A Pinacol Coupling Approach to *N*-Heterocycles

- Synthesis of Iminosugars

Thesis submitted for the degree of Doctor of Philosophy

At the University of Leicester

by

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Statement

The accompanying thesis submitted for the degree of Ph.D. entitled "A Pinacol Coupling Approach to *N*-Heterocycles – Synthesis of Iminosugars" is based on work conducted by the author in the Department of Chemistry at the University of Leicester between the period October 2000 to September 2003.

All the work recorded in this thesis is original unless otherwise acknowledged in the text or by references. None of the work has been submitted for another degree in this or any other university.

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Abstract

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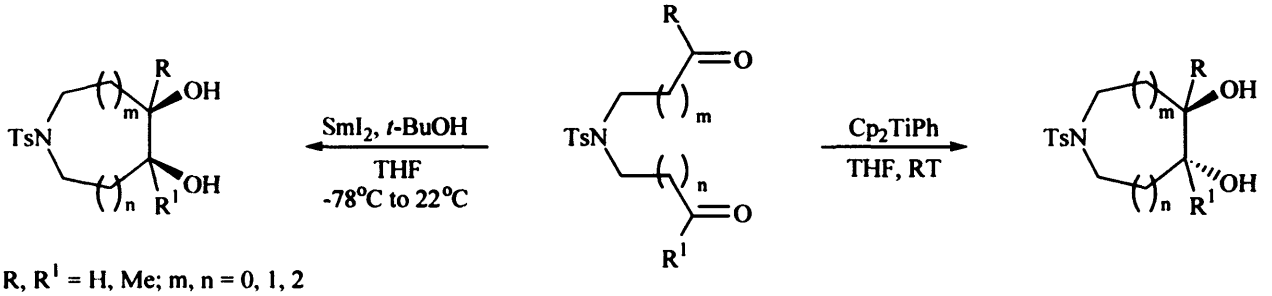
by Manpreet S. Kachala

The pinacol coupling reaction has enjoyed resurgence as a method for synthesising 1,2-diols made possible due to the advent of a variety of low-valent metal reagents that can be employed in the reaction. Intramolecular pinacol couplings to produce carbocyclic sugar analogues is well documented however, there are relatively few reports of the same reaction being applied to the synthesis of heterocyclic compounds.

A series of 5-8 membered *N*-heterocyclic diols have been prepared from dicarbonyls (shown below), *via* intramolecular pinacol reactions. The *cis*- or *trans*-stereoselectivity of these reactions is controlled by judicious choice of the low-valent metal reagent employed. The diastereoselectivity of the pinacol products is pleasingly comparable with literature examples, albeit with lower levels of stereocontrol in some cases than the corresponding carbocylic systems. Deprotection to yield the corresponding novel amino diols has also been undertaken so that biological testing could be performed.



R, R^1 = H, Me; m, n = 0, 1, 2

In addition a novel reaction has been developed whereby an ozonide precursor is treated with SmI_2 to carry out both ozonide reduction and pinacol coupling in the same pot to yield the corresponding *N*-heterocyclic diol.

Trihydroxypiperidines, such as 1,5-dideoxy-1,5-imino-arabinitol have been synthesised in order to investigate and explain the 'directing' effects α-alkoxy substituents have on the stereoselectivity of the pinacol reaction. The levels of stereoselectivity of the reaction were good, but lower that the comparable carbocylic cases. To the best of our knowledge we have also carried out the first titanium-mediated (Cp_2TiPh) pinacol coupling of an α-alkoxy substituted dicarbonyl which proceeds with a good level of diastereoselectivity.

Ring-closing metathesis with Grubb's catalyst and dihydroxylation with osmium tetroxide reactions have been applied as an alternative method for the synthesis of a series 6- and 7-membered of *N*-heterocycles. These products were compared to the products synthesised *via* pinacol coupling reactions to confirm their stereochemistry.

Dedicated

to

Mum, Dad, my Brother and Sister who are always there for me

and with their love and support have got me to where I am

today

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Abbreviations

Ac	acetyl
AIBN	azobisisobutyrylnitrile
AIDS	Acquired Immuno Deficiency Syndrome
Bn	benzyl
Bu	butyl
Cbz	carboxybenzyl
COSY	Correlated SpectroscopY
Cy	cyclohexyl
D	doublet
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethylazodicarboxylate
DHAP	dihydroxyacetone phosphate
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropyl ethylamine
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethyl formamide
DMPU	1,3-dimethyltetrahydro-2(1*H*)-pyrimidone
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
EI	electron ionisation
Et	ethyl
ES	electrospray
FAB	fast atom bombardment
FDP	fructose-1,6-diphosphate
FT-IR	fourier transform infra-red
GLC	gas liquid chromatography
HIV	Human Immunodeficiency Virus
HMPA	hexamethylphosphoric triamide
HOMO	highest occupied molecular orbital
J	coupling constant
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
Me	methyl

MOM	methoxymethyl
Ms	methylsulfonyl (mesyl)
NMO	*N*-morpholine oxide
nOe	nuclear Overhauser effect
NMR	nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect SpectroscopY
Ns	nitrobenzenesulfonyl (nosyl)
PCC	pyridinium chloro chromate
Py	pyridine
(*rac*)	racemic
RCM	ring closing metathesis
RT	room temperature
S_N2	bimolecular nucleophilic substitution
TBAF	*tert*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEMPO	tetramethylpiperidine *N*-oxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tr	triphenylmethyl
Ts	*para*-toluenesulfonyl

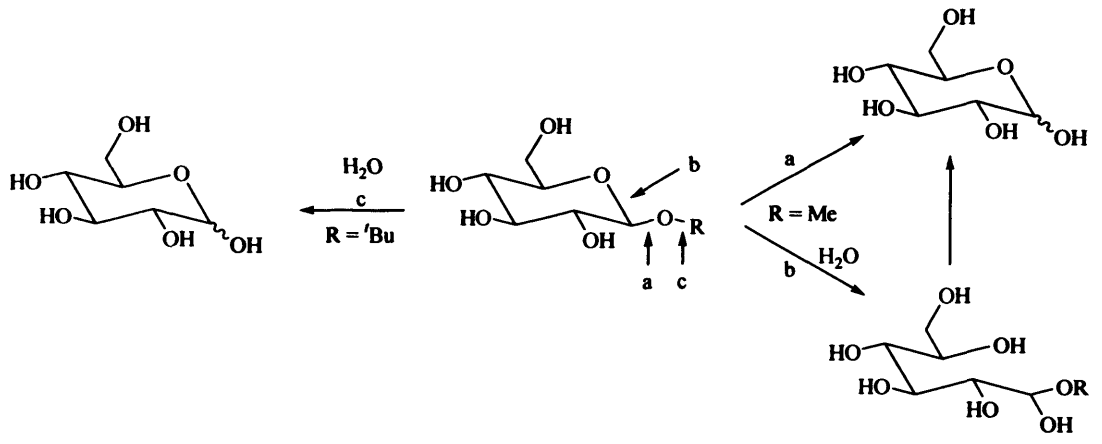
1. Chapter 1: Glycosides

1.1 Introduction

Carbohydrates are one of the most diverse classes of organic molecules in the biosphere with respect to stereochemistry, type of assembly, chain length and their conjugation to a large variety of non-carbohydrate aglycones. Carbohydrates can be converted into various polymeric, oligomeric and monomeric products that are of importance in the food, textile, pharmaceutical and agrochemical industries. They perform a multitude of functions in living organisms and are involved in structural, metabolic, defence and communication roles. Thus, carbohydrates and their conjugates such as glycoproteins and glycolipids are now recognized to act as freestanding chemical mediators and as cell surface receptors. Through this transmission of chemical signals carbohydrates mediate an enormous range of biologically important events such as cell-cell recognition, cell growth, cell development, inflammation and metastasis.[1]

1.2 Glycosides

The term glycoside is given to derivatives of sugars in which an alkyl or aryl group has replaced the hydrogen atom of the hemiacetal hydroxyl.[2] The alkyl or aryl substituent is referred to as the aglycon group and the carbohydrate part is called the glycon group. Glycosides have also been defined as any compound that contains a carbohydrate molecule, which is convertible by hydrolytic cleavage into sugar and non-sugar components. Glycosides are named on the basis of the sugar moiety *i.e.* glucoside, pentoside and fructoside contain glucose, pentose and fructose respectively as their carbohydrate component. Since glycosides are acetals they undergo acid catalysed hydrolysis to give the free sugars, a method usually used for the isolation of monosaccharides. The hydrolysis of glycosides can be initiated by the cleavage of three different carbon-oxygen bonds as shown (Scheme 1).[3] In most cases cleavage occurs directly at one of the C-O bonds at the acetal carbon (a or b). However, when the aglycone R can stabilise a positive charge and cleavage of bond c is also possible.

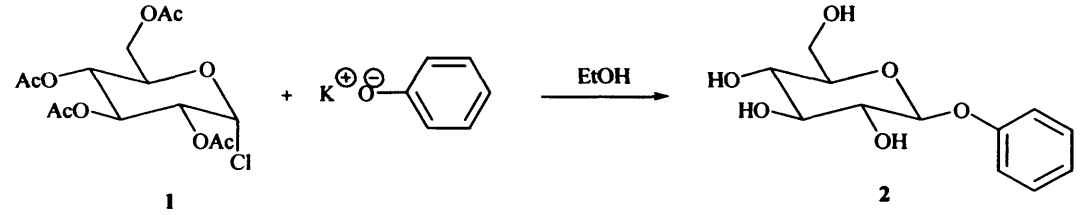


Scheme 1

It should be noted that during acidic hydrolysis of glycosides small amounts of dimeric products could be formed, even in dilute solutions, by competitive attack on the intermediate oxocarbocations from free sugar or glycoside molecule(s).

Perhaps the greatest synthetic challenge in carbohydrate chemistry has been the development of methods for the synthesis of the glycosidic bond. Whilst there are many methods available to synthesize glycosides few have found wide or general application. Numerous reviews have been published in this area[4] and only a brief discussion will follow.

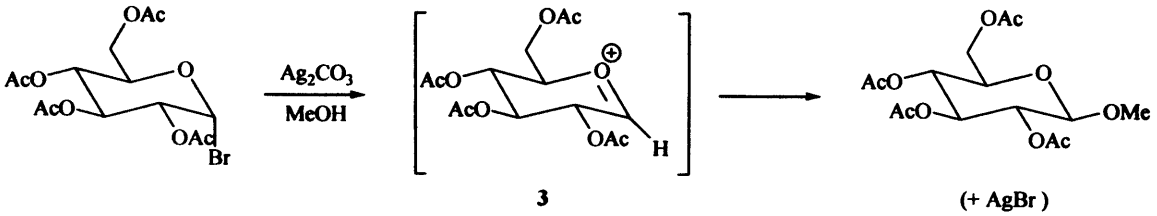
In 1879 Michael and co-workers reported the first glycosylation reaction between tetra-O-acetyl-α-D-glucopyranosylchloride **1** and potassium phenolate to yield phenyl β-D-glucopyranoside **2** (Scheme 2).[5] It should be noted that the acetyl groups are hydrolysed under the reaction conditions.



1 2

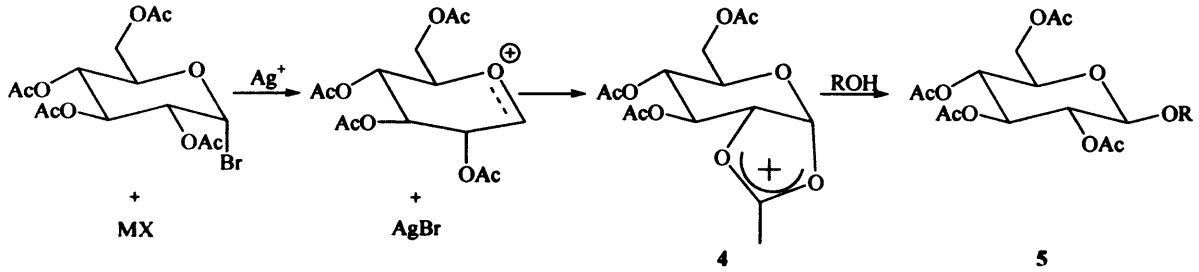
Scheme 2

Following on from this report Koenigs and Knorr[6] introduced silver (I) oxide or silver (I) carbonate as a hydrogen halide acceptor (Scheme 3). This facilitates leaving of the halide and reaction proceeds *via* the stabilised carbocation **3** shown. In general bromides are preferred over the corresponding chlorides due to the lower reaction temperatures required and glycosyl fluorides do not react under Koenigs-Knorr conditions.



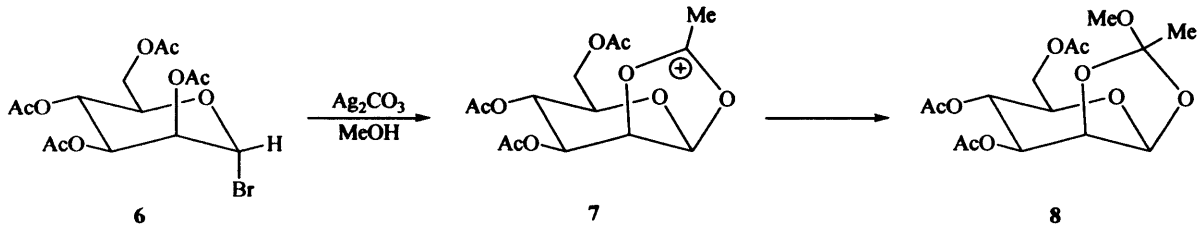
Scheme 3

Improvements were made to the Koenigs-Knorr reaction once the mechanism had been realized (Scheme 4). Isabell and Frush proposed that once the halide had departed, an acetooxonium cation **4** was formed and subsequent reaction with a glycosyl acceptor could lead to the 1,2-*trans* glycoside **5**.[7]



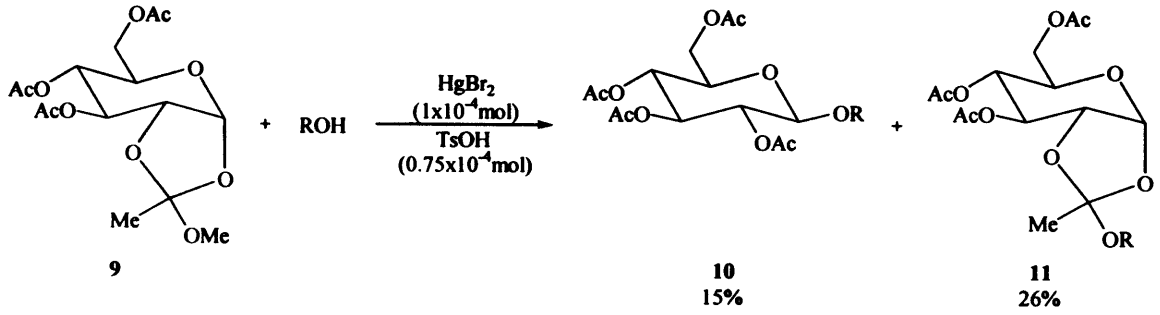
Scheme 4

Glycosides can also be synthesized from orthoester derivatives. These orthoesters are formed as a side reaction from the corresponding bromide **6** under Koenigs-Knorr reaction conditions (Scheme 5). The reaction again involves neighbouring participation to generate the intermediate cation **7**, which undergoes nucleophilic attack to give the stable orthoester **8**.



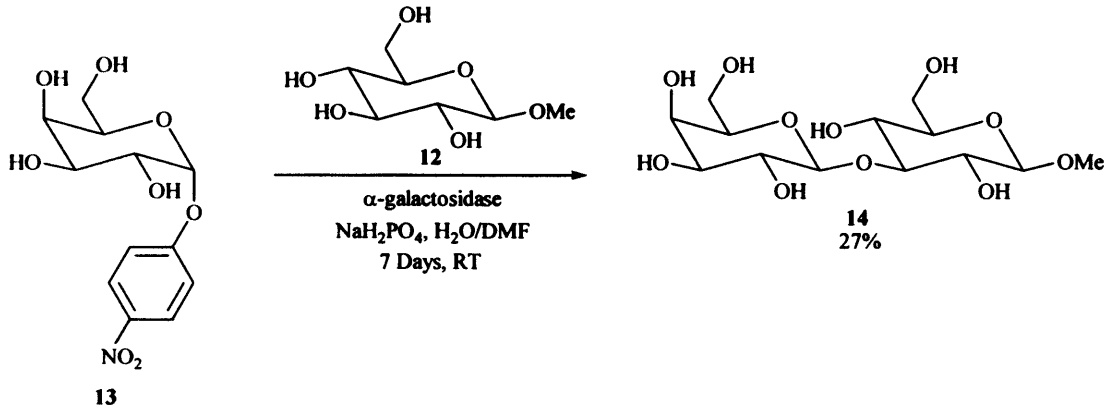
Scheme 5

Since the formation of these orthoesters lowers the yield of the Koenigs-Knorr process methods have been developed for their conversion into glycosides. Thus, Kochetkov *et. al.* have reported that the orthoester **9** will react with alcohols in the presence of a Lewis acid to yield the 1,2-*trans* glycoside **10** together with another orthoester **11** (Scheme 6).[8]



Scheme 6

Transglycosidation involves the exchange of the aglycon group of a glycoside. In general this can be achieved by treatment of an alcoholic solution of the glycoside with an acid catalyst and this method is useful in preparing glycosides from polysaccharides. Thus, methyl and benzyl α-D-fructofuranosides yield benzyl β-D-fructofuranoside when dissolved in benzyl alcohol and treated with hydrogen chloride.[9] Transglycosidation can also be brought about using enzymes known as glycosidases. These enzymes are normally involved in the biosynthetic cleavage of oligosaccharides to give glycosides. However, they can be used synthetically to prepare glycosides by employing a suitable glycosyl donor together with large excess of a glycosyl acceptor. An example is shown below (Scheme 7) where regioselective glycosylation of methyl α-D-glucopyranoside **13** with *p*-nitrophenyl α-D-galactoside **12** in the presence of the enzyme α-galactosidase produces the galactosylglucose derivative **14**.[10]

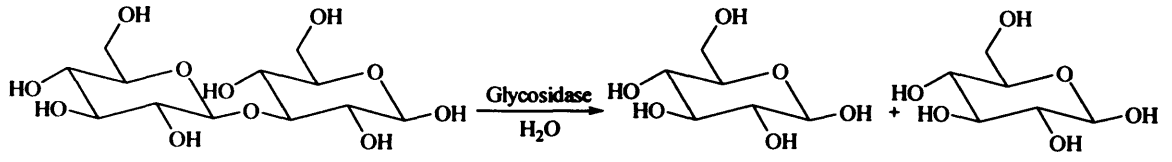


Scheme 7

1.3 Glycosidase Enzymes

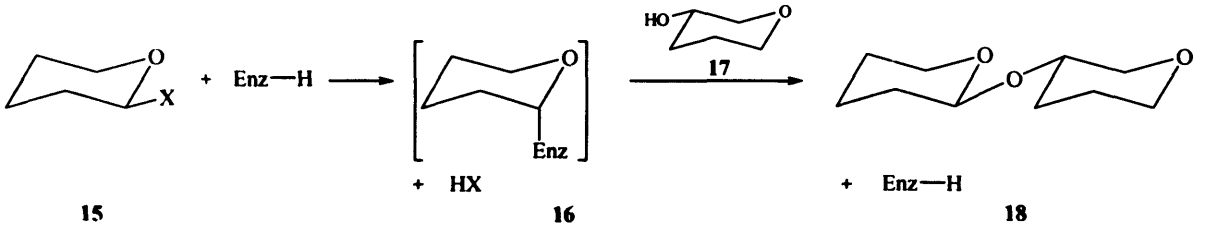
Glycoside hydrolases, or glycosidases as they are commonly known are an important class of carbohydrate and glycoconjugate processing enzymes, which are extremely widespread in organisms. Their exploitation in the bio- and food technology areas as well as medical research has become a major area of research over the past 30 years.[11] These enzymes

catalyse the hydrolysis of glycosidic bonds in carbohydrates and glycoconjugates, the effect being the release of low molecular weight saccharide units (Scheme 8). This hydrolysis of polysaccharides is of great importance in the digestion of saccharides as well as in cell-recognition processes.



Scheme 8

As mentioned above enzymatic glycosylation involves the combination of a glycosyl donor and acceptor by use of a suitable enzyme. The glycosyl donors are usually monosaccharide components that provide the non-reducing end of the product whereas the acceptors are saccharide moieties, which contain a nucleophilic hydroxyl group and supply the reducing end of the product. The donor **15** is activated by formation of a glycosyl-enzyme intermediate **16**, which is subsequently attacked by a hydroxyl group of the acceptor **17** generating the product **18** (Scheme 9).

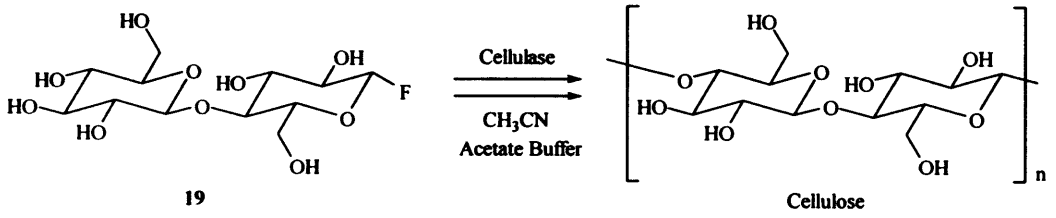


Scheme 9

The synthesis of oligo- and polysaccharides by enzyme-mediated reaction can be advantageous over more classic chemical methods due to increased chemo- and regioselectivity- thus circumventing long-winded protection strategies. However, under certain circumstances (*e.g.* low yields or low availability of the enzyme) traditional chemical methods may still prove to be best.

Glycosidase enzymes can bring about the synthesis of a new glycosidic bond by either direct reversal of the hydrolysis reaction that they normally catalyse or by formation of a glycosyl-enzyme intermediate. In the first of these approaches the reaction is driven in the direction of glycoside formation by increasing the concentration of the donor compound, decreasing the amount of water present and removing the final product from the reaction system by extraction or precipitation. Alternatively the use of activated glycosyl donors leads to the formation of a glycosyl-enzyme intermediate, which is subsequently attacked by a

nucleophilic group on the acceptor molecule.[12] An example is in the synthesis of cellulose in a single step *via* polycondensation of β-D-cellobiosyl fluoride **19** catalysed by the enzyme cellulase (Scheme 10).[13]



Scheme 10

1.4 Enzyme mechanism

Glycosidase enzymes are involved in the hydrolysis of poly- or oligosaccharides. Sites that are able to bind the sugar units on either side of the glycoside bond undergoing hydrolysis usually surround the catalytic centre of these enzymes. Conversely in the reverse reaction (bond forming) these sites bind the donor and acceptor moieties. There are two major types of glycosidase enzymes known: *exo*- and *endo*-glycosidases. *Exo*-glycosidases catalyse the removal of sugar moieties one at a time from the non-reducing end of an oligo- or polysaccharide and are involved in the breakdown of starch and glycogen, and the biosynthesis and modifications of glycosphingolipids. *Exo*-glycosidases have a low preference towards the aglycon moiety (*i.e.* they are able to cleave a variety of glycosides) and have a small catalytic site. *Endo*-glycosidases cleave non-terminal glycosidic bonds within polysaccharides. These enzymes are involved in the catabolism of aged glycoproteins and the alteration of bacterial and plant cell walls. A general feature of *endo*-glycosidase enzymes when compared to *exo*-glycosidases is depicted in figure 1. Thus, *endo*-glycosidases have multiple recognition subsites on both sides of the glycosidic linkage to be cleaved and these subsites are heavily involved in substrate specificity.[14]

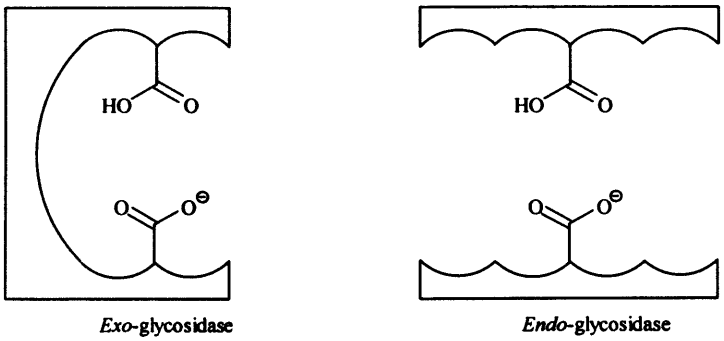
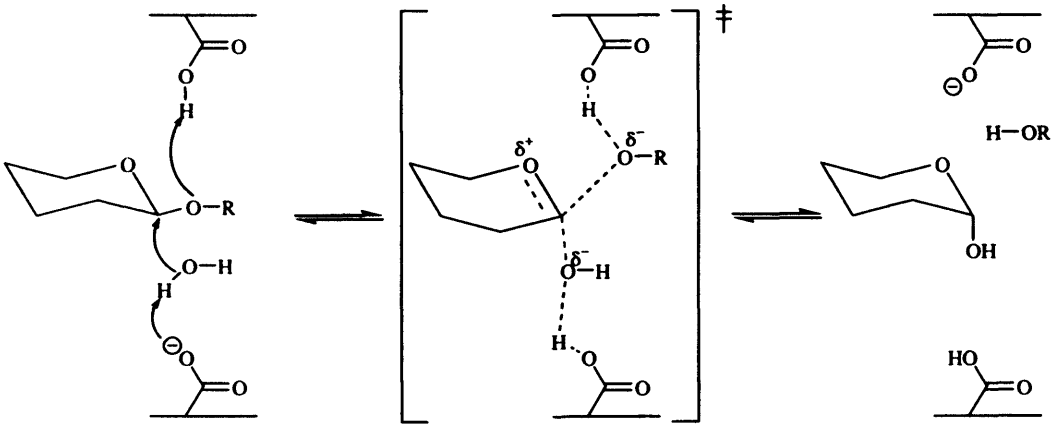


Figure 1

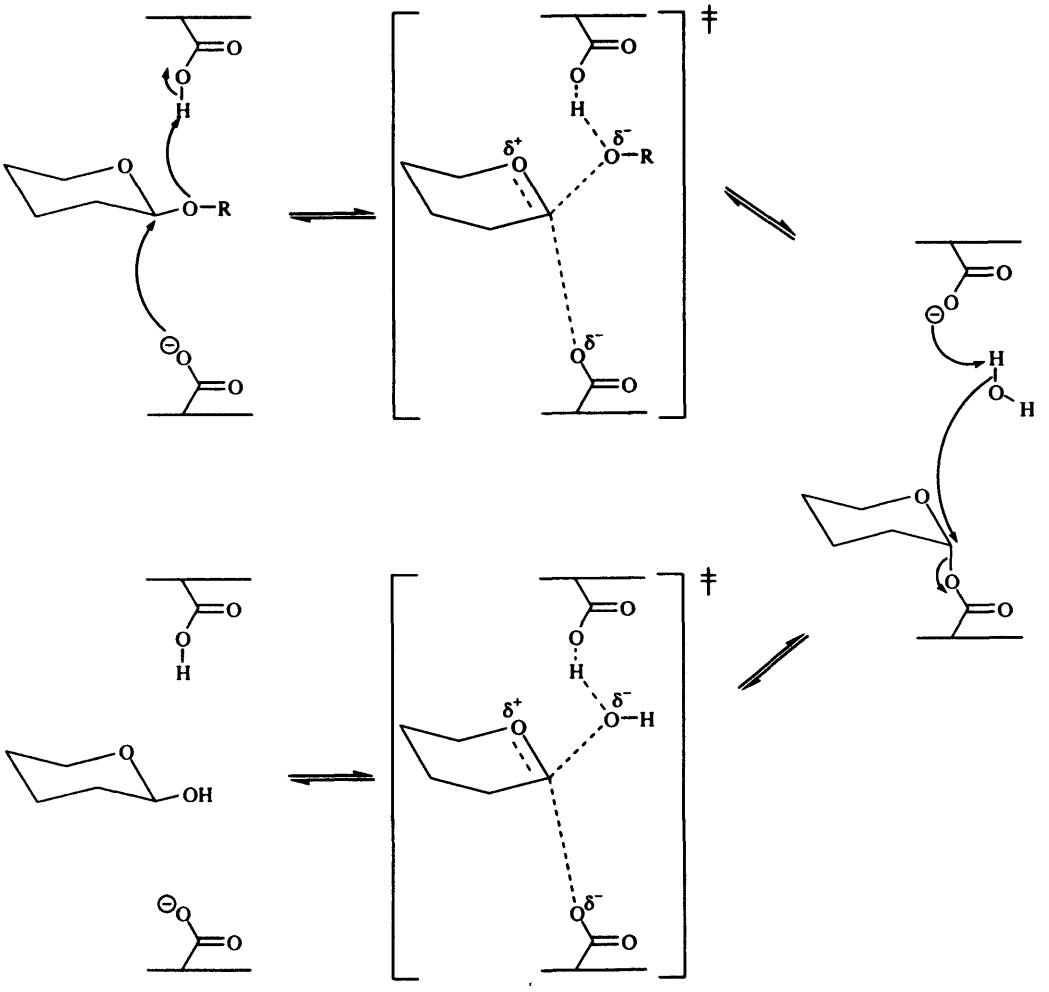
Enzyme-mediated hydrolysis of the glycosidic linkage can occur with two possible stereochemical outcomes:[15]

- inversion of configuration at the anomeric centre (Scheme 11);
- retention of configuration of the anomeric centre (Scheme 12);

the enzymes involved in each case are known as inverting and retaining glycosidases respectively.



Scheme 11



Scheme 12

Although the mechanisms of both types of enzymes share some similarities there are a few distinct differences in how the two diverse stereochemical outcomes are brought about. Thus, inverting enzymes employ both carboxylic acid and carboxylate groups to achieve general acid and base catalysis respectively in the direct attack of water at the anomeric centre. The two carboxyl groups are found 10.5 Å apart so as to allow both the substrate and a water molecule to bind in the active site. The overall reaction occurs *via* a single displacement resulting in inversion of stereochemistry.

By contrast the mechanism of retaining glycosidase enzymes, one of the carboxylate group acts as a nucleophile in a process whereby a glycosyl-enzyme intermediate is formed. Additionally the two carboxylate groups are positioned only 5.5 Å apart, and the mechanism involves a double displacement reaction whereby a covalent glycosyl-enzyme intermediate is formed and subsequently hydrolysed with general acid and base assistance (for the respective steps). Both steps occur with inversion of stereochemistry at the anomeric centre resulting in overall retention.

Whilst there are these important differences between the mechanisms of inverting and retaining glycosidases they do share some common features. Most notably with both types of enzyme the displacement of the aglycone group involves transition states, which have substantial oxocarbenium ion **20** character as shown (Figure 2).

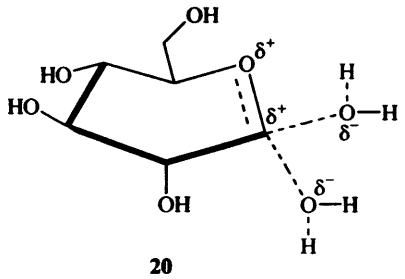


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Figure 2

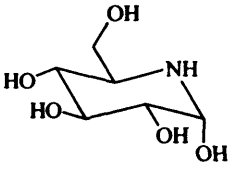
1.5 Inhibition of Glycosidase Enzymes

Carbohydrates play many important roles in the biology of animal and plant life and hence the control of carbohydrate biochemistry is an important target in both pharmaceutical and agrochemical research fields. Thus the search for inhibitors of enzymes that metabolise carbohydrates is an ongoing process. Carbohydrates themselves are rarely used as enzyme inhibitors for this purpose due to the possibility that they are themselves degraded rapidly and so research has focussed on other compounds that are similar to carbohydrates and are known

collectively as glycomimetics. Glycomimetics as a term describes the group of naturally occurring or artificially derived compounds that resemble sugars by shape, polarity and reactivity. Monosaccharide analogues include carbasugars,[16] thiosugars[17] and iminosugars. It is this last group that have perhaps been the most successful glycosidase inhibitors and which will be discussed here.

1.6 Iminosugars: Introduction

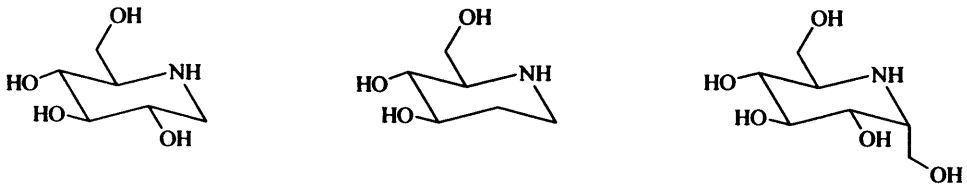
Sugar mimics in which the ring oxygen has been replaced with nitrogen are by far the most widely reported (family of) glycosidase inhibitors. The class of compounds as a whole are often referred to as iminosugars or azasugars. Iminosugars act as inhibitors of carbohydrate-processing enzymes and this behaviour has resulted in great chemical and biochemical interest these compounds. Thus, there has been increasing interest in simple hydroxylated derivatives of mono- and bicyclic nitrogen heterocycles for their potential usefulness as anti-viral,[18] anti-tumoural and anti-diabetic compounds.[19] The first naturally occurring iminosugar to be discovered was nojirimycin **21**[20] (which is the *N*-heterocyclic analogue of D-glucose) isolated from *S. roseochromogenes* R-468 and *S. lavendulae* SF-425.[21, 22]



21

Figure 3

Nojirimycin was found to have antimicrobial activity and was also shown to be a potent inhibitor of α- and β-glucosidases.[23] After the discovery of this biologically active compound, chemists began to search for and isolate other polyhydroxylated piperidine alkaloids from plant sources. Examples of some of the other naturally occurring piperidine iminosugars that have been isolated include 1-deoxynojirimycin[24] (DNJ) **22,** isolated from the roots of Mulberry trees as well as being produced by strains of *Bacillus* and *Streptomyces*[25] and 1,2-dideoxynojirimycin **23** (more commonly called fagomine).[26] Particularly interesting was the isolation of α-homonojirimycin **34** from *O. diandra* as it showed that carbon substituents at C-1 on the piperidine ring were naturally occurring (Figure 4).



22 23 24

Figure 4

In addition to naturally occurring piperidines a whole family of polyhydroxylated pyrrolidine iminosugars are also known. One of the first isolated was 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine (DMDP) **25** which is related to the oxysugar α-D-arabinose **26** (Figure 5). Since this discovery many other pyrrolidine-based iminosugars have been isolated and these have been reviewed.[27]

25 26

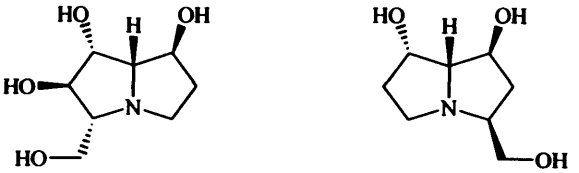
Figure 5

Bicyclic iminosugars in the form of indolizidines and pyrrolizidines ring systems are also known. The first of the indolizidines discovered was swainsonine **27**[28] which was followed by the isolation of castanospermine **28** (Figure 6).[29] Castanospermine **28** is sometimes referred to as the bicyclic derivative of deoxynojirimycin **22** due to the structural and stereochemical resemblance between the two.

27 28

Figure 6

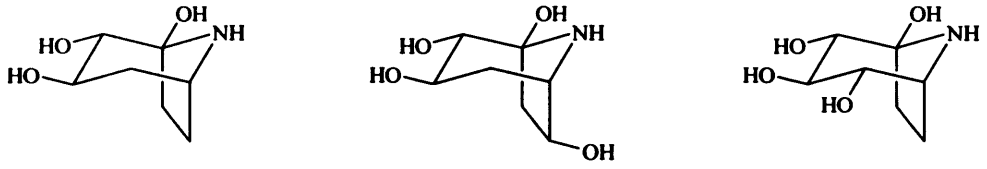
The first iminosugar to be isolated that contained the pyrrolizidine ring system was alexine[30] **29**, which was followed soon afterwards by the isolation of australine[31] **30**.



29 30

Figure 7

A recently recognised class of iminosugars, which have been discovered are compounds known as calystegines. These compounds consist of tri-, tetra- and pentahydroxy nortropane alkaloids and they all possess a novel aminoketal functionality, generating a tertiary hydroxyl group at the bicyclic ring bridgehead. The first calystegines to be extracted from natural sources were classified into two groups, calystegines A and B having 3 or 4 hydroxyl groups respectively. Each of calystegines A and B were resolved into their isomeric components using liquid chromatography to give calystegines A_1-A_4, B_1 and B_2. A few examples of these compounds are shown in figure 8.[32] A new class of calystegines having five hydroxyl groups have also been reported.[33,34]



Calystegine A_3 Calystegine B_1 Calystegine B_2

Figure 8

The majority of naturally occurring polyhydroxylated azasugars have been isolated from plants and there are only a few examples that have been isolated from bacteria. Additionally polyhydroxylated alkaloids (iminosugars) can be released by the producing plants into the soil and can be readily taken up and aggregated in plant tissues of neighbouring species. Thus there may be many more naturally occurring polyhydroxylated alkaloids still awaiting discovery.

1.7 Biological Activity of Iminosugars

Iminosugars have been found to inhibit glycosidases by binding specifically to the active sites of enzymes. As glycosidase enzymes are involved in a wide range of important biological processes their inhibition is of great importance. Thus, glycosidase enzymes digest dietary carbohydrates down to monosaccharides, which are then absorbed in the intestine. Inhibition

of these enzymes can therefore help regulate the breakdown, release and absorption of carbohydrates, which could potentially lead to benefits for people with diabetes. Thus, deoxynojirimycin **22** (Figure 4) was originally isolated from extracts of mulberry leaves due to the ability of these leaves to suppress the rise in blood glucose which follows eating.

Iminosugars have also been shown to have anti-viral activity particularly against the HIV virus, which is responsible for AIDS.[35] Many viruses that infect humans have an outer envelope of glycoproteins that are important factors in the stages of the life cycle of the viral agent. Compounds that can disrupt the outer glycoprotein envelope can be potentially used against viral infections. Sunkara and co-workers[36] tested the possible activity of iminosugars against the HIV virus using Moloney murine leukaemia virus as a model and found that whilst castanospermine **28** (Figure 6) and deoxynojirimycin **22** were active against this virus and that deoxymannojirimycin **78** and swainsonine **27** were inactive. Additionally *N*-alkylated derivatives of DNJ were found to be more potent than the natural product which in itself was shown to be cytotoxic.[37] A particular point to note is that *N*-butyl DNJ was developed as a drug candidate and was put through phase II clinical trials.[38]

There is growing evidence that oligosaccharides on the surface of tumour cells play an important role in the growth and spread of the tumour.[39] Glycoprotein processing glycosidases are involved in the change of normal cells to cancerous cells. The ability of compounds to inhibit the glycosylation of oligosaccharides can thus lead to the inhibition of tumour growth. There are a number of polyhydroxylated alkaloids that have been shown to possess anti-cancer activity however, research has mainly concentrated on the development of swainsonine **27** (Figure 6). This compound has been shown to inhibit tumour growth and stimulate the immune system response.[38]

The enzymatic activity of iminosugars has been attributed to their structural resemblance to 'natural' sugars. The specificity of inhibition was thought to be dependent on the position, number and stereochemistry of the hydroxyl groups on these molecules however, the chirality of the hydroxy groups on the iminosugar was not sufficient to predict the compounds ability to inhibit enzymes.[40] As was discussed in section 1.4, the transition state structure in the enzyme mediated hydrolysis of glycosides is believed to be an oxocarbenium ion intermediate (Figure 9). This means that compounds that mimic this structure would be expected to be strong inhibitors of glycosidases. Thus, the inhibitory potency of nojirimycin was first ascribed to its reversible conversion to the iminium ion **31** and the resemblance of this species to the transition state oxocarbenium ion **20**.

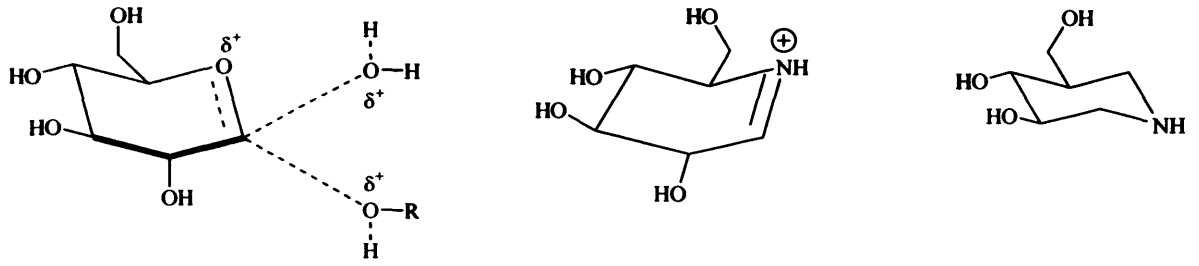


Figure 9

This is a very simplified explanation of how iminosugars interact and occupy the active site of glycosidase enzymes. For 2-deoxy analogues (*i.e.* most of the iminosugars) there are other factors that are important. Recent studies[41] have shown that the following features have great influence in determining the inhibitory potency of iminosugars.

i) Position of the basic centre – A general explanation as to why hydroxylated alkaloids are more potent inhibitors of glycosidases than natural sugars (*i.e.* hexoses) is due to the formation of an ion-pair between the protonated inhibitor and a carboxylate group in the enzyme active site. Thus, position of the basic centre is important for the inhibitory potency of iminosugars, as shown by Jesperson and co-workers[42] who synthesized the non-natural iminosugar isofagomine **32** and investigated its enzyme inhibition (Figure 9).

In comparison with deoxynojirimycin **22**, isofagomine **32** has the basic nitrogen atom at the pseudo anomeric position. Whilst deoxynojirimycin is an inhibitor of both α- and β-glucosidases[43] isofagomine shows strong inhibition only against β-glucosidases.[44] This difference in specificity is thought to arise from the differences in location of the carboxylic acid sites in these two classes of enzyme (Figure 10).

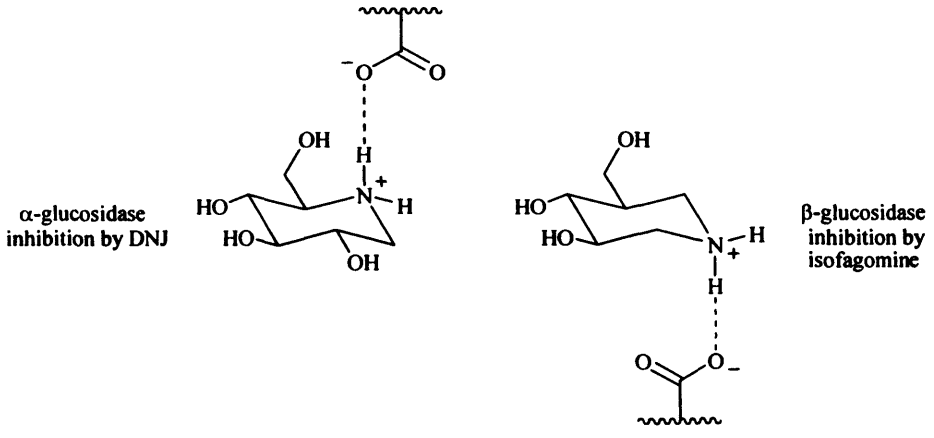
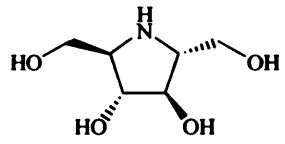


Figure 10

ii) Geometry and charge distribution at the anomeric position – The importance of charge distribution was emphasised by Leaback[45] who described the strong inhibition of β-glycosidases by lactones due to their resemblance to the oxocarbenium ion intermediate. It was shown by X-ray crystallographic analysis that the enzyme mechanism involved stabilisation of the oxocarbenium ion intermediate by a carboxylate group suitably placed in the active site (without the formation of a glycosyl ester). The interaction of this carboxylate group with the dipole of the lactone contributed to the strong inhibitory ability of this class of compounds.

iii) Ring size and hydroxylation pattern – Pyrrolidine iminosugars (*e.g.* **33**, Figure 11) are often more potent inhibitors[46] than the corresponding 6-membered iminosugars and Sinnott[47] postulated that this was due to the closer resemblance of these five-membered heterocycles to the enzyme transition state. Thus, pyrrolidine based inhibitors could adopt conformations resembling a twisted half-chair to reduce ring strain.



33

Figure 11

In contrast 7-membered iminosugars such as polyhydroxylated azepanes are more flexible in shape and can therefore adopt several conformations compared to the 5- and 6-membered heterocycles. In accordance with this azepanes can more readily adapt to the space filling and polar requirements of glycosidase enzyme active sites and in certain cases this leads to better inhibition of β-galactosidase than is found with the analogous piperidine compounds.[48]

Bicyclic iminosugars such as the indolizidines swainsonine **27** and castanospermine **28** (Figure 6); and pyrrolizidines like australine **30** (Figure 7) have restricted flexibility in comparison to monocyclic systems. Studies[49] have shown that in most cases the bicyclic compounds are more potent inhibitors than the corresponding monocyclic iminosugars suggesting that this restricted flexibility plays an important role. However, there are some reports of bicyclic iminosugars showing no inhibition of glycosidases at all, and the reason postulated is that the bicyclic analogues may be just too big to fit into the active site of certain enzymes.

iv) Hydrogen bonding – as mentioned earlier, the position of the basic centre is important in determining the inhibitory effects of an iminosugar due to ion-pair formation. In a similar way hydrogen bonding with the carboxylate group is also an important factor. In the example shown below (Figure 12) the hydrogen bond between the carboxylate group and the nitrogen of the 'azole' ring causes an increase in positive charge at the anomeric carbon centre, thus increasing the ion-ion interaction with the other carboxylate nucleophile.[14]

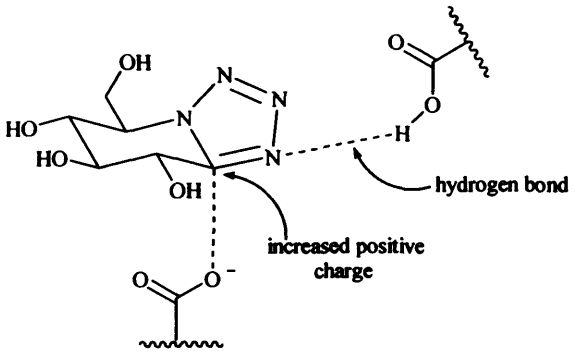
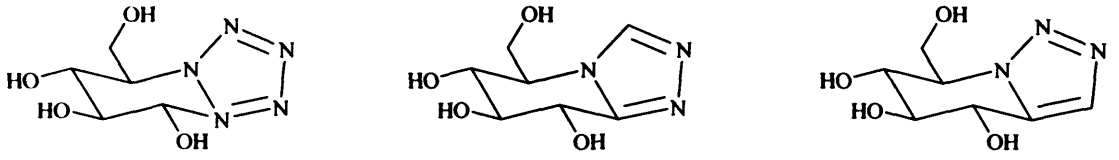


Figure 12

Another factor in this example was that the nitrogen of the azole ring needed to be adjacent to the anomeric centre for the inhibitory potency. Thus, nojintetrazol **34** and **35** had inhibitory effects against β-glucosidases, but the triazole **36** (Figure 13) was not an inhibitor of β-glucosidases.



34 **35** **36**

Figure 13

1.8 Previous Synthetic Strategies towards Iminosugars

The potential chemotherapeutic application of iminosugars has stimulated a great deal of interest towards the synthesis of this class of compounds. Existing synthetic strategies have been used to produce iminosugars of both natural and 'non-natural' origin. A great variety of synthetic approaches have been employed including both chemical and enzymatic methods. The existing procedures for iminosugar synthesis can be classified into different categories based upon the starting material utilised. Thus the synthetic approaches can be divided into:

- those employing carbohydrate starting materials, and
- those using non-carbohydrate starting materials (*i.e.* chiral pool reagents).

This area has been extensively reviewed[41] and only a few examples will be briefly discussed below.

1.9 Approaches Employing Carbohydrate-based Starting Materials

Iminosugars bear a striking resemblance to monosaccharides and due to this close structural relation natural sugars have often been suggested as starting materials for iminosugar synthesis. In fact Nature uses carbohydrate starting compounds in the biosynthesis of natural iminosugars, an example being the formation of mannojirimycin **41** from D-fructose **37** (Figure 14).[50]

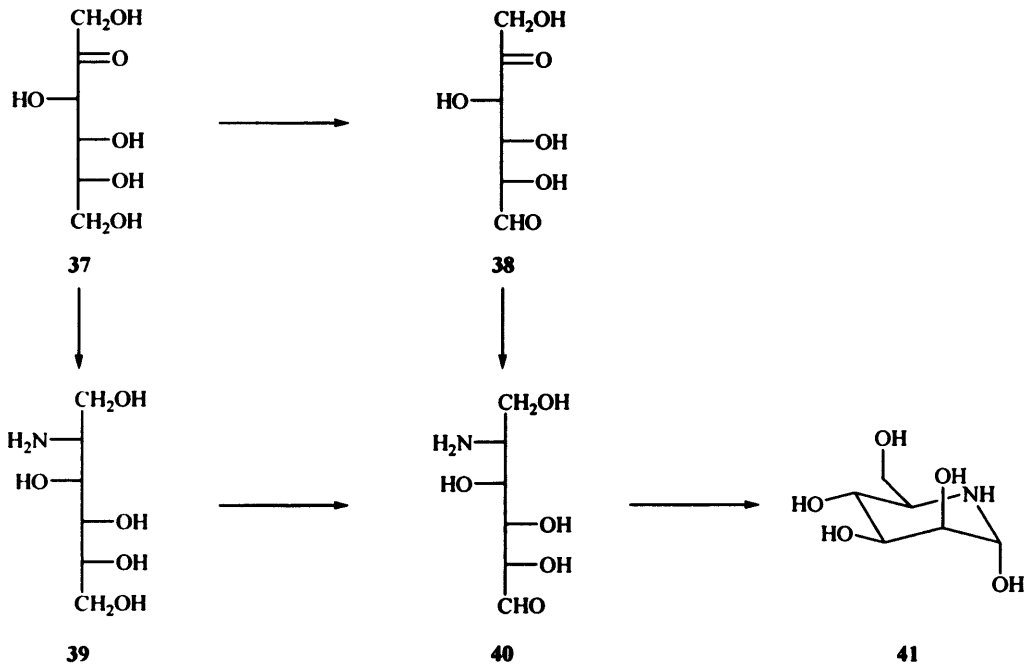
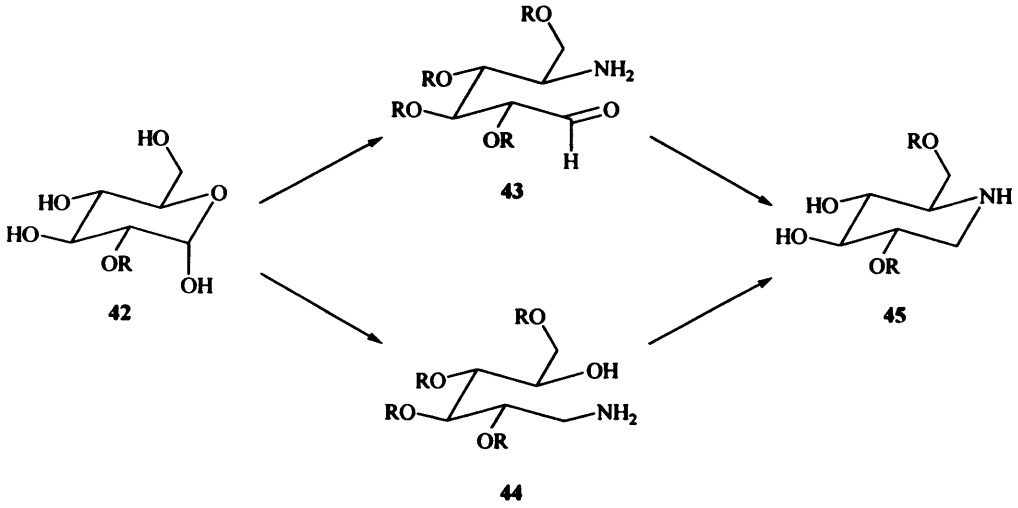


Figure 14

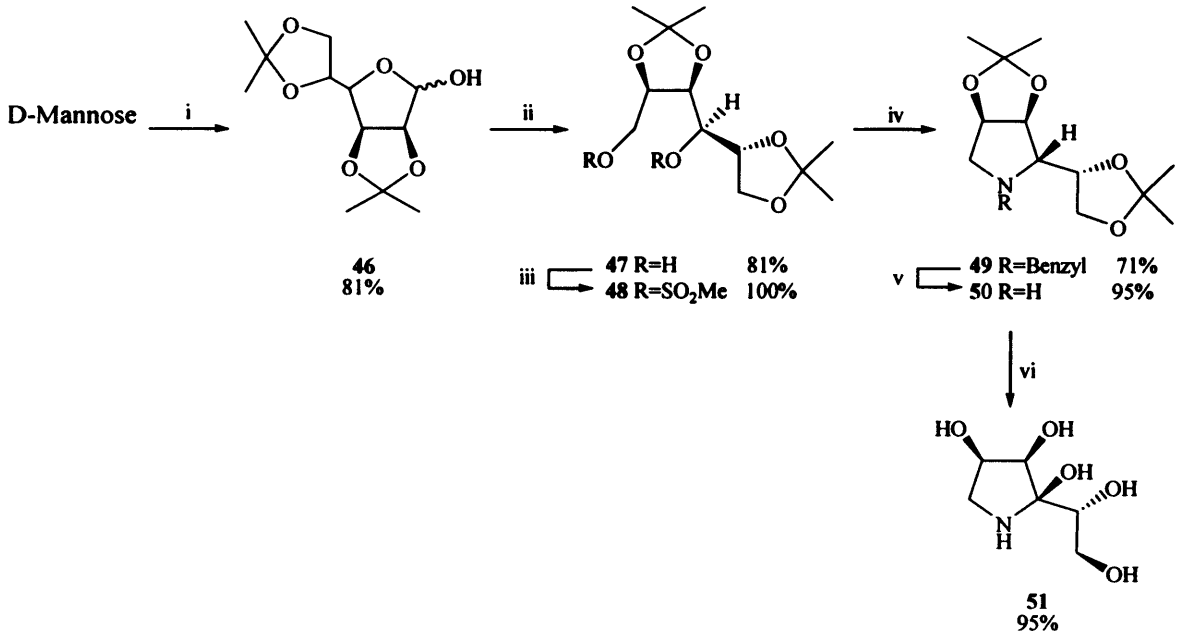
Studies have shown that **37** undergoes biosynthetic oxidation to the dialdehyde **38** followed by reductive amination of the keto group to give **40,** which is the open chain form of the hemiaminal, mannojirimycin. Alternatively reductive amination may occur before oxidation (*i.e.* **37** → **39** → **40**) as the specific timings of these events are uncertain.

The majority of conversions of true sugars into iminosugars tend to follow similar general strategies. These involve ring opening of the oxysugar and introduction of the amino functionality followed by a subsequent cyclisation to the target molecule. As shown below (Scheme 13) the amine functionality can either be introduced at the anomeric position (*i.e.* **42** → **44** → **45**) or at the C-5 (sugar numbering) carbon (*i.e.* **42** → **43** → **45**). Many examples exist of both these approaches and only a few will be discussed.



Scheme 13

Fleet *et. al.*[51] have reported the synthesis of 1,4-dideoxy-1,4-imino-D-talitol **51** from diacetone mannose **46** (Scheme 14). The pyrrolidine **51** is the open chain analogue of an epimer of swainsonine **27** (Figure 6).

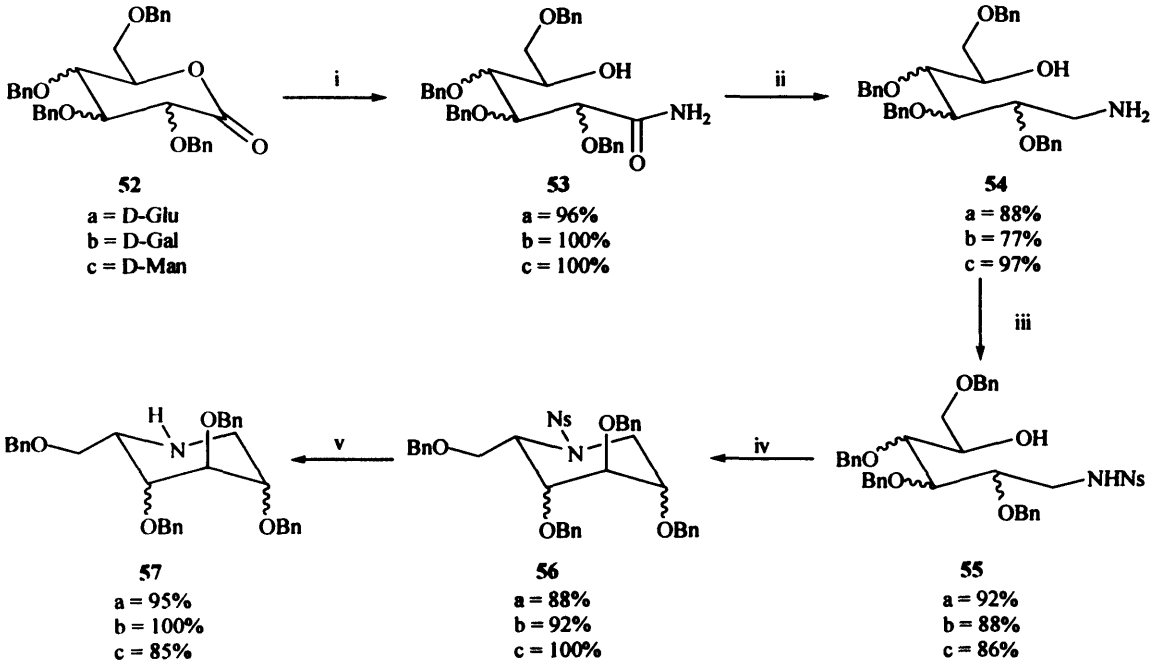


i. H_2SO_4, Acetone; ii. $NaBH_4$, EtOH; iii. MsCl, DMAP, Py, 0°C; iv. $BnNH_2$, reflux, 60 h; v. H_2, Pd/C, EtOH; vi TFA (aq).

Scheme 14

In this synthesis D-mannose was converted to the protected diacetal **46**, which was then reduced to give diol **47**. Reaction of **47** with methanesulfonyl chloride gave the dimesylate **48** and the amino functionality was then introduced by reaction with benzyl amine to give **49**. Finally acid-mediated deprotection of the benzyl and acetal groups gave the target iminosugar **51**.

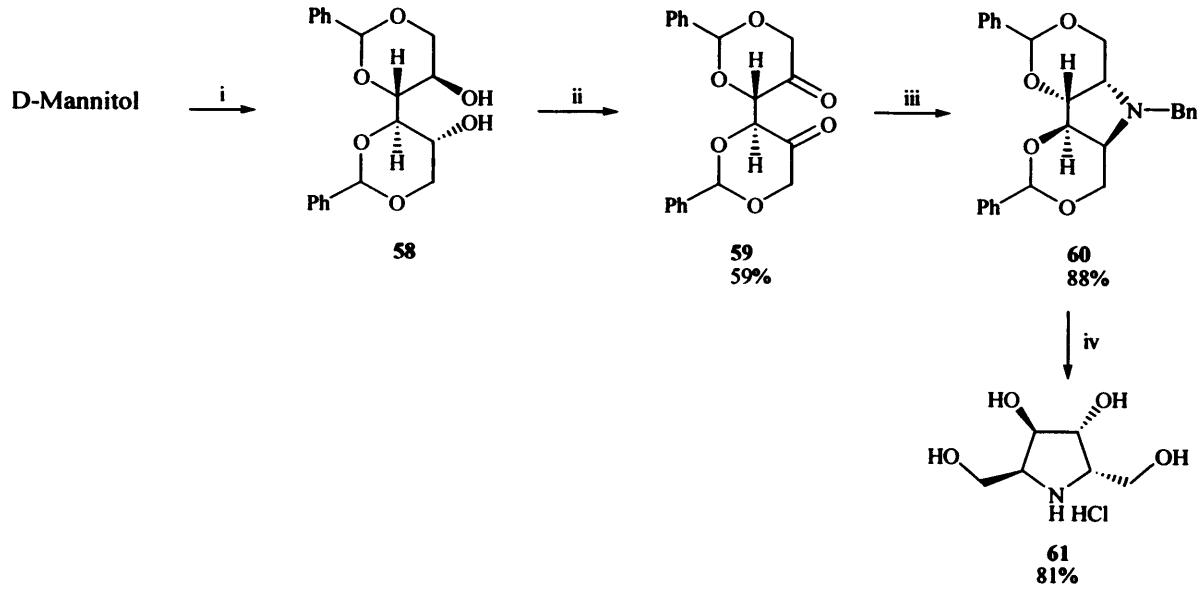
Sugar lactones have also been employed as starting materials for iminosugar synthesis usually *via* initial conversion to the corresponding amide. Sawada *et. al.*[52] reported the synthesis of 1-deoxy-iminosugars from D-glucono-1,5-lactones, derived from D-glucose, D-galactose and D-mannose (Scheme 15). The lactones **52** were converted to the corresponding amides **53** by treatment with ammonia. Reduction of the amides with $LiAlH_4$ gave amines **54**, which were then *N*-protected using NsCl to give **55**. Subsequent cyclisation using Mitsunobu conditions occurred with inversion of stereochemistry as expected and afforded the L-1-deoxy-iminosugars **56**. Finally the nosyl group was removed by using $PhSH/K_2CO_3$ to yield the iminosugar derivatives **57**.



i. NH_3, MeOH; ii. $LiAlH_4$, THF, reflux; iii. NsCl, NEt_3, DCM; iv. PPh_3, DEAD, THF; v. PhSH, K_2CO_3, DMF.

Scheme 15

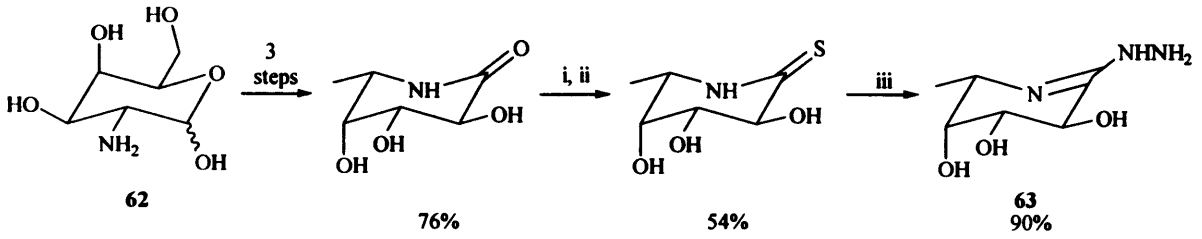
Alditols have also been employed in the synthesis of iminosugars as shown in scheme 16.[53] Thus, D-mannitol is converted to the di-benzylidene derivative **58** followed by oxidation of the free hydroxyl groups with PCC to give the diketone **59** (usually isolated as a cyclic hydrate). Reductive amination of **59** with benzyl amine and sodium cyanoborohydride gave **60**, which after hydrogenolysis gave the iminosugar **61**.



i. PhCHO, DMF, H_2SO_4, RT; ii. PCC, NaOAc, CH_3CN/DCM (3/1), 4Å molecular sieves, reflux; iii. a. $BnNH_2$, oxolane/MeOH (1/1), 4Å molecular sieves, b. $NaBH_3CN$, AcOH; iv. H_2 (50psi), Pd/C, MeOH, HCl (aq).

Scheme 16

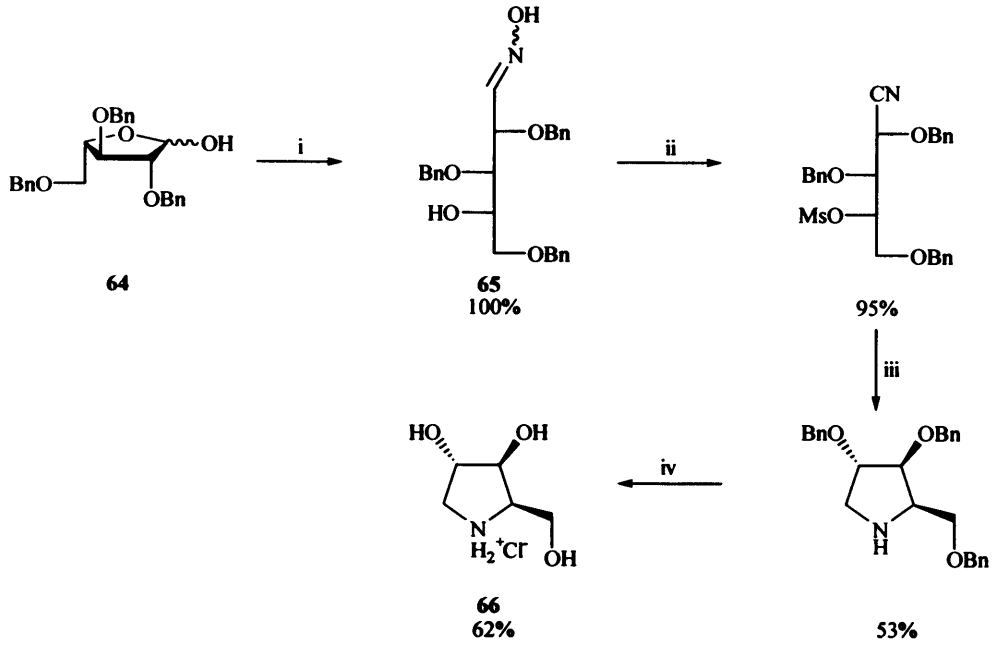
Using aminosugars as starting materials for the synthesis of iminosugars removes the steps necessary for the introduction of the nitrogen functionality. This strategy is of convenience when the structure of the target molecule is related to that of a commercially available aminosugar. For example D-galactosamine **62** has been converted to the iminosugar analogue **63** of L-fucose, as shown (Scheme 17).[54]



i. TMSCl, $(TMS)_2NH$, Py; ii. Lawesson's reagent, benzene, reflux then MeOH/HCl; iii. NH_2NH_2/MeOH, 0°C.

Scheme 17

Amination of the anomeric centre of a sugar can also be used to introduce the nitrogen functionality. An example is given in scheme 18[55] where 2,3,5-tri-*O*-benzyl-L-arabinose **64** is reacted with hydroxylamine to give **65** that is subsequently converted to the pyrrolidine **66** as shown.

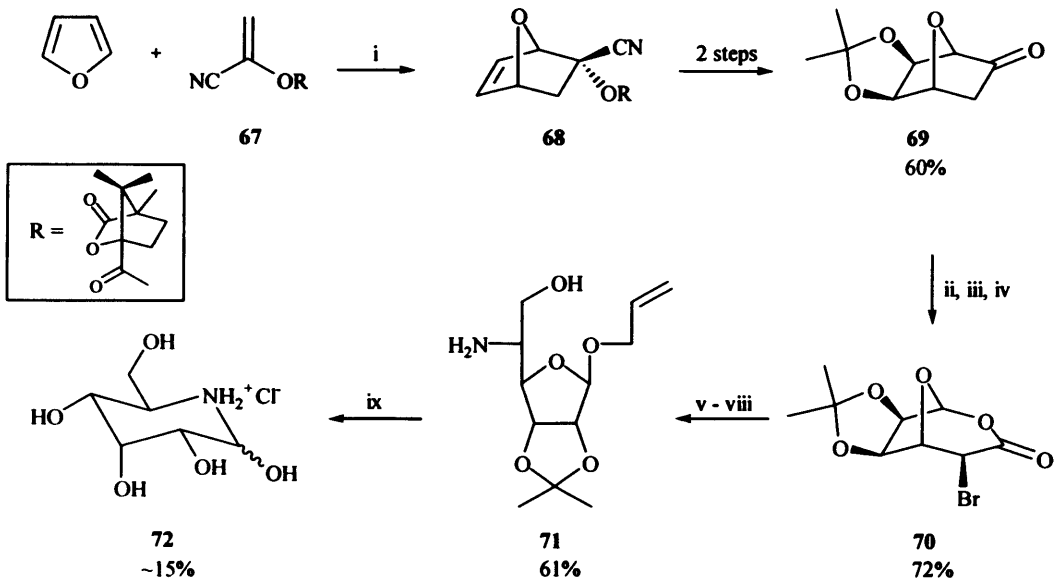


i. $NH_2OH.HCl$, NaOMe, MeOH; ii. MsCl, Py; iii. $NaBH_4$, $CoCl_2.6H_2O$, MeOH; iv H_2, Pd/C, EtOH, HCl (aq).

Scheme 18

1.10 Iminosugars from Non-Carbohydrate Starting Materials

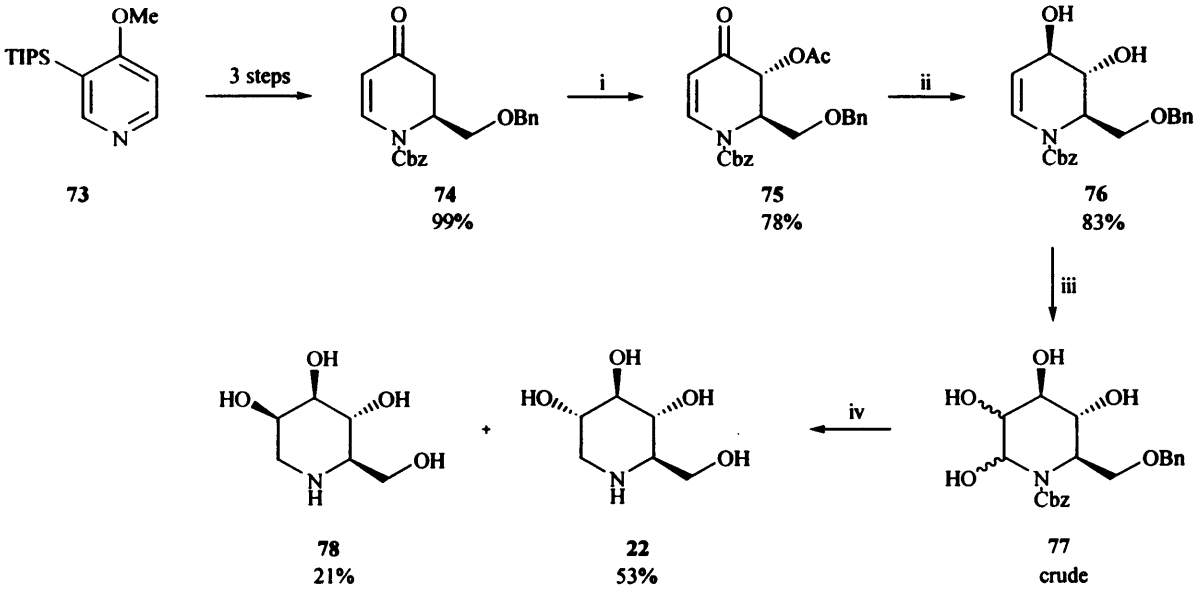
The synthesis of iminosugars from oxy sugars is perhaps the most 'obvious' route to these species. However, it is not always the most efficient method. Many synthetic strategies have been employed where the polyhydroxylated chiral skeleton of the target molecule has been built up from non-carbohydrate starting materials by either chemical or enzymatic processes. The strategies have been reviewed[56] and only a few illustrative examples will be discussed here. Chemical methods for iminosugar synthesis are mainly based upon stereoselective condensation reactions and in a few cases cycloaddition reactions where the final product of this reaction is manipulated to yield the target iminosugar. For example Diels-Alder reactions using furan as a diene have been employed to produce different iminosugars (Scheme 19).[57] Thus reaction of furan with the 1-cyanovinyl ester of (1*S*)-camphanic acid **67** gave the adduct **68** which was then transformed to the ketone **69**. Subsequent bromination of **69** followed by Bayer-Villiger reactions then gave the bromolactone **70**. A series of steps involving introduction of the nitrogen by displacement of the bromide by azide then gave the amine **71**, which was converted to **72** on treatment with acid.



(i) ZnI_2; (ii) *N*-^{t}BDMS-*N*-Me-trifluoroacetamide; (iii) Br_2; (iv) CF_3CO_2OH, Na_2HPO_4; (v) $CH_2{=}CHCH_2OH$, CH_3SO_3H; (vi) EtOH/H_2O (9:1), $[Rh(PPh_3)_3Cl]$, DABCO; (vii) CsN_3 then $PhCH_2Br$; (viii) $LiAlH_4$; (ix) HCl.

Scheme 19

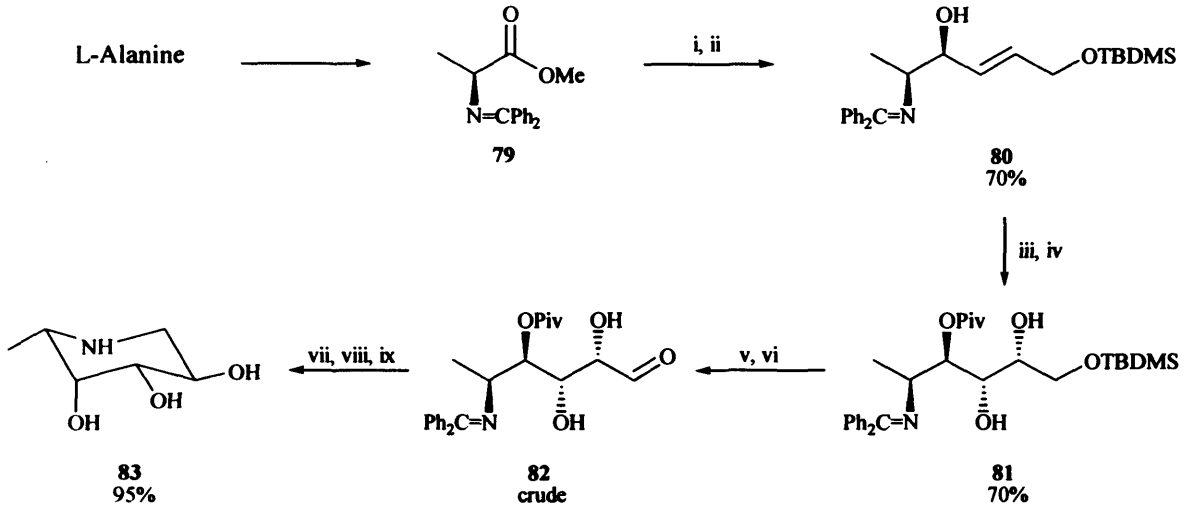
Comins and Fulp[58] have used substituted pyridines as the starting point for the asymmetric synthesis of 1-deoxynojirimycin as shown (Scheme 20). Thus the pyridine **73** was converted in three steps to the enone **74**, which was subsequently hydroxylated at the α-position to give **75**. Diastereoselective reduction of the keto group next gave **76**, which was converted to a crude mixture of aminals **77** upon *cis*-dihydroxylation. Finally reduction of **77** gave both 1-deoxynojirimycin **22** and 1-deoxymannojirimycin **78**.

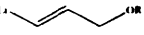


i. $Pb(OAc)_4$, toluene, reflux; ii. HCl (aq)/EtOH then $Me_4NBH(OAc)_3$, acetone/AcOH; iii. OsO_4, NMO; iv. H_2, $Pd(OH)_2$, HCl (aq).

Scheme 20

Iminosugars can also be synthesised using stereoselective chemical condensation reactions. Here the skeleton of the iminosugar is built up by stereoselective reactions, which lengthen the enantiomerically pure starting materials. A common choice for the starting material in this type of synthesis are amino acids, an example being the use of L-alanine to prepare the piperidine **83** as shown (Scheme 21).[59]

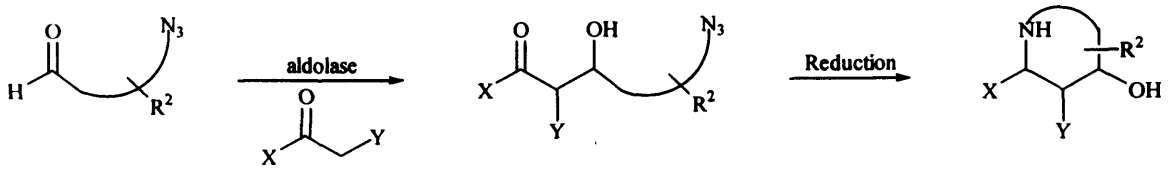


i. DIBAL; ii.  ; iii. PivCl; iv. Sharpless osmylation; v. Bu_4NF; vi. NaOCl, TEMPO; vii. $NaBH_3CN$; viii. Bu_4NOH; ix. H_2, Pd/C, HCl (aq).

Scheme 21

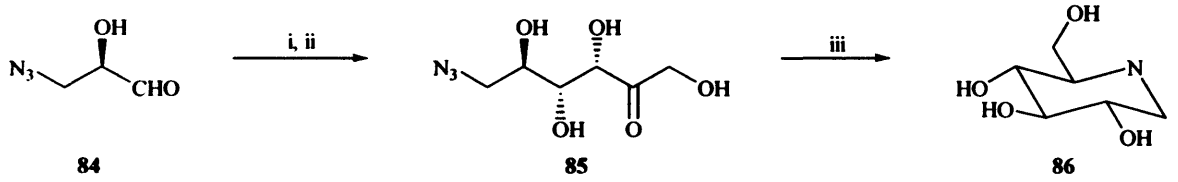
Thus, L-alanine methyl ester benzophenone imine **79** was converted to the corresponding aldehyde followed by diastereoselective nucleophilic addition to give alcohol **80**, which was protected as its pivaloyl ester. Sharpless asymmetric hydroxylation next gave the tetrol **81**, which was deprotected and oxidised to furnish the aldehyde **82**. Reduction of the benzophenone imine in **82** lead to spontaneous cyclisation and finally ester and benzyl deprotection gave the target molecule **83**.

The polyhydroxylated skeleton of iminosugars has in many cases been built up by exploiting the ability of aldolases enzymes to condense dihydroxyacetone phosphate (DHAP) with a variety of aldehydes. The general strategy is to initially form an open chain azido sugar analogue, which is then reduced (usually hydrogenation) to the amine, which undergoes a spontaneous cyclisation *via* reductive amination (Scheme 22).



Scheme 22

One such aldolase used is fructose-1,6-diphosphate aldolases (FDP-aldolase) – an inexpensive readily available enzyme. The reaction of DHAP with a suitably modified aldehyde **84** in the presence of FDP-aldolase resulted in the stereoselective generation of two new stereocentres **85** as shown (Scheme 23). Reduction of the product **85** then efficiently gave 1-deoxynojirimycin **22**.[60]

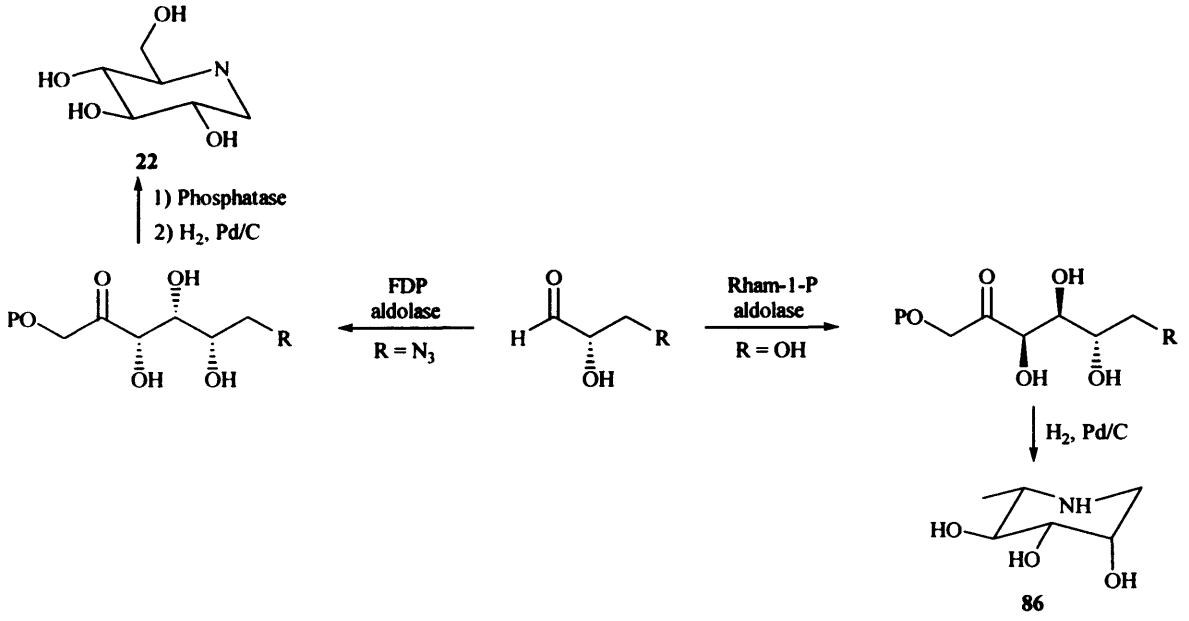


84 **85** **86**

i. DHAP, FDP aldolases; ii. Acid phosphatase; iii. H_2, Pd/C.

Scheme 23

The use of different aldolases, such as L-fuculose 1-phosphate (FDP) aldolases and L-rhamnulose 1-phosphate (Rham-1-P) aldolase allows for the generation of other possible stereoisomers and these enzymes have been used in the synthesis of different iminosugars as shown below for the divergent synthesis of 1-deoxynojirimycin **22** and 1,6-dideoxymannojirimycin **86** (Scheme 24).[43]



Scheme 24

1.11 Potential Disadvantages of Previous Synthetic Strategies

A number of the more important synthetic strategies towards iminosugars have been described above. However, the need to develop new routes to these molecules is still relevant as some of the previous methods can suffer from potential limitations. For example the use of synthetic routes based on carbohydrate (or carbohydrate derived) starting materials may limit the number of structural and/or stereochemical analogues of a particular iminosugar that can be produced by a given synthetic route. Additionally these carbohydrate-based syntheses can suffer from lengthy and involved synthetic routes and in the main include multiple protection/deprotection steps.

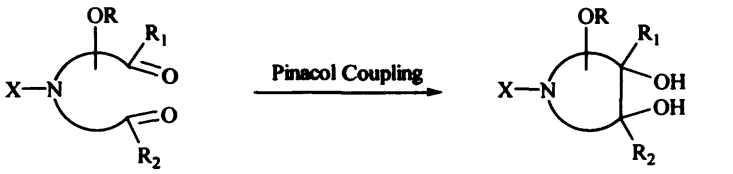
Similarly the enzyme-based synthetic routes can be limited by enzyme availability and/or substrate tolerance, the latter especially important for access to structural analogues. Additionally the inherent stereoselectivity associated with the enzyme reaction may in fact be a potential disadvantage in the synthesis of stereochemical isomers of a given iminosugar. Finally several groups of enzymes require co-factors, these co-factors can be too expensive to use stoichiometrically, thus possibly limiting the use of enzymes in synthesis.

Thus, although numerous methods have been developed for the synthesis of iminosugars the development of new routes to these potentially biologically significant molecules is still relevant. A synthetic route that will allow for the production of various stereoisomers and/or structural analogues is highly desirable. This is because the biological properties of iminosugars are often influenced by their overall structure and/or stereochemistry. Thus, 1-deoxynojirimycin **22** has anti-viral properties[61] the stereoisomeric 1-deoxymannojirimycin **78** blocks human B-cell development.[62]

2. Chapter 2: The Pinacol Coupling

2.1 Research Aims

The general aims of this research project were the exploration of a new synthetic route for the formation of *N*-heterocyclic diols and polyols in general and more specifically iminosugars. In developing such a route we wished to address some of the limitations of current synthetic strategies towards these compounds that have been outlined in chapter 1 section 1.11. The key reaction of our proposed new synthetic procedure is an intramolecular pinacol coupling of a suitable dicarbonyl precursor as shown (Figure 15).



R, R^1, R^2 = alkyl, aryl *etc*
X = N-protecting group

Figure 15

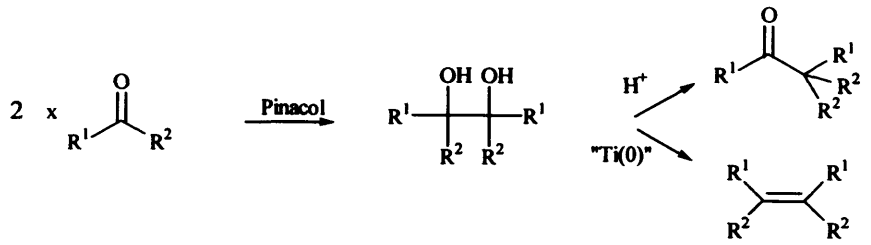
During this project we hoped to develop a highly specific, flexible and divergent synthetic route, which could allow access to different stereoisomers of a given iminosugar together with a variety of structural analogues. The pinacol coupling reaction in this route will dictate the ring size of the heterocycle together with the stereochemistry of the newly formed diol functionality. Consequently this chapter will discuss the background to this key reaction.

2.2 The Pinacol Coupling Reaction

The pinacol coupling reaction was first described over 140 years ago in a report into the formation of 1,2-diols (commonly called pinacols).[63] The reaction involves the reductive coupling of carbonyl compounds to give vicinal diols (or after *in situ* deoxygenation, alkenes) and is an important method for C-C bond formation.[64]

2.3 Introduction

The pinacol reaction usually requires the use of 1-electron reducing agents and transition and lanthanide metal-based reagents have found most application. The reaction has been comprehensively reviewed[65] and the discussion that follows will mainly deal with aspects having some relevance to this project.

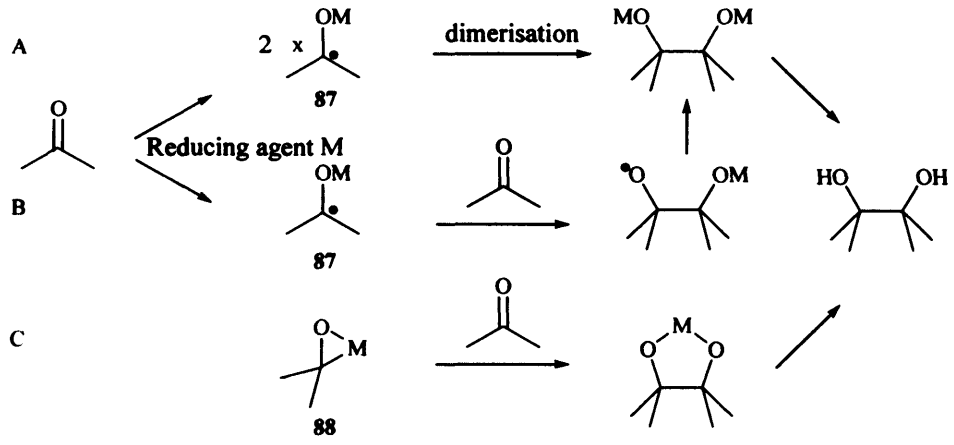


Scheme 25

The product 1,2-diols are versatile synthetic intermediates in their own right but can also be converted to ketones (*via* a pinacol rearrangement) or to alkenes (*via* deoxygenation, usually under McMurry conditions). The synthetic utility of the pinacol reaction has been employed in the synthesis of the natural products taxol© [66] and grayanotoxin IV,[67] amongst others.

2.4 Reaction Mechanism and Stereochemistry

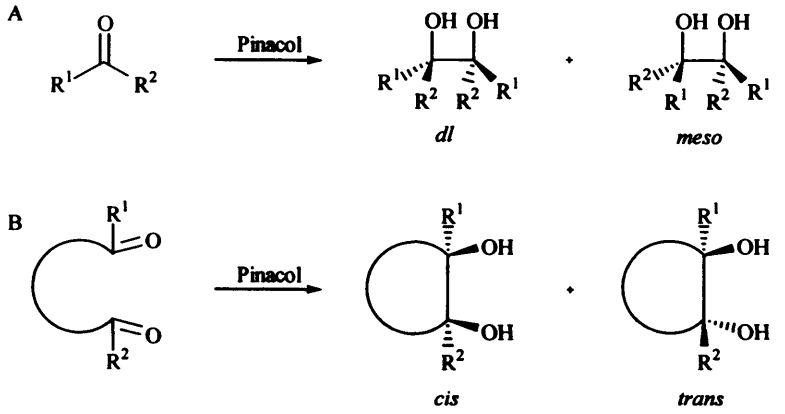
There are at least three possible mechanisms for the pinacol coupling (shown for an intermolecular reaction in Scheme 26).



Scheme 26

In mechanisms A and B the first step is the formation of a ketyl radical **87** from the carbonyl compound by single electron transfer (SET) from a reducing agent, usually a low valent metal. The ketyl radical **87** can either dimerise (mechanism A) or add to a second carbonyl group (mechanism B). An alternative mechanism C follows the insertion of the metal into the carbonyl group to form a metal-carbon bonded intermediate **88**, which reacts subsequently with another carbonyl moiety. Although some initial mechanistic studies of the pinacol-related reactions of carbonyl-hydrazones have been reported[68] there are no literature reports that define which mechanism is operating. It may be that different mechanisms are involved with different starting materials. The pinacol coupling reaction generally leads to the formation of two new stereocentres, the intermolecular homocoupling reaction can lead to the

formation of either *dl* or *meso* products (Scheme 27; A). In a similar manner the intramolecular reaction can generate *cis*- or *trans*-diols as shown (Scheme 27; B).



Scheme 27

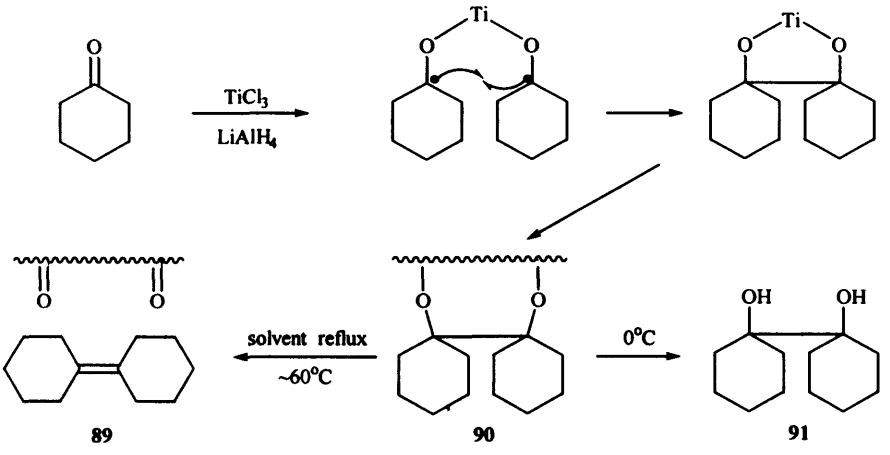
The stereochemical outcome of the reaction will depend upon the reducing reagent used and the structure of the starting carbonyl compound and these factors are discussed below.

2.5 Reducing Reagents Employed

There are a number of reducing reagents that have been used successfully in pinacol coupling reactions; these include Group 1 metals, transition metals, lanthanides and organometallic compound(s). In general these reagents will mediate both inter- and intramolecular pinacol coupling reactions although with varying levels of efficiency, stereoselectivity and functional group tolerance.

2.6 Titanium-mediated Pinacol Reactions

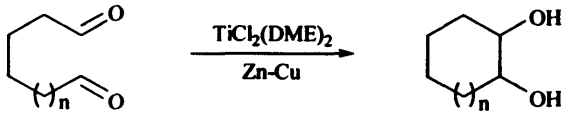
Titanium-mediated carbonyl coupling reactions were introduced with the discovery by McMurry[69] that ketones and aldehydes can be reductively dimerised to yield olefins in the presence of low-valent titanium reagents (Scheme 28).



Scheme 28

The titanium reagent for this reaction was produced from the reduction of $TiCl_3$ with $LiAlH_4$. The formation of the alkene **89** presumably occurs *via* the intermediate product **90** and the reaction can be stopped prior to deoxygenation of **90** by lowering the temperature to 0°C leading to the isolation of the diol product **91** (as shown). The low valent titanium species required for this reaction can also be produced from titanium (II) chloride and zinc. For intermolecular reactions the diastereoselectivity of the product diols is usually modest.

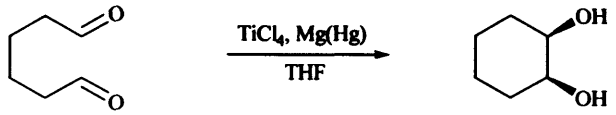
The McMurry reaction has also been applied to intramolecular pinacol reactions of dicarbonyl compounds to produce carbocyclic diols in high yields (Scheme 29).[65]



n	*cis* : *trans*	yield (%)
1	100 : 0	85
2	70 : 30	80
4	25 : 75	80

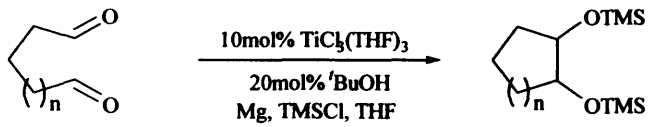
Scheme 29

As can be seen small, medium and large rings could be generated although the latter two require high dilution conditions to avoid competing intermolecular reactions. Additionally the formation of rings with less than 10 carbons occurred with *cis*-selectivity for the product diol whereas larger rings gave *trans*-selective reactions. Similar results have been reported using Corey's reagent, $TiCl_4$ and Mg(Hg) in THF (Scheme 30)[70] and using catalytic $TiCl_3(THF)_3$ in the presence of magnesium as co-reductant as reported by Lipski *et. al.* (Scheme 31).[71]



cis : *trans*	yield (%)
100 : 0	32

Scheme 30

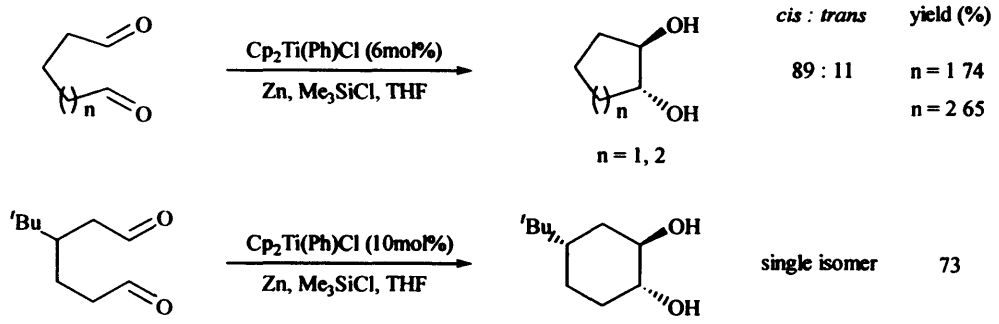


n	*cis* : *trans*	yield (%)
1	89 : 11	74
2	52 : 48	73

Scheme 31

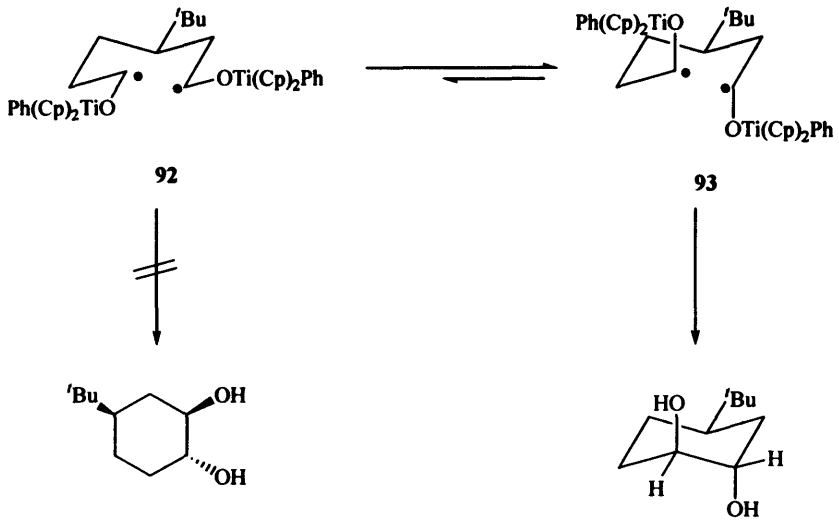
Thus the majority of titanium-induced intramolecular pinacol reactions give small to medium ring diols with *cis*-selectivity. However, recently Yamamoto and co-workers[72] have reported the use of Cp_2TiPh as a reducing reagent for effective intermolecular pinacol coupling of aromatic and aliphatic aldehydes. The authors developed a system using $Cp_2Ti(Ph)Cl$ (catalytic) in the presence of trimethylsilylchloride and zinc, which carried out intramolecular

pinacol reactions of dials to give carbocyclic 1,2-diols in good yields and with excellent *trans*-selectivity (Scheme 32).



Scheme 32

This high *trans*-selectivity makes this method highly important. The mechanism shown below (Scheme 33) is that proposed by the authors, and the selectivity is thought to arise due to the fact that the bulky Ti (IV) (surrounded by two cyclopentadienyl and one phenyl ligand) cannot co-ordinate to the other carbonyl terminus (**92**) and thus cyclisation must occur *via* the conformation **93** (Scheme 33) in which the two bulky $Cp_2(Ph)TiO$ moieties occupy axial positions in order to reduce steric interactions between each other. However no conclusive experiments to confirm the intermediary of the diradical **93** have been reported.



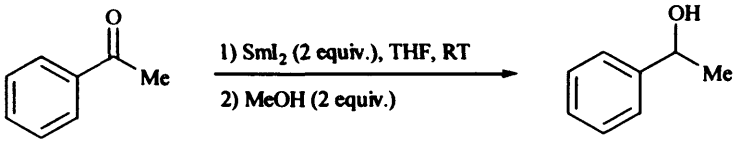
Scheme 33

It should be noted that the more commonly used Ti (III) reagent, Cp_2TiCl will not carry out the same reaction. Presumably the Ti (III)-Ph σ-bond is necessary for the titanium centre to have the correct reduction potential to form the ketyl radical (or diradical).

2.7 Samarium-mediated Pinacol Reactions

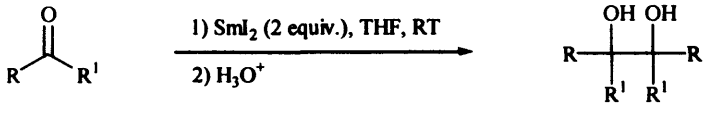
One of the most widely used low-valent metal species employed as a single electron transfer, (SET), agent in pinacol reactions is the lanthanide (II) salt samarium diiodide (SmI_2). Kagan and colleagues first introduced this reagent over 20 years ago[73] and it has rapidly gained importance and is now used in a variety of synthetic processes. These include radical cyclisations, Barbier- and Grignard-type reactions, ketyl-olefin coupling reactions, pinacol coupling reactions, aldol reactions and many more, and the area has been reviewed.[74] In the majority of these reactions SmI_2 exhibits remarkable chemoselectivity and efficiency. The reagent can promote both one- and two-electron processes and significantly its oxidation potential can be tailored to the needs of a particular reaction by changes in reaction conditions and/or the use of catalysts or additives (*e.g.* HMPA).[75] In addition the reagent is commercially available and can also be readily prepared by reacting samarium metal and either 1,2-diiodoethane,[73] 1,2-diiodomethane[76] or iodine.[74]

Kagan and co-workers were the first to fully show the general ability of SmI_2 to chemoselectively reduce a large variety of functional groups mainly through SET processes.[73] Thus, the reduction of aldehydes and ketones to the corresponding alcohols could be achieved using SmI_2 in THF in the presence of a small amount of methanol (Scheme 34).



Scheme 34

Additionally the reduction was shown to be faster for aldehydes than for ketones and no evidence for any competing pinacol reactions was presented. In comparison treatment of aromatic and aliphatic aldehydes and ketones with SmI_2 (equimolar) at room temperature in THF in the absence of a proton source (no water or alcohol) lead to the formation of the pinacol products (Scheme 35).[77]

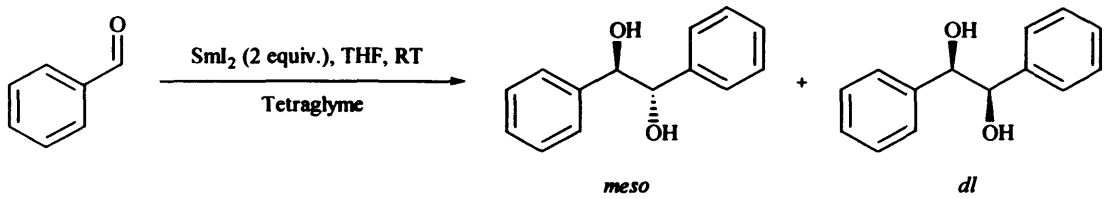


R, R^1 = H, alkyl, aryl

66-95%

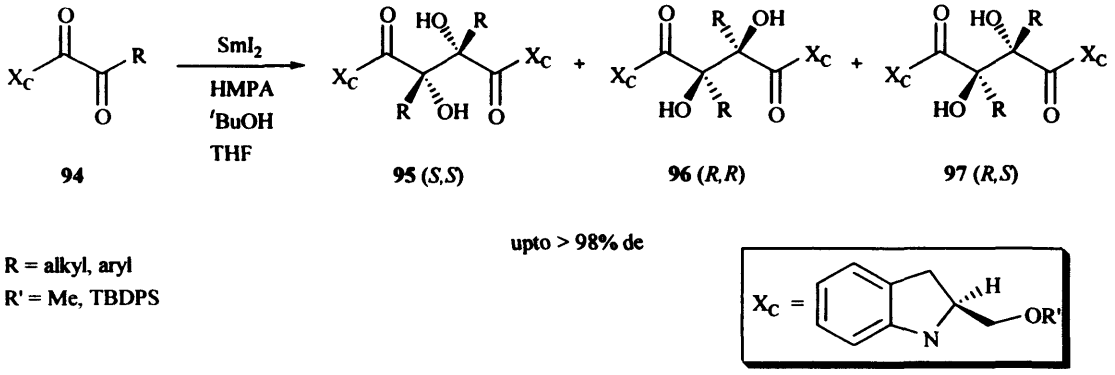
Scheme 35

In general aromatic aldehydes and ketones were coupled in < 1 min, aliphatic aldehydes in a few hours and aliphatic ketones proved to be the least reactive requiring around 1 day for reaction. The stereoselectivity of the reaction was only examined for benzaldehyde, which produced a mixture of isomers in the ratio *dl* : *meso* = 56 : 44 with a total yield of 95 %. Following on from these initial observations by Kagan, SmI_2 has been applied in a variety of intermolecular pinacol reactions. Thus ligand effects in the diastereoselectivity of the reaction have been examined and formation of the *dl* isomer from the homocoupling of benzaldehyde has been shown to be disfavoured by the addition of tetraglyme (Scheme 36).[78]



Scheme 36

The stereoselective intermolecular reaction of chiral α-ketoamides **94** has also been exploited to produce quaternary tartaric acid derivatives **95** - **97** as shown (Scheme 37).

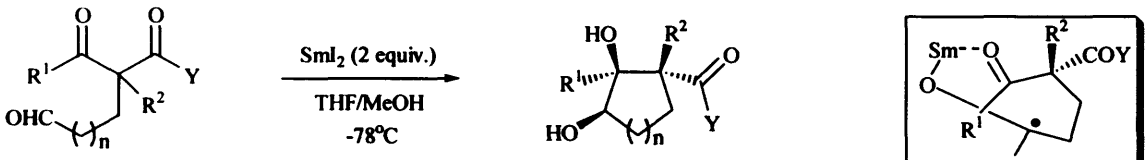


Scheme 37

It was found that the pinacol coupling of **94** using SmI_2, HMPA and ^tBuOH in THF gave pinacol **95** in extremely high diastereoselectivity (> 98 % de). However, if no HMPA and ^tBuOH is used then the reaction was less stereoselective. This was said to be because HMPA[75] is known to increase the rate of reaction and stereoselectivity of SmI_2-mediated pinacol coupling reactions and ^tBuOH is a well-used proton source. Additionally it should be noted that trimethylsilyl chloride has been found to accelerate the SmI_2-mediated pinacol coupling of carbonyl compounds.[79]

In a further advance the intermolecular pinacol reaction has been carried out using catalytic quantities of SmI_2 together with magnesium as a co-reductant.[80] In this report a preliminary investigation into a catalytic cycle of SmI_2 for the reduction of carbonyl compounds is established. Magnesium is used as a co-reductant because of the similar reduction potential between samarium and magnesium (-2.41 V and –2.37 V respectively).

In contrast to the low levels of stereocontrol often seen in the SmI_2-mediated intermolecular pinacol reactions considerable stereochemical control can be achieved in intramolecular cases. The first report of such a reaction was by Molander and Kenny who explored the synthesis of five and six membered carbocycles as shown (Scheme 38).[81]



Scheme 38

The authors showed that the reaction was highly diastereoselective with preferential formation of the *cis*-diol that had an *anti*-orientation to the adjacent carbonyl functionality. To explain this *cis*-diol selectivity the authors proposed the existence of a chelated ketyl intermediate **98** as shown.

Subsequently Chiara and co-workers[82] also reported the stereocontrolled formation of carbocyclic *cis*-diols *via* a samarium diiodide pinacol coupling reaction. These authors showed that a variety of five and six membered carbocycles could be formed by this synthetic strategy, again with selectivity for the *cis*-diol (explained once more by the existence of chelated ketyl intermediates such as **99**, Figure 16).

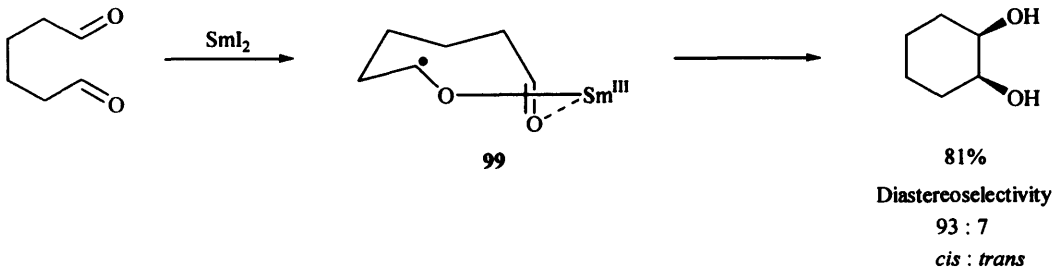
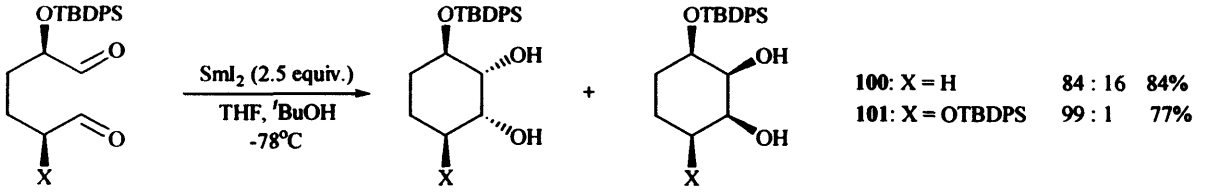


Figure 16

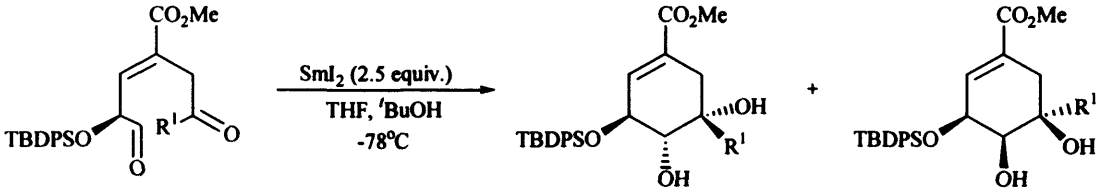
2.8 The Directing Effects of α-Substituents in Pinacol Reactions

Chiara and colleagues investigated the effect of α-substituents on the stereochemical outcome of the SmI_2-mediated pinacol coupling reaction.[82] When hydroxy- or alkoxy-substituents were present on the carbon atoms adjacent to the reacting carbonyl group, the *cis*-diol was produced with an *anti*-orientation to the substituent group(s) (*e.g.* Scheme 39).



Scheme 39

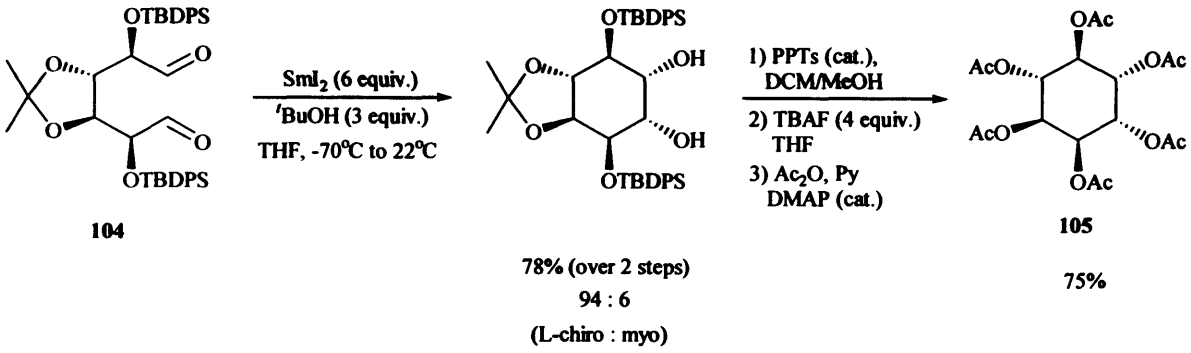
The diastereoselectivity was good when one substituent was present (*e.g.* **100**) and excellent when two alkoxy groups were included (*e.g.* **101**). Additionally it seemed that the coupling of keto-aldehydes (*e.g.* **102**) was more stereoselective than that of the corresponding dialdehydes (**103**) as shown in scheme 40.



Scheme 40

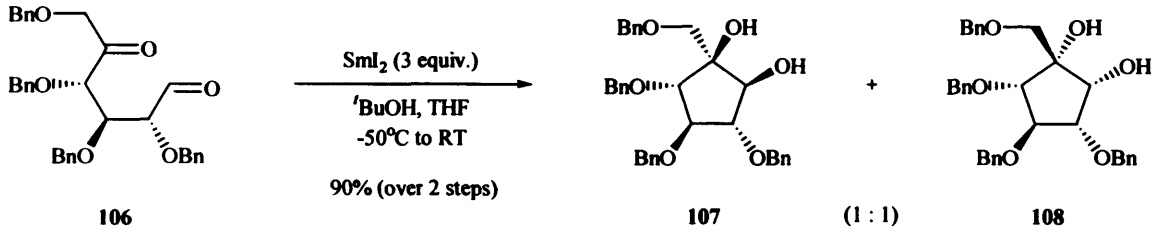
In the presence of one alkoxy substituent, the orientation was attributed to steric and dipolar effects involving the ketyl radical and the adjacent alkoxy group. It should also be noted that reduction of the α-alkoxy substituent was not observed even though SmI_2 is known to carry out the facile deoxygenation of α-heterosubstituted aldehydes and ketones.[83]

This directing effect of α-alkoxy substituents has also been observed by other research groups and has been exploited in the synthesis of carbasugars. Thus, Chiara and Valle employed the stereoselective pinacol coupling reaction of the dial **104** in their synthesis of L-chiro-Inositol hexaacetate **105** (Scheme 41).[84]



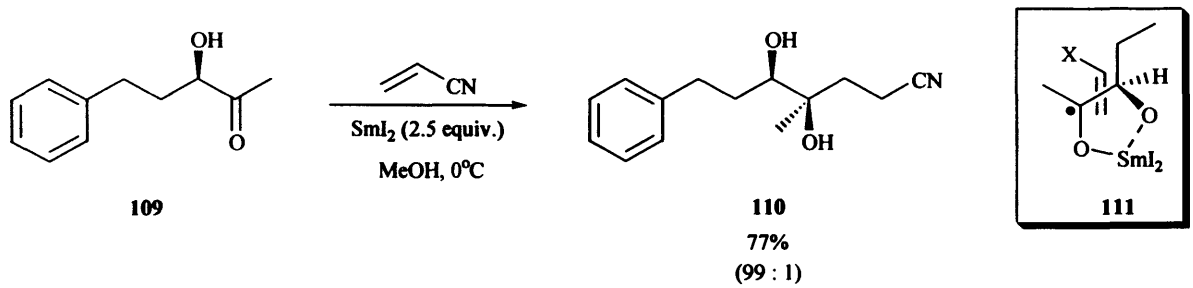
Scheme 41

However, in other cases the directing properties of α-alkoxy substituents can differ. Thus, SmI_2-mediated cyclisation of the D-glucose-derived dialdehyde **106** leads to a 1 : 1 mixture of the two *cis*-diols **107** and **108** (Scheme 42).[85]



Scheme 42

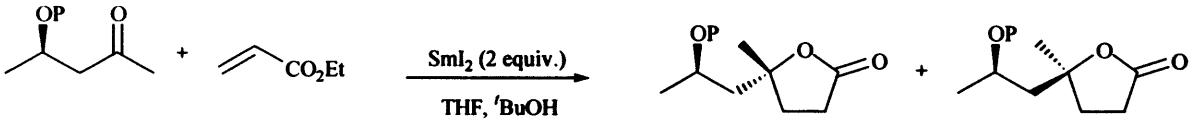
The stereodirecting effect of α-hydroxy substituents in SmI_2-mediated pinacol reactions to form carbocyclic systems all employ dicarbonyl starting materials with protected α-hydroxy substituent(s). The use of starting materials with free α-hydroxy groups is not known for intramolecular pinacol reactions however there are examples in the literature whereby ketyl radicals are reacted intermolecularly with alkenes *via* chelation with the free α-hydroxy group. In a paper by Kawatsura and co-workers it was shown that a free α-hydroxyl group could direct the stereoselectivity of the product from the intermolecular coupling of ketone and olefin precursors (Scheme 43).[86]



Scheme 43

It was proposed that the free hydroxyl group of **109** chelates to the SmI_2 and the oxygen of the radical to give the 5-membered chelate **111**, thus directing the reaction of this ketyl radical with the olefin to give **110**.

Additionally Inanaga and co-workers reported the chelation and stereocontrol of the reaction between a β-hydroxy substituted ketone (**112**) and an alkene (**113**). In this case the β-hydroxy substituent was differentially protected and proved again that this β-hydroxy substituent can control the stereoselectivity of the forming product(s) (Scheme 44).[87]



112 **113**

P =	Bn	RT	1.5 : 1
	$P(O)(OEt)_2$	RT	11 : 1
		-78°C	20 : 1
	$P(O)(NMe_2)_2$	-78°C	24 : 1

Scheme 44

Interestingly if the β-hydroxy substituent was benzyl protected the diastereoselectivity was low however when it was protected as a phosphoate of phosphoamide the stereoselectivity of the products increases and the authors proposed this was due to the formation of an eight-membered ring chelate (Figure 17) and not, as anticipated, a six-membered ring chelate.

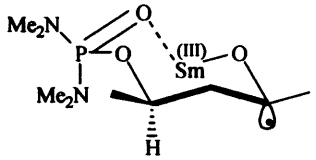
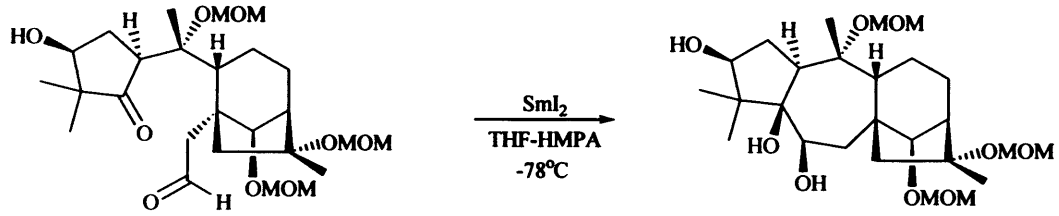


Figure 17

As mentioned above the intramolecular pinacol reaction of a free α-hydroxy substituted precursor is not known, but there is one example whereby a free β-hydroxyl group can dictate the stereoselectivity of the product of the pinacol reaction of a dicarbonyl compound. Kan and co-workers employed this in the synthesis of the 7-membered B-ring of grayanotoxins.[88] In this paper keto-aldehyde **114** possessing a free β-hydroxy group was treated with SmI_2 to produce the diol **115** exclusively. The authors proposed that the observed stereochemistry of the *cis*-diol moiety of **115** was due to chelation between the Sm (III) cation (generated in the process) and the neighbouring β-hydroxy substituent.

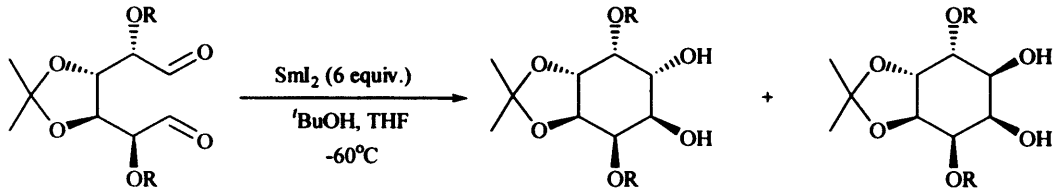


114

115
50%

Scheme 45

It has been shown that the group used to protect the α-hydroxy group is a non-innocent bystander in determining stereoselectivity. Hence cyclisation of *O*-benzyl protected dialdehyde **116** gave the expected *cis*-diol **117** as the major diastereoisomer as shown (Scheme 46).



116 R = Bn, 76%
118 R = TBDPS, 85%

119

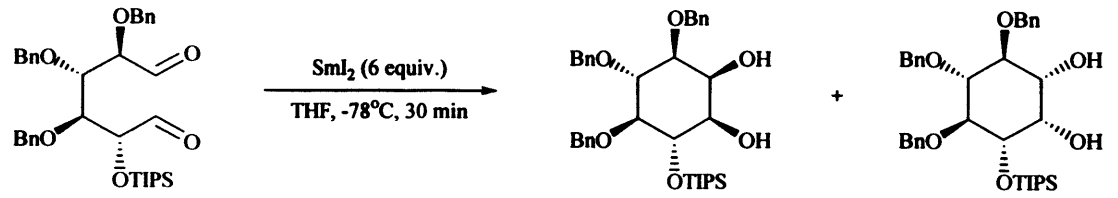
11 : 89
93 : 7

117

Scheme 46

However, somewhat surprisingly the corresponding *O*-silyl protected dicarbonyl **118** gave the *trans*-diol **119** as the major product. The authors remarked that this was the first example of a pinacol coupling reaction where the stereoselectivity is driven by the choice of protecting group at the adjacent position. Whilst α-silyloxy and benzyloxy groups work in pinacol reactions the corresponding α-hydroxy esters gave no reaction. In addition the presence of an acetal group at this position gave low yields of products, which the authors postulated was due to non-determinal side reactions.

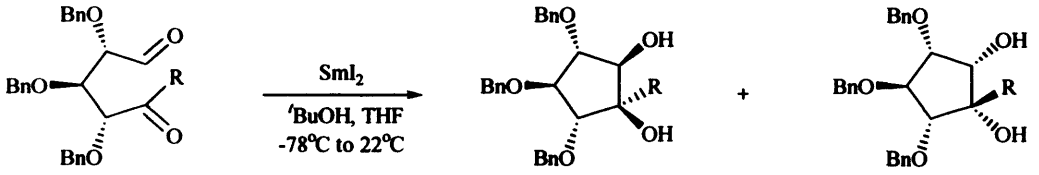
There are other reports in the literature whereby a dicarbonyl precursor with two α-hydroxy/alkoxy groups is treated with SmI_2 to form products in which the stereoselectivity of the diol groups can be dictated. An example is in a paper by Kornienko and co-workers, whereby a dicarbonyl precursor **120** (used in the synthesis of a differentially protected *myo*-inositol) was treated with an excess of SmI_2 to give two products **121** and **122** with good selectivity for the former. This result seems to suggest that the silyl group is more 'important' in directing the newly formed diol *anti* than the benzyl group (Scheme 47).[89]



120 121 20 : 1 70% 122

Scheme 47

Adinolfi *et. al.* have investigated how the stereoselectivity of pinacol reactions can be directed by α-hydroxy substituents and ketone/aldehyde functionalities (Scheme 48).[90]



123: R = Me
125: R = H

124 97 : 3
126 75 : 25

Scheme 48

Thus, diketone **123** was reacted with SmI_2 to give the expected product **124** with the newly formed *cis*-diol *trans*-orientated to the adjacent alkoxy groups. Interestingly, the reaction of dialdehyde **125**, again gave the expected product **126** as the major isomer, however the diastereoselectivity of the overall reaction had somewhat decreased. The authors proposed that due to the greater electron-donating power of a methyl group with respect to the hydrogen atom and the higher stereoselectivity of the reaction of ketone **123** suggested that an important role is played by electrostatic interactions in the stereochemical control of this type of reaction.

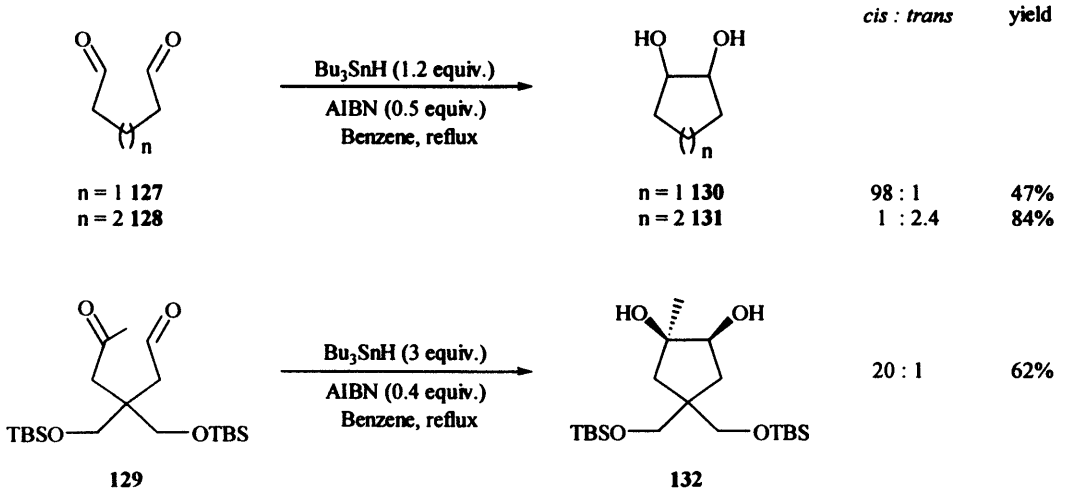
The powerful influence of appropriately positioned hydroxyl (free and protected) groups in facilitating intermolecular ketyl-olefin coupling and intramolecular dicarbonyl coupling reactions has been eluded to above and has been shown to greatly enhance the reactivity of the substrate(s) and control the stereochemistry of the product(s) through chelation and polar effects.

In addition to being used for the formation of small (5 and 6 membered) carbocycles SmI_2-mediated pinacol reactions have also been employed successfully for the formation of larger rings. Notable examples include the synthesis of the BC ring system of Taxol[91] and ring B of (-)-Grayanotoxin III.[67]

The pinacol coupling reaction employing SmI_2 is very rapid and chemoselective with respect to many reducible functional groups. Kagan and co-workers[92] have reported that substituents such as -CN, $-NO_2$ and $-CO_2R$ remain intact if stoichiometric amounts of SmI_2 are used, it is well known that ester[73] and carboxylic[73] functions are not readily reduced using SmI_2. Interestingly, even though the nitro-functionality is normally reduced by reaction with SmI_2 Kagan *et. al.* reported that reaction of *p*-nitrobenzaldehyde with SmI_2 (1 equiv) gave the corresponding intermolecular pinacol product without reduction of the nitro-functionality.[92]

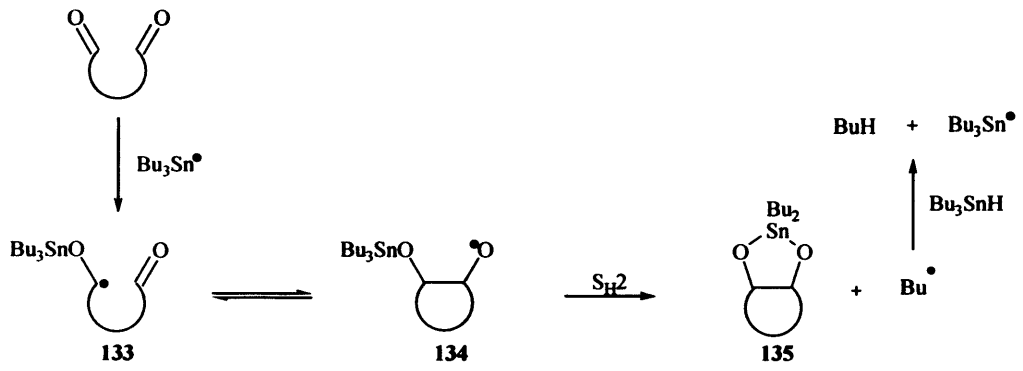
2.9 Tributyltin hydride-mediated Pinacol Reactions

Hays and coworkers[93] have described the intramolecular pinacol coupling of 1,5- and 1,6-dicarbonyl compounds employing tributyltin hydride (Bu_3SnH) as the reducing agent. This work followed the precedent of Beckwith *et. al.* who had established that Bu_3SnH effected the reductive cyclisation of a δ,ε-unsaturated aldehydes to yield cyclic hydroxy products – a reaction proceeding *via* ketyl radical intermediates.[94] Starting from this precedent Hays and Fu investigated the analogous reductive cyclisation of dicarbonyl compounds. These authors showed that Bu_3SnH successfully mediated the pinacol coupling of a series of 1,5 and 1,6 dicarbonyls to the corresponding carbocyclic diols (Scheme 49).



Scheme 49

The results showed that both dialdehydes **127** and **128** as well as the keto-aldehyde **129** undergo successful reactions in good to excellent yields. The stereoselectivity of the reaction is such that 1,5-dicarbonyls (**127** and **129**) furnish *cis*-diols (**130** and **132**) as the major diastereoisomer whilst the 1,6-dicarbonyl gave a mixture of *cis* and *trans* products. Hays and Fu's proposed pathway for the reaction entails a radical chain process whereby the key step is the addition of a tin ketyl radical **133** to the second carbonyl group (*i.e.* **133** → **134**) generating a high-energy oxygen centred radical **134** (Scheme 50).



Scheme 50

This alkoxy radical **134** can potentially abstract a hydrogen atom *inter*molecularly from Bu_3SnH however, on the basis of further studies the authors proposed that **134** effects an *intra*molecular homolytic substitution (S_H2) at the tin centre generating the 1,3-dioxa-2-stannalane **135**. The butyl radical thus liberated then abstracts hydrogen from Bu_3SnH propagating the chain. The stereoselectivity of the reaction can be explained by the formation of the bicyclic intermediate **135**. Thus, for 5-membered carbocycles **135** necessarily has to have a *cis*-ring junction whereas for 6-membered systems both *cis* and *trans*-fused bicycles are possible. Presumably selective formation of the *trans*-diol from **128** indicates that the addition of the ketyl radical to the carbonyl group is reversible. Interestingly whilst this Bu_3SnH-mediated methodology has been exploited in other intramolecular pinacol-type reactions (see section 2.17) there are no reports for its successful use in the corresponding intermolecular pinacol couplings.

2.10 Other metal-mediated Pinacol Reactions

In addition to the use of titanium, SmI_2 and Bu_3SnH a wide variety of other low-valent metal-based systems have been employed in pinacol reactions. This section will briefly discuss some of the more commonly employed reagents concentrating on intramolecular ring forming reactions.

2.11 Magnesium-mediated Pinacol Reactions

Fürstner and co-workers[95] have reported that magnesium dispersed on graphite can be used to carry out both inter- and intramolecular pinacol coupling reactions of dicarbonyl compounds. Thus a number of dialdehydes and diketones could be successfully employed to give the products diols in good to excellent yields (Scheme 51). The stereochemical assignments of the products and hence diastereoselectivity of the reaction were only reported for the reaction of

dialdehyde **136** which gave product diol in a 3 : 2 (*cis* : *trans*) ratio. Additionally this method required the use of high dilution conditions (syringe pumps) to avoid competing intermolecular reactions. This magnesium-mediated strategy has seen little reported use subsequently.

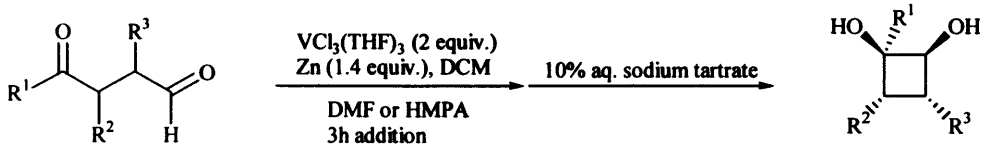
136: R = H, n = 3
R = Ph, n = 1

R = H, n = 3, 48% (*cis* : *trans*, 3 : 2)
R = Ph, n = 1, 66%

Scheme 51

2.12 Vanadium-mediated Pinacol Reactions

Vanadium (II)-species have also been used with great success mainly in intermolecular pinacol coupling reactions. Thus, Cozzi and co-workers have reported the pinacol coupling of some aliphatic aldehydes with aromatic aldehydes bearing a chiral auxiliary promoted by $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ to give *cis* 1,2-diols.[96] Pederson and Raw have employed the $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ reagent for the intramolecular pinacol reaction of the 1,4-dicarbonyl (**137**) to yield *cis* 1,2-cyclobutanediols (**138**) as shown (Scheme 52).[97] The *cis*-stereochemistry of the product diols was expected of this reaction and good to excellent yields were produced. The authors stated that these yields were very high due to DMF and HMPA being employed as additives in the reaction however, their role was not well understood at the time.



137

R^1 = alkyl, aryl
R^2 = H, Et
R^3 = H, OTBDMS

138

yields 72 - 93%

Scheme 52

2.13 Cerium-mediated Pinacol Reactions

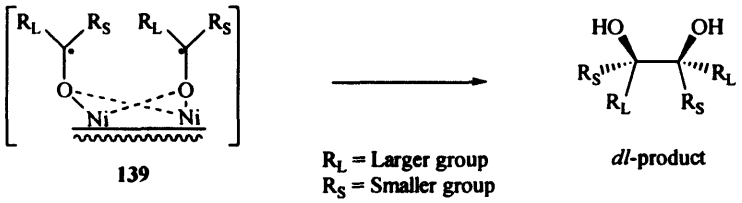
Low-valent cerium reagents have also been employed as reagents for pinacol reactions although only intermolecular cases have been reported to date. Thus, aromatic and aliphatic carbonyls have been homocoupled using a Ce-I_2 system[98] and a $Ce(O^iPr)_3$-$ZnEt_2$-Me_3SiCl system has also been reported.[99]

2.14 Manganese-mediated Pinacol Reactions

Manganese and manganese complexes have been used as single electron sources in free-radical cyclisations, and on this point Rieke and Kim postulated that their active manganese species might be a good reagent for pinacol coupling reactions.[100] These authors prepared active manganese species (reduction of manganese halides by lithium in the presence of naphthalene) and showed that they could be used to carry out the intermolecular pinacol homocoupling of a variety of aryl aldehydes to give diols in moderate to good yields (51 – 90 %) albeit with low diastereoselectivities.

2.15 Nickel-mediated Pinacol Reactions

Shi and co-workers have developed the pinacol coupling of carbonyl compounds mediated by nickel reagents.[101] The reagent was prepared by addition to $NiCl_2$ of lithium and naphthalene in THF at room temperature and can carry out the successful intermolecular homocoupling of a variety of aromatic aldehydes and ketones in good yields (54 – 99 %) and with good stereoselectivity for the *dl*-products. The authors explained this stereoselectivity on the basis of the reaction *via* the chelated intermediate **139** (formed by SET from Ni to the carbonyl functionality) (Scheme 53). No reports of Ni-mediated intramolecular pinacol reactions have appeared.



139

R_L = Larger group
R_S = Smaller group

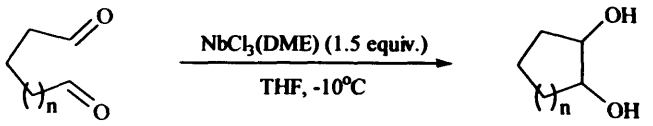
dl-product

Scheme 53

2.16 Niobium-mediated Pinacol Reactions

Niobium has also been used in the pinacol coupling of aromatic aldehydes and ketones. Thus, Szymoniak and co-workers have used $NbCl_3$(DME) to successfully homocouple a variety of aromatic aldehydes with good selectivity for the *threo*-isomer.[102] Arai and co-workers have reported analogous intermolecular couplings of aromatic aldehydes using a low-valent niobium reagent, generated by the reduction of $NbCl_5$ with zinc metal.[103] The $NbCl_3$(DME) reagent has also been used to obtain cyclic diols *via* intramolecular pinacol reactions of dicarbonyls.[64] Thus, the reaction of two α, ω-dialdehydes **140** and **141** with $NbCl_3$(DME) at −10°C using high dilution conditions (syringe pump over 6 h, to suppress intermolecular

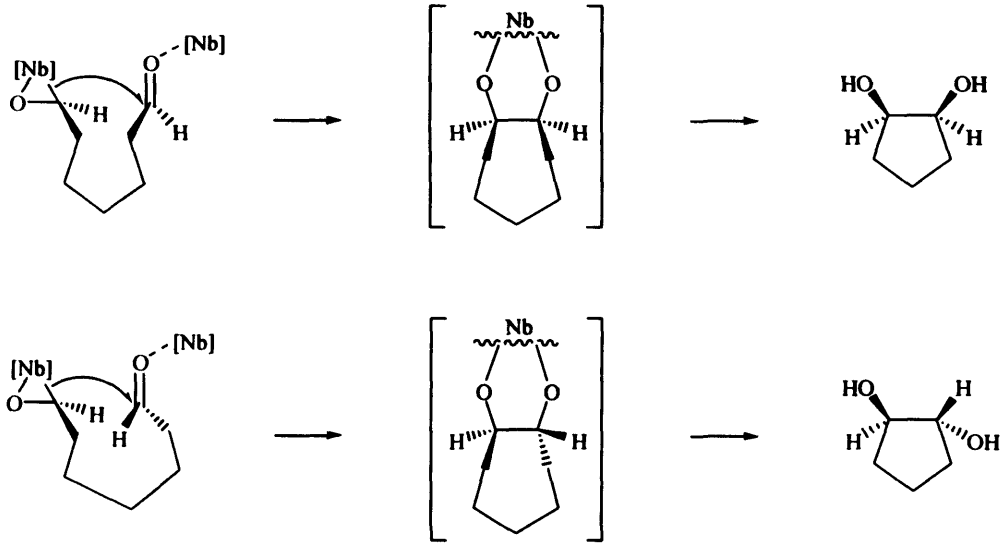
reactions) resulted in the formation of the corresponding cyclic diols **142** and **143** in moderate yields (Scheme 54).



		cis : *trans*	yield (%)
140 (n = 2)	**142** (n = 2)	9 : 11	48
141 (n = 4)	**143** (n = 4)	1 : 1	43

Scheme 54

The diols **142** and **143** were produced in a 9 : 11 and 1 : 1 *cis* : *trans* ratio respectively and the authors postulated that this low stereoselectivity may be due to the two competitive pathways shown (Scheme 55).



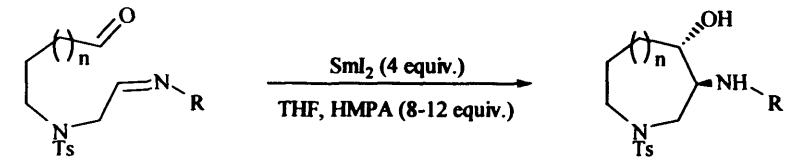
Scheme 55

2.17 Pinacol-type Coupling Reactions to Form *N*-Heterocycles

In sections 2.6–2.16 the inter and intramolecular pinacol reactions of dicarbonyl precursors were discussed and it was seen that a numerous variety of examples of these reactions have been reported in the literature. In contrast low-valent metal-mediated pinacol reactions to produce *N*-heterocycles are relatively rare and the few that have been reported employed carbonyl derivatives.

A report by Skrydstrup *et. al.* showed that the hexahydroazepine ring of balanol (a protein kinase C inhibitor) could be synthesised by SmI_2-mediated pinacol reactions (Scheme 56).[68] They reported that cyclisation of carbonylhydrazones **144** to seven-membered cyclic amino

alcohols **145** is an efficient process, which affords the product in high *trans*-selectivity. The corresponding attempt to access an eight membered heterocycle failed.



144

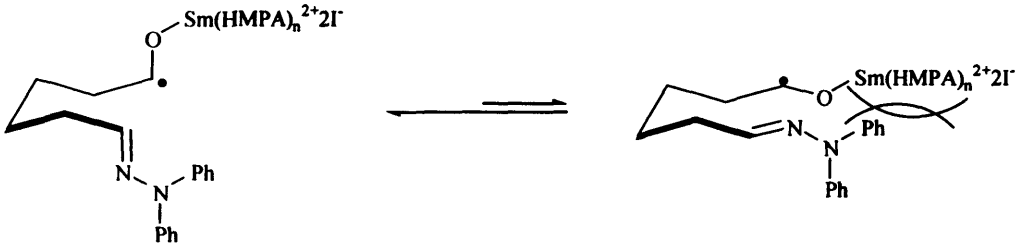
a. n = 0, R = NPh_2
b. n = 0, R = OBn
c. n = 1, R = NPh_2

145

	cis : *trans*	yield (%)
a.	1 : 10	59
b.	1 : 5	40
c.		0

Scheme 56

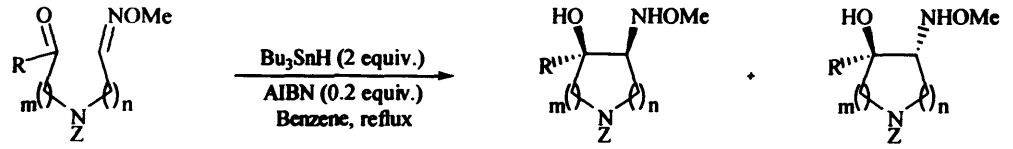
The *trans*-selectivity of the reaction was greater with the *N,N*-diphenylhydrazone **145a** (10 : 1, *trans* : *cis*) than for the benzyloxime hydrazone **145b** (5 : 1, *trans* : *cis*). The authors explained the *trans*-selectivity by proposing the chelated intermediate **146** (Figure 18) in which the co-solvent HMPA prevents chelation. Similar *trans*-selective pinacol type cyclisations of carbonylhydrazones[104] and oximes[85] have been reported for carbocyclic systems.



146

Figure 18

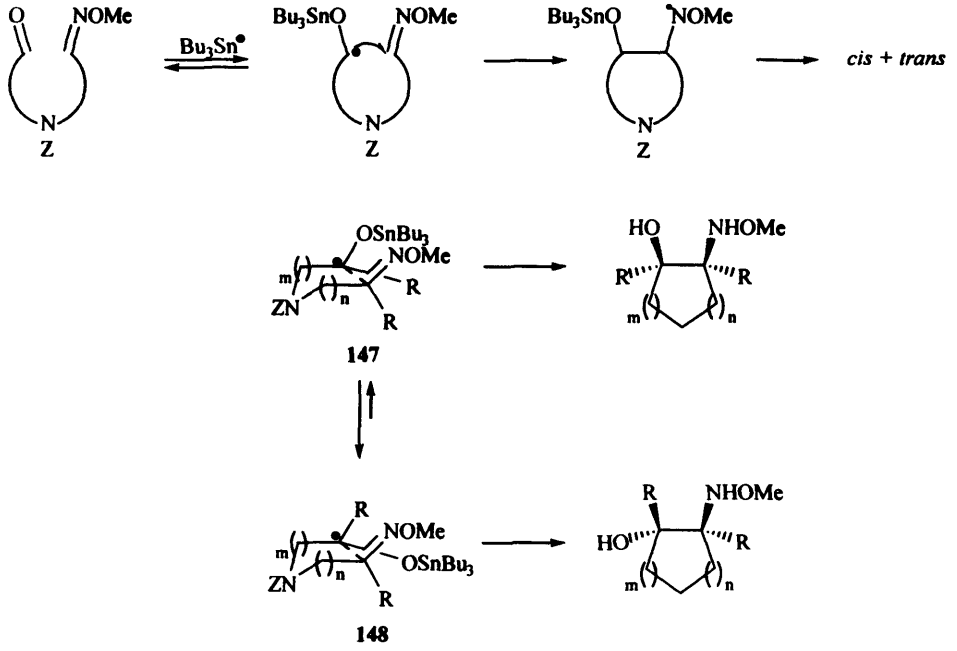
The tributyltin hydride-mediated intramolecular cyclisation of oxime ethers with aldehydes or ketones has been reported by Naito *et. al.*.[105] The reaction is analogous to the pinacol reaction discussed in section 2.9 and can be used to access five to seven-membered cyclic amino alcohols in good yields in which the *trans*-isomers were the major product (Scheme 57).



Substrate	R	m	n	Ratio *cis* : *trans*	yield (%)
a	H	1	1	30 : 70	54
b	H	2	1	39 : 61	62
c	H	1	2	20 : 80	70
d	H	3	1	32 : 68	44
e	Me	1	1	21 : 79	52

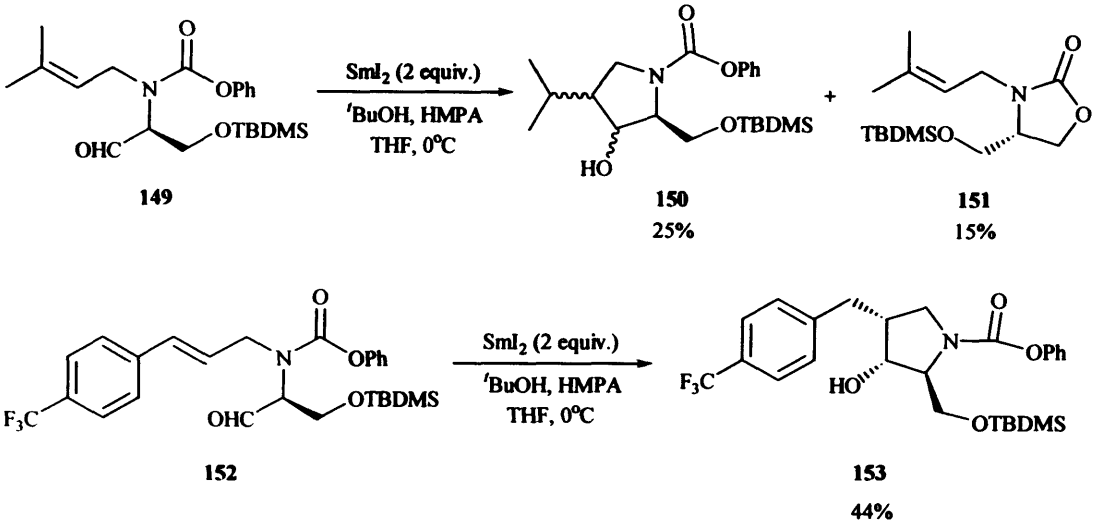
Scheme 57

A mechanistic pathway was proposed by Naito and co-workers to account for this stereoselectivity (Scheme 58).[106] Thus, *trans*-selectivity could be explained by the electrostatic repulsions between the stannyloxy group and the nitrogen or oxygen of the oxime ether group in conformation **147**. The steric repulsion between the two R groups (particularly Me) along with this electronic repulsion will increase the instability of **147**, thus giving *trans*-isomer *via* conformation **148**.



Scheme 58

Five membered ring nitrogen heterocycles have also been accessed by 5-exo-trig cyclisations of ketyl radicals onto unstabilised alkenes. However, generally low yields and diastereoselectivities were observed in the synthesis of pyrrolidine derivatives (Scheme 59).[107]

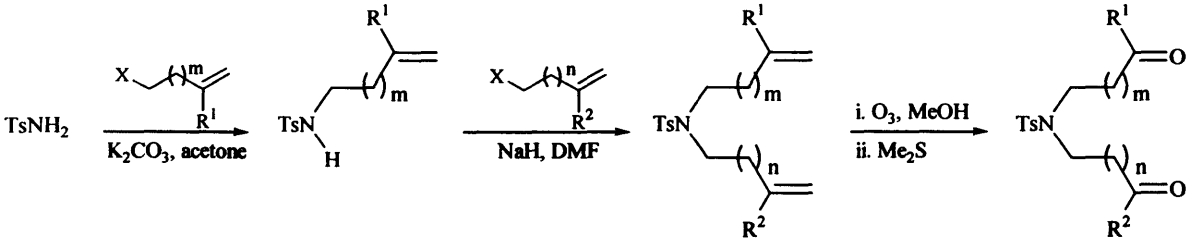


Scheme 59

Thus treatment of aldehyde **149** with SmI_2 gave two products **150** and **151** in 25 % and 15 % yields respectively. The authors showed that the expected cyclised product, **150**, was a mixture of all 4 diastereoisomers and separation was unsuccessful by chromatography. The reduced product, **151**, was formed by reduction of **149** to the alkoxide and subsequent intramolecular attack on the carbamate carbonyl. Activating the alkene, as in **152** could increase the yields of the cyclised products. However, the pyrrolidine **153** was still obtained as a mixture of diastereoisomers.

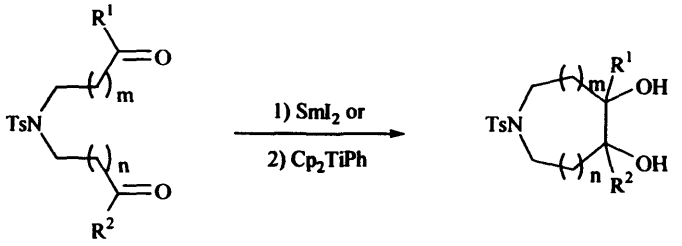
2.18 Previous Studies on the Synthesis of *N*-Heterocycles *via* Pinacol Reactions

Previous work at Leicester by S. Lowe had investigated a pinacol approach to *N*-heterocyclic diols.[108] She was able to synthesise the three dicarbonyls **180**, **190** and **192** using the ozonolysis route shown below (Scheme 60).



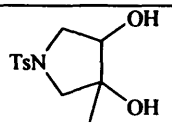
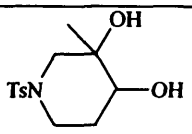
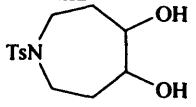
Scheme 60

Having isolated these dicarbonyl precursors the key pinacol reaction were explored using both SmI_2 and Cp_2TiPh-mediated conditions, the results are summarised in scheme 61 and table 1.



Scheme 61

Table 1.

R^1	R^2	M	N	Product	SmI_2, *cis* : *trans* (Yield)	Cp_2TiPh, *cis* : *trans* (Yield)
H	Me	0	0		> 90 % *cis* (29 %)	25 : 75 (20 %)
Me	H	0	1		> 85 % *cis* (38 %)	Undetermined (37 %)
H	H	1	1		96 : 4 (30 %)	

As can be seen from the results presented Lowe was able to successfully carry out a number of pinacol reactions to produce *N*-heterocyclic diols. Thus, the keto-aldehyde **180** was successfully and selectively transformed to both the *cis*- **201** and *trans*-diol **202** using SmI_2 and Cp_2TiPh reagents respectively. Similar results were obtained with the keto-aldehyde **190** giving *cis*- and *trans*-piperidine diols **205** and **206** and with dialdehyde **192**, which gave the *cis*-diol **207** upon reaction with SmI_2.

However, whilst these initial results established the proof of concept- *i.e.* that stereoselective pinacol reactions could be applied to the synthesis of *N*-heterocyclic diols there were a number of issues, which needed addressing:-

- Yields – low and unoptimised
- Selectivity – was not determined for Cp_2TiPh reaction to form 6-membered diol.
- Stereoassignments – were done on the basis of NOESY spectra and nOe experiments. Although this gave some evidence, it was far from conclusive and needed to be re-investigated (especially for 6- and 7-membered diols)

- Only limited ranges of substrates were used, so to further explore this investigation and any possible limitations to this methodology more substrates were required.

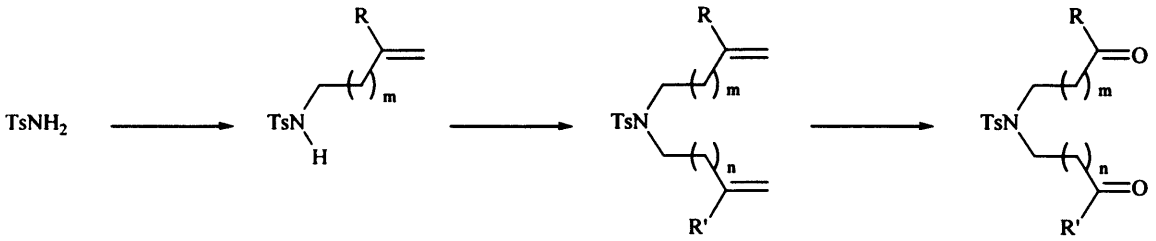
Thus at the start of this project the initial aims were:-

- The optimisation of reactions leading to improvements in yields.
- To investigate a full range of dicarbonyl precursors *i.e.* cyclisation of diketones as well as other dialdehyde and keto-aldehyde substrates.
- To investigate the effect of ring size on the diastereoselectivity of the reaction.
- To fully establish the stereochemistry of the products (and hence the stereoselectivity of the reaction) using NMR spectroscopy or X-ray crystallography as necessary.
- To investigate the effect of α-substituents on the stereochemical outcome of the reaction.

3. Chapter 3: Results and Discussion 1

In the previous chapter (section 2.18) the initial work of S. Lowe[108] regarding the proposed pinacol-based strategy to *N*-heterocyclic diols was discussed. This had been successful for the production of dienes precursors for 5, 6 and 7-membered heterocycles, their conversion to the corresponding dicarbonyl compounds and finally their samarium (II)- and titanium (III)-mediated pinacol reactions. During these studies S. Lowe undertook preliminary investigations into the stereochemistry of the diols produced in the pinacol coupling reactions using nOe spectral data. These studies showed that this pinacol coupling of dicarbonyl compounds is a feasible route for the production of *N*-heterocycles. However these initial studies did not fully investigate the effect of varying experimental conditions and/or functional groups on the yields and stereoselectivity of the reactions. Additionally some of the stereochemical assignments made during this work were not totally conclusive. Therefore the starting point for this project was to optimise and build upon the results of this initial study.

The general strategy employed for the formation of the majority of the dicarbonyl precursors is shown (Scheme 62) and the steps are discussed in greater detail below. Toluene sulfonamide **154** is a favourable starting material for the formation of the required precursors as it already incorporates an *N*-protecting group and because it is commercially available.



154

Scheme 62

3.1 Diene Synthesis

The initial diene targets were chosen so as to allow for the investigation of different ring size and functional groups (aldehyde or ketone) on the yield and stereoselectivity of the key pinacol coupling reactions. The ten targets are shown below and cover precursors of 5-8 membered heterocycles together with a selection of dialdehydes, diketones and keto aldehydes (Figure 19).

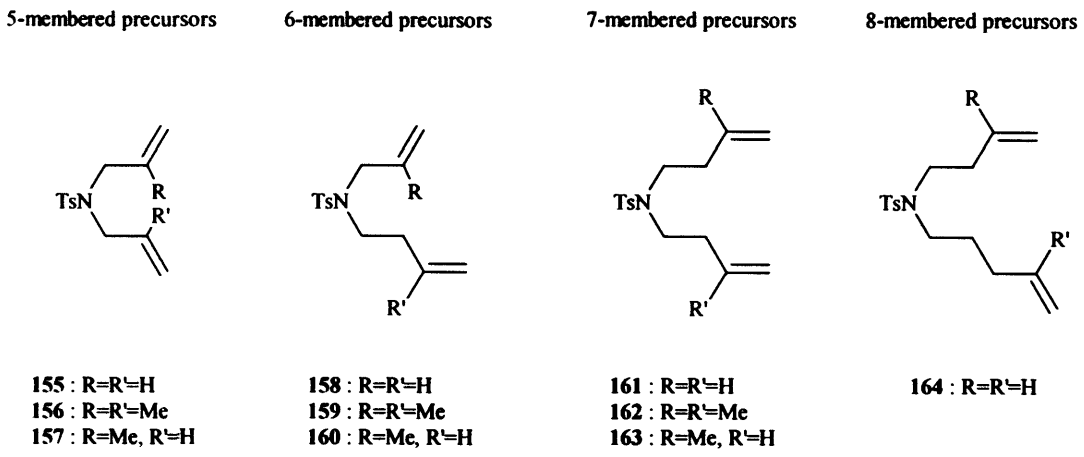
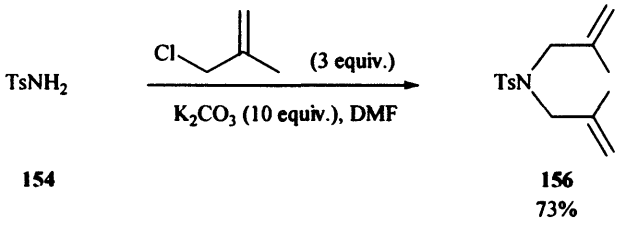


Figure 19

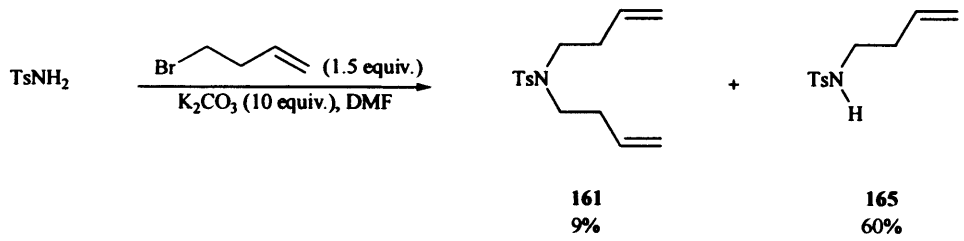
3.2 Formation of Symmetrical Dienes 156, 161 and 162

The synthesis of the three symmetrical dienes **156, 161** and **162** was readily achieved by the one-pot double alkylation of *p*-toluene sulfonamide **154**. The amide **154** is readily alkylated by electrophiles such as alkyl halides and tosylates in the presence of a suitable base. In this context both sodium hydride NaH[109] and potassium carbonate K_2CO_3[110] have been previously employed. Thus, reaction of **154** with commercially available methallyl chloride (3 equiv.) in DMF in the presence of K_2CO_3 (10 equiv.) gave the dialkylated sulfonamide **156** in good yield after purification by chromatography on silica (Scheme 63).



Scheme 63

The two symmetrical seven-membered ring precursors **161** and **162** were prepared in an analogous manner. Thus, reaction of **154** with commercially available 4-bromo-1-butene (1.5 equiv.) and K_2CO_3 (10 equiv.) in DMF gave both the dialkylated **161** and monoalkylated **165** products (Scheme 64), which could be readily separated by flash column chromatography on silica. The formation of **165** as the major product is presumably due to the use of less equivalents of the alkylating agent (compared to the reaction of methallyl chloride) but may also be a result of the competing elimination reaction possible with the bromobutene. However, as compound **165** was going to be employed in the synthesis of unsymmetrical dienes (see section 3.3) this was not a problem.

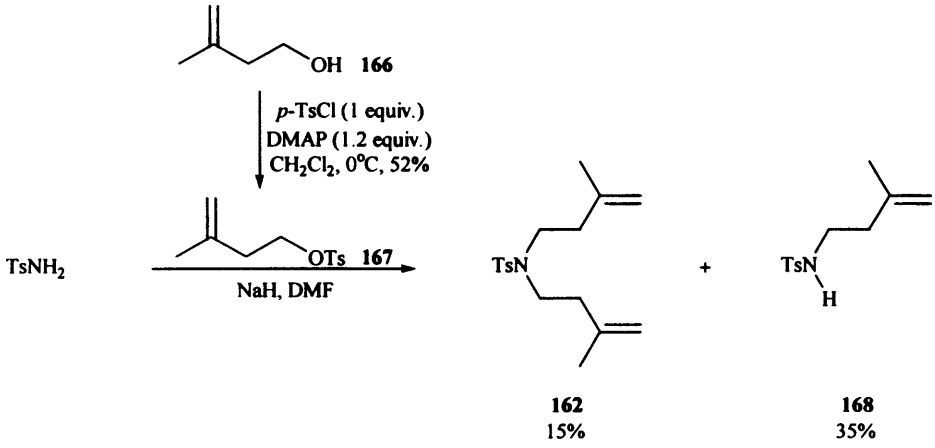


161 9%

165 60%

Scheme 64

The synthesis of **162** proved slightly more problematic. Firstly the required alkylating agent was not commercially available but could be readily accessed from the available alcohol **166** by tosylation as shown (Scheme 65). Alkylation of *p*-toluene sulfonamide with the tosylate **167** was not straight forward due to problems separating the product **162** from the tosylate **167** as they had very similar R_F values in a wide variety of solvent systems. Therefore, the reaction conditions were chosen such that all of the alkylating agent **167** would react thus easing separation. Alkylation was carried out with the stronger base NaH (1.2 equiv.) and only using a limiting amount of **167** (1 equiv.) to give the di- and monoalkylated products **162** and **168** as shown (Scheme 65) which again could be readily separated. Again product **168** was utilised in the formation of unsymmetrical diene precursors as discussed in section 3.3.

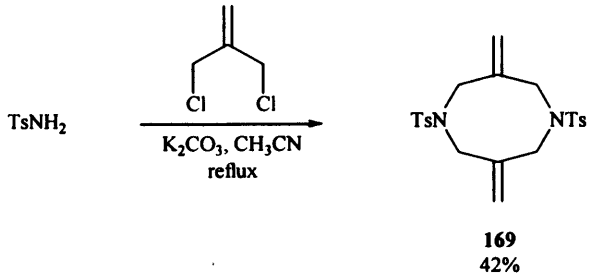


162 15%

168 35%

Scheme 65

Finally a 5-membered symmetrical bicyclic ring precursor, **169** was prepared following literature precedent[111] *via* the alkylation of *p*-toluene sulfonamide with 3-chloro-2-chloromethyl-propene using potassium carbonate as base in acetonitrile (Scheme 66).

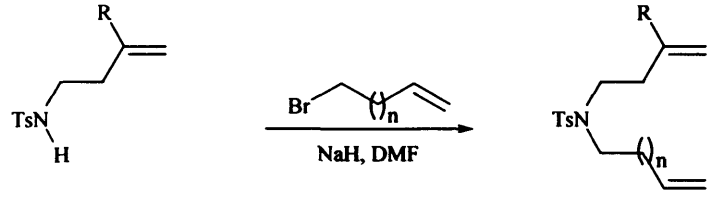


169 42%

Scheme 66

3.3 Formation of the Unsymmetrical Dienes 157, 159, 160, 163 and 164

The general strategy for the formation of unsymmetrical dicarbonyl precursors involved the stepwise alkylation of *p*-toluene sulfonamide. Thus, the monoalkylated sulfonamides **165** and **168** (isolated during the synthesis of symmetrical dienes **161** and **162**) were readily alkylated under standard conditions[112] to produce the diene precursors **163** and **164** (Scheme 67) as shown.

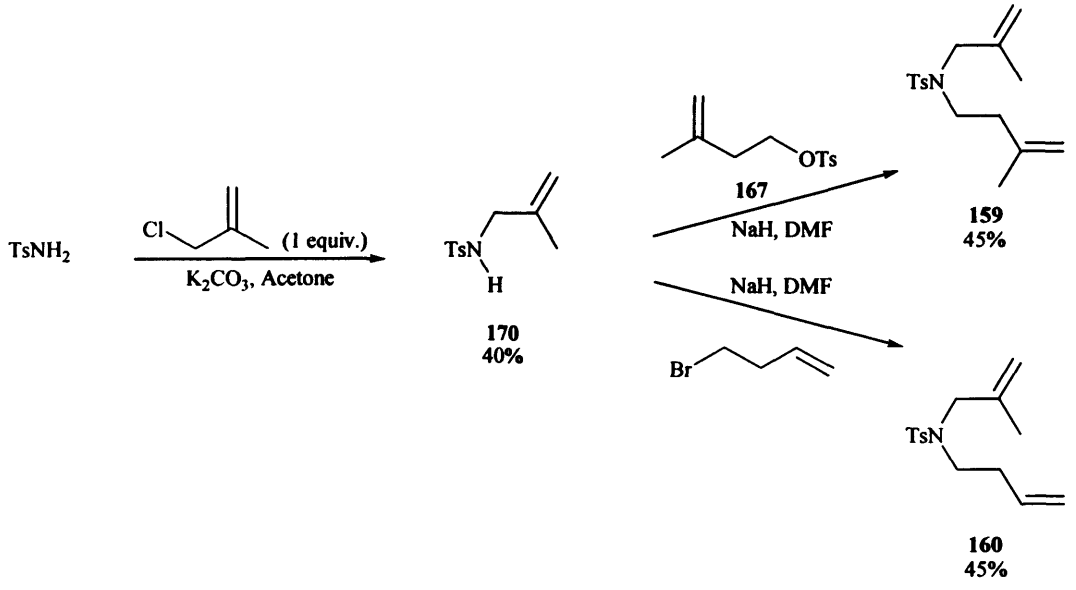


165: R = H, n = 2
168: R = Me, n = 1

164: 87%
163: 71%

Scheme 67

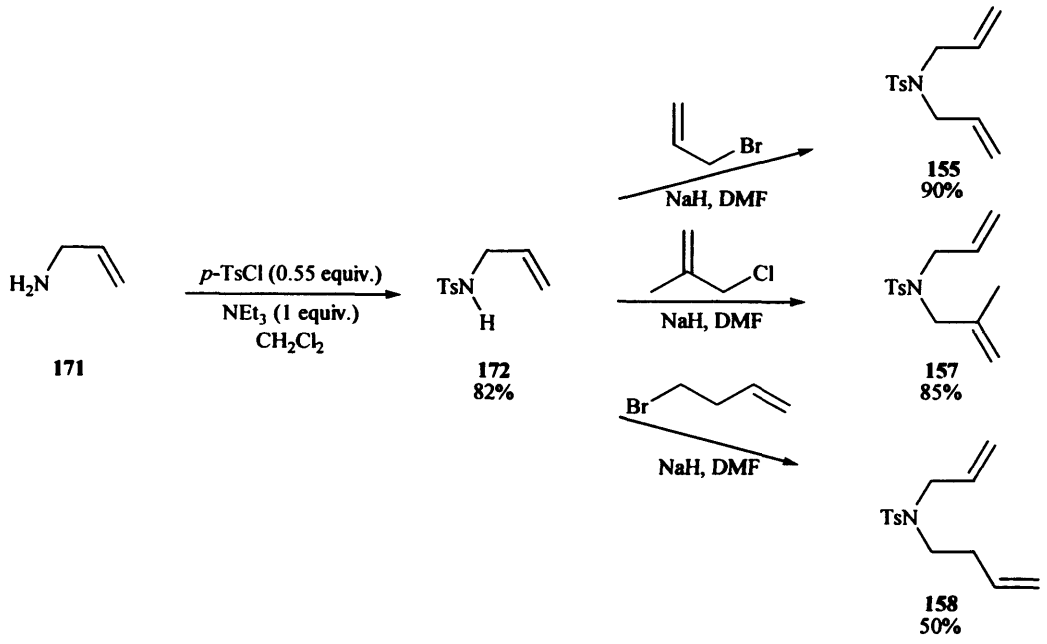
Further diene precursors were synthesised as shown in scheme 68. Thus, alkylation of *p*-toluene sulfonamide with only 1 molar equivalent of methallyl chloride gave the monoalkylated sulfonamide **170** in moderate yield (together with 10 % of the dialkylated compound **156**). Alkylation of **170** with either the tosylate **167** or 4-bromo-1-butene then gave the dienes **159** and **160** respectively in moderate yields.



170
40%

Scheme 68

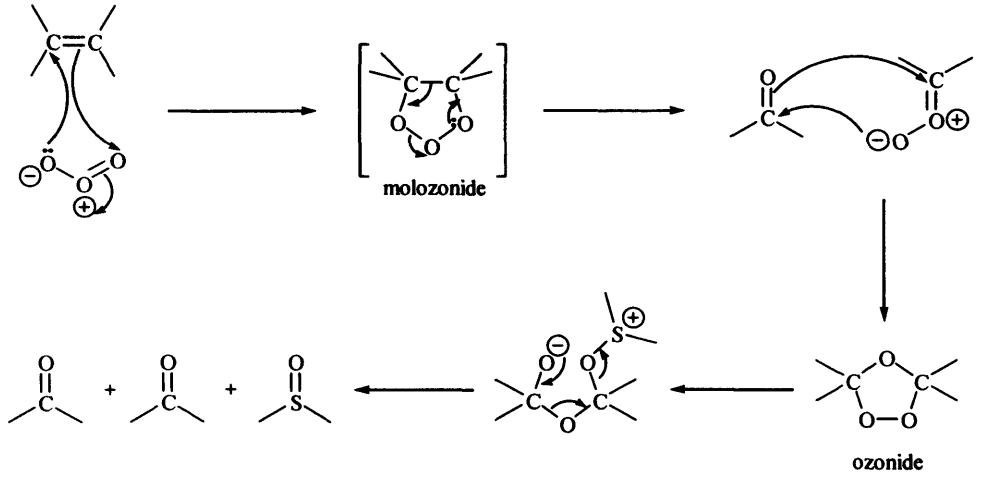
Finally three further dienes were synthesised from *N*-tosyl protected allylamine **172** as shown (Scheme 69). Thus tosylation of commercially available allylamine **171** gave **172** in excellent yield. Subsequent alkylation with the appropriate allyl bromide or chloride then furnished the three dienes **155**, **157** and **158**.



Scheme 69

3.4 Diene Ozonolysis

With a variety of *N*-toluene sulfonamide precursors to hand we next investigated their ozonolysis to the corresponding dicarbonyl compounds. The oxidation of double bonds with ozone followed by the subsequent cleavage of the resultant ozonides to the carbonyl(s) is a procedure that is commonly employed for the synthesis of aldehydes and ketones that are not commercially available (Scheme 70).[113]

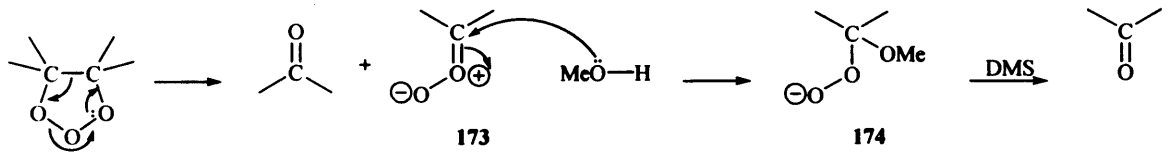


Scheme 70

The reduction of the ozonide to the corresponding carbonyl compound(s) can be achieved by a variety of reagents including Zn,[114] PPh_3,[115] urea[116] and dimethyl sulfide.[117] In general dimethyl sulfide has several advantages over the other reagents used primarily the fact that its

volatility means that it is easily removed from the reaction mixture and its oxidation product dimethyl sulfoxide, DMSO can also be removed under reduced pressure or *via* an aqueous wash. In contrast the use of PPh_3, for example, is often complicated by its removal or, more frequently, by removal of the oxidation product PPh_3=O. The one disadvantage of dimethyl sulfide is its irritable pungent odour and toxicity. In spite of these it was used as the reductant in all of our studies. The reaction is generally very efficient producing the carbonyl(s) in a clean fashion and in good yield. Other methods, which are used to oxidise dienes (*e.g.* potassium permanganate and osmium tetraoxide) can be costly and time-consuming, may produce toxic waste products and work up of the reactions is often long winded.

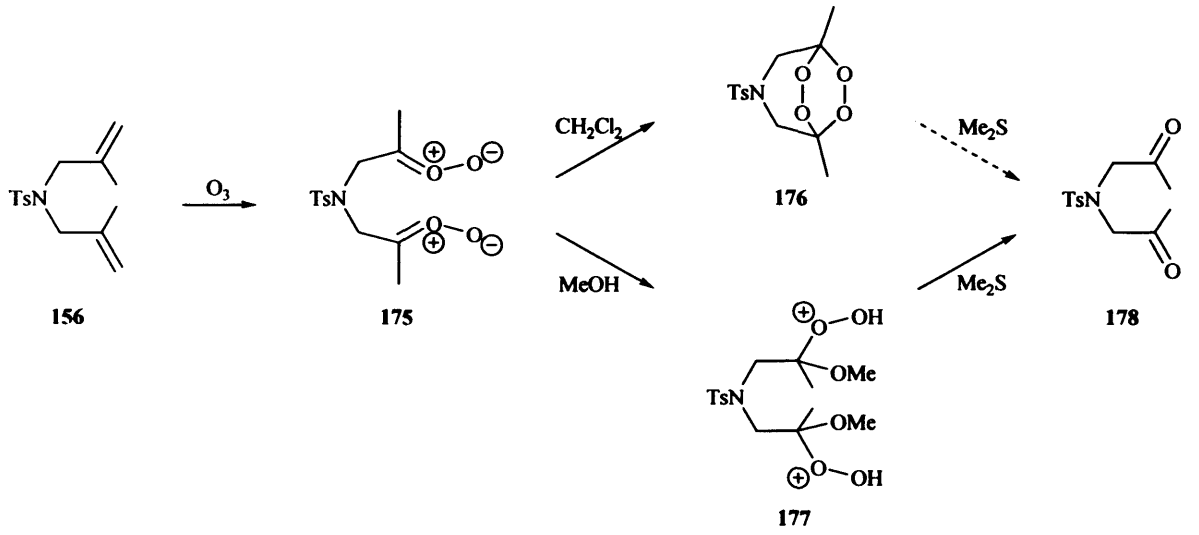
Ozonolysis reactions can be carried out in either participating (*e.g.* MeOH) or non-participating (*e.g.* DCM) solvents. In the latter case the reaction mechanism is as shown above in scheme 70. In contrast reactions in methanol can involve attack by the solvent on the intermediate **173** as shown, generating the methoxy hydroperoxide acetal **174**, which is subsequently reduced to the carbonyl (Scheme 71).



173 **174**

Scheme 71

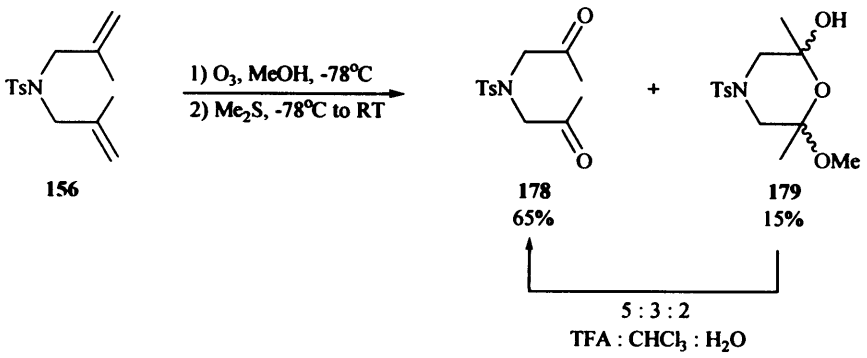
The initial studies by S. Lowe[108] had suggested that ozonolysis of the diene **156** in dichloromethane lead to significant formation of stable peroxides resistant to reduction by dimethyl sulfide. A possible explanation, involving intramolecular cyclisation of **175** giving **176** is shown (Scheme 72). The result being that Lowe observed very low yields of the corresponding diketone in these reactions.



Scheme 72

In contrast when methanol was employed as a participating solvent the yields of the desired diketone were shown to increase significantly. This can be attributed to the reaction of methanol with the intermediate **175** leading to the peroxyacetal **177**, which is subsequently converted to the diketone **178** (Scheme 72). Consequently the majority of the ozonolysis reactions carried out in this study used methanol solvent. The ozonolysis reactions were carried out using the procedure employed by Sawada *et. al.*[118] where ozone was bubbled through a solution of the diene and methanol at -78°C until a pale blue colour was observed, this was then left for 5 minutes while nitrogen gas was purged through it. Excess dimethyl sulfide was added at -78°C and the reaction left to warm to room temperature overnight (approximately 16 hours).

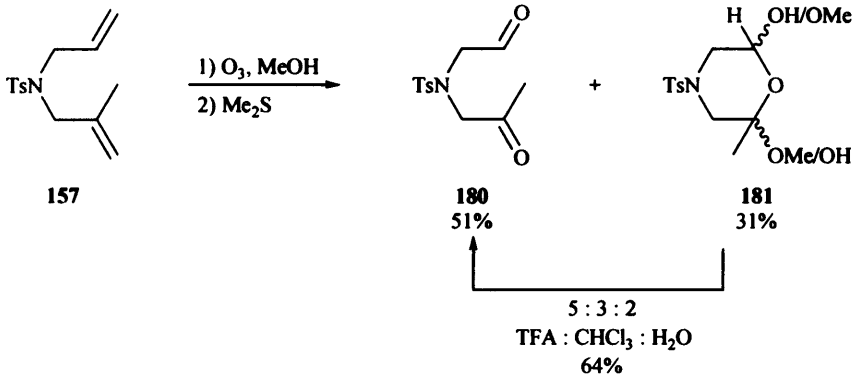
We first explored the ozonolysis of the diene precursors for the five-membered heterocycles *i.e.* **155**, **156** and **157**. Thus, ^{1}H NMR and mass spectroscopy of the resulting reaction mixture followed the ozonolysis of the diene **156** indicated that the desired carbonyl **178** and a second species, thought to be cyclic ketal **179**, had formed during the reaction (Scheme 73). The two products were separated by column chromatography to give pure diketone **178** (65 %) and ketal **179** (15 %). Spectroscopic analysis of the side product **179** confirmed it as the cyclic ketal and ^{13}C NMR analysis (indicating 4 quaternary *C* peaks in the 'ketyl region' 102 - 107 ppm) suggested that **179** had been produced as a mixture of two stereoisomers (although their respective stereochemistry was not assigned). Interestingly electrospray mass spectroscopy of diketone **178** also showed a peak at *m/z* 315 suggesting that a species similar to **179** is formed in the mass spectroscopy process.



Scheme 73

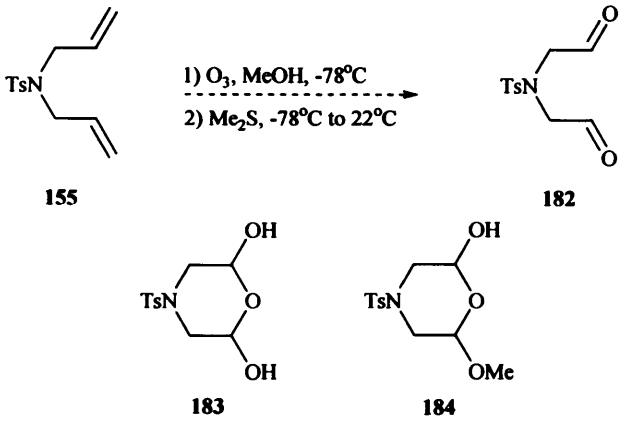
Fortunately formation of the ketal **179** was not problematic because previous work by Lowe[108] had shown that it could be converted to **178** upon treatment with trifluoroacetic acid: chloroform: water in a 5:3:2 ratio (Scheme 73) - although this transformation was not carried out in the course of these studies.

In an analogous manner ozonolysis of diene **157** gave a mixture of the keto-aldehyde **180** (51 %) and acetal(s) **181** (31 %) which could be readily separated by flash column chromatography. The acetal(s) **181** were readily converted to the keto-aldehyde **180** on treatment with acid to give an overall yield of 71 % of **180** from **157**.



Scheme 74

S. Lowe has previously attempted the ozonolysis of diene **155** using standard reaction conditions.[108] She had analysed the mass spectrum and NMR data and the indication was that none of the desired dial **182** had been formed (Scheme 75). Instead signals corresponding to the hydrated acetal **183** and the acetal **184** were observed. S. Lowe had isolated the hydrated acetal **183** by flash column chromatography on silica. The NMR spectrum had 6 separate proton signals at appropriate chemical shifts however, the spectrum could not be assigned as it was poorly resolved.



Scheme 75

There is literature precedent for the synthesis of hydrate **183** type molecules. In a report by Barry and co-workers precursor diol compounds were oxidized using sodium periodate and instead of the desired dialdehyde product the reaction gave the hydrate compounds as side products.[119] It was stated by the authors that the 1,5-dialdehyde **185** is only known as the hydrate **186** (Figure 20).

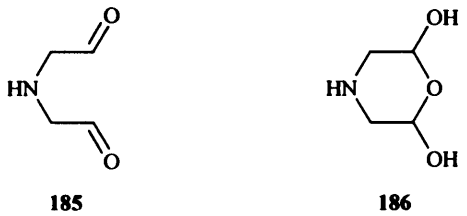
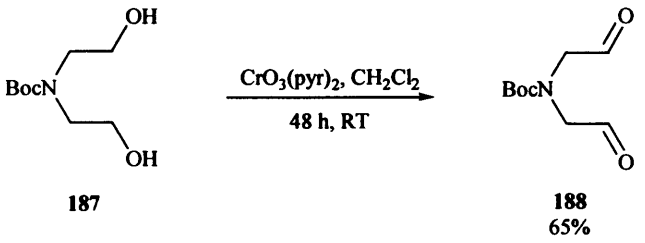


Figure 20

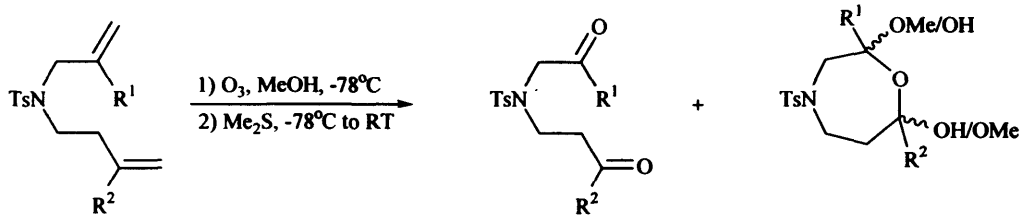
There is only one report in the literature whereby a 1,5-dial is successfully synthesised and isolated. In a report by Garrigues and Lazraq diol **187** was oxidised using $CrO_3(pyr)_2$ in dichloromethane to give dial **188** in good isolated yield (65 %) (Scheme 76).[120]



Scheme 76

However, previous work in our laboratory had failed to replicate this result.[108]

Ozonolysis of the precursor to the six-membered heterocycles gave similar results to those above (Scheme 77).

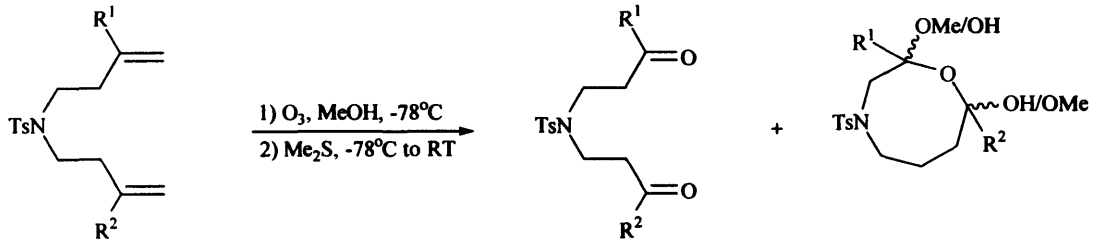


158 : $R^1 = R^2 = H$		
159 : $R^1 = R^2 = Me$	**189** : $R^1 = R^2 = Me$ (80%)	
160 : $R^1 = Me$, $R^2 = H$	**190** : $R^1 = Me$, $R^2 = H$ (78%) +	**191** (9%)

Scheme 77

Thus diene **159** gave the diketone **189** in excellent (80 %) yield with no sign of any cyclic ketal. The keto-aldehyde **190** was also formed in good yield (78 %) from diene **160**, however in this case a small amount of cyclic acetal(s) **191** (9 %) was also isolated. Finally ozonolysis of diene **158** gave a crude reaction product that showed very little indication of an aldehyde functional group by ^1H NMR spectroscopy. Mass spectroscopy did indicate the presence of a signal for the dial product however this could have been formed during the mass spectrometry process. Attempted purification gave many unidentifiable products in very small amounts.

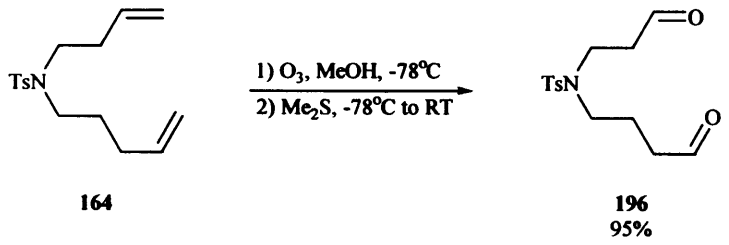
The results from the ozonolysis with the seven-membered ring precursors are given in scheme 78. Reaction of dienes **161** and **162** gave only the corresponding dicarbonyl compounds **192** and **193** respectively in excellent yields. In contrast ozonolysis of diene **163** gave both the desired keto-aldehyde **194** (72%) and acetal species **195** (13%) which were readily separated by chromatography.



161 : $R^1 = R^2 = H$	**192** : $R^1 = R^2 = H$, (90%)	
162 : $R^1 = R^2 = Me$	**193** : $R^1 = R^2 = Me$, (96%)	
163 : $R^1 = Me$, $R^2 = H$	**194** : $R^1 = Me$, $R^2 = H$, (72%)	**195** (13%)

Scheme 78

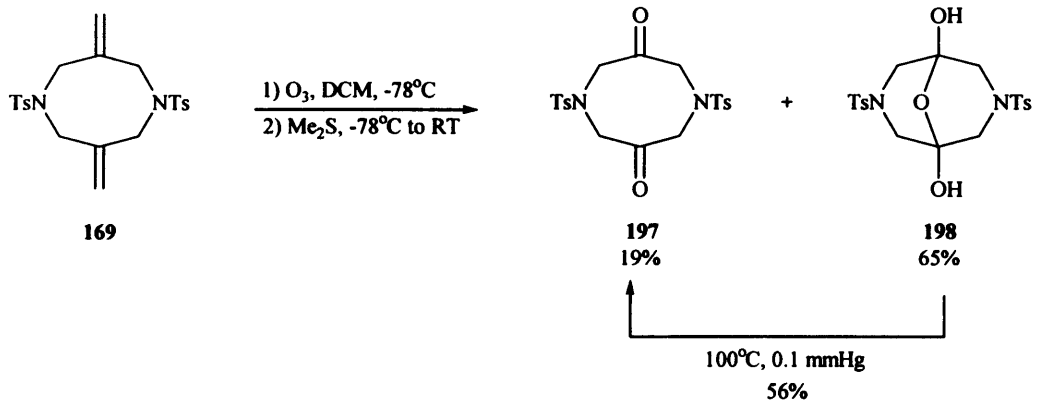
The two remaining dienes also successfully underwent ozonolysis. In the case of **164** the dialdehyde **196** was produced in excellent yield (95 %) (Scheme 79).



164 **196** 95%

Scheme 79

Ozonolysis of the diene **169** has been reported previously to give both the diketone **197** and the bicyclic hydrate **198** (Scheme 80).[121] In our hands the ozonolysis followed by purification by column chromatography gave **197** as the minor component (19%) together with **198** (65%) as the major product isolated from the reaction. Fortunately the hydrate **198** could be converted cleanly to the diketone **197** by heating at 100°C under reduced pressure (0.1 mmHg Kugel-Röhr) albeit in a moderate 56% yield.



169 **197** 19% **198** 65%

Scheme 80

To summarise the results of the ozonolysis reactions, the oxidation of dienes by ozonolysis has proved to be a good method for the synthesis of pinacol precursors generally giving targets in good yield. However, there was one major issue in the formation of cyclic ketals. As expected this was especially prominent in the formation of 6-membered acetals (*e.g.* **179** and **181**) and less so for larger rings (*e.g.* compare **178** to **189** and **193**). Additionally acetal formation was more evident with the more reactive aldehydes compared to the ketone precursors (*e.g.* **191** *c.f.* **189**). However, in the majority of cases these acetals could be converted to the parent dicarbonyls by treatment with acid and water. This acetalisation was a significant problem in the attempted preparation of the two dials **182** and **242** (from dienes **155** and **158**) where the aldehyde functionality was not observed (by ^{1}H and ^{13}C NMR) and attempts to convert the presumed acetal products to the dialdehydes met with failure.

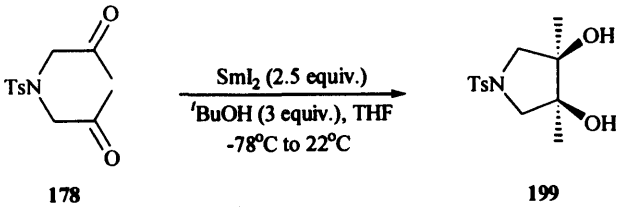
3.5 The Pinacol Coupling Reactions

With a wider range of dicarbonyl precursors to hand we next turned our attention to examining the pinacol-coupling step for the stereoselective synthesis of *N*-heterocyclic diols to build upon the original work of Lowe.[108] The stereochemical outcome of the coupling reactions will play a key role in the potential future application for forming more complicated systems. The two pinacol coupling reagents we chose to investigate were SmI_2 and Cp_2TiPh. SmI_2 is commercially available as a 0.1 M THF solution; however it goes off rapidly on contact with air. It was therefore more reliable to freshly prepare SmI_2 each time the reaction is performed. In general SmI_2 (0.1 M in THF) was prepared from samarium and diiodomethane[122] (or diiodoethane)[73, 76] using dry degassed THF (freeze-pump-thaw) under argon. Excess SmI_2 (2.5 equivalents with respect to the dicarbonyl) was used and a solution of the dicarbonyl and ^{t}BuOH (used as an *in situ* protonating agent) in dry degassed THF was added at -78°C and the reaction allowed to warm up to room temperature. The reactions of samarium and samarium diiodide were carried out under an inert atmosphere, argon or nitrogen, because both these reagents are extremely air sensitive.

The pinacol reagent Cp_2TiPh was readily prepared[123] by the *in situ* reduction of Cp_2TiCl_2 with ^{i}PrMgCl followed by the addition of PhMgCl. It is also air sensitive so the reactions are performed under an inert atmosphere, in fact argon was used because Cp_2TiPh readily reacts with elemental nitrogen to form a dinitrogen complex $(Cp_2TiPh)_2N_2$.[124] Reactions were carried out with excess Cp_2TiPh (3.0 equivalents with respect to the dicarbonyl) at room temperature. The dicarbonyl was added and the reaction stirred overnight at room temperature.

3.6 Pinacol Coupling Reactions Generating Pyrrolidines

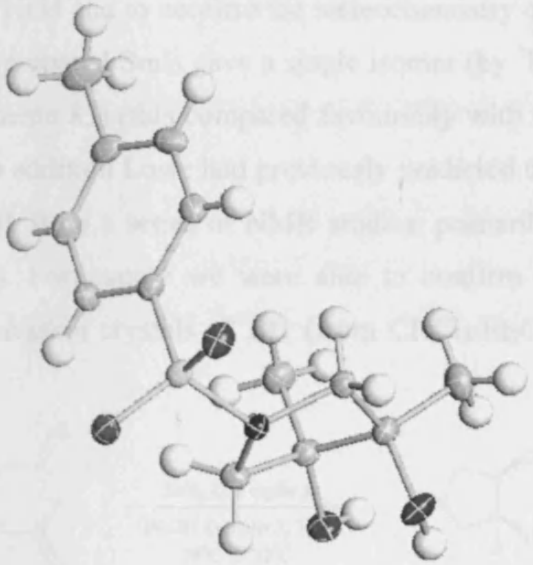
The reaction of diketone **178** with SmI_2 under the general conditions stated above gave a single isomer of the pyrrolidine **199** (by ^{1}H and ^{13}C NMR of the crude reaction mixture) that could be isolated in good (62 %) yield (Scheme 81).



178 199 62%

Scheme 81

Due to the symmetrical nature of **199** nOe analysis could not be used to determine the diol geometry. Fortunately crystals of **199** (from CH_2Cl_2:MeOH) could be grown that were suitable for X-ray diffraction analysis. The results[125] are shown (Figure 21, see appendix 2.1) and indicate that the diol **199** had been produced exclusively with *cis*-stereochemisty as would be predicted from the formation of carbocyclic diols using SmI_2.[82] It should be noted that this is the first reported example for the formation of a *N*-heterocycle by pinacol coupling of a diketone precursor.



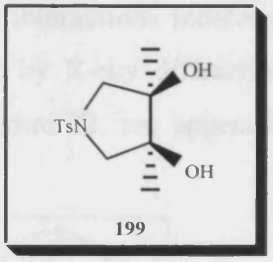
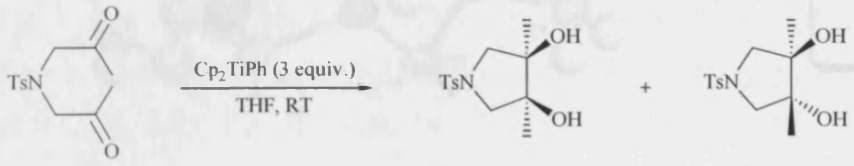


Figure 21

In comparison treatment of **178** with Cp_2TiPh under the general reaction conditions gave a mixture of the two isomeric diols **199** and **200** as judged by the ^1H NMR of the crude reaction mixture (Scheme 82).



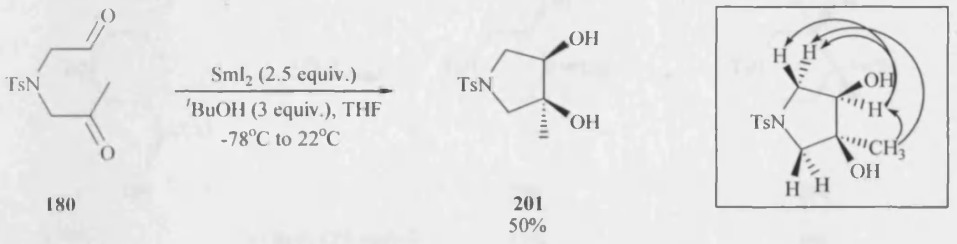
178 **199** 5% **200** 64%

Scheme 82

Separation of this mixture by flash column chromatography gave the *trans*-diol **200** as the major product (64 %) together with a small amount of the *cis*-stereoisomer **199** (5 %). The

trans-stereochemistry was assigned to **200** on the basis of ^{1}H and ^{13}C NMR analysis. The stereoselective formation of the *trans*-diol **200** in this reaction is in accordance to the results reported for carbocyclic systems.[72, 126] The stereoselectivity of the reaction (14 : 1, **200** : **199**) is slightly lower than the corresponding SmI_2-mediated reaction. However, this is the first example of the use of this low valent titanium species to produce a nitrogen heterocycle.

Having successfully completed the stereoselective pinacol coupling of **178** we next turned our attention to reactions of the keto-aldehyde **180** with SmI_2 and Cp_2TiPh. Both these reactions were previously investigated by S. Lowe[108] and were repeated here in an effort to improve the yield and to confirm the stereochemistry of the products. Thus, treatment of **180** with freshly prepared SmI_2 gave a single isomer (by ^{1}H and ^{13}C NMR) of the diol **201** in 50 % yield (Scheme 83) (this compared favourably with the yield of 29 % previously achieved by Lowe). In addition Lowe had previously predicted the *cis* relationship of the two hydroxyl groups in **201** from a series of NMR studies, primarily from the nOe interactions indicated (Scheme 83). Fortunately we were able to confirm this assignment by X-ray diffraction analysis of suitable crystals of **201** (from $CHCl_3$:Et_2O) as shown (Figure 22, see appendix 2.2).



180 **201** 50%

Scheme 83

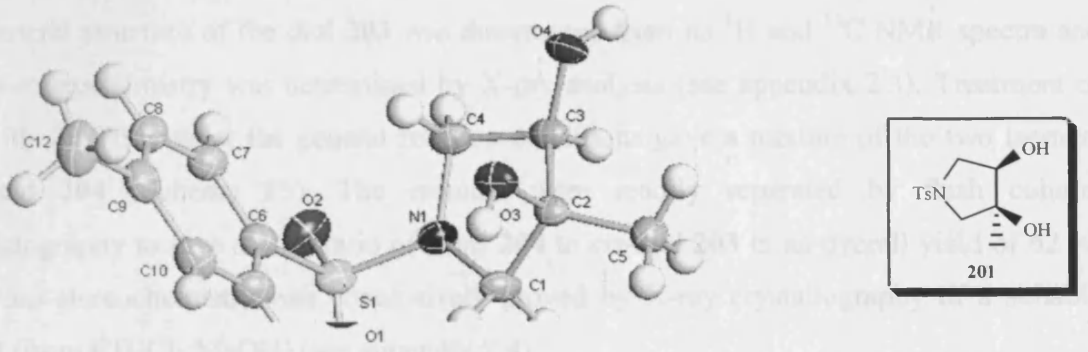
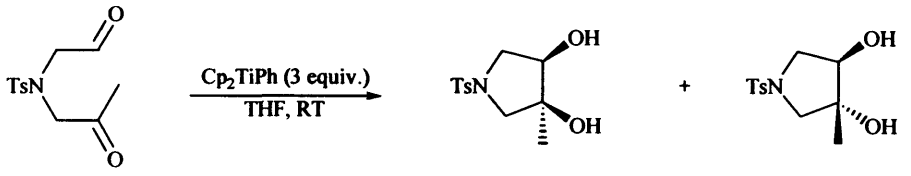


Figure 22

Reaction of **180** with Cp_2TiPh gave a mixture of two products which could be separated by column chromatography to give both *cis*-diol **201** and *trans*-diol **202** in overall 77 % yield

and in a 4 : 1 ratio (**202** : **201**) (Scheme 84). This yield is considerably improved to the initial studies (20 %) in which the stereoselectivity was also not reported.[108]

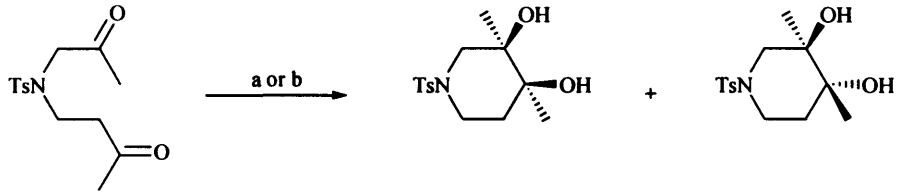


180 **201** 18% **202** 59%

Scheme 84

3.7 Pinacol Coupling Reactions Generating Piperidines

Diketone **189** underwent pinacol coupling with SmI_2 to give only the *cis* piperidine diol **203** in excellent yield (73 %) (Scheme 85) with no evidence for formation of any of the *trans*-isomer **204** (by inspection of the ^1H and ^{13}C NMR of the crude reaction mixture).



189 **203** **204**

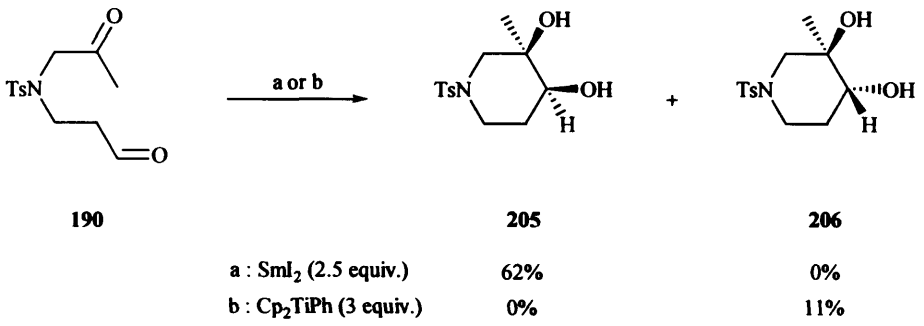
a : SmI_2 (2.5 equiv.)	73%	0%
b : Cp_2TiPh (3 equiv.)	9%	53%

Scheme 85

The general structure of the diol **203** was determined from its ^1H and ^{13}C NMR spectra and the *cis*-stereochemistry was determined by X-ray analysis (see appendix 2.3). Treatment of **189** with Cp_2TiPh under the general reaction conditions gave a mixture of the two isomers **203** and **204** (Scheme 85). The isomers were readily separated by flash column chromatography to give a 6 : 1 ratio of *trans* **204** to *cis*-diol **203** in an overall yield of 62 %. The *trans*-stereochemistry was conclusively proved by X-ray crystallography of a suitable crystal (from CH_2Cl_2:MeOH) (see appendix 2.4).

Again S. Lowe has reported the reaction of the keto-aldehyde **190** with SmI_2 and Cp_2TiPh and both reactions were repeated to improve the yield and confirm the stereoselectivity of the pinacol coupling (Scheme 86). Thus treatment of **190** with SmI_2 gave a single isomer of the diol **205** in 62 % yield; the yield was pleasingly improved from the 38 % reported previously.

Fortunately crystals of **205** suitable for X-ray analysis could be obtained (from $CHCl_3$:MeOH) and this proved the *cis*-stereochemistry shown (see appendix 2.5).



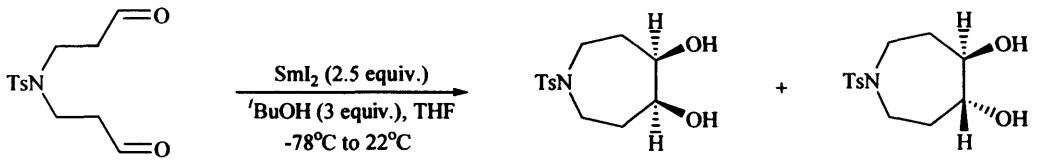
190	205	206
a : SmI_2 (2.5 equiv.)	62%	0%
b : Cp_2TiPh (3 equiv.)	0%	11%

Scheme 86

By comparison reaction of **190** with Cp_2TiPh gave diol **206** (Scheme 86) in a very low yield (11 %). There were also other unidentifiable products isolated which may explain why diol **206** was isolated in lower yield compared to the yield previously achieved by Lowe (37 %).[108] The *trans*-relationship of the hydroxyl groups in diol **206** was determined from comparison of the ^1H and ^{13}C NMR spectra to that of the *cis*-diol **205**.

3.8 Pinacol Coupling Reactions Generating Azepanes

Having successfully synthesised a number of pyrrolidine and piperidine systems we next turned our attention to accessing azepanes. We first explored the pinacol reaction of the dialdehyde **192**. The SmI_2-mediated pinacol reaction of **192** had already been carried out by S. Lowe and shown to give a heterocyclic diol in 30 % yield although the stereochemistry of the product had not been established. In our hands reaction of **192** with SmI_2 gave the seven membered heterocyclic diol as a 4 : 1 mixture (as judged from ^1H and ^{13}C NMR spectroscopy) of isomers in 46 % total yield (Scheme 87).



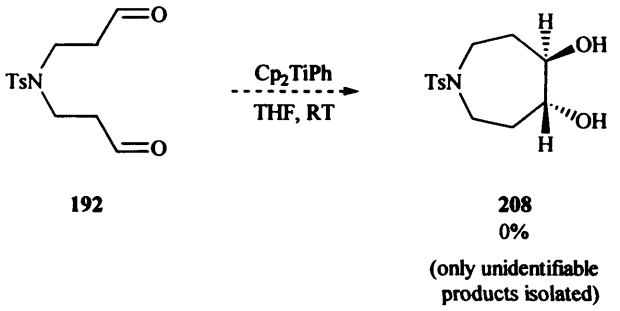
192	207	208
	37%	9%

Scheme 87

Separation of these two isomers proved difficult but careful chromatography gave a small amount (20 %) of the major isomer **207** in pure form. Assignment of the *cis*-stereochemistry to **207** proved somewhat difficult. Attempts to derivatise **207** to provide crystals suitable for

X-ray crystallography were unsuccessful. Thus, the *cis*-stereochemistry of **207** was finally assigned by synthesis of **207** *via* an alternative synthetic pathway involving ring closing metathesis of diene **161** and subsequent dihydroxylation which necessarily gives a *cis*-diol (these reactions are discussed in section 3.13).

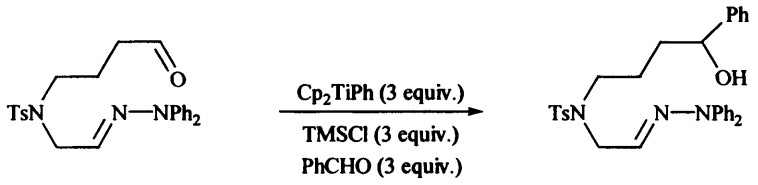
In comparison, reaction of the dialdehyde **192** with Cp_2TiPh gave only unidentifiable products and there was no sign of the formation of either the diols **207** or **208** from the crude NMR of the reaction mixture.



192 → **208** 0% (only unidentifiable products isolated)

Scheme 88

The failure of the Cp_2TiPh reagent to give any pinacol product on reaction with **192** is disappointing. However, there are no reports of this reagent having been successfully used for the formation of a seven membered ring and it may be a reagent limitation. Indeed Skrydstrup and co-workers[68] have reported their attempts to carry out a pinacol-type coupling of the carbonylhydrazone **144c** using Cp_2TiPh (Scheme 89). These authors attempts turned out to be ineffective. The major product isolated from this reaction was the alcohol **209** which had been produced by transfer of the phenyl group from the titanium centre to the aldehyde. These observations could indicate why the reaction of dialdehyde **192** with Cp_2TiPh (Scheme 88) did not give desired diol **208**, but gave unidentifiable products.

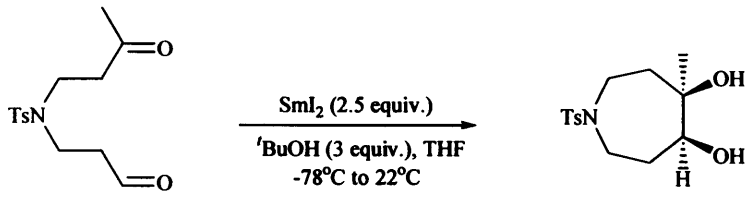


144c → **209** 53%

Scheme 89

Reaction of the keto-aldehyde **194** with SmI_2 gave a single isomer (by ^1H and ^{13}C NMR) of diol **210** in a modest 25 % yield (Scheme 90). The rest of the reaction mixture could not be identified although there was no evidence for any formation of the corresponding *trans*-diol. Assignment of the *cis*-stereochemistry to **210** was attempted from NOESY spectra however

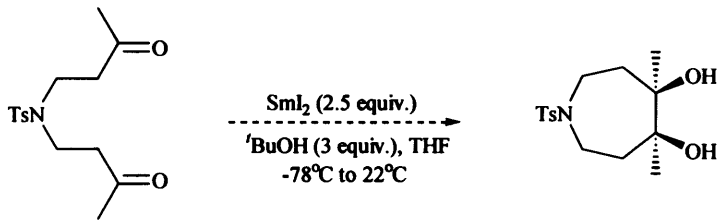
this proved inconclusive. Thus recourse was made to the alternative synthesis of **210** by *cis*-dihydroxylation of the corresponding cyclic olefin (discussed in section 3.13), which gave material identical to the pinacol product thus confirming the *cis*-stereoselectivity of the reaction.



194 **210** 25%

Scheme 90

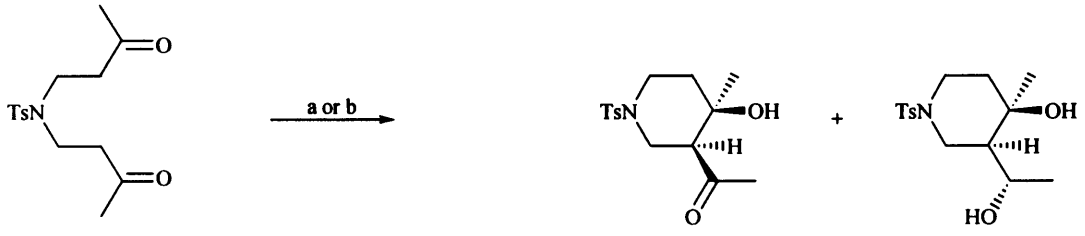
Finally in this azepanes series SmI_2-mediated cyclisation of diketone **193** was attempted in the expectation of producing the *cis*-diol **211** (Scheme 91).



193 **211**

Scheme 91

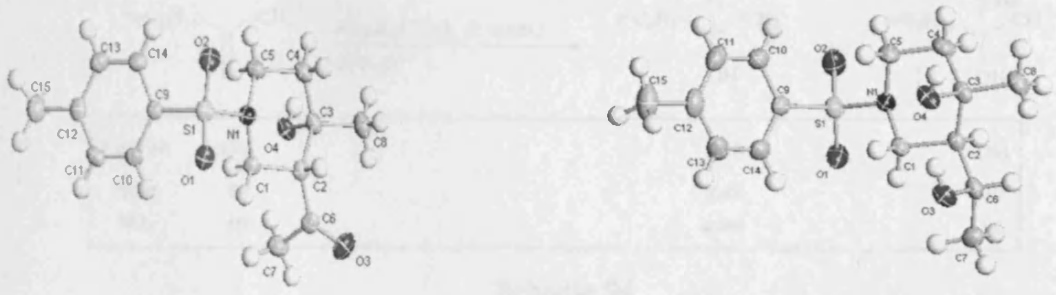
However, whilst reaction of **193** under the standard SmI_2 conditions resulted in conversion of all of the starting material, NMR analysis of the crude reaction mixture did not indicate the presence of **211**. Careful chromatography allowed for the isolation of four components from the reaction mixture. NMR analysis of two of these components **212** (47 %) and **213** (11 %) showed them to be the piperidines indicated (Scheme 92) and their relative stereochemistries were confirmed by X-ray crystallographic analysis (Figure 23, see appendix 2.6 and 2.7). Unfortunately the other two products (33 % and 9 %) could not be identified on the basis of their ^1H and ^{13}C NMR spectra.



193 **212** **213**

a. SmI_2 (2.5 equiv.), ^{t}BuOH (3 equiv.), THF, -78 °C to 22°C	47%	11%
b. SmI_2 (2.5 equiv.), NiI_2 (1mol%) ^{t}BuOH (3 equiv.), THF, -78 °C to 22°C	43%	18%

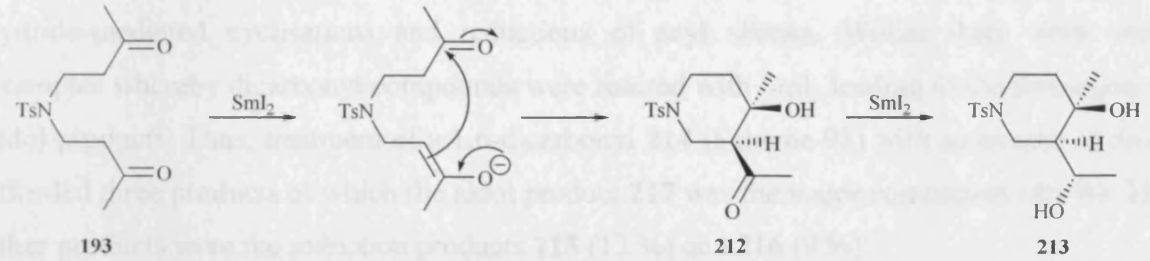
Scheme 92



212 **213**

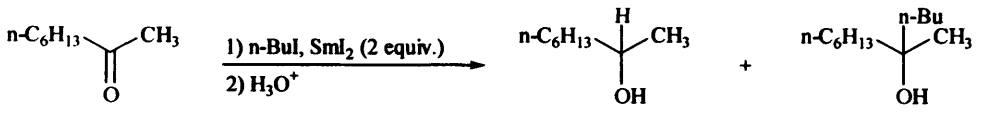
Figure 23

The formation of these unexpected products can be explained by stereoselective intramolecular aldol condensation of diketone **193** to form ketone **212**, which is subsequently stereoselectively reduced by SmI_2 to diol **213** (Scheme 93). The fact that the diketone **193** seemingly undergoes an aldol reaction in preference to a pinacol coupling is interesting. We initially thought that by increasing the reducing ability of the SmI_2 we may be able to 'force' formation of the ketyl radical from **193** thus generating the expected pinacol product diol.



Scheme 93

The reduction potential of SmI_2 solutions can be modified by the addition of suitable co-solvents and/or transition metal salts.[127] Thus the addition of HMPA to THF solutions of SmI_2 has been shown to increase the reduction potential.[128] In addition Kagan and co-workers have shown that the addition of small amounts (*ca.* 1 mol%) of NiI_2 can significantly accelerate SmI_2-mediated reactions.[127] An example from this study is given in scheme 94 showing the dramatic increase in reactivity on addition of NiI_2 (presumably due to the increased reduction potential).

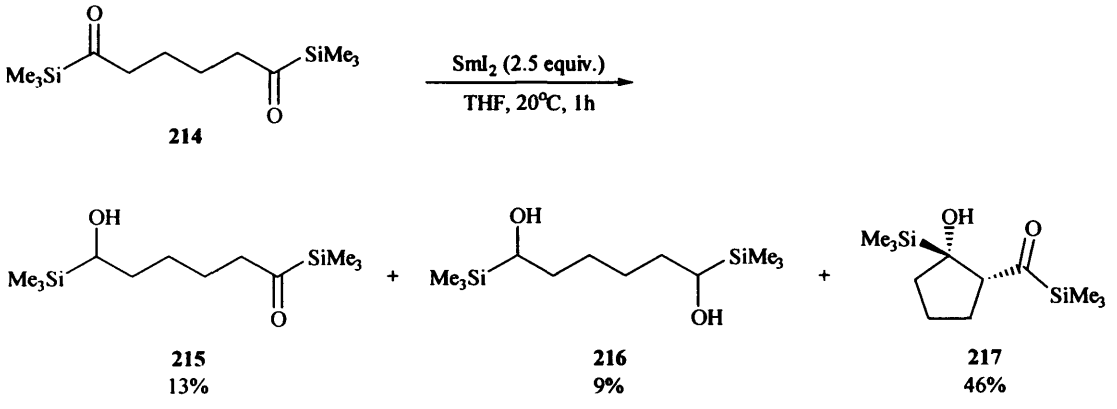


Catalyst	(%)	(%)	(%)
None	80	trace	20
NiI_2	10	trace	90

Scheme 94

Reaction of the diketone **193** under our standard conditions and employing 1 mol% of NiI_2 catalyst, however, still failed to give any of the expected diol **211**. Again only two compounds isolated from the reaction were identifiable, the aldol products **212** and **213** in comparable yields to the previous reaction (Scheme 92).

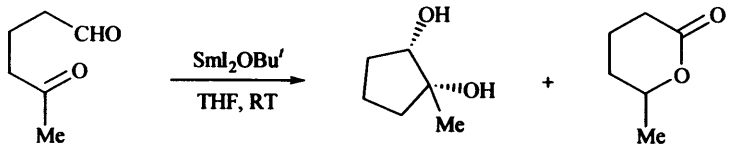
The preference of diketone **193** to undergo an aldol reaction over the pinacol coupling was unexpected. Analogous aldol side products are not well documented in SmI_2-mediated reactions. There are only two reports of this type of reaction and one being the work by Chuang and co-workers.[129] These authors were investigating the SmI_2- and tributyltin hydride-mediated cyclisations and reductions of acyl silanes. Within their work were examples whereby dicarbonyl compounds were reacted with SmI_2 leading to the formation of aldol products. Thus, treatment of a 1,6-dicarbonyl **214** (Scheme 95) with an excess of SmI_2 afforded three products of which the aldol product **217** was the major component (46 %). The other products were the reduction products **215** (13 %) and **216** (9 %).



Scheme 95

A second report has been published by Unenishi and co-workers concerning Sm^{2+}- and Sm^{3+}-mediated reactions of γ-oxy-δ-keto aldehydes.[130] In this study reaction of the keto aldehyde **218** with SmI_2OBu^t did not give desired diol **219** but gave a very low yield of lactone **220**.

The authors observed that this reaction was messy and aldol products were also isolated although further details were not elaborated.



218 **219** 0% **220** ~10%

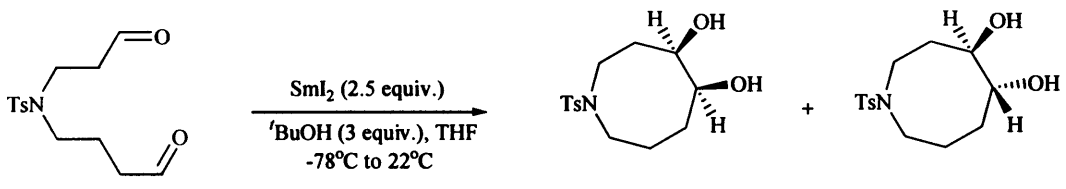
Scheme 96

Catalysis of the aldol reaction of **193** may have been facilitated by some Sm^{3+} species present in the reaction mixture. However, reaction of **193** with 20 mol% SmI_3 gave no aldol products and only starting material was re-isolated. Thus, the reasons for formation of **212** and **213** in preference to the azepane diol are not clear at present.

The failure of Cp_2TiPh to furnish 7-membered rings (Scheme 88) is in accordance with the analogous reactions of carbonylhydrazones, thus Cp_2TiPh-mediated pinacol coupling reactions of the keto-aldehyde **194** and diketone **193** were not investigated.

3.9 Pinacol Coupling Reactions Generating Azocane and 5,5-bicyclic systems

The use of SmI_2-mediated pinacol reactions to generate 8-membered *N*-heterocyclic diols **221** and **222** from dialdehyde **196** was also successful albeit in low yield (16 %) (Scheme 97). Examination of the ^1H and ^{13}C NMR of the diol mixture indicated a ratio of 3 : 1 for **221** : **222** respectively and careful chromatography allowed isolation of the major isomer **221** in 10 % yield. This *cis*-stereochemistry for **221** was confirmed by X-ray diffraction analysis of suitable crystals (from CH_2Cl_2:MeOH) (see appendix 2.8).

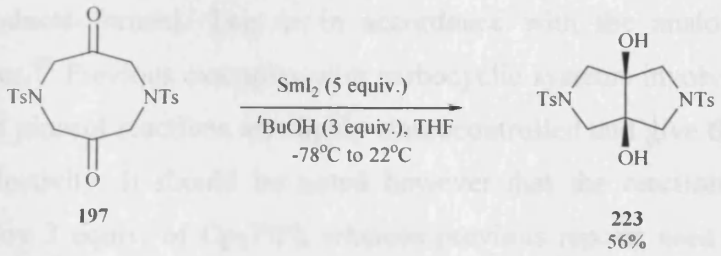


196 **221** 10% **222** 6%

Scheme 97

Treatment of diketone **197** with SmI_2 successfully generated 5-5 fused bicyclic diol **223** in good yield (Scheme 98). Only the *cis*-diol stereochemistry is possible in the product and this

was confirmed by X-ray diffraction analysis (Figure 24 and see appendix 2.9), which showed that **223** adopted an interesting 'W-conformation' in the crystal lattice.



Scheme 98

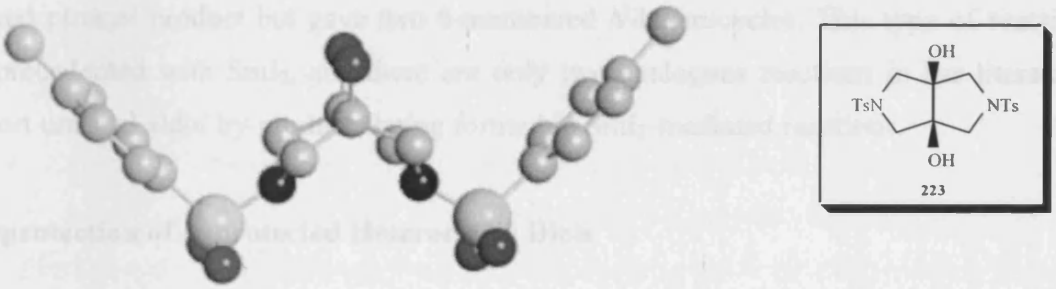


Figure 24

3.10 Summary of the Pinacol Coupling Results

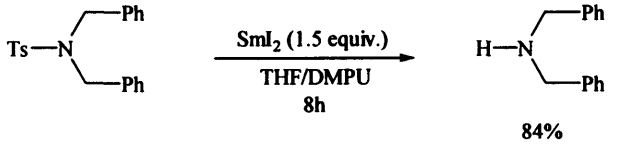
From the results above it can be stated that these are the first successful diastereoselective pinacol coupling reactions of dicarbonyls to produce *N*-protected heterocyclic diols using both SmI_2 and Cp_2TiPh. The use of SmI_2 reagent conclusively shows that this agent mediates the successful cyclisation of 5-8-membered rings to form dominantly the *cis*-diol. The formation of pyrrolidines (**199** and **201**) and piperidines (**203** and **205**) resulted in good yields and with complete diastereoselectivity for the *cis*-diols. Not surprisingly the formation of 7- and 8-membered ring systems (**207** and **221**) were less efficient and occurred with lower levels of stereocontrol producing significant amounts of the *trans*-diols. The trends for the SmI_2-mediated pinacol reactions are very comparable to those reported for intramolecular pinacol reactions of carbocyclic systems. These similarities are that the *cis*-diols are formed with high diastereocontrol in the formation of 5- and 6–membered ring systems (compare diol **203**; Scheme 85 with Figure 22; Chapter 3 section 3.6). The Cp_2TiPh-mediated pinacol reactions have successfully produced pyrrolidines (**200** and **202**) and piperidines (**204** and **206**) with *trans*-orientated diols. The levels of diastereoselectivity, 4 : 1 to 8 : 1 *trans* : *cis* are

lower than for the corresponding SmI_2-mediated pinacol reactions, however the *trans*-diol could be obtained in pure form in moderate to good yields. The only drawback was the failure of Cp_2TiPh to mediate the formation of 7- and 8-membered ring systems with only unidentifiable products formed. This is in accordance with the analogous reactions of carbonylhydrazones.[68] Previous examples with carbocyclic systems involving intramolecular Cp_2TiPh-mediated pinacol reactions are highly stereocontrolled and give the *trans*-diol in 91 : 9 or greater selectivity. It should be noted however that the reaction conditions differ slightly (we employ 3 equiv. of Cp_2TiPh whereas previous reports used catalytic Cp_2TiPh with Zn and/or Me_3SiCl).

Interestingly the reaction of the diketone **193** with SmI_2 gave none of the desired 7-membered pinacol product but gave two 6-membered *N*-heterocycles. This type of reaction was unprecedented with SmI_2, and there are only two analogous reactions in the literature that report unusual aldol by-products being formed in SmI_2-mediated reactions.

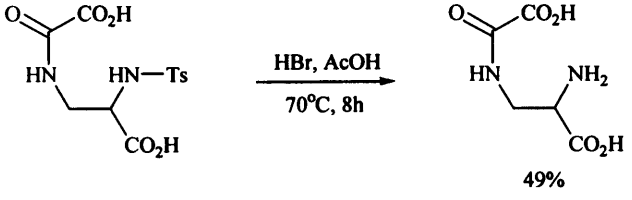
3.11 Deprotection of *N*-protected Heterocyclic Diols

Having successfully produced a number of novel *N*-protected heterocyclic diols we next turned our attention to the removal of the tosyl protecting group. This would allow the generation of a series of novel amino-diols that could be tested for any biological activity (*e.g.* glycosidase inhibition). There are a number of possible methods for the deprotection of a *N*-tosyl group. These include heating with excess SmI_2 in THF/DMPU.[131] and an example is shown (Scheme 99).



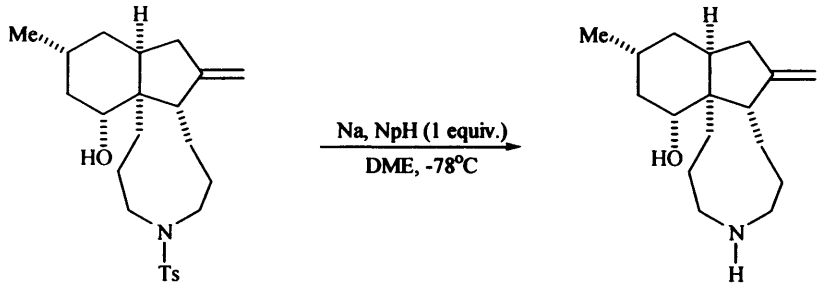
Scheme 99

Another method for tosyl deprotection involves the use of hydrobromic acid in acetic acid. An example is given[132] (Scheme 100) for a substrate which proved resistant to other deprotection methods.



Scheme 100

Tosyl groups can also be removed using sodium naphthalenide. An example is in the synthesis of (±)-fawcettimine,[133] where deprotection of **224** was achieved using sodium naphthalenide in DME to give **225** in excellent yield (94 %). Other methods had lead to the reduction of the exocyclic methylene group.

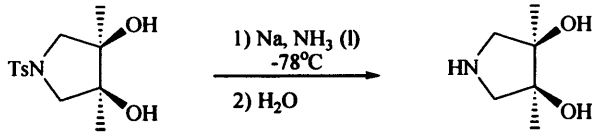


224 **225** 94%

Scheme 101

However, in choosing a method for the deprotection of the heterocyclic diols in this study we were aware of potential problems that could arise due to the possible water solubility of the product amino alcohols. Consequently we decided to employ a method that would allow us to remove any aqueous work-up from the reaction procedure. Thus, we chose to employ sodium in liquid ammonia to remove the *N*-tosyl group. This deep blue solution contains solvated electrons, which readily reduce the *p*-toluene sulfonyl group resulting in N-S bond cleavage. Work-up of the reactions simply involved evaporation of all volatiles followed by flash column chromatography of the resulting crude material on silica to furnish the amino alcohols.

We initially explored the deprotection of the pyrrolidine diol **199**. Thus, **199** was treated with sodium metal (3 molar equivalents) in liquid ammonia at -78°C. After 30 mins a blue colouration remained and excess ammonia was allowed to evaporate at RT (Scheme 102).

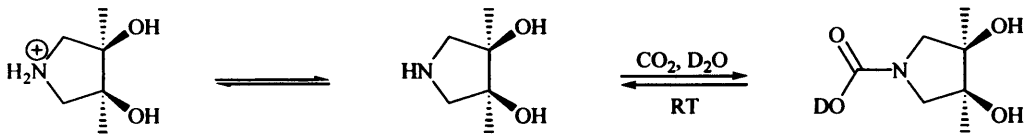


199 **226** 56%

Scheme 102

We initially attempted to purify the product amino alcohol **226** from this crude material using ion-exchange chromatography using freshly regenerated Dowex-50 (H^+ form). Unfortunately

despite repeated attempts we could only isolate material that was not particularly pure by ^1H NMR spectroscopy after elution with ammonia solution. Pleasingly, however, repetition of this reaction followed by purification by flash column chromatography on silica using methanol and 2M ammonia in methanol as eluent, gave the pure amine **226** in moderate yield (56 %) (Scheme 102). The ^1H spectrum of the product **226** is expected to be very simple and easy to assign. Examination of the ^1H and ^{13}C NMR spectra in D_2O for the isolated product indicated a doubling up of the signals. Upon addition of a drop of DCl these signals collapsed to a single set with the expected pattern (*i.e.* an AB quartet at 3.46 ppm and a singlet at 1.40 ppm). Basification of this solution with NaOD again gave only a single AB quartet and singlet at 2.86 ppm and 1.19 ppm respectively. From these experiments we proposed that the original 'doubling up' of signals was due to an equilibrium between the free base **226** and protonated form **227** as shown (Scheme 103).



227 **226** **228**

Scheme 103

Interestingly it was found that if a sample of amine **226** was left for prolonged periods in D_2O then on NMR analysis the ^{13}C spectrum exhibited an extra quaternary carbon signal in the 160 - 170 ppm region. These signals are consistent with the carbon of the carbonyl group of a carbamate such as **228** and suggest that the amine **226** is reacting with carbon dioxide dissolved in the D_2O (Scheme 103). Such carbamic acids are relatively stable under basic conditions[134] however they are unstable under acidic conditions undergoing spontaneous decarboxylation. Pleasingly on addition of DCl to this NMR sample the resulting spectrum showed only the presence of a single species, which was presumably the deuterochloride salt of the amine **226**. Based on this observation the amines isolated from the other deprotection reactions were kept in D_2O only for a minimum amount of time.

Following the successful deprotection of the diol **199** the other *N*-tosyl heterocycles were also subjected to the same deprotection procedure. The purified yields of the product amino diols are shown in table 2.

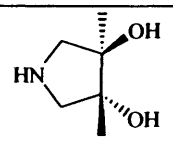
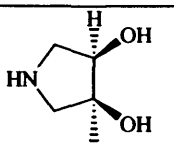
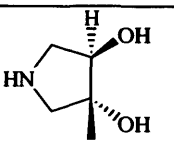
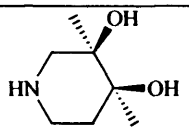
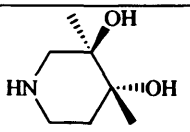
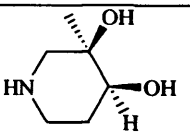
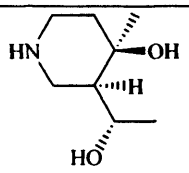
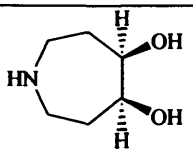
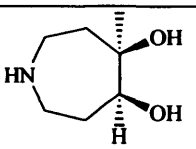
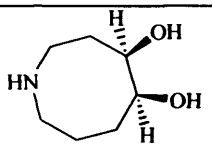
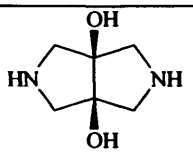
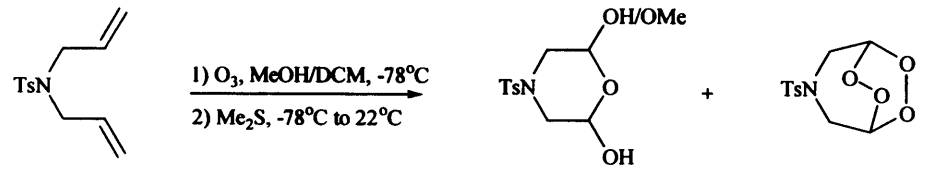
 **229** 82%	 **230** 58%	 **231** 73%
 **232** 83%	 **233** 82%	 **234** 83%
 **235** 83%	 **236** 60%	 **237** 75%
 **238** 63%	 **239** 78%	

Table 2

As can be seen all the deprotections successfully gave the amino-diols generally in good yield. The one exception was the attempted deprotection of the aldol product **212** which gave only unidentifiable material when subjected to the standard Na/NH_3 (l) conditions. Whilst this was not explored further the failure of this deprotection may be due to the reactive ketone moiety in **212**.

3.12 Pinacol Coupling Reactions Involving 'Unstable' Dicarbonyl Compounds

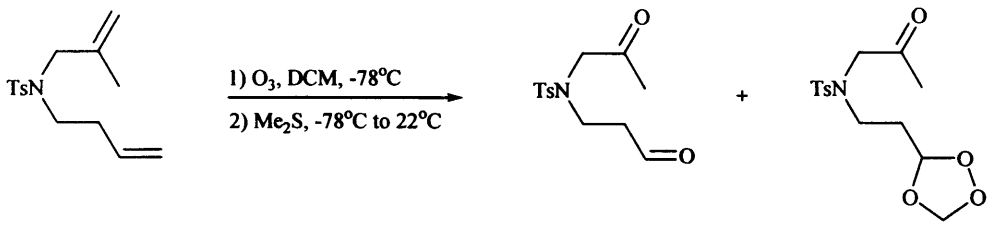
In section 3.4 the successful ozonolysis of a variety of dienes to give the corresponding dicarbonyl compounds was discussed. These reactions were carried out in the participating solvent methanol and although in a few cases cyclic acetal formation was observed, this side-reaction was not problematic. However, in two cases ozonolysis of the diene precursors **155** and **158** gave very little formation of the corresponding dicarbonyl. Thus, ozonolysis of **155** gave crude material having no observable aldehyde peak in the ^1H NMR spectrum and which gave signals around 90 - 95 ppm in ^{13}C NMR spectrum and on peaks at *m/z* 272 and 288 in the electrospray mass spectrum suggesting the formation of **240** and/or **241**. Similar results had also been observed previously by Lowe (Scheme 104).[108]



155 240 241

Scheme 104

Similarly ozonolysis of diene **158** gave, after workup, crude material that did show aldehyde signals in the ^{1}H and ^{13}C NMR. Attempted purification of this material was unsuccessful as no dial **242** could be isolated, although this may have been due to the potential instability of **242** on silica. Thus, it seemed likely that the instability of the dials **182** and **242** would prevent their use in pinacol coupling reactions therefore possibly limiting the scope of this methodology. In an effort to address this potential limitation we decided to investigate the ozonolysis of both **155** and **158** in the non-participating solvent dichloromethane in an attempt to prevent any possible cyclic acetal formation due to the solvent methanol. However, we initially chose to look at the reaction of the diene **160** under these conditions to see what effect, if any, there would be on changing from methanol to dichloromethane as the reaction solvent (previous ozonolysis of **160** in methanol had given both the keto-aldehyde **190** together with some of the cyclic ketal **191** (see Scheme 77). Thus treatment of **160** with ozone in dichloromethane followed by a reductive work up with dimethyl sulfide gave, after flash column chromatography, two products as shown (Scheme 105). The first of these was the expected keto-aldehyde **190** but unexpectedly the ozonide **243** was also isolated from this reaction (structure determined from ^{1}H and ^{13}C NMR analysis). The formation of **243** is presumably due to the lack of a participating solvent that can attack the molozonide intermediate (see section 3.4). Ozonide **243** proved to be relatively stable and was not converted to **190** even with prolonged treatment with dimethyl sulfide.

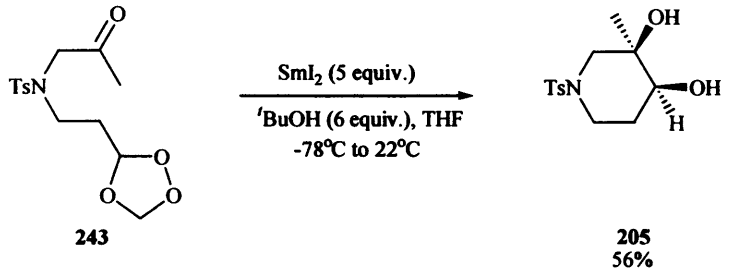


160 190 21% 243 28%

Scheme 105

The isolation of the ozonide **243** lead us to explore a possible novel one-pot two-step ozonide reduction-pinacol coupling reaction. We envisioned that treatment of **243** with excess SmI_2 would lead to sequential O-O bond reduction generating the keto-aldehyde **190** *in situ* which

would subsequently undergo a SmI_2-mediated pinacol coupling. Pleasingly treatment of **243** with SmI_2 (5 molar equivalents) gave the diol **205** in good yield (56 %) (Scheme 106) and with the same complete *cis*-stereoselectivity that had been observed in the pinacol coupling of **190** to generate **205**.

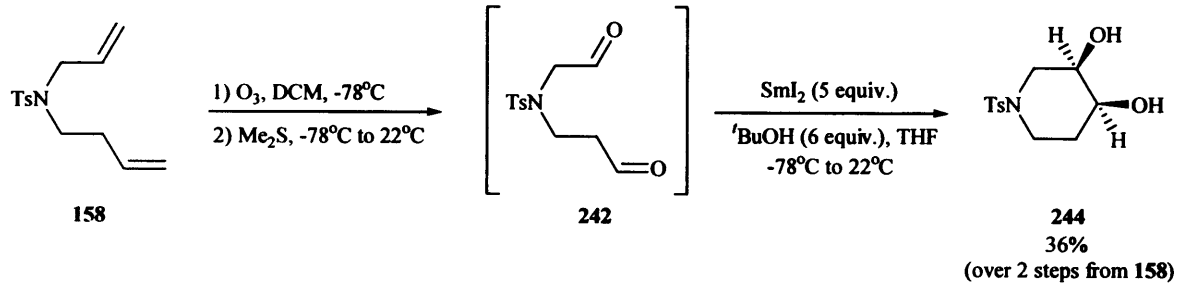


243 **205** 56%

Scheme 106

The successful formation of **205** from **243** in a comparable yield to the reduction of keto-aldehyde **190** (56 % v's 62 %) is the first ever report of such a sequential transformation. Additionally it opened up the possibility of directly converting ozonide products (from other ozonolysis reactions) to *N*-heterocyclic diols *without* the need to isolate potentially unstable dicarbonyls.

With this goal in mind we re-examined the ozonolysis and subsequent pinacol reaction of the diene **158** (Scheme 107). Thus ozonolysis of **158** in dichloromethane was followed by the usual reductive work up (Me_2S). ^1H and ^{13}C NMR analysis of the resulting crude reaction mixture showed very small signals (approximately 20 % from ^1H and ^{13}C NMR measurements) in the aldehyde region (^1H, 9 - 10 ppm; ^{13}C 200 - 210 ppm) although the majority of the signals observed were in the 5 - 6 ppm and 90 - 100 ppm region of the ^1H and ^{13}C NMR spectra respectively. Additionally electrospray mass spectrometry indicated that various acetals, peroxy or hydrated species had been formed but we could not use this data to conclusively assign the species present. This crude material from the ozonolysis reaction was treated with SmI_2 (5 molar equivalents) under standard pinacol coupling conditions. Pleasingly work up and purification of the reaction by column chromatography gave the diol **244** in moderate yield of 36 % over two steps (*i.e.* from **158**). Only one stereoisomer of the diol **244** was observed and the *cis*-diol stereochemistry assigned by comparison to material produced using the complementary RCM-dihydroxylation approach (see section 3.13).



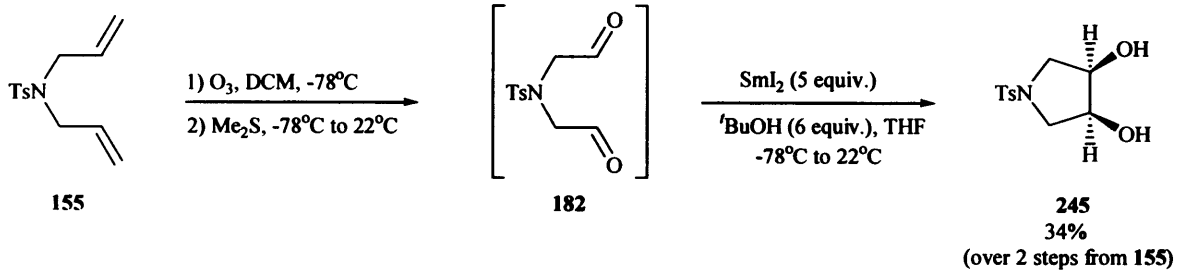
158 242 244

36%

(over 2 steps from **158**)

Scheme 107

The successful formation of the diol **244** without the need to isolate the unstable dial **242** was very encouraging and we next turned our attention to the analogous reaction of the diene **155** (Scheme 108).



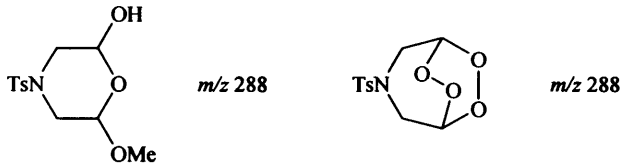
155 182 245

34%

(over 2 steps from **155**)

Scheme 108

Again ozonolysis of diene **155** in dichloromethane followed by reductive work up (Me_2S) gave a crude reaction product. Analysis by ^1H and ^{13}C NMR showed no indication of any aldehyde functionality and gave numerous signals in the 4.7 - 5.5 ppm region of the ^1H NMR spectrum and the 90 - 95 ppm region of the ^{13}C spectrum. These presumably arise from cyclic acetals/hydrates and/or ozonides. Mass spectrometric analysis (electrospray) indicated significant peaks at *m/z* 272 and 288. These fit with the possible formation of the cyclic acetal **246** (in the mass spectrometer) or the peroxy species **241**.

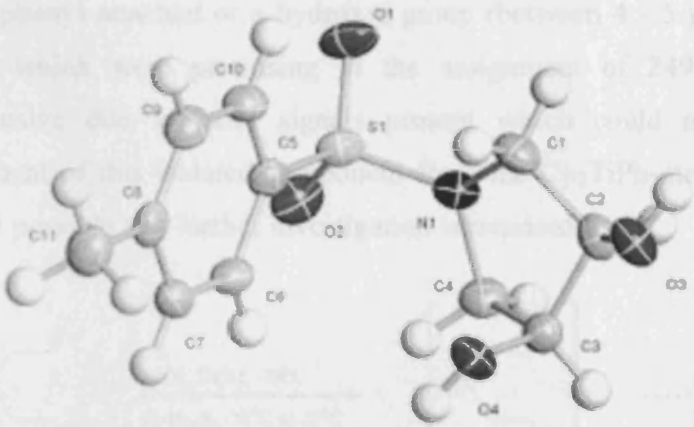


246 241

Figure 25

Reaction of this crude ozonolysis product(s) with SmI_2 (5 molar equivalents) gave, after purification by column chromatography, the diol **245** as a single isomer in moderate yield (34 % over the two steps). This exclusive *cis*-stereoselectivity was shown by X-ray diffraction analysis of the product **245** (Figure 26, see appendix 2.10). The crude material

isolated after the ozonolysis reaction contained DMSO. It is known that DMSO reacts with SmI_2,[73] however it didn't seem to be a problem in these two reactions.



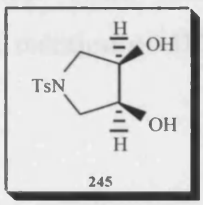
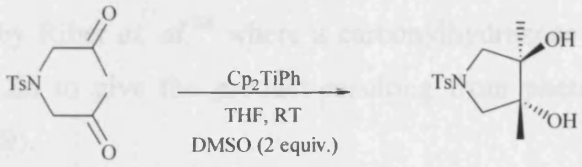


Figure 26

Having successfully carried out two SmI_2-mediated pinacol coupling on the crude ozonolysis products we turned our attention to the corresponding Cp_2TiPh-mediated reactions. As mentioned above a small quantity of DMSO is sometimes present in the crude ozonolysis products and so initially we examined the effect this could possibly have on the Cp_2TiPh-mediated reaction. Pleasingly reaction of the diketone **178** with Cp_2TiPh in the presence of two equivalents of DMSO gave the *trans*-diol **200** in good yield (*cf.* 64 % in absence of DMSO) (Scheme 109). This suggested that any sulfoxide present would not significantly interfere with the pinacol reaction.

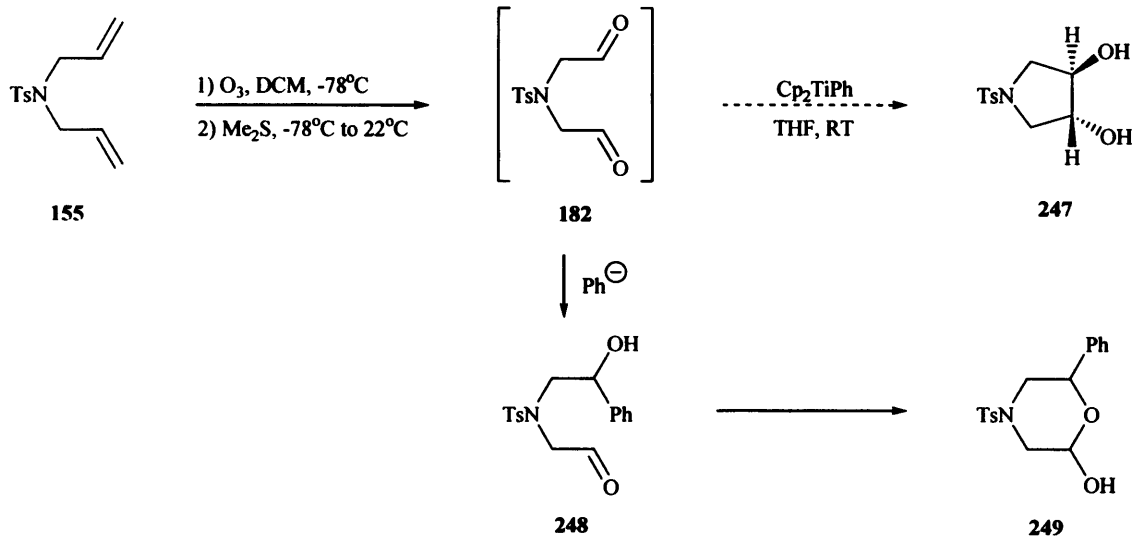


178 **200**
53%

Scheme 109

The reaction of the crude ozonolysis product from **155** with Cp_2TiPh was next attempted. Unfortunately none of the expected diol **247** was isolated (Scheme 110). TLC analysis indicated a couple of components and purification by flash column chromatography on silica gave only one identifiable product from the reaction in low yield (12 %). Mass spectroscopy was not very informative towards the structure of this product. However, NMR analysis showed that this isolated product to possibly be formed by attack of the phenyl group onto one aldehyde functionality (**248**) after reduction of the crude products (isolated from the

ozonolysis reaction) to the dialdehyde **182**. Subsequent cyclisation would then generate the possible cyclic acetal species (**249**). The ^{1}H spectrum of this isolated product showed signals for phenyl group protons (7 - 7.5 ppm) and two signals, which could be assigned to the -C-H with a phenyl attached or a hydroxyl group (between 4 - 5 ppm). The ^{13}C NMR exhibited signals which were promising in the assignment of **249** again spectral analysis was inconclusive due to extra signals present which could not be identified. Thus, final assignment of this isolated component from the Cp_2TiPh-mediated pinacol reaction of **182** was not possible and further investigation is required.

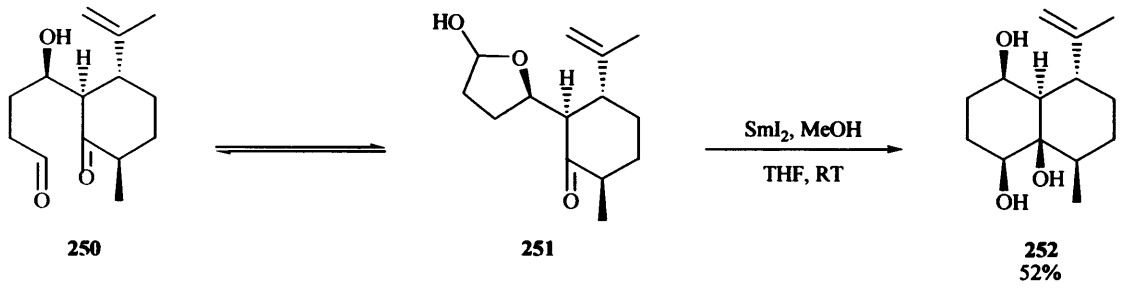


Scheme 110

A possible mechanism to explain this formation is the reduction of the ozonide to the dial and subsequent transfer of the phenyl (Ph) group by nucleophilic attack. The phenyl group would be expected to be nucleophilic on the Ti (IV) fragment than on the Ti (III) reagent. This result agrees with the report by Riber *et. al.*[68] where a carbonylhydrazone compound was reacted with $Cp_2Ti(Ph)Cl$ and Zn to give the product resulting from phenyl group attack on the carbonyl (see Scheme 89).

The successful SmI_2-mediated reactions generating the pyrrolidine **245** and piperidine **246** show that it is not necessary to isolate unstable dialdehydes prior to pinacol coupling. These novel transformations may be occurring by two possible pathways. Firstly, although dials **182** and **242** are not present to a large extent in the crude ozonolysis products they may be in equilibrium with cyclic hydrates. Pinacol coupling on any small amount of dialdehyde present would give the heterocyclic diols observed and further dialdehydes could be produced by re-establishment of the equilibrium. A similar situation has been previously reported by Kawatsura *et. al.*[135] where SmI_2-mediated pinacol coupling of a keto-aldehyde

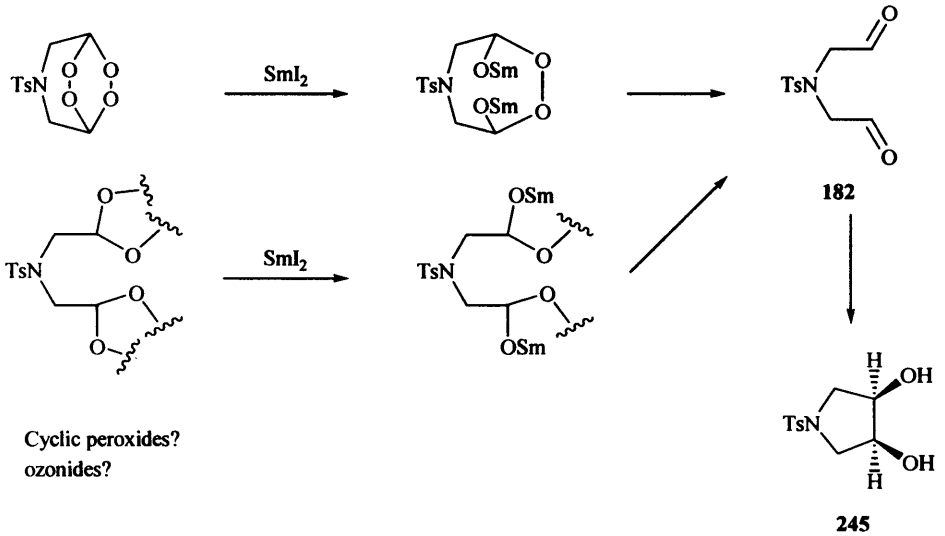
250 which is in equilibrium with the hemiacetal **251** to the corresponding triol **252** was achieved (Scheme 111).



250 **251** **252** 52%

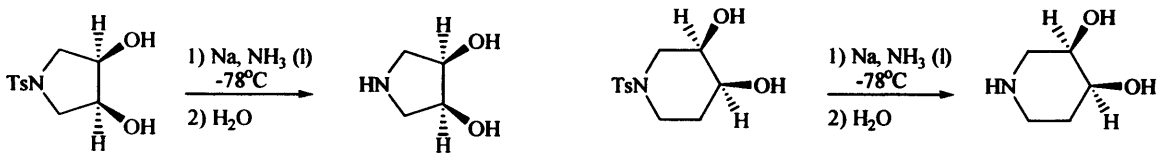
Scheme 111

However, previous studies by Lowe[108] had indicated that the cyclic hydrate **183** did *not* undergo pinacol reaction when treated with SmI_2. This was maybe due to the fact that the reduction of the cyclic hydrate to the dial would result in the loss of water and not simply a shift in equilibrium; and whilst this doesn't rule out this explanation it suggests that it is unlikely. An alternative explanation is based upon the results seen with stable ozonide **243**. It is possible (NMR and mass spectroscopic evidence) that the crude extracts from the ozonolysis reactions contain 'stable' peroxy species such as **241** (Figure 25). These species may react in similar manner to the ozonide **243** (Scheme 104) and be reduced by the SmI_2 to generate the dials **182** and **242** *in situ* which subsequently undergo pinacol coupling before they can form cyclic acetals or hydrates (Scheme 112).



Scheme 112

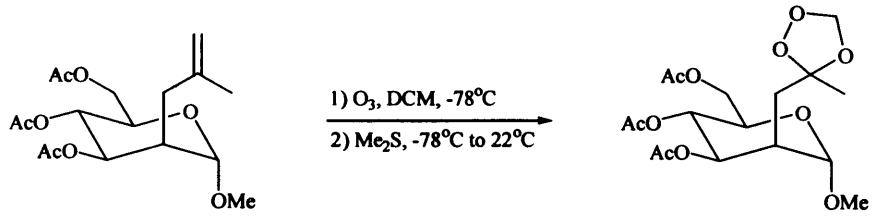
The 5-membered *N*-heterocyclic pyrrolidine **245** was tosyl deprotected under standard conditions to afford the amine **253** as shown (Scheme 113). Additionally piperidine **244** was also deprotected to give the amine **254** in moderate yield (43 %).



245 **253** 75% **244** **254** 43%

Scheme 113

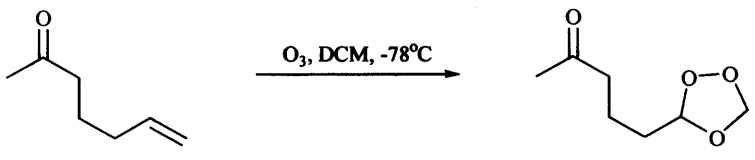
In an effort to examine this novel transformation further we investigated the potential isolation of stable ozonides or peroxides from the ozonolysis reactions. In certain cases ozonide compounds have been shown to be stable and can be successfully isolated.[136] Thus, Chen and Wiemer reported the isolation of a stable carbohydrate-derived ozonide **256**[137] from the reaction of **255** with ozone in CH_2Cl_2 at -78°C followed by reductive workup with dimethyl sulfide (Scheme 114). The authors postulated that the ozonides were formed and not further reduced to the carbonyl compounds due to the low reactivity of dimethyl sulfide.



255 **256** 71%

Scheme 114

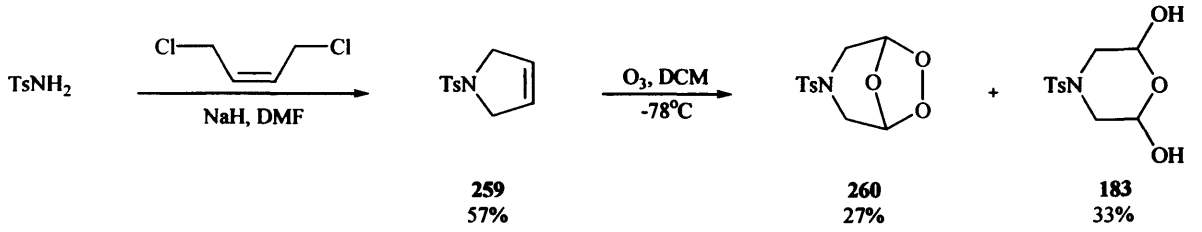
Another example where ozonides have been isolation is in a paper by Hon and co-workers.[138] The authors were synthesising ozonides to be subsequently treated with phosphonium ylides to give (*E*)-α,β-unsaturated carbonyl compounds. Thus, terminal alkene **257** was treated with ozone in dichloromethane at -78°C (no reducing reagent was used as the ozonide products were desired) to give ozonide **258** in excellent yield (93 %) (Scheme 115). Once again the ozonide was isolated by flash column chromatography and found to be very stable in the freezer for two weeks and decomposed only slowly at RT.



257 **258** 93%

Scheme 115

In our studies we employed the cyclic olefin **259** (produced from *p*-toluene sulfonamide as shown[139] (Scheme 116). Ozonolysis of **259** without reductive work up gave the stable ozonide **260** in moderate yield. However, reaction of **260** with SmI_2 did not give any of the expected pyrrolidine diol **245** and instead gave only a mixture of unidentifiable products. Unfortunately limitation in time meant that this initial result could not be pursued further.



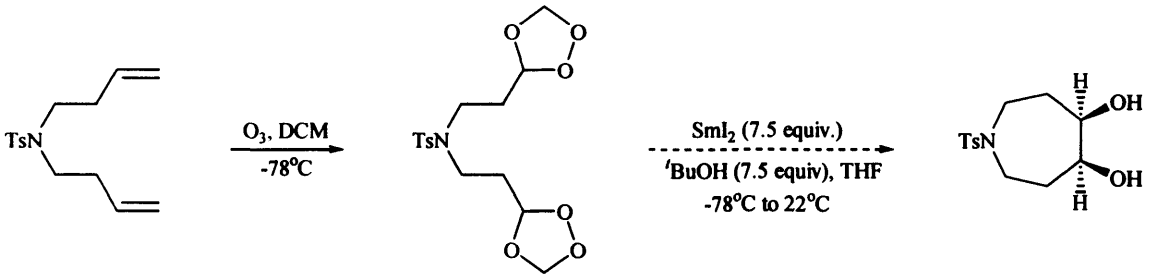
259 57%

260 27%

183 33%

Scheme 116

In an analogous manner ozonolysis of diene **161** without dimethyl sulfide work up gave a small amount of the ozonide **261** (Scheme 117) in addition to other unidentifiable products. However, treatment of **261** with excess SmI_2 (7.5 molar equivalents) again failed to generate any of the azepane **207** and lead only to unidentifiable products.



161

261 18%

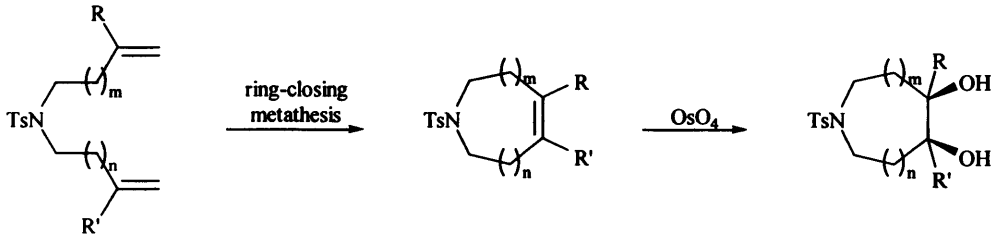
207

Scheme 117

Thus, in summary these results do not shed any further light on the mechanism of the pinacol reaction of crude ozonolysis products. The initial results seem to suggest that this novel transformation does not involve ozonides such as **260** and **261** although time limitations meant that these studies could not be completed. This does not rule out the possibility that other ozonides or peroxides are involved in the reaction as successful conversion of the stable ozonide **243** is possible. Further studies will be necessary to clarify this area.

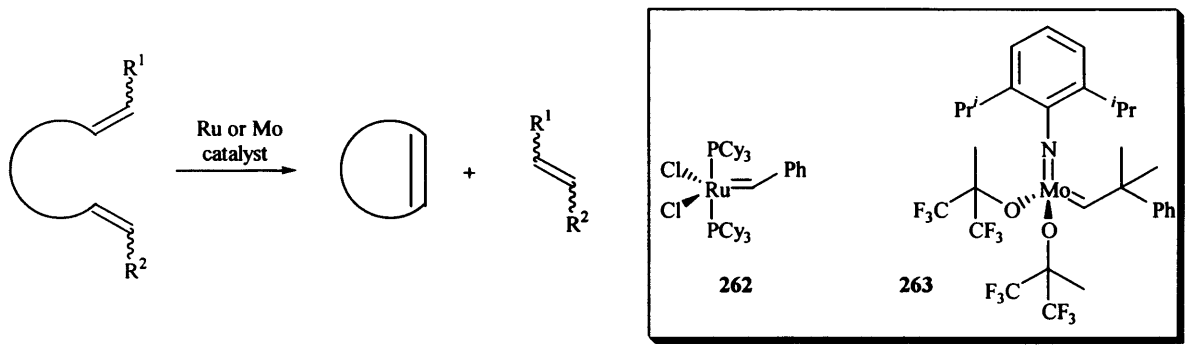
3.13 A Complementary Ring Closing Metathesis-Dihydroxylation Approach to Diols 207, 210 and 244

In sections 3.5-3.10 the synthesis of a number of *N*-heterocyclic diols by stereoselective pinacol coupling reactions was discussed. The stereochemistry of the majority of products was determined by a combination of NMR analysis (^{1}H and nOe studies) and where possible X-ray diffraction analysis. However, in a few cases NMR analysis proved insufficient and suitable crystals for X-ray analysis could not be grown. To confirm the stereochemistry of the diol in these cases we took recourse to their synthesis by an alternative route that would unambiguously generate the *cis*-diol isomer, namely a ring closing metathesis-dihydroxylation approach (Scheme 118).



Scheme 118

The ring closing metathesis reaction has recently enjoyed a great prominence in synthetic organic chemistry.[140] The reaction usually involves treatment of a suitable diene with a transition metal catalyst (those based on Molybdenum (Mo) and Ruthenium (Ru) are the most common) and results in the formation of a cyclic olefin together with loss of another alkene (Scheme 119) in a very efficient and high yielding process. The reaction is readily applied for the synthesis of *N*-heterocycles.[141]

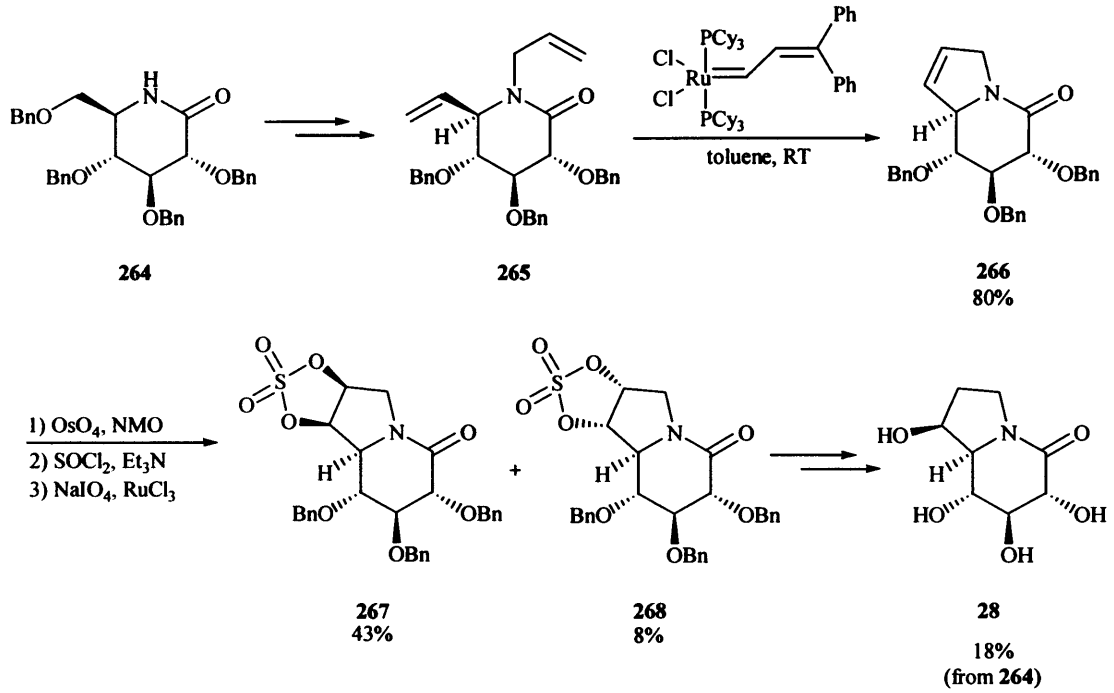


Scheme 119

The resulting cyclic alkene can then be further derivatised and one common transformation in the OsO_4-mediated *cis*-dihydroxylated reaction. The Grubb's catalyst **262** is the most widely

used catalyst for RCM reactions due to its increased tolerance towards functional groups and the somewhat higher selectivity and also sensitivity to the substitution pattern of alkenes than that exhibited by Mo-based Schrock catalysts, **263**.[142] This is shown by exceptional compatibility with ketone and aldehyde functionalities whereas Schrock catalysts are known to react with these groups.[141]

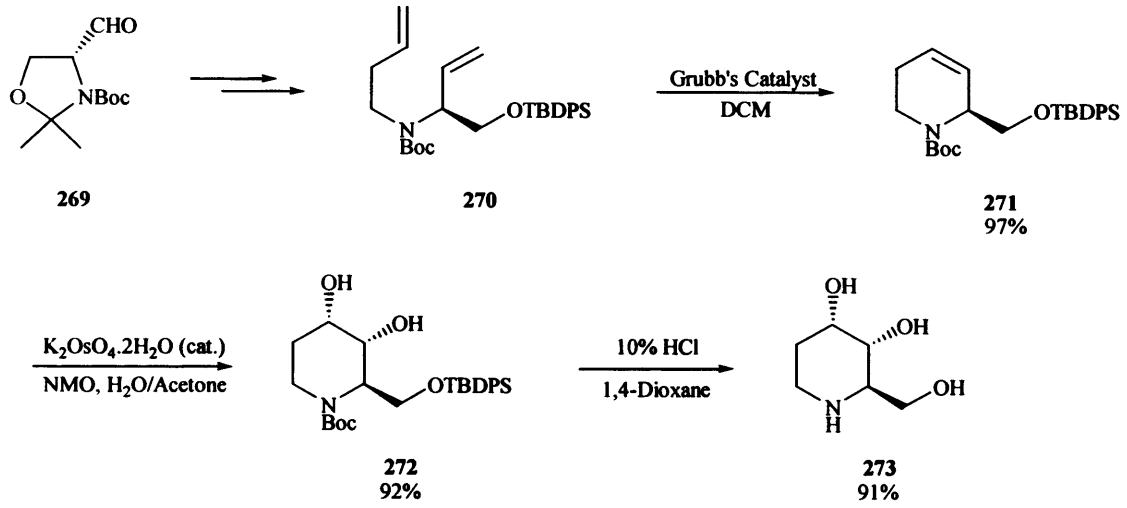
The combination of these two reactions has been employed in the synthesis of *N*-heterocyclic polyols including iminosugars and as such is a complementary synthetic strategy to the pinacol coupling approach discussed in this thesis. Examples of reported RCM-dihydroxylation based synthesis of iminosugars include a report by Pandit and co-workers who synthesised the bicyclic iminosugar castanospermine **28** (Scheme 120).[141] The authors started the synthesis by using sugar lactam **264** and manipulation gave diene **265**. Subsequent RCM employing a Ru catalyst gave olefin **266** in excellent yield. Dihydroxylation using OsO_4 and NMO gave an inseparable mixture of the expected diols. These diols were converted to the corresponding cyclic sulfates (**267** and **268**) of which the major compound **267** was isolated pure. Further manipulations of **267** lead to the desired iminosugar castanospermine **28**.



Scheme 120

In another paper the use of RCM and dihydroxylation reactions were employed by Takahata *et. al.* to synthesis various isomers of fagomine, as shown (Scheme 121).[143] The synthesis was initiated by the use of D-serine drived Garner aldehyde **269**. This aldehyde was manipulated over 3 steps to give the diene **270**, which was subsequently treated with Grubb's

catalyst to yield olefin **271**. This was dihydroxylated using catalytic $K_2OsO_4.2H_2O$ and NMO to give exclusively the diol **272** in excellent yield (91 %). Deprotection with 10 % HCl and purification lead to the isolation of 3-*epi*-fagomine **273**.



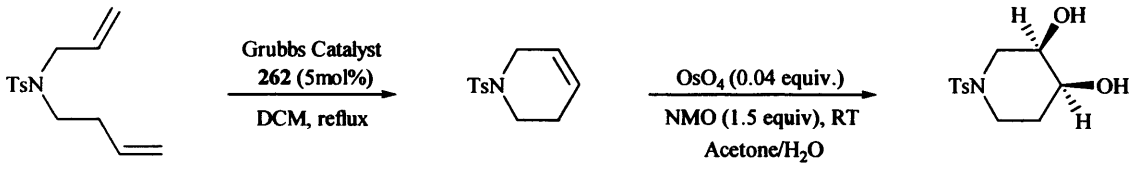
269 **270** **271** 97%

272 92% **273** 91%

Scheme 121

In this study we wanted to employ this approach to generate *cis*-diols so as to confirm the stereochemistry of some of our pinacol products. Additionally we could use the results we obtained to compare the relative merits of the two complementary strategies with the systems under investigation.

Treatment of diene **158** with Grubb's catalyst **262** in dichloromethane gave the olefin **274** in excellent isolated yield (98 %). Subsequently reaction of **274** with OsO_4 and NMO under Upjohn conditions[144] gave the diol **244** in 65 % yield (Scheme 122).

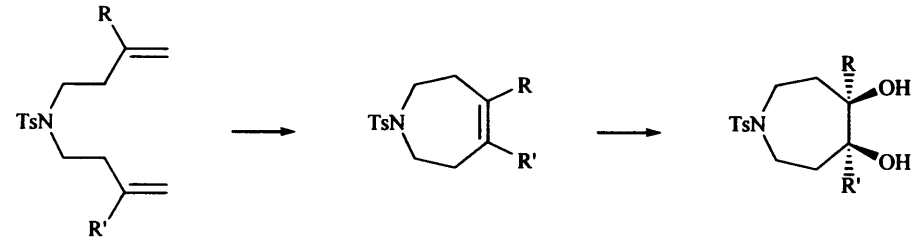


158 **274** 98% **244** 65%

Scheme 122

As stated above the stereochemistry of diol **244** is predetermined as OsO_4 carries out a *cis*-selective dihydroxylation reaction. Comparison of the data for **244** formed in this process to the diol isolated from the comparable SmI_2-mediated pinacol reaction (see Scheme 105) confirmed that the latter also possessed this *cis*-stereochemistry.

In an analogous manner the diols **207** and **210** were also synthesised (Scheme 123).



161: R = R' = H
163: R = Me, R' = H

275: 83%
276: 97%

207: 81%
210: 67%

Scheme 123

In general the RCM reactions gave the corresponding cyclic alkenes in good to excellent yields and the dihydroxylation reactions produced the diols in good yield. In all cases comparison of the spectral data for the product diols to those compounds formed from the corresponding SmI_2-mediated pinacol reactions confirmed the *cis*-stereoselectivity of the latter method.

3.14 Conclusions of RCM and Dihydroxylation Investigations

As a result of this investigation it has been shown that RCM and dihydroxylation can be used to synthesise *N*-heterocyclic diols **207**, **210** and **244**. The NMR spectral data from the synthesis of these diols *via* RCM and dihydroxylation were compared with the same diols synthesised from SmI_2-mediated pinacol reactions and aided in confirming the *cis*-stereoselectivity of the pinacol reactions. However, in comparison with the synthesis of these diols by pinacol coupling reactions the synthesis of the diols **207**, **210** and **244** by RCM and dihydroxylation reactions proved to be much more efficient and gave better yields (compare for diol **207** – SmI_2-mediated pinacol reaction the yield was 37 % but RCM-dihydroxylation gave a yield of 81%, this result being repeated for the diols **210** and **244**). So from the above results it can be seen that the complementary synthesis of *N*-heterocyclic diols by RCM-dihydroxylation is advantageous over pinacol coupling reactions. However, the synthesis of a tetrasubstituted alkene (which may have lead to the synthesis of the diols **199** or **203**) was not attempted because there may be potentials problems. However, pinacol reactions have been very successful in the synthesis of *N*-heterocyclic diols from diketone precursors (Schemes 81 and 85). The RCM reaction may not have worked with first generation Grubb's catalyst **262** due to Ru-based catalysts being more sensitive to the substitution pattern of alkenes than other catalysts.[145] The only known catalyst capable of producing tetrasubstituted cycloalkenes is Schrock's catalyst (a Mo-based catalyst). To overcome this the use of the

second generation Grubb's catalyst may have been successful but this was not pursued due to this catalyst not being commonly available at the start of this project.

An advantage of the pinacol reactions over RCM-dihydroxylation reactions is that it allows access to the *trans*-diol. This is done by simply using a pinacol reagent that stereoselectively forms the *trans*-isomeric diol product. However, using RCM extra steps would be required to synthesise a *trans*-diol from a cyclic olefin (*e.g.* forming an epoxide from the cyclic olefin and then stereoselective ring opening of the epoxide to afford the *trans*-isomer). Thus, in conclusion both approaches are complementary in that they allow access to both isomers of the diol in good yields.

3.15 Biological Testing of *N*-Heterocyclic Diols

The work outlined in this chapter had led to the synthesis of a number of novel *N*-heterocyclic diols. Although glycosidase inhibitors normally have 3 or more hydroxyl substituents (see Chapter 1, section 1.7) we nevertheless decided to test the biological activity of the diols produced in this study. The diols **229, 230, 233, 234, 235** and **239** were tested for inhibition against a range of glycosidase enzymes.[≠] As can be seen none of the diols tested showed significant levels of enzyme inhibition as would be predicted for these "simple" compounds.

Table 3 Results of biological testing of *N*-heterocyclic diols.

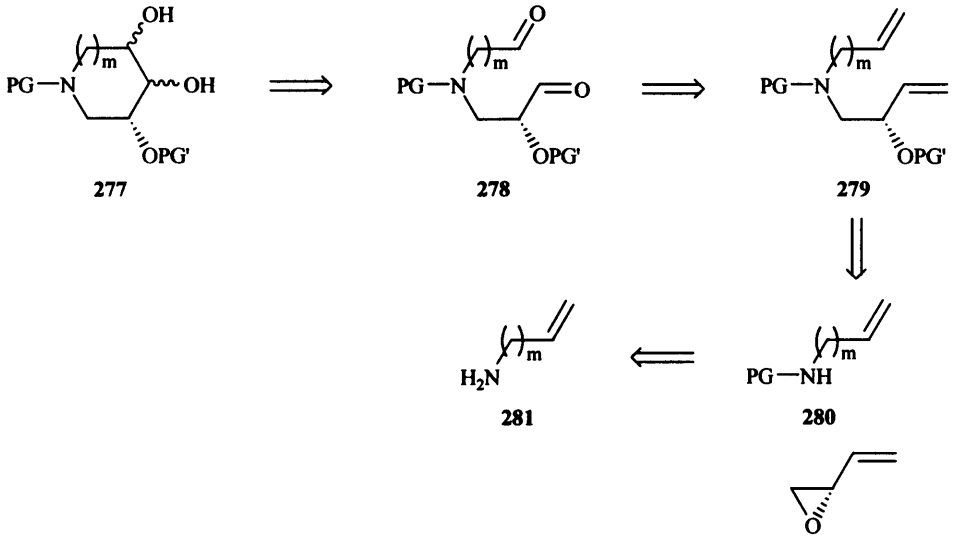
Assay	% inhibition by 1mg/11 solution					
	230	**233**	**235**	**234**	**229**	**239**
α-D-glucosidase (yeast)	6.4	1	2.4	1	3.6	-2.1
α-D-glucosidase (Bacillus)	13.2	1.1	3.3	0	-2.9	-5.6
α-D-glucosidase (rice)	2.8	3.3	2.5	-5.9	5.8	-4.2
β-D-glucosidase	**36**	-5.2	-6	-2.4	-6.6	-6.3
α-D-galactosidase	-1	-4.4	2.6	-2.8	1.2	-0.8
α-L-fucosidase	9.1	11.6	16	8.5	7.1	3.1
α-D-mannosidase	-1	-3.4	0.7	-1.8	-1	5.9
Naringinase	-3.3	2	-2.7	-1.4	-5.2	0.2
N-acetyl-β-D-glucosaminidase (bovine kidney)	1.2	-6.8	-1.7	-1.1	0.3	-5.2
N-acetyl-β-D-glucosaminidase (Jack bean)	0.3	2.3	3.1	1.8	-0.7	-0.9
N-acetyl-β-D-hexosaminidase	-5.1	-2.6	-3.8	-7.6	1.3	3.1
Amyloglucosidase	-0.5	0.4	2.7	-3.9	-6.2	0.8

≠ Biological testing was carried out at Molecular Nature (MNL) in collaboration with Professor Nash. The protocol is given in appendix 1.

4. Chapter 4: Results and Discussion 2

4.1 Pinacol Reactions to Generate α-Substituted *N*-Heterocyclic Systems

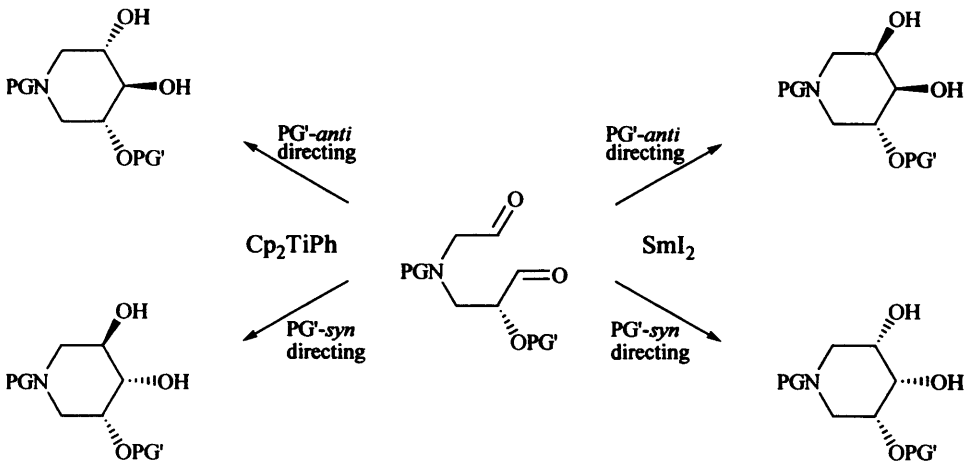
In the previous chapter the successful synthesis of a variety of dicarbonyls and their subsequent stereoselective Sm(II)- and Ti(III)-mediated pinacol reactions were discussed. This methodology allowed us to synthesise a range of *N*-heterocyclic diols and their stereochemistry was established by a combination of NMR and X-ray diffraction studies. In order to employ this method for the synthesis of *N*-heterocylic polyols the next step was to investigate the effect of α-hydroxy substituents upon the diastereoselectivity of the reaction. The retrosynthetic analysis for these studies is shown below (Scheme 124).



Scheme 124

This retrosynthesis was chosen, as we believed it would give maximum flexibility for the synthesis of a wide range of analogues (*e.g.* starting with different amines could lead to *N*-heterocyclic polyols of different ring size and with different substitution patterns). We were also keen to explore the effect of the α-hydroxy substituent upon the stereoselectivity of the pinacol reaction as we supposed that by choice of suitable directing groups (PG') together with suitable low-valent metal reagents for the pinacol coupling (*i.e.* SmI_2 → *cis*-diol; Cp_2TiPh → *trans*-diol) we would be able to access many, if not all, of the stereoisomers of **277**.

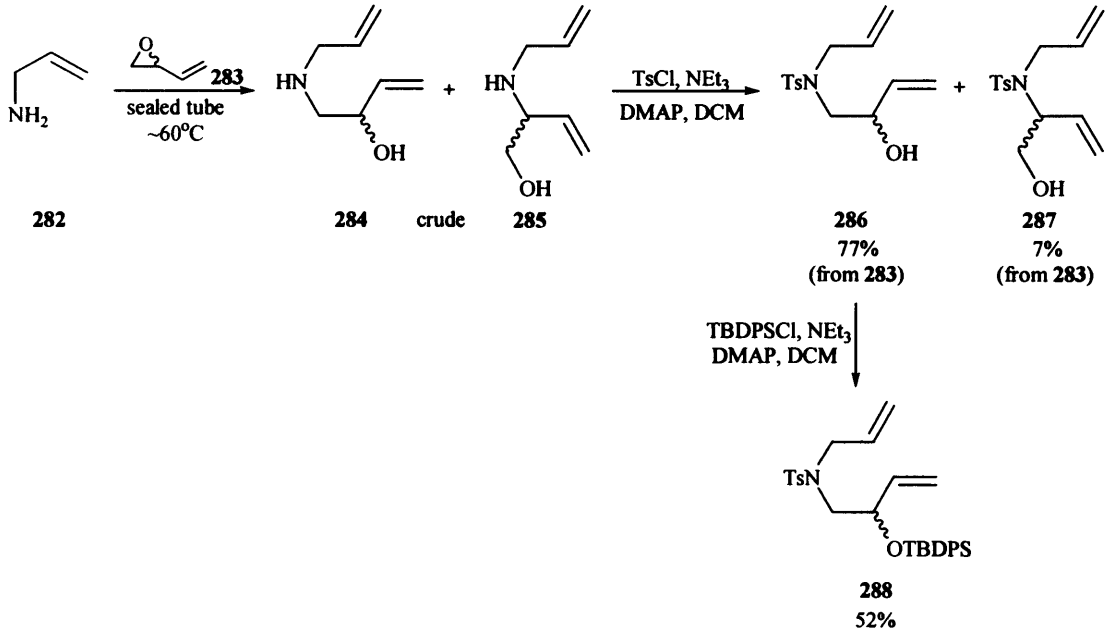
We started this section with the view to investigating if we could employ these directing effects in our key pinacol coupling reaction. We anticipated that if successful such a strategy could allow us to control the stereoselectivity of the pinacol reaction as shown below (Scheme 125).



Scheme 125

4.2 Studies Towards the Synthesis of 1,5-dideoxy-1,5-iminoarabinitol and Stereo Analogues

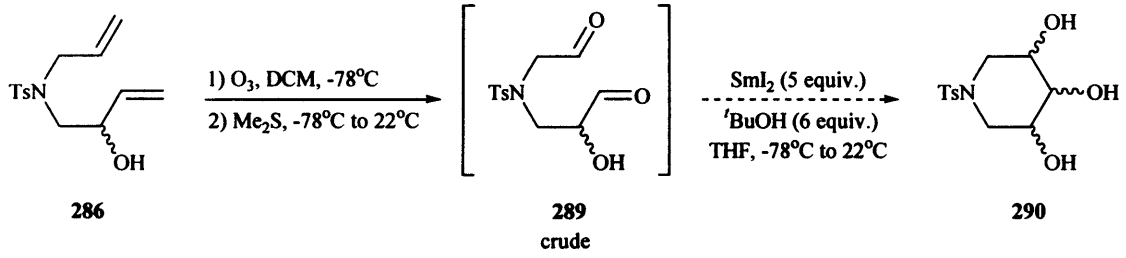
The first system we targeted was the piperidine triol 1,5-dideoxy-1,5-iminoarabinitol **296** and its stereoisomers.



Scheme 126

Thus allylamine **282** was reacted with butadiene monoxide **283** in a sealed (Young's) tube and heated for 18h (Scheme 126). The desired product, amino alcohol **284**, was expected from attack of the amine on the least hindered end of epoxide carbon atom. However, ^{1}H and ^{13}C NMR analysis of the crude reaction mixture indicated that in addition to **284** a small amount of another product tentatively assigned as the amino alcohol **285**, was also present – ratio **284** : **285** *ca.* 6 : 1 (as measured by ^{13}C NMR). This mixture of **284** and **285** could not be separated by column chromatography and so it was taken through to the next stage and

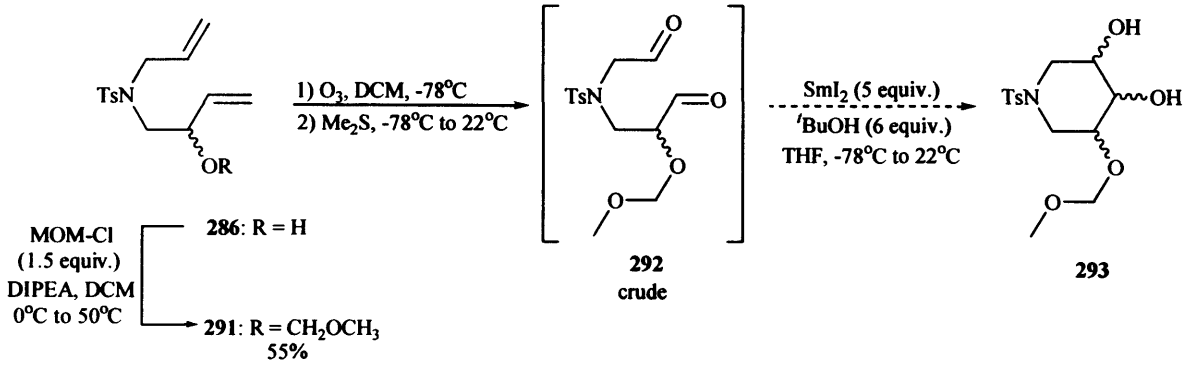
treated with *p*-toluenesulfonyl chloride, NEt_3 and DMAP in dichloromethane. Pleasingly purification of the resulting mixture by column chromatography on silica gave the two tosylates **286** and **287** in 77 % and 7 % yield (over 2 steps, from **283**) respectively. Analysis by ^1H and ^{13}C NMR proved that the epoxide opening had indeed given the two amino alcohols **284** and **285** as proposed. Treatment of the diene **286** with ozone, followed by reductive (Me_2S) work up gave a mixture that was analysed by ^1H and ^{13}C NMR (Scheme 127). This showed that the ozonolysis of the diene **286** gave a crude reaction mixture which by ^1H NMR analysis gave two aldehyde signals as expected at 9 - 10 ppm together with signals at 4.8 - 5.7 ppm which were expected signals for acetal/hydrate and/or ozonide compounds (see section 3.12). Integration of the CHO signal in comparison with the methyl from the tosyl group indicated that < 10 % dialdehyde was present in the crude reaction mixture. ^{13}C NMR analysis also indicated two aldehyde signals at around 199 ppm, as well as many signals between 89 - 100 ppm indicative for the presence of acetal/hydrate and/or ozonide compounds.



286 **289** crude **290**

Scheme 127

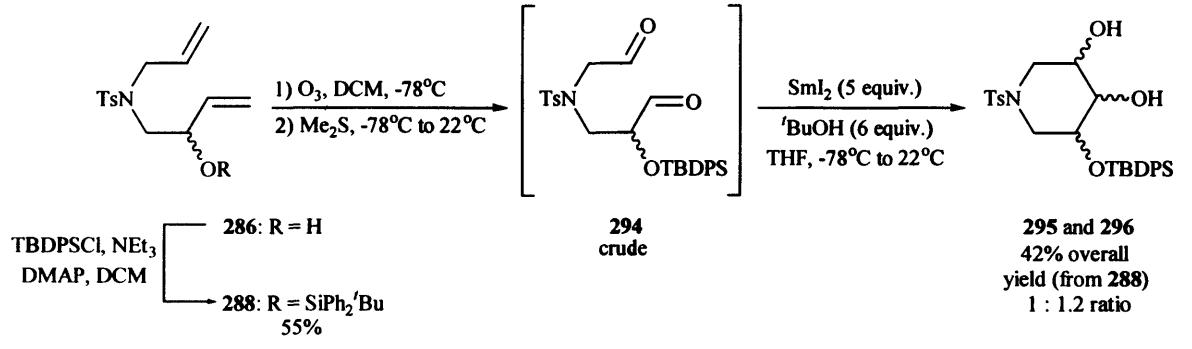
In the previous studies (see chapter 3, section 3.12) we had observed that dialdehyde precursors of piperidines (*e.g.* **242**) were unstable and had therefore been taken on into the pinacol reaction without further purification. Thus, the crude material from the ozonolysis reaction of **286** was treated with excess SmI_2 (5 molar equivalents) at -78°C under our standard conditions. Work up of this reaction, however, gave a mixture of numerous products (from ^1H and ^{13}C NMR analysis) from which no identifiable products could be isolated. The failure of this reaction lead us next to explore the analogous transformation of protected α-hydroxy systems. Thus, treatment of the key intermediate alcohol **285** with methoxymethyl chloride (MOM-Cl) in the presence of Hunigs base (diisopropyl ethylamine – DIPEA) gave the acetal protected diene **291** in moderate yield (Scheme 128).



Scheme 128

The diene was treated with ozone in dichloromethane followed by the usual reductive work up. Examination of this crude material by NMR again indicated aldehyde signals and signals for acetal/hydrate and/or ozonide compounds between 4.5 - 5.6 ppm however, due to the complexity of the NMR spectrum integration of the aldehyde signals was not possible and so an approximation of the amount of aldehyde in the crude mixture was not possible. This crude material was treated with excess SmI_2 (5 molar equivalents) but once again no identifiable products could be isolated from the reaction mixture.

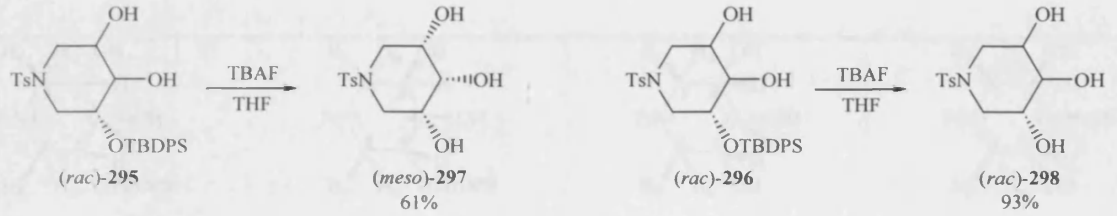
We next turned our attention to protection of the free hydroxyl group of **286** with the silyloxy TBDPS group. Therefore, the alcohol **286** was treated with TBDPSCl, NEt_3 and DMAP in dichloromethane to give the silyl ether **288** in moderate yield (Scheme 129).



Scheme 129

Ozonolysis of the diene **288** again gave a crude reaction mixture which by ^1H NMR analysis gave two aldehyde signals as expected at 9 - 10 ppm together with signals at 4.5 - 5.2 ppm which were expected signals for acetal/hydrate and/or ozonide compounds (see section 3.12). Integration of the CHO signal in comparison with the methyl from the tosyl group indicated that < 30 % dialdehyde was present in the crude reaction mixture. Mass spectroscopy (electrospray) showed that the expected dialdehyde was present but gave no information on the presence of any acetal/hydrate or ozonide species. The isolated crude mixture from the

ozonolysis of **294** was subsequently treated with excess SmI_2 using the standard conditions. Pleasingly purification of the resulting mixture by column chromatography on silica afforded two products (Scheme 129) in a 1 : 1.2 ratio (**295** : **296**), and a total overall yield of 42 % (over 2 steps, from **288**). Whilst ^{1}H and ^{13}C NMR analysis of the two isolated compounds **295** and **296** indicated that they were indeed the *N*-heterocyclic triol shown (Scheme 129) this data did not allow us to assign their relative stereochemistry. Additionally neither **295** or **296** were solids and so in an effort to obtain crystals suitable for X-ray diffraction both compounds were deprotected by treatment with tetrabutyl ammonium fluoride (TBAF) to give the corresponding triols **297** and **298** as shown (Scheme 130).



Scheme 130

Whilst the triol **298** was not a solid compound, **297** gave crystals suitable for X-ray diffraction analysis which indicated that the triol had been produced with all three hydroxyl groups *syn* (Figure 27; see also appendix 2.11).

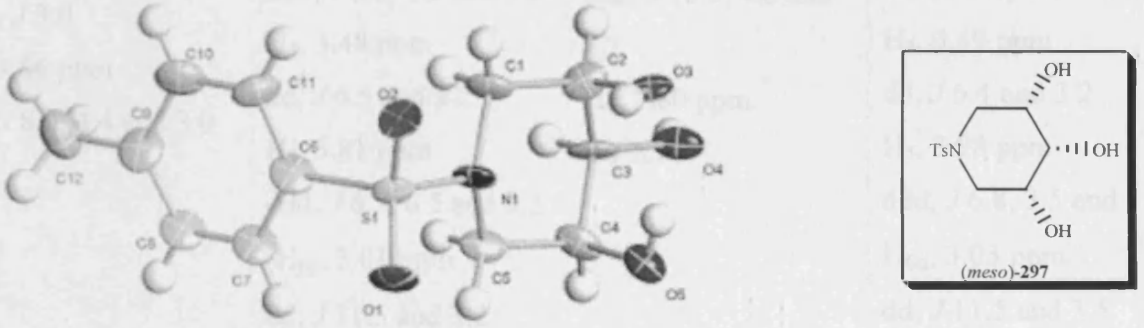


Figure 27

This also meant that the minor isomer **295** from the SmI_2-mediated pinacol reaction was the all *syn* isomer. This result is in agreement with the predictions based upon previous reactions with carbocyclic systems (see section 2.8) and these would also allow us to predict that the major isomer **296** from the pinacol reaction had the stereochemistry shown (Figure 28).

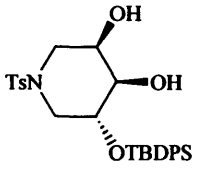
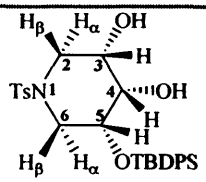
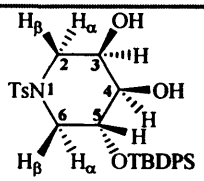
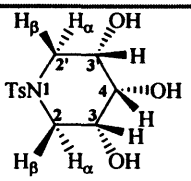
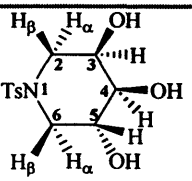


Figure 28

In order to confirm this we examined the ^{1}H-^{1}H coupling constants of the four compounds **295 - 298**. Some of the most useful *J* values are given in table 4.

Table 4: ^{1}H-^{1}H values (in Hz) for the *N*-heterocyclic diols – only piperidine ring protons shown.

 **295**	 **296**	 **297**	 **298**
*H_3, 3.62 ppm br m H_4, 3.68 ppm app t, *J* 3.0 *H_5, 3.86 ppm ddd, *J* 8.0, 4.4 and 3.0	‡$H_{2\alpha}$, 2.97 ppm dd, *J* 11.5 and 3.2 ‡$H_{2\beta}$, 3.06 ppm dd, *J* 11.5 and 6.5 H_3, 4.02 ppm ddd, *J* 6.5, 3.2 and 3.2 H_4, 3.48 ppm dd, *J* 6.5 and 3.2 H_5, 3.81 ppm ddd, *J* 6.5, 6.5 and 3.2 ‡$H_{6\beta}$, 3.01 ppm dd, *J* 11.5 and 3.2 ‡$H_{6\alpha}$, 2.71 ppm dd, *J* 11.5 and 6.5	$H_{2\alpha}$, 2.60 ppm app t, *J* 10.0 $H_{2\beta}$, 3.35 ppm dd, *J* 10.0 and 4.6 $H_{3/3'}$, 3.67 ppm ddd, *J* 10.0, 4.6 and 2.7 H_4, 3.80 ppm t, *J* 2.7	$H_{2\alpha}$, 2.85 ppm dd, *J* 11.5 and 6.4 $H_{2\beta}$, 3.22 ppm dd, *J* 11.5 and 3.2 H_3, 3.84 ppm ddd, *J* 6.4, 6.4 and 3.2 H_4, 3.49 ppm dd, *J* 6.4 and 3.2 H_5, 3.98 ppm ddd, *J* 6.8, 3.5 and 3.4 $H_{6\alpha}$, 3.03 ppm dd, *J* 11.5 and 3.5 $H_{6\beta}$, 3.11 ppm dd, *J* 11.5 and 6.5

*H_3 and H_5 are unassigned and maybe interchanged.

‡H_2 and H_6 are unassigned and maybe interchanged.

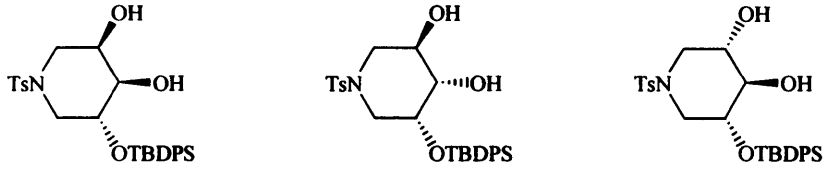
Taking as the starting point, the triol **297** with defined stereochemistry (from X-ray diffraction analysis) we can use the ^3J values to obtain stereochemical information as follows. Firstly we assume that the piperidine can take up two possible chair conformations and that

these will represent the lowest energy conformations of the molecule. Secondly we will employ the average ^3J values as follows: $J_{ax\text{-}ax} \approx 11$ Hz, $J_{ax\text{-}eq} \approx 4$ Hz and $J_{eq\text{-}eq} \approx 3$ Hz. Employing this analysis on **297** gives the following two conformations **297a** and **297b** (Figure 29).

297a **297b**

Figure 29

We would predict H-3 to be a ddd, $^3J_{H3\text{-}H2\beta} \approx 11$, $^3J_{H3\text{-}H2\alpha} \approx 4$, $^3J_{H3\text{-}H4} \approx 4$ in **297a** and a ddd, $^3J_{H3\text{-}H2\beta} \approx 3$, $^3J_{H3\text{-}H2\alpha} \approx 4$, $^3J_{H3\text{-}H4} \approx 4$ in **297b**. The actual values for the ^3J couplings for H-3 are 10.0, 4.6 and 2.7 Hz that agrees with the pattern predicted and suggests **297a** is the more populated conformer. The similar ^3J for H-3 or H-5 in the silyl protected compound **295** (8.0, 4.4 and 3.0 Hz) also seem to agree with this simple conformational analysis. For the major (unassigned) stereoisomer **296** (and **298**) there are three possible diastereoisomers **296, 299** and **300**.



296 **299** **300**

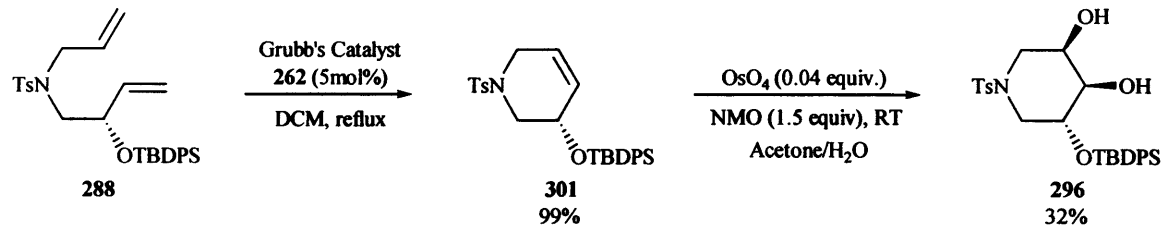
Figure 30

Whilst we would predict the product to have the *cis*-diol moiety **296** we cannot discount the potential formation of the *trans*-diols **299** or **300**. There is literature precedent that shows SmI_2-mediated pinacol couplings of α-alkoxy substituted dicarbonyls giving *trans*-diols especially similar systems to our one.[146]

However desilylation of the diol **300** would give a symmetrical triol and the complexity of the ^{1}H NMR of the actual triol product formed therefore rules out the formation of **300** as the major product in the pinacol reaction. To distinguish between the two remaining possibilities (*i.e.* **296** and **299**) we can again analyse ^3J constants of the silyl protected intermediate **296** (examination of the ^{1}H NMR of the deprotected systems is of little use here as desilylation of **296** and **299** gives the same triol). Examination of the *J* values for H-5 in **296** shows a ddd with couplings of 6.5, 6.5 and 3.2 Hz. Using a similar conformational analysis to that described above we would predict that the two 'large' couplings (> 6 Hz) would only arise if

the H-3 hydrogen had two diaxial hydrogen neighbours. This suggests **296** has the predicted stereochemistry **296** rather than **299**. However, to further confirm this assignment we decided to carry out a complementary synthesis of **296** using RCM-dihydroxylation approach previously discussed in chapter 3, section 3.13.

Thus, treatment of diene **288** with Grubb's catalyst **262** in dichloromethane gave the olefin **301** in excellent isolated yield (99 %). Subsequent reaction of **301** with OsO_4 and NMO under Upjohn conditions[144] gave the diol **296** in moderate yield (32 %)(Scheme 131).

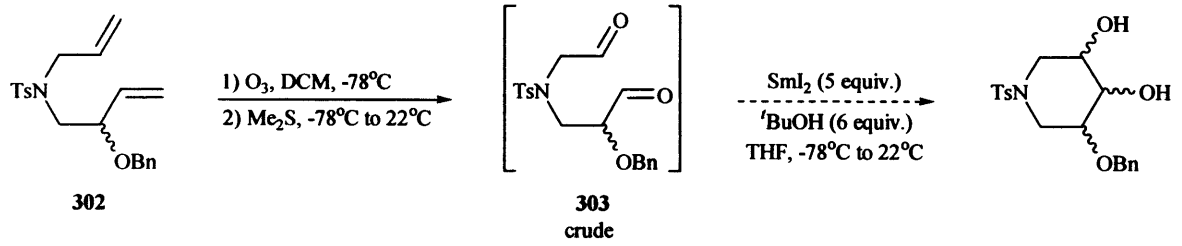


288 **301** 99% **296** 32%

Scheme 131

The stereochemistry of the diol **296** is predetermined as OsO_4 carries out a *cis*-selective dihydroxylation reaction which is normally *anti*-orientated to the α-alkoxy substituent, as was stated in a report by Kishi and co-workers who were investigating the stereochemistry of osmium tetroxide oxidation of allylic alcohol systems.[147] A important preliminary finding was that the relative stereochemistry between the pre-existing hydroxyl/alkoxyl group and the newly introduced hydroxyl group in all cases is *anti*. Comparison of the data for **296** formed in this process to the diol isolated from the comparable SmI_2-mediated pinacol reaction (see Scheme 129) confirmed that the same diol had formed.

Additionally we investigated the pinacol coupling of a benzyl protected α-hydroxy precursor (Scheme 132). Thus, diene **302**[148] was treated with ozone in dichloromethane and reductively worked up (Me_2S) to give a crude reaction mixture of **303**. Examination of this crude material by ^1H NMR again indicated the presence of a small amount of aldehyde signals between 9 - 10 ppm and signals for acetal/hydrate and/or ozonide compounds between 4.5 - 5.6 ppm. This crude material was treated with excess SmI_2 (5 equiv.) using the standard conditions and from TLC analysis purification was attempted. Using flash column chromatography one product was isolated (18 % over 2 steps, from **302**) and analysis of ^1H and ^{13}C NMR indicated that the reaction had produced an *N*-heterocyclic diol however ^{13}C NMR showed that it was a possible mixture of three isomers, stereochemical assignments were not assigned. Having already investigated the silyloxy protected precursor this investigation into the benzyl protected precursor was not further pursued.



302 **303** crude

Scheme 132

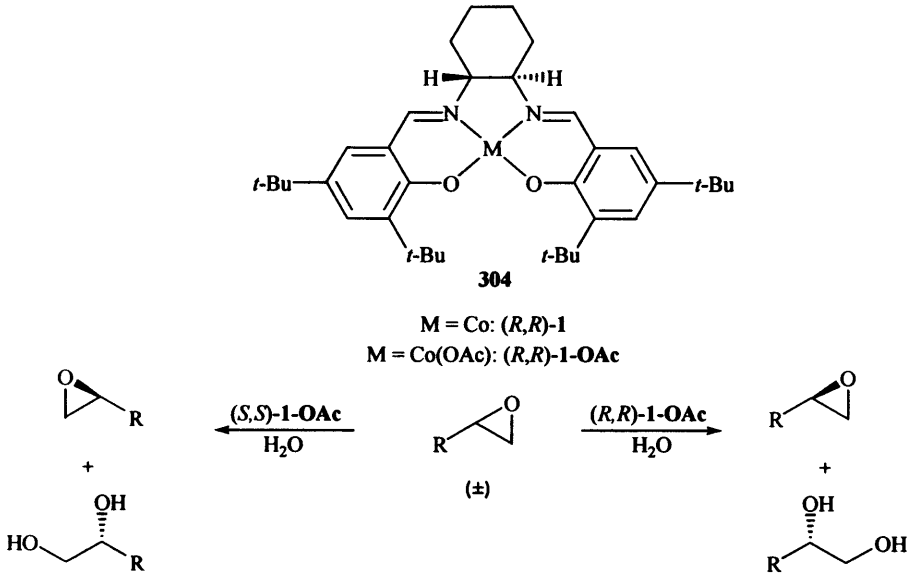
4.3 Conclusion on Studies towards the Synthesis of 1,5-dideoxy-1,5-iminoarabinitol and Stereo analogues

The evidence above has proved that *N*-heterocyclic triols can be effectively formed using SmI_2-mediated pinacol reactions. This reaction did form two isomers (**295** and **296**) and the stereochemistry of these two products was assigned using X-ray crystallography data and RCM-dihydroxylation reactions as well as ^1H-^1H coupling constants. The ratio of this reaction was 1 : 1.2 (**295** : **296**) and this compares unfavourably with that reported for carbocyclic ring systems in the literature (see Scheme 39, Chapter 2). In fact our reaction did yield a low ratio compared to that reported by Chiara and co-workers,[82] but it did give the same major isomer *i.e.* with the *cis*-diol *anti* to the silyloxy substituent. The low ratio of this reaction may be attributed to the fact that our systems are *N*-heterocycles and are different to the systems reported. Another possible reason could be that the crude reaction mixture that we perform the SmI_2-mediated pinacol reaction on has other compounds present, such as acetal/hydrates and/or ozonides and we do not know the possible effects these may have on the overall reaction stereoselectivity. A report by Pederson and co-workers investigated the effect of ligands on the diastereoselectivities of intermolecular SmI_2-mediated reactions.[78] These authors found that the addition of polyether complexing agents significantly affected the diastereoselectivities of the pinacol reaction and it may be the case that the other species present in the crude dial preparations are resulting in the low stereoselectivity observed.

4.4 Synthesis of Enantiopure 1,5-dideoxy-1,5-iminoarabinitol 296

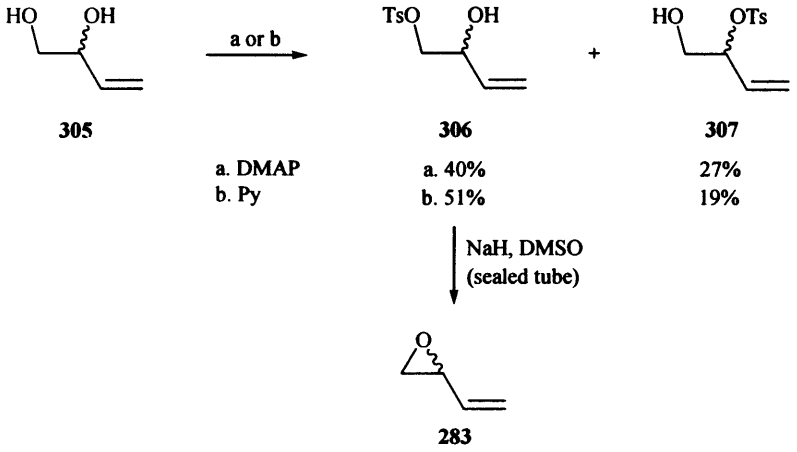
Having successfully carried out the racemic synthesis of **296** we turned our attention to working with the homochiral series. In the first instance we examined the possibility of carrying out the same synthetic route but starting with a single enantiomer of butadiene monoxide **283**. Whilst this starting material is commercially available as either isomer it is relatively expensive to purchase. Alternatively either enantiomer of the epoxide **283** can access by kinetic resolution of the racemic material using a protocol developed by Jacobsen and co-workers.[149] However, this would require the additional synthetic steps necessary to

make ligand **304** (Scheme 133).



Scheme 133

In view of these potential hurdles we decided to slightly modify our route such that we could start with a readily available homochiral starting material. As our starting point we took butene-1,2-diol **305**, a compound that can be prepared as a single enantiomer from D-mannitol (see later). Initially work with racemic material was investigated whereby conversion of diol **305** to butadiene monoxide **283** was tried by the scheme below (Scheme 134).



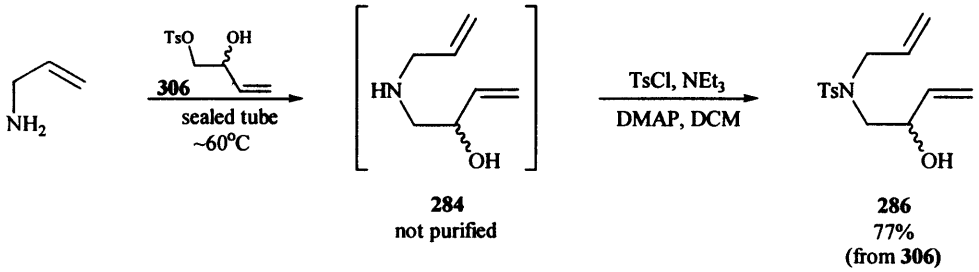
Scheme 134

The monotosylation of the diol **305** was carried out using a similar method to that reported by Kabalka and colleagues.[150] In this report a variety of alcohols were reacted with *p*-toluenesulfonyl chloride and pyridine in chloroform. The reaction gave selective tosylation of the primary alcohol (*i.e.* **306**) over the secondary one (*i.e.* **307**) in a 3 : 1 ratio and 70 % overall yield. Although the two isomers **306** and **307** were readily separable by column

chromatography on silica and identified by their characteristic ^{1}H NMR shifts (deshielding of the -CH or -CH_2 protons is seen on formation of the sulfonate); we wanted to improve the ratio in favour of **306**. Thus, we attempted the reaction under slightly different conditions. Hence diol **305** was treated with *p*-toluenesulfonyl chloride, triethylamine and DMAP in dichloromethane to give tosylates **306** and **307** in a 3 : 2 ratio in overall 67 % yield. Instead of improving the ratio in favour of primary tosylate **306** we observed the opposite with the increase in favour of tosylate **307**.

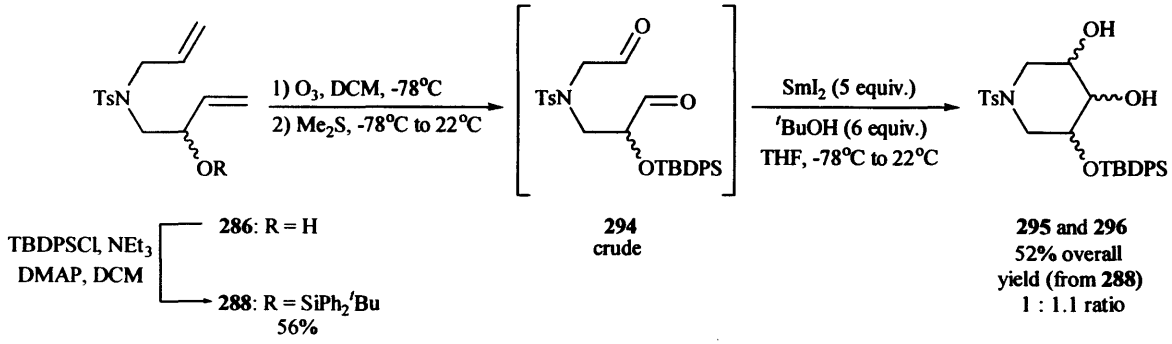
With the monotosylate **306** to hand we next attempted its conversion to the epoxide **283**. Again this is a known reaction[151] involving treatment of **306** with sodium hydride in DMSO. However, in our hands we were unable to isolate any of epoxide **283** from this reaction even though all of the starting material was consumed. This may have been due to the volatility of the epoxide (b. pt. 65 - 66°C), which meant that the product was lost on opening of the sealed tube followed by work up and isolation.

In view of this failure we next examined the direct reaction of allylamine and the tosylate **306** at 60°C in a sealed tube in the absence of solvent (Scheme 135). Pleasingly work up of the reaction followed by ^{1}H NMR analysis suggested that the target amine **284** had indeed been formed. This was confirmed by reaction of this unpurified material with *p*-toluenesulfonyl chloride which allowed isolation of the toluenesulfonamide **286** in 77 % overall yield from **309**.



Scheme 135

Interestingly none of the isomeric sulfonamide **287** (see section 4.2, Scheme 126) was isolated suggesting that reaction of allylamine with **306** involves a direct nucleophilic displacement and does not proceed *via* formation of butadiene monoxide followed by subsequent attack. The diene **286** was taken through the same sequence as before **286** → **288** → [**294**]→ **295** and **296** (Scheme 136) and gave similar results as before suggesting that the stereoselectivity of the pinacol reaction was a reproducible result.

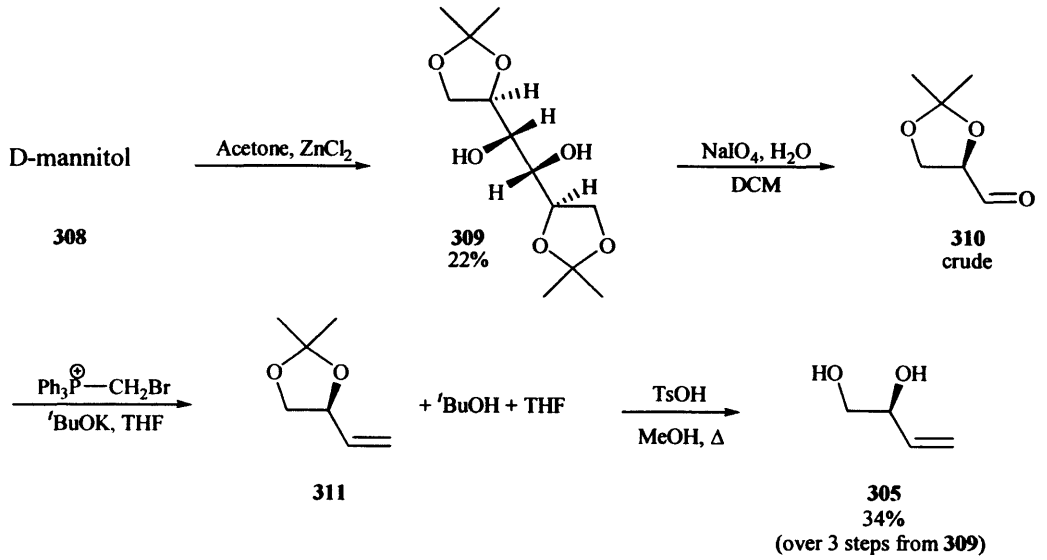


Scheme 136

4.5 Asymmetric Synthesis of 1,5-dideoxy-1,5-iminoarabinitol 296

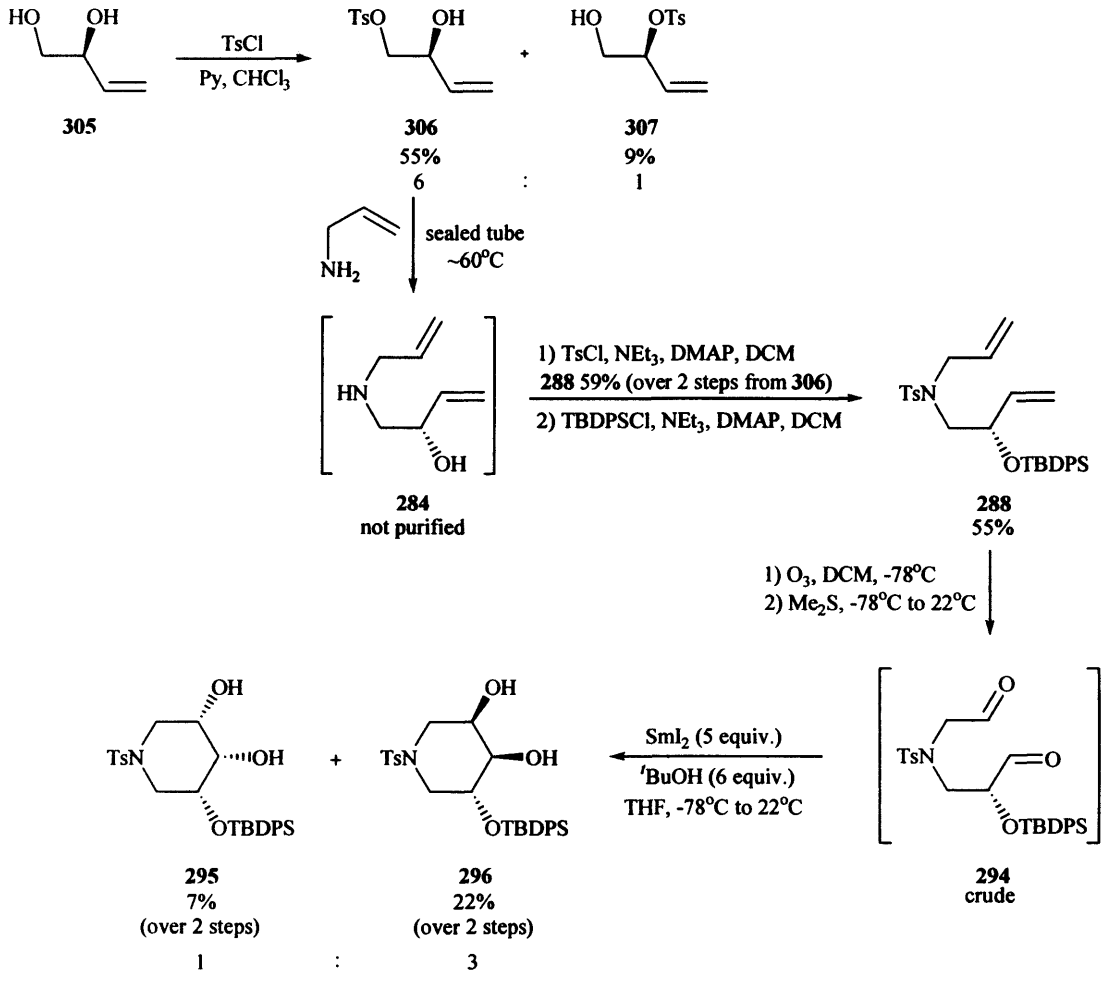
Having successfully carried out the racemic synthesis of the piperidine triol **296** we now turned our attentions to the homochiral series. In order to access enantiomerically pure butane-1,2-diol we chose to start with D-mannitol **308**. Thus conversion of **308** to the corresponding bis-acetonide was carried out using standard literature conditions[152] (Scheme 137).

Treatment of the diol **309** in dichloromethane with sodium *meta*-periodate and water next gave aldehyde **310**.[153] The aldehyde **310** was not purified due to anticipated problems associated with its high volatility and was reacted directly with the ylide generated from methyltriphenylphosphonium bromide and ^{t}BuOK following a literature procedure.[154] Again due to problems of volatility and the losses associated with them the alkene **311** was only partially purified by distillation at atmospheric pressure to remove volatiles. This gave **311** contaminated with small amounts of THF and ^{t}BuOH – a small sample of **311** was freed from these contaminants to allow for full analysis. Removal of the acetal group from **311** was achieved by reaction with *p*-toluene sulfonic acid in refluxing methanol. This reaction was best followed by GC chromatography due to the volatile nature of **311** making the analysis difficult and using this protocol a 34 % isolated yield of the diol **305** from **309** was achieved.



Scheme 137

With the homochiral diol **305** to hand we completed the rest of the synthetic route following the steps discussed previously (Scheme 138).



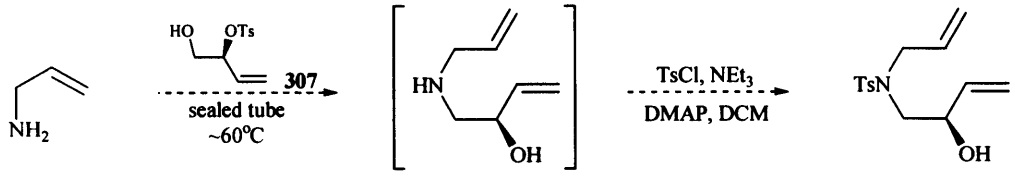
Scheme 138

The steps proved generally uneventful although it should be noted that the chemoselectivity

of the monotosylation step (**305** → **306**) was improved by more careful control of the reaction temperature. Ozonolysis of the homochiral diene **288** gave material that was again reacted with excess SmI_2 without purification. Analysis of the ^1H NMR and electrospray mass spectrum of the crude material from the ozonolysis reaction suggested that it was composed of similar compounds as with the racemic series although full characterisation was again not possible.

Purification of the key pinacol reaction gave the homochiral piperidine triols (3*S*, 4*S*, 5*R*)-**295** and (3*R*, 4*S*, 5*R*)-**296** in slightly lower (7 % and 22 % respectively) but comparable yield to the racemic series. Interestingly the diastereoselectivity of this reaction (*ca.* 75 % selective for the *anti*-isomer **296**) is greater than the previous reactions with racemic material. There seems no direct explanation for this finding and we can only propose that these different selectivities are the result of difference in the composition of the material isolated from the ozonolysis reactions in the two cases. Whilst comparison of the ^1H NMR of these reactions suggests that they contain similar components, the resolution of the spectra introduces a degree of uncertainty in this conclusion. Pederson and co-workers have shown the affect of added ligands on the diastereoselectivity of intermolecular SmI_2-mediated pinacol reactions[78] and as also mentioned earlier it may be the case that the various species produced in the ozonolysis reaction (*e.g.* cyclic acetals and hydrates, ozonides, peroxides) can affect the diastereoselectivity of the pinacol reaction.

In view of the success of the reaction between allylamine and tosylate **306**, we examined the direct reaction of allylamine and the secondary tosylate **307**, which if it occurred *via* butadiene monoepoxide would give access to another enantiomer. Therefore, **307** was reacted with allylamine in the absence of solvent in a sealed tube heated at ~ 60°C (Scheme 139). After work up the crude reaction mixture **284** was directly reacted with *p*-toluenesulfonyl chloride, NEt_3 and DMAP in dichloromethane. Initial examination of TLC and ^1H NMR indicated that none of the expected diene **286** had formed. This suggests that the epoxide **283** was not being formed as an intermediate during the reaction.



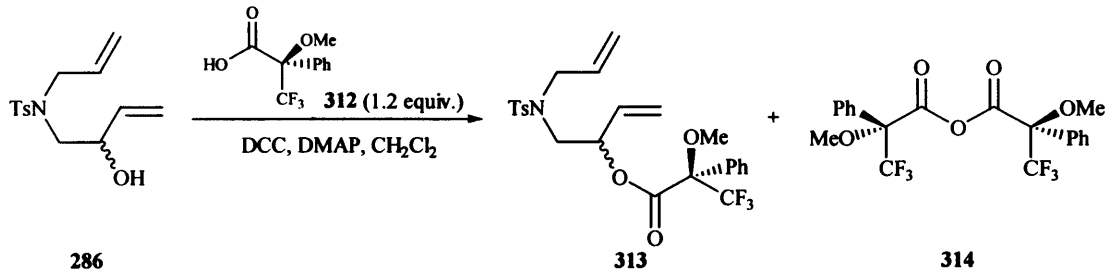
282 **284** not purified **286**

Scheme 139

4.6 Establishing the Enantiomeric Excess of the Piperidine Triol 296

Having completed the synthesis of the target homochiral piperidine **296** we needed to establish the stereochemical integrity of the chiral centre during the synthesis. We were especially concerned with possible epimerisation during the synthesis, purification or reaction of the glyceraldehyde derivative **310** and during the ozonolysis-pinacol protocol (*i.e.* **288** → **[294]** → **296**. In both these steps the chiral centre would be α- to a carbonyl group and so particularly prone to epimerisation. To investigate this possible racemisation we employed a Moshers-ester based analysis as discussed below.

We initially examined the alcohol **286** and both the racemic and homochiral compounds were converted to the corresponding Moshers esters by reaction with the acid **312** (1.2 equiv.) in the presence of DCC and DMAP (Scheme 140).

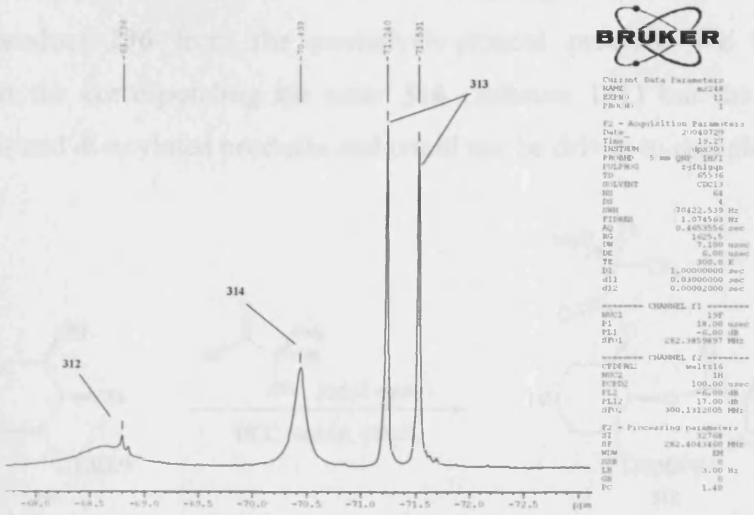


286 **313** **314**

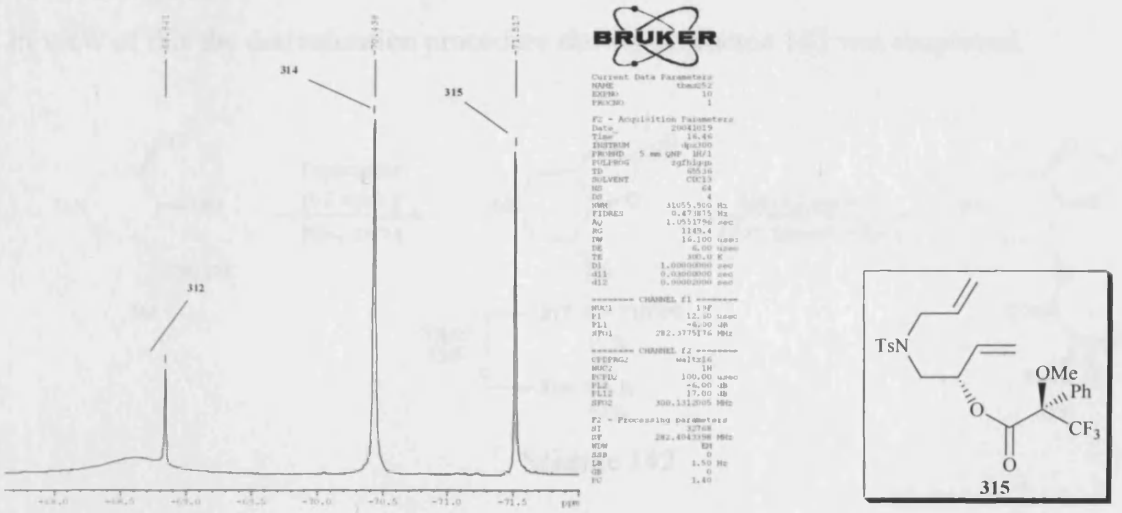
Scheme 140

Reaction of the racemate gave material which was simply worked up but not purified (to avoid loss of any diastereoisomer) and analysed by ^{19}F NMR. This spectrum showed two singlet signals for the diastereoisomeric products in a 1 : 1 ratio together with signals for remaining acid **312** and the anhydride **314** formed during the reaction. The assignment of the signals for **312** and **314** were confirmed by carrying out the derivatisation procedure in the absence of the alcohol **286**. Reaction of the homochiral alcohol **286** was carried out by exactly the same procedure and analysis of the ^{19}F NMR of **315** showed only a single peak for one of the two diastereoisomers (together with a signal for the anhydride **314**) showing the material to be enantiomerically pure. This result was confirmed by 'spiking' experiments as necessary (Figure 31).

^{19}F NMR of **313**



^{19}F NMR of **315**



315 'spiked' with **313**

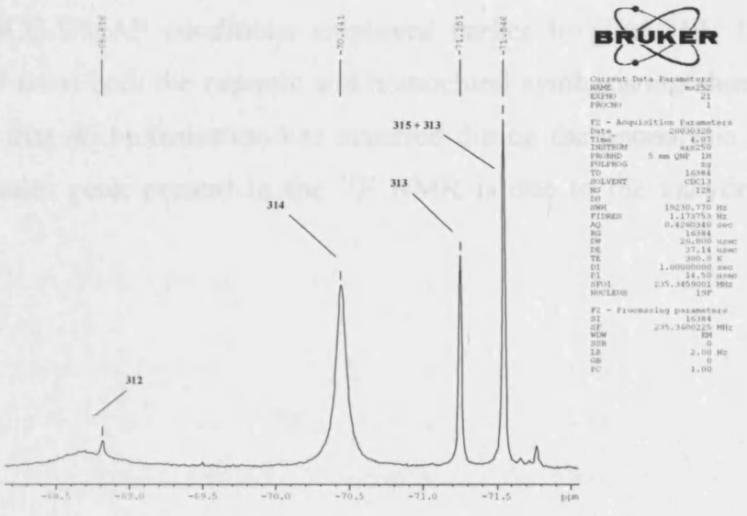
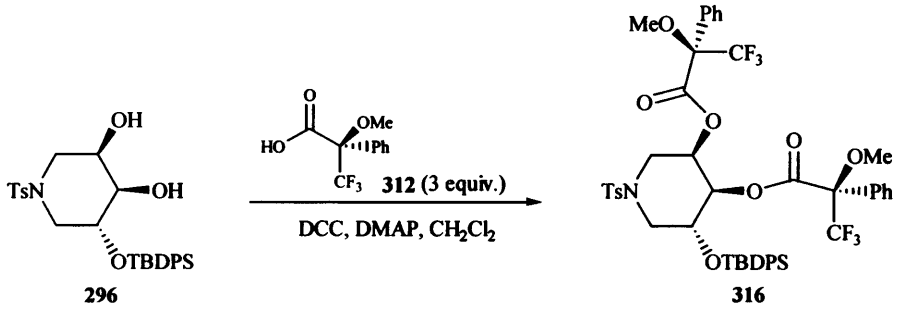


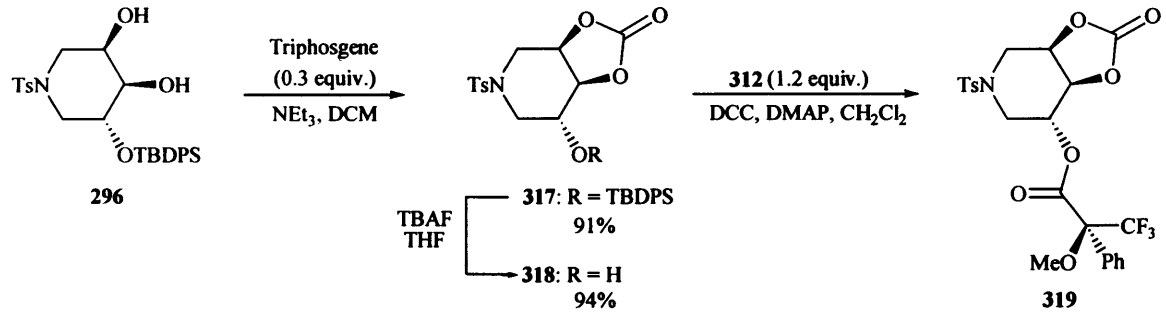
Figure 31

Having established that there was no racemisation during the formation of **286** we next examined the product **296** from the ozonolysis-pinacol process. We initially tried to derivatise **296** to the corresponding bis ester **316** (Scheme 141) but the reaction gave a mixture of mono- and di-acylated products and could not be driven to completion.



Scheme 141

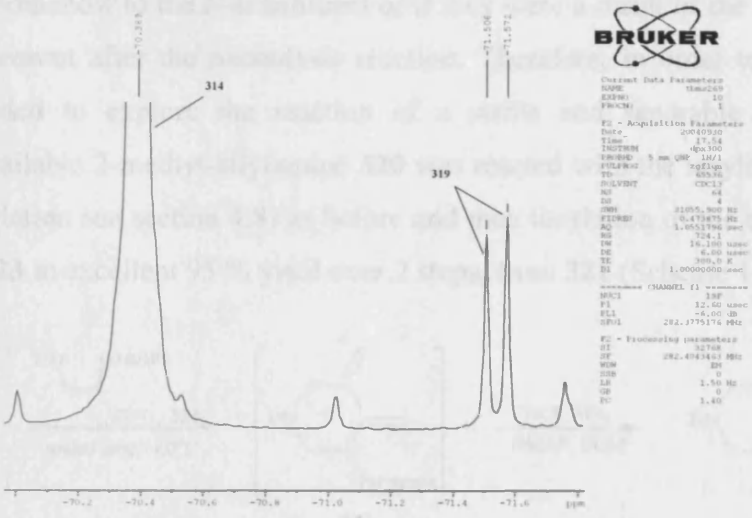
In view of this the derivatisation procedure shown in scheme 142 was employed.



Scheme 142

Thus reaction of **296** with triphosgene gave the carbonate **317** in good yield. Removal of the silyl protecting group gave the alcohol **318**, which was acylated with the Mosher's acid **312** using the DCC-DMAP conditions employed earlier to give **319**. The ^{19}F NMR of the products **319** from both the racemic and homochiral synthesis are shown in figure 32 and it can be seen that *no* racemisation has occurred during the ozonolysis and pinacol reactions (the other major peak present in the ^{19}F NMR is due to the anhydride **314** as explained previously).

^{19}F NMR of (*rac*)-**319**



^{19}F NMR of **319**

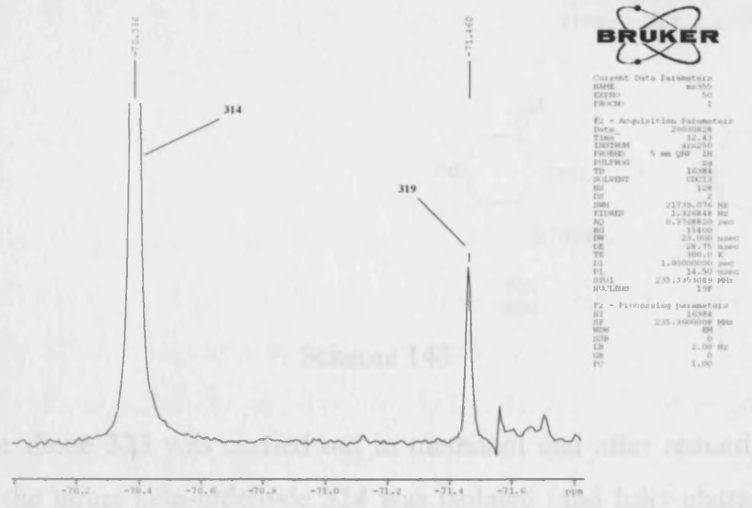


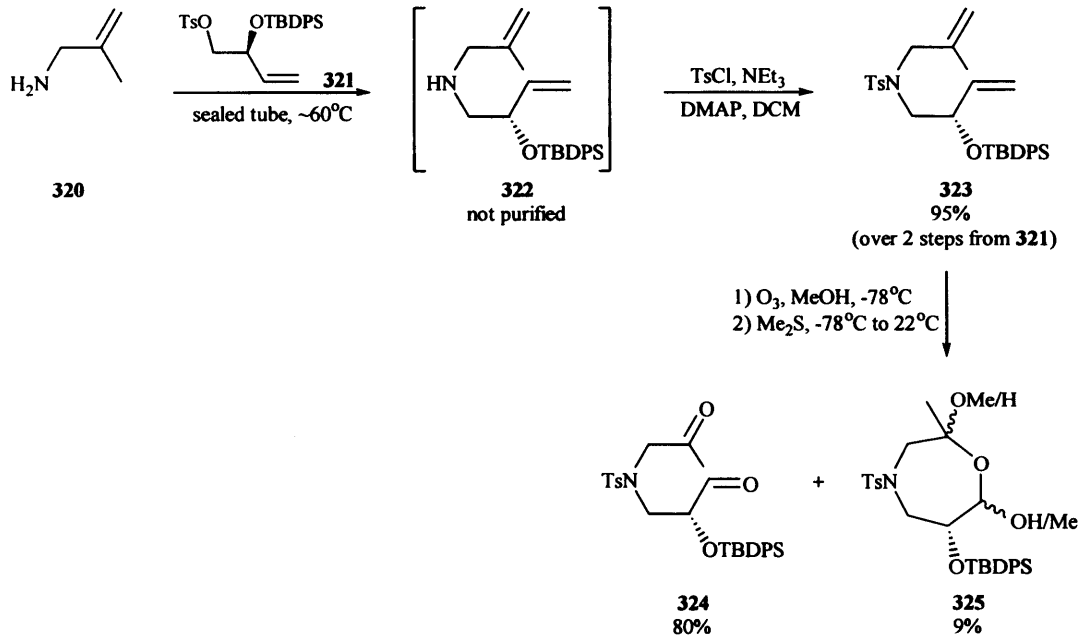
Figure 32

Thus these studies have proved that no racemisation takes place during the synthetic routes shown in scheme 137 and 138 and that the pinacol product **296** is enantiomerically pure. These findings suggest that such a strategy could therefore be employed for the synthesis of homochiral iminosugars and their analogues.

4.7 Further Investigations into the Diastereoselectivity of the Pinacol Reaction

The studies discussed in section 4.2 show that the pinacol reaction can be used to access trihydroxylated piperidines (*e.g.* **296**). However, the diastereoselectivity of the key pinacol reaction was found to vary between an essentially non-stereoselective reaction (**295** : **296**; 1 : 1.2) and a modest level of stereoselection (**295** : **296**; 1 : 3). These levels were considerably lower than with the corresponding carbocyclic systems (see section 2.8) where

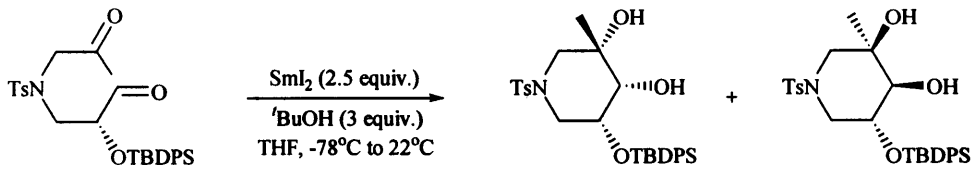
stereoselectivity is normally in the region of > 90 : 10. We could not be sure if these lower levels were due somehow to the *N*-substituent or if they were a result of the complex mixture of compounds present after the ozonolysis reaction. Therefore, in order to investigate this further we decided to explore the reaction of a stable and separable dicarbonyl. The commercially available 2-methyl-allylamine **320** was reacted with the tosylate **321** (prepared from **306** by silylation see section 4.8) as before and then tosylation of the resulting material gave the diene **323** in excellent 95 % yield over 2 steps, from **321** (Scheme 143).



320 **322** not purified **323** 95% (over 2 steps from **321**) **324** 80% **325** 9%

Scheme 143

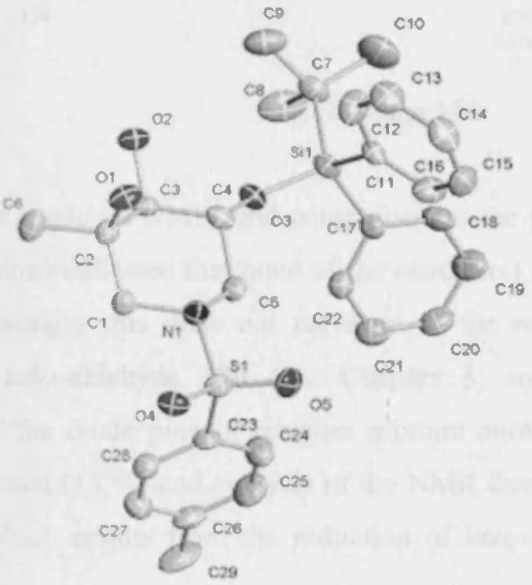
Ozonolysis of the diene **323** was carried out in methanol and after reductive work up with dimethyl sulfide the target keto-aldehyde **324** was isolated (and fully characterised) in good yield together with a small amount of cyclic acetal **325** (the stereo- and regiochemistry of **325** was not determined, although ^{1}H NMR analysis suggested a single isomer had been produced). Subsequent treatment of the dicarbonyl **324** with SmI_2 (2.5 equiv.) under our standard conditions gave the two isomeric products **326** and **327,** which could be readily separated by flash column chromatography (Scheme 144).



324 **326** 17% **327** 48% 1 : 3

Scheme 144

^{1}H and ^{13}C NMR analysis confirmed the general structure of the two isomers and fortunately crystals suitable for X-ray analysis could be grown for the major product (3*S*, 4*R*, 5*S*)-**327** and confirmed its *anti-cis* stereochemistry as shown (Figure 33; see also appendix 2.12).



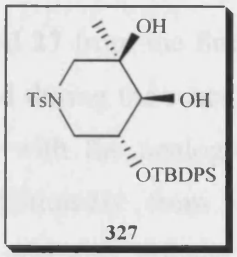
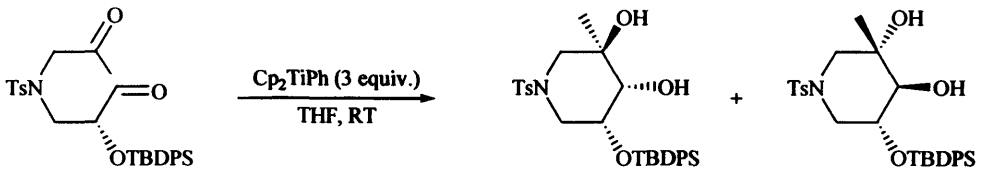


Figure 33

The stereostructure of the minor isomer **327** was assigned by comparison of its NMR spectra to the product **295** synthesised previously. Thus, the SmI_2-mediated pinacol reaction of the pure keto-aldehyde **324** resulted in a modestly stereoselective reaction (50 % diastereomeric excess) favouring formation of the *anti-cis* diol **327**. Additionally repetition of the pinacol reaction gave a reproducible 3 : 1 ratio of the stereoisomers **327** : **326**. This result suggests that the nitrogen functionality is affecting the diastereoselectivity of the reaction resulting in lower levels than seen with comparable carbocyclic systems. In comparison with the pinacol reaction of the "dialdehyde" **294** discussed in section 4.2 we can also make the preliminary conclusion that the presence of a variety of potential ligands in the crude mixture resulting from the ozonolysis reaction may also lower the diastereoselectivity of the pinacol reaction giving levels from 0 - 50 % diastereomeric excess.

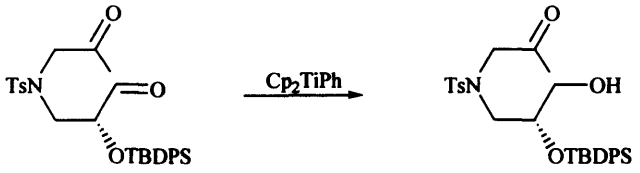
Having the keto-aldehyde **324** in hand we also investigated the diastereoselectivity of the analogous Cp_2TiPh-mediated pinacol reaction (this had been impossible with the unstable dialdehyde **294**). Thus, treatment of **324** with Cp_2TiPh (3 equiv.) under our standard conditions gave, after flash column chromatography, two isomeric diols **328** and **329** in moderate 21 % and 7 % yield respectively (Scheme 145).



324 **328** 21% 3 : **329** 7% 1

Scheme 145

Analysis of the crude ^{1}H NMR (and comparison to the products **326** and **27** from the SmI_2-mediated reaction) indicated that none of the *cis*-diol(s) had been formed during the reaction of **324**. Interestingly this does not correlate to the results observed with the analogous unsubstituted keto-aldehyde **190** (see Chapter 3; section 3.7). Additionally from the purification of the crude pinacol reaction mixture another compound was also isolated in significant amount (13 %) and analysis of the NMR data suggest this compound is the keto-alcohol **330** which results from the reduction of keto-aldehyde **324** by Cp_2TiPh (Scheme 146).



324 **330** 13%

Scheme 146

The stereochemical assignments of pinacol products **328** and **329** were made by analysis of the coupling constants for the H-4 hydrogen in all of the piperidine systems shown in figure 34. The stereostructures of compounds **295** – **298** have been established by either X-ray analysis or *J* coupling constant analysis from unambiguous synthesis (see section 4.2). We can see that hydrogen *anti* to H-4 couple with *J* values of ≈ 6.4 Hz whilst those *syn* give lower values of ≈ 3 Hz. If we make the assumption that the additional C-5 methyl substituent in **326**, **327** and **328**, **329** will have minimal effect on the conformation of these systems we can see that the *J* value for the H-4 to H-3 coupling 'matches' those predicted from the structures **295** – **298**. Thus, compound **327** (having stereochemistry established by X-ray diffraction analysis) shows the expected *anti*-coupling of ≈ 6.5 Hz. Applying this analysis to the products from the Cp_2TiPh-mediated pinacol reaction gives the two stereostructures for **328** and **329** as shown.

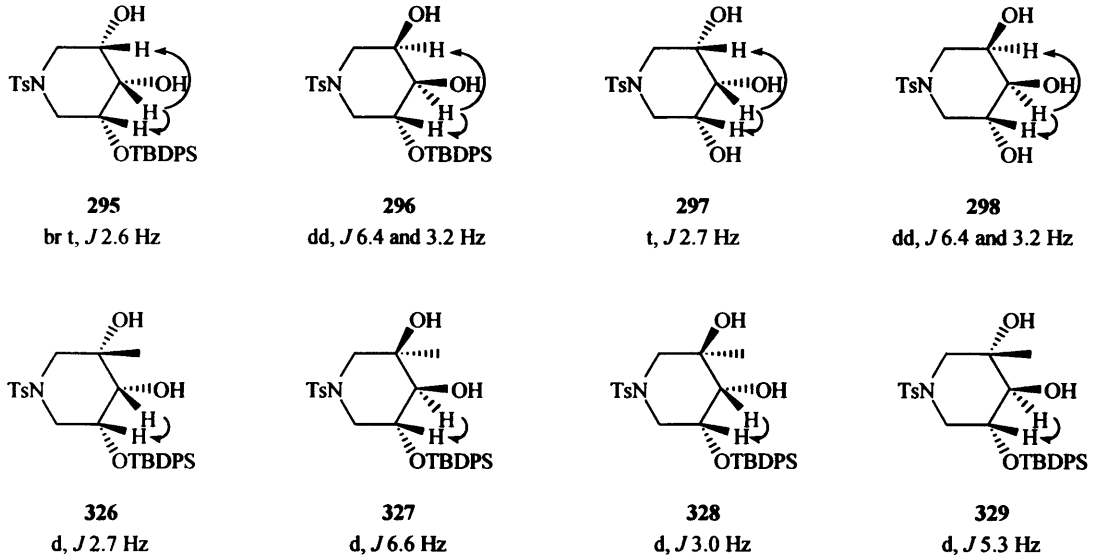


Figure 34

From these results above it can be stated that this was the first successful diastereoselective Cp_2TiPh-mediated pinacol coupling of an α-alkoxy substituted dicarbonyl to produce an *N*-heterocyclic triol. The two piperidines formed **328** and **329** were produced with good stereoselectivity, favouring **328** over **329** in a 3 : 1 ratio. This result can be compared with the Cp_2TiPh-mediated pinacol reaction of the unsubstituted keto-aldehyde **190**, and the difference with this reaction is that only one product (**206**) was isolated albeit in low yield whereas a likeness is that both reactions did not yield any of the *cis*-diol products, which were prevalent in the reactions to form pyrrolidines (*cf.* **200** and **202**).

4.8 Synthesis of an α-Substituted Azepane

As mentioned in chapter 1, section 1.7 polyhydroxyazepanes are known to be potent inhibitors of glycosidase enzymes. This has been shown in the literature by the considerable attention from synthetic, medicinal chemists and biologists. These types of compounds, polyhydroxyazepanes have several properties that make them potentially useful as inhibitors. One property is the flexibility of the seven-membered ring allowing the hydroxyl groups to adopt different positions and a second important property is the high water solubility, this circumvents the problem of bioavailability. Some trihydroxyazepanes that are known to be glycosidase inhibitors are shown (Figure 35).

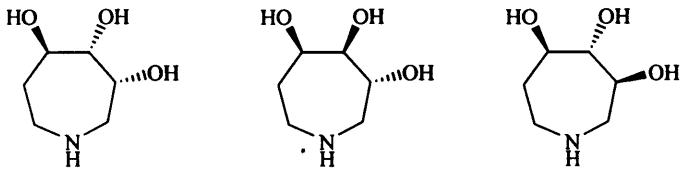
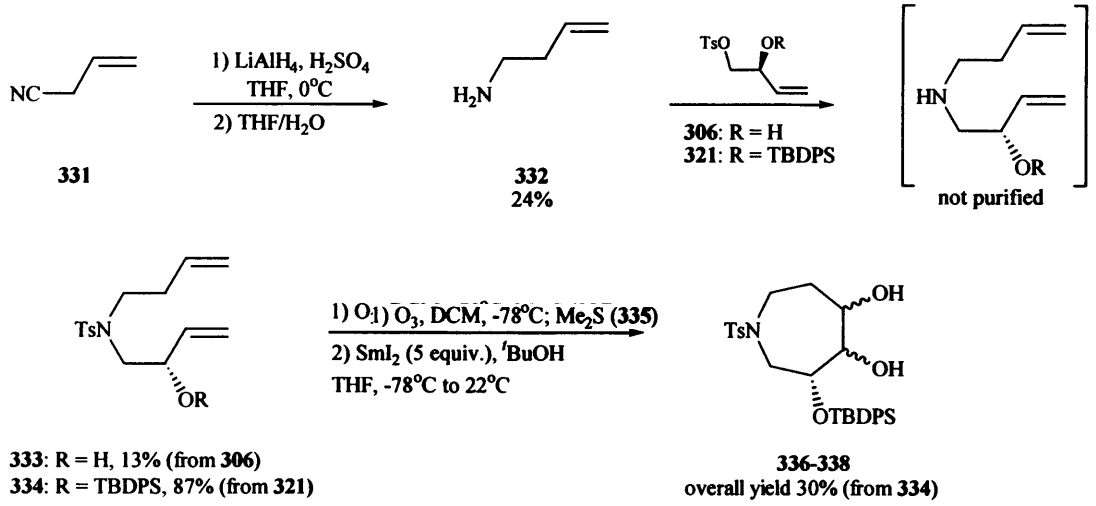


Figure 35

Following on from the successful synthesis of four different piperidine diols from dicarbonyl precursors having an α-silyloxy substituent we turned our attentions to employing a similar synthetic strategy to access the corresponding azepane systems. The synthetic route employed is shown below (Scheme 147).

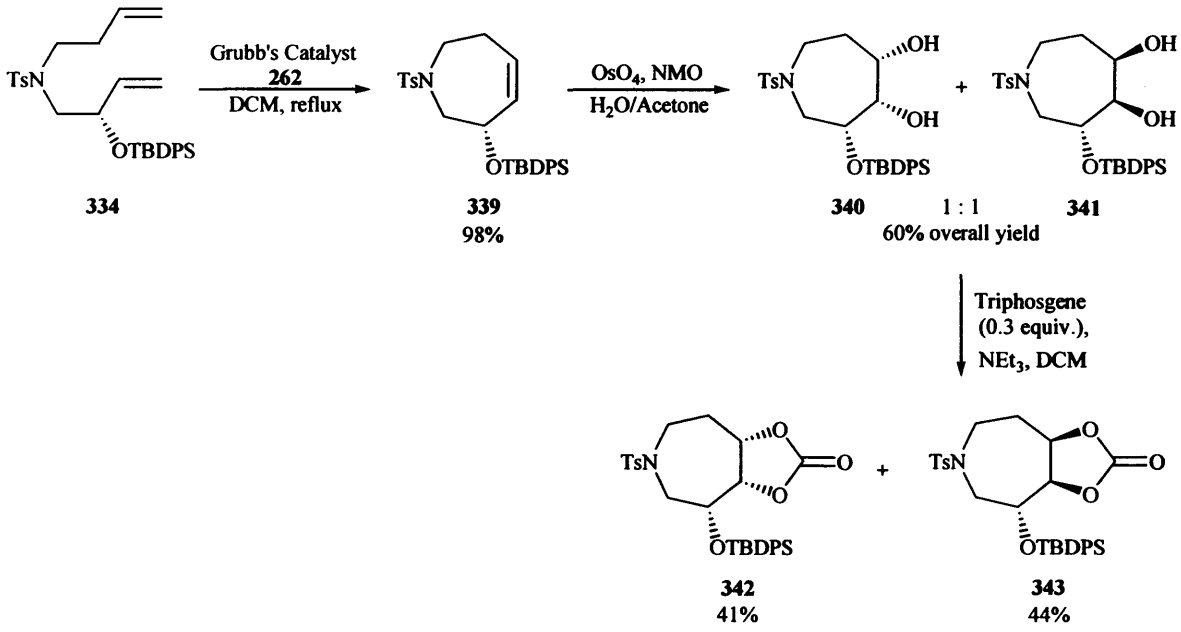


Scheme 147

Thus, allyl cyanide **331** was reduced with aluminium hydride (generated *in situ* from $LiAlH_4$ and H_2SO_4) according to the literature procedure[155] to give but-3-enylamine **332**. Reaction of the amine **332** with the homochiral tosylate **306** as before, followed by subsequent *N*-tosylation gave the target diene **333** albeit in poor yield (13 % from **306**) together with substantial amounts of *N*-tosyl but-3-enylamine. However, this could be overcome by reaction of the amine **332** with silyl protected tosylate **321** (produced from **306** by standard silylation protection TBDPS-Cl, DIPEA, DMAP) which gave, after *N*-tosylation the diene **334** in 87 % over two steps, from **321**. Ozonolysis of the diene **334** in the non-participating solvent dichloromethane gave crude material whose ^1H NMR spectrum indicated a mixture of the corresponding dialdehyde together with other unidentifiable components. This crude material (**335**) was reacted with excess SmI_2 using our standard pinacol conditions. Analysis of the resulting products by ^1H and ^{13}C NMR prior to purification suggested that there were three diols having the hoped for structure **336** - **338** shown (Scheme 147) with an overall yield of 30 %. Purification by column chromatography was only partially successful and only one of the components diols could be isolated pure; the other two proved inseparable. Additionally whilst NMR suggested that the three diols were stereoisomers it was difficult to assign their stereostructures with any certainty and so we made recourse to a complementary method to access the target *cis*-diols.

In chapter 3, section 3.13 the RCM-dihydroxylation approach to *N*-heterocyclic diols was discussed as a complementary method to our pinacol studies. This approach would

unequivocally give only the *cis*-diol product(s) and we decided to employ it here in an effort to assign the products produced from the pinacol reaction just discussed. The synthetic scheme is shown below (Scheme 148).



334 → 339 (98%) → 340 + 341 (1 : 1, 60% overall yield) → 342 (41%) + 343 (44%)

Scheme 148

Thus reaction of the diene **334** with Grubb's catalyst **262** gave the cycloalkene **339** in excellent yield (98 %). Subsequent dihydroxylation using UpJohn conditions gave a 1 : 1 mixture of the two stereoisomeric diols **340** and **341** in 60 % overall yield. These two diols proved inseparable by column chromatography and comparison of their ^{1}H and ^{13}C NMR data to the inseparable diols produced in the pinacol reaction of **334** (see above) showed them to be identical.

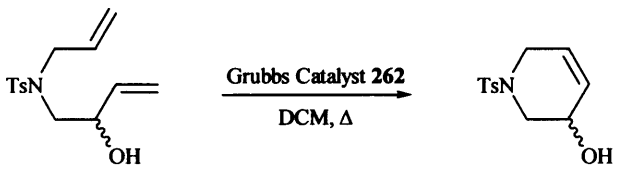
The conclusion from this is that the pure diol isolated from the SmI_2-mediated pinacol reaction must have a *trans*-diol configuration. This result is in agreement with the earlier studies with the non-substituted dial **192** which showed a small but measurable amount (9 %) of *trans*-diol formation in the preparation of the azepane system **207** (see chapter 3; section 3.8). In an effort to separate the two *cis*-diols **340** and **341** the mixture was reacted with triphosgene to give the two corresponding carbonates **342** and **343**. These compounds were readily separable by column chromatography unfortunately detailed NMR analysis including 2D COSY failed to allow us to conclusively assign their relative stereostructures. Additionally due to time constraints no further work could be done to investigate and secure these stereochemistries.

4.9 Conclusions on the Synthesis of an α-Substituted Azepane System

As shown above the SmI_2-mediated pinacol coupling to form an α-substituted azepane gave interestingly three different pinacol products, it was found that we could isolate one of the three products and the other two remained inseparable. Also RCM-dihydroxylation reactions yielded us the *cis* products and confirmed that the two inseparable products from the SmI_2 pinacol reaction were the same and also helped in the confirmation that the isolated product is the *trans*-isomer. This agrees with the result previously (see chapter 3; section 3.8) and again shows that the stereocontrol of 7-membered rings is not ideal. The ratio of the two inseparable *cis*-products from the SmI_2 pinacol reaction was measured (^{13}C NMR) and indicated that these products had formed in a 1 : 1 ratio which can be interpreted that the α-substituent is not having any directing effect on the formation of the final product(s). This is in accordance with the ratio of the products from the SmI_2-mediated pinacol coupling of the dialdehyde **294**. Another reason maybe because crude material isolated after the ozonolysis of the diene **334** was taken forward into the pinacol reaction and because pure dialdehyde was not used other species (ozonides/acetals/hydrates) may be present and again the effect they may have on the stereoselectivity of the pinacol product(s) is not known.

4.10 Miscellaneous Synthetic Studies on Piperidines

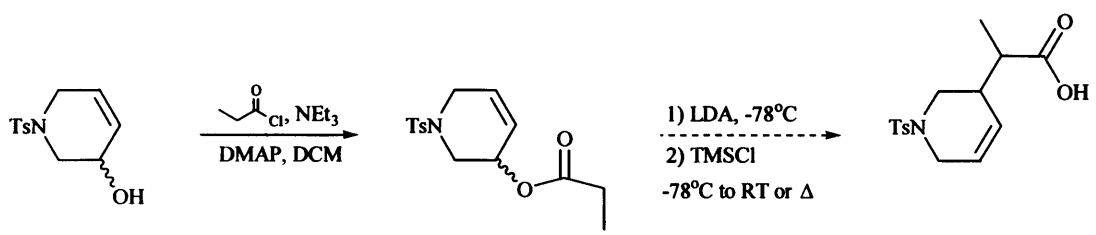
During the course of this work we had synthesised the heterocyclic allylic alcohol **344** by the RCM reaction of the diene **286** as shown (Scheme 149).



286 **344** 99%

Scheme 149

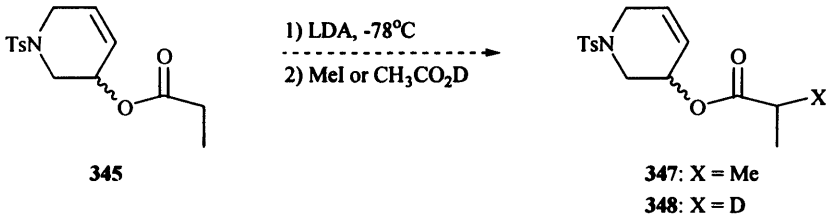
We wished to explore the use of **344** to access further piperidine based intermediates. To this end **344** was reacted with propionyl chloride to give the ester **345** in excellent yield (Scheme 150).



Scheme 150

Reaction of the ester **345** under standard Ireland-Claisen conditions[156] was expected to furnish the substituted piperidine **346** *via* a [3,3]-sigmatropic rearrangement. However, the only product isolated from the reaction of **345** with LDA followed by the addition of trimethylsilyl chloride was the alcohol **344**, presumably arising by base-mediated hydrolysis during work up of the reaction. Attempts to facilitate the rearrangement by extended reaction times and/or heating after addition of the trimethylsilyl chloride also failed and only **344** was isolated.

To test for enolate formation the silylchloride was replaced by MeI and deuterated acetic acid, however no evidence for either the methylated or deuterated products **347** or **348** was seen even on prolonged reaction times for enolate formation (Scheme 151).



Scheme 152

From these results we can only propose that enolate formation from **345** is failing to occur. There seems no reasonable explanation for this and further work will have to explore this reaction further if carbon-substituted piperidines are to be accessed.

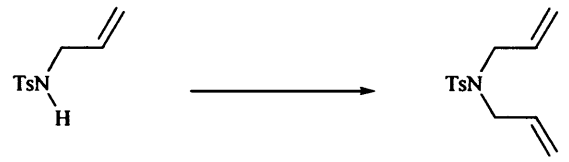
5. Experimental

5.1 General Experimental

All the reactions were performed under an inert atmosphere, nitrogen gas was routinely used except for SmI_2- and Cp_2TiPh-mediated pinacol coupling reactions Wittig reactions which were performed under argon. All solvent extractions were routinely dried with magnesium sulphate (unless otherwise stated). Tetrahydrofuran was distilled from sodium metal and benzophenone. Diethyl ether was distilled from lithium aluminium hydride. Dichloromethane, methanol and triethylamine were distilled from calcium hydride and dry DMF was purchased from Aldrich. All other reagents and solvents were purified by standard literature procedures.[157] Petroleum ether refers to the 40 – 60°C boiling fraction. Thin layer chromatography (TLC) analysis was performed using silica gel 60 F_{254} aluminium TLC plates, Merck 5554. Flash column chromatography was carried out using sorbsil C60 silica gel 40–60μm. Gas liquid chromatography (GLC) was carried out using a Perkin Elmer Autosystems XL gas chromatograph with P. E. elite series 5 column 30.0 x 0.25 μL. Melting points were measured using a Kofler hotstage and are uncorrected. Infrared (IR) spectra collected as liquid films between NaCl discs or solution cells using dichloromethane were recorded using a Perkin Elmer 1310 and 1600 FT-IR spectrometers. Mass spectra obtained by electrospray as methanolic solutions on a micromass Quattro LC. Accurate masses obtained by FAB on a Kratos high res spectrometer. Optical rotations were measured using a Perkin Elmer 341 polarimeter. NMR spectra were recorded using an ARX 250 (250 MHz ^1H, 62.9 MHz ^{13}C, 235.4 MHz ^{19}F), Bruker AM 300 (300 MHz ^1H, 75.5 MHz ^{13}C, 282.4 MHz ^{19}F) or a Bruker DRX 400 (400 MHz ^1H, 100.6 MHz ^{13}C) spectrometer. Chemical shifts are reported in parts per million (δ) downfield from TMS. *J* coupling constants are reported in Hertz (Hz). Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent peak), br (broad peak). ^{13}C NMR experiments were all accumulated with proton decoupling and DEPT experiments were used to aid carbon assignment. Samarium powder (-40 mesh) purchased from Acros Organics. SmI_2 prepared as reported by Kagan *et al.*.[73]

5.2 Compounds from Chapter 3

N,N-Diallyl-4-methylbenzenesulfonamide **155**

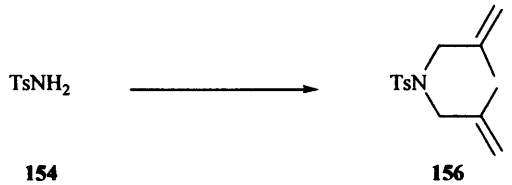


172 **155**

The sulfonamide **172** (3.0 g, 14.2 mmol) was reacted NaH (60 % dispersion in mineral oil, 0.681 g, 17.0 mmol) in DMF (30 cm^3). The reaction was stirred for 15 min then allyl bromide (1.40 cm^3, 17.0 mmol) added dropwise. After 18 h the reaction mixture was poured into saturated aqueous ammonium chloride (50 cm^3) and water (50 cm^3). The organic compound was extracted with ethyl acetate (3 x 50 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to leave the crude product, which was purified by flash column chromatography on silica using petrol:diethyl ether (90:10 to 70:30) to give the *diene* **155** (3.21 g, 90 %) as a colourless oil. ν_{max} (cm^{-1}, film) 2922, 1643, 1598, 1344 (SO_2), 1160 (SO_2). δ_H (300 MHz, $CDCl_3$) 2.42 (3H, s, Ar-CH_3), 3.80 (4H, d, *J* 6.1, NCH_2CH), 5.11-5.17 (4H, m, 2 x $NCH_2CH=CH_2$), 5.60 (2H, ddd, *J* 17.2, 9.9 and 6.1, 2 x $NCH_2CH=CH_2$), 7.30 (2H, d, *J* 8.0, Ar-*H* x 2), 7.70 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.29 (CH_3), 49.18 (2 x CH_2), 118.75 (2 x CH_2), 126.97 (2 x CH), 129.52 (2 x CH), 132.51 (2 x CH), 137.24 (C), 143.08 (C). *m/z* (FAB) 252.1058 (MH^+. $C_{13}H_{18}NO_2S$ requires 252.1058), 252 (100 %), 224 (6), 155 (57), 109 (19), 91 (60), 81 (37), 69 (48).

This is a literature compound.[158]

4-Methyl-*N,N*-bis-(2-methylallyl)-benzenesulfonamide **156**

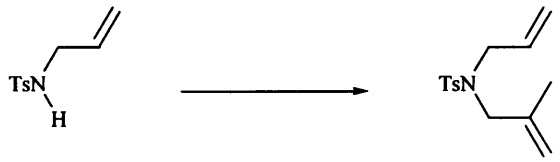


154 **156**

p-Toluene sulfonamide **154** (10 g, 58.4 mmol) was added to a suspension of K_2CO_3 (80.7 g, 584 mmol) in DMF (200 cm^3) and left to stir for 15 min, after which methallyl chloride (17.3 cm^3, 175 mmol) was added. The reaction was stirred for 18 h after which time TLC showed it to be complete. Water (200 cm^3) was added and the organic species extracted with ethyl acetate (3 x 50 cm^3). The organic extracts were combined, dried ($MgSO_4$) and the solvent

evaporated under reduced pressure to leave the crude product, which was purified by flash column chromatography on silica using petrol:diethyl ether (70:30 to 30:70) to elute the *diene* **156** (11.95 g, 73 %) as a colourless oil. ν_{max} (cm^{-1}, film) 3060, 2920, 1655, 1590, 1450, 1345 and 1170 (SO_2). δ_H (250 MHz, $CDCl_3$) 1.53 (6H, s, 2 x C(C*H*$_3$)=CH_2), 2.34 (3H, s, Ar-C*H*$_3$), 3.63 (4H, s, 2 x NC*H*$_2$C(CH_3)), 4.71 (2H, br s, 2 x C(CH_3)=C*H*H), 4.78 (2H, br s, 2 x C(CH_3)=C*H*H), 7.21 (2H, d, *J* 8.0, Ar-*H* x 2), 7.63 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 19.93 (2 x CH_3), 21.42 (CH_3), 53.07 (2 x CH_2), 114.43 (2 x CH_2), 127.21 (2 x CH), 129.44 (2 x CH), 137.44 (C), 140.06 (2 x C), 143.02 (C). *m/z* (ES) 280 (49 %), 224 (59), 184 (46), 155 (92), 109 (100). *m/z* (FAB) 280.1372 (MH^+. $C_{15}H_{22}NO_2S$ requires 280.1371).

N-Allyl-4-methyl-*N*-(2-methylallyl)-benzenesulfonamide **157**

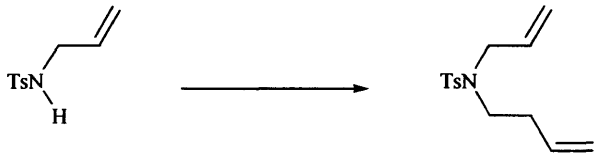


172 **157**

The method for the alkylation with methallyl chloride is based upon the procedure employed by Parsons and Pettifer.[112] The sulfonamide **172** (7.5 g, 35.5 mmol) was added to a solution of NaH (60 % dispersion in mineral oil, 1.71 g, 42.8 mmol) in DMF (120 cm^3). The reaction was stirred for 15 min then methallyl chloride (9.6 cm^3, 98 mmol) was added. The reaction was monitored by TLC and stirred for 16 h until complete. The reaction mixture was poured into saturated aqueous ammonium chloride (100 cm^3) and water (100 cm^3). The organic compound was extracted with ethyl acetate (3 x 50 cm^3). The combined extracts were dried ($MgSO_4$) evaporated under reduced pressure to leave a brown oil which was purified by flash column chromatography on silica using petrol:diethyl ether (95:5 to 80:20) to give the *diene* **157** (8.05 g, 85 %) as a yellow oil. ν_{max} (cm^{-1}, film) 3060, 2980, 1650, 1595, 1445, 1345 (SO_2), 1165 (SO_2). δ_H (250 MHz, $CDCl_3$) 1.71 (3H, s, C(C*H*$_3$)=CH_2), 2.45 (3H, s, Ar-C*H*$_3$), 3.72 (2H, s, NC*H*$_2$C(CH_3)), 3.79 (2H, br d, *J* 6.7, NC*H*$_2$CH=CH_2), 4.87 (1H, br s, C(CH_3)=C*H*H), 4.93 (1H, br s, C(CH_3)=CH*H*), 5.06-5.10 (1H, m, CH=C*H*H), 5.13-5.15 (1H, m, CH=CH*H*), 5.56 (1H, ddd, *J* 17.4, 9.6 and 6.7, C*H*=CH_2), 7.32 (2H, d, *J* 8.0, Ar-*H* x 2), 7.73 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 19.75 (CH_3), 21.43 (CH_3), 49.32 (CH_2), 52.73 (CH_2), 114.41 (CH_2), 119.11 (CH_2), 127.14 (2 x CH), 129.57 (2 x CH), 132.28 (CH), 137.42 (C), 140.01 (C), 143.11 (C). *m/z* (FAB) 266.1215 (MH^+. $C_{14}H_{20}NO_2S$ requires 266.1214), 266 (100 %), 224 (13), 155 (49), 139 (19).

This is a literature compound.[159]

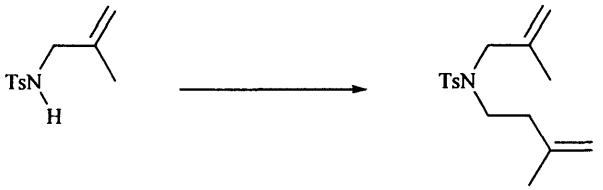
N-Allyl-*N*-but-3-enyl-4-methylbenzenesulfonamide **158**



172 **158**

The reaction was carried out as for the preparation of **156**, except that NaH was used as the base.The *p*-toluene sulfonamide **172** (2 g, 9.5 mmol) was reacted NaH (95 % dispersion in mineral oil, 0.296 g, 12.3 mmol) in DMF (50 cm^3) and 4-bromo-1-butene (1.12 cm^3, 7.1 mmol) added. After 18 h the reaction was worked up as before and the crude product purified by flash column chromatography on silica using petrol:diethyl ether (80:20 to 30:70) to give the *diene* **158** (1.25 g, 50 %) as a colourless oil together with recovered **172** (38 %). ν_{max} (cm^{-1}, film) 3079, 2923, 1642, 1598, 1343 and 1159 (SO_2), 1091. δ_H (400 MHz, $CDCl_3$) 2.28 (2H, app qt, *J* 7.1 and 1.3, $CH_2CH_2CH{=}CH_2$), 2.42 (3H, s, Ar-CH_3), 3.16-3.20 (2H, m (2^{nd} order), $CH_2CH_2CH{=}CH_2$), 3.81 (2H, dt, *J* 6.4 and 1.3 $NCH_2CH{=}CH_2$), 4.99-5.06 (2H, m, $CH_2CH_2CH{=}CH_2$), 5.12-5.21 (2H, m, $NCH_2CH{=}CH_2$), 5.59-5.75 (2H, m, $NCH_2CH_2CH{=}CH_2$ and $NCH_2CH{=}CH_2$), 7.29 (2H, d, *J* 8.0, Ar-*H* x 2), 7.70 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (100.6 MHz, $CDCl_3$) 21.45 (CH_3), 32.82 (CH_2), 46.65 (CH_2), 50.66 (CH_2), 116.92 (CH_2), 118.71 (CH_2), 127.12 (2 x CH), 129.62 (2 x CH), 133.19 (CH), 134.69 (CH), 137.16 (C), 143.14 (C). *m/z* (FAB) 266.1215 (MH^+. $C_{14}H_{20}NO_2S$ requires 266.1214), 266 (59 %), 224 (100), 155 (48), 139 (14), 91 (44).

4-Methyl-*N*-(2-methylallyl)-*N*-(3-methylbut-3-enyl)-benzenesulfonamide **159**

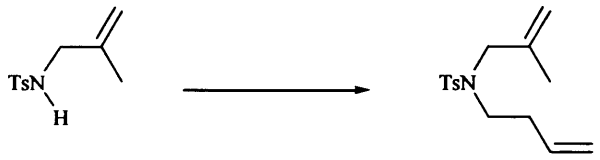


170 **159**

The reaction was carried out as for the preparation of **157**. The sulfonamide **170** (1 g, 4.44 mmol) was reacted with NaH (95 %, 0.135 g, 5.33 mmol) in DMF (50cm^3) and then the tosylate **167** (1.17 g, 4.88 mmol) was added and the reaction left to stir for 18 h. The reaction was worked up as before and purified by flash column chromatography on silica using petrol:diethyl ether (100:0 to 80:20) to give the *diene* **159** (0.58 g, 45 %) as a colourless oil. ν_{max} (cm^{-1}, film) 3075, 2922, 1650, 1598, 1454, 1340 and 1159 (SO_2). δ_H (400 MHz, $CDCl_3$) 1.67 (3H, s, $NCH_2CH_2C(CH_3)$), 1.72 (3H, s, $NCH_2C(CH_3)$), 2.14-2.18 (2H, m,

$NCH_2CH_2C(CH_3)$), 2.42 (3H, s, Ar-CH_3), 3.17-3.21 (2H, m, $NCH_2CH_2C(CH_3)$), 3.71 (2H, s, $NCH_2C(CH_3)$), 4.60 (1H, br s, $CH_2CH_2C(CH_3)=CHH$), 4.72 (1H, br s, $CH_2CH_2C(CH_3)=CHH$), 4.89 (1H, br s, $NCH_2C(CH_3)=CHH$), 4.91 (1H, br s, $NCH_2C(CH_3)=CHH$), 7.29 (2H, d, *J* 8.0, Ar-*H* x 2), 7.70 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (100.6, $CDCl_3$) 19.81 (CH_3), 21.48 (CH_3), 22.42 (CH_3), 36.17 (CH_2), 46.39 (CH_2), 54.47 (CH_2), 111.82 (CH_2), 114.49 (CH_2), 127.17 (2 x CH), 129.61 (2 x CH), 137.19 (C), 140.85 (C), 142.59 (C), 143.11 (C). *m/z* (ES) 294 (59 %), 252 (66), 238 (100), 184 (12), 102 (15). *m/z* (FAB) 294.1527 (MH^+. $C_{16}H_{24}NO_2S$ requires 294.1528).

N-But-3-enyl-4-methyl-*N*-(2-methylallyl)-benzenesulfonamide **160**

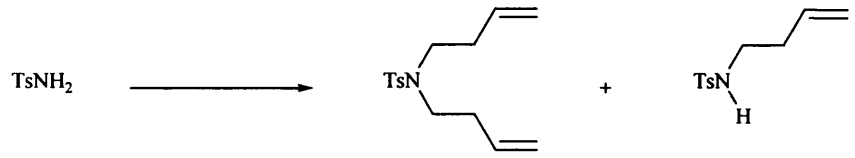


170 **160**

The reaction was carried out as for the preparation of **157**. The sulfonamide **170** (2.22 g, 9.85 mmol) was added to a suspension of NaH (95 %, 0.373 g, 14.8 mmol) in DMF (100 cm^3) and stirred for 15 min. 4-Bromo-1-butene (1.5 cm^3, 14.8 mmol) was added dropwise and after 16 h the reaction was worked up as for **157** and the crude product purified by chromatography on silica using petrol:diethyl ether (70:30 to 40:60) to give the *diene* **160** (1.23 g, 45 %) as a colourless oil. ν_{max} (cm^{-1}, film) 2920, 1642, 1598, 1455, 1161 (SO_2). δ_H (250 MHz, $CDCl_3$) 1.84 (3H, s, $C(CH_3)=CH_2$), 2.45 (2H, app q, *J* 7.0, $CH_2CH_2CH=CH_2$), 2.65 (3H, s, Ar-CH_3), 3.33-3.40 (2H, m (2^{nd} order), $CH_2CH_2CH=CH_2$), 3.93 (2H, s, $NCH_2C(CH_3)=CH_2$), 5.11-5.13 (2H, m, ($NCH_2C(CH_3)=CH_2$), 5.18 (1H, br s, $CH_2CH_2CH=CHH$), 5.22-5.25 (1H, m, $CH_2CH_2CH=CHH$), 5.88 (1H, ddd, *J* 17.0, 9.6 and 7.0, $NCH_2CH_2CH=CH_2$), 7.52 (2H, d, *J* 8.0, Ar-*H* x 2), 7.92 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 19.75 (CH_3), 21.40 (CH_3), 32.58 (CH_2), 47.18 (CH_2), 54.56 (CH_2), 114.38 (CH_2), 116.75 (CH_2), 127.09 (2 x CH), 129.55 (2 x CH), 134.75 (CH), 137.05 (C), 140.73 (C), 143.08 (C). *m/z* (ES) 280 (65 %), 238 (54), 226 (45), 184 (82), 155 (100), 109 (84). *m/z* (FAB) 280.1371 (MH^+. $C_{15}H_{22}NO_2S$ requires 280.1371).

N,N-Dibut-3-enyl-4-methylbenzenesulfonamide **161** and

N-But-3-enyl-4-methylbenzenesulfonamide **165**



154 **161** **165**

The reaction was carried out as for the preparation of **157**, except that K_2CO_3 was used as the base. *p*-Toluene sulfonamide **154** (11.5 g, 67.1 mmol) was dissolved in DMF (100 cm^3) and K_2CO_3 (9.27 g, 67.1 mmol) was added. The reaction mixture was stirred for 15 min before the addition of 4-bromo-1-butene (7.95 cm^3, 67.1 mmol). After stirring for 4 h a further portion of 4-bromo-1-butene (2 cm^3, 16.9 mmol) was added. The reaction was stirred for 12 h and workup as before gave an oil that was purified by flash column chromatography on silica using petrol:ethyl acetate (90:10) to give the disubstituted *diene* **161** (1.73 g, 9 %) and petrol:ethyl acetate (50:50) to elute the monosubstituted *olefin* **165** (9.17 g, 60 %) as colourless oils.

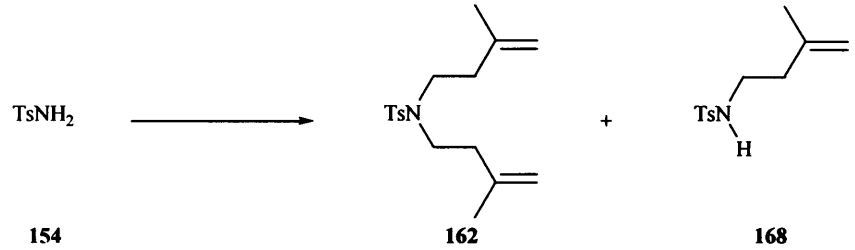
161: ν_{max} (cm^{-1}, film) 3020, 2930, 1640, 1595, 1500, 1460, 1345 and 1175 (SO_2). δ_H (250 MHz, $CDCl_3$) 2.27 (4H, app qt, *J* 6.9 and 1.2, 2 x NCH_2CH_2), 2.40 (3H, s, Ar-CH_3), 3.14-3.20 (4H, m (2nd order), 2 x NCH_2CH_2), 4.99-5.03 (2H, m, 2 x $CH_2CH{=}CHH$ *cis*), 5.03-5.08 (2H, m, 2 x $CH_2CH{=}CHH$ *trans*), 5.69 (2H, ddd (overlapping), *J* 17.2, 10.3 and 6.9, 2 x $CH_2CH{=}CH_2$) 7.27 (2H, d, *J* 8.0, Ar-*H* x 2), 7.75 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.41 (CH_3), 33.15 (2 x CH_2), 47.70 (2 x CH_2), 116.98 (2 x CH_2), 127.08 (2 x CH), 129.57 (2 x CH), 134.61 (2 x CH) 137.00 (C), 143.07 (C). *m/z* (FAB) 280.1371 (MH^+. $C_{15}H_{22}NO_2S$ requires 280.1371), 280 (81 %), 238 (100), 184 (23), 155 (60), 139 (20), 91 (55).

165: ν_{max} (cm^{-1}, film) 3265 (NH), 3060, 2970, 1640, 1600, 1435, 1330 and 1165 (SO_2). δ_H (250 MHz, $CDCl_3$) 2.41 (2H, app qt, *J* 7.0 and 1.2, NCH_2CH_2), 2.63 (3H, s, Ar-CH_3), 3.21 (2H, app q, *J* 7.0, NCH_2CH_2), 5.13-5.22 (2H, m, $NCH_2CH_2CH{=}CH_2$), 5.26 (1H, br s, N*H*), 5.84 (1H, ddd, *J* 17.5, 10.8 and 7.0, $CH{=}CH_2$), 7.51 (2H, d, *J* 8.0, Ar-*H* x 2), 7.97 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.36 (CH_3), 33.49 (CH_2), 42.09 (CH_2), 117.72 (CH_2), 126.99 (2 x CH), 129.57 (2 x CH), 134.14 (CH) 136.87 (C), 143.25 (C). *m/z* (FAB) 226.0901 (MH^+. $C_{11}H_{16}NO_2S$ requires 226.0902), 226 (100 %), 184 (43), 155 (63), 139 (27), 91 (46).

This is a literature compound.[160]

4-Methyl-*N,N*-bis-(3-methylbut-3-enyl)-benzenesulfonamide **162** and

4-Methyl-*N*-(3-methylbut-3-enyl)-benzenesulfonamide **168**



154 **162** **168**

The reaction carried out as for the preparation of **157**. *p*-Toluene sulfonamide **154** (5 g, 29.2 mmol) in DMF (100 cm^3) and NaH (95 %, 0.88 g, 35 mmol) were reacted with **167** (7 g, 29.2 mmol). Workup as before gave an oil that was purified by flash column chromatography on silica using petrol:ethyl acetate (70:30) to give the disubstituted *diene* **162** (1.10 g, 15 %) and petrol:ethyl acetate (90:10) to elute the monosubstituted *olefin* **168** (2.20 g, 35 %) as colourless oils.

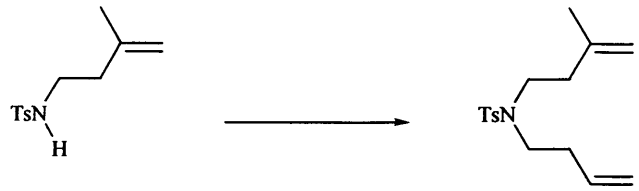
162: ν_{max} (cm^{-1}, film) 3079, 2934, 1649, 1598, 1456, 1340 and 1158 (SO_2). δ_H (250 MHz, $CDCl_3$) 1.86 (6H, s, 2 x C(C*H*$_3$)=CH_2), 2.38 (4H, br t, *J* 7.6, 2 x C*H*$_2$C(CH_3)=CH_2), 2.56 (3H, s, Ar-C*H*$_3$), 3.37-3.43 (4H, m (2nd order), 2 x NC*H*$_2$$CH_2$C($CH_3$)), 4.82 (2H, br s, 2 x CH_2CH_2C(CH_3)=CH*H*), 4.91 (2H, br s, 2 x CH_2CH_2C(CH_3)=C*H*H), 7.43 (2H, d, *J* 8.0, Ar-*H* x 2), 7.84 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.42 (CH_3), 22.42 (2 x CH_3), 36.76 (2 x CH_2), 46.65 (2 x CH_2), 111.97 (2 x CH_2), 127.09 (2 x CH), 129.59 (2 x CH), 137.08 (C), 142.34 (2 x C), 143.06 (C). *m/z* (FAB) 308.1684 (MH^+. $C_{17}H_{26}NO_2S$ requires 308.1684), 308 (18 %), 252 (100), 184 (76), 155 (51), 139 (16).

This is a literature compound.[159]

168: ν_{max} (cm^{-1}, film) 3284 (NH), 3079, 2935, 1650, 1598, 1467-1408, 1324 and 1158 (SO_2). δ_H (250 MHz, $CDCl_3$) 1.72 (3H, s, C(C*H*$_3$)=CH_2), 2.27 (2H, t, *J* 6.9, CH_2C*H*$_2$C(CH_3)=CH_2), 2.55 (3H, s, Ar-C*H*$_3$), 3.17 (2H, app q, *J* 6.9, C*H*$_2$$CH_2$C($CH_3$)=$CH_2$), 4.76 (2H, br s, C($CH_3$)=C*H*H and N*H*), 4.91 (1H, br s, C(CH_3)=CH*H*), 7.43 (2H, d, *J* 8.0, Ar-*H* x 2), 7.87 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.42 (CH_3), 21.68 (CH_3), 37.13 (CH_2), 40.58 (CH_2), 113.02 (CH_2), 127.05 (2 x CH), 129.62 (2 x CH), 136.84 (C), 141.44 (C), 143.32 (C). *m/z* (FAB) 240.1058 (MH^+. $C_{12}H_{18}NO_2S$ requires 240.1058), 240 (24 %), 184 (100), 155 (47), 139 (15).

This is a literature compound.[160]

N-But-3-enyl-4-methyl-*N*-(3-methylbut-3-enyl)-benzenesulfonamide **163**

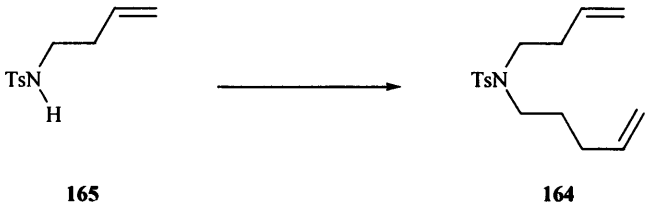


168 **163**

The reaction was carried out as for the preparation of **157**. The olefin **168** (1 g, 4.2 mmol) in DMF (20 cm^3) and NaH (95 %, 0.127 g, 5 mmol) were reacted with 4-bromo-1-butene (0.58 cm^3, 5.3 mmol). Workup as before gave an oil that was purified by flash column chromatography on silica using petrol:ethyl acetate (80:20) to give the *diene* **163** (0.86 g, 69 %) as a yellow oil. ν_{max} (cm^{-1}, film) 3079, 2927, 1647, 1599, 1456, 1340 and 1158 (SO_2). δ_H (250 MHz, $CDCl_3$) 1.83 (3H, s, $CH_2CH_2C(CH_3)=CH_2$), 2.32–2.46 (4H, overlapping m, $CH_2CH_2C(CH_3)=CH_2$ and $CH_2CH_2CH=CH_2$), 2.53 (3H, s, Ar-CH_3), 3.29–3.39 (4H, overlapping m, $CH_2CH_2CH=CH_2$ and $CH_2CH_2C(CH_3)=CH_2$), 4.79 (1H, br s, $CH_2CH_2C(CH_3)=CHH$), 4.88 (1H, br s, $CH_2CH_2C(CH_3)=CHH$), 5.13–5.22 (2H, m, $CH_2CH_2CH=CH_2$), 5.84 (1H, ddd, *J* 16.9, 10.1 and 6.7, $CH_2CH_2CH=CH_2$), 7.40 (2H, d, *J* 8.0, Ar-*H* x 2), 7.81 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 20.93 (CH_3), 21.38 (CH_3), 33.11 (CH_2), 36.74 (CH_2), 46.78 (CH_2), 47.52 (CH_2), 111.92 (CH_2), 116.94 (CH_2), 127.05 (2 x CH), 129.55 (2 x CH), 134.61 (CH), 137.01 (C), 142.29 (C), 143.04 (C). *m/z* (ES) 294 (66 %), 252 (10), 238 (100), 184 (10), 140 (7). *m/z* (FAB) 294.1528 (MH^+. $C_{16}H_{24}NO_2S$ requires 294.1528).

This is a literature compound.[159]

N-But-3-enyl-4-methyl-*N*-pent-4-enylbenzenesulfonamide **164**

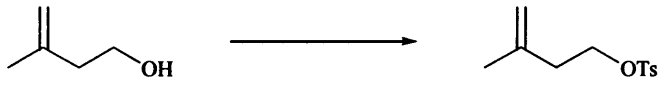


165 **164**

The reaction was carried out as for the preparation of **157**. The olefin **165** (2 g, 8.8 mmol) was reacted with NaH (95 %, 0.269 g, 10.66 mmol) in DMF (50 cm^3) and 4-bromo-1-butene (1.16 cm^3, 9.77 mmol) added. After 18 h the reaction was worked up as before and the crude product purified by flash column chromatography on silica using petrol:ethyl acetate (90:10 to 70:30) to give the *diene* 14 (2.25 g, 87 %) as a colourless oil. ν_{max} (cm^{-1}, film) 3077, 2928,

1641, 1338, 1158 (SO_2) and 1090. δ_H (250 MHz, $CDCl_3$) 1.65 (2H, pentet, *J* 7.3, $NCH_2CH_2CH_2$), 2.06 (2H, app q, *J* 7.3, $NCH_2CH_2CH_2$), 2.26-2.35 (2H, m, $NCH_2CH_2CH{=}CH_2$), 2.42 (3H, s, Ar-CH_3), 3.11-3.16 (2H, m (2^{nd} order), $NCH_2CH_2CH_2CH{=}CH_2$), 3.17-3.22 (2H, m (2^{nd} order), $NCH_2CH_2CH{=}CH_2$), 4.96-5.04 (4H, m, $NCH_2CH_2CH{=}CH_2$ and $NCH_2CH_2CH_2CH{=}CH_2$), 5.65-5.87 (2H, m, 2 x $CH_2CH{=}CH_2$), 7.30 (2H, d, *J* 8.0, Ar-*H* x 2), 7.71 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.36 (CH_3), 27.72 (CH_2), 30.67 (CH_2), 33.21 (CH_2), 47.69 (CH_2), 47.83 (CH_2), 115.16 (CH_2), 116.89 (CH_2), 127.02 (2 x CH), 129.51 (2 x CH), 134.61 (CH), 136.90 (C), 137.37 (CH), 142.97 (C). *m/z* (ES) 294 (92 %), 252 (100), 240 (23), 198 (55), 184 (58), 155 (59), 138 (36), 98 (29). *m/z* (FAB) 294.1527 (MH^+. $C_{16}H_{24}NO_2S$ requires 294.1528).

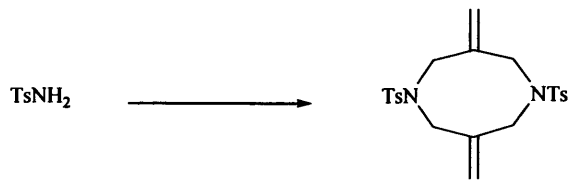
Toluene-4-sulfonic acid 3-methylbut-3-enyl ester **167**



166 **167**

p-Toluenesulfonyl chloride (9.44 g, 49.5 mmol) and DMAP (7.26 g, 59.4 mmol) were added to dichloromethane (200 cm^3) and the mixture stirred for 15 min at 0°C before 3-methyl-3-buten-1-ol **166** (5 cm^3, 49.5 mmol) was added dropwise to the reaction mixture which was stirred at room temperature for 18 h. The reaction was quenched by addition of water (100 cm^3) and the organic species extracted with DCM (3 x 50 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to leave a yellow oil, which was purified by flash column chromatography on silica using petrol:diethyl ether (80:20 to 60:40) to give the *tosylate* **167** (6.08 g, 52 %) as a colourless oil. ν_{max} (cm^{-1}, film) 3060, 2920, 1650, 1595, 1455, 1360 (SO_2), 1200, 1185 (SO_2). δ_H (250 MHz, $CDCl_3$) 1.66 (3H, s, $CH_2C(CH_3){=}CH_2$), 2.34 (2H, t, *J* 6.9, $CH_2C(CH_3){=}CH_2$), 2.44 (3H, s, Ar-CH_3), 4.12 (2H, t, *J* 6.9, OCH_2), 4.78 (1H, br s, $C(CH_3){=}CHH$), 4.90 (1H, br s, $C(CH_3){=}CHH$), 7.34 (2H, d, *J* 8.0, Ar-*H* x 2), 7.70 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.52 (CH_3), 22.21 (CH_3), 36.66 (CH_2), 68.46 (CH_2), 113.00 (CH_2), 127.80 (2 x CH), 129.74 (2 x CH), 133.09 (C), 140.50 (C), 144.67 (C). *m/z* (FAB) 241.0898 ($C_{12}H_{17}O_3S$ requires 241.0898), 241 (100 %), 223 (11), 173 (30), 155 (70), 137 (46).

3,7-Dimethylene-1,5-bis-(toluene-4-sulfonyl)-[1,5]diazocane **169**

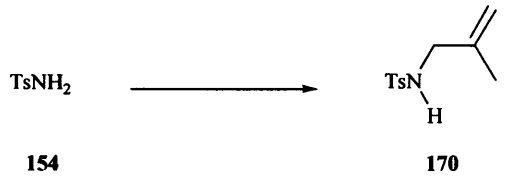


154 **169**

This method for the alkylation of *p*-toluene sulfonamide with 3-chloro-2-chloromethyl-propene is based upon the procedure employed by Dave and Forohar.[111] *p*-Toluene sulfonamide **154** (7 g, 40.9 mmol) was added to a solution of K_2CO_3 (8.07 g, 81.8 mmol) in acetonitrile (70 cm^3). The reaction was stirred for 15 min, then 3-chloro-2-chloromethyl-propene (4.73 cm^3, 40.9 mmol) was added dropwise over 15 min. The reaction was heated under reflux for 16 h after which it was allowed to cool and the solvent was removed by evaporation under reduced pressure. The crude product was extracted using hot ethyl acetate and on cooling gave the *sulfonamide* **169** (3.82 g, 42 %) as a white solid. Further purification was not required. M.p. 192-193°C (EtOAc)(Literature m.p. 194-197°C).[111] ν_{max} (cm^{-1}, solid) 3069, 2923, 1597, 1330 (SO_2), 1090. δ_H (250 MHz, $CDCl_3$) 2.44 (6H, s, Ar-C*H*$_3$), 3.83 (8H, s, 4 x NC*H*$_2$C=CH$_2$), 5.19 (4H, s, 2 x NCH$_2$C=C*H*$_2$), 7.32 (4H, d, *J* 8.0, Ar-*H* x 4), 7.68 (4H, d, *J* 8.0, Ar-*H* x 4). δ_C (62.9 MHz, $CDCl_3$) 21.49 (2 x CH_3), 53.02 (4 x CH_2), 118.16 (2 x CH_2), 127.15 (4 x CH), 129.77 (4 x CH), 135.93 (2 x C), 141.84 (2 x C), 143.55 (2 x C). *m/z* (FAB) 447.1412 (MH^+. $C_{22}H_{27}N_2O_4S_2$ requires 447.1412), 447 (88 %), 393 (7), 322 (10), 291 (50), 154 (98), 136 (100).

This is a literature compound.[111]

N-(2-methylallyl)-4-methylbenzenesulfonamide **170**



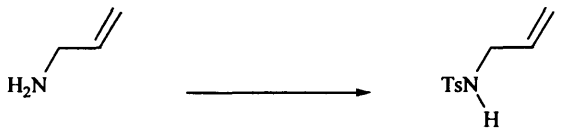
154 **170**

p-Toluene sulfonamide **154** (10 g, 58.4 mmol) was added to a suspension of K_2CO_3 (8.07 g, 58.4 mmol) in acetone (150 cm^3). The reaction was left to stir for 15 min and then methallyl chloride (5.8 cm^3, 58.4 mmol) was added. The reaction was heated under reflux for 4 h then stirred for a further 16 h at room temperature. The K_2CO_3 and KCl were filtered off and the solvent was removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography on silica using petrol:diethyl ether (70:30 to 30:70) to give

the *sulfonamide* **170** (4.71 g, 40 %) as a white solid. M.p. 49-50°C (petrol 40-60)(literature m.p. 50-52°C).[161] ν_{max} (cm^{-1}, CH_2Cl_2) 3285 (NH), 3079, 2973, 1598, 1422, 1325 (SO_2), 1265, 1161 (SO_2). δ_H (250 MHz, $CDCl_3$) 1.69 (3H, s, $C(CH_3)=CH_2$), 2.44 (3H, s, Ar-CH_3), 3.44 (2H, d, *J* 6.0 $NCH_2C(CH_3)$), 4.56 (1H, t, *J* 6.0, NH), 4.83 (1H, s, $C(CH_3)=CHH$), 4.86 (1H, s, $C(CH_3)=CHH$), 7.31 (2H, d, *J* 8.0, Ar-*H* x 2), 7.76 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 20.07 (CH_3), 21.49 (CH_3), 49.03 (CH_2), 112.74 (CH_2), 127.10 (2 x CH), 129.67 (2 x CH), 136.98 (C), 140.50 (C), 143.42 (C). *m/z* (ES) 226 (61 %), 184 (24), 155 (100), 108 (90). *m/z* (FAB) 226.0902 (MH^+. $C_{11}H_{16}NO_2S$ requires 226.0902).
Some of the *disubstituted diene* **156** was also isolated (1.10 g, 10 %), data as shown above.

This is a literature compound.[161]

N-Allyl-4-methylbenzenesulfonamide **172**

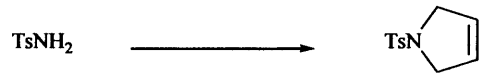


171 **172**

To a solution of allylamine **171** (6 g, 105 mmol) in DCM (100 cm^3) was added triethylamine (14.8 cm^3, 106mmol). The reaction mixture was then cooled to 0°C and *p*-toluenesulfonyl chloride (10.5 g, 55 mmol) was added portion-wise. The reaction was stirred at 0°C for 1 h until TLC analysis showed no remaining starting material. The mixture was quenched by addition of water (70 cm^3) and extracted with DCM (3 x 50 cm^3). The extracts were combined, dried ($MgSO_4$) and the solvent was removed by evaporation under reduced pressure to leave the *sulfonamide* **172** as a white solid (9.56 g, 82 %). M.p. 58-60°C (petrol 40-60) (Literature m.p. 59-61°C).[162] ν_{max} (cm^{-1}, solid) 3285 (NH), 3059, 2987, 1645, 1598, 1422, 1325 (SO_2), 1266, 1160 (SO_2). δ_H (250 MHz, $CDCl_3$) 2.45 (3H, s, Ar-CH_3), 3.59 (2H, tt, *J* 5.7 and 1.4, $NCH_2CH=CH_2$), 4.51 (1H, br t, *J* 5.7, NH), 5.13-5.26 (2H, m, $CH=CH_2$), 5.78 (1H, ddd, *J* 17.2, 10.3 and 5.7, $CH_2CH=CH_2$), 7.37 (2H, d, *J* 8.0, Ar-*H* x 2), 7.81 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.50 (CH_3), 45.77 (CH_2), 117.71 (CH_2), 127.14 (2 x CH), 129.72 (2 x CH), 132.99 (CH), 136.98 (C), 143.51 (C). *m/z* (FAB) 212.0745 (MH^+. $C_{10}H_{14}NO_2S$ requires 212.0745), 212 (100 %), 155 (40), 137 (19), 107 (8), 91 (38).

This is a literature compound.[162]

1-(Toluene-4-sulfonyl)-2,5-dihydro-1*H*-pyrrole **259**

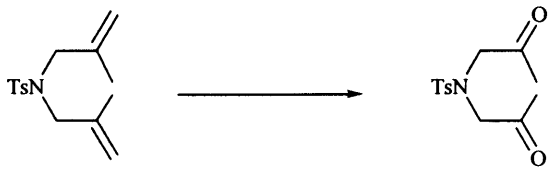


154 **259**

This method for the alkylation of *p*-toluene sulfonamide with 1,4-dichloro-but-2-ene is based upon the procedure employed by Greenwood and Greenwood.[139] *p*-Toluene sulfonamide **154** (2 g, 11.7 mmol) was reacted with NaH (60 % dispersion in mineral oil, 0.560 g, 14.0 mmol) in DMF (20 cm^3) and 1,4-dichloro-but-2-ene (1.35cm^3, 12.8mmol) added. After 16 h the reaction was worked up as for the preparation of **157** and the crude product purified by flash column chromatography on silica using petrol:diethyl ether (70:30 to 60:40) to give the *diene* **259** (1.48 g, 57 %) as a white solid. M.p. 127-129°C (hexane)(literature m.p. 130-131°C).[139] δ_H (300 MHz, $CDCl_3$) 2.40 (3H, s, Ar-C*H*$_3$), 4.09 (4H, s, 2 x NC*H*$_2$CH=CH), 5.63 (2H, s, NCH$_2$C*H*=C*H*), 7.31 (2H, d, *J* 8.0, Ar-*H* x 2), 7.71 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (75.5 MHz, $CDCl_3$) 21.04 (CH_3), 54.47 (2 x CH_2), 125.05 (2 x CH), 126.96 (2 x CH), 129.40 (2 x CH), 133.74 (C), 143.09 (C).

This is a literature compound.[158]

4-Methyl-*N,N*-bis-(2-oxopropyl)-benzenesulfonamide **178**



156 **178**

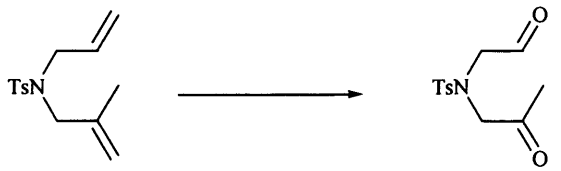
Ozone was bubbled through a stirred solution of **156** (1.74 g, 6.14 mmol) in dry methanol (50 cm^3) at -78°C until a pale blue colour was observed. Nitrogen was then bubbled through until the solution turned colourless. Then Me_2S (1.5 cm^3, 24 mmol) was added and the reaction allowed to warm to room temperature and stirred for a further 18 h. The solvent was removed by evaporation under reduced pressure and the crude product purified by flash column chromatography on silica using diethyl ether:petrol (70:30 to 100:0) to elute the *diketone* **178** (1.12 g, 64 %) as a white solid. M.p. 105-106°C (Et_2O)(literature m.p. 104-105°C).[163] ν_{max} (cm^{-1}, sol^n) 3053, 2925, 1736 (C=O), 1422, 1265, 1158 (SO_2). δ_H (250 MHz, $CDCl_3$) 2.08 (6H, s, 2 x NCH$_3$COC*H*$_3$), 2.36 (3H, s, Ar-C*H*$_3$), 4.06 (4H, s, 2 x NC*H*$_2$COCH$_3$), 7.24 (2H, d, *J* 8.0, Ar-*H* x 2), 7.61 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.56 (CH_3), 27.02 (2 x

CH_3), 56.71 (2 x CH_2), 127.36 (2 x CH), 129.72 (2 x CH), 135.76 (C), 143.92 (C), 203.08 (2 x C). *m/z* (FAB) 284.0956 (MH^+. $C_{13}H_{18}NO_4S$ requires 284.0957), 284 (100 %), 240 (82), 155 (81), 139 (37).

This is a literature compound.[163]

Cyclised ketal **179** was also eluted (as a mixture of stereoisomers)(0.28g, 14 %). **179**: δ_H (250 MHz, $CDCl_3$) 1.30 (3H, s, $NCH_2C(CH_3)$), 1.49 (3H, s, $NCH_2C(CH_3)$), 2.43 (3H, s, Ar-CH_3), 2.68 (1H, d, *J* 13.0, NCH_2), 2.87 (1H, dd, *J* 14.2 and 0.7, NCH_2), 3.33 (3H, s, $NCH_2C(CH_3)(OCH_3)$), 3.78 (1H, dd, *J* 13.0 and 1.4, NCH_2), 3.88 (1H, dd, *J* 14.2 and 1.4, NCH_2) 4.74 (1H, s, O*H*), 7.34 (2H, d, *J* 8.0, Ar-*H* x 2), 7.66 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 17.82 (CH_3), 17.97 (CH_3), 21.39 (2 x CH_3), 21.81 (CH_3), 22.62 (CH_3), 49.37 (CH_2), 49.61 (CH_2), 57.67 (CH_2), 58.40 (CH_2), 60.24 (2 x CH_2), 101.93 (C), 103.87 (C), 106.82 (C), 107.31 (C), 126.90 (2 x CH), 127.05 (2 x CH), 129.84 (2 x CH), 129.95 (2 x CH), 134.69 (C), 135.14 (C), 143.77 (C), 144.08 (C).

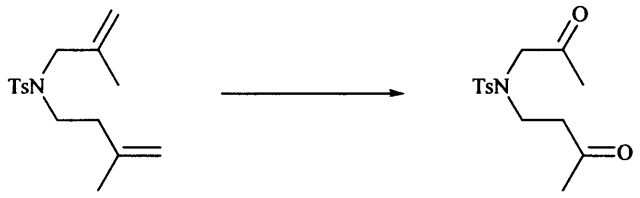
4-Methyl-*N*-(2-oxoethyl)-*N*-(2-oxopropyl)-benzenesulfonamide **180**



157 **180**

The diene **157** (1.5 g, 5.65 mmol) in dry methanol (70 cm^3) was treated with ozone then Me_2S (1.7 cm^3, 22.6 mmol) as for the preparation of **178**. After evaporation the crude material was purified by flash column chromatography on silica using diethyl ether:petrol (50:50 to 100:0) to give the *keto-aldehyde* **180** (0.769 g, 50 %) as a brown oil. ν_{max} (cm^{-1}, film) 3460, 3060, 2930, 1725 (C=O), 1600, 1500. δ_H (400 MHz, $CDCl_3$) 2.15 (3H, s, $COCH_3$), 2.44 (3H, s, Ar-CH_3), 3.91 (2H, br s, NCH_2CHO), 4.16 (2H, s, NCH_2COCH_3), 7.33 (2H, d, *J* 8.0, Ar-*H* x 2), 7.68 (2H, d, *J* 8.0, Ar-*H* x 2), 9.66 (1H, t, *J* 1.1, NCH_2CHO). δ_C (100.6 MHz, $CDCl_3$) 21.54 (CH_3), 26.94 (CH_3), 57.35 (CH_2), 57.65 (CH_2), 127.33 (2 x CH), 129.91 (2 x CH), 135.45 (C), 144.27 (C), 197.67 (CH), 202.4 (C). *m/z* (FAB) 270.0800 (MH^+. $C_{12}H_{16}NO_4S$ requires 270.0800), 270 (61 %), 240 (15), 154 (100), 136 (77).

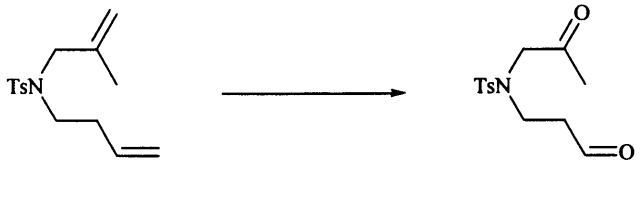
4-Methyl-*N*-(3-oxobutyl)-*N*-(2-oxopropyl)-benzenesulfonamide **189**



159 **189**

The diene **159** (1.18 g, 4.01 mmol) in dry methanol (50 cm^3) was treated with ozone and then Me_2S (1.0 cm^3, 16 mmol) as for the preparation of **178**. Removal of the solvent under high vacuum (0.1 mmHg) gave the *diketone* **189** (0.95 g, 80 %) as a colourless oil. ν_{max} (cm^{-1}, film) 3060, 2989, 2921, 2303, 1715 (C=O), 1349, 1265, 1159 (SO_2). δ_H (250 MHz, $CDCl_3$) 2.12 (6H, br s, 2 x ($COCH_3$), 2.43 (3H, s, Ar-CH_3), 2.85 (2H, t, *J* 6.4, $NCH_2CH_2COCH_3$), 3.36 (2H, t, *J* 6.4, $NCH_2CH_2COCH_3$), 4.10 (2H, s, NCH_2COCH_3), 7.31 (2H, d, *J* 8.0, Ar-*H* x 2), 7.68 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.48 (CH_3), 26.67 (CH_3), 30.03 (CH_3), 43.63 (CH_2), 43.96 (CH_2), 58.66 (CH_2), 127.30 (2 x CH), 129.65 (2 x CH), 136.06 (C), 143.65 (C), 203.33 (C), 207.28 (C). *m/z* (ES) 298 (MH^+, 35 %), 240 (78), 228 (93), 155 (57).

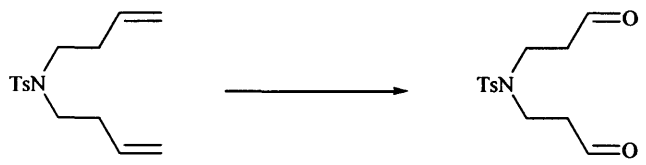
4-Methyl-*N*-(3-oxopropyl)-*N*-(2-oxopropyl)-benzenesulfonamide **190**



160 **190**

The diene **160** (0.240 g, 0.86 mmol) in dry methanol (10 cm^3) was treated with ozone then Me_2S (0.252 cm^3, 3.44 mmol) as for the preparation of **178**. After evaporation, the crude material was purified by flash column chromatography on silica using diethyl ether:petrol (80:20 to 100:0) to give the *keto-aldehyde* **190** (0.187 g, 78 %) as a colourless oil. ν_{max} (cm^{-1}, film) 2920, 1732 (C=O), 1716 (C=O), 1647, 1597, 1338 and 1155 (SO_2). δ_H (250 MHz, $CDCl_3$) 2.12 (3H, s, NCH_2COCH_3), 2.42 (3H, s, Ar-CH_3), 2.86 (2H, br t, *J* 6.4, NCH_2CH_2), 3.43 (2H, t, *J* 6.4, NCH_2CH_2), 4.10 (2H, s, NCH_2COCH_3), 7.31 (2H, d, *J* 8.0, Ar-*H* x 2), 7.68 (2H, d, *J* 8.0, Ar-*H* x 2), 9.71 (1H, br s, NCH_2CH_2CHO). δ_C (62.9 MHz, $CDCl_3$) 21.41 (CH_3), 27.21 (CH_3), 42.48 (CH_2), 43.78 (CH_2), 58.09 (CH_2), 127.22 (2 x CH), 129.65 (2 x CH), 135.84 (C), 143.73 (C), 200.45 (CH), 203.17 (C). *m/z* (ES) 284 (14 %), 240 (20), 228 (47), 155 (8). *m/z* (FAB) 284.0957 (MH^+. $C_{13}H_{18}NO_4S$ requires 284. 0957).

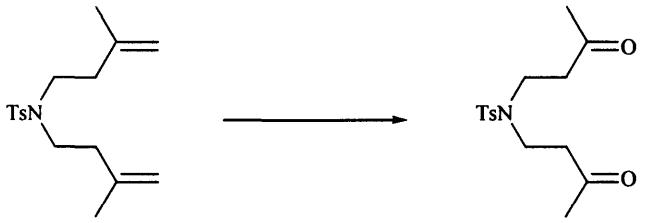
4-Methyl-*N,N*-bis-(3-oxopropyl)-benzenesulfonamide **192**



161 **192**

The diene **161** (0.34 g, 1.22 mmol) in dry methanol (10 cm^3) was treated with ozone then Me_2S (0.358 cm^3, 4.88 mmol) as for the preparation of **178**. After evaporation, the crude material was purified by flash column chromatography on silica using ethyl acetate:petrol (70:30 to 90:10) to give the *dialdehyde* **192** (0.31 g, 90 %) as a colourless oil. δ_H (250 MHz, $CDCl_3$) 2.42 (3H, s, Ar-C*H*$_3$), 3.02 (4H, br t, *J* 6.9, 2 x NCH_2CH_2CHO), 3.62 (4H, t, *J* 6.9, 2 x NCH_2CH_2CHO), 7.53 (2H, d, *J* 8.0, Ar-*H* x 2), 7.89 (2H, d, J 8.0, Ar-*H* x 2), 9.96 (2H, br s, 2 x NCH_2CH_2CHO). δ_C (62.9 MHz, $CDCl_3$) 21.51 (CH_3), 42.86 (2 x CH_2), 43.79 (2 x CH_2), 127.27 (2 x CH), 129.93 (2 x CH), 135.39 (C), 143.92 (C), 200.01 (2 x CH). *m/z* (ES) 284 (21 %), 240 (36), 184 (8). *m/z* (FAB) 284.0957 (MH^+. $C_{13}H_{18}NO_4S$ requires 284. 0957).

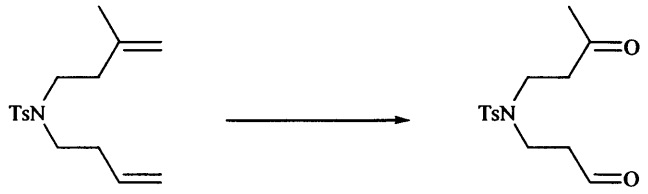
4-Methyl-*N,N*-bis-(3-oxobutyl)-benzenesulfonamide **193**



162 **193**

The diene **162** (0.9 g, 2.93 mmol) in dry methanol (50 cm^3) was treated with ozone then Me_2S (0.86 cm^3, 11.7 mmol) as for the preparation of **178**. After evaporation, the crude material was purified by flash column chromatography on silica using diethyl ether:petrol (80:20 to 100:0) to give the *diketone* **193** (0.873 g, 96 %) as a colourless oil. ν_{max} (cm^{-1}, film) 2922, 1711 (C=O), 1598, 1336 (SO_2), 1089. δ_H (250 MHz, $CDCl_3$) 2.15 (6H, s, 2 x $NCH_2CH_2COCH_3$), 2.43 (3H, s, Ar-C*H*$_3$), 2.79 (4H, t, *J* 7.0, 2 x $NCH_2CH_2COCH_3$), 3.32 (4H, t, *J* 7.0, 2 x $NCH_2CH_2COCH_3$), 7.32 (2H, d, *J* 8.0, Ar-*H* x 2), 7.67 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.37 (CH_3), 30.09 (2 x CH_3), 43.31 (2 x CH_2), 44.36 (2 x CH_2), 127.16 (2 x CH), 129.79 (2 x CH), 135.39 (C), 143.58 (C), 206.70 (2 x C). *m/z* (FAB) 312.1269 (MH^+. $C_{15}H_{22}NO_4S$ requires 312.1270), 312 (50 %), 268 (16), 254 (100), 242 (15), 219 (36), 184 (16), 155 (86), 136 (43).

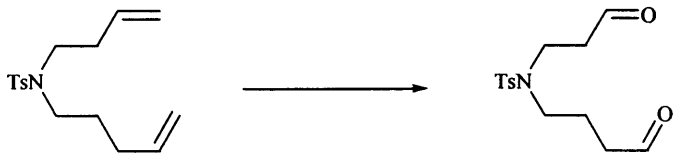
4-Methyl-*N*-(3-oxobutyl)-*N*-(3-oxopropyl)-benzenesulfonamide **194**



163 **194**

The diene **163** (0.702 g, 2.39 mmol) in dry MeOH (30 cm^3) was treated with ozone then Me_2S (0.7 cm^3, 9.56 mmol) as for the preparation of **178**. After evaporation, the crude material was purified by flash column chromatography on silica using diethyl ether:petrol (60:40 to 80:20) to give the *keto-aldehyde* **194** (0.509 g, 72 %) as a colourless oil. δ_H (250 MHz, $CDCl_3$) 2.15 (3H, s, CH_2COCH_3), 2.43 (3H, s, Ar-CH_3), 2.76-2.83 (4H, m, $CH_2CH_2COCH_3$ and NCH_2CH_2CHO), 3.32 (2H, t, *J* 6.9, $NCH_2CH_2COCH_3$), 3.42 (2H, t, *J* 6.9, NCH_2CH_2CHO), 7.32 (2H, d, *J* 8.0, Ar-*H* x 2), 7.67 (2H, d, *J* 8.0, Ar-*H* x 2), 9.74 (1H, br s, CH_2CH_2CHO). δ_C (62.9 MHz, $CDCl_3$) 21.41 (CH_3), 30.11 (CH_3), 43.08 (CH_2), 43.36 (CH_2), 43.58 (CH_2), 44.11 (CH_2), 127.17 (2 x CH), 129.81 (2 x CH), 135.35 (C), 143.72 (C), 200.11 (CH), 206.65 (C). Cyclised acetal **195** was also eluted (0.102 g, 13 %).

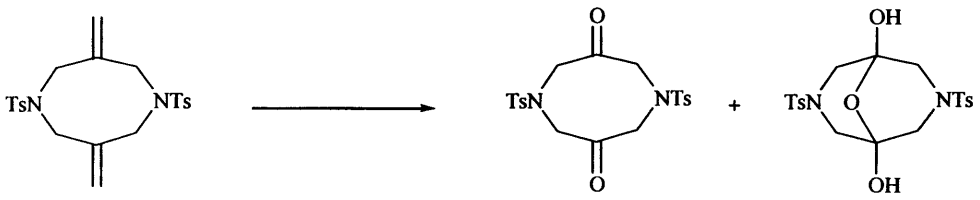
4-Methyl-*N*-(4-oxobutyl)-*N*-(3-oxopropyl)-benzenesulfonamide **196**



164 **196**

The diene **164** (0.145 g, 0.49 mmol) in dry methanol (5 cm^3) was treated with ozone and then Me_2S (0.135 cm^3, 1.96 mmol) as for the preparation of **178**. Removal of the solvent under high vacuum (0.1 mmHg) gave the *dialdehyde* **196** (0.14 g, 95 %) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 1.84 (2H, app pentet, *J* 6.9, $NCH_2CH_2CH_2CHO$), 2.41 (3H, s, Ar-CH_3), 2.53 (2H, td, *J* 6.9 and 1.0, $NCH_2CH_2CH_2CHO$), 2.81 (2H, td, *J* 7.2 and 1.0, NCH_2CH_2CHO), 3.10 (2H, t, *J* 6.9, $NCH_2CH_2CH_2CHO$), 3.41 (2H, t, *J* 7.2, NCH_2CH_2CHO), 7.31 (2H, d, *J* 8.0, Ar-*H* x 2), 7.66 (2H, d, *J* 8.0, Ar-*H* x 2), 9.74 (1H, br d, *J* 1.0, $NCH_2CH_2CH_2CHO$) 9.76 (1H, br s, NCH_2CH_2CHO). δ_C (75.5 MHz, $CDCl_3$) 20.73 (CH_2), 21.27 (CH_3), 40.25 (CH_2), 41.92 (CH_2), 43.49 (CH_2), 48.19 (CH_2), 126.94 (CH), 129.67 (CH), 135.59 (C), 143.52 (C), 199.95 (CH), 201.10 (CH).

1,5-Bis-(toluene-4-sulfonyl)-[1,5]-diazocane-3,7-dione **197**



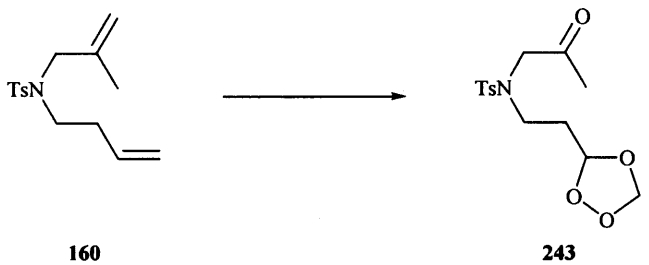
169 **197** **198**

The diene **169** (0.323 g, 0.72 mmol) in dry dichloromethane (10 cm^3) was treated with ozone then Me_2S (0.211 cm^3, 2.88 mmol) as for the preparation of **178**. After evaporation, the crude material was purified by flash column chromatography using diethyl ether:petrol (40:60 to 70:30) to give the *diketone* product **197** (0.062 g, 19 %) and the hydrated product **198** (0.218 g, 65 %) as white solids. The product **198** was dehydrated at 100°C under reduced pressure (0.1 mmHg) using KugelRöhr apparatus to give a further amount of the *diketone* **197** (0.118 g, 36 %) as a white solid. M.p. 277°C (Et_2O) (Literature m.p. 275°C (dec.)).[111] δ_H (250 MHz, $CDCl_3$) 2.48 (6H, s, Ar-CH_3), 4.11 (8H, s, NCH_2C=O), 7.39 (4H, d, *J* 8.0, Ar-*H* x 2), 7.74 (4H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.61 (CH_3), 59.94 (CH_2), 127.19 (CH), 130.30 (CH), 133.99 (C), 145.09 (C), 204.19 (C). *m/z* (ES) 451 (MH^+, 32 %), 309 (8), 153 (15).

198: δ_H (250 MHz, d_6-acetone) 2.38 (4H, br d, *J* 10.5, 4 x NC*H*H), 2.44 (3H, s, Ar-CH_3), 3.71 (4H, d, *J* 10.5, 4 x NCH*H*), 7.47 (2H, d, *J* 8.0, Ar-*H* x 2), 7.70 (2H, d, *J* 8.0, Ar-*H* x 2). δ_H (62.9 MHz, d_6-acetone) 21.39 (CH_3), 52.21 (CH_2), 93.82 (C), 128.78 (CH), 130.61 (CH), 132.83 (C), 144.81 (C). *m/z* (ES) 486 (63 %), 469 (MH^+, 33), 451 (100).

These are literature compounds.[111]

4-Methyl-*N*-(2-oxo-propyl)-*N*-(2-[1,2,4]trioxolan-3-yl-ethyl)-benzenesulfonamide **243**



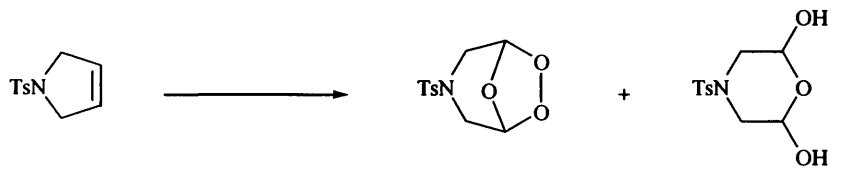
160 **243**

The diene **160** (0.5 g, 1.79 mmol) in dry dichloromethane (25 cm^3) was treated with ozone then Me_2S (0.525 cm^3, 7.16 mmol) as for the preparation of **178**. After evaporation, the crude material was purified by flash column chromatography on silica using diethyl ether:petrol (70:30 to 100:0) to give the *ozonide* **243** (0.147 g, 28 %) and the *keto-aldehyde* **190** (0.104 g,

21 %) as colourless oils. **243**: δ_H (250 MHz, $CDCl_3$) 1.95-2.04 (2H, m, $NCH_2CH_2CHOCH_2$), 2.19 (3H, s, NCH_2COCH_3), 2.44 (3H, s, Ar-CH_3), 3.31 (2H, t, *J* 7.5, NCH_2CH_2CH), 4.03 (2H, s, NCH_2COCH_3), 5.05 (1H, s, $NCH_2CH_2CHOCHH$), 5.12 (1H, s, $NCH_2CH_2CHOCHH$), 5.24 (1H, app t, *J* 5.0, $NCH_2CH_2CHOCH_2$), 7.32 (2H, d, *J* 8.0, Ar-*H* x 2), 7.71 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (100.6 MHz, $CDCl_3$) 21.54 (CH_3), 26.91 (CH_3), 30.66 (CH_2), 44.13 (CH_2), 57.25 (CH_2), 94.07 (CH_2), 101.30 (CH), 127.43 (2 x CH), 129.72 (2 x CH), 135.94 (C), 143.81 (C), 203.34 (C). *m/z* (ES) 330 (MH^+, 37 %), 317 (3), 240 (8), 228 (9).

Data for *keto-aldehyde* **190** as above (page 126).

3-(Toluene-4-sulfonyl)-6,7,8-trioxa-3-aza-bicyclo[3,2,1]octane **260** and
4-(Toluene-4-sulfonyl)-morpholine-2,6-diol **183**



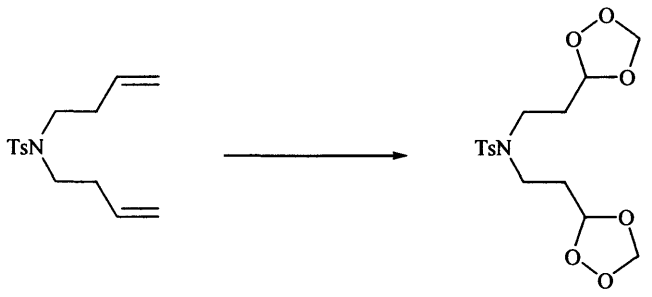
259 **260** **183**

Ozone was bubbled through a stirred solution of **259** (0.1 g, 0.45 mmol) in dry dichloromethane (5 cm^3) at -78°C until a pale blue colour was observed. Nitrogen was then bubbled through until the solution turned colourless and the reaction allowed to warm up to room temperature and stirred for a further 3 h. The solvent was removed by evaporation under reduced pressure and the crude product purified by flash column chromatography on silica using diethyl ether:petrol (70:30 to 90:10) to elute the *ozonide* **260** (0.033 g, 27 %) and the *hydrate* **183** (0.04 g, 33 %) as colourless oils.

260: δ_H (300 MHz, $CDCl_3$) 2.45 (3H, s, Ar-CH_3), 3.02 (2H, d, *J* 12.5, 2 x $NCHHCHO$), 3.73 (2H, d, *J* 12.5, 2 x $NCHHCHO$), 5.80 (2H, s, 2 x NCH_2CHO), 7.34 (2H, d, *J* 8.0, Ar-*H* x 2), 7.70 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (75.5 MHz, $CDCl_3$) 21.55 (CH_3), 47.60 (2 x CH_2), 97.14 (CH), 127.57 (2 x CH), 129.76 (2 x CH), 133.70 (C), 144.11 (C). *m/z* (ES) 272 (34 %), 226 (61), 155 (54), 139 (27). *m/z* (FAB) 272.0593 (MH^+. $C_{11}H_{14}NO_5S$ requires 272.0593).

183: δ_H (300 MHz, d_6-Acetone) 2.43 (3H, s, Ar-CH_3), 2.83 (2H, dd, *J* 9.0 and 14.0, 2 x $NCHHCHOH$), 3.99 (2H, dd, *J* 4.0 and 14.0, $NCHHCHOH$), 5.35 (2H, ddd, *J* 5.5, 9.0 and 14.0, 2 x NCH_2CHOH), 6.29 (2H, d, *J* 5.5, 2 x NCH_2CHOH), 7.44 (2H, d, *J* 8.0, Ar-*H* x 2), 7.77 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (75.5 MHz, d_6-Acetone) 22.15 (CH_3), 54.61 (2 x CH_2), 101.33 (2 x CH), 128.51 (2 x CH), 131.52 (2 x CH), 138.68 (C), 145.22 (C).

4-Methyl-*N*,*N*-bis-(2-[1,2,4]trioxalan-3-ylethyl)-benzenesulfonamide **261**



161 **261**

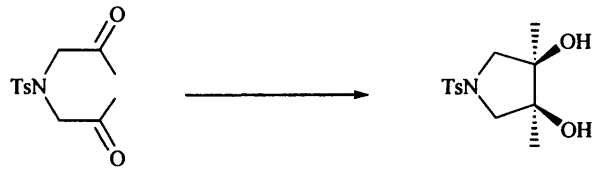
Ozone was bubbled through a stirred solution of the diene **161** (0.1 g, 0.36 mmol) in dry dichloromethane (5 cm^3) at -78°C until a pale blue colour was observed. Nitrogen was then bubbled through until the solution turned colourless and the reaction allowed to warm up to room temperature and stirred for a further 3 h. The solvent was removed by evaporation under reduced pressure and the crude product purified by flash column chromatography on silica using diethyl ether:petrol (20:80 to 40:60) to elute the *ozonide* **261** (0.024 g, 18 %) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 1.99-2.06 (4H, m, 2 x NCH_2CH_2CHO), 2.44 (3H, s, Ar-CH_3), 3.26 (4H, t, *J* 7.5, 2 x NCH_2CH_2), 5.07 (2H, s, 2 x $NCH_2CH_2CHOCHH$), 5.14 (2H, s, 2 x $NCH_2CH_2CHOCHH$), 5.24 (2H, t, *J* 4.5, 2 x $NCH_2CH_2CHOCH_2$), 7.33 (2H, d, *J* 8.0, Ar-*H* x 2), 7.71 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (75.5 MHz, $CDCl_3$) 21.49 (CH_3), 31.04 (2 x CH_2), 43.69 (2 x CH_2), 94.08 (2 x CH_2), 101.31 (2 x CH), 127.22 (2 x CH), 129.82 (2 x CH), 135.83 (C), 143.65 (C). *m/z* (ES) 376 (16 %), 286 (65), 256 (28), 240 (42), 198 (75), 184 (34), 155 (100). *m/z* (FAB) 376.1066 (MH^+. $C_{15}H_{22}NO_8S$ requires 376.1066).
An unidentified compound was isolated (0.025 g).

The coupling reactions were carried out in flame-dried glassware using freshly distilled THF, under an argon atmosphere. Samarium diiodide, SmI_2 (0.1 M in THF) was freshly prepared immediately before use by the procedure described by Kagan *et al.*[73] An example procedure is as follows: Samarium metal (0.36 g, 2.4 mmol, -40 mesh, weighed out in inert atmosphere, flame dried under vacuum (approximately 0.1 mmHg) was suspended in dry degassed (four cycles freeze-pump-thaw) THF (20 cm^3). Then diiodomethane CH_2I_2 (0.16 cm^3, 2.0 mmol) or diiodoethane ICH_2CH_2I (0.56 g, 2.0 mmol) was dissolved in dry degassed THF (5 cm^3) and the solution subjected to two more cycles of freeze-pump-thaw. This solution was added by canula to the suspension of samarium and the reaction mixture was stirred under argon for between 1-4 h until a deep blue colour was observed. A solution of the dicarbonyl compound in THF was also degassed (three cycles of freeze-pump-thaw) then ^tBuOH was added and

solution subjected to two more cycles of freeze-pump-thaw. This solution was added dropwise by canula to the samarium diiodide reaction mixture. The reaction vessel was maintained at -78°C before being allowed to warm to room temperature and left stirring for 18 h.

Cp_2TiPh (0.1 M in THF) was freshly prepared before use by the procedure of Yamamoto *et al.*.[123] Cp_2TiCl_2 (0.35 g, 1.41 mmol, weighed out in inert atmosphere, flame dried under vacuum (approximately 0.1 mmHg) and then subjected to four cycles of vacuum-argon purge). Dry degassed (four cycles freeze-pump-thaw) THF (6 cm^3) was added by canula to ^iPrMgCl (2.0 M in THF, 0.7 cm^3, 1.4 mmol) and subjected to two more cycles of freeze-pump-thaw. This was then added by canula to the suspension and left to stir for 30 min. A dark green colour was observed. Then PhMgCl (2.0 M solution in THF, 0.7 cm^3, 1.4 mmol) in dry degassed (two cycles freeze-pump-thaw) THF (2 cm^3) was also subjected to two more cycles freeze-pump-thaw and added to suspension by canula. The mixture was stirred under argon for 1 h until a dark brown colour is observed. A solution of the dicarbonyl compound in THF was degassed (3 cycles freeze-pump-thaw) and added to the Cp_2TiPh *via* canula. The reaction was stirred at room temperature for 16 h.

cis 3,4-Dimethyl-1-(toluene-4-sulfonyl)-pyrrolidine-3,4-diol **199**



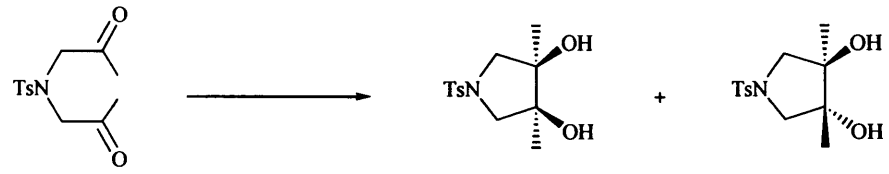
178 **199**

To a -78°C solution of SmI_2 (0.1 M THF, Sm, 0.32 g, 2.12 mmol, CH_2I_2, 0.14 cm^3, 1.8 mmol, reacted in degassed THF (18 cm^3)) was added *via* canula a solution of the diketone **178** (0.2 g, 0.71 mmol) and ^tBuOH (0.2 cm^3, 2.1 mmol) in THF (5 cm^3, four cycles freeze-pump-thaw). The reaction was stirred for 16 h whilst warming to room temperature and then poured into saturated aqueous sodium bicarbonate (50 cm^3) and water (50 cm^3). The organic species were extracted with ethyl acetate (3 x 50 cm^3) and the extracts washed respectively with sodium thiosulphate (10% solution, 50 cm^3) and saturated sodium chloride (50 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica using dichloromethane:methanol (98:2 to 95:5) to give the *cis diol* **199** (0.124 g, 62 %) as a white solid. (Found: C, 54.7; H, 6.7; N, 4.8; Calc. for $C_{13}H_{19}NO_4S$: C, 54.7; H, 6.7; N, 4.9 %). Mp 139-141°C (from EtOAc). ν_{max} (cm^{-1}, solid) 3300 (br, OH), 3066, 2921, 1265, 1159 (SO_2). δ_H (400 MHz, $CDCl_3$) 1.14 (6H, s, 2 x

$NCH_2C(CH_3)OH$), 2.43 (3H, s, Ar-CH_3), 3.31 (2H, d, *J* 10.2, 2 x NC*H*HC$(CH_3)OH$), 3.35 (2H, d, *J* 10.2, 2 x NCH*H*C$(CH_3)OH$), 7.32 (2H, d, *J* 8.0, Ar-*H* x 2), 7.71 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (100.6 MHz, $CDCl_3$) 20.49 (2 x CH_3), 21.54 (CH_3), 57.86 (2 x CH_2), 77.99 (2 x C), 127.45 (2 x CH), 129.67 (2 x CH), 133.87 (C), 143.63 (C). *m/z* (FAB) 286.1113 (MH^+. $C_{13}H_{20}NO_4S$ requires 286.1113), 286 (43 %), 268 (24), 154 (67), 136 (73), 107 (39), 91 (100), 77 (56).

Crystals suitable for X-ray were grown from MeOH:CH_2Cl_2 (see appendix 2, section 2.1 for crystallographical data).

trans 3,4-Dimethyl-1-(toluene-4-sulfonyl)-pyrrolidine-3,4-diol **200**

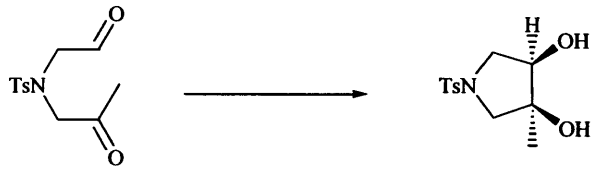


178 **199** **200**

To a solution of Cp_2TiPh (made from Cp_2TiCl_2, 0.53 g, 2.13 mmol, ^iPrMgCl (2.0 M in THF), 1.0 cm^3, 2.0 mmol and PhMgCl (2.0 M in THF), 1.0 cm^3, 2.0 mmol) in degassed THF (20 cm^3) was added *via* canula a solution of the diketone **178** (0.226 g, 0.8 mmol) in THF (5 cm^3, four cycles freeze-pump-thaw). The reaction was stirred at room temperature for 16 h, poured in 1.0 M HCl (30 cm^3) and extracted with ethyl acetate (5 x 50 cm^3). The extracts were combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude material was purified by flash column chromatography using diethyl ether:petrol (1:2 to 1:0) to give the *trans diol* **200** (0.145 g, 64 %) as a white solid in pure form together with *cis diol* **199** (0.011 g, 5 %). Data for **200**: M.p. 143-145°C (from EtOAc). ν_{max} (cm^1, solid) 3452 (OH), 2967, 1383, 1319, 1147 (SO_2), 1097. δ_H (250 MHz, $CDCl_3$) 1.23 (6H, s, 2 x $NCH_2C(CH_3)OH$), 1.60 (2H, br s, 2 x CHO*H*), 2.42 (3H, s, Ar-CH_3), 3.32 (2H, d, *J* 10.8, NC*H*HC$(CH_3)OH$), 3.47 (2H, d, *J* 10.8, NCH*H*C$(CH_3)OH$), 7.31 (2H, d, *J* 8.0, Ar-*H* x 2), 7.73 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 17.58 (2 x CH_3), 21.51 (CH_3), 58.98 (2 x CH_2), 79.94 (2 x C), 127.45 (2 x CH), 129.64 (2 x CH), 134.22 (C), 143.53 (C). *m/z* (FAB) 286.1112 (MH^+. $C_{13}H_{20}NO_4S$ requires 286.1113), 286 (24 %), 268 (8), 228 (8), 154 (100), 136 (83).

Data for **199** as above.

cis 3-Methyl-1-(toluene-4-sulfonyl)-pyrrolidine-3,4-diol **201**

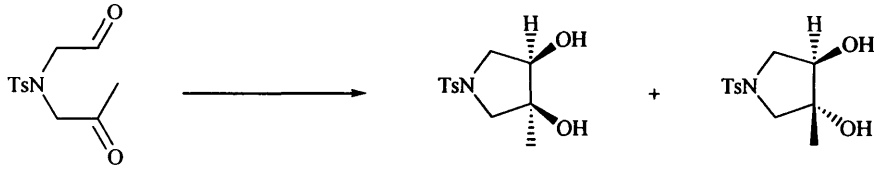


180 **201**

To a -78°C solution of SmI_2 (prepared from Sm, 0.39 g, 2.4 mmol, CH_2I_2, 0.16 cm^3, 2.0 mmol reacted in degassed THF (20 cm^3)) was added *via* canula a solution of the keto-aldehyde **180** (0.217 g, 0.8 mmol) and ^tBuOH (0.225 cm^3, 2.4 mmol) in THF (5 cm^3, four cycles freeze-pump-thaw). The reaction was warmed to room temperature over 16 h and worked up as before. The crude material was purified by flash column chromatography on silica using ethyl acetate:petrol (40:60 to 70:30) to elute the *cis diol* **201** (0.105 g, 50 %) as a white solid. M.p. 115-117°C (from EtOAc). ν_{max} (cm^{-1}, solid) 3519, 3468, 3049, 2970, 1598, 1324, 1154 (SO_2), 1087. δ_H (400 MHz, $CDCl_3$) 1.24 (3H, s, $NCH_2C(CH_3)OH$), 2.43 (3H, s, Ar-CH_3), 3.17 (1H, dd, *J* 10.5 and 5.5, $NCHHCHOH$), 3.27 (1H, s, $NCHHC(CH_3)OH$), 3.28 (1H, s, $NCHHC(CH_3)OH$), 3.59 (1H, dd, *J* 10.5 and 5.5, $NCHHCHOH$), 3.80 (1H, app t, *J* 5.5, NCH_2CHOH), 7.32 (2H, d, *J* 8.0, Ar-*H* x 2), 7.71 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (100.6 MHz, $CDCl_3$) 21.55 (CH_3), 23.04 (CH_3), 52.73 (CH_2), 57.16 (CH_2), 75.16 (2 x CH), 76.16 (C), 127.54 (2 x CH), 129.71 (2 x CH), 133.61 (C), 143.72 (C). *m/z* (ES) 272 (100 %), 254 (60). *m/z* (FAB) 272.0957 (MH^+. $C_{12}H_{18}NO_4S$ requires 272.0957).

Crystals suitable for X-ray were grown from $CHCl_3$:Et_2O (see appendix 2, section 2.2 for crystallographical data).

trans 3-Methyl-1-(toluene-4-sulfonyl)-pyrrolidine-3,4-diol **202**



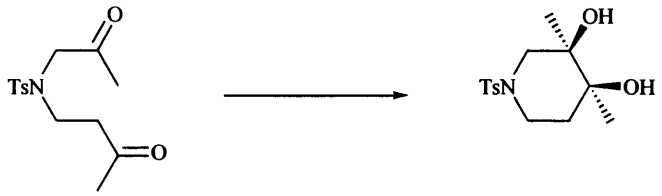
180 **201** **202**

To a solution of Cp_2TiPh (made from Cp_2TiCl_2, 0.53 g, 2.13 mmol, ^iPrMgCl (2.0 M in THF), 1.0 cm^3, 2.0 mmol and PhMgCl (2.0 M in THF), 1.0 cm^3, 2.0 mmol) in degassed THF (20 cm^3) was added a solution of the keto-aldehyde **180** (0.207 g, 0.77 mmol) in THF (5 cm^3, four cycles freeze-pump-thaw). The reaction was stirred at room temperature for 16 h and worked up as before. The crude material was purified by flash column chromatography using ethyl acetate:petrol (30:70 to 80:20) to give the *trans diol* **202** (0.122 g, 59 %) in pure form as an

oil together with the *cis* isomer **201** (0.038 g, 18 %). Data for **202**: ν_{max} (cm^{-1}, film) 3441, 3066, 2936, 1598, 1325, 1150 (SO_2), 1087. δ_H (250 MHz, $CDCl_3$) 1.21 (3H, s, $NCH_2C(CH_3)OH$), 2.38 (3H, s, Ar-CH_3), 3.12-3.25 (1H, m, $NCHHCHOH$), 3.18 (1H, d, *J* 10.5, $NCHHC(CH_3)OH$), 3.25 (1H, d, *J* 10.5, $NCHHC(CH_3)OH$), 3.64 (1H, dd, *J* 10.6 and 4.6, $NCHHCHOH$), 3.83-3.90 (1H, br m, NCH_2CHOH), 7.28 (2H, d, *J* 8.0, Ar-*H* x 2), 7.67 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 19.57 (CH_3), 21.46 (CH_3), 54.39 (CH_2), 57.37 (CH_2), 76.84 (CH), 79.06 (C), 127.42 (2 x CH), 129.68 (2 x CH), 133.56 (C), 143.68 (C). *m/z* (FAB) 272.0956 (MH^+. $C_{12}H_{18}NO_4S$ requires 272.0957), 272 (100 %), 254 (31), 228 (17), 154 (80), 136 (80).

Data for **201** as above.

cis 3,4-Dimethyl-1-(toluene-4-sulfonyl)-piperidine-3,4-diol **203**

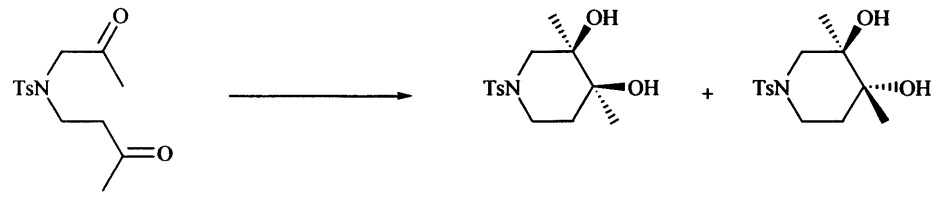


189 **203**

To a -78°C solution of SmI_2 (prepared from Sm, 0.28 g, 2.17 mmol, CH_2I_2, 0.132 cm^3, 1.55 mmol reacted in degassed THF (16 cm^3)) was added *via* canula a solution of the diketone **189** (0.185 g, 0.62 mmol) and ^tBuOH (0.175 cm^3, 1.86 mmol) in THF (5 cm^3, four cycles freeze-pump-thaw). The reaction was warmed to room temperature over 16 h and worked up as before. The crude material was purified by flash column chromatography on silica using dichloromethane:methanol (100:0 to 96:4) to give the *cis diol* **203** (0.135 g, 73 %) as a white solid. M.p. 174-176°C (from EtOAc) δ_H (400 MHz, $CDCl_3$) 1.16 (3H, s, $NCH_2CH_2C(CH_3)OH$), 1.31 (3H, s, $NCH_2C(CH_3)OH$), 1.77 (2H, dd, *J* 5.0 and 6.6, NCH_2CH_2), 2.44 (3H, s, Ar-CH_3), 2.85 (1H, d, *J* 11.2, $NCHHC(CH_3)OH$), 2.93 (1H, dt, *J* 11.5 and 6.6, $NCHHCH_2$), 3.03 (1H, dd, *J* 11.2 and 1.1, $NCHHC(CH_3)OH$), 3.15-3.20 (1H, m, $NCHHCH_2$), 7.33 (2H, d, *J* 8.0 Hz, Ar-*H* x 2), 7.63 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (100.6 MHz, $CDCl_3$) 21.31 (CH_3), 21.47 (CH_3), 22.61 (CH_3), 35.72 (CH_2), 42.83 (CH_2), 53.16 (CH_2), 71.67 (C), 72.39 (C), 127.53 (2 x CH), 129.71 (2 x CH), 133.10 (C), 143.67 (C). *m/z* (FAB) 300.1269 (MH^+. $C_{14}H_{22}NO_4S$ requires 300.1270), 300 (51 %), 282 (38), 242 (15), 154 (100), 136 (84), 107 (31).

Crystals suitable for X-ray were grown from $CHCl_3$ (see appendix 2, section 2.3 for crystallographical data).

trans 3,4-Dimethyl-1-(toluene-4-sulfonyl)-piperidine-3,4-diol **204**



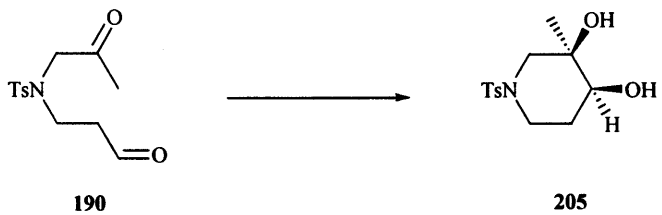
189 **203** **204**

To a solution of Cp_2TiPh (made from Cp_2TiCl_2, 0.627 g, 2.52 mmol, $^{i}PrMgCl$ (2.0 M in THF), 1.26 cm^3, 2.52 mmol and PhMgCl (2.0 M in THF), 1.26 cm^3, 2.52 mmol) in degassed THF (25cm^3) was added *via* canula a solution of the diketone **189** (0.25 g, 0.84 mmol) in THF (5 cm^3, four cycles freeze-pump-thaw). The reaction was stirred at room temperature for 16 h and worked up as before. The crude material was purified by flash column chromatography using ethyl acetate:petrol (30:70 to 60:40) to give the *trans diol* **204** (0.131 g, 53 %) and the *cis diol* **203** (0.023 g, 9 %) as white solids. (Found: C, 56.4; H, 7.0; N, 4.5; Calc. for $C_{14}H_{21}NO_4S$: C, 56.2; H, 7.1; N, 4.7 %). Mp 183-185°C (from EtOAc). ν_{max} (cm^{-1}, solid) 3491 (OH), 2972, 1599, 1341, 1165 (SO_2), 1094. δ_H (250 MHz, $CDCl_3$) 1.17 (3H, s, $CH_2C(CH_3)$), 1.25 (3H, s, $CH_2CH_2C(CH_3)$), 1.47 (1H, d app t, *J* 14.0 and 3.0, NCH_2CHH), 1.63 (2H, br s, 2 x *OH*), 2.07 (1H, ddd, *J* 14.0, 12.8 and 5.0, NCH_2CHH), 2.44 (3H, s, Ar-CH_3), 2.61 (1H, ddd, *J* 13.0, 12.8 and 3.0, $NCHHCH_2$), 2.71 (1H, d, *J* 11.5, $NCHHC(CH_3)$), 3.29 (1H, dd, *J* 11.5 and 2.0, $NCHHC(CH_3)$), 3.52-3.61 (1H, m, $NCHHCH_2$), 7.33 (2H, d, *J* 8.0, Ar-*H* x 2), 7.64 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, CD_3OD) 19.40 (CH_3), 21.31 (CH_3), 22.74 (CH_3), 34.68 (CH_2), 42.26 (CH_2), 52.78 (CH_2), 70.67 (C), 71.50 (C), 127.48 (2 x CH), 129.68 (2 x CH), 132.76 (C), 143.79 (C). *m/z* (FAB) 300.1270 (MH^+. $C_{14}H_{22}NO_4S$ requires 300.1269), 300 (24 %), 242 (7), 154 (100), 136 (75).

Data for **203** as above.

Crystals suitable for X-ray were grown from MeOH:CH_2Cl_2 (see appendix 2, section 2.4 for crystallographical data).

cis 3-Methyl-1-(toluene-4-sulfonyl)-piperidine-3,4-diol **205**

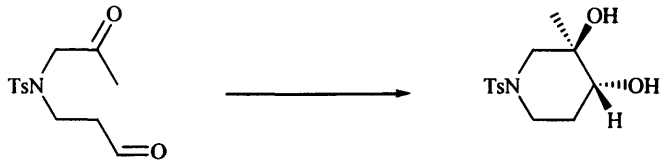


190 **205**

To a solution a -78°C solution of SmI_2 (prepared from Sm, 0.389 g, 2.59 mmol, CH_2I_2, 0.15 cm^3, 1.85 mmol reacted in degassed THF (25 cm^3)) was added *via* canula a solution of the

keto-aldehyde **190** (0.21 g, 0.74 mmol) and ^{t}BuOH (0.21 cm^3, 1.85 mmol) in THF (5 cm^3, four cycles freeze-pump-thaw). The reaction was warmed to room temperature over 16 h and worked up as before. The crude material was purified by flash column chromatography on silica using ethyl acetate:petrol (60:40 to 90:10) to elute the *cis diol* **205** (0.131 g, 62 %) as a white solid. (Found: C, 54.6; H, 6.8; N, 4.7; Calc. for $C_{13}H_{19}NO_4S$: C, 54.7; H, 6.7; N, 4.9 %). Mp 128-130°C (from EtOAc). ν_{max} (cm^{-1}, solid) 3467 (OH), 3360, 3095, 2969, 1597, 1340, 1086. δ_H (400 MHz, $CDCl_3$) 1.30 (3H, s, C(C*H*$_3$)OH), 1.72-1.81 (1H, m, NCH$_2$CH*H*CHOH), 1.89-1.96 (1H, m, NCH$_2$C*H*HCHOH), 2.44 (3H, s, Ar-C*H*$_3$), 2.64 (1H, d, *J* 11.7, NC*H*HC(CH$_3$)OH), 2.73 (1H, dt, *J* 10.3 and 3.5, NC*H*HCH$_2$CHOH), 3.23 (1H, dd, *J* 11.7 and 1.4, NCH*H*C(CH$_3$)OH), 3.33-3.36 (2H, m, NCH$_2$CH$_2$C*H*OH and NCH*H*CH$_2$), 7.34 (2H, d, *J* 8.0, Ar-*H* x 2), 7.64 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (100.6 MHz, $CDCl_3$) 21.52 (CH_3), 22.88 (CH_3), 29.71 (CH_2), 43.54 (CH_2), 53.96 (CH_2), 69.89 (C), 71.94 (CH), 127.64 (2 x CH), 129.79 (2 x CH), 132.99 (C), 143.87 (C). *m/z* (FAB) 286.1113 (MH$^+$. $C_{13}H_{20}NO_4S$ requires 286.1113), 286 (66 %), 268 (20), 184 (9), 154 (100), 136 (78), 107 (31), 91 (45).
Crystals suitable for X-ray were grown from MeOH:$CHCl_3$ (see appendix 2, section 2.5 for crystallographical data).

trans 3-Methyl-1-(toluene-4-sulfonyl)-piperidine-3,4-diol **206**

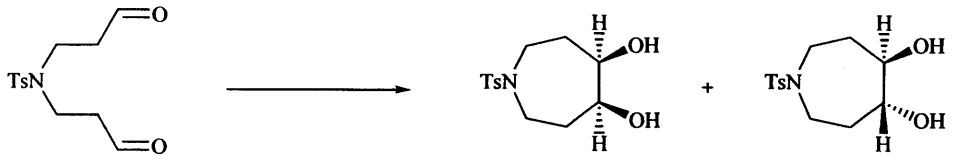


190 **206**

To a solution of Cp_2TiPh (made from Cp_2TiCl_2, 0.493 g, 1.98 mmol, ^{i}PrMgCl (2.0 M in THF), 2.5 cm^3, 1.98 mmol and PhMgCl (2.0 M in THF), 2.5 cm^3, 1.9 8mmol) in degassed THF (20 cm^3) was added v*ia* canula a solution of the keto-aldehyde **190** (0.187 g, 0.66 mmol) in THF (5 cm^3, four cycles freeze-pump-thaw). The reaction was stirred at room temperature for 16 h and worked up as before. The crude material was purified by flash column chromatography using ethyl acetate:petrol (50:50 to 80:20) to give the *trans diol* **206** (0.02 g, 11 %) as a colourless oil. ν_{max} (cm^{-1}, film) 3551-3461 (OH), 2923, 2854, 1599, 1335, 1155 (SO_2), 1034. δ_H (250 MHz, $CDCl_3$) 1.29 (3H, s, CH$_2$C(C*H*$_3$)OH), 1.58 (1H, br s, CHO*H*), 1.67 (1H, ddd, *J* 13.9, 6.9 and 3.0, NCH$_2$C*H*HCHOH), 1.74 (1H, br s, CHO*H*), 2.09 (1H, dd app. t, *J* 13.9 and 4.0, NCH$_2$CH*H*CHOH), 2.45 (3H, s, Ar-C*H*$_3$), 2.80 (1H, d, *J* 11.5, NC*H*HC(CH$_3$)OH), 2.95-3.06 (1H, m, NC*H*HCH$_2$CHOH), 3.05 (1H, d, *J* 11.5, NCH*H*C(CH$_3$)OH), 3.07-3.17 (1H, m, NCH*H*CH$_2$CHOH), 3.50 (1H, br s, C*H*OH), 7.34 (2H,

d, *J* 8.0, Ar-*H* x 2), 7.65 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (100.6 MHz, $CDCl_3$) 20.77 (CH_3), 21.51 (CH_3), 28.95 (CH_2), 42.65 (CH_2), 53.47 (CH_2), 70.69 (C), 72.45 (CH), 127.62 (2 x CH), 129.77 (2 x CH), 132.99 (C), 143.81 (C). *m/z* (FAB) 286.1113 (MH^+. $C_{13}H_{20}NO_4S$ requires 286.1113), 286 (21 %), 268 (5), 154 (100), 136 (88).

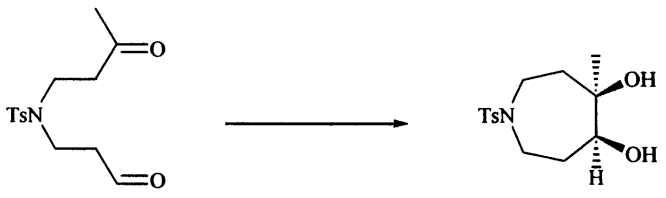
cis 1-(Toluene-4-sulfonyl)-azepane-4,5-diol **207**



192 **207** **208**

To a -78°C solution of SmI_2 (prepared from Sm, 0.46 g, 3.1 mmol, CH_2I_2, 0.21 cm^3, 2.6 mmol, reacted in degassed THF (28 cm^3)) was added *via* canula to a solution of the dialdehyde **192** (0.145 g, 0.51 mmol) and ^tBuOH (0.29 cm^3, 3.1 mmol) in THF (5 cm^3, four cycles freeze-pump-thaw). The reaction was warmed to room temperature over 16 h and worked up as before. The crude material was purified by flash column chromatography on silica using ethyl acetate:petrol (60:40 to 90:10) to elute the *cis diol* **207** (0.029 g, 20 %) in pure form as a white solid. A mixture of **207** and **208** was also isolated (0.038 g, 26 %, approx. ratio ~4 : 1, **207** : **208**). **207**: M.p. 111-113°C (from EtOAc). ν_{max} (cm^{-1}, solid) 3400 (br, OH), 3053, 1265, 1159. δ_H (250 MHz, $CDCl_3$) 1.71-1.83 (2H, m, 2 x $NCH_2CHHCHOH$), 1.98-2.12 (2H, m, 2 x $NCH_2CHHCHOH$), 2.42 (3H, s, Ar-CH_3), 3.18 (2H, ddd, *J* 13.5, 7.8 and 4.0, $NCHHCH_2CHOH$), 3.41 (2H, ddd, *J* 13.5, 7.8 and 4.4, $NCHHCH_2CHOH$), 3.95 (2H,dd, *J* 6.0 and 2.1, NCH_2CH_2CHOH) 7.30 (2H, d, *J* 8.0, Ar-*H* x 2), 7.65 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.46 (CH_3), 30.94 (2 x CH_2), 42.08 (2 x CH_2), 72.33 (2 x CH), 126.97 (2 x CH), 129.71 (2 x CH), 135.65 (C), 143.31 (C). *m/z* (FAB) 286.1113 (MH^+. $C_{13}H_{20}NO_4S$ requires 286.1113), 286 (46 %), 268 (7), 154 (100), 136 (76).

cis 4-Methyl-1-(toluene-4-sulfonyl)-azepane-4,5-diol **210**

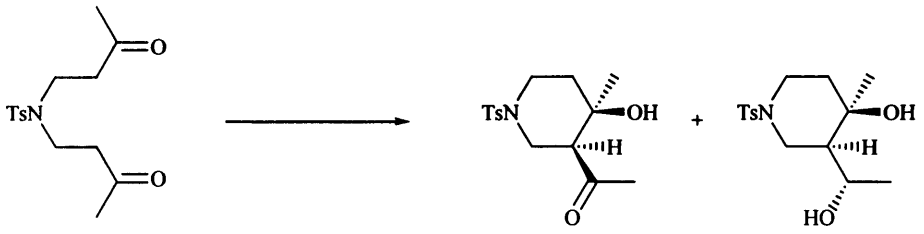


194 **210**

To a -78°C solution of SmI_2 (prepared from Sm, 0.576 g, 3.83 mmol, CH_2I_2, 0.257 cm^3, 3.19mmol reacted in degassed THF (35 cm^3)) was added *via* canula a solution of the

keto-aldehyde **194** (0.38 g, 1.28 mmol) and ^{t}BuOH (0.36 cm^3, 3.83 mmol) in THF (5 cm^3, four cycles freeze-pump-thaw). The reaction was warmed to room temperature over 16 h and worked up as before. The crude material was purified by flash column chromatography on silica using ethyl acetate:petrol (70:30 to 90:10) to elute the *cis diol* **210** (0.097 g, 25 %) as a colourless oil. ν_{max} (cm^{-1}, film) 3429 (br OH), 2965, 1598, 1326, 1153 (SO_2), 1092. δ_H (400 MHz, CD_3OD) 1.27 (3H, s, $CH_2C(CH_3)$), 1.61 (1H, ddd, *J* 15.0, 8.0 and 3.5, $NCH_2CHHC(CH_3)$), 1.75 (1H, ddt, *J* 15.0, 8.0 and 3.0, $NCH_2CHHCHOH$), 1.93-2.02 (2H, m, NCH_2CH_2), 2.42 (3H, s, Ar-CH_3), 3.15 (1H, ddd, *J* 13.5, 8.0 and 3.0, $NCHHCH_2C(CH_3)$), 3.26 (1H, ddd, *J* 13.5, 8.0 and 3.0, $NCHHCH_2CHOH$), 3.37-3.46 (2H, m, $NCHHCH_2C(CH_3)$ and $NCHHCH_2CHOH$), 3.47 (1H, dd, *J* 8.0 and 3.0, NCH_2CH_2CHOH), 7.30 (2H, d, *J* 8.0, Ar-*H* x 2), 7.64 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (100.6 MHz, CD_3OD) 21.44 (CH_3), 26.41 (CH_3), 32.47 (CH_2), 37.68 (CH_2), 42.62 (CH_2), 43.17 (CH_2), 74.10 (C), 76.79 (CH), 128.15 (2 x CH), 130.83 (2 x CH), 137.11 (C), 144.83 (C). *m/z* (ES) 300 (30 %), 282 (14), 154 (100), 136 (80), 120 (14), 107 (26). *m/z* (FAB) 300.1270 (MH^+. $C_{14}H_{22}NO_4S$ requires 300.1270).

1-[3-Hydroxy-3-methyl-1-(toluene-4-sulfonyl)-piperidin-4-yl]-ethanone **212** and
4-(Hydroxy-ethyl)-3-methyl-1-(toluene-4-sulfonyl)-piperidin-3-ol **213**



193 **212** **213**

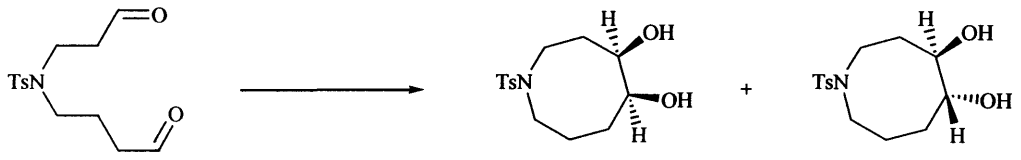
To a -78°C solution of SmI_2 (0.1 M) was added *via* canula a solution of the diketone **193** (0.1 g, 0.32 mmol) and ^{t}BuOH (0.09 cm^3, 0.94 mmol) in THF (5 cm^3, four cycles freeze-pump-thaw). The reaction was warmed to room temperature over 16 h and worked up as before. The crude material was purified by flash column chromatography on silica using ethyl acetate:petrol (20:80 to 80:20) to elute the *aldol* products **212** (0.047 g, 47 %) and **213** (0.011 g, 11 %) as white solids.

212: Mp 103-105°C (from EtOAc). ν_{max} (cm^{-1}, solid) 3494 (OH), 3068, 2964, 1699 (C=O), 1676, 1597, 1335, 1156 (SO_2). δ_H (400 MHz, $CDCl_3$) 1.20 (3H, s, $CH_2C(CH_3)OH$), 1.60-1.69 (2H, m, NCH_2CH_2), 2.31 (3H, s, $CHCOCH_3$), 2.43 (3H, s, Ar-CH_3), 2.61 (1H, t, *J* 11.3, $NCHHCHCOCH_3$), 2.70 (1H, td, *J* 11.5 and 4.0, $NCHHCH_2$), 2.91 (1H, dd, *J* 11.3 and 3.8, $NCH_2CHCOCH_3$), 3.56 (1H, dddd, *J* 11.5, 9.2, 4.0 and 2.0, $NCHHCH_2$), 3.66 (1H, br s, O*H*),

3.71 (1H, ddd, *J* 11.3, 3.8 and 2.0, NCH*H*CHCOCH$_3$), 7.32 (2H, d, *J* 8.0, Ar-*H* x 2), 7.62 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (100.6 MHz, $CDCl_3$) 21.49 (CH_3), 28.29 (CH_3), 32.03 (CH_3), 37.31 (CH_2), 42.01 (CH_2), 43.76 (CH_2), 55.65 (CH), 67.86 (C), 127.54 (2 x CH), 129.79 (2 x CH), 133.05 (C), 143.79 (C), 212.76 (C). *m/z* (FAB) 312.1270 (MH^+. $C_{15}H_{22}NO_4S$ requires 312.1270), 312 (100 %), 294 (28), 252 (48), 184 (34), 154 (51), 136 (46).
Crystals suitable for X-ray were grown from MeOH:$CHCl_3$ (see appendix 2, section 2.6 for crystallographical data).

213: Mp 113-115°C (from EtOAc). ν_{max} (cm^{-1}, solid) 3481 (OH), 3025, 2970, 1712, 1688, 1599, 1332, 1157 (SO_2). δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.5, CHOHC*H*$_3$), 1.32 (3H, s, $CH_2C(CH_3)OH$), 1.53 (1H, ddd, *J* 11.5, 4.5 and 1.8, $NCH_2CHCHOH$), 1.58 (1H, dt, *J* 13.5 and 2.5, NCH_2CHH), 1.72 (1H, td, *J* 13.5 and 4.5, NCH_2CHH), 2.43 (3H, s, Ar-C*H*$_3$), 2.59-2.69 (2H, m, $NCHHCH_2C(CH_3)OH$ and $NCHHCH_2$), 3.58 (1H, dddd, *J* 11.5, 4.5, 2.5 and 2.0, $NCHHCH_2$), 3.73 (1H, ddd, *J* 11.5, 4.5 and 2.0, $NCHHCH_2C(CH_3)OH$), 4.50 (1H, br q, *J* 6.5, $NCH_2CHHCOHCH_3$), 7.32 (2H, d, *J* 8.0, Ar-*H* x 2), 7.66 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (100.6 MHz, $CDCl_3$) 21.28 (CH_3), 21.49 (CH_3), 28.31 (CH_3), 39.26 (CH_2), 40.47 (CH_2), 41.95 (CH_2), 47.91 (CH), 65.16 (CH), 70.17 (C), 127.65 (2 x CH), 129.68 (2 x CH), 133.21 (C), 143.45 (C). *m/z* (ES) 314 (68 %), 278 (47), 252 (100), 184 (63), 155 (27). *m/z* (FAB) 314.1425 (MH^+. $C_{15}H_{24}NO_4S$ requires 314.1426).
Crystals suitable for X-ray were grown from MeOH:$CHCl_3$ (see appendix 2, section 2.7 for crystallographical data).

cis 1-(Toluene-4-sulfonyl)-azocane-4,5-diol **221**



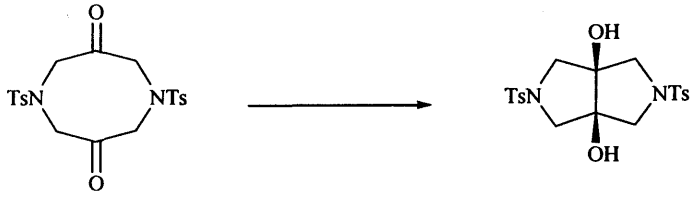
196 **221** **222**

To a -78°C solution of SmI_2 (0.1 M THF, Sm, 0.227 g, 1.25 mmol, CH_2I_2, 0.101 cm^3, 1.25 mmol reacted in degassed THF (15 cm^3)) was added *via* canula a solution of the dialdehyde **196** (0.15 g, 0.5 mmol) and ^tBuOH (0.142 cm^3, 1.5 mmol) in THF (5 cm^3, four cycles freeze-pump-thaw). The reaction was stirred for 16 h whilst warming to room temperature and worked up as before. The crude material was purified by flash column chromatography on silica using ethyl acetate:petrol (70:30 to 100:0) to elute the *cis diol* **221** (0.015 g, 10 %) in pure form as a white solid. A mixture of **207** and **208** was also isolated (0.01 g, 6 %, approx.

ratio 1 : ~2.0, **221** : **222**). **221**: Mp 130-132°C (from EtOAc). ν_{max} (cm^{-1}, solid) 3391 (OH), 2937, 1328, 1153 (SO_2), 1088. δ_H (250 MHz, CD_3OD) 1.64-2.05 (6H, m, NCH_2CH_2CHOH and $NCH_2CH_2CH_2CHOH$), 2.41 (3H, s, Ar-CH_3), 2.71 (1H, ddd, *J* 13.9, 7.8 and 3.7, $NCHHCH_2CHOH$), 2.82 (1H, ddd, *J* 13.9, 6.2 and 4.4, $NCHHCH_2CH_2CHOH$), 3.47 (2H, m, $NCHHCH_2CHOH$ and $NCHHCH_2CH_2CHOH$), 3.94 (1H, dt, *J* 8.5 and 3.0, CH_2CHOH), 4.13 (1H, dt, *J* 8.5 and 3.0, CH_2CHOH), 7.38 (2H, d, *J* 8.0, Ar-*H* x 2), 7.66 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 Hz, MeOD) 21.42 (CH_3), 26.42 (CH_2), 30.78 (CH_2), 32.87 (CH_2), 46.10 (CH_2), 49.23 (CH_2), 73.53 (CH), 73.72 (CH), 128.21 (2 x CH), 130.85 (2 x CH), 136.67 (C), 144.92 (C). *m/z* (ES) 300 (66 %), 282 (100), 256 (23), 126 (100). *m/z* (FAB) 300.1269 (MH^+. $C_{14}H_{22}NO_4S$ requires 300.1269).

Crystals suitable for X-ray were grown from MeOH:CH_2Cl_2 (see appendix 2, section 2.8 for crystallographical data).

2,5-Bis-(toluene-4-sulfonyl)-tetrahydropyrrolo[3,4-c]pyrrole-3a,6a-diol **223**

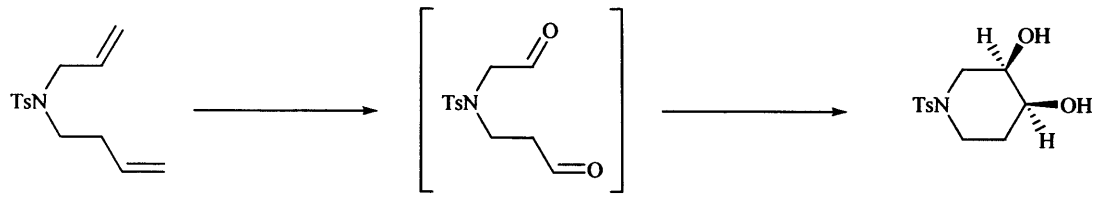


197 **223**

To a -78°C solution of SmI_2 (prepared from Sm, 0.15 g, 1 mmol, CH_2I_2, 0.040 cm^3, 0.5 mmol, reacted in degassed THF (6 cm^3)) was added *via* canula a solution of the diketone **197** (0.09 g, 0.2 mmol) and ^tBuOH (0.056 cm^3, 0.6 mmol) in THF (2 cm^3, four cycles freeze-pump-thaw). The reaction was warmed to room temperature over 16 h and worked up as before. The crude material was purified by recrystallisation using ethyl acetate to give the *diol* **223** (0.051 g, 56 %) as a white solid. (Found: C, 52.9; H, 5.1; N, 6.1; Calc. for $C_{20}H_{24}N_2O_6S_2$: C, 53.1; H, 5.3; N, 6.2 %). M.p. 268-270°C (from EtOAc). ν_{max} (cm^{-1}, solid) 3446 (OH), 3068, 2921, 1599, 1337, 1151 (SO_2), 1092. δ_H (250 MHz, d_6-acetone) 2.43 (6H, s, 2 x Ar-CH_3), 3.09 (4H, d, *J* 10.1, 4 x $NCHHCOH$), 3.26 (4H, d, *J* 10.1, 4 x $NCHHCOH$), 7.43 (4H, d, 8.0, Ar-*H* x 4), 7.65 (4H, d, 8.0, Ar-*H* x 4). δ_C (100.6 MHz, d_6-acetone) 20.63 (2 x CH_3), 57.17 (4 x CH_2), 82.28 (2 x C), 127.84 (4 x CH), 129.83 (4 x CH), 132.85 (2 x C), 143.99 (2 x C). *m/z* (ES) 453 (84), 331 (100), 279 (16). *m/z* (FAB) 453.1154 ($C_{20}H_{25}N_2O_6S_2$ requires 453.1154).

Crystals suitable for X-ray were grown from EtOAc:CH_2Cl_2 (see appendix 2, section 2.9 for crystallographical data).

cis 1-(Toluene-4-sulfonyl)-piperidine-3,4-diol **244**

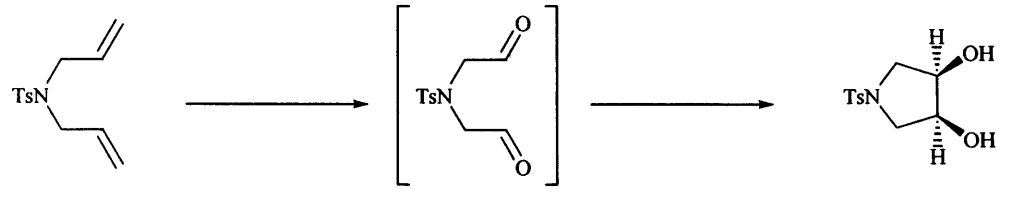


158 **242** **244**

The diene **158** (0.25 g, 0.94 mmol) in dry dichloromethane (10 cm^3) was treated with ozone then Me_2S (0.277 cm^3, 3.76 mmol) as for the preparation of **178**. After evaporation the crude product dialdehyde was not isolated due to decomposition on silica. Thus the crude material was taken through to the SmI_2-mediated pinacol coupling reaction.

To a -78°C solution of SmI_2 (0.1 M THF, Sm, 0.837 g, 5.58 mmol, CH_2I_2, 0.374 cm^3, 4.65 mmol reacted in degassed THF (46 cm^3)) was added *via* canula to a crude solution of the dialdehyde **242** (0.25 g, 0.93 mmol) and ^{t}BuOH (0.522 cm^3, 5.58 mmol) in THF (5 cm^3, four cycles freeze-pump-thaw). The reaction was stirred for 16 h whilst warming to room temperature and worked up as before. The crude material was purified by flash column chromatography on silica using ethyl acetate:petrol (60:40 to 80:20) to give the *cis diol* **244** (0.092 g, 36 % (over two steps, from **158**). Mp 108-110°C (from EtOAc). ν_{max} (cm^{-1}, solid) 3327 (br, OH), 3064, 2921, 1599, 1336, 1087. δ_H (400 MHz, $CDCl_3$) 1.74-1.90 (2H, m, NCH_2CH_2CHOH), 2.42 (3H, s, Ar-CH_3), 2.94-3.07 (3H, m, NCH_2CH_2CHOH and $NCHHCHOH$), 3.13 (1H, dd, *J* 11.6 and 3.6, $NCHHCHOH$), 3.74 (1H, dt, *J* 6.6 and 3.5, NCH_2CH_2CHOH), 3.84 (1H, dt, *J* 7.5 and 3.6, NCH_2CHOH), 7.32 (2H, d, *J* 8.0, Ar-*H* x 2), 7.63 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (100.6MHz, $CDCl_3$) 21.46 (CH_3), 29.25 (CH_2), 41.92 (CH_2), 47.76 (CH_2), 67.41 (CH), 67.71 (CH), 127.53 (2 x CH), 129.74 (2 x CH), 132.97 (C), 143.79 (C). *m/z* (ES) 272 (68 %), 254 (100), 198 (29), 155 (83). *m/z* (FAB) 272.0956 (MH^+. $C_{12}H_{18}NO_4S$ requires 272.0957).

cis 1-(Toluene-4-sulfonyl)-pyrrolidine-3,4-diol **245**



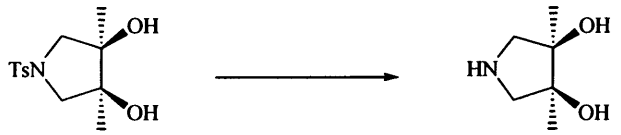
155 **182** **245**

The diene **155** (0.145 g, 0.58 mmol) in dry dichloromethane (10 cm^3) was treated with ozone then Me_2S (0.170 cm^3, 2.32 mmol) as for the preparation of **178**. After evaporation the crude

product dialdehyde was not isolated due to decomposition on silica. Thus the crude material was taken through to the SmI_2-mediated pinacol coupling reaction.

To a -78°C solution of SmI_2 (0.1 M THF, Sm, 0.53 g, 3.54 mmol, CH_2I_2, 0.237 cm^3, 2.95 mmol reacted in degassed THF (30 cm^3)) was added *via* canula a crude solution of the dialdehyde **182** (0.15 g, 0.59 mmol) and ^tBuOH (0.331 cm^3, 3.54 mmol) in THF (5 cm^3, four cycles freeze-pump-thaw). The reaction was stirred for 16 h whilst warming to room temperature and worked up as before. The crude material was purified by flash column chromatography on silica using ethyl acetate:petrol (60:40) to remove impurities and then using methanol to give the *cis diol* **245** (0.051 g, 34 % (over 2 steps, from **155**)) as a white solid. M.p. 127-129°C (from EtOAc). ν_{max} (cm^{-1}, solid) 3484 (OH), 3094, 2957, 1598, 1321, 1147 (SO_2), 1085, 1041. δ_H (250 MHz, CD_3OD) 2.47 (3H, s, Ar-C*H*$_3$), 3.19 (2H, dd, *J* 10.3 and 5.0, 2 x NC*H*HCHOH), 3.48 (2H, dd, *J* 10.3 and 5.0, 2 x NCH*H*CHOH), 3.99-4.05 (2H, m, 2 x NCH_2CHOH), 7.44 (2H, d, *J* 8.2, Ar-*H* x 2), 7.75 (2H, d, *J* 8.2, Ar-*H* x 2). δ_C (62.9 MHz, CD_3OD) 21.45 (CH_3), 53.13 (2 x CH_2), 71.87 (2 x CH), 128.65 (2 x CH), 130.79 (2 x CH), 135.20 (C), 145.13 (C). *m/z* (FAB) 258.0800 (MH^+. $C_{11}H_{16}NO_4S$ requires 258.0800), 258 (20 %) 242 (8), 226 (4), 176 (10), 154 (100), 136 (90).
Crystals suitable for X-ray were grown from MeOH:CH_2Cl_2 (see appendix 2, section 2.10 for crystallographical data).

cis 3,4-Dimethylpyrrolidine-3,4-diol **226**

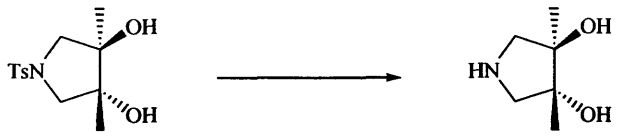


199 **226**

To a three-necked flask fitted with a dry ice-acetone condenser was added the diol **199** (0.04 g, 0.14 mmol). The flask was cooled to -78°C and a stream of ammonia gas was allowed to flow through the reaction vessel until all of the diol **199** had dissolved in liquid ammonia (5 cm^3). Sodium metal (0.01 g, 0.42 mmol) was added to the solution until a dark blue colour was persistent. The reaction vessel was removed from the dry ice-acetone bath and the ammonia evaporated. The reaction was quenched by addition of water (5 cm^3) and stirred for 5 min. The resultant solution was evaporated under reduced pressure to leave a residue, which was purified by flash column chromatography on silica using methanol:2M ammonia in methanol (100:0 to 80:20) to give the *amino diol* **226** (0.01 g, 56 %) as a pale yellow oil. δ_H (300 MHz, D_2O) 1.26 (6H, s, 2 x $NCH_2C(CH_3)OH$), 3.26 (2H, d, *J* 12.5, NC*H*HC(CH_3)OH), 3.35 (2H, d, *J* 12.5, NCH*H*C(CH_3)OH). δ_C (75.5 MHz, D_2O) 19.56 (2 x CH_3), 53.70 (2 x

CH_2), 77.78 (2 x C). *m/z* (ES) 132 (57 %), 114 (100), 109 (6), 96 (18). *m/z* (FAB) 132.1025 (MH^+. $C_6H_{14}NO_2$ requires 132.1025).

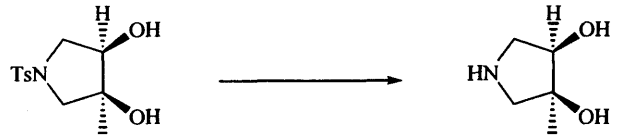
trans 3,4-Dimethylpyrrolidine-3,4-diol **229**



200 **229**

To a -78°C solution of the diol **200** (0.021 g, 0.074 mmol) in liquid ammonia (5 cm^3) was added sodium metal (0.005 g, 0.22 mmol) until a dark blue colour was persistent. Workup as before gave a residue, which was purified by flash column chromatography on silica using methanol:2M ammonia in methanol (100:0 to 80:20) to give the *amino diol* **229** (0.008 g, 82 %) as a yellow oil. δ_H (300 MHz, D_2O) 1.27 (6H, s, 2 x $NCH_2C(CH_3)OH$), 3.21 (2H, d, *J* 12.3, $NCHHC(CH_3)OH$), 3.38 (2H, d, *J* 12.3, $NCHHC(CH_3)OH$). δ_C (75.5 MHz, D_2O) 16.06 (2 x CH_3), 55.46 (2 x CH_2), 79.87 (2 x C). *m/z* (ES) 132 (81 %), 114 (100), 96 (18). *m/z* (FAB) 132.1024 (MH^+. $C_6H_{14}NO_2$ requires 132.1025).

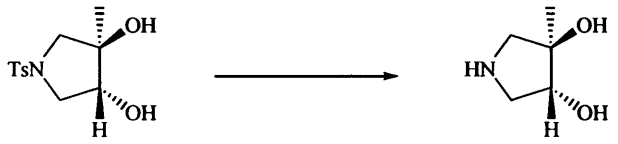
cis 3-Methylpyrrolidine-3,4-diol **230**



201 **230**

To a -78°C solution of the diol **201** (0.02 g, 0.074 mmol) in liquid ammonia (5 cm^3) was added sodium metal (0.005 g, 0.22 mmol) until a dark blue colour was persistent. Workup as before gave a residue, which was purified by flash column chromatography on silica using methanol:2M ammonia in methanol (100:0 to 80:20) to give the *amino diol* **230** (0.005 g, 58 %) as a yellow oil. δ_H (400 MHz, D_2O) 1.33 (3H, s, $NCH_2C(CH_3)OH$), 3.18 (1H, dd, *J* 12.0 and 7.5, $NCHHCH_2CHOH$), 3.22 (1H, d, *J* 12.4, $NCHHC(CH_3)OH$), 3.34 (1H, d, *J* 12.4, $NCHHC(CH_3)OH$), 3.56 (1H, dd, *J* 12.0 and 7.5, $NCHHCHOH$), 4.13 (1H, t, *J* 7.5, NCH_2CHOH). δ_C (100.6 MHz, D_2O) 20.51 (CH_3), 47.92 (CH_2), 53.67 (CH_2), 73.68 (CH), 75.46 (C). *m/z* (ES) 118 (73 %), 109 (39), 100 (100), 82 (56). *m/z* (FAB) 118.0868 (MH^+. $C_5H_{12}NO_2$ requires 118.0868).

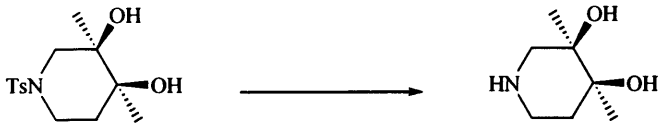
trans 3-Methylpyrrolidine-3,4-diol **231**



202 **231**

To a -78°C solution of the diol **202** (0.013 g, 0.047 mmol) in liquid ammonia (5 cm^3) was added sodium metal (0.0032 g, 0.14 mmol) until a dark blue colour was persistent. Workup as before gave a residue, which was purified by flash column chromatography on silica using methanol:2M ammonia in methanol (100:0 to 80:20) to give the *amino diol* **231** (0.004 g, 73 %) as a yellow oil. δ_H (300 MHz, D_2O) 1.33 (3H, s, $NCH_2C(CH_3)OH$), 3.20 (1H, dd, *J* 11.1 and 6.0, $NCHHCHOH$), 3.33 (2H, AB quartet, *J* 11.1, $NCH_2C(CH_3)OH$), 3.63 (1H, dd, *J* 11.1 and 6.0, $NCHHCHOH$), 3.99 (1H, t, *J* 6.0, NCH_2CHOH). δ_C (75.5 MHz, D_2O) 21.90 (CH_3), 50.61 (CH_2), 55.66 (CH_2), 74.64 (CH), 76.10 (C). *m/z* (ES) 118 (100 %), 100 (90), 82 (56). *m/z* (FAB) 118.0868 (MH^+. $C_5H_{12}NO_2$ requires 118.0868).

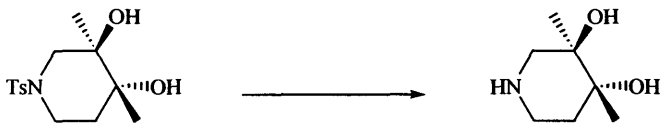
cis 3,4-Dimethylpiperidine-3,4-diol **232**



203 **232**

To a -78°C solution of the diol **203** (0.03 g, 0.1 mmol) in liquid ammonia (5 cm^3) was added sodium metal (0.007 g, 0.3 mmol) until a dark blue colour was persistent. Workup as before gave a residue, which was purified by flash column chromatography on silica using methanol:2M ammonia in methanol (100:0 to 80:20) to give the *amino diol* **232** (0.012 g, 83 %) as a yellow oil. δ_H (400 MHz, D_2O) 1.29 (3H, s, $NCH_2CH_2C(CH_3)OH$), 1.33 (3H, s, $NCH_2C(CH_3)OH$), 1.79 (1H, dt, *J* 4.4 and 14.4, NCH_2CHH), 2.18 (1H, ddd, *J* 14.4, 11.2 and 4.4, NCH_2CHH), 3.09-3.16 (2H, m, $NCHHCH_2$ and $NCHHC(CH_3)OH$), 3.22 (1H, dd, *J* 13.5 and 1.5, $NCHHC(CH_3)OH$), 3.33-3.37 (1H, m, $NCHHCH_2$). δ_C (100.6 MHz, D_2O) 19.62 (CH_3), 21.22 (CH_3), 32.12 (CH_2), 41.43 (CH_2), 50.40 (CH_2), 71.09 (C), 71.27 (C). *m/z* (ES) 146 (57 %), 128 (100), 99 (66). *m/z* (FAB) 146.1182 (MH^+. $C_7H_{16}NO_2$ requires 146.1181).

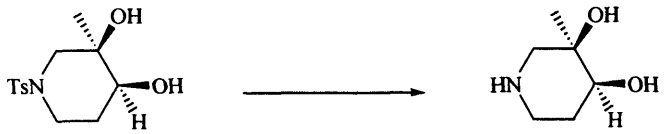
trans 3,4-Dimethylpiperidine-3,4-diol **233**



204 **233**

To a -78°C solution of the diol **204** (0.02 g, 0.065 mmol) in liquid ammonia (5 cm^3) was added sodium metal (0.004 g, 0.2 mmol) until a dark blue colour was persistent. Workup as before gave a residue, which was purified by flash column chromatography on silica using methanol:2M ammonia in methanol (100:0 to 80:20) to give the *amino diol* **233** (0.008 g, 82 %) as a yellow oil. δ_H (400 MHz, D_2O) 1.19 (3H, s, one of CH_3), 1.25 (3H, s, one of CH_3), 1.51 (1H, td, *J* 3.6 and 14.4, NCH_2CHH), 1.86 (1H, ddd, *J* 14.4, 9.6 and 7.0, NCH_2CHH), 2.62 (1H, d, *J* 13.6, $NCHHC(CH_3)OH$), 2.80-2.84 (2H,m (2^{nd} order), NCH_2CH_2), 2.87 (1H, d, *J* 13.6, $NCHHC(CH_3)OH$). δ_C (100.6 MHz, D_2O) 19.08 (CH_3), 21.70 (CH_3), 31.16 (CH_2), 39.82 (CH_2), 49.71 (CH_2), 70.16 (C), 70.57 (C). *m/z* (ES) 146 (100 %), 128 (48), 99 (24), 70 (32). *m/z* (FAB) 146.1181 (MH^+. $C_7H_{16}NO_2$ requires 146.1181).

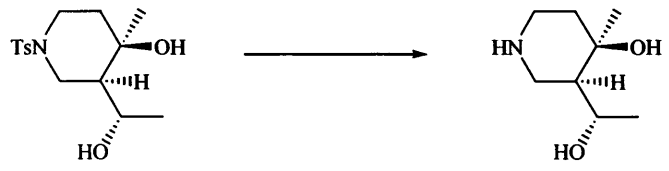
cis 3-Methylpiperidine-3,4-diol **234**



205 **234**

To a -78°C solution of diol the **205** (0.021 g, 0.074 mmol) in liquid ammonia (5 cm^3) was added sodium metal (0.005 g, 0.22 mmol) until a dark blue colour was persistent. Workup as before gave a residue, which was purified by flash column chromatography on silica using methanol:2M ammonia in methanol (100:0 to 80:20) to give the *amino diol* **234** (0.008 g, 83 %) as a yellow oil. δ_H (400 MHz, D_2O) 1.26 (3H, s, $NCH_2C(CH_3)OH$), 1.76-1.88 (2H, m, NCH_2CH_2), 2.77 (1H, d, *J* 13.6, $NCHHC(CH_3)OH$), 2.76-2.84 (1H, m, $NCHHCH_2$), 3.03 (1H, d, *J* 13.6, $NCHHC(CH_3)OH$), 3.20 (1H, br d, *J* 12.8, $NCHHCH_2$), 3.62 (1H, dd, *J* 9.5 and 6.0, $CHOH$). δ_C (100.6 MHz, D_2O) 22.30 (CH_3), 27.56 (CH_2), 42.91 (CH_2), 52.91 (CH_2), 69.49 (C), 71.50 (CH). *m/z* (ES) 132 (52 %), 114 (100), 96 (9), 85 (22), 70 (42). *m/z* (FAB) 132.1025 (MH^+. $C_6H_{14}NO_2$ requires 132.1025).

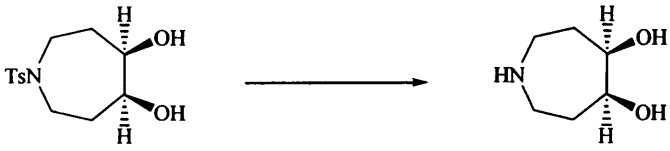
cis 4-(1-Hydroxyethyl)-3-methylpiperidin-4-ol **235**



213 **235**

To a -78°C solution of diol the **213** (0.031 g, 0.099 mmol) in liquid ammonia (5 cm^3) was added sodium metal (0.007 g, 0.3 mmol) until a dark blue colour was persistent. Workup as before gave a residue, which was purified by flash column chromatography on silica using methanol:2M ammonia in methanol (100:0 to 80:20) to give the *amino diol* **235** (0.013 g, 83 %) as a yellow oil. δ_H (400 MHz, D_2O) 1.17 (3H, d, *J* 6.8, $NCH_2CHCHOHCH_3$), 1.36 (3H, s, $NCH_2CH_2C(CH_3)OH$), 1.73 (1H, ddd, *J* 12.5, 4.0 and 2.0, $NCH_2CHCHOH$), 1.78-1.82 (2H, m), 3.19-3.25 (3H, m), 3.38 (1H, dd, *J* 4.0 and 12.5, $NCHHCHCHOHCH_3$), 4.50 (1H, dq, *J* 2.0 and 6.8, $CHOHCH_3$). δ_C (100.6 MHz, D_2O) 20.07 (CH_3), 26.56 (CH_3), 35.35 (CH_2), 39.01 (CH_2), 39.87 (CH_2), 45.14 (CH), 64.98 (CH), 69.07 (C). *m/z* (ES) 160 (32 %), 142 (3), 124 (100), 109 (4). *m/z* (FAB) 160.1337 (MH^+. $C_8H_{18}NO_2$ requires 160.1338).

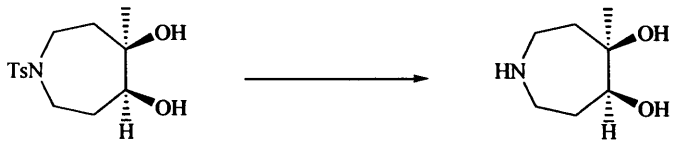
cis Azepane-4,5-diol **236**



207 **236**

To a -78°C solution of the diol **207** (0.01 g, 0.036 mmol) in liquid ammonia (5 cm^3) was added sodium metal (0.0025 g, 0.11 mmol) until a dark blue colour was persistent. Workup as before gave a residue, which was purified by flash column chromatography on silica using methanol:2M ammonia in methanol (100:0 to 80:20) to give the *amino diol* **236** (0.003 g, 60 %) as a yellow oil. δ_H (400 MHz, D_2O) 1.86-1.97 (2H, m, 2 x NCH_2CHH), 2.04-2.14 (2H, m, NCH_2CHH), 3.10-3.21 (2H, m, 2 x $NCHHCH_2$), 3.33-3.42 (2H, m, 2 x $NCHHCH_2$), 3.70-3.75 (2H, m), 3.95-4.00 (2H, m). *m/z* (ES) 132 (62 %), 114 (31), 109 (100). *m/z* (FAB) 132.1025 (MH^+. $C_6H_{14}NO_2$ requires 132.1025).

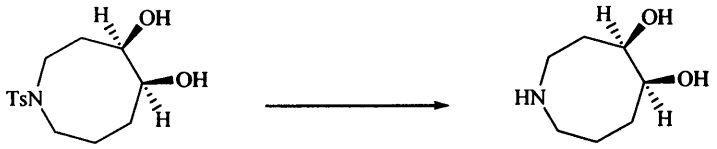
cis 4-Methyl-azepane-4,5-diol **237**



210 **237**

To a -78°C solution of diol the **210** (0.011 g, 0.036 mmol) in liquid ammonia (5 cm^3) was added sodium metal (0.0025 g, 0.11 mmol) until a dark blue colour was persistent. Workup as before gave a residue, which was purified by flash column chromatography on silica using methanol:2M ammonia in methanol (100:0 to 80:20) to give the *amino diol* **237** (0.004 g, 75 %) as a yellow oil. δ_H (400 MHz, D_2O) 1.25 (3H, s, $NCH_2CH_2C(CH_3)OH$), 1.85-1.93 (3H, m), 1.95-2.08 (1H, m), 3.03-3.12 (2H, m), 3.31-3.39 (2H, m), 3.56 (1H, dd, *J* 10.0 and 3.0, NCH_2CH_2CHOH). *m/z* (ES) 146 (100 %), 128 (87), 110 (89), 99 (72). *m/z* (FAB) 146.1181 (MH^+. $C_7H_{16}NO_2$ requires 146.1181).

cis Azocane-4,5-diol **238**



221 **238**

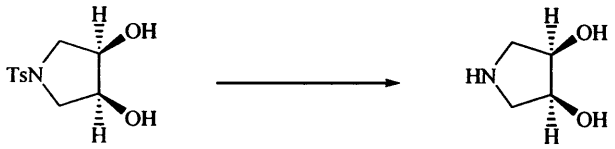
To a -78°C solution of the diol **221** (0.01 g, 0.033 mmol) in liquid ammonia (5 cm^3) was added sodium metal (0.0023 g, 0.1 mmol) until a dark blue colour was persistent. Workup as before gave a residue, which was purified by flash column chromatography on silica using methanol:2M ammonia in methanol (100:0 to 80:20) to give the *amino diol* **238** (0.003 g, 63 %) as a yellow oil. δ_H (400 MHz, D_2O) 1.80-1.90 (4H, m), 2.00-2.10 (2H, m), 2.95-3.03 (2H, m), 3.13-3.20 (1H, m), 3.27-3.33 (1H, m), 3.97 (1H, ddd, *J* 2.5, 4.0 and 7.2, one of C*H*OH), 4.07-4.11 (1H, m, one of C*H*OH). *m/z* (ES) 146 (100 %), 130 (29), 128 (61), 112 (68), 110 (87). *m/z* (FAB) 146.1181 (MH^+. $C_7H_{16}NO_2$ requires 146.1181).

cis Tetrahydro-pyrrolo[3,4-*c*]pyrrole-3*a*-6*a*-diol **239**

223 **239**

To a -78°C solution of the diol **223** (0.028 g, 0.062 mmol) in liquid ammonia (5 cm^3) was added sodium metal (0.009 g, 0.43 mmol) until a dark blue colour was persistent. Workup as before gave a residue, which was purified by flash column chromatography on silica using methanol:2M ammonia in methanol (100:0 to 80:20) to give the *amino diol* **239** (0.007 g, 78 %) as a yellow oil. δ_H (300 MHz, D_2O) 3.53 (4H, d, *J* 13.5, 2 x NC*H*HCOH), 3.62 (4H, d, *J* 13.5, 2 x NCH*H*COH). δ_C (75.5 MHz, D_2O) 52.30 (4 x CH_2), 83.23 (2 x C). *m/z* (ES) 145 (100 %), 129 (44), 91 (14), 80 (14). *m/z* (FAB) 145.0977 ($C_6H_{13}N_2O_2$ requires 145.0977).

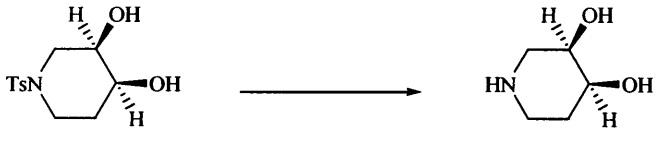
cis Pyrrolidine-3,4-diol **253**



245 **253**

To a -78°C solution of diol the **245** (0.031 g, 0.12 mmol) in liquid ammonia (5 cm^3) was added sodium metal (0.008 g, 0.36 mmol) until a dark blue colour was persistent. Workup as before gave a residue, which was purified by flash column chromatography on silica using methanol:2M ammonia in methanol (100:0 to 80:20) to give the *amino diol* **253** (0.009 g, 75 %) as a yellow oil. δ_H (400 MHz, D_2O) 3.27 (2H, dd, *J* 12.4 and 4.5, 2 x NCH_2CHOH), 3.49 (2H, dd, *J* 12.4 and 4.5, 2 x NCH_2CHOH), 4.39-4.43 (2H, m (2nd order), 2 x NCH_2CHOH). δ_C (75.5 MHz, D_2O) 50.03 (CH_2), 70.74 (*C*-H). *m/z* (ES) 104 (70 %), 91 (54), 86 (31), 68 (29). *m/z* (FAB) 104.0711 (MH^+. $C_4H_{10}NO_2$ requires 104.0712).

cis Piperidine-3,4-diol **254**



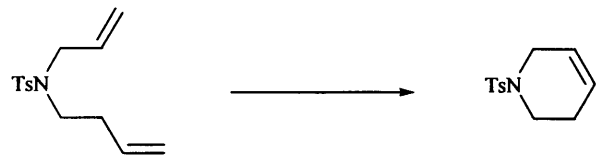
244 **254**

To a -78°C solution of the diol **244** (0.027 g, 0.099 mmol) in liquid ammonia (5 cm^3) was added sodium metal (0.007 g, 0.3 mmol) until a dark blue colour was persistent. Workup as before gave a residue, which was purified by flash column chromatography on silica using methanol:2M ammonia in methanol (100:0 to 80:20) to give the *amino diol* **254** (0.005 g, 43 %) as a yellow oil. δ_H (400 MHz, D_2O) 1.91 (1H, ddd, *J* 14.0, 8.5 and 4.5, NC*H*HCH_2), 2.03 (1H, ddd (overlapping), *J* 14.0, 9.6 and 4.5, NCH_2CHH), 3.07 (1H, dt, *J* 4.5 and 14.0, NC*H*HCH_2), 3.17 (1H, dd, *J* 2.5 and 13.2, NCH_2CHH), 3.29-3.36 (2H, m, NCH*H*CHOH and

NCH*H*CH$_2$), 3.96 (1H, ddd, *J* 9.6, 4.5 and 2.5, NCH$_2$CH$_2$C*H*OH), 4.08 (1H, ddd, *J* 5.5, 4.5 and 2.5, NCH$_2$C*H*OH). δ_C (75.5 MHz, D_2O) 28.62 (CH_2), 41.20 (CH_2), 47.21 (CH_2), 67.65 (CH), 68.23 (CH). *m/z* (ES) 118 (82 %), 100 (100), 82 (13), 71 (53). *m/z* (FAB) 118.0868 (MH^+. $C_5H_{12}NO_2$ requires 118.0868).

This is a literature compound.[164]

1-(Toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridine **274**

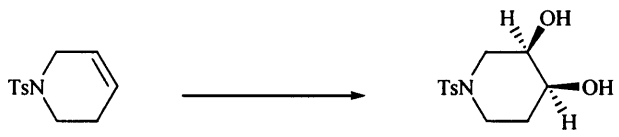


158 **274**

A solution of the diene **158** (0.05 g, 0.19 mmol) in dichloromethane (5 cm^3) was added to $RuCl_2$(=CHPh)(PCy_3)$_2$ (5 mol%, 0.008 g, 0.01 mmol) *via* canula, under an atmosphere of nitrogen. The mixture was stirred for 3 h under reflux then cooled and the solution was filtered through silica gel, which was washed thoroughly with dichloromethane. The solvent was removed under reduced pressure and the resulting material was purified by flash column chromatography on silica using diethyl ether:petrol (70:30 to 50:50) to elute the *olefin* **274** (0.044 g, 98 %) as a colourless oil. ν_{max} (cm^{-1}, film) 3039, 2944, 2893, 1597 (C=C), 1328. δ_H (250 MHz, $CDCl_3$) 2.18-2.25 (2H, m, NCH$_2$C*H*$_2$), 2.43 (3H, s, Ar-C*H*$_3$), 3.18 (2H, t, *J* 5.7, NC*H*$_2$CH$_2$), 3.58 (2H, m, NC*H*$_2$CH=CH), 5.57-5.65 (1H, m, NCH$_2$CH$_2$C*H*=CH), 5.72-5.80 (1H, m, NCH$_2$C*H*=CH), 7.32 (2H, d, *J* 8.0, Ar-*H* x 2), 7.68 (2H, d, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.48 (CH_3), 25.24 (CH_2), 42.61 (CH_2), 44.74 (CH_2), 122.75 (CH), 125.04 (CH), 127.66 (2 x CH), 129.59 (2 x CH), 133.45 (C), 143.44 (C). *m/z* (ES) 238 (100 %), 184 (87), 155 (79). *m/z* (FAB) 238.0902 (MH^+. $C_{12}H_{16}NO_2S$ requires 238.0902).

This is a literature compound.[165]

cis 1-(Toluene-4-sulfonyl)-piperidine-3,4-diol **244**



274 **244**

A solution of the olefin **274** (0.031 g, 0.13 mmol) in acetone (2 cm^3) and osmium tetroxide, OsO_4 (0.053 cm^3, 2.5 wt% in ^tBuOH, 0.005 mmol) was prepared at room temperature. This was added *via* canula to a solution of NMO (0.023 g, 0.20 mmol) in H_2O (1 cm^3). The reaction mixture was stirred for 16 h at room temperature and then quenched by the addition of saturated aqueous $Na_2S_2O_4$. After further stirring for 30 min the solution was filtered through celite and washed thoroughly with acetone. The solvent was evaporated under reduced pressure to leave a residue which was purified by flash column chromatography on silica using ethyl acetate:petrol (60:40 to 80:20) to afford the *cis diol* **244** (0.023 g, 65 %) as a white solid.

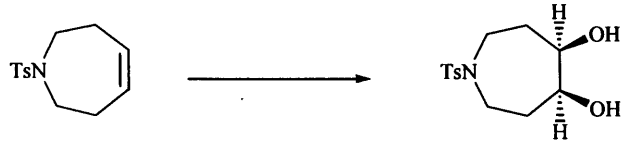
Analytical data as before (page 142).

1-(Toluene-4-sulfonyl)-2,3,6,7-tetrahydro-1*H*-azepine **275**

161 **275**

The reaction was carried out as for **158** thus the diene **161** (0.065 g, 0.23 mmol) in dichloromethane (2 cm^3) was added to $RuCl_2(=CHPh)(PCy_3)_2$ (5 mol%, 0.009 g, 0.01 mmol) *via* canula under an atmosphere of nitrogen and the mixture was stirred under reflux for 3 h. The reaction was worked up as before and purified by flash column chromatography on silica using dichloromethane:petrol (70:30 to 90:10) to elute the *olefin* **275** (0.048 g, 83 %) as a white solid. M.p. 118-120°C (petrol 40-60). ν_{max} (cm^{-1}, solid) 3039, 2893, 1597 (C=C), 1451, 1328, 1283, 1160 (SO_2), 1092. δ_H (250 MHz, $CDCl_3$) 2.21-2.26 (4H, br app q, *J* 4.1, 2 x NCH_2CH_2), 2.34 (3H, s, Ar-CH_3), 3.18-3.22 (4H, m (2^{nd} order), 2 x NCH_2CH_2), 5.66-5.68 (2H, m (2^{nd} order), 2 x NCH_2CH_2CH), 7.22 (2H, d, *J* 8.0, Ar-*H* x 2), 7.59 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.41 (CH_3), 29.84 (2 x CH_2), 48.19 (2 x CH_2), 126.99 (2 x CH), 129.6 (2 x CH), 130.15 (2 x CH), 136.28 (C), 143.03 (C). *m/z* (FAB) 252.1058 (MH^+. $C_{13}H_{18}NO_2S$ requires 252.1058), 252 (100 %), 238 (7), 184 (6), 154 (29), 136 (27).

cis 1-(Toluene-4-sulfonyl)-azepane-4,5-diol **207**

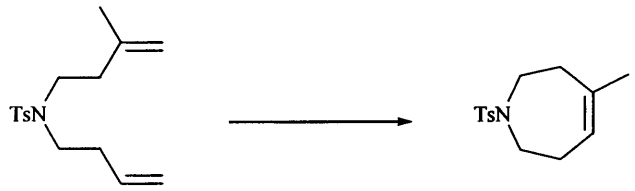


275 **207**

The reaction was carried out as described for **274** thus the olefin **275** (0.033 g, 0.13 mmol) in acetone (2 cm^3) and osmium tetroxide, OsO_4 (0.053 cm^3, 2.5 wt% in ^tBuOH, 0.005 mmol) was prepared at room temperature. This was added *via* canula to a solution of NMO (0.023 g, 0.20mmol) in H_2O (1 cm^3) and the reaction mixture was stirred for 16 h at room temperature. The reaction was worked up as before and purified by flash column chromatography on silica using ethyl acetate:petrol (60:40 to 80:20) to afford the *cis diol* **207** (0.03 g, 81 %) as a white solid.

Analytical data as before (page 138).

4-Methyl-1-(toluene-4-sulfonyl)-2,3,6,7-tetrahydro-1*H*-azepine **276**

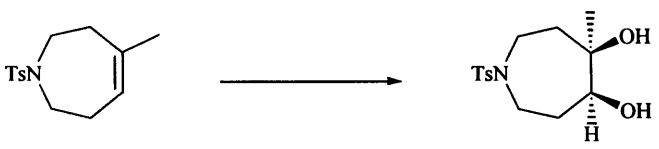


163 **276**

The reaction was carried out as for **158** thus the diene **163** (0.05 g, 0.17 mmol) in dichloromethane (17 cm^3) was added to $RuCl_2(=CHPh)(PCy_3)_2$ (5 mol%, 0.007 g, 0.0085 mmol) under an atmosphere of nitrogen and the mixture was stirred under reflux for 3 h. The reaction was worked up as before and purified by flash column chromatography on silica using dichloromethane:petrol (80:20 to 100:0) to elute the *alkene* **276** (0.044 g, 97 %) as a colourless oil. δ_H (250 MHz, $CDCl_3$) 1.65 (3H, s, $NCH_2CH_2C(CH_3)$), 2.11-2.17 (4H, m, 2 x NCH_2CH_2), 2.39 (3H, s, Ar-CH_3), 3.16-3.20 (4H, m, 2 x NCH_2CH_2), 5.43 (1H, t, *J* 5.7, NCH_2CH_2CH), 7.22 (2H, d, *J* 8.0, Ar-*H* x 2), 7.63 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.44 (CH_3), 25.98 (CH_3), 28.25 (CH_2), 46.79 (CH_2), 48.15 (2 x CH_2), 123.84 (CH), 127.12 (2 x CH), 129.59 (2 x CH), 136.01 (C), 138.74 (C), 143.03 (C).

This is a literature compound.[159]

4-Methyl-1-(toluene-4-sulfonyl)-azepane-4,5-diol **210**



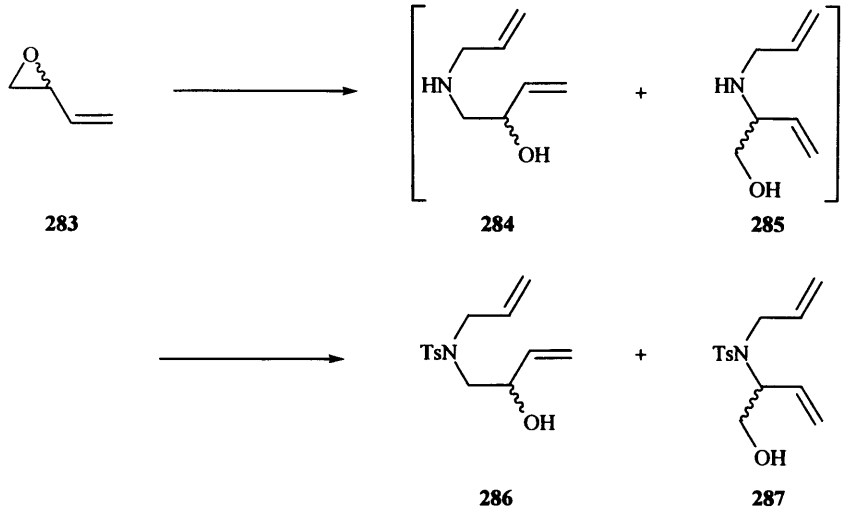
276 **210**

The reaction was carried out as described for **274** thus the olefin **276** (0.027 g, 0.108 mmol) in acetone (2 cm^3) and osmium tetroxide, OsO_4 (0.041 cm^3, 2.5 wt% in ^tBuOH, 0.004 mmol) was prepared at room temperature. This was added *via* canula to a solution of NMO (0.019 g, 0.16 mmol) in H_2O (1 cm^3) and the reaction mixture was stirred for 16 h at room temperature. The reaction was worked up as before and purified by flash column chromatography on silica using ethyl acetate:petrol (50:50 to 70:30) to afford the *cis diol* **210** (0.028g, 87 %) as a colourless oil.

Analytical data as before (page 139).

5.3 Compounds from Chapter 4

N-Allyl-*N*-(2-hydroxy-but-3-enyl)-4-methylbenzenesulfonamide **286** and
N-Allyl-*N*-(1-hydroxymethylallyl)-4-methylbenzenesulfonamide **287**



283 **284** **285**

286 **287**

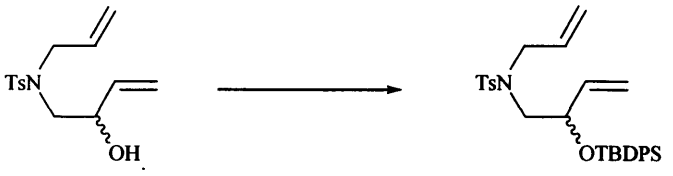
A solution of 2-vinyl-oxirane (*rac*)-**283** (2 g, 28 mmol) in allylamine (21.4 cm^3, 285 mmol) in a sealed tube was heated under reflux for 18 h after which the reaction was cooled and excess allylamine was evaporated under reduced pressure to leave a dark brown oil. Further purification was not required and the crude amines (*rac*)-**284** and (*rac*)-**285** were taken through to the next stage.

Under an atmosphere of nitrogen, the crude amines **284** and **285** from above in dichloromethane (50 cm^3) was added triethylamine (3.8 cm^3, 27 mmol) and DMAP (0.333 g, 2.7 mmol). The reaction mixture was cooled to 0°C and *p*-toluenesulfonyl chloride (5.72 g, 30 mmol) was added portion-wise. The reaction was stirred for 18 h while warming to room temperature after which the reaction was quenched by addition of water (50 cm^3) and the organic species were extracted with DCM (3 x 50 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to leave a brown oil, which was purified by flash column chromatography on silica using petrol:diethyl ether (90:10 to 70:30) to give the *alcohol* (*rac*)-**286** (6.17 g, 77 % (over 2 steps, from **283**)) and the *alcohol* (*rac*)-**287** (0.567 g, 7 % (over 2 steps, from **283**)) as colourless oils.
Analytical data for (*rac*)-**286** found on page 163.

(*rac*)-**287**: δ_H (250 MHz, $CDCl_3$) 2.40 (3H, s, Ar-CH_3), 3.64-3.73 (3H, m, NC*H*HCH=CH_2 and NCHCH_2OH), 3.95 (1H, dd, *J* 16.4 and 5.3, NCH*H*CH=CH_2), 4.43 (1H, AB quartet, *J* 6.4, NC*H*CH_2OH), 4.99-5.28 (4H, m, NCH_2CH=CH_2 and NCHCH=CH_2), 5.54 (1H, ddd *J*

17.0, 10.6 and 6.4, one of C*H*=CH_2), 5.77-5.93 (1H, m, one of C*H*=CH_2), 7.28 (2H, d, *J* 8.0, Ar-*H* x 2), 7.72 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.31 (CH_3), 47.23 (CH_2), 61.63 (CH), 62.42 (CH_2), 117.62 (CH_2), 119.49 (CH_2), 127.12 (2 x CH), 129.47 (2 x CH), 132.41 (CH), 135.37 (CH), 137.41 (C), 143.28 (C).

N-Allyl-*N*-[2-(*tert*-butyldiphenylsilanyloxy)-but-3-enyl]-4-methylbenzenesulfonamide **288**

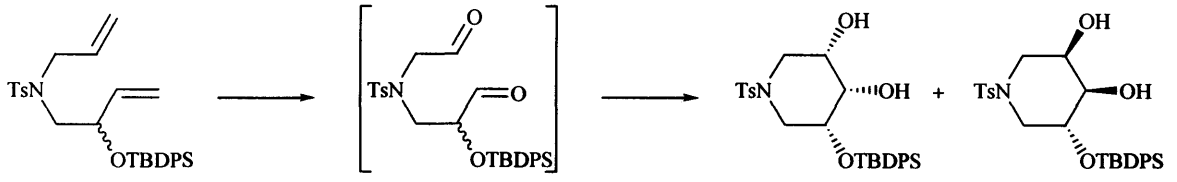


286 **288**

The alcohol (*rac*)-**286** (0.3 g, 1.07 mmol) in dichloromethane (10 cm^3) was added triethylamine (0.163 cm^3, 1.17 mmol) and DMAP (0.01 g, 0.107 mmol). The reaction mixture was cooled to 0°C and TBDPSCl (0.3 cm^3, 1.17 mmol) was added dropwise. The reaction was stirred for 18 h while warming to room temperature after which the reaction was worked up by addition of water (25 cm^3). The organic species was extracted with DCM (3 x 25 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to leave a yellow oil. The product was purified by flash column chromatography on silica using petrol:dichloromethane (60:40 to 20:80) to give the *silyl-protected diene* (*rac*)-**288** (0.34 g, 55 %) as a colourless oil.

Data as for diene (2*S*)-**288** found on page 164.

(*rac*)-*syn,syn* 5-(*tert*-Butyldiphenylsilanyloxy)-1-(toluene-4-sulfonyl)-piperidine-3,4-diol **295**
(*rac*)-*anti,syn* 5-(*tert*-Butyldiphenylsilanyloxy)-1-(toluene-4-sulfonyl)-piperidine-3,4-diol **296**



288 **294** **295** **296**

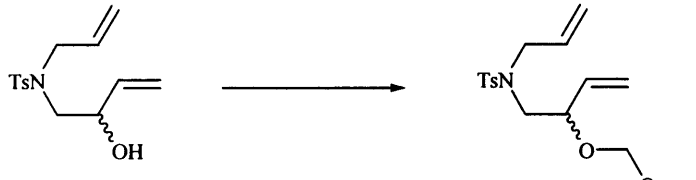
The diene (*rac*)-**288** (0.338 g, 0.65 mmol) in dry dichloromethane (10 cm^3) was treated with ozone then Me_2S (0.19 cm^3, 2.6 mmol) as for the preparation of **178**. After evaporation the product dialdehyde was not isolated due to decomposition on silica but was taken through to the SmI_2-mediated pinacol coupling reaction.

To a -78°C solution of SmI_2 (0.1 M THF, Sm, 0.582 g, 3.8 mmol, CH_2I_2, 0.26 cm^3, 3.2 mmol, in degassed THF 32 cm^3) was added *via* canula a crude solution of the dialdehyde (*rac*)-**294** (0.338 g, 0.64 mmol) and ^tBuOH (0.363 cm^3, 3.2 mmol) in THF (5 cm^3, four cycles freeze-pump-thaw). The reaction was stirred for 16 h whilst warming to room temperature and then poured into saturated sodium bicarbonate (30 cm^3) and water (30 cm^3). The organic species were extracted with ethyl acetate (3 x 50 cm^3) and washed with sodium thiosulphate (10% solution, 30 cm^3) and saturated sodium chloride (30 cm^3). The organic species were combined, dried (Na_2SO_4) and evaporated under reduced pressure and the crude material was purified by flash column chromatography on silica using dichloromethane:diethyl ether (98:2 to 95:5) to give the *pinacol* (*rac*)-**295** (0.063 g, 19 % (over 2 steps, from (*rac*)-**288**)) and the *pinacol* (*rac*)-**296** (0.077 g, 23 % (over 2 steps, from (*rac*)-**288**)) as colourless oils.

Repetition of the reaction using 0.3 g of the diene (*rac*)-**288** gave (*rac*)-**295** (0.075 g, 25 % from (*rac*)-**288**) and (*rac*)-**296** (0.082 g, 27 % from from (*rac*)-**288**) in a ratio of 1 : 1.1 respectively.

Analytical data found on page 165.

(*rac*)-*N*-Allyl-*N*-(2-methoxy-but-3-enyl)-4-methylbenzenesulfonamide **291**

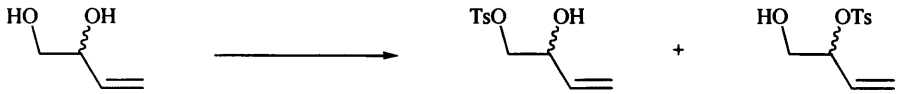


286 **291**

The alcohol (*rac*)-**286** (0.5 g, 1.77 mmol) in dichloromethane (20 cm^3) was added DIPEA (0554 cm^3, 3.2 mmol). The reaction mixture was cooled to 0°C and MOM-Cl (0.202 cm^3, 2.66 mmol) was added dropwise. The reaction was stirred for 18 h while warming to room temperature then refluxed (~50°C) for a further 12 h after which the reaction was worked up by addition of water (25 cm^3). The organic species was extracted with DCM (3 x 50 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to leave a yellow oil. The product was purified by flash column chromatography on silica using diethyl ether:petrol (40:60 to 70:30) to give the *acetal-protected diene* (*rac*)-**291** (0.319 g, 55 %) as a colourless oil. δ_H (250 MHz, $CDCl_3$) 2.41 (3H, s, Ar-CH_3), 3.26 (2H, d, *J* 6.5, NCH_2CHO), 3.30 (3H, s, OCH_3), 3.93 (2H, d, *J* 6.5, NCH_2CH=CH_2), 4.29 (1H, app q, *J* 6.5, NCH$_2$C*H*OCH_2), 4.51 (1H, d, *J* 6.5, OC*H*HOCH_3), 4.63 (1H, d, *J* 6.5, OCH*H*OCH_3), 5.10-5.31 (4H, m, 2 x CH=CH_2), 5.61 (2H, m (overlapping), 2 x C*H*=CH_2), 7.29 (2H, d, *J* 8.0, Ar-*H* x 2), 7.71 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.18 (CH_3), 50.26 (CH_2), 51.36 (CH_2), 55.23 (CH_3) 75.84 (CH), 93.77 (CH_2), 118.74 (CH_2), 118.95 (CH_2),

127.01 (2 x CH), 129.36 (2 x CH), 132.52 (CH), 135.27 (CH), 137.11 (C), 143.14 (C). *m/z* (ES) 326 (MH^+, 9 %), 294 (41), 264 (85), 224 (12), 155 (16), 130 (100).

(*rac*)-Toluene-4-sulfonic acid 2-hydroxy-but-3-enyl ester **306** and
(*rac*)-Toluene-4-sulfonic acid 1-hydroxy methylallyl ester **307**

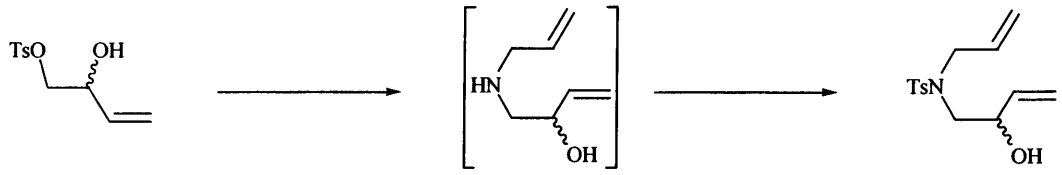


305 **306** **307**

Butene-1,2-diol (*rac*)-**305** (0.3 g, 3.4 mmol) in chloroform (6 cm^3) was cooled to 0°C using an ice-bath and pyridine (0.55 cm^3, 6.8 mmol) was added. The reaction mixture was stirred for 15 min then *p*-toluenesulfonyl chloride (0.974 g, 5.1 mmol) was added portion-wise to the reaction and stirred for 16 h. The reaction was quenched by addition of diethyl ether (10 cm^3) and water (8 cm^3). The organic extract was washed with hydrochloric acid (1M, 15 cm^3), saturated aqueous sodium hydrogen carbonate (10 cm^3) and water (10 cm^3). The organic extract was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to leave yellow oil, which was purified by flash column chromatography using dichloromethane (100:0) as the eluent to give the *2° tosylate* (*rac*)-**307** (0.154 g, 19 %) and then using petrol:ethyl acetate (50:50) to elute the *1° tosylate* (*rac*)-**306** (0.422 g, 51 %) as colourless oils.

Data for (*rac*)-**306** and (*rac*)-**307** found on page 162.

(*rac*)-*N*-Allyl-*N*-(2-hydroxy-but-3-enyl)-4-methylbenzenesulfonamide **286**



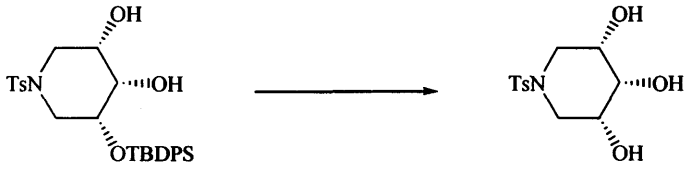
306 **284** **286**

A solution of the tosylate (*rac*)-**306** (0.2 g, 0.83 mmol) in allylamine (0.62 cm^3, 8.3 mmol) in a sealed tube in the absence of solvent was heated under reflux for 18 h after which the reaction was cooled and excess allylamine was evaporated under reduced pressure to leave a dark brown oil. Further purification was not required and the crude material was taken through to the next stage.

Under an atmosphere of nitrogen, a crude solution of the amine (*rac*)-**284** in dichloromethane (5 cm^3) was added NEt_3 (0.24 cm^3, 1.83 mmol) and DMAP (0.019 g, 0.083 mmol). The

reaction mixture was cooled to 0°C and *p*-toluenesulfonyl chloride (0.33 g, 0.91 mmol) was added portion-wise. The reaction was stirred for 18 h while warming to room temperature after which the reaction was quenched by addition of water (5 cm^3) and the organic species was extracted with DCM (3 x 10 cm^3). The combined extracts were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a brown oil, which was purified by flash column chromatography on silica using petrol:diethyl ether (60:40 to 40:60) to give the *tosylate* (*rac*)-**286** (0.18g, 77 % (over 2 steps, from (*rac*)-**306**)) as a colourless oil.
Data as for alcohol (2*S*)-**286** found on page 163.

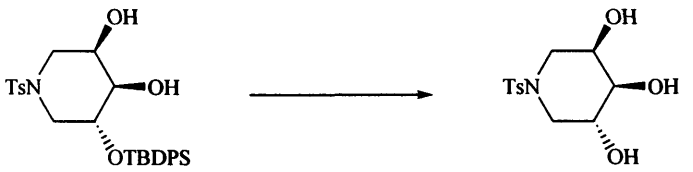
(*meso*)-*syn,syn* 1-(Toluene-4-sulfonyl)-piperidine-3,4,5-diol **297**



295 **297**

To a solution of the diol (*rac*)-**295** (0.027 g, 0.051 mmol) in THF (2 cm^3) was added TBAF (0.016 cm^3, 0.056 mmol) and the reaction was stirred for 1 h. The reaction was quenched by addition of saturated aqueous ammonium chloride (3 cm^3) and extracted using ethyl acetate (3 x 5 cm^3). The combined extracts were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a yellow oil, which was purified by flash column chromatography on silica using dichloromethane:methanol (99:1 to 97:3) to give the *triol* (*meso*)-**297** (0.009 g, 61 %) as a white solid. M.p. 199-201°C. δ_H (300 MHz, CD_3OD) 2.44 (3H, s, Ar-C*H*$_3$), 2.60 (2H, app t, *J* 10.0, 2 x NC*H*HCHOH), 3.35 (2H, dd, *J* 10.0 and 4.6, 2 x NCH*H*CHOH), 3.67 (2H, ddd, *J* 10.0, 4.6, 2.7, NCH_2CHOH), 3.80 (1H, t, *J* 2.7, $NCH_2CHOHCHOH$), 7.42 (2H, d, *J* 8.0, Ar-*H* x 2), 7.66 (2H, d, *J* 8.0, Ar-*H* x 2). *m/z* (ES) 288 (MH^+, 39 %), 242 (100).
Crystals suitable for X-ray were grown from MeOH:CH_2Cl_2 (see appendix 2, section 2.11 for crystallographical data).

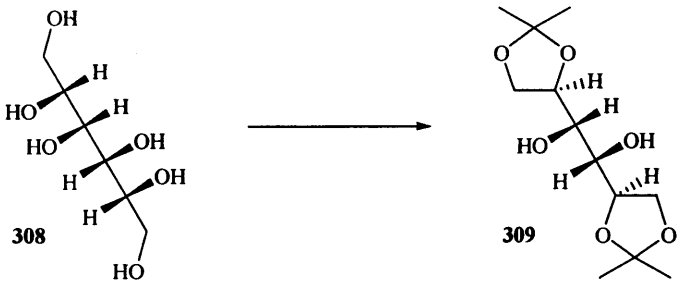
(*rac*)-*anti,syn* 1-(Toluene-4-sulfonyl)-piperidine-3,4,5-diol **298**



296 **298**

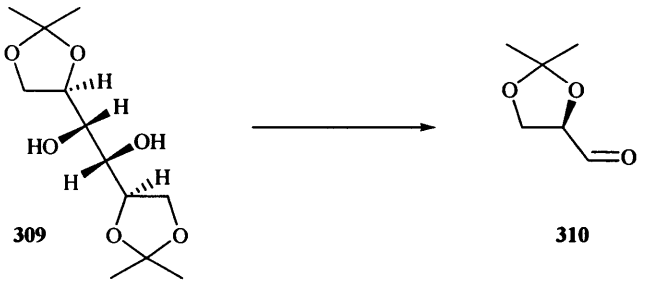
The reaction was carried out as described for (*meso*)-**297** thus diol (*rac*)-**296** (0.028 g, 0.053 mmol) in THF (2 cm^3) was added TBAF (0.017 cm^3, 0.059 mmol) and stirred for 1 h. Workup and purification by flash column chromatography on silica using dichloromethane:methanol (99:1 to 97:3) gave the *triol* (*rac*)-**298** (0.013 g, 93 %) as a colourless oil. δ_H (250 MHz, CD_3OD) 2.48 (3H, s, Ar-C*H*$_3$), 2.85 (1H, dd, *J* 11.5 and 6.5, one of NC*H*H), 3.03 (1H, dd, *J* 11.5 and 3.5, one of NCH*H*), 3.11 (1H, dd, *J* 11.5 and 6.5, one of NC*H*H), 3.22 (1H, dd, *J* 11.5 and 3.5, one of NCH*H*), 3.49 (1H, dd, *J* 6.5 and 3.2, NCH_2CHOHC*H*OH), 3.84 (1H, td, *J* 6.5 and 3.5, one of NCH_2C*H*OH), 3.98 (1H, d app t, *J* 6.5 and 3.5, one of NCH_2C*H*OH), 7.45 (2H, d, *J* 8.0, Ar-*H* x 2), 7.71 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, MeOD) 21.45 (CH_3), 49.74 (CH_2), 49.98 (CH_2), 67.62 (CH), 69.01 (CH), 73.29 (CH), 128.81 (2 x CH), 130.82 (2 x CH), 134.73 (C), 145.28 (C). *m/z* (ES) 288 (MH^+, 23 %), 242 (10), 186 (100).

1,2:5,6-diisopropylidene-D-mannitol **309**



The method for the conversion of **308** to **309** is based upon a procedure employed by Kuszmann and co-workers.[152] $ZnCl_2$ (42 g, 308 mmol) was added to distilled acetone (175 cm^3) and stirred. The resulting milky solution was allowed to settle and the clear solution was added *via* canula to a flask containing D-mannitol **308** (20 g, 109 mmol) and stirred for 3 h at RT. The reaction mixture was poured into aqueous K_2CO_3 (300 cm^3) and stirred for a further 1 h. After this time the precipitate was filtered and washed with DCM (3 x). The combined DCM extracts were re-extracted with cold H_2O, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a solid residue, which was recrystallised from hexane to give the pure *mannitol diacetonide* **309** (6.18 g, 22 %). $[\alpha]^{22}_D$ +2.5° (c = 2.7 in MeOH) (Literature $[\alpha]^{22}_D$ +2.1° (c = 2.1 in MeOH).[166] M.p. 119-120°C (Literature m. p. 118-120°C).[167] δ_H (250 MHz, $CDCl_3$) 1.36 (6H, s, 2 x CH_2OCCH_3), 1.42 (6H, s, 2 x CH_2OCCH_3), 2.66 (2H, d, *J* 6.5, 2 x CHO*H*), 3.75 (2H, app t, *J* 6.5, 2 x Me_2COCHC*H*), 3.98 (2H, dd, *J* 8.3 and 5.3, 2 x C*H*HO), 4.09-4.23 (4H, m, 2 x C*H*HO and 2 x Me_2COC*H*). δ_C (62.9 MHz, $CDCl_3$) 25.17 (2 x CH_3), 26.69 (2 x CH_3), 66.72 (2 x CH_2), 71.19 (2 x CH), 76.24 (2 x CH), 109.36 (2 x C). *m/z* (ES) 263 (MH^+, 12 %), 205 (10), 147 (33). This is a literature compound.[166]

(4*R*)-2,2-Dimethyl-[1,3]dioxolane-4-carbaldehyde **310**

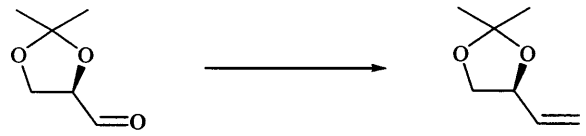


309 **310**

The method for the coversion of **309** to (2*S*)-**310** is based upon a procedure employed by Ladame and co-workers.[153] To a solution of **309** (15.3 g, 58 mmol) in dichloromethane (100 cm^3) was added sodium *meta* periodate (25 g, 116 mmol) and water (6 cm^3). The reaction was stirred for 3 h. To the reaction mixture was added magnesium sulfate (30 g) and stirring was continued for a further 30 min. The solvent was evaporated under reduced pressure keeping the water bath temperature below 5°C, to leave the *aldehyde* (4*R*)-**310** as a colourless oil. The crude product (4*R*)-**310** was taken without purification to the next stage. A small sample was retained for data analysis. $[\alpha]^{22}_D$ +31.3° (c = 4.8 in DCM) (Literature $[\alpha]^{20}_D$ +61.6° (c = 2.3 in DCM).[168] δ_H (250 MHz, $CDCl_3$) 1.42 (3H, s, C*H*$_3$), 1.49 (3H, s, C*H*$_3$), 4.10 (1H, dd, *J* 8.7 and 5.0, C*H*HO), 4.17 (1H, app t, *J* 8.7, CH*H*O), 4.36-4.42 (1H, m, CH_2CH), 9.71 (1H, d, *J* 1.8, *H*C=O). δ_C (62.9 MHz, $CDCl_3$) 25.02 (CH_3), 26.12 (CH_3), 65.44 (CH_2), 79.75 (CH), 111.17 (C), 201.67 (CH).

This is a literature compound.[168]

(4*S*)-2,2-Dimethyl-4-vinyl-[1,3]dioxolane **311**



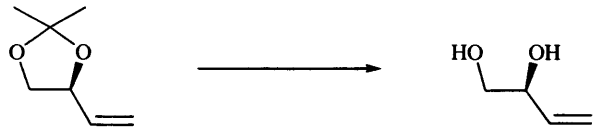
310 **311**

The method for the Wittig reaction employing ^{t}BuOK is based upon a procedure employed by Izquierdo and co-workers.[154] Under an atmosphere of argon a stirred solution of ^{t}BuOK (12.9 g, 115 mmol) in THF (150 cm^3), which has been cooled to 0°C, was added methyltriphenylphosphonium bromide (41 g, 115 mmol) and stirred for 1.5 h. Then a crude solution of the aldehyde **310** (15 g, 115 mmol) in diethyl ether (100 cm^3) was added to the reaction mixture and stirred for a further 3 h. The reaction was quenched by addition of diethyl ether saturated with water (50 cm^3) and water (50 cm^3). The organic phase was separated and washed with brine (100 cm^3) and concentrated (using flash distillation). From

the crude residue the *alkene* (4*S*)-**311** was distilled (containing THF and ^{t}BuOH). The distillate was taken, without further distillation to the next stage. However, a small amount was evaporated under reduced pressure (to remove THF and ^{t}BuOH) for data analysis. $[\alpha]^{22}_D$ +13.5 (c = 2.2 in MeOH) (literature $[\alpha]^{23}_D$ +32° (c = 1.2 in $CHCl_3$).[154] δ_H (250 MHz, $CDCl_3$) 1.40 (3H, s, C*H*$_3$), 1.44 (3H, s, C*H*$_3$), 3.61 (1H, app t, *J* 8.0, C*H*HO), 4.12 (1H, dd, *J* 8.0 and 6.5, CH*H*O), 4.51 (1H, app q, *J* 6.5, C*H*CH=CH$_2$), 5.22 (1H, dd, *J* 10.3 and 1.0, CH=C*H*H), 5.35 (1H, dt, *J* 17.2 and 1.0, CH=CH*H*), 5.84 (1H, ddd, *J* 17.2, 10.3 and 6.5, C*H*=CH$_2$).

This is a literature compound.[154]

(2*S*)-Butene-1,2-diol **305**

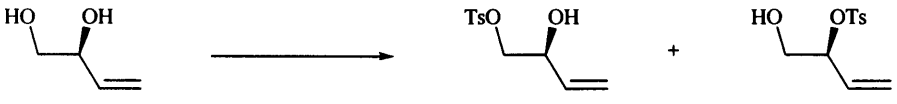


311 **305**

To a crude solution of the alkene (4*S*)-**311** (14 g, 111 mmol) in methanol (40 cm^3) was added *p*-toluenesulfonic acid (0.42 g, 2 mmol) and stirred under reflux for 16 h. The reaction was continuously monitored by gas liquid chromatography (GLC) until completion. The reaction was cooled and methanol was evaporated under reduced pressure to leave a residue, which was purified by flash column chromatography on silica to give the *diol* (2*S*)-**305** (1.75 g, 34 % (over 3 steps, from **309**)) as a colourless oil. $[\alpha]^{22}_D$ –31.3° (c = 5 in EtOAc) (Literature $[\alpha]^{22}_D$ –28.4° (c = 5 in EtOAc).[169] ν_{max} (cm^{-1}, film) 3329 (OH), 2924, 1647, 1426, 1320. δ_H (250 MHz, $CDCl_3$) 3.40 (1H, br d, *J* 11.3, C*H*HOH), 3.59 (1H, br d, *J* 11.3, CH*H*OH), 4.07 (1H, br s, CH$_2$C*H*OH), 4.19 (2H, br s, 2 x O*H*), 5.15 (1H, d, *J* 10.0, CH=C*H*H, *cis*), 5.29 (1H, d, *J* 17.0, CH=CH*H*, *trans*), 5.78 (1H, ddd, *J* 17.0, 10.0 and 5.5, C*H*=CH$_2$). δ_C (62.9 MHz, $CDCl_3$) 66.08 (CH_2), 73.20 (CH), 116.34 (CH_2), 136.68 (CH).

This is a literature compound.[169]

(2*S*)-Toluene-4-sulfonic acid 2-hydroxy-but-3-enyl ester **307** and
(2*S*)-Toluene-4-sulfonic acid 1-hydroxy methyl-allyl ester **306**



305 **306** **307**

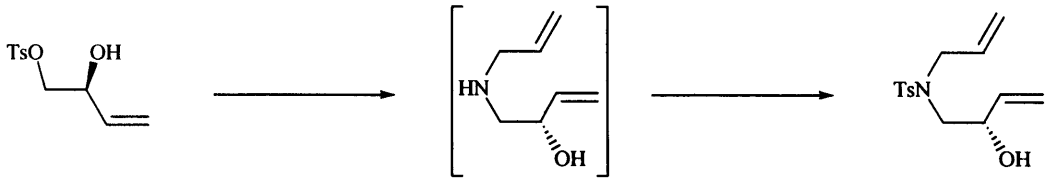
The reaction was carried out as described for (*rac*)-**306** and (*rac*)-**307** thus the diol (2*S*)-**305** (0.8 g, 9 mmol) in chloroform (20 cm^3) was cooled to 0°C and pyridine (1.47 cm^3, 18 mmol) was added. The reaction mixture was stirred for 15 min then *p*-toluenesulfonyl chloride (2.59 g, 13.6 mmol) was added portion-wise to the reaction which was stirred for 16 h. Work up and purification as before gave the *2° tosylate* (2*S*)-**307** (0.196 g, 9 %) and the *1° tosylate* (2*S*)-**306** (1.204 g, 55 %) as colourless oils.

(2*S*)-**307**: $[\alpha]^{22}_D$ –5.3° (c = 2 in MeOH) (Literature $[\alpha]^{22}_D$ +2.5° (c = 2.7 in MeOH). ν_{max} (cm^{-1}, film) 3665-3561 (OH), 3063, 2954, 1597 (C=C), 1364, 1177 (SO_2), 1095. δ_H (250 MHz, $CDCl_3$) 2.47 (3H, s, Ar-C*H*$_3$), 4.14-4.18 (2H, m, OHC*H*$_2$CH), 4.49 (1H, app q, *J* 7.0, C*H*OTs), 5.29 (1H, d, *J* 10.1, CH=C*H*H, *cis*), 5.39 (1H, d, *J* 17.0, CH=CH*H*, *trans*), 5.79 (1H, ddd, *J* 17.0, 10.1 and 7.0, C*H*=CH_2), 7.37 (2H, d, *J* 8.0, Ar-*H* x 2), 7.82 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.68 (CH_3), 57.68 (CH), 71.26 (CH_2), 120.28 (CH_2), 128.02 (2 x CH), 129.03 (2 x CH), 133.32 (C and CH), 145.21 (C).

(2*S*)-**306**: $[\alpha]^{22}_D$ –8.6° (c = 1.9 in MeOH). ν_{max} (cm^{-1}, film) 3349 (OH), 3071, 2923, 1649, 1564, 1356, 1174 (SO_2). δ_H (250 MHz, $CDCl_3$) 2.41 (3H, s, Ar-C*H*$_3$), 2.83 (1H, s, CHO*H*), 3.88 (1H, dd, *J* 10.3 and 7.0, C*H*HOTs), 4.02 (1H, dd, *J* 10.3 and 3.7, CH*H*OTs), 4.31-4.39 (1H, m, C*H*OH), 5.18 (1H, dt, *J* 10.3 and 1.4, CH=C*H*H, *cis*), 5.32 (1H, dt, *J* 17.2 and 1.4, CH=CH*H*, *trans*), 5.72 (1H, ddd, *J* 17.2, 10.3 and 5.5, C*H*=CH_2), 7.32 (2H, *J* 8.0, Ar-*H* x 2), 7.76 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.42 (CH_3), 70.07 (CH), 72.82 (CH_2), 117.69 (CH_2), 127.93 (2 x CH), 129.78 (2 x CH), 132.38 (C), 134.69 (CH), 144.94 (C). *m/z* (FAB) 243.0691 (MH^+. $C_{11}H_{15}O_4S$ requires 243.0691), 243 (14 %), 225 (17), 173 (8), 154 (100), 136 (74).

This is a literature compound.[170]

(2*S*)-*N*-Allyl-*N*-(2-hydroxy-but-3-enyl)-4-methylbenzenesulfonamide **286**



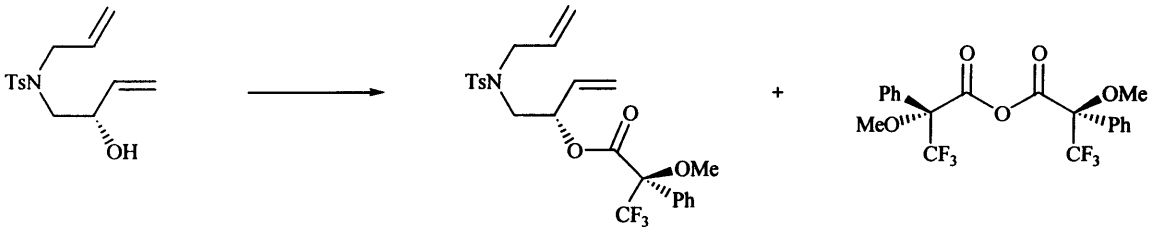
306 **284** **286**

The reaction was carried out as described for (*rac*)-**286** thus the tosylate (2*S*)-**306** (0.5 g, 2 mol) in allylamine (1.62 cm^3, 20 mmol) in the absence of solvent in a sealed tube was heated

under reflux for 18 h. Further purification was not required and the crude amine (2*S*)-**284** was taken through to the next stage.

The crude solution of the amine (2*S*)-**284** in dichloromethane (5 cm^3) was added NEt_3 (1.2 cm^3, 8.65 mmol) and DMAP (0.05 g, 0.39 mmol). The reaction mixture was cooled to 0°C and *p*-toluenesulfonyl chloride (0.82 g, 4.3 mmol) was added portion-wise and stirred for 18 h. Work up and purification as before gave the *tosylate* (2*S*)-**286** (0.34 g, 59 % (over 2 steps, from (2*S*)-**306**)) as a colourless oil. $[\alpha]^{22}_D$ +1.7° (c = 1.5 in EtOAc). ν_{max} (cm^{-1}, film) 3512-3284 (OH), 3084, 2924, 1598, 1420, 1325, 1091. δ_H (250 MHz, $CDCl_3$) 2.41 (3H, s, Ar-C*H*$_3$), 3.10 (1H, dd, *J* 15.0 and 4.6, NC*H*HCHOH), 3.20 (1H, dd, *J* 15.0 and 7.8, NCH*H*CHOH), 3.84 and 3.94 (2 x 1H, dd (overlapping), *J* 15.6 and 6.0, NC*H*$_2$CH=CH), 4.34-4.35 (1H, br m, C*H*OH), 5.12-5.21 (3H, m, CH=C*H*$_2$ and CH=C*H*H), 5.33 (1H, dt, *J* 17.2 and 1.5, one of CH=CH*H trans*), 5.63 (1H, ddd (overlapping), *J* 16.0, 10.0 and 6.0, one of C*H*=CH_2), 5.80 (1H, ddd, *J* 17.2, 10.0 and 6.0, CHOHC*H*=CH_2), 7.31 (2H, d, *J* 8.0, Ar-*H* x 2), 7.71 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9 MHz, $CDCl_3$) 21.22 (CH_3), 52.03 (CH_2), 52.82 (CH_2), 70.86 (CH), 116.16 (CH_2), 119.18 (CH_2), 127.01 (2 x CH), 129.55 (2 x CH), 132.57 (CH), 136.14 (C), 137.38 (CH), 143.38 (C). *m/z* (FAB) 282.1163 (MH^+. $C_{14}H_{20}NO_3S$ requires 282.1164), 282 (64 %), 264 (54), 224 (100), 212 (27), 155 (85), 139 (24).

3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid-1-{[allyl-(toluene-4-sulfonyl)-amino]-methyl}allyl ester **315**

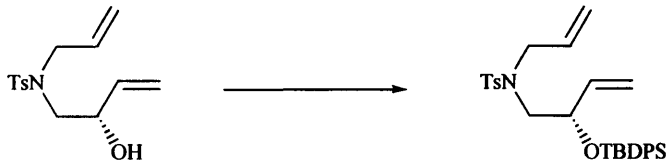


286 **315** **314**

To a solution of the alcohol (2*S*)-**286** (0.01 g, 0.036 mmol) in DCM (1 cm^3) was added DCC (0.009 g, 0.043 mmol), DMAP (0.0004 g, 0.004 mmol) and Moshers Acid **312** (0.01 g, 0.043 mmol) and the resulting mixture was stirred at room temperature. After 2 h stirring at RT the reaction was complete by TLC and was filtered through celite washing with ethyl acetate (3 x 5 cm^3), evaporation under reduced pressure gave a residue of the Moshers ester **315**. Further purification was not carried out and the crude material was analysed by ^{19}F NMR. δ_F (282.4 MHz, $CDCl_3$) –71.52 (**315**), -70.44 (signal for anhydride **314**).

(*rac*)-**286** was also treated with Moshers acid **312** and gave a residue of the Moshers ester **313**, anhydride **314** and acid **312** and analysed by ^{19}F NMR. δ_F (282.4 MHz, $CDCl_3$) –71.53 and -71.24 (1 : 1 ratio), -70.44 and -68.80 respectively.

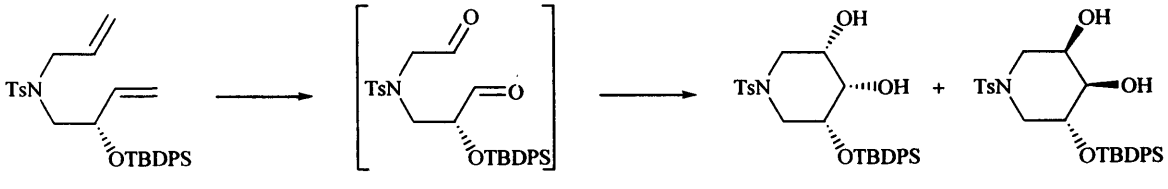
(2*S*)-*N*-Allyl-*N*-[2-(*tert*-butyldiphenylsilanyloxy)-but-3-enyl]-4-methylbenzenesulfonamide **288**



286 **288**

The reaction was carried out as described for (*rac*)-**288** thus the alcohol (2*S*)-**286** (0.34 g, 1.2 mmol) in dichloromethane (10 cm^3) was added triethylamine (0.2 cm^3, 1.45 mmol) and DMAP (0.015 g, 0.12 mmol). The reaction mixture was cooled to 0°C and TBDPSCl (0.38 cm^3, 1.45 mmol) was added dropwise and continuously stirred for 18 h while warming to room temperature. Work up and purification as before gave the *silyl-protected diene* (2*S*)-**288** (0.34 g, 55 %) as a colourless oil. ν_{max} (cm^{-1}, film) 3053, 2932, 1599, 1428, 1344, 1265, 1157 (SO_2), 1112. $[\alpha]^{22}_D$ –35.5° (c = 2.1 in MeOH). δ_H (300 MHz, $CDCl_3$) 1.06 (9H, s, $SiC(CH_3)_3$), 2.39 (3H, s, Ar-CH_3), 3.10 (2H, d, *J* 7.0, NCH_2CHOSi), 3.59 (1H, dd, *J* 15.6 and 6.5, $NCHHCH=CH_2$), 3.76 (1H, dd, *J* 15.6 and 6.5, $NCHHCH=CH_2$), 4.39 (1H, app q, *J* 7.0, NCH_2CHOSi), 4.86-5.03 (4H, m, 2 x $CH=CH_2$), 5.39 (1H, dd app t (overlapping), *J* 17.0, 10.0 and 6.5, $CH_2CH=CH_2$), 5.80 (1H, ddd, *J* 17.0, 10.0 and 7.0, $CHCH=CH_2$), 7.20 (2H, d, *J* 8.0, Ar-*H* x 2), 7.32-7.44 (6H, m, Ar-*H* x 6), 7.50 (2H, d, *J* 8.0, Ar-*H* x 2), 7.62-7.69 (4H, m, Ar-*H* x 4). δ_C (75.5 MHz, $CDCl_3$) 18.97 (C), 21.44 (CH_3), 26.96 (3 x CH_3), 51.99 (CH_2), 52.48 (CH_2), 73.05 (CH), 116.75 (CH_2), 118.93 (CH_2), 127.19 (2 x CH), 127.41 (2 x CH), 127.56 (2 x CH), 129.47 (2 x CH), 129.60 (CH), 129.68 (CH), 132.69 (CH), 133.60 (C), 133.80 (C), 135.91 (2 x CH), 135.96 (2 x CH), 137.01 (C), 138.20 (CH), 143.00 (C). *m/z* (ES) 520 (83 %), 442 (49), 380 (5), 264 (12). *m/z* (FAB) 520.2341 (MH^+. $C_{30}H_{38}NO_3SSi$ requires 520.2342).

(3*S*,4*S*,5*R*)-5-(*tert*-Butyldiphenylsilanyloxy)-1-(toluene-4-sulfonyl)-piperidine-3,4-diol **295**
(3*R*,4*R*,5*R*)-5-(*tert*-Butyldiphenylsilanyloxy)-1-(toluene-4-sulfonyl)-piperidine-3,4-diol **296**



288 **294** **295** **296**

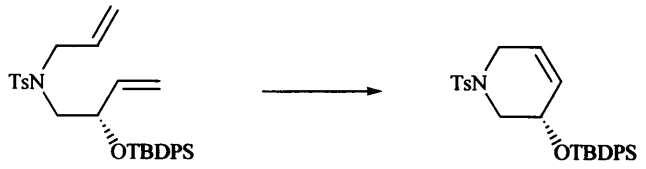
The diene (2*S*)-**288** (0.264 g, 0.51 mmol) in dry dichloromethane (10 cm^3) was treated with ozone then Me_2S (0.15 cm^3, 2 mmol) as for the preparation of **178**. After evaporation the product dialdehyde was not isolated due to decomposition on silica but was taken through to the SmI_2-mediated pinacol coupling reaction.

To a -78°C solution of SmI_2 (0.1 M THF, Sm, 0.455 g, 3 mmol, CH_2I_2, 0.203 cm^3, 2.5 mmol, in degassed THF 26 cm^3) was added *via* canula a crude solution of the dialdehyde (2*S*)-**294** (0.27 g, 0.52 mmol) and ^tBuOH (0.284 cm^3, 3 mmol) in THF (5 cm^3). Work up and purification as before gave the *diol* (3*S*,4*S*,5*R*)-**295** (0.016 g, 7 % (over 2 steps, from (2*S*)-**288**)) and the *diol* (3*R*,4*R*,5*R*)-**296** (0.06 g, 22 % (over 2 steps, from (2*S*)-**288**)) as colourless oils.

(3*S*,4*S*,5*R*)-**295**: ν_{max} (cm^{-1}, film) 3499 (OH), 3072, 2931, 1744, 1598, 1428, 1346, 1165 (SO_2), 1111. δ_H (300 MHz, $CDCl_3$) 1.11 (9H, s, $C(CH_3)_3$), 2.43 (3H, s, Ar-CH_3), 2.77-2.87 (2H, 2 x dd (overlapping), NC*H*H and NCH*H*), 3.10 (1H, dd, *J* 11.5 and 4.4, one of NCH*H*), 3.29 (1H, dd, *J* 11.5 and 4.4, one of NCH*H*), 3.57-3.68 (1H, m, NCH_2CH), 3.68 (1H, br app t, *J* 3.0, $NCH_2CHOSiCHOH$), 3.86 (1H, ddd, *J* 8.0, 4.4, 3.0, one of NCH_2CH), 7.27 (2H, d, *J* 8.0, Ar-*H* x 2), 7.38-7.50 (6H, m, Ar-*H* x 6), 7.51 (2H, d, *J* 8.0, Ar-*H* x 2), 7.65-7.72 (4H, m, Ar-*H* x 4). δ_C (75.5 MHz, $CDCl_3$) 19.20 (C), 21.52 (CH_3), 26.97 (3 x CH_3), 46.27 (CH_2), 46.94 (CH_2), 67.71 (CH), 69.65 (CH), 70.39 (CH), 127.44 (2 x CH), 128.03 (4 x CH), 129.76 (2 x CH), 130.32 (2 x CH), 130.37 (2 x CH), 132.43 (2 x C), 133.77 (C), 135.66 (2 x CH), 135.82 (2 x CH), 143.68 (C). *m/z* (FAB) 526.2084 (MH^+. $C_{28}H_{36}NO_5SSi$ requires 526.2084), 526 (63), 468 (100), 448 (88), 390 (22), 370 (22).

(3*R*,4*R*,5*R*)-**296**: $[\alpha]^{22}_D$ –19.3° (c = 1 in EtOAc). ν_{max} (cm^{-1}, film) 3474 (OH), 3072, 2931, 1599, 1344, 1162 (SO_2), 1087. δ_H (400 MHz, $CDCl_3$) 1.10 (9H, s, $C(CH_3)_3$), 2.43 (3H, s, Ar-CH_3), 2.71 (1H, dd, *J* 11.5 and 6.5, one of NC*H*H), 2.97 (1H, dd, *J* 11.5 and 3.2, one of NC*H*H), 3.01 (1H, dd, *J* 11.5 and 3.2, one of NCH*H*), 3.06 (1H, dd, *J* 11.5 and 6.5, one of NCH*H*), 3.48 (1H, dd, *J* 6.5 and 3.2, $NCH_2CHOHCHOH$), 3.81 (1H, ddd, *J* 6.5, 6.5 and 3.5, one of NCH_2CH), 4.02 (1H, ddd, *J* 6.5, 3.2 and 3.2, one of NCH_2CH), 7.17 (2H, d, *J* 8.0, Ar-*H* x 2), 7.29-7.40 (6H, m, Ar-*H* x 6), 7.45 (2H, d, *J* 8.0, Ar-*H* x 2), 7.57-7.62 (4H, m, Ar-*H* x 4). δ_C (75.5 MHz, $CDCl_3$) 19.18 (C), 21.48 (CH_3), 26.87 (3 x CH_3), 47.57 (CH_2), 48.09 (CH_2), 66.55 (CH), 69.59 (CH), 72.75 (CH), 127.49 (2 x CH), 127.80 (4 x CH), 129.98 (2 x CH), 130.02 (2 x CH), 133.06 (2 x C), 133.52 (C), 135.66 (2 x CH), 135.85 (2 x CH), 143.52 (C). *m/z* (ES) 526 (65), 448 (100), 400 (59), 370 (22), 279 (19). *m/z* (FAB) 526.2084 (MH^+. $C_{28}H_{36}NO_5SSi$ requires 526.2084).

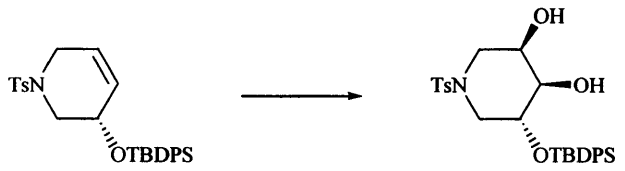
(3*S*)-3-(*tert*-Butyldiphenylsilanyloxy)-1-toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridine **301**



288 **301**

The reaction was carried out as described for **158** thus the diene (2*S*)-**288** (0.076g, 0.15mmol) in dichloromethane (10 cm^3) was added to $RuCl_2(=CHPh)(PCy_3)_2$ (5 mol%, 0.006g, 0.007 mmol) *via* canula, under an atmosphere of nitrogen and the mixture was stirred for 3 h under reflux. The reaction was worked up as before and purified by flash column chromatography on silica using dichloromethane:petrol (50:50 to 80:20) to elute the *cycloalkene* (3*S*)-**301** (0.071g, 99 %) as a colourless oil. $[\alpha]^{22}_D$ –19.6° (c = 1.9 in EtOAc). ν_{max} (cm^{-1}, film) 3071, 2930, 1598 (C=C), 1428, 1349, 1165 (SO_2), 1103. δ_H (300 MHz, $CDCl_3$) 0.97 (9H, s, $C(CH_3)_3$), 2.33 (3H, s, Ar-CH_3), 2.60 (1H, dd, *J* 11.7 and 7.5, NC*H*HCHOSi), 3.24 (1H, d, *J* 17.2, NC*H*HCH=CH), 3.46 (1H, dd, *J* 11.7 and 5.3, NCH*H*CHOSi), 3.63 (1H, d, *J* 17.2, NCH*H*CH=CH), 4.19-4.25 (1H, m, NCH_2CHOSi), 5.52 (2H, s, $NCH_2CH{=}CH$), 7.17 (2H, d, *J* 8.0, Ar-*H* x 2), 7.27-7.40 (6H, m, Ar-*H* x 6), 7.47 (2H, d, *J* 8.0, Ar-*H* x 2), 7.55-7.60 (4H, m, Ar-*H* x 4). δ_C (75.5 MHz, $CDCl_3$) 19.09 (C), 21.49 (CH_3), 26.83 (3 x CH_3), 44.33 (CH_2), 48.98 (CH_2), 65.16 (CH), 123.75 (CH), 127.45 (2 x CH), 127.66 (2 x CH), 127.76 (2 x CH), 129.59 (2 x CH), 129.81 (2 x CH), 129.91 (CH), 133.49 (2 x C), 133.80 (C), 135.69 (4 x CH), 143.44 (C). *m/z* 492 (18 %), 414 (76), 236 (100), 155 (13). *m/z* (FAB) 492.2029 (MH^+. $C_{28}H_{34}NO_3SSi$ requires 492.2029).

(3*R*,4*R*,5*R*)-5-(*tert*-Butyldiphenylsilanyloxy)-1-(toluene-4-sulfonyl)-piperidine-3,4-diol **296**

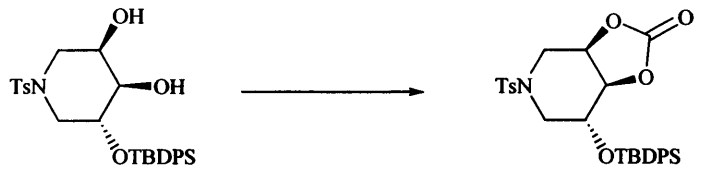


301 **296**

The reaction was carried out as described for **274** thus the cyclocalkene (3*S*)-**301** (0.068 g, 0.14 mmol) in acetone (2 cm^3) and osmium tetroxide, OsO_4 (0.056 cm^3, 2.5 wt% in ^tBuOH, 0.0055 mmol) was prepared at room temperature. This was added *via* canula to a solution of NMO (0.024 g, 0.21 mmol) in H_2O (1 cm^3) and the reaction mixture was stirred for 16 h at room temperature. The reaction was worked up as before and purified by flash column

chromatography on silica using dichloromethane:diethyl ether (100:0 to 80:20) to afford the *cis diol* (3*R*, 4*R*, 5*R*)-**296** (0.023 g, 32 %) as a colourless oil.
Analytical data as reported above.

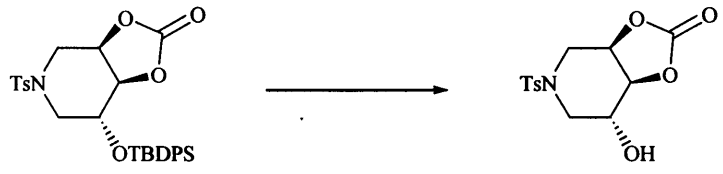
(1*R*,3*R*,7*R*)-7-(*tert*-Butyldiphenylsilanyloxy)-5-(toluene-4-sulfonyl)-hexahydro-[1,3] dioxolo[4,5-c]pyridin-2-one **317**



296 **317**

To a solution of the piperidine (3*R*, 4*R*, 5*R*)-**296** (0.016 g, 0.03 mmol) in dichloromethane (2 cm^3) was added NEt_3 (0.005 cm^3, 0.03 mmol) and stirred for 15 min. Then triphosgene (0.003 g, 0.009 mmol) was added to the reaction mixture and stirred for a further 2 h. Then addition of saturated aqueous ammonium chloride (3 cm^3) quenched the reaction and extracted with ethyl acetate (3 x 5 cm^3). The combined extracts were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a yellow oil, which was purified by flash column chromatography on silica using diethyl ether:petrol (50:50 to 80:20) to give the *carbonate* (1*R*,3*R*,7*R*)-**317** (0.015 g, 91 %) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 1.01 (9H, s, $C(CH_3)_3$), 2.42 (3H, s, Ar-CH_3), 3.19 (1H, dd, *J* 12.9 and 3.5, NC*H*HCHOSi), 3.26 (1H, dd, *J* 12.9 and 3.5, NCH*H*CHOSi) 3.52 (1H, dd, *J* 14.1 and 3.0, NC*H*HCHOC=O), 3.88 (1H, dd, *J* 14.1 and 3.0, NCH*H*CHOC=O), 4.10 (1H, app q, *J* 3.5, NCH_2CHOSi), 4.45 (1H, dd, *J* 7.8 and 3.5, $NCH_2CHOCHO$), 4.85 (1H, dt, *J* 7.8 and 3.0, $NCH_2CHOC{=}O$), 7.29 (2H, d, *J* 8.0, Ar-*H* x 2), 7.38-7.52 (6H, m, Ar-*H* x 6), 7.55-7.62 (6H, m, Ar-*H* x 6). δ_C (75.5 MHz, $CDCl_3$) 18.94 (C), 21.52 (CH_3), 26.68 (3 x CH_3), 43.49 (CH_2), 45.73 (CH_2), 66.41 (CH), 73.26 (CH), 73.83 (CH), 127.38 (2 x CH), 128.10 (2 x CH), 128.14 (2 x CH), 129.85 (2 x CH), 130.52 (2 x CH), 131.79 (C), 131.90 (C), 133 .90 (C), 135.47 (2 x CH), 135.63 (2 x CH), 144.06 (C), 152.84 (C).

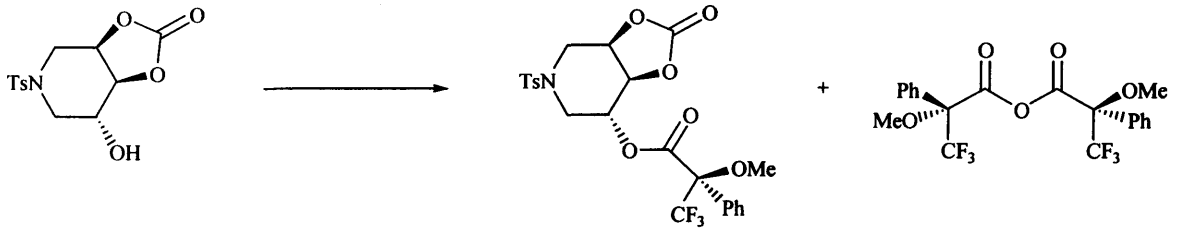
(1*R*,3*R*,7*R*)-7-Hydroxy-5-(toluene-4-sulfonyl)-hexahydro-[1,3]dioxolo[4,5-c]pyridin-2-one **318**



317 **318**

The reaction was carried out as described for **297** thus the carbonate (1*S*,3*R*,7*R*)-**317** (0.015 g, 0.027 mmol) in tetrahydrofuran (1 cm^3) was added TBAF (0.009 cm^3, 0.03 mmol) and stirred for 1 h. The reaction was worked up as before and purified by flash column chromatography on silica using ethyl acetate:petrol (50:50 to 80:20) to give the *alcohol* (1*S*, 3*R*, 7*R*)-**318** (0.008 g, 94 %) as a colourless oil. $[\alpha]^{22}_D$ –8.6° (c = 0.5 in EtOAc). δ_H (300 MHz, $CDCl_3$) 2.46 (3H, s, Ar-C*H*$_3$), 2.64 (1H, br s, NCH$_2$CHO*H*), 3.29 (1H, dd, *J* 13.0 and 4.8, NC*H*HCHOH), 3.36 (1H, dd, *J* 13.0 and 3.6, NCH*H*CHOH), 3.49 (1H, dd, *J* 13.8 and 4.5, NC*H*HCHOC=O), 3.58 (1H, dd, *J* 13.8 and 4.5, NCH*H*CHOC=O), 4.17-4.22 (1H, br m, NCH$_2$C*H*OH), 4.61 (1H, dd, *J* 7.2 and 4.5, NCH$_2$CHOC*H*O), 4.91 (1H, dt, *J* 7.2 and 4.5, NCH$_2$C*H*OC=O), 7.37 (2H, d, *J* 8.0, Ar-*H* x 2), 7.69 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (75.5 MHz, $CDCl_3$) 21.59 (CH_3), 44.53 (CH_2), 46.64 (CH_2), 65.41 (CH), 72.60 (CH), 75.48 (CH), 127.47 (2 x CH), 130.11 (2 x CH), 133.90 (C), 144.61 (C), 153.50 (C).

(1*S*,3*R*,3'*R*,7*R*)-3',3',3'-Trifluoro-2-methoxy-2-phenyl-propionic acid 2-oxo-5-(toluene-4-sulfonyl)-hexahydro[1,3]dioxolo[4,5-*c*]pyridine-7-yl ester **319**



318 **319** **314**

To a solution of the alcohol (1*S*, 3*R*, 7*R*)-**318** (0.008 g, 0.026 mmol) in DCM (1 cm^3) was added DCC (0.0024 g, 0.03 mmol), DMAP (0.00003 g, 0.00026 mmol) and Moshers Acid **312** (0.0072 g, 0.03 mmol) and the resulting mixture was stirred at RT. After 2 h stirring at room temperature the reaction was complete by TLC and was filtered through celite washing ethyl acetate (3 x 5 cm^3). Evaporation under reduced pressure gave a residue of the *ester* **319**. Further purification was not carried out and the crude material was analysed by ^{19}F NMR. δ_F (235.4 MHz, 250 MHz, $CDCl_3$) –71.46 (**318**), -70.39 (signal for anhydride **314**).

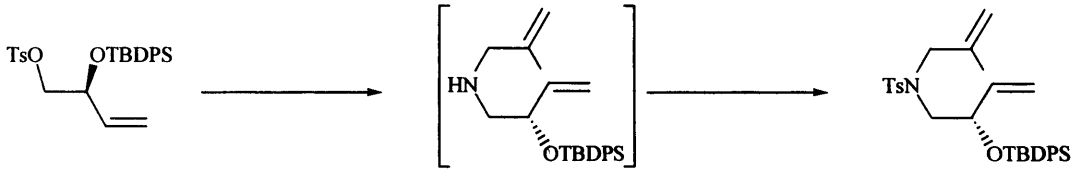
The same sequence of reactions was carried out with racemic material (*rac*)-**296** → (*rac*)-**314** → (*rac*)-**318** to Moshers ester of alcohol (*rac*)-**318** which was analysed by ^{19}F NMR. δ_F (282.4 MHz, 300 MHz, $CDCl_3$) –71.57 and -71.50 (**319**, 1:1 ratio), -70.39 (signal for anhydride **314**).

(2*S*)-Toluene-4-sulfonic acid 2-(*tert*-butyldiphenylsilanyloxy)-but-3-enyl ester **321**

306 **321**

To a solution of the alcohol (2*S*)-**306** (0.5 g, 2.06 mmol) in dichloromethane (5 cm^3) was added DIPEA (0.431 cm^3, 2.47 mmol) and the reaction was stirred for 15 min. Then TBDPSCl (0.59 cm^3, 2.27 mmol) was added dropwise to the reaction and stirred for 16 h. The reaction was quenched with water (10 cm^3) and then extracted with dichloromethane (3 x 20 cm^3). The combined extracts were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a brown oil, which was purified by flash column chromatography on silica using toluene:petrol (70:30 to 90:10) to give the *tosylate* (2*S*)-**321** (0.794 g, 80 %) as a colourless oil. $[\alpha]^{22}_D$ –54.2 (c = 3 in EtOAc). ν_{max} (cm^{-1}, film) 3073, 2933, 1598, 1429, 1367, 1175 (SO_2), 1103, 1092. δ_H (300 MHz, $CDCl_3$) 1.03 (9H, s, C(C*H*$_3$)$_3$), 2.41 (3H, s, Ar-C*H*$_3$), 3.83 (1H, dd, *J* 9.6 and 5.1, OC*H*H), 3.90 (1H, dd, *J* 9.6 and 6.0, OCH*H*), 4.28 (1H, app q, *J* 6.0, CH_2C*H*OSi), 5.03-5.10 (2H, m, CH=C*H*$_2$), 5.70 (1H, ddd, *J* 17.0, 10.5 and 6.0, C*H*=CH_2), 7.25 (2H, d, *J* 8.0, Ar-*H* x 2), 7.28-7.44 (6H, m, Ar-*H* x 6), 7.55-7.65 (6H, m, Ar-*H* x 6). δ_C (75.5 MHz, $CDCl_3$) 19.21 (C), 21.54 (CH_3), 26.81 (3 x CH_3), 71.93 (CH), 72.39 (CH_2), 117.59 (CH_2), 127.43 (2 x CH), 127.52 (2 x CH), 127.86 (2 x CH), 129.65 (2 x CH), 129.72 (2 x CH), 132.81 (C), 133.12 (C), 133.21 (C), 135.82 (4 x CH), 135.84 (CH), 144.55 (C). *m/z* (ES) 498 (58), 374 (100), 333 (31), 155 (34). *m/z* (FAB) 481.1869 (MH^+. $C_{27}H_{33}O_4SSi$ requires 481.1869).

(2*S*)-*N*-[2-(*tert*-Butyldiphenylsilanyloxy)-but-3-enyl]-4-methyl-*N*-(2-methylallyl)-benzenesulfonamide **323**

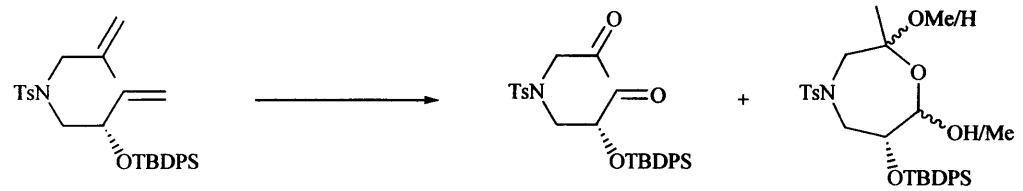


321 **322** **323**

The reaction was carried out as for (2*S*)-**286** thus the tosylate (2*S*)-**321** (0.23 g, 0.48 mmol) and 2-methylallylamine **320** (0.13 cm^3, 1.44 mmol) in the absence of solvent and the mixture heated under reflux for 16 h. The reaction was worked up as before and with further purification not required the crude amine (2*S*)-**322** was taken through to the next stage.

The unpurified amine (2*S*)-**322** in dichloromethane (5 cm^3) was added NEt_3 (0.122 cm^3, 0.87 mmol) and DMAP (0.007 g, 0.058 mmol). The reaction mixture was cooled to 0°C and *p*-toluenesulfonyl chloride (0.133 g, 0.7 mmol) was added portion-wise and stirred for 18h while warming to room temperature. The reaction was worked up as before and purified by flash column chromatography on silica using petrol:diethyl ether (70:30 to 50:50) to give the *tosylate* (2*S*)-**323** (0.243 g, 95 % (over 2 steps, from (2*S*)-**321**)) as a colourless oil. $[\alpha]^{22}_D$ –27.5° (c = 3.2 in EtOAc). ν_{max} (cm^{-1}, film) 3072, 2931, 1590 (C=C), 1447, 1381, 1341, 1159 (SO_2). δ_H (300 MHz, $CDCl_3$) 1.09 (9H, s, $C(CH_3)_3$), 1.56 (3H, s, $NCH_2C(CH_3)=CH_2$), 2.42 (3H, s, Ar-CH_3), 3.11-3.26 (2H, m (2nd order), NCH_2CH), 3.53 (1H, d, *J* 15.0, $NCHHC(CH_3)=CH_2$), 3.73 (1H, d, *J* 15.0, $NCHHC(CH_3)=CH_2$), 4.39 (1H, app q, *J* 6.9, NCH_2CHOSi), 4.61 (1H, br s, $NCH_2C(CH_3)=CHH$), 4.77 (1H, br s, $NCH_2C(CH_3)=CHH$), 4.90 (1H, d, *J* 17.1, CH=CH*H trans*), 4.99 (1H, d, *J* 10.0, CH=CH*H cis*), 5.80 (1H, ddd, *J* 17.1, 10.0 and 6.9, $NCH_2CHOSiCH=CH_2$), 7.22 (2H, d, *J* 8.0, Ar-*H* x 2), 7.36-7.48 (6H, m, Ar-*H* x 6), 7.53 (2H, d, *J* 8.0, Ar-*H* x 2), 7.65-7.71 (4H, m, Ar-*H* x 4). δ_C (75.5 MHz, $CDCl_3$) 19.20 (C), 19.93 (CH_3), 21.40 (CH_3), 26.92 (3 x CH_3), 55.68 (CH_2), 53.09 (CH_2), 72.77 (CH), 114.67 (CH_2), 116.91 (CH_2), 127.17 (2 x CH), 127.37 (2 x CH), 127.51 (2 x CH), 129.36 (2 x CH), 129.57 (CH), 129.65 (CH), 133.60 (C), 133.78 (C), 135.87 (2 x CH), 135.91 (2 x CH), 136.99 (C), 138.29 (CH), 140.09 (C), 142.89 (C). *m/z* (ES) 534 (17 %), 456 (61), 380 (100), 302 (86) 278 (72), 224 (5). *m/z* (FAB) 534.2499 (MH^+. $C_{31}H_{40}NO_3SSi$ requires 534.2498).

(2*S*)-*N*-(2-*tert*-Butyldiphenylsilanyloxy)-3-oxopropyl]-4-methyl-*N*-(2-oxopropyl)-benzenesulfonamide **324**



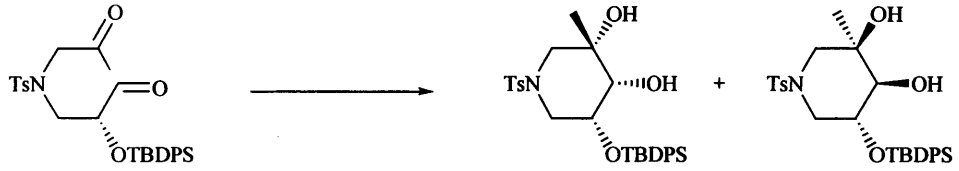
323 **324** **325**

The diene (2*S*)-**323** (0.13 g, 0.24 mmol) in dry methanol (10 cm^3) was treated with ozone then Me_2S (0.036 cm^3, 0.48 mmol) as for the preparation of **178**. After evaporation, the crude material was purified by flash column chromatography on silica using diethyl ether:petrol (40:60 to 60:40) to elute the *dicarbonyl* (2*S*)-**324** (0.103 g, 80 %) as a colourless oil. $[\alpha]^{22}_D$ – 29.8° (c = 4.5 in DCM). δ_H (300 MHz, $CDCl_3$) 1.10 (9H, s, $C(CH_3)_3$), 2.00 (3H, s, NCH_2COCH_3), 2.40 (3H, s, Ar-CH_3), 3.43 (1H, dd, *J* 15.2 and 5.5, $NCHHCHOSi$), 3.52 (1H, dd *J* 15.2 and 5.5, $NCHHCHOSi$), 4.12 (2H, s, NCH_2COCH_3), 4.27 (1H, d app t, *J* 0.9 and 5.5, NCH_2CHOSi), 7.24 (2H, d, *J* 8.0, Ar-*H* x 2), 7.34-7.46 (6H, m, Ar-*H* x 6), 7.57 (2H, d, *J*

8.0, Ar-*H* x 2), 7.59-7.62 (4H, m, Ar-*H* x 4), 9.48 (1H, d, *J* 0.9, C*H*=O). δ_C (75.5 MHz, $CDCl_3$) 19.17 (C), 21.50 (CH_3), 26.76 (CH_3), 26.84 (CH_3), 49.68 (CH_2), 57.87 (CH_2), 77.16 (CH), 127.46 (2 x CH), 127.91 (2 x CH), 129.53 (2 x CH), 130.20 (CH), 130.26 (CH), 132.10 (C), 132.34 (C), 135.65 (2 x CH), 135.77 (2 x CH and C), 143.71 (C), 200.17 (CH), 202.77 (C). *m/z* (ES) 538 (61 %), 460 (16), 325 (17), 240 (94), 233 (60), 176 (30), 155 (18), 90 (100). *m/z* (FAB) 538.2085 (MH^+. $C_{29}H_{36}NO_5SSi$ requires 538.2084).

Acetal **325** was also isolated (0.012 g, 9 %). δ_H (300 MHz, $CDCl_3$) 1.09 (9H, s, C(C*H*$_3$)$_3$), 1.30 (3H, s, NCH$_2$C(C*H*$_3$)), 2.44 (3H, s, Ar-C*H*$_3$), 2.60 (1H, dd, *J* 14.5 and 9.5, NC*H*HCHOSi), 2.99 (1H, br d, *J* 14.5, NC*H*HC(CH_3)), 3.30 (3H, s, C(CH_3)(OC*H*$_3$), 3.76 (1H, br d, *J* 14.5, NCH*H*C(CH_3)), 3.81 (1H, br d, *J* 14.5, NC*H*HCHOSi), 4.23 (1H, ddd, *J* 10.0, 6.4 and 1.4, NCH$_2$C*H*OSi), 4.77 (1H, br d, 6.7, C*H*OH), 7.26 (2H, d, *J* 8.0, Ar-*H* x 2), 7.39-7.63 (6H, m, Ar-*H* x 6), 7.68-7.80 (6H, m, Ar-*H* x 6). δ_C (75.5 MHz, $CDCl_3$) 17.09 (C), 19.29 (CH_3), 21.52 (CH_3), 26.97 (CH_3), 49.21 (CH_3), 54.78 (CH_2), 55.42 (CH_2), 77.21 (CH), 102.72 (CH), 104.77 (C), 127.49 (2 x CH), 127.65 (2 x CH), 127.70 (2 x CH), 129.63 (CH), 129.76 (2 x CH), 129.87 (CH), 132.74 (C), 133.58 (C), 134.75 (C), 135.69 (CH), 135.99 (CH), 136.12 (2 x CH), 143.54 (C).

(3*R*,4*S*,5*S*)-5-(*tert*-Butyldiphenylsilanyloxy)-3-methyl-(toluene-4-sulfonyl)-piperidine-3,4-diol **326** and
(3*S*,4*R*,5*S*)-5-(*tert*-Butyldiphenylsilanyloxy)-3-methyl-(toluene-4-sulfonyl)-piperidine-3,4-diol **327**



324 **326** **327**

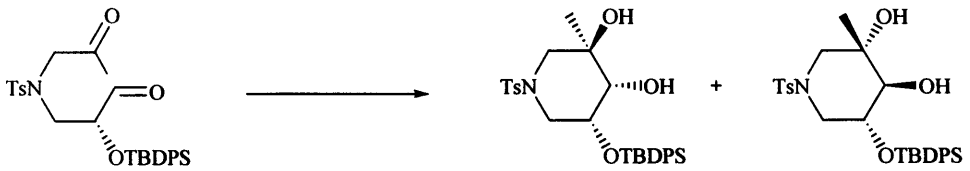
To a -78°C solution of SmI_2 (0.1 M THF, Sm, 0.086 g, 0.57 mmol, CH_2I_2, 0.04 cm^3, 0.48 mmol reacted in degassed THF (8cm^3)) was added *via* canula a solution of the dicarbonyl **324** (0.103 g, 0.19 mmol) and ^{t}BuOH (0.054 cm^3, 0.57 mmol) in THF (5 cm^3, 4 cycles freeze-pump-thaw). The reaction was stirred for 16 h whilst warming to room temperature and worked up as before. The crude material was purified by flash column chromatography on silica using dichloromethane:diethyl ether (100:0 to 90:10) to give the *diol* **326** (0.017 g, 17 %) as a colourless oil and the *diol* **327** (0.049 g, 48 %) as a white solid.

(3*R*,4*S*,5*S*)-**326**: $[\alpha]^{22}_D$ –26.4° (c = 1.2 in EtOAc). δ_H (300 MHz, CD_3OD) 1.02 (3H, s, NCH$_2$C(C*H*$_3$)OH), 1.13 (9H, s, C(C*H*$_3$)$_3$), 2.46 (3H, s, Ar-C*H*$_3$), 2.76 (2H, overlapping d and

dd, *J* 11.0 and 11.0 and 4.2, NC*H*HC(CH_3) and NC*H*HCH), 2.92 (1H, br d, *J* 11.0, NCH*H*C(CH_3)OH), 3.06 (1H, dd, *J* 11.0 and 3.0, NCH*H*CHOSi), 3.33-3.35 (1H, m, C*H*OH masked by solvent signal), 3.92 (1H, ddd, *J* 8.7, 4.2 and 3.0, NCH_2CHOSi), 7.39-7.55 (8H, m, Ar-*H* x 8), 7.72-7.78 (6H, m, Ar-*H* x 6). δ_C (75.5 MHz, CD_3OD) 19.99 (C), 21.45 (CH_3), 23.12 (CH_3), 27.50 (3 x CH_3), 47.81 (CH_2), 52.71 (CH_2), 70.98 (CH), 71.67 (C), 75.38 (CH), 128.54 (2 x CH), 128.87 (2 x CH), 128.96 (2 x CH), 130.88 (2 x CH), 131.20 (CH), 131.30 (CH), 134.22 (C), 134.44 (C), 134.93 (C), 137.06 (4 x CH), 145.32 (C). *m/z* (ES) 540 (100 %), 462 (99), 444 (100), 384 (42), 372 (81), 228 (27). *m/z* (FAB) 540.2240 (MH^+. $C_{29}H_{38}NO_5SSi$ requires 540.2240).

(3*S*, 4*R*, 5*S*)-**327**: $[\alpha]^{22}_D$ –22.3° (c = 1.3 in EtOAc). Mp 195-197 °C (from EtOAc). ν_{max} (cm^{-1}, solid) 3540 (OH), 3072, 2931, 2857, 1340, 1109, 1090. δ_H (300 MHz, CD_3OD) 1.11 (9H, s, C(CH_3)$_3$), 1.37 (3H, s, $NCH_2C(CH_3)OH$), 2.46 (3H, s, Ar-CH_3), 2.53 (1H, dd, *J* 11.6 and 7.0, NC*H*HCHOSi), 2.71 (1H, d, *J* 12.0, NC*H*HC(CH_3)OH), 3.03 (1H, dd, *J* 11.6 and 3.5, NCH*H*CHOSi), 3.10 (1H, d, *J* 12.0, NCH*H*C(CH_3)OH), 3.29 (1H, d, *J* 7.0, $NCH_2CHOSiCHOH$), 3.97 (1H, td, *J* 7.0 and 3.5, NCH_2CHOSi), 7.37 (2H, d, *J* 8.0, Ar-*H* x 2), 7.42-7.53 (8H, m, Ar-*H* x 8), 7.72-7.78 (4H, m, Ar-*H* x 4). δ_C (75.5 MHz, CD_3OD) 20.09 (C), 21.45 (CH_3), 24.37 (CH_3), 27.50 (3 x CH_3), 50.76 (CH_2), 54.92 (CH_2), 71.41 (C), 71.93 (CH), 77.79 (CH), 128.64 (2 x CH), 128.80 (2 x CH), 128.84 (2 x CH), 130.76 (2 x C-H), 131.00 (CH), 131.10 (CH), 133.02 (C), 134.43 (C), 135.22 (C), 137.11 (4 x CH), 145.19 (C). *m/z* (ES) 540 (100 %), 462 (91), 444 (87), 370 (18). *m/z* (FAB) 540.2241 (MH^+. $C_{29}H_{38}NO_5SSi$ requires 540.2240).
Crystals suitable for X-ray were grown from MeOH:CH_2Cl_2 (see appendix 2, section 2.12 for crystallographical data).

(3*S*,4*S*,5*S*)-5-(*tert*-Butyldiphenylsilanyloxy)-3-methyl-(toluene-4-sulfonyl)-piperidine-3,4-diol **328** and
(3*R*,4*R*,5*S*)-5-(*tert*-Butyldiphenylsilanyloxy)-3-methyl-(toluene-4-sulfonyl)-piperidine-3,4-diol **329**



324 **329** **330**

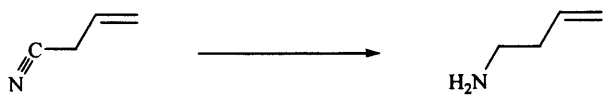
To a solution of Cp_2TiPh (made from Cp_2TiCl_2, 0.222 g, 0.9 mmol, ^iPrMgCl (2.0 M in THF), 0.425 cm^3, 0.9 mmol and PhMgCl (2.4 M in THF), 0.372 cm^3, 0.9 mmol) in THF (10 cm^3) was added a solution of the dicarbonyl (2*S*)-**324** (0.16 g, 0.3 mmol) in THF (5 cm^3). The

reaction was stirred at room temperature for 16 h and worked up as before. The crude material was purified by flash column chromatography using dichloromethane:diethyl ether (100:0 to 96:4) to give the *diol* **328** (0.034 g, 21 %) as a white solid and the *diol* **329** (0.012 g, 7 %) as a colourless oil.

(3*S*,4*S*,5*S*)-**328**: $[\alpha]^{22}_D$ –60.9° (c = 1 in EtOAc). M.p. 150-152°C (from EtOAc). δ_H (300 MHz, $CDCl_3$) 1.09 (9H, s, $C(CH_3)_3$), 1.23 (3H, s, $NCH_2C(CH_3)OH$), 2.37 (1H, app t, *J* 10.5, NC*H*HCHOSi), 2.45 (3H, s, Ar-CH_3), 2.57 (1H, d, *J* 12.0, NC*H*HC(CH_3)OH), 3.24 (1H, d, *J* 12.0, NCH*H*C(CH_3)OH), 3.36 (1H, ddd, *J* 10.5, 5.4, 1.0, NCH*H*CHOSi), 3.47 (1H, d, *J* 3.0, $NCH_2CHOSiCHOH$), 4.21 (1H, ddd, *J* 10.5, 5.4 and 3.0, NCH_2CHOSi), 7.31 (2H, d, *J* 8.0, Ar-*H* x 2), 7.40-7.52 (8H, m, Ar-*H* x 8), 7.63-7.67 (4H, m, Ar-*H* x 4). δ_C (75.5 MHz, $CDCl_3$) 19.13 (C), 21.53 (CH_3), 22.93 (CH_3), 26.93 (3 x CH_3), 45.29 (CH_2), 50.94 (CH_2), 67.99 (CH), 70.42 (C), 73.58 (CH), 127.45 (2 x CH), 127.97 (2 x CH), 128.03 (2 x CH), 129.76 (2 x CH), 130.22 (2 x CH), 132.28 (C), 132.90 (C), 133.37 (C), 135.55 (4 x CH), 143.79 (C). *m/z* (ES) 540 (100 %), 444 (26). *m/z* (FAB) 540.2239 (MH^+. $C_{29}H_{38}NO_5SSi$ requires 540.2240).

(3*R*,4*R*,5*S*)-**329**: $[\alpha]^{22}_D$ –6.8° (c = 0.5 in EtOAc). ν_{max} (cm^{-1}, film) 3558-3410 (OH), 2928, 2857, 1344, 1113 (SO_2), 1045. δ_H (300 MHz, $CDCl_3$) 1.11 (9H, s, $C(CH_3)_3$), 1.18 (3H, s, $NCH_2C(CH_3)OH$), 2.42 (3H, s, Ar-CH_3), 2.80-2.90 (2H, overlapping d, *J* 11.4, NC*H*HC(CH_3)OH and m, NC*H*HCHOSi), 2.97-3.04 (2H, overlapping t, *J* 11.4, NCH*H*C(CH_3)OH and m, NCH*H*CHOSi), 3.45 (1H, d, *J* 5.3, $NCH_2CHOSiCHOH$), 3.74-3.77 (1H, m, NCH_2CHOSi), 7.28 (2H, d, *J* 8.0, Ar-*H* x 2), 7.39-7.51 (6H, m, Ar-*H* x 6), 7.56 (2H, d, *J* 8.0, Ar-*H* x 2), 7.67-7.76 (4H, m, Ar-*H* x 4). δ_C (75.5 MHz, $CDCl_3$) 19.13 (C), 21.49 (CH_3), 21.81 (CH_3), 26.92 (3 x CH_3), 48.08 (CH_2), 53.11 (CH_2), 70.69 (C), 71.12 (CH), 74.92 (CH), 127.53 (2 x CH), 127.94 (4 x CH), 129.65 (2 x CH), 130.16 (CH), 130.28 (CH), 132.30 (C), 132.67 (C), 133.63 (C), 135.71 (2 x CH), 136.07 (2 x CH), 143.52 (C). *m/z* (ES) 540 (84 %), 462 (100), 444 (67), 384 (63). *m/z* (FAB) 540.2241 (MH^+. $C_{29}H_{38}NO_5SSi$ requires 540.2240).

But-3-enylamine **332**

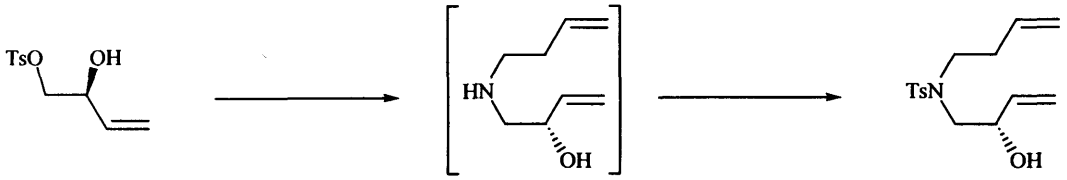


331 **332**

The reaction was carried out using the procedure reported by Yoon and Brown.[155] Lithium aluminium hydride (16 g, 417 mmol) in THF (200 cm^3) was cooled to 0°C using an ice-bath, then sulphuric acid (11 cm^3, 198 mmol) was added cautiously dropwise over 15 min while the

solution was vigorously stirred. The solution was stirred for a further 1 h at 0°C. After this time a solution of the allyl cyanide **331** (20 g, 290 mmol) in THF (10 cm^3) was added slowly over 30 min and the mixture stirred for a further 30 min. The reaction was quenched by careful addition of a 100 cm^3 1 : 1 solution of THF:H_2O. The clear THF solution was decanted and treated with hydrochloric acid (2.0 M, 60 cm^3) after which it was basified with NaOH (10 %, 150 cm^3) and then extracted using diethyl ether (3 x 200 cm^3). The combined extracts were dried (KOH) and the resulting solution was distilled to yield the *amine* **332** (5.13 g, 24 %) as a colourless oil. B. pt. 74°C. δ_H (300 MHz, $CDCl_3$) 1.14 (2H, br s, NH_2), 2.02 (2H, app q, *J* 6.7, NCH_2CH_2), 2.58 (2H, t, *J* 6.7, NCH_2CH_2), 4.87-4.95 (2H, m, $NCH_2CH_2CH{=}CH_2$), 5.60 (1H, ddd, *J* 17.2, 10.0, 6.7, $CH{=}CH_2$). δ_C (75.5 MHz, $CDCl_3$) 37.45 (CH_2), 40.60 (CH_2), 115.98 (CH_2), 135.64 (CH).

(2*S*)-*N*-Butyl-3-enyl-*N*-(2-hydroxy-but-3-enyl)-4-methylbenzenesulfonamide **333**



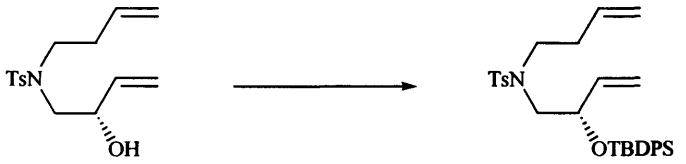
306 **333**

The reaction was carried out as described for (2*S*)-**286** thus the tosylate (2*S*)-**306** (0.09 g, 0.37 mmol) in but-3-enylamine **332** (0.264 g, 3.7 mmol) in the absence of solvent in a sealed tube was heated under reflux for 18 h. Further purification was not required and the crude amine was taken through to the next stage.

Under an atmosphere of nitrogen, a solution of the amine in dichloromethane (5 cm^3) was added NEt_3 (0.2 cm^3, 1.41 mmol) and DMAP (0.008 g, 0.064 mmol). The reaction mixture was cooled to 0°C and *p*-toluenesulfonyl chloride (0.134 g, 0.7 mmol) was added portion-wise. The reaction was stirred for 18 h while warming to RT. The reaction was worked up as before and purified by flash column chromatography on silica using dichloromethane:petrol (70:30 to 100:0) to give the *diene* (2*S*)-**333** (0.014 g, 13 % (over 2 steps, from (2*S*)-**306**)) as a colourless oil. (Found: C, 61.1; H, 7.0; N, 4.6; Calc. for $C_{15}H_{21}NO_3S$: C, 61.0; H, 7.2; N, 4.7 %). ν_{max} (cm^{-1}, film) 3516 (OH), 2925, 1641 (C=C), 1598, 1333, 1152 (SO_2). δ_H (250 MHz, $CDCl_3$) 2.34 (2H, app q, *J* 6.5, NCH_2CH_2), 2.42 (3H, s, Ar-CH_3), 3.18 (2H, br d, *J* 6.5, NCH_2CH), 3.26 (1H, br s, CHO*H*), 3.29 (2H, dd, *J* 7.0 and 3.0, NCH_2CHOH), 4.35-4.39 (1H, br m, C*H*OH), 5.01-5.41 (4H, m, $NCH_2CH_2CH{=}CH_2$ and $NCH_2CHOHCH{=}CH_2$), 5.72 (1H, ddt, *J* 17.0, 10.3 and 7.0, $NCH_2CH_2CH{=}CH_2$), 5.86 (1H, ddd, *J* 17.2, 10.3 and 5.5, $NCH_2CHOHCH{=}CH_2$), 7.32 (2H, d, *J* 8.0, Ar-*H* x 2), 7.72 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (62.9

MHz, $CDCl_3$) 21.23 (CH_3), 32.77 (CH_2), 49.28 (CH_2), 54.29 (CH_2), 71.12 (CH), 116.14 (CH_2), 116.93 (CH_2), 127.03 (2 x CH), 129.57 (2 x CH), 134.55 (CH), 136.03 (C), 137.56 (CH), 143.36 (C). *m/z* (FAB) 296.1321 (MH^+. $C_{15}H_{22}NO_3S$ requires 296.1320), 296 (93 %), 278 (28), 238 (93), 184 (23), 155 (100), 139 (27).

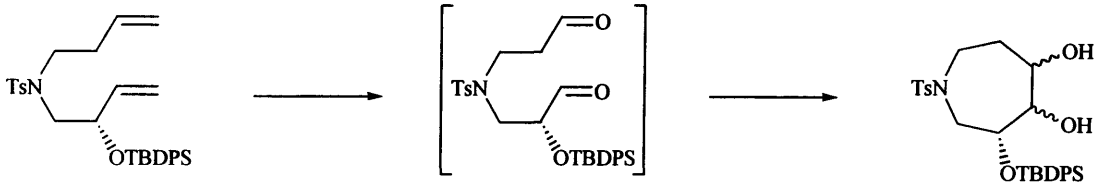
(2*S*)-*N*-But-3-enyl-*N*-[2-(*tert*-butyldiphenylsilanyloxy)-but-3-enyl]-4-methyl benzenesulfonamide **334**



333 **334**

The reaction was carried out as described for (2*S*)-**288** thus the diene (2*S*)-**333** (0.346 g, 1.17 mmol) in dichloromethane (10 cm^3) was added triethylamine (0.179 cm^3, 1.29 mmol) and DMAP (0.012 g, 0.12 mmol). The reaction mixture was cooled to 0°C and TBDPSCl (0.335 cm^3, 1.29 mmol) was added dropwise and the reaction was stirred for 18 h while warming to room temperature. The reaction was worked up as before and purified by flash column chromatography on silica using petrol:dichloromethane (80:20 to 20:80) to give the *silyl-protected diene* (2*S*)-**334** (0.372 g, 60 %) as a colourless oil. Data for **334** on page 175.

3-(*tert*-Butyldiphenylsilanyloxy)-1-(toluene-4-sulfonyl)-azepane-4,5-diol **336-338**



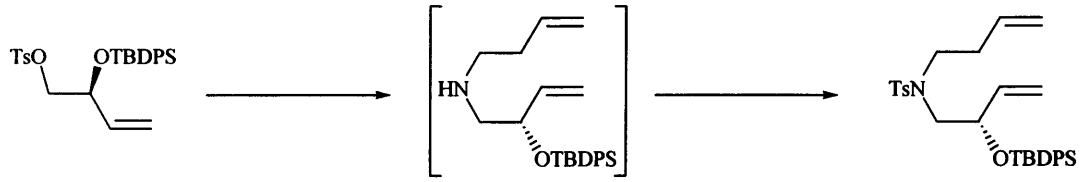
334 **335** **336-338**

The diene (2*S*)-**334** (0.21 g, 0.39 mmol) in dry dichloromethane (10 cm^3) was treated with ozone then Me_2S (0.116 cm^3, 1.56 mmol) as for the preparation of **178**. After evaporation the product dialdehyde was not isolated due to decomposition on silica but the crude was taken through to the SmI_2-mediated pinacol coupling reaction.

To a -78°C solution of SmI_2 (0.1 M THF, Sm, 0.352 g, 2.34 mmol, CH_2I_2, 0.157 cm^3, 1.95 mmol reacted in degassed THF (20 cm^3)) was added *via* canula a crude solution of the dialdehyde (2*S*)-**335** (0.21 g, 0.39 mmol) and ^{t}BuOH (0.22 cm^3, 2.34 mmol) in THF (5 cm^3, 4 cycles freeze-pump-thaw). The reaction was stirred for 16 h whilst warming to room temperature. The reaction was worked up as before to leave a residue of the crude material as a mixture of three isomers **336-338** (established by ^{1}H and ^{13}C NMR). However, purification

by flash column chromatography on silica gave one pure product (0.011 g, 5 % (over 2 steps, from (2*S*)-**334**)) as a colourless oil. Data for this compound is as follows. δ_H (250 MHz, $CDCl_3$) 1.12 (9H, s, $C(CH_3)_3$), 1.63-1.82 (1H, m, NCH_2CHH), 1.86-2.07 (2H, m), 2.41 (3H, s, Ar-CH_3), 2.75 (1H, dd, *J* 14.4 and 10.1, $NCH_2CH_2CHOHCHOH$), 2.93 (1H, ddd, *J* 12.2, 6.2 and 2.8, $NCHHCH_2$), 3.34-3.46 (2H, m), 3.50-3.60 (1H, m, NCH_2CH_2CHOH), 3.76-3.92 (1H, m, NCH_2CHOSi), 7.21 (2H, d, *J* 8.0, Ar-*H* x 2), 7.35 (2H, d, *J* 8.0, Ar-*H* x 2), 7.45-7.52 (6H, m, Ar-*H* x 6), 7.71-7.76 (4H, m, Ar-*H* x 4). δ_C (100.6 MHz, $CDCl_3$) 19.32 (CH_3), 21.48 (3 x CH_3), 30.55 (CH_2), 43.98 (CH_2), 47.86 (CH_2), 69.37 (CH), 75.58 (CH), 81.76 (CH), 127.04 (2 x CH), 127.91 (2 x CH), 128.07 (2 x CH), 129.52 (2 x CH), 130.09 (CH), 130.13 (CH), 133.09 (C), 133.19 (C), 135.08 (C), 135.76 (2 x CH), 136.01 (2 x CH), 143.28 (C).
A mixture of two isomers was also isolated (0.058 g, 28 % (over 2 steps, from (2*S*)-**334**)).

(2*S*)-*N*-But-3-enyl-*N*-[2-(*tert*-butyldiphenylsilanyloxy)-but-3-enyl]-4-methyl benzenesulfonamide **334**



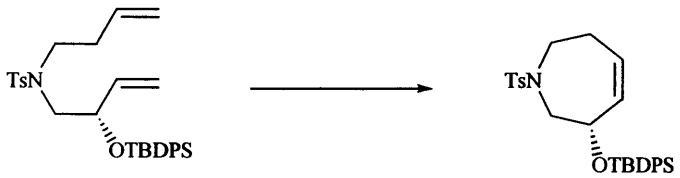
321 **334**

The reaction was carried out as described for (2*S*)-**333** thus the tosylate (2*S*)-**321** (0.24 g, 0.5 mmol) and but-3-enylamine (0.354 g, 5 mmol) in the absence of solvent in a sealed tube was heated under reflux for 18 h. Work up as before and further purification was not required so the crude was taken through to the next stage.

The crude amine in dichloromethane (10 cm^3) was added triethylamine (0.132 cm^3, 0.95 mmol) and DMAP (0.007 g, 0.063 mmol). The reaction mixture was cooled to 0°C and *p*-toluenesulfonyl chloride (0.132 g, 0.69 mmol) was added portion-wise. The reaction was worked up as before and purified by flash column chromatography on silica using dichloromethane:petrol (30:70 to 60:40) to give the *diene* (2*S*)-**334** (0.233 g, 87 % (over 2 steps, from (2*S*)-**321**)) as a colourless oil. $[\alpha]^{22}_D$ –35.2° (c = 2 in EtOAc). ν_{max} (cm^{-1}, film) 3072, 2931, 1428, 1342, 1155 (SO_2), 1111. δ_H (300 MHz, $CDCl_3$) 1.12 (9H, s, $C(CH_3)_3$), 2.03 (2H, app q, *J* 8.0, $NCH_2CH_2CH=CH_2$), 2.42 (3H, s, Ar-CH_3), 3.07 (2H, dt, *J* 12.5 and 8.0, $NCH_2CH_2CH=CH_2$), 3.16 (2H, d, *J* 6.7, NCH_2CHOSi), 4.42 (1H, app q, *J* 6.7, NCH_2CHOSi), 4.90-4.99 (2H, m, $NCH_2CH_2CH=CH_2$), 5.07-5.12 (2H, m, $CHOSiCH=CH_2$), 5.56 (1H, ddd, *J* 17.2, 10.5 and 8.0, $NCH_2CH_2CH=CH_2$), 5.89 (1H, ddd, *J* 17.0, 10.0 and 6.7,

CHOSiC*H*=CH_2), 7.23 (2H, d, *J* 8.0, Ar-*H* x 2), 7.36-7.48 (6H, m, Ar-*H* x 6), 7.54 (2H, d, *J* 8.0, Ar-*H* x 2), 7.67-7.75 (4H, m, Ar-*H* x 4). δ_C (75.5 MHz, $CDCl_3$) 19.20 (C), 21.39 (CH_3), 26.94 (3 x CH_3), 32.35 (CH_2), 49.01 (CH_2), 53.71 (CH_2), 72.97 (CH), 116.57 (CH_2), 116.79 (CH_2), 127.14 (2 x CH), 127.45 (2 x CH), 127.60 (2 x CH), 129.43 (2 x CH), 129.67 (CH), 129.74 (CH), 133.40 (C), 133.75 (C), 134.49 (CH), 135.84 (2 x CH), 135.90 (2 x CH), 136.85 (C), 138.07 (CH), 142.94 (C). *m/z* (ES) 534 (76 %), 456 (49), 278 (16). *m/z* (FAB) 534.2497 (MH^+. $C_{31}H_{40}NO_3SSi$ requires 534.2498).

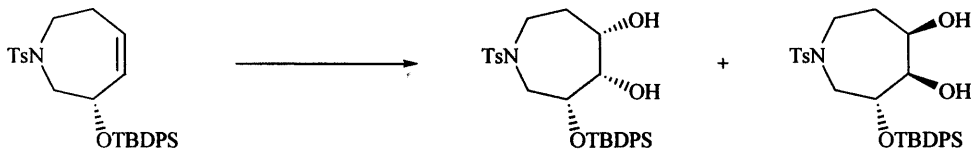
(3*S*)-3-(*tert*-Butyldiphenylsilanyloxy)-1-(toluene-4-sulfonyl)-2,3,6,7-tetrahydro-1*H*-azepine **339**



334 **339**

The reaction was carried out as described for (3*S*)-**301** thus the diene (2*S*)-**334** (0.09 g, 0.17 mmol) in dichloromethane (10 cm^3) was added to $RuCl_2$(=CHPh)(PCy_3)$_2$ (5 mol%, 0.007 g, 0.008 mmol) *via* canula, under an atmosphere of nitrogen and stirred for 3 h under reflux. The reaction was worked up as before and purified by flash column chromatography on silica using diethyl ether:petrol (10:90 to 30:70) to elute the *cycloalkene* (3*S*)-**339** (0.083 g, 98 %) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 1.09 (9H, s, C(CH_3)$_3$), 2.22 (2H, app q, *J* 5.0, NCH_2CH_2CH=CH), 2.41 (3H, s, Ar-CH_3), 2.72-2.82 (2H, m), 3.68-3.80 (2H, m), 4.50-4.53 (1H, br m, NCH_2CHOSi), 5.55-5.64 (1H, m, one of C*H*=CH), 5.69-5.73 (1H, m, one of C*H*=CH), 7.21 (2H, d, *J* 8.0, Ar-*H* x 2), 7.37-7.49 (8H, m, Ar-*H* x 8), 7.65-7.70 (4H, m, Ar-*H* x 4). δ_C (75.5 MHz, $CDCl_3$) 19.17 (C), 21.46 (CH_3), 26.92 (3 x CH_3), 29.81 (CH_2), 48.22 (CH_2), 53.76 (CH_2), 71.65 (CH), 126.93 (3 x CH), 127.65 (2 x CH), 127.71 (2 x CH), 129.57 (2 x CH), 129.77 (2 x CH), 133.53 (C), 133.68 (C), 135.85 (CH), 136.45 (C), 136.94 (4 x CH), 142.96 (C). *m/z* (FAB) 506.2186 (MH^+. $C_{29}H_{36}NO_3SSi$ requires 506.2186), 506 (12 %), 448 (92), 428 (25), 250 (100), 197 (40), 155 (26), 135 (87).

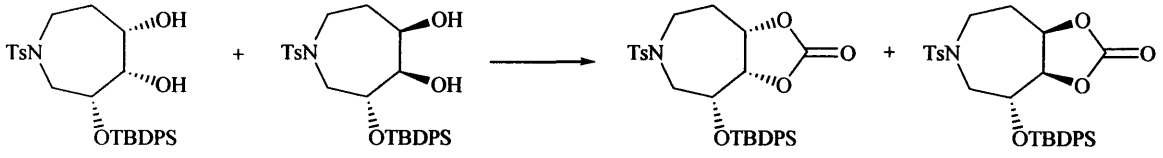
3-(*tert*-Butyldiphenylsilanyloxy)-1-(toluene-4-sulfonyl)-azepane-4,5-diol **340** and **341**



339 **340** **341**

The reaction was carried as described for (3*R*,4*R*,5*R*)-**296** thus the *cycloalkene* (3*S*)-**339** (0.055 g, 0.11 mmol) in acetone (2 cm^3) and osmium tetroxide, OsO_4 (0.044 cm^3, 2.5 wt% in ^tBuOH, 0.0044 mmol) was prepared at room temperature. This was added *via* canula to a solution of NMO (0.019 g, 0.164 mmol) in H_2O (1 cm^3) and the reaction mixture was stirred for 16 h at room temperature. The reaction was worked up as before and purified by flash column chromatography on silica using ethyl acetate:petrol (30:70 to 60:40) to afford the *diols* **340** and **341** (0.035 g, 60 %) in a 1 : 1 ratio as a white solid which was a mixture of two inseparable products. δ_H (300 MHz, $CDCl_3$) 1.09 (9H, s, $C(CH_3)_3$), 1.10 (9H, s, $C(CH_3)_3$), 1.74-1.89 (4H, m), 2.15-2.28 (2H, m), 2.40 (3H, s, Ar-CH_3), 2.41 (3H, s, Ar-CH_3), 2.83-2.93 (2H, m), 3.04 (1H, ddd, *J* 13.2, 9.1 and 3.8), 3.12-3.26 (2H, m), 3.39 (1H, dd, *J* 14.0 and 4.4), 3.53-3.63 (1H, m), 3.78 (2H, dd, *J* 7.5 and 2.0), 3.93 (1H, br s), 4.02 (1H, ddd, *J* 10.2, 7.0 and 3.0), 4.07-4.16 (1H, m), 7.20 (2H, d, *J* 8.0, Ar-*H* x 2), 7.21 (2H, d, *J* 8.0, Ar-*H* x 2), 7.33-7.46 (16H, m, Ar-*H* x 16), 7.66-7.70 (8H, m, Ar-*H* x 8). δ_C (75.5 MHz, $CDCl_3$) 19.20 (C), 21.47 (2 x CH_3), 27.00 (2 x CH_3), 28.59 (CH_2), 31.79 (CH_2), 42.82 (CH_2), 44.57 (CH_2), 46.68 (CH_2), 50.26 (CH_2), 69.28 (CH), 69.79 (CH), 70.81 (CH), 72.80 (CH), 75.38 (CH), 77.21 (CH), 126.91 (4 x CH), 127.02 (4 x CH), 127.82 (4 x CH), 127.91 (4 x CH), 127.99 (4 x CH), 129.59 (4 x CH), 130.13 (2 x CH), 130.22 (2 x CH), 132.46 (2 x C), 132.71 (2 x C), 133.09 (2 x C), 135.39 (2 x C), 135.78 (4 x CH), 135.85 (4 x CH), 135.96 (4 x CH), 143.19 (2 x C).

(1*R*,3*R*,4*S*)-4-(*tert*-Butyldiphenylsilanyloxy)-6-(toluene-4-sulfonyl)-hexahydro-1,3-dioxa-6-aza azulen-2-one **342** and
(1*S*,3*S*,4*S*)-4-(*tert*-Butyldiphenylsilanyloxy)-6-(toluene-4-sulfonyl)- hexahydro-1,3-dioxa-6-aza azulen-2-one **343**



340 **341** **342** **343**

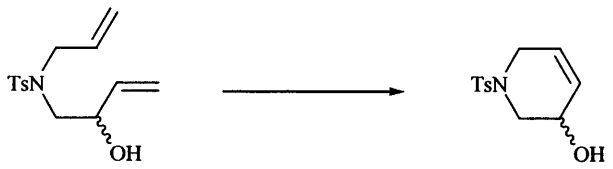
To a solution of the diols **340** and **341** (a mixture of 2 isomers) (0.035 g, 0.065 mmol) in dichloromethane (1 cm^3) was added NEt_3 (0.009 cm^3, 0.065 mmol) and the reaction was stirred for 15 min. Then triphosgene (0.006 g, 0.02 mmol) was added to the reaction mixture and stirred for a further 2 h. Addition of saturated aqueous ammonium chloride (3 cm^3) quenched the reaction which was extracted with ethyl acetate (3 x 10 cm^3). The combined extracts were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a yellow oil, which was purified by flash column chromatography on silica using dichloromethane:petrol (70:30 to 90:10) to give the *carbonate* **342** (0.016 g, 41 %) and

carbonate **343** (0.017 g, 44 %) as colourless oils. The stereochemistries of **342** and **343** have not been assigned.

(1*R*,3*R*,4*S*)-**342**: δ_H (300 MHz, $CDCl_3$) 1.15 (9H, s, C(CH_3)$_3$), 2.13 (1H, ddd, *J* 14.0, 7.5 and 6.5, NCH_2CHH), 2.43 (3H, s, Ar-CH_3), 2.46-2.53 (1H, m, NCH_2CHH), 2.68 (1H, ddd, *J* 14.0, 9.0 and 2.0, $NCHHCH_2$), 2.84 (1H, dd, *J* 14.0 and 2.0, NCHHCHOSi), 3.63 (1H, m, $NCHHCH_2$), 3.82 (1H, ddd, *J* 14.0, 6.4 and 2.0, NCHHCHOSi), 4.18 (1H, td, *J* 6.4 and 2.0, NCH_2CHOSi), 4.49 (1H, dd, *J* 9.0 and 6.4, $NCH_2CHOSiCHO$), 4.85 (1H, ddd, *J* 9.0, 6.5 and 2.5, NCH_2CH_2CHO), 7.29 (2H, d, *J* 8.0, Ar-*H* x 2), 7.40-7.51 (6H, m, Ar-*H* x 6), 7.57 (2H, d, *J* 8.0, Ar-*H* x 2), 7.68-7.80 (4H, m, Ar-*H* x 4). δ_C (75.5 MHz, $CDCl_3$) 19.18 (C), 21.50 (CH_3), 26.88 (3 x CH_3), 31.44 (CH_2), 43.00 (CH_2), 49.15 (CH_2), 69.70 (CH), 77.00 (CH), 78.74 (CH), 127.03 (2 x CH), 127.96 (2 x CH), 128.11 (2 x CH), 129.90 (2 x CH), 130.31 (CH), 130.41 (CH), 132.04 (C), 132.65 (C), 134.99 (C), 135.70 (2 x CH), 136.08 (2 x CH), 143.74 (C), 153.30 (C).

(1*S*,3*S*,4*S*)-**343**: δ_H (300 MHz, $CDCl_3$) 1.11 (9H, s, C(CH_3)$_3$), 2.06-2.13 (1H, m, NCH_2CHH), 2.46 (3H, s, Ar-CH_3), 2.48-2.55 (1H, m, NCH_2CHH) 2.65 (2H, m), 3.63-3.73 (2H, m), 4.37 (1H, br t, *J* 6.0, NCH_2CHOSi), 4.79 (2H, br s, 2 x CHO(C=O)), 7.29 (2H, d, *J* 8.0, Ar-*H* x 2), 7.41-7.53 (8H, m, Ar-*H* x 8), 7.67-7.74 (4H, m, Ar-*H* x 4). δ_C (75.5 MHz, $CDCl_3$) 19.06 (C), 21.53 (CH_3), 26.80 (3 x CH_3), 30.19 (CH_2), 43.07 (CH_2), 50.28 (CH_2), 71.12 (CH), 75.70 (CH), 80.24 (CH), 127.03 (2 x CH), 127.99 (2 x CH), 128.03 (2 x CH), 129.90 (2 x CH), 130.26 (2 x CH), 132.03 (C), 132.92 (C), 134.29 (C), 135.90 (2 x CH), 135.98 (2 x CH), 143.91 (C), 153.93 (C).

(*rac*)-1-(Toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridin-3-ol **344**

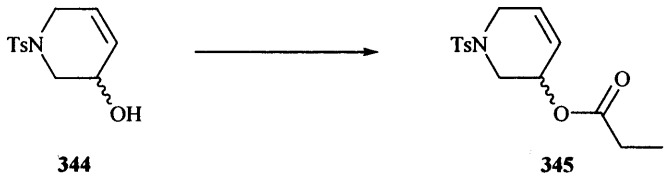


286 **344**

The reaction was carried out as described for (3*S*)-**339** thus the diene (*rac*)-**286** (0.3 g, 1.1 mmol) in dichloromethane (10 cm^3) was added to $RuCl_2$(=CHPh)(PCy_3)$_2$ (5 mol%, 0.044 g, 0.054 mmol) *via* canula, under an atmosphere of nitrogen and stirred for 3 h under reflux. The reaction was worked up as before and purified by flash column chromatography on silica using diethyl ether:petrol (50:50 to 70:30) to elute the *cycloalkene* (*rac*)-**344** (0.269 g, 99 %) as a colourless oil. ν_{max} (cm^{-1}, film) 3524 (OH), 3052, 2923, 1596 (C=C), 1332, 1159 (SO_2),

1095. δ_H (300 MHz, $CDCl_3$) 2.40 (3H, s, Ar-C*H*$_3$), 2.63 (1H, br s, CHO*H*), 3.12 (1H, dd, *J* 11.7 and 4.5, NC*H*HCHOH), 3.22 (1H, dd, *J* 11.7 and 4.5, NCH*H*CHOH), 3.38 (1H, dq, *J* 16.8 and 2.0, NC*H*HCH=CH), 3.66 (1H, dm, *J* 16.8 and long-range coupling, NCH*H*CH=CH), 4.18-4.22 (1H, br m, NCH_2CHOH), 5.75 (1H, dt, *J* 10.2 and 2.0, NCH_2CH=CH), 5.85 (1H, m, $NCH_2CH(OH)CH$=CH), 7.31 (2H, d, *J* 8.0, Ar-*H* x 2), 7.65 (2H, d, *J* 8.0, Ar-*H* x 2). δ_C (75.5 MHz, $CDCl_3$) 21.38 (CH_3), 44.69 (CH_2), 49.85 (CH_2), 63.26 (CH), 125.38 (CH), 127.54 (2 x CH), 128.16 (CH), 129.68 (2 x CH), 132.76 (C), 143.78 (C). *m/z* (ES) 254 (43 %), 236 (100), 155 (39). *m/z* (FAB) 254.0850 (MH^+. $C_{12}H_{16}NO_3S$ requires 254.0851).

(*rac*)-Propionic acid (toluene –4-sulfonyl)-1,2,3,6-tetrahydro-pyridin-3-yl ester **345**



344 **345**

A solution of the cycloalkene (*rac*)-**344** (0.102 g, 0.4 mmol) in dichloromethane (5 cm^3) was added NEt_3 (0.12 cm^3, 0.88 mmol) and DMAP (0.005 g, 0.04 mmol). The mixture was cooled to 0°C and stirred for 15 min after which propionyl chloride (0.07 cm^3, 0.8 mmol) was added dropwise to the reaction and stirred for 2 h. The reaction was quenched by addition of dichloromethane (20 cm^3) and the organic extract was washed with aqueous sodium hydrogen bicarbonate (10 cm^3) and brine (10 cm^3). The organic extract was dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a yellow oil, which was purified by flash column chromatography on silica using diethyl ether:petrol (40:60 to 60:40) to give the *ester* (*rac*)-**345** (0.123 g, 98 %) as a colourless oil. ν_{max} (cm^{-1}, film) 3477 (OH), 2943, 1732 (C=O), 1597, 1348, 1160 (SO_2), 1090. δ_H (300 MHz, $CDCl_3$) 1.13 (3H, t, *J* 7.8, $OCOCH_2CH_3$), 2.33 (2H, q, *J* 7.8, $OCOCH_2CH_3$), 2.43 (3H, s, Ar-C*H*$_3$), 3.23 (1H, dd, *J* 12.6 and 4.5, NC*H*HCHO), 3.37 (1H, dd, *J* 12.6 and 4.5, NCH*H*CHO), 3.48 (1H, dd, *J* 17.0 and 2.0, NC*H*HCH=CH), 3.78 (1H, dm, *J* 17.0, NCH*H*CH=CH), 5.23-5.27 (1H, br m, NCH_2CHOCO), 5.81 (1H, m, NCH_2CHOCH=CH), 5.93 (1H, m, NCH_2CH=CH), 7.34 (2H, d, *J* 8.0, Ar-*H* x 2), 7.67 (2H, d, *J* 8.0, Ar-*H* x 2), δ_C (75.5 MHz, $CDCl_3$) 8.80 (CH_3), 21.27 (CH_3), 27.31 (CH_2), 44.24 (CH_2), 46.38 (CH_2), 64.88 (CH), 123.83 (CH), 127.37 (2 x CH), 127.83 (CH), 129.57 (2 x CH), 133.19 (C), 143.64 (C), 173.64 (C). *m/z* (FAB) 310.1113 (MH^+. $C_{15}H_{20}NO_4S$ requires 310.1113), 310 (44 %), 282 (6), 236 (100), 155 (65), 136 (43).

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Appendices

Appendix 1: ENZYME BIOASSAY METHODS

The basis for the majority of the glucosidase assays is the reaction between the enzyme solution and the selected substrate, causing the release of the *p*-nitrophenol conjugated group, which has a yellow colour in solution that can be quantified spectrophotometrically.

The amyloglucosidase assay works on the principle that glucose monomers are released from starch chains in the presence of the enzyme – glucose is then detected using Trinder glucose reagent, which gives a red colour when reacted with glucose solution.

In both assays, the extent of enzyme inhibition is measured with respect to water or the sample solvent, which is used as a blank (assume 0 % inhibition with dH_2O).

Enzyme	Source	pH	Conc. (U/ml)	Substrate
α-D-glucosidase	*Saccharomyces cerevisiae*	6.0	1.5	PNP-α-D-glucopyranoside
α-D-glucosidase	*Bacillus sterothermophilus*	6.8	5.0	PNP-α-D-glucopyranoside
α-D-glucosidase	Rice (*Oryzae sativa*)	4.0	5.0	PNP-α-D-glucopyranoside
β-D-glucosidase	Almond (*Prunus* sp.)	5.0	0.2	PNP-β-D-glucopyranoside
α-D-galactosidase	Green coffee beans (*Coffea* sp.)	6.5	0.25	PNP-α-D-galactopyranoside
α-D-mannosidase	Jack bean (*Canavalia ensiformis*)	4.5	0.2	PNP-α-D-mannopyranoside
α-L-fucosidase	Bovine kidney	5.5	0.5	PNP-α-L-fucopyranoside
Naringinase	*Penecillium decumbens*	4.0	1.0	PNP-α-D-rhamnopyranoside
N-acetyl-β-D-glucosaminidase	Bovine kidney	4.25	0.2	PNP-N-acetyl-β-D-glucosaminide
N-acetyl-β-D-glucosaminidase	Jack bean (*Canavalia ensiformis*)	7.0	0.25	PNP-N-acetyl-β-D-glucosaminide
N-acetyl-β-D-hexosaminidase	*Aspergillus oryzae*	5.0	0.25	PNP-N-acetyl-β-D-glucosaminide
Amyloglucosidase	*Aspergillus niger*	4.5	0.5	1 % soluble starch & Trinder reagent

All enzymes and substrate compounds are purchased from Sigma (including the Trinder reagent).

Substrate solutions should be made up to 5 m*M* concentration using McIlvaine citrate-phosphate buffer, at the optimum pH for the enzyme as suggested by the supplier.

Once made up, all solutions should be stored at 4°C and discarded after a month if not used – they should be allowed to warm up to room temperature before use.

The Trinder glucose detection reagent (required for the amyloglucosidase assay) should be diluted in 100 ml of dH_2O before use – the instructions supplied with the reagent give information about storage and handling. The starch solution should be made using McIlvaine buffer, pH 4.5 – the solution may need to be boiled or autoclaved to get the starch into solution (it makes a cloudy, thinly-gelatinous solution on heating, that remains stable but needs mixing well after refrigeration).

The other assays also require 0.4 *M* glycine solution, pH 10.4, which should be made using dH_2O and pH-adjusted using NaOH pellets.

The assay method has been designed for use with 96-well microtitre plates, which are read using a microplate reader at 405 nm (550 nm for the amyloglucosidase assay). All samples (and blanks) are assayed in triplicate.

Method (all assays except amyloglucosidase)

Combine the following (in this order):

10 µl enzyme solution
10 µl sample solution/water/sample solvent (containing 10 µg sample)
50 µl substrate solution

Incubate the reaction mixture at room temperature – the length of time required depends on the concentration and activity of the enzyme, and should usually be 5 – 20 minutes. In practice, I test the enzyme solutions when I make them up to determine the time needed to

give approximately 0.5 – 1.0 U absorbance at the end of the reaction period (after the glycine solution has been added). Endpoint absorbances outside the linear response range of the microplate reader (> 2.5 U) mean that the reaction time needs to be reduced, or the enzyme solution needs diluting. The enzyme solution concentrations given above usually require about 10 minutes' reaction time, but this varies with enzyme batch, so it's always worth checking the reaction time at the start of each set of assays.

When the reaction period is complete, add 70 µl glycine solution, and measure the absorbance at 405 nm.

Amyloglucosidase assay

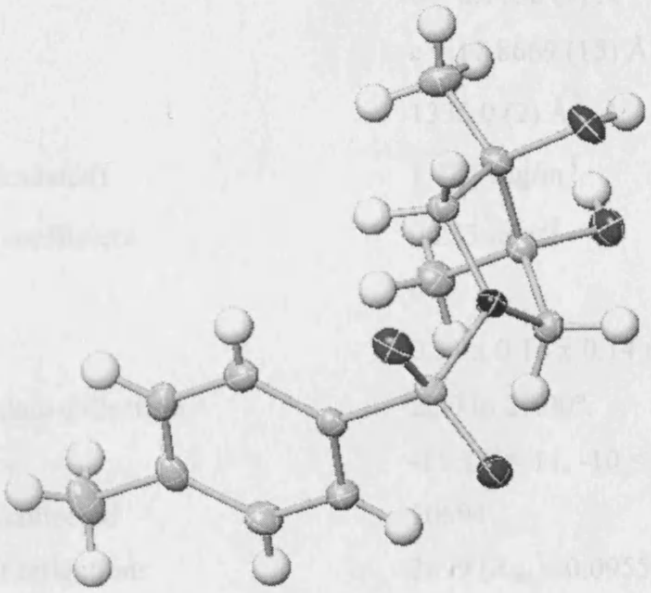
This follows the same method as the other assays (see above), except 100 µl of Trinder solution are added at the end of the reaction period. The colour reaction needs at least 10 minutes to complete at room temperature, after which the absorbance is read at 550 nm. There is no need to stop the reaction between the Trinder solution and the reaction mix. *NB – samples made up in solvents other than water may cause solubility problems with the starch.*

Calculating % inhibition

Enzyme inhibition is calculated with respect to the blank samples:

First, calculate the mean of the triplicate assays per sample.

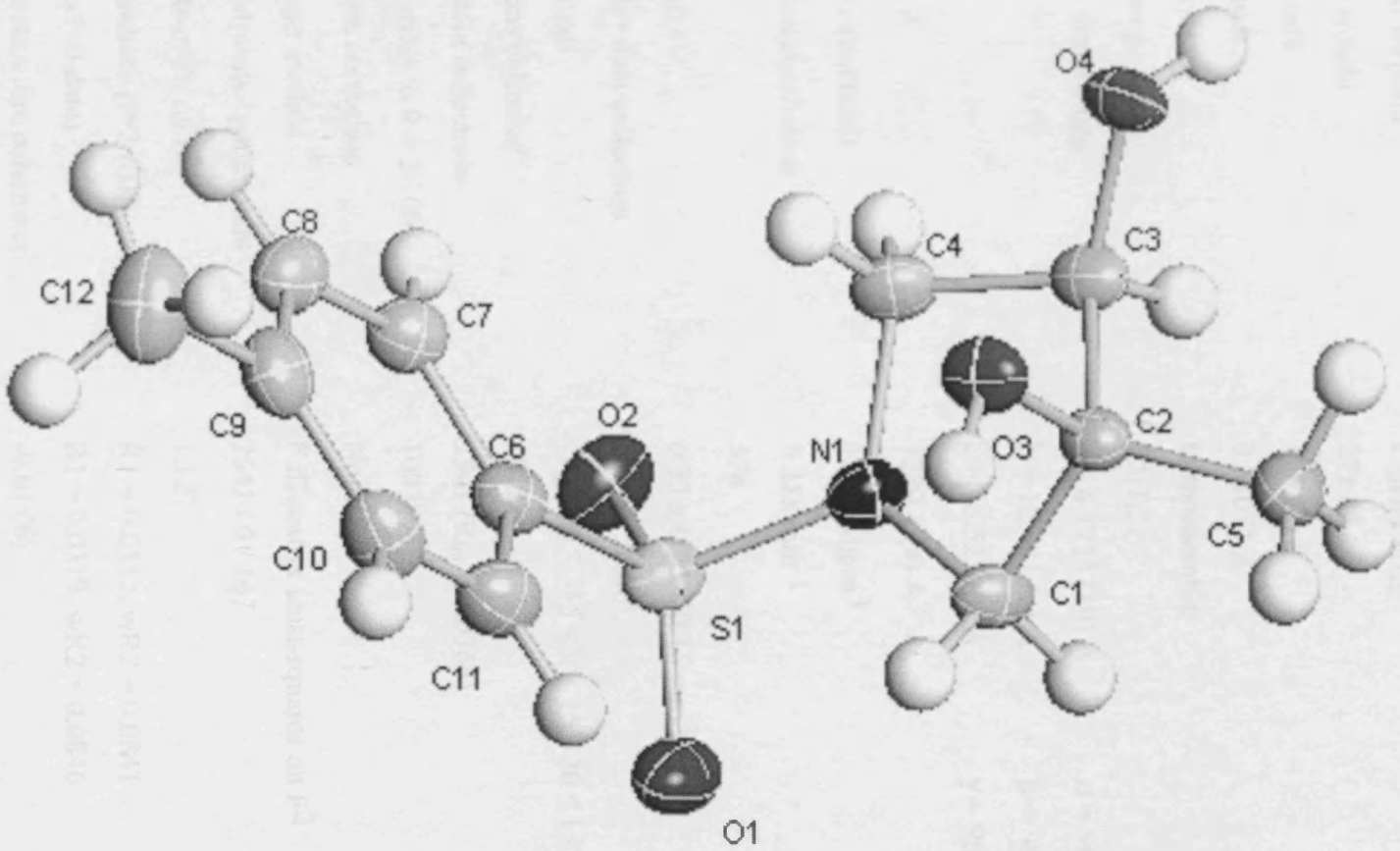
Then, % inhibition = (100 - [(Mean absorbance sample / Mean absorbance blank) x 100])



Appendix 2.1

Table 1. Crystal data and structure refinement for **199**

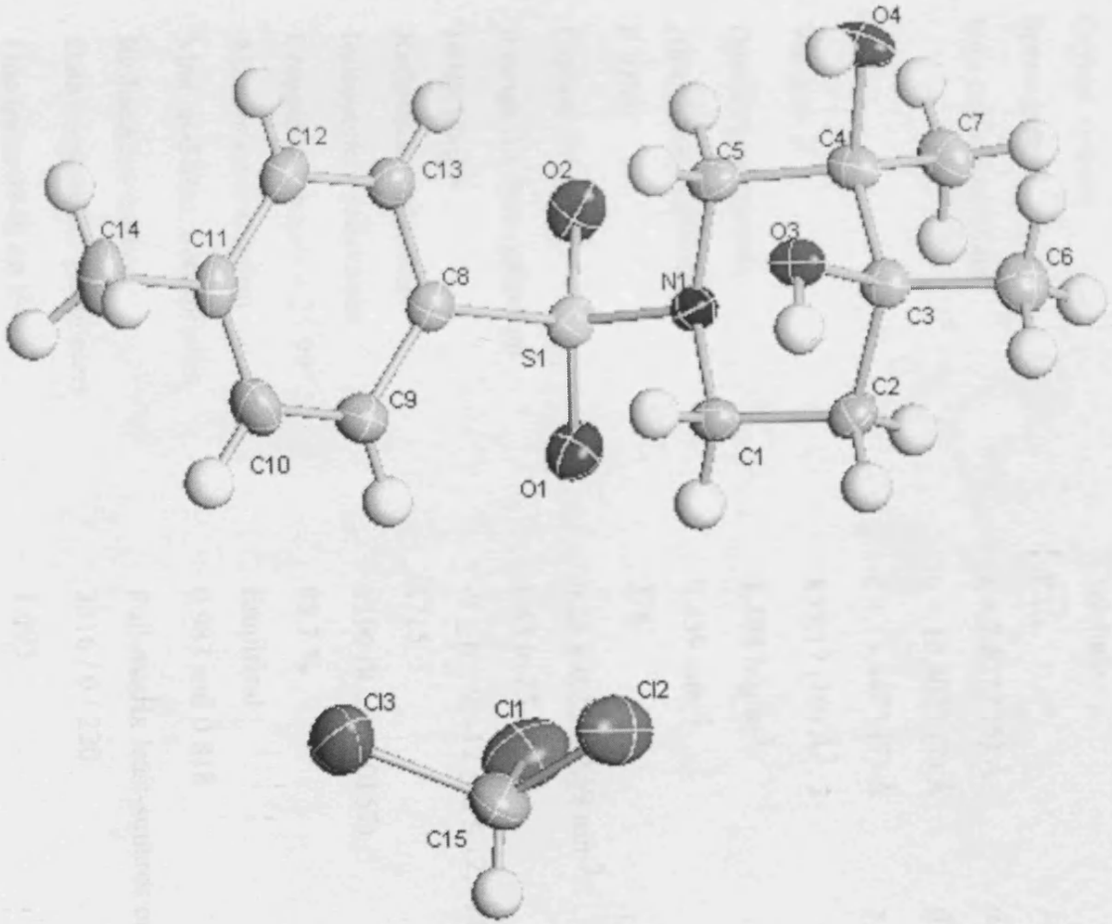
Identification code	**199**	
Empirical formula	$C_{13}H_{19}NO_4S$	
Formula weight	285.35	
Temperature	160 (2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_{1/n}$	
Unit cell dimensions	a = 9.3202 (8) Å	α = 90°
	b = 8.1758 (7) Å	β = 101.3060 (10)°
	c = 17.8669 (15) Å	γ = 90°
Volume, Z	1335.0 (2) $Å^3$, 4	
Density (calculated)	1.420 Mg/m^3	
Absorption coefficient	0.253 mm^{-1}	
F (000)	608	
Crystal size	0.31 x 0.16 x 0.14 mm^3	
θ range for data collection	2.30 to 27.00°.	
Index ranges	$-11 \leq h \leq 11, -10 \leq k \leq 10, -22 \leq l \leq 22$	
Reflections collected	10694	
Independent reflections	2899 (R_{int} = 0.0955)	
Completeness to θ = 27.00°	99.6 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2899 / 0 / 177	
Goodness-of-fit on F^2	1.079	
Final R indices [I >2σ(I)]	R1 = 0.0515, wR2 = 0.1174	
R indices (all data)	R1 = 0.0601, wR2 = 0.1233	
Largest diff. peak and hole	0.462 and -1.028 $eÅ^{-3}$	


O4
C8
C12
C7
C4
C3
C9
O2
C6
N1
O3
C2
C10
C5
C1
S1
C11
O1

Appendix 2.2

Table 1. Crystal data and structure refinement for **201**

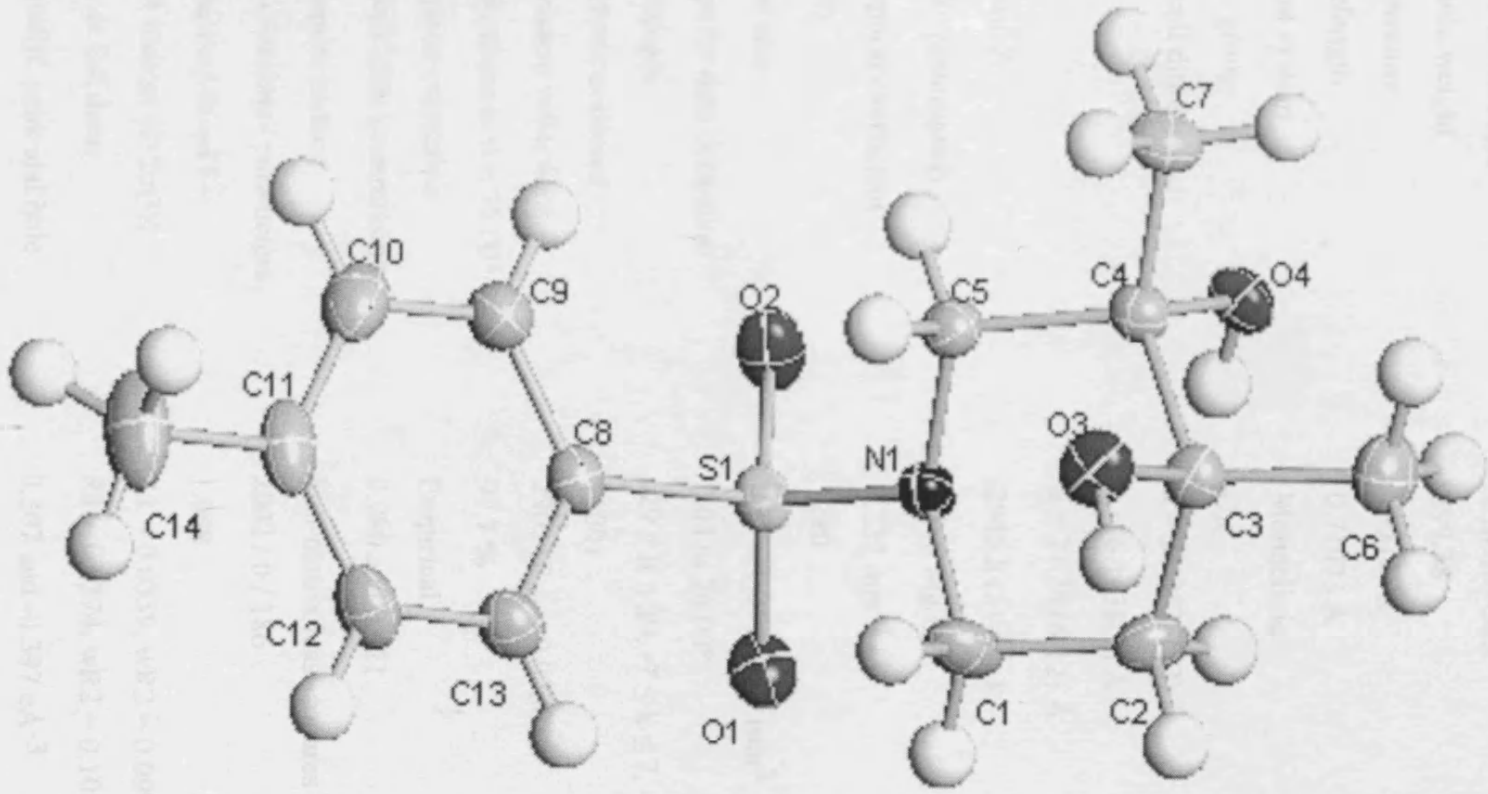
Identification code	**201**	
Empirical formula	$C_{12}H_{17}NO_4S$	
Formula weight	271.33	
Temperature	160 (2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.1728 (10) Å	α = 90°
	b = 12.641 (2) Å	β = 90°
	c = 16.525 (3) Å	γ = 90°
Volume, Z	1289.4 (4) $Å^3$, 4	
Density (calculated)	1.398 Mg/m^3	
Absorption coefficient	0.258 mm^{-1}	
F (000)	576	
Crystal size	0.33 x 0.25 x 0.16 mm^3	
θ range for data collection	2.03 to 26.00°.	
Index ranges	$-7 \leq h \leq 7, -15 \leq k \leq 15, -20 \leq l \leq 20$	
Reflections collected	10127	
Independent reflections	2541 (R_{int} = 0.0364)	
Completeness to θ = 26.00°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2541 / 0 / 167	
Goodness-of-fit on F^2	1.127	
Final R indices [I>2σ(I)]	R1 = 0.0312, wR2 = 0.0841	
R indices (all data)	R1 = 0.0319, wR2 = 0.0846	
Absolute structure parameter	-0.01 (6)	
Largest diff. peak and hole	0.296 and -0.215 $eÅ^{-3}$	


O4
C12
C13
O2
C5
C4
C7
C14
C11
O3
C6
C8
N1
C3
S1
C2
C9
C10
C1
O1
Cl3
Cl1
Cl2
C15

Appendix 2.3

Table 1. Crystal data and structure refinement for **203**

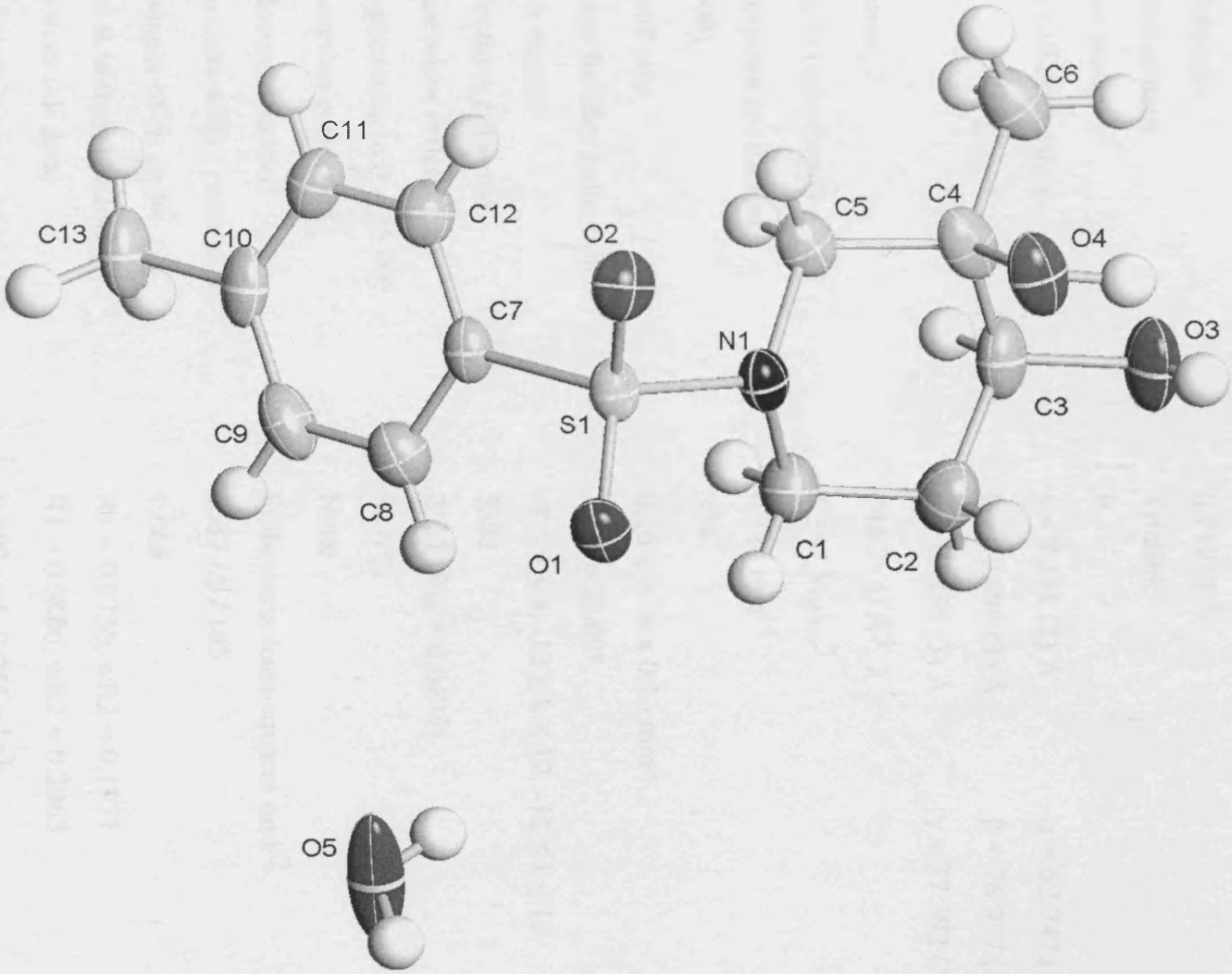
Identification code	**203**	
Empirical formula	$C_{14}H_{21}NO_4S$	
Formula weight	359.06	
Temperature	160 (2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P_{-1}	
Unit cell dimensions	a = 7.6277 (5) Å	α = 87.5670 (10)°
	b = 10.3021 (7) Å	β = 76.6880 (10)°
	c = 11.4473 (7) Å	γ = 77.6730 (10)°
Volume, Z	855.17 (10) $Å^3$, 2	
Density (calculated)	1.394 Mg/m^3	
Absorption coefficient	0.439 mm^{-1}	
F (000)	378	
Crystal size	0.28 x 0.23 x 0.19 mm^3	
θ range for data collection	1.83 to 25.99°.	
Index ranges	$-9 \leq h \leq 9, -12 \leq k \leq 12, -14 \leq l \leq 14$	
Reflections collected	6715	
Independent reflections	3316 (R_{int} = 0.0157)	
Completeness to θ = 25.99°	98.7 %	
Absorption correction	Empirical	
Max. and Min. transmission	0.983 and 0.818	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3316 / 0 / 220	
Goodness-of-fit on F^2	1.093	
Final R indices [I >2σ(I)]	R1 = 0.0386, wR2 = 0.1111	
R indices (all data)	R1 = 0.0434, wR2 = 0.1140	
Largest diff. peak and hole	0.518 and -0.340 $eÅ^{-3}$	


C7
C10
C9
O2
C5
C4
O4
C11
C8
S1
N1
O3
C3
C6
C14
C12
C13
O1
C1
C2

Appendix 2.4

Table 1. Crystal data and structure refinement for **204**

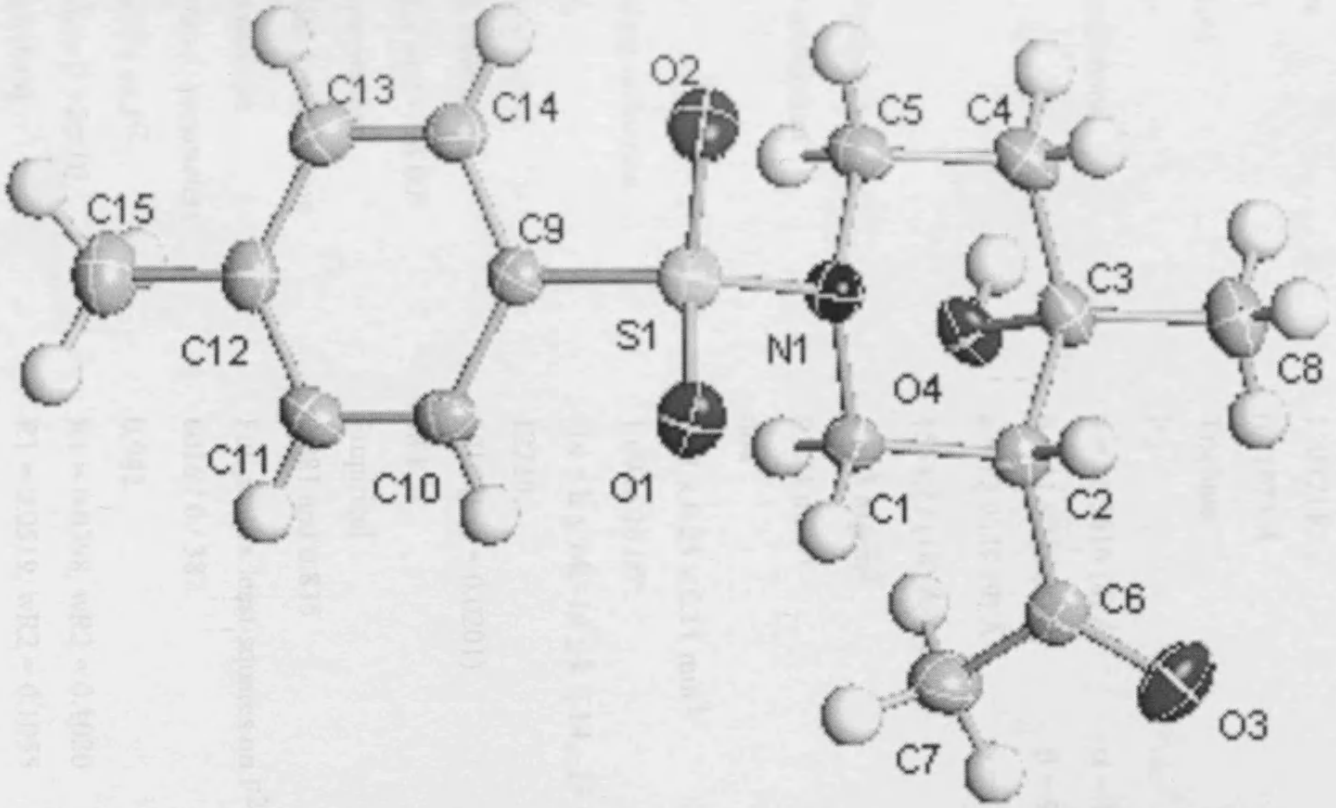
Identification code	**204**	
Empirical formula	$C_{14}H_{21}NO_4S$	
Formula weight	299.38	
Temperature	150 (2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$C_{2/c}$	
Unit cell dimensions	a = 23.9827(12) Å	α = 90°
	b = 6.1438(3) Å	β = 110.768 (2)°
	c = 21.3816(12) Å	γ = 90°
Volume, Z	2945.8 (3) $Å^3$, 8	
Density (calculated)	1.350 Mg/m^3	
Absorption coefficient	0.232 mm^{-1}	
F (000)	1280	
Crystal size	0.38 x 0.35 x 0.15 mm^3	
θ range for data collection	2.04 to 26.00°.	
Index ranges	$-29 \leq h \leq 29, -7 \leq k \leq 7, -26 \leq l \leq 26$	
Reflections collected	11001	
Independent reflections	2902 (R_{int} = 0.0230)	
Completeness to θ = 26.00°	99.7 %	
Absorption correction	Empirical	
Max. and Min. transmission	0.980 and 0.821	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2902 / 0 / 186	
Goodness-of-fit on F^2	1.068	
Final R indices [I>2σ(I)]	R1 = 0.0359, wR2 = 0.0999	
R indices (all data)	R1 = 0.0374, wR2 = 0.1010	
Largest diff. peak and hole	0.307 and -0.397 $eÅ^{-3}$	


C11
C12
C13
C10
C7
O2
C6
C5
C4
O4
O3
N1
C3
S1
C9
C8
O1
C1
C2
O5

Appendix 2.5

Table 1. Crystal data and structure refinement for **205**

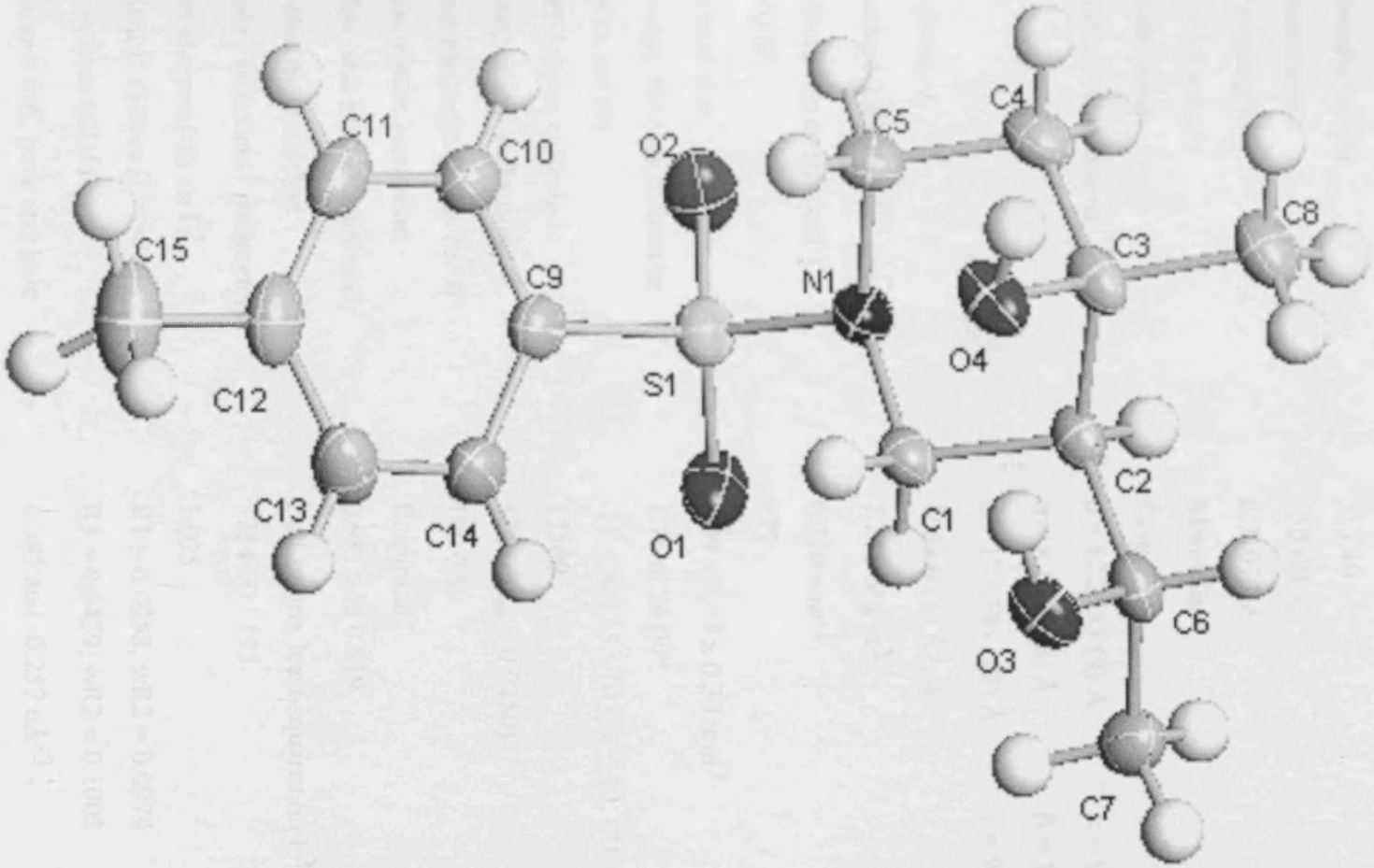
Identification code	**205**	
Empirical formula	$C_{13}H_{21}NO_5S$	
Formula weight	303.37	
Temperature	150 (2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P_{-1}	
Unit cell dimensions	a = 7.511 (2) Å	α = 62.742 (5)°
	b = 10.690 (3) Å	β = 76.977 (5)°
	c = 10.855 (3) Å	γ = 77.392 (5)°
Volume, Z	748.2 (4) $Å^3$, 2	
Density (calculated)	1.347 Mg/m^3	
Absorption coefficient	0.234 mm^{-1}	
F (000)	324	
Crystal size	0.16 x 0.14 x 0.13 mm^3	
θ range for data collection	2.13 to 25.00°.	
Index ranges	$-8 \leq h \leq 8, -12 \leq k \leq 12, -12 \leq l \leq 12$	
Reflections collected	5381	
Independent reflections	2587 (R_{int} = 0.0495)	
Completeness to θ = 25.00°	98.6 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2587 / 0 / 185	
Goodness-of-fit on F^2	1.068	
Final R indices [I >2σ(I)]	R1 = 0.0736, wR2 = 0.1971	
R indices (all data)	R1 = 0.0886, wR2 = 0.2063	
Largest diff. peak and hole	0.882 and -0.255 $eÅ^{-3}$	


C13
C14
O2
C5
C4
C15
C9
C3
S1
N1
C8
C12
O4
C11
C10
O1
C1
C2
C6
O3
C7

Appendix 2.6

Table 1. Crystal data and structure refinement for **212**

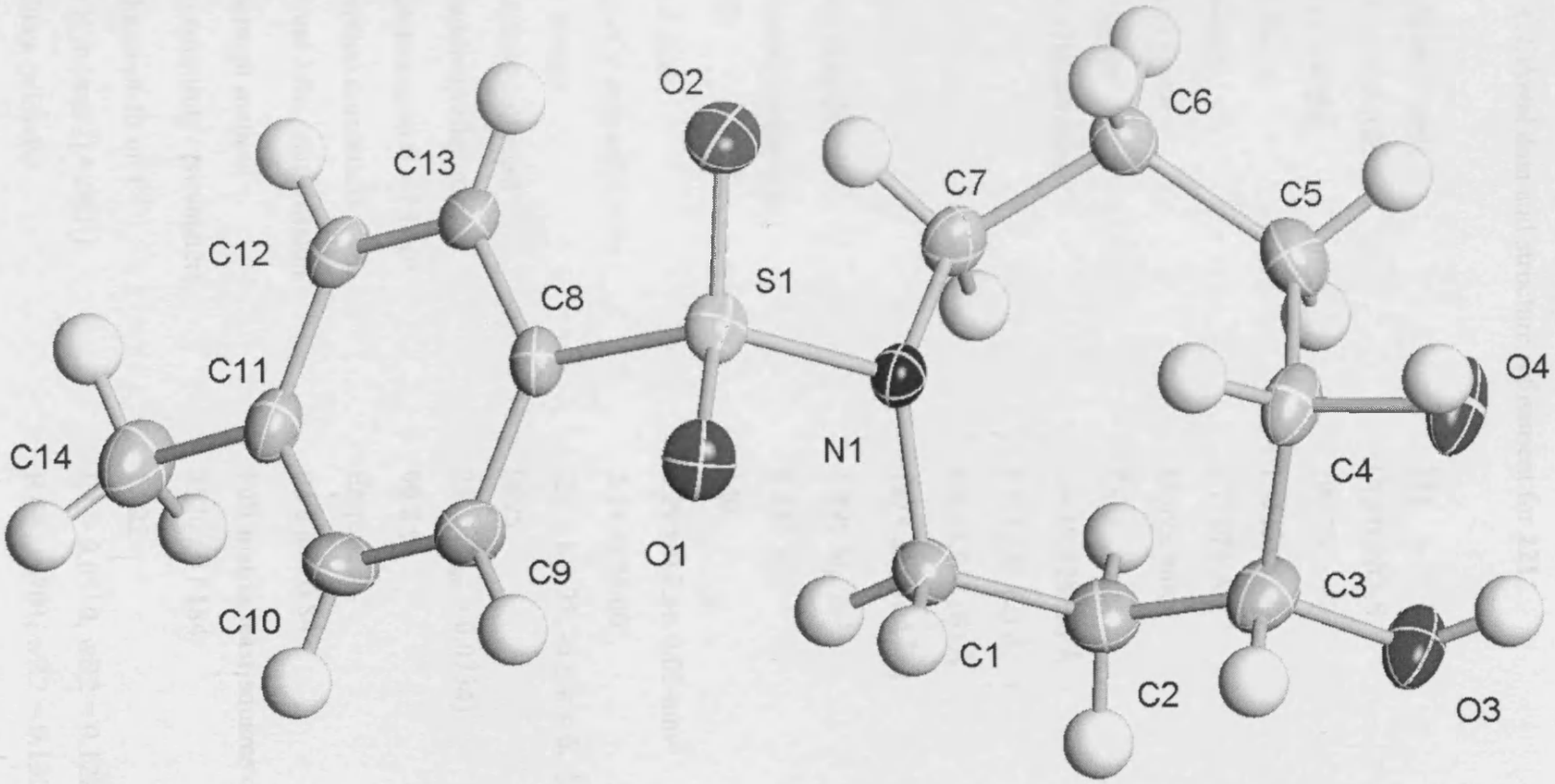
Identification code	**212**	
Empirical formula	$C_{15}H_{21}NO_4S$	
Formula weight	311.39	
Temperature	150 (2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P_{-1}	
Unit cell dimensions	a = 11.5616 (8) Å	α = 104.033 (1)°
	b = 11.9745 (8) Å	β = 99.202 (1)°
	c = 12.9339 (9) Å	γ = 111.642 (1)°
Volume, Z	1551.77 (18) $Å^3$, 4	
Density (calculated)	1.333 Mg/m^3	
Absorption coefficient	0.224 mm^{-1}	
F (000)	664	
Crystal size	0.31 x 0.25 x 0.11 mm^3	
θ range for data collection	1.69 to 26.00°.	
Index ranges	$-14 \leq h \leq 14$, $-14 \leq k \leq 14$, $-15 \leq l \leq 15$	
Reflections collected	12210	
Independent reflections	6016 (R_{int} = 0.0201)	
Completeness to θ = 26.00°	98.8 %	
Absorption correction	Empirical	
Max. and Min. transmission	0.981 and 0.835	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6016 / 0 / 387	
Goodness-of-fit on F^2	0.942	
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0398, wR2 = 0.1020	
R indices (all data)	R1 = 0.0519, wR2 = 0.1055	
Largest diff. peak and hole	0.423 and -0.270 $eÅ^{-3}$	


C11
C10
O2
C5
C4
C15
C9
N1
C3
C8
O4
S1
C12
C2
C13
C14
O1
C1
O3
C6
C7

Appendix 2.7

Table 1. Crystal data and structure refinement for **213**

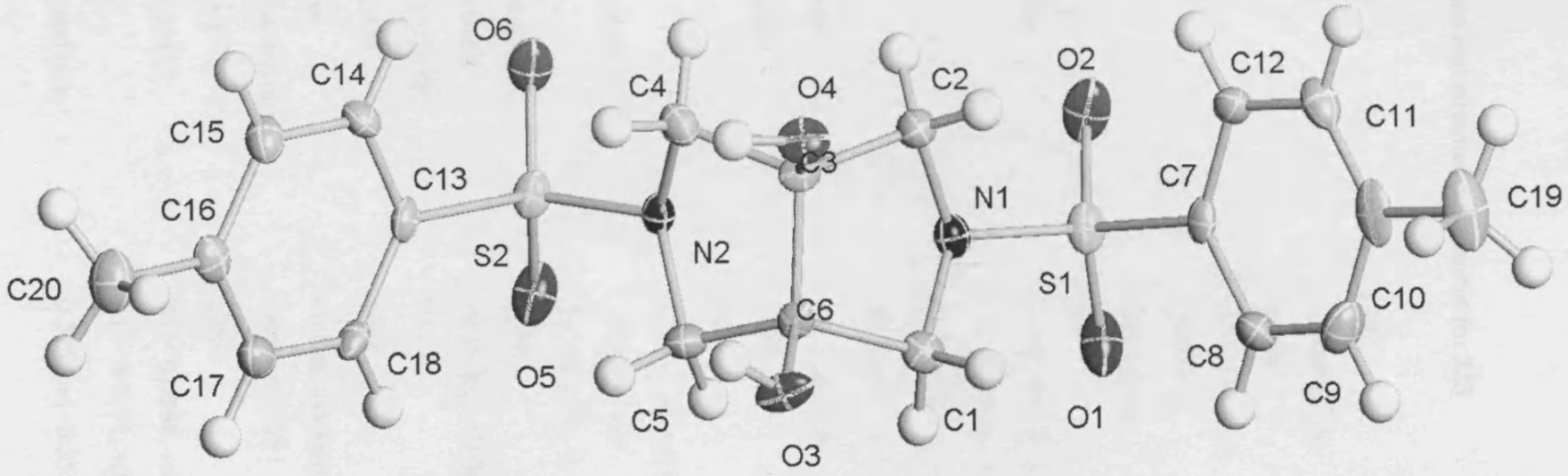
Identification code	**213**	
Empirical formula	$C_{15}H_{23}NO_4S$	
Formula weight	313.40	
Temperature	150 (2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P_{2(1)/c}$	
Unit cell dimensions	a = 12.2853 (9) Å	$\alpha = 90°$
	b = 8.1976 (6) Å	$\beta = 109.406\ (1)°$
	c = 17.4535 (12) Å	$\gamma = 90°$
Volume, Z	1657.9 (2) $Å^3$, 4	
Density (calculated)	1.256 Mg/m^3	
Absorption coefficient	0.210 mm^{-1}	
F (000)	672	
Crystal size	0.09 x 0.13 x 0.39 mm^3	
θ range for data collection	1.76 to 26.00°.	
Index ranges	$-15 \leq h \leq 15, -10 \leq k \leq 10, -21 \leq l \leq 21$	
Reflections collected	12569	
Independent reflections	3254 (R_{int} = 0.0250)	
Completeness to θ = 26.00°	100.0 %	
Absorption correction	Empirical	
Max. and Min. transmission	0.981 and 0.819	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3254 / 0 / 193	
Goodness-of-fit on F^2	1.025	
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0358, wR2 = 0.0974	
R indices (all data)	R1 = 0.0439, wR2 = 0.1002	
Largest diff. peak and hole	0.385 and -0.257 $eÅ^{-3}$	


O2
C6
C13
C7
C5
C12
S1
C8
O4
C11
N1
C14
C4
O1
C9
C3
C10
C1
C2
O3

Appendix 2.8

Table 1. Crystal data and structure refinement for **221**

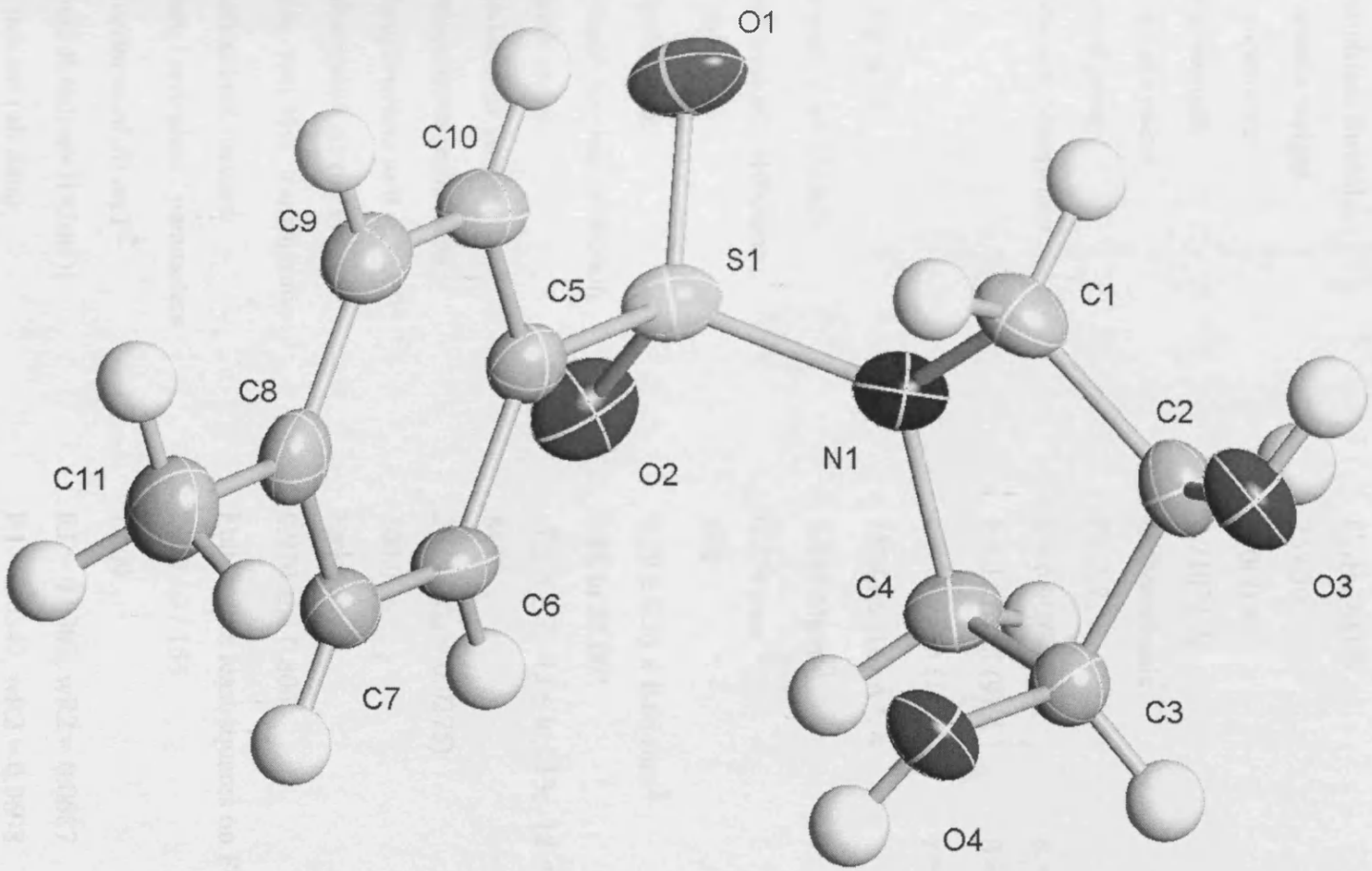
Identification code	**221**	
Empirical formula	$C_{14}H_{21}NO_4S$	
Formula weight	299.38	
Temperature	150 (2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P_{2(1)/c}$	
Unit cell dimensions	a = 19.628 (8) Å	α = 90°
	b = 5.381 (2) Å	β = 104.057(7)°
	c = 13.912 (6) Å	γ = 90°
Volume, Z	1425.4 (10) $Å^3$, 4	
Density (calculated)	1.395 Mg/m^3	
Absorption coefficient	0.240 mm^{-1}	
F (000)	640	
Crystal size	0.29 x 0.23 x 0.05 mm^3	
θ range for data collection	2.14 to 25.00°.	
Index ranges	$-23 \leq h \leq 23$, $-6 \leq k \leq 6$, $-16 \leq l \leq 16$	
Reflections collected	9595	
Independent reflections	2520 (R_{int} = 0.0734)	
Completeness to θ = 25.00°	99.8 %	
Absorption correction	Empirical	
Max. and Min. transmission	0.98 and 0.84	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2520 / 0 / 184	
Goodness-of-fit on F^2	1.022	
Final R indices [I >2σ(I)]	R1 = 0.0510, wR2 = 0.1223	
R indices (all data)	R1 = 0.0701, wR2 = 0.1308	
Largest diff. peak and hole	0.500 and -0.290 $eÅ^{-3}$	


O6
C14
C4
O4
C2
O2
C12
C15
C3
C11
C13
C7
C16
N1
C19
S2
N2
S1
C20
C6
C10
C18
C8
C17
O5
C5
C1
O1
C9
O3

Appendix 2.9

Table 1. Crystal data and structure refinement for **223**

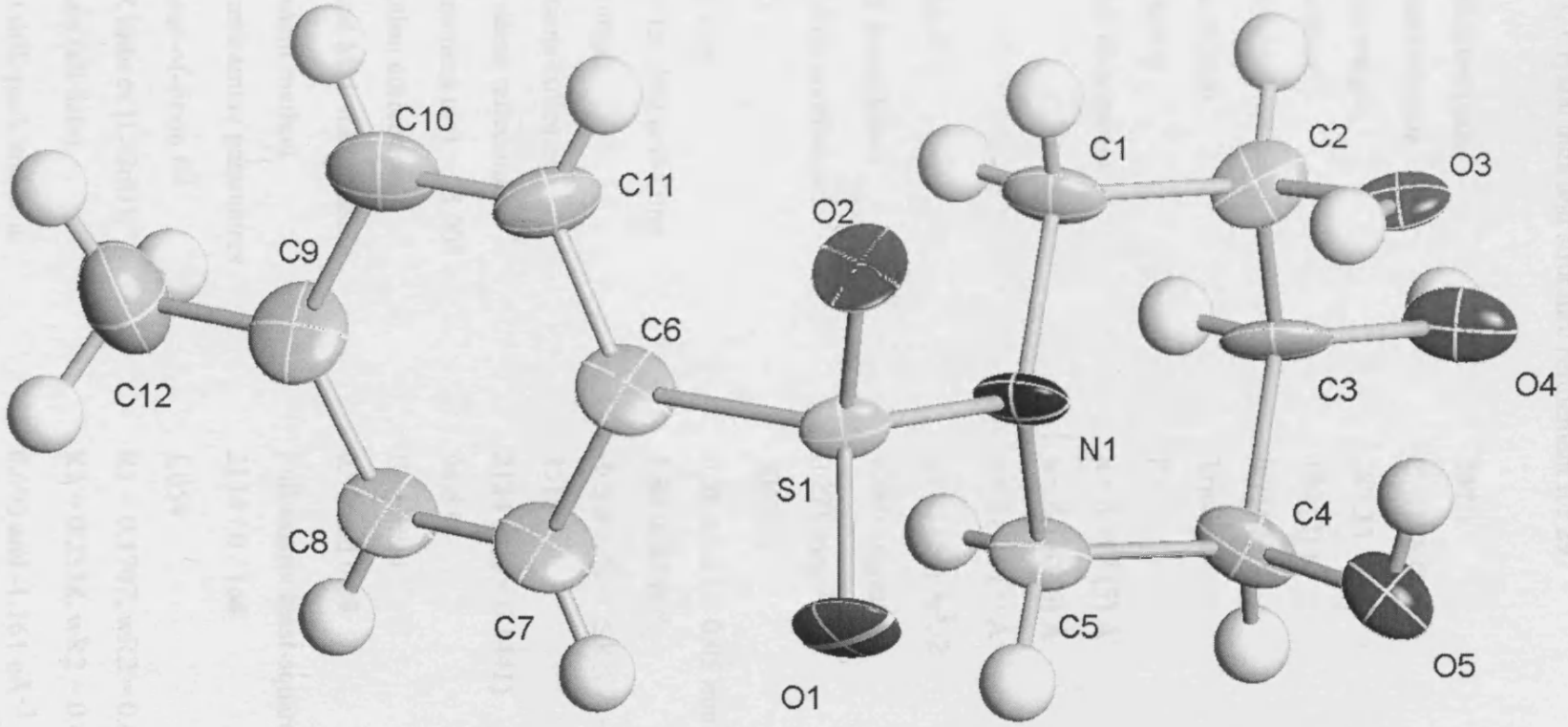
Identification code	**223**	
Empirical formula	$C_{20}H_{24}N_2O_6S_2$	
Formula weight	452.53	
Temperature	150 (2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$C_{2/c}$	
Unit cell dimensions	a = 33.508 (5) Å	α = 90°
	b = 5.5153 (8) Å	β = 112.943 (2)°
	c = 23.133 (3) Å	γ = 90°
Volume, Z	3937.0 (10) $Å^3$, 8	
Density (calculated)	1.527 Mg/m^3	
Absorption coefficient	0.314 mm^{-1}	
F (000)	1904	
Crystal size	0.22 x 0.12 x 0.08 mm^3	
θ range for data collection	1.32 to 25.00°.	
Index ranges	$-39 \leq h \leq 39$, $-6 \leq k \leq 6$, $-27 \leq l \leq 27$	
Reflections collected	12921	
Independent reflections	3469 (R_{int} = 0.0457)	
Completeness to θ = 25.00°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3469 / 0 / 275	
Goodness-of-fit on F^2	1.216	
Final R indices [I>2σ(I)]	R1 = 0.0868, wR2 = 0.1804	
R indices (all data)	R1 = 0.1071, wR2 = 0.1895	
Largest diff. peak and hole	0.795 and -0.355 $eÅ^{-3}$	


O1
C10
C9
S1
C5
C1
C8
C2
C11
O2
N1
C6
C4
O3
C7
C3
O4

Appendix 2.10

Table 1. Crystal data and structure refinement for **245**

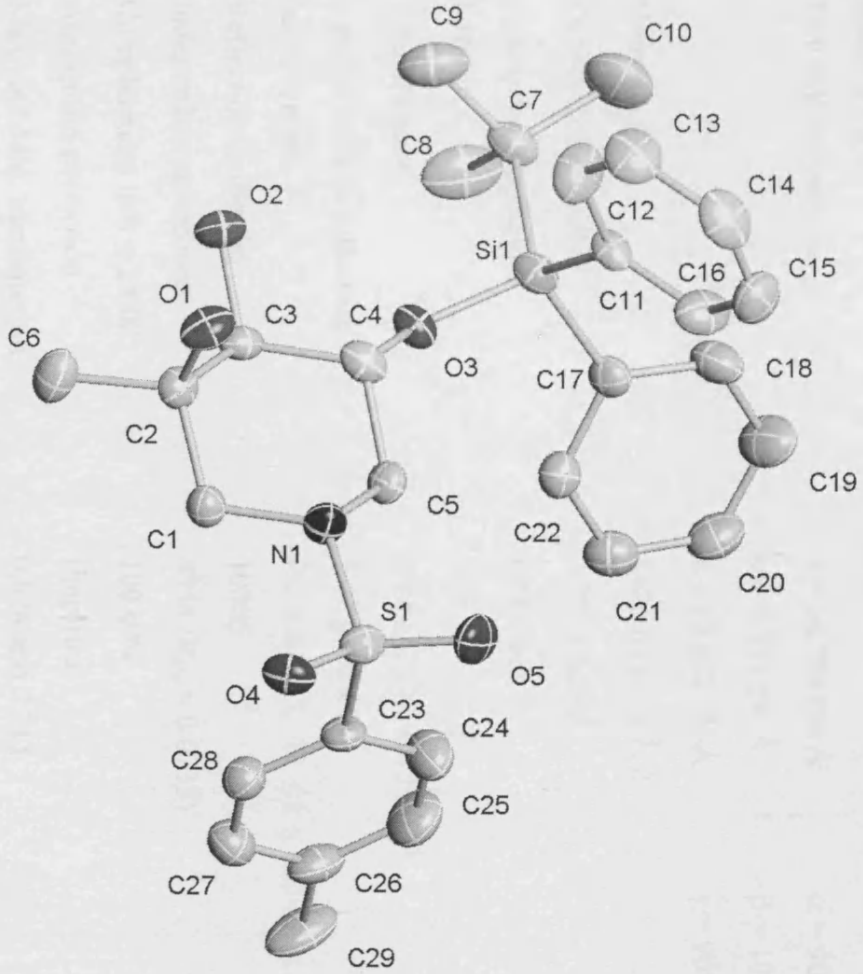
Identification code	**245**	
Empirical formula	$C_{11}H_{15}NO_4S$	
Formula weight	257.30	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.4098 (5) Å	$\alpha = 90°$
	b = 11.6188 (9) Å	$\beta = 90°$
	c = 15.7646 (12) Å	$\gamma = 90°$
Volume, Z	1174.06 (16) $Å^3$, 4	
Density (calculated)	1.456 Mg/m^3	
Absorption coefficient	0.279 mm^{-1}	
F (000)	544	
Crystal size	0.29 x 0.23 x 0.05 mm^3	
θ range for data collection	2.18 to 25.00°	
Index ranges	$-7 \leq h \leq 7, -13 \leq k \leq 13, -18 \leq l \leq 18$	
Reflections collected	8490	
Independent reflections	2079 (R_{int} = 0.0275)	
Completeness to θ = 25.00°	100.0 %	
Absorption correction	Empirical	
Max. and Min. transmission	0.970 and 0.806	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2079 / 0 / 155	
Goodness-of-fit on F^2	1.009	
Final R indices [I>2σ(I)]	R1 = 0.0302, wR2 = 0.0687	
R indices (all data)	R1 = 0.0342, wR2 = 0.0698	
Absolute structure parameter	-0.03 (8)	
Largest diff. peak and hole	0.253 and -0.133 $eÅ^{-3}$	


C10
C11
C9
C6
C12
C8
C7
O2
S1
O1
N1
C1
C2
O3
C3
O4
C4
C5
O5

Appendix 2.11

Table 1. Crystal data and structure refinement for **297**

Identification code	**297**	
Empirical formula	$C_{12}H_{17}NO_5S$	
Formula weight	287.33	
Temperature	150 (2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P_{-1}	
Unit cell dimensions	a = 5.292 (5) Å	α = 84.959(19)°
	b = 6.180 (6) Å	β = 83.221(19)°
	c = 21.73 (2) Å	γ = 64.671(16)°
Volume, Z	637.2 (11) $Å^3$, 2	
Density (calculated)	1.497 Mg/m^3	
Absorption coefficient	0.271 mm^{-1}	
F (000)	304	
Crystal size	0.38 x 0.21 x 0.05 mm^3	
θ range for data collection	1.89 to 25.00°.	
Index ranges	$-6 \leq h \leq 6, -7 \leq k \leq 7, -25 \leq l \leq 25$	
Reflections collected	3515	
Independent reflections	2134 (R_{int} = 0.1441)	
Completeness to θ = 25.00°	94.6 %	
Absorption correction	Empirical	
Max. and Min. transmission	0.99 and 0.89	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2134 / 0 / 164	
Goodness-of-fit on F^2	1.054	
Final R indices [$I > 2\sigma(I)$]	R1 = 0.1707, wR2 = 0.4097	
R indices (all data)	R1 = 0.2338, wR2 = 0.4531	
Largest diff. peak and hole	0.690 and -1.161 $eÅ^{-3}$	


C9
C10
C7
C13
C8
C14
O2
C12
Si1
C15
C16
O1
C3
C4
C11
C6
O3
C17
C18
C2
C19
C5
C22
C1
N1
C20
S1
C21
O5
O4
C23
C24
C28
C25
C27
C26
C29

Appendix 2.12

Table 1. Crystal data and structure refinement for **327**

Identification code	**327**	
Empirical formula	$C_{29}H_{37}NO_5SSi$	
Formula weight	539.75	
Temperature	150 (2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 10.784 (6) Å	α = 90°
	b = 9.723 (5) Å	β = 100.802 (10)°
	c = 13.842 (7) Å	γ = 90°
Volume, Z	1425.6 (13) $Å^3$, 2	
Density (calculated)	1.257 Mg/m^3	
Absorption coefficient	0.194 mm^{-1}	
F (000)	576	
Crystal size	0.44 x 0.19 x 0.12 mm^3	
θ range for data collection	1.50 to 25.00°.	
Index ranges	$-12 \leq h \leq 12, -11 \leq k \leq 11, -16 \leq l \leq 16$	
Reflections collected	10305	
Independent reflections	4954 (R_{int} = 0.0733)	
Completeness to θ = 25.00°	100.0 %	
Absorption correction	Empirical	
Max. and Min. transmission	0.928 and 0.711	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4954 / 1 / 339	
Goodness-of-fit on F^2	0.796	
Final R indices [I >2σ(I)]	R1 = 0.0562, wR2 = 0.0733	
R indices (all data)	R1 = 0.0863, wR2 = 0.0821	
Absolute structure parameter	-0.04 (10)	
Largest diff. peak and hole	0.366 and -0.243 $eÅ^{-3}$	