of biologically active molecules.[106]

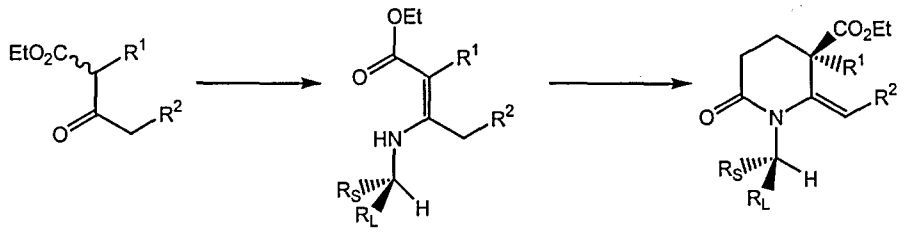
In principle two mechanistic pathways could be followed leading to the product (Scheme 4.3). Route (a) involves initial formation of the C-N bond by *N*-acylation of the tautomeric enamine (**200b**) to give (**201a**). Route (b) involves initial formation of the C-C bond through Michael addition of the β-enaminoester (**200b**) to the acrylate derivative producing (**201b**).



Scheme 4.3

4.3. Asymmetric formation of quaternary centres via aza-annulation.

As part of the ongoing research in this field, Stille investigated the asymmetric formation of quaternary centres through aza-annulation of chiral β-enamino esters with acrylate derivatives.[107] Tetrasubstituted secondary enamines, in which the enamine tautomer was stabilised through conjugation with an ester carbonyl, were prepared from the optically active primary amine (*R*)-α-phenylethylamine and the amino esters of (*S*)-valine and (*R*)-phenylglycine. Treatment of enamine (**204**) with either acryloyl chloride or sodium acrylate/ethyl chloroformate resulted in aza-annulation to give the corresponding δ-lactam (**205**) with high diastereoselectivity. A general strategy for asymmetric aza-annulation is shown in scheme 4.4.



203 204 205

Scheme 4.4

The cyclic β-keto ester substrate (**206**) was converted to diastereomer (**207**) in 85% yield for the two-step enamine formation/aza-annulation procedure as shown in Table 4.1. The quaternary centre was generated with >97:3 diastereoselectivity. An important feature for effective 1,4-asymmetric induction during the annulation reaction is the geometry of the intermediate β-enamino ester. Although substrates (**206**) and (**208**) were restricted to a single enamine geometry, the acyclic substrates (**210**), (**211**), and (**212**) could form two possible geometric isomers. However, in this example, the intramolecular hydrogen bonding with the ester carbonyl served to produce the *Z*-enamine (**204**). Consequently, the annulation was highly stereoselective in each case. Changing the chiral auxiliary led to significant loss of stereoselectivity.[112]

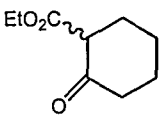
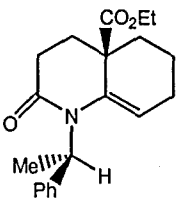
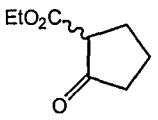
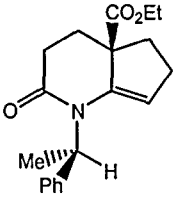
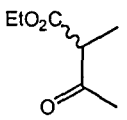
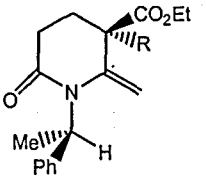
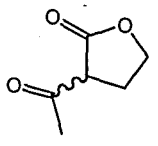
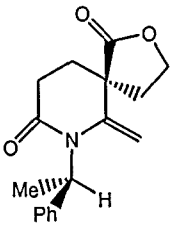
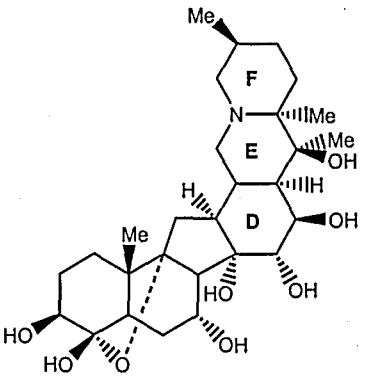
Substrate	Product	Diastereomer ratio	Yield%
		>97:3	85
206	**207**		
		>97:3	76
208	**209**		
		R = Me 97:3 R = OBz 92:8	76 58
210; R = Me **211**; R = OBz			
		94:6	80
212			

Table 4.1

4.4. Previous routes to the DEF-rings of model germine.

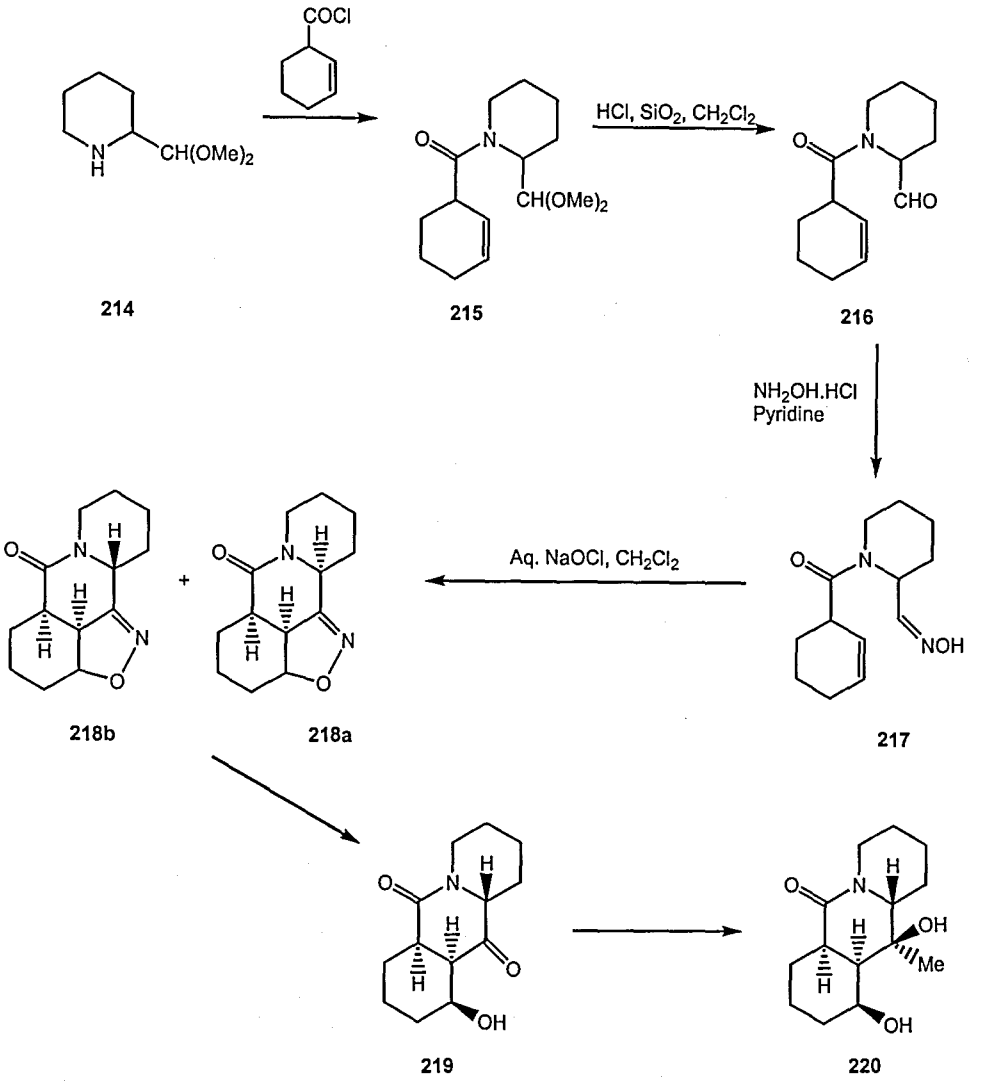
An abundance of knowledge has been gathered on natural germine (Figure 4.1) and its esters. However, there has been little synthetic work reported in the literature on the *ceveratrum* alkaloids. Germine is one of the parent alkamines of this class of natural products and was first isolated in 1937.[108] The structure and stereochemistry of germine was determined in a classic piece of work by Kupchan.[109] This target model compound contains nine stereocentres found in the DEF portion of germine.



213

Figure 4.1.

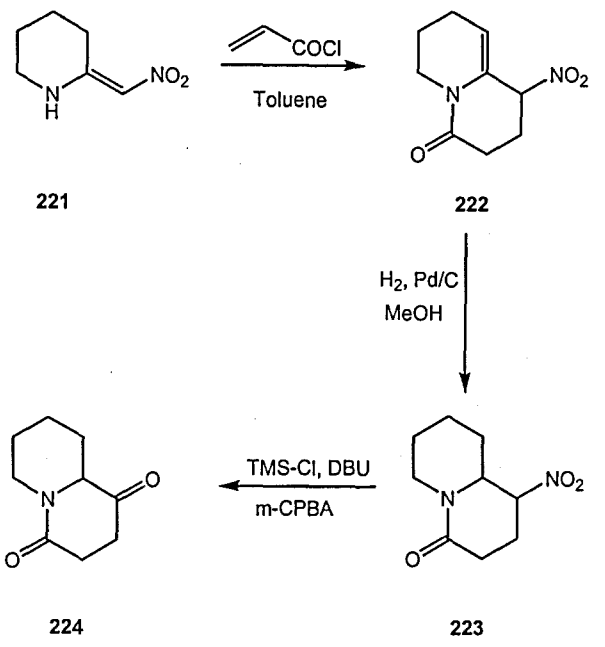
Our interest in this molecule is in the synthises of the DEF-ring system of germine (**213**). Early approaches in the group (Scheme 4.5) towards the synthesis of DEF-rings of germine relied on a key [3+2] intramolecular nitrile oxide cycloaddition (INOC) as a key step in the route. If the Huisgen method of nitrile oxide formation were to be used then 2-(1,1-dimethyloxymethyl)-piperidine (**214**), would become the F-ring within germine. Huisgen studied the reactions of nitrile oxides with alkenes for over twenty years and has provided detailed information about a variety of 1,3-dipoles and the mechanism of their addition to unsaturated systems.[110]



Scheme 4.5

4.5. An aza-annulation approach to the DEF-rings of germine.

Our proposed route towards the synthesis of the DEF-rings of germine (**213**) relies on a key aza-annulation reaction to form the E-ring thus completing the DEF-ring skeleton. The advantages over the previous routes are twofold. In the nitrile-oxide method, the precursor for the cycloaddition reaction is racemic at both chiral centres. Secondly, in the aza-annulation route the F-ring component is formed from a concise synthesis repeatable on a multi-gram scale. Conversely, many steps are required for Huisgen's method for nitrile-oxide generation (Scheme 4.5). We thought to explore this aza-annulation reaction using the nitroenamine (**221**) as shown in scheme 4.6.

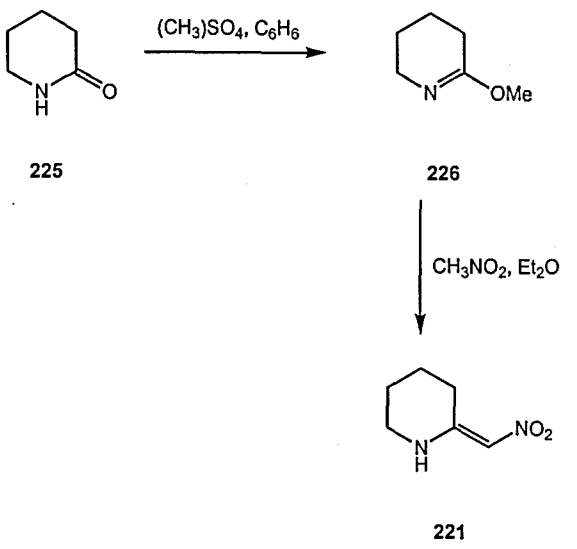


Scheme 4.6

4.6. Synthesis of 2-(nitromethylene piperidine) (221).

The nitroenamine (**221**) has been described in a Shell patent[111] in 1977. We synthesised (**221**) following the chemistry outlined in the patent. This is shown in scheme 4.7. Imidate (**226**) was prepared from commercially available δ-valerolactam (**225**). Thus, δ-valerolactam (**225**) was treated with dimethyl sulfate in refluxing benzene. Removal of the organic solvent *in vacuo* gave the required imidate (**226**) as an oil in 35.6% yield, which was used without further purification. Owing to this very poor yield and the instability and volatility of the imidate, we explored extensively a variety of other reagents and methods that would furnish an appropriate precursor to form the nitroenamine in good yields. We were unsuccessful in finding a suitable method.

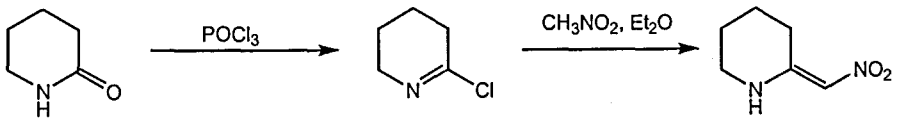
Conversion of imidate (**226**) to 2-(nitromethylene)-piperidine (**221**) was unproblematic and was achieved by refluxing (**226**) in neat nitromethane for three days. The crude product obtained was purified by continuous ether extraction through a soxhlet thimble for 18 hours. Pale yellow crystals of (**221**) were obtained upon cooling in a yield of 52% yield. Evidence for the nitroenamine (**221**) was provided by ^{1}H NMR. The triplet at δ 6.43 ppm integrating for 1 H was assigned as the proton α-to the nitro group. The yield for the two step synthesis although only moderate was repeatable on a 300 mmol scale (Scheme 4.7).



225 226 221

Scheme 4.7

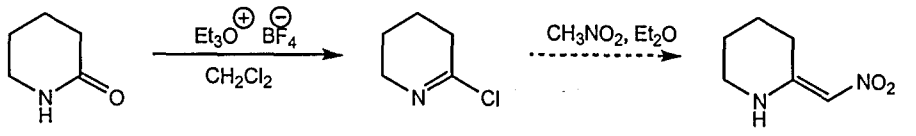
Other methods of synthesising the nitroenamine (**221**) were explored due to the low-yielding reaction in forming the imidate (**226**). Firstly, we thought to synthesise the imino chloride (**227**), scheme 4.8.[112] In this reaction, δ-valerolactam (**225**) was reacted with phosphorus oxychloride. Owing to the fact that this imine (**227**) is very unstable and prone to hydrolysis it was immediately subjected to the aza-annulation reaction. Unfortunately, this method failed to give the desired nitro-enamine (**221**).



225 227 221

Scheme 4.8

Secondly, the option of forming an imino ether (Scheme 4.9) was explored.[113] δ-valerolactam (**225**) was reacted with triethyloxonium, tetrafluoroborate. This reaction produced very low yields of imino ether (**228**), which meant that (**228**) was not subjected to the aza-annulation reaction.

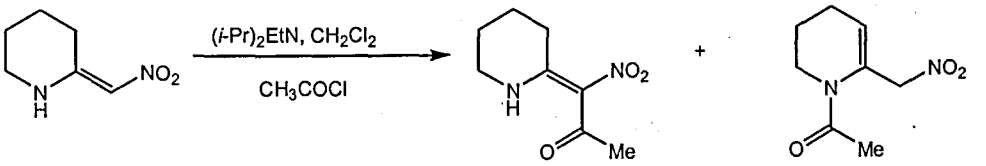


225 228 221

Scheme 4.9

4.7. Aza-annulation of 2-(nitromethylene)-piperidine (221).

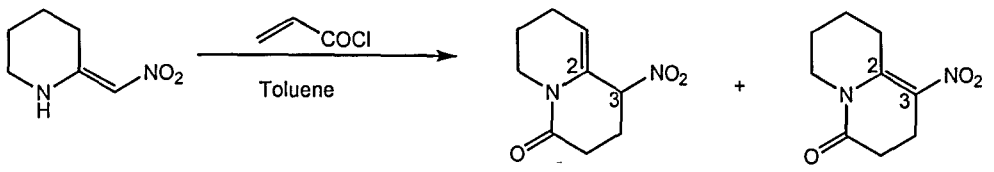
Previous work carried out by Jones and Yarnold using (**221**) suggested that both the *N*-acylated and *C*-acylated products were formed on reaction of 2-(nitromethylene)-piperidine with acid chlorides.[114] In such systems (**221**) there are two sites at which acylaton can occur[116], the nitrogen or carbon α to the nitro group. They found that reaction of (**221**) with acetyl chloride gave two acylated products. *N*-Acylation occurred with migration of the double bond to give (**229b**) in 4% yield. The *C*-acylated product (**229a**) was also obtained in 10% yield. This preference in a nitroenamine has been noted previously.[115] (Scheme 4.10).



221 229a 229b

Scheme 4.10

In order to explore the aza-annulation reactions of 2-(nitromethylene)-piperidine (**221**) the first reaction simply involved the use of acryloyl chloride. Nitroenamine (**221**) was heated under reflux with acryloyl chloride in dry toluene. After two hours, thin layer chromatography indicated one new spot but a large amount of unreacted starting material remained. Heating was continued for twelve hours by which time thin layer chromatography indicated two spots. The reaction was worked up and the crude product was subjected to flash chromatography. The ^{1}H NMR spectra confirmed that these products were isomers. The major isomer (**230a**) gave a yield of 24.8%, while the minor isomer (**230b**) gave a yield of 7.2%. (Scheme 4.11).



221 230a 230b

Scheme 4.11

A signal at δ 5.07 ppm was assigned to the hydrogen α-to the nitro group in compound (**230a**). This signal shifted from δ 6.43 ppm in the nitroenamine (**221**) to δ 5.07 ppm for the aza-annulated product (**230a**), with a decrease in multiplicity from triplet to doublet. This signal is consistent for a proton α-to both a nitro group and an olefin. The new multiplet at δ 5.14 ppm integrating for 1 H was assigned as the proton at C-3. This assignment was consistent with the shift expected for an olefinic proton. This new product was identified as the aza-annulation product with migration of the enamine double bond. However, the proton α-to the nitro group is not observed in the ^{1}H NMR spectra of compound (**230b**). Comparing the ^{13}C NMR DEPT spectrums for both isomers, five CH_2 signals were evident and thus assigned to the major isomer (**230a**), while the other ^{13}C NMR dept spectrum showed six CH_2 signals, thus indicating that this compound is the major isomer (**230b**). (**230b**) is the expected product but is in minority due to the 1,3-allylic strain between the nitro group and the β- hydrogen. (Figure 4.2)

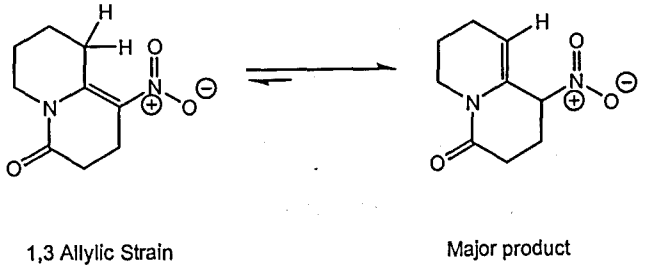
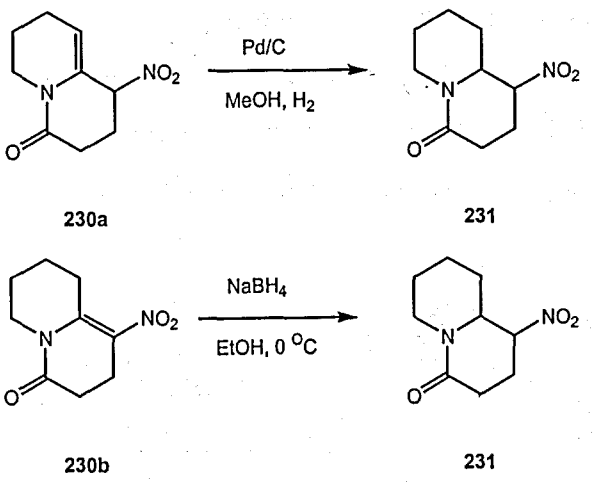


Figure 4.2

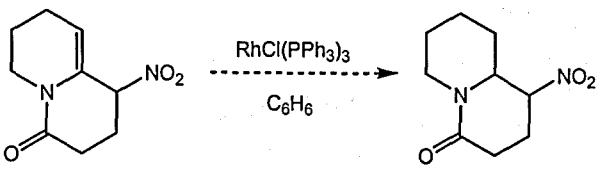
4.8. Hydrogenation of quinolizidines (230 and 230b).

The next step was hydrogenation of the carbon-carbon double bond of (**230a**). A methanolic solution of quinolizidine was reduced under an atmosphere of hydrogen (25 psi) using palladium on carbon as catalyst. After 3 hours at room temperature, thin layer chromatography indicated that no reaction had occurred. Therefore the reaction was continued for a further 12 hours by which time a new spot appeared by thin layer chromatography but an insufficient amount of material for sufficient analysis to be carried out. Thus, by thin layer chromatography, this method only furnished 10% of the quinolizidine product. (Scheme 4.12). Owing to the very low yield, it was difficult to confirm this compound by ^{1}H NMR. Moreover, we were thus unable to determine the stereochemistry at the newly formed ring junction as this would be based on the coupling constants found in the ^{1}H NMR spectrum.



Scheme 4.12

Alternative methods of hydrogenation were explored. A rhodium catalyst was used for this selective reduction.[116] However, this reaction was also unsuccessful. (Scheme 4.13).



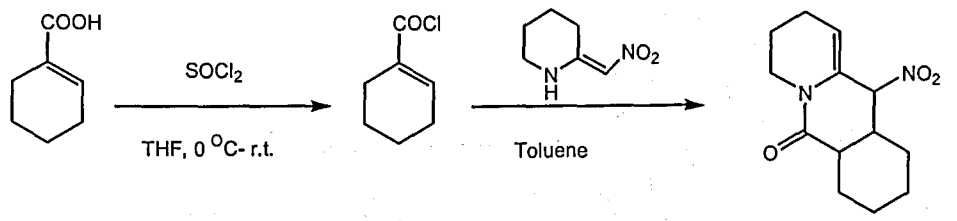
230a 231

Scheme 4.13

4.9. Aza-annulation with 1-cyclohexene-1-carboxylic acid (232).

With the knowledge that simple annulations work, our next aim was to explore the attractive possibility of forming the tricycle in one synthetic step utilising the aza-annulation reaction.

1-Cyclohexene-1-carboxylic acid chloride (**233**) was prepared from the commercially available acid (**232**) using thionyl chloride, which afforded (**233**). We subsequently carried out an aza-annulation reaction with nitroenamine (**227**). Unfortunately, we were unable to determine the outcome of this reaction, as the ^{1}H NMR spectrum was extremely complicated (Scheme 4.13).



232 233 234

Scheme 4.13

4.10. Conclusion

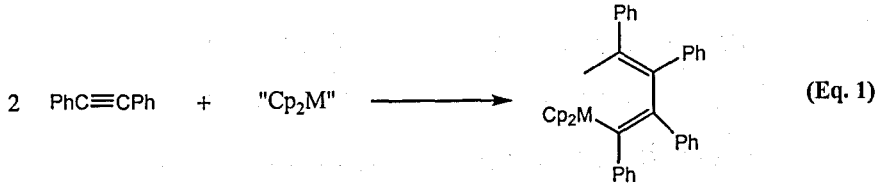
The aza-annulation reaction proved to be a useful method to produce DEF-rings system of germine.

CHAPTER V

A Novel Titanium Mediated Radical Cyclisation Approach to Substituted Pyrrolidines.

5.1 Introduction

Although there are important exceptions, the substrates for transition metal-mediated reactions are typically organic molecules containing carbon-carbon unsaturations (eg. alkenes, alkynes, arenes). This represents both an advantage and a disadvantage to the synthetic chemist: on the one hand, such molecules are readily prepared by simple, high yielding reactions. They are stable toward many reaction conditions (base, nucleophiles, reductions) required to assemble other portions of a complex organic molecule. On the other hand, with such molecules lacking the intrinsic polarisation of carbonyl derivatives, the control of regiochemistry can be problematic. This difficulty applies to the "oxidative coupling" reaction (**Eq. 1**), which has been observed by several workers[117] upon treating diphenylacetylene with various titanocene or zirconocene precursors.



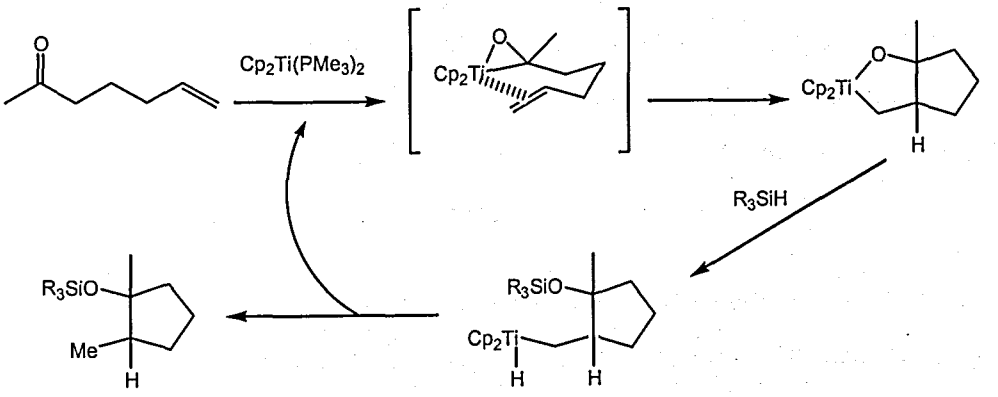
(Eq. 1)

235a, M = Ti
235b, M = Zr

It was reported[118] however that this regiochemical problem could be circumvented when such a reaction was applied to the intramolecular cyclisation of diacetylene. Ample precedent for this approach is found in the elegant studies of Vollhardt on the cobalt-catalysed cyclotrimerisation of acetylenes.[119] The viability of this approach was demonstrated using a titanocene-based reagent that provided higher yields with many simple substrates.[120]

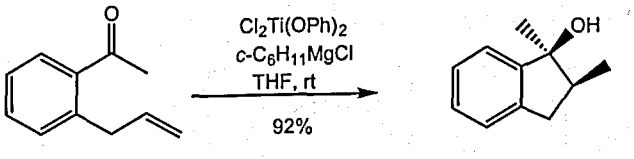
The reductive coupling of two unsaturated molecules by the use of low valent metals from the two extremes of the transition series (Ni, Ti, Zr) has been well documented to provide a convenient carbon-carbon bond formation via a

metallocycle intermediate. The group IV metal-mediated cyclisations of diynes, enynes, and dienes were first developed, and have successfully been extended to those involving heteroatom-containing unsaturated functionalities.[121] For example, the titanocene-mediated, stoichiometric reductive cyclisation of δ,ε-enones was shown by Whitby to afford oxatitanabicyclopentanes in good yields (Scheme 5.1).[122] Recent developments by the Buchwald and Crowe groups independently developed a useful catalytic variant by employing an *in situ* σ-bond metathesis with a silane [e.g. Ph_2SiH_2 or $(EtO)_3SiH$].[123]



Scheme 5.1

Further to this, building upon the Kulinkovich cyclopropanation reactions,[124] a dichlorotitanium diphenoxide-cyclohexylmagnesium chloride-mediated cyclisation of δ,ε-enones was found to parallel the stoichiometric and catalytic titanocene-mediated reactions for the formation of *cis*-substituted cycpopentanols as illustrated in scheme 5.2.[125]



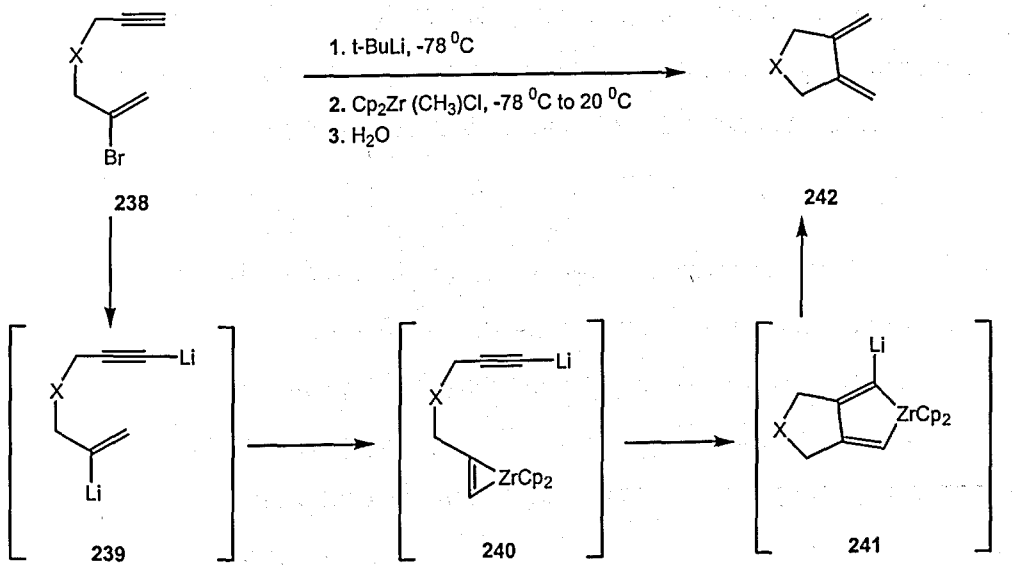
236 **237**

Scheme 5.2

In the last few years, organozirconium compounds have been developed into useful reagents and intermediates for organic synthesis, and transformations mediated by them have gained recognition as a powerful means for achieving

reaction selectivity.[126] In particular, the cyclisation of unsaturated functionalities, using a zirconocene equivalent prepared from zirconocene dichloride and butyllithium,[127] affords zirconabicycles, which are fairly stable. Treatment of these metallabicycles with protons, halogens,[128] isocyanides,[129] or oxygen[130] produces mono- and bicyclic organic compounds with high regio- and stereoselectivity. Electrophilic cleavage with various main-group halides affords a number of unusual heterocycles.[131] Of special interest is the direct and facile generation of conjugated bicyclic enones by carbonylation of these intermediates. Despite the large number of carbocycles that have been obtained in this way, few nitrogen heterocycles have been synthesised. However, a major restriction of these reactions is that substrates containing terminal alkynes cannot be used, presumably owing to the ready oxidative addition of the acidic acetylene hydrogen to the electron-rich metallocene.[118]

Barluenga and Sanz[132] reported the first zirconium-mediated intramolecular coupling of terminal alkynes, as well as their carbonylation and subsequent reaction with electrophiles to form a new type of zirconabicyclopentene. The key steps involve the generation of zirconocene-alkyne complexes (**240**) from 2-bromoalkenes (**238**) and subsequent intramolecular carbometallation to afford unexpected products and therefore allow access to polyfunctionalised molecules from simple starting materials (Scheme 5.3).

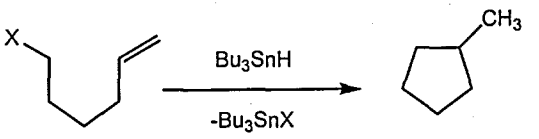


Scheme 5.3 Intramolecular cyclisation of terminal alkynes

The formation of these compounds can be understood by assuming an intramolecular insertion of the acetylide moiety into the zirconacyclopropanes leading to zirconacyclopentadienes (**241**), which generate (**242**) on protonation.

5.2 Radical Cyclisation.

The explosive growth in free radical chemistry in recent years reflects its significance as a powerful tool in modern synthetic chemistry.[133] Hexenyl radical cyclisations are a powerful method for the synthesis of cyclopentane derivatives.[134] Nevertheless, one significant limitation in the usual synthetic procedure has been noted.[135] Treatment of an alkenyl halide with tributyltin hydride as exemplified by (**Eq.2**) necessarily results in a net loss of two functional groups. Termination is largely limited to H-atom abstraction.

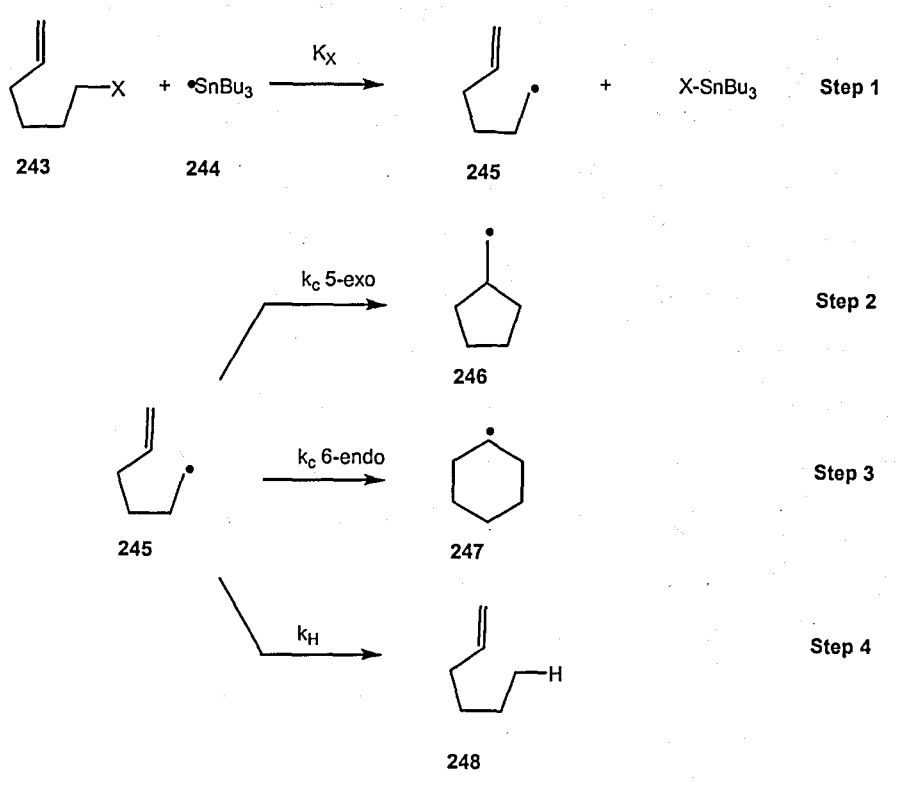


(Eq. 2)

The intramolecular addition of a radical to a π bond leads to the formation of a new ring system. Most of the ring systems produced by radical cyclisation are five- or six-membered, and either partly of fully saturated. Heterocycles are formed if there is a heteroatom present in the linking chain. Less commonly, one of the atoms forming the new bond, usually at the radical centre, can be a heteroatom.

Tri-n-butyltin hydride is now the most commonly used reagent for performing free radical carbon-carbon bond formation reactions.[136] This method involves a controlled chain mechanism, which consists of three distinctive processes: chain initiation, propagation and termination. The first step in the propagation sequence (step 1) involves an atom or group abstraction from (**243**) to provide the hexenyl radical (**245**) (Scheme 5.4).

Propagation:



Scheme 5.4

The hexenyl radical (**245**) can then undergo one of three chain transfer steps. Firstly, a 5-*exo*-trig cyclisation (step 2), in a first order reaction ($k_{c\ (5\text{-}exo)} \sim 2 \times 10^5$ s^{-1} at 25 °C), to give the kinetic product (**246**). Secondly, a 6-*endo*-trig cyclisation (step 3), to give the thermodynamic product (**247**). Finally, the radical (**245**) can abstract a hydrogen atom from the initiator, tri-butyltin hydride in a second-order reaction ($k_H \sim 2 \times 10^6$ M^{-1} s^{-1} at 25 °C)[137] to give the reduced product, 1-hexene (**248**), and tri-n-butyltin radical (step 4). The cyclopentylmethyl radical (**246**) can abstract hydrogen from tin hydride to give methylcyclopentane in another chain transfer reaction.

In order to plan and predict radical reactions, it is important to recognise the factors, which affect the selectivity in these radical processes. The various forms of selectivity include chemoselectivity (preference for one functional group over another), regioselectivity (preference for one position over another) and diastereoselectivity (preference of one diastereoisomer over another).

The outcome of simple addition and β-elimination processes (Figure 5.1) can be reliably predicted using the thermochemical approach. That is, radical reactions

follow the most exothermic available pathway or afford the most stable possible product.[138] The thermochemical approach utilises the bond dissociation energies to estimate relative rates of related reactions. However, thermochemistry alone is incapable of predicting the outcome of many radical processes. Other important factors have to be considered. They are stereoelectronic, polar and steric effects. Stereoelectronic effects reveal the relationship between the energy of the transition structure and the need for overlap of frontier orbitals. A phenomenon studied extensively by Giese[139] is the polar effect. This reflects the stabilising or destabilising capabilities of the relative electronegativities of constituent atoms on the transition structure. Finally, steric effects reflect the contribution of non-bonded interactions to the energy of the transition state. The evaluation of all these factors must be carried out in order to predict the outcome of any particular reaction.

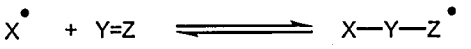
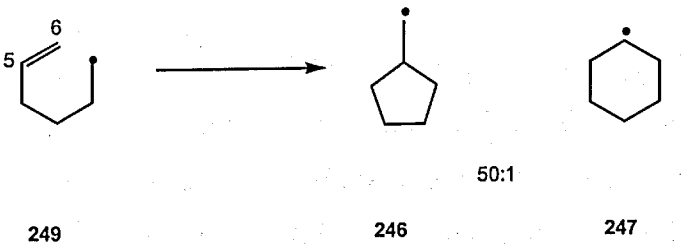


Figure 5.1 **Addition / β fission**

The regioselective cyclisation of the 5-hexenyl radical (**249**) to give the less stable primary cyclopentylmethyl radical (**246**) in preference to the more stable secondary cyclohexyl radical (**247**), demonstrates the inadequacies of the predictions based on thermochemical criteria. Unless the radicals are highly stabilised, the intramolecular addition step is irreversible. Such reactions are thus kinetically controlled. (Scheme 5.5).



Scheme 5.5

The transition state for intermolecular homolytic addition reactions is also found in intramolecular reactions. The transition complex is formed by the interaction of the semi-occupied 2p orbital of the carbon centred radical with the vacant π^* orbital of the olefin as shown in (Figure 5.2). When a radical centre approaches an acceptor such as an alkene or alkyne, the approach is perpendicular to the nodal plane of the π-system at an angle of 109° for alkenes and 114° for alkynes. The transition state that results is unsymmetrical in which the distances between the attacking radical and the two vinylic or alkynic carbon atoms are unequal.

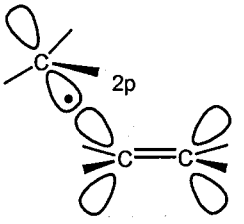


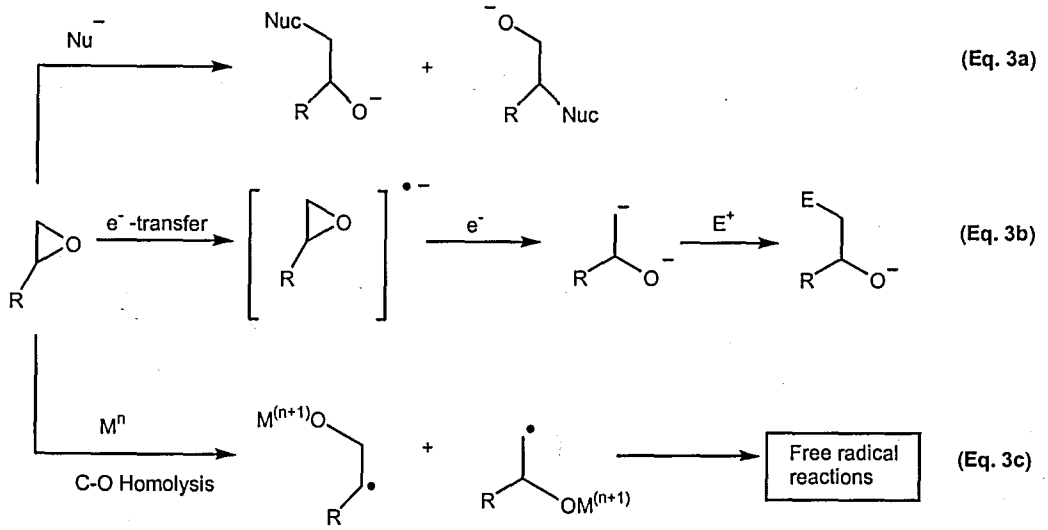
Figure 5.2

Beckwith used theoretically-calculated transition structures as models for 5-*exo*- and 6-*endo*-trig ring closure respectively.[140] These structures resemble a distorted chair form of cyclohexane in preference to the boat form, from which enabled Beckwith to rationalise the observed stereochemical outcomes. Beckwith's guidelines state that 1,5-*exo* ring closure of 2- or 4- substituted hexenyl radicals yields mainly the *trans*-disubstituted cyclic product, whereas 1- or 3- substituted systems afford mainly the *cis*- product.[141]

5.3 Selective generation of free radicals from epoxides.

In spite of the explosive growth in free radical chemistry, the number of synthetically useful radical precursors remains limited.[142] Rajanbabu and Nugent[143] proposed that the use of epoxides would provide an excellent source of functionalised radicals. Epoxides are among the most versatile synthons in organic chemistry. They are readily accessible, often in enantiomerically pure form, from olefins, diols, and carbonyl compounds. The considerable utility of epoxides as building blocks for organic synthesis reflects both their ready availability and their ability to under go selective nucleophilic substitution

reactions (**Eq 3a**) with predictable stereochemistry.[144] In contrast, the two-electron reduction of epoxides to the corresponding carbanionic species (**Eq 3b**)[145] allows the elaboration of epoxides with electrophiles, thus providing an "umpolung" of their usual reaction mode. However, as compared to the reaction with nucleophiles, several serious limitations of this approach have been noted. These include incompatibility of the highly reducing conditions with a number of common functional groups, instability of such carbanionic species toward elimination, and the narrow range of electrophiles that can be used in this sequence.



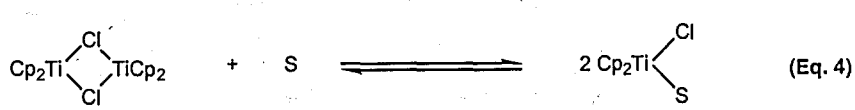
However, Rajanbabu and Nugent have successfully established that the selective one-electron reduction of an epoxide to a radical intermediate (**Eq. 3c**) would represent an invaluable synthetic tool, provided the intermediate radical could be trapped in subsequent reactions. As compared to reactions involving polar intermediates, free radical-mediated reactions are compatible with a wider array of functional groups. Furthermore, the product distributions are different from those of classical reactions of epoxides. The regio- and stereochemistries of the epoxide opening via C-O homolysis will be guided by the relative stability of the intermediate radicals rather than the ease of approach to the epoxide termini as is the case in nucleophilic (S_N2) openings. The stability of a carbon radical is affected by both the substitution pattern (tertiary > secondary > primary) and stereoelectronic factors.[146] They reported that reduction (**Eq. 3c**) might be accomplished with a low-valent transition-metal reagent. Precedent for this approach exists in the mechanistic proposal of Kochi, Singleton, and Andrews.[147]

These researchers suggested that the deoxygenation of epoxides by chromium (II) reagents proceeds by discrete one-electron steps via the carbon-centred radical. Formation of a carbon-centred radical from a transition-metal-centred radical and its subsequent reactions is ubiquitous in living systems.[148] However, the application of this type of transformation in organic synthesis is largely limited to redox reactions.[149]

5.4 The Reagent: Bis (cyclopentadienyl) titanium (III) chloride.

Rajanbabu and Nugent reported that a titanium (III) reagent, bis-(cyclopentadienyl) titanium (III) chloride, promotes such a homolytic process (**Eq. 3c**) with remarkable selectivity at or below room temperature. The reagent is easily generated *in situ* from inexpensive Cp_2TiCl_2 and is compatible with many organic functional groups. Production of free radicals in this manner allowed the development of a variety of unique transformations of epoxides including selective reduction and deoxygenation processes and intra- and intermolecular carbon-carbon bond forming reactions.[150]

Bis (cyclopentadienyl) titanium (III) chloride was first reported by Green and co-workers in 1972.[151] In the solid state, the complex exists as a chloride-bridged dimer. However, in the presence of donor solvents such as THF, the dimer dissociates (**Eq. 4**) to afford the monomeric species which may be regarded as a loosely solvated "transition-metal-centred radical."



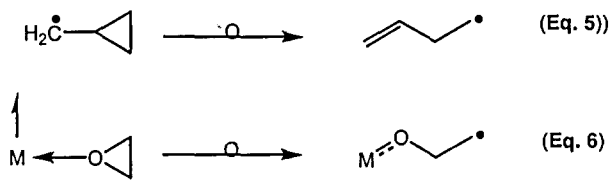
(Eq. 4)

S = Coordinating solvent

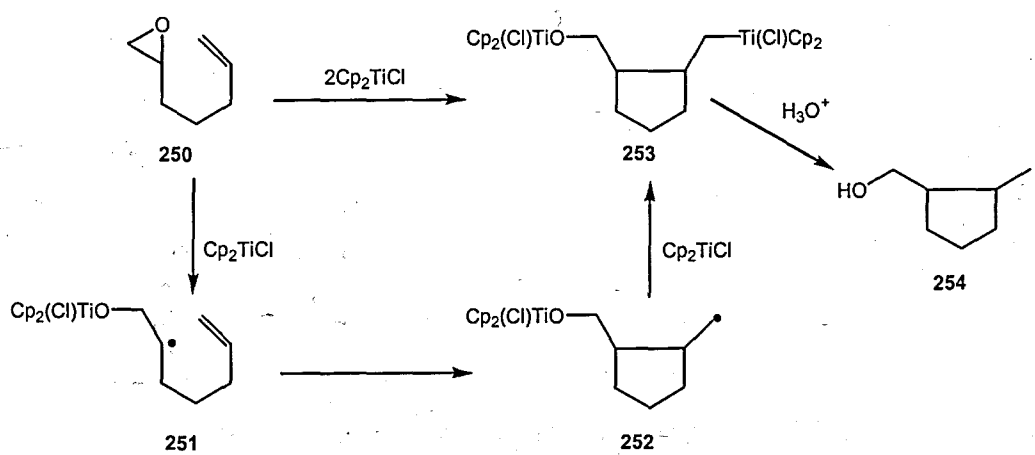
A satisfactory reagent can be prepared by stirring a red THF solution of commercially available titanocene dichloride with powered zinc dust. After 15 minutes, the solution turns lime green and the formation of Cp_2TiCl is complete.

Nugent and Rajanbabu[150] reported a direct synthesis of functionalised cyclopentane derivatives. This reaction is based on an analogy to the extremely

facile rearrangment of cyclopropylmethyl radical to homoallyl radical (**Eq. 5**). A σ-complex of an epoxide with a paramagnetic transition metal[152] having a half-filled (π-symmetry) d orbital represents an electronic analogue of the cyclpropylmethyl moiety. By analogy, to (**Eq. 5**), release of ring strain might be expected to drive the homolytic C-O bond cleavage in (**Eq. 6**).



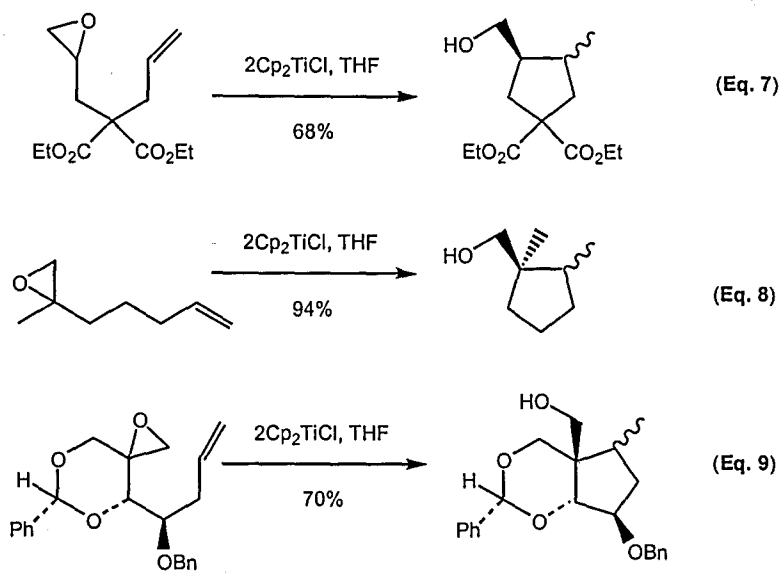
As shown in scheme 5.6, when this reaction was applied to the intramolecular cyclisation of 6,7-epoxy-1-heptene (**250**), the result suggests that after C-O bond cleavage, hexenyl radical cyclisation can indeed occur (**252**). Moreover, the resultant primary radical is efficiently scavenged by a second equivalent of titanium (III) affording the indicated alkyl-titanium (IV) species (**253**).



Scheme 5.6

The most frequent workup procedure involves protonolysis of (**253**) to give product (**254**). This then regenerates one functional group, which can be derivatised later. This sequence was applied to a series of substituted epoxyolefins containing synthetically useful functionality. As shown in Scheme 5.7, several observations are noteworthy from these examples. Successful synthesis of (**Eq.7**) indicates that the reaction conditions are compatible with

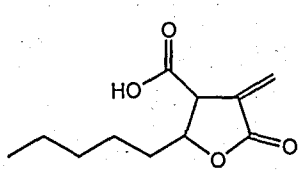
carbonyl functionality. Products (**Eq. 8**) and (**Eq. 9**) demonstrate that this procedure is especially well suited to the introduction of quaternary centres.



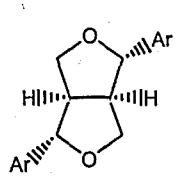
Scheme 5.7

5.5 Applications of this Cyclisation Strategy towards Natural Products.

The titanium-mediated radical cyclisation of Rajanbabu and Nugent has been applied to the synthesis of heterocycles. Although no pyrrolidine syntheses using this chemistry have been reported, there are examples of the synthesis of tetrahydrofuran-containing natural products (Fig. 5.3).[153] The furofuran ligan, (±) sesamin has been synthesised[154] by the intramolecular radical cyclisation of an epoxide using a Ti (III) species as the radical source. Previous work within the group applied this epoxide radical cyclisation strategy towards the synthesis of the functionalised anti-tumor antibiotic (±) methylenolactocin.[155] Methylenolactocin, a small but densely functionalised and isomerisation-prone antibiotic has attracted interest because of its selective antibacterial activity against Gram-positive bacteria including *Baciillus*, *Micrococcus*, *Staphylococcus* and *Corynebacterium*. Nakayama et al first isolated it in 1988[156] from the culture filtrate of *Pencillium* sp.



Methylenolactocin



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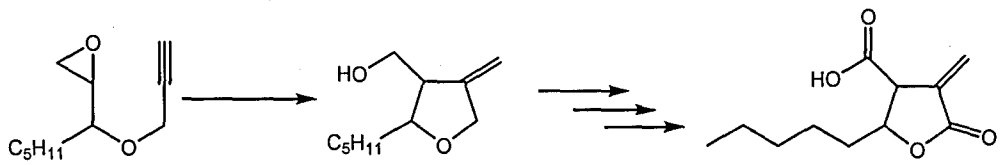
Maiti and Roy[157] reported the total syntheses of racemic methylenolactocin using radical cyclisation as the key step (Scheme 5.8).

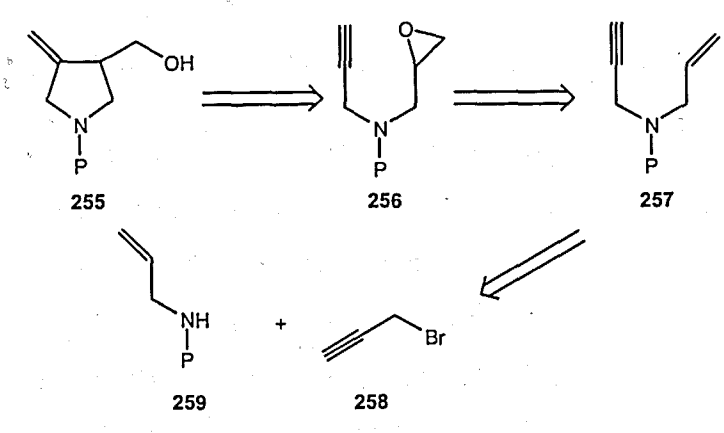


Scheme 5.8

5.6 Application of Rajanbabu Chemistry to the synthesis of Pyrrolidines.

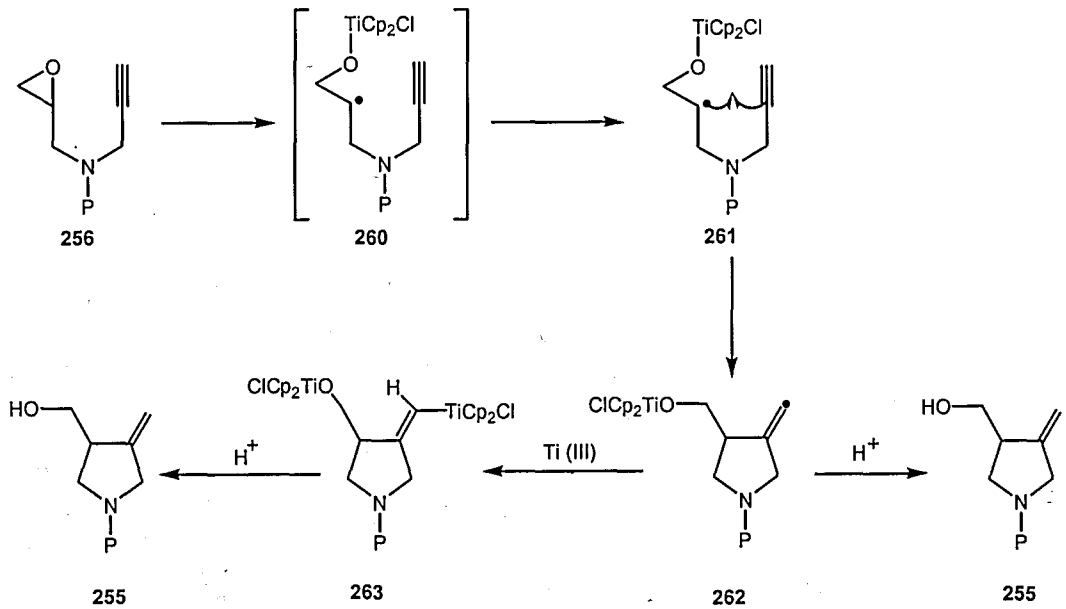
As discussed, while there are several examples of synthesising cyclopentane and tetrahydrofuran-based ring systems using the titanium-mediated epoxide opening method, to the best of our knowledge pyrrolidine synthesis has yet to be explored. We decided to exploit the use of this titanium species to promote a radical cyclisation of epoxides to generate substituted pyrrolidine ring systems. The key step in our synthetic strategy involves initiating a radical cyclisation reaction using a low valent titanium species.

Our synthetic approach towards the synthesis of substituted pyrrolidines, outlined in scheme 5.9, is based on the reported synthesis of methylenolactocin.[153] The key step involves the formation of the pyrrolidine (**255**) via an intramolecular radical cyclisation of an epoxide (**256**) using Cp_2TiCl. The intermediate for the synthesis of the desired radical cyclisation precursor is the olefinic substituent on the protected propargyl amine (**257**).



Scheme 5.9

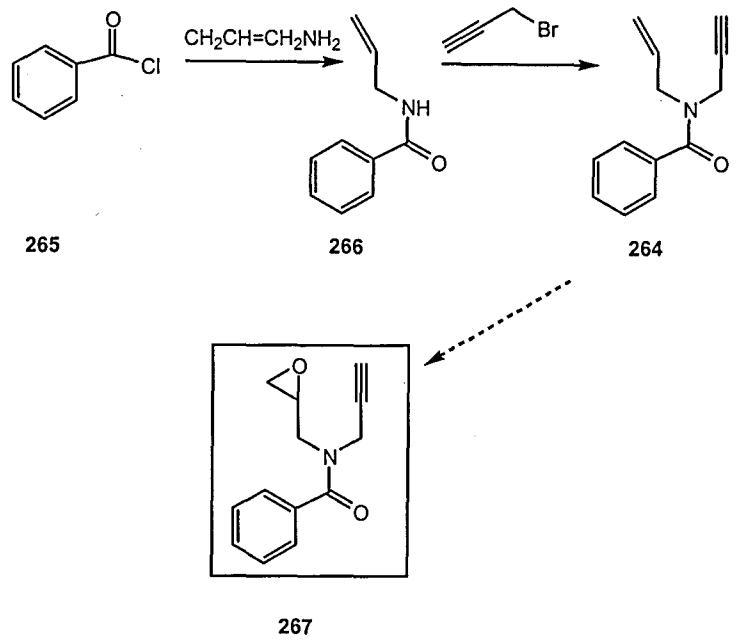
Our proposed titanium radical cyclisation reaction is illustrated in scheme 5.10. The titanium species being very oxophilic chelates readily with the oxygen of the epoxide, causing the C-O bond of the epoxide to cleave homolytically generating a carbon radical (**260**). The acetylenic chain then forms a C-C bond with the carbon (**261**) to afford a five-membered nitrogen heterocycle. The pyrrolidine ring bears a vinyl radical group (**257**) which is quenched by Ti (III) to give (**263**). Alternatively, the vinyl radical (**257**) can abstract a hydrogen atom from the solvent to give (**255**) directly. The protecting group has two functions, firstly to prevent internal S_N reactions taking place, for example, ring opening of the epoxide by the lone pair on the unprotected nitrogen atom. Secondly, the protecting group prevents co-ordination of the nitrogen to the Ti (III) species.



Scheme 5.10 Proposed Mechanism of Titanium Radical Cyclistaion

5.7 Synthesis of the radical cyclisation precursor (267).

Our exploration in this area involved the synthesis of cyclisation precursor (**267**), scheme 5.11. The *N*-benzoyl group was chosen as the protecting group on nitrogen for reasons of convenience and simplicity. Reaction of benzoyl chloride with allylamine in the presence of Hünigs base gave *N*-allylbenzamide (**266**) in 92% yield. This compound was then reacted with propargyl bromide using sodium hydride in THF to give the tertiary amide (**264**) in 85% yield.



Scheme 5.11

The ^{1}H NMR spectrum is quite broad due to the fact that rotamers are present. The rotamers are due to the planar benzoyl group, which leads to the molecule existing with the benzoyl group lying in both directions (Figure 5.3).

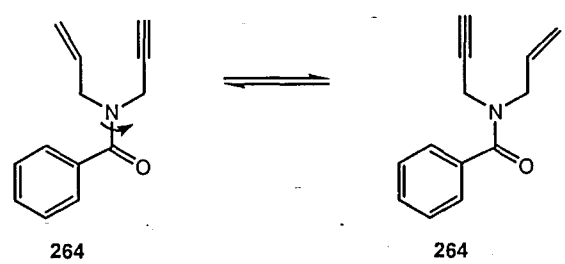


Figure 5.3

The acetylenic hydrogen is evident at δ 2.2 ppm. The final step in the synthesis of (**267**) is the apparently straightforward epoxidaton of the alkene (**264**). The initial epoxidising reagent used was *m*-CPBA (*meta*-chloroperbenzoic acid)[158] which was purified by literature methods.[159] Surprisingly, this reaction proved very difficult.

Although there are several methods of epoxidising acyclic and cyclic alkenes, the epoxidation of tertiary amides bearing a terminal alkene with a nearby electron-withdrawing group has so far been unreported. A range of reagents and conditions were explored to achieve the epoxidation of (**264**). The results will be discussed and presented later.

It became apparent that these terminal alkenes with a nearby electron-withdrawing group are resistant to classic epoxidising reagents such as *m*-CBPA. From our studies, we can try to explain why *N*-allyl-*N*-propargyl benzamide was proving difficult to epoxidise. The reasons for this lack of reactivity are unclear. Two possible explanations are:

1). The electron withdrawing effect from the *N*-benzoyl group decreases the nucleophilicty of the alkene functionality, thereby lowering its electron density to attack the electrophilic oxygen of the per-oxyacid.

2). The *m*-CPBA can form a hydrogen bond with the benzoyl group. Owing to this, the carbonyl group can easily form a bond with the hydrogen of *m*-CPBA, also reducing its ability to be attacked by the alkene, as illustrated in figure 5.5

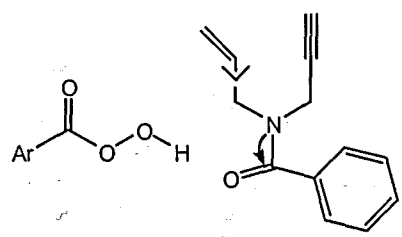
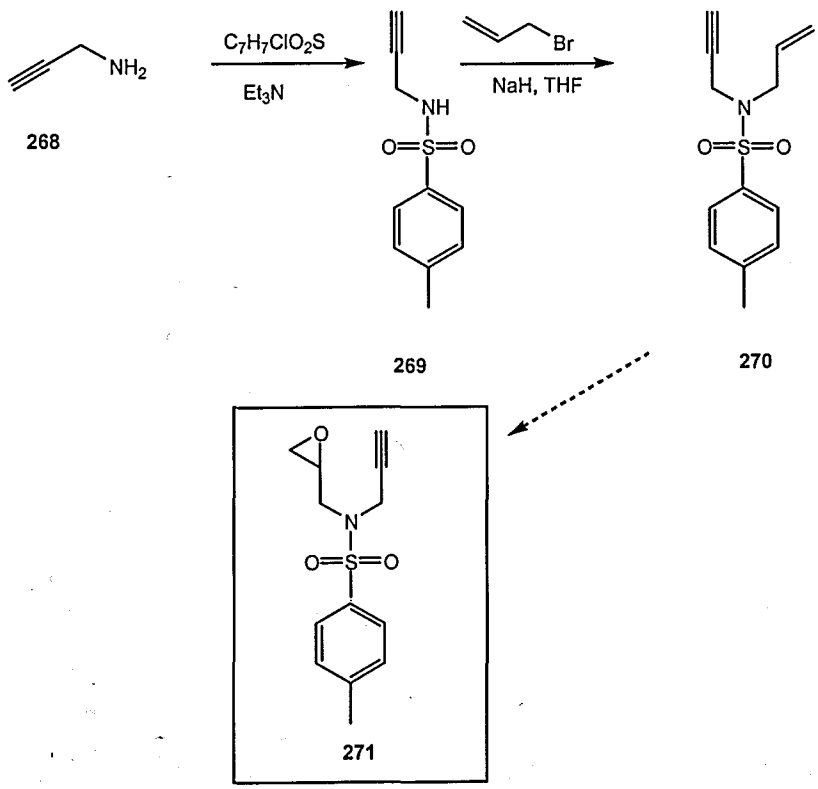


Figure 5.4

In order to overcome some of the problems related with the benzoyl-protecting group we decided to change the protecting group on the nitrogen to a tosyl group. The tosyl protecting group is tetrahedral in shape and so its overlap of orbitals is much weaker than that of the benzoyl group. This would therefore avoid the problem of rotamers and enhance the nucleophilicity of the terminal alkene bond. This reaction was carried out on propargylamine (**268**) using triethylamine in DCM and para-toluenesulfonyl chloride.[160] The reaction afforded 96% of *N*-

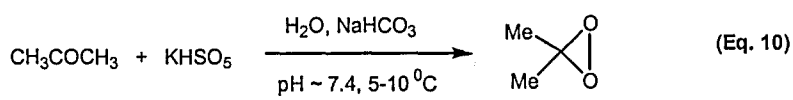
propargyl-p-toluenesulfonamide (**269**) as white crystals. The protected propargyl amine (**269**) was then treated with allyl bromide in THF containing sodium hydride and was readily converted[161] into *N*-allyl-*N*-propargyl-toluenesulfonamide (**270**) as shown in scheme 5.13. Analysis of ^{1}H NMR spectra showed the acetylenic proton at δ 1.94 ppm and the olefinic protons at δ 5.15-δ 5.24 ppm. By using the tosyl protecting group, we overcame the problem associated with rotamers. The ^{1}H NMR spectrum was thus much sharper and easier to analyse. Again, we used *m*-CPBA to epoxidise the double bond of (**270**). This reaction also failed.



Scheme 5.12

To overcome the problem of potential hydrogen bonding between the protecting group and the epoxidising reagent, we decided to use NBS in DMSO and water[162] as an alternative method for epoxidising the terminal alkene. The key step in this reaction is the formation of the bromonium ion intermediate which is then attacked by water. Subsequent elimination of HBr with cyclisation should yield the epoxide. Reaction of (**270**) with NBS in DMSO gave only recovered starting material. This suggests that the difficulty of this epoxidation step is due to electronic effects.

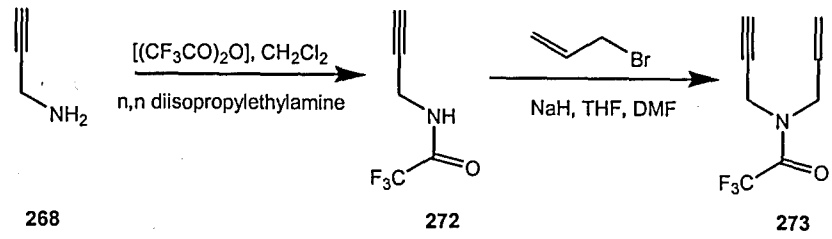
We therefore decided to try the most reactive epoxidising reagent, dimethyl dioxirane (DMDO) in acetone, (**Eq. 10**).[163] The epoxidation of double bonds has been the major area for the application of DMDO methodology and a wide range of alkenes are effectively converted to epoxides by solutions of DMDO.[164] However, in the ^{1}H NMR spectrum of the crude product, signals assignable to the desired epoxide could be observed but amounted to less than 10% of the total product. A limitation of DMDO is that the absolute yields of dioxirane are quite low. Efforts to improve on this reaction followed the work of Adam, Bialas and Hadjiarapoglou [165] who provided a simplified version of previous procedures. A significant benefit of this new version is the fact that the originally required[166] amounts of peroxide reagent and buffer can be cut back to (0.195 mol) of potassium monoperoxysulfate [the triple salt 2 $KHSO_5$. $KHSO_4$. K_2SO_4; trade name caroat] and (0.690 mol) of $NaHCO_3$ to afford ca. 150 ml of ca. 0.1 M dioxirane solution in acetone. Although the absolute yield of dioxirane is still quite low (*ca.* 5%), it represents a *ca.* threefold improvement. Unfortunately, this methodology was too low yielding to make this a feasible route.



(Eq. 10)

5.8 Alternative Routes towards the Epoxide Precursor:

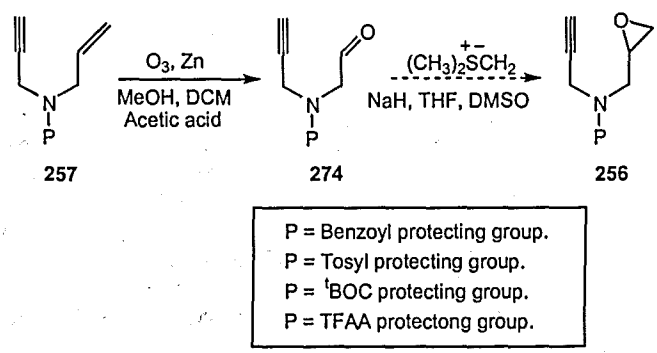
At this stage, it was apparent that epoxidation of (**264**) and (**270**) is very difficult to achieve and an alternative route to epoxide (**256**) was explored. We envisaged that the epoxide could be made via a two-step process, which would involve synthesising an aldehyde, which would then be transformed into the epoxide utilising sulfur ylide chemistry. To explore the feasibility of this route, we decided to carry out this reaction sequence on the three substrates that had been synthesised for the direct epoxidation route. The benzoyl group for convenience, the tosyl group to overcome the electronic effects and ^{t}BOC as it is easily removed. In addition, the trifluoroacetic anhydride-protecting group was also studied (Scheme 5.13).



Scheme 5.13

Again, propargylamine (**268**) was treated with trifluoroacetic anhydride in dichloromethane and Hünigs base to afford *N*-(2-propynyl)-2,2,2-trifluoroacetamide (**272**)[167] in 85% yield. The acetylenic proton was evident at δ 2.2 ppm in the ^{1}H NMR spectrum. The protected propargylamine (**272**) was then treated with allyl bromide in THF containing sodium hydride to give *N*-allyl-(2-propynyl)-2,2,2,trifluoroacetamide (**273**)[168] Analysis of the ^{1}H NMR spectra showed the acetylenic proton at δ 2.28 ppm and the olefinic protons at δ 5.2 ppm.

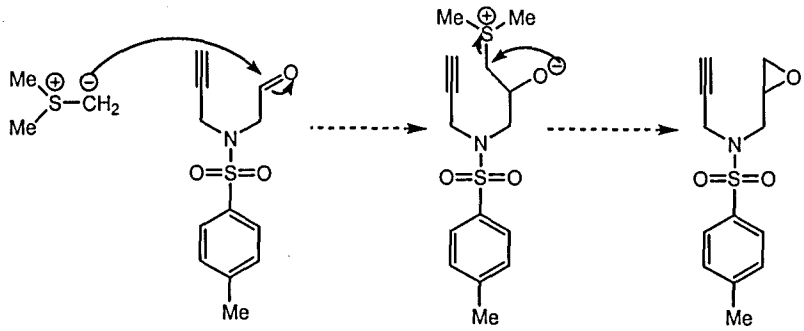
The proposed synthesis of the desired epoxide (**256**) is outlined in the pathway shown in scheme 5.14.



Scheme 5.14

The *N*-tosyl compound was investigated initially owing to its simpler ^{1}H NMR spectrum. *N*-Allyl-*N*-propargyl-toluenesulfonamide (**270**) dissolved in a mixture of methanol and DCM at -78°C was treated with ozone. Zinc and acetic acid were added and the reaction was left to stir overnight.[169] The ^{1}H NMR spectrum of the crude product showed a signal assigned to the aldehyde proton at δ 9.53 ppm. As we felt the aldehyde would be somewhat unstable it was immediately subjected to the ylide chemistry.[170] The dimethylsulfonium methylide was generated by

treating trimethylsulfonium iodide in dry DMSO with sodium hydride (under nitrogen) at -10°C. Enough THF was added to prevent freezing.



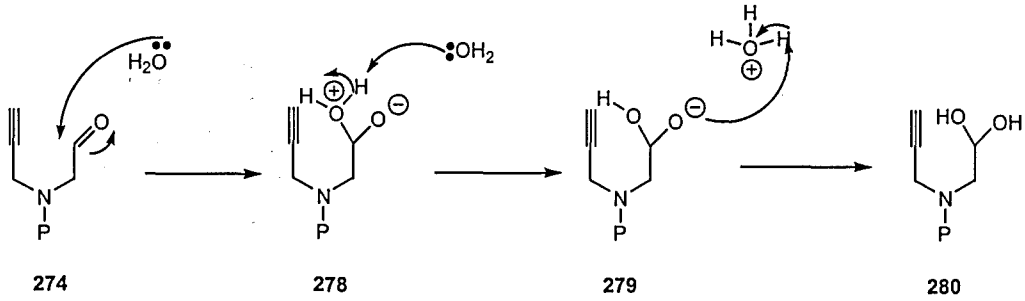
275 276 277

Scheme 5.15

At 0 °C or below, the stability of the ylide is much greater. Since the process of ylide formation is rapid, it is possible to conduct the reaction without significant loss of the reagent by immediate addition of the aldehyde (**275**) with continued cooling. The reaction failed to yield the desired epoxide.

The failure of the sulfur ylide chemistry was thought to be an intrinsic problem with the substrate involved (**275**). However, it was noted on subsequent occasions that ozonolysis of the alkene frequently failed to give the aldehyde, indicating a possible stability problem with the aldehyde. In the case of 4-methyl-*N*-(2-oxo-ethyl)-*N*-prop-2-ynyl benzenesulfonamide (**275**), ozonolysis appeared to be successful as judged by the singlet in the ^{1}H NMR spectrum at δ 9.53ppm. However, the preparation of this compound proved difficult to repeat.

One explanation for the difficulty of this reaction could be due to the formation of a hydrate. This process is illustrated in scheme 5.16.

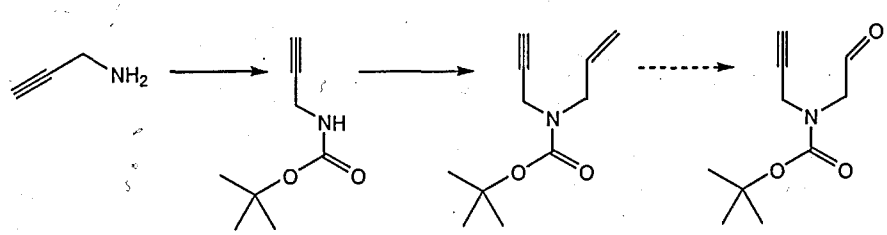


274 278 279 280

Scheme 5.16

The ozonolysis reaction was tried on different substrates. The protecting group was changed to ^{t}Boc (*tert*-butyloxycarbonyl). Again, propargylamine (**268**) was treated with triethylamine and di-*tert* butyl dicarbonate in diethyl ether to afford *N*-(*tert*-butyloxycarbonyl)prop-2-ynylamine (**281**).[171] This reaction gave the product in 84% yield. The acetylenic proton was evident at δ 2.16 ppm in the ^{1}H NMR spectrum. The protected propargyl amine (**281**) was then treated with allyl bromide in THF containing sodium hydride to give *N*-allyl-prop-2-ynyl-carbamic acid *tert*-butyl ester (**282**).[168] Analysis of the ^{1}H NMR spectrum showed the acetylenic proton at δ 2.1 ppm and the olefinic protons at δ 5.02 ppm. This compound was then submitted to the ozonolysis reaction as described earlier but no aldehyde signal was observed in the ^{1}H NMR spectrum.

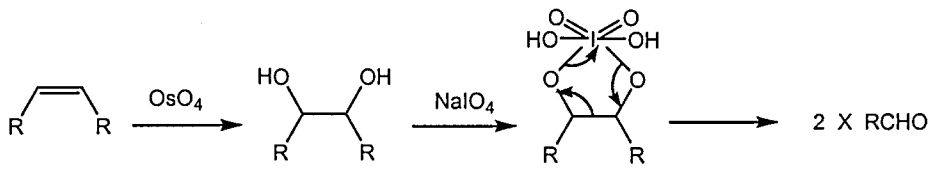
Benzamide (**282**) was also submitted to this ozonolysis reaction and again, the reaction failed to afford the desired aldehyde (Scheme 5.17).



268 281 282 283

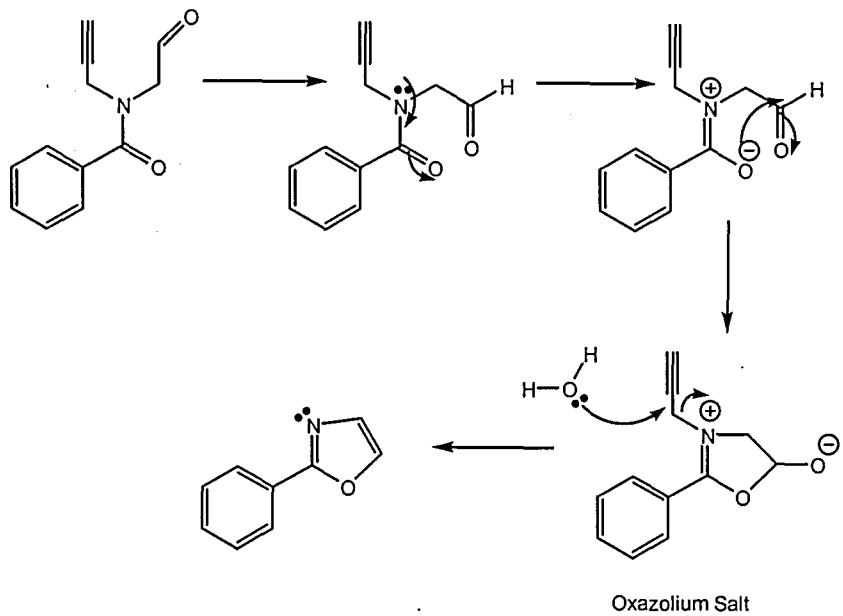
Scheme 5.17

An alternative method of cleaving C=C bonds is to use osmium tetraoxide (OsO_4) in conjunction with $NaIO_4$ (sodium periodate). The diol product forms a periodate ester, which decomposes to give two molecules of aldehyde (Scheme 5.18).



Scheme 5.18

The tosyl-protected amine was submitted to these conditions[172] but no aldehyde was produced. The paper by Grahams and Williams proposed a reason as to why some olefins display resistance to forming the desired aldehyde. They reported that the oxidation of benzylidenecyclobutane gives rise to both rearranged and unrearranged products. The differences observed in the tendencies of alkylidene cyclobutanes and cyclobutylmethanols to rearrange in the course of oxidations (or dehydrations) is ascribed in part to a steric effect. Ozonolysis of the olefin gave an aldehyde, a diol and a monoacetate. This theory may begin to explain why the ozonolysis of these tertiary amides was proving difficult. Perhaps the aldehyde forms but rearranges itself as outlined in scheme 5.19 and so prevents any formation of the epoxide. This can be described as a 1,5-*exo* addition rearrangement. This theory could potentially occur in all reactions carried out to form the aldehyde as carbonyl functionality is present in all substrates.

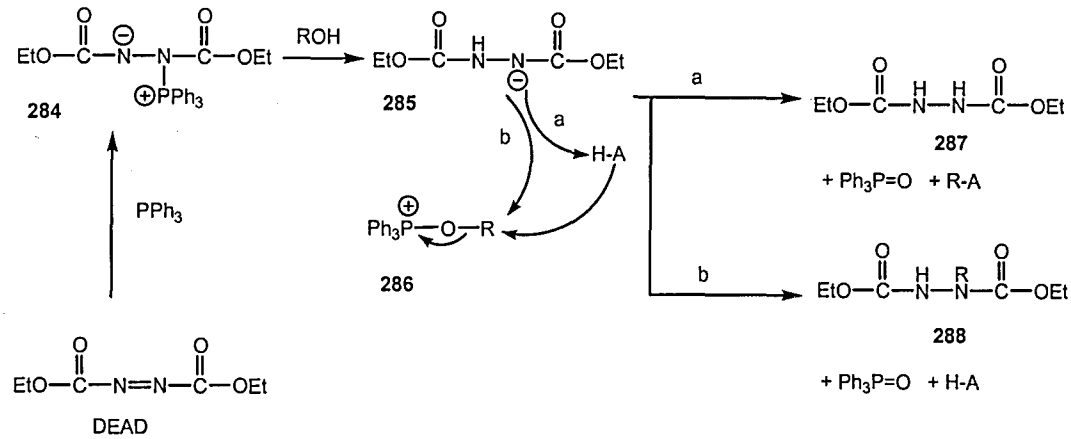


Scheme 5.19 Proposed Rearrangement of Aldeheyde.

At this stage it was concluded that the direct epoxidation of the terminal alkene fails and so too does the formation of the aldehyde. We therefore abandoned these methods of synthesising the epoxide.

5.9 Alternative approaches to "Epoxy Alkenes"

The Mitsunobu reaction[29] is an S_N2 reaction using phosphorus chemistry. It utilises a diethyl azodicarboxylate (DEAD)-triphenylphosphine (TPP) system and proceeds probably through the generally accepted path as shown in scheme 5.20.[173] It is a very versatile method for the condensation of alcohols (ROH) and various nucleophiles (or acids, HA) to give the products (RA), which are widely used in organic synthesis. However, the reaction has a serious limitation; the acidic hydrogen in HA has to have a pK_a lower than 11 for the reaction to proceed satisfactorily. If HA has a pK_a larger than 11, the yield of RA lowers considerably, and with HA having larger pK_a than 13, the desired reaction does not occur. For example, the yield of the products in the reactions with propanol is as follows: ethyl acetoacetate (pK_a 10.7) 42% (a mixture of C- and O-alkylated products);[167] malononitrile (pK_a 11.2) 51%;[174] diethyl malonate (pK_a 13.3) 0%. The major byproduct in these cases is the alkylated hydrazine derivative (**288**) formed through path b in the scheme.



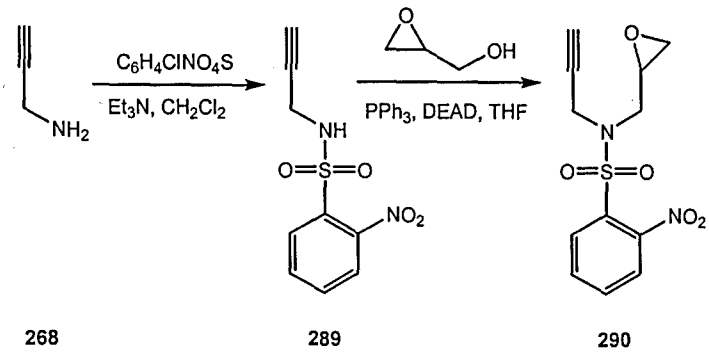
Scheme 5.20 Proposed Mechanism of Mitsunobu Reaction

The phosphine adds to the weak N=N π bond (**284**) to give an anion stabilised by one of the ester groups. The anion produced in this first stage is basic enough to remove a proton from the alcohol. Oxygen and phosphorus have a strong affinity and so the new alkoxide ion immediately attacks the positively charged phosphorus atom displacing a second nitrogen anion, which is stabilised in the same way as the first. This is the S_N2 reaction at carbon. The other basic nitrogen (**285**) removes a proton from the nucleophile. The true nucleophile is now revealed as an anion. Finally, the anion of the nucleophile attacks the phosphorus derivative of the alcohol (**286**) in a normal S_N2 reaction at carbon with the phosphine oxide as the leaving group.

The whole process takes place in one operation. The four reagents are all added to one flask and the products are phosphine oxide, the reduced azo diester with two NH bonds replacing the N=N double bond, and the product of an S_N2 reaction on the alcohol. These atoms end up in very stable molecules- the P=O and N-H bonds are very stable while the N=N bond is weak.

5.10 Mitsunobu Chemistry towards the Epoxide (290)

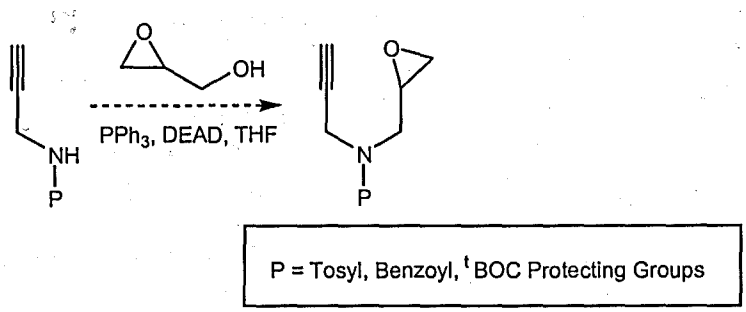
It was decided to utilise this chemistry to directly form the epoxide. First, the Mitsunobu chemistry was carried out on a model compound, which has a pKa lower than 11. The preparation of *N*-propynyl-2-nitro-*N*-oxiranylmethylbenzenesulfonamide (**290**) was achieved as shown in scheme 5.21.



Scheme 5.21

N-Propargyl-2-nitrobenzenesulfonamide (**289**) was treated with DEAD, and triphenylphosphine in dry THF. Glycidol was then rapidly added to this solution to afford *N*-propynyl-2-nitro-*N*-oxiranyl-methylbenzenesulfonamide (**290**) in 86% yield. It was concluded that the epoxide was synthesised on the basis of the observed epoxide protons in the ^{1}H NMR spectrum. The ^{1}H NMR spectrum showed resonances for three protons. A double doublet at δ 2.53 ppm with *J* values of 4.6 and 2.6 Hz and a triplet at δ 2.71 ppm with a *J* value of 4.3 Hz integrated for the two protons next to the oxygen of the epoxide. A multiplet at δ 3.06 ppm intregrated for the single proton next to the oxygen of the epoxide. These features, along with an accurate high-resolution mass spectrum data, confirmed the formation of the epoxide (**290**).

As expected, when this chemistry was applied to our original compounds having either the tosyl, benzoyl, ^{t}BOC or trifluoroacetic anhydride protecting groups, the reaction fails (Scheme 5.22).



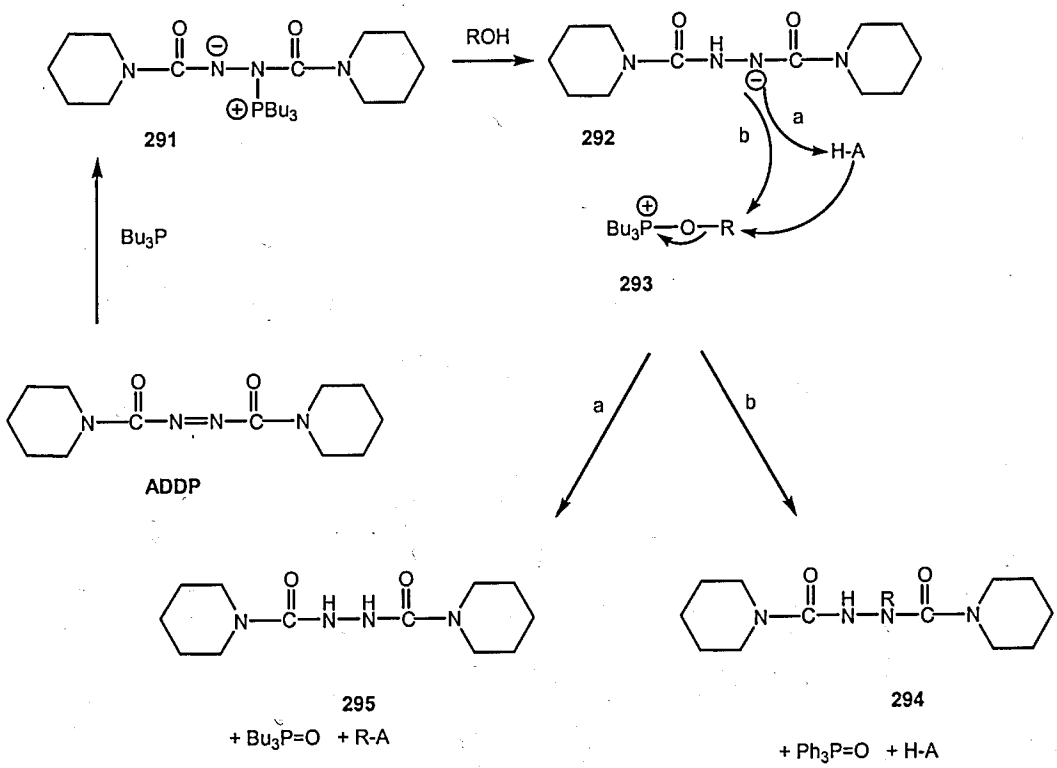
Scheme 5.22

This confirms the limitations of this chemistry, as the nucleophile must have a pKa lower than 11. However, Japanese workers; Tsunoda, Yamamiya and Itô[175] reported new reagents, 1,1[1]-(azodicarbonyl)dipiperidine (ADDP)-tributylphosphine (TBP), which can satisfactorily be applied to substrates with pKa higher than 11. These reagents have the following improvements on the classical Mitsunobu reagents. (Scheme 5.23).

1) an increase in the nucleophilicity of phosphine in the formation of intermediate (**291**),

2) the positive charge on phosphorus in (**291**) and (**293**) is localised in order to facilitate the nucleophilic attack of the RO anion or the A anion, respectively,

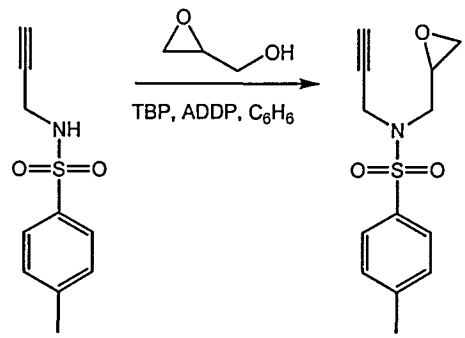
3) the negative charge at the azo-nitrogen is localised in order to increase its basicity in intermediate (**292**). The first two considerations arrived at TBP, while the third culminated in ADDP.



Scheme 5.23

5.11 The ADDP-TBP System towards the Epoxide (297)

The preparation of 4-methyl-*N*-(prop-2-enyl)-*N*-oxiranyl-N-benzenesulfonamide (297) was achieved as shown in scheme 5.24.

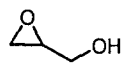
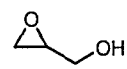
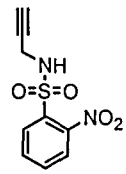
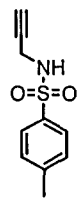
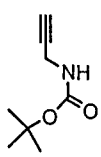
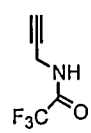


296 297

Scheme 5.23

Under an atmosphere of nitrogen, glycidol, tributylphosphine and the starting material 4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (296) were successively dissolved in dry benzene with stirring at 0 °C, and solid ADDP was added to the solution. This reaction afforded a yellow solid in 62% yield. The two hydrogen protons of the epoxide were observed as a double doublet at δ 2.55 ppm and as a triplet at δ 2.72 ppm in the ^{1}H NMR spectrum. A multiplet at δ 3.09ppm was assigned to the single proton on the epoxide. These features, along with an accurate high-resolution mass spectrum, confirmed the formation of the epoxide (297).

The efficiency of the ADDP-TBP system was compared with DEAD-TPP in benzene for the reactions of *N*-propargyl-2-nitrobenzenesulfonamide (289), 4-methyl-*N*-prop-ynyl-benzenesulfonamide (296), *N*-(*tert*-butyloxycarbonyl)prop-2-ynylamine (281) and 2,2,2-triflouro-*N*-prop-2-ynyl-acetamide (272) with the alcohol glycidol. The results are shown in table 5.1.

	HA	ROH	
			
		D	A
1		86%	-
2		0%	62%
3		0%	0%
4		0%	40%

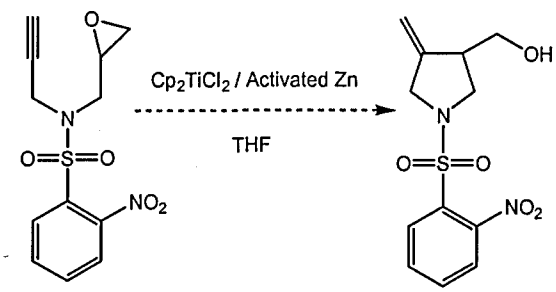
D : DEAD-TPP in C_6H_6. A : ADDP-TBP in C_6H_6 - : No Experiment

Table 5.1.

Entry 1 worked well under classical Mitsunobu conditions giving 86% yield. This is due to the fact that the acidic hydrogen in (**290**) has a pK_a lower then 11. Entry 2 failed to proceed under classical conditions but under the improved ADDP-TBP system yielded 62% of product. Entry 3 failed to afford product under either set of reaction conditions. This could be due to steric factors associated with the bulky BOC group, rendering it difficult for the nucleophile to abstract a hydrogen from H-A. Finally, entry 4 was successful using ADDP-TBP but still fails with DEAD-TPP despite the fact that this protecting group makes the N-H bond more acidic. Base-promoted alkylation of all four substrates (entry 1-4) shown in Table 5.1 with epichlorohydrin failed to give the desired product.

5.12 Titanium-Mediated Radical Cyclisation of Precursor (298).

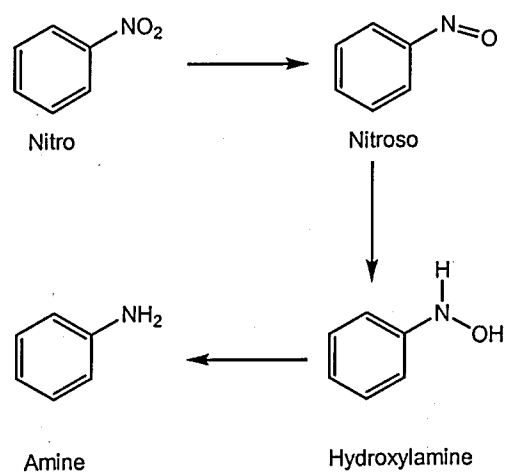
We anticipated the possibility of this radical cyclisation reaction of (**290**) being unsuccessful due to the presence of the nitro group. The nitro group was ideal for the Mitsunobu chemistry as it lowered the pK_a sufficiently to allow the reaction to proceed. However, when we subjected our *N*-propynyl-2-nitro-*N*-oxiranylmethyl-benzenesulfonamide (**290**) to the titanium radical chemistry we were not surprised to discover that the desired cyclised product was not formed.



290 **298**

The most notable points that can be made about this cyclisation are:

1. The NO_2 group can be easily reduced under these conditions. The titanium/zinc complex can reduce the nitro group as follows:



This reduction from NO_2 to NH_2 is evident in the ^1H NMR spectrum as the benzylic group multiplet moves upfield from δ 7.6 ppm to δ 6.9 ppm.

In addition, the protons assigned to the epoxide are not evident although the acetylenic proton is still present at δ 2.2 ppm. One possibility is that the carbon radical is formed, but undergoes a rapid ipso attack on the benzene ring (Figure 5.6). There is good precedent for this reaction in the work of Motherwell.[176]

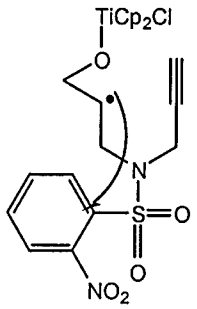
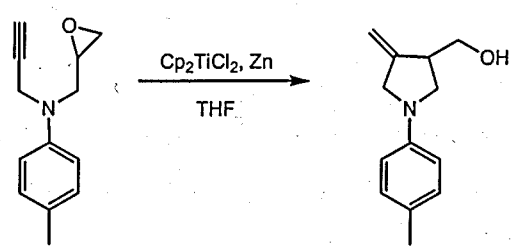


Figure 5.6

5.13 Titanium-Mediated Radical Cyclisation of Precursor (297).

The radical cyclisation of 4-methyl-*N*-(prop-2-ynyl)-*N*-oxiranylmethyl-*N*-benzenesulfonamide (**297**) was carried out under the same conditions. Quenching the reaction with 10% H_2SO_4, resulted in a substantial amount of emulsions forming. The crude product was extracted with Et_2O after washing with $NaHCO_3$.

The product with an R_f value of 0.27 was isolated in 39% yield. In the ^1H NMR spectrum the vinylic protons were observed at δ 4.92 ppm and δ 4.96 ppm respectively as a singlet and a doublet both integrating for one proton. Further evidence for the successful cyclisation to the pyrrolidine product was the disappearance of the epoxide protons. A double doublet appearing at δ 3.8 ppm with *J* values of 14 and 2 Hz and integrating for two protons also can be assigned to the CH_2OH group. This successful cyclisation demonstrates the feasibility of this approach to functionalised pyrrolidines (Scheme 5.24).

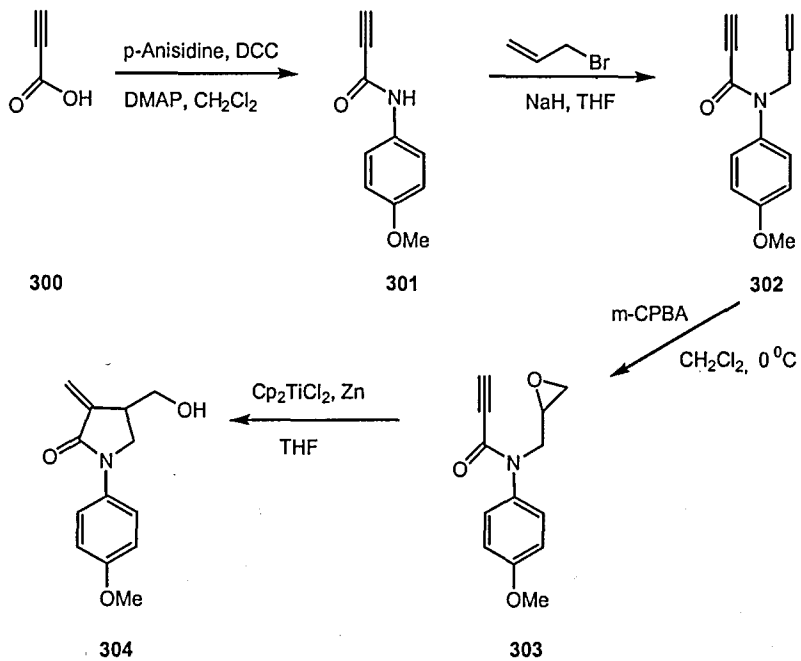


297 299

Scheme 5.24

5.14 An Alternative Route towards the substituted pyrrolidine (304)

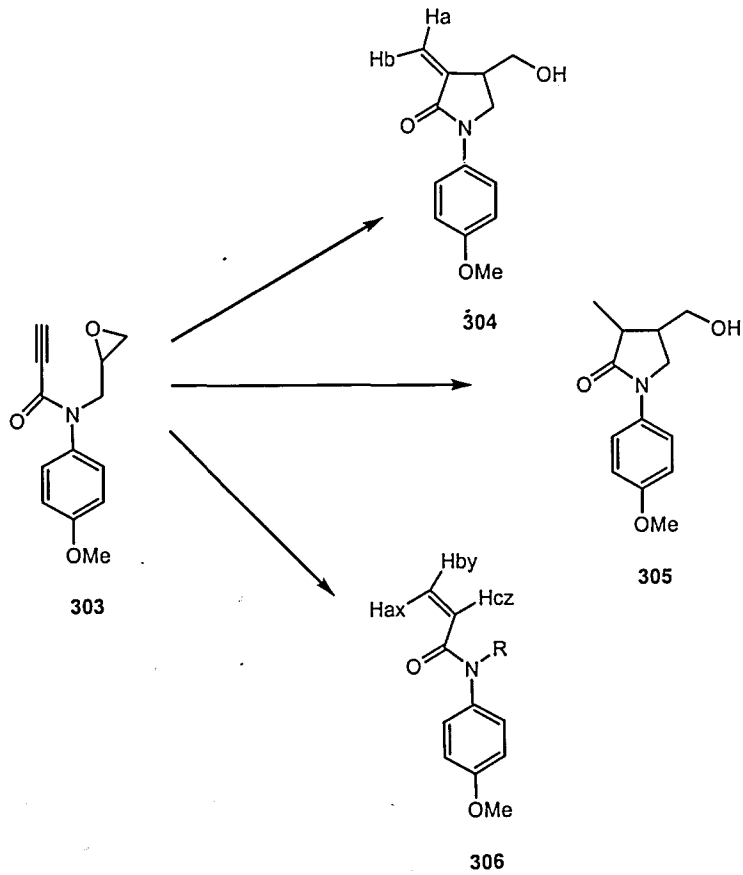
To further explore the failure of the simple *N*-substituted-*N*-propenylallylamines to epoxidise, we decided to transpose the carbonyl group. Thus, we synthesised epoxidation substrate (**302**) with the carbonyl group conjugated with the alkyne as shown in scheme 5.25.



Scheme 5.25

Addition of *p*-anisidine to propiolic acid (**300**) using dicyclohexylcarbodiimide (DCC)[177] gave (**301**) in 88% yield. Reaction of this alkynyl amide (**301**) with sodium hydride and allyl bromide in THF gave the tertiary amide (**302**) in 65% yield. This was confirmed in the ^{1}H NMR spectrum as the acetylenic proton was observed as a singlet at δ 2.77 ppm. The allylic protons were observed as double doublets at δ 5.04 ppm and δ 5.07 ppm respectively. Epoxidation of (**302**) was carried out using *m*-CPBA in dichloromethane at 0 °C, which successfully afforded propynoic acid (4-methoxy-phenyl)-oxiranylmethylamide (**303**) in 56% yield. The evidence for the epoxide moiety came from the ^{1}H NMR spectrum. A double doublet appeared at δ 2.4 ppm with *J* values of 2.5 and 4.4 Hz integrating for one hydrogen of NCH_2CHCH_2O. The second of these hydrogens appears as a triplet with a *J* value of 4.4 Hz at δ2.7 ppm. The acetylenic proton appears as a singlet at δ 2.8 ppm. The third epoxide proton appears as a double doublet at δ 4.02 ppm.

The radical cyclisation of the acetylenic-epoxy amide (**303**) was carried out as discussed previously using bis(cyclopentadienyl)titanium(III)chloride with activated zinc in dry THF. The ^{1}H NMR spectrum of the crude product showed three compounds to be present as shown in scheme 5.26.



Scheme 5.26

5.15 Products observed

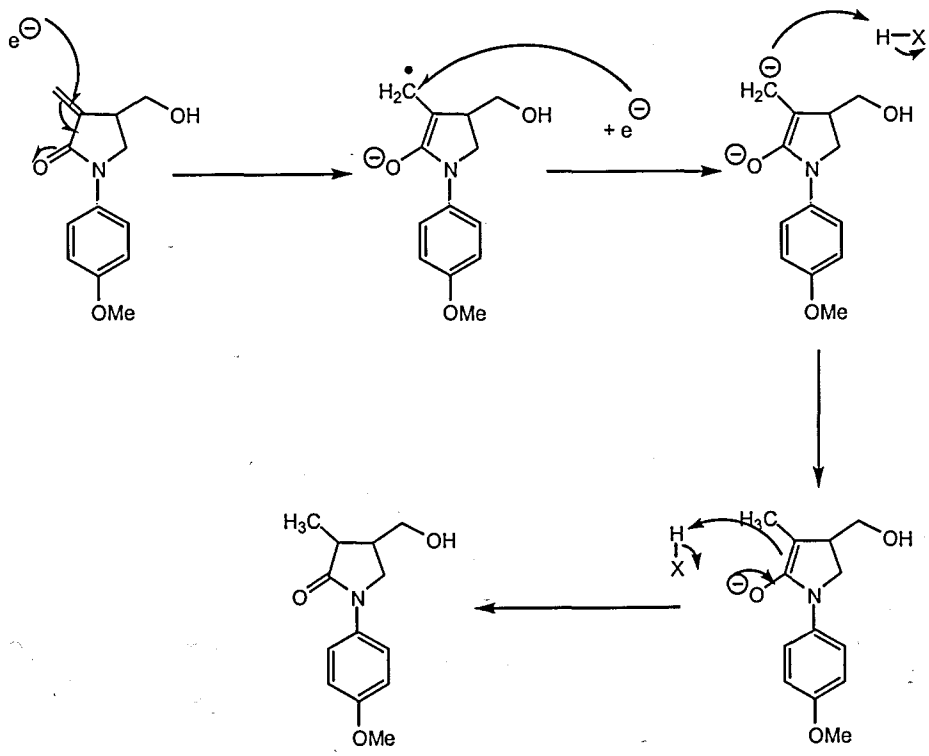
Three products in a ratio of 2:2:1 were observed for (**304**), (**305**) and (**306**) respectively.

Product (304):

Evidence for this product was seen in the ^{1}H NMR spectrum. The olefinic protons H_a and H_b were observed as resonances at δ 5.31 ppm and δ 6.05 ppm. Both H_a and H_b appear as doublets with a *J* value of 2.5 Hz, each integrating for one proton. The two protons of $CHCH_2OH$ appear as a doublet with a *J* value of 5 Hz at δ 3.68 ppm. We concluded that this is the desired reaction product, 4-hydroxymethyl-1-(4-methoxy-phenyl)3-methylene-pyrrolidin-2-one (**304**) and is the product of the titanium-mediated cyclisation reaction.

Product (305):

An excess of titanium reagent is present in the reaction, the structure (**305**) was tentatively assigned to this product which forms by reduction of (**304**) (Scheme 5.27). This product is clearly not simply a double bond isomerisation of (**304**) as the resulting methyl group would be vinylic and appear as a singlet in the ^1H NMR spectrum. A doublet was observed at δ 1.25 ppm integrating for three protons.

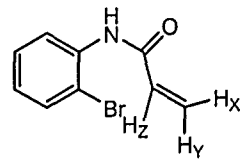


305

Scheme 5.27

Product (306):

In the ^1H NMR spectrum we observed a resonance at δ 5.9 ppm, which appears as a double doublet with *J* values of 17 and 10 Hz, which could be assigned to Hcz. A signal at δ 5.5 ppm (dd, *J* 10 and 2 Hz) integrating for one proton was assigned to Hby. Finally, a signal at δ 6.3 ppm (dd, *J* 17 and 2 Hz) could be assigned to Hax. These chemical shifts fit very well to those found in the molecule (**307**), figure 5.5.[178] Compound (**306**) is also a reduction product presumably formed by excess titanium reagent.



307

Figure 5.5

5.16 Conclusion

From our studies we can conclude that tertiary amides (sulfonamides) do not epoxidise. However, tertiary amides with a carbonyl group in the propargyl sidechain do epoxidise. Secondary amides epoxidise easily.

The classical Mitsunobu reaction conditions (DEAD, TPP) failed to furnish suitable substrates for our titanium-mediated cyclisation reaction. However modified Mitsunobu reaction conditions (ADDP, TBP) afforded the desired cyclisation precursor. The N-Ts epoxide substrate successfully cyclised to afford the pyrrolidine utilising the titanium-based radical chemistry. The propiolic amide also gave cyclised material but a side reaction occurred owing to the position of the C=O bond.

Chapter VI

Experimental

Tetramethylsilane (TMS) was adopted as the internal standard for ^{1}H NMR spectra and the solvent peaks for ^{13}C NMR spectra. Chemical shifts (δ_H and δ_C) are quoted as downfield from trimethylsilane. The multiplicity of a ^{1}H and deuterium NMR signal is designated by one of the following abbreviations: s = singlet, d = doublet, t – triplet, q = quartet, quin = quintet, br = broad and m = multiplet. High-resolution mass spectra were performed at the chemistry department, Kings College, London University. High-resolution mass spectra were recorded on either a Katos MS89MS with Katos DS90 software or a Jeol complement data system. Samples were ionised electronically (EI), with an accelerating voltage of ≈6 kV or by low-resolution fast atom bombardment (FAB) in thioglycerol matrix. High-resolution fast atom bombardment (FAB) was carried out at ULIRS mass spectrometry facility at the School of Pharmacy, University of London.

All melting points were determined on a Gallenkamp melting point apparatus or a kofler hot plate apparatus and were uncorrected. Infrared spectra were recorded on a Perkin Elmer 1605 FT-IR spectrophotometer. ^{1}H NMR, ^{13}C NMR and deuterium NMR spectra were recorded on a Brucker AM360 spectrometer operating at 300 Mz for proton and deuterium and 75 MHz for carbon.

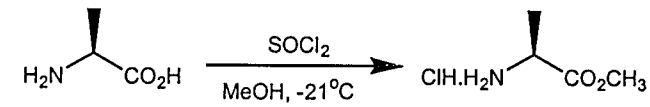
All moisture sensitive reactions were carried out under argon. All glassware, syringes and needles were pre-dried in an oven (110 °C) and cooled in an argon atmosphere prior to use. Stirring was by internal magnetic follower unless otherwise stated. All reactions were followed by TLC. Organic phases are dried with magnesium sulfate or sodium sulfate.

Diethyl ether, tetrahydrofuran (THF) and toluene were distilled from sodium benzophenone ketyl immediately before use. Methanol and ethanol were distilled

form magnesium turnings under argon, either directly into the reaction vessel or kept over activated 3Å molecular sieves prior to use. Dichloromethane was refluxed over calcium hydride and distilled directly into the reaction vessel. Dimethylformamide was heated to reflux over calcium hydride, distilled and stirred over activated molecular sieves prior to use. Acetone was dried and purified by refluxing over a mixture of potassium permanganate and anhydrous potassium carbonate before distilling onto 3Å molecular sieves. 40-60 °C Petroleum ether (petrol) was distilled before use in column chromatography. Thionyl chloride was distilled from iron turnings before use. Acryloyl chloride and dimethyl sulphoxide were freshly distilled before use. Tri-*n*-butyltin hydride was made by the procedure of Szammer and Ötvös. It was distilled under an argon atmosphere and could be stored refrigerated in an atmosphere of argon for several months.

Purification was carried out by column chromatography using the flash chromatography technique as reported by Still.[179] The silica gel used was Merck 7734 or Merck 60 (230-400 mesh). Thin layer chromatographic analysis was performed using Polygram and Merck plastic-backed silica plates (Merck 5735). Glass TLC plates have also been used. Components were visualised using either ultraviolet light, iodine vapour or potassium permanganate indicator.

L-Alanine methyl ester hydrochloride (139)

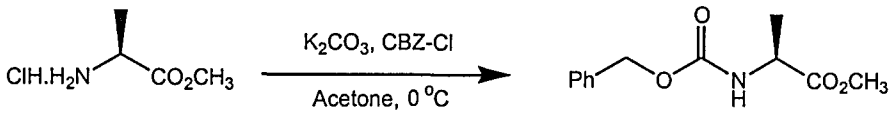


$C_3H_7NO_2$ — Mol. Wt.: 89.0932

$C_4H_7NO_2HCl$ — Mol. Wt.: 139.58

Thionyl chloride (160 g, 1.34 mol, 98.1 mL) was slowly added dropwise to a solution of L-alanine (100 g, 1.122 mol) in dry methanol (500 mL) at –21 °C. The mixture was allowed to warm to room temperature, and stirring was continued for 4 hours. The excess thionyl chloride and solvent were removed under reduced pressure to yield the title compound (**139**) as a white crystalline solid. (155.93 g, 99 %) m.p. 109 - 112°C [Lit.[79] 109 - 111°C]; $[\alpha]_D^{20}$ + 6.1 (methanol, $c = 0.13$) [Lit.[2] $[\alpha]_D^{20}$ + 7]; (found M^+-HCl, 103.0633 $C_4H_9NO_2$ requires M^+-HCl 103.0633; ν_{max} (NaCl)/cm^{-1} 1740.3 (ester C=O), 2988.5 (C-H); δ_H (300 MHz; $CDCl_3$) 1.42 (3H, d, *J* 7.1, CH_3), 3.71 (3H, s, OCH_3), 4.03 (1H, q, *J* 7.1, $CHCH_3$), 8.77 (2H, br. s, NH_2); δ_C (75 MHz; $CDCl_3$) 17.9 (CH_3), 51.7 (CH_3), 56.5 (CH), 174.1 (C=O); m/z 105.1 (9.8 %), 104.1 (49.9), 103.1 (49.9), 88.0 (16.3).

N-Benzyloxycarbonyl-(*2S*)-alanine methyl ester (140)[77]



$C_4H_9NO_2.HCl$

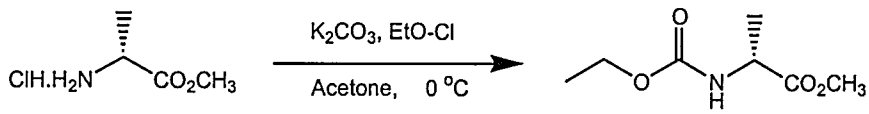
Mol. Wt.: 139.58

$C_{12}H_{15}NO_4$

Mol. Wt.: 237.3

Benzyl chloroformate (61.12 g, 0.36 mol) was added dropwise to a stirred solution of L-alanine methyl ester hydrochloride (**139**) (50.0 g, 0.36 mol) and potassium carbonate (188.02 g, 1.360 mol) in dry acetone (715 mL) under argon, and the reaction mixture was stirred overnight. Water (715 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 300 mL). The combined extracts were washed with an aqueous solution of hydrochloric acid (300 mL, 2 M) and then with water (300 mL). The organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give the title compound contaminated with benzyl alcohol. The benzyl alcohol contaminant was removed under reduced pressure (34 °C / 0.7 mmHg) to afford the title compound (**140**) (67.91 g, 79 %) as a light yellow oily residue; R_f (2:1 hexane: ethyl acetate) 0.57; $[\alpha]_D^{20}$ – 28.1 (methanol, $c = 0.13$) [Lit.[78] $[\alpha]_D^{20}$ – 26.8]; (Found M^+, 237.0966. $C_{12}H_{15}NO_4$ requires M^+ 237.1001); ν_{max} (NaCl)/cm^{-1} 1535 (aromatic ring), 1701 (NCOO), 1745.6 (ester C=O), 3343.3 (N-H); δ_H (300 MHz; $CDCl_3$) 1.33 (3H, d, *J* 7, $CHCH_3$), 3.6 (3H, s, OCH_3), 4.31 (1H, quintet, *J* 7, $NHCHCH_3$), 5.03 (2H, s, $PhCH_2$), 5.3 (1H, d, *J* 7, NH), 7.23 - 7.33 (5H, m, aryl C-H); δ_C (75 MHz; $CDCl_3$) 18.6 ($CHCH_3$), 49.6 (OCH_3), 52.5 ($NHCHCH_3$), 66.9 ($PhCH_2$), 128.1 + 128.2 + 128.6 (aryl C-H), 136.2 (quaternary aryl-C), 155.6 (NCOO), 173.5 (CO_2Me); m/z 127.1 (7.4%, M^+), 107.1 (7.2%, $PhCH_2O^+$), 91.1 (100%, $PhCH_2^+$), 77.0 (3.2%, $C_6H_5^+$).

N-Ethoxycarbonyl-(*2R*)-alanine methyl ester (152)[180]



$C_4H_9NO_2.HCl$

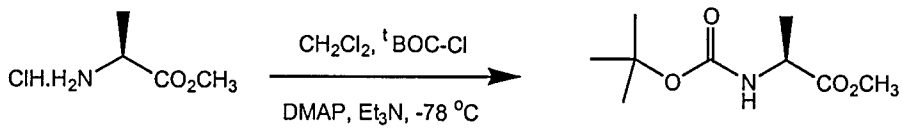
Mol. Wt.: 139.6

$C_7H_{13}NO_4$

Mol. Wt.: 175.2

Ethyl chloroformate (51.1 mL, 0.535 mol) was added dropwise to a stirred solution of *R*-alanine methyl ester hydrochloride (**151**) (15 g, 0.107 mol) and potassium carbonate (125.5 g, 0.909 mol) in acetone (200 mL) under argon, and the reaction mixture was stirred overnight. Water (100 mL) was added and the reaction was extracted with ethyl acetate (3 x 100 mL). The combined extracts were washed with an aqueous solution of hydrochloric acid (100 mL, 10 %) and then with water (100 mL). The organic layers were dried ($MgSO_4$), and the solvent removed under reduced pressure. The crude material was purified by column chromatography (2:1 hexane: ethyl acetate) to give the title compound (**152**) (11.1 g, 59 %) as a light yellow oily residue; R_f (2:1 hexane: ethyl acetate) 0.56; $[\alpha]_D^{20}$ −2.3 ($CHCl_3$, $c = 0.03$); ν_{max} (NaCl)/cm^{-1} 1705.6 (NCOO), 1723.0 (ester C=O), 3341.7 (N-H); δ_H (300 MHz; $CDCl_3$) 1.2 (3H, t, *J* 7.1, $CH_2\mathbf{CH_3}$), 1.3 (3H, d, *J* 7.2, $NCH\mathbf{CH_3}$), 3.66 (3H, s, $O\mathbf{CH_3}$), 4.03 (2H, q, *J* 7.1, $O\mathbf{CH_2}$), 4.27 (1H, quintet, *J* 7.2, $NH\mathbf{C}HCH_3$), 5.5 (1H, d, *J* 7.2, N**H**); δ_C (75 MHz; $CDCl_3$) 14.1 ($\mathbf{C}H_3$), 17.8 ($\mathbf{C}H_3$), 49.2 (N**C**H), 51.9 ($\mathbf{C}H_3$), 60.6 ($\mathbf{C}H_2$), 155.8 (**C**=O), 173.5 (**C**=O). Found $[M + Na]^+$, 198.0745; $C_7H_{13}NO_4$ requires *M* + Na 198.0737.

N-tert-butoxycarbonyl-(*S*)-alanine methyl ester (154)[181]



$C_4H_9NO_2.HCl$

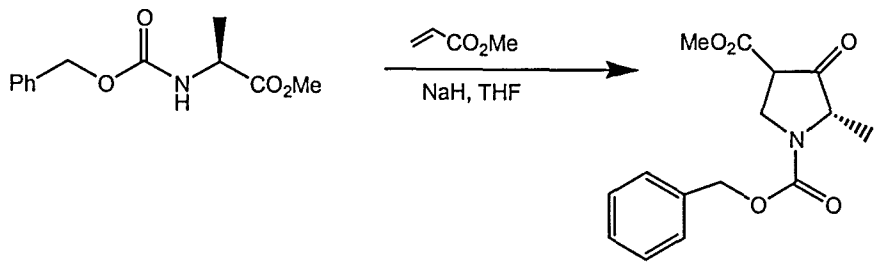
Mol. Wt.: 139.6

$C_9H_{17}NO_4$

Mol. Wt.: 203.2

Di-*tert*-butyl dicarbonate (20.9 g, 96.0 mmol), 4-dimethylamino-pyridine (DMAP) (0.78 g, 6.4 mmol), and triethylamine (8.9 mL, 64.5 mmol) were added to a solution of L-alanine methyl ester hydrochloride (**151**) (9 g, 64.48 mmol) in dichloromethane (128 mL) at –78 °C. The solution was stirred for 7 hours under an atmosphere of nitrogen. The dichloromethane was removed *in vacuo* and the residue was reconstituted in water (30 mL). The latter mixture was quenched with saturated NH_4Cl (20 mL) and extracted with diethyl ether (3 x 50 mL). The extracts were washed with brine (3 x 40 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to furnish the title compound (**154**). The crude material was purified by column chromatography on silica gel (4:1 hexane: ethyl acetate) to give the title compound (**154**) (8.0 g, 62 %) as a light yellow oily residue; R_f (4:1 hexane: ethyl acetate) 0.52; $[\alpha]_D^{20}$ +2.4 ($CHCl_3$, $c = 0.02$); ν_{max} (NaCl)/cm^{-1} 1367.1 (CH_3), 1710.0 (NCOO), 1740.3 (ester C=O), 3342.6 (N-H); δ_H (300 MHz; $CDCl_3$) 1.3 (3H, d, *J* 6, NCHC**H**$_3$), 1.37 (9H, s, (C**H**$_3$)$_3$), 3.67 (3H, s, OC**H**$_3$), 4.24 (1H, quintet, *J* 6, NHC**H**), 5.06 (1H, br. s, N**H**); δ_C (75 MHz; $CDCl_3$) 18.56 (**C**H$_3$), 28.26 (C(**C**H$_3$)$_3$), 49.10 (O**C**H$_3$), 52.26 (NH**C**H), 79.7 (quaternary-**C**), 156.5 (**C**=O), 173.8 (**C**=O). Found $[M + Na]^+$, 226.1056; $C_9H_{17}NO_4$ requires *M* + Na 226.1050.

_N_-Benzyloxycarbonyl-(2_S_)-4-methoxycarbonyl-2-methylpyrrolidin-3-one (141)



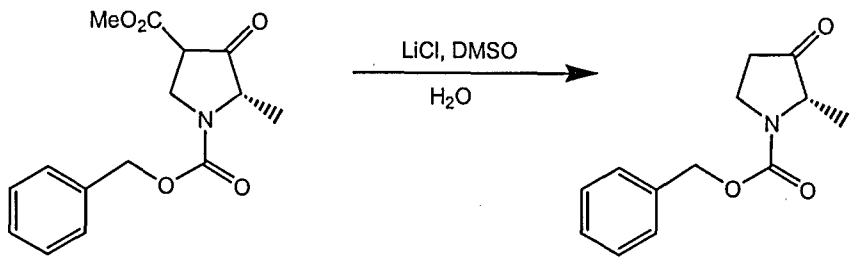
$C_{12}H_{15}NO_4$
Mol. Wt.: 237.3

$C_{15}H_{17}NO_5$
Mol. Wt.: 291.3

A solution of *N*-benzyloxycarbonyl-(2S) alanine methyl ester (**140**) (50.0 g, 210.7 mmol) in dry THF (120 mL) was added to a stirred suspension of sodium hydride (10.03 g of 60 % dispersion in mineral oil, 250.73 mmol, hexane washed) in THF (250 mL) under an atmosphere of nitrogen followed by methyl acrylate (19.74 g, 20.66 mL, 229.7 mmol), and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was heated under reflux for 2 hours, then allowed to cool to room temperature. Water (250 mL) was then added carefully. The aqueous layer was separated, washed with diethyl ether (2 x 250 mL), acidified (pH < 2) with concentrated hydrochloric acid and extracted with ethyl acetate (3 x 150 mL). The combined extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to give the title compound (**141**) (31.7 g, 51 %) as a viscous orange oil, which was not further purified. R_f (1:5 ethyl acetate: petroleum ether 40-60 °C) 0.75; $[\alpha]_D^{20}$ + 4.5 (methanol, $c = 0.12$); ν_{max} (NaCl)/cm^{-1} 1530 (aromatic ring), 1641.0 (C=O), 2956 (C-H), 3409 (O-H); δ_H (300 MHz; $CDCl_3$) spectrum shows evidence of restricted rotation: 1.26 - 1.41 (3H, m, CH_3), 3.40 - 3.75 (4H, m, OCH_3, CHCO), 3.85 - 3.90 (1H, m, $NCHCH_3$), 3.95 - 4.23 (2H, m, NCH_2), 5.05 (2H, m, $PhCH_2$), 7.25 (5H, m, aryl-H); δ_C (75 MHz; $CDCl_3$) 17.4 (CCH_3), 18.4 (CCH_3), 44.2 (CH_2N), 44.8 (CH_2N), 47.9 (CH_2N), 48.2 (CH_2N), 51.4 (OCH_3), 53.1 (OCH_3), 57.7 ($CHCO_2Me$), 58.3 ($NCHCH_3$), 66.9 + 67.2 + 67.4 ($PhCH_2$), 127.9 + 128.1 + 128.2 + 128.3 + 128.5 + 128.6 + 128.7 (aryl C-H), 136.1 (quaternary aryl-C), 154.9 (NCOO), 155.0 (NCOO), 167.7 (CO_2Me), 168.9 (CO_2Me), 171.5 (CO),

171.6 (CO); HRMS m/z 292.1185 (M + H^+). Found $[M + Na]^+$, 314.1024; $C_{15}H_{17}NO_5$ requires *M* + Na 314.0999.

N-Benzyloxycarbonyl-(*2S*)-2-methyl-pyrrolidin-3-one (142)

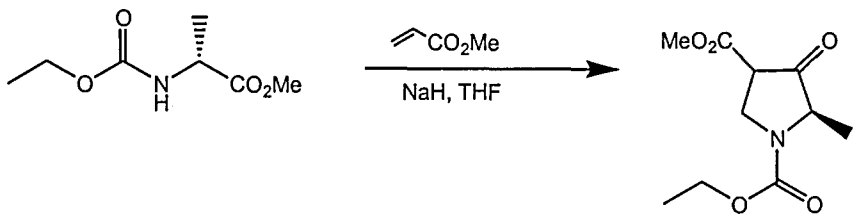


$C_{15}H_{17}NO_5$
Mol. Wt.: 291.3

$C_{13}H_{15}NO_3$
Mol. Wt.: 233.3

Lithium chloride (4.85 g, 0.12 mol) and water (5.56 g, 0.31 mol) were added to a stirred solution of *N*-benzyloxycarbonyl-(*2S*)-4-methoxycarbonyl-2-methylpyrrolidin-3-one (**141**) (30 g, 0.103 mol) in dimethyl sulfoxide (236 mL). The reaction mixture was heated to 100 °C under nitrogen for 2 hours, allowed to cool, and water (250 mL) was added. The reaction mixture was extracted with ethyl acetate (5 x 75 mL), and the combined organic extracts were washed with saturated sodium bicarbonate solution (3 x 100 mL), saturated sodium chloride solution (3 x 100 mL) and water (3 x 100 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to give the crude product, which was purified by column chromatography. The title compound (**142**) was obtained as a pale yellow oil (15.07 g, 63 %); R_f (1:1 ethyl acetate: hexane) 0.68; $[\alpha]_D^{20}$ + 16.34 (methanol, $c = 0.21$); ν_{max} (NaCl)/cm^{-1} 1367 (C-O) 1758 (C=O), 3444 (O-H); δ_H (300 MHz; $CDCl_3$) 1.92 (3H, d, *J* 5.1, NCHC**H**$_3$), 3.13 - 3.21 (2H, m, C(4)**H**$_2$), 4.2 - 4.3 (1H, m, NC**H**), 4.5 (2H, t, *J* 6.7, C(5)**H**$_2$), 5.74, 5.79 (2H, ABq, *J* 12, PhC**H**$_2$), 7.8 - 8.0 (5H, m, aryl C-**H**); δ_C (75 MHz; $CDCl_3$) 30.9 (C**C**H$_3$), 35.6 (**C**H$_2$), 40.7 (N**C**H), 41.2 (**C**H$_2$), 65.1, (Ph**C**H$_2$), 67.2 (Ph**C**H$_2$), 126.9, 127.4, 128.0, 128.2, 128.4, 128.6 (aryl **C**-H), 136.3 (quaternary aryl-**C**), 189.0 (**C**=O); m/z 233 (12.5%, M^+), 91 (100% $PhCH_2^+$). Found $[M + Na]^+$, 256.0947; $C_{13}H_{15}NO_3$ requires *M* + Na 256.0944.

_N_-Ethyoxycarbonyl-(2_R_)-4-methoxycarbonyl-2-methyl-pyrrolidin-3-one (153)



$C_7H_{13}NO_4$

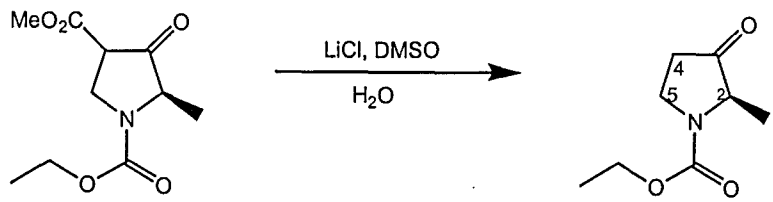
Mol. Wt.: 175.2

$C_{10}H_{15}NO_5$

Mol. Wt.: 229.2

A solution of _N_-ethoxycarbonyl-(2_R_)-alanine methyl ester (**152**) (10.0 g, 57.16 mmol) in dry THF (30 mL) was added to a stirred suspension of sodium hydride (2.72 g of 60 % dispersion in mineral oil, 67.89 mmol, hexane washed) in THF (50 mL) under nitrogen, followed by the addition of methyl acrylate (5.34 g, 5.59 mL, 62.13 mmol). The resulting mixture was stirred at room temperature for 30 minutes, and was then heated under reflux for 2 hours. The contents of the flask were then allowed to cool to room temperature, and water (50 mL) was carefully added. The aqueous layer was separated, washed with diethyl ether (2 x 50 mL), made acidic (pH < 2) with concentrated hydrochloric acid and extracted with ethyl acetate (3 x 50 mL). The combined extracts were dried with magnesium sulfate and the solvent removed under reduced pressure to give the title compound (**153**), (7.23 g, 55.4 %) as a viscous orange oil which was not further purified. R_f (1:3 ethyl acetate: petroleum ether 40-60 °C) 0.67; $[\alpha]_D^{20}$ + 11.2 (methanol, $c = 0.002$); ν_{max} (NaCl)/cm^{-1} 1683 (C=O), 2991.2 (C-H), 3397.2 (O-H); δ_H (300 MHz; $CDCl_3$) 1.16 - 1.32 (3H, m, $OCH_2\mathbf{CH_3}$), 1.34 - 1.43 (3H, m, $\mathbf{CH_3}$), 3.68 (2H, dd, _J_ 11.2, 4.1, $NC\mathbf{H_2}$), 3.73 (3H, s, OCH_3), 4.03 - 4.34 (3H, m, $OC\mathbf{H_2}$, $\mathbf{CH}CO_2CH_3$), 4.37 - 4.53 (1H, m, NC**H**); δ_C (75 MHz; $CDCl_3$) 14.1 ($\mathbf{CH_3}$), 14.5 ($\mathbf{CH_3}$), 18.3 ($\mathbf{CH_3}$), 29.4 ($\mathbf{CH_2}$), 31.6 ($\mathbf{CH_2}$), 53.1 ($\mathbf{CH_3}$), 57.7 ($\mathbf{C}HCO_2Me$), 58.7 ($\mathbf{C}HCO_2Me$), 61.2 ($\mathbf{CH_2}$), 61.4 ($\mathbf{CH_2}$), 63.8 (N**C**H), 152.0 (**C**=O), 176.34 (**C**=O), 189.0 (**C**=O).

N-Ethoxycarbonyl-(*2R*)-2-methyl-pyrrolidin-3-one (311)[182]



$C_{10}H_{15}NO_5$

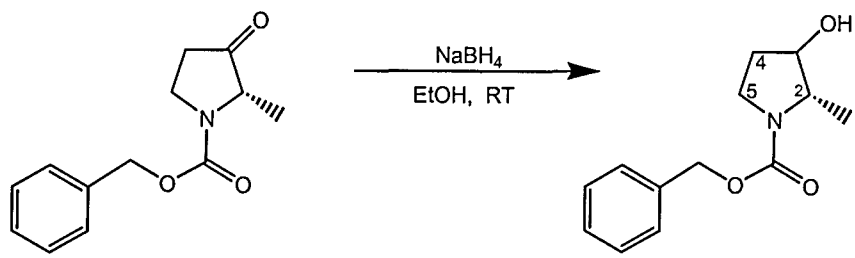
Mol. Wt.: 229.2

$C_8H_{13}NO_3$

Mol. Wt.: 171.2

Lithium chloride (0.56 g, 0.013 mol) and water (0.6 g, 0.037 mol) were added to a stirred solution of *N*-ethoxycarbonyl-(*2R*)-4-methoxycarbonyl-2-methyl-pyrrolidin-3-one (**153**) (2.8 g, 0.012 mol) in dimethyl sulfoxide (27.68 mL). The reaction mixture was heated to 100 °C under nitrogen for 2 hours, allowed to cool, and water (25 mL) was added. The reaction mixture was extracted with ethyl acetate (5 x 10 mL) and the combined organic extracts were washed with saturated sodium bicarbonate solution (3 x 10 mL), saturated sodium chloride solution (3 x 10 mL) and water (3 x 10 mL). The organic layer was dried with magnesium sulfate, filtered, and the solvent removed *in vacuo* to give the crude product which was purified by column chromatography to give the title compound (**x**) (1.2 g, 58.4 %) as a viscous orange oil; R_f (4:1 petroleum ether 40-60 °C: ethyl acetate) 0.58; $[\alpha]_D^{20}$ + 1.3 (methanol, $c = 0.02$); ν_{max} (NaCl)/cm^{-1} 1684.1 (C=O), 3421.0 (O-H); δ_H (300 MHz; $CDCl_3$) 1.19 - 1.27 (6H, m, CH_3, CH_2CH_3), 2.69 - 2.76 (2H, m, NCH_2), 3.75 (1H, q, *J* 8.7, NC**H**), 4.08 (2H, t, *J* 6.6, C(4)H_2), 4.31 (2H, m, OCH_2); δ_C (75 MHz; $CDCl_3$); 14.8 (CH_3), 16.5 (CH_3), 35.8 (CH_2), 41.2 (CH_2), 57.9 (CCH_3), 61.5 (CH_2), 155.3(**C**=O), 189.1 (**C**=O).

Benzyl-(*2S*)-3-hydroxy-2-methyltetrahydro-1*H*-pyrrolecarboxylate (156)

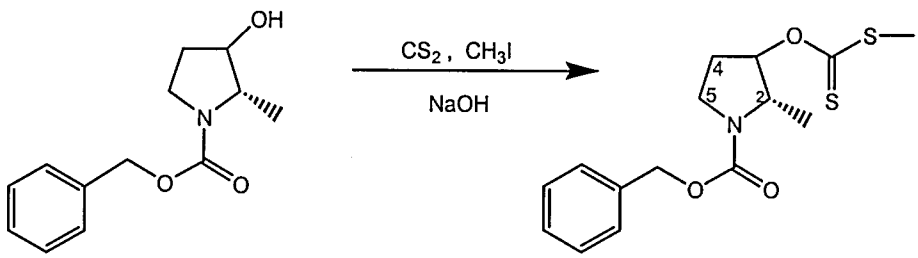


$C_{13}H_{15}NO_3$
Mol. Wt.: 233.3

$C_{13}H_{17}NO_3$
Mol. Wt.: 235.3

Sodium borohydride (0.12 g, 3.21 mmol) was added in small portions to a stirred solution of *N*–benzyloxycarbonyl–(*2S*)–2-methyl-pyrrolidin-3-one (**142**) (0.5 g, 2.14 mmol) in ethanol (150 mL). The reaction mixture was stirred for 8 hours at room temperature and then quenched with water (70 mL). The excess ethanol was removed under reduced pressure leaving a residue, which was then dissolved in water, and extracted with ethyl acetate (3 x 100 mL). The organic phase was dried using magnesium sulfate, filtered and concentrated under reduced pressure to give the title compound (**156**) (0.8748 g, 86.7 %) as a cloudy, slightly yellow oil; R_f (4:1 diethyl ether: hexane) 0.34; $[\alpha]_D^{20}$ + 5.06 (methanol, $c = 0.116$); ν_{max} (NaCl)/cm^{-1}), 3416 (O-H), 1530 (aromatic ring), 1678 (NC=O), 2978 (C-H), 3416.7 (O-H); δ_H (300 MHz; $CDCl_3$) 1.10 (3H, br. s, CH_3), 1.86 – 1.89 (1H, m, C(4)H_a), 1.94 – 2.04 (1H, m, C(4)H_b), 2.47 (1H, br. s, OH), 3.24 – 3.49 (2H, m, C(5)H_2), 3.82 (1H, quintet, *J* 6.4, C(2)H), 4.17 (1H, br. m, C(3)H), 5.01 (2H, br. s, PhCH_2), 7.16 – 7.31 (5H, m, aryl C-H); δ_C (75 MHz; $CDCl_3$) 13.9 (CH_3), 30.3 (C(4)H_2), 43.4 (C(5)H_2), 57.9 ($CHCH_3$), 66.8 (PhCH_2), 71.3 (CHOH), 127.8, 128.0, 128.5 (aryl C-H), 136.8 (quaternary aryl-C), 157.9 (C=O). Found [M + Na]$^+$, 258.1105; $C_{13}H_{17}NO_3$ requires *M* + Na 258.1101.

Benzyl-(*2S*)-3-xanthate-ester-2-methyltetrahydro-1*H*-pyrrolecarboxylate (157)



$C_{13}H_{17}NO_3$

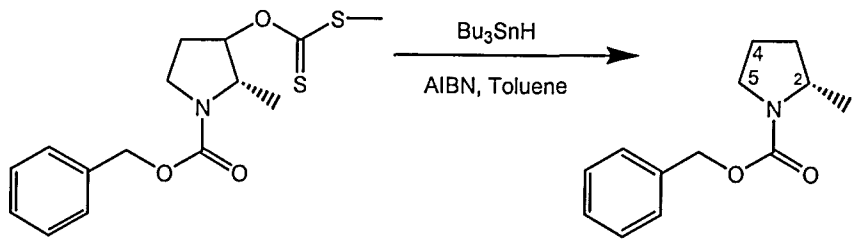
Mol. Wt.: 235.3

$C_{15}H_{19}NO_3S_2$

Mol. Wt.: 325.4

A solution of benzyl-(*2S*)-3-hydroxy-2-methyltetrahydro-1*H*-pyrrolecarboxylate (**156**) (6.0 g, 25.5 mmol) and methyl iodide (1.71 mL, 27.5 mmol) were added to a two-phase system consisting of carbon disulphide (25.64 mL, 426.4 mmol) and aqueous sodium hydroxide (29.45 mL, 50 % w/v) containing nBu_4NHSO_4 (0.87 g, 2.55 mmol) and stirred for 1 hr at room temperature. The reaction mixture was extracted with dichloromethane (3 x 20 mL). The organic extracts were dried and evaporated *in vacuo* affording the crude product which was purified by flash chromatography to give the title compound (**157**) (3.95 g, 48 %) as a bright yellow coloured oil. R_f (4:1 diethyl ether: hexane) 0.34; $[\alpha]_D^{20}$ + 2.1 ($CHCl_3$, c = 0.198); ν_{max} (NaCl)/cm^{-1} 1208 (C=S), 1679 (C=O), 680 (5 adjacent aryl C-H); δ_H (300 MHz; $CDCl_3$) 1.0 - 1.2 (3H, 2 br. s, CCH_3), 2.0 - 2.25 (2H, m, C(4)H_2), 2.48 (3H, s, SCH_3), 3.45 (2H, t, J 7.2, NCH_2), 4.24 (1H, quintet, J 6.5, $NCHCH_3$), 5.0 (2H, br. s, $PhCH_2$), 5.82 (1H, m, C(3)**H**), 7.18 - 7.35 (5H, m, aryl C-**H**); δ_C (75 MHz; $CDCl_3$) 14.2 ($CHCH_3$), 19.2 (SCH_3), 28.9 (CH_2), 43.2 (NCH_2), 54.5 ($NCHCH_3$), 66.7 ($PhCH_2$), 82.1 (**C**HOCS), 127.9, 128.0, 128.5 (aryl **C**-H), 136.7 (quaternary aryl-**C**), 156.0 (**C**=O), 177 (**C**SS). Found $[M + Na]^+$, 348.0709; $C_{15}H_{19}NO_3S_2$ requires M + Na 348.0699.

(*S*) 2-methyl-1-pyrrolidine carboxylic acid phenylmethyl ester (158)[81]



$C_{15}H_{19}NO_3S_2$

Mol. Wt.: 325.4

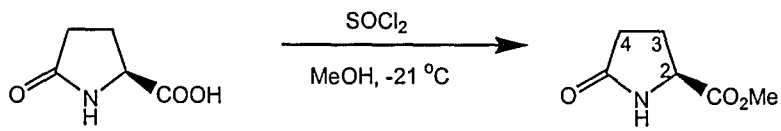
$C_{13}H_{17}NO_2$

Mol. Wt.: 219.3

The xanthate (**157**) (50 mg, 0.17 mmol) and Bu_3SnH (123.7 mg, 0.425 mmol) were dissolved in toluene (5 mL) and heated to 110 °C under reflux conditions. Aza–iso-butylnitrile (AIBN) (*ca* 8.5 mg, 0.0816 mmol) was added and the reaction stirred at 110 °C for 2 hours under an atmosphere of nitrogen. The toluene was evaporated *in vacuo* and the residue was purified by chromatography to yield the title compound (**158**) (0.01 g, 27 %) as a colourless oil. R_f (hexane followed by 50 % diethyl ether: hexane) 0.31, $[\alpha]_D^{20}$ + 21.40 ($CHCl_3$, $c = 0.16$) [Lit. (enantiomer) $[\alpha]_D^{20}$ -24.9]; ν_{max} (NaCl)/cm^{-1} 1698 (C=O), 780.1 (5 adjacent aryl C-H); δ_H (300 MHz; $CDCl_3$) 1.21 (3H, *J* 6.2, CH_3), 1.5 - 2.1 (4H, m, C(3)H_2, C(4)H_2), 3.3 - 3.5 (2H, br. m, NCH_2), 3.8 - 4.0 (1H, br. s, NCH), 5.12 (2H, br. s, PhCH_2), 7.34 (5H, m, aryl C-H); δ_C (75 MHz; $CDCl_3$) 20.0, 20.9 (CH_3), 22.9, 23.7 (C(4)H_2), 32.6, 33.2 (C(3)H_2), 46.3, 46.6 (C(5)H_2), 53.5 (NCH), 66.4, 66.6 (PhCH_2), 127.8, 128.4 (aryl-C), 139.0 (quaternary aryl-C), 189.0 (CO). Found $[M + Na]^+$, 242.1160; $C_{13}H_{17}NO_2$ requires *M* + Na 242.1151.

*Restricted rotation is evident in the ^1H NMR spectrum.

(*S*)-5-methoxycarbonyl-2-pyrrolidin-2-one (309)[183]



$C_5H_7NO_3$

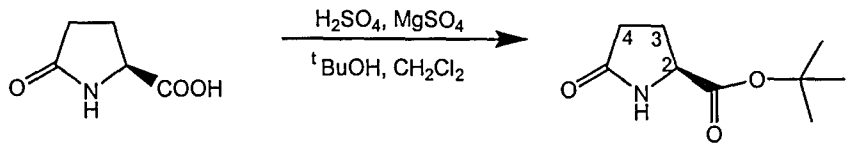
Mol. Wt.: 129.1

$C_6H_9NO_3$

Mol. Wt.: 143.1

To a solution of *S*-pyroglutamic acid (10 g, 77.46 mmol) in methanol (100 mL) at –21 °C, freshly distilled thionyl chloride (6.26 mL, 85.71 mmol) was added over a period of 15 minutes. The mixture was warmed to room temperature and the stirring was continued for four hours. Removal of the excess solvent gave an oil which was distilled under reduced pressure (bp 90 °C at 12 mmHg) to give the title compound as a colourless oil (**309**) (8.2 g, 74 %). R_f (5 % methanol: dichloromethane) 0.65; $[\alpha]_D^{20}$ + 11.46 ($CHCl_3$, $c = 0.01$) [Lit. $[\alpha]_D^{20}$ + 11 (MeOH, $c = 6.2$]; ν_{max} (NaCl)/cm^{-1} 1698 (C=O), 2960.3 (C-H), 3407 (N-H); δ_H (300 MHz; $CDCl_3$) 2.04 - 2.25 (1H, m, C(3)$\mathbf{H}_2$), 2.26 - 2.44 (3H, m, C(3)$\mathbf{H}_2$, C(4)$\mathbf{H}_2$), 3.66 (3H, s, OC$\mathbf{H}_3$), 4.17 - 4.21 (1H, m, NC**H**), 7.44 (1H, br. s, N**H**); δ_C (75 MHz; $CDCl_3$) 24.7 (**C**H_2), 29.2 (**C**H_2), 52.4 (**C**H_3), 55.5 (N**C**H), 172.7 (**C**=O), 178.5 (**C**=O).

(*S*)-5-(*tert*-butoxycarbonyl) pyrrolidin-2-one (310)



$C_5H_7NO_3$

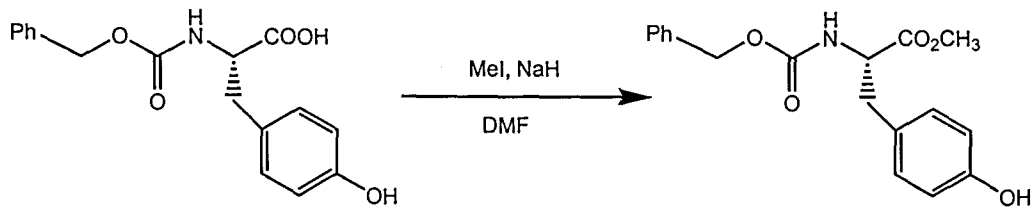
Mol. Wt.: 129.1

$C_9H_{15}NO_3$

Mol. Wt.: 185.2

Concentrated sulfuric acid (2.91 mL, 38.72 mmol) was added to a vigorously stirred suspension of anhydrous magnesium sulfate (14.43 g, 120 mmol), in 150 mL dichloromethane. The mixture was stirred for 15 minutes after which time the S-pyroglutamic acid (5 g, 38.72 mmol) was added. Tertiary butanol (14.05 mL, 150 mmol) was added last. The mixture was stoppered tightly, stirred for 18 hours at 25 °C and the reaction monitored by TLC analysis. The reaction mixture was quenched with saturated sodium bicarbonate solution (75 mL). The solvent phase was separated, washed with brine, dried ($MgSO_4$) and concentrated to afford the crude product, which was purified by column chromatography, which furnished the product (**310**) as white crystals (4.2 g, 75.6 %). m.p. 108 - 109 °C (Lit. 109 - 110° C); R_f (1:1 ethyl acetate: hexane) 0.42; $[\alpha]_D^{20}$ + 8.4 ($CHCl_3$, $c = 0.02$) [Lit. $[\alpha]_D^{20}$ + 8.3 (MeOH, $c = 3$]; ν_{max} (NaCl)/cm^{-1} 1395 (C-$(CH_3)_3$), 1736 (C=O), 3451 (N-H); δ_H (300 MHz; $CDCl_3$) 1.34 (9H, s, $(CH_3)_3$), 2.07 - 2.14 (1H, m, C(3)H_2), 2.25 - 2.42 (3H, m, C(3)H_2, C(4)H_2), 4.09 (1H, m, NC**H**), 6.74 (1H, br. s, N**H**); δ_C (75 MHz; $CDCl_3$) 24.8 (CH_2), 27.9 ($C(CH_3)_3$), 29.4 (CH_2), 56.2 (NCH), 82.2 (quarternary-**C**), 171.2 (**C**=O), 178.3 (**C**=O). Found $[M + Na]^+$, 208.0949; $C_9H_{15}NO_3$ requires M + Na 208.0944.

2-Benzyloxycarbonylamino-(*2S*)-3-(-4-hydroxy-phenyl)-propionic acid methyl ester (193)[184]



$C_{17}H_{17}NO_5$

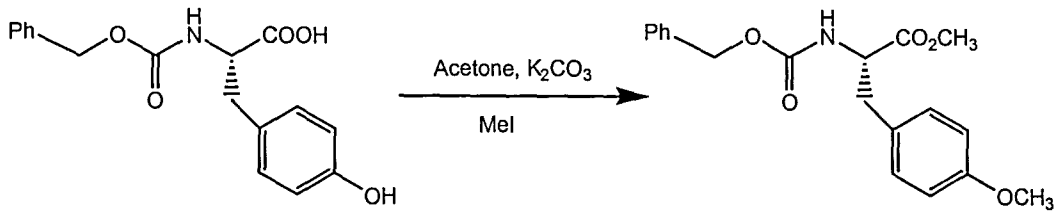
Mol. Wt.: 315.3

$C_{18}H_{19}NO_5$

Mol. Wt.: 329.3

CBZ-(*S*)-tyrosine (5 g, 15.86 mmol) was dissolved in DMF (75 mL), the solution was cooled to 10 °C, and a sodium hydride suspension (60 % in mineral oil, 1.47 g, 36.8 mmol) was added all at once. After stirring for 1 hour at 10 °C, methyl iodide (0.99 mL, 15.86 mmol) was added. After the reaction mixture had stirred for 3 hours ice water (150 mL) and ethyl acetate (400 mL) were added. The aqueous phase was separated, extracted twice with ethyl acetate (75 mL), and acidified with 6 N HCl with cooling. The product was extracted into ethyl acetate (3 x 75 mL), washed with brine and dried ($MgSO_4$). The crude product was obtained on evaporation and was purified by column chromatography (1:1 dichloromethane: hexane 1 % Et_3N). This furnished the title compound (**193**) as an orange oil (2.17 g, 41.3 %). R_f (1:1 ethyl acetate: hexane) 0.33; $[\alpha]_D^{20}$ - 26.2 ($CHCl_3$, $c = 0.01$) [Lit. $[\alpha]_D^{20}$ - 30.1]; ν_{max} (NaCl)/cm^{-1} 1514 (aromatic ring), 1702 (C=O), 2837 (O-CH_3), 3065 (NH stretch), 3354 (sharp, O-H); δ_H (300 MHz; $CDCl_3$) 2.92 (2H, m, CH_2PhOH), 3.60 (3H, s, CO_2CH_3), 4.51 (1H, m, NC**H**), 4.98 (2H, s, PhCH_2), 5.30 (1H, d, *J* 8.4, N**H**), 6.60 (2H, d, *J* 8.2, aryl C-**H**), 6.81 (2H, d, *J* 8.2, aryl C-**H**), 7.22 (5H, m, aryl C-**H**); δ_C (75 MHz; $CDCl_3$) 37.3 (CH_2), 55.1 (CH_3), 55.2 (N**C**H), 67.2 (CH_2), 114.0 (aryl **C**-H), 115.6 (aryl **C**-H), 126.9 (quaternary aryl-**C**), 128.1 + 128.3 + 128.6 (aryl **C**-H), 136.1 (quaternary aryl-**C**), 155.4 (**C**OH), 156.0 (**C**=O), 172.4 (**C**=O). Found $[M + Na]^+$, 352.1163; $C_{18}H_{19}NO_5$ requires *M* + Na 352.1155.

2-Benzyloxycarbonylamino-(*2S*)-3-(-4-methoxy-phenyl)-propionic acid methyl ester (189)[185]



$C_{17}H_{17}NO_5$

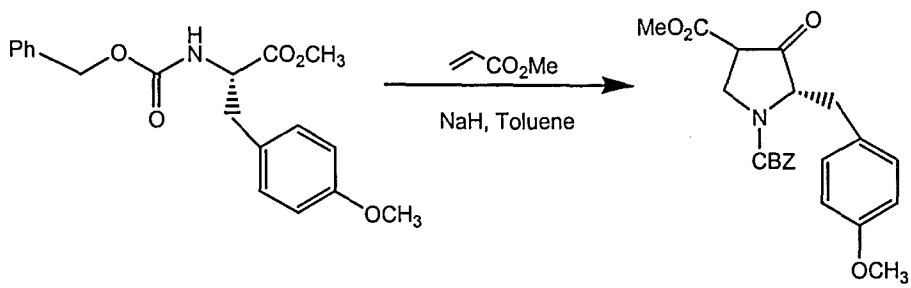
Mol. Wt.: 315.3

$C_{19}H_{21}NO_5$

Mol. Wt.:343.4

Potassium carbonate (11.06 g, 80 mmol) was dissolved in acetone (100 mL) and stirred for 30 minutes. CBZ-(L)-tyrosine (10 g, 31.7 mmol) was dissolved in acetone (75 mL) and added to the K_2CO_3 solution. Methyl iodide (11.96 mL, 192 mmol) was then added and the solution was heated gently at 38 °C and left to stir for 16 hours. The reaction mixture was filtered and the acetone removed *in vacuu*. The residue was dissolved in diethyl ether, washed with water (3 x 30 mL) and dried with $MgSO_4$ to yield the crude product, which was purified by column chromatography. This furnished the title compound (**189**) as a yellow solid (4.8 g, 44 %). m.p. 60 - 63 °C; R_f (1:1 ethyl acetate: hexane) 0.5; $[\alpha]_D^{20}$ + 47.0 ($CHCl_3$, $c = 0.01$) [Lit. $[\alpha]_D^{20}$ + 46.8]; ν_{max} (NaCl)/cm^{-1} 1513.7 (aromatic ring), 1718.3 (C=O), 3347.0 (NH), 2954.0 (CO-CH_3); δ_H (300 MHz; $CDCl_3$) 2.94 (1H, dd, *J* 15, 6, CH_2PhOCH_3), 2.80 (1H, dd, *J* 15, 6, CH_2PhOCH_3), 3.55 (3H, s, CO_2CH_3), 3.60 (3H, s, OCH_3), 4.48 (1H, q, *J* 6, NCH), 4.95 (2H, s, $PhCH_2$), 5.40 (1H, d, *J* 2.5, NH), 6.66 (2H, d, *J* 8.5, aryl C-H), 6.87 (2H, d, *J* 8.5, aryl C-H), 7.17 (5H, s, aryl C-H); δ_C (75 MHz; $CDCl_3$) 37.3 (CH_2), 52.3 (CH_3), 55.1 (CH_3), 60.4 (NCH), 66.9 (CH_2), 114.0 (aryl C-H), 128.1 + 128.5 + 130.2 (aryl C-H), 136.2 (quaternary aryl-C), 155.7 (quaternary aryl-C), 158.7 (C=O), 172.1 (C=O).

5-(4-Methoxy-benzyl)-(*2S*)-4-oxo-pyrrolidine-1,3-dicarboxylic acid 1-benzyl ester 3-methyl ester (187)



$C_{19}H_{21}NO_5$

Mol. Wt.:343.4

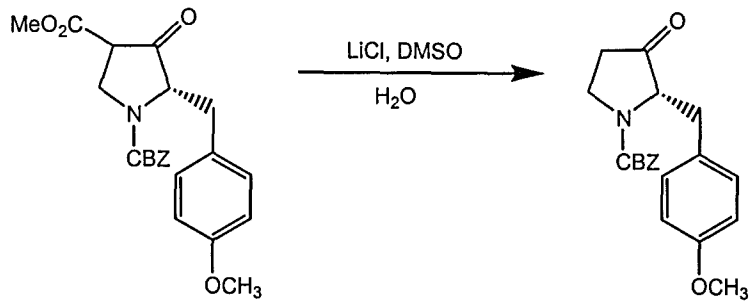
$C_{22}H_{23}NO_6$

Mol. Wt.: 397.4

A solution of 2-benzyloxycarbonylamino-(*2S*)-3-(-4-phenylmethoxy-)-propionic acid methyl ester (**189**) (0.5 g, 1.46 mmol) in dry toluene (10 mL) was added to a stirred suspension of sodium hydride (0.069 g of 60 % dispersion in mineral oil, 1.74 mmol, hexane washed) in toluene (10 mL) under nitrogen followed by methyl acrylate (0.14 g, 0.14 mL, 1.59 mmol) and the reaction mixture was stirred at room temperature for 30 min. The reaction was then heated under reflux for 2 hours, then allowed to cool to room temperature. Water (20 mL) was then added carefully. The aqueous layer was separated, washed with diethyl ether (2 x 20 mL), made acidic (pH < 2) with concentrated hydrochloric acid and extracted with ethyl acetate (3 x 20 mL). The combined extracts were dried with magnesium sulphate and the solvent removed under reduced pressure to give the title compound (**187**), which was purified by column chromatography (1:1 ethyl acetate: hexane, 1 % acetic acid). This furnished the title compound (**187**) as a pink viscous oil (0.39 g, 67 %). R_f (1:1 ethyl acetate: hexane, 1 % acetic acid) 0.53; $[\alpha]_D^{20}$ + 17.4 (methanol, $c = 0.02$); ν_{max} (NaCl)/cm^{-1} 1535.2 (aromatic ring), 1701.6 (NCOO), 1746.0 (ester C=O); δ_H (300 MHz; $CDCl_3$) 2.28 (2H, m, $\mathbf{CH_2}PhOCH_3$), 3.33 - 3.65 (6H, m, $CO_2\mathbf{CH_3}$, NCH_2, $CHCO_2CH_3$), 3.67 (3H, s, OCH_3), 4.3 (1H, m, NCH), 5.09 (2H, m, $PhCH_2$), 6.62 - 6.9 (4H, m, aryl C-H), 7.1 - 7.3 (5H, m, aryl C-H); δ_C (75 MHz; $CDCl_3$) 34.2 + 35.7 (CH_2), 48.4 + 48.6 (CH_2), 51.4 ($CHCO_2CH_3$), 52.7 (OCH_3), 55.0 (OCH_3), 63.1 (NCH), 66.8 + 67.4 (CH_2Ph), 113.4 + 113.5 (aryl C-H), 127.9 + 128.1 + 128.2 + 128.3 + 128.5 +

129.4 + 130.0 (aryl **C**-H), 136.7 (quaternary aryl-**C**), 154.3 (quaternary aryl-**C**), 158.7 (**C**=O), 169.0 (**C**=O). Found $[M + Na]^+$, 420.1453; $C_{22}H_{23}NO_6$ requires *M* + Na 420.1418.

2-(4-Methoxy-benzyl)-(*2S*)-3-oxo-pyrrolidine-1-carboxylic acid benzyl ester (192)



$C_{22}H_{23}NO_6$

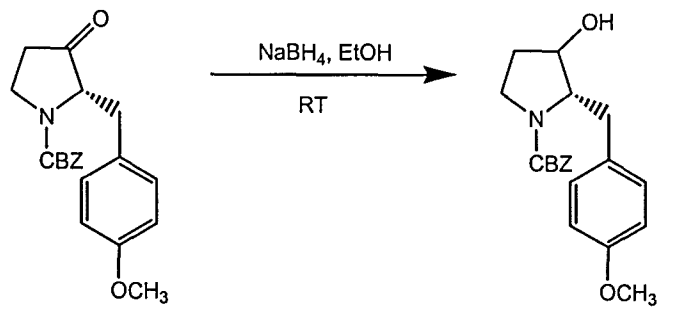
Mol. Wt.: 397.4

$C_{20}H_{21}NO_4$

Mol. Wt.: 339.4

Lithium chloride (0.36 g, 0.84 mmol) and water (4 mL) were added to a stirred solution of *N*-benzyloxycarbonyl-(*2S*)-4-methoxycarbonyl–2-methylpyrrolidin-3-one (**187**) (0.3 g, 0.76 mmol) in dimethyl sulfoxide (1.7 mL). The reaction mixture was heated to 100 °C under an atmosphere of nitrogen for 2 hour's, allowed to cool, and water (20 mL) was added. The reaction was extracted with ethyl acetate (5 x 20 mL) and the combined organic extracts washed with saturated sodium bicarbonate solution (3 x 30 mL), saturated sodium chloride solution (3 x 30 mL) and water (3 x 30 mL). The organic layer was then dried with magnesium sulphate, filtered, and the solvent removed *in vacuo* to give a crude product which was purified by column chromatography to give the title compound (**192**). (0.17 g, 68 %) as a pale yellow oil; R_f (1:1 diethyl ether: hexane) 0.54; $[\alpha]_D^{20}$ + 19.3 (methanol, $c = 0.01$); ν_{max} (NaCl)/cm^{-1} 820.1 (2 adjacent H), 1530.1 (aromatic ring), 1718.2 (C=O), 2820.1 (O-CH_3); δ_H (300 MHz; $CDCl_3$) 2.33 - 2.42 (1H, m, C**H**$_2$PhOCH$_3$), 2.83 (1H, m, C**H**$_2$PhOCH$_3$), 3.05 (2H, m, NC**H**$_2$), 3.72 - 3.77 (4H, m, NC**H**$_2$, OC**H**$_3$), 4.19 (1H, br. s, NC**H**), 5.28 (2H, m, PhC**H**$_2$), 6.63 - 6.99 (4H, m, aryl C-**H**), 7.27 - 7.42 (5H, m, aryl C-**H**); δ_C (75 MHz; $CDCl_3$) 34.7 (**C**H$_2$), 36.0 (**C**H$_2$), 42.1 (**C**H$_2$), 55.1 (O**C**H$_3$), 63.3 (N**C**H), 67.0 (**C**H$_2$), 95.86 (quaternary aryl **C**-H), 113.9 (aryl **C**-H), 128.4 (aryl **C**-H), 128.6 (aryl **C**-H), 130.8 (aryl **C**-H), 135.0 (quaternary aryl-**C**), 155.0 (**C**O), 158.6 (**C**O). Found [M + Na]$^+$, 364.1523; $C_{20}H_{21}NO_4$ requires *M* + Na 364.1519.

3-Hydroxy-2-(4-methyloxybenzyl)-(*2S*)-pyrrolidine-1-carboxylic acid benzylester (185)[186]



$C_{20}H_{21}NO_4$
Mol. Wt.: 339.4

$C_{20}H_{23}NO_4$
Mol. Wt.: 341.4

Sodium borohydride (0.02 g, 0.59 mmol) was added in small portions to a stirred solution of 2-(4-methyloxybenzyl)-(*2S*)-3-oxopyrrolidine-1-carboxylic acid benzyl ester (**192**) (0.1 g, 0.29 mmol) in ethanol (30 mL). The reaction mixture was stirred for 8 hours at room temperature and then quenched with water (20 mL). The excess ethanol was removed under reduced pressure leaving a residue, which was then dissolved in water, and extracted with ethyl acetate (3 x 20 mL). The organic phase was dried using magnesium sulphate, filtered and concentrated under reduced pressure to give the title compound (**185**) (0.076 g, 77 %) as an orange oil; R_f (1:1, ethyl acetate: hexane) 0.28; $[\alpha]_D^{20}$ 0, (methanol, $c = 0.005$) [Lit. $[\alpha]_D^{20}$ - 6.0]; ν_{max} (NaCl)/cm^{-1} 1420.3 (O-H bend), 1536.7 (aromatic ring), 1690 (NC=O), 2970 (C-H), 3436 (O-H); δ_H (300 MHz; $CDCl_3$) 1.64 - 1.73 (2H, m, CH_2), 1.88 (1H, br. s, OH), 2.85 (2H, m, CH_2Ph), 3.37 - 3.48 (2H, m, NCH_2), 3.70 (3H, s, OCH_3), 3.98 (1H, m, CHOH), 4.21 (1H, br. s, NCH), 5.06 (2H, br. s, CH_2Ph), 6.71 (4H, br. s, aryl C-H), 7.28 (5H, s, aryl C-H); δ_C (75 MHz; $CDCl_3$) 30.9 (CH_2), 32.8 (CH_2), 43.0 (CH_2), 55.2 (OCH_3), 61.9 (NCH), 65.2 (CHOH), 70.9 (CH_2), 113.9 (aryl C-H), 128.0 + 128.5 (aryl C-H), 130.4 (quaternary aryl-C), 131.1 (quaternary aryl-C), 155.0 (quaternary aryl-C), 158.0 (CO). Found $[M + Na]^+$, 364.1511; $C_{20}H_{23}NO_4$ requires *M* + Na 364.1519.

HPLC (Chiracel OD-H, 5 mm, 2-propanol/hexane 15:85, 0.5 mL/min failed to give conclusive results.

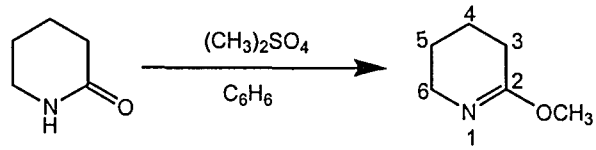
Literature Data for supposed enantiomer:

$[\alpha]_D^{20}$ -6.0 (chloroform, $c = 1.3$) [Lit.[187] $[\alpha]_D^{20}$ - 4.9 (chloroform, $c = 1.145$)]; δ_H (300 MHz; $CDCl_3$) 1.72 - 1.83 (m, 1 **H**), 1.93 - 2.04 (m, 1 **H**), 2.84 - 2.92 (m, 1 **H**), 3.0 - 3.15 (br. s, 1 **H**), 3.40 - 3.60 2.85 (m, 1 **H**), 3.75 (s, 3 **H**), 4.10 (br. q, J = 6.3 Hz, 1 **H**), 4.32 (q, J = 6.0 Hz, 1 **H**), 5.10 (deformed Abq, $\delta_a = 5.07$, δ_b = 5.13, J_{ab} = 12.0 Hz, 2 **H**), 6.93 (deformed Abq, $\delta_a = 6.77$, $\delta_b = 7.09$, $J_{ab} = 8.5$ Hz, 4 **H**), 7.30 - 7.36 (m, 5 **H**);

δ_C (50.3 MHz; C_6D_6) δ 32.8, 34.3, 44.9, 55.5, 63.6, 67.6, 72.3, 114.9, 129.2, 131.6, 132.6, 138.5, 155.9, 159.5.

HPLC (Chiracel OD-H, 5 mm, 2-propanol/hexane 15:85, 0.5 mL/min, t_R 20.7 min (Vs 24.5 min)) indicated an ee of ≥ 99 %).

2-Methyoxy--3,4,5,6-tetrahydro-pyridine (226)[188]



C_5H_9NO

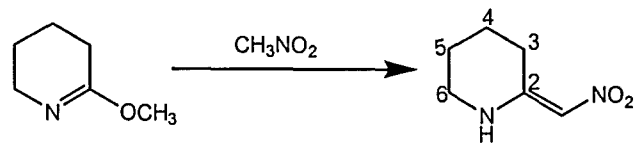
Mol. Wt.: 99.1

$C_6H_{11}NO$

Mol. Wt.: 113.2

Dimethylsulfate (12.59 g, 100 mmol) was added over 2.5 hours to a refluxing solution of δ-valerolactam (10 g, 100 mmol) in benzene (30 mL). The solution was refluxed for 16 hours. The two-phase system was cooled with an ice bath and slowly treated with triethylamine (14 mL) to quench the reaction. The resultant salt was filtered and the aqueous phase extracted with benzene (4 x 30 mL). The combined organic extracts were dried ($MgSO_4$). Evaporation of the solvent under reduced pressure at room temperature followed by distillation the title compound (**226**) (3.36 g, 35.6 %) as a colourless oil. B.p. 68 - 71°C/45 mmHg [Lit.[189] 68 - 70°C/60 mmHg]; ν_{max} (NaCl)/cm^{-1} 1649 (C=N), 2945 (C-H); δ_H (300 MHz; $CDCl_3$) 1.46 - 1.50 (2H, m, C(4)$\mathbf{H_2}$), 1.62 - 1.66 (2H, m, C(5)$\mathbf{H_2}$), 2.08 (2H, t, *J* 6.6, C(3)$\mathbf{H_2}$), 3.40 (2H, t, *J* 5.6, C(6)$\mathbf{H_2}$), 3.5 (3H, s, O$\mathbf{CH_3}$); δ_C (75 MHz; $CDCl_3$) 20.3 (**C**(4)H_2), 22.4 (5)**C**H_2), 25.7 (**C**(3)H_2), 46.7 (**C**(6)H_2), 51.7 (OCH3), 162.9 (**C**-N).

2-(Nitromethylene)–piperidine (221)



$C_6H_{11}NO$

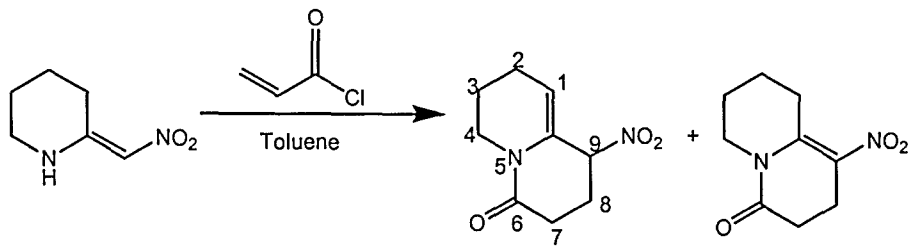
Mol. Wt.: 113.2

$C_6H_{10}N_2O_2$

Mol. Wt.: 142.2

A solution of 2-methoxy–3,4,5,6-tetrahydropyridine (**226**) (1.617 g, 14.31 mmol) and nitromethane (1.7 g, 28 mmol) were refluxed for 3 days, cooled and quenched in cold diethyl ether (50 mL). This solution was filtered to give a crude product. The crude product was continuously extracted from a soxhlet thimble with ether for 18 hours after which time a small amount of dark solid residue remained. The solvent now containing crystallised product was cooled and the orange solid filtered. This product was then recrystallised from methanol to yield pale yellow needle like crystals (**221**) (1.042 g, 52 %), m.p. 76 - 77 °C [Lit.[190] 80.5 - 81 °C]; ν_{max} (NaCl)/cm^{-1} 1469 (C-NO_2), 1605 (C=C), 2954 (C-H); δ_H (300 MHz; $CDCl_3$), 1.62 - 1.8 (4H, m, C(5)$\mathbf{H_2}$, C(4)$\mathbf{H_2}$), 2.3 (2H, t, *J* 6.3, C(3)$\mathbf{H_2}$), 3.42 (2H, m, $\mathbf{CH_2}$N), 6.43 (1H, t, *J* 20.1, CC**H**NO_2), 10.58 (1H, br. s, N**H**); δ_C (75 MHz; $CDCl_3$), 18.4 (**C**(4)H_2), 21.7 (**C**(5)H_2), 26.6 (**C**(3)H_2), 41.6 (**C**(6)H_2), 109.2 (**C**H), 189.7 (**C**N).

2,3,4,5,6,7,8,9, - Heptahydro–9-nitro–quinolizin-6-one (230a) & (230b)



$C_6H_{10}N_2O_2$ — Mol. Wt.: 142.2

$C_9H_{12}N_2O_3$ — Mol. Wt.: 196.2 **(230a)**

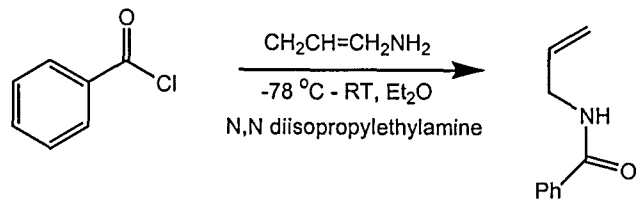
$C_9H_{12}N_2O_3$ — Mol. Wt.: 196.2 **(230b)**

To a solution of 2-(nitromethylene)-piperidine (**221**) (500 mg, 3.5 mmol) in dry toluene (10 mL), a solution of acryloyl chloride (0.3 mL, 3.5 mmol) in dry toluene (20 mL) was added drop wise over 10 minutes. The solution was heated under reflux for 12 hours. The reaction mixture was cooled and the organic phase washed with sodium bicarbonate solution (10 mL), brine (10 mL) and dried over magnesium sulphate. Removal of the solvent *in vacuo* and the purification of the residue by flash chromatography (1:1 petroleum ether: ethyl acetate) gave the product (**230**) which contained both the major (**230a**) and the minor (**230b**) regioisomer (0.17 g, 25 %; 0.05 g,7% respectively). R_f 0.23 major regioisomer, 0.36 minor regioisomer. ν_{max} (NaCl)/cm^{-1} 1547 + 1379 (NO_2), 1643.2 (C=O), 2930 (C-H); *Major regioisomer*: δ_H (300 MHz; $CDCl_3$), 1.68 - 1.89 (2H, m, C(3)$\mathbf{H_2}$), 2.10 - 2.41 (3H, m, C(1)$\mathbf{H_{ax}}$, C(2)$\mathbf{H_{eq}}$, C(2)$\mathbf{H_{ax}}$), 2.10 - 2.41 (3H, m, C(8)$\mathbf{H_{eq}}$, C(7)$\mathbf{H_{eq}}$ and $\mathbf{H_{ax}}$), 3.38 – 3.47 (1H, m, C(4)$\mathbf{H_{ax}}$), 4.0 - 4.07 (1H, m, C(4)$\mathbf{H_{eq}}$), 5.07 (1H, d, *J* 4.1, C**H**NO2), 5.14 (1H, m, (C(8)$\mathbf{H_{ax}}$); δ_C (75 MHz; $CDCl_3$), 20.8 (**C**H_2), 22.5 (**C**H_2), 24.0 (**C**H_2), 27.6 (**C**H_2), 40.1 (**C**H_2), 82.0 (**C**H), 113.7 (quaternary-**C**), 130.0 (**C**-NO_2), 165.6 (**C**=O). Found $[M + Na]^+$, 196.0857; $C_9H_{12}N_2O_3$ requires *M* + Na 196.0842.

Minor regioisomer: δ_H (300 MHz; $CDCl_3$), 1.78 - 1.87 (4H, m, C(2)$\mathbf{H_2}$ and C(3)$\mathbf{H_2}$), 2.55 (2H, t, *J* 6.3, C(1)$\mathbf{H_2}$), 2.69 - 2.7 (2H, m, C(8)$\mathbf{H_2}$), 3.12 (2H, t, *J* 6.2,

C(7)$\mathbf{H_2}$), 3.69 (2H, m, C(4)$\mathbf{H_2}$); δ_C (75 MHz; $CDCl_3$), 18.5 (**C**H_2), 19.9 (**C**H_2), 25.2 (**C**H_2), 27.6 (**C**H_2), 32.7 (**C**H_2), 40.6 (**C**H_2), 131.0 (quaternary-**C**), 147.6 (**C**-NO_2), 170.0 (**C**=O).

N-Allylbenzamide (266)[191]



C_7H_5OCl

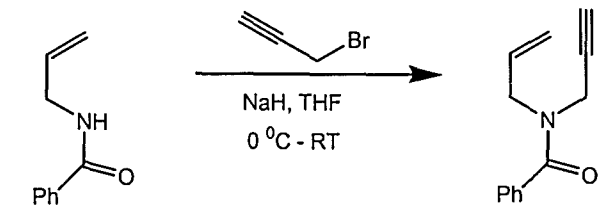
Mol. Wt.:140.6

$C_{10}H_{11}NO$

Mol. Wt.: 161.2

Benzoyl chloride (2.23 mL, 19.25 mmol,) was added dropwise to a solution of allylamine (1.32 mL, 17.52 mmol) and Hünigs base (3.35 mL, 19.25 mmol) at 0 °C. This mixture was warmed to room temperature, monitored by TLC and stirred for 1 hour. *N*-Allylbenzamide was washed with 1M HCl (3 x 30 mL), Sodium bicarbonate solution (2 x 10 mL), water (1 x 10 mL), and dried with magnesium sulphate. The compound was then purified by column chromatography on silica gel. This furnished the title compound (**266**) as a yellow oil (2.86 g, 92.6 %). R_f (1:1ethyl acetate: hexane, 5 % Et_3N) 0.39; ν_{max} (NaCl)/cm^{-1} 694.1 (5 adjacent aryl C-H), 1640.1 (C=O), 3066.0 ($CH=CH_2$), 3316.0 (N-H); δ_H (300 MHz; $CDCl_3$) 3.98 (2H, t, *J* 5.7, $NC\mathbf{H_2}$), 4.9 (1H, dd, *J* 10, 1.5, $NCH_2CHC\mathbf{H_2}$), 5.09 (1H, dd, *J* 17, 1.5, $NCH_2CHC\mathbf{H_2}$), 5.8 (1H, q, *J* 10, $NCH_2C\mathbf{H}$), 6.5 (1H, br. s, N**H**), 7.28 - 7.79 (5H, m, aryl C-**H**); δ_C (75 MHz; $CDCl_3$) 42.4 ($N\mathbf{C}H_2$), 116.4 ($NHCH_2C\mathbf{H}CH_2$), 127.1 + 128.5 (aryl-**C**), 131.4 ($NHCH_2\mathbf{C}H$), 134.2 + 134.4 (quaternary aryl-**C**), 167.6 (**C**=O). Found $[M + Na]^+$, 184.0737; $C_{10}H_{11}NO$ requires *M* + Na 184.0733.

N-Allyl–*N*–benzoyl-*N*-prop-2-ynylamine (264)



$C_{10}H_{11}NO$

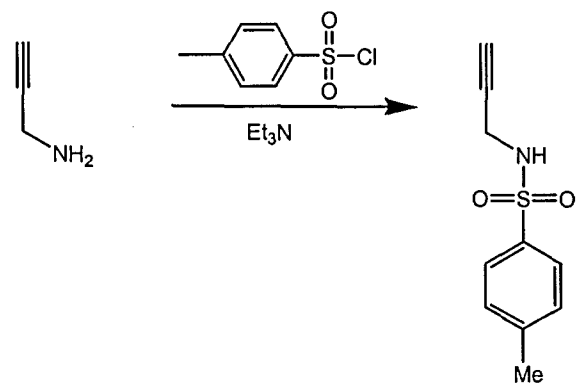
Mol. Wt.: 161.2

$C_{13}H_{13}NO$

Mol. Wt.: 199.2

A solution of *N*-allylbenzamide (**266**) (1.5 g, 9.32 mmol) in THF (30 mL) was treated with sodium hydride (0.45 g of 60 % dispersion in mineral oil, 11.1 mmol, hexane washed) and propargyl bromide (3.2 g, 2.4 mL, 27.0 mmol) at 0 °C. After 36 hours the reaction mixture was quenched with water and extracted with Et_2O. The combined organic layers were dried over K_2CO_3, concentrated *in vacuo* and chromatographed on silica gel to give the title compound (**264**) as a colourless oil (1.63 g, 88 %). R_f (1:1 hexane: diethyl ether, 5 % Et_3N) 0.25; ν_{max} (NaCl)/cm^{-1} 1530.0 (aromatic ring), 1640 (C=O), 2116 (acetylenic stretch), 3327 (C-H); δ_H (300 MHz; $CDCl_3$) 2.20 (1H, br. s, $NCH_2CC\mathbf{H}$), 3.9 (2H, br. s, $NC\mathbf{H}_2CHCH_2$), 4.2 (2H, br. d, $NC\mathbf{H}_2CCH$), 5.1 – 5.3 (2H, m, $NCH_2CHC\mathbf{H}_2$), 5.7 (1H, br. s, $NCH_2C\mathbf{H}$), 7.2 – 7.3 (5H, m, aryl C-**H**); δ_C (75 MHz; $CDCl_3$) 37.0 ($N\mathbf{C}H_2CCH$), 50.8 ($N\mathbf{C}H_2CHCH_2$), 71.9 ($NCH_2\mathbf{C}CH$), 78.8 ($NCH_2\mathbf{C}CH$), 118.3 ($NCH_2CH\mathbf{C}H_2$), 126.9 + 128.4 + 130.1 (aryl **C**-H), 132.4 ($NCH_2\mathbf{C}HCH_2$), 135.6 (quaternary aryl-**C**), 172.0 (**C**O). Found $[M + Na]^+$, 222.0897; $C_{13}H_{13}NO$ requires *M* + Na 222.0889.

4-Methyl-*N*-prop-2-ynyl-benzezesulfonamide (269)[192]



C_3H_5N

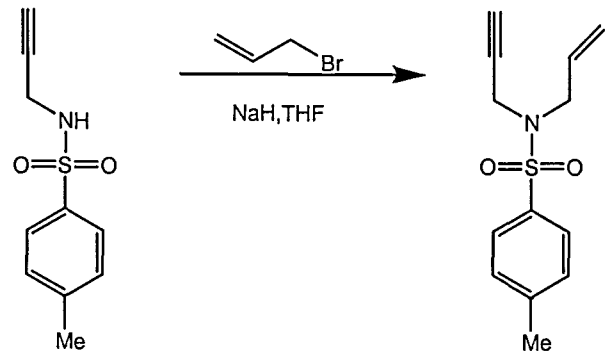
Mol. Wt.: 55.1

$C_{10}H_{11}NO_2S$

Mol. Wt.: 209.3

Triethylamine (5.02 mL, 0.036 mol) was added dropwise to a stirred suspension of propargylamine (2.49 mL, 0.036 mol) and p-toluenesulfonyl chloride (7.28 g, 0.038 mol) in a solvent of dry dichloromethane (15 mL) at 0 °C under an atmosphere of nitrogen. 4-dimethylaminopyridine (DMAP) (0.37 g, 0.0036 mol) was added to the mixture. The solution was stirred for 48 hours and monitored by TLC. The solution, which was slightly cloudy and darker in colour was quenched with 0.5 M aq.HCl (32 mL), ice and Et_3N (40 mL). The organic layer was washed with brine (40 mL), dried ($MgSO_4$), and the solvents were removed *in vacuo*. The residue was chromatographed on silica gel furnishing a white solid (**269**) (7.22g, 96 %); m.p. 72 - 75 °C (Lit. 73.5 - 74 °C); R_f (3:1 hexane: ethyl acetate) 0.3; ν_{max} (NaCl)/cm^{-1} 2129 (acetyenic stretch), 3417 (N-H); δ_H (300 MHz; $CDCl_3$) 2.02 (1H, t, *J* 2.5, $NHCH_2CC\mathbf{H}$), 2.35 (3H, s, $PhC\mathbf{H}_3$), 3.7 (2H, dd, *J* 2.5, 6, $NHC\mathbf{H}_2$), 5.05 (1H, t, *J* 6, **NH**), 7.2 (2H, d, *J* 8.5, aryl-**H**), 7.7 (2H, d, *J* 8.5, aryl-**H**); δ_C (75 MHz; $CDCl_3$) 21.6 ($PhCH_3$), 32.8 ($NHCH_2$), 72.9 (NCH_2CCH), 78.0 ($NHCH_2CCH$), 127.4 (aryl **C**-H), 129.7 (aryl C-H), 136.5 (quaternary aryl-**C**), 143.8 (quaternary aryl-**C**). Found $[M + Na]^+$, 232.0397; $C_{10}H_{11}NO_2S$ requires *M* + Na 232.0403.

N-Allyl-*N*-propargyl-toluenesulfonamide (270)[193]



$C_{10}H_{11}NO_2S$

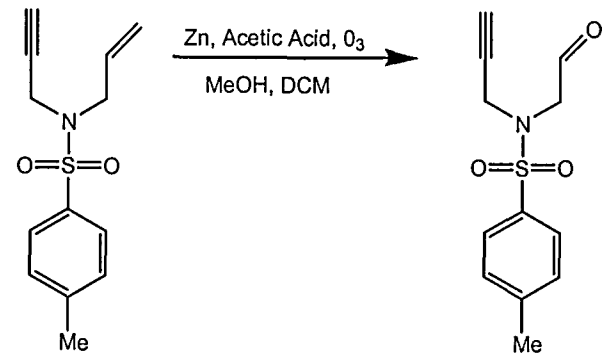
Mol. Wt.: 209.3

$C_{13}H_{15}NO_2S$

Mol. Wt.: 249.3

Sodium hydride (1.4 g, of 60 % dispersion in mineral oil, 0.035 mol, hexane washed) was added to a solution of 4-methyl-*N*-propargylbenzenesulfonamide (6 g, 0.02 mol) in THF (10 mL) and DMF (1 mL). *N*-Allylbromide (6.9 mL, 0.08 mol) was then added dropwise to this solution. After 36 hours the reaction mixture was quenched with water and extracted with diethyl ether. The combined extracts were dried over K_2CO_3, concentrated and chromatographed. This furnished the title compound (**270**) as a white crystalline solid (6.53 g, 91.8 %); m.p 96 - 98 °C (Lit. 97 - 99 °C); R_f (2:1 hexane: ethyl acetate) 0.36; ν_{max} (NaCl)/cm^{-1} 989 and 931 ($CH{=}CH_2$), 2116 (acetylenic stretch); δ_H (300 MHz; $CDCl_3$) 1.94 (1H, t, *J* 2.4, $NCH_2CC\mathbf{H}$), 2.34 (3H, s, CH_3), 3.74 (2H, d, *J* 6.4, NCH_2CHCH_2), 3.9 (2H, d, *J* 2.4, NCH_2CCH), 5.18 (2H, m, NCH_2CHCH_2), 5.6 (1H, m, NCH_2CHCH_2), 7.2 (2H, d, *J* 8.2, aryl C-**H**), 7.6 (2H, d, *J* 8.2, aryl C-**H**); δ_C (75 MHz; $CDCl_3$) 21.6 (CH_3), 35.7 (CH_2), 48.9 (CH_2), 73.8 (NCH_2CCH), 76.4 (NCH_2CCH), 120.0 (CH_2), 127.7 (aryl **C**-H), 129.5 (aryl **C**-H), 131.8 (NCH_2CHCH_2), 135.9 (quaternary aryl-**C**), 143.6 (quaternary aryl-**C**). Found [M + Na]$^+$, 272.0726; $C_{13}H_{15}NO_2S$ requires *M* + Na 272.0716.

4-Methyl-*N*-(2-oxo-ethyl)-*N*-prop-2-ynyl-benzezesulfonamide (275)[194]



$C_{13}H_{15}NO_2S$

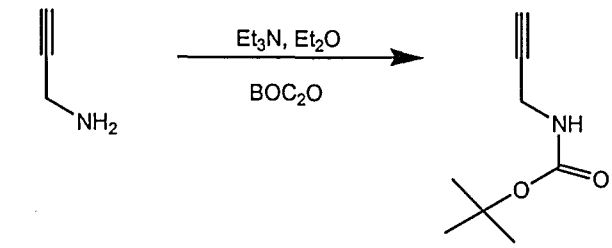
Mol. Wt.: 249.3

$C_{12}H_{13}NO_3S$

Mol. Wt.: 251.3

4-Methyl-*N*-(prop-2-enyl)-*N*-(prop-2-ynyl) benzenesulfonamide (**270**) (1.0 g, 4.0 mmol) was dissolved in a solution of dichloromethane (50 mL) and methanol (5 mL) and cooled to –78 °C. A steady stream of ozone was passed through the solution until a blue colour persisted and continued for a further 60 minutes. The reaction mixture was treated with starch-iodine paper to confirm the generation of ozone. Zinc (0.6 g) and glacial acetic acid (1 mL) were added and the solution stirred at room temperature for 16 hours. The reaction mixture was filtered, concentrated *in vacuo* and then rapidly chromatographed on silica gel (1:1 hexane: ethyl acetate) to afford the aldehyde (**274**) (0.96 g, 96 %) as a colourless oil. R_f (1:1 hexane: ethyl acetate) 0.34; ν_{max} (NaCl)/cm^{-1} 1530.0 (aromatic ring), 1740.6 (CHO), 2350.2 (acetylenic stretch); δ_H (300 MHz; $CDCl_3$) 1.92 (1H, s, $NCH_2CC\mathbf{H}$), 2.3 (3H, s, $\mathbf{CH_3}$), 3.87 (2H, s, $NC\mathbf{H_2}CCH$), 4.07 (2H, d, *J* 2.4, $NC\mathbf{H_2}CHO$), 7.2 (2H, d, *J* 8.2, aryl-**H**), 7.6 (2H, d, *J* 8.2, aryl-**H**), 9.53 (1H, br. s, $NCH_2C\mathbf{H}O$); δ_C (75 MHz; $CDCl_3$); 21.4 ($\mathbf{C}H_3$), 38.6 (NCH_2CCH), 55.7 (NCH_2CHO), 76.0 ($NCH_2\mathbf{C}CH$), 77.3 ($NCH_2\mathbf{C}CH$), 127.7 (aryl **C**-H), 129.5 (aryl **C**-H), 134.7 (quaternary aryl-**C**), 144.3 (quaternary aryl-**C**), 199.5 (**C**HO). Found $[M + Na]^+$, 274.0517; $C_{12}H_{13}NO_3S$ requires *M* + Na 274.0508.

N-(*Tert*-butyloxycarbonyl)prop-2-ynylamine (281)[195]



C_3H_5N

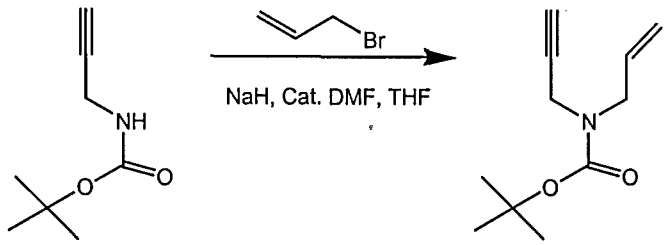
Mol. Wt.: 55.1

$C_8H_{13}NO_2$

Mol. Wt.: 155.2

To an ice cooled solution of propargylamine (4.44 g, 79.8 mmol) and triethylamine (11.15 mL, 79.8 mmol) in diethyl ether (30 mL) was added di-*tert* butyl dicarbonate in diethyl ether. The resulting solution was stirred overnight at 25 °C. The reaction mixture was washed with saturated ammonium chloride (100 mL) followed by water (100 mL) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and purified by column chromatography (1:1 ethyl acetate: hexane) to give a clear oil (**281**) (10.3 g, 84 %). R_f (1:1 hexane: ethyl acetate) 0.67; ν_{max} (NaCl)/cm^{-1} 1392 ($C(CH_3)_3$), 1713 (C=O), 2121 (acetylenic stretch), 3385 (N-H); δ_H (300 MHz; $CDCl_3$) 1.38 (9H, s, $(CH_3)_3$), 2.16 (1H, t, *J* 2.5, NCH_2CCH), 3.8 (2H, s, NCH_2), 4.8 (1H, br. s, NH); δ_C (75 MHz; $CDCl_3$); 28.3 ($(CH_3)_3$), 30.4 (NCH_2), 71.0 (NCH_2CCH), 80.1 (NCH_2CCH), 97.1 ($C(CH_3)_3$), 155.0 (CO).

Allyl-prop-2-ynyl-carbamic acid *tert*-butyl ester (282)



$C_8H_{13}NO_2$

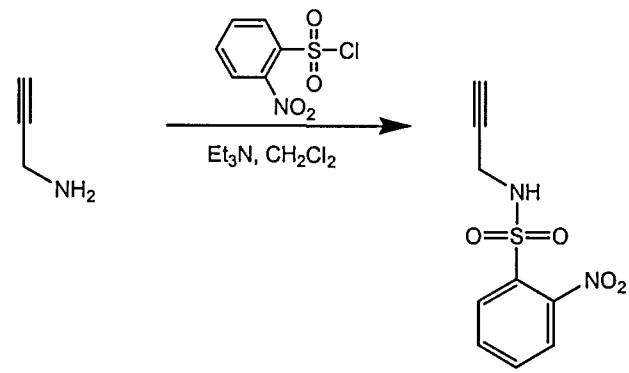
Mol. Wt.: 155.2

$C_{11}H_{17}NO_2$

Mol. Wt.: 195.3

Sodium hydride (1.4 g, of 60 % dispersion in mineral oil, 35.0 mmol, hexane washed) was added to a solution of *N*--*tert*-butoxycarbonyl)prop-2-ynylamine (5 g, 32.26 mmol) in a 9:1 mixture of THF and DMF. Allylbromide (3.25 mL, 38.4 mmol) was then added dropwise to this solution. After 36 hours the reaction mixture was quenched with H_2O and extracted with Et_2O. The combined extracts were dried over K_2CO_3, concentrated and chromatographed (2:1 hexane: ethyl acetate). This furnished the title compound (**282**) as a yellow oil (4.8 g, 77 %). R_f (2:1 hexane: ethyl acetate) 0.53; ν_{max} (NaCl)/cm^{-1} 993 + 923 ($CH=CH_2$), 1367 ($C(CH_3)_3$), 1694 (C=O), 3307 + 2118 (acetylenic stretch), δ_H (300 MHz; $CDCl_3$) 1.35 (9H, s, $(CH_3)_3$), 2.1 (1H, t, *J* 2.3, NCH_2CCH), 3.78 (4H, m, CH_2NCH_2), 5.02 (2H, m, NCH_2CHCH_2), 5.67 (1H, m, NCH_2CHCH_2); δ_C (75 MHz; $CDCl_3$) 28.20 ($C(CH_3)_3$), 35.5 (CH_2), 48.4 (CH_2), 76.7 (NCH_2CCH), 79.4 (quaternary-**C**), 80.1 (NCH_2CCH), 116.0 (NCH_2CHCH_2), 133.2 (NCH_2CHCH_2).154 (**C**=O). Found $[M + Na]^+$, 218.1154; $C_{11}H_{17}NO_2$ requires *M* + Na 218.1151.

N-Propargyl-2-nitrobenzenesulfonamide (289)



C_3H_5N

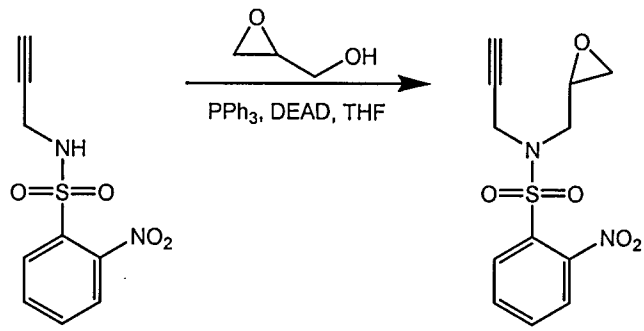
Mol. Wt.: 55.1

$C_9H_8N_2O_4S$

Mol. Wt.: 240.2

2-Nitrobenzenesulfonylchloride (11.97 g, 54.47 mmol) in dry dichloromethane (20 mL) was added via cannular to a solution of propargylamine (3 g, 54.47 mol) and triethylamine (16.56 mL, 118.8 mmol) in dry DCM (20 mL) at 0°C under an atmosphere of nitrogen. The resulting solution was allowed to warm to room temperature and left to stir overnight (16 hrs.). The solution was then washed with water (3 x 30 mL), dried ($MgSO_4$), filtered and evaporated to dryness *in vacuo* furnishing an orange oil (**289**) (11.63 g, 89 %). R_f (3:1 hexane: ethyl acetate) 0.33; ν_{max} (NaCl)/cm^{-1} 1368 (N=O), 1538 (C-NO_2), 2125 (acetylenic stretch), 3425 (N-H); δ_H (300 MHz; $CDCl_3$) 1.90 (1H, t, *J* 2.5, $NCH_2CC\mathbf{H}$), 3.95 (2H, dd, *J* 6, 2.5, $NC\mathbf{H}_2$), 5.6 (1H, br. s, N**H**), 7.69 (2H, m, aryl C-**H**), 7.85 (1H, dd, *J* 6, 3, aryl C-**H**), 8.13 (1H, m, aryl C-**H**); δ_C (75 MHz; $CDCl_3$); 33.4 (NCH_2CCH), 73.3 ($NCH_2C\mathbf{C}H$), 77.0 ($NCH_2\mathbf{C}CH$), 125.5, 131.6, 132.0, 133.9 (aryl **C**-H), 135.1 (quaternary aryl-**C**), 148.00 (**C**-NO_2).

N-Propynyl-2-nitro-*N*-oxiranylmethylbenzenesulfonamide (290)



$C_9H_8N_2O_4S$

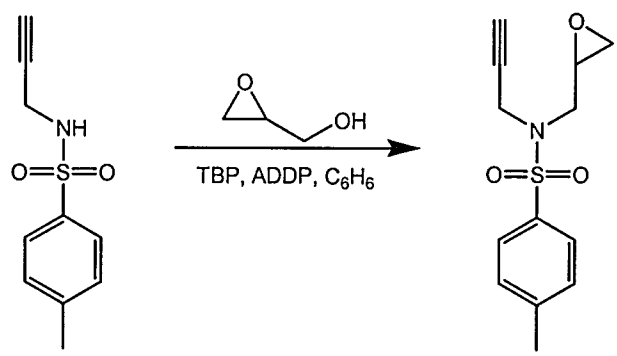
Mol. Wt.: 240.2

$C_{12}H_{12}N_2O_5S$

Mol. Wt.: 296.3

Diethylazodicarboxylate (DEAD) (0.95 g, 5.5 mmol, 0.86 mL) was added dropwise to a stirred solution of (**289**) (1 g, 4.17 mmol) and triphenylphosphine (1.4 g. 5.5 mmol) in dry THF (50 mL) at 0 °C. To this solution, glycidol (0.37 g, 5.0 mmol, 0.33 mL) was rapidly added. The solution was left to warm to room temperature and stirred overnight. The organic solvent was removed *in vacuo* and the crude product was immediately purified by column chromatography, furnishing a yellow oil (**290**) (0.95 g, 86 %); m.p. 71 - 74 °C; R_f (3:5:1 dichloromethane: diethyl ether: hexane) 0.52; ν_{max} (NaCl)/cm^{-1} 1350 (N=O), 1545 (C-NO_2), 2121 (acetylenic stretch), 3276 (CH); δ_H (300 MHz; $CDCl_3$) 2.12 (1H, t, *J* 2.4, $NCH_2CC\mathbf{H}$), 2.53 (1H, dd, *J* 4.5, 2.6, $CHOC\mathbf{H}_2$), 2.71 (1H, t, *J* 4.5, $CHOC\mathbf{H}_2$), 3.06 (1H, m, $C\mathbf{H}OCH_2$), 3.29 (1H, dd, *J* 15.2, 6.2 $NC\mathbf{H}_2$), 3.7 (1H, dd, *J* 15.2, 3.4, $NC\mathbf{H}_2$), 4.21 (2H, d, *J* 2.4, $NC\mathbf{H}_2CCH$), 7.67 - 7.72 (3H, m, aryl C-**H**), 7.95 - 7.99 (1H, m, aryl C-**H**); δ_C (75 MHz; $CDCl_3$) 38.0 (NCH_2), 44.8 (NCH_2), 49.0 (CH_2), 50.3 (**C**H), 74.3 (NCH_2CCH), 76.7 (NCH_2CCH), 124.3 + 130.9 + 132.0 + 132.2 (aryl **C**-H), 134.3 (quaternary aryl-**C**), 148.1 (**C**-NO_2). Found [M + Na]$^+$, 319.0367; $C_{12}H_{12}N_2O_5S$ requires *M* + Na 319.0359.

4-Methyl-*N*-(prop-2-ynyl)-*N*-oxiranylmethyl-*N*-benzenesulfonamide (297)



$C_{10}H_{11}NO_2S$

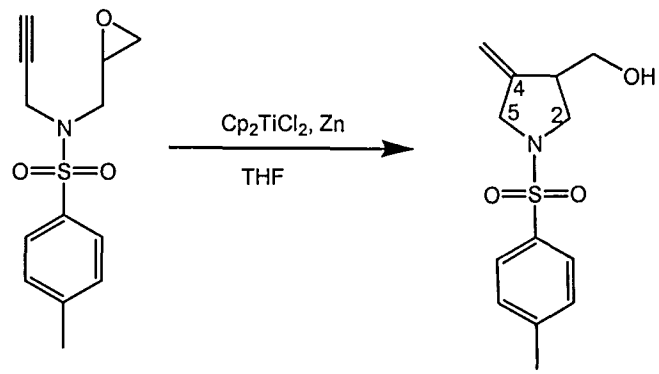
Mol. Wt.: 209.3

$C_{13}H_{15}NO_3S$

Mol. Wt.: 265.3

Under an atmosphere of nitrogen, glycidol (2.59 g, 35.0 mmol, 2.32 mL), tributylphosphine (TBP) (2.8 g, 14.0 mmol, 3.49 mL), and 4-methyl-*N*-propargyl-benzenesulfonamide (**269**) (3 g, 14.0 mmol) were successively dissolved in dry benzene (50 mL) with stirring at 0 °C. 1,1-(Azodicarbonyl)-dipiperidine (ADDP) (3.5 g, 14.0 mmol) was added to the solution. After 10 minutes, the reaction mixture was brought to room temperature and the stirring was continued for 24 hours. Hexane was added to the reaction mixture and the dihydro-ADDP, which separated out, was filtered off. The desired product (**297**) was purified by column chromatography after evaporation of the solvent *in vacuo* furnishing a yellow oil (2.4 g, 62 %); R_f (2:1 hexane: ethyl acetate) 0.57; ν_{max} (NaCl)/cm^{-} 1572 (aromatic ring), 2152 (acetylenic stretch), 3309 (CH), δ_H (400 MHz; $CDCl_3$) 2.0 (1H, s, $NCH_2CC\mathbf{H}$), 2.35 (3H, s, $C\mathbf{H}_3$), 2.55 (1H, dd, *J* 4.5, 2.5, $CHOC\mathbf{H}_2$), 2.72 (1H, t, *J* 4.5, $CHOC\mathbf{H}_2$), 3.09 (1H, m, $C\mathbf{H}OCH_2$), 3.16 (1H, dd, *J* 14.5, 5.7, $NC\mathbf{H}_2$), 3.47 (1H, dd, *J* 14.5, 3.5, $NC\mathbf{H}_2$), 4.1 (2H, s, $NC\mathbf{H}_2CCH$), 7.15 - 7.28 (2H, d, *J* 8.2, aryl C-**H**), 7.65 - 7.7 (2H, d, *J* 8.2, aryl C-**H**); δ_C (75 MHz; $CDCl_3$) 21.6 ($\mathbf{C}H_3$), 38.0 ($\mathbf{N}CH_2$), 45.0 ($\mathbf{N}CH_2$), 48.2 ($\mathbf{N}CH_2$), 50.5 ($NCH_2\mathbf{C}HOCH_2$), 66.0 ($NCH_2\mathbf{C}CH$), 74.0 ($NCH_2\mathbf{C}CH$), 127.7+129.6 (aryl-**C**), 135.7 (quaternary-**C**), 143.8 (quaternary-**C**). Found $[M + Na]^+$, 288.0676; $C_{13}H_{15}NO_3S$ requires *M* + Na 288.0665.

[4-Methylene-1-(toluene-4-sulfonyl)-pyrrolidin-3-yl]-methanol (299)



$C_{13}H_{15}NO_3S$

Mol. Wt.: 265.3

$C_{13}H_{17}NO_3S$

Mol. Wt.: 267.3

Activation of Zinc Powder:

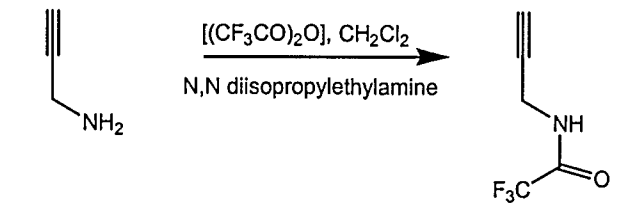
Zinc powder (4 g) was stirred with HCl (10 %, 10 mL) for 2 minutes, filtered and washed with water (30 mL) followed by acetone (10 mL) to give the activated zinc.

In situ preparation of Cp_2TiCl from Cp_2TiCl_2 and activated zinc.

Dicyclopentadienyl titanium dichloride (0.67 g, 2.72 mmol), dissolved in THF (25 mL) was added to the activated zinc (0.27 g, 4.08 mmol) and the mixture vigorously stirred for 60 minutes under an atmosphere of nitrogen with rigorous exclusion of oxygen. The solution was then added to another flask containing the starting material (**297**) (0.18 g, 0.68 mmol) dissolved in THF also under an atmosphere of nitrogen. The solution was left to stir for 10 minutes. A 10 % solution of H_2SO_4 (10 mL) was added to quench the reaction and left to stir for another 10 minutes. The reaction mixture was then washed with sat. $NaHCO_3$ and the aqueous layer carefully extracted with Et_2O (3 x 20 mL). The solvent was evaporated *in vacuo* to yield the crude product which was purified by column chromatography which afforded (**299**) (0.07 g, 39 %); R_f (1:1 hexane: ethyl acetate, followed by 4:1 hexane: ethyl acetate) 0.27; ν_{max} (NaCl)/cm^{-1} 813.7 (2 adjacent H), 906.5 (C=CH_2), 3374.0 (O-H); δ_H (300 MHz; $CDCl_3$) 2.33 (3H, s, CH_3), 2.76 (1H, m, $CHCH_2OH$), 3.3 (2H, ABq, *J* 9.7, 2.4, C(2)H_2), 3.57 (2H, d, *J* 5.7, C(5)H_2), 3.8 (2H, dd, *J* 14, 2, CH_2OH), 4.96 (2H, d, *J* 2, CCH_2), 7.2 (2H, m, aryl C-H), 7.7 (2H, m, aryl C-H); δ_C (75 MHz; $CDCl_3$) 21.6 (CH_3), 30.0 (CCH_2),

45.5 (**C**HCH$_2$OH), 50.7 (N**C**H$_2$), 52.0 (N**C**H$_2$), 63.4 (**C**H$_2$OH), 108.6 (C**C**H$_2$), 128.0 (aryl **C**-H), 130.0 (aryl **C**-H), 143.9 (quaternary-**C**), 144.7 (quaternary-**C**). Found $[M + Na]^+$, 290.0859; $C_{13}H_{17}NO_3S$ requires M + Na 290.0821.

2,2,2-Trifluoro-*N*-prop-2-ynyl-acetamide (272)[196]



C_3H_5N

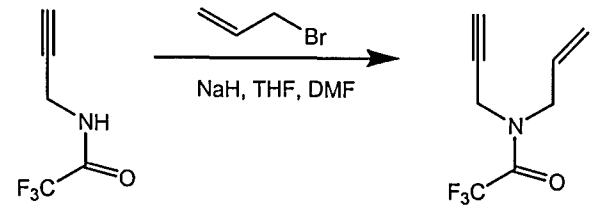
Mol. Wt.: 55.1

$C_5H_4F_3NO$

Mol. Wt.: 151.1

Trifluoroacetic anhydride (15.5 mL, 110 mmol,) was added dropwise to a solution of propargylamine (6.9 mL, 100.0 mmol) in dichloromethane (100 mL) and Hünigs base (52.3 mL, 300 mmol) at 0 °C. This mixture was warmed to room temperature, monitored by TLC and stirred overnight. The solution was washed with 1M HCl (3 x 50 mL), Sodium bicarbonate solution (2 x 30 mL), water (1 x 50 mL) and dried with magnesium sulfate. The compound was then purified by column chromatography on silica gel (2:1 hexane: ethyl acetate). This furnished the title compound (**272**) as a yellow oil (12.9 g, 85.2 %). R_f (2:1 hexane: ethyl acetate) 0.55; ν_{max} (NaCl)/cm^{-1} 1641 (C=O), 3130 (N-H); δ_H (300 MHz; $CDCl_3$) 2.2 (1H, t, *J* 2.5, $NCH_2CC\mathbf{H}$), 4.1 (2H, dd, *J* 5.4, 2.5, $NC\mathbf{H_2}CCH$), 7.1 (1H, br. s, N**H**); δ_C (75 MHz; $CDCl_3$) 29.2 ($\mathbf{C}H_2$), 72.2 ($NCH_2\mathbf{C}CH$), 77.1 ($NCH_2C\mathbf{C}H$), 115.6 (q, *J* 250, $\mathbf{C}F_3$), 157.4 (q, *J* 38, **C**O).

N-Allyl-(2-propynyl)-2,2,2,trifluoroacetamide (273)



$C_5H_4F_3NO$

Mol. Wt.: 151.1

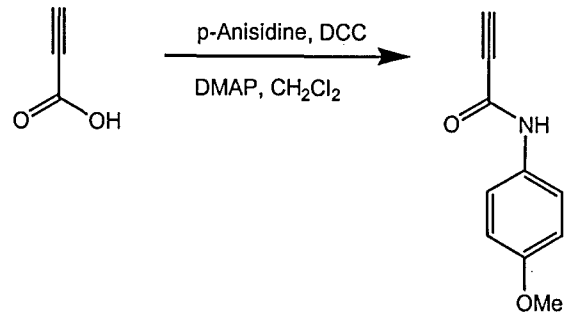
$C_8H_8F_3NO$

Mol. Wt.:191.2

To a solution of trifluoro-*N*-prop-2-ynyl-acetamide (2.5 g, 16.55 mmol) in THF (50 mL), sodium hydride (0.81 g, of 60 % dispersion in mineral oil, 20.2 mmol, hexane washed) was added and the solution left to stir for 30 minutes. Neat allyl bromide (3.8 mL, 120.9 mmol) was added at 0°C to the reaction mixture and left for 36 hours. The reaction was quenched with water and extracted with diethyl ether. The combined extracts were concentrated, dried with K_2CO_3 and chromatographed on silica gel (1:1 diethyl ether: hexane). This furnished the title compound (**273**) as a yellow oil (1.9 g, 59 %). R_f (1:1 diethyl ether: hexane) 0.53; ν_{max} (NaCl)/cm^{-1} 985 + 909 (CH=CH_2), 1697 (NC=O); δ_H (300 MHz; $CDCl_3$) [mixture of rotamers]*, 2.23 (1H, t, *J* 2.4, NCH_2CCH), 2.28 (0.7H, *J* 2.4, NCH_2CCH), 4.09 - 4.16 (7H, m "2 x CH_2"), 5.2 - 5.28 (3.4H, m, NCH_2CHCH_2), 5.63 - 5.76 (1.7H, m, NCH_2CHCH_2); δ_C(75 MHz; $CDCl_3$) 34.8 (NCH_2), 36.1 (NCH_2), 48.4 (NCH_2), 49.0 (NCH_2), 73.1 (CCH), 73.4 (CCH), 73.4 76.6 (CCH), 76.8 (CCH), 116 (q, *J* 280, CF_3), 119.8 ($CHCH_2$), 120.1 ($CHCH_2$), 130.3 ($CHCH_2$), 130.9 ($CHCH_2$), carbonyl carbon not observed. Found $[M + Na]^+$, 214.0449; $C_8H_8F_3NO$ requires *M* + Na 214.0450.

*Mixture of rotamers: Ratio of rotamers is indicated by integration.

N-(-4-methoxyphenyl)-N-propiolamide (301)[197]

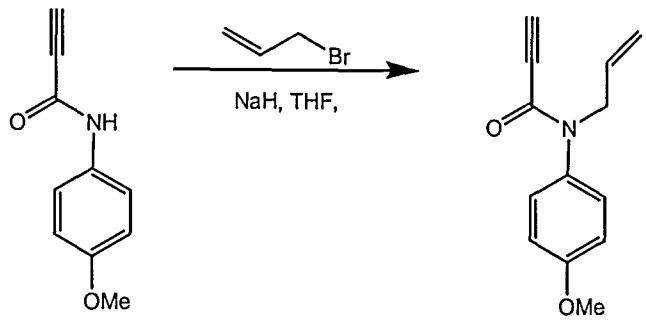


$C_3H_2O_2$
Mol. Wt.: 70.0

$C_{10}H_9NO_2$
Mol. Wt.: 175.2

p-Anisidine (9.4 g, 76.3 mmol) was added to a solution of propiolic acid (5 g, 71.4 mmol) in dichloromethane (70 mL). To this mixture, 4-dimethylaminopyridine (DMAP) was added (1.7 g, 14 mmol). A solution of 1,3 dicyclohexylcarbodiimide (DCC) (15.9 g, 77.0 mmol) in DCM (30 mL) was then added dropwise to the solution at 0 °C. The resulting solution was stirred for 30 minutes after, which time a white precipitate formed. The reaction mixture was then stirred for a further 3 hours at room temperature, cooled in ice and filtered. The residue was washed with dichloromethane. The filtrate was then washed with 2 M HCl (3 x 100 mL), $NaHCO_3$ (3 x 100 mL), $NaHCO_3$ (3 x 100 mL) and water (3 x 100 mL). The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to yield the crude product, which was purified by column chromatography (1:1 ethyl acetate: hexane). This furnished the title compound (**301**) as an orange oil (2.15 g, 88 %). R_f (1:1 diethyl ether: hexane) 0.21; ν_{max} (NaCl)/cm^{-1} 860 (2 adjacent H), 2218 (acetylenic stretch), 1675.0 (C=O); 3287.6 (N-H); δ_H (300 MHz; $CDCl_3$) 2.83 (1H, s, NCOCC**H**), 3.69 (3H, s, OCH_3), 6.7 (2H, d, *J* 9, aryl C-**H**), 7.4 (2H, d, *J* 9, aryl C-**H**), 8.2 (1H, br. s, N**H**); δ_C (75 MHz; $CDCl_3$) 55.5 (OCH_3), 74.2 (NCOCCH), 77.7 (NCOCCH), 114.2 (aryl **C**-H), 122.0 (aryl **C**-H), 130.2 (quaternary aryl-**C**), 149.9 (**C**=O), 156.9 (quaternary aryl-$COCH_3$). Found $[M + Na]^+$, 197.0425; $C_{10}H_9NO_2$ requires *M* + Na 197.0447.

Propynoic acid-allyl(4-methoxyphenyl)amide (302)



$C_{10}H_9NO_2$

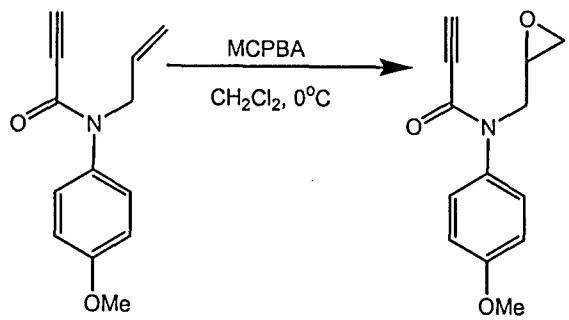
Mol. Wt.: 175.2

$C_{13}H_{13}NO_2$

Mol. Wt.: 215.2

To a solution of *N*-(-4-methoxyphenyl)-*N*-propiolamide (x) (2 g, 11.43 mmol) in THF (150 mL), sodium hydride (0.3 g, 13.1 mmol) was added and immediately after, the allyl bromide (2.7 mL, 31.9 mmol). After 36 hours the reaction mixture was quenched with water (200 mL) and extracted with Et_2O (3 x 100 mL). The combined extracts were dried over potassium carbonate (K_2CO_3), concentrated *in vacuo* to yield the crude product, which was purified by column chromatography (1:1 ethyl acetate: hexane). This furnished the title compound (**302**) as an orange oil (1.49 g, 65 %). R_f (1:1 ethyl acetate: hexane) 0.43; ν_{max} (NaCl)/cm^{-1} 872 (2 adjacent H), 932 ($CH=CH_2$), 1634 (C=O), 2100 (acetylenic stretch); δ_H (300 MHz; $CDCl_3$) 2.77 (1H, s, NCOCC**H**), 3.74 (3H, s, OCH_3), 4.22 (2H, d, *J* 6.3, NCH_2CHCH_2), 5.04 (1H, dd, *J* 9, 1, NCH_2CHCH_2), 5.07 (1H,dd, *J* 17, 1, NCH_2CHCH_2), 5.7 (1H, m, NCH_2CHCH_2), 6.8 (2H, d, *J* 6.7, aryl C-**H**), 7.1 (2H, d, *J* 6.7, aryl C-**H**); δ_C (75 MHz; $CDCl_3$) 51.7 (CH_2), 55.4 (OCH_3), 76.4 (NCOCCH), 79.8 (NCOCCH), 114.4 (aryl **C**-H), 118.7 (CH_2), 129.5 (aryl **C**-H), 131.9 (quaternary aryl-**C**), 133.9 (quaternary-**C**), 153.0 (quaternary aryl-**C**), 159.3 (**C**=O). Found $[M + Na]^+$, 238.0841; $C_{13}H_{13}NO_2$ requires *M* + Na 238.0838.

Propynoic acid (*N*-4-methoxy-phenyl)-oxiranylmethyl-amide (303)

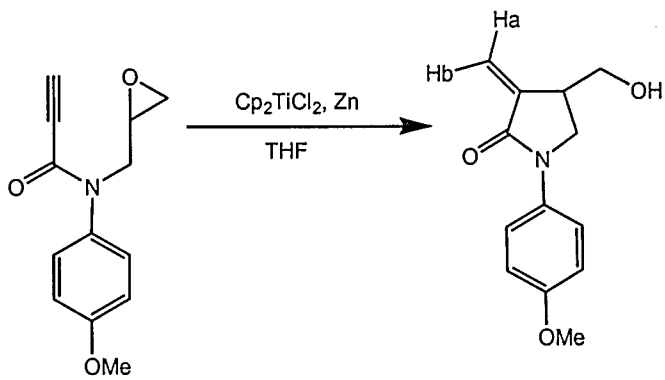


$C_{13}H_{13}NO_2$
Mol. Wt.: 215.2

$C_{13}H_{13}NO_3$
Mol. Wt.: 231.2

Metachloroperbenzoic acid (*m*-CPBA) (0.13 g, 0.74 mmol) was dissolved in dry dichloromethane (5 mL) and cooled in an ice bath to 0 °C. Propanoic acid allyl(4-methoxy-phenyl)amide (**302**) (0.02 g, 0.09 mmol) was then added to the MCPBA solution over 20 minutes and left to stir overnight. The reaction mixture was then washed with Na_2SO_3 (3 x20 mL), sat. $NaHCO_3$ (3 x20 mL) and extracted with dichloromethane. The combined extracts were then washed with brine and dried with sodium sulphate. The organic solvent was evaporated *in vacuo* to yield the crude product, which was purified by column chromatography (1:1 ethyl acetate: hexane). This furnished the title compound (**303**) as an orange oil (1.2 g, 56 %). R_f (1:1 ethyl acetate: hexane) 0.38; ν_{max} (NaCl)/cm^{-1} 848.8 (2 adjacent H), 1686.0 (C=O); δ_H (300 MHz; $CDCl_3$) 2.4 (1H, dd, *J* 4.4, 2.5, NCH_2CHCH_2O), 2.7 (1H, t, *J* 4.4, NCH_2CHCH_2O), 2.8 (1H, s, NCOCC**H**), 3.16 (1H, quintet, *J* 3.9, NCH_2), 3.5 (1H, dd, *J* 14.2, 6.4 NCH_2), 3.7 (3H, s, OCH_3), 4.02 (1H, dd, *J* 14.2, 3.9, NCH_2CHCH_2O), 6.8 (2H, d, *J* 4.4, aryl C-**H**), 7.1 (2H, d, *J* 4.4, aryl C-**H**); δ_C (75 MHz; $CDCl_3$) 45.7 (CH_2), 49.4 (NCH_2CHCH_2O) 51.5 (CH_2), 55.5 (OCH_3), 76.1 (NCOCCH), 80.4 (NCOCCH), 114.4 (aryl **C**-H), 129.3 (aryl **C**-H), 134.0 (quaternary aryl-**C**), 153.5 (quaternary aryl-**C**), 159.5 (**C**=O). Found $[M + Na]^+$, 254.0795; $C_{13}H_{13}NO_3$ requires *M* + Na 254.0788.

4-Hydroxymethyl-1-(-4-methoxy-phenyl)-3-methylene-pyrrolidin2-one (304)



$C_{13}H_{13}NO_3$

Mol. Wt.: 231.2

$C_{13}H_{15}NO_3$

Mol. Wt.: 233.3

Activation of Zinc Powder:

Zinc powder (4 g) was stirred with HCl (10%, 10 mL) for 2 minutes, filtered and washed with water (30 mL) followed by acetone (10 mL) to give the activated zinc.

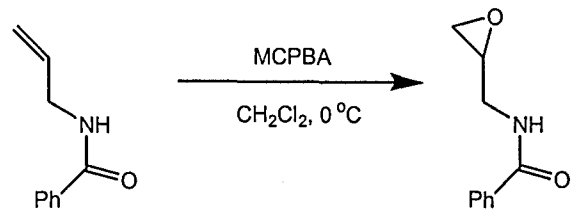
In situ preparation of Cp_2TiCl from Cp_2TiCl_2 and activated zinc.

Dicyclopentadienyl titanium dichloride (0.28 g, 1.12 mmol), dissolved in THF (15 mL) was added to the activated zinc (0.11 g, 1.68 mmol) and the mixture was vigorously stirred for 60 minutes under an atmosphere of nitrogen with rigorous exclusion of oxygen. The solution was then added to another flask containing the starting material (**303**) (0.06 g, 0.28 mmol) dissolved in THF also under an atmosphere of nitrogen. The solution was left to stir for 10 minutes. A 10 % solution of H_2SO_4 (10 mL) was added to quench the reaction and then left to stir for another 10 minutes. The reaction mixture was then washed with sat. $NaHCO_3$ and the aqueous layer carefully extracted with diethyl ether (3 x 15 mL). The solvent was evaporated *in vacuo* to yield the crude product, which was purified by column chromatography to afford the title product (**304**). R_f (1:1:2 diethyl ether: dichloromethane: hexane) 0.37; ν_{max} (NaCl)/cm^{-1} 840.2 (2 adjacent H), 1642.5 (C=O), 3604.1 (O-H);

Evidence of product (**304**)

δ_H (300 MHz; $CDCl_3$) 3.02 (1H, m, C**H**CH_2OH), 3.32 (2H, m, NC**H**$_2$), 3.68 (2H, d, *J* 5, $CHCH_2$**O**H), 3.74 (3H, s, OC**H**$_3$), 5.31 (1H, d, *J* 2.5, C**H**$_a$), 6.05 (1H, d, *J* 2.5, C**H**$_b$), 6.81 – 6.88 (2H, m, aryl C-**H**), 7.49 – 7.56 (2H, m, aryl C-**H**), δ_C (75 MHz; $CDCl_3$) 34.5 (**C**HCH_2OH), 48.9 (**C**H_2), 56.0 (**C**H_3), 66.7 (**C**H_2), 114.3 (aryl **C**-H), 121.4 (aryl **C**-H), 117.1 (**C**H_2), 130.5 (quaternary aryl-**C**), 149.5 (quaternary **C**), 157.6 (quaternary aryl-**C**), 162.0 (**C**=O).

N-Oxiranylmethyl-benzamide (308)



$C_{10}H_{11}NO$
Mol. Wt.: 161.2

$C_{10}H_{11}NO_2$
Mol. Wt.: 177.2

Metachloroperbenzoic acid (MCPBA) (2.1 g, 12 mmol) was dissolved in dry dichloromethane (15 mL) and cooled in an ice bath to 0 °C. The *N*-Allyl-benzamide (0.33 g, 2 mmol) was then added to the MCPBA solution over 20 minutes and left to stir overnight. The reaction mixture was then washed with Na_2SO_3 (3 x20 mL), sat. $NaHCO_3$ (3 x 20 mL) and extracted with dichloromethane. The combined extracts were then washed with brine and dried with sodium sulphate. The organic solvent was evaporated *in vacuo* to yield the crude product (**x**), which was purified by column chromatography (1:1 ethyl acetate: hexane). This furnished the title compound (**308**) as a yellow oil (0.21 g, 60 %). R_f (1:1 ethyl acetate: hexane) 0.17; ν_{max} (NaCl)/cm^{-1} 1644.0 (CO), 3421.7 (N-H); δ_H (300 MHz; $CDCl_3$) 3.6 (1H, dd, *J* 12.3, 5.7, NCH_2CHCH_2O), 3.7 (1H, m, NCH_2CHCH_2O), 3.8 (1H, m, NCH_2CHCH_2O), 4.06 (1H, m, NCH_2), 4.7 (1H, m, NCH_2), 7.39 (3H, m, aryl C-**H**), 7.8 (2H, m, aryl C-**H**); δ_C (75 MHz; $CDCl_3$) 55.9 (CH_2), 63.9 (CH_2), 80.2 (NCH_2CHCH_2O), 128.2 + 128.4 + 129.8 (aryl **C**-H), 131.5 (quaternary **C**), 164.4 (**C**O).

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