

# **"Asymmetric Piperidine Synthesis"**

by

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## Abstract

It has been demonstrated that bakers' yeast reduction of 1-*tert*-butyl-2-methyl 3-oxo-piperidine-1,2-dicarboxylate gives (2*R*, 3*S*), 1-*tert*-butyl-2-methyl 3-hydroxy-piperidine-1,2-dicarboxylate in 80% chemical yield with >99% d.e. and >97% e.e. Also bakers' yeast reduction of 1-*tert*-butyl-3-ethyl 4-oxo-piperidine-1,3-dicarboxylate gives (3*R*, 4*S*), 1-*tert*-butyl-3-ethyl 4-hydroxy-piperidine-1,3-dicarboxylate in 74% chemical yield with >99% d.e. and >93% e.e. The optical purity and absolute configurations of the hydroxy-ester derivatives were determined by conversion into the corresponding chiral *bis*-tosylate derivatives of 2- and 3-piperidinemethanol respectively.

It has also been shown that bakers' yeast reduction of 1-*tert*-butyl-4-methyl 3-oxo-piperidine-1,4-dicarboxylate gives (3*R*, 4*R*)-1-*tert*-butyl-4-methyl 3-hydroxy-piperidine-dicarboxylate in 81% chemical yield with >99% d.e. and 87% e.e. The optical purity and absolute configuration of the hydroxy-ester derivative were determined by utilisation of the compound in the total synthesis of (*R*)-3-quinuclidinol *via* chain elongation at C-4 of the piperidine followed by cyclisation to produce the bicyclic structure.

Further work is reported on the diastereoselective synthesis of polyhydroxylated indolizidine alkaloids. 1-Acetoxy-2-hydroxy-3-(hydroxymethyl)-indolizidine has been synthesised as a single diastereomer from 2-piperidinemethanol *via* attack of an amine onto an epoxide functionality thus producing the bicyclic system.

## **Dedication**

*To Mum and Dad*

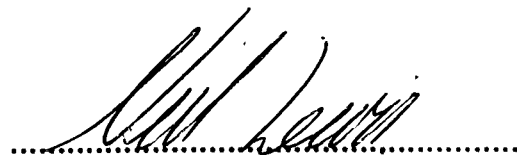
## **Acknowledgements**

I would like to express my sincere thanks to my supervisor Dr. D. W. Knight and my industrial supervisor, Dr. D. Haigh, for their invaluable contributions during the course of this work. I would also like to express my thanks to the technical staff at Nottingham University and SB Pharmaceuticals, Great Burgh, for their assistance throughout this time. I acknowledge SB Pharmaceuticals and the Science and Engineering Research Council for financial support through the CASE scheme.

## Declaration

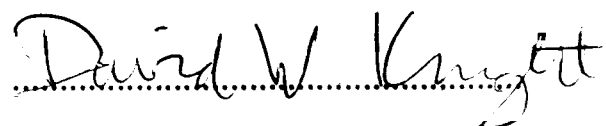
I hereby declare that the substance of this thesis has not been nor is being currently submitted in candidature for any other degree.

I also declare that the work embodied in this thesis is the result of my own investigations and where work of other investigators has been used this is fully acknowledged in the text.

A handwritten signature in black ink, appearing to read 'Neil Lewis', written over a horizontal dotted line.

(Neil Lewis)

DIRECTOR OF STUDY

A handwritten signature in black ink, appearing to read 'David W. Knight', written over a horizontal dotted line.

(Dr. D. W. Knight)

### Abbreviations used in the text

<b>Ac</b>	Acetyl
<b>AIBN</b>	Azo- <i>bis</i> -isobutyronitrile
<b>Bn</b>	Benzyl
<b>BOC</b>	<i>t</i> -Butyl carbonate
<b>Bu</b>	Butyl
<b>BY</b>	Bakers' yeast
<b>CDI</b>	1,1'-Carbonyldiimidazole
<b>DBU</b>	1,8-diazobicyclo[5.4.0]undecene-7
<b>DBY</b>	Dried bakers' yeast
<b>DCC</b>	Dicyclohexylcarbodiimide
<b>d.e.</b>	Diastomeric excess
<b>DEAD</b>	Diethylazodicarboxylate
<b>DIBAL-H</b>	Diisobutylaluminium hydride
<b>DMAP</b>	4-Dimethylaminopyridine
<b>DMF</b>	Dimethylformamide
<b>DMSO</b>	Dimethylsulphoxide
<b>e.e.</b>	Enantiomeric excess
<b>Et</b>	Ethyl
<b>Im</b>	Imidazole
<b>IMBY</b>	Immobilised bakers' yeast
<b>LDA</b>	Lithium diisopropylamine
<b>mCPBA</b>	m-Chloroperoxybenzoic acid
<b>Me</b>	Methyl
<b>MOM</b>	Methoxymethyl
<b>Ms</b>	Methane sulphonyl



<b>NMR</b>	Nuclear magnetic resonance
<b>NOE</b>	Nuclear Overhauser Effect
<b>Ph</b>	Phenyl
<b>Pr</b>	Propyl
<b>TBDMS</b>	<i>t</i> -Butyldimethylsilyl
<b>TBDPS</b>	<i>t</i> -Butyldiphenylsilyl
<b>Tf</b>	CF <sub>3</sub> SO <sub>2</sub>
<b>TFA</b>	Trifluoroacetic acid
<b>THF</b>	Tetrahydrofuran
<b>Ts</b>	<i>p</i> -Toluene sulphonyl
<b>TMS</b>	Trimethylsilyl / Tetramethylsilane
<b>Z</b>	Benzyl carbonate

## **Chapter One**

### **The use of Bakers' Yeast in Enantioselective Synthesis**

## Introduction to bakers' yeast

In the past few years a growing interest in chiral compounds arose in synthetic organic chemistry. This interest has in the main been fuelled by the pressure that has been put on the pharmaceutical industry to produce enantiomerically pure drugs since unwanted enantiomers can in theory have harmful and sometimes fatal effects. The use of naturally occurring chiral building blocks has been known for quite some time and indeed sugars and amino acids are commonplace chiral compounds used in enantioselective synthesis. The so called 'chiral pool' which is a selection of readily available chiral compounds is increasing in size, which makes for a wide choice of chiral building blocks for the organic chemist interested in enantioselective synthesis.

Accompanying the growth of the chiral pool has been a surge in the amount of scientific papers appearing in the literature regarding stereo- and enantioselective transformations. Indeed comprehensive reviews have been written on general areas of stereoselective transformations such as enantioselective addition of titanium compounds to carbonyl groups,<sup>1</sup> addition of organozinc compounds to aldehydes<sup>2</sup> and asymmetric conjugate addition<sup>3</sup> to name but three. During the same time, synthetic organic chemists have appreciated the input received from microbiologists and indeed microbial and enzymatic mediated transformations are becoming increasingly popular in the laboratory.

The chemists desire to satisfy the hunger for chirality has led to a revived interest in bakers' yeast (*Saccharomyces cerevisiae*) mediated stereoselective transformations<sup>4</sup>. The use of bakers yeast as a laboratory reagent was reported nearly a century ago<sup>5,6</sup> and by the mid 1950s over one hundred and sixty scientific works had been published in this area.<sup>7</sup> The numbers of scientific works devoted to this micro-organism has grown tremendously since the 1970s and it is

interesting to note that over three hundred enzymes have been purified from bakers' yeast and doubtless many more exist.<sup>8</sup> It has also been shown that many of these isolated enzymes show activity under very similar conditions: neutral to mildly acidic aqueous media. This may seem a good thing in that bakers' yeast shows a wide range of chemical capabilities under these mild conditions. However this 'versatility' has the price of making bakers' yeast reactions potentially non-selective in the mode of action on the substrate used. This is, in fact, a common argument among chemists who prefer the selectivity of often expensive isolated enzymes and brand bakers' yeast reactions as 'intrinsically messy'.<sup>9</sup> This is of course true to varying degrees but their argument against the use of bakers' yeast is strengthened when one considers that the products from such reactions are often difficult to isolate from the fermentation broth and are sometimes contaminated with the cell mass, nutrients, metabolites and unreacted substrate.

A great deal of effort has been focused on these inherent problems and a greater understanding of the mode of action of the micro-organism has been established.<sup>10</sup> New and novel abilities of the micro-organism are continually being reported in the scientific press as new substrates are subjected to the various reactions.<sup>11,12</sup> As more effort is focused on the use of bakers' yeast, the greater the understanding of the enzymatic processes involved becomes.

It has been the experience of many synthetic chemists that in addition to the desired transformation, the substrate also undergoes multi-stage transformations leading to a mixture of products. This problem of selectivity, i.e. controlling the various enzymatic processes involved with bakers' yeast has become a major area for research and discussion. As it is already understood that bakers' yeast displays most of its activity under very similar conditions, chemists have used structure modifications as the major tool in controlling selectivity. However other methods have been reported for controlling the reaction such as the control of pH during reaction,<sup>13</sup> immobilisation of the cellular mass,<sup>14</sup> the nature of nutrients used,<sup>15,16</sup>

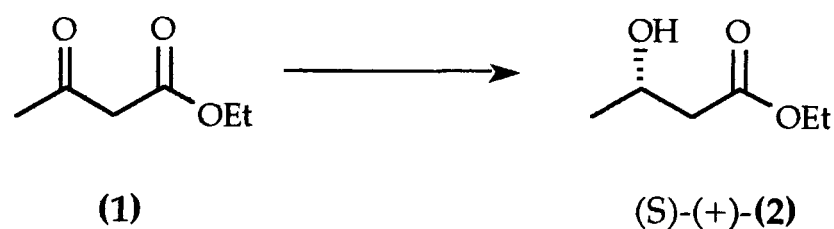
concentration,<sup>17</sup> pre-treatment of the cellular mass,<sup>18</sup> use of enzyme inhibitors<sup>15</sup> and varying the cellular mass/substrate ratio. This list is by no means exhaustive and indeed a constant stream of new methods continue to appear in the scientific literature. When appropriate extraction methodology is used with relatively inexpensive starting materials at an early point in the synthesis, then the convenience of obtaining valuable chiral intermediates of high optical purity will not be significantly influenced by any lack of efficiency.

In general, knowledge of the requirements of bakers' yeast and its mode of action is limited. This is because the isolated enzymes have only been compared to the whole microbial system in a few cases. This continues to be an area of great interest and doubtless will remain so for some time to come.

## **The Reactions of Bakers' Yeast**

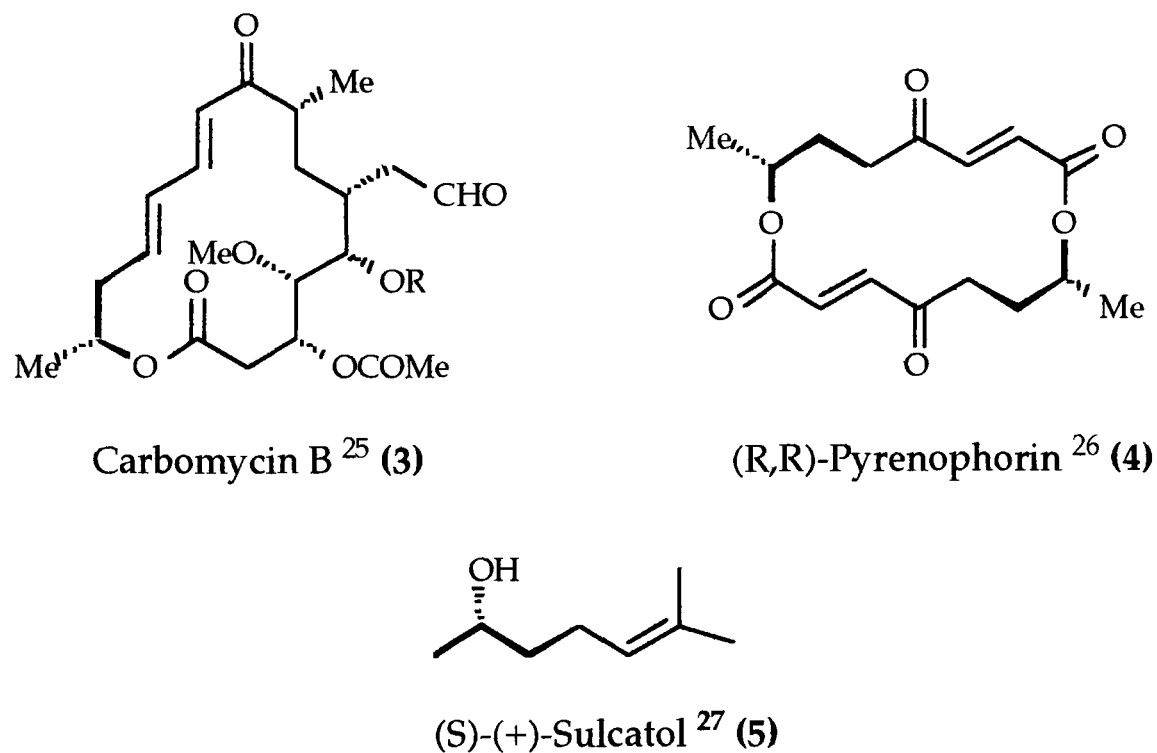
### **(1) The stereoselective reduction of $\beta$ -keto esters**

The use of bakers' yeast to transform small molecule  $\beta$ -keto-esters into chiral intermediates is certainly one of the most popular microbial transformation used by synthetic organic chemists. The reaction was first reported back in the early 1930s<sup>19</sup> but major discrepancies in enantiomeric excess (e.e) and yield meant that it was not until recently that the reaction was re-examined<sup>20-24</sup>. Seebach and co-workers studied the effect of the micro-organism on the simple  $\beta$ -keto ester, ethyl acetoacetate (1), in an attempt to produce chiral ethyl 3-hydroxybutanoate (2) as shown in Scheme 1.<sup>23</sup> They found the method easy to perform and observed enantiomeric excesses of greater than 85% in favour of the (S)-(+)-isomer (2).



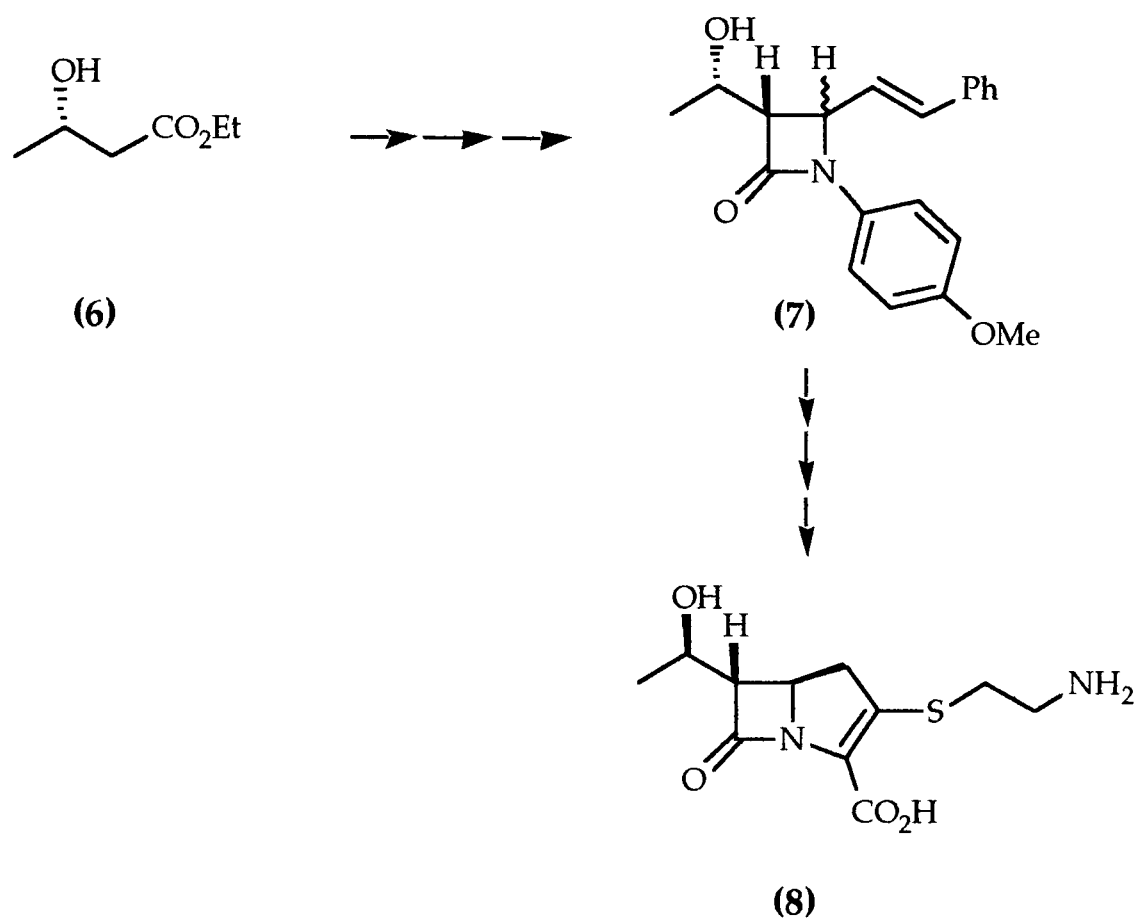
(Scheme 1)

Furthermore, the results were found to be reproducible using different brands of commercially available bakers' yeast and commercially available sugar (sucrose) overcoming a problem that earlier chemists had encountered. The product was later crystallised to optical purity *via* its 3,5-dinitrobenzoate derivative. Optically active ethyl 3-hydroxybutanoate (2) was shown to be an extremely useful intermediate in the synthesis of a number of important natural products as shown in Figure 1 in which the ethyl 3-hydroxybutanoate skeleton is highlighted.



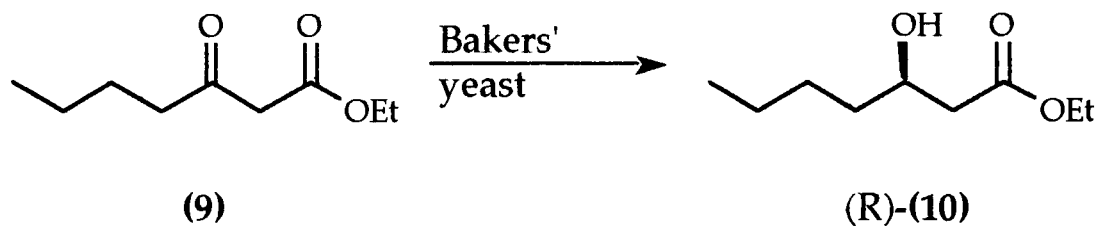
(Figure 1)

Georg and co-workers have also utilised (*S*)-(+)-ethyl 3-hydroxybutanoate (**2**) derived from bakers' yeast reduction in the synthesis of thienomycin (**8**)<sup>28,29</sup>. This is shown in Scheme 2.



(Scheme 2)

Further work on  $\beta$ -keto esters by Seebach showed that bakers' yeast reduction of 3-oxoheptanoate (**9**) gave 3-hydroxyheptanoate (**10**) with again high enantiomeric excess (>90%) as shown in Scheme 3 but in this case the (*R*) enantiomer was favoured.<sup>23</sup>



(Scheme 3)

A hypothesis put forward for this apparent change in selectivity is that the microbial system has a number of enzymes operating at the same time and these enzymes are substrate specific and in some way competing against each other. The need for a rational of these selectivity effects has become a major area of study.

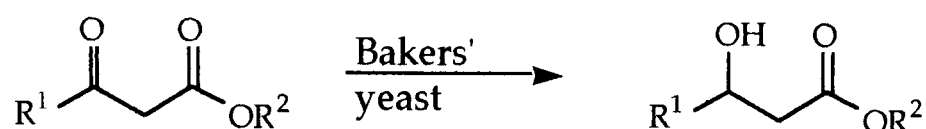
Sih and co-workers propose that there is a relationship between selectivity and the size of the groups attached to the carbonyl group.<sup>31,32</sup> Sih has shown that the microbial system of bakers' yeast has competing enzymes that deliver hydrogen selectively to both faces of the molecule. He has also shown that the rates of reaction of the competing enzymes, when different, lead to an excess of one enantiomer over the other and chirality is induced.

It follows therefore that the difference in size of the groups adjoining the carbonyl group should regulate the rate of reduction from each side and thus stereoselective reduction is observed. In other words the microbial system of bakers' yeast consists of a number of oxido-reductases each able to distinguish large and small groups in an enantiomeric way but operating at different rates.

From this came the proposal that the greatest factor that will influence selectivity will be structure modifications.

Examples of this approach are shown in Table 1 where both ends of a  $\beta$ -keto acid derivative have been manipulated and the stereochemical outcome of the bakers' yeast reduction deduced. Results from this approach have afforded enhanced yields and more importantly enhanced enantiomeric excesses.



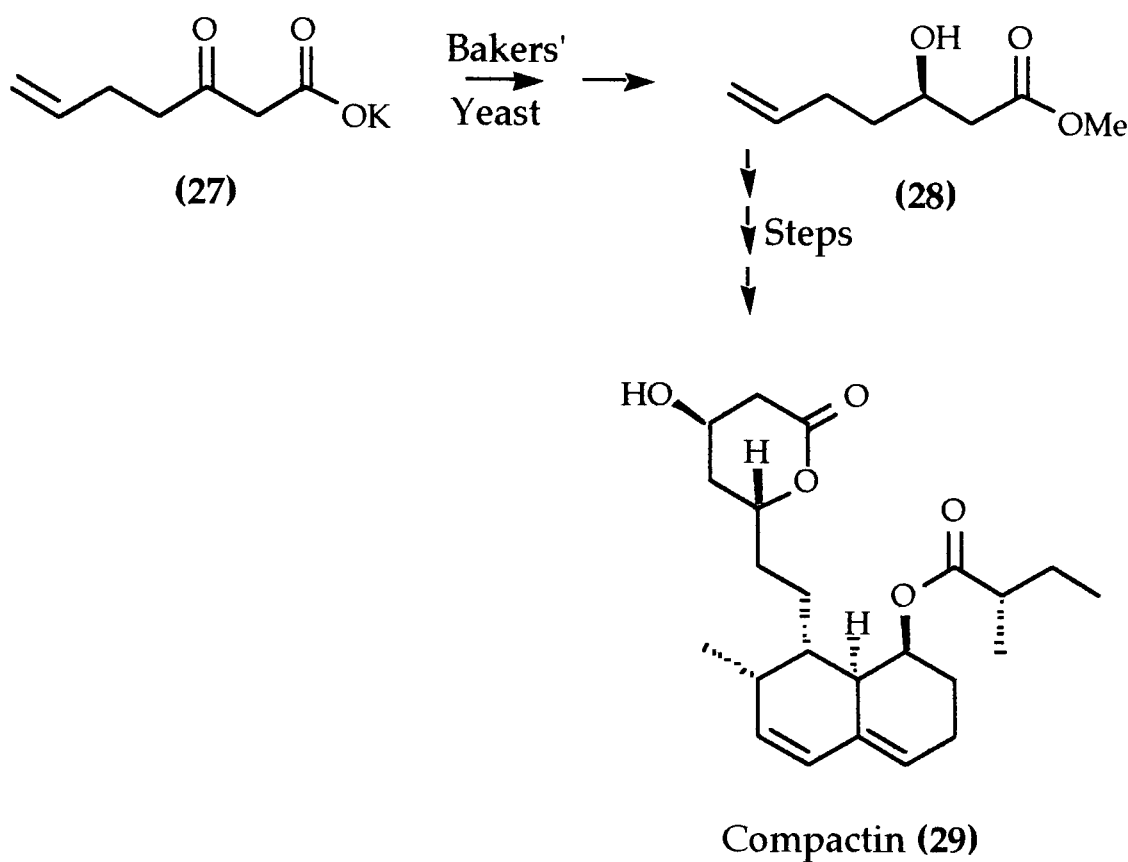


Substrate	R <sup>1</sup>	R <sup>2</sup>	Product	ee (%)	Ref
(1)	Me	Et	(2)-(S)	100	33
(11)	Et	Me	(12)-(R)	100	34
(13)	Et	<i>n</i> -C <sub>8</sub> H <sub>17</sub>	(14)-(S)	40	10
(15)	CH <sub>2</sub> N <sub>3</sub>	<i>n</i> -C <sub>8</sub> H <sub>17</sub>	(16)-(R)	98	35
(17)	<i>n</i> -Pr	H	(18)-(R)	100	36
(19)	Ph	Et	(20)-(S)	100	37
(21)	3-butenyl	K	(22)-(R)	100	33
(23)	3-pentenyl	K	(24)-(R)	100	33
(25)	(CH <sub>2</sub> ) <sub>3</sub> OCH <sub>2</sub> Ph	K	(26)-(R)	89	38

(Table 1)

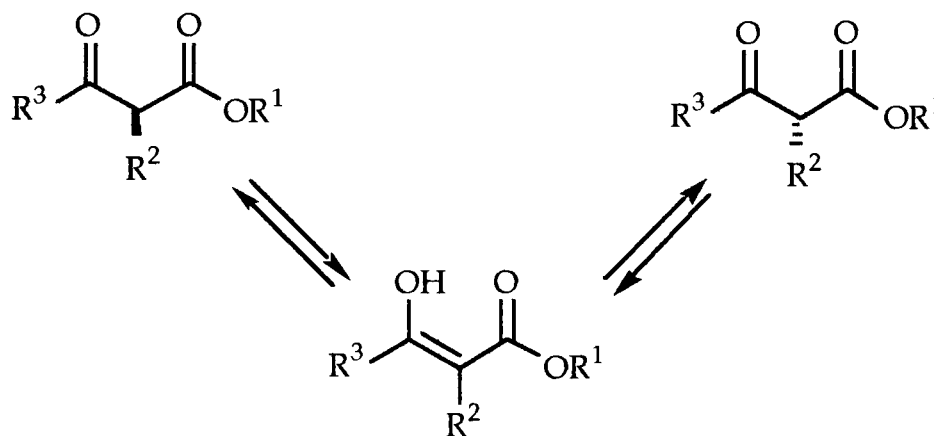
Enhancement of enantiomeric excess is observed when potassium carboxylates are used in place of carboxylic esters.<sup>39,40</sup> In the 3 examples (21), (23) and (25) of this shown in Table 1 the reduction has occurred with excellent enantiomeric excess. This method of enhancement of optical purity has been used *en route* to a number of important natural products, one of which is depicted in Scheme 4.<sup>41</sup>

A number of other significant improvements to the experimental procedure have been reported which enhance selectivity and chemical yield. These procedures and modifications will be discussed in a later section.



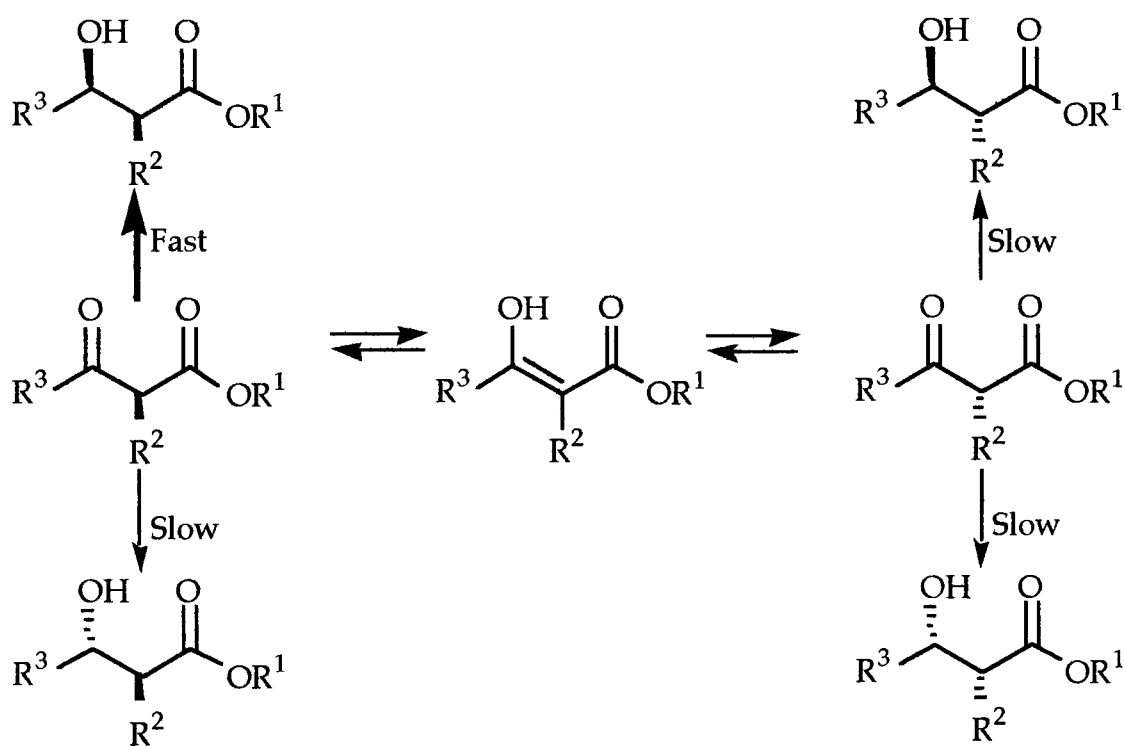
(Scheme 4)

There has been much interest in the bakers' yeast reduction of  $\alpha$ -substituted  $\beta$ -keto esters. Here both enantio- and diastereoselection have to be considered when predicting the likely stereochemistry of reaction products. The racemic substrate can interconvert and equilibrate *via* its enolic form as shown in Scheme 5.



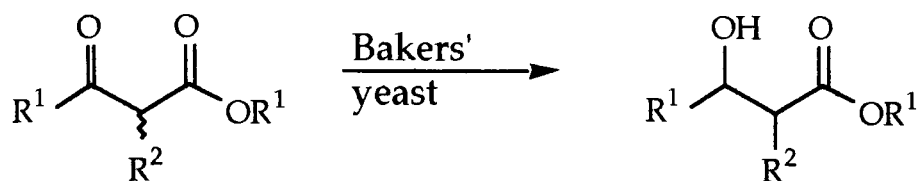
(Scheme 5)

From a mechanistic standpoint the reduction is likely to occur *via* one of two pathways. The first and less likely of these is by enantioselective “hydrogenation” of the carbon-carbon double bond of the enolic intermediate, although it is known that tetrasubstituted double bonds are not normally reduced by bakers' yeast. In the second and more likely case, one of the two enantiomers of the keto tautomer is reduced at a much faster rate than the other and this drives the equilibrium towards the formation of predominantly one stereoisomer. This is more pronounced the larger the difference in rates between the formation of one isomer versus the other three. This process is outlined in Scheme 6.



(Scheme 6)

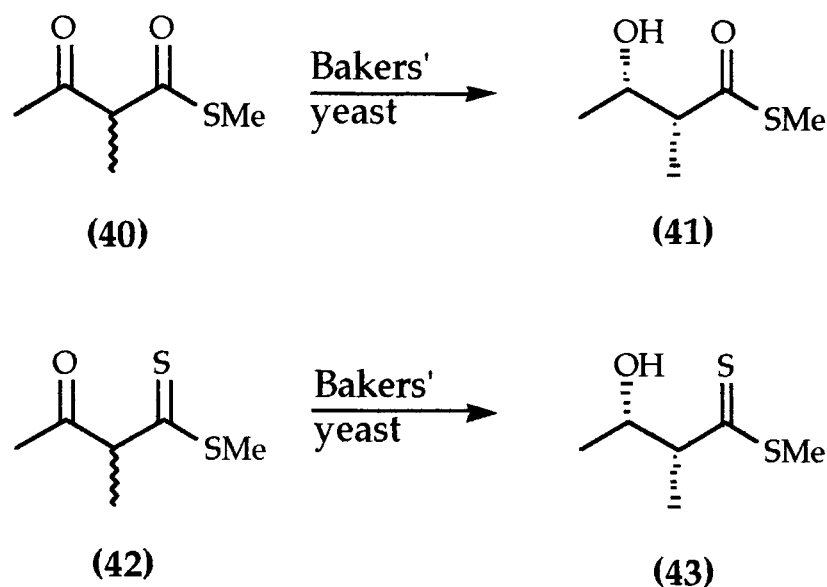
A number of representative examples of this type of reduction are shown in Table 2.



Substrate	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield (%)	% ee	% de	Ref
(30)	H	Me	Et	25	100	--	42
(31)	H	Et	Et	70	90	--	43
(32)	H	Me	<i>i</i> -Pr	78	90	--	44
(33)	Me	Me	Et	75	100	66	45
(34)	Me	Me	<i>t</i> -Bu	57	100	92	46
(35)	Me	Me	<i>n</i> -C <sub>8</sub> H <sub>17</sub>	82	98	98	45
(36)	Me	CH <sub>2</sub> CH=CH <sub>2</sub>	Et	84	100	90	47
(37)	Me	CH <sub>2</sub> CH=CH <sub>2</sub>	<i>t</i> -Bu	36	100	88	46
(38)	Me	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	Et	22	100	34	47
(39)	CH=CHPh	Me	Me	7	95	90	48

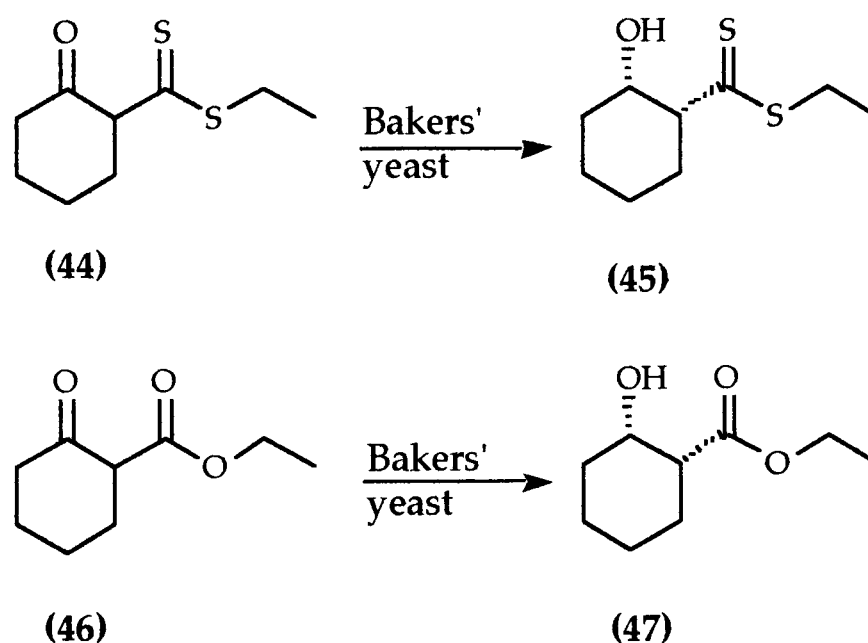
(Table 2)

By analogy to  $\beta$ -keto-esters, thio- and dithioesters are also reduced with outstanding *syn* selectivity by the micro-organism.<sup>49</sup> Indeed compounds (42) and (43) show enantiomeric excesses for the reaction of greater than 96% with *syn* preferences of greater than 88%, as shown in Scheme 7.



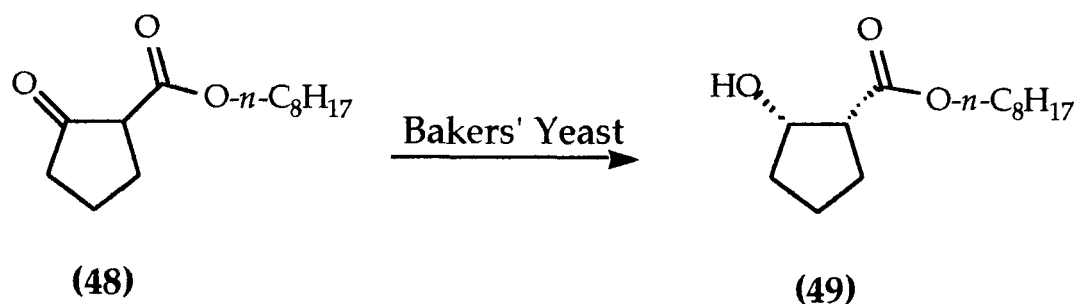
(Scheme 7)

The dithioester (43) can subsequently be transformed into the corresponding 3-hydroxy-ester in high yield and its optical purity is maintained. Similar selectivities are observed with compound (44) which is reduced with 96% enantiomeric excess and 100% diastereomeric excess (d.e).<sup>49</sup> These figures are higher than for the corresponding oxygen analogue (46).



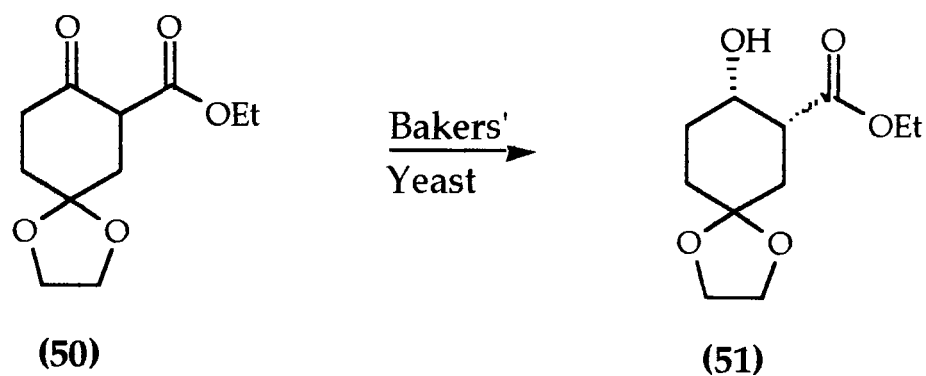
(Scheme 8)

The reaction has also been applied with some success to the corresponding cyclic systems and the reduction of 2-ketocycloalkane carboxylates has been studied in some depth.<sup>20,51</sup> An example of this is shown in Scheme 9 where the cyclopentanone derivative (48) is transformed to the corresponding alcohol (49) in 62% chemical yield, with 100% diastereomeric excess and greater than 96% enantiomeric excess.



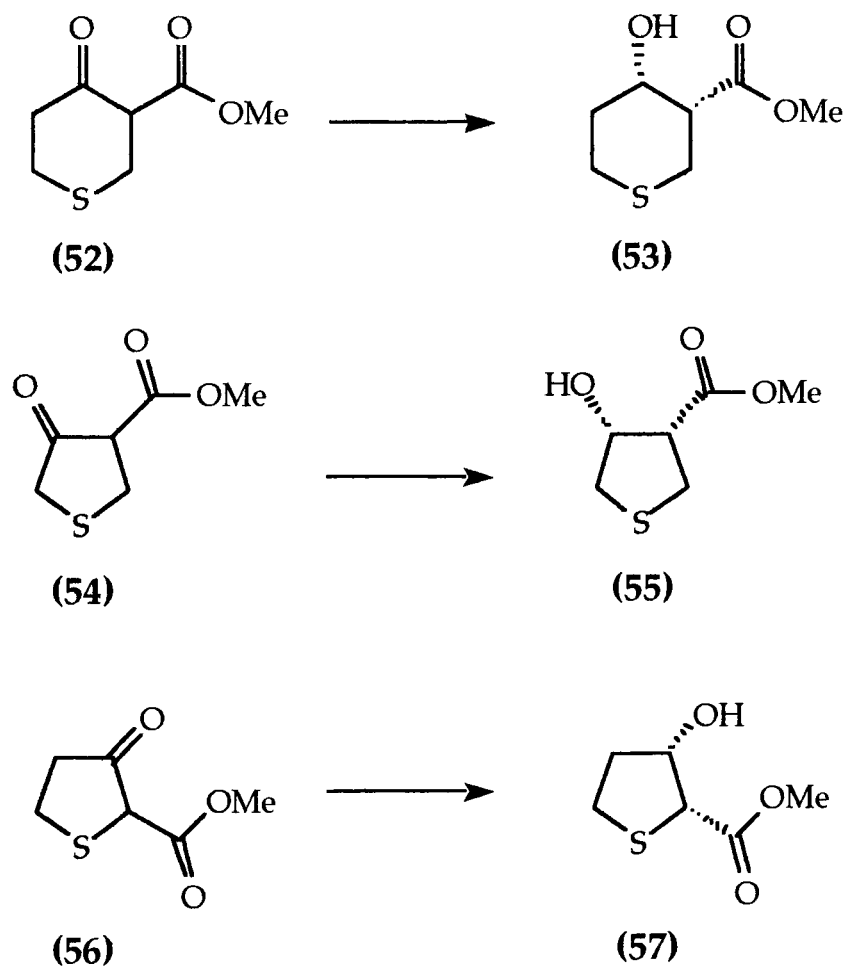
(Scheme 9)

In the case of cyclohexanone derivatives, it has been found that substitution at the 4-position of 2-oxocyclohexanecarboxylates results in enhanced optical purity in the reduced product.<sup>20,50</sup> This is shown in Scheme 10 where the substituted cyclohexanone derivative (50) is reduced in 74% yield with an excellent 98% e.e.



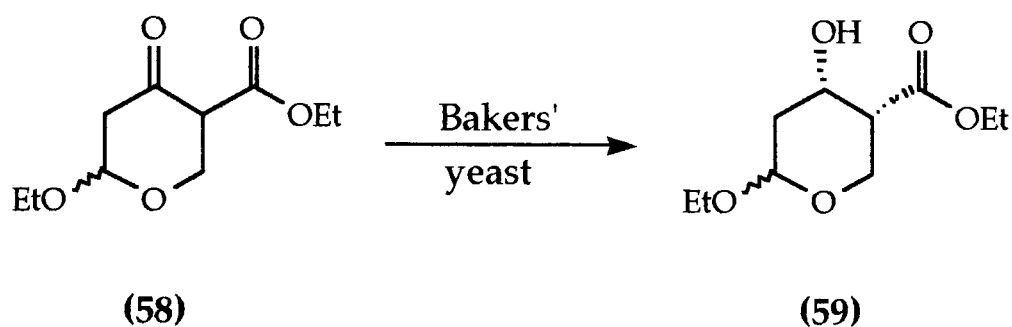
(Scheme 10)

The reaction has been extended even further to accommodate heterocyclic systems. In the case of the sulphur containing heterocycles shown in Scheme 11 the *cis*-isomers were obtained in all three cases. The β-hydroxy-ester (53) was obtained with 85% optical purity<sup>52</sup> and the β-hydroxy-ester (57) in 95% optical purity<sup>53</sup>.



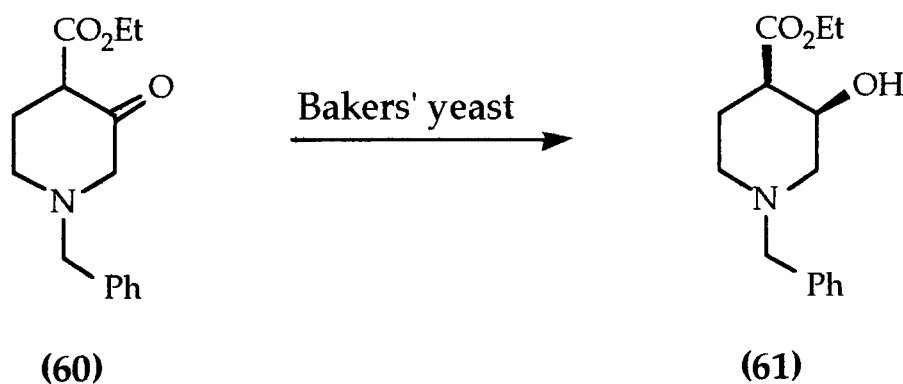
(Scheme 11)

The reduction of oxygen heterocycles is also possible using the micro-organism. For example the highly substituted six membered oxygen heterocycle (58) is reduced by bakers' yeast with the reduced product (59) being obtained with modest diastereoselection (43% e.e.) *via* kinetic resolution as shown in Scheme 12.<sup>54</sup>



(Scheme 12)

The piperidine derivative (60) was reduced to the corresponding *cis*-isomer (61) by Seebach and co-workers in a reported yield of 73% with an enantiomeric excess of greater than 95% but using a large excess of yeast and no added sucrose.<sup>55</sup>

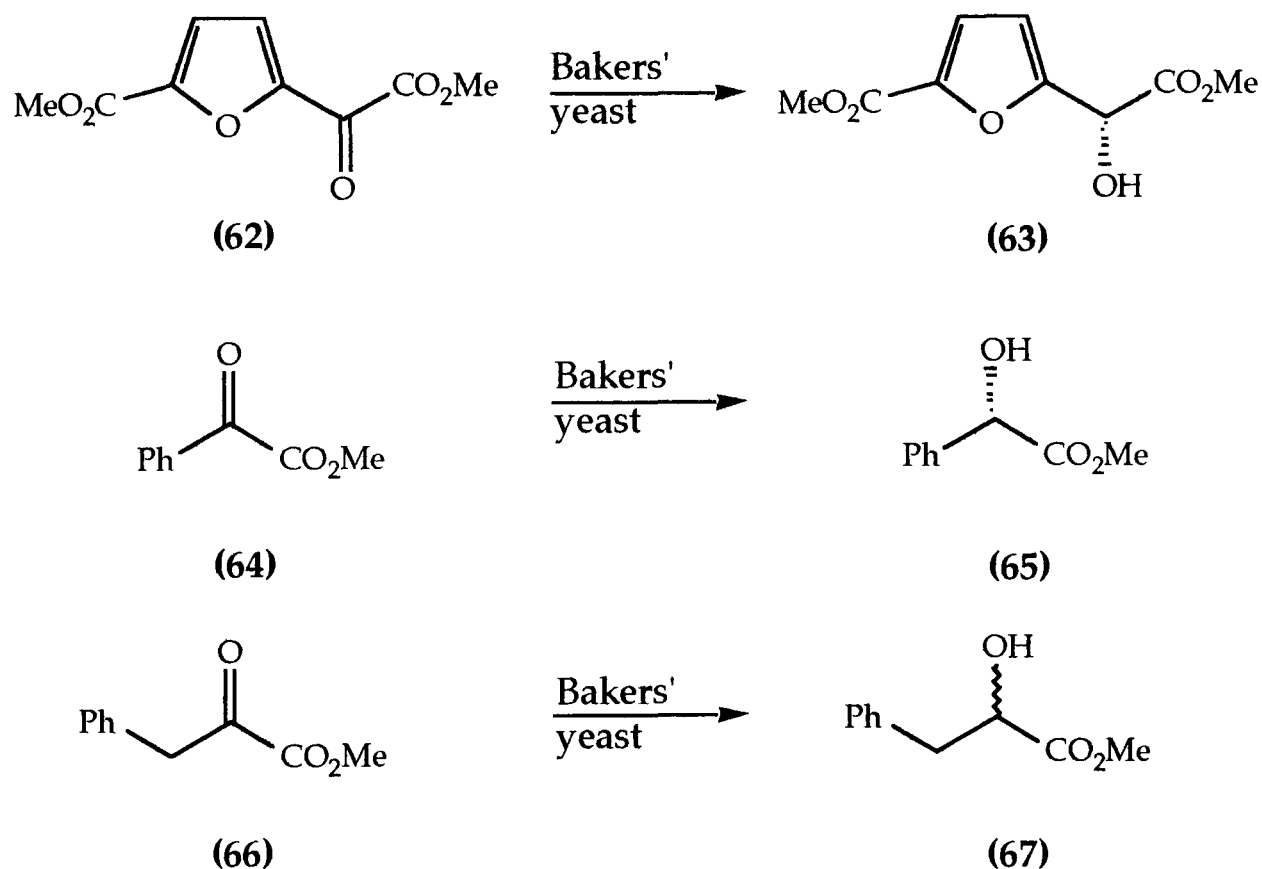


(Scheme 13)



## 2) Stereoselective reduction of $\alpha$ -keto esters and $\alpha$ -keto acids

$\alpha$ -keto esters are readily reduced by bakers' yeast; however, enantiomerically pure compounds are not always produced.  $\alpha$ -Hydroxy ester (63) was obtained in 92% enantiomeric excess when (62) was fermented with bakers' yeast and the aryl acetic ester (64) was reduced with almost complete enantioselectivity. The higher homolog (66), was however, reduced to give the corresponding alcohol (67) in racemic form demonstrating the unreliability of bakers' yeast on this type of substrate.<sup>20</sup> These results are outlined in Scheme 14.



(Scheme 14)

A study was carried out on a number of linear  $\alpha$ -keto esters in the hope of producing a relationship between chain length and optical purity of products.<sup>56</sup>

The chain length was varied between 3 and 7 as shown in Table 3 and the substrate was incubated in normal bakers' yeast, immobilised bakers' yeast in water and immobilised bakers' yeast in hexane. The resulting enantiomeric excesses varied between 30 and 94%, with a trend of decreasing optical purity of products with increasing chain length being observed as depicted in Figure 3.



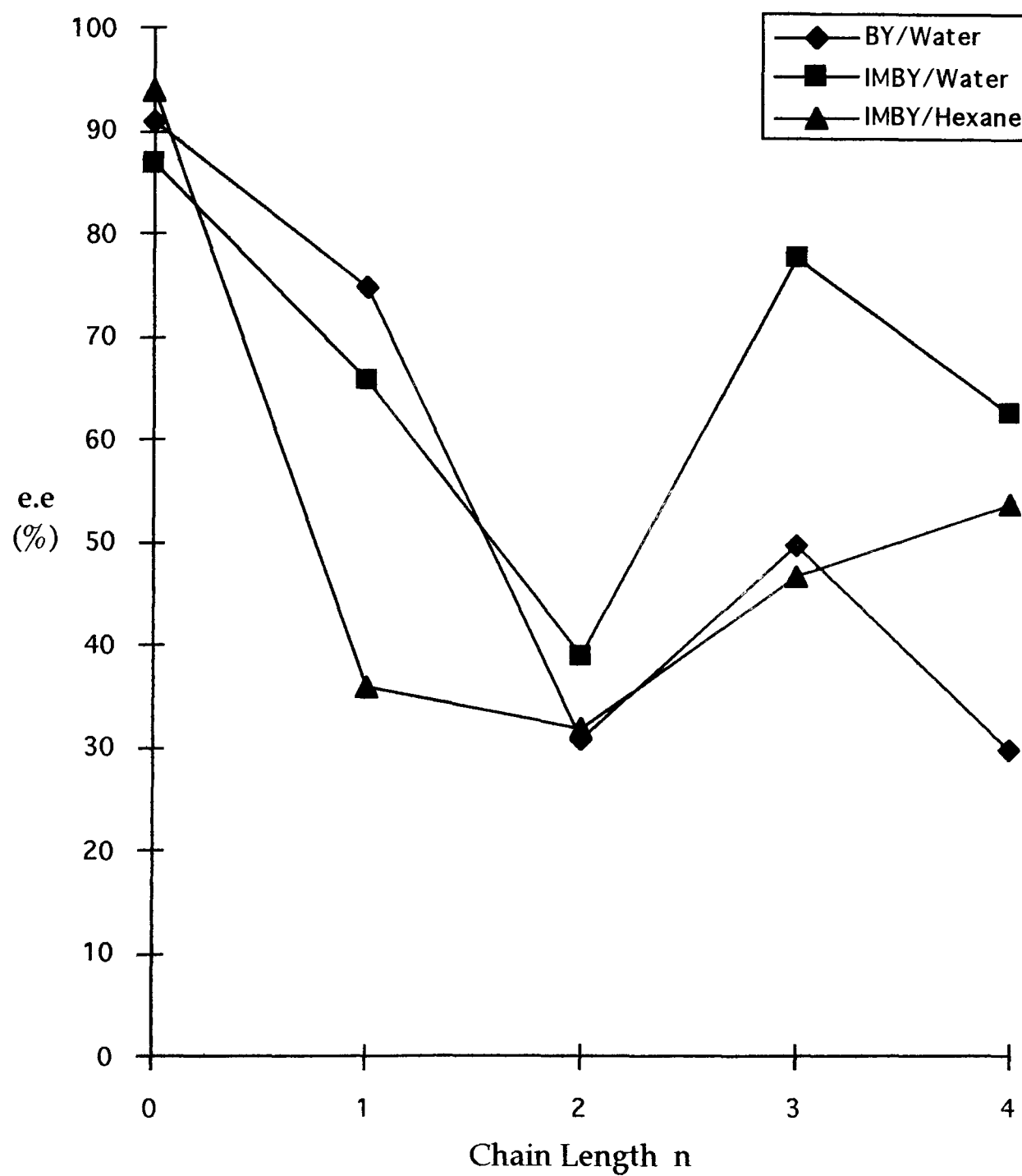
Substrate n		BY in H <sub>2</sub> O	IMBY in H <sub>2</sub> O	IMBY in Hexane
(ee : Chemical Yield : Configuration)				
a	0	91:47:S	87:43:S	94:33:S
b	1	75:42:S	66:42:S	36:28:S
c	2	31:36:S	39:36:S	32:27:S
d	3	50:29:S	78:20:S	47:41:R
e	4	30:23:S	63:31:S	54:36:R

BY=Bakers' Yeast

IMBY=Immobilised Bakers' Yeast

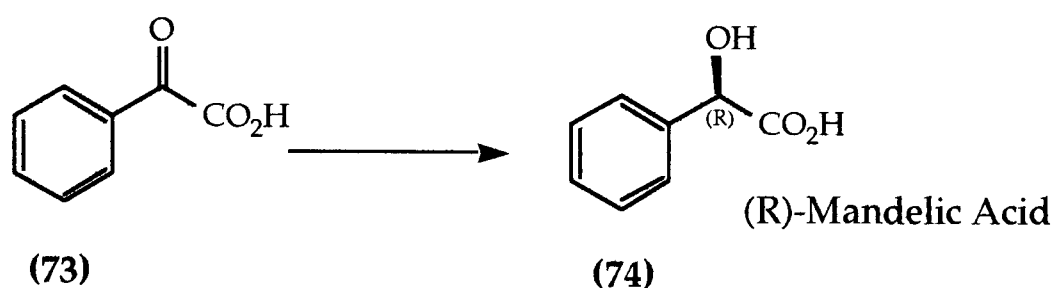
(Table 3)

The effect of increasing chain length on the Bakers' yeast reduction of  $\alpha$ -keto esters.



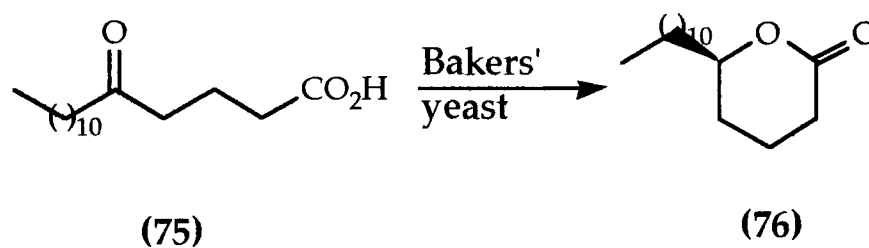
(Figure 2)

$\alpha$ -Keto-acids have been successfully reduced using bakers' yeast to furnish optically active  $\alpha$ -hydroxy-acids. In 1910, Neuberg obtained mandelic acid (74) in optically active form using this approach.<sup>57</sup>



(Scheme 15)

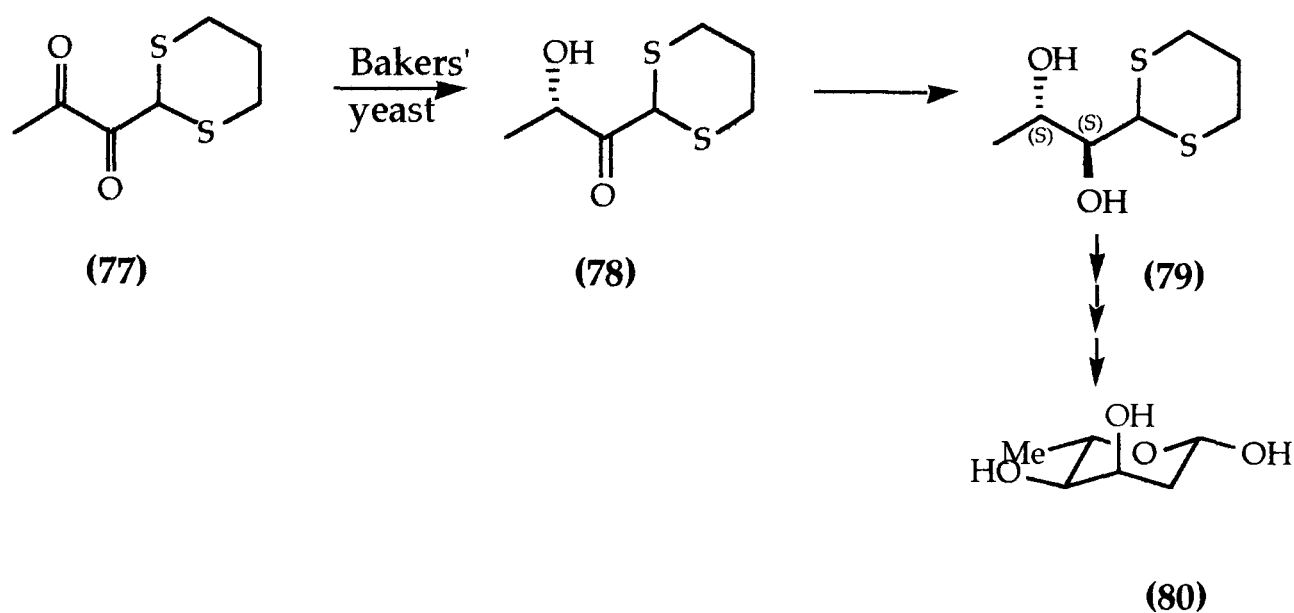
The insect pheromone (*R*)-5-hexadecanolide (76) has been prepared by Utaka and co-workers in enantiomerically pure form using bakers' yeast.<sup>58</sup> This is outlined briefly in Scheme 16.



(Scheme 16)

### (3) Stereoselective reduction of 1,2- and 1,3-diketones

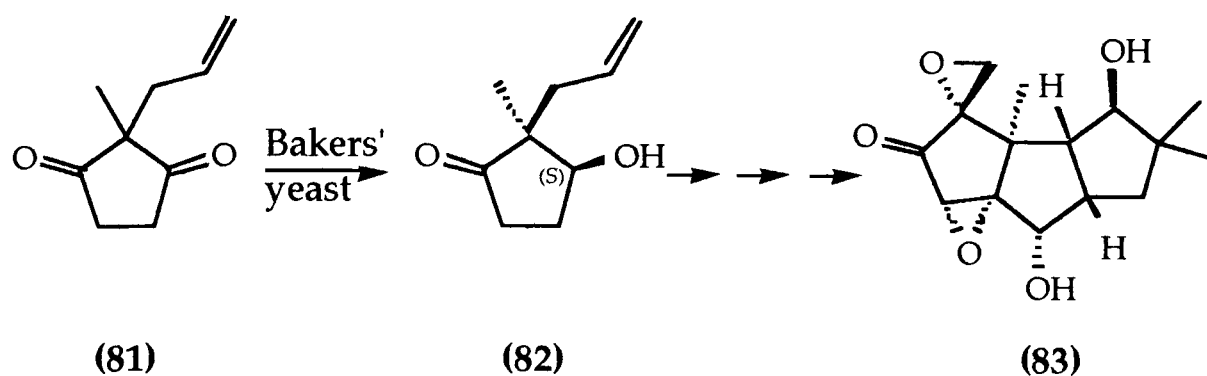
1,2-Diketones have been converted into the corresponding diols using bakers' yeast. The diols are often obtained in good yield and with good to excellent e.e's. The  $\alpha$ -diketone (77) was smoothly converted to the diol (79) in a chemical yield of 82% and 97% enantiomeric excess, as shown in Scheme 17.



(Scheme 17)

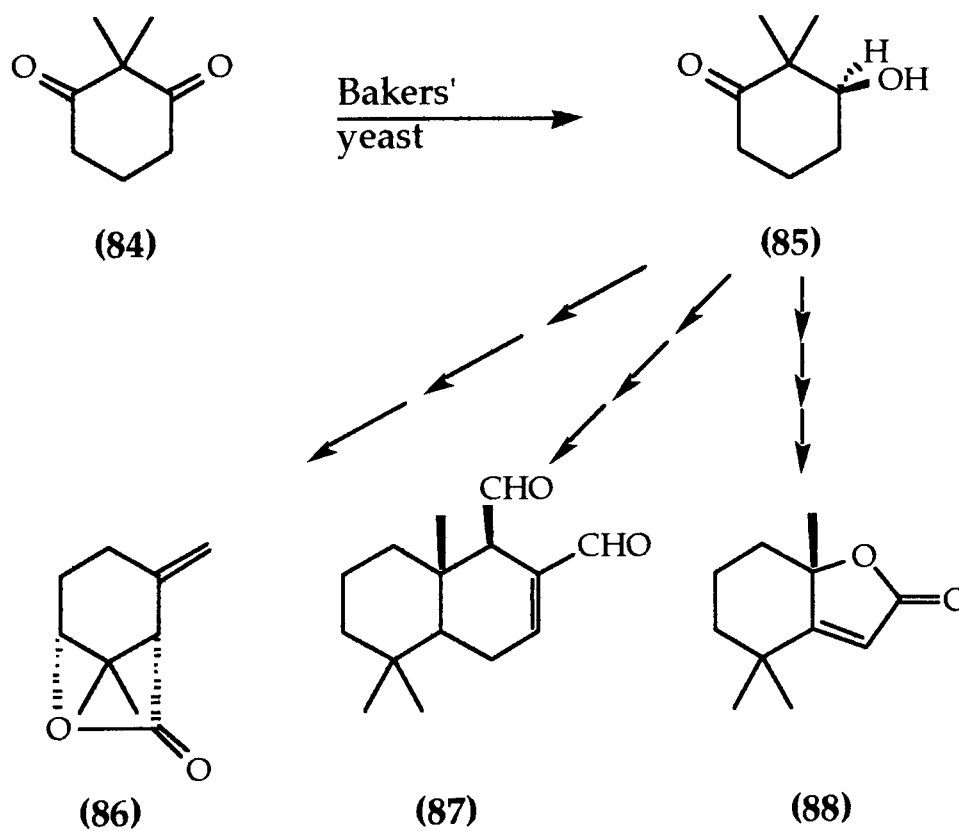
The resulting diol (79) was subsequently converted to L-digitoxose (80) which is a sugar component of digitalis.<sup>59</sup>

The reduction of 1,3-diketones (particularly 2,2-disubstituted cyclopentane-1,3-diones) has been extensively studied. The reactions usually furnish products with a high degree of optical purity. Brooks used this approach in the reduction of cyclopentane dione (81) to give the optically active synthon (82) in the synthesis of the natural product coriolin (83), as shown in Scheme 18.<sup>60,61</sup>



(Scheme 18)

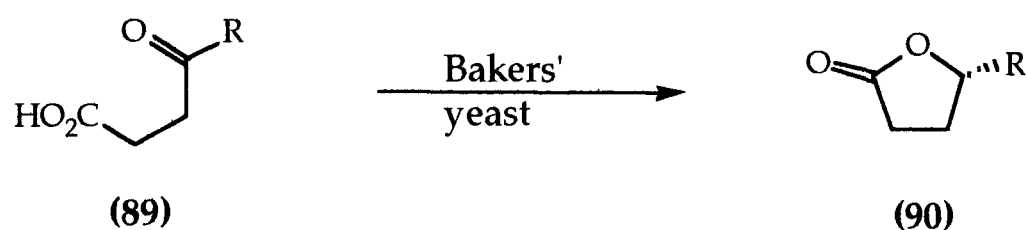
In general, reductions of 2,2-disubstituted-cyclohexane-1,3-diones with bakers' yeast give (*S*)-hydroxyketones.<sup>62</sup> Mori and co-workers have reduced 2,2-dimethylcyclohexane-1,3-dione (84) in this manner to produce (*S*)-3-hydroxy-2,2-dimethylcyclohexanone (85) in 79% yield and with >99% optical purity. This was used as an intermediate in the total synthesis of karahana lactone (86), polygodial (87) and (+)-dihydroactinidiolide (88) as outlined in Scheme 19.<sup>63-66</sup>



(Scheme 19)

#### (4) Stereoselective reduction of 4 & 5-oxoalkanoic acids and esters

Much interest has been shown in the use of bakers' yeast in the preparation of naturally occurring  $\gamma$  and  $\delta$  lactones<sup>67</sup>. The reduction of 4- and 5-oxoalkanoic acids and esters have been achieved with variable success and a variety of lactones have been prepared by this method with reported enantiomeric excesses usually exceeding 95%. An example is shown in Figure 4.



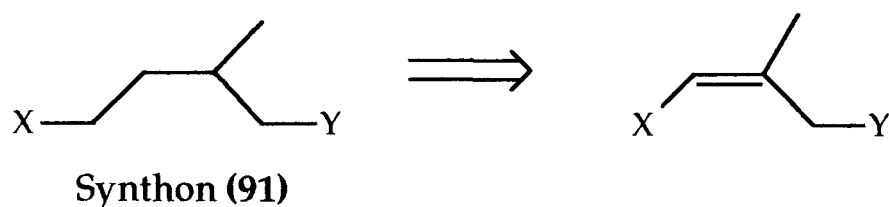
(Figure 3)

#### (5) Stereoselective reduction of carbon-carbon double bonds

Enantioselective microbial reduction of  $\alpha,\beta$ -unsaturated aldehydes is well established. Bakers' yeast has been used for the stereoselective reduction of 'activated' double bonds which have in the main been trisubstituted.<sup>68-71</sup> Work in this field started when Fischer, in 1940, applied the bakers' yeast reduction to a number of  $\alpha,\beta$ -unsaturated alcohols and aldehydes.<sup>72</sup> His work ranged from the simple crotyl and cinnamyl derivatives through to citral, geraniol and triglinaldehyde derivatives. His results were only based on optical rotation values, with relative configurations being assigned where possible. This has led scientists

to rediscover his work and particular attention has been paid to the preparative value of this type of intermediate in asymmetric synthesis.<sup>73,74</sup>

Particular interest has been shown in intermediates with a methyl substituent present on the  $\beta$ -carbon atom. Synthons (91) are useful intermediates *en route* to a number of important natural products containing the isoprenoid unit. The isoprenoid unit is found in such natural products as tocopherol, phylloquinones, phytol and insect pheromones. It is synthetically useful if the X and Y groups are distinguishable and can therefore be manipulated independently. Bakers' yeast gives a quick and efficient way of producing synthons (91) in chiral form.

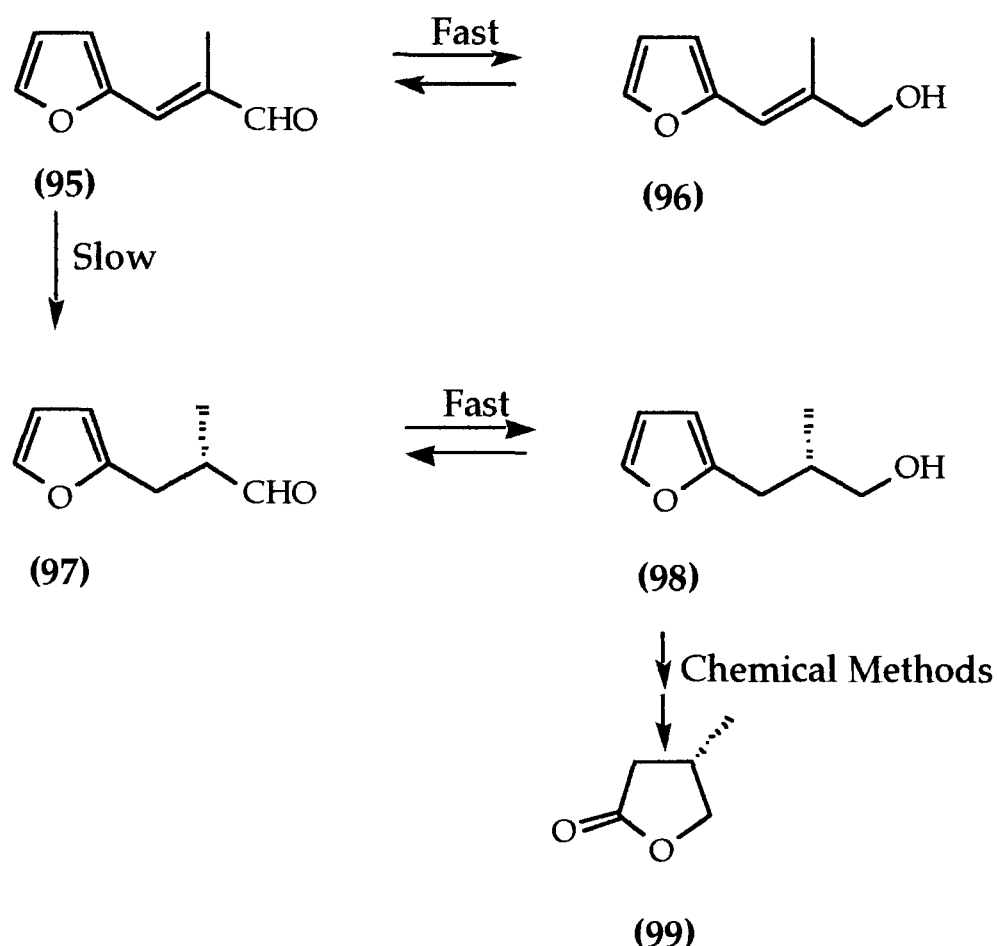


(Figure 4)

An example of this procedure is a synthesis of the intermediate lactone (99) which has been used successfully in the synthesis of a number of important natural products such as Vitamin E and the pheromone of *Tiboleum castaneum*.  $\beta$ -Furylacrolein (95) has been incubated with bakers' yeast to produce the corresponding alcohol (98) as the major product.<sup>68</sup> The chemical yield is reported as 72% with virtually 100% e.e. The authors also show that the allylic alcohol (96) is reduced by bakers' yeast to give the same product (98) and it is proposed that the reaction follows the pathway outlined in Scheme 20. The allylic alcohol (96) is



in equilibrium with the aldehyde (97) which is itself slowly reduced by the micro-organism. Once reduced, the saturated aldehyde (97) is quickly further reduced to the saturated alcohol (98). The resulting saturated alcohol (98) was then smoothly converted to the corresponding lactone (99) by ozonolysis.

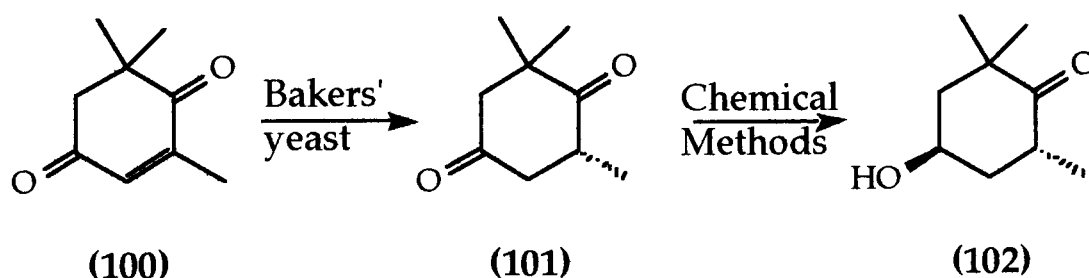


(Scheme 20)

Successful bakers' yeast reduction of trisubstituted olefins has also been observed, to furnish optically active saturated molecules of synthetic interest. Several dienes containing alcohol or aldehyde functionality have been chosen for this reaction in order to obtain larger chiral units. These products often contain a proportion of the functionality of the target molecule already in place. This has been illustrated in the synthesis of optically active phytol<sup>75</sup> and a number of other saturated pheromones.

Studies of the reduction of carbon-carbon double bonds have shown that the presence of electron withdrawing groups on the alkene are essential for reduction to take place.  $\alpha,\beta$ -Unsaturated esters are not considered to be good candidates for this type of reaction<sup>76,77</sup>. The use of fluoro-substituted- $\alpha,\beta$ -unsaturated esters and alcohols have been well documented<sup>78</sup> and indeed the reductions occur with good chemical yield and between 67 and 87% optical purities.

A number of examples of the reduction of cyclic olefins have also been reported. An example of this is the reduction of the cyclohexene (100) with bakers' yeast to give the corresponding saturated cyclohexane-dione (101). This procedure has been carried out on a 10 kg scale with a concentration of 20g/L being possible without yeast poisoning and has led to an isolated yield of 80% in enantiomerically pure form. This product (101) was then smoothly converted to zeaxanthin (102) by chemical methods<sup>79</sup>.



(Scheme 21)

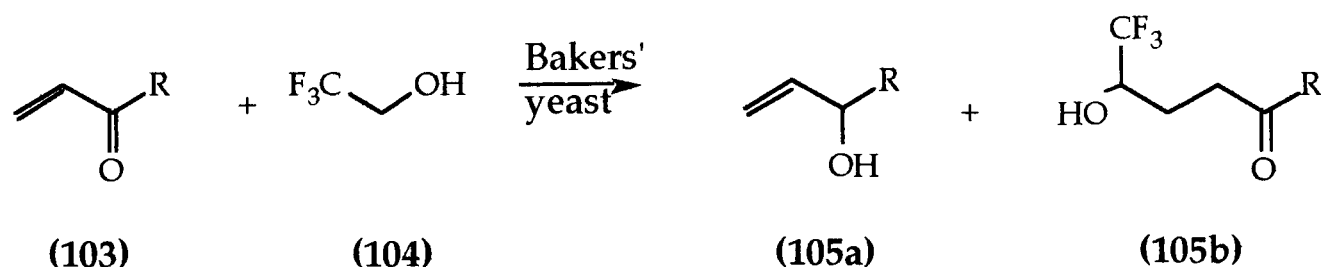
## (6) Carbon-carbon bond forming reactions.

The formation of carbon-carbon bonds is of fundamental importance to any synthetic organic chemist. Enzyme-mediated carbon-carbon bond forming

reactions are in the main very limited and indeed the few reactions available are related to enzymatic systems operating within a narrow substrate range<sup>80</sup>. Bakers' yeast mediated carbon-carbon bond forming reactions are so far limited to Michael addition of a carbon nucleophile, sterol formation and acyloin condensation.

**(a) Michael-type addition of a carbon nucleophile.**

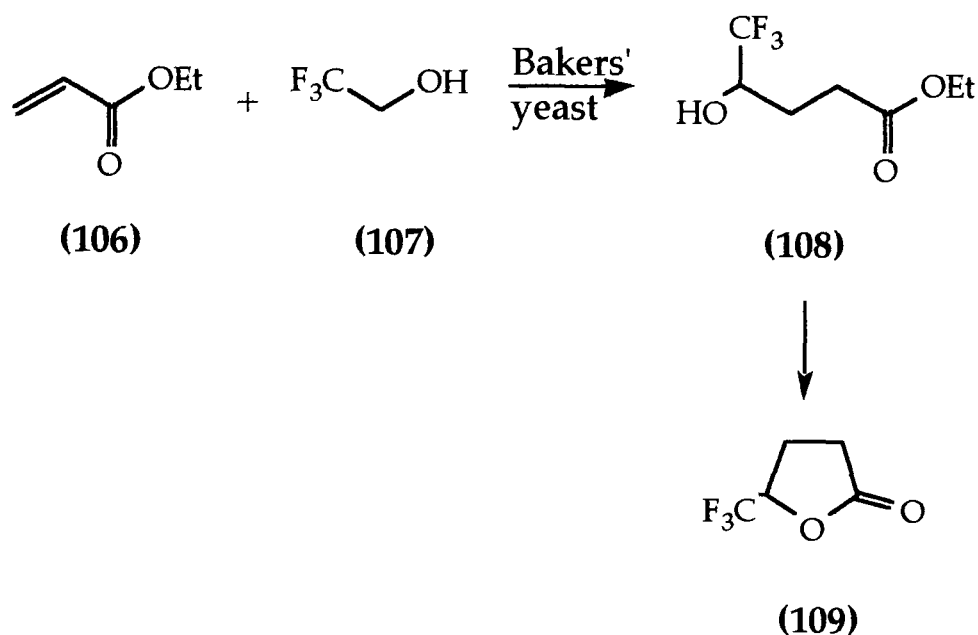
It has recently been observed that addition of 2,2,2-trifluoroethanol (104) to a fermenting mixture of bakers' yeast and an  $\alpha,\beta$ -unsaturated ketone or ester proceeds with the formation of optically active fluorinated carbinols as well as the expected alcohol reduction product. This type of reaction is outlined in Scheme 22.



(Scheme 22)

Trifluoromethyl carbinols have been shown to be produced in 26-40% isolated yield with enantiomeric excesses exceeding 90%. When the transformation is applied to  $\alpha,\beta$ -unsaturated esters the corresponding lactones are produced *via* enzymatic hydrolysis to the intermediate hydroxy-acid. An example of this

procedure is shown in Scheme 23 where ethyl acrylate (106) is smoothly converted into the lactone (109) in 47% yield and 79% enantiomeric excess.

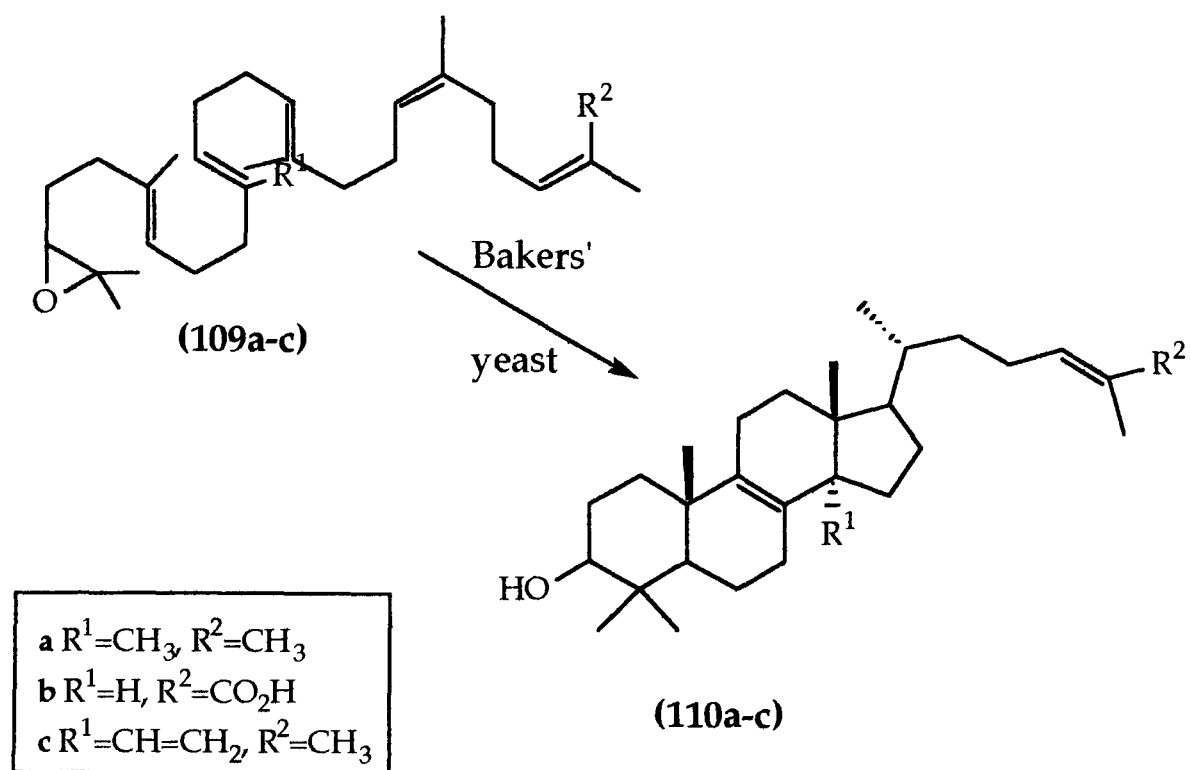


(Scheme 23)

## (b) Sterol Formation

Studies have shown that optically active lanosterol derivatives can be derived from racemic squalene oxides by the use of bakers' yeast. The process is thought to involve kinetic resolution of the squalene oxide followed by cyclisation of the polymeric structure. This transformation has been carried out on gram scales and natural products such as lanosterol (110a), ganoderic acid (110b) and (-)-loanostatatriene (110c) have been prepared by this method (Scheme 24).<sup>81-83</sup> Reported yields for the reaction are high, in the region of 60-80%, but using

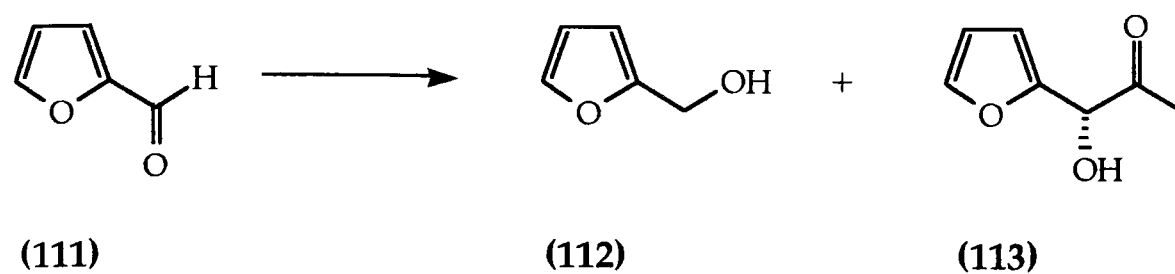
modified yeast. The yeast in question is modified by pretreatment of the cellular mass with ultrasonic radiation, which has the effect of activating the required enzymes. Bakers' yeast not activated in this way was found to give poor results in this type of reaction.



(Scheme 24)

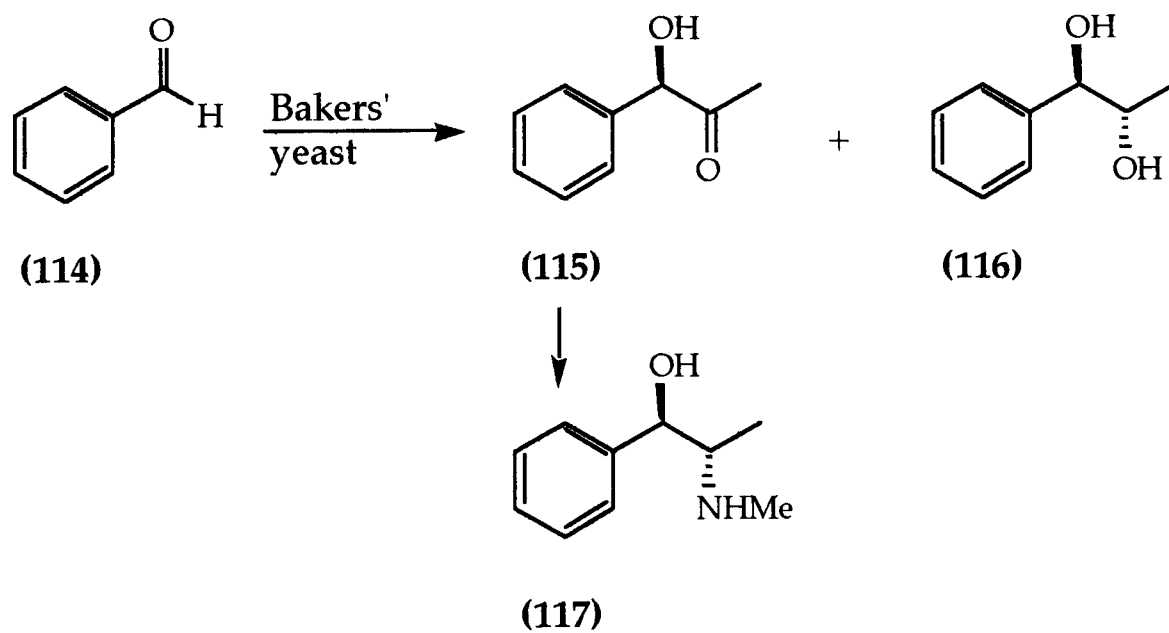
### (c) The Acyloin Condensation

H. J von Liebig found, in 1913, that during the yeast fermentation of furfural (111), a second product (113) was produced in addition to the expected reduction product (112)<sup>84</sup>. Upon further investigation by Neuberg<sup>85</sup> this product was found to be furylic alcohol formed as the acyloin condensation product.



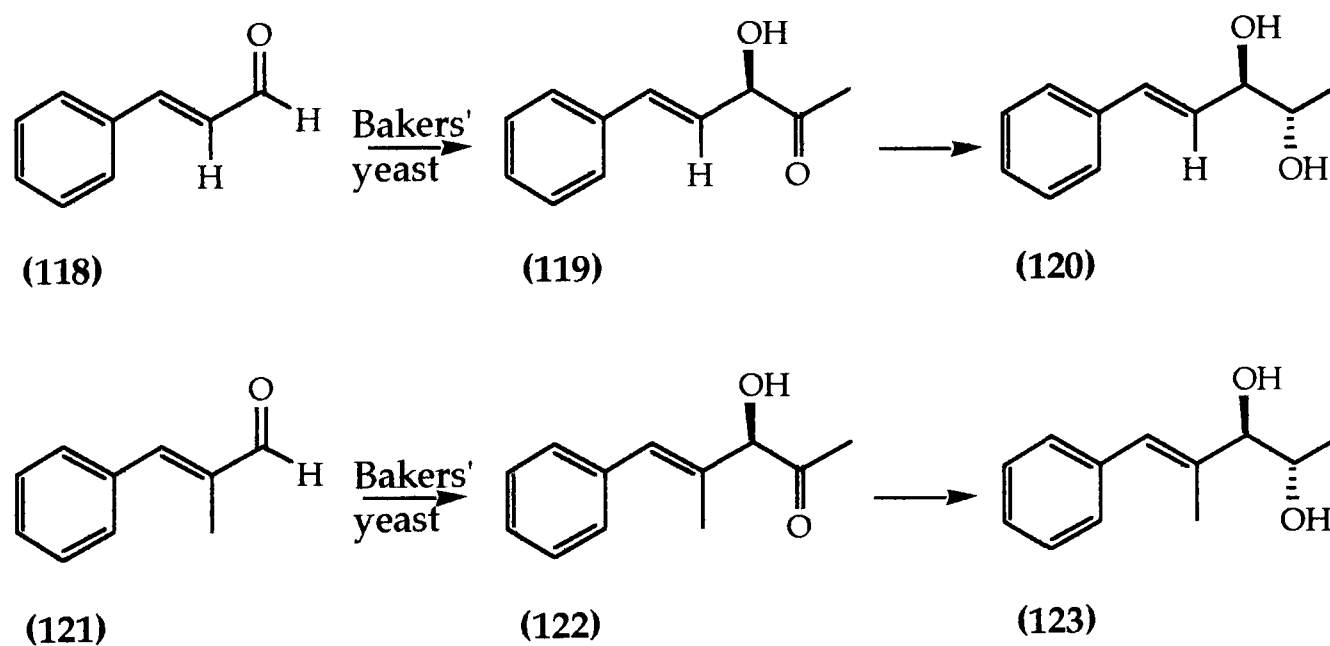
(Scheme 25)

This reaction has been exploited by many organic chemists and indeed the process has found its uses in industry including the large scale preparation of (L)-ephedrine (117).<sup>86</sup> Benzaldehyde (114) is used as starting material and is converted to the desired product as shown in Scheme 26.



(Scheme 26)

Benzaldehyde (114) is reacted with the formal equivalent of acetaldehyde to furnish the  $\alpha$ -hydroxy-ketone (115) and the *erythro*-diol (116). Enantioselectivity in both steps is very high and the diol (116) is produced with 95% enantiomeric excess as shown. This procedure has also been extended to a number of monosubstituted benzaldehydes with very little depreciation in selectivity.<sup>87</sup> The bakers' yeast mediated acyloin condensation is by no means limited to the use of benzaldehydes and its derivatives and  $\alpha,\beta$ -unsaturated aldehydes have been successfully converted into optically active diols in moderate yield and high enantiomeric excesses. In the case of cinnamaldehyde (118) and  $\alpha$ -methyl cinnamaldehyde (121) as shown in Scheme 27, the (2*S*, 3*R*) diols are produced in 25% isolated yield and 85-95% ee.<sup>89,90</sup>



(Scheme 27)

It has been shown that the steric bulk of the  $\alpha$ -substituent has a part to play in the reaction in that its presence can hinder the process. Indeed  $\alpha$ -ethyl and  $\alpha$ -propyl substituted  $\alpha,\beta$ -unsaturated aldehydes do not undergo bakers' yeast mediated acyloin condensations.

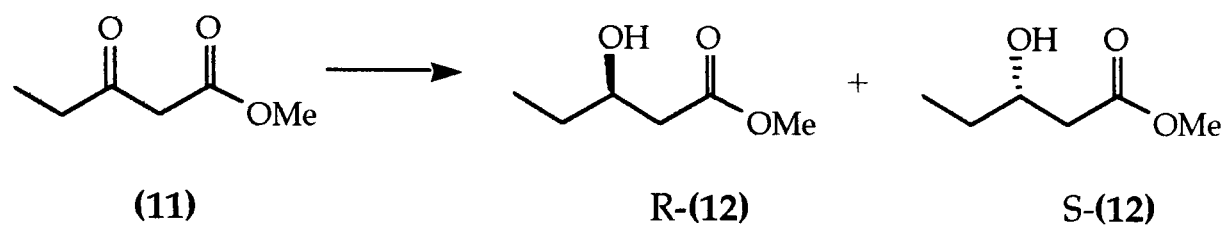
## **Enhancement of chemical yield and enantioselectivity in Bakers' yeast mediated reactions.**

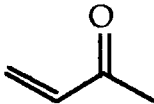
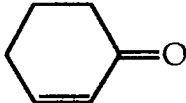

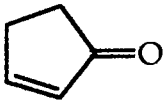
In the majority of cases reported so far in the scientific literature, bakers' yeast reductions of carbonyl compounds afford satisfactory results, with high chemical yield and high stereoselectivity. However, there are many examples that have afforded unsatisfactory results, low chemical yield and/or low stereoselectivities. Usually these results are discarded and moreover they are not reported in the literature. At the same time, the micro-organism may not afford the compound of desired configuration for further use as a synthetic intermediate. In such cases, the reduction can be controlled or reversal of stereochemistry can be performed by a number of reported methods. In this section a number of key experimental procedures will be outlined which can be used to control both stereochemistry and chemical yield.

### **(a) Addition of a third reagent to the reaction system.<sup>15</sup>**

Unsatisfactory stereoselectivity during bakers' yeast reduction occurs when two or more dehydrogenases operate simultaneously with a number of enzymes producing the (*R*)-alcohol and a number producing the (*S*)-alcohol, each with a high degree of stereoselectivity.<sup>31</sup> It follows, therefore, that if appropriate enzymes can be inhibited or activated, this will result in higher stereoselectivities. Nakurama and co-workers adopted this approach and studied the effect of various additives on the reduction of methyl 3-oxopentanoate (11) with bakers' yeast. The addition of  $\alpha,\beta$ -unsaturated carbonyl and hydroxy compounds was found to be particularly effective and a number of results are outlined in Table 4.





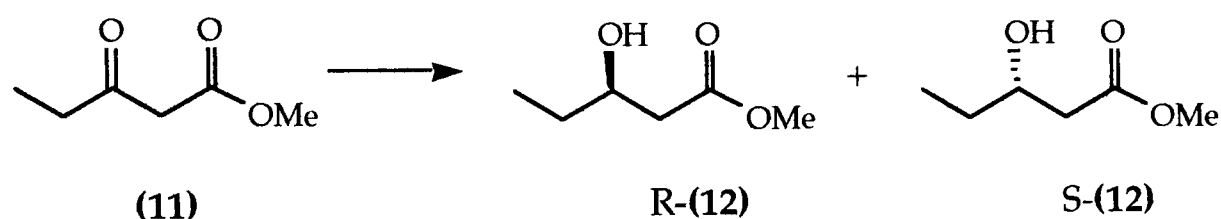
Additive	Yeast	Configuration	ee (%)	Yield (%)
	DBY	R	68	51
	BY	R	89	22
	DBY	R	61	71
	BY	R	78	50
	DBY	R	60	68
	BY	R	89	67
	DBY	R	44	67
	BY	R	66	68
None	DBY	R	12	46
	BY	R	37	38

DBY = Dried Bakers' yeast  
 BY = Bakers' Yeast

**(Table 4)**

In the absence of any additive, the reduction of methyl 3-oxopentanoate (11) with dried bakers' yeast proceeds with only 12% enantiomeric excess, indicating that a number of competing enzymes are operating at the same time producing both the (*R*)- and (*S*)-enantiomers. As can be seen from the results, addition of  $\alpha,\beta$ -unsaturated carbonyl and hydroxy compounds enhance the optical purity of the product in favour of the (*R*)-enantiomer.

Nakurama went on to study the effect of adding different nutrients to the reaction mixture and found that glucose was particularly good at enhancing both chemical yield and stereoselectivity. A number of his results of the reduction of methyl 3-oxopentanoate (11) with bakers' yeast are outlined in Table 5.



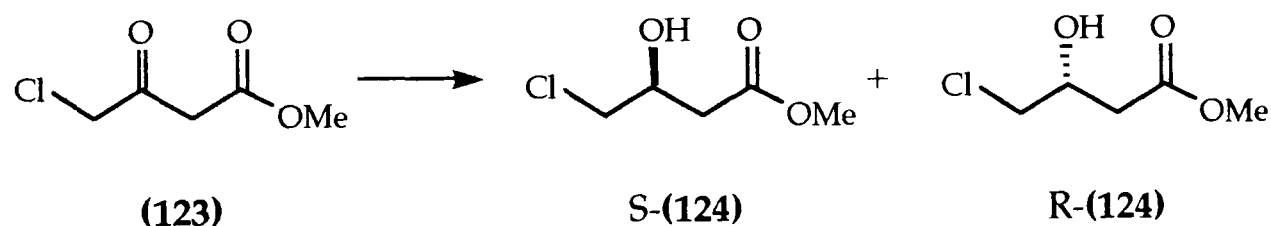
DBY/g	Glucose/g	Configuration	ee (%)	Yield (%)
2	0	<i>R</i>	7	41
2	1	<i>R</i>	23	43
4	0	<i>R</i>	12	31
4	1	<i>R</i>	31	61

(Table 5)

The enhancement of chemical yield and stereoselectivity observed when  $\alpha,\beta$ -unsaturated carbonyl and hydroxy compounds is believed to result from Michael type addition of the (*S*)-producing enzymes onto the additive. This has the effect of 'tying' the enzymes up and prevents them from reacting with the substrate. It is also believed that the (*R*)-producing enzymes are located in different sites which renders them unable to encounter these inhibitors. In the case of the addition of glucose, it is believed that the dehydrogenase levels are altered in the yeast and therefore a change in stereoselectivity can be expected.

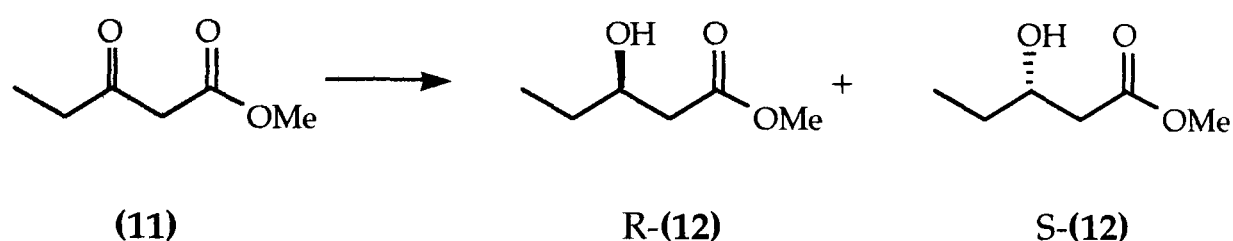
### (b) Immobilisation of the Cellular Mass<sup>14,92</sup>.

It has been shown recently by Ohno and co-workers that the configuration and optical purity of products obtained from bakers' yeast reduction can be dramatically changed by entrapment of the cellular mass in dense polyurethane matrices.<sup>14,93</sup> It is also reported that such entrapment improves the rather troublesome isolation procedure from the fermentation broth as the immobilised cells are easily removed from the reaction mixture by rapid filtration. Ohno found that in the bakers' yeast reduction of  $\beta$ -keto esters (123) and (11), enantiomeric excesses were enhanced substantially by the use of this entrapment procedure. His results are shown in Tables 6 and 7.



Concentration (g/L)	Method of Immobilisation	Configuration	ee (%)
10	-	<i>R</i> -(124)	31
20	-	<i>R</i> -(124)	12
20	Polyurethane	<i>S</i> -(124)	90

(Table 6)

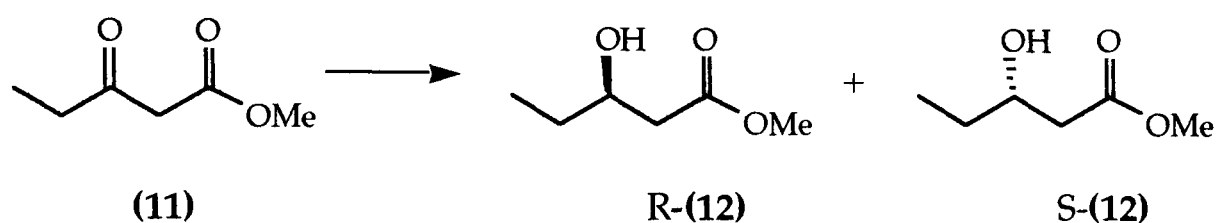


Concentration (g/L)	Method of Immobilisation	Product	ee (%)
20	-	<i>R</i> -(12)	5
20	Polyurethane	<i>R</i> -(12)	86

(Table 7)

Further work by this group has shown similar results when the micro-organism is immobilised using magnesium alginate and the reaction is run under a high concentration of magnesium ion.<sup>92</sup> Work has been carried out using both ordinary and immobilised yeast and the effect of various metal salts has been investigated. Addition of sodium and potassium ions was found to reverse the selectivity of the reaction and indeed methyl (*S*)-3-hydroxypentanoate (12) was formed from methyl 3-oxopentanoate (11) instead of the expected (*R*)-isomer which is formed under normal fermentation conditions. As enantiomeric excesses and chemical

yields were only found to be moderate using sodium and potassium salts further studies were conducted. Attention was focused on Group II metal salts and in particular magnesium and calcium salts. Again reversal of configuration was observed with greatly enhanced enantioselectivity (75-86%) but with only moderate chemical yield. Once the cells were immobilised however the chemical yield was enhanced to the region of 44-58% making the reaction a viable process for the synthetic organic chemist. A summary of the results is outlined in Table 8.



Additive (conc)	Configur- ation	e.e (%)	Yield (%)
none	R	12	46
KCl (1.0)	S	8	54
KCl (2.0)	S	24	47
KCl (4.0)	S	45	41
NaCl (2.0)	S	43	37
NaCl (4.0)	S	47	14
MgCl <sub>2</sub> (2.0)	S	80	20
MgCl <sub>2</sub> (3.0)	S	86	1
CaCl <sub>2</sub> (2.0)	S	75	19
MgCl <sub>2</sub> (2.0) (IMBY)	S	81	58
MgCl <sub>2</sub> (4.0) (IMBY)	S	89	44

(Table 8)

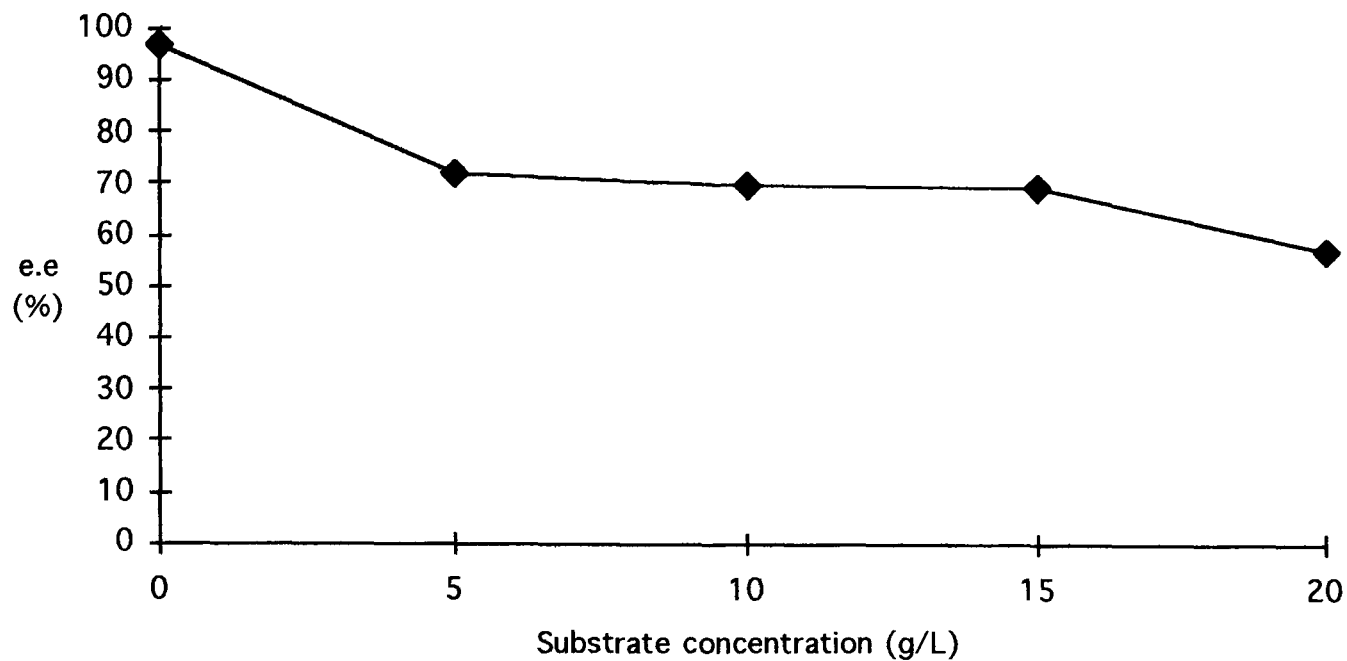
### (c) Substrate Concentration.<sup>17</sup>

Wipf and co-workers demonstrated that the production of (S)-ethyl 3-hydroxybutyrate (2) from ethyl acetoacetate (1) was observed with enhanced yield and optical purity by keeping the concentration of substrate constant during the reaction. This was achieved by constant addition of a solution of the substrate and a solution of sucrose to the fermentation vessel. Wipf showed that an optimum concentration of 0-1g/L during reaction led to the isolated product having an optical purity in the range of 95-97%. He also showed that there is a dramatic loss in optical purity as the concentration of substrate increases above 1g/L. These results are shown in Table 9 and Figure 6. The course of reaction was also studied and this is shown in Figure 7.

Substrate Concentration (g/L)	Optical Purity (ee %)
0-1	95-97
5	72
10	70
15	70
20	58

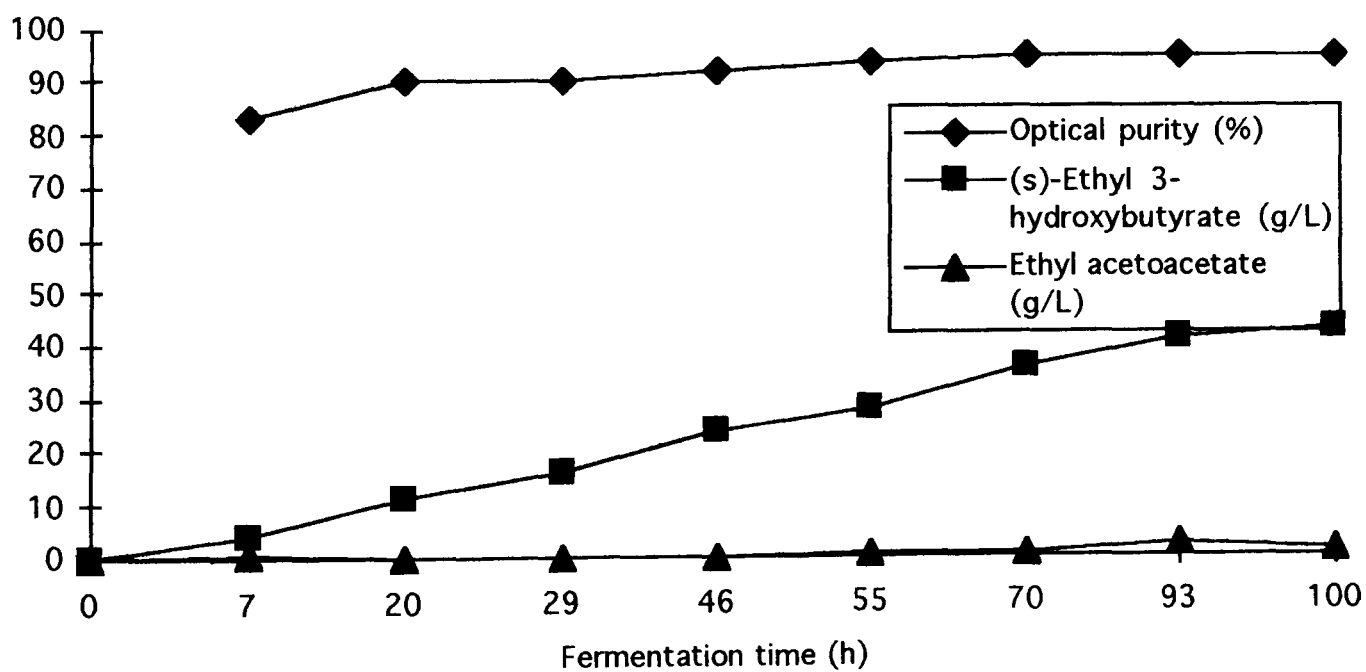
(Table 9)

The effect of increasing concentration on optical purity in the bakers' yeast  
reduction of ethyl acetoacetate (1)



(Figure 5)

The course of the reduction of ethyl acetoacetate with bakers' yeast.



(Figure 6)

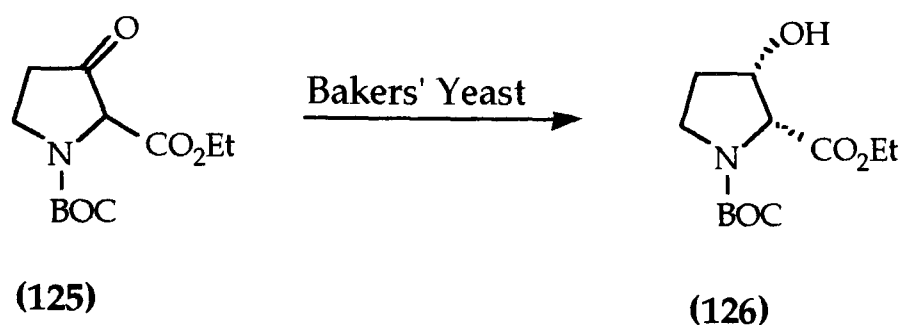
## **Chapter Two**

### **Preparation and yeast reduction of the piperidine derivatives**



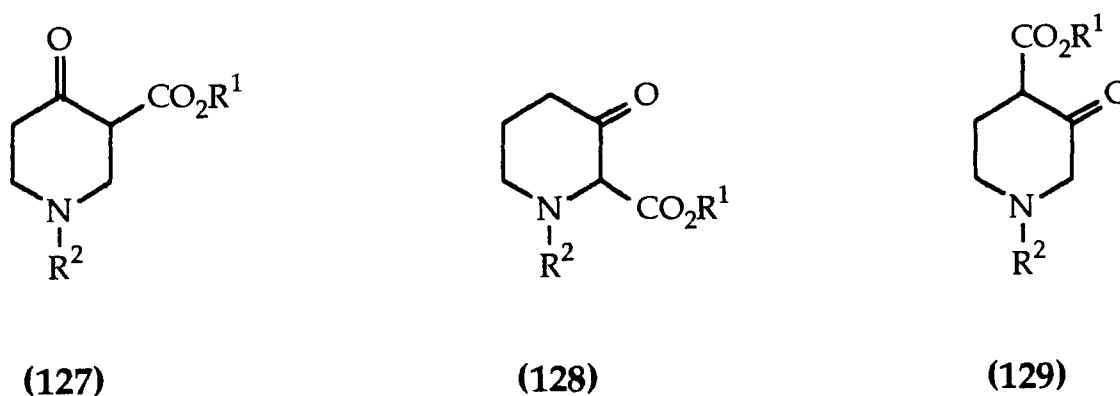
## Preparation of the Piperidine Derivatives

During previous work within the group it was shown that racemic keto-proline (125) could be reduced stereoselectively to the corresponding *cis*- $\beta$ -hydroxyproline (126) with excellent optical purity using dried bakers' yeast and sucrose<sup>94</sup>.



(Scheme 28)

We decided that it would be interesting and useful from a synthetic standpoint if the three possible piperidine  $\beta$ -keto-esters (127), (128) and (129) were subjected to the bakers' yeast reduction and the subsequent products identified. It is worthy of note that all three of these piperidine  $\beta$ -keto-esters possess considerable synthetic potential which make them desirable synthetic targets for organic chemists.



(Figure 7)

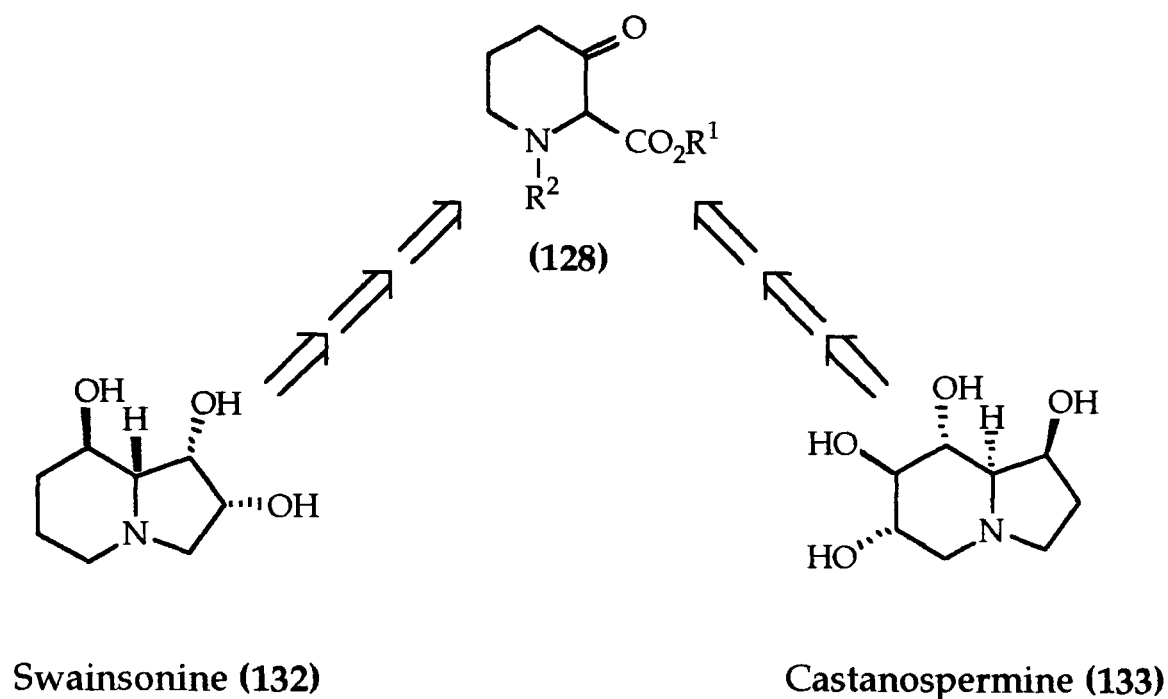
The hydroxy-piperidinecarboxylic acids (130) and (131) have been shown to influence the functioning of the central  $\gamma$ -aminobutyric acid neurotransmitter system. This is interesting from the point of view of the development of certain psychiatric and neurological disorders.<sup>95</sup> 4-Hydroxypiperidine-3-carboxylic acid (130) has been shown to be a potent substrate competitive inhibitor of the neuronal  $\gamma$ -aminobutyric acid uptake process<sup>96</sup> and 3-hydroxypiperidine-4-carboxylic acid (131) has been shown to be a specific  $\gamma$ -aminobutyric acid receptor agonist.<sup>97</sup>



(Figure 8)

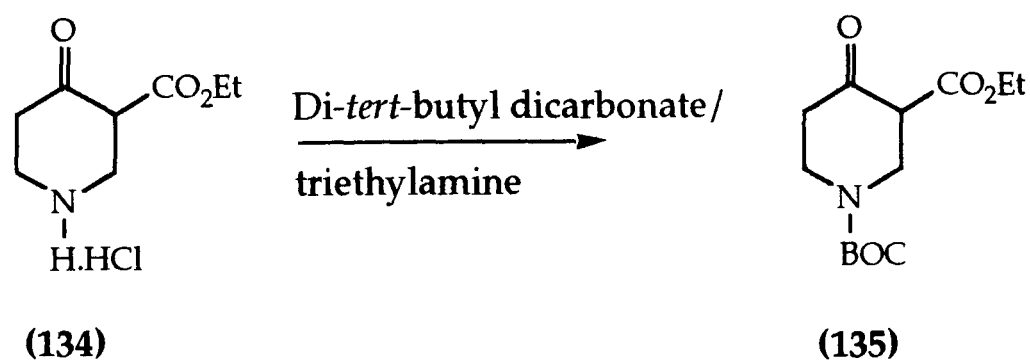
From the point of view of both synthetic and pharmacological interest, it is surprising to find that these compounds have only been available in racemic form until the present work featuring the use of bakers' yeast on the corresponding  $\beta$ -keto-esters provided the compounds in chiral form.

It can be easily envisaged that the piperidine  $\beta$ -keto ester (128) can be utilised as a synthetic intermediate *en-route* to a number of naturally occurring indolizidine alkaloids including compounds such as swainsonine (132) and castanospermine (133). To this end the reduction of this intermediate in chiral form may prove useful in the total synthesis of such compounds, again in chiral form.



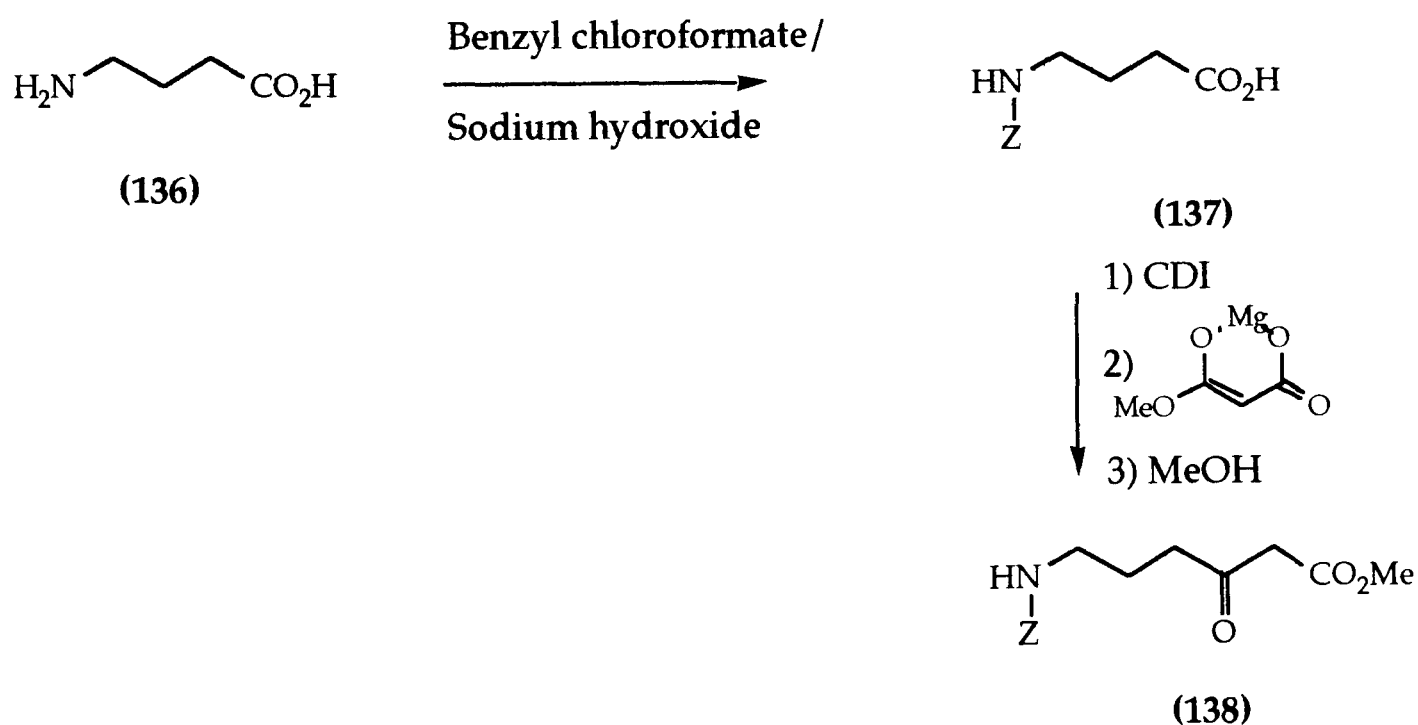
(Scheme 29)

Of the three  $\beta$ -keto-esters we wished to subject to the bakers' yeast reduction, we were pleased to find that the 3-ethoxycarbonyl-4-oxopiperidine derivative was commercially available as its hydrochloride salt (134) from the Fluka Chemical Company. This was subsequently protected at nitrogen as its BOC derivative (135) by reaction with di-*tert*-butyl dicarbonate with the use of triethylamine as base.<sup>98</sup>



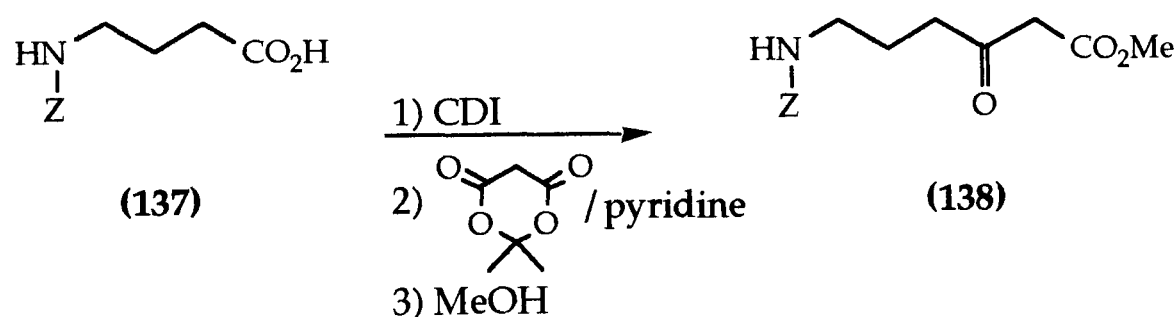
(Scheme 30)

The 2-alkoxycarbonyl-3-oxopiperidine (128) was unfortunately not available from a commercial source and so the search for an expedient synthesis of such a compound was undertaken in the chemical literature. We were pleased to find that Rapoport and co-workers had published an article showing the preparation of the desired compound by a rhodium(II) acetate dimer-catalysed carbenoid insertion /cyclisation reaction.<sup>99</sup> Work was immediately undertaken on the synthesis of this compound which started with the protection of 4-aminobutyric acid (136) as its benzyloxycarbonyl derivative. Schotten-Baumann conditions of simultaneous addition of benzyl chloroformate and aqueous sodium hydroxide were utilised to furnish the desired protected amino acid (137).<sup>100</sup> This was subsequently activated using *N,N'*-carbonyldiimidazole and reacted with the dianion formed by the action of isopropylmagnesium bromide on hydrogen methyl malonate<sup>101-103</sup> to produce the corresponding  $\beta$ -keto-ester (138).



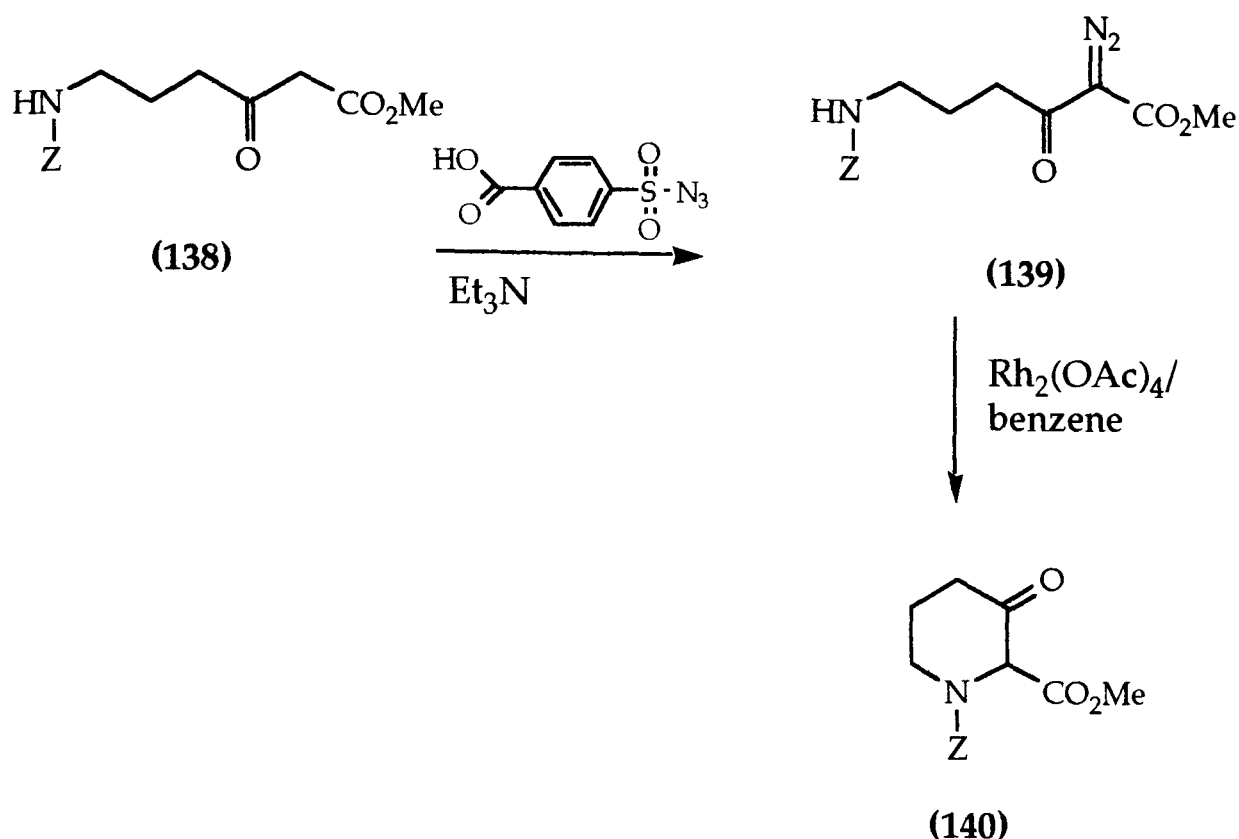
(Scheme 31)

In practise this reaction was found to be cumbersome and poor yielding. We found that the multi-stage reaction involved here was not tolerant of minor variations in the experimental procedure and this led to rather variable results. In order that the desired  $\beta$ -keto-ester (138) be produced by a more viable pathway we turned our attention to the use of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid).<sup>104</sup> Again the Z-protected 4-aminobutyric acid (136) was activated using *N,N'*-carbonyldiimidazole and the intermediate was reacted with Meldrum's acid in the presence of pyridine as base.<sup>105</sup> Subsequent breakdown of the intermediate complex using refluxing methanol led to the desired compound (138) in 80% isolated yield and high purity, making Meldrum's acid the reagent of choice for this particular step.



(Scheme 32)

Next came the introduction of the diazo functionality between the two carbonyl groups. This was cleanly achieved using a mixture of *p*-carboxybenzenesulphonyl azide<sup>106</sup> and triethylamine as base. The final cyclisation step to produce the desired piperidine  $\beta$ -keto-ester was achieved by the rhodium(II) acetate dimer-catalysed carbenoid insertion into the N-H bond to furnish the desired piperidine  $\beta$ -keto-ester (140) after silica gel chromatography

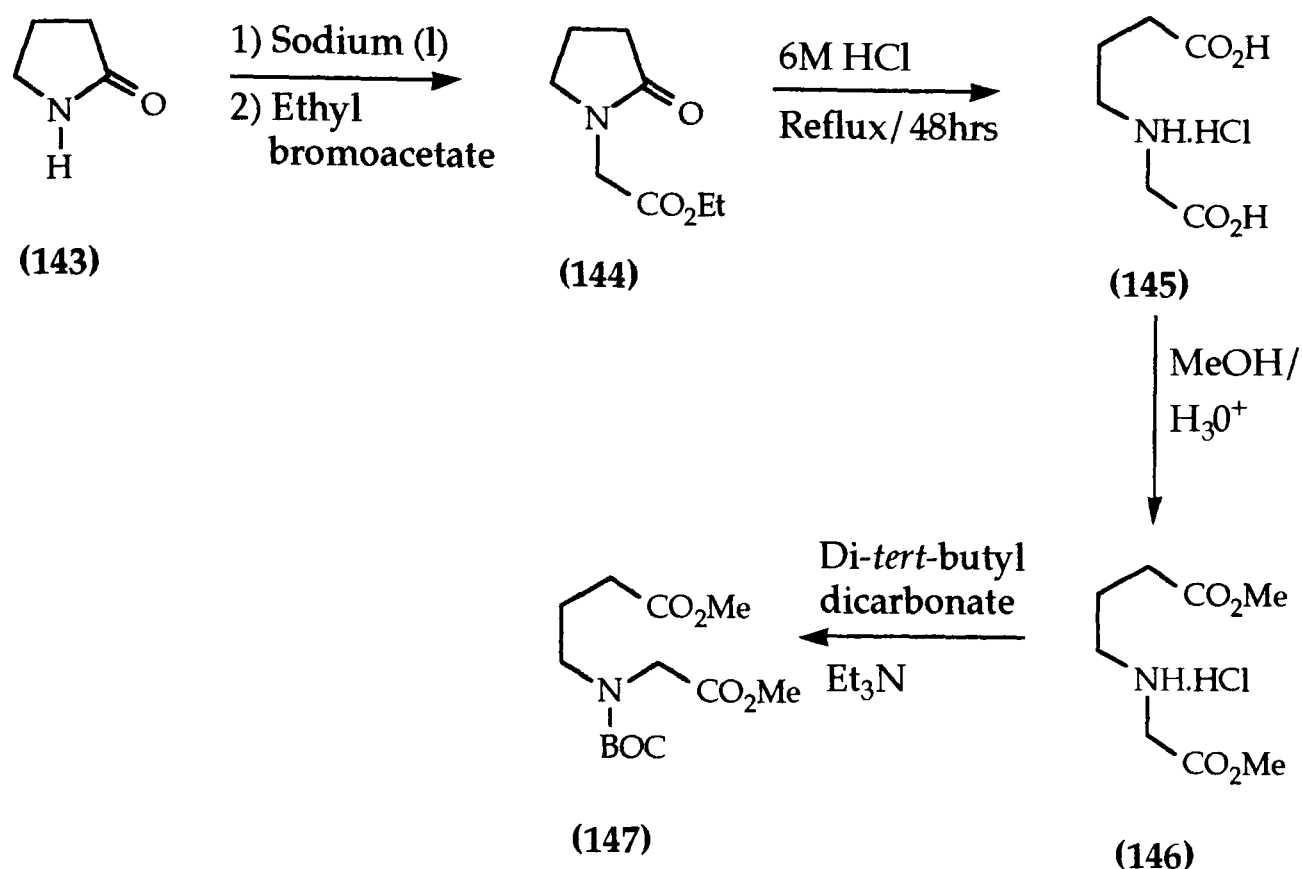


(Scheme 33)

This final reaction proved particularly stubborn in that the course of reaction was greatly influenced by the time taken for the reaction mixture to reach reflux and also by minor contaminants in the reagents or substrate. At best a mixture of compounds was isolated which resulted from the competing reactions of N-H and C-H insertion and a reaction of unknown mechanism. These results were also experienced by Rapoport and co-workers.<sup>99</sup>

It soon became apparent that a completely new synthetic strategy would need to be adopted for the synthesis of this piperidine and to this end a Dieckmann cyclisation approach was considered.<sup>107</sup> 2-Pyrrolidinone (143) was reacted with a finely divided suspension of molten sodium in refluxing toluene to produce the corresponding sodium salt which was then quenched with ethyl bromoacetate to produce the alkylated derivative (144) in 83% yield. Subjection of this product to the rather harsh conditions of refluxing 6M hydrochloric acid over a period of 2 days furnished the hydrolysed product (145) which was immediately re-esterified in acidic methanol to give the diester (146) as a thick gum in an overall yield of 66% for both steps. Without purification, this gum was protected at nitrogen as its

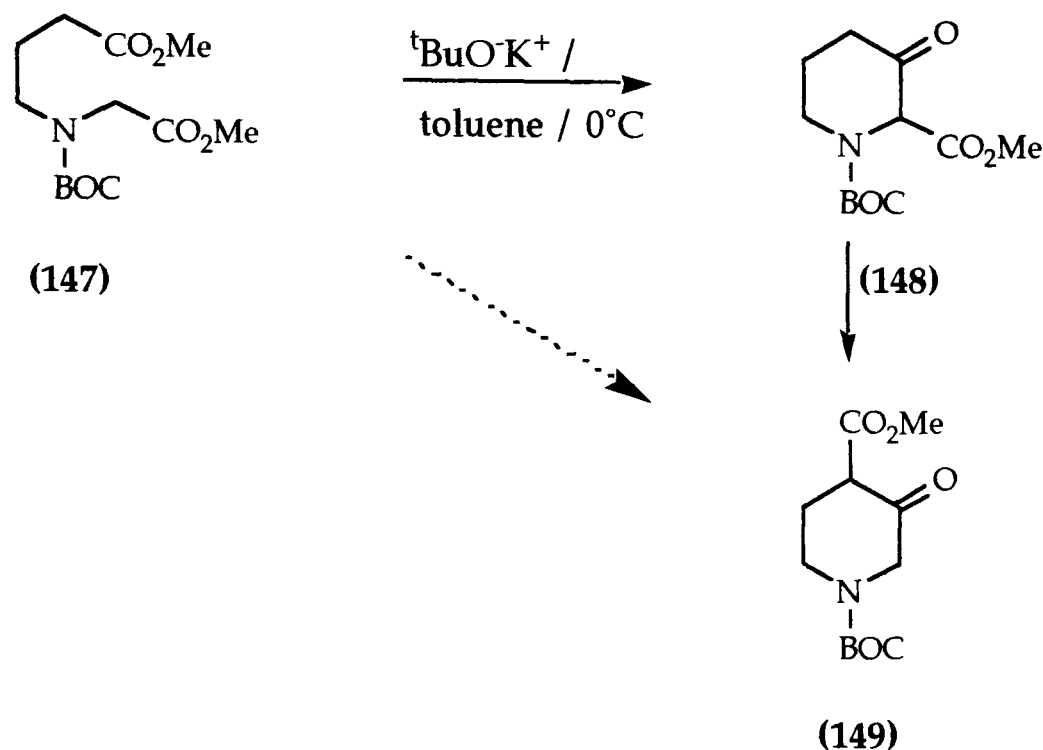
BOC derivative (147) using di-*tert*-butyl dicarbonate and triethylamine and we were pleased to isolate the protected diester (147) as a thick oil in 85% yield.



(Scheme 34)

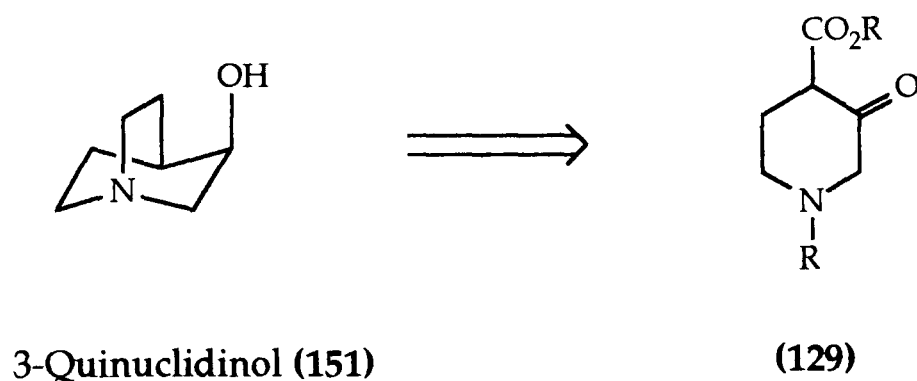
Dieckmann ring closure of this compound using the so called 'non equilibrating' conditions of potassium *tert*-butoxide in dry toluene<sup>108</sup> furnished the desired piperidine  $\beta$ -keto-ester (148) in moderate yield. It was found that this product, which was the kinetic product from the reaction, rapidly isomerised under the reaction conditions to produce the thermodynamic product (149). This showed that the 'non-equilibrating' reaction conditions were in fact allowing equilibration to occur and indeed the thermodynamic product became the major product from the reaction. Much work was carried out on this reaction and we were satisfied to obtain a 2:1 mixture of the two products in favour of the thermodynamic product (149) by using low temperature and fast reaction times. With appropriate

purification techniques this became a viable route to the desired 2-methoxycarbonyl-3-oxo-piperidine protected as its BOC derivative (148).



(Scheme 35)

The third and final  $\beta$ -keto-ester (129) has been prepared using the thermodynamic conditions for Dieckmann ring closure and reduced using bakers' yeast. The resulting  $\beta$ -hydroxy-ester has been used as an intermediate *en-route* to the naturally occurring compound 3-quinuclidinol (151). This chemistry will be outlined in a later section (p 82).

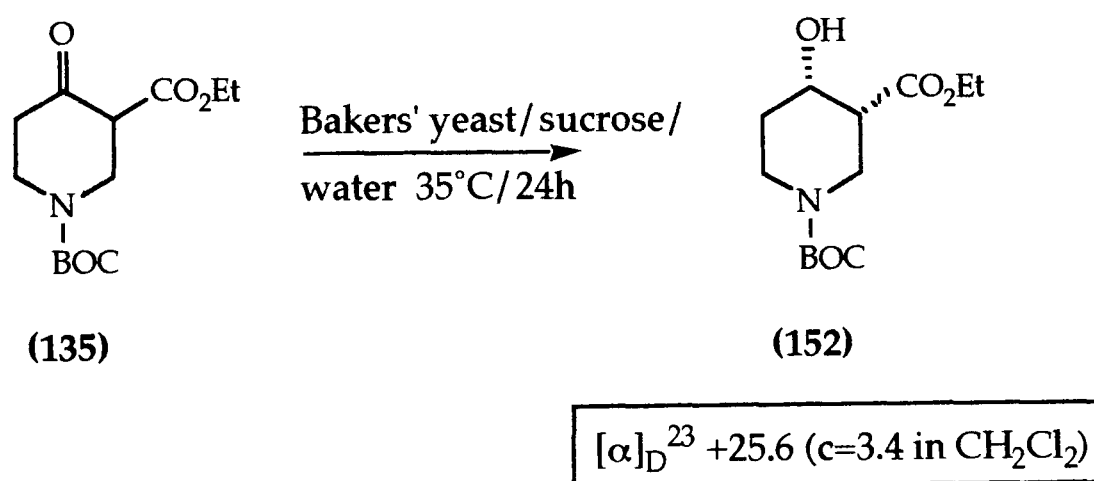


(Scheme 36)



## Yeast reduction of the piperidine $\beta$ -keto-ester derivatives

The piperidine  $\beta$ -keto-ester (135) was added to a fermenting solution of bakers' yeast and sucrose in tap water at 35°C.<sup>109</sup> Tap water was required as it was found that the reduction did not go to completion if deionised or distilled water was used. Fermentation continued for a period of 24 hours at which time the cellular mass was removed by filtration through kieselguhr. Extraction of the filtrate with dichloromethane and subsequent work up of the organic phases led to the isolation of the desired  $\beta$ -hydroxy-ester (152) in 74% yield as an off white solid (m.p 58-60°C). This looked extremely pure by both  $^1\text{H}$  and  $^{13}\text{C}$  NMR and appeared to be a single diastereomer which was fortunate in that any attempts to purify the compound by silica gel chromatography led to its complete degradation.<sup>111</sup> Furthermore we were pleased to find that the product was chiral and showed an optical rotation of +25.6°. However, in order that this compound can be used as an intermediate in any stereoselective synthesis the relative and absolute stereochemistries of the two newly created chiral centres must firstly be deduced.



(Scheme 37)

In order to determine relative chemistry of the hydroxyl and carboxylate functions, we decided to analyse the coupling of the protons geminal to these groups. Coupling is mediated by the interaction of orbitals within the bonding framework and is therefore dependant upon overlap and hence upon the dihedral angle.

The relationship between dihedral angle and the vicinal coupling constant  $^3J$  is given theoretically by the Karplus equations.

$$^3J_{ab} = J^0 \cos^2\phi - 0.28 \quad (0^\circ \leq \phi \leq 90^\circ)$$

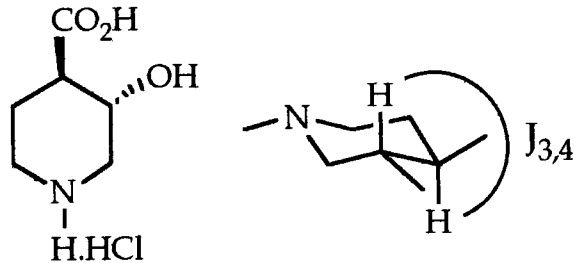
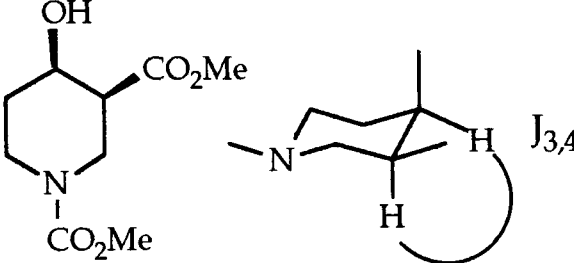
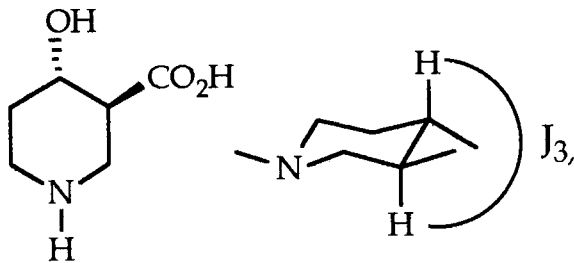
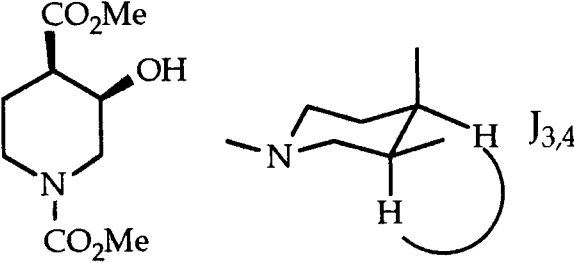
$$^3J_{ab} = J^{180} \cos^2\phi - 0.28 \quad (90^\circ \leq \phi \leq 180^\circ)$$

where  $J^0$  and  $J^{180}$  are constants which depend upon the constituents on the carbon atoms and  $\phi$  is the dihedral angle.

From this relationship it can be calculated that the coupling constant is largest when the dihedral angle is  $180^\circ$  (hydrogens in an anti-periplanar arrangement), slightly lower when the dihedral angle is  $0^\circ$  (hydrogens in a syncliplanar arrangement) and smallest when the dihedral angle is  $90^\circ$  (hydrogens in an orthogonal arrangement).

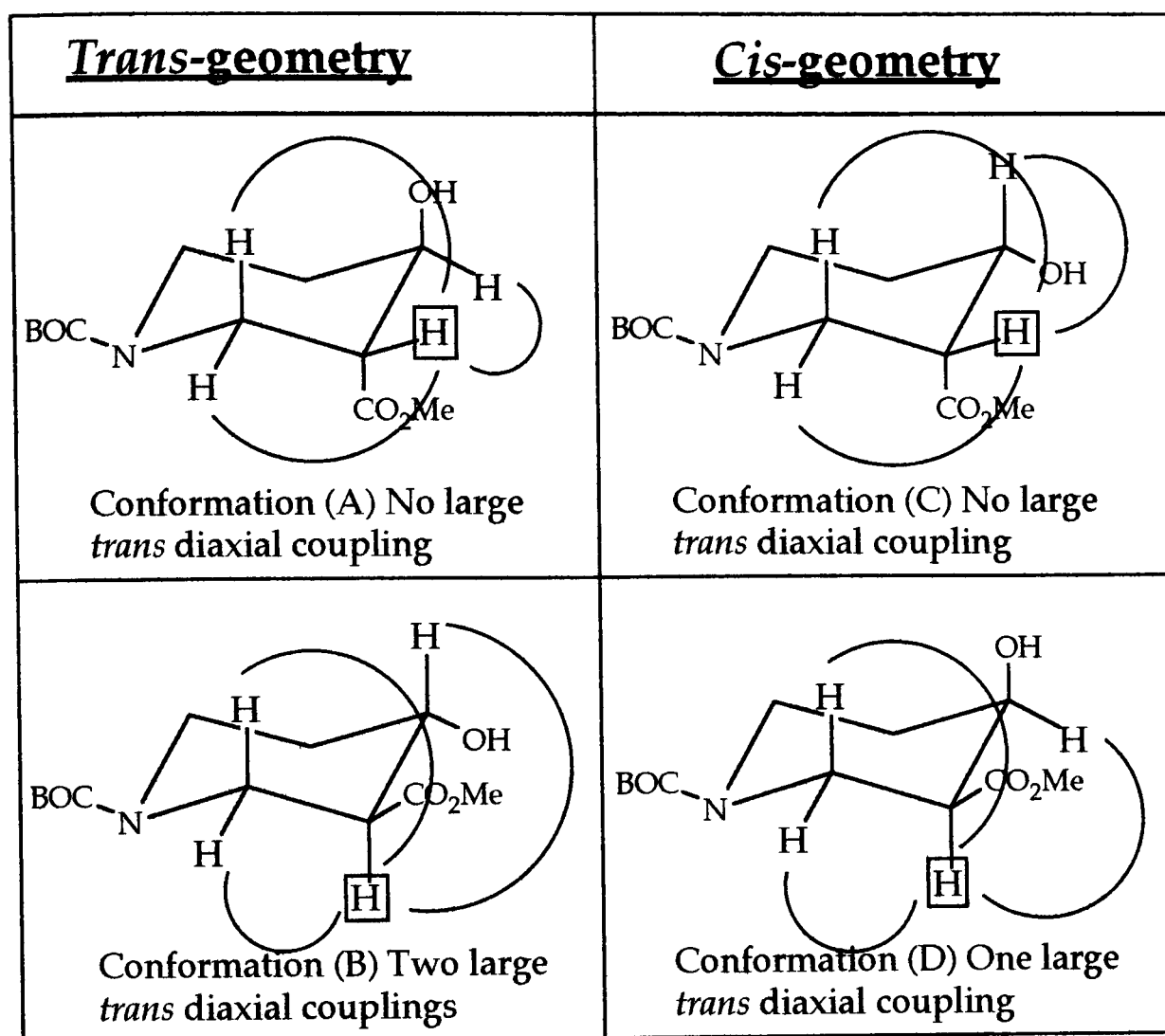
In rigid cyclohexanes the axial axial coupling is usually large, in the range 9-13 Hz, because the dihedral angle is close to  $180^\circ$ . The axial-equatorial and equatorial-equatorial coupling constants are much smaller, in the range 2-5 Hz because the dihedral angles are close to  $60^\circ$ . For our purposes the results found for cyclohexane systems should bear close resemblance to the piperidine systems.

Turning our attention to similar compounds in the literature we found that *trans* geometry of the protons between the newly created stereo-centres led to a coupling constant in the order of 10Hz and *cis* geometry of 2.5Hz (Figure 9).

<u><b>Trans-geometry</b></u>	<u><b>Cis-geometry</b></u>
 <p><math>J_{3,4}</math> 10.05 Hz (154)</p>	 <p><math>J_{3,4}</math> 2.5 Hz (155)</p>
 <p><math>J_{3,4}</math> 8.25 Hz (156)</p>	 <p><math>J_{3,4}</math> 2.5 Hz (157)</p>

(Figure 9)

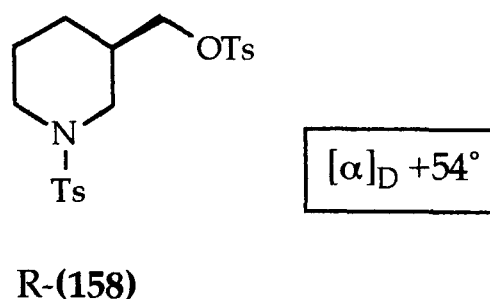
To determine the relative stereochemistry of the yeast reduction product we analysed the coupling constants between the protons on the 3 and 4 positions ( $J_{3,4}$ ) of the yeast reduction product (152). The proton at the 3-position showed 3 couplings (ddd) one large ( $J$  10.4) and two small ( $J$  4.4 and 2.6). If we consider the conformations for both diastereomers as shown in Figure 10, we can deduce that conformation (D) is present i.e. with only one large *trans* diaxial coupling and 2 smaller axial-equatorial couplings being observed. Thus the data is consistent with a *cis* orientation of the ester and hydroxyl functions.



(Figure 10)

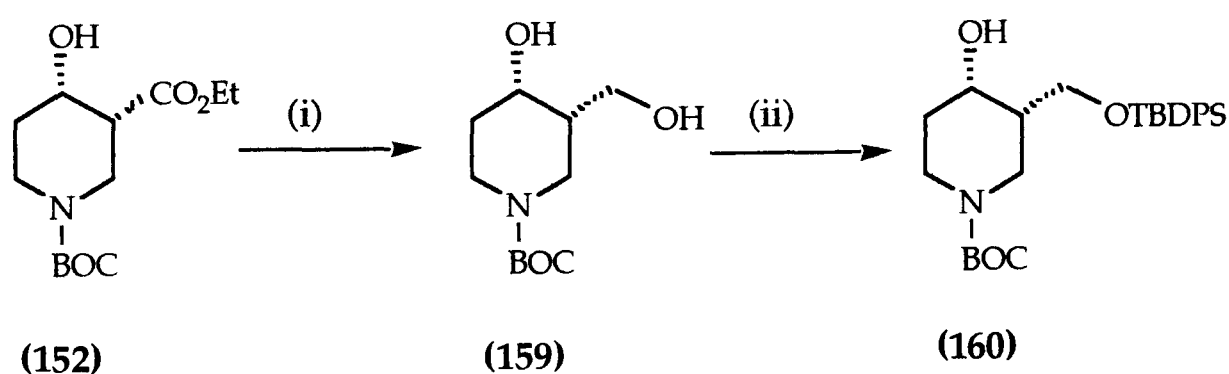
In order to determine the absolute stereochemistry of the yeast reduction product (152), it was necessary to convert this compound into one of known stereochemistry and subsequently compare optical rotations. To this end we chose to use the yeast reduction product (152) to synthesise the *bis*-tosylate (158) which had a literature  $[\alpha]_D$  of  $+54^{\circ 115}$  and (*R*) geometry as shown in Figure 11.

We envisaged that such a synthesis would involve deoxygenation at the 4 position of the yeast reduction product (152) followed by relevant functional group interconversions.



(Figure 11)

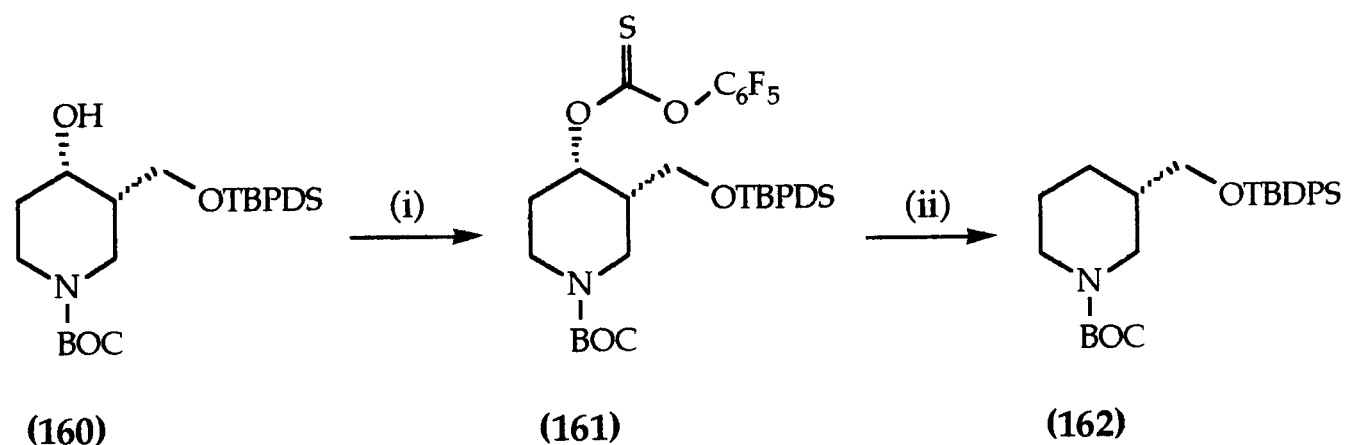
Firstly the yeast reduction product was further reduced to the corresponding diol (159) using diisobutylaluminium hydride in toluene.<sup>116</sup> This procedure produced the desired compound (159) only in moderate yield with evidence of unreduced starting material being present. To this end we decided to use the more powerful reducing agent lithium aluminium hydride and were pleased to isolate the desired diol (159) in good yield using this reagent. As we wished to deoxygenate the secondary alcohol at the C-(4) position of the piperidine, it was necessary to protect the primary alcohol functionality prior to this. This was smoothly achieved using *tert*-butylchlorodiphenylsilane<sup>117</sup> and triethylamine with a catalytic amount of 4-dimethylaminopyridine<sup>118</sup> and we were pleased to isolate the desired *tert*-butyldiphenylsilyl (TBDPS)-derivative (160) in 79% yield.



Reagents: (i),  $\text{LiAlH}_4$   
(ii), TBDPSCl,  $\text{Et}_3\text{N}$ , DMAP

(Scheme 38)

In order to deoxygenate the mono-protected diol (160), we adopted the Barton methodology of radical deoxygenation<sup>119,120</sup> as alternative attempts at reductive deoxygenation within the group had proved unfruitful.<sup>121</sup> The secondary alcohol moiety was converted into the corresponding thionocarbonate using pentafluorophenyl chlorothionoformate, pyridine and catalytic *n*-hydroxy succinimide. This compound (161) was stable to silica gel chromatography and we were able to isolate the intermediate in high purity. We then treated this intermediate (161) with tri-*n*-butyltin hydride and the radical initiator azo-*bis*-isobutyronitrile (AIBN) in refluxing benzene for a period of 30 minutes and we were pleased to isolate the desired deoxygenated product (162) in an overall 53% yield for the two steps.

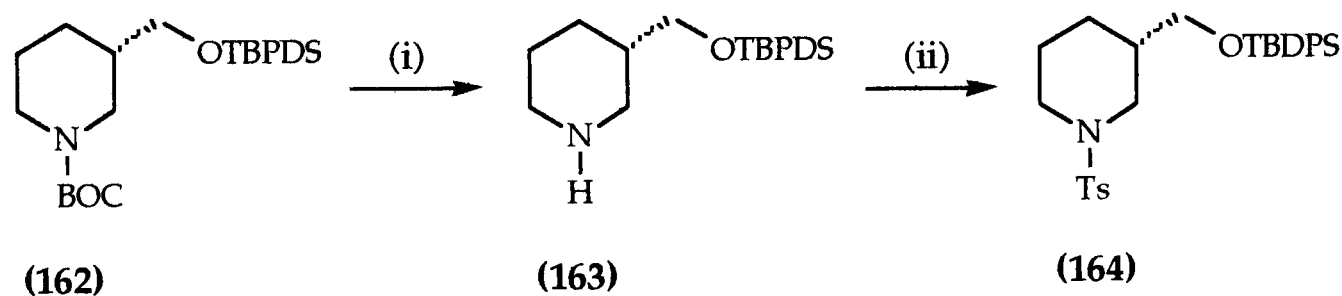


Reagents: (i),  $\text{C}_6\text{F}_5\text{O}(\text{CS})\text{Cl}$ , pyridine, *n*-hydroxysuccinimide  
(ii), Tri-*n*-butyltin hydride, AIBN, benzene, reflux

(Scheme 39)

With the basic skeleton of the desired *bis*-tosylate (158) now in place, we turned our attention to the necessary functional group conversions that were required to complete the synthesis. Removal of the nitrogen protecting group was cleanly accomplished using an excess of trifluoroacetic acid, which upon basification

liberated the free amine (163).<sup>123</sup> It was decided to reprotect this amine functionality as the tosylate instead of removing the oxygen protecting group at this stage. We feared that the resulting amino alcohol might have proven difficult to isolate. The tosylation was achieved using standard tosylation methodology of tosyl chloride and pyridine<sup>124,125</sup> although a catalytic amount of 4-dimethylaminopyridine<sup>118</sup> was required to drive the reaction through to completion. We were pleased to isolate the desired tosylated derivative (164) in 74% overall yield for the two steps.

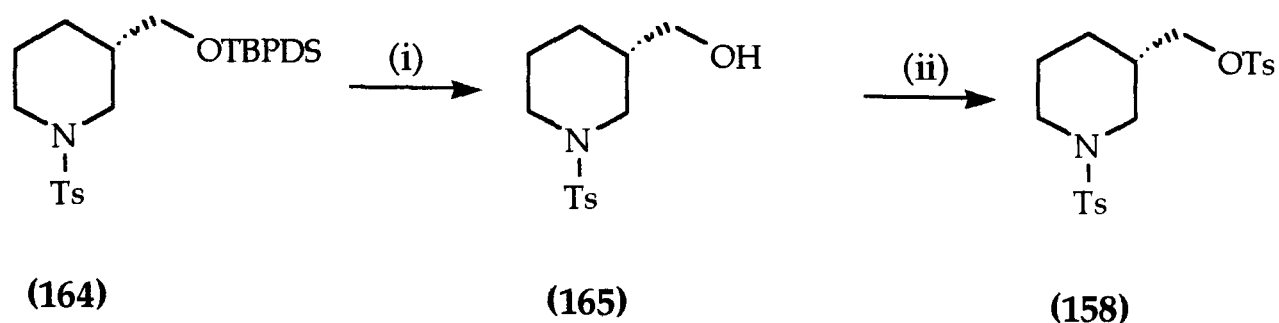


Reagents: (i), Trifluoroacetic acid then NaHCO<sub>3</sub>  
(ii), Tosyl chloride, pyridine, DMAP

**(Scheme 40)**

Turning our attention finally to the oxygen portion of the molecule, we smoothly deprotected the silyl moiety using the standard conditions of tetra-*n*-butylammonium fluoride in tetrahydrofuran.<sup>126</sup> This liberated the free alcohol (165) which was subsequently tosylated using the conditions outlined for the nitrogen portion<sup>118,124,125</sup> and we were very pleased to isolate the desired target

*bis*-tosylate (**158**) as a white crystalline solid with a melting point of 88-89°C [lit 87-89°C for the (*R*)-enantiomer<sup>115</sup>].

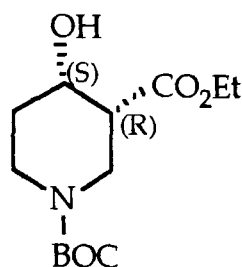


Reagents: (i), Tetra-*n*-butylammonium fluoride  
(ii), Tosyl chloride, pyridine, DMAP

(Scheme 41)

We were now left to measure the optical rotation ( $[\alpha]_D$ ) of this compound and compare it to the literature value<sup>115</sup> for the (*R*)-*bis*-tosylate (**158**) of +54°. We were subsequently very satisfied to find that the *bis*-tosylate (**158**) derived from our bakers' yeast reduction product (**152**) showed an optical rotation of -50.2° under identical conditions to the literature thus indicating (*S*)-configuration. Furthermore this figure allowed us to calculate an enantiomeric excess for the (*S*)-*bis* tosylate (**158**) derived from the bakers' yeast reduction product (**152**) of 93%. As we were careful not to enrich the optical purity of the compound during the synthesis by making relevant checks on column fractions etc., we can also suggest that the bakers' yeast reduction product (**152**) has an enantiomeric excess of 93%. As we had already deduced the relative stereochemistry as being *cis* and we now know that the absolute stereochemistry at the 3 position of the yeast reduction product (**152**) is (*R*), we can deduce the absolute stereochemistry at the 4 position will be (*S*) as shown in Figure 12.

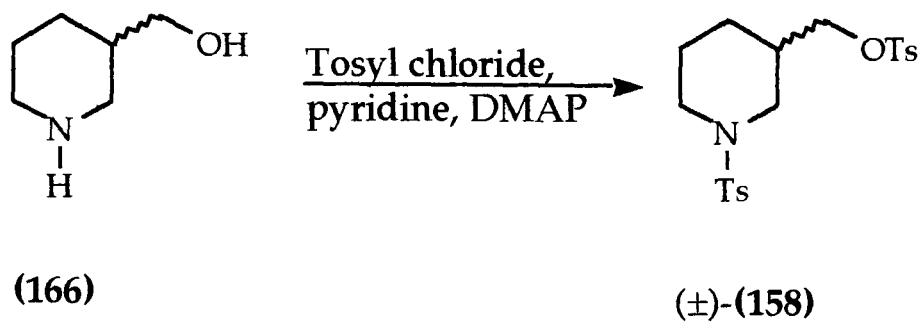




(152)

(Figure 12)

As a more accurate check of the optical purity of the yeast reduction product (152) we decided to undertake chiral shift NMR experiments on both the racemic and chiral *bis*-tosylates (158). The racemic product ( $\pm$ )-(158) was synthesised by subjecting 3-piperidinemethanol (166) to the tosylating conditions of tosyl chloride and pyridine catalysed by 4-dimethylaminopyridine.<sup>118,124,125</sup> We again isolated the desired compound ( $\pm$ )-(158) as a white crystalline solid.



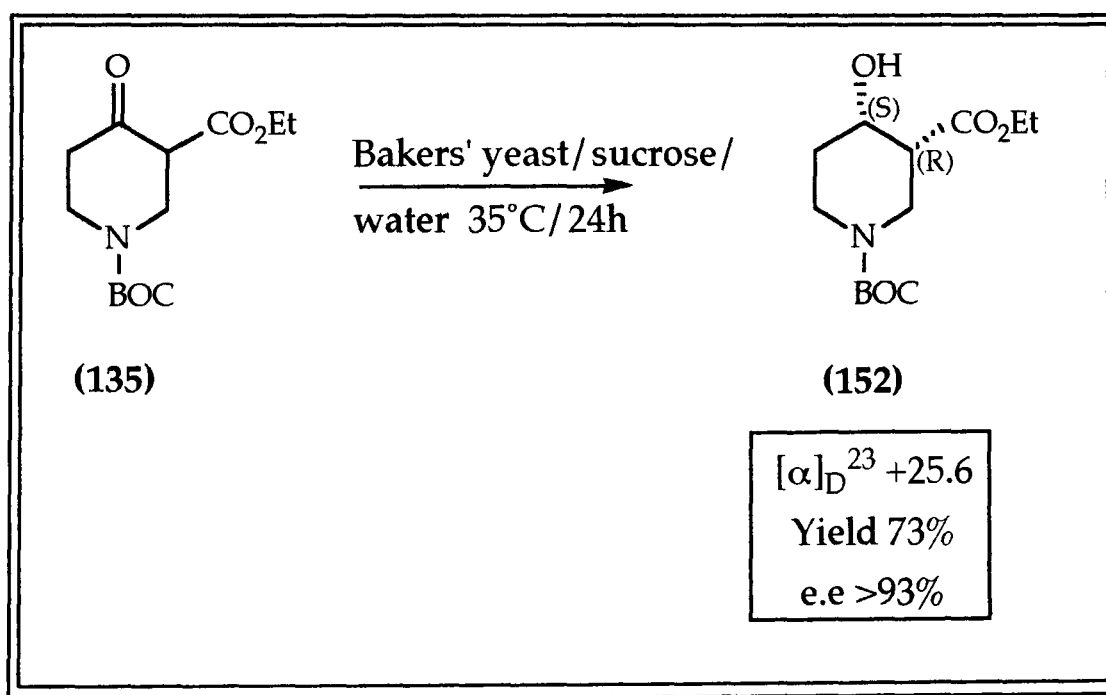
(Scheme 42)

A measured amount of the racemic material was dissolved in deuteriochloroform and to this solution were added small quantities of the europium shift reagent *tris*-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium (III). After a number of attempts we were excited to see splitting of a signal corresponding to one of the aromatic ring protons in the  $^1\text{H}$  NMR spectrum. Addition of the shift reagent was continued and the splitting eventually gave 2

distinct signals although complete base line separation could not be achieved. When the chiral material was subjected to the same experiments we saw only one of the two signals in the  $^1\text{H}$  NMR spectrum which indicated the complete absence of one of the enantiomers of the *bis*-tosylate (158). This indicated that the observed optical purity of 93% from optical rotation values should be taken as a minimum value for the reaction.

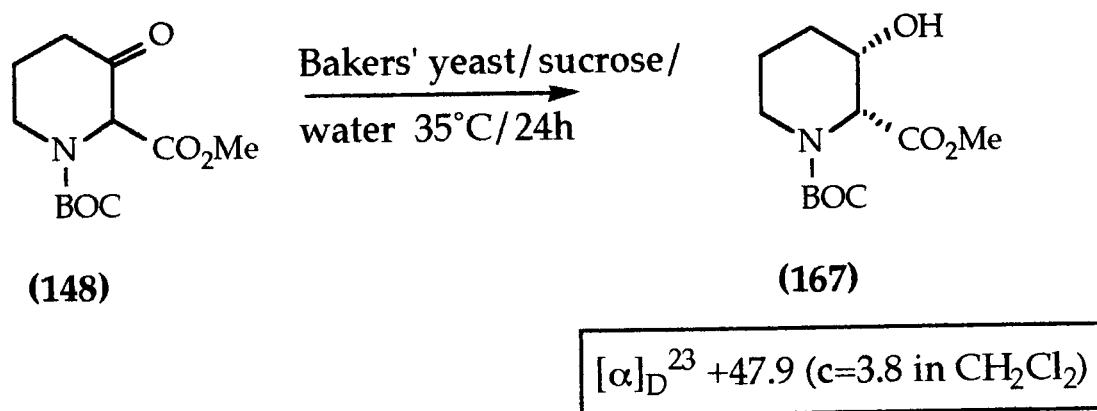
## Conclusion

In conclusion we can say that the bakers' yeast reduction of 1-*tert*-butyl-3-ethyl 4-oxopiperidine-1,3-dicarboxylate (135) gives (3*R*, 4*S*)-1-*tert*-butyl-3-ethyl 4-hydroxypiperidine-1,3-dicarboxylate (152) in 74% chemical yield and with an enantiomeric excess greater than 93% as shown in Figure 13.



(Figure 13)

1-*tert*-Butyl-2-methyl 3-oxopiperidine-1,2-dicarboxylate (148) was also subjected to the bakers' yeast reduction methodology.<sup>109</sup> The piperidine  $\beta$ -keto-ester (148) was added to a fermenting solution of bakers' yeast and sucrose in tap water and fermentation was continued for a period of 24hrs. Removal of the cellular mass by filtration through kieselguhr followed by extraction into dichloromethane and the usual work up furnished the desired piperidine- $\beta$ -hydroxy ester (167) as a pale oil in 80% isolated yield. As in the previous example we were pleased to find the crude product looked extremely pure by  $^1\text{H}$  NMR and also appeared to be a single diastereomer by  $^{13}\text{C}$  NMR. All rotameric line splittings were eliminated when the sample was heated to 333K.<sup>110</sup> We were also happy to observe that chirality had been induced in the product as it displayed an optical rotation of  $+47.9^\circ$ . No attempts were made to purify this compound by silica gel chromatography as we feared this would result in its degradation as in the previous example.<sup>111</sup>



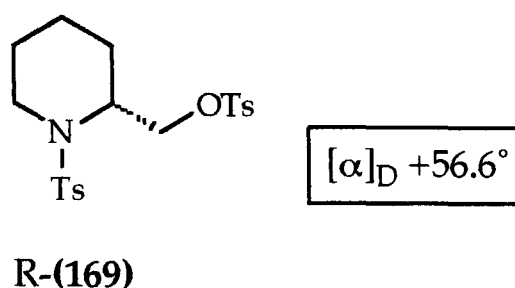
(Scheme 43)

In order to determine the relative stereochemistry of the product we again looked at the coupling constant between the protons of the newly created chiral centres (J<sub>2,3</sub>). However, we believed this case would be a little more complicated than the last in that we had predicted that the ester functionality would adopt an axial configuration in the product to avoid steric interactions with the nitrogen protecting group, a phenomenon often observed with these systems.<sup>127</sup> We were unable to predict whether this would have any influence on the stereochemical outcome of the bakers' yeast reduction at this stage.

Again an attempt was made to analyse the coupling constants of the newly created stereo-centres the yeast reduction product (167) and its corresponding acetate<sup>110</sup>. We were unable to measure coupling constants for the C(2)-H or C(3)-H of the yeast reduction product (167) or the C(2)-H and C(3)-H signals of the corresponding acetate<sup>110</sup> as the signals were obscured in the <sup>1</sup>H NMR spectrum. No attempts at reducing rotameric line broadening resolved this problem. In order to confirm relative stereochemistry we hoped that one of the derivatives of the yeast reduction product would display a clear signal for one of these protons. If not we predicted double irradiation or NOE experiments would have to be performed.

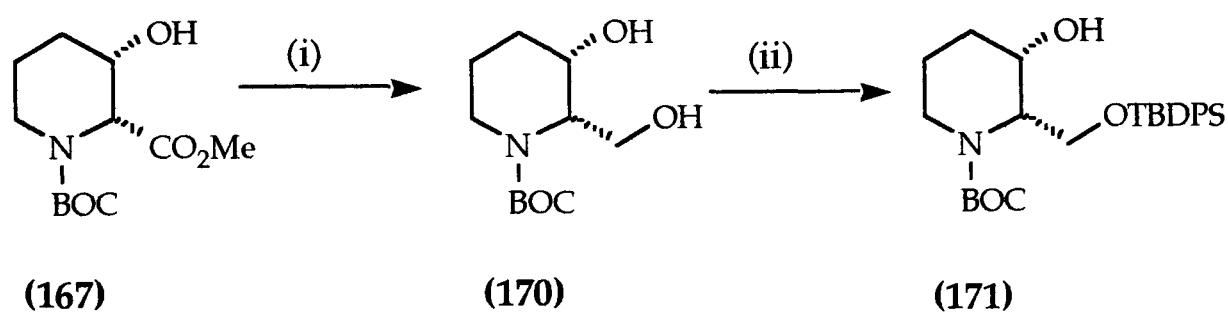
In order to determine absolute stereochemistry we again turned to the scientific literature in the hope that a suitable compound could be found that the yeast reduction product (167) could be elaborated to. To our delight we came across the corresponding *bis*-tosylate of 2-piperidine methanol (169) which had been synthesised in chiral form with the (*R*)-form showing an optical rotation of +56.6°. <sup>128</sup> This meant that the chemistry used in the previous example could be adapted to the purpose of proving absolute stereochemistry of the second yeast reduction product in the series (167). We were again required therefore to deoxygenate the yeast reduction product followed by relevant functional group

interconversions to create the desired *bis*-tosylate (169) and compare its optical rotation to that of the literature compound.<sup>128</sup>



(Figure 14)

Lithium aluminium hydride reduction of the yeast reduction product (167) resulted in its smooth conversion to the corresponding diol (170) in 72% isolated yield. It was again necessary to protect the primary hydroxyl function prior to the radical deoxygenation sequence. This was smoothly achieved using *tert*-butylchlorodiphenylsilane and triethylamine with a catalytic amount of 4-dimethylaminopyridine<sup>117,118</sup> and we were pleased to isolate the desired *tert*-butyldiphenylsilyl (TBDPS)-derivative (171) in 78% yield after silica gel chromatography.

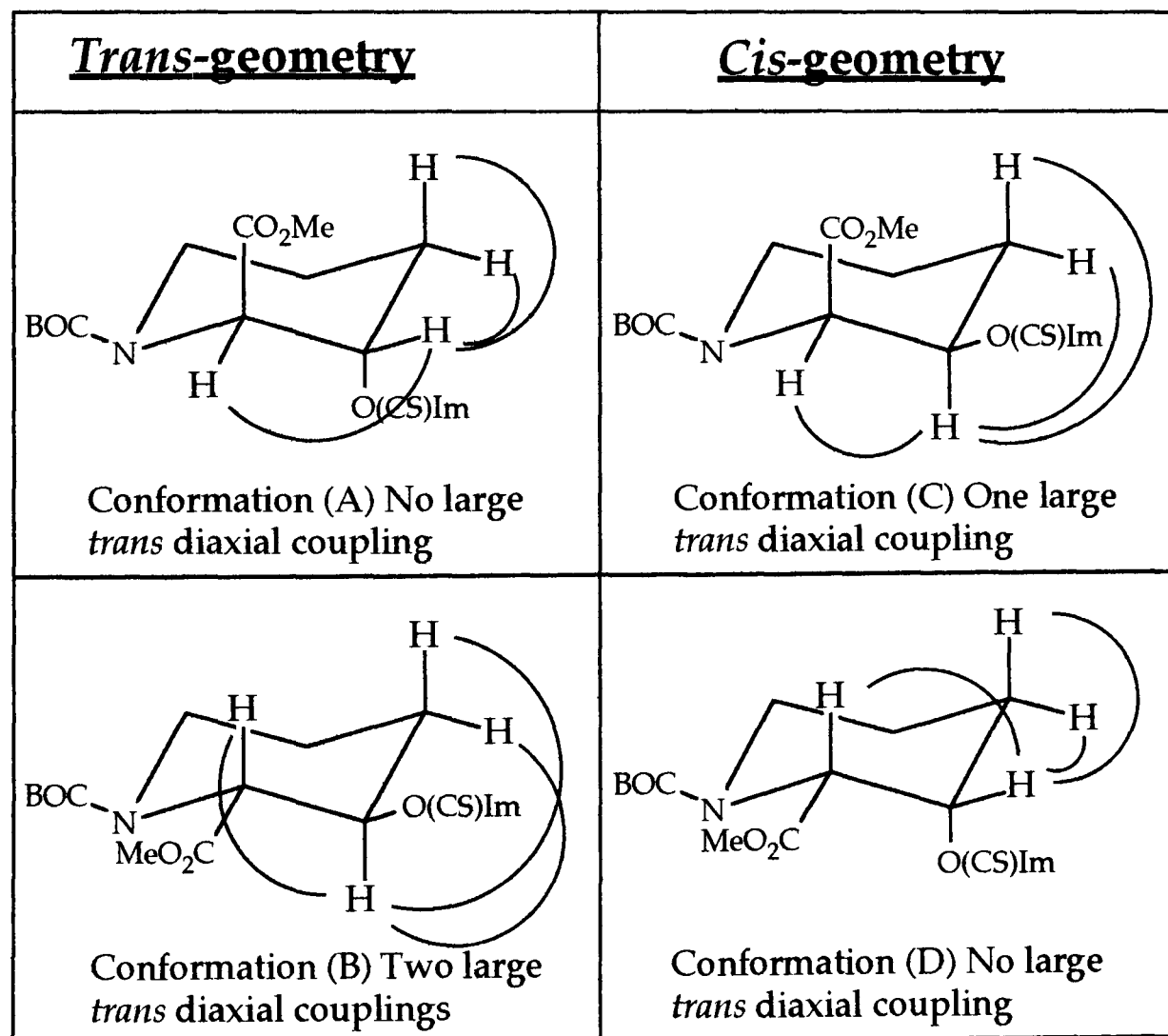


Reagents: (i),  $\text{LiAlH}_4$   
(ii), TBDPSCl,  $\text{Et}_3\text{N}$ , DMAP

(Scheme 44)

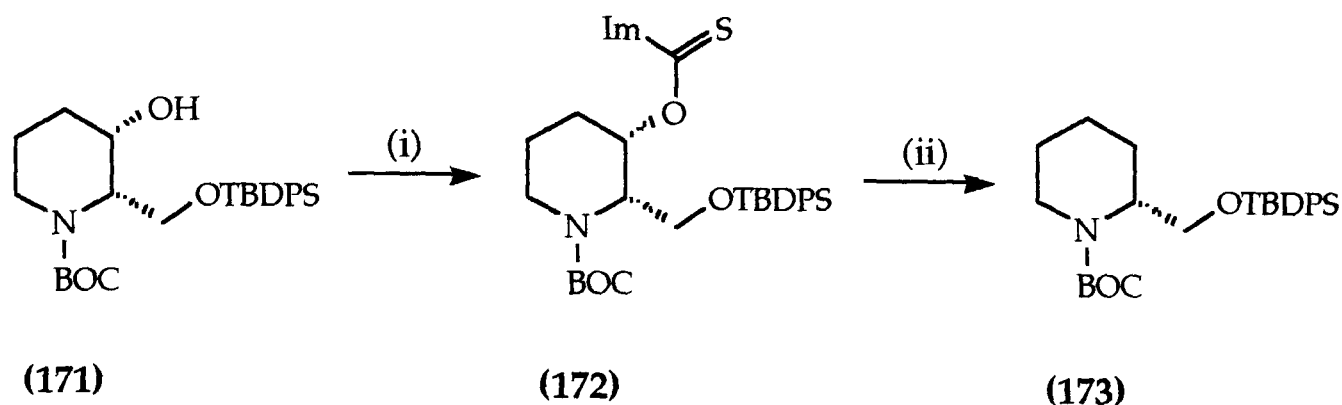
We were disappointed to find that the Barton deoxygenation procedure adopted previously using pentafluorophenyl chlorothionoformate<sup>122</sup> proved unsuccessful on this molecule. We were unable to offer an adequate explanation of this anomaly

but decided to modify the radical deoxygenation procedure by using *N,N'*-thiocarbonyldiimidazole.<sup>129</sup> On this occasion we were relieved to isolate the desired thionourethane intermediate (172) after silica gel chromatography. This compound was to prove even more valuable than we first thought as we were able to unambiguously measure the coupling constant ( $J_{2,3}$ ) of the C(3)-H which had been pulled down to  $\delta 5.53$ , and appeared as a double double doublet in the  $^1\text{H}$  NMR spectrum. The three couplings consisted of one large ( $J$  10.4) and two small ( $J$  4.4 and 2.6). If we consider the conformations for both diastereomers as shown in Figure 15, we can deduce that conformation (C) is present i.e. with only one large *trans* diaxial coupling and 2 smaller axial-equatorial couplings being observed. Thus the data is consistent with a *cis* orientation of the ester and hydroxyl functions in the yeast reduction product (167).



(Figure 15)

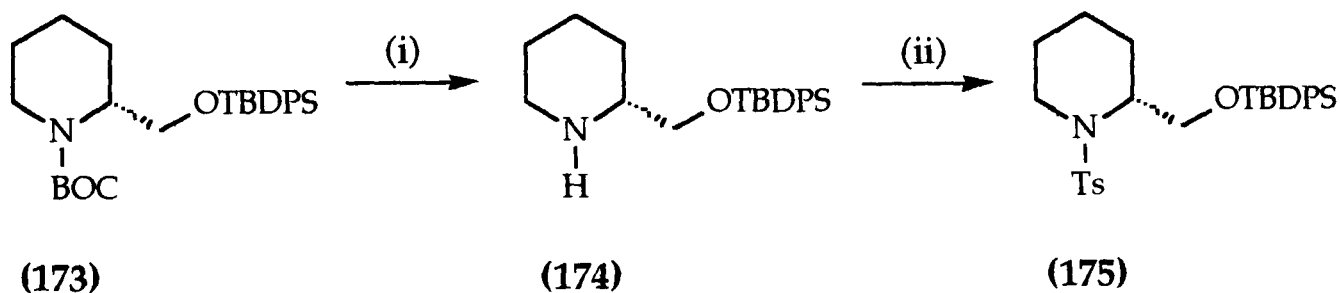
Focusing on the deoxygenation of the thiourethane derivative (172), the use of tri-*n*-butyltin hydride in refluxing benzene furnished the desired deoxygenated derivative (173) in 53% yield after column chromatography.



Reagents: (i), Im<sub>2</sub>CS, pyridine  
(ii), Tri-*n*-butyltin hydride, AIBN, benzene

(Scheme 45)

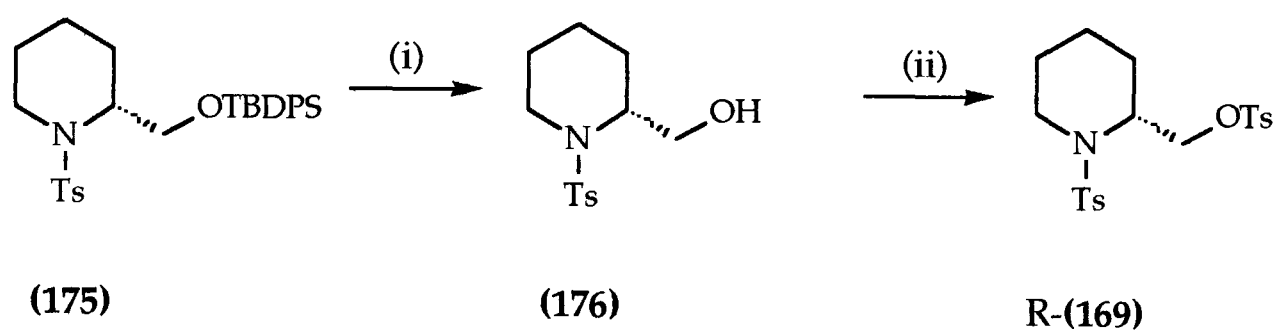
Removal of the nitrogen protecting group was again cleanly accomplished using excess trifluoroacetic acid which upon basification liberated the free amine (174)<sup>123</sup>. Tosylation was achieved using tosylation methodology of tosyl chloride and 4-dimethylamino-pyridine<sup>118,124,125</sup>. We were pleased to isolate the desired tosylated derivative (175) in a yield of 70% after silica gel chromatography.



Reagents: (i), Trifluoroacetic acid  
(ii), Tosyl chloride, pyridine, DMAP

(Scheme 46)

Turning our attention finally to the oxygen portion of the molecule we smoothly deprotected the silyl moiety using the standard conditions of tetra-*n*-butylammonium fluoride in tetrahydrofuran.<sup>126</sup> This liberated the free alcohol (176) which was subsequently tosylated using the conditions outlined for the nitrogen portion and we were pleased to isolate the desired target *bis*-tosylate (169) as a viscous colourless oil in 75% yield.



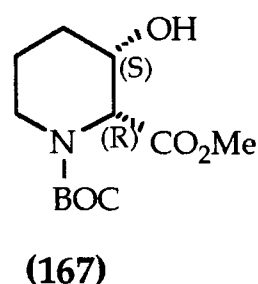
Reagents: (i), Tetra-*n*-butylammonium fluoride  
 (ii), Tosyl chloride, pyridine, DMAP

(Scheme 47)

We were left now to measure the optical rotation ( $[\alpha]_D$ ) of this compound and compare it to the literature value for the (*R*)-*bis*-tosylate (169) of +56.6°. <sup>128</sup> We were subsequently very satisfied to find that the *bis*-tosylate (169) derived from our bakers' yeast reduction product (167) showed an optical rotation of +55.0° thus indicating (*R*)-geometry also. Furthermore this figure allowed us to calculate an enantiomeric excess for the *bis*-tosylate derived from the bakers' yeast reduction product (167) of 97%. As we were careful not to enrich the optical purity of the compound during the synthesis by making relevant checks on column fractions etc we can also state that the bakers' yeast reduction product (167) also has an enantiomeric excess of 97%. As we had already deduced the relative stereochemistry as being *cis* and we now know the absolute stereochemistry at the 2 position of the yeast reduction product (167) is (*R*), we

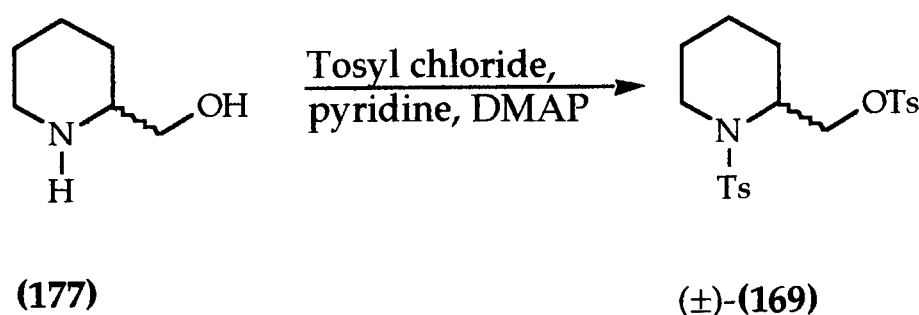


can deduce the absolute stereochemistry at the 3 position will be (*S*) as shown in Figure 16.



(Figure 16)

As a more accurate check of the optical purity of the yeast reduction product, we again decided to undertake chiral shift NMR experiments on both the racemic and chiral bis-tosylates (169). The racemic product ( $\pm$ )-(169) was synthesised by subjecting 2-piperidinemethanol (177) with the tosylating conditions of tosyl chloride and pyridine catalysed by 4-dimethylaminopyridine. We again isolated the desired compound ( $\pm$ )-(169) as a thick colourless oil.



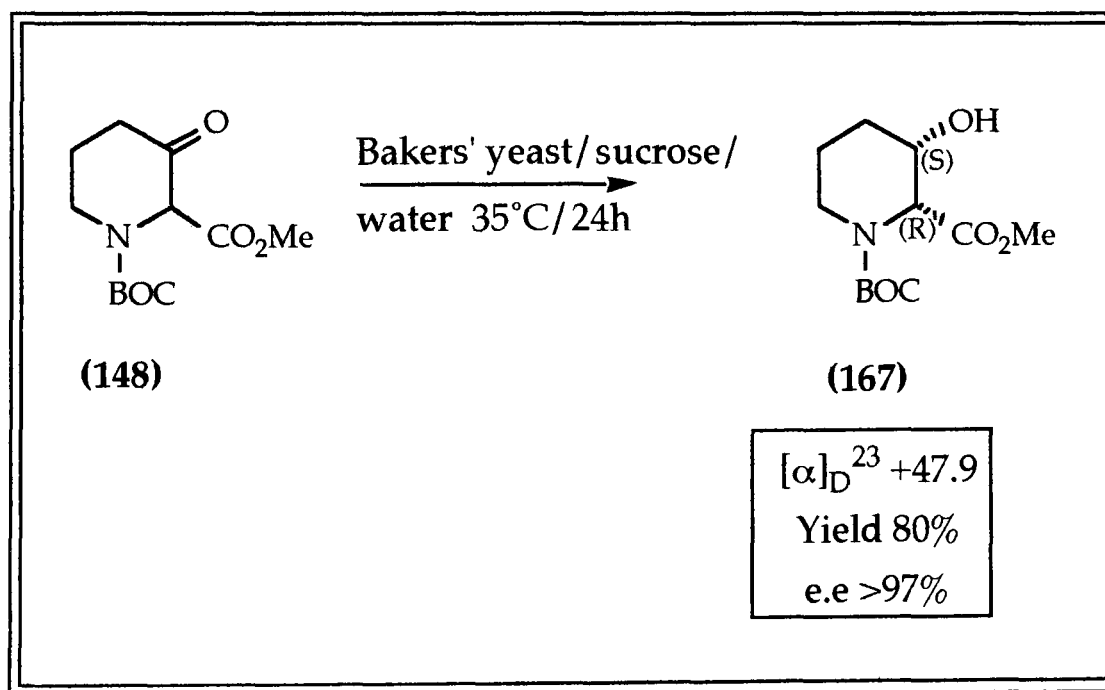
(Scheme 48)

A measured amount of the racemic material was dissolved in deuteriochloroform and to this solution were added small quantities of the europium shift reagent *tris*- [3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium (III). After a number of additions of the reagent we saw splitting of a signal

corresponding to one of the aromatic protons in the  $^1\text{H}$  NMR spectrum. Addition of the shift reagent was continued and the splitting eventually gave 2 distinct signals although complete base line separation could not be achieved. When the chiral material was subjected to the same experiments we saw only one of the two peaks in the  $^1\text{H}$  NMR spectrum which indicated the complete absence of one of the enantiomers of the *bis*-tosylate (169). This indicated that the observed optical purity of 97% from optical rotation values again should be taken as a minimum value for the reaction.

## Conclusion

In conclusion we can say that the bakers' yeast reduction of 1-*tert*-butyl-2-methyl 3-oxopiperidine-1,2-dicarboxylate gives (2*R*, 3*S*)-1-*tert*-butyl-2-methyl 3-hydroxypiperidine-1,2-dicarboxylate in 80% chemical yield and with an enantiomeric excess greater than 97% as shown in Figure 17.



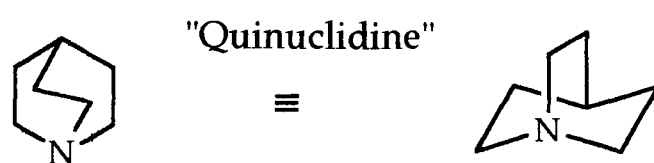
(Figure 17)

## **Chapter Three**

### **Synthesis of (*R*)-3-quinuclidinol**

## Introduction to quinuclidines

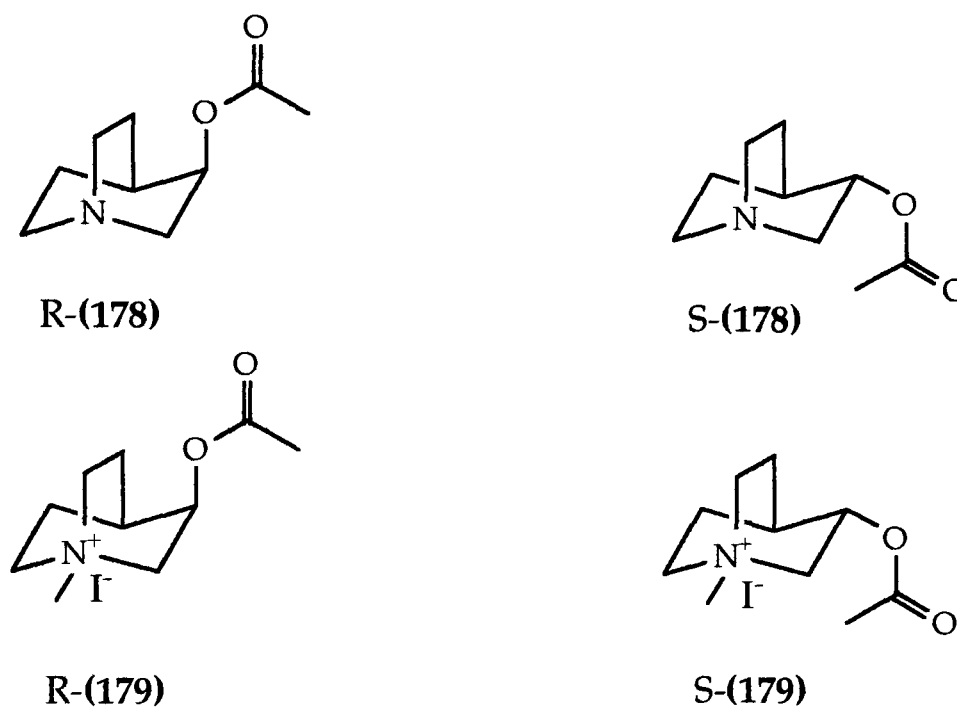
The quinuclidine nucleus is of synthetic interest to the organic chemist in connection with the number of naturally occurring alkaloids that contain this unit. Indeed large families of alkaloids such as the sarpagine, ajamine and cincona families boast this nucleus as part of their structure.<sup>130, 131, 132, 134</sup>



(Figure 18)

It is interesting to note that the chemistry surrounding quinuclidine is limited with only a small amount of work being reported in this area. Moreover there have been hardly any reports of the enantioselective synthesis of quinuclidines and their associated analogues in the scientific literature to date. Optically active quinuclidines and their derivatives are extremely important to both chemists and pharmacologists alike. In particular, 3-quinuclidinol (**151**) is interesting in the fact that its associated esters show anticholinergic properties.<sup>135</sup> 3-Acetoxyquinuclidine (**178**) is one such compound which is one of the few muscarinic agents that are more active as tertiary amines than as quaternary ammonium salts.<sup>136</sup> In addition to its peripheral effects, 3-acetoxyquinuclidine (**178**) also shows central effects upon systemic administration causing tremor, analgesia and hypothermia in mice.<sup>137</sup> Barlow and Casy have shown that the enantiomers of 3-acetoxyquinuclidine (**178**) display different levels of biological activity.<sup>138</sup> (*S*)-3-Acetoxyquinuclidine (**178**) has 10 times the level of activity on guinea pig ileum than the corresponding (*R*) enantiomer. Furthermore, the

methiodate (179) of (*R*)-3-acetoxyquinuclidine (178) displays a 40 fold increase in activity over the corresponding (*S*) enantiomer.



(Figure 19)

Barlow and Casy as well as Weinstein and co-workers have shown that 3-acetoxyquinuclidine (178) embodies all the functional groups of acetylcholine (180) in a fairly rigid structure.<sup>138,139</sup> Furthermore, it is proposed that the (*S*)-enantiomer is a particularly good model for discussing fit to the muscarinic receptor.



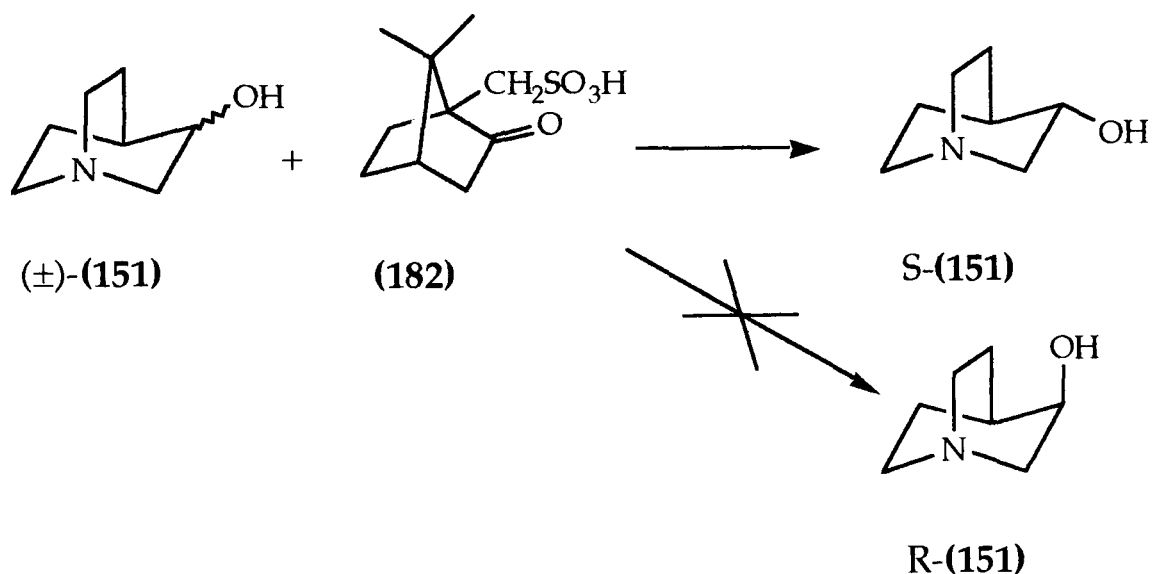
(Figure 20)

The differing levels of biological activity associated with the enantiomers of 3-acetoxyquinuclidine (178) is not uncommon in this and indeed many other areas of work. 3-Quinuclidinyl benzilate (181) also shows a widely different level of activity in each enantiomer<sup>140</sup>.



(Figure 21)

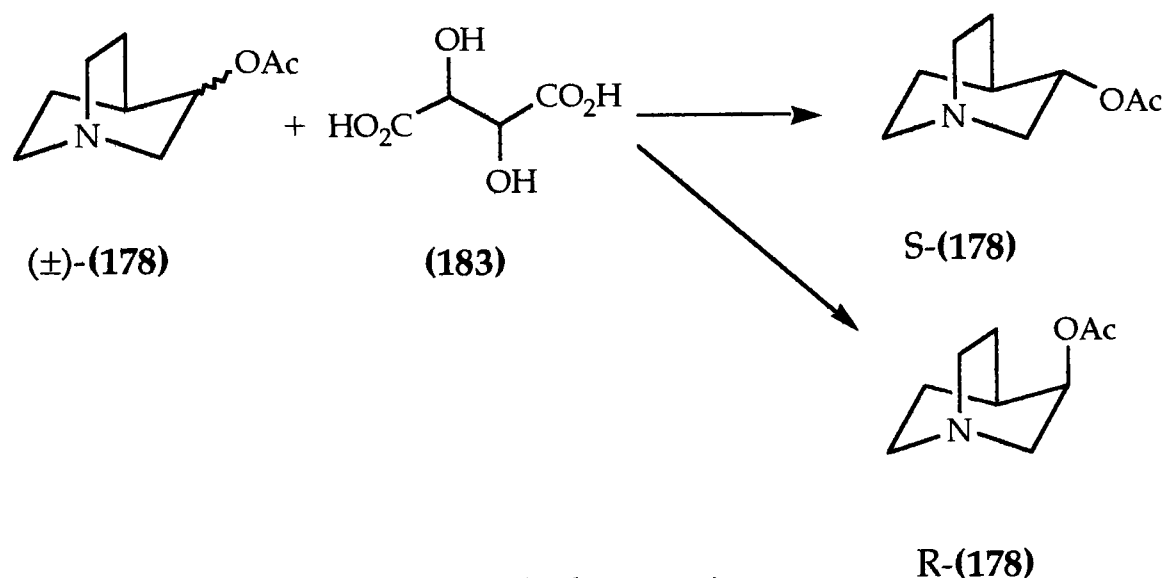
In general, the enantiomers of 3-quinuclidinol (151) have been separated by resolution of their corresponding diastereomeric salts. Sternbach and Kaiser were able to obtain (*S*)-3-quinuclidinol (151) in optically pure form back in 1952 by resolution of the racemate with 10-camphorsulphonic acid (182).<sup>141</sup> However the method was found to be low yielding and moreover the (*R*)-enantiomer could not be isolated by this method.



(Scheme 49)

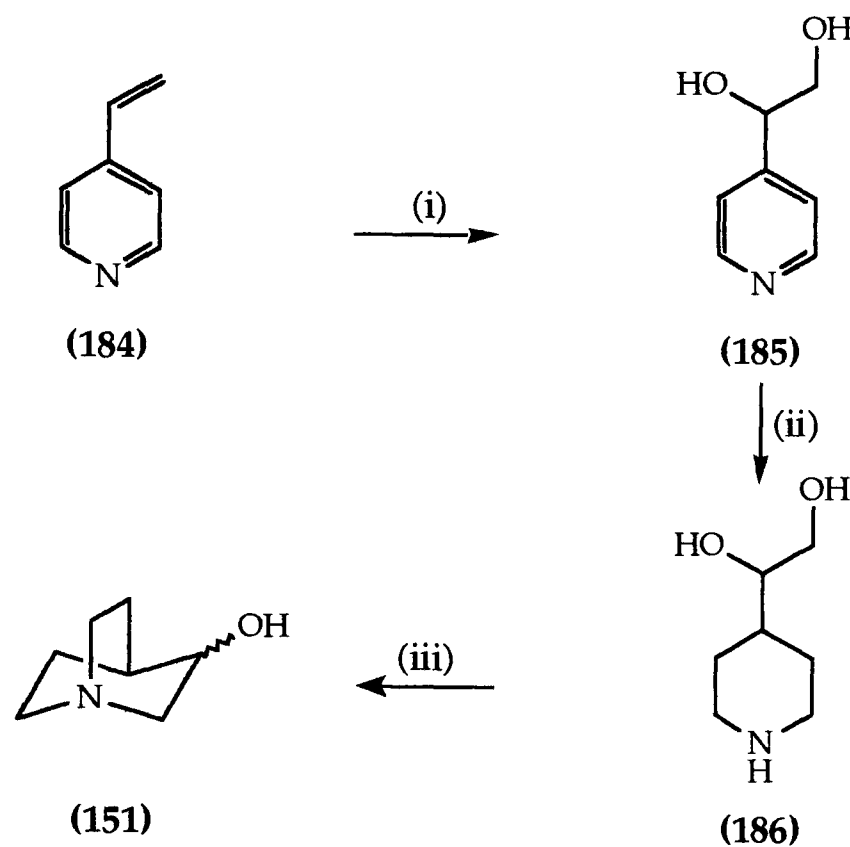
Kalir and co-workers later prepared (*S*)-3-quinuclidinol (**151**) by *N*-benzylation of the racemate followed by conversion of the quaternary base into the dibenzoyl-D-tartrate salt. Subsequent resolution of the salt followed by hydrogenolysis yielded the desired (3)-quinuclidinol (**151**) in chiral form.<sup>142</sup>

Dahlbom and co-workers simplified this procedure significantly by resolving racemic 3-acetoxyquinuclidine into its (*R*) and (*S*) enantiomers using (+) and (-)-tartaric acid (**183**).<sup>143</sup> The enantiomeric esters were obtained in high yield and with high optical purities by this method. In order to obtain chiral 3-quinuclidinol by this method it was simply necessary to hydrolyse the chiral esters in alkaline media.



As mentioned earlier in the chapter, research into the area of quinuclidines and their derivatives has been somewhat scarce. This has also been the case for 3-quinuclidinol with only a handful of syntheses reported for the racemate and even less for the chiral material. Aaron and co-workers published a synthesis of the racemic material by cyclodehydration of (4-piperidyl)-1,2-ethanediol (**186**), in 1965.<sup>144</sup> 4-Vinylpyridine (**184**) was oxidised in cold aqueous potassium permanganate to furnish 4-(pyridyl)-1,2-ethanediol (**185**) which was subsequently

hydrogenated to produce the desired material ready for cyclodehydration (186). Treatment of this compound with activated alumina at 300°C for 1 hr led to the desired racemic 3-quinuclidinol (151).



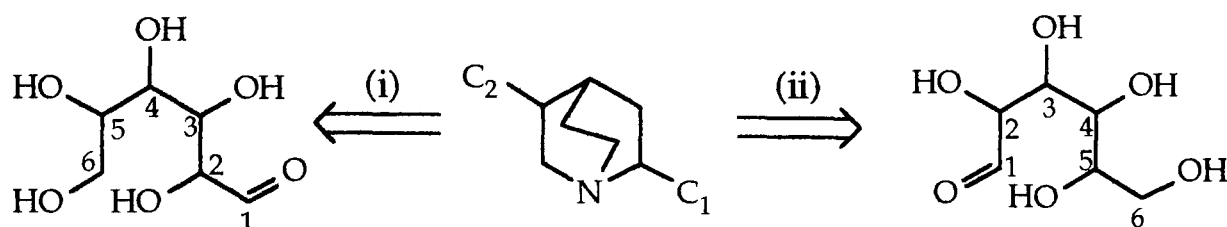
Reagents: (i)  $\text{KMnO}_4(\text{aq})$   
(ii)  $\text{H}_2/\text{PtO}_2$   
(iii) Alumina/ 300°C

(Scheme 51)

Interestingly, Fleet and co-workers have published a number of syntheses of chiral 3-quinuclidinol (151) that will allow introduction of key functionality into the final cyclised product.<sup>145,146</sup> It is a common feature of the alkaloids that contain 3-quinuclidinol, that the base is substituted with a one carbon chain on one of the ring bridges and a two carbon chain on one of the other ring bridges.



Fleet proposes that such a system could be generated by either of the two strategies outlined in Scheme 52.

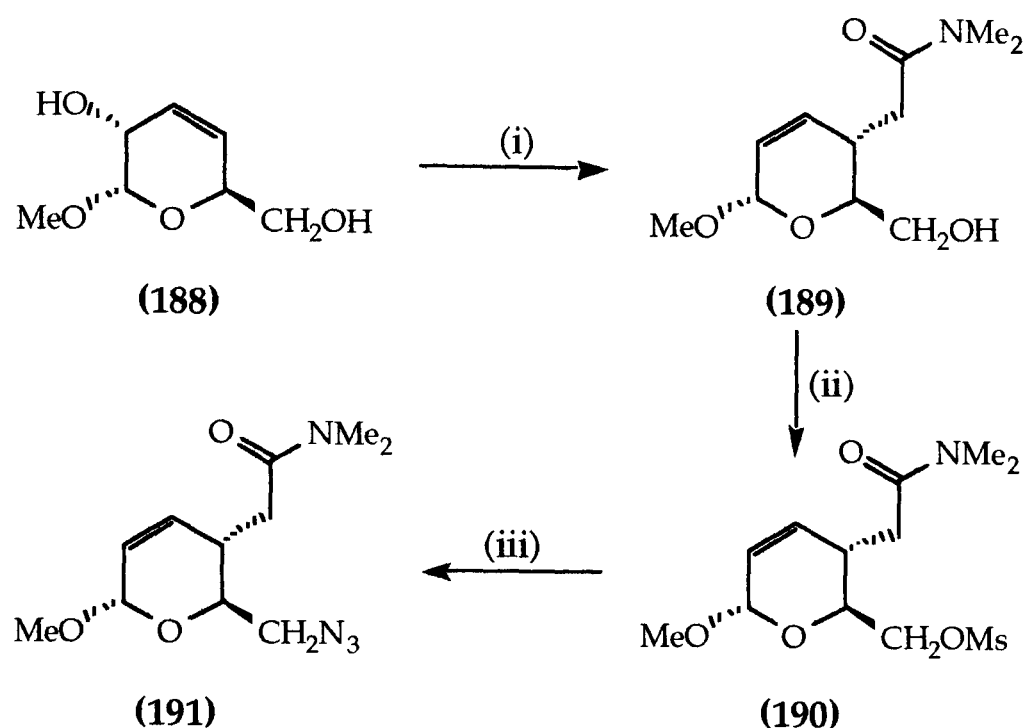


(Scheme 52)

The first approach (i) involves the introduction of the two carbon chain destined to become the bridge of the quinuclidine at C-(4) of the hexose; the two carbon substituent is therefore introduced at C-(5). The second approach (ii) involves the introduction of the bridge of the quinuclidine at C-(3) of the hexose and therefore the two carbon substituent is at C-(2).

In the first approach (i) Fleet synthesised (*S*)-3-quinuclidinol (**151**) from (*D*)-glucose. A two carbon unit is introduced initially at C-(4) of glucose which is subsequently joined by nitrogen to the C-(6) position of the sugar to form an intermediate lactam (**192**) which is further elaborated to form the quinuclidine framework. Methyl  $\alpha$ -D-glucopyranoside is converted to the corresponding diol (**188**) by known methods.<sup>147</sup> Treatment of the diol with *N,N*-dimethylacetamide dimethyl acetal<sup>148</sup> gave the amide (**189**). This was mesylated and the corresponding mesylate group in the product (**190**) displaced by azide to furnish

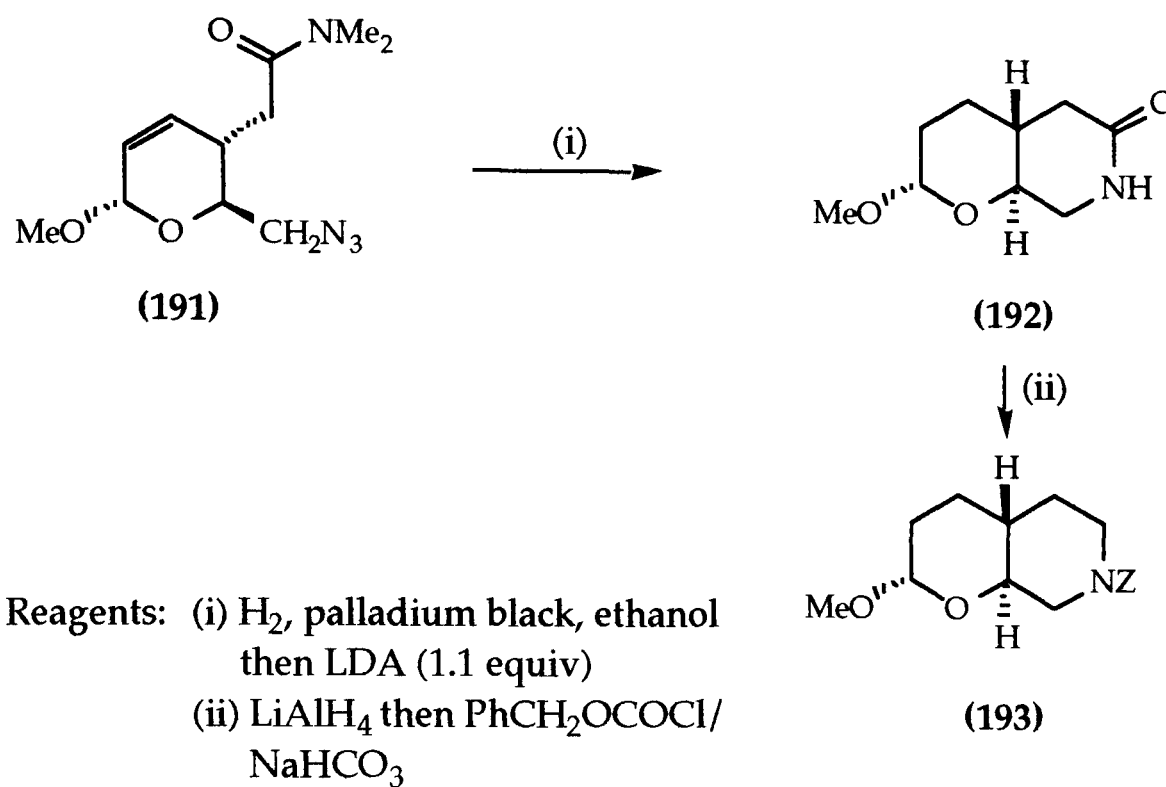
the azidoamide (191).



Reagents: (i)  $\text{MeC(OMe)}_2\text{NMe}_2$ , diglyme then  $\text{K}_2\text{CO}_3$   
(ii)  $\text{MeSO}_2\text{Cl}$ /pyridine  
(iii)  $\text{NaN}_3$ /DMF

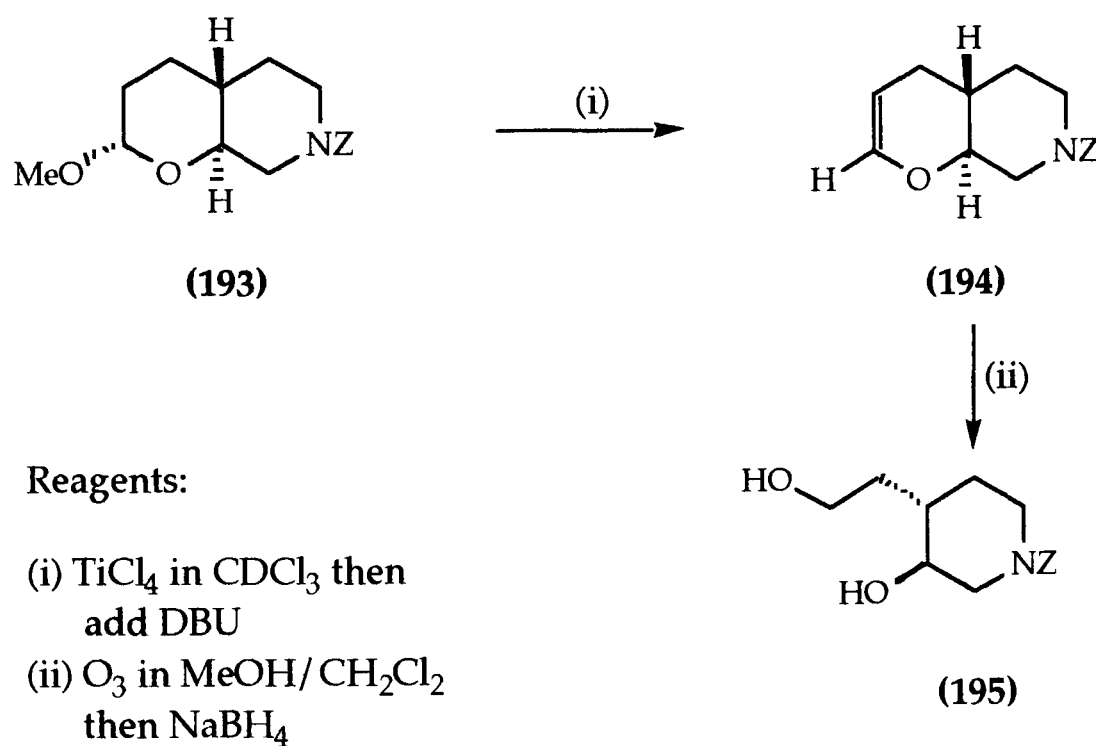
(Scheme 53)

The resulting azidoamide (191) was hydrogenolysed over palladium black which resulted in saturation of the double bond and reduction of the azide portion to the corresponding amine which cyclised in the presence of lithium diisopropylamide to the intermediate lactam (192) which was further reduced with lithium aluminium hydride and protected as the benzyl carbamate (193).



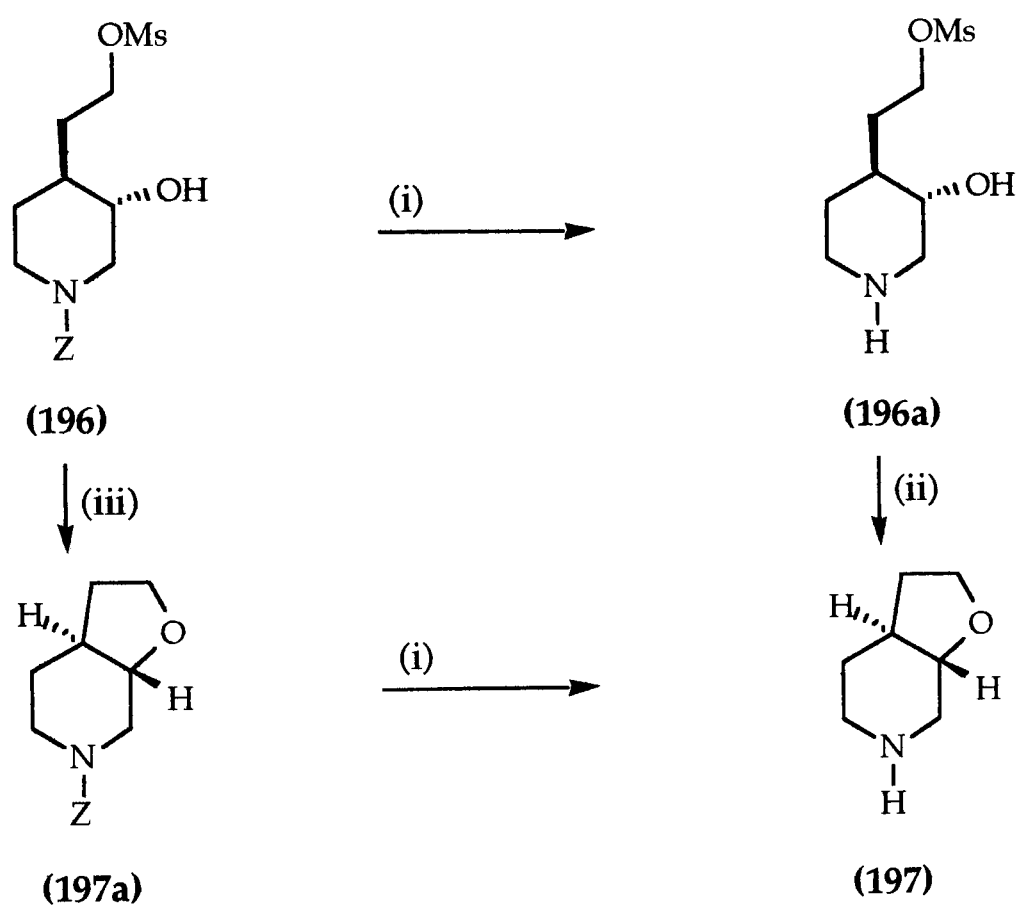
(Scheme 54)

Reaction of (193) with titanium tetrachloride<sup>149-150</sup> in CDCl<sub>3</sub> (to allow monitoring of reaction by NMR) followed by addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to the formation of the vinyl ether (194) which was subjected to ozonolysis and sodium borohydride reduction<sup>151</sup> to furnish the diol (195).



(Scheme 55)

Fleet envisaged the final cyclisation to produce (*S*)-3-quinuclidinol would involve mesylation and subsequent deprotection at nitrogen to allow cyclisation to take place. However, release of the amine functionality by hydrogenation of the mesylate (196) led to spontaneous ring closure with the formation of the tetrahydrofuran (197) in which intramolecular attack by oxygen had competed successfully with the anticipated attack by nitrogen. Fleet also found that the tetrahydrofuran (197a) could be formed by treatment of the protected piperidine mesylate (196) with base.

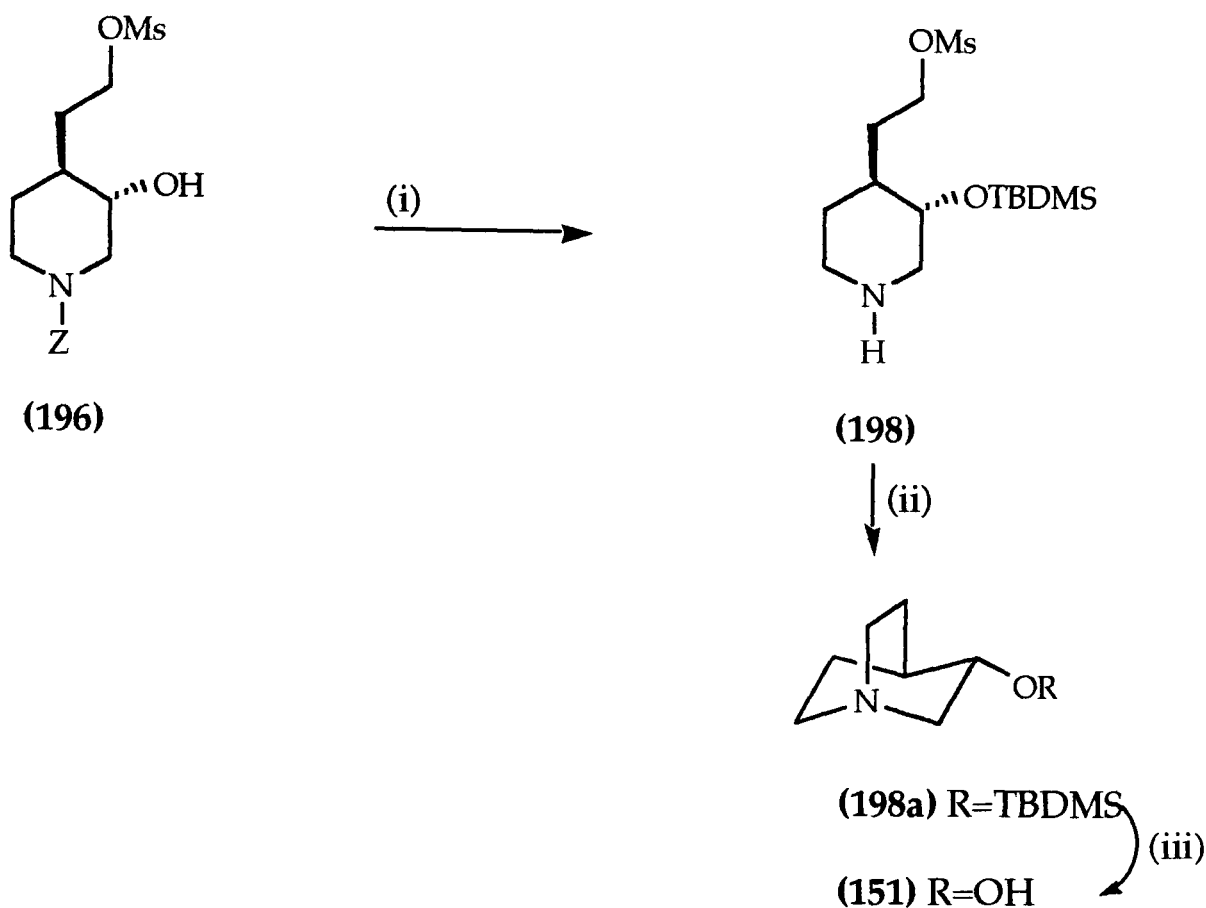


Reagents: (i)  $\text{H}_2$ /palladium black, ethanol  
(ii) Ethanol  $60^\circ$   
(iii) NaH/THF

(Scheme 56)

It was therefore necessary to protect the secondary hydroxyl function of the piperidine mesylate (196) prior to deprotection at nitrogen. This method furnished

the desired quinuclidinol (198a) as its silyl ether which was deprotected at oxygen using trifluoroacetic acid to give the target compound (151) with an optical rotation of  $+35.2^\circ$  (c, 0.23 in 1N HCl) [lit  $+43.8^\circ$  (c, 3.0 in 1N HCl)].<sup>152,153</sup>

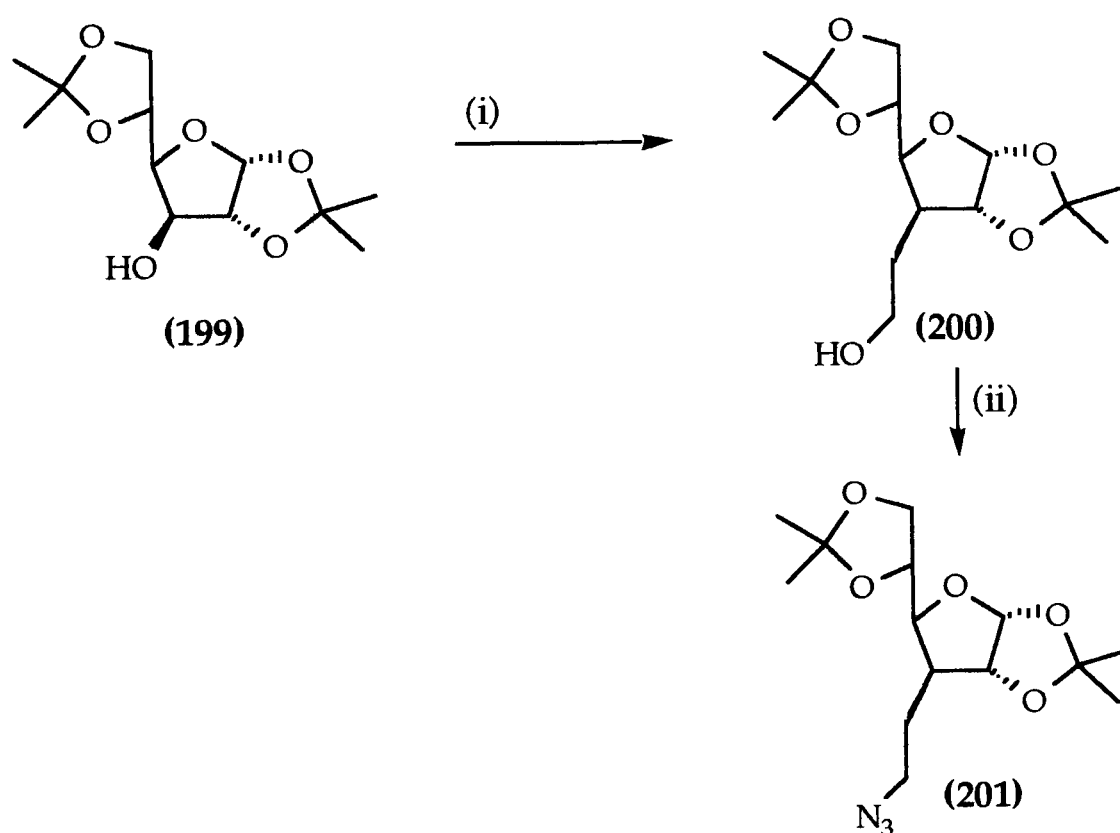


Reagents: (i)  $\text{CF}_3\text{SO}_3\text{SiMe}_2^t\text{Bu}$  / lutidine  
(ii)  $\text{H}_2$  / palladium black then ethanol  $60^\circ$   
(iii) TFA (aq)

(Scheme 57)

In the case of Fleet's second approach (ii), the introduction of the 2-carbon bridge of the quinuclidine was achieved at C-(3) of the hexose. Oxidation of diacetone glucose (199) with pyridium chlorochromate was followed by treatment with

carbomethoxymethylene triphenylphosphorane. Subsequent hydrogenation over palladium and reduction with lithium aluminium hydride gave the primary alcohol (200).<sup>154</sup> Mesylation followed by displacement of the mesylate functionality with azide gave 3-(2-azidoethyl)-3-deoxy-1,2:5,6-di-O-isopropylidene-allofuranose (201).

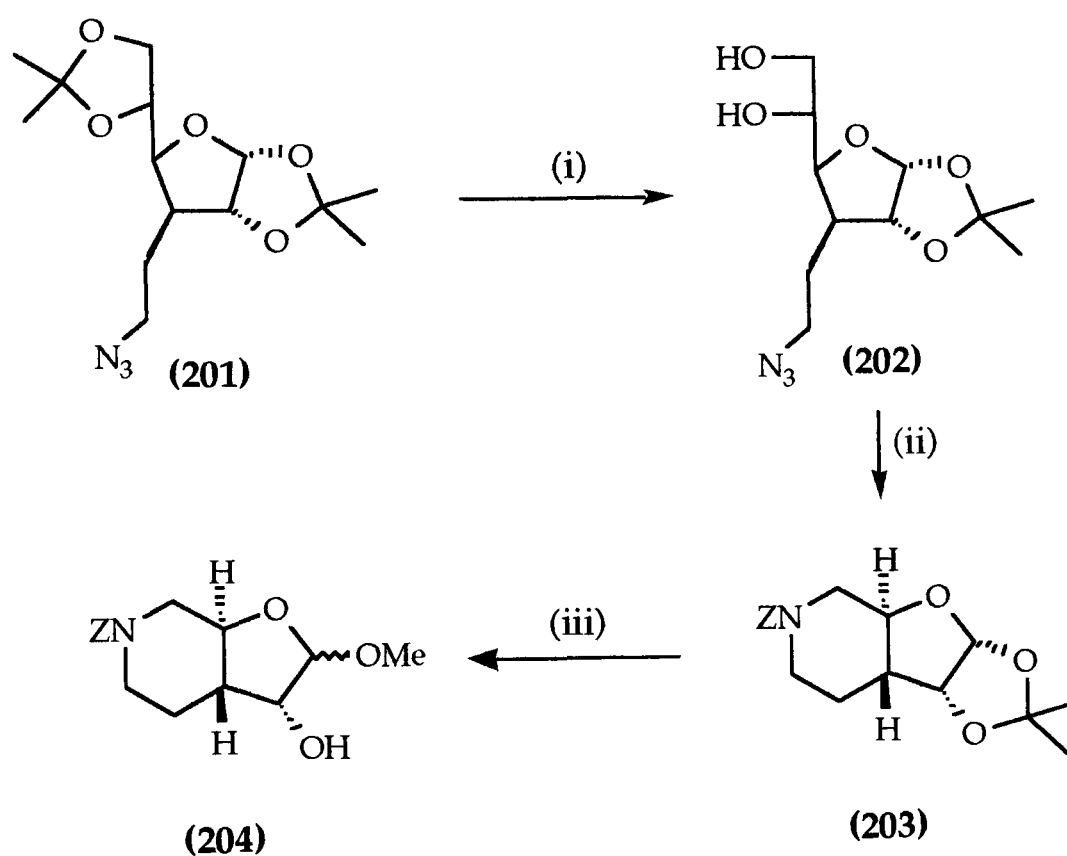


Reagents: (i) Pyridinium chlorochromate;  $\text{Ph}_3\text{PCHCO}_2\text{Me}$ ;  
 $\text{H}_2/\text{Pd}/\text{MeOH}$ ;  $\text{LiAlH}_4/\text{THF}$   
(ii)  $\text{MsCl}/\text{pyridine}$ ;  $\text{NaN}_3/\text{DMF}$

(Scheme 58)

Mild hydrolysis of (201) gave the diol (202) which was oxidised with periodate and hydrogenated over palladium black. The resulting amine was protected using

benzyl chloroformate to give (203) in which the first of the required rings of the target molecule had been formed. Methanolysis of this intermediate in the presence of acid ion exchange resin gave a mixture of  $\alpha$ - and  $\beta$ -furanosides (204).

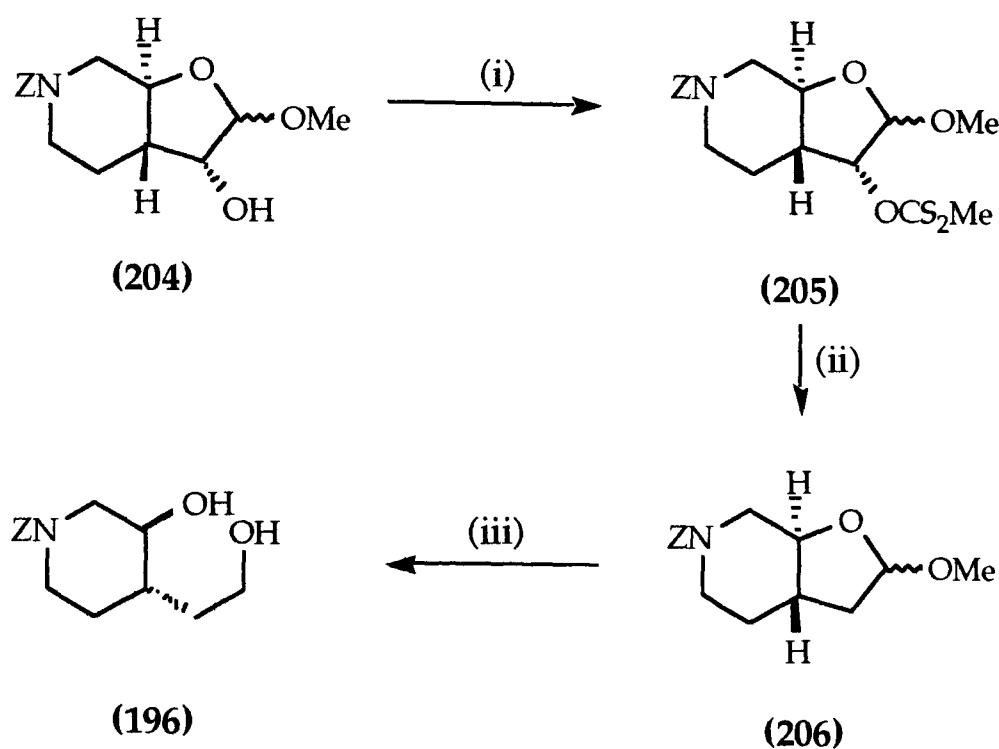


Reagents: (i) AcOH/ MeOH/ H<sub>2</sub>O  
(ii) NaIO<sub>4</sub>/ MeOH; H<sub>2</sub>/ palladium black, AcOH;  
PhCH<sub>2</sub>OCOCl/ NaHCO<sub>3</sub>  
(iii) Dowex (H<sup>+</sup>) resin/ MeOH

(Scheme 59)

Deoxygenation using Barton methodology<sup>119</sup> followed by hydrolysis of the

intermediate (206) gave the lactol which was reduced with sodium borohydride to give the diol (196).



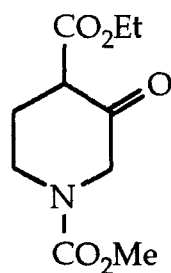
Reagents: (i) NaH, CS<sub>2</sub>, MeI  
(ii) Bu<sub>3</sub>SnH, AIBN, xylene  
(iii) CF<sub>3</sub>CO<sub>2</sub>H; NaBH<sub>4</sub>/EtOH

(Scheme 60)

As (196) has already been converted to chiral (*S*)-3-quinuclidinol (151) this approach represents another enantioselective synthesis of the molecule.



In the case of the third and final piperidine- $\beta$ -keto ester we wished to subject to the bakers' yeast reduction methodology<sup>109</sup> we were pleased to find that it was initially available commercially as its methyl carbamate from the Aldrich Chemical Company.

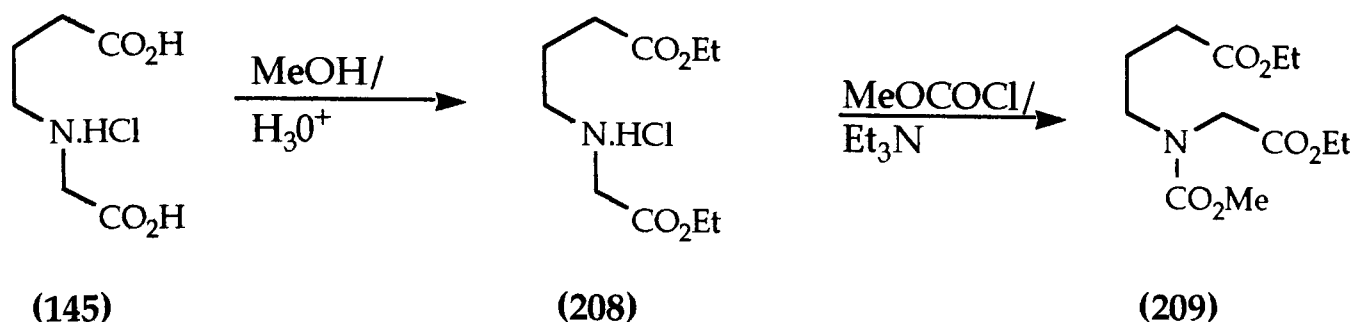


(207)

(Figure 22)

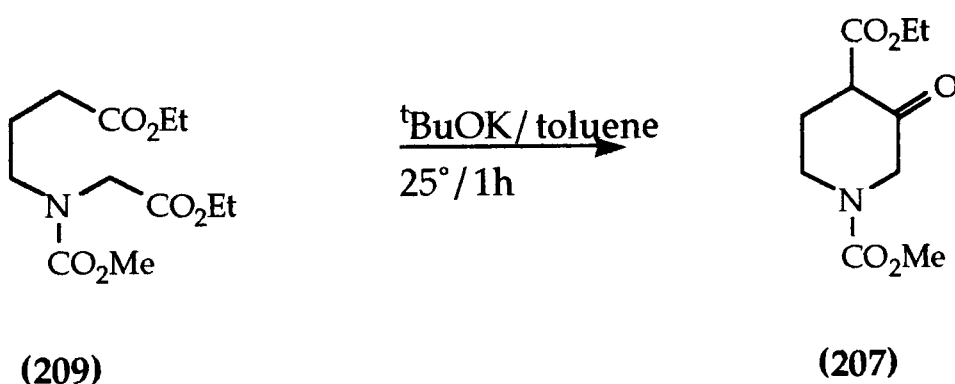
However with work well underway in this area, we were disappointed to find that the compound had been discontinued by the company in question and we were forced to design our own synthesis in order to carry on the project. Having received considerable success with the preparation of one of the previous piperidine  $\beta$ -keto esters (148) *via* Dieckmann cyclisation,<sup>107</sup> we decided that it would be a good idea to adopt this approach here. We also recalled the fact that a similarly substituted piperidine- $\beta$ -keto ester protected as the *tert*-butyl carbamate (149) could be formed as the major product from a Dieckmann cyclisation.

The diacid (145) produced as described earlier was re-esterified, this time using acidic ethanol in place of methanol to afford the corresponding diethyl ester (208) in a satisfying 84% yield. This was subsequently protected at nitrogen as its methyl carbamate using methyl chloroformate and triethylamine and we were pleased to isolate the desired protected material (209) as a colourless oil in 70% yield.



(Scheme 61)

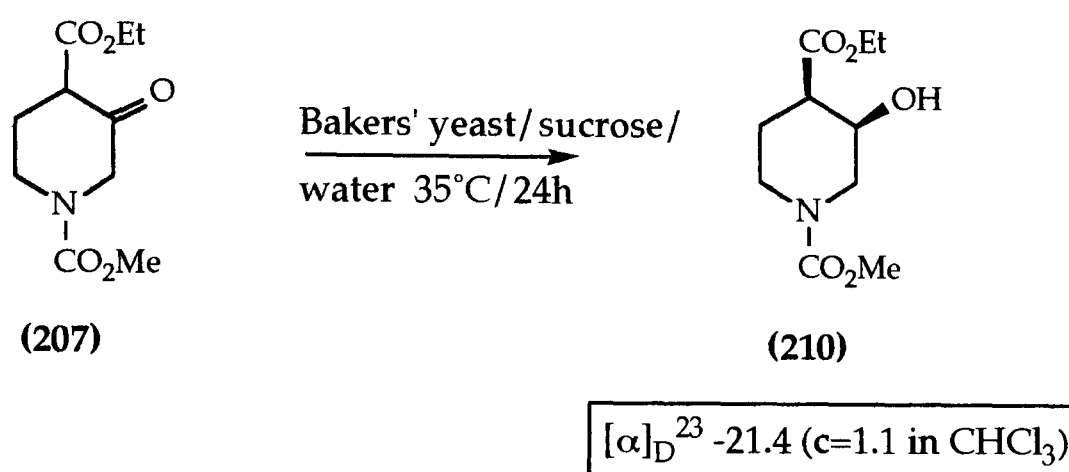
We had already learned from previous work on the cyclisation that the kinetic product from the Dieckmann cyclisation (the 3-oxo, 2-ester moiety) rapidly isomerised under the reaction conditions of potassium *tert*-butoxide and dry toluene at 0°C to give the thermodynamic product (namely the 3-oxo, 4-ester moiety). To this end we decided to adapt the reaction conditions to favour the thermodynamic product we now desired even more by running the reaction for longer periods at room temperature to allow even further equilibration. Potassium *tert*-butoxide was again used as the base and we were satisfied to obtain a yield of 51% for the isolated product after column chromatography.



(Scheme 62)

Once a plentiful supply of the required starting material (207) was at hand we decided to subject it to the bakers' yeast reduction reaction as before.<sup>109</sup> The compound was added to a fermenting solution of bakers' yeast and sucrose in

tap water and fermentation continued for 24hrs. After this time the cellular mass was removed by filtration through kieselguhr and the product extracted into dichloromethane. Work up of the organic fractions led to the desired piperidine- $\beta$ -hydroxyester (210) in an isolated yield of 89%. Again we were fortunate in that the product looked extremely pure by  $^1\text{H}$  NMR and therefore did not require purification by silica gel chromatography. Furthermore the compound appeared to be a single diastereomer by  $^{13}\text{C}$  NMR and as importantly showed an optical rotation of  $-21.4^\circ$ .

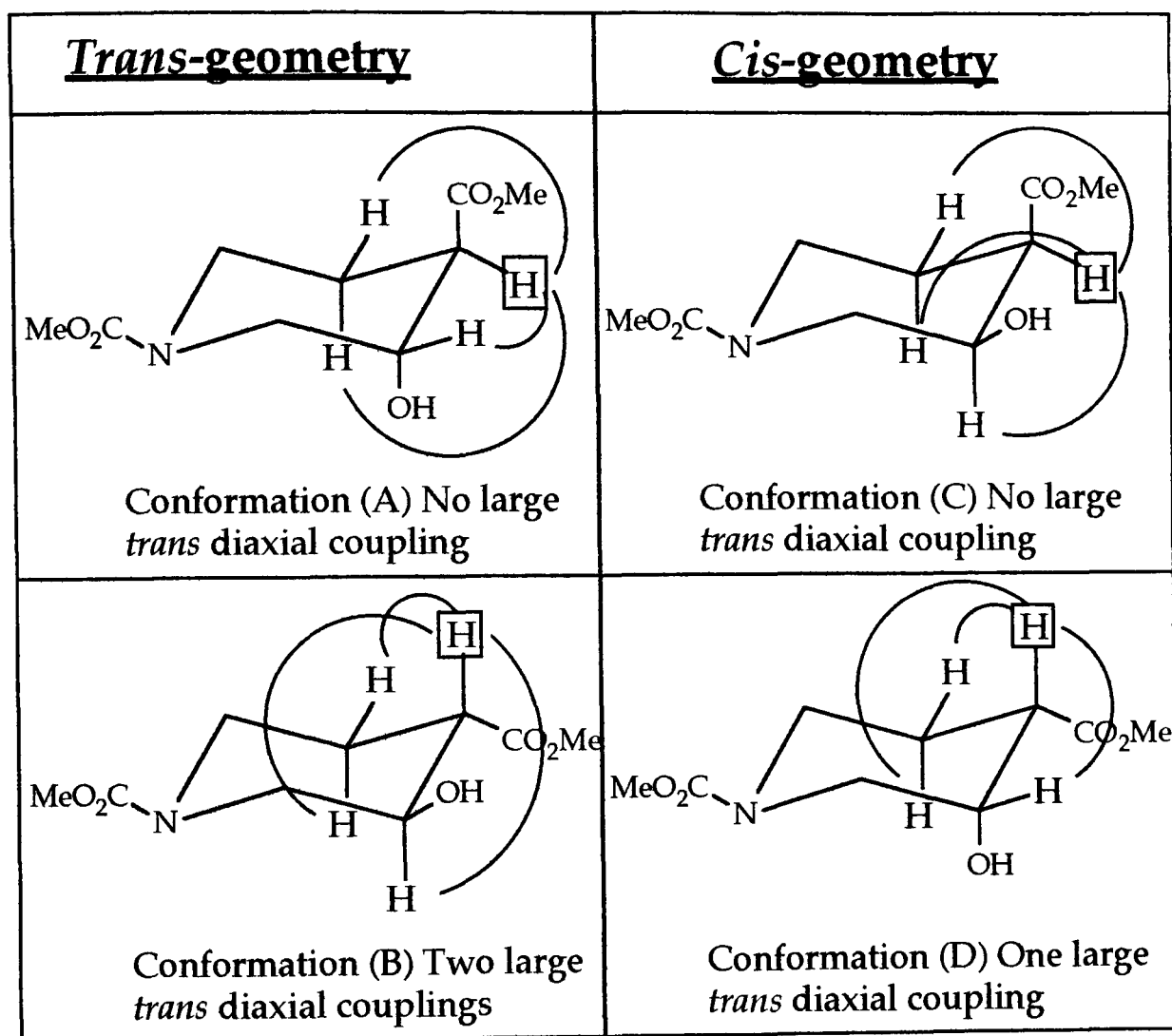


(Scheme 63)

Previous work within the group has shown that the isolated piperidine- $\beta$ -hydroxyester (210) shows a diastereomeric excess of 99.5% and an enantiomeric excess of 89.4% by chiral column gas chromatography.<sup>133</sup>

In order to determine the relative stereochemistry of the yeast reduction product we again analysed the coupling constants between the protons on the 3 and 4 positions ( $J_{3,4}$ ) of the yeast reduction product (210). The 3-proton was obscured in the  $^1\text{H}$  NMR spectrum, however the proton at the 4-position showed 3 couplings (ddd) one large ( $J$  10.6) and two small ( $J$  4.7 and 2.4). If we consider the conformations for both diastereomers as shown in Figure 23, we can deduce that conformation (D) is present i.e. only one large *trans* diaxial

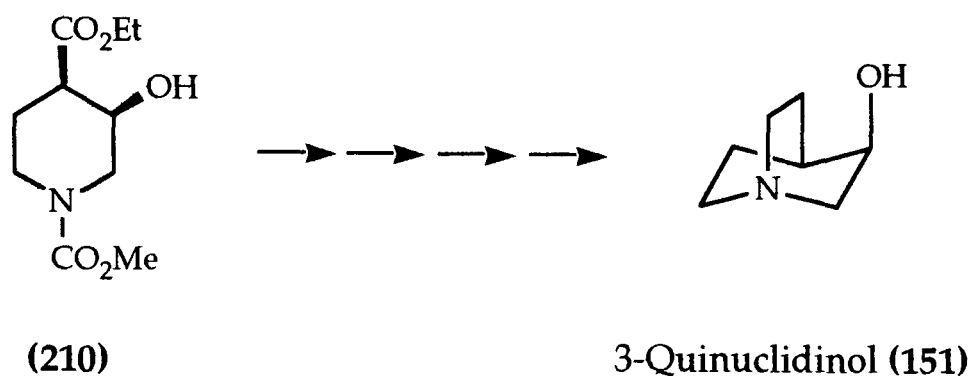
coupling and 2 smaller axial-equatorial couplings being observed. Thus the data is consistent with a *cis* orientation of the ester and hydroxyl functions.



(Figure 23)

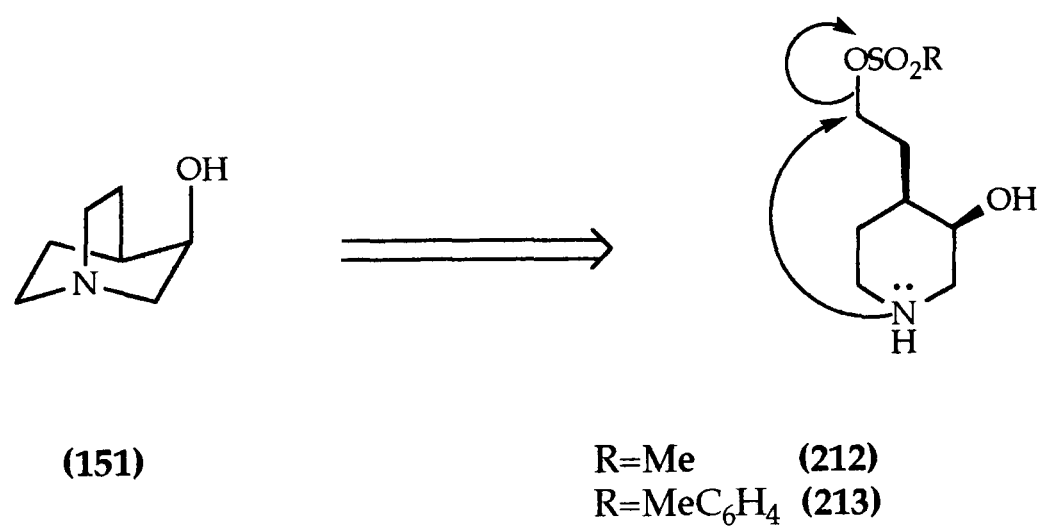
In the previous two cases, we degraded the yeast reduction products (152) and (167) in order to determine their absolute stereochemistries. In this example we were excited when we realised that the yeast reduction product (210) could be elaborated to the natural product 3-quinuclidinol (151). 3-Quinuclidinol (151) is well documented in the literature and the optical rotation of its enantiomers are known<sup>152,153</sup>. Once the compound is synthesised from the

piperidine- $\beta$ -hydroxyester (210) it will be a matter of comparing optical rotations to determine absolute stereochemistry.



(Scheme 64)

In a retrosynthetic sense we envisaged the penultimate step being the cyclisation of a free amine onto a tosylate or mesylate as shown in Scheme 65.



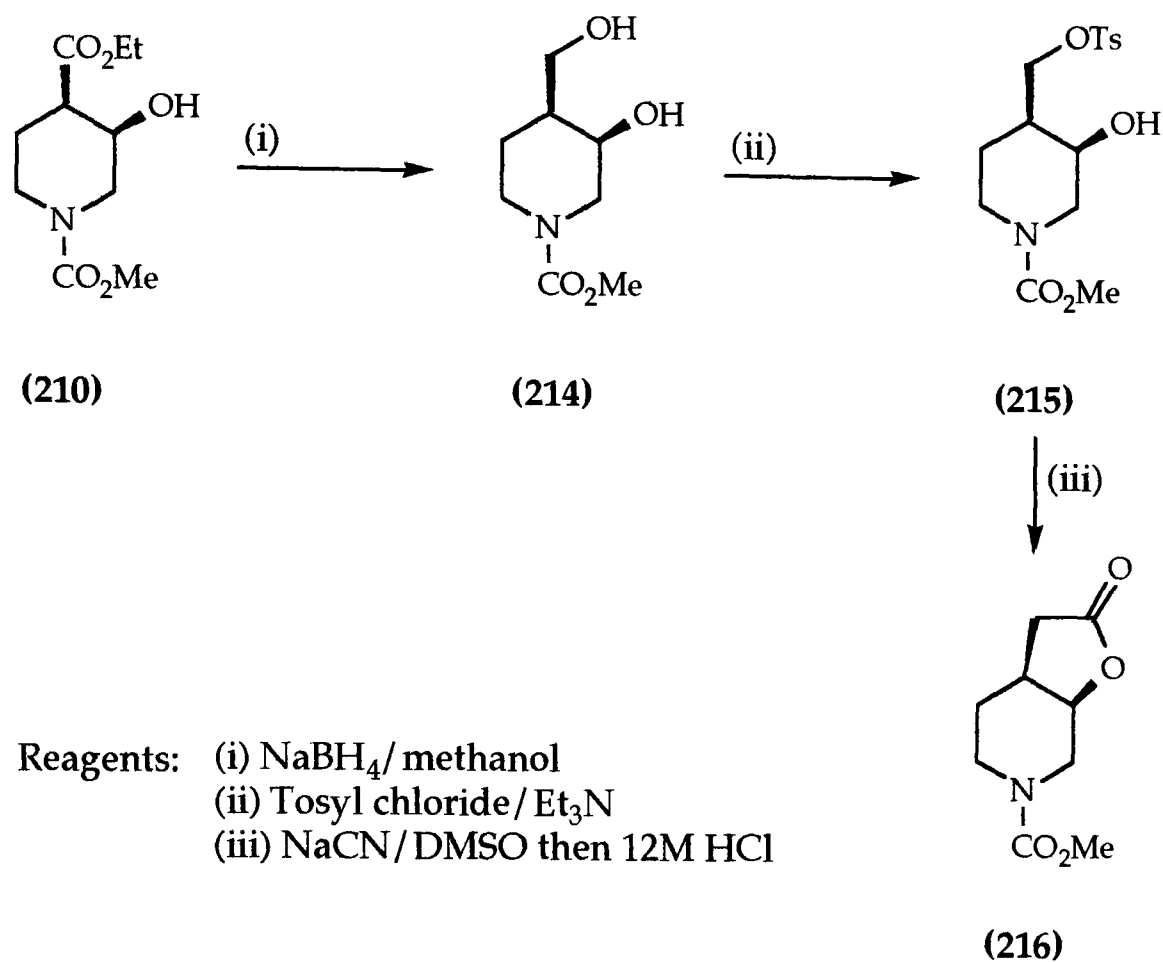
(Scheme 65)

It can be easily envisaged that such a precursor will be derived from the bakers' yeast reduction product (210) by a one carbon homologation at the 4-position side chain of the piperidine. One problem that we saw from the onset was the removal of the methyl carbamate group in order to effect cyclisation. We realised the conditions of iodotrimethylsilane would be too harsh in the presence of the tosylate/mesylate functionality so we aimed to exchange protecting groups at a suitable point in the synthesis.

In a forward sense we further reduced the bakers' yeast reduction product (210) using sodium borohydride in methanol and we were pleased to isolate the desired diol (214) in 68% yield after column chromatography. The use of lithium aluminium hydride as in the previous two examples would not be possible as this would reduce the methyl carbamate to the corresponding N-methyl derivative which would not allow the remainder of the envisaged synthesis to be carried out.

We envisaged chain extension at the 4-position would be afforded by cyanide displacement of a suitable leaving group. The piperidine diol (214) was smoothly converted to the corresponding mono-tosylate (215) in 84% yield using a mixture of tosyl chloride and triethylamine in dichloromethane.<sup>124,125</sup> It is interesting to note that none of the corresponding *bis*-tosylate was isolated and indeed the compound refused to form even with the assistance of 4-dimethylaminopyridine.<sup>118</sup> Subsequent cyanide displacement of the tosylate portion was achieved using sodium cyanide in dimethylsulphoxide at 50°C for 6h. The resulting nitrile was hydrolysed *in situ* for 16h by the addition of 12M hydrochloric acid to the reaction mixture. We were pleased to isolate the desired lactone (216) from the reaction mixture as a colourless oil in 88% yield

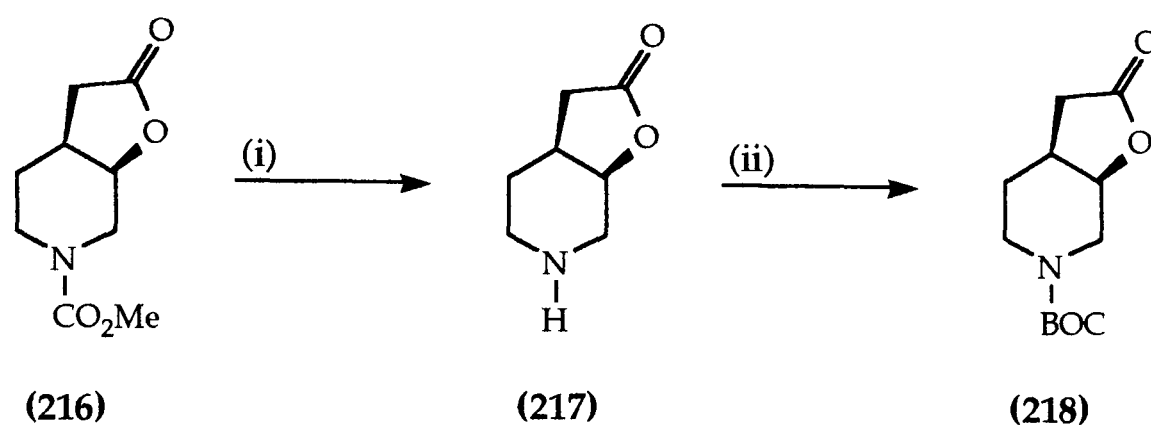
after column chromatography.



(Scheme 66)

With the lactone (216) in hand we believed that this might be a good point in the synthesis to effect protecting group exchange at nitrogen. To this end the lactone was treated with iodotrimethylsilane in chloroform. After heating for 5 hours at  $50^\circ\text{C}$  we were pleased to see the disappearance of the methyl carbamate by  $^1\text{H}$  NMR. The resulting free amine (217) was reprotected this time as the *tert*-butyl carbamate and we were pleased to isolate the desired

lactone (218) in an overall yield for the two steps of 95% after column chromatography.



Reagents: (i) TMSI then MeOH  
(ii) Di-*tert*-butyl dicarbonate/Et<sub>3</sub>N

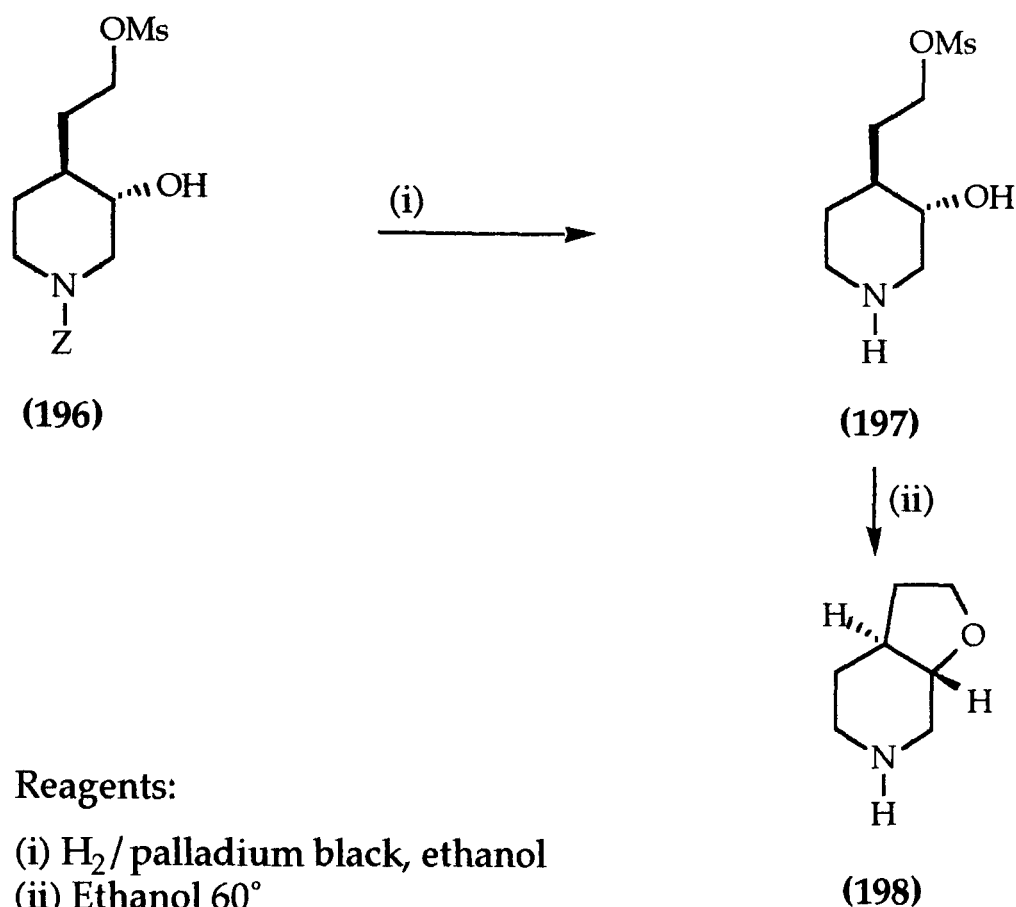
(Scheme 67)

We envisaged the remainder of the synthesis would involve reduction of the lactone (218) to the corresponding diol (219) followed by esterification of the primary hydroxyl function as the mesylate (221). The final cyclisation would then be achieved by removal of the nitrogen protecting group in mild acid followed by heating of the resulting amino mesylate.

Reduction of the lactone (218) proceeded smoothly with sodium borohydride in ethanol<sup>151</sup> and the corresponding diol (219) was isolated in 68% yield. Mesylation of the resulting diol however did not furnish the expected product (221) as there was no methyl signal associated with the mesyl group in the <sup>1</sup>H NMR spectrum. Turning our attention to the literature we found that Fleet and co-workers had also experienced a similar problem<sup>145</sup> and they had

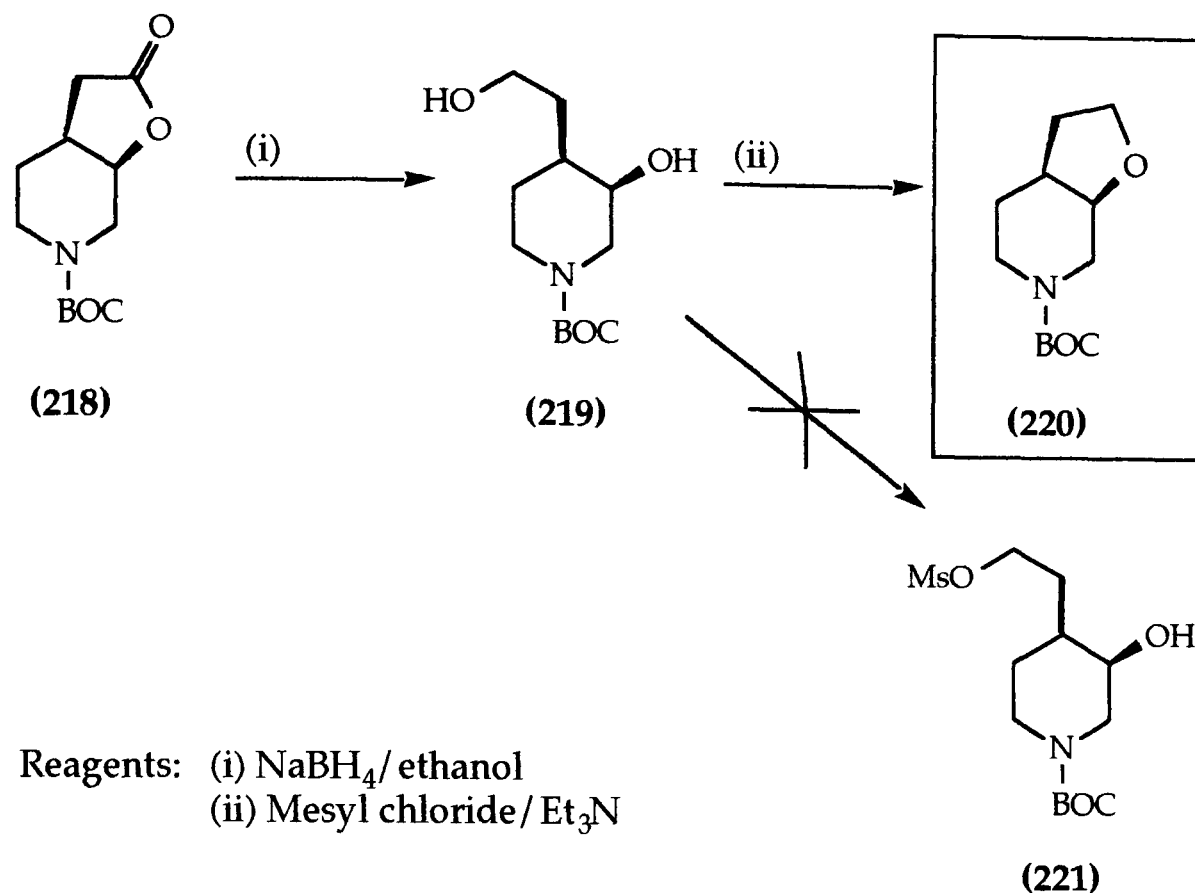


produced the *trans*-tetrahydrofuran (198) instead of the desired quinuclidine skeleton in their synthesis of 3-quinuclidinol (151).



(Scheme 68)

It was felt that our system was even further disadvantaged than Fleet's in that there was a even stronger possibility that the *cis*-tetrahydrofuran could be formed. Preliminary data on the compound indicated this to be the case and indeed we believe that the hydroxy-mesylate underwent spontaneous ring closure under the reaction conditions to produce the aforesaid tetrahydrofuran (220).

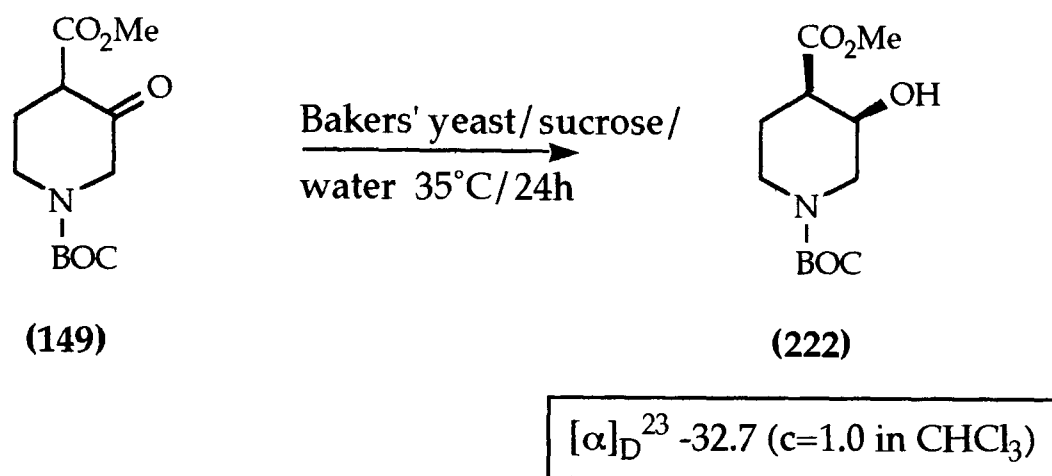


(Scheme 69)

We felt that one possible solution to the problem would be to protect the secondary hydroxyl function prior to the cyclisation procedure. We were disappointed to find that we were unable to achieve any derivatisation of the secondary alcohol, a phenomenon we experienced earlier when *bis*-tosylation of the diol (214) was attempted. At this point in the synthesis we decided to adopt a new route to 3-quinuclidinol (151) and to this end the original sequence was abandoned.

By this time we had collected a plentiful supply of the piperidine- $\beta$ -keto ester (149) which, as discussed earlier, had been the “unwanted” thermodynamic product from the Dieckmann cyclisation which produced 1-*tert*-butyl-2-methyl-3-oxopiperidine-1,2-dicarboxylate (148). It was therefore decided that it would be advantageous to subject this compound to the bakers' yeast reduction methodology<sup>109</sup> and use the resulting reduced material as the precursor to our target compound 3-quinuclidinol (151). The compound was

added to a fermenting solution of bakers' yeast and sucrose in tap water and fermentation continued for 24hrs. After this time the cellular mass was removed by filtration through kieselguhr and the product extracted into dichloromethane. Work up of the organic fractions led to the desired piperidine- $\beta$ -hydroxyester (222) in an isolated yield of 81%. Again we were fortunate in that the product looked extremely pure by  $^1\text{H}$  NMR and therefore did not require purification by silica gel chromatography. Furthermore the compound appeared to be a single diastereomer by  $^{13}\text{C}$  NMR and as importantly showed an optical rotation of  $-32.7^\circ$ .

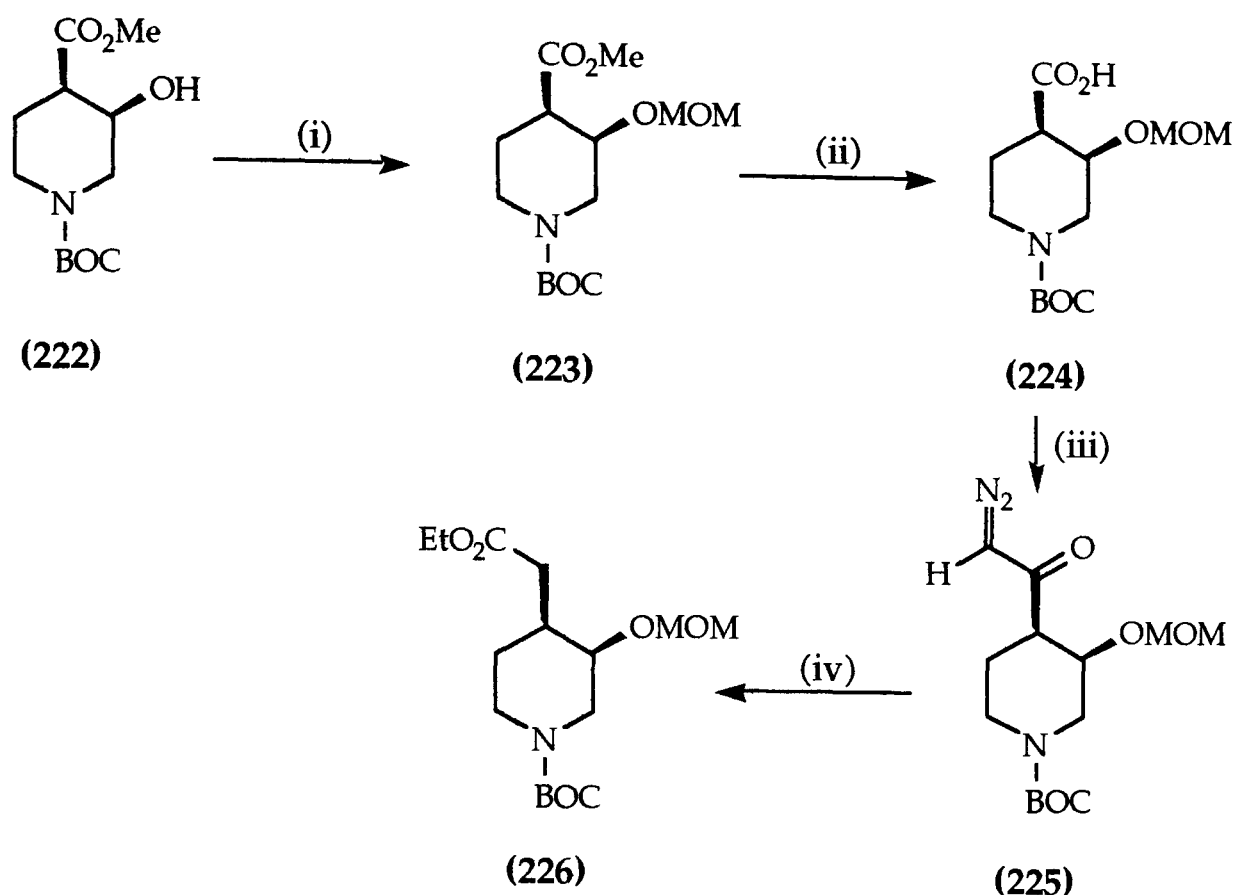


(Scheme 70)

In order to determine the relative stereochemistry of the yeast reduction product we analysed the coupling constants of the 4-proton as in the previous example as the 3-proton was obscured in the  $^1\text{H}$  NMR spectrum. Again 3 couplings (ddd) were present for this proton, one large ( $J$  10.6) and two small ( $J$  3 and 3). If we consider the conformations for both diastereomers as shown in Figure 23 then we can deduce that conformation (D) is again present i.e. only one large *trans* diaxial coupling is present with 2 smaller axial-equatorial couplings being observed. Thus the data is again consistent with a *cis* orientation of the ester and hydroxyl functions.

Turning our attention to the synthesis of 3-quinuclidinol (151) in order to determine absolute stereochemistry of the yeast reduction product (222), we recalled the problems we encountered previously with the secondary hydroxyl function attacking the mesylate moiety and effecting spontaneous ring closure to form the tetrahydrofuran (220). We decided to protect the secondary hydroxyl function from the onset as the methoxymethyl ether (223). This was smoothly achieved by treatment with chloromethyl methyl ether<sup>154</sup> and diisopropylethyl amine (Hunig's base)<sup>155</sup> and we were pleased to isolate the desired protected product (223) in 92% yield after silica gel column chromatography. Turned our attention now to the chain elongation that was required at the C-4 position of the piperidine ring, we decided to adopt Arndt Eistert homologation methodology<sup>156-158</sup> which was to involve treatment of the protected hydroxy acid derivative (224) with oxalyl chloride followed by diazomethane and silver benzoate in methanol<sup>159-160</sup>

The required hydroxy acid (224) was produced by hydrolysis of the protected yeast reduction product (223) in aqueous potassium hydroxide in almost quantitative yield. Reaction of the carboxylic acid (224) firstly with freshly distilled oxalyl chloride furnished the acid chloride which was treated *in situ* with an excess of an ice cold ethereal solution of diazomethane. Chromatography of the residue gave the intermediate diazoketone (225) which showed a characteristic peak for the proton adjacent to the diazoketone group at 5.31 ppm in the <sup>1</sup>H NMR spectrum. This intermediate was subsequently treated with silver benzoate and triethylamine in ethanol to effect the Wolff rearrangement and we were pleased to isolate the desired homologated ester (226) as a colourless oil after silica gel chromatography in good yield.

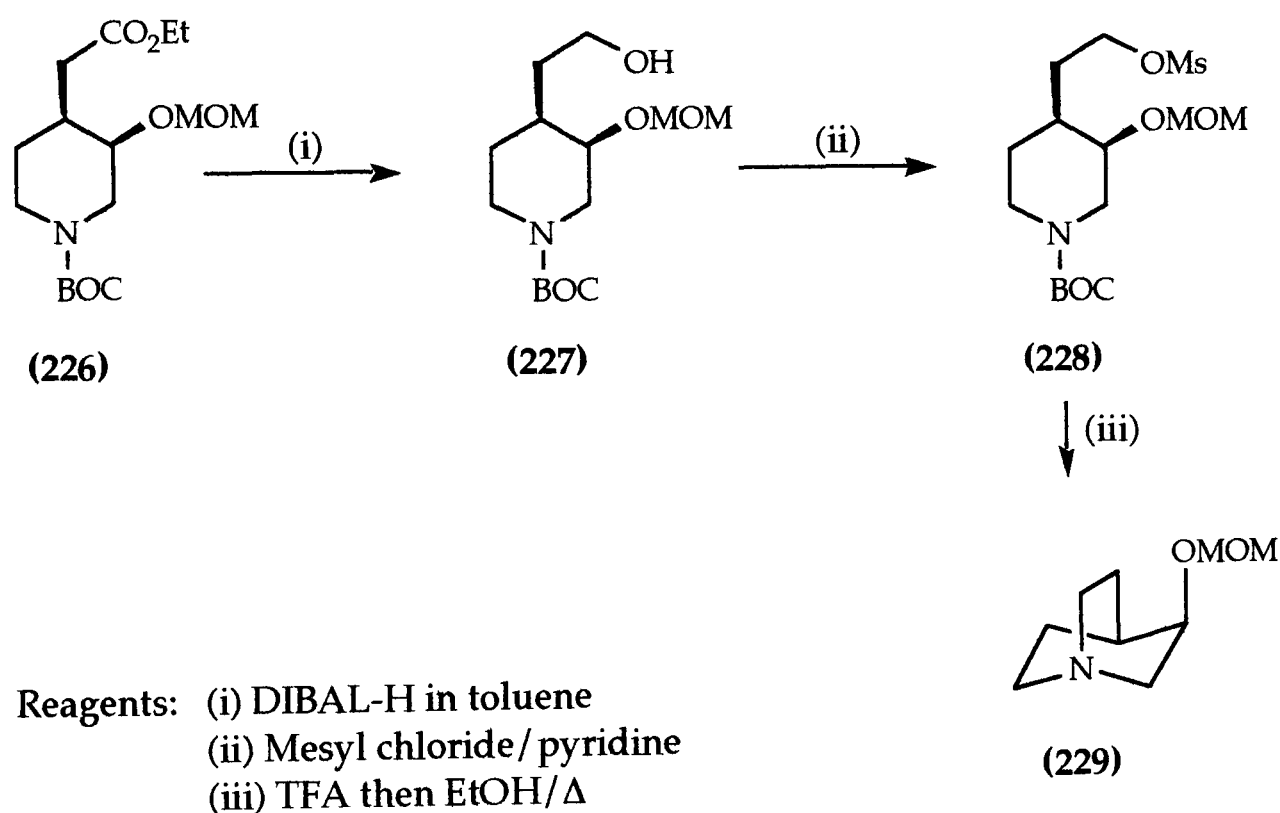


Reagents: (i) MOM-Cl/Hunigs base  
(ii) KOH (aq)  
(iii) Oxalyl chloride/DMF then diazomethane  
(iv) Silver benzoate/ $\text{Et}_3\text{N}$ /ethanol

(Scheme 71)

Reduction of the ethyl ester functionality to the corresponding alcohol was achieved by treatment with diisobutylaluminium hydride in toluene at  $-78^\circ\text{C}$ <sup>161</sup>. After work up with potassium tartrate the desired material (227) was isolated in an adequate 55% yield. To effect cyclisation to the required quinuclidine framework we again decided to esterify the hydroxy function as the corresponding mesylate and release the free amine in the hope that cyclisation would occur. Standard mesylation conditions<sup>162</sup> of methanesulphonyl chloride and pyridine in dichloromethane afforded the desired mesylate (228) which we were pleased to be able to isolate from the reaction mixture on this occasion. Removal of the nitrogen protecting group was subsequently achieved using trifluoroacetic acid<sup>123</sup> in dichloromethane

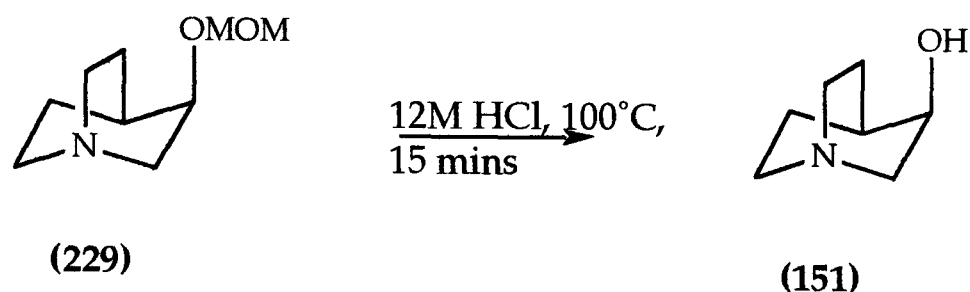
and we were delighted that after heating of the residue in ethanol for 6h, the desired 3-quinuclidinol protected as the hydroxymethyl-methyl ether (**229**) was isolated in a moderate 27% yield. Furthermore the compound showed an optical rotation of  $-23.4^\circ$ .



(Scheme 72)

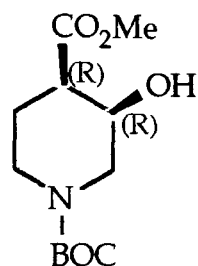
Elaboration of the MOM-protected intermediate (**229**) to the desired 3-quinuclidinol (**151**) was achieved by brief treatment with refluxing concentrated hydrochloric acid and the desired 3-quinuclidinol (**151**) was

isolated in 83% yield after silica gel chromatography.



(Scheme 73)

We were left now to measure the optical rotation ( $[\alpha]_D$ ) of this compound and compare it to the literature value for the (*R*)-3-quinuclidinol (151) of  $+45.3^\circ$ <sup>152,153</sup>. We were subsequently very satisfied to find that the 3-quinuclidinol (151) derived from our bakers' yeast reduction product (222) showed an optical rotation of  $+39.5^\circ$  thus indicating (*R*)-geometry also. This compound was indistinguishable from the authentic material by  $^1\text{H}$  and  $^{13}\text{C}$  NMR. Furthermore this figure allowed us to calculate an enantiomeric excess for the quinuclidinol derived from the bakers' yeast reduction product of 87%. As we were careful not to enrich the optical purity of the compound during the synthesis by making relevant checks on column fractions etc., we can also state that the bakers' yeast reduction product (222) also shows an enantiomeric excess of 87%. As we had already deduced the relative stereochemistry as being *cis* and we now know the absolute stereochemistry at the 3 position of the yeast reduction product (222) is (*R*) we can deduce the absolute stereochemistry at the 4 position will be also (*R*) as shown in Figure 24.

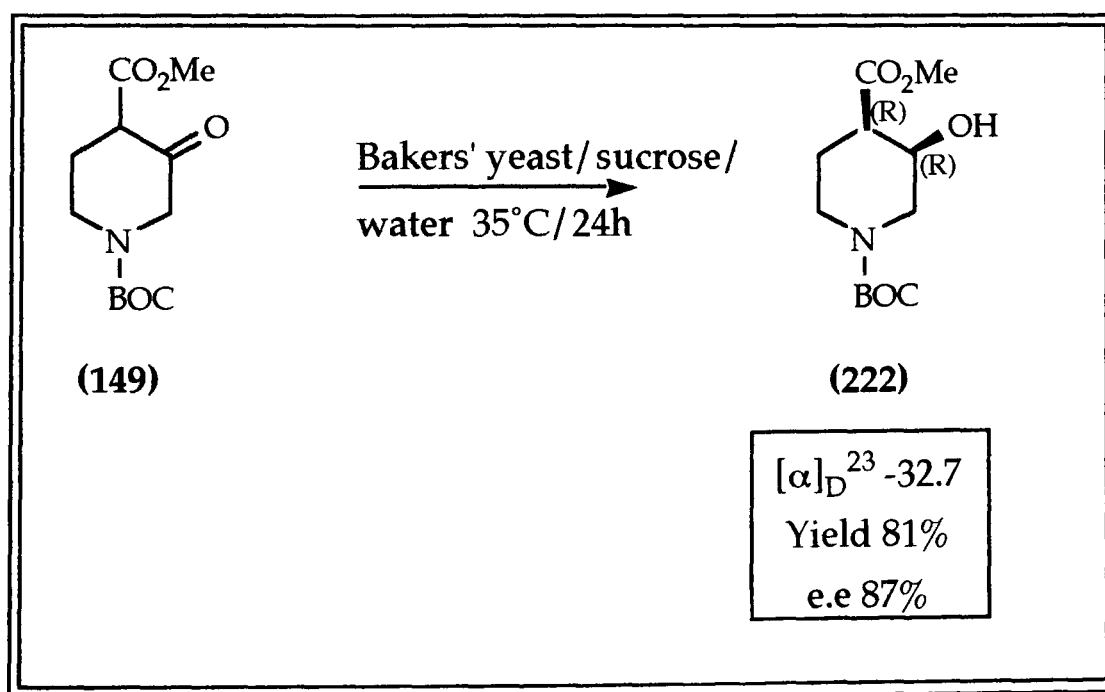


(222)

(Figure 24)

## Conclusion

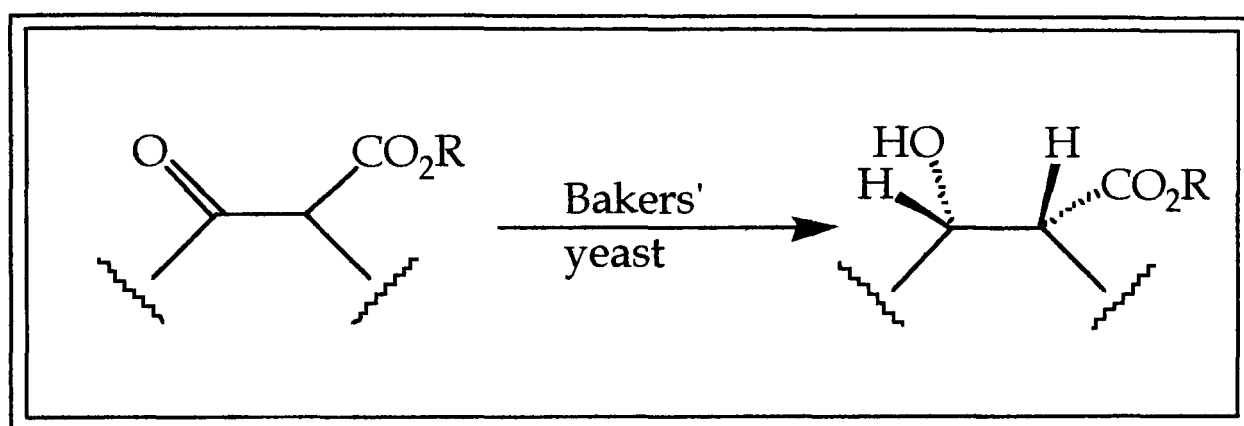
In conclusion we can say that the bakers' yeast reduction of 1-*tert*-butyl-4-methyl 3-oxopiperidine-1,4-dicarboxylate (149) gives (3*R*, 4*R*)-1-*tert*-butyl-4-methyl 3-hydroxypiperidine-1,4-dicarboxylate (222) in 81% chemical yield and with an enantiomeric excess of 87% as shown in Figure 25.



(Figure 25)



From the work carried out on the bakers' yeast reduction of piperidine- $\beta$ -keto esters so far we can say that in general bakers' yeast delivers hydrogen in a *syn* fashion to the top face of the molecule as drawn in Figure 26, ie with the keto functionality drawn on the left and the carboxylate functionality drawn on the right, hydrogen is delivered into the page.



(Figure 26)

## **Chapter Four**

### **Indolizidine Alkaloid Synthesis**

## Introduction to Indolizidines

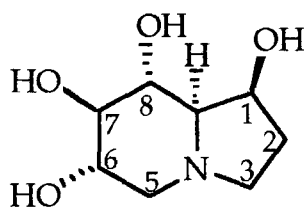
Polyhydroxylated indolizidine alkaloids have recently gained considerable synthetic interest as possible candidates for glycosidase inhibitor design. The major driving force is attributable to the biological activity associated with two such indolizidines, castanospermine (133)<sup>163</sup> and swainsonine (132).<sup>164,165</sup> The compounds have been shown to inhibit various glycosidase and specifically swainsonine (132) functions as a powerful inhibitor of lysosomal, jack bean  $\alpha$ -mannosidase and the glycoprotein golgi mannosidase. Swainsonine (132) has been also shown to inhibit the processing of asparagine linked glycoproteins.<sup>166-169</sup> Castanospermine (133) on the other hand is a potent inhibitor of various glycosidases including lysosomal  $\alpha$ -glucosidase,  $\alpha$ - and  $\beta$ -glucosidase in fibroblast extracts as well as inhibiting  $\beta$ -xylosidase<sup>170-172</sup> and sucrase.<sup>173-175</sup>

The ability of such compounds to disrupt glycoprotein processing has resulted in their use to modify glycoprotein biosynthesis and thus provide more insight into the role of oligosaccharides in glycoprotein function.<sup>176-179</sup> Recently, castanospermine (133) and swainsonine (132) have been observed to inhibit metastasis of some cancers.<sup>180</sup> Additionally castanospermine (133) has been implicated as an inhibitor of the human immunodeficiency virus (HIV) syncytium formation<sup>180-186</sup> and virus replication.<sup>187</sup>

For the purpose of this review a number of syntheses of these two molecules will be described along with another important indolizidine alkaloid allopumiliotoxin 339A (230). A further indolizidine alkaloid cyclizidine (231) will also be described.

## Castanospermine (133)

Castanospermine (133) [(1*S*, 6*S*, 7*R*, 8*R*, 8*aR*)-1, 6, 7, 8-tetrahydroxyindolizidine] has been isolated from the seeds of *castanospermum australe* <sup>175</sup> as well as *alexia leiopetala*.<sup>188</sup>

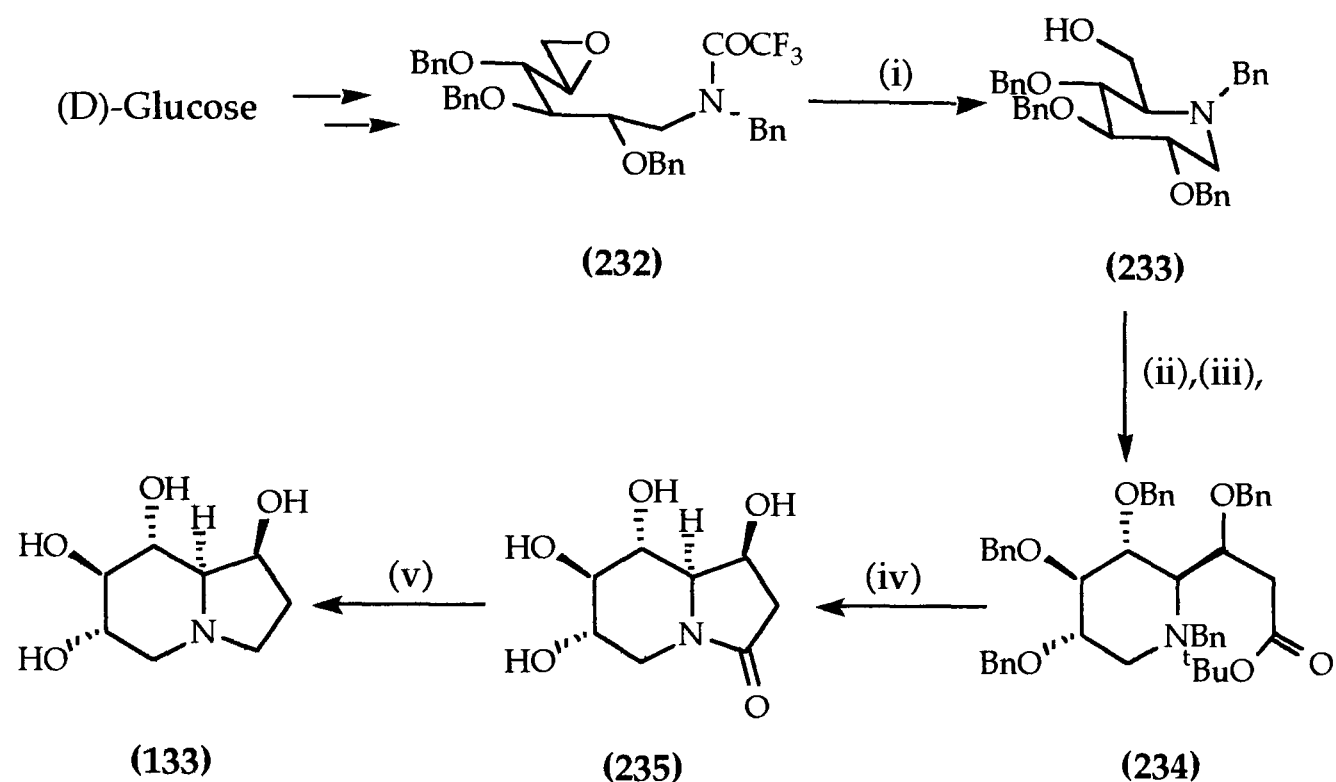


Castanospermine (133)

(Figure 27)

The compound was first synthesised in 1984 by Bernotas and Ganem from D-glucose and from this synthesis the absolute configuration of the molecule was determined.<sup>189</sup> The synthesis involved treatment of the epoxide (232) with sodium borohydride which facilitated loss of the trifluoroacetyl group and subsequent attack by nitrogen on both carbons of the epoxide. One of the resulting piperidines (233) was oxidised by the method of Swern (DMSO-oxalyl chloride),<sup>190,191</sup> condensed with lithio *tert*-butylacetate, hydrogenolysed and treated with trifluoroacetic acid to furnish the corresponding lactam (235). The lactam (235) was reduced with diisobutylaluminium hydride to give

castanospermine (133) which was identical to the natural material by 300MHz  $^1\text{H}$  NMR. The observed rotation was  $+71^\circ$  with a literature value for the natural material of  $+80^\circ$ .<sup>175</sup>

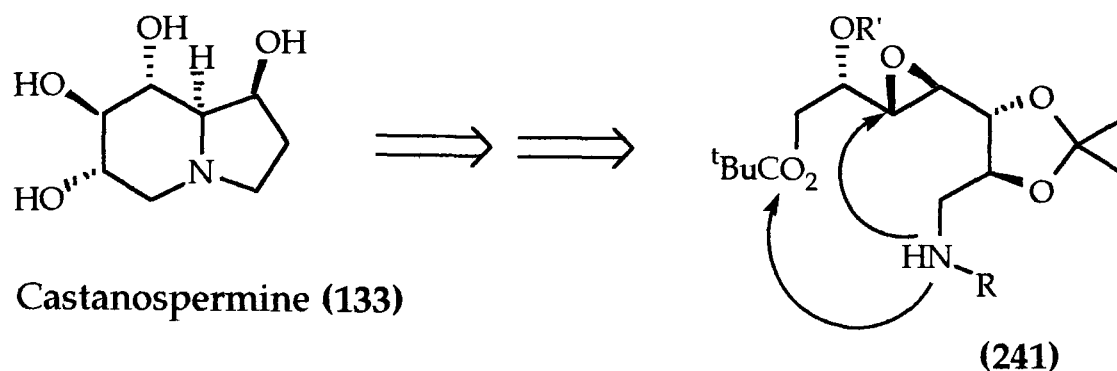


Reagents: (i)  $\text{NaBH}_4$  in ethanol      (ii) Oxalyl chloride/DMSO  
 (iii) Lithio *tert*-butylacetate    (iv)  $\text{H}_2$  then TFA (Aq)  
 (v) DIBAL-H

(Scheme 74)

Shortly after this synthesis was reported Hashimoto and co-workers reported the synthesis of castanospermine (133) from D-mannose utilising a

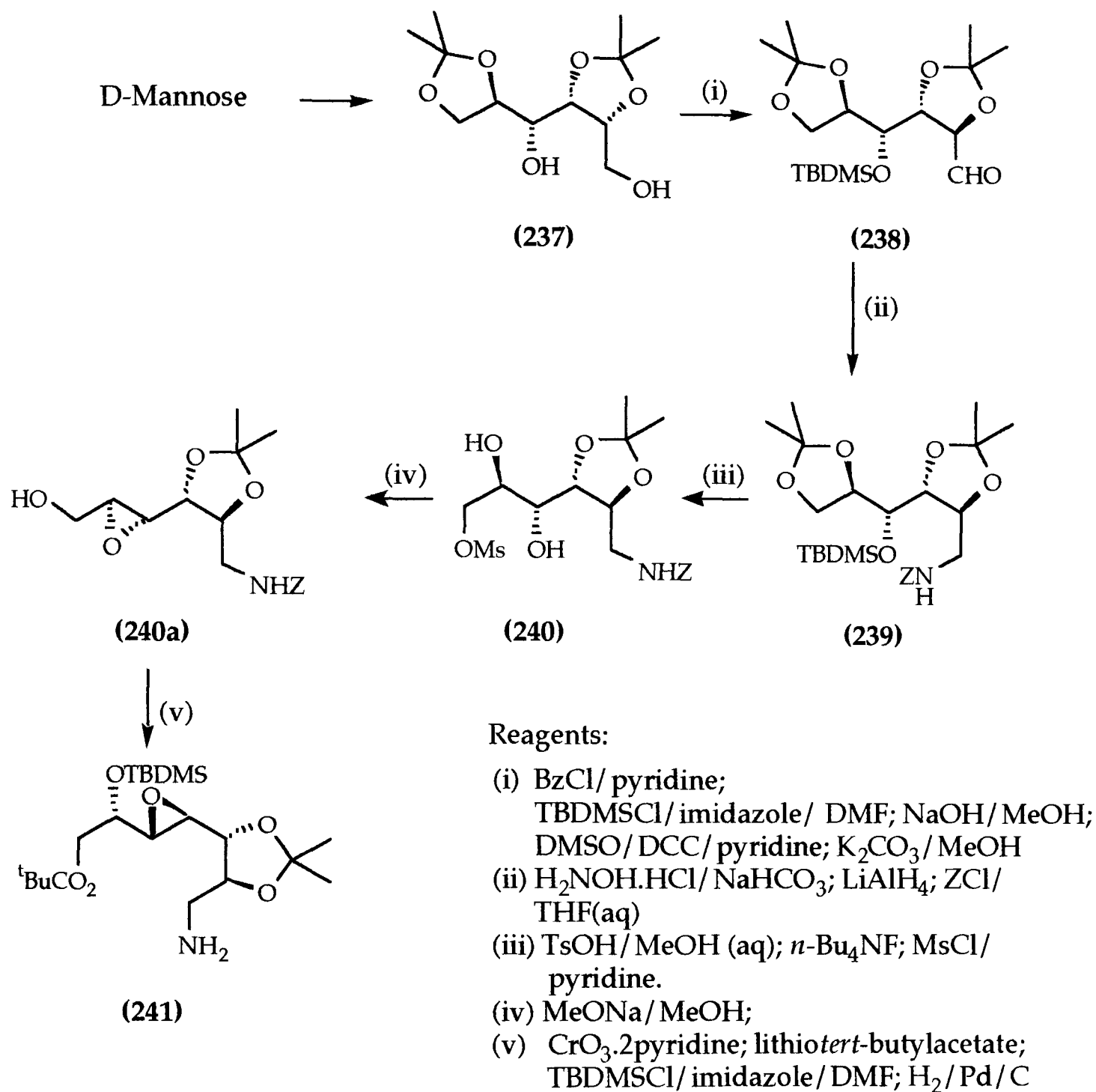
double cyclisation reaction of the amino ester (241).<sup>192</sup>



(Scheme 75)

In a forward sense successive selective protections of the diol functionalities gave the alcohol (237). Moffatt oxidation<sup>193,194</sup> and subsequent treatment of the resulting aldehyde with potassium carbonate in methanol gave the 2,3 trans aldehyde (238). This intermediate was converted to the corresponding oxime followed by reduction with lithium aluminium hydride and the resulting amine function protected as the benzyl carbamate (239). Partial hydrolysis of this material followed by selective deprotection of the hydroxyl functions with tosic acid and subsequent mesylation of the primary hydroxyl gave (240) which was treated with sodium methoxide and cyclised to form an intermediary end epoxide which readily isomerised in the presence of sodium methoxide to produce the epoxide (240a). Oxidation of the primary alcohol of (240a), reaction with *tert*-butyl lithioacetate, protection of the hydroxyl function and deprotection of the amine gave the desired epoxy-amino-ester (241) in

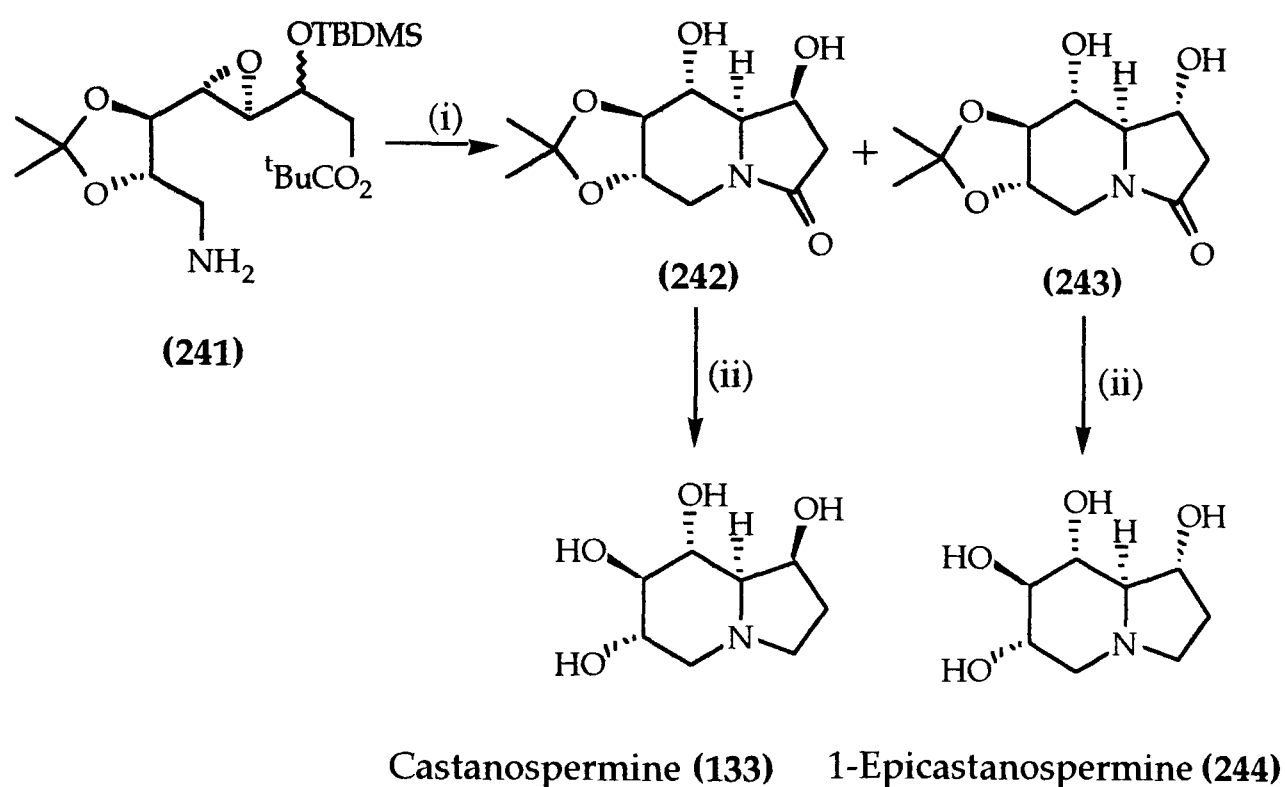
preparation for the double cyclisation reaction.



(Scheme 76)

The resulting amine (241) was refluxed in methoxyethanol to give a mixture of the indolizidines (242) and (243) which were readily separable by silica gel

chromatography. Finally (242) was reduced with borane-THF complex and subsequent treatment with 6M HCl gave castanospermine (133). Similar treatment of (243) gave 1-epicastanospermine (244).



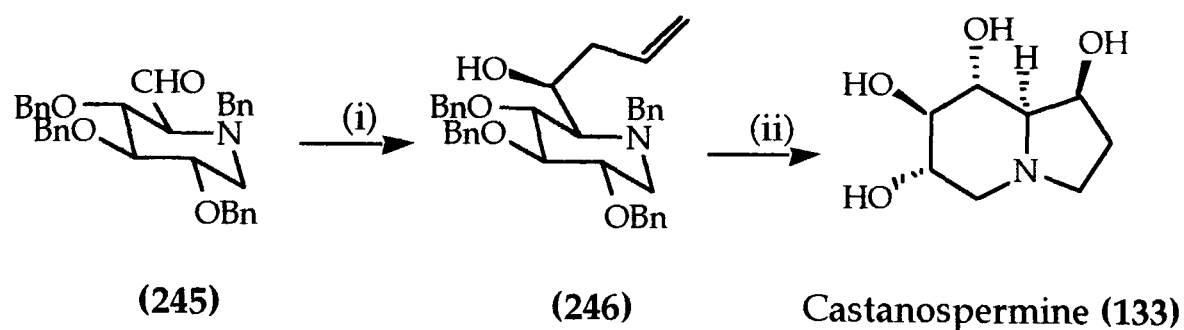
Reagents: (i) Methoxyethanol/  $\Delta$   
 (ii) Borane.THF then 6M HCl

(Scheme 77)

Ganem and co-workers reported the enantioselective synthesis of (+)-castanospermine (133) from (D)-glucose<sup>195</sup> using a highly selective chelation controlled Sakurai reaction of the type Keck,<sup>196,197</sup> Danishefsky<sup>198,199</sup> and others<sup>200,201</sup> have observed with  $\alpha$ - and  $\beta$ -alkoxy aldehydes. To this end the aldehyde (245) which is available enantiomerically pure from D-glucose by oxidation of the protected (+)-amino alditol (245),<sup>202</sup> underwent the Sakurai condensation with allyltrimethylsilane and titanium tetrachloride to furnish the desired olefin (246). Ozonolysis followed by reduction with sodium borohydride furnished the diol which was further elaborated to (+)-



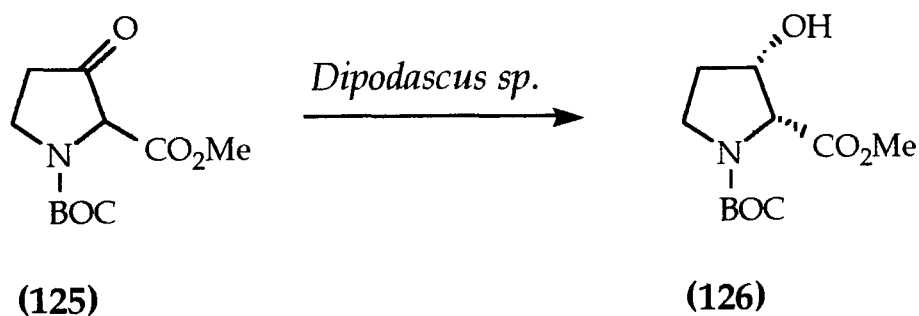
castanospermine (133) by esterification with mesyl chloride followed by hydrogenation/cyclisation.



Reagents: (i) Allyltrimethylsilane, TiCl<sub>4</sub>  
(ii) O<sub>3</sub>; NaBH<sub>4</sub>/ethanol; MsCl, Et<sub>3</sub>N; H<sub>2</sub>, Pd/C

(Scheme 78)

Of particular interest to the Knight group was the synthesis of (+) castanospermine (133) reported by Sih and co-workers.<sup>203</sup> This involves the stereoselective reduction of pyrrolidine β-keto ester (125) using *Dipodascus sp.*

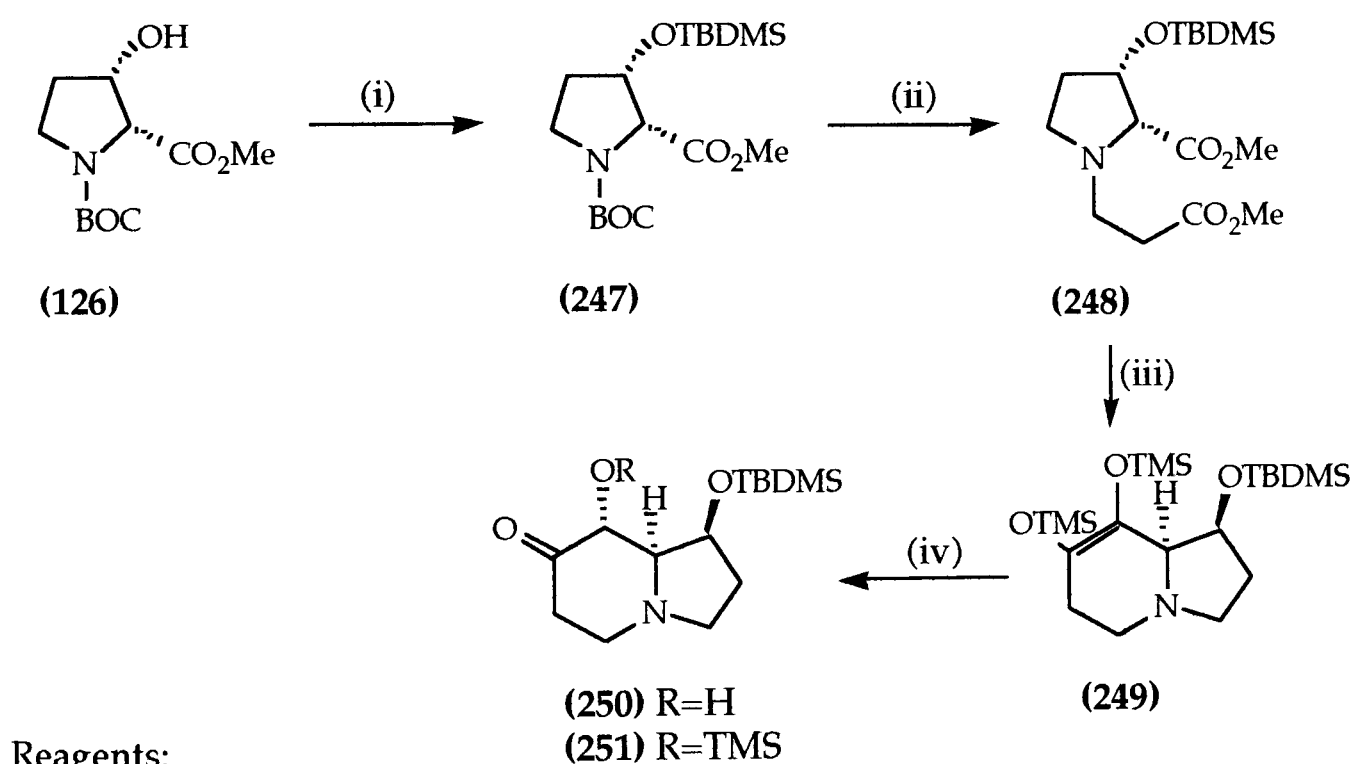


(Scheme 79)

As was reported earlier in the text, Knight and co-workers achieved the stereoselective reduction with 80% optical purity using baker's yeast.<sup>94</sup> Sih was able to achieve 99% optical purity using *Dipodascus sp.* and he attributes the

lower enantiomeric excess observed for the baker's yeast reduction being the result of multiple enzymes operating with opposite stereochemical preferences during the reaction.<sup>31</sup>

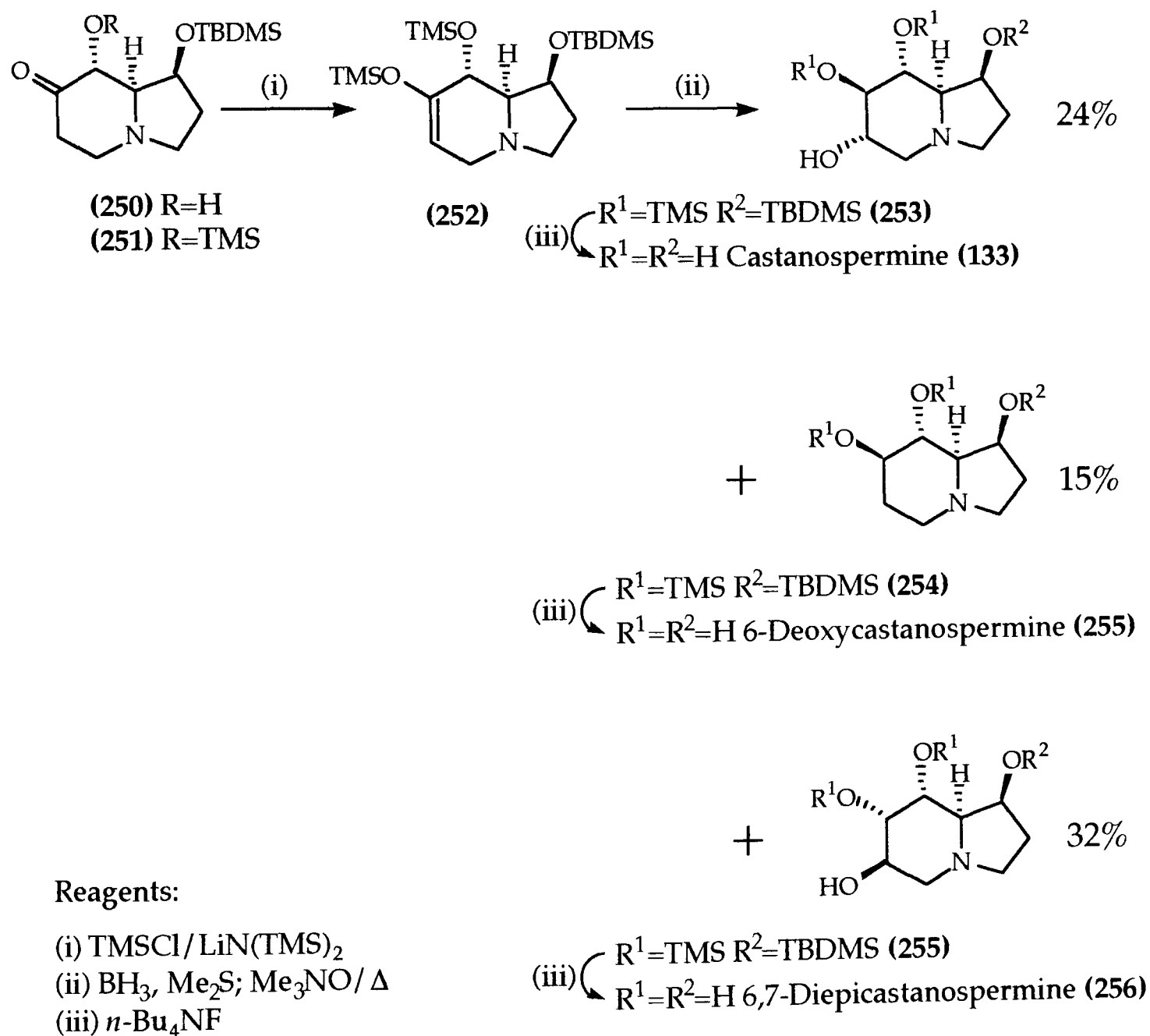
The initial reduction product (126) was protected as its silyl ether (247) and transformed into the diester (248) by treatment with 2% trifluoroacetic acid followed by removal of volatiles and treatment of the salt with methyl acrylate and triethylamine. Acyloin condensation<sup>204</sup> of (248) in the presence of chlorotrimethylsilane led to the *bis*-trimethylsiloxy derivative (249). (249) was smoothly converted to a mixture of (250) and (251) using excess DBU in dichloromethane.



(Scheme 80)

Both of these compounds were converted to (252) by reaction with LiN(TMS)<sub>2</sub>

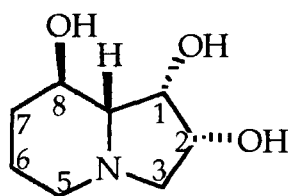
and chlorotrimethylsilane. Hydroboration of the intermediate followed by oxidation<sup>205</sup> gave a mixture of (253), (254) and (255) which were readily separable by chromatography. Desilylation led to (+)-castanospermine (133), 6-deoxycastanospermine (255) and 6,7-diepicastanospermine (256) respectively.



(Scheme 81)

## Swainsonine (132)

Swainsonine [(1*S*, 2*R*, 8*R*, 8*aR*)-octahydro-1, 2, 8-indolizidinetriol] has been isolated from the fungus *rhizoctonia leguminicola*,<sup>164,165</sup> the legume *leniginosus*, the spotted locoweed *astragalus lentiginosus*<sup>206-208</sup> and *swainsona canescens*.<sup>166</sup>



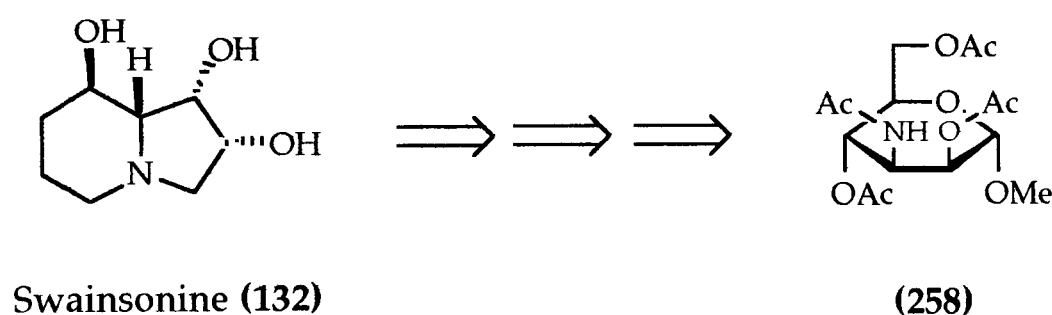
Swainsonine (132)

(Figure 28)

This alkaloid is believed to be the cause of locoism, a disease contracted by animals upon ingestion of swainsonine containing plants.<sup>206-208</sup> It has also been suggested by Elbein that the physiological effects of the alkaloid may in part be due to its ability to inhibit various enzymes including lysosomal  $\alpha$ -mannosidase<sup>167</sup> and mannosidase II.<sup>209</sup> Lysosomal  $\alpha$ -mannosidase is involved in the cellular degradation of polysaccharides while mannosidase II is a key enzyme in the processing of asparagine linked glycoproteins.<sup>210</sup>

Recent reports have indicated that swainsonine exhibits immunoregulatory activity and this has led to it being considered as a possible candidate for cancer chemotherapy<sup>211,212</sup>.

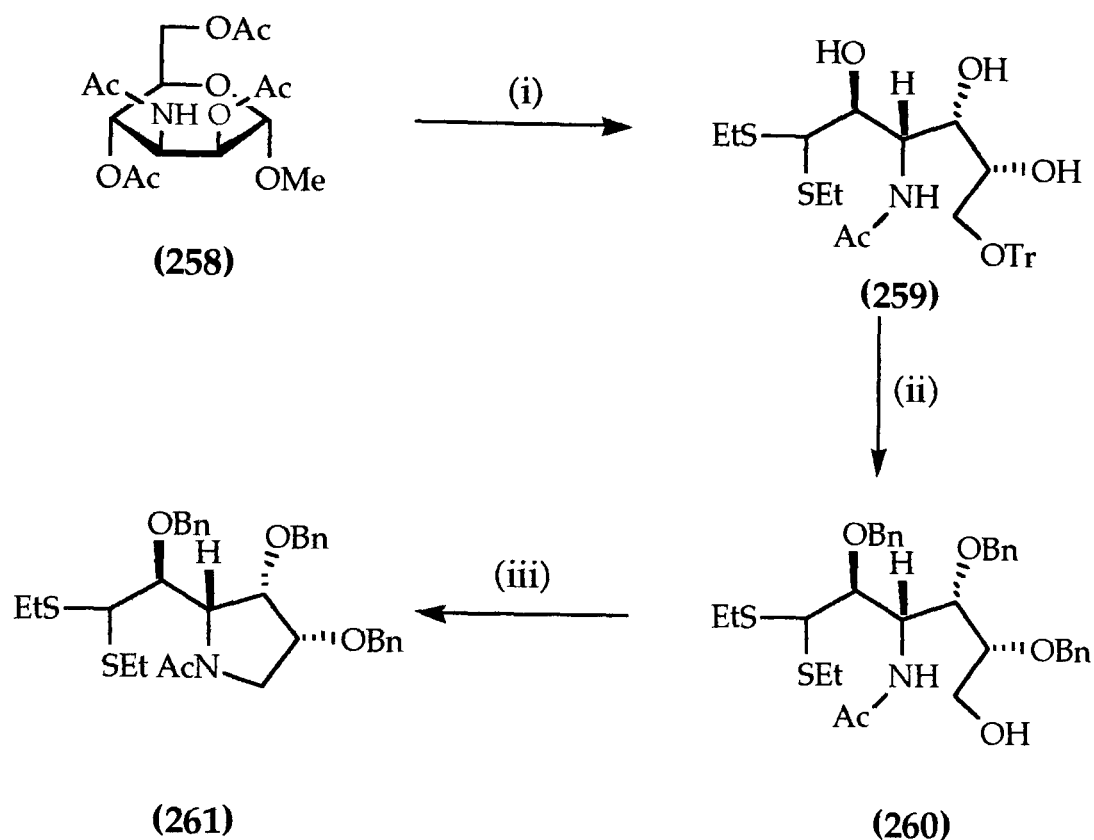
Soon after its isolation the structure of the alkaloid was established<sup>166</sup> and by 1983 Sharpless had reported its total synthesis at the 103rd Annual Meeting of the Pharmaceutical Society of Japan in Tokyo. Soon afterwards Suami and co-workers published the total synthesis of the alkaloid starting from methyl 3-acetamido-2, 4, 6-tri-*O*-acetyl-3-deoxy- $\alpha$ -D-mannopyranoside (258).<sup>213</sup>



(Scheme 82)

Hydrolysis of this material (258) followed by *O*-deacetylation in methanolic sodium methoxide, treatment with ethanethiol and tritylation with trityl chloride in pyridine gave the dithioacetal (259). *O*-Benzylation of (259) followed by removal of the *O*-trityl group afforded the tri-*O*-benzyl derivative (260). (260) was converted to the pyrrolidine derivative (261) by tosylation followed by *N*-

deacetylation and subsequent cyclisation.

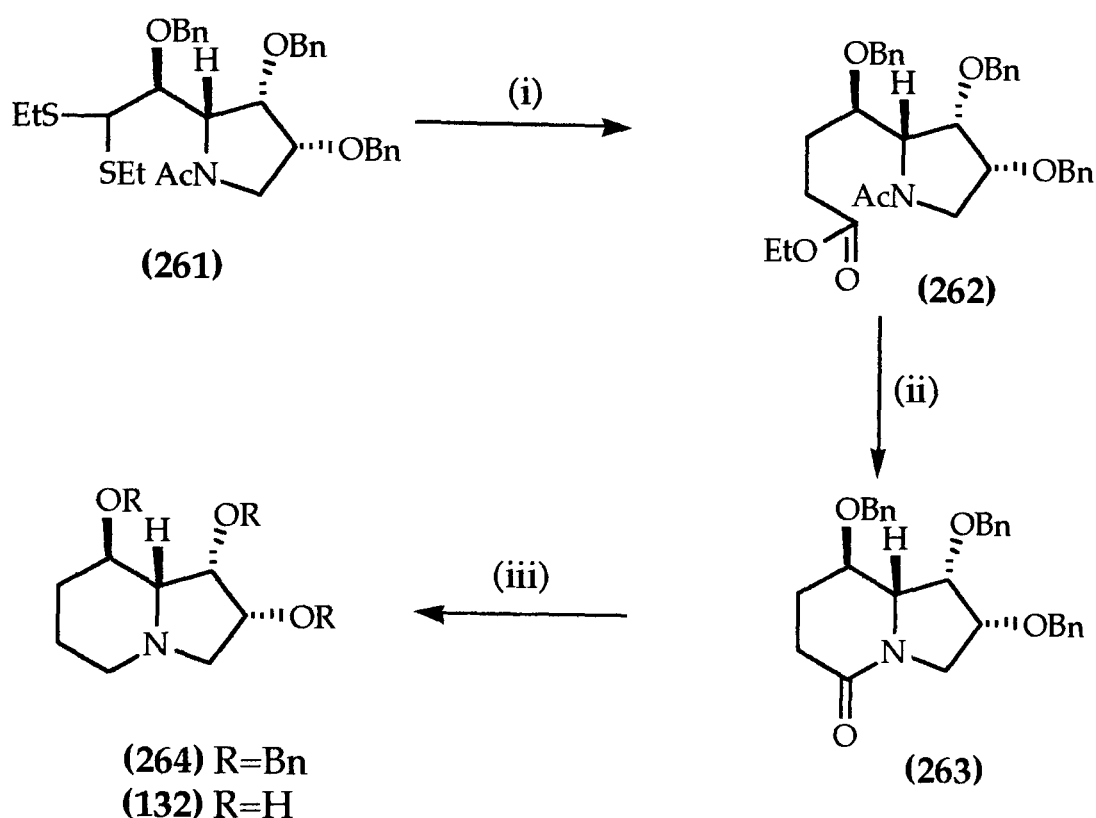


Reagents: (i) HCl/  $\Delta$ ; Ac<sub>2</sub>O; MeONa, MeOH; EtSH;  
 Trityl chloride/ pyridine  
 (ii) Benzyl bromide/ NaH/ DMF; Mild acid  
 (iii) Tosyl chloride/ pyridine; NaOH/  $\Delta$

(Scheme 83)

The pyrrolidine derivative (261) was converted to the corresponding aldehyde moiety and Horner-Emmons reaction with diethyl ethoxycarbonylmethylphosphonate and sodium hydroxide gave a mixture of epimers which could be successfully separated. Hydrogenation of the epimeric mixture over Raney nickel afforded the saturated ester (262). Preparation of the lactam (263) was achieved by heating the ester (262) in aqueous ethanolic potassium hydroxide and subsequent reduction using lithium aluminium hydride and O-

debenzylation<sup>213</sup> gave (-)-swainsonine (132) which showed identical spectral properties to that of the natural product.

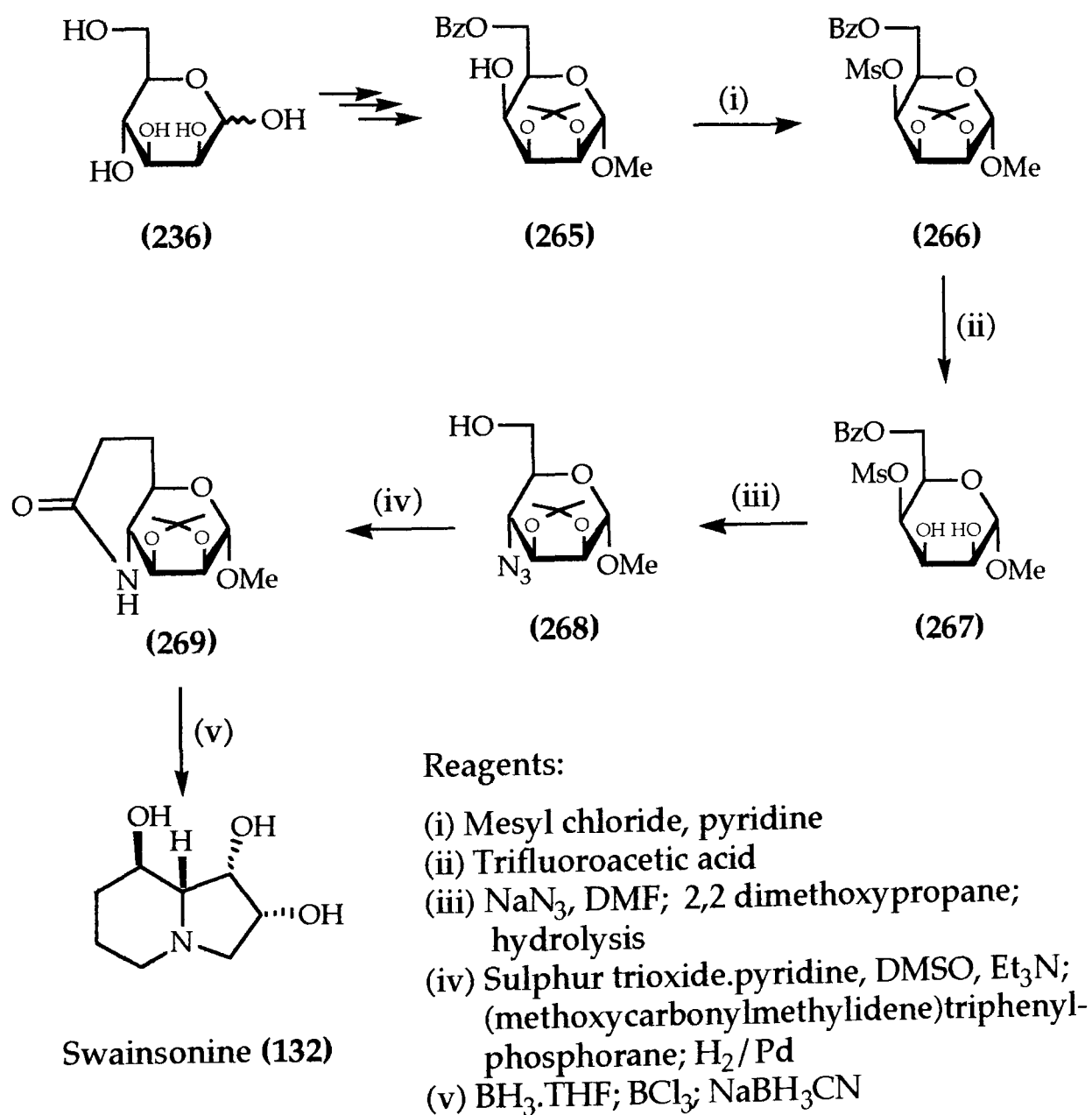


Reagents: (i)  $\text{HgCl}_2/\text{CaCO}_3$ ; diethyl ethoxycarbonylmethylphosphonate/ $\text{NaH}$ ;  $\text{H}_2$ /Raney nickel  
(ii)  $\text{KOH}$ , ethanol,  $\Delta$ , 6 days  
(iii)  $\text{LiAlH}_4$ ;  $\text{Pd}(\text{OH})_2/\text{C}$ , cyclohexene

(Scheme 84)

At the same time Takaya and co-workers published the synthesis of swainsonine (132) starting from (D)-mannose (236).<sup>215</sup> Methyl-6-O-benzoyl-2,3-O-isopropylidene- $\alpha$ -D-talopyranoside (265) derived from D-mannose according to the method of Evans<sup>216</sup> was mesylated and deprotected as shown in Scheme 85. Reaction of the intermediate (267) with sodium azide in DMF followed by protection with 2,2-dimethoxypropane and alkaline hydrolysis gave the azido

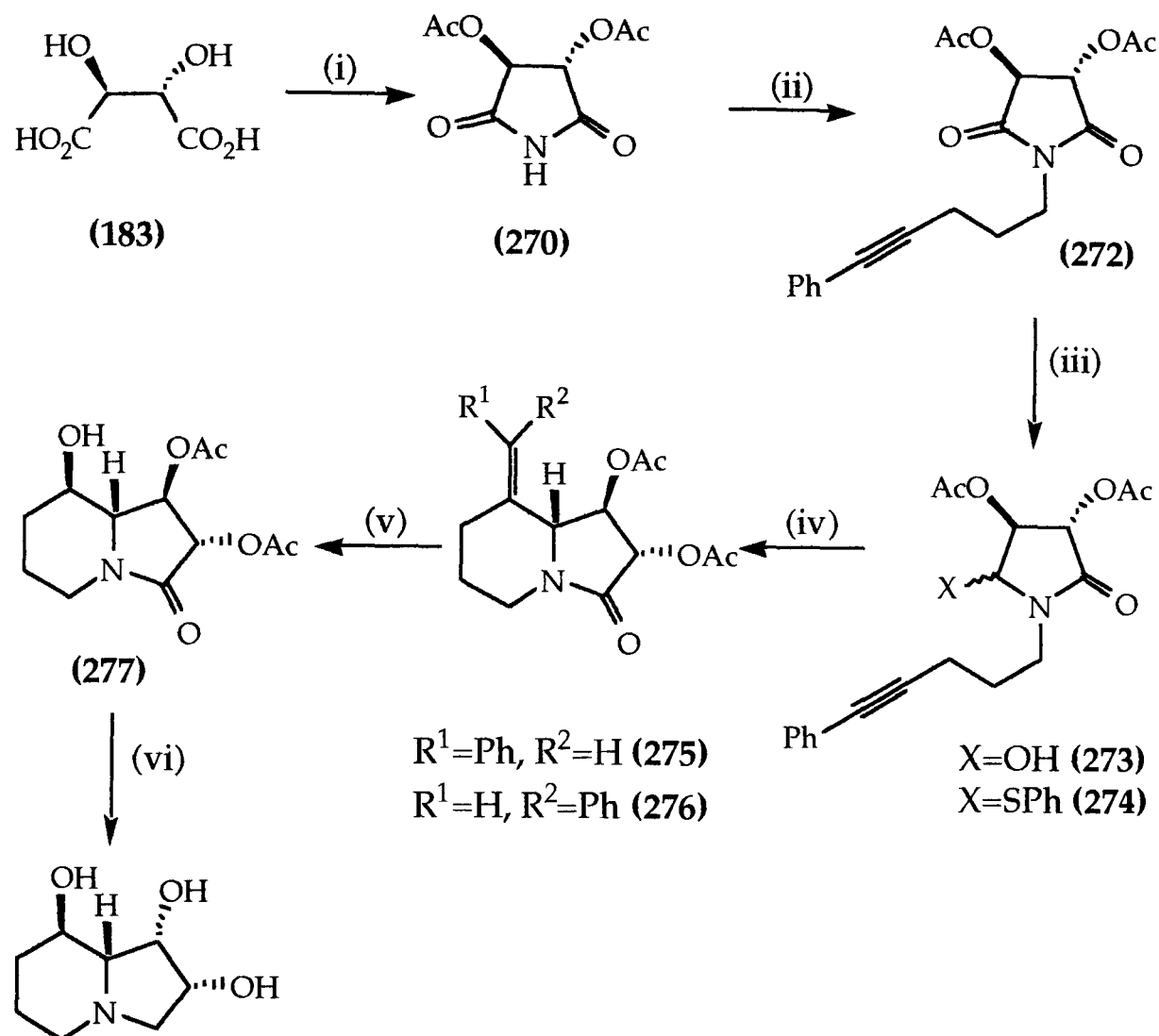
derivative (268) in almost quantitative yield. Oxidation of the primary alcohol followed by Wittig reaction with (methoxycarbonylmethylidene) triphenyl phosphorane gave the vinyl ether which was hydrogenated and cyclised to the corresponding amide (269). The amide was further elaborated to swainsonine (132) by demethylation with boron trichloride and subsequent treatment with sodium cyanoborohydride. Again the final product was spectroscopically identical to the natural product.



(Scheme 85)



Hart and co-workers adopted a different approach to the synthesis of the alkaloid in that instead of using carbohydrate precursors they utilised an  $\alpha$ -acylamino radical approach.<sup>217</sup>



Swainsonine (132)

Reagents: (i) Acetyl chloride, NH<sub>3</sub>, Acetyl chloride  
 (ii) Ph<sub>3</sub>P, DEAD, PhC≡CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OH (271)  
 (iii) NaBH<sub>4</sub>, MeOH; Ac<sub>2</sub>O, Et<sub>3</sub>N, DMAP; *n*-Bu<sub>3</sub>P, PhSSPh  
 (iv) *n*-Bu<sub>3</sub>SnH, AIBN, PhH  
 (v) O<sub>3</sub>, MeOH; Me<sub>2</sub>S; NaBH<sub>4</sub>, MeOH  
 (vi) Me<sub>3</sub>CCOCl, DMAP, pyridine; NH<sub>3</sub>, MeOH; Me<sub>3</sub>CCOCl, DMAP, pyridine, Tf<sub>2</sub>O; KOAc, 18-crown 6, DMF; Ac<sub>2</sub>O, Et<sub>3</sub>N, DMAP; (p-MeOC<sub>6</sub>H<sub>4</sub>PS<sub>2</sub>)<sub>2</sub>; Raney Ni, EtOH; MeNH<sub>2</sub>

(Scheme 86)

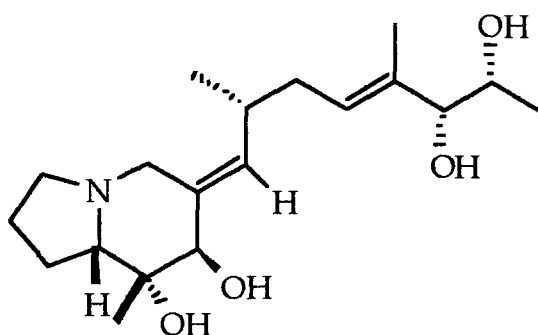
The imide (270) was prepared by the sequential treatment of D-tartaric acid (183) with acetyl chloride, ammonia and acetyl chloride. Treatment of the imide (270) with a mixture of triphenyl phosphine, diethylazodicarboxylate (DEAD) and the acetylenic alcohol (271) afforded the tartarimide (272) in close to quantitative yield. Reduction of the intermediate gave the carbinol lactam (273) as a mixture of diastereomers. The lactam was subsequently treated with diphenyl disulphide in the presence of tri-*n*-butylphosphine to furnish the desired radical precursor (274). Reaction of (274) with tri-*n*-butyltin hydride in the presence of the radical initiator azo-*bis*-isobutyronitrile gave the epimeric mixture (275)/(276). The mixture was ozonised and reduced with sodium borohydride to furnish the indolizidine (277) which was further elaborated to swainsonine (132) as shown in Scheme 86.

### Allopumiliotoxin 339A (230)

Several members of the pumiliotoxin A class of amphibian alkaloids display significant cardiotonic activity.<sup>218-222</sup> Recent pharmacological studies demonstrate that pumiliotoxin B enhances sodium influx by binding to a unique modulatory site on the voltage dependant sodium channel.<sup>223,224</sup> This interaction has been shown to stimulate phosphoinositide breakdown with the effect on this secondary messenger system being ultimately expressed at cardiotonic and myotonic activities.

The most complex and rare members of the pumiliotoxin A group are the allopumiliotoxins<sup>225,226</sup> which contain oxidation at both C-(7) and C-(8) of the indolizidine ring.

Allopumiliotoxin 339A (230) is the only pumiliotoxin A alkaloid to be more effective at stimulating both sodium influx and phosphoinositide breakdown than pumiliotoxin B.<sup>224</sup>

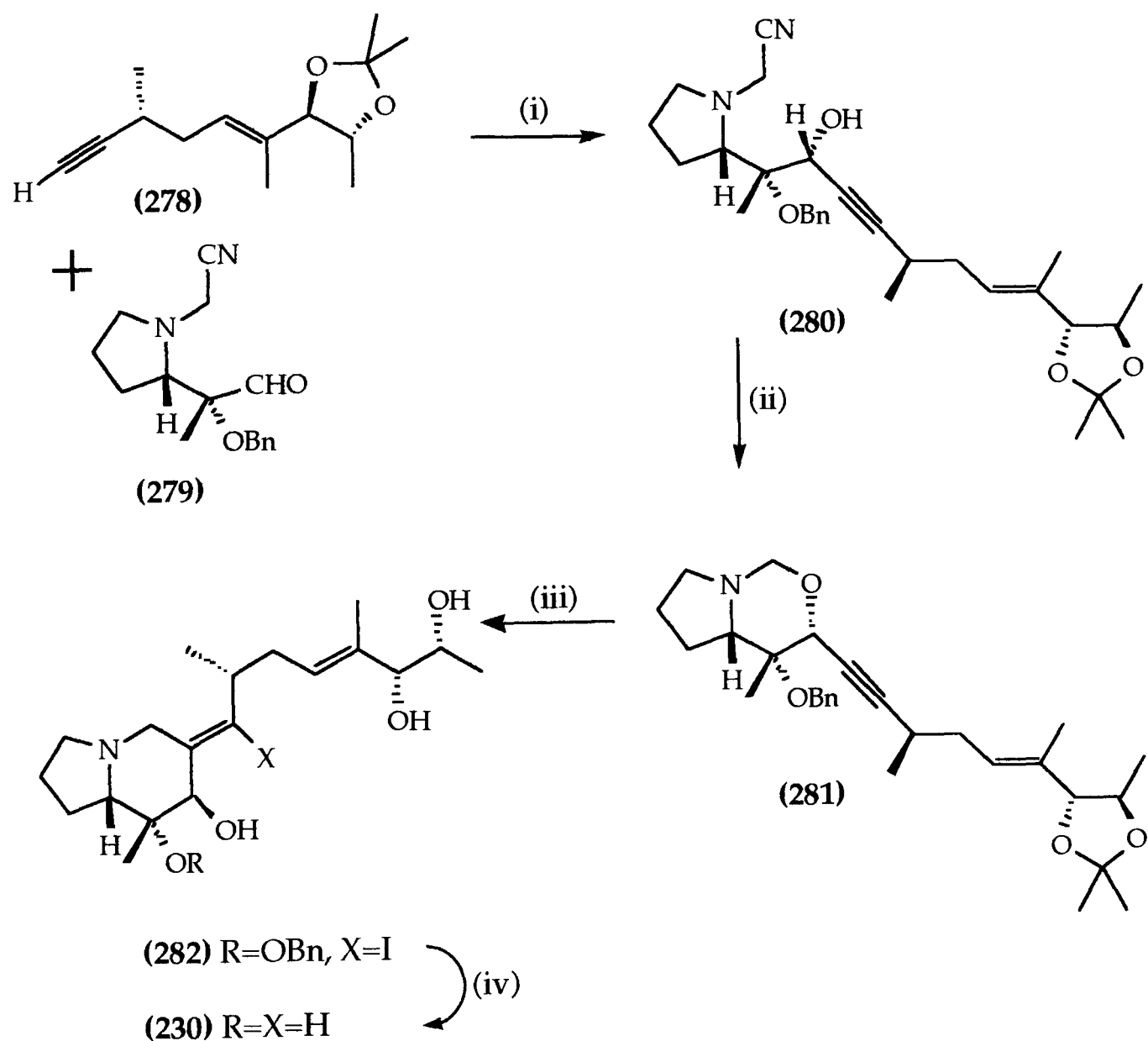


Allopumiliotoxin 339A (230)

(Figure 29)

Overman and co-workers have published the total synthesis of this molecule<sup>228</sup> which involves the combination of the proline derived aldehyde (279) with the side chain alkyne (278). Addition of the alkynyl derivative of (278) to the  $\alpha$ -benzyloxyaldehyde (279) gave mainly (280) which was further treated with silver triflate to yield the cyclopentaoxazine (281) in high yield. Cyclisation to give the indolizidine skeleton (282) was achieved with tosic acid and sodium iodide in aqueous acetone. Elaboration to the natural product (230) was achieved by de-iodination followed by cleavage of the benzyl ether. The

isolated product was indistinguishable from the natural toxin by TLC and  $^{13}\text{C}$  NMR.

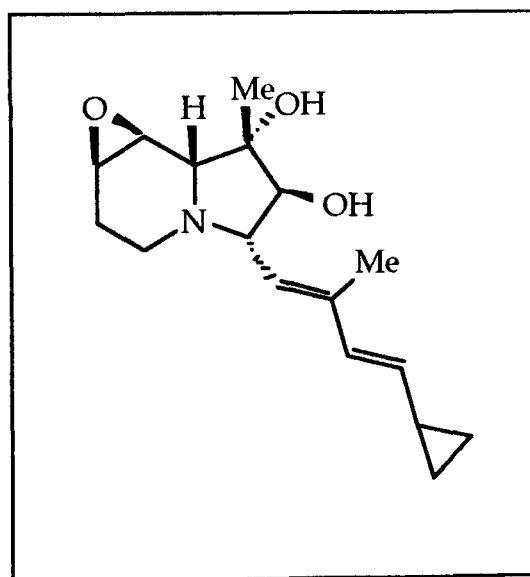


Reagents: (i)  $n\text{-BuLi}$   
(ii)  $\text{AgOSO}_2\text{CF}_3$   
(iii)  $\text{TsOH}$ ,  $\text{NaI}$   
(iv)  $n\text{-BuLi}$ ;  $\text{MeOH}$ ;  $\text{Li}$ ,  $\text{NH}_3$

(Scheme 87)

## Cyclizidine (231)

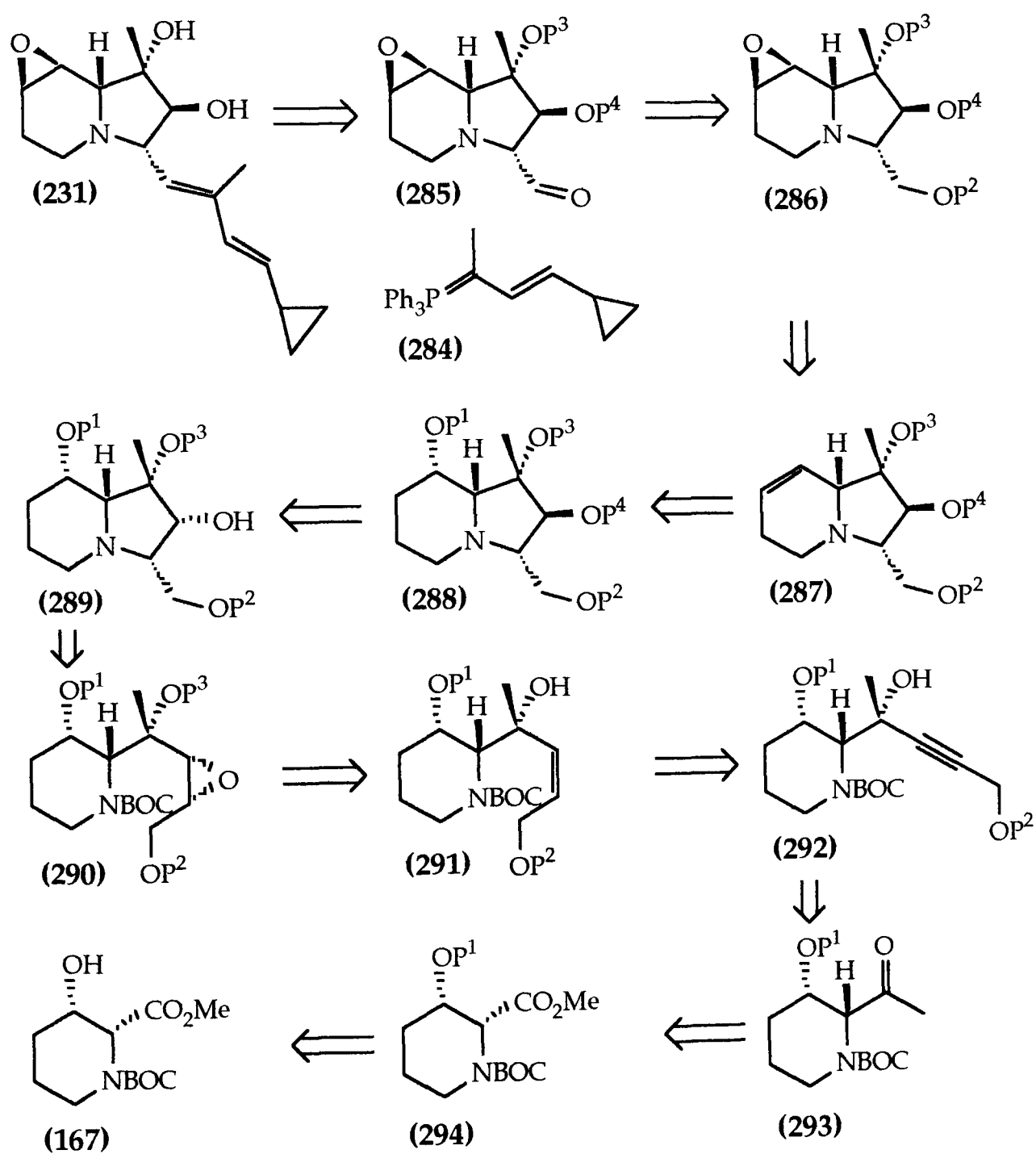
An indolizidinediol with an unusual  $\alpha,\beta,\gamma,\delta$ -unsaturated cyclopropyl side-chain has been isolated from a new *streptomyces* species NCIB 11649 which itself has been isolated from hedgerow soil samples in the Greater Manchester area. In 1982 the crystal structure was determined by Sim and co-workers<sup>229</sup> but the compound has not yet been synthesised by chemical methods. Interestingly the compound shows non-selective immunostimulatory properties and furthermore its acetate causes a reduction in the frequency of cultured heart cells, an effect seen with certain  $\beta$ -blocking drugs.



Cyclizidine (231)

(Figure 30)

We were particularly interested in the indolizidine alkaloid Cyclizidine (231) by virtue of the fact that it has not yet been synthesised in the laboratory. We envisaged the use of the piperidine  $\beta$ -hydroxy ester (167) derived from baker's yeast reduction as a chiral building block in our proposed synthesis. One such retrosynthetic analysis is shown in Scheme 88 which is one of our many ideas of how the total synthesis of Cyclizidine (231) may be accomplished.

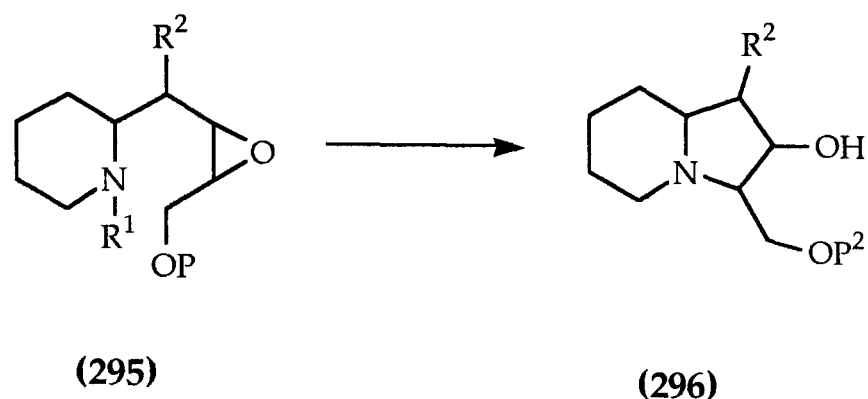


(Scheme 88)

In a forward sense protection of the initial yeast reduction product (167) as its silyl ether (294)<sup>117</sup> followed by Grignard reaction of the ester functionality with methylmagnesium bromide should afford the corresponding methyl ketone (293).<sup>230</sup> Treatment of this ketone (293) with the anion produced by the action of *n*-butyl lithium on propargyl alcohol protected as its silyl ether should then form the corresponding acetylene (292). It is hoped that the two chiral centres formed by the baker's yeast will direct the nucleophilic attack as drawn. Hydrogenation of the acetylene (292) using palladium on barium sulphate poisoned with quinoline<sup>231</sup> should allow selective reduction of the triple bond to produce the corresponding *cis*-olefin (291). It is envisaged that the allylic alcohol (291) will then be epoxidised in a stereoselective manner using Sharpless methodology<sup>232-236</sup> followed by protection of the free hydroxyl function to furnish the differentially protected epoxy-triol (290). Deprotection of the amine function should result in attack by the free amine onto the epoxide thus forming the indolizidine skeleton (289). Mitsunobu inversion<sup>237</sup> of the C-(2) hydroxyl followed by protection should then furnish the desired indolizidine skeleton (288) with the correct stereochemistry of the target molecule Cyclizidine (231). Deprotection of the C-(8) hydroxyl followed by dehydration and subsequent stereoselective epoxidation should yield the epoxy derivative (286). In order to complete the synthesis the hydroxyl function on the C-(3) side-chain will be oxidised to the corresponding aldehyde (285)<sup>238</sup> and the side chain (284) introduced in one piece in a Wittig type reaction<sup>239-240</sup> to furnish Cyclizidine (231).

We realised that much work will have to be carried out on this synthesis and realised that some of our ideas may only look good on paper. However, we are confident that the general synthetic ideas are of sound judgement and to this end we decided to undertake model reactions to prove that the synthetic scheme is viable. For the purpose of this project we decided to model the ring closure reaction of the amine group attacking the epoxide to form the

indolizidine ring structure to firstly see if the reaction would take place and if so to determine whether or not it would be stereoselective. To this end work was undertaken in the synthesis of the required amino epoxide (295) which we intended to cyclise to give the indolizidine skeleton (296).

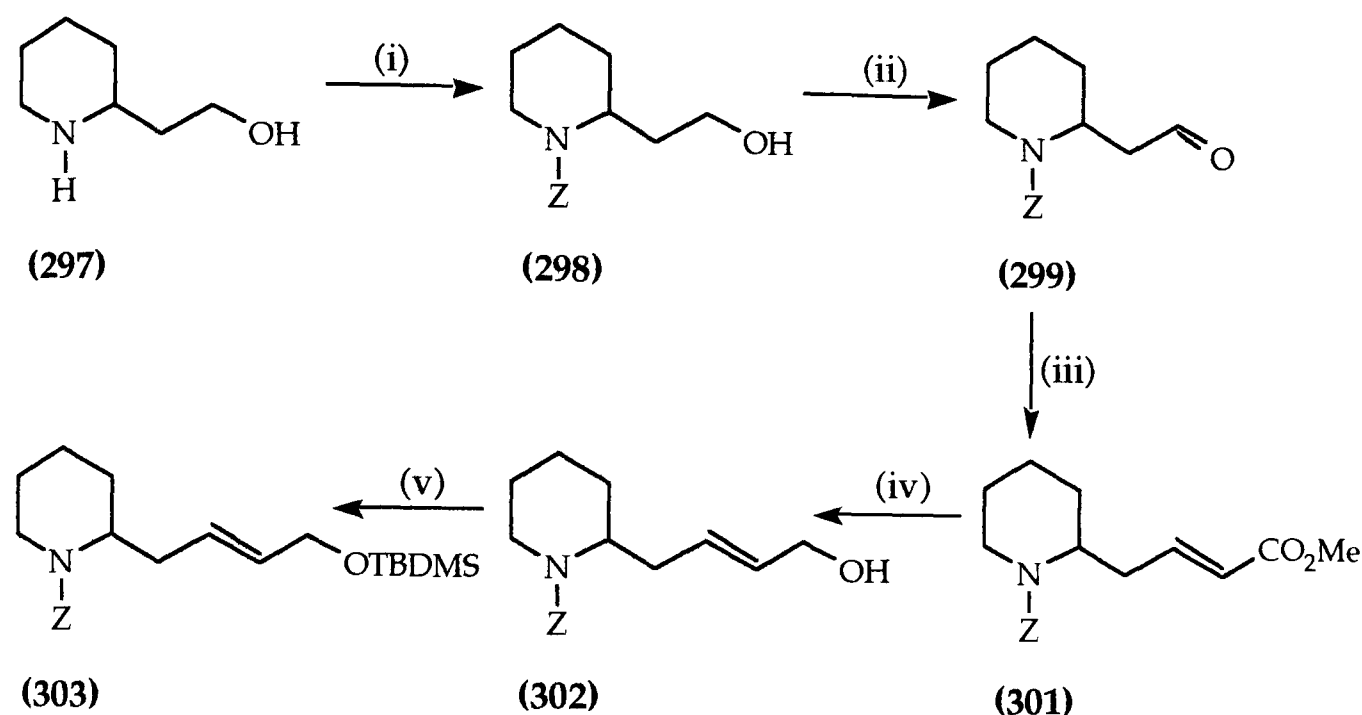


(Scheme 89)

Protection of 2-piperidineethanol (297) as its benzyl carbamate was achieved using Schotten Baumann methodology<sup>100</sup> and we were able to isolate the desired protected material (298) in high yield. This was subsequently oxidised to the corresponding aldehyde (299) using the Parikh-Doering procedure of DMSO, sulphur trioxide-pyridine complex and triethylamine.<sup>238,241-246</sup> We were pleased to isolate the desired aldehyde (299) in 82% yield after column chromatography. Wittig reaction of the aldehyde (299) using the stabilised ylide methyltriphenylphosphorylideneacetate (300) gave the  $\alpha,\beta$ -unsaturated ester (301). Reduction of the ester moiety to the corresponding alcohol was achieved using diisobutylaluminium hydride in toluene at  $-78^\circ\text{C}$ <sup>116</sup> and the desired allylic alcohol (302) was isolated in 87% yield after purification by silica gel chromatography. Protection of the hydroxyl function was performed by the



action of *tert*-butyldimethylsilyl chloride<sup>117</sup>, triethylamine and DMAP<sup>118</sup> and the corresponding silyl ether (303) was isolated in a yield of 79%.



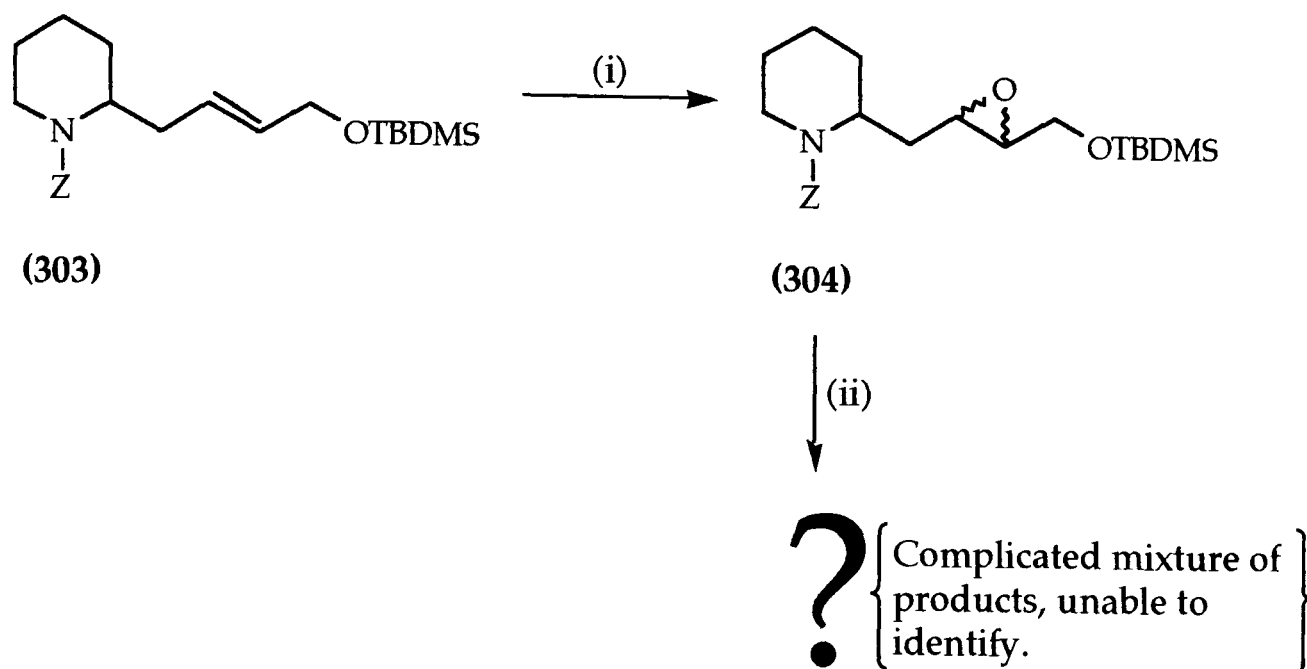
Reagents:

- (i) Benzyl chloroformate/ NaOH
- (ii) DMSO, sulphur trioxide.pyridine complex, Et<sub>3</sub>N
- (iii) Ph<sub>3</sub>P=CHCO<sub>2</sub>Me (300)
- (iv) DIBAL-H in toluene
- (v) TBDMSCl, Et<sub>3</sub>N, DMAP

(Scheme 90)

Epoxidation of this moiety (303) was achieved using *meta*-chloroperoxybenzoic acid<sup>247</sup> and the epoxide (304) was isolated as a mixture of inseparable diastereomers. We were disappointed by the fact that we were unable to separate these diastereomers and found that this caused problems in the final cyclisation step. Deprotection of the amine functionality by hydrogenation over 5% palladium on carbon<sup>248,249</sup> followed by stirring for 24 hours in methanol led to a complicated mixture of diastereomers which made structure elucidation of the product virtually impossible. To this end we decided to

adopt a different approach to the preparation of the amino-epoxide (295) in the hope that more stereochemical control could be achieved.



Reagents:

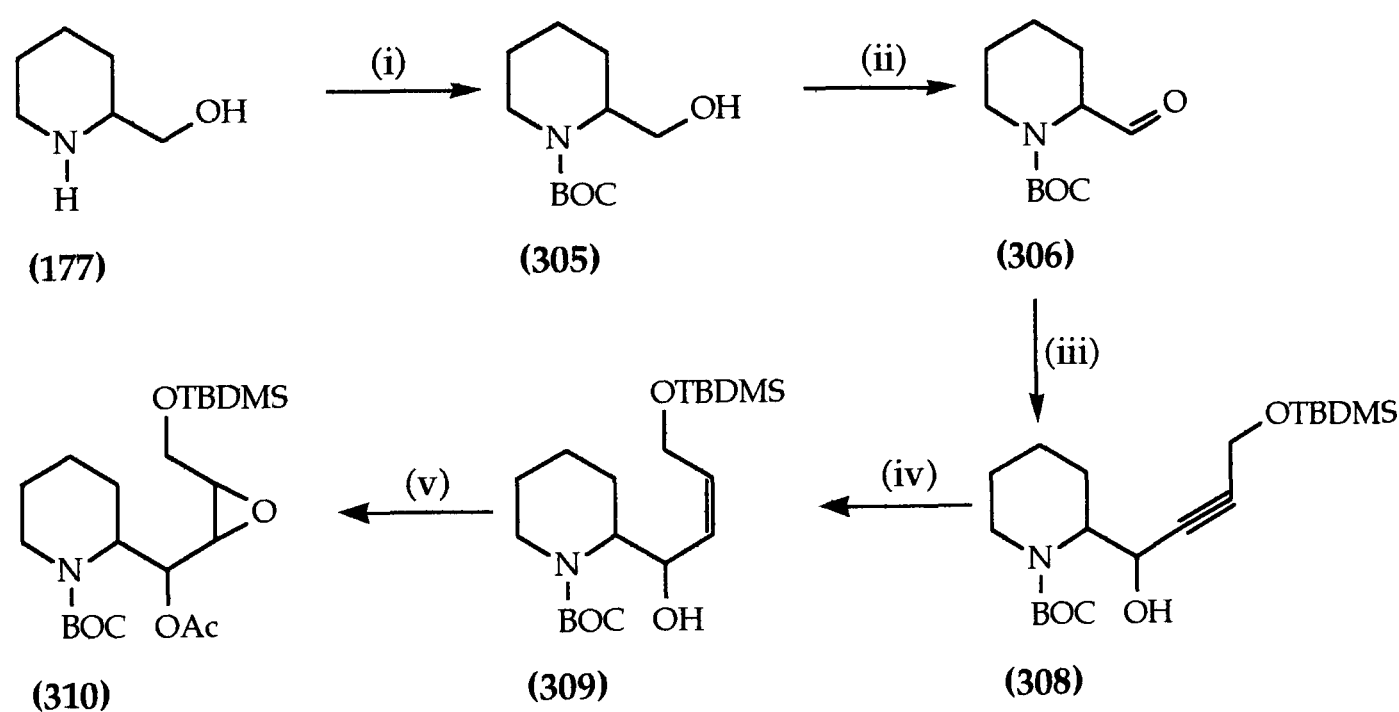
(i) *m*-CPBA

(ii) H<sub>2</sub>/ 5% Pd on C; MeOH 36h

(Scheme 91)

2-Piperidinemethanol (177) was protected as its *tert*-butyl carbamate using di-*tert*-butyl dicarbonate and triethylamine<sup>98</sup> and the desired protected derivative (305) was isolated in 80% yield. Oxidation of the hydroxyl function was achieved as before by using the Parikh-Doering procedure of DMSO, sulphur trioxide-pyridine complex and triethylamine<sup>241-246</sup>. We were pleased to isolate the desired aldehyde (306) in 74% yield after column chromatography. Treatment of the aldehyde (306) with the anion generated by the action of *n*-butyl lithium on *O-tert*-butyldimethylsilyl-propyn-1-ol (307) led to the acetylenic derivative (308) as largely a single diastereomer by <sup>13</sup>C NMR which

was selectively reduced to the corresponding *cis*-olefin (**309**) by hydrogenolysis over palladium on barium sulphate poisoned with quinoline<sup>231</sup>. We envisaged the use of Sharpless methodology<sup>232-236</sup> would need to be adopted to stereoselectively epoxidise the allylic alcohol. However we were pleased to isolate the desired acetoxy epoxide (**310**) as a single diastereomer after treatment with *meta*-chloroperoxybenzoic acid<sup>247</sup> followed by protection of the free hydroxyl function as its acetate (acetic anhydride/pyridine) to prevent Payne rearrangement from occurring<sup>250</sup>.



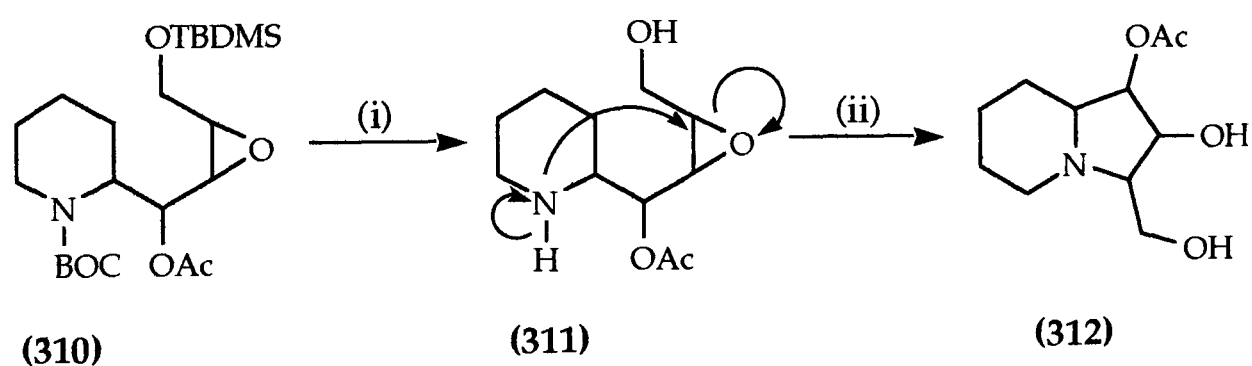
#### Reagents:

- (i) Di-*tert*-butyl dicarbonate
- (ii) DMSO, sulphur trioxide.pyridine complex, Et<sub>3</sub>N
- (iii) TBDMSOCH<sub>2</sub>-C≡C-OH (**307**), n-BuLi
- (iv) H<sub>2</sub>, Pd on BaSO<sub>4</sub> quinoline
- (v) *m*-CPBA; Ac<sub>2</sub>O, pyridine

(Scheme 92)

We were again in a position to model the cyclisation of the free amine function onto the epoxide in an attempt to produce the indolizidine ring

structure. Removal of the *tert*-butyl carbamate was smoothly achieved using trifluoroacetic acid<sup>123</sup> and the free base (311) formed by neutralisation of the reaction mixture cyclised to form the desired indolizidine (312) by stirring in methanol for 36 hours. <sup>1</sup>H NMR indicated that the product isolated after silica gel chromatography was extremely pure and <sup>13</sup>C NMR indicated the presence of a single diastereomer.



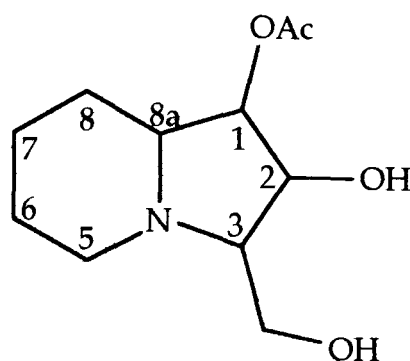
Reagents:

(i) Trifluoroacetic acid

(ii) MeOH, room temp, 36h

(Scheme 93)

We were excited at our findings and decided to undertake NOE experiments in the hope of elucidating the relative stereochemistry of the product (312).



(312)

(Figure 31)

Irradiation at  $\delta 5.15$  (1-H) led to an enhancement of signal at  $\delta 3.58$ - $3.72$  (3-H) and also at  $\delta 1.97$  (8- $H_AH_B$ ) which indicates a *syn* arrangement of the C-(1)-acetate and the C-(3) side chain.

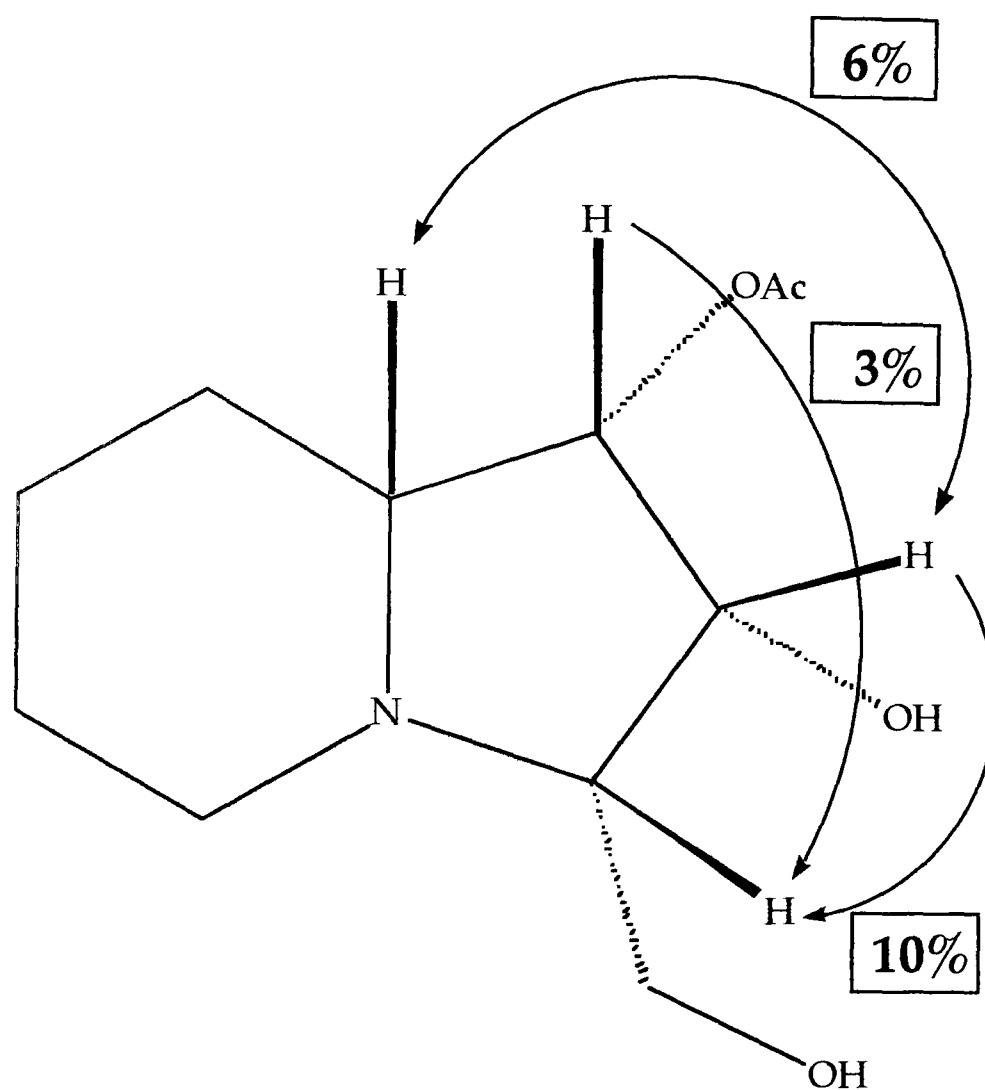
Irradiation at  $\delta 4.31$  (2-H) led to an enhancement of signal at  $\delta 3.58$ - $3.72$  (3-H),  $\delta 3.29$ - $3.38$  (8a-H) and also at  $\delta 4.24$  (5- $H_AH_B$ ) which indicates a *syn* arrangement of the C-(2) hydroxyl to the C-(3) side-chain and an anti arrangement of the C-(2) hydroxyl to the bridge proton. This means the functional groups at C-(1), C-(2) and C-(3) are all *syn* to each other and *anti* to the bridge proton (8a-H).

Irradiation at  $\delta 3.29$ - $3.38$  (8a-H) led to an enhancement of signal at  $\delta 4.31$  (2-H),  $\delta 1.97$  (8- $H_AH_B$ ), and  $\delta 4.24$  (5- $H_AH_B$ ) confirming the anti arrangement of the C-(2) hydroxyl to the bridgehead proton 8a-(H).

Irradiation at  $\delta 4.24$  (5- $H_AH_B$ ) led to an enhancement of signal at  $\delta 2.79$  (5 $H_AH_B$ ) and also at  $\delta 1.97$  (8- $H_AH_B$ ).

Irradiation at  $\delta 1.97$  (8- $H_AH_B$ ) led to an enhancement of signal at  $\delta 1.25$ - $1.35$  (5- $H_AH_B$ ).

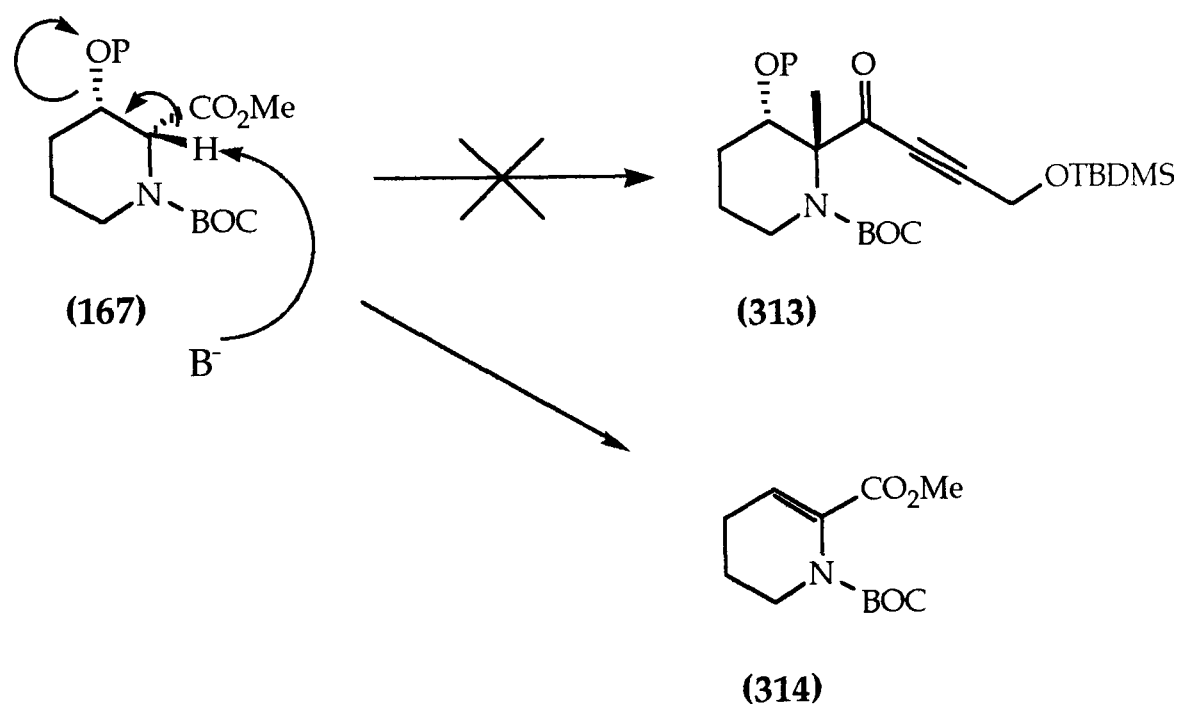
From these experiments we are able to assign the relative stereochemistry of the diastereomer (312) produced from the cyclisation as shown in Figure 32.



(Figure 32)

To follow on from these rather pleasing results we decided to substitute our yeast reduction product (167) for the protected 2-piperidinemethanol

derivative (305) used in the previous synthesis. We were disappointed to find that preliminary results of the addition of the anion of *O*-*tert*-butyldimethylsilyl-propyn-1-ol (307) onto the piperidine- $\beta$ -hydroxy ester (167) led to the elimination of the hydroxyl function to form the corresponding olefin (314) presumably by base extraction of the proton  $\alpha$ - to the ester function.



(Scheme 94)

However this reaction was only attempted on one occasion and time did not permit further study in this area.

## **Chapter Five**

### **Experimental**



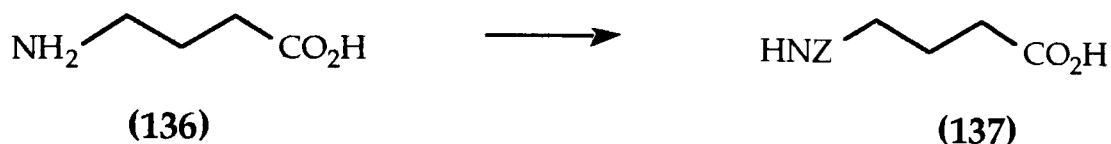
## General Details -

Melting points were determined on a K f ler hot stage apparatus and are uncorrected. Optical rotations are determined using an Optical Activity AA-10 polarimeter. Infrared spectra were recorded using a Perkin-Elmer 1600 series Fourier transform spectrometer using neat films unless otherwise stated.  $^1\text{H}$  NMR spectra were determined using a Perkin-Elmer R32 (90 MHz), a Bruker WM-250 (250 MHz), a Jeol EX-270 (270 MHz) or a Bruker AM-400 (400 MHz).  $^{13}\text{C}$  NMR spectra were recorded using a Jeol EX-270 (270) operating at 67.8 MHz, a Bruker WM-250 (250 ) operating at 62.5 MHz or a Bruker AM-400 (400) operating at 100.1 MHz. Dilute solutions in deuteriochloroform were used throughout unless otherwise stated and tetramethylsilane was used as an internal standard throughout. All J values are in Hz. Mass spectra were determined using either an A. E. I. MS902 or VG 7070E spectrometer. All molecular formulae, quoted both for molecular ions ( $\text{M}^+$ ) and fragments, are accurate to  $\pm 3$  ppm.

Tetrahydrofuran was dried over potassium and benzophenone and distilled as required. Ether, toluene and benzene were dried over sodium. Dichloromethane, dimethyl formamide, diisopropylamine, dimethyl sulphoxide and chloroform were dried over calcium hydride and distilled onto 4  molecular sieves. Pyridine, triethylamine and diisopropylethyl amine were dried over potassium hydroxide. Oxalyl chloride was freshly distilled before use. Acetonitrile was dried over phosphorus pentoxide and distilled onto 4  molecular sieves. Methanol was dried using magnesium methoxide and distilled onto 4  molecular sieves. Ethanol was dried using magnesium ethoxide and distilled onto 4  molecular sieves

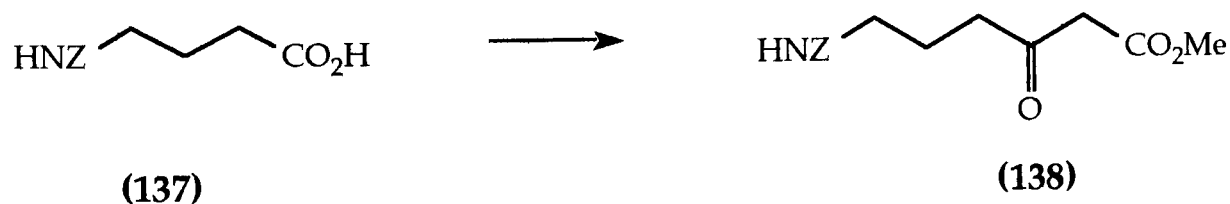
All organic solutions were dried over anhydrous magnesium sulphate. Sorbsil silica gel was used throughout.

### N-(Benzyloxycarbonyl)-4-aminobutyric acid (137)



Benzyl chloroformate (136) (36.4 g, 214 mmol) and sodium hydroxide (8.5 g, 214 mmol) in water (100 ml) were simultaneously added to a stirred, ice-cooled solution of 4-aminobutyric acid (20 g, 194 mmol) and sodium hydroxide (7.8 g, 194 mmol) in water (100 ml). The reaction mixture was warmed to room temperature, stirred for 16h, washed with ether (50 ml) acidified to pH 1 with 2M aqueous hydrochloric acid then extracted with dichloromethane (3 x 150 ml). The combined organic extracts were washed with brine (30 ml) and concentrated *in vacuo* to give the title compound (137) (40.5 g, 88%) as a white solid, m.p 110-112°C,  $\nu_{\text{max}}$  1700, 1710 and 3440  $\text{cm}^{-1}$ ,  $\delta_{\text{H}}$  (90) 1.58-1.97 (2H, m,  $\text{NHCH}_2\text{CH}_2$ ), 2.33 (2H, t, J 7.5,  $\text{CH}_2\text{CO}_2\text{H}$ ), 3.20 (2H, td, J 7.5 and 6,  $\text{NHCH}_2$ ), 5.60 (2H, s,  $\text{PhCH}_2$ ), 7.30 (5H, s,  $\text{C}_6\text{H}_5$ ) and 9.84 (1H, br s,  $\text{CO}_2\text{H}$ ).

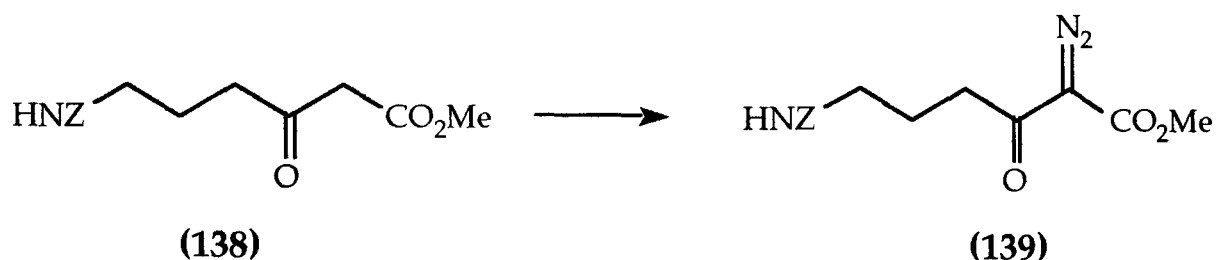
### Methyl 6-[(benzyloxycarbonyl)amino]-3-oxohexanoate (138)



1,1'-Carbonyl diimidazole (4.1 g, 25 mmol) was added to a stirred solution of the protected amino-acid (137) (5 g, 21 mmol) in dry dichloromethane (100 ml). The reaction mixture was stirred at room temperature for 16h, and subsequently added to a stirred solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (3.6 g, 25 mmol) and pyridine (2 g, 25 mmol) in dichloromethane (100 ml) at 0°C. After 90min at 0°C the reaction mixture was warmed to room temperature, stirred for 1h diluted with dichloromethane (150 ml) then washed with 2M citric acid (2 x

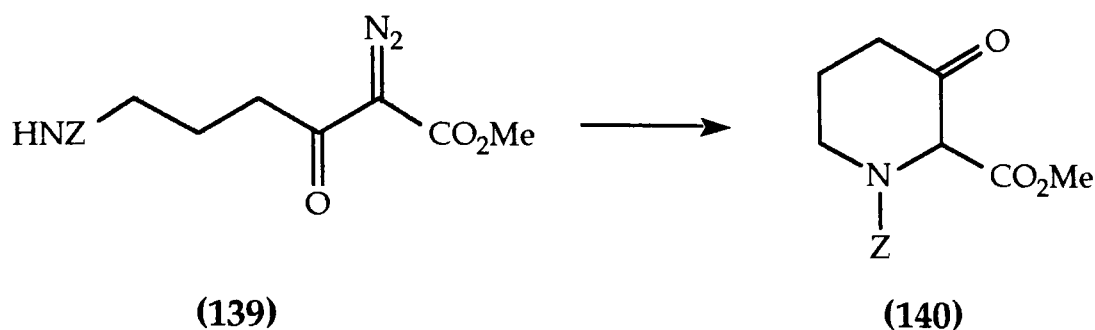
50 ml) and brine (50 ml). The organic phase was dried and concentrated *in vacuo*. The residue was dissolved in methanol (100 ml), refluxed for 3h and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) gave the title compound (138) (4.95g, 80%) as a clear colourless oil,  $R_F$  0.65,  $\nu_{\max}$  1700, 1740, 2940 and 3440 $\text{cm}^{-1}$ ,  $\delta_H$  (90) 1.60-1.95 (2H, m,  $\text{CH}_2\text{CH}_2\text{C}=\text{O}$ ), 2.555 (2H, t, J 7,  $\text{CH}_2\text{C}=\text{O}$ ), 3.15 (2H, m,  $\text{NHCH}_2$ ), 3.40 (2H, s,  $\text{O}=\text{CCH}_2\text{C}=\text{O}$ ), 3.70 (3H, s,  $\text{CH}_3\text{CO}_2$ ), 5.00 (1H, br s, NH), 5.10 (2H, s,  $\text{PhCH}_2$ ) and 7.35 (5H, s,  $\text{C}_6\text{H}_5$ ).

#### Methyl 6-[(benzyloxycarbonyl)amino]-2-diazo-3-oxohexanoate (139)



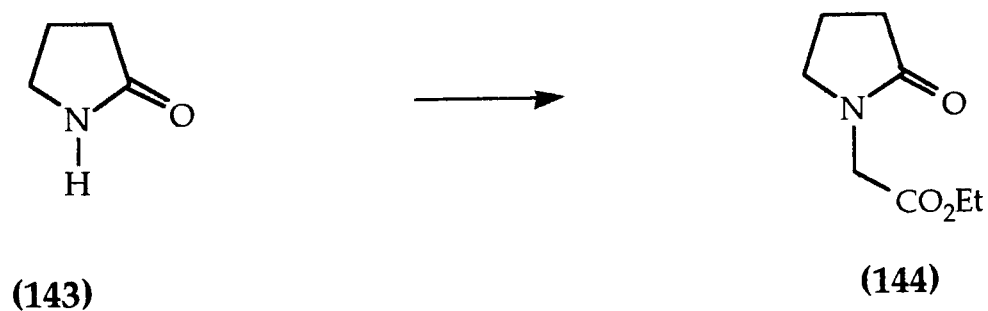
Triethylamine (1.45 g, 14.3 mmol) was added in a single portion to an ice-cooled stirred solution of the  $\beta$ -keto-ester (138) (1.4 g, 4.8 mmol) and *p*-(carboxybenzene)sulphonyl azide (1.2 g, 5.3 mmol) in acetonitrile (20 ml). The reaction mixture was warmed to room temperature, stirred for 90 minutes, diluted with dichloromethane (200 ml) then washed with saturated aqueous sodium hydrogen carbonate (40 ml) and brine (40 ml). The combined organic extracts were dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) gave the title compound (139) (1.28g, 84%) as a colourless oil,  $R_F$  0.45,  $\nu_{\max}$  1710, 2140, 3000 and 3440 $\text{cm}^{-1}$ ,  $\delta_H$  (90) 1.65-2.00 (2H, m,  $\text{NHCH}_2\text{CH}_2$ ), 2.85 (2H, t, J 7,  $\text{NHCH}_2\text{CH}_2\text{CH}_2$ ), 3.18 (2H, m,  $\text{NHCH}_2$ ), 3.78 (3H, s,  $\text{CH}_3\text{CO}_2\text{C}$ ), 5.08 (2H, s,  $\text{PhCH}_2$ ) and 7.35 (5H, s,  $\text{C}_6\text{H}_5$ ).

**(±)-1-Benzyl-2-methyl-3-oxopiperidine-1,2-dicarboxylate (140)**



Rhodium (II) acetate dimer (22 mg, 0.06 mmol) was added to a solution of the  $\alpha$ -diazo- $\beta$ -keto-ester and the resulting suspension immediately immersed in an oil bath pre heated at 90°C. The reaction mixture was heated at this temperature for 30 minutes and cooled. The resulting solution was filtered through kieselguhr and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) gave the title compound **(140)** (178mg, 49%) as a colourless oil,  $R_F$  0.85,  $\nu_{\max}$  1710 and 2960cm<sup>-1</sup>,  $\delta_H$  (90) 1.73-2.15 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>), 2.30 and 2.67 (2H, 2t, J 6.4 and 6.1, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.32-3.65 (1H, m, 6-H<sub>ax</sub>), 3.71 and 3.77 (3H, 2s, CH<sub>3</sub>CO<sub>2</sub>C), 3.80-4.20 (1H, m, 6-H<sub>eq</sub>), 5.17 (2H, s, PhCH<sub>2</sub>) and 7.35 (5H, s, C<sub>6</sub>H<sub>5</sub>).

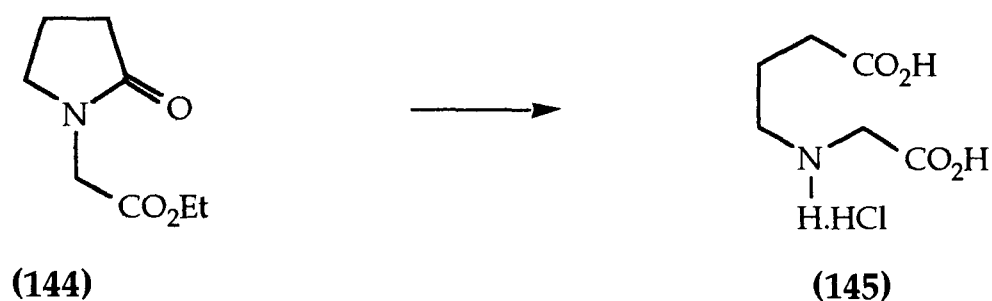
**Ethyl 2-pyrrolidinone-N-acetate (144)**



2-Pyrrolidinone **(143)** (85 g, 1 mol) was added to a rapidly stirred suspension of molten sodium (23 g, 1 mol) in refluxing toluene (600 ml). Heating was continued for 1h after which time ethyl bromoacetate (167 g, 1 mol) was introduced dropwise over a period of 20min. The reaction mixture was heated for 1h, cooled, filtered and concentrated *in vacuo*. The residue was distilled under reduced pressure (b.p.

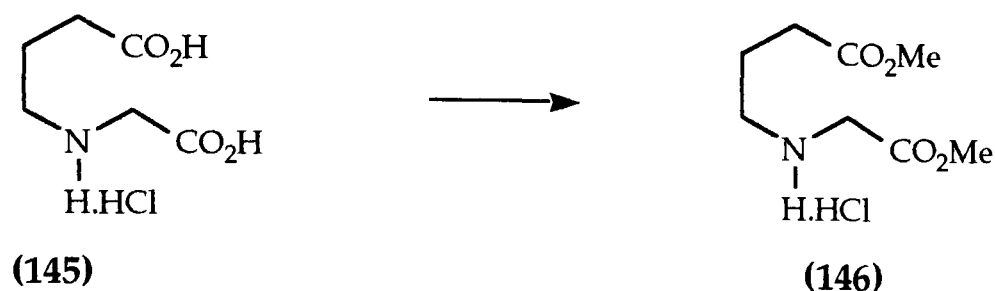
127°C / 0.1 mmHg) to give the **title compound (144)** (142g, 83%) as a colourless oil,  $\nu_{\max}$  1740  $\text{cm}^{-1}$ ,  $\delta_{\text{H}}$  (270) 1.28 (3H, t, J 7.25,  $\text{CH}_3\text{CH}_2\text{O}_2\text{C}$ ), 2.02-2.12 (2H, m,  $\text{CH}_2\text{CH}_2\text{C}=\text{O}$ ), 2.39 (2H, t, J 8,  $\text{CH}_2\text{CH}_2\text{C}=\text{O}$ ), 3.50 (2H, t, J 7, N- $\text{CH}_2\text{CH}_2$ ), 4.05 (2H, s,  $\text{NCH}_2\text{CO}_2\text{Et}$ ) and 4.19 (2H, q, J 7.25,  $\text{CH}_3\text{CH}_2\text{O}_2\text{C}$ ),  $\delta_{\text{C}}$  (68.5) 13.50 ( $\text{CH}_3$ ), 17.30 ( $\text{CH}_2$ ), 29.65 ( $\text{CH}_2$ ), 43.36 ( $\text{CH}_2$ ), 47.03 ( $\text{CH}_2$ ), 60.52 ( $\text{CH}_2$ ), 168.01 (C) and 174.88 (C),  $m/z$  171 (20%, M), 125 (5, M-EtO), 98 (100, M- $\text{CO}_2\text{Et}$ ), 84 (19, M- $\text{CH}_2\text{CO}_2\text{Et}$ ), 70 (26, M- N $\text{CH}_2\text{CO}_2\text{Et}$ ) and 68 (3, M-O- $\text{CH}_2\text{CO}_2\text{Et}$ ), [Found: M, 171.0900.  $\text{C}_8\text{H}_{13}\text{NO}_3$  requires M, 171.0895].

### 3-Azahepta-1,7- dioic acid hydrochloride (145)



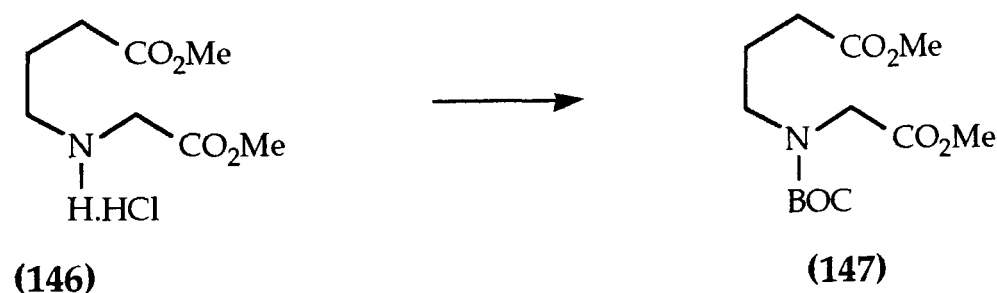
A solution of the pyrrolidine **(144)** (120 g, 702 mmol) in aqueous 6M hydrochloric acid (800 ml) was refluxed for a period of 48h. The resulting solution was cooled and concentrated *in vacuo*. The residue was dissolved in methanol (400 ml) and concentrated *in vacuo*. This procedure was repeated to give the **title compound (145)** (115g, 83%) as a colourless gum,  $\delta_{\text{H}}$  (400) ( $\text{D}_2\text{O}$ ) 1.67 (2H, m,  $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ ), 2.21 (2H, t, J 7.2,  $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ ), 2.86 (2H, t, J 7.80, N $\text{CH}_2\text{CH}_2$ ) and 3.67 (2H, s, N $\text{CH}_2\text{CO}_2\text{H}$ ),  $\delta_{\text{C}}$  (100) ( $\text{D}_2\text{O}$ ) 23.13 ( $\text{CH}_2$ ), 33.03 ( $\text{CH}_2$ ), 49.24 ( $\text{CH}_2$ ), 49.79 ( $\text{CH}_2$ ), 171.22 (C) and 179.06 (C),  $m/z$  144 (9%, M-HCl-OH), 143 (50, M-HCl-H-OH), 116 (7, M-HCl- $\text{CO}_2\text{H}$ ), 99 (51, M-HCl- $\text{CO}_2\text{H}$ -OH), 98 (100, M-HCl- $\text{CO}_2\text{H}$ -OH-H), 71 (8, M-HCl- $\text{CO}_2\text{H}$ - $\text{CO}_2\text{H}$ ) and 70 (81, M-HCl- $\text{CO}_2\text{H}$ - $\text{CO}_2\text{H}$ -H), [Found: M-HCl-OH, 144.0660.  $\text{C}_6\text{H}_{10}\text{NO}_3$  requires M-HCl-OH, 144.0660].

**Dimethyl 3-azahepta-1,7- dicarboxylate hydrochloride(146)**



The diacid (145) (88 g, 446 mmol) was dissolved in methanol (500 ml) to which acetyl chloride (50 ml) had been added. The resulting solution was refluxed for 5h, cooled and concentrated *in vacuo* to give the title compound (146) (80.3 g, 80%) as a colourless oil,  $\nu_{\max}$  1728, 1741 and 3360  $\text{cm}^{-1}$ ,  $\delta_{\text{H}}$  (400) ( $\text{CD}_3\text{OD}$ ) 2.01-2.16 (2H, m,  $\text{CH}_2\text{CH}_2\text{CO}_2\text{Me}$ ), 2.57 (2H, t, J 7.3,  $\text{CH}_2\text{CH}_2\text{CO}_2\text{Me}$ ), 3.24 (2H, t, J 7.7,  $\text{NCH}_2\text{CH}_2$ ), 3.71 (3H, s,  $\text{CH}_3\text{CO}_2\text{C}$ ), 3.87 (3H, s,  $\text{CH}_3\text{CO}_2\text{C}$ ), 4.10 (2H, s,  $\text{NCH}_2\text{CO}_2\text{Me}$ ) and 5.48 (1H, br s, NH),  $\delta_{\text{C}}$  (100) ( $\text{CD}_3\text{OD}$ ) 18.84 ( $\text{CH}_2$ ), 27.21 ( $\text{CH}_2$ ), 31.56 ( $\text{CH}_2$ ), 49.00 ( $\text{CH}_2$ ), 52.44 ( $\text{CH}_3$ ), 53.70 ( $\text{CH}_3$ ), 168.02 (C) and 174.40 (C),  $m/z$  189 (3%, M-HCl), 130 (89, M- $\text{CO}_2\text{Me}$ ), 99 (7, M- $\text{CO}_2\text{Me-Me}$ ), 98 (100, M- $\text{CO}_2\text{Me-Me-H}$ ), 71 (4, M- $\text{CO}_2\text{Me-CO}_2\text{Me}$ ), 70 (46, M- $\text{CO}_2\text{Me-CO}_2\text{Me-H}$ ) and 59 (17,  $\text{CO}_2\text{Me}$ ), [Found: M-HCl, 189.0992.  $\text{C}_8\text{H}_{15}\text{NO}_4$  requires M-HCl, 189.1001].

**Dimethyl N-(tert-butyloxycarbonyl)-3-azahepta-1,7- dicarboxylate (147)**

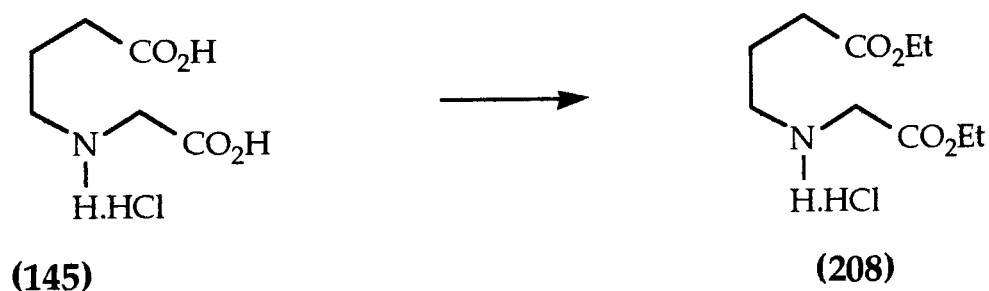


Di-*tert*-butyl dicarbonate (32 g, 146 mmol) was added dropwise to a solution of the diester (146) (30 g, 113 mmol) and triethylamine (14.8 g, 146 mmol) in dichloromethane (200 ml) at room temperature. The reaction mixture was stirred for 16h, diluted with dichloromethane (200 ml), washed with 2M aqueous citric



a colourless oil,  $R_F$  0.9,  $\nu_{\max}$  1662, 1690 and 3361  $\text{cm}^{-1}$ ,  $\delta_H$  (270) 1.47 (9H, s,  $(\text{CH}_3)_3\text{C}$ ), 2.32-2.40 (2H, m,  $\text{NCH}_2\text{CH}_2$ ), 3.49 (2H, t,  $J$  6,  $\text{NCH}_2\text{CH}_2$ ), 3.78 (3H, s,  $\text{CH}_3\text{CO}_2\text{C}$ ), 4.03 (2H, s,  $\text{NCH}_2\text{C}=\text{O}$ ) and 12.00 (1H, s, OH),  $\delta_C$  (68.5) 21.91 and 2.38 ( $\text{CH}_2$ ), 28.1 and 28.10 ( $\text{CH}_3$ ), 39.90 and 41.23 ( $\text{CH}_2$ ), 44.96 and 45.53 ( $\text{CH}_2$ ), 51.51 ( $\text{CH}_3$ ), 79.37 and 80.34 (C), 96.58 and 98.46 (C), 154.03 and 154.37 (C), 166.97 (C) and 172.99 (C),  $m/z$  156 (6%, M-BOC), 125 (13, M-BOC-OMe), 101 (3, BOC), 97 (8, M-BOC- $\text{CO}_2\text{Me}$ ), 59 (10,  $\text{CO}_2\text{Me}$ ) and 57 (100,  $(\text{CH}_3)_3\text{C}$ ), [Found: M-BOC, 156.0634.  $\text{C}_7\text{H}_{10}\text{NO}_3$  requires M-BOC, 156.0661] and the **title compound (149)** (6 g, 27%) as a colourless oil,  $R_F$  0.8,  $\nu_{\max}$  1698, 1740 and 3407  $\text{cm}^{-1}$ ,  $\delta_H$  (270) 1.44 (9H, s,  $(\text{CH}_3)_3\text{C}$ ), 1.95-2.08 (2H, m,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 2.42-2.60 (2H, m,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 3.28-3.52 (1H, m, 6-H<sub>ax</sub>), 3.79 (3H, s,  $\text{CH}_3\text{O}_2\text{C}$ ), 3.86-4.10 (1H, m, 6-H<sub>eq</sub>) and 11.12 (1H, br s, OH),  $\delta_C$  (68.5) 22.32 ( $\text{CH}_2$ ), 26.52 ( $\text{CH}_2$ ), 27.87 ( $\text{CH}_3$ ), 37.82 ( $\text{CH}_2$ ), 53.05 ( $\text{CH}_3$ ), 81.17 (C), 107.92 (C), 154.79 (C), 167.40 (C) and 169.40 (C),  $m/z$  257 (2%, M), 156 (10, M-BOC), 125 (18, M-BOC-OMe), 97 (6, M-BOC- $\text{CO}_2\text{Me}$ ), 59 (11,  $\text{CO}_2\text{Me}$ ) and 57 (10,  $(\text{CH}_3)_3\text{C}$ ), [Found: M, 257.1235.  $\text{C}_{12}\text{H}_{19}\text{NO}_5$  requires M, 257.1263].

#### Diethyl 3-azahepta-1,7-dicarboxylate hydrochloride(208)

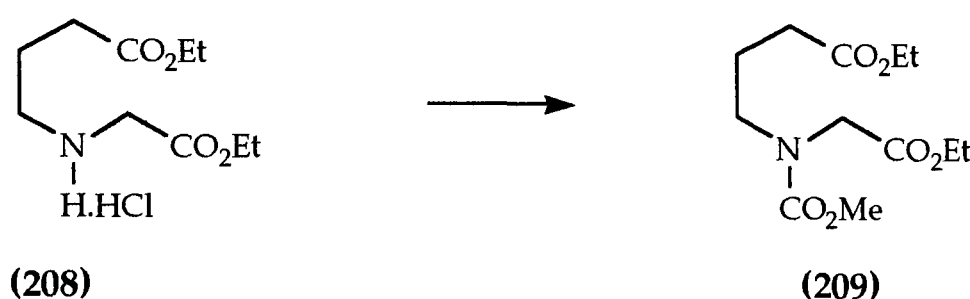


The diacid **(145)** (105 g, 532 mmol) was dissolved in ethanol (500 ml) to which acetyl chloride (50 ml) had been added. The resulting solution was refluxed for 5h, cooled and concentrated *in vacuo* to give the **title compound (208)** (113 g, 84%) as a pale yellow oil,  $\nu_{\max}$  1735, 1738 and 3290  $\text{cm}^{-1}$ ,  $\delta_H$  (400) ( $\text{CD}_3\text{OD}$ ) 1.28 (3H, t,  $J$  7,  $\text{CH}_3\text{CH}_2\text{O}_2\text{C}$ ), 1.35 (3H, t,  $J$  7,  $\text{CH}_3\text{CH}_2\text{O}_2\text{C}$ ), 2.10 (2H, m,  $\text{CH}_2\text{CH}_2\text{CO}_2\text{Et}$ ), 2.55 (2H, t,  $J$  7,  $\text{CH}_2\text{CH}_2\text{CO}_2\text{Et}$ ), 3.22 (2H, t,  $J$  6.5,  $\text{NCH}_2\text{CH}_2$ ), 4.05 (2H, s,  $\text{NCH}_2\text{CO}_2\text{Et}$ ),



4.16 (2H, q, J 7, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 4.32 (2H, q, J 7, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>) and 4.88 (1H, br s, NH),  $\delta_C$  (100) (CD<sub>3</sub>OD) 14.39 (CH<sub>3</sub>), 14.54 (CH<sub>3</sub>), 22.27 (CH<sub>2</sub>), 31.88 (CH<sub>2</sub>), 48.80 (CH<sub>2</sub>), 58.22 (CH<sub>2</sub>), 61.65 (CH<sub>2</sub>), 63.50 (CH<sub>2</sub>), 167.49 (C) and 173.94 (C),  $m/z$  217 (3%, M-HCl), 172 (5, M-EtO), 144 (89, M-CO<sub>2</sub>Et), 115 (14, M-CO<sub>2</sub>Et-Et), 99 (22, M-CO<sub>2</sub>Et-OEt) and 84 (18, M-CO<sub>2</sub>Et-CO<sub>2</sub>Et-H), [Found: M-HCl, 217.1002. C<sub>10</sub>H<sub>19</sub>NO<sub>4</sub> requires M-HCl, 217.1314].

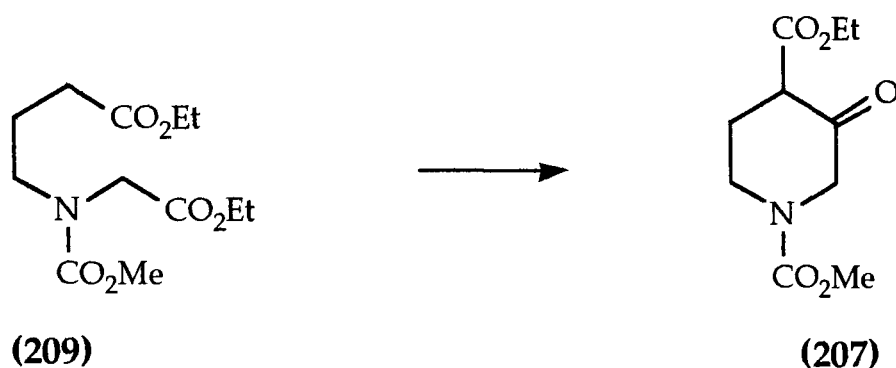
### Diethyl N-(methoxycarbonyl)-3-azahepta-1,7-dicarboxylate (209)



Methyl chloroformate (8.2 g, 87 mmol) was added dropwise to a solution of the diester **(208)** (20 g, 78 mmol) and triethylamine (8.8 g, 87 mmol) in dichloromethane (200 ml) at 0°C. The reaction mixture was warmed to room temperature, stirred for 16h, diluted with dichloromethane (200ml), washed with aqueous 2M hydrochloric acid (2 x 30 ml), saturated aqueous sodium chloride (40 ml), and dried. The resulting solution was passed through a pad of silica gel and concentrated *in vacuo* to give the title compound **(209)** (15.2 g, 70%) as a colourless oil,  $\nu_{\max}$  1670, 1732 and 1736 cm<sup>-1</sup>,  $\delta_H$  (400) 1.07 (3H, t, J 7, CH<sub>3</sub>CH<sub>2</sub>O<sub>2</sub>CCH<sub>2</sub>CH<sub>2</sub>), 1.11 (3H, t, J 7, CH<sub>3</sub>CH<sub>2</sub>O<sub>2</sub>CCH<sub>2</sub>N), 1.55-1.75 (2H, m, CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>Et), 2.08-2.28 (2H, m, CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>Et), 3.16 and 3.19 (2H, 2 x t, J 7 and 7, NCH<sub>2</sub>CH<sub>2</sub>), 3.46 and 3.51 (3H, 2xs, CH<sub>3</sub>CO<sub>2</sub>CN), 3.75 and 3.80 (2H, 2 x s, NCH<sub>2</sub>CO<sub>2</sub>C), 3.93 (2H, q, J 7, CH<sub>3</sub>CH<sub>2</sub>O<sub>2</sub>CCH<sub>2</sub>CH<sub>2</sub>) and 3.93 (2H, q, J 7, CH<sub>3</sub>CH<sub>2</sub>O<sub>2</sub>CCH<sub>2</sub>N),  $\delta_C$  (100) 13.10 (CH<sub>3</sub>), 13.16 (CH<sub>3</sub>), 22.31 and 22.61 (CH<sub>2</sub>), 30.05 and 30.21 (CH<sub>2</sub>), 46.42 and 46.60 (CH<sub>2</sub>), 47.89 and 48.14 (CH<sub>2</sub>), 51.59 and 51.66 (CH<sub>3</sub>), 59.14 and 59.44 (CH<sub>2</sub>), 59.92 and 60.04 (CH<sub>2</sub>), 155.58 and 155.94 (C), 168.71 and 167.72 (C) and 171.90 (C),  $m/z$

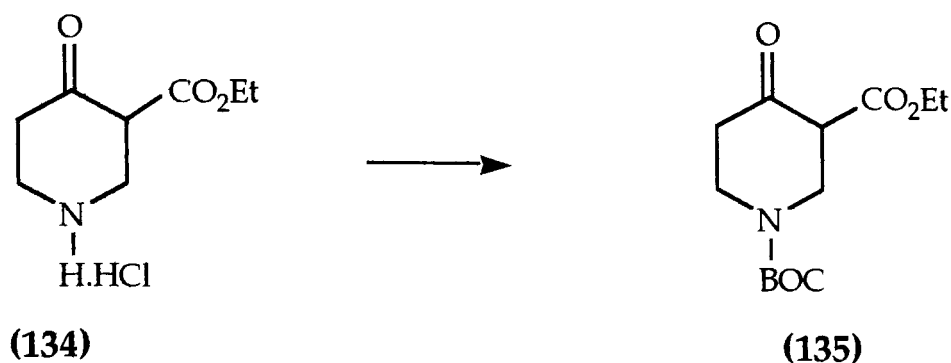
275 (3%, M), 230 (9, M-OEt), 216 (6, M-CO<sub>2</sub>Me) 202 (2, M-CO<sub>2</sub>Et), 188 (6, M-CH<sub>2</sub>CO<sub>2</sub>Et), 128 (8, M-CO<sub>2</sub>Et-OEt) and 70 (33, M-CO<sub>2</sub>Et-CO<sub>2</sub>Et-CO<sub>2</sub>Me), [Found: M, 275.1350. C<sub>12</sub>H<sub>21</sub>NO<sub>6</sub> requires M, 275.1369].

**(±)-1-Methyl-4-ethyl 3-oxopiperidine-1,4-dicarboxylate (207)**



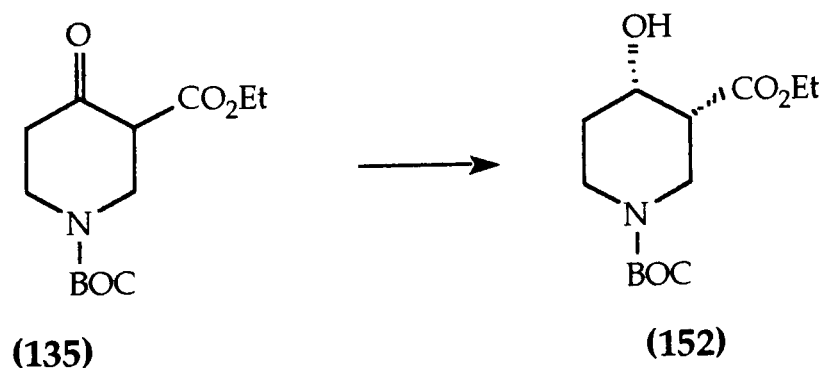
Potassium *tert*-butoxide (4 g, 36.4 mmol) was added in portions over 10min to a solution of the N-protected diester **(209)** (10 g, 36.4 mmol) in dry toluene (150 ml). After a further 30min the reaction mixture was acidified to pH1 with 2M aqueous hydrochloric acid, the organic layer separated and the aqueous phase further extracted with dichloromethane (3 × 100 ml). The organic phases were combined, washed with saturated aqueous sodium chloride (50 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) gave the title compound **(207)** (4.25g, 51%) as a colourless oil,  $R_F$  0.9,  $\nu_{max}$  1668, 1701 and 3350cm<sup>-1</sup>,  $\delta_H$  (400) 1.31 (3H, t, J 7, CH<sub>3</sub>CH<sub>2</sub>O<sub>2</sub>C), 2.34 (2H, br s, NCH<sub>2</sub>CH<sub>2</sub>), 3.54 (2H, br s, NCH<sub>2</sub>CH<sub>2</sub>), 3.73 (3H, s, CH<sub>3</sub>O<sub>2</sub>CN), 4.06 (2H, s, NCH<sub>2</sub>C=O), 4.23 (2H, q, J 7, CH<sub>3</sub>CH<sub>2</sub>O<sub>2</sub>C) and 12.01 (1H, br s, OH),  $\delta_C$  (100) 13.31 (CH<sub>3</sub>), 21.48 (CH<sub>2</sub>), 40.23 (CH<sub>2</sub>), 44.07 (CH<sub>2</sub>), 51.66 (CH<sub>3</sub>), 59.64 (CH<sub>2</sub>), 95.87 (C), 154.77 (C), 166.62 (C) and 170.85 (C),  $m/z$  229 (55%, M), 184 (16, M-EtO), 168 (9, M-EtO<sub>2</sub>), 156 (36, M-CO<sub>2</sub>Et), 140 (50, M-CO<sub>2</sub>Et-O), 59 (67, CO<sub>2</sub>Me) and 45 (36, EtO), [Found: M, 229.0952. C<sub>10</sub>H<sub>15</sub>NO<sub>5</sub> requires M, 229.0950].

**(±)-1-tert-Butyl-3-ethyl 4-oxopiperidine-1,3-dicarboxylate (135)**



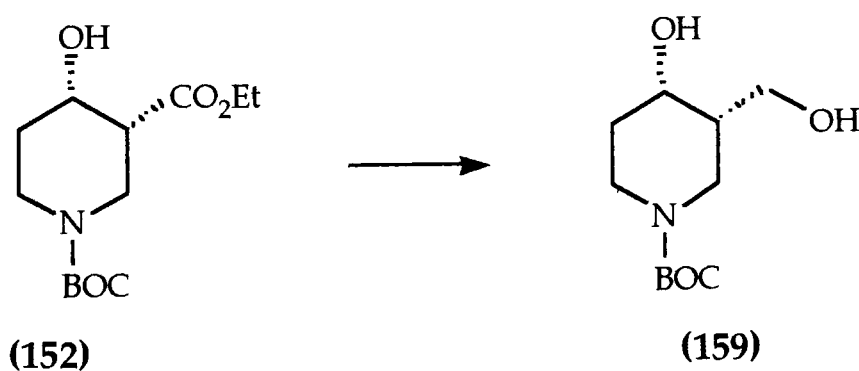
Di-*tert*-butyl dicarbonate (5.8 g, 26.5 mmol) was added dropwise to a solution of ethyl 4-oxopiperidine-3-carboxylate hydrochloride (**134**) (5 g, 24.1 mmol; Fluka) and triethylamine (2.68 g, 26.5 mmol) in dichloromethane. (100 ml) The reaction mixture was stirred overnight at room temperature, diluted with dichloromethane (200 ml), washed with 2M aqueous hydrochloric acid (2 x 30 ml), and saturated aqueous sodium chloride (30 ml), dried and concentrated *in vacuo* to give the **title compound (135)** (5.1 g, 78%) as a colourless oil,  $\nu_{\max}$  1665, 1698 and 3369  $\text{cm}^{-1}$ ,  $\delta_{\text{H}}$  (400, 333K) 1.31 (3H, t, J 7,  $\text{CH}_3\text{CH}_2\text{O}$ ), 1.48 (9H, s,  $(\text{CH}_3)_3\text{C}$ ), 2.37 (2H, br t, J 5.8,  $\text{NCH}_2\text{CH}_2$ ), 3.57 (2H, t, J 5.9,  $\text{NCH}_2\text{CH}_2$ ), 4.06 (2H, s,  $\text{NCH}_2\text{C}(\text{CO}_2\text{Et})$ ), 4.24 (2H, q, J 7,  $\text{CH}_3\text{CH}_2\text{O}_2\text{C}$ ) and 12.07 (1H, s, OH),  $\delta_{\text{C}}$  (68.5) 13.66 ( $\text{CH}_3$ ), 27.93 ( $\text{CH}_3$ ), 28.45 ( $\text{CH}_2$ ), 38.89 ( $\text{CH}_2$ ), 39.84 ( $\text{CH}_2$ ), 60.07 ( $\text{CH}_2$ ), 84.58 (C), 95.53 (C), 154.11 (C), 169.49 (C) and 169.85 (C),  $m/z$  214 (40%,  $\text{M}-(\text{CH}_3)_3\text{C}$ ), 198 (9,  $\text{M}-\text{CO}_2\text{Et}$ ), 170 (10,  $\text{M}-\text{BOC}$ ), 142 (12,  $\text{M}-(\text{CH}_3)_3\text{C}-\text{CO}_2\text{Et}+\text{H}$ ), 98 (28,  $\text{M}-\text{BOC}-\text{CO}_2\text{Et}+\text{H}$ ) and 57 (100,  $(\text{CH}_3)_3\text{C}$ ), [Found:  $\text{M}-(\text{CH}_3)_3\text{C}$ , 214.0743.  $\text{C}_9\text{H}_{12}\text{NO}_5$  requires  $\text{M}-(\text{CH}_3)_3\text{C}$ , 214.0715].

**(3R, 4S)-1-tert-Butyl-3-ethyl 4-hydroxypiperidine-1,3-dicarboxylate (152)**



The piperidine  $\beta$ -keto-ester (135) (5 g, 18.5 mmol) was added to a fermenting solution of dried baker's yeast (30 g) and sucrose (50 g) in tap water (500 ml). Fermentation continued for 16h and the yeast residues were removed by filtration. The filtrate was filtered 5 x through kieselguhr and extracted with dichloromethane (5 x 200 ml). The combined organic extracts were washed with saturated aqueous sodium chloride (100 ml), dried and concentrated *in vacuo* to give the title compound (152) (3.73 g, 74%) as an off white solid, m.p. 58-60°C,  $[\alpha]_D^{23} +25.6$  (c=3.4 in CH<sub>2</sub>Cl<sub>2</sub>),  $\nu_{\max}$  1668, 1732 and 3414cm<sup>-1</sup>,  $\delta_H$  (400, 333K) 1.21 (3H, t, J 7, CH<sub>3</sub>CH<sub>2</sub>O<sub>2</sub>C), 1.40 (9H, s, (CH<sub>3</sub>)<sub>3</sub>CO), 1.55-1.62 (1H, m, NCH<sub>2</sub>CH<sub>A</sub>H<sub>B</sub>), 1.72-1.78 (1H, m, NCH<sub>2</sub>H<sub>A</sub>H<sub>B</sub>), 2.51 (2H, ddd, J 10.4, 4.4 and 2.6, CHCO<sub>2</sub>Et), 3.19 (1H, ddd, J 14, 11 and 3, 6-H<sub>ax</sub>), 3.34 (1H, dd, J 14 and 11, 2-H<sub>ax</sub>), 3.59 (1H, m, 6-Heq), 3.86 (1H, dd, J 14 and 4.1, 2-Heq), 4.12 (2H, q, J 7, CH<sub>3</sub>CH<sub>2</sub>CO<sub>2</sub>C) and 4.20-4.23 (1H, m, CHOH),  $\delta_C$  (68.5) 13.9 (CH<sub>3</sub>), 28.1 (CH<sub>3</sub>), 31.3 (CH<sub>2</sub>), 38.1 (CH<sub>2</sub>), 40.3 (CH<sub>2</sub>), 45.6 (CH), 60.7 (CH<sub>2</sub>), 64.8 (CH), 79.5 (C), 154.5 (C) and 172.5 (C),  $m/z$  273 (1%, M), 216 (13, M-(CH<sub>3</sub>)<sub>3</sub>C), 200 (7, M-CO<sub>2</sub>Et), 172 (11, M-BOC), 143 (4, M-(CH<sub>3</sub>)<sub>3</sub>C-CH<sub>3</sub>CH<sub>2</sub>), 100 (14, M-BOC-CO<sub>2</sub>Et+H), 82 (43, M-BOC-CO<sub>2</sub>Et-OH), 73 (5, EtO<sub>2</sub>C) and 57 (100, (CH<sub>3</sub>)<sub>3</sub>C), [Found: M, 273.1600. C<sub>13</sub>H<sub>23</sub>NO<sub>5</sub> requires M, 273.1576].

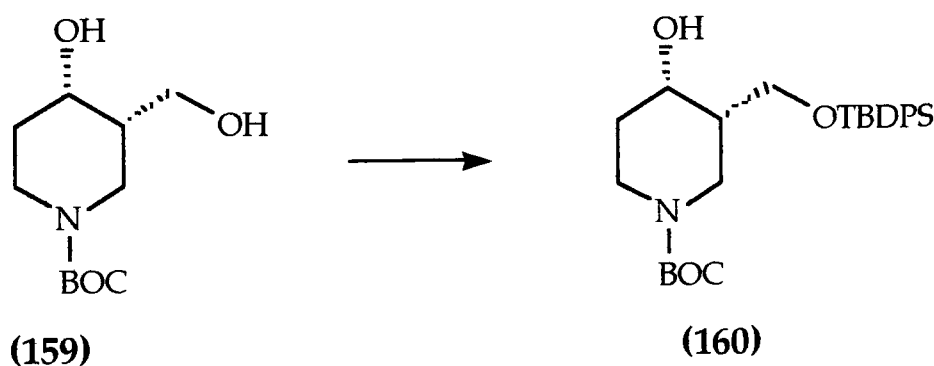
**(3S, 4S)-1-tert-Butyl 4-hydroxy3-hydroxymethylpiperidine-1-carboxylate (159)**



The hydroxy ester (152) (2 g, 7.3 mmol) was added to a stirred ice-cooled suspension of lithium aluminium hydride (1.1 g, 29.3 mmol) in tetrahydrofuran

(40 ml). After 3h 2M aqueous sodium hydroxide solution (1.1 ml) was introduced and the reaction mixture filtered. The solid residue was washed with dichloromethane (200 ml) and the combined organic filtrates washed with water (20 ml), and saturated aqueous sodium chloride (20 ml), dried and concentrated *in vacuo* to give the title compound (159) (1.22 g, 72%) as a thick colourless oil,  $[\alpha]_D^{23} +14.0$  ( $c=1.8$  in  $\text{CH}_2\text{Cl}_2$ ),  $\nu_{\text{max}}$  1670 and  $3420\text{cm}^{-1}$ ,  $\delta_{\text{H}}$  (400) 1.45 (9H, s,  $(\text{CH}_3)_3\text{CO}$ ), 1.6-1.91 (3H, m,  $\text{CHCH}_2\text{OH}$  and  $\text{NCH}_2\text{CH}_2$ ), 2.40-2.52 (2H, m, 2-H<sub>ax</sub> and 6-H<sub>ax</sub>) and 3.7-4.18 (5H, m, 2-Heq, 6-Heq,  $\text{CH}_2\text{OH}$  and  $\text{CHOH}$ ),  $\delta_{\text{C}}$  (68.5) 25.57 ( $\text{CH}_2$ ), 28.41 ( $\text{CH}_3$ ), 39.25 ( $\text{CH}_2$ ), 41.46 ( $\text{CH}_2$ ), 41.74 ( $\text{CH}$ ), 67.40 ( $\text{CH}$ ), 67.94 ( $\text{CH}_2$ ), 79.80 (C) and 155.31 (C),  $m/z$  158 (16%, M- $(\text{CH}_3)_3\text{C}$ ), 113 (6, M-BOC-OH) and 57 (100,  $(\text{CH}_3)_3\text{C}$ ), [Found: M- $(\text{CH}_3)_3\text{C}$ , 158.0770.  $\text{C}_9\text{H}_{12}\text{NO}_3$  requires M- $(\text{CH}_3)_3\text{C}$ , 158.0817].

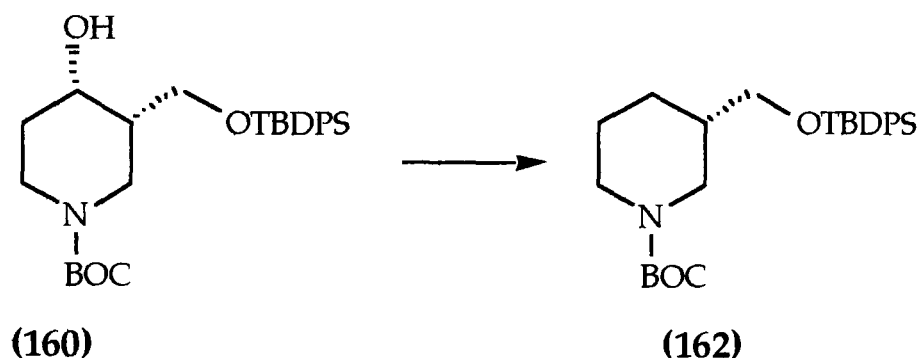
**(3S, 4S)-1-*tert*-Butyl 4-hydroxy-3-*O*-*tert*-butyldiphenylsilyloxymethyl-piperidine-1-carboxylate (160)**



*tert*-Butylchlorodiphenylsilane (1.31 g, 4.76 mmol) was added to a stirred solution of the piperidine diol (159) (1 g, 4.3 mmol), triethylamine (0.48 g, 4.8 mmol) and 4-dimethylaminopyridine (26 mg, 0.33 mmol) in dichloromethane (100 ml) and the reaction mixture stirred at room temperature for 16h. The reaction mixture was diluted with dichloromethane (200 ml), washed with water (50 ml), and saturated aqueous sodium chloride (50 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane :

ethyl acetate (9:1) gave the **title compound (160)** (1.60 g, 79%) as a colourless oil,  $R_F$  0.7,  $[\alpha]_D^{21} +10.6$  ( $c=2.0$  in  $CH_2Cl_2$ ),  $\nu_{max}$  1665 and  $3422\text{cm}^{-1}$ ,  $\delta_H$  (270) 1.06 (9H, s,  $(CH_3)_3CSi$ ), 1.43 (9H, s,  $(CH_3)_3CO$ ), 1.49-1.78 (3H, m,  $NCH_2CH_2$  and  $CHCH_2OTBDPS$ ), 3.20-3.35 (2H, m, 2-**Hax** and 6-**Hax**), 3.75-3.92 (4H, m, 2-**Heq**, 6-**Heq** and  $CH_2OTBDPS$ ), 4.21 (1H, br s,  $CHOH$ ), 7.26-7.67 (10H, m,  $2 \times C_6H_5$ ),  $\delta_C$  (68.5) 19.08 (C), 26.79 ( $CH_3$ ), 28.43 ( $CH_3$ ), 32.29 ( $CH_2$ ), 38.71 ( $CH_2$ ), 41.37 ( $CH_2$ ), 41.51 ( $CH_2$ ), 65.61 ( $CH_2$ ), 67.85 (CH), 79.41 (C), 127.89 (CH), 129.97 (CH), 132.54 (C), 135.60 (CH) and 154.98 (C),  $m/z$  470 (45%,  $M+H$ ), 396 (3,  $M-(CH_3)_3C$ ) and 312 (12,  $M-BOC-(CH_3)_3C$ ), [Found:  $M+H$ , 470.2801.  $C_{27}H_{39}NO_4Si$  requires  $M+H$ , 470.2727].

**(3S)-1-tert-Butyl 3-O-tert-butyldiphenylsilyloxymethylpiperidine-1-carboxylate (162)**

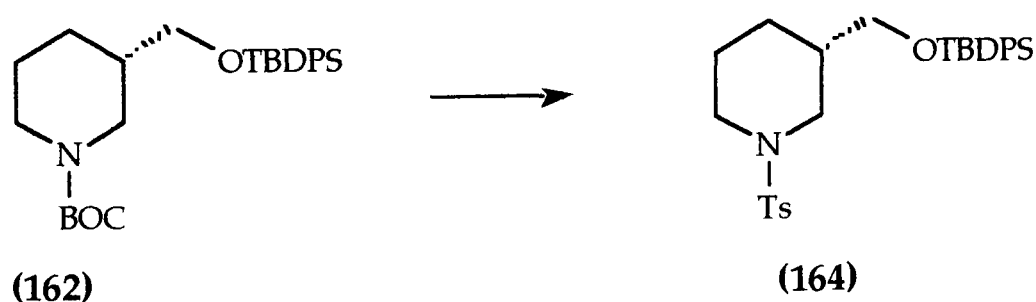


Pentafluorophenyl chlorothionoformate (1.24 g, 4.7 mmol) was added to a stirred solution of the piperidine **(160)** (0.37 g, 0.79 mmol), pyridine (0.13 g, 1.6 mmol) and *N*-hydroxysuccinimide (18 mg, 0.16 mmol) in benzene (20 ml). The reaction mixture was refluxed for 5h, cooled and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) gave the **thionocarbonate (161)** (500mg, 91%) as a colourless oil.  $R_F$  0.85,  $\delta_H$  (270) 0.83 (9H, s,  $(CH_3)_3CSi$ ), 1.49-2.38 (3H, m,  $CHCH_2OTBDPS$  and  $NCH_2CH_2$ ), 1.41 (9H, s,  $(CH_3)_3CO$ ), 2.55-3.23 (2H, m, 2-**Hax** and 6-**Hax**), 3.40-3.62 (2H, m,  $CH_2OTBDPS$ ),

3.72-4.04 (2H, m, 2-**Heq** and 6-**Heq**), 5.64 (1H, br s, CHO(CS)OC<sub>6</sub>F<sub>5</sub>) and 7.24-7.65 (10H, m, 2xC<sub>6</sub>H<sub>5</sub>), which was used directly.

The thionocarbonate (500 mg, 0.72 mmol) was refluxed with tri-*n*-butyltin hydride (0.21 g, 0.72 mmol) and azo-*bis*-iso-butyronitrile (6 mg, 0.04 mmol) in benzene (20 ml) for 30min. The reaction mixture was cooled and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) gave the **title compound (162)** (280 mg, 58%) as a colourless oil, *R*<sub>F</sub> 0.70, [α]<sub>D</sub><sup>25</sup> +12.6 (c=1.15 in CHCl<sub>3</sub>), *ν*<sub>max</sub> 1665 cm<sup>-1</sup>, δ<sub>H</sub> (400) 1.0-1.3 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.11 (9H, s, (CH<sub>3</sub>)<sub>3</sub>Si), 1.45-1.60 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>), 1.47 (9H, s, (CH<sub>3</sub>)<sub>3</sub>CO), 1.75 (1H, m, CHCH<sub>2</sub>OTBDPS), 2.5-2.62 (1H, m, 6-**Hax**), 2.62-2.75 (1H, m, 2-**Hax**), 3.49-3.56 (2H, m, CH<sub>2</sub>OTBDPS), 4.0 (1H, m, 6-**Heq**), 4.2 (1H, m, 2-**Heq**) and 7.3-7.75 (10H, m, 2xC<sub>6</sub>H<sub>5</sub>), δ<sub>C</sub> (100, 333K) 19.34 (C), 24.72 (CH<sub>2</sub>), 26.93 (CH<sub>3</sub>), 27.23 (CH<sub>2</sub>), 28.55 (CH<sub>3</sub>), 38.74 (CH), 44.40 (CH<sub>2</sub>), 47.53 (CH<sub>2</sub>), 66.41 (CH<sub>2</sub>), 79.80 (C), 129.69 (CH), 133.71 (CH), 133.72 (C), 135.41 (CH) and 155.07 (C), *m/z* 454 (10%, M+H), 396 (7, M-<sup>t</sup>Bu), 352 (35, M-BOC), 199 (90, M-BOC-(2xPh)+H) and 198 (46, M-BOC-(2xPh)), [Found: M+H, 454.2778. C<sub>27</sub>H<sub>40</sub>NO<sub>3</sub>Si requires M+H, 454.2777].

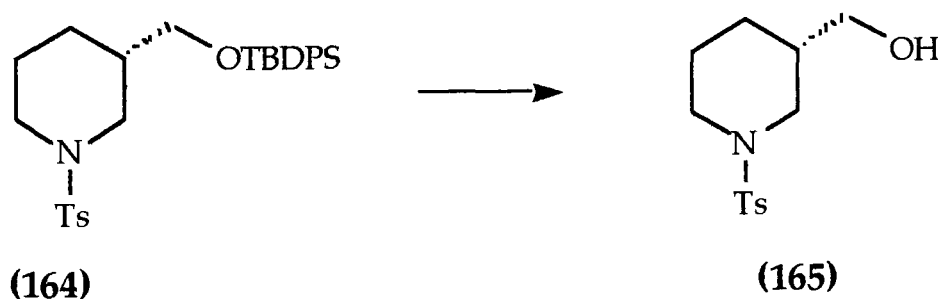
**(3*S*)-1-(*p*-Toluenesulphonyl) 3-*O*-*tert*-butyldiphenylsilyloxymethylpiperidine (164)**



Trifluoroacetic acid (1.51 g, 13.25 mmol) was added to a stirred solution of the piperidine **(162)** (200 mg, 0.44 mmol) in dichloromethane (20 ml). After 1h the reaction mixture was diluted with dichloromethane (100 ml), washed with saturated sodium hydrogen carbonate (2 x 20 ml), dried and concentrated *in vacuo*.

The residue was dissolved in dichloromethane (5 ml) and added to a stirred solution of *p*-toluenesulphonyl chloride (168 mg, 0.88 mmol), triethylamine (178 mg, 1.77 mmol) and 4-dimethylaminopyridine (3 mg, 0.02 mmol) in dichloromethane (5 ml). After 16h the reaction mixture was diluted with dichloromethane (50 ml), washed with water (10 ml), saturated aqueous sodium chloride (10 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) gave the **title compound (164)** (166 mg, 74%) as a colourless oil,  $R_F$  0.60,  $[\alpha]_D^{22}$  -22.3 ( $c=1.1$  in  $CHCl_3$ ),  $\nu_{max}$  1114, 1361 and 1673  $cm^{-1}$ ,  $\delta_H$  (270) 1.03 (9H, s,  $(CH_3)_3CSi$ ), 1.42-1.97 (4H, m,  $NCH_2CH_2CH_2$  and  $NCH_2CH_2$ ), 2.12 (1H, app. t,  $J$  10.5, 6-**Hax**), 2.26 (1H, dt,  $J$  11.7 and 3.5, 6-**Hax**), 2.43 s (3H, s,  $CH_3C_6H_4$ ), 3.41-3.78 (5H, m, 2-**Heq**, 6-**Heq**,  $CHCH_2OTBDPS$  and  $CHCH_2OTBDPS$ ) and 7.28-7.68 (14H, m,  $2 \times C_6H_5$  and  $SO_2C_6H_4CH_3$ ),  $\delta_C$  (68.5) 14.02 ( $CH_3$ ), 19.23 (C), 24.12 ( $CH_2$ ), 25.59 ( $CH_2$ ), 26.34 ( $CH_3$ ), 38.15 (CH), 46.70 ( $CH_2$ ), 60.39 ( $CH_2$ ), 66.02 ( $CH_2$ ), 127.56 (CH), 129.40 (CH), 133.19 (C), 134.30 (CH), 134.98 (CH), 135.63 (CH), 143.29 (C) and 171,21 (C),  $m/z$  450 (1%,  $M-tBu$ ), 199 (100,  $M-Ts-(2 \times Ph)+H$ ), 78 (7,  $C_6H_6$ ) and 77 (12,  $C_6H_5$ ), [Found:  $M-tBu$ , 450.1576.  $C_{25}H_{28}NO_3SSi$  requires  $M-tBu$ , 450.1550].

**(3S)-1-(*p*-Toluenesulphonyl) 3-hydroxymethylpiperidine (165)**

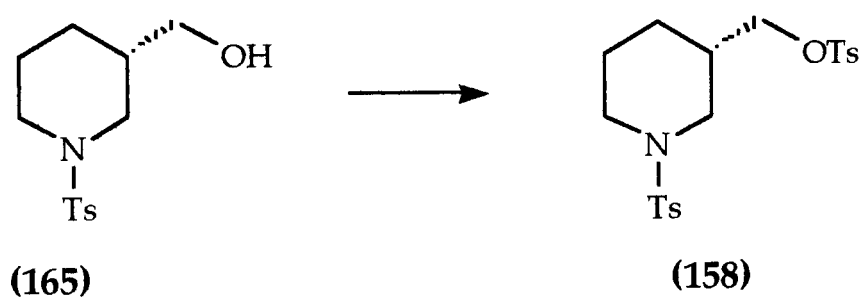


Tetrabutylammonium fluoride (0.397 ml, 1M in tetrahydrofuran, 0.4 mmol) was added to a stirred solution of the piperidine **(164)** (100 mg, 0.2 mmol) in tetrahydrofuran (0.5 ml). The reaction mixture was stirred for 16h at room temperature, diluted with dichloromethane (100 ml), washed with water (10 ml),



and saturated aqueous sodium chloride (10 ml), dried and concentrated *in vacuo* to give the **title compound (165)** (53 mg, 78%) as a colourless oil,  $[\alpha]_{\text{D}}^{21} -16.52$  ( $c=3.0$  in  $\text{CHCl}_3$ ),  $\nu_{\text{max}}$  1149, 1379 and  $3304\text{cm}^{-1}$ ,  $\delta_{\text{H}}$  (270) 0.99-1.10 (1H, m,  $\text{NCH}_2\text{CH}_2\text{CH}_\text{A}\text{H}_\text{B}$ ), 1.50-1.97 (3H, m,  $\text{NCH}_2\text{CH}_2\text{CH}_\text{A}\text{H}_\text{B}$  and  $\text{NCH}_2\text{CH}_2$ ), 2.24 (1H, br t, 6-H<sub>ax</sub>), 2.44 (3H, s,  $\text{CH}_3\text{C}_6\text{H}_4$ ), 2.29-2.53 (1H, m, 2-H<sub>ax</sub>), 3.18-3.71 (5H, m, 2-Heq, 6-Heq,  $\text{CHCH}_2\text{OH}$  and  $\text{CH}_2\text{OH}$ ), 7.30 (2H, d,  $J$  8.3,  $\text{CH}(\text{Tosyl})$ ) and 7.62 (2H, m,  $\text{CH}(\text{Tosyl})$ ),  $\delta_{\text{C}}$  (68.5) 21.42 ( $\text{CH}_3$ ), 23.85 ( $\text{CH}_2$ ), 26.06 ( $\text{CH}_2$ ), 38.01 ( $\text{CH}$ ), 46.52 ( $\text{CH}_2$ ), 48.97 ( $\text{CH}_2$ ), 64.67 ( $\text{CH}_2$ ), 127.57 ( $\text{CH}$ ), 129.54 ( $\text{CH}$ ), 132.96 (C) and 143.38 (C),  $m/z$  269 (1%, M), 238 (1, M- $\text{CH}_2\text{OH}$ ), 156 (2,  $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{H}$ ), 115 (8, M-Ts+H), 114 (100, M-Ts), 91 (69,  $\text{CH}_3\text{C}_6\text{H}_4$ ), 84 (7, M-Ts- $\text{CH}_2\text{OH}$ +H) and 83 (6, M-Ts- $\text{CH}_2\text{OH}$ ), [Found: M, 269.0972,  $\text{C}_{13}\text{H}_{19}\text{NO}_3\text{S}$  requires M, 269.1086].

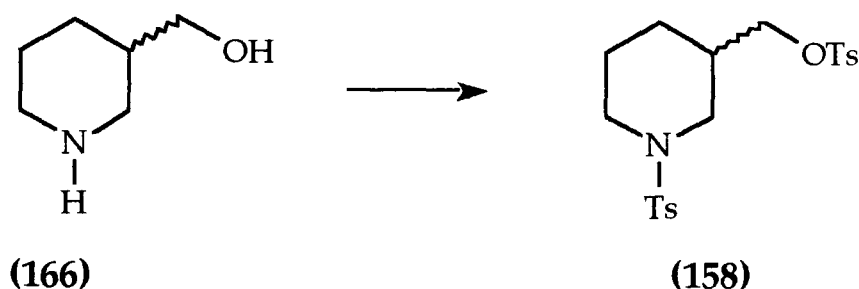
**(3S)-N,O-di-(p-Toluenesulphonyl)-3-oxymethylpiperidine (158)**



*p*-Toluenesulphonyl chloride (39 mg, 0.20 mmol) was added to a solution of the piperidine **(165)** (50 mg, 0.19 mmol), triethylamine (21 mg, 0.20 mmol), and 4-dimethylaminopyridine (0.01 mmol) in dichloromethane (10 ml). The reaction mixture was stirred for 16h at room temperature, diluted with dichloromethane (100 ml), washed with water (5 ml), and saturated aqueous sodium chloride (5 ml), dried and concentrated *in vacuo*. The residue was recrystallised from hot methanol to give the **title compound (158)** (46 mg, 63%) as a white solid, mp  $88-89^\circ$ ,  $[\alpha]_{\text{D}}^{25} -50.2$  ( $c=1.1$  in  $\text{CHCl}_3$ ), [Lit m.p  $87-89^\circ$ ,  $[\alpha]_{\text{D}}^{25} +54$  for the *R*-enantiomer],<sup>115</sup>  $\nu_{\text{max}}$  1175, 1342 and  $1359\text{cm}^{-1}$ ,  $\delta_{\text{H}}$  (400) 1.03-1.11 (1H, m,  $\text{NCH}_2\text{CH}_2\text{CH}_\text{A}\text{H}_\text{B}$ ), 1.49-1.65 (3H, m,  $\text{NCH}_2\text{CH}_2\text{CH}_\text{A}\text{H}_\text{B}$  and  $\text{NCH}_2\text{CH}_2$ ), 1.93-1.97 (1H, m,  $\text{CHCH}_2\text{OTs}$ ), 2.27

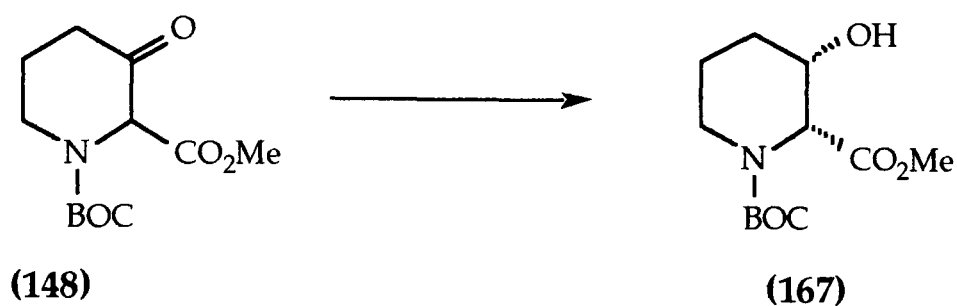
(1H, t, J 9.5, 6-**Hax**), 2.38 (3H, s, CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>N), 2.41 (3H, s, CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>O), 2.48-2.55 (1H, m, 2-**Hax**), 3.39-3.47 (2H, m, 2-**Heq** and 6-**Heq**), 3.83 (1H, dd, J 10 and 6.6, CH<sub>A</sub>H<sub>B</sub>OTs), 3.91 (1H, dd, J 10 and 6, CH<sub>A</sub>H<sub>B</sub>OTs), 7.25 (2H, d, J 8.3, CH(N-Tosyl)), 7.30 (2H, d, J 8.3, CH(O-Tosyl)), 7.55 (2H, d, J 8.3, CH(N-Tosyl)) and 7.72 (2H, d, J 8.3, CH(O-Tosyl)),  $\delta_C$  (100) 21.51 (CH<sub>3</sub>), 21.65 (CH<sub>3</sub>), 23.49 (CH<sub>2</sub>), 25.68 (CH<sub>2</sub>), 35.10 (CH), 46.64 (CH<sub>2</sub>), 48.29 (CH<sub>2</sub>), 71.39 (CH<sub>2</sub>), 127.62 (CH), 127.89 (CH), 129.04 (CH), 129.67 (CH), 132.56 (CH), 132.56 (C), 132.87 (C), 143.63 (C) and 145.01 (C),  $m/z$  269 (4%, M-Ts+H), 268 (27, M-Ts), 252 (4, M-OTs), 156 (2, TsOH), 113 (3, M-2xTs), 97 (7, M-Ts-OTs) and 91 (50, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>), [Found: M-Ts+H, 269.1059. C<sub>13</sub>H<sub>18</sub>NO<sub>3</sub>S requires M-Ts+H, 269.1086].

**(±)O,N-di-(*p*-Toluenesulphonyl)-3-oxymethylpiperidine (158)**



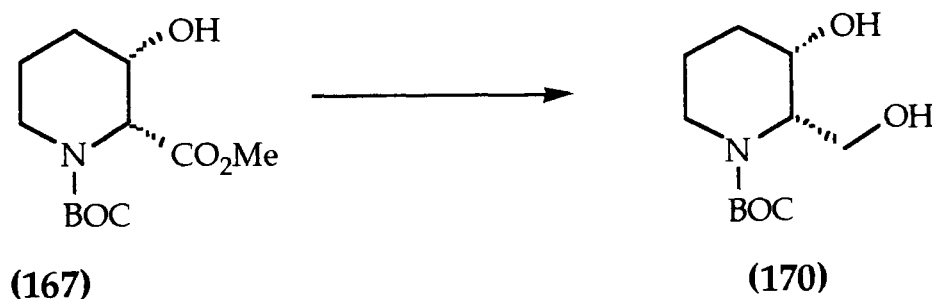
*p*-Toluenesulphonyl chloride (780 mg, 4.0 mmol) was added to a solution of 3-piperidinemethanol (**166**) (440 mg, 3.8 mmol), triethylamine (420 mg, 4.0 mmol), and 4-dimethylaminopyridine (0.2 mmol) in dichloromethane (100 ml). The reaction mixture was stirred for 16h at room temperature, diluted with dichloromethane (100 ml), washed with water (25 ml), and saturated aqueous sodium chloride (25 ml), dried and concentrated *in vacuo*. The residue was recrystallised from hot methanol to give the **title compound (158)** (730 mg, 50%) as a white solid, mp 87-89° [Lit 87-89° for the *R*-enantiomer];<sup>115</sup> all spectroscopic data was consistent with the chiral material.

**(2R, 3S)-1-(*tert*-Butyl)-2-methyl 3-hydroxypiperidine-1,2-dicarboxylate (167)**



The piperidine  $\beta$ -keto-ester (5g, 18.5mmol) was reacted with a solution of dried baker's yeast by the method outlined for (3R, 4S)-1-*tert*-butyl-3-ethyl 4-hydroxypiperidine-1,3-dicarboxylate (152) to give the title compound (167) (4.00 g, 80%) as a pale oil,  $[\alpha]_D^{22} +47.9$  ( $c=3.8$  in  $\text{CH}_2\text{Cl}_2$ ),  $\nu_{\text{max}}$  1695, 1739 and  $3437\text{ cm}^{-1}$ ,  $\delta_{\text{H}}$  (400) 1.41-1.59 (1H, m,  $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOH}$ ), 1.43 (9H, s,  $(\text{CH}_3)_3\text{CO}$ ), 1.67-1.78 (1H, m,  $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOH}$ ), 1.91-2.00 (2H, m,  $\text{NCH}_2\text{CH}_2$ ), 2.79 (1H, br s, 6-**Hax**), 3.70-3.82 (1H, m,  $\text{CHOH}$ ), 3.74 (3H, s,  $\text{CH}_3\text{CO}_2\text{C}$ ), 3.92 (1H, br d,  $J$  13.3, 6-**Heq**) and 4.54 (1H, br s, 2-**Heq**),  $\delta_{\text{C}}$  (100) 23.40 and 24.00 ( $\text{CH}_2$ ), 28.28 ( $\text{CH}_3$ ), 30.08 ( $\text{CH}_2$ ), 40.00 and 41.40 ( $\text{CH}_2$ ), 52.26 ( $\text{CH}_3$ ), 57.30 and 58.90 ( $\text{CH}$ ), 68.91 ( $\text{CH}$ ), 80.62 (C), 154.90 (C) and 172.41 (C),  $m/z$  200 (6%,  $\text{M}-\text{CO}_2\text{Me}$ ), 158 (12,  $\text{M}-\text{BOC}$ ), 127 (2,  $\text{M}-\text{BOC}-\text{OMe}$ ), 100 (91,  $\text{M}-\text{BOC}-\text{CO}_2\text{Me}+\text{H}$ ), 59 (2,  $\text{CO}_2\text{Me}$ ) and 57 (100,  $(\text{CH}_3)_3\text{C}$ ), [Found:  $\text{M}-\text{CO}_2\text{Me}$ , 200.1289.  $\text{C}_{10}\text{H}_{18}\text{NO}_3$  requires  $\text{M}-\text{CO}_2\text{Me}$ , 200.1287].

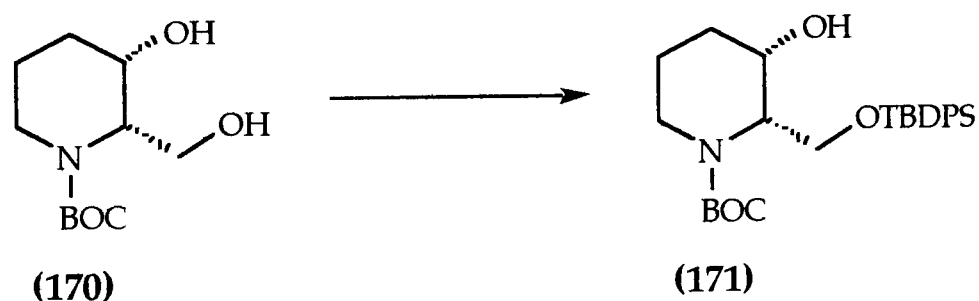
**(2S, 3S)-1-*tert*-Butyl 3-hydroxy-2-hydroxymethylpiperidine-1-carboxylate (170)**



The hydroxy ester (167) (2 g, 7.7 mmol) was added to a stirred ice-cooled suspension of lithium aluminium hydride (1.17 g, 30.9 mmol) in tetrahydrofuran (50 ml). After 3h 2M aqueous sodium hydroxide solution (1.2 ml) was introduced

and the reaction mixture filtered. The solid residue was washed with dichloromethane (200 ml) and the combined organic filtrates washed with water (20 ml), and saturated aqueous sodium chloride (20 ml), dried and concentrated *in vacuo* to give the title compound (170) (1.28 g, 72%) as a colourless oil,  $[\alpha]_{\text{D}}^{22} +19.5$  ( $c=1.6$  in  $\text{CH}_2\text{Cl}_2$ ),  $\nu_{\text{max}}$  1678 and  $3425\text{cm}^{-1}$ ,  $\delta_{\text{H}}$  (400, 333K) 1.39 (9H, s,  $(\text{CH}_3)_3\text{CO}$ ), 1.42-1.78 (4H, m), 2.81 (1H, app br t,  $J$  13.5, 6-**Hax**), 3.68-3.72 (1H, m, 6-**Heq**), 3.7 (1H, dd,  $J$  11.3 and 6.5,  $\text{CH}_\text{A}\text{H}_\text{BOH}$ ), 3.87 (1H, dt,  $J$  10.3 and 4.9,  $\text{CHOH}$ ), 4.03 (1H, dd,  $J$  11.3 and 6.4,  $\text{CH}_\text{A}\text{H}_\text{BOH}$ ) and 4.25 (1H, dt,  $J$  5.7 and 6.1, 2-**Heq**),  $\delta_{\text{C}}$  (68.5) 23.74 ( $\text{CH}_2$ ), 28.36 ( $\text{CH}_2$ ), 28.41 ( $\text{CH}_3$ ), 39.70 ( $\text{CH}_2$ ), 55.97 ( $\text{CH}$ ), 59.37 ( $\text{CH}_2$ ), 69.47 ( $\text{CH}$ ), 80.34 (C) and 155.68 (C),  $m/z$  158 (12%,  $\text{M}-(\text{CH}_3)_3\text{CO}$ ) and 57 (95,  $(\text{CH}_3)_3\text{C}$ ), [Found:  $\text{M}-(\text{CH}_3)_3\text{CO}$ , 158.0808.  $\text{C}_7\text{H}_{12}\text{NO}_3$  requires  $\text{M}-(\text{CH}_3)_3\text{CO}$ , 158.0817].

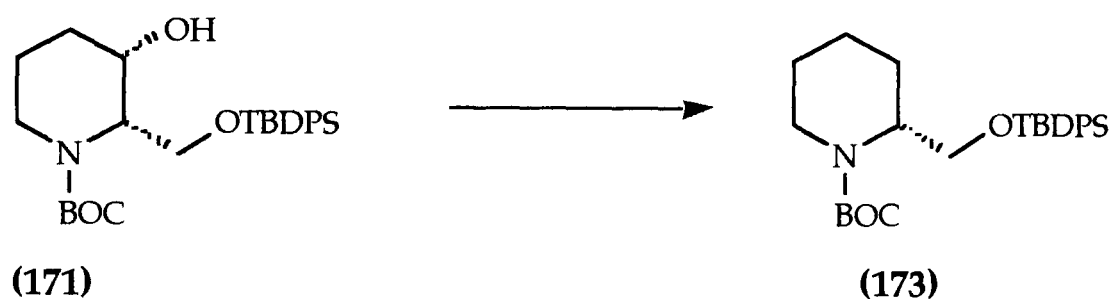
**(2S, 3S)-1-*tert*-Butyl 3-hydroxy-2-*O-tert*-butyldiphenylsilyloxymethyl-piperidine-1-carboxylate (171)**



*tert*-Butylchlorodiphenylsilane (1.31 g, 4.76 mmol) was added to a stirred solution of the piperidine diol (170) (1 g, 4.3 mmol), triethylamine (0.48 g, 4.8 mmol) and 4-dimethylaminopyridine (26 mg, 0.33 mmol) in dichloromethane (100 ml) and the reaction mixture stirred at room temperature for 16h. The reaction mixture was diluted with dichloromethane (200 ml), washed with water (50 ml), and saturated aqueous sodium chloride (50 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) gave the title compound (171) (1.59 g, 78%) as a colourless oil,

$R_F$  0.65,  $[\alpha]_D^{22} +42.8$  ( $c=3.5$  in  $CH_2Cl_2$ ),  $\nu_{max}$  1668 and  $3424cm^{-1}$ ,  $\delta_H$  (400, 333K) 1.09 (9H, s,  $(CH_3)_3CSi$ ), 1.44 (9H, s,  $(CH_3)_3CO$ ), 1.47-1.65 (3H, m), 1.88 (1H, br d, J 9.2,  $NCH_2CH_AH_B$ ), 2.64 (1H, br t, J 13.3, 6-**Hax**), 2.89 (1H, br s, OH), 3.84-3.90 (3H, m, 6-**Heq**, CHOH,  $CH_AH_BOTBDPS$ ), 4.10 (1H, dd, J 10.4 and 7.2,  $CH_AH_BOTBDPS$ ), 4.58 (1H, dt, J 6.3 and 6.2, 2-**Heq**) and 7.38-7.72 (10H, 2m,  $2 \times C_6H_5$ ),  $\delta_C$  (100) 19.11 (C), 23.99 ( $CH_2$ ), 26.83 ( $CH_3$ ), 28.42 ( $CH_3$ ), 28.94 ( $CH_2$ ), 38.88 ( $CH_2$ ), 54.91 (CH), 60.72 ( $CH_2$ ), 69.92 (CH), 79.11 (C), 127.88 (CH), 129.94 (CH), 132.81 (C), 135.65 (CH) and 154.85 (C),  $m/z$  396 (3%, M- $(CH_3)_3CO$ ), 143 (4, M-OTBDPS-BOC), 100 (100, M- $CH_2OTBDPS$ -BOC+H) and 57 (45,  $(CH_3)_3C$ ), [Found: M- $(CH_3)_3CO$ , 396.1897.  $C_{23}H_{30}NO_3Si$  requires M- $(CH_3)_3CO$ , 396.1995].

**(2R)-1-tert-Butyl 2-O-tert-butyldiphenylsilyloxymethylpiperidine-1-carboxylate (173)**

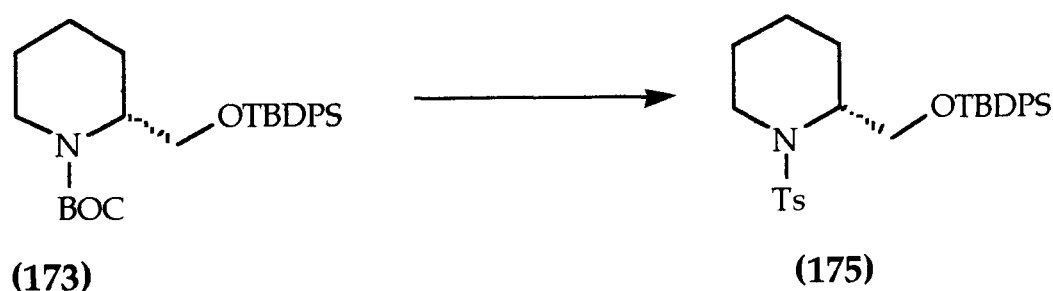


1,1'-Thiocarbonyl diimidazole (380 mg, 2.1 mmol) was added to a stirred solution of the piperidine (171) (0.5 g, 1.1 mmol) in dichloromethane (20 ml). The reaction mixture was refluxed for 24h, cooled and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) gave the thionourethane (172) (570mg, 95%) as a colourless oil,  $R_F$  0.3,  $\delta_H$  (270) 1.02 (9H, s,  $(CH_3)_3CSi$ ), 1.48 (9H, s,  $(CH_3)_3CO$ ), 1.62-2.05 (4H, m), 3.00 (1H, br t, J 13.5, 6-**Hax**), 3.80-4.05 (3H, m,  $CH_2OTBDPS$  and 6-**Heq**), 4.75-4.82 (1H, m, 2-**Heq**), 5.53 (1H, ddd, J 12, 6 and 6,  $CHO(CS)Im$ ), 7.01 (1H, br s,  $NCH=CHN$ ), 7.26-7.66 (11H, m,  $2 \times C_6H_5$  and  $NCH=CHN$ ) and 8.23 (1H, br s,  $NCH=N$ ),  $\delta_C$  (68.5) 18.99 (C), 23.67 ( $CH_2$ ), 25.14 ( $CH_2$ ), 26.72 ( $CH_3$ ), 28.41 ( $CH_3$ ), 39.00 ( $CH_2$ ), 60.10 (CH), 60.14 ( $CH_2$ ),

79.59 (CH), 80.27 (C), 117.90 (C), 127.78 (CH), 127.89 (CH), 129.88 (CH), 129.94 (CH), 132.90 (C), 135.52 (CH), 135.60 (CH) and 154.70 (C).

The thiourethane (172) (570 mg, 1 mmol) was refluxed with tri-*n*-butyltin hydride (0.29 g, 1 mmol) and azo-*bis*-iso-butyronitrile (6 mg, 0.04 mmol) in toluene (10 ml) for 2h. The reaction mixture was cooled and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) gave the title compound (173) (243 mg, 53%) as a colourless oil,  $R_F$  0.60,  $[\alpha]_D^{21} +21.7$  ( $c=1.4$  in  $CH_2Cl_2$ ),  $\nu_{max}$  1693  $cm^{-1}$ ,  $\delta_H$  (270) 0.91 (9H, s,  $(CH_3)_3CSi$ ), 1.22-2.01 (6H, m), 1.29 (9H, s,  $(CH_3)_3CO$ ), 2.61 (1H, br t, J 13.5, 6-**Heq**), 3.68 (2H, d, J 10.5,  $CH_2OTBDPS$ ), 3.95 (1H, br d, J 13.5, 6-**Heq**), 4.36 (1H, br s, 2-**Heq**) and 7.18-7.60 (10H, 2m,  $2 \times C_6H_5$ ),  $\delta_C$  (68.5) 19.07 ( $CH_2$ ), 19.12 (C), 24.78 ( $CH_2$ ), 25.28 ( $CH_2$ ), 26.78 ( $CH_3$ ), 28.41 ( $CH_3$ ), 39.84 ( $CH_2$ ), 51.61 (CH), 61.48 ( $CH_2$ ), 79.08 (C), 127.64 (CH), 129.60 (CH), 133.55 (C), 135.63 (CH) and 155.08 (C),  $m/z$  454 (4%, M+H), 397 (21, M- $tBu$ +H), 352 (12, M-BOC) and 199 (100, M-BOC-( $2 \times Ph$ )+H), [Found: M+H, 454.2777.  $C_{27}H_{40}NO_3Si$  requires M+H, 454.2777].

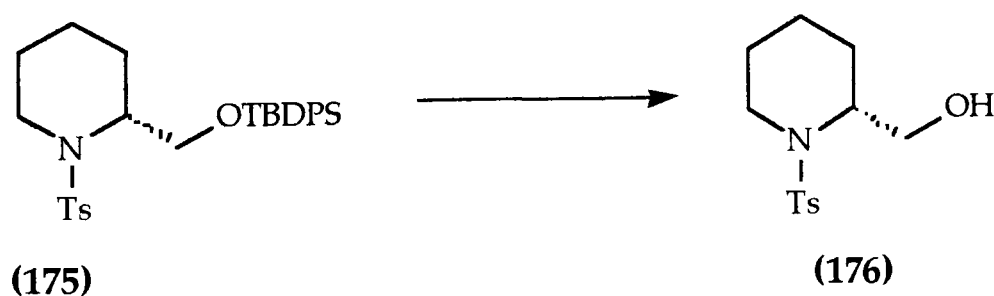
**(2R)-1-(*p*-Toluenesulphonyl) 2-*O*-*tert*-butyldiphenylsilyloxymethylpiperidine**  
(175)



Trifluoroacetic acid (1.9 g, 16.6 mmol) was added to a stirred solution of the piperidine (175) (250 mg, 0.55 mmol) in dichloromethane (20 ml). After 1h the reaction mixture was diluted with dichloromethane (100 ml), washed with saturated sodium hydrogen carbonate (2 x 20 ml), dried and concentrated *in vacuo*. The residue was dissolved in dichloromethane (5 ml) and added to a stirred

solution of *p*-toluenesulphonyl chloride (210 mg, 1.1 mmol), triethylamine (223 mg, 2.2 mmol) and 4-dimethylaminopyridine (3.4 mg, 0.03 mmol) in dichloromethane (5 ml). After 16h, the reaction mixture was diluted with dichloromethane (50 ml), washed with water (10 ml), saturated aqueous sodium chloride (10 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) gave the title compound (175) (196 mg, 70%) as a colourless oil,  $R_F$  0.45,  $[\alpha]_D^{22}$  -20.1 ( $c=1$  in  $CH_2Cl_2$ ),  $\nu_{max}$  1112, 1161 and 1343  $cm^{-1}$ ,  $\delta_H$  (270) 0.97 (9H, s,  $(CH_3)_3CSi$ ), 1.16-1.48 (5H, m), 1.90 (1H, br d,  $J$  11,  $NCH_2CH_AH_B$ ), 2.30 (3H, s,  $CH_3C_6H_4$ ), 2.76 (1H, br t,  $J$  11.4, 6-**Hax**), 3.53-3.72 (3H, m,  $CH_2OTBDPS$  and 6-**Heq**), 4.09-4.20 (1H, m, 2-**Heq**), 7.13 (1H, d,  $J$  8.2, CH (Tosyl)) and 7.28-7.64 (12H, m,  $2 \times C_6H_5$  and CH (Tosyl)),  $\delta_C$  (68.5) 18.31 (CH), 19.12 (C), 21.17 ( $CH_2$ ), 21.44 ( $CH_3$ ), 24.42 ( $CH_2$ ), 26.78 ( $CH_3$ ), 41.75 ( $CH_2$ ), 53.37 (CH), 61.12 ( $CH_2$ ), 126.81 (CH), 127.67 (CH), 129.52 (CH), 129.69 (CH), 133.32 (C), 135.54 (CH), 138.58 (C) and 142.66 (C),  $m/z$  450 (69%,  $M-(CH_3)_3C$ ), 239 (14,  $M-CH_2OTBDPS+H$ ), 238 (100,  $M-CH_2OTBDPS$ ) and 155 (13,  $CH_3C_6H_4SO_2$ ), [Found:  $M-(CH_3)_3C$ , 450.1557.  $C_{25}H_{28}NO_3SiS$  requires  $M-(CH_3)_3C$ , 450.1559].

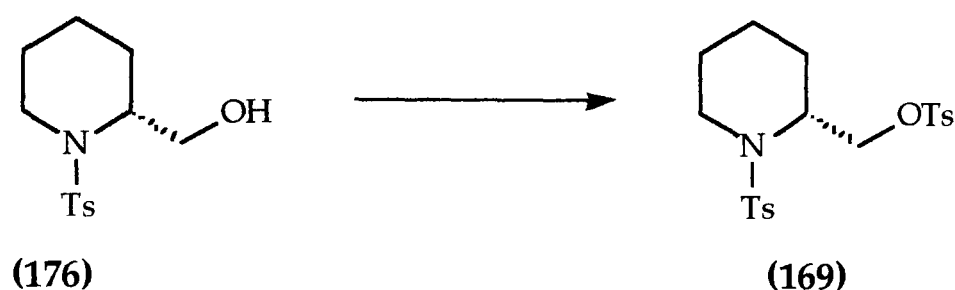
**(2*R*)-1-(*p*-Toluenesulphonyl) 2-hydroxymethylpiperidine (176)**



Tetrabutylammonium fluoride (0.59 ml, 1M in tetrahydrofuran, 0.6 mmol) was added to a stirred solution of the piperidine (175) (150 mg, 0.2 mmol) in tetrahydrofuran (0.5 ml). The reaction mixture was stirred for 16h at room temperature, diluted with dichloromethane (100 ml), washed with water (10 ml),

and saturated aqueous sodium chloride (10 ml), dried and concentrated *in vacuo* to give the **title compound (176)** (54 mg, 68%) as a colourless oil,  $[\alpha]_{\text{D}}^{23} +17.3$  ( $c=1.5$  in  $\text{CH}_2\text{Cl}_2$ ),  $\nu_{\text{max}}$  1115, 1184 and  $1354\text{ cm}^{-1}$ ,  $\delta_{\text{H}}$  (400) 1.00-1.38 (5H, m), 1.52 (1H, d,  $J$  13.5,  $\text{NCH}_2\text{CH}_A\text{H}_B$ ), 2.24 (3H, s,  $\text{CH}_3\text{C}_6\text{H}_4$ ), 2.90 (1H, br t,  $J$  11.4, 6-**Hax**), 3.46 (1H, dd,  $J$  11.2 and 7, 6-**Heq**), 3.61 (2H, dd,  $J$  11.2 and 7.6,  $\text{CH}_2\text{OH}$ ), 3.87-3.95 (1H, m, 2-**Heq**), 7.13 (1H, d,  $J$  8.2, CH (Tosyl)) and 7.59 (1H, d,  $J$  8.2, CH (Tosyl)),  $\delta_{\text{C}}$  (100) 18.41 ( $\text{CH}_2$ ), 20.98 ( $\text{CH}_3$ ), 23.61 ( $\text{CH}_2$ ), 23.98 ( $\text{CH}_2$ ), 41.02 ( $\text{CH}_2$ ), 53.91 (CH), 59.83 ( $\text{CH}_2$ ), 128.54 (CH), 129.32 (CH), 137.99 (C) and 142.89 (C),  $m/z$  238 (100%,  $\text{M}-\text{CH}_2\text{OH}$ ), 84 (12,  $\text{M}-\text{CH}_2\text{OH}-\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2+\text{H}$ ), 83 (8,  $\text{M}-\text{CH}_2\text{OH}-\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2$ ), [Found:  $\text{M}-\text{CH}_2\text{OH}$ , 238.0863.  $\text{C}_{12}\text{H}_{16}\text{NO}_2\text{S}$  requires  $\text{M}-\text{CH}_2\text{OH}$ , 238.0902].

**(2R)-N,O, -di-(*p*-Toluenesulphonyl) 2-hydroxymethylpiperidine (169)**

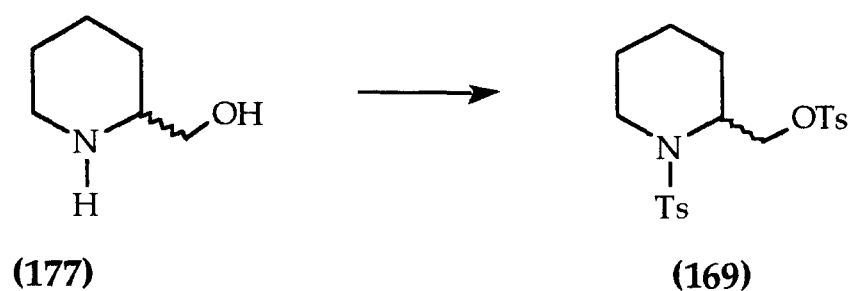


*p*-Toluenesulphonyl chloride (39 mg, 0.20 mmol) was added to a solution of the piperidine **(176)** (50 mg, 0.19 mmol), triethylamine (21 mg, 0.20 mmol), and 4-dimethylaminopyridine (0.01 mmol) in dichloromethane (10 ml). The reaction mixture was stirred for 16h at room temperature, diluted with dichloromethane (100 ml), washed with water (5 ml), and saturated aqueous sodium chloride (5 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) gave the **title compound (169)** (55 mg, 75%) as a colourless oil,  $R_{\text{F}}$  0.40,  $[\alpha]_{\text{D}}^{23} +55.0$  ( $c=0.8$  in  $\text{CH}_2\text{Cl}_2$ ), [Lit +56.6 for the (*R*)-enantiomer],<sup>128</sup>  $\nu_{\text{max}}$  1160, 1177, 1190 and  $1362\text{ cm}^{-1}$ ,  $\delta_{\text{H}}$  (400) 1.20-1.53 (5H, m), 1.68 (1H, br d,  $J$  12.4,  $\text{NCH}_2\text{CH}_A\text{H}_B$ ), 2.40 (3H, s,  $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{O}$ ), 2.44 (3H, s,  $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{N}$ ), 2.81 (1H, br t,  $J$  12.2, 6-**Hax**), 3.69 (1H, br d,  $J$  12.2, 6-**Heq**),



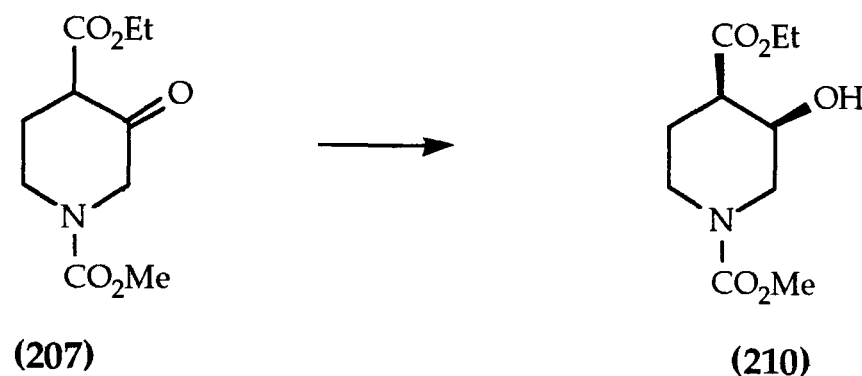
4.01-4.12 (2H, m, CH<sub>2</sub>OTs), 4.18-4.29 (1H, m, 2-Heq), 7.26 (2H, d, J 8.2, CH (N-Tosyl)), 7.4 (2H, d, J 8.2, CH (O-Tosyl)), 7.66 (2H, d, J 8.2, CH (N-Tosyl)) and 7.73 (2H, d, J 8.2, CH (O-Tosyl)),  $\delta_C$  (100) 18.20 (CH<sub>2</sub>), 21.38 (CH<sub>3</sub>), 21.54 (CH<sub>3</sub>), 23.99 (CH<sub>2</sub>), 24.29 (CH<sub>2</sub>), 41.26 (CH<sub>2</sub>), 50.37 (CH), 66.78 (CH<sub>2</sub>), 126.65 (CH), 127.80 (CH), 129.65 (CH), 129.86 (CH), 132.42 (C), 137.74 (C), 143.22 (C) and 145.00 (C),  $m/z$  238 (100%, M-CH<sub>2</sub>OSO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>Me) and 91 (43, CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>), [Found: M-CH<sub>2</sub>OSO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>Me, 238.0889. C<sub>12</sub>H<sub>16</sub>NO<sub>2</sub>S requires M-CH<sub>2</sub>OSO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>, 238.0902].

**(±)N,O-di-(*p*-Toluenesulphonyl) 2-oxymethylpiperidine (169)**



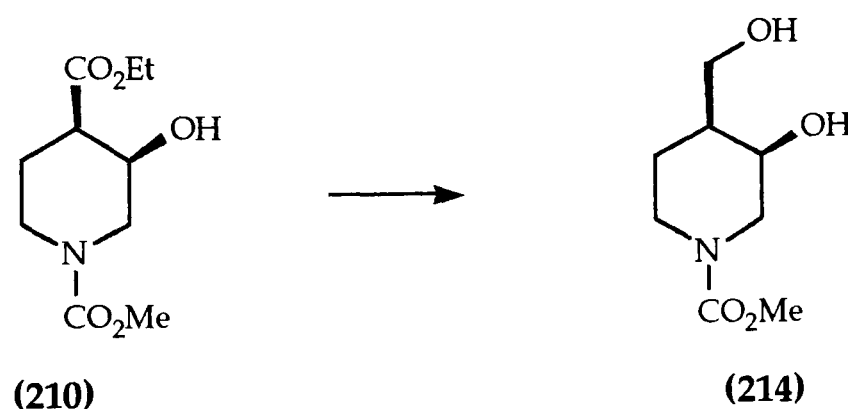
*p*-Toluenesulphonyl chloride (1.17 g, 6.0 mmol) was added to a solution of 3-piperidinemethanol (**166**) (660 mg, 5.7 mmol), triethylamine (630 mg, 6.0 mmol), and 4-dimethylaminopyridine (0.3 mmol) in dichloromethane (100 ml). The reaction mixture was stirred for 16h at room temperature, diluted with dichloromethane (100 ml), washed with water (25 ml), and saturated aqueous sodium chloride (25 ml), dried and concentrated *in vacuo*. to give the title compound (**169**) (1.5 g, 70%) as a colourless oil; all spectroscopic data displayed was consistent with the chiral material.

**(3*R*, 4*R*)-1-Methyl-4-ethyl 3-hydroxypiperidine-1,4-dicarboxylate (210)**



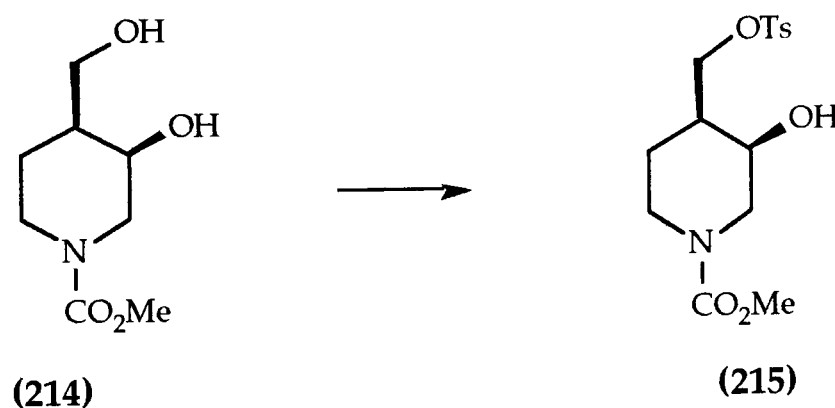
The piperidine  $\beta$ -keto-ester (**207**) (5 g, 21.8 mmol) was reacted with a solution of dried baker's yeast by the method outlined for (3*R*, 4*S*)-1-*tert*-butyl-3-ethyl 4-hydroxypiperidine-1,3-dicarboxylate (**152**) to give the title compound (**210**) (4.49 g, 89%) as a pale oil,  $[\alpha]_{\text{D}}^{21}$  -21.4 ( $c=1.10$  in  $\text{CHCl}_3$ ),  $\nu_{\text{max}}$  1690, 1732 and 3460  $\text{cm}^{-1}$ ,  $\delta_{\text{H}}$  (400) 1.28 (3H, t,  $J$  7.1,  $\text{CH}_3\text{CH}_2\text{CO}_2\text{C}$ ), 1.76 (1H, br d,  $J$  13.5,  $\text{NCH}_2\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.07 (1H, ddd,  $J$  13.5, 10.6 and 4.4,  $\text{NCH}_2\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.56 (1H, ddd,  $J$  10.6, 4.7 and 2.4,  $\text{CHCO}_2\text{Et}$ ), 2.87 (1H, br t,  $J$  13.5, 6- $\text{H}_{\text{ax}}$ ), 3.00 (1H, br d,  $J$  13, 2- $\text{H}_{\text{ax}}$ ), 3.70 (3H, s,  $\text{CH}_3\text{CO}_2\text{C}$ ) 4.10-4.20 (3H, m, 2- $\text{H}_{\text{eq}}$ , 6- $\text{H}_{\text{eq}}$  and  $\text{CHOH}$ ) and 4.21 (2H, q,  $J$  7.1,  $\text{CH}_3\text{CH}_2\text{CO}_2\text{C}$ ),  $\delta_{\text{C}}$  (68.5) 13.96 ( $\text{CH}_3$ ), 22.18 ( $\text{CH}_2$ ), 42.88 ( $\text{CH}_2$ ), 45.07 ( $\text{CH}$ ), 48.93 ( $\text{CH}_2$ ), 52.58 ( $\text{CH}_3$ ), 60.74 ( $\text{CH}_2$ ), 64.93 ( $\text{CH}$ ), 156.59 (C) and 171.03 (C),  $m/z$  254 (15%,  $\text{M}+\text{Na}$ ), 232 (100,  $\text{M}+\text{H}$ ), 214 (14,  $\text{M}-\text{OH}$ ), 200 (21,  $\text{M}-\text{MeO}$ ), 172 (6,  $\text{M}-\text{CO}_2\text{Me}$ ) and 186 (13,  $\text{M}-\text{EtO}$ ), [Found:  $\text{M}+\text{H}$ , 232.1175.  $\text{C}_{10}\text{H}_{18}\text{NO}_5$  requires  $\text{M}+\text{H}$ , 232.1185].

**(3*R*, 4*S*)-1-Methyl 3-hydroxy-4-hydroxymethylpiperidine-1-carboxylate (214)**



Sodium borohydride (4.84 g, 130 mmol) was added in portions over 10min to a solution of the hydroxy ester (210) (3 g, 13.0 mmol) in methanol (100 ml) at 0°C. After 16h the reaction mixture was concentrated *in vacuo*, dissolved in dichloromethane (300 ml), washed with water (20 ml), and saturated aqueous sodium chloride (20 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with ethyl acetate gave the title compound (214) (1.7 g, 68%) as a colourless oil,  $R_F$  0.2,  $\nu_{\max}$  1680 and 3430  $\text{cm}^{-1}$ ,  $\delta_H$  (270) 1.18-1.85 (3H, m,  $\text{NCH}_2\text{CH}_2$  and  $\text{CHCH}_2\text{OH}$ ), 2.62-3.06 (2H, m, 2-H<sub>ax</sub> and 6-H<sub>ax</sub>), 3.55-3.84 (2H, m,  $\text{CH}_2\text{OH}$ ), 3.61 (3H, s,  $\text{CH}_3\text{CO}_2\text{C}$ ) and 3.90-4.20 (3H, m, 2-Heq, 6-Heq and  $\text{CHOH}$ ),  $\delta_C$  (68.5) 22.19 ( $\text{CH}_2$ ), 41.22 ( $\text{CH}$ ), 43.67 ( $\text{CH}_2$ ), 50.08 ( $\text{CH}_2$ ), 52.62 ( $\text{CH}_3$ ), 64.40 ( $\text{CH}_2$ ), 66.13 ( $\text{CH}$ ) and 156.93 (C),  $m/z$  189 (10%, M), 141 (14, M- $\text{CH}_2\text{OH}$ -OH), 130 (23, M- $\text{CO}_2\text{Me}$ ), 82 (7, M- $\text{CO}_2\text{Me}$ - $\text{CH}_2\text{OH}$ -OH) and 59 (20,  $\text{CO}_2\text{Me}$ ), [Found: M, 189.1045.  $\text{C}_8\text{H}_{15}\text{NO}_4$  requires M, 189.1001].

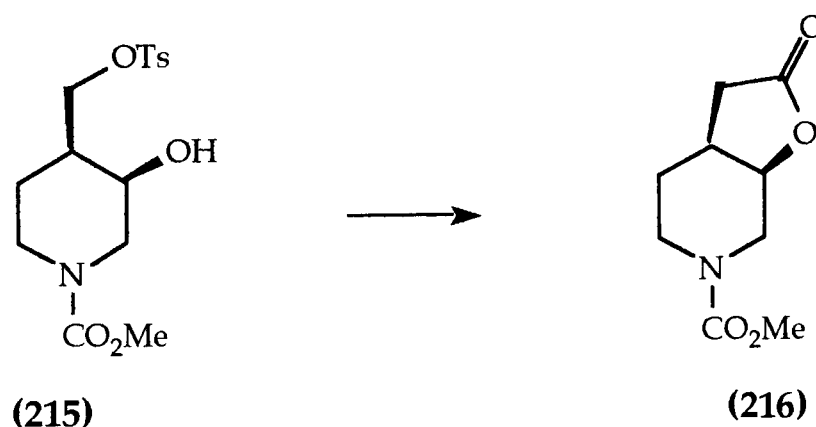
**(3*R*, 4*S*)-1-Methyl 3-hydroxy-4-*O*-*p*-toluenesulphonyloxymethylpiperidine-1-carboxylate (215)**



The piperidine diol (214) (1 g, 5.3 mmol) was dissolved in dichloromethane (25 ml) and added to a stirred solution of *p*-toluenesulphonyl chloride (1.11 g, 5.8 mmol) and triethylamine (590 mg, 5.8 mmol) in dichloromethane (25 ml). After 16h the reaction mixture was diluted with dichloromethane (100 ml), washed with water (10 ml), 2M hydrochloric acid (30 ml) and saturated aqueous sodium chloride (10 ml), dried and concentrated *in vacuo*. Chromatography of the residue over

silica gel eluting with dichloromethane : ethyl acetate (1:1) gave the title compound (215) (1.52 g, 84%) as a colourless oil,  $R_F$  0.60,  $\nu_{\max}$  1160, 1190, 1678 and  $3425\text{ cm}^{-1}$ ,  $\delta_H$  (400) 1.25-1.56 and 1.94-2.00 (3H, 2 x m,  $\text{NCH}_2\text{CH}_2$  and  $\text{CHCH}_2\text{OTs}$ ), 2.45 (3H, s,  $\text{CH}_3\text{C}_6\text{H}_4$ ), 2.73 (1H, br t,  $J$  11.8, 6-Hax), 2.87 (1H, br d,  $J$  13.9, 2-Hax), 3.68 (3H, s,  $\text{CH}_3\text{CO}_2\text{C}$ ), 3.70-3.93 (2H, m,  $\text{CH}_2\text{OTs}$ ), 4.07-4.19 (3H, m, 2-Heq, 6-Heq and  $\text{CHOH}$ ), 7.35 (2H, d,  $J$  8.2, CH (Tosyl)) and 7.79 (2H, d,  $J$  8.2, CH (Tosyl)),  $\delta_C$  (68.5) 14.02 ( $\text{CH}_3$ ), 21.84 ( $\text{CH}_2$ ), 39.57 ( $\text{CH}_2$ ), 43.18 ( $\text{CH}_2$ ), 49.80 ( $\text{CH}_2$ ), 52.56 ( $\text{CH}_3$ ), 60.24 (CH), 71.16 ( $\text{CH}_2$ ), 127.71 (CH), 129.74 (CH), 132.58 (C), 144.74 (C) and 156.71 (C),  $m/z$  188 (5%,  $\text{M-SO}_2\text{C}_6\text{H}_4\text{CH}_3$ ), 172 (6,  $\text{M-OSO}_2\text{C}_6\text{H}_4\text{CH}_3$ ), 155 (7,  $\text{M-OSO}_2\text{C}_6\text{H}_4\text{CH}_3\text{-OH}$ ) and 82 (5,  $\text{C}_5\text{H}_8\text{N}$ ), [Found:  $\text{M-SO}_2\text{C}_6\text{H}_4\text{CH}_3$ , 188.0879.  $\text{C}_8\text{H}_{14}\text{NO}_4$  requires  $\text{M-SO}_2\text{C}_6\text{H}_4\text{CH}_3$ , 188.0923].

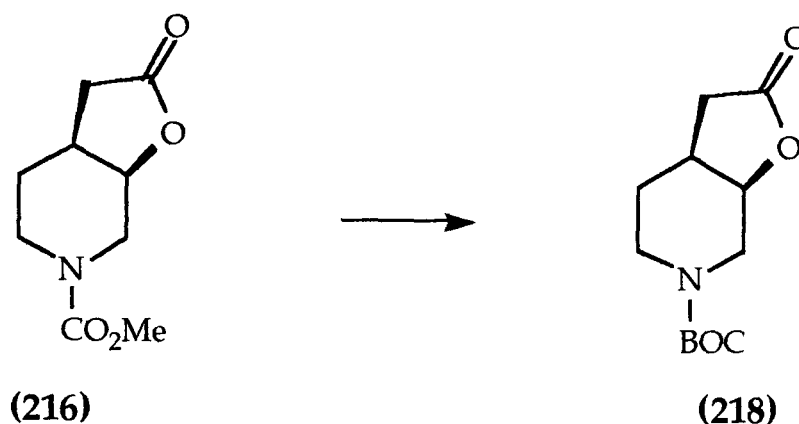
**(1*R*, 5*S*)-8-Aza-*N*-(methyloxycarbonyl)-2-oxabicyclo-[3.4.0]-nonan-3-one (216)**



The piperidine tosylate (215) (500 mg, 1.5 mol) was added to a stirred suspension of sodium cyanide (179 mg, 3.6 mmol) in dimethyl sulphoxide (10 ml). The reaction mixture was heated at  $50^\circ\text{C}$  for 6h, cooled and 12M hydrochloric acid (50 ml) was introduced. After 16h the reaction mixture was extracted with dichloromethane (2 x 100 ml) and chloroform (50 ml). The combined organic extracts were washed with water (20 ml) and saturated aqueous sodium chloride (20 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (1:1) gave the title

**compound (216)** (255 mg, 88%) as a colourless oil,  $R_F$  0.50,  $[\alpha]_D^{23}$  -22.4 ( $c=1.13$  in  $CHCl_3$ ),  $\nu_{max}$  1701 and  $1780\text{cm}^{-1}$ ,  $\delta_H$  (400) 1.27-1.55 (1H, m,  $NCH_2CH_AH_B$ ), 1.69-1.83 (1H, m,  $NCH_2CH_AH_B$ ), 2.26 (1H, dd,  $J$  17.8 and 2,  $CH_AH_BC=O$ ), 2.44-2.58 (1H, m,  $NCH_2CH_2CH$ ), 2.67 (1H, dd,  $J$  17.8 and 7.6,  $CH_AH_BC=O$ ), 2.76-3.05 (1H, m, 6-**Hax**), 3.25 (1H, br d,  $J$  13.5, 2-**Hax**), 3.65 (3H, s,  $CH_3CO_2C$ ), 4.0-4.15 (1H, m, 6-**Heq**), 4.20 (1H, br d,  $J$  13.5, 2-**Heq**) and 4.37 (1H, br s,  $CH-O$ ),  $\delta_C$  (68.5) 26.53 ( $CH_2$ ), 30.14 ( $CH_2$ ), 33.23 ( $CH$ ), 41.57 ( $CH_2$ ), 44.60 ( $CH_2$ ), 53.32 ( $CH_3$ ), 76.41 ( $CH$ ), 156.60 (C) and 176.80 (C),  $m/z$  199 (42%, M), 168 (12, M-OMe), 140 (100, M- $CO_2Me$ ) and 59 (18,  $CO_2Me$ ), [Found: M, 199.0840.  $C_9H_{13}NO_4$  requires M, 199.0845].

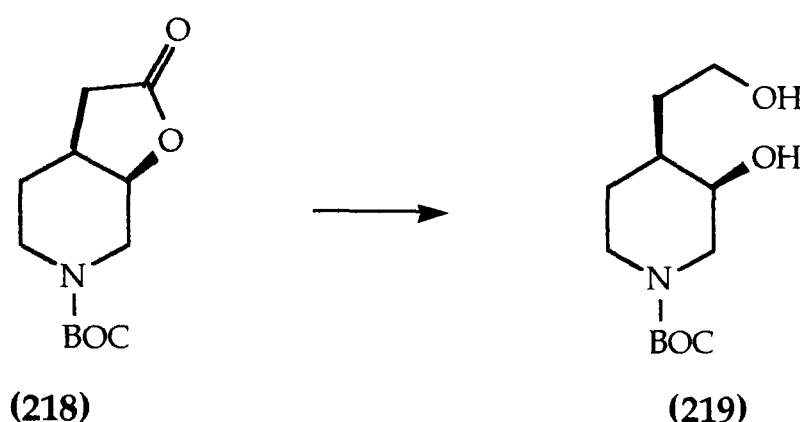
**(1R, 5S)-8-Aza-N-(tert-butyloxycarbonyl)-2-oxabicyclo-[3.4.0]-3-nonanone (218)**



Iodotrimethylsilane (603 mg, 3 mmol) was added to a stirred solution of the lactone **(216)** (300 mg, 1.5 mmol) in chloroform (15 ml). The reaction mixture was heated at 50 °C for 8h, methanol (50 ml) was introduced, heating continued for 1h and the reaction mixture was then concentrated *in vacuo*. The residue was dissolved in dichloromethane (20 ml), triethylamine (305 mg, 3 mmol) and di-*tert*-butyl dicarbonate (660 mg, 3 mmol) were added and the reaction mixture stirred at room temperature for 16h, diluted with dichloromethane (200 ml), washed with 2M aqueous citric acid (2 x 30 ml), and saturated aqueous sodium chloride (30 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (1:1) gave the title compound

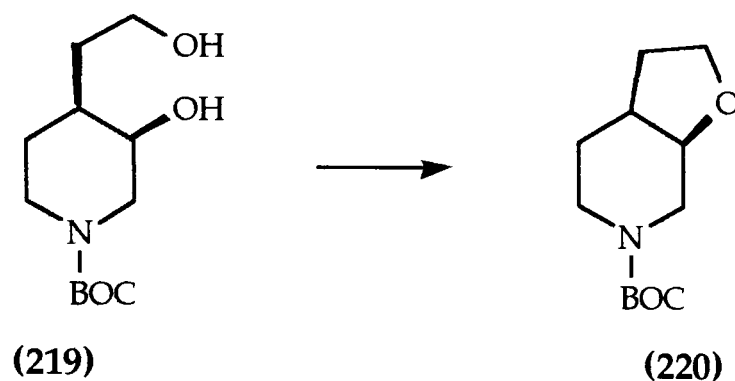
(218) (345 mg, 95%) as a colourless oil,  $R_F$  0.50,  $[\alpha]_D^{23}$  -19.7 ( $c=1.3$  in  $\text{CHCl}_3$ ),  $\nu_{\text{max}}$  1686 and  $1776\text{cm}^{-1}$ ,  $\delta_H$  (400) 1.33-1.49 (1H, m,  $\text{NCH}_2\text{CH}_A\text{H}_B$ ), 1.43 (9H, s,  $(\text{CH}_3)_3\text{C}$ ), 1.68-1.85 (1H, m,  $\text{NCH}_2\text{CH}_A\text{H}_B$ ), 2.27 (1H, br d,  $J$  17.8,  $\text{CH}_A\text{H}_B\text{C}=\text{O}$ ), 2.49-2.62 (1H, m,  $\text{NCH}_2\text{CH}_2\text{CH}$ ), 2.70 (1H, dd,  $J$  17.8 and 7.6,  $\text{CH}_A\text{H}_B\text{C}=\text{O}$ ), 2.75-3.10 (1H, m, 6-H<sub>ax</sub>), 3.25 (1H, br d,  $J$  13.5, 2-H<sub>ax</sub>), 3.62-4.01 (1H, m, 6-Heq), 4.20 (1H, br d,  $J$  13.5, 2-Heq) and 4.45 (1H, br s, CH-O).

**(3R, 4S)-N-(tert-Butyloxycarbonyl)-3-hydroxy-4-piperidineethanol (219)**



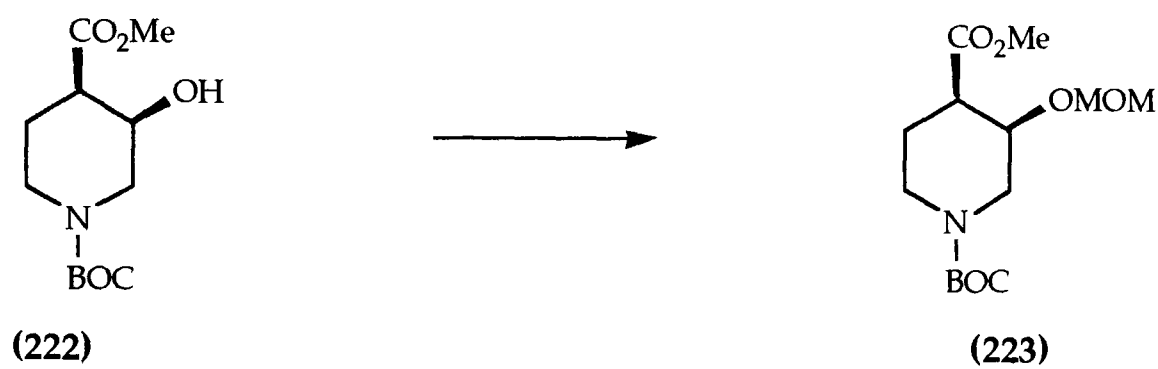
Sodium borohydride (189 mg, 5 mmol) was added to a solution of the lactone (300 mg, 1.2 mmol) in ethanol (20 ml) at  $0^\circ\text{C}$  and the reaction mixture allowed to warm to room temperature. After 16h the suspension was concentrated *in vacuo*, the residue dissolved in dichloromethane (100 ml) and the solution washed with water (5 ml) and saturated aqueous sodium chloride (10 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with ethyl acetate gave the title compound (207 mg, 68%) as a colourless oil,  $R_F$  0.2,  $\nu_{\text{max}}$  1666 and  $3419\text{cm}^{-1}$ ,  $\delta_H$  (400) 1.41-1.92 (4H, m,  $\text{NCH}_2\text{CH}_2$  and  $\text{CH}_2\text{CH}_2\text{OH}$ ), 1.45 (9H, s,  $(\text{CH}_3)_3\text{C}$ ), 2.42-2.9 (1H, m, 6-H<sub>ax</sub>), 2.78 (1H, m,  $\text{CHCH}_2\text{CH}_2\text{OH}$ ), 2.93 (1H, br d,  $J$  13.5, 2-H<sub>ax</sub>), 3.62-3.90 (4H, m, 2-Heq, 6-Heq and  $\text{CH}_2\text{OH}$ ) and 4.0-4.15 (1H, m, CHOH) which was used directly without further purification.

**(1*R*,5*S*)-8-Aza-*N*-(*tert*-butyloxycarbonyl)-2-oxabicyclo-[3.4.0]-nonane (220)**



hydroxypiperidine-1,3-dicarboxylate (152) to give the **title compound (222)** (4.08 g, 81%) as a pale oil,  $[\alpha]_{\text{D}}^{25} -32.7$  ( $c=1.0$  in  $\text{CHCl}_3$ ),  $\nu_{\text{max}}$  1690, 1735 and  $3450\text{ cm}^{-1}$ ,  $\delta_{\text{H}}$  (270) 1.46 (9H, s,  $(\text{CH}_3)_3\text{CO}$ ), 1.73 (1H, dt,  $J$  3.6 and 13.5, 5- $\text{H}_{\text{A}}\text{H}_{\text{B}}$ ), 2.07 (1H, ddd,  $J$  13.5, 11.5 and 7.3, 5- $\text{H}_{\text{A}}\text{H}_{\text{B}}$ ), 2.56 (1H, ddd,  $J$  10.6, 3.0 and 3.0, 4-H), 2.83 (1H, dt,  $J$  11.9 and 3.6, 6- $\text{H}_{\text{ax}}$ ), 2.97 (1H, br d,  $J$  13.2, 2- $\text{H}_{\text{ax}}$ ), 3.73 and 3.78 (3H, 2 s,  $\text{CH}_3\text{O}$ ) and 4.03-4.19 (3H, m, 2- $\text{H}_{\text{eq}}$ , 6- $\text{H}_{\text{eq}}$  and 3-H),  $\delta_{\text{C}}$  (68.5) 22.41 (CH), 28.32 (CH<sub>3</sub>), 42.80 (CH<sub>2</sub>), 45.21 (CH<sub>2</sub>), 48.93 (CH<sub>2</sub>), 51.84 (CH<sub>3</sub>), 65.24 (CH), 79.84 (C), 155.54 (C) and 171.97 (C),  $m/z$  200 (7%, M- $\text{CO}_2\text{Me}$ ), 158 (16, M-BOC), 141 (8, M-BOC-OH), 101 (5, BOC), 82 (7, M-BOC- $\text{CO}_2\text{Me}$ -OH), 59 (5,  $\text{CO}_2\text{Me}$ ) and 57 (100,  $^t\text{Bu}$ ), [Found: M- $\text{CO}_2\text{Me}$ , 200.1269.  $\text{C}_{10}\text{H}_{18}\text{NO}_3$  requires M- $\text{CO}_2\text{Me}$ , 200.1287].

**(3*R*, 4*R*)-1-*tert*-Butyl-4-methyl 3-(methyloxymethoxy)-1,4-piperidine-dicarboxylate (223)**

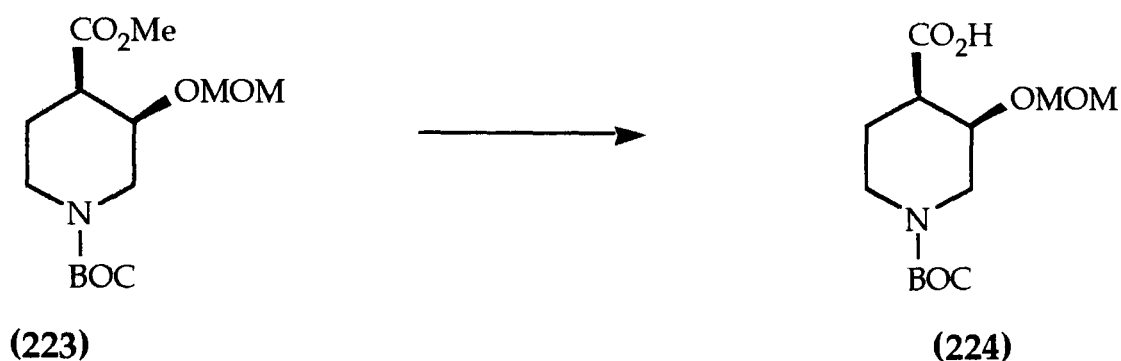


Chloromethyl methyl ether (6.22 g, 77.2 mmol) was added to an ice-cooled solution of the piperidine (222) (4 g, 15.4 mmol) and diisopropylethylamine (5 g, 38.6 mmol) in dichloromethane (200 ml) and the reaction mixture allowed to warm to room temperature. After 16h the resulting solution was diluted with dichloromethane (100 ml), washed with 2M hydrochloric acid (2 x 40ml), and saturated aqueous sodium chloride (50 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with ethyl acetate : dichloromethane (9:1) gave the **title compound (223)** (4.3 g, 92%) as a colourless oil,  $R_{\text{F}}$  0.6,  $[\alpha]_{\text{D}}^{25} +23.4$  ( $c=0.9$  in  $\text{CHCl}_3$ ),  $\nu_{\text{max}}$  1687 and  $1734\text{ cm}^{-1}$ ,  $\delta_{\text{H}}$  (270) 1.46



(9H, s, (CH<sub>3</sub>)<sub>3</sub>CO), 1.60-2.17 (2H, m, 5-H), 2.49-2.90 (3H, m, 2-H<sub>ax</sub>, 6-H<sub>ax</sub> and 4-H), 3.33 (3H, s, CH<sub>3</sub>OCH<sub>2</sub>O), 4.02-4.48 (3H, m, 2-Heq, 6-Heq and 3-H), 4.55 (1H, d, J 7, OCH<sub>A</sub>H<sub>B</sub>O) and 4.76 (1H, d, J 7, OCH<sub>A</sub>H<sub>B</sub>O), δ<sub>C</sub> (68.5) 22.54 (CH<sub>2</sub>), 28.79 (CH<sub>3</sub>), 42.64 (CH<sub>2</sub>), 45.82 (CH), 46.06 (CH<sub>2</sub>), 52.13 (CH<sub>3</sub>), 56.03 (CH<sub>3</sub>), 69.97 (CH), 80.02 (C), 95.19 (CH<sub>2</sub>), 155.40 (C) and 173.08 (C), m/z 244 (8%, M-CO<sub>2</sub>Me), 202 (7, M-BOC), 183 (5, M-CO<sub>2</sub>Me-OMOM), 143 (5, M-CO<sub>2</sub>Me-BOC), 141 (8, M-BOC-OMOM), 82 (8, M-BOC-CO<sub>2</sub>Me-OMOM), 59 (11, CO<sub>2</sub>Me) and 57 (100, <sup>t</sup>Bu), [Found: M-BOC, 202.1051. C<sub>9</sub>H<sub>16</sub>NO<sub>4</sub> requires M-BOC, 202.1079].

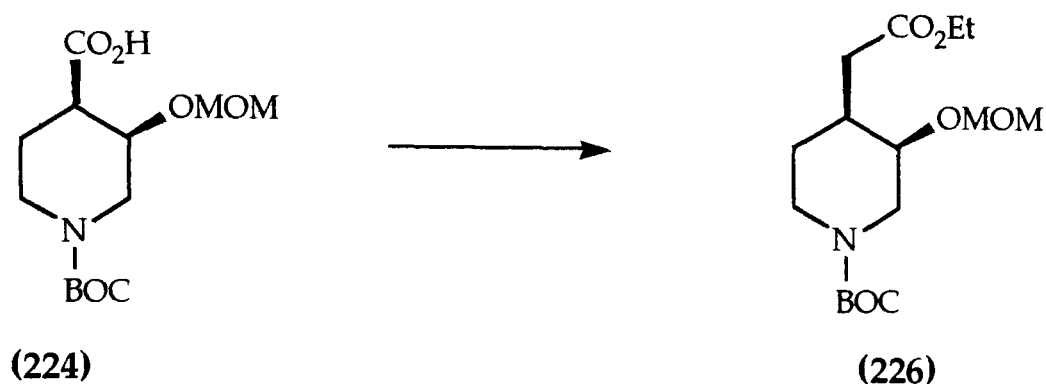
**(3R, 4R)-1-(tert-Butyloxycarbonyl) 3-(methyloxymethoxy)-4-piperidine-carboxylic acid (224)**



The piperidine (223) (1 g, 3.3 mmol) was added to a stirred solution of potassium hydroxide (0.92 g, 16.5 mmol) in water (10 ml) and the reaction stirred for 16h. The resulting solution was washed with diethyl ether (2 ml), acidified to pH 2 with 2M citric acid and extracted with chloroform (3 x 30 ml). The combined extracts were dried and concentrated *in vacuo* to give the title compound (224) (935 mg, 98%) as a thick colourless oil, ν<sub>max</sub> 1691 and 3275 cm<sup>-1</sup>, δ<sub>H</sub> (400) 1.45 (9H, s, (CH<sub>3</sub>)<sub>3</sub>CO), 1.68-1.80 (1H, m, 5-H<sub>A</sub>H<sub>B</sub>), 1.99-2.12 (1H, m, 5-H<sub>A</sub>H<sub>B</sub>), 2.48-2.88 (3H, m, 2-H<sub>ax</sub>, 6-H<sub>ax</sub> and 4-H), 3.36 (3H, s, CH<sub>3</sub>OCH<sub>2</sub>O), 3.92-4.49 (3H, m, 2-Heq, 6-Heq and 3-H), 4.61 (1H, d, J 7, OCH<sub>A</sub>H<sub>B</sub>O) and 4.78 (1H, d, J 7, OCH<sub>A</sub>H<sub>B</sub>O), δ<sub>C</sub> (68.5) 20.81 (CH<sub>2</sub>), 28.16 (CH<sub>3</sub>), 42.70 (CH<sub>2</sub>), 45.07 (CH), 46.20 (CH<sub>2</sub>), 55.47 (CH<sub>3</sub>), 69.00 (CH), 79.66 (C), 94.50 (CH<sub>2</sub>), 154.93 (C) and 176.93 (C), m/z 312 (35%, M+Na), 290 (66,

M+H), 258 (14, M-OMe), 232 (13, M-<sup>t</sup>Bu), 188 (21, M-BOC) and 128 (33, M-BOC-OCH<sub>2</sub>OCH<sub>3</sub>+H), [Found: M+H, 290.1614. C<sub>13</sub>H<sub>24</sub>NO<sub>6</sub> requires M+H, 290.1604].

**Ethyl-(3R, 4S)-N-(tert-butyloxycarbonyl)-3-(methyloxymethoxy)-4-piperidine-acetate (226)**

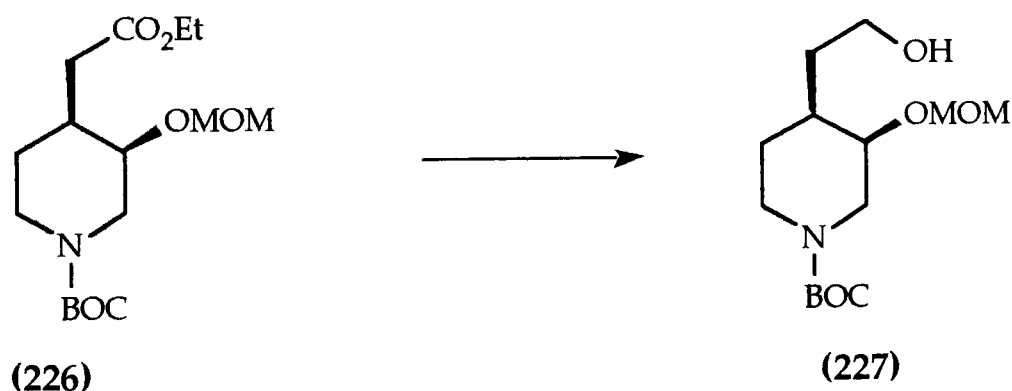


Freshly distilled oxalyl chloride (1.1 g, 8.6 mmol) was added to a stirred solution of the piperidine carboxylic acid (224) (500 mg, 1.7 mmol) and dimethylformamide (6.3 mg, 0.09 mmol) in diethyl ether (25 ml). The mixture was stirred at 0°C for 30 mins and 90 mins at room temperature. The solvent and excess reagent were evaporated *in vacuo* and the residue dissolved in diethyl ether (10 ml). An excess of an ice cold ethereal solution of diazomethane was added, the solution left to stand for 16h then concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with ethyl acetate : dichloromethane (9:1) gave the diazoketone (225) (411 mg, 75%) as a colourless oil, R<sub>F</sub> 0.5,  $\nu_{\max}$  1686, 1734 and 2253 cm<sup>-1</sup>,  $\delta_{\text{H}}$  (250) 1.35-1.72 (2H, m, 5-H), 1.45 (9H, s, (CH<sub>3</sub>)<sub>3</sub>CO), 2.8-3.12 (3H, m, 2-H<sub>ax</sub>, 6-H<sub>ax</sub> and 4-H), 3.40 (3H, s, CH<sub>3</sub>OCH<sub>2</sub>O), 4.0-4.3 (3H, m, 2-Heq, 6-Heq and 3-H), 4.68 (1H, d, J 7, OCH<sub>A</sub>H<sub>B</sub>O), 4.72 (1H, d, J 7, OCH<sub>A</sub>H<sub>B</sub>O) and 5.31 (1H, s, HC=N<sub>2</sub>).

Silver benzoate (14 mg, 0.06 mmol) and triethylamine (0.05 ml) were added to a solution of the diazoketone (225) (411 mg, 1.2 mmol) in ethanol (15 ml) and the reaction mixture stirred for 16h then concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with ethyl acetate : dichloromethane (9:1) gave the title compound (226) (237 mg, 62%) as a colourless oil, R<sub>F</sub> 0.6,  $[\alpha]_{\text{D}}^{25}$  +18.0

( $c=1.4$  in  $\text{CHCl}_3$ ),  $\nu_{\text{max}}$  1684 and 1740  $\text{cm}^{-1}$ ,  $\delta_{\text{H}}$  (400) 1.27 (3H, t, J 7,  $\text{CH}_3\text{CH}_2\text{O}$ ), 1.4-1.58 (1H, m, 4-H), 1.45 (9H, s,  $(\text{CH}_3)_3\text{CO}$ ), 1.67-1.81 (1H, m, 5- $\text{H}_\text{A}\text{H}_\text{B}$ ), 2.03 (1H, ddd, J 13.5, 11 and 7.3, 5- $\text{H}_\text{A}\text{H}_\text{B}$ ), 2.55 (1H, br d, J 11.9, 6- $\text{H}_\text{ax}$ ), 3.28-3.40 (1H, m, 2- $\text{H}_\text{ax}$ ), 3.55 (3H, s,  $\text{CH}_3\text{OCH}_2$ ), 4.1-4.4 (3H, m, 2- $\text{H}_\text{eq}$ , 6- $\text{H}_\text{eq}$  and 3-H), 4.17 (2H, q, J 7,  $\text{OCH}_2\text{CH}_3$ ), 4.57 (1H, d, J 7,  $\text{CH}_\text{A}\text{H}_\text{BO}$ ) and 4.75 (1H, d, J 7,  $\text{CH}_\text{A}\text{H}_\text{BO}$ ),  $\delta_{\text{C}}$  (68.5) 13.95 ( $\text{CH}_3$ ), 21.81 ( $\text{CH}_2$ ), 28.17 ( $\text{CH}_3$ ), 40.03 ( $\text{CH}_2$ ), 45.50 ( $\text{CH}$ ), 46.20 ( $\text{CH}_2$ ), 55.42 ( $\text{CH}_3$ ), 56.00 ( $\text{CH}_2$ ), 60.38 ( $\text{CH}_2$ ), 69.71 ( $\text{CH}$ ), 79.46 (C), 94.59 ( $\text{CH}_2$ ), 154.84 (C) and 172.01 (C),  $m/z$  216 (10%, M-BOC), 143 (4, M-BOC- $\text{CH}_2\text{CO}_2\text{Me}$ ), 142 (7, M-BOC- $\text{CO}_2\text{Me-Me}$ ), 126 (40, M-BOC- $\text{CH}_2\text{CO}_2\text{Me-Me}$ ), 82 (45, M- $\text{CH}_2\text{CO}_2\text{Me-OCH}_2\text{OMe-BOC}$ ) and 57 (100,  $\text{tBu}$ ), [Found: M-BOC, 216.1038.  $\text{C}_{10}\text{H}_{18}\text{NO}_4$  requires M-BOC, 216.1236].

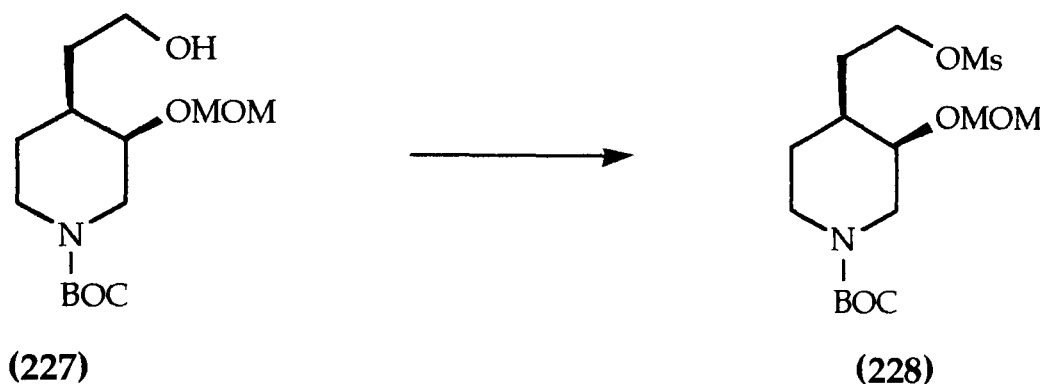
**(3*R*, 4*S*)-1-*tert*-Butyl 3-(methyloxymethoxy)-4-hydroxyethylpiperidine-1-carboxylate (227)**



Diisobutylaluminum hydride (1.7 ml, 2.52 mmol, 1.5M in toluene) was added to a solution of the piperidine (226) (200 mg, 0.63 mmol) in toluene (10 ml) at  $-78^\circ\text{C}$ . After 6h, saturated aqueous potassium tartrate (2 ml) was added, the suspension diluted with dichloromethane (100 ml), washed with water (5 ml), and saturated aqueous sodium chloride (10 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with ethyl acetate: dichloromethane (1:1) gave the title compound (227) (100 mg, 55%) as a colourless oil,  $R_F$  0.6,  $\nu_{\text{max}}$  1688 and 3270  $\text{cm}^{-1}$ ,  $\delta_{\text{H}}$  (250) 1.27-1.52 (1H, m, 4-H), 1.42 (9H, s,

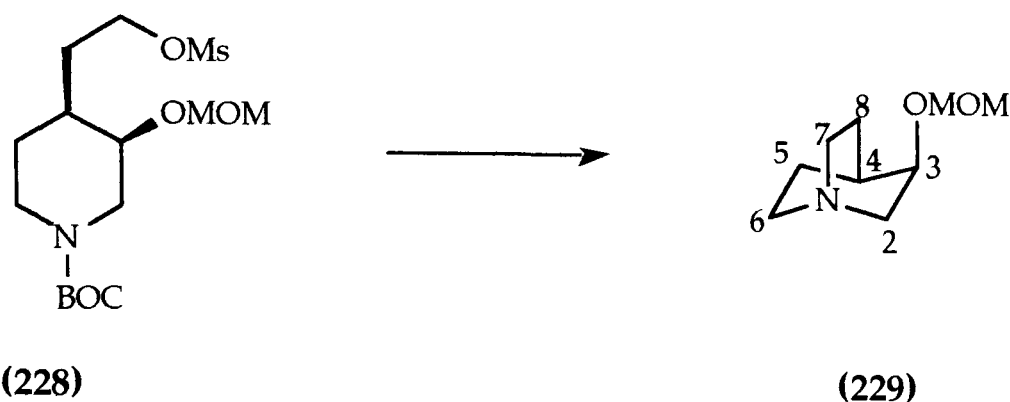
(CH<sub>3</sub>)<sub>3</sub>CO), 1.63 (2H, ddd, J 13.6, 11.2 and 7.3, 5-H), 1.70-1.90 (2H, m, CH<sub>2</sub>CH<sub>2</sub>OH), 2.60-2.85 (2H, m, 2-H<sub>ax</sub> and 6-H<sub>ax</sub>), 3.40 (3H, s, CH<sub>3</sub>OCH<sub>2</sub>), 3.54-3.71 (2H, m, CH<sub>2</sub>OH), 3.89 (1H, br s, 6-Heq), 3.94-4.40 (2H, m, 2-Heq and 3-H), 4.61 (1H, d, J 7, OCH<sub>A</sub>H<sub>B</sub>O) and 4.80 (1H, d, J 7, OCH<sub>A</sub>H<sub>B</sub>O).

**(3R, 4S)-1-tert-Butyl 3-(methyloxymethoxy)-4-(O-methanesulphonyloxyethyl)-piperidine (228)**



Methanesulphonyl chloride (63 mg, 0.55 mmol) was added to a solution of the piperidine **(227)** (80 mg, 0.28 mmol) and pyridine (44 mg, 0.55 mmol) in dichloromethane (5 ml) at 0°C. The reaction mixture was stirred at this temperature for 3h, diluted with dichloromethane (100 ml), washed with water (5 ml) and saturated aqueous sodium chloride (5 ml), dried and concentrated *in vacuo* to give the title compound **(228)** (63mg, 62%) as a colourless oil,  $\nu_{\text{max}}$  1690, 1112 and 1160cm<sup>-1</sup>,  $\delta_{\text{H}}$  (250) 1.36-1.78 (3H, m, 5-H and 4-H), 1.46 (9H, s, (CH<sub>3</sub>)<sub>3</sub>CO), 1.98-2.16 (2H, m, CH<sub>2</sub>CH<sub>2</sub>OMs), 2.49-2.87 (2H, m, 2-H<sub>ax</sub> and 6-H<sub>ax</sub>), 3.01 (3H, s, CH<sub>3</sub>SO<sub>2</sub>), 3.49 (3H, s, CH<sub>3</sub>OCH<sub>2</sub>), 3.85 (1H, br s, 6-Heq), 4.03-4.51 (3H, m, 2-Heq and CH<sub>2</sub>OMs), 4.57 (1H, d, J 7, OCH<sub>A</sub>H<sub>B</sub>O) and 4.80 (1H, d, J 7, OCH<sub>A</sub>H<sub>B</sub>O).

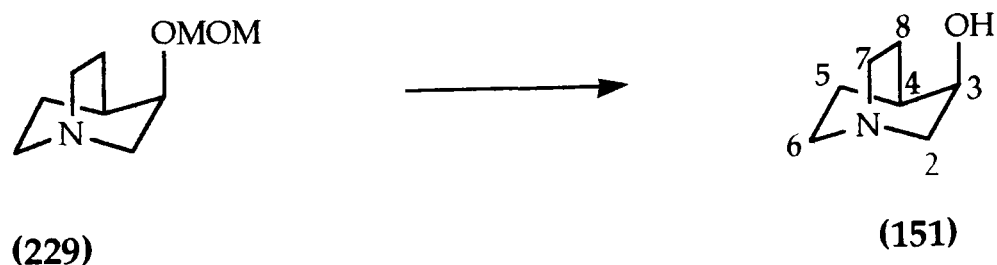
**(3R)-1-Aza-3-(methyloxymethoxy)-bicyclo-[2.2.2]-heptane (229)**



Trifluoroacetic acid (560 mg, 4.9 mmol) was added to a stirred solution of the piperidine (228) (60 mg, 0.16 mmol) in dichloromethane (10 ml). After 1h the reaction mixture was diluted with dichloromethane (100 ml), washed with saturated sodium hydrogen carbonate (2 x 4 ml), dried and concentrated *in vacuo*. The residue was dissolved in ethanol (15 ml), refluxed for 6h and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with methanol : ammonia (19:1) gave the title compound (229) (7.5 mg, 27%) as a colourless oil,  $R_F$  0.4,  $[\alpha]_D^{25}$  -23.4 ( $c=1$  in 1N HCl),  $\delta_H$  (400) 1.86-1.97 (2H, m, 5- $H_AH_B$ , 7- $H_AH_B$ ), 2.06-2.12 (1H, m, 5- $H_AH_B$ ), 2.19-2.25 (1H, m, 7- $H_AH_B$ ), 2.28-2.40 (1H, m, 4-H), 3.14 (1H, dt, J 13 and 3, 6- $H_AH_B$ ), 3.29-3.49 (4H, m, 2- $H_AH_B$ , 6- $H_AH_B$  and 8-H), 3.71 (1H, ddd, J 3, 8 and 13, 2- $H_AH_B$ ) and 4.24-4.26 (1H, m, CHOMOM),  $\delta_C$  (100) 18.25 ( $CH_2$ ), 21.91 ( $CH_2$ ), 28.52 (CH), 51.94 ( $CH_2$ ), 53.09 ( $CH_2$ ), 61.13 (CH), 61.57 ( $CH_2$ ), 65.03 ( $CH_3$ ) and 92.76 ( $CH_2$ ).

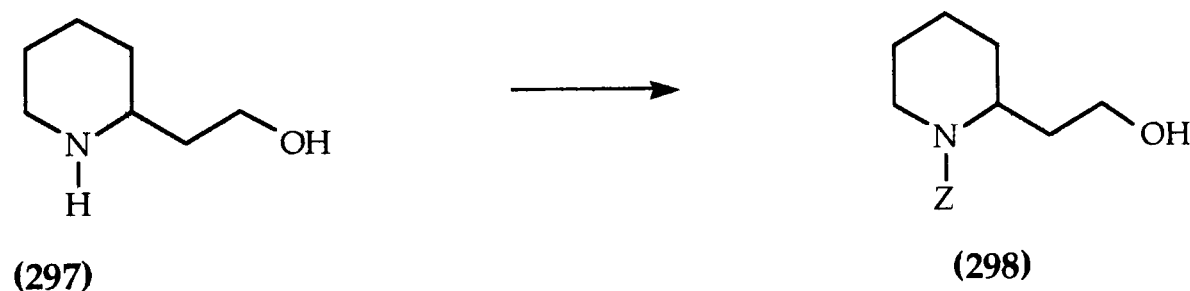
**3-(R)-1-Aza-3-hydroxy-bicyclo-[2.2.2]-heptane**

**[3-(R)-quinuclidinol] (151)**



12M hydrochloric acid (5 ml) was added to a solution of the quinuclidinol (**229**) (20 mg, 0.012 mmol) in ethanol (5 ml), the resulting solution was refluxed for 15 mins and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with methanol : ammonia (9:1) gave the **title compound (151)** (12 mg, 83%) as a colourless oil,  $R_F$  0.15,  $[\alpha]_D^{25}$  -39.5 ( $c=0.5$  in 1N HCl), Lit  $[\alpha]_D^{20}$  +45.8° ( $c=3.0$  in 1N HCl) for the (*S*) enantiomer,  $^{133}\nu_{max}$  3450  $cm^{-1}$ ,  $\delta_H$  (400) 1.12-1.47 (2H, m, 5- $H_AH_B$  and 7- $H_AH_B$ ), 1.48-1.78 (2H, m, 4-H and 5- $H_AH_B$ ), 1.79-2.00 (1H, m, 7- $H_AH_B$ ), 2.39-2.90 (5H, m, 2- $H_AH_B$ , 8-H and 6-H), 2.91-3.09 (1H, m, 2- $H_AH_B$ ), 3.61-3.78 (1H, m, 3-H) and 5.31 (1H, br s, OH),  $\delta_C$  (400) 18.67 ( $CH_2$ ), 28.53 ( $CH_2$ ), 28.12 (CH), 46.06 ( $CH_2$ ), 47.12 ( $CH_2$ ), 57.72 ( $CH_2$ ) and 66.72 (CH). This data is consistent with an authentic sample of the racemic material from the Aldrich Chemical Company.

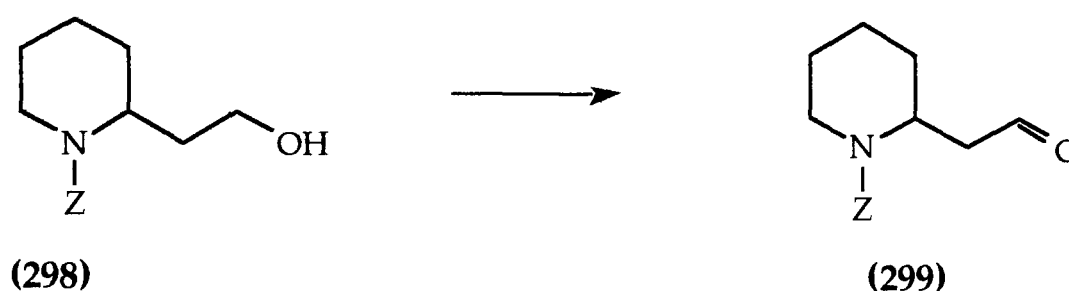
**(±) 1-Benzyl-2-hydroxyethylpiperidine-1-carboxylate (298)**



Benzyl chloroformate (13.2 g, 85.3 mmol) and 2M aqueous sodium hydroxide (40 ml, 85.3 mmol) were added simultaneously to a stirred solution of 2-piperidineethanol (**297**) (10 g, 77.5 mmol) and sodium hydroxide (3.1 g, 77.5 mmol) in water (40 ml) at 0°C. The reaction mixture was warmed to room temperature and the resulting solution stirred for 16h, then acidified to pH1 with 2M aqueous hydrochloric acid and extracted with dichloromethane (3 x 150 ml). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (50 ml) and saturated aqueous sodium chloride (50 ml), dried and concentrated *in vacuo* to give the **title compound (298)** (18.35 g, 90%) as a colourless oil,  $\nu_{max}$  ( $CH_2Cl_2$ ) 1680 and 3220  $cm^{-1}$ ,  $\delta_H$  (270) 1.29-1.58 (7H, m, 3- $CH_2$ , 4- $CH_2$ , 5-

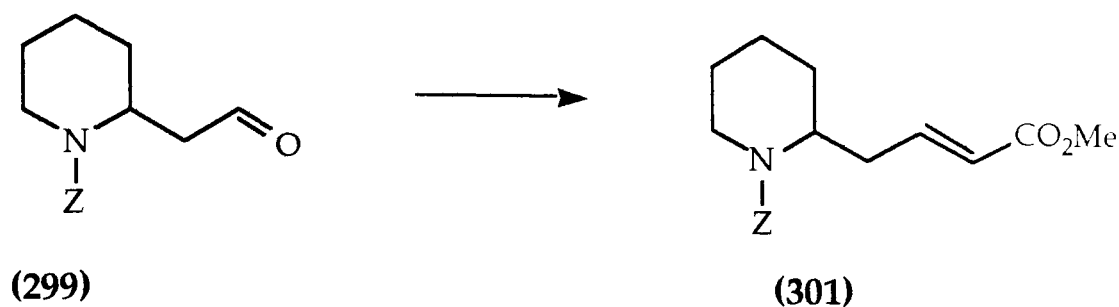
CH<sub>2</sub>CH<sub>A</sub>H<sub>B</sub>CH<sub>2</sub>OH), 1.81 (1H, app br t, J 13.3, CH<sub>A</sub>H<sub>B</sub>CH<sub>2</sub>OH), 2.84 (1H, br t, J 13, 6-**Hax**), 3.39 (2H, m, CH<sub>2</sub>OH), 3.91 (1H, br d, J 13, 6-**Heq**), 4.34 (1H, m, 2-**Heq**), 5.08 (2H, br s, PhCH<sub>2</sub>), 7.28-7.39 (5H, m, C<sub>6</sub>H<sub>5</sub>), δ<sub>C</sub> (100) 18.53 (CH<sub>2</sub>), 25.27 (CH<sub>2</sub>), 28.08 (CH<sub>2</sub>), 32.47 (CH<sub>2</sub>), 38.80 (CH<sub>2</sub>), 47.88 (CH), 58.32 (CH<sub>2</sub>), 66.02 (CH<sub>2</sub>), 127.32 (CH), 127.66 (CH), 128.34 (CH), 137.20 (C), and 154.65 (C), m/z 264 (100%, M + H), 218 (2, M<sup>+</sup> - CH<sub>2</sub>CH<sub>2</sub>OH), 173 (2, M - C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>), and 156 (18, M - C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>O), [Found: M + H, 264.1600. C<sub>15</sub>H<sub>21</sub>NO<sub>3</sub> requires M+H, 264.1600].

**(±) N-(Benzyloxycarbonyl)-2-piperidineethanal (299)**



A solution of pyridine-sulphur trioxide complex (9.1 g, 19.0 mmol) in dimethyl sulphoxide (29.6 ml, 380 mmol) was added to an ice-cooled solution of the piperidine **(298)** (5 g, 19.0 mmol) and triethylamine (9.6 g, 95 mmol) in dichloromethane (200 ml) under an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature and, after 16h, the resulting solution was diluted with dichloromethane (200 ml), washed with water (3 x 30 ml) and saturated aqueous sodium chloride (50 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) gave the title compound **(299)** (4.0 g, 82%) as a colourless oil. R<sub>F</sub> 0.65, δ<sub>H</sub> (90) 1.3-2.15 (6H, m), 2.95 (1H, br t, J 13, 6-**Hax**), 2.75 (2H, m, CH<sub>2</sub>CHO), 4.35 (1H, br d, J 12, 6-**Heq**), 5.05 (1H, br s, 2-**Heq**), 5.20 (2H, s, PhCH<sub>2</sub>), 7.42 (5H, s, C<sub>6</sub>H<sub>5</sub>) and 9.3 (1H, s, CHO) which was used directly without further purification.

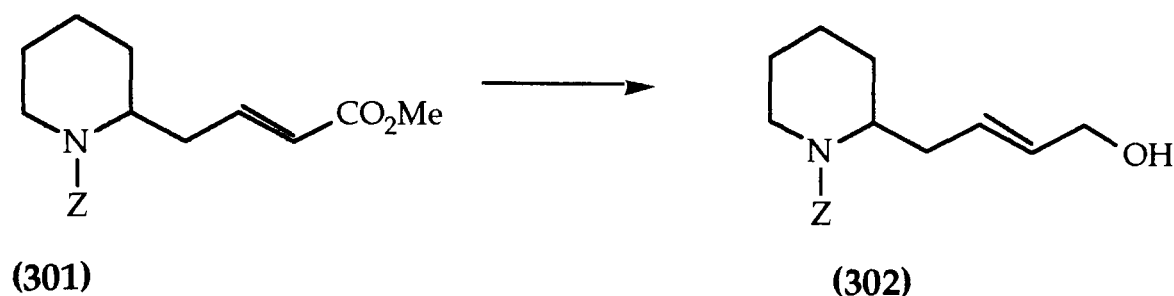
**Methyl 4-[(±) N-(Benzyloxycarbonyl)-2-piperidiny]-2-butenate (301)**



A solution of the aldehyde **(299)** (4.0 g, 15 mmol) and methyl triphenylphosphorylidene acetate **(300)** (5.6 g, 16.8 mmol) in dichloromethane (100 ml) were stirred under a nitrogen atmosphere for 16h. The resulting solution was filtered, the solid residue washed with dichloromethane (200 ml) and the combined organic extracts concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) to give the title compound **(301)** (3.65 g, 75%) as a colourless oil,  $R_F$  0.6,  $\nu_{\max}$  1685 and 1710  $\text{cm}^{-1}$ ,  $\delta_H$  (400) 1.18-1.30 (1H, m), 1.31-1.84 (5H, m), 2.21-2.27 (1H, m,  $\text{CH}_A\text{H}_B\text{CH}=\text{CH}$ ), 2.32-2.38 (1H, m,  $\text{CH}_A\text{H}_B\text{CH}=\text{CH}$ ), 2.64, (1H, br t, J 12.9, 6-**H**<sub>ax</sub>), 3.51 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 3.95 (1H, br d, J 12.9, 6-**H**<sub>eq</sub>), 4.27 (1H, br s, 2-**H**<sub>eq</sub>), 4.92 (2H, s,  $\text{PhCH}_2$ ), 5.66 (1H, d, J 15.6,  $\text{CH}=\text{CHCO}_2\text{Me}$ ), 6.69 (1H, dt, J 15.6 and 7.5,  $\text{CH}=\text{CHCO}_2\text{Me}$ ) and 7.15 (5H, s,  $\text{C}_6\text{H}_5$ ),  $\delta_C$  (68) 18.35 ( $\text{CH}_2$ ), 24.71 ( $\text{CH}_2$ ), 27.39 ( $\text{CH}_2$ ), 32.20 ( $\text{CH}_2$ ), 38.64 ( $\text{CH}_2$ ), 49.36 (CH), 50.75 ( $\text{CH}_3$ ), 66.43 ( $\text{CH}_2$ ), 122.41 (CH), 127.22 (CH), 127.87 (CH), 127.49 (CH), 144.94 (CH), 154.73 (C) and 165.82 (C),  $m/z$  335 (92%,  $\text{M} + \text{NH}_4$ ) and 318 (100,  $\text{M} + \text{H}$ ), [Found:  $\text{M} + \text{H}$ , 318.1704.  $\text{C}_{18}\text{H}_{24}\text{NO}_4$  requires  $\text{M} + \text{H}$ , 318.1705].

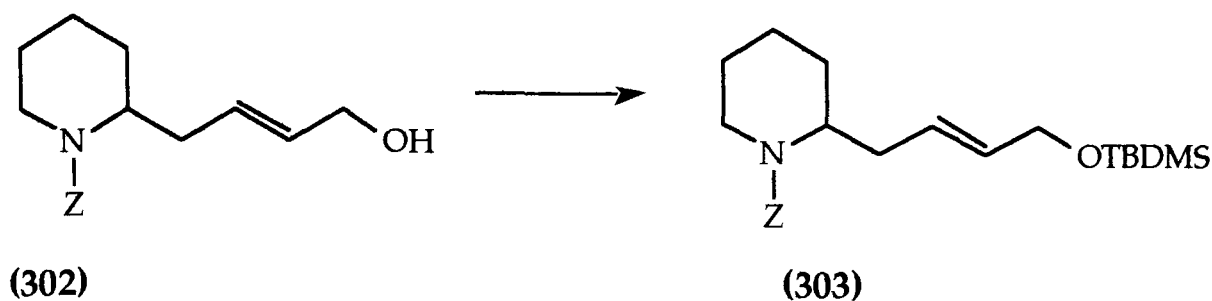


4-[(±)-N-(Benzyloxycarbonyl)-2-piperidiny]-2-buten-1-ol (302)



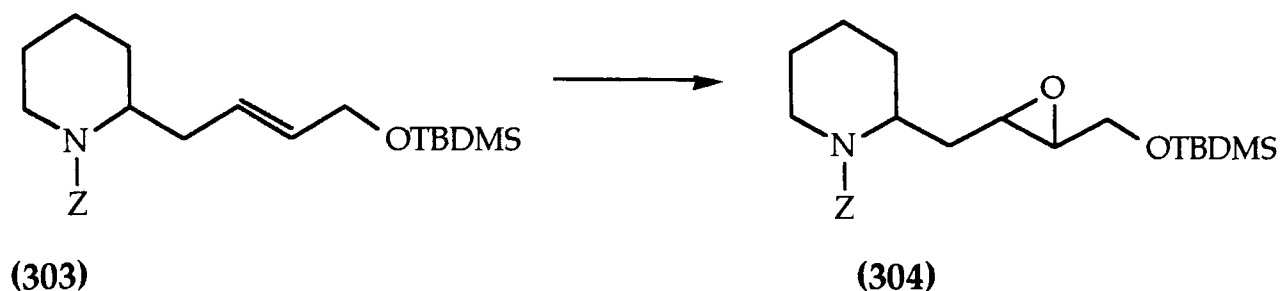
A solution of diisobutylaluminium hydride (16.8 ml, 25 % wt soln, 1.5 M, 25 mmol) was added to a solution of the piperidine (301) (2 g, 6.3 mmol) in toluene (50 ml) at  $-78^{\circ}\text{C}$  under an atmosphere of nitrogen. After 6h saturated aqueous potassium tartrate was added (15 ml). The reaction mixture was warmed to room temperature, filtered, and the residue washed with dichloromethane (200 ml). The combined filtrates were washed with water (25 ml) and saturated aqueous sodium chloride (25 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) gave the title compound (302) (1.6 g, 87%) as a colourless oil,  $R_F$  0.4,  $\nu_{\text{max}}$  1680 and  $3240\text{ cm}^{-1}$ ,  $\delta_{\text{H}}$  (250) 1.35-1.82 (6H, m), 2.19-2.34 (1H, m,  $\text{CH}_A\text{H}_B\text{CH}=\text{CH}$ ), 2.39-2.65 (1H, m,  $\text{CH}_A\text{H}_B\text{CH}=\text{CH}$ ), 2.94, (1H, br t,  $J$  13.5, 6-H<sub>ax</sub>), 3.19 (1H, br s, OH), 3.98-4.30 (3H, m,  $\text{CH}_2\text{OH}$ , 6-Heq), 4.43 (1H, br s, 2-Heq), 5.19, (2H, s,  $\text{PhCH}_2$ ), 5.32-5.63, (2H, m,  $\text{CH}=\text{CH}$ ) and 7.43 (5H, s,  $\text{C}_6\text{H}_5$ ),  $\delta_{\text{C}}$  (75) 18.74 ( $\text{CH}_2$ ), 25.37 ( $\text{CH}_2$ ), 27.81 ( $\text{CH}_2$ ), 32.79 ( $\text{CH}_2$ ), 39.23 ( $\text{CH}_2$ ), 50.52 (CH), 63.32 ( $\text{CH}_2$ ), 66.85 ( $\text{CH}_2$ ), 127.81 (CH), 127.90 (CH), 128.42 (CH), 128.98 (CH), 131.53 (CH) and 155.68 (C),  $m/z$  290 (32%,  $M + H$ ), 218 (24,  $M - \text{CH}_2\text{CH}=\text{CHCH}_2\text{OH}$ ), 92 (22,  $\text{C}_6\text{H}_5\text{CH}_3$ ), 91 (100,  $\text{C}_6\text{H}_5\text{CH}_2$ ) and 57 (3,  $\text{CH}=\text{CHCH}_2\text{OH}$ ), [Found:  $M+H$ , 290.1756.  $\text{C}_{17}\text{H}_{23}\text{NO}_3$  requires  $M+H$ , 290.1756].

**4-[(±)-N-(Benzyloxycarbonyl)-2-piperidiny]-2-penten-1-ol (302)**



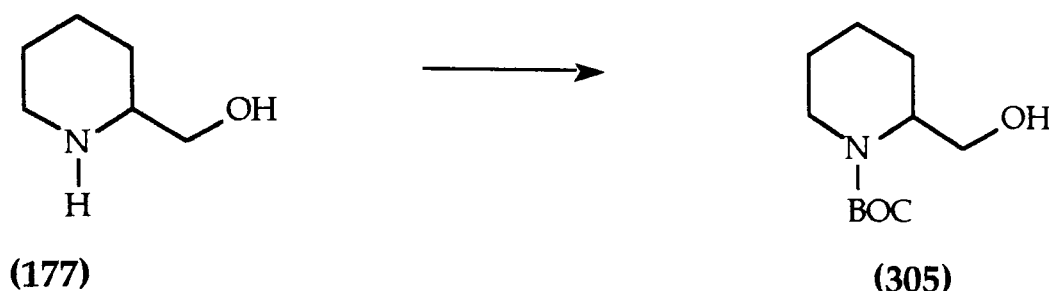
*tert*-Butyldimethylsilyl chloride (0.57 g, 3.8 mmol) was added to a solution of the allylic alcohol (302) (1.0 g, 3.5 mmol), triethylamine (0.38 g, 3.8 mmol) and DMAP (20 mg, 0.17 mmol) in dichloromethane (40 ml) under a nitrogen atmosphere. The reaction mixture was stirred for 16 h, diluted with dichloromethane (100 ml), washed with 2M aqueous citric acid (30 ml), water (10 ml) and saturated aqueous sodium chloride (30 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) gave the title compound (303) (1.10 g, 79%) as a colourless oil,  $R_F$  0.8,  $\nu_{\max}$  1690  $\text{cm}^{-1}$ ,  $\delta_H$  (400) 0.01 (6H, s,  $\text{Si}(\text{CH}_3)_2$ ), 0.86 (9H, s,  $\text{SiC}(\text{CH}_3)_3$ ), 1.22-1.64 (6H, m), 2.21-2.27 (1H, m,  $\text{CH}_A\text{H}_B\text{CH}=\text{CHCH}_2\text{OSi}$ ), 2.28-2.34 (1H, m,  $\text{CH}_A\text{H}_B\text{CH}=\text{CHCH}_2\text{OSi}$ ), 2.80 (1H, br t,  $J$  11, 6-**H**<sub>ax</sub>), 3.90-4.09 (1H, m, 6-**H**<sub>eq</sub>), 4.18-4.38, (1H, m, 2-**H**<sub>eq</sub>), 5.08 (2H, s,  $\text{PhCH}_2$ ), 5.51-5.54 (2H, m,  $\text{CH}=\text{CH}$ ) and 7.30 (5H, s,  $\text{C}_6\text{H}_5$ ),  $\delta_C$  (100) -5.17 and -5.30 ( $\text{CH}_3$ ), 18.29 ( $\text{CH}_2$ ), 18.91 and 18.70 ( $\text{CH}_2$ ), 22.53 ( $\text{CH}_2$ ), 25.58 and 25.41 ( $\text{CH}_2$ ), 25.93 ( $\text{CH}_3$ ), 32.66 ( $\text{CH}_2$ ), 39.25 and 39.04 ( $\text{CH}_2$ ), 50.75 and 50.34 ( $\text{CH}$ ), 63.01 and 63.73 ( $\text{CH}$ ), 66.79 ( $\text{CH}_2$ ), 127.25 ( $\text{CH}$ ), 127.69 ( $\text{CH}$ ), 127.77 ( $\text{CH}$ ), 128.38 ( $\text{CH}$ ) and 155.44 (C),  $m/z$  218 (28%,  $\text{M}-\text{CH}_2\text{CH}=\text{CHCH}_2\text{OTBDMS}$ ), 212 (7,  $\text{M}-\text{PhCH}_2\text{O}_2\text{C}-t\text{Bu} + \text{H}$ ), 92 (20,  $\text{C}_6\text{H}_5\text{CH}_3$ ), 91 (100,  $\text{C}_6\text{H}_5\text{CH}_2$ ) and 77 (3,  $\text{C}_6\text{H}_5$ ), [Found:  $\text{M}-\text{CH}_2\text{CH}=\text{CHCH}_2\text{OTBDMS}$ , 218.1214.  $\text{C}_{13}\text{H}_{16}\text{NO}_2$  requires  $\text{M}-\text{CH}_2\text{CH}=\text{CHCH}_2\text{OTBDMS}$ , 218.1181].

**4-[(±)-N-(Benzyloxycarbonyl)-2-piperidiny]-2,3-epoxy-butan-1-ol (304)**



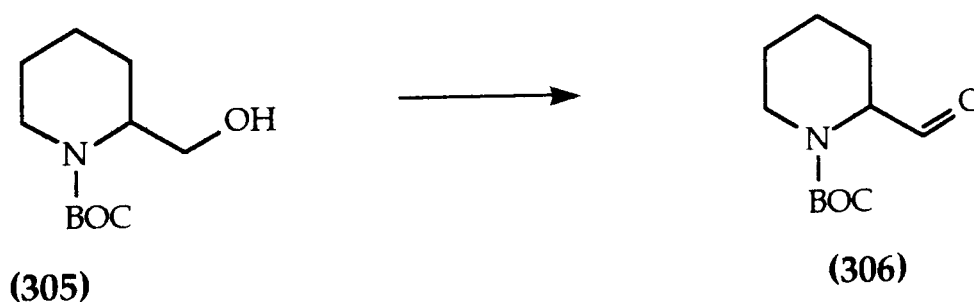
*meta*-Chloroperoxybenzoic acid (342 mg, 50% pure, 2 mmol) was added to a stirred solution of the alkene (303) at room temperature. After 90min the reaction mixture was diluted with dichloromethane (100 ml), washed with saturated sodium hydrogen carbonate (30 ml) and saturated aqueous sodium chloride (30 ml), dried and concentrated *in vacuo* to give the title compound (304) (148 mg, 71%) as a colourless oil,  $R_F$  0.8,  $\delta_H$  (400) 0.04-0.09 (6H, m, Si(CH<sub>3</sub>)<sub>2</sub>), 0.89 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.12-1.75 (7H, m), 1.8-2.05 (1H, m), 2.65-2.9 (3H, m, 6-H<sub>ax</sub> and CH<sub>2</sub>CH(O)CH), 3.48-3.58 (1H, m, CH<sub>A</sub>H<sub>B</sub>OTBDMS), 3.60-3.8 (1H, m, CH<sub>A</sub>H<sub>B</sub>OTBDMS), 4.00 (1H, br s, 6-Heq), 4.55 (1H, br s, 2-Heq), 5.12-5.17 (2H, m, PhCH<sub>2</sub>) and 7.27-7.36 (5H, m, C<sub>6</sub>H<sub>5</sub>),  $\delta_C$  (68) -5.20 (CH<sub>3</sub>), 18.00 (CH<sub>2</sub>), 18.41 (C), 25.51 and 25.89 (CH<sub>2</sub>), 25.94 and 26.04 (CH<sub>3</sub>), 28.32 (CH<sub>2</sub>), 32.27 and 32.88 (CH<sub>2</sub>), 39.19 and 39.48 (CH<sub>2</sub>), 48.88 and 49.08 (CH), 53.83 and 54.14 (CH), 58.61 (CH), 63.17 and 63.88 (CH<sub>2</sub>), 67.08 and 67.15 (CH<sub>2</sub>), 127.85 (CH), 127.97 (CH), 128.50 (CH), 137.00 (C) and 155.48 (C),  $m/z$  362 (5%, M-(CH<sub>3</sub>)<sub>3</sub>C), 218 (7, M-CH<sub>2</sub>CHOCHCH<sub>2</sub>OTBDMS), 108 (5, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>OH), 107 (5, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>O) and 91 (100, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>), [Found: M-(CH<sub>3</sub>)<sub>3</sub>C, 362.1803. C<sub>19</sub>H<sub>28</sub>NO<sub>4</sub>Si requires M-(CH<sub>3</sub>)<sub>3</sub>C, 362.1788].

**(±) N-(tert-Butyloxycarbonyl)-2-piperidinemethanol (305)**



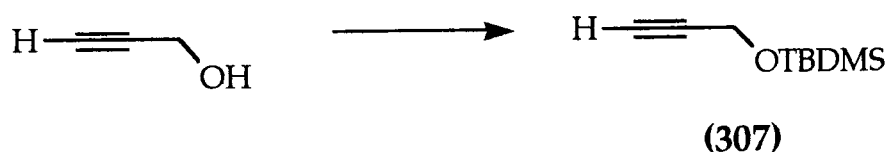
Di-*tert*-butyl dicarbonate (4.18 g, 19.1 mmol) was added to a stirred solution of 2-piperidinemethanol (**177**) (2 g, 17.4 mmol) and triethylamine (1.93 g, 19.1 mmol) in dichloromethane (100 ml). The reaction mixture was stirred for 16h, then acidified to pH1 with 2M aqueous citric acid and extracted with dichloromethane (3 x 150 ml). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (50 ml), saturated aqueous sodium chloride (50 ml), dried and concentrated *in vacuo* to give the title compound (**305**) (3.0 g, 80%) as a colourless oil,  $\nu_{\max}$  1688 and 3430  $\text{cm}^{-1}$ ,  $\delta_{\text{H}}$  (400) 1.34-1.68 (5H, m), 1.41 (9H, s,  $(\text{CH}_3)_3\text{CO}$ ), 1.74 (1H, ddd, J 13.1, 13.1 and 3.0, 5- $\text{H}_{\text{A}}\text{H}_{\text{B}}$ ), 3.57 (1H, ddd, J 13.1, 13.1 and 3.0, 6- $\text{H}_{\text{ax}}$ ), 3.71 (2H, dd, J 10.9 and 8.2,  $\text{CH}_2\text{OH}$ ), 3.87 (1H, br d, J 13, 6- $\text{H}_{\text{eq}}$ ) and 4.17-4.21 (1H, m, 2- $\text{H}_{\text{eq}}$ ).  $\delta_{\text{C}}$  (100) 19.61 ( $\text{CH}_2$ ), 25.23 ( $\text{CH}_2$ ), 28.44 ( $\text{CH}_3$ ), 28.70 ( $\text{CH}_2$ ), 40.18 ( $\text{CH}_2$ ), 52.80 ( $\text{CH}$ ), 61.60 ( $\text{CH}_2$ ), 79.59 (C) and 156.08 (C),  $m/z$  238 (15%,  $\text{M}+\text{Na}$ ), 216 (65,  $\text{M}+\text{H}$ ), 184 (53,  $\text{M}-\text{CH}_2\text{OH}$ ), 158 (25,  $\text{M}-\text{tBu}$ ), 142 (42,  $\text{M}-\text{tBuO}$ ) and 114 (59,  $\text{M}-\text{BOC}$ ), [Found:  $\text{M}+\text{H}$ , 216.1613.  $\text{C}_{11}\text{H}_{22}\text{NO}_3$  requires  $\text{M}+\text{H}$ , 216.1600].

**(±) N-(tert-Butyloxycarbonyl)-2-piperidinemethanal (306)**



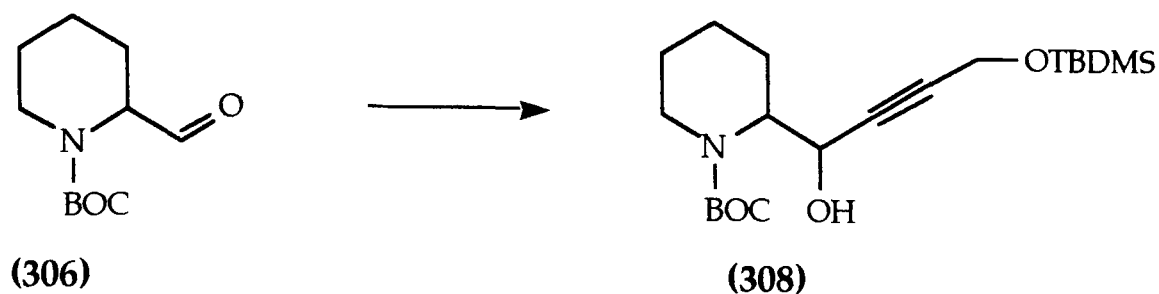
A solution of pyridine-sulphur trioxide complex (2.1 g, 13.1 mmol) in dimethyl sulphoxide (7 ml, 96 mmol) was added to an ice-cooled solution of the piperidine (305) (0.95 g, 4.4 mmol) and triethylamine (2.2 g, 21.8 mmol) in dichloromethane (50 ml). The reaction mixture was allowed to warm to room temperature and after 16h the resulting solution was diluted with dichloromethane (100 ml), washed with water (3 x 20 ml) and saturated aqueous sodium chloride (20 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) gave the title compound (306) (0.70 g, 74%) as a colourless oil,  $R_F$  0.75,  $\delta_H$  (270) 1.15-1.63 (5H, m), 1.39 (9H, s,  $(CH_3)_3CO$ ), 1.92-2.1 (1H, m, 5- $H_AH_B$ ), 2.87 (1H, br t,  $J$  12.4, 6- $H_{ax}$ ), 3.84 (1H, br d,  $J$  12.4, 6- $H_{eq}$ ), 4.43-4.55 (1H, m, 2- $H_{eq}$ ) and 9.50 (1H, s, CHO),  $\delta_C$  (68.5) 20.41 ( $CH_2$ ), 23.11 ( $CH_2$ ), 24.26 ( $CH_2$ ), 27.72 ( $CH_3$ ), 42.12 ( $CH_2$ ), 60.71 (CH), 79.46 (C), 154.90 (C) and 199.84 (CH). The sample was used directly.

#### 1-*tert*-butyldimethylsilyloxy-2-propyne (307)



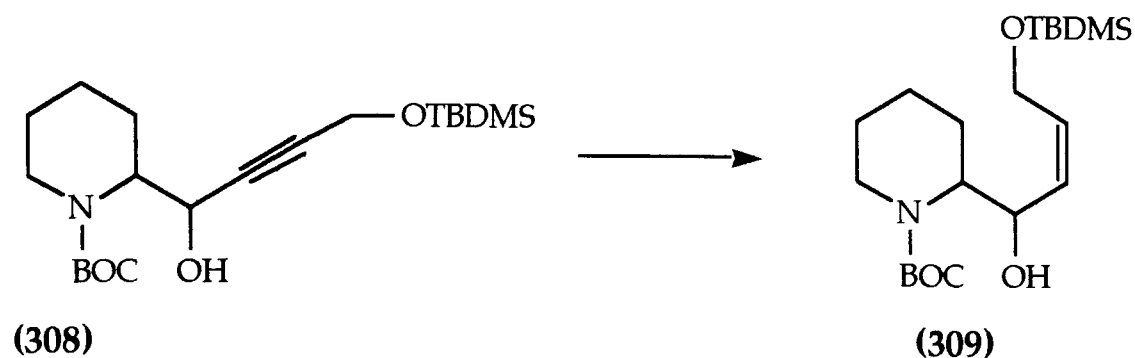
*tert*-Butyldimethylsilyl chloride (29.6 g, 196 mmol) was added to a stirred solution of propargyl alcohol (10 g, 179 mmol), triethylamine (19.8 g, 196 mmol) and 4-dimethylaminopyridine (1.1 g, 9 mmol) in dichloromethane (200 ml). The reaction mixture was stirred for 16h, washed with 2M aqueous hydrochloric acid (2 x 40 ml) and brine (40 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (4:1) gave the title compound (307) (24.9 g, 82%) as a colourless oil,  $R_F$  0.3,  $\delta_H$  (250) 0.05 (6H, s,  $(CH_3)_3Si$ ), 0.88 (9H, s,  $(CH_3)_3CSi$ ), 2.36 (1H, s, C-H) and 4.27 (2H, s,  $CH_2-O$ ).

**4-[(±)-N-(*tert*-Butyloxycarbonyl)-2-piperidinyl]-4-hydroxy-(*O*-*tert*-butyl-dimethylsilyl)-2-butyne-1-ol (308)**



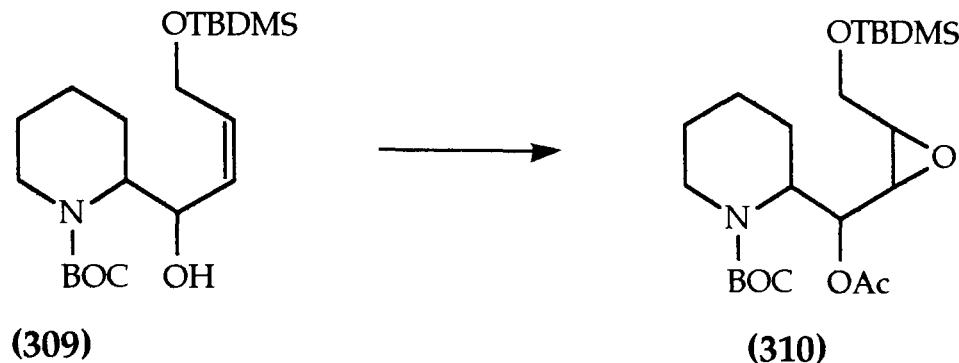
Butyl lithium (1.46 ml, 1.6M in hexanes, 2.35 mmol) was added dropwise to a solution of the alkyne (307) (439 mg, 2.58 mmol) in tetrahydrofuran (10 ml) at  $-78^{\circ}\text{C}$ . The reaction mixture was stirred at this temperature for 20min and at room temperature for a further 20min. The resulting solution was cooled to  $-78^{\circ}\text{C}$  and the piperidine aldehyde (306) (500 mg, 2.35 mmol) was slowly added. Stirring continued for 45min at this temperature and at room temperature for a further 45min. Saturated aqueous ammonium chloride (1 ml) was introduced, the reaction mixture was diluted with dichloromethane (200 ml), washed with water (10 ml) and saturated aqueous sodium chloride (10 ml), dried and concentrated *in vacuo*. Chromatography of the residue over silica gel eluting with dichloromethane : ethyl acetate (9:1) gave the title compound (308) (791 mg, 88%) as a colourless oil,  $R_F$  0.85,  $\nu_{\text{max}}$  1687, 3240  $\text{cm}^{-1}$ ,  $\delta_H$  (400) 0.08 (6H, s,  $(\text{CH}_3)_2\text{Si}$ ), 0.88 (9H, s,  $(\text{CH}_3)_3\text{CSi}$ ), 1.14-1.67 (5H, m), 1.44 (9H, s,  $(\text{CH}_3)_3\text{CO}$ ), 1.94-1.99 (1H, m, 5- $\text{H}_A\text{H}_B$ ), 2.98 (1H, br t, J 11, 6- $\text{H}_{ax}$ ), 3.92 (1H, br d, J 11, 6- $\text{H}_{eq}$ ), 4.10-4.18 (1H, m,  $\text{CHOH}$ ), 4.29 (2H, s,  $\text{CH}_2\text{OSi}$ ) and 4.62 (1H, d, J 6.4, 2- $\text{H}_{eq}$ ),  $\delta_C$  (100) -5.10 ( $\text{CH}_3$ ), 18.29 (C), 19.47 ( $\text{CH}_2$ ), 24.41 ( $\text{CH}_2$ ), 24.66 ( $\text{CH}_2$ ), 25.87 ( $\text{CH}_3$ ), 28.54 ( $\text{CH}_3$ ), 40.81 ( $\text{CH}_2$ ), 51.84 ( $\text{CH}_2$ ), 55.93 (CH), 63.66 (CH), 79.77 (C), 84.17 (C), 84.70 (C) and 155.84 (C),  $m/z$  406 (3%,  $\text{M}+\text{Na}$ ), 384 (7,  $\text{M}+\text{H}$ ), 326 (5,  $\text{M}-t\text{Bu}$ ), 310 (28,  $\text{M}-t\text{BuO}$ ), 184 (20,  $\text{M}-\text{CH}(\text{OH})\text{C}-\text{CCH}_2\text{OTBDMS}$ ) and 128 (100,  $\text{M}-\text{CH}(\text{OH})\text{CCCH}_2\text{OTBDMS}-t\text{Bu}+\text{H}$ ), Found:  $\text{M}+\text{H}$ , 386.2716.  $\text{C}_{20}\text{H}_{40}\text{NO}_4\text{Si}$  requires  $\text{M}+\text{H}$ , 386.2727].

**4-[(±)-N-(*tert*-Butyloxycarbonyl)-2-piperidiny]-4-hydroxy-(*O*-*tert*-butyldimethylsilyl)-2-buten-1-ol (309)**



The alkyne (308) (200 mg, 0.54 mmol) was added to a rapidly stirred solution of palladium on barium sulphate (200 mg, 5%) and quinoline (30  $\mu$ L) in ethyl acetate (4 ml) under an atmosphere of hydrogen. The reaction mixture was stirred until the requisite amount of hydrogen had been absorbed (ca 0.5h), filtered through kieselguhr and concentrated *in vacuo* to give the title compound (309) (185 mg, 92%) as a colourless oil,  $\nu_{\text{max}}$  1680 and 3254  $\text{cm}^{-1}$ ,  $\delta_{\text{H}}$  (400) 0.26 (6H, s,  $(\text{CH}_3)_2\text{Si}$ ), 0.86 (9H, s,  $(\text{CH}_3)_3\text{CSi}$ ), 1.22-1.62 (5H, m), 1.39 (9H, s,  $(\text{CH}_3)_3\text{CO}$ ), 2.03 (1H, br d, J 15, 5- $\text{H}_{\text{A}}\text{H}_{\text{B}}$ ), 2.68 (1H, ddd, J 13, 13 and 3, 6- $\text{H}_{\text{ax}}$ ), 4.00-4.07 (2H, m,  $\text{CHOH}$  and 6- $\text{H}_{\text{eq}}$ ), 4.19 (1H, ddd, J 13, 4.4 and 1.2,  $\text{CH}_{\text{A}}\text{H}_{\text{B}}\text{OSi}$ ), 4.28 (1H, ddd, J 13, 4.9 and 1.2,  $\text{CH}_{\text{A}}\text{H}_{\text{B}}\text{OSi}$ ) and 5.51-5.63 (2H, m,  $\text{CH}=\text{CH}$ ),  $\delta_{\text{C}}$  (100) -5.1 ( $\text{CH}_3$ ), 18.13 (C), 19.40 ( $\text{CH}_2$ ), 24.29 ( $\text{CH}_2$ ), 25.07 ( $\text{CH}_2$ ), 25.81 ( $\text{CH}_3$ ), 28.36 ( $\text{CH}_3$ ), 40.44 ( $\text{CH}_2$ ), 55.20 ( $\text{CH}_2$ ), 59.63 ( $\text{CH}_2$ ), 65.87 (CH), 79.23 (C), 131.83 (CH), 132.14 (CH) and 155.12 (C),  $m/z$  408 (3%,  $\text{M}+\text{Na}$ ), 386 (20,  $\text{M}+\text{H}$ ), 284 (15,  $\text{M}-\text{BOC}$ ), 272 (9,  $\text{M}-\text{TBDMS}+\text{H}$ ), 228 (10,  $\text{M}-\text{BOC}-t\text{Bu}+\text{H}$ ), 184 (27,  $\text{M}-\text{CH}(\text{OH})\text{CH}=\text{CHCH}_2\text{OTBDMS}$ ) and 128 (100,  $\text{M}-\text{CH}(\text{OH})\text{CH}=\text{CHCH}_2\text{OTBDMS}-t\text{Bu}+\text{H}$ ), [Found:  $\text{M}+\text{H}$ , 386.2716.  $\text{C}_{20}\text{H}_{40}\text{NO}_4\text{Si}$  requires  $\text{M}+\text{H}$ , 386.2727].

**4-[(±)-N-(*tert*-Butyloxycarbonyl)-2-piperidiny]-4-acetoxy-(*O*-*tert*-butyldimethylsilyl)-2,3-epoxy-butan-1-ol (310)**

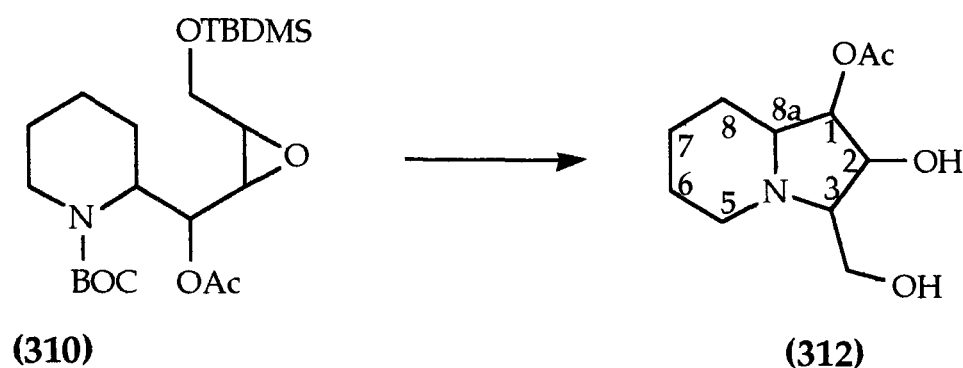


*m*-Chloroperoxybenzoic acid (269 mg, 0.8 mmol, 50% pure) was added to a solution of the alkene **(309)** (150 mg, 0.4 mmol) in dichloromethane (15 ml) at 0°C. The reaction mixture was warmed to room temperature, stirred for 90min, diluted with dichloromethane (100 ml), washed with saturated aqueous sodium hydrogen carbonate (5 ml), and saturated aqueous sodium chloride (5 ml), dried and concentrated *in vacuo* to yield the epoxide. The crude epoxide was dissolved in dichloromethane (20 ml), acetic anhydride (159 mg, 1.6 mmol) and pyridine (123 mg, 1.6 mmol) were added and the reaction mixture stirred at room temperature for 16h. The resulting solution was diluted with dichloromethane (100 ml), washed with 2M aqueous hydrochloric acid (2 × 7 ml), and saturated aqueous sodium chloride (2 ml), dried and concentrated *in vacuo*. Chromatography of the residue over alumina eluting with hexane : ethyl acetate (9:1) gave the title compound **(310)** (124 mg, 72%) as a colourless oil,  $R_F$  0.90,  $\delta_H$  (400) 0.10 (6H, s, (CH<sub>3</sub>)<sub>2</sub>Si), 0.91 (9H, s, (CH<sub>3</sub>)<sub>3</sub>CSi), 1.06-1.72 (6H, m), 1.46 (9H, s, (CH<sub>3</sub>)<sub>3</sub>CO), 2.09 (3H, s, CH<sub>3</sub>CO), 2.74 (1H, br t, J 12.7, 6-H<sub>ax</sub>), 3.10 (1H, dt, J 4.2 and 6.3, CHCH<sub>2</sub>OSi), 3.17 (1H, dd, J 8.8 and 4.2, CHCHOAc), 3.72 (1H, dd, J 11.8 and 3.6, CH<sub>A</sub>H<sub>B</sub>OSi), 3.91 (1H, dd, J 11.8 and 6.2, CH<sub>A</sub>H<sub>B</sub>OSi), 4.02 (1H, br d, J 12.7, 6-Heq), 4.39-4.48 (1H, m, 2-Heq) and 5.19 (1H, dd, J 8.8 and 10, CHOAc),  $\delta_C$  (100) -5.07 (CH<sub>3</sub>), 18.43 (C), 19.51 (CH<sub>2</sub>), 20.92 (CH<sub>3</sub>), 24.62 (CH<sub>2</sub>), 25.10 (CH<sub>2</sub>), 26.01 (CH<sub>3</sub>), 28.55 (CH<sub>3</sub>), 40.61 (CH<sub>2</sub>), 51.58 (CH<sub>2</sub>), 57.11 (CH), 58.60 (CH), 62.04 (CH<sub>2</sub>), 68.94 (CH), 80.09 (C), 154.84 (C) and 169.70 (C),  $m/z$  466 (1%, M+Na), 444 (2,



M+H), 443 (1, M), 386 (3, M-<sup>t</sup>Bu) and 342 (12, M-BOC), [Found: M, 443.2698. C<sub>22</sub>H<sub>41</sub>NO<sub>6</sub>Si requires M, 443.2703].

### 1-Acetoxy-2-hydroxy-3-(hydroxymethyl)-indolizidine (312)



Trifluoroacetic acid (455 mg, 0.14 mmol) was added to a stirred solution of the piperidine (310) (60 mg, 0.14 mmol) in dichloromethane (20 ml). After 1h the reaction mixture was diluted with dichloromethane (100 ml), washed with saturated sodium hydrogen carbonate (2 x 20 ml), dried and concentrated *in vacuo*. The residue was dissolved in methanol (20 ml), stirred at room temperature for 36h and concentrated *in vacuo* to give the title compound (312) (17 mg, 54%) as a thick colourless oil,  $\delta_{\text{H}}$  (400) 1.25-1.35 (1H, m, 8- $\text{H}_{\text{A}}\text{H}_{\text{B}}$ ), 1.4-1.55 (2H, m, 6- $\text{CH}_{\text{A}}\text{H}_{\text{B}}$  and 7- $\text{H}_{\text{A}}\text{H}_{\text{B}}$ ), 1.65-1.74 (1H, m, 6- $\text{H}_{\text{A}}\text{H}_{\text{B}}$ ), 1.82-1.91 (1H, m, 7- $\text{H}_{\text{A}}\text{H}_{\text{B}}$ ), 1.97 (1H, br d, J 13, 8- $\text{H}_{\text{A}}\text{H}_{\text{B}}$ ), 2.12 (3H, s,  $\text{CH}_3\text{CO}_2$ ), 2.79 (1H, dt, J 3 and 13, 5- $\text{H}_{\text{ax}}$ ), 2.97-3.38 (1H, m, 8a-H), 3.58-3.72 (3H, m,  $\text{CHCH}_2\text{OH}$ ), 4.24 (1H, br d, J 13, 5- $\text{H}_{\text{eq}}$ ), 4.31 (1H, d, J 10, 2-H) and 5.15 (1H, dd, J 8 and 10, 1-H),  $\delta_{\text{C}}$  (100) 20.48 ( $\text{CH}_3$ ), 24.05 ( $\text{CH}_2$ ), 25.97 ( $\text{CH}_2$ ), 31.88 ( $\text{CH}_2$ ), 46.28 ( $\text{CH}_2$ ), 59.62 (CH), 62.57 ( $\text{CH}_2$ ), 68.30 (CH), 67.00 (CH), 75.98 (CH) and 171.07 (C).

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## **Publication**

## New Members of the Chiral Pool: $\beta$ -Hydroxypiperidine Carboxylates from Baker's Yeast Reductions of the Corresponding Keto-esters

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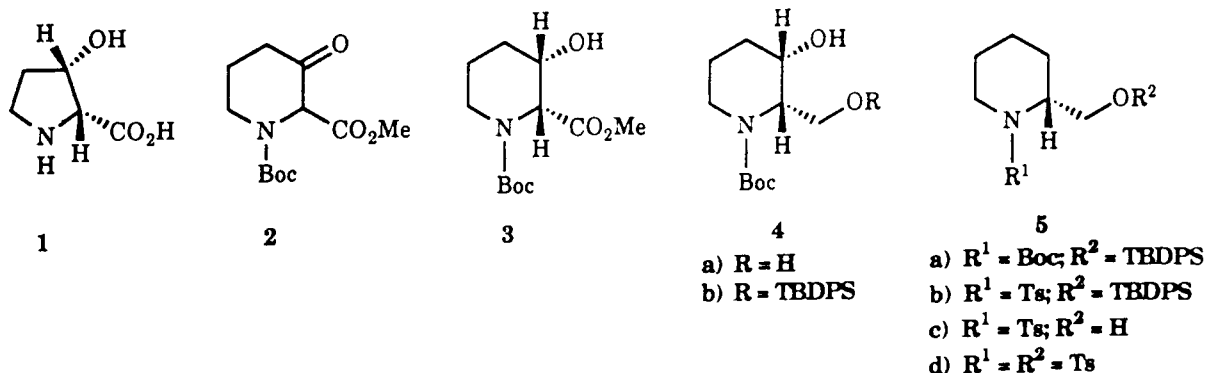
David Haigh

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KT18 5XQ.

(Received in UK 25 January 1993)

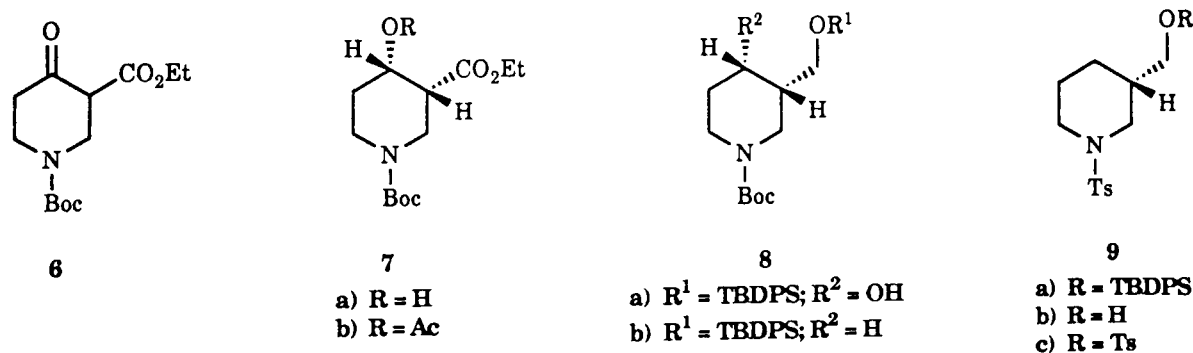
**Summary:** Baker's yeast reduction of the keto-piperidinecarboxylates **2** and **6** leads to the corresponding hydroxy-esters **3** and **7a** in good chemical yields and with >99% d.e. and >93% e.e. in both cases.

Amongst the many applications of baker's yeast in asymmetric synthesis, the reduction of (racemic)  $\beta$ -keto-esters to the corresponding  $\beta$ -hydroxy-esters is one of the most useful transformations which can be achieved using this organism.<sup>1</sup> Thus, when we recently required access to 3-hydroxyproline **1**, yeast reductions of 3-ketoprolines, protected at nitrogen, proved to be a viable option.<sup>2,3</sup> The success of this conversion encouraged us to examine similar reactions of related ketopiperidine carboxylates, in the hope of gaining access to some useful new chiral pool members in an area which is somewhat depleted in terms of the availability of homochiral starting materials.



Exposure of the keto-piperidine carboxylate **2** to fermenting baker's yeast in aqueous sucrose<sup>5</sup> (48h, 30°C) followed by filtration through kieselguhr, saturation of the filtrate with sodium chloride and ethyl acetate extraction (5x) gave a hydroxypiperidine carboxylate in 75-80% yield (5-10 g scale) as an oil, which was a single diastereoisomer according to <sup>13</sup>C NMR

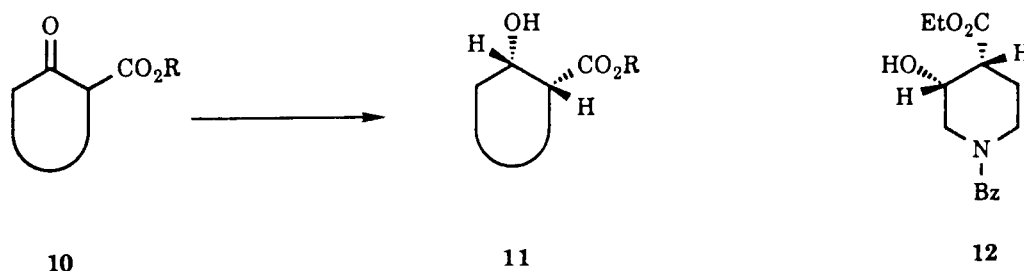
A similar reduction of the 4-ketopiperidine-3-carboxylate **6**<sup>11</sup> also led, in 78% isolated yield, to a single diastereoisomer of a hydroxypiperidine carboxylate **7a**, m.p. 58 - 60°C,<sup>12</sup> [ $\alpha$ ]<sub>D</sub> +25.6, (c, 2.4, CH<sub>2</sub>Cl<sub>2</sub>), the identity of which was proven in a similar manner and in similar yields to the foregoing example.



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induced desilylation to give the alcohol **9b** and tosylation. The *bis*-tosylate **9c**, m.p. 88-89°C, (Lit.<sup>15</sup> m.p. 87-89°C for the (*R*)-enantiomer) showed  $[\alpha]_D - 50.2$ , (c, 1.1, CHCl<sub>3</sub>) [Lit.<sup>15</sup>  $[\alpha]_D + 54.0$ , (c, 1.4, CHCl<sub>3</sub>) for the (*R*)-enantiomer]. Thus, our sample is clearly the (*S*)-enantiomer as shown and has an enantiomeric enrichment of 93%, according to the optical rotation data. However, chiral shift reagent experiments (Tris [3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium (III), CDCl<sub>3</sub>) using *rac*-**9c** as a standard, did not show the presence of any of the (*R*)-enantiomer in the *bis*-tosylate **9c** indicating that this is also a minimum value for the e.e. of the initial yeast reduction product **7a**. Appropriate checks on other column fractions and mother liquors showed that no significant enantiomeric enrichment was occurring during the foregoing transformations and therefore that the initial reduction product **7a** has at least 93% e.e.

Finally, we note that similar reductions of the carbon and sulfur analogues of these piperidines (*ie.* **6** with CH<sub>2</sub> or S in place of NBoc, respectively) also produce very high optical yields of the corresponding hydroxy-esters.<sup>1,16</sup> In addition, the sense of the reduction is the same, as indicated by the general transformation **10** → **11**. The same absolute configuration has also been found in a reduction of ethyl *N*-benzyl-3-ketopiperidine-4-carboxylate to the hydroxy-ester **12**, using non-fermenting baker's yeast.<sup>17</sup> However, this method requires a very large excess of yeast and special isolation techniques and, although the chemical and optical yields are excellent (65% and 95% respectively), the d.e. (73%) is relatively poor. The excellent levels of chiral induction achieved in these present reductions suggests that the two products (**3** and **7a**) will find a number of applications in the synthesis of chiral piperidine derivatives; efforts in this direction are in progress.



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