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The Stereoselective Synthesis of Iodinated Analogues of Reboxetine; New Imaging Agents for the Noradrenaline Transporter

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A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy.

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Abstract

The noradrenaline reuptake transporter is located on the pre-synaptic membrane of noradrenic neurons. Its main function is to terminate the action of the neurotransmitter noradrenaline by reuptake back into the nerve terminal. Changes in the function and density of the noradrenaline reuptake transporter have been implicated in neurological disorders such as clinical depression and Alzheimer’s disease. In vivo imaging of the noradrenaline transporter using single photon emission computed tomography has been hampered by the lack of a suitable imaging agent. The information from imaging studies could lead to a better understanding of transporter function and the development of more efficient and faster acting drugs to treat the diseases associated it.

For the first time, all four stereoisomers of an iodinated analogue of reboxetine were stereoselectively synthesised and biologically evaluated in an effort to understand the relationship between stereochemistry and potency. All four compounds were found to have nanomolar affinity for the noradrenaline transporter.

Of most interest was the (2R,3S)-stereoisomer, which was identified as being as potent as the more studied (2S,3S)-stereoisomer. Therefore, a new series of iodoanalogues based on the (2R,3S)-stereochemical scaffold were synthesised and tested for their affinity with the noradrenaline transporter. This study revealed the derivative with ortho substitution on the phenoxy ring to be a potential lead for the development of a novel imaging agent for the noradrenaline transporter.
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Author’s Declaration

This thesis represents the original work of Nicola Kathryn Jobson unless explicitly stated otherwise in the text. The research was carried out at the University of Glasgow in the Henderson Laboratory and the Loudon Laboratory under the supervision of Dr Andrew Sutherland during the period October 2005 to September 2008. Portions of the work described herein have been published elsewhere as listed below.


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<td>Boc</td>
<td>tert-butoxycarbonyl</td>
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<td>broad</td>
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<td>°C</td>
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<td>catechol O-methyl transferase</td>
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<td>dopamine</td>
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<td>NARI</td>
<td>noradrenaline reuptake inhibitor</td>
</tr>
<tr>
<td>NAT</td>
<td>noradrenaline transporter</td>
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<tr>
<td>NMR</td>
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<tr>
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<td>nuclear Overhauser effect</td>
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<tr>
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<td>pyridinium $p$-toluenesulfonate</td>
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<td>serotonin transporter</td>
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<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitors</td>
</tr>
<tr>
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<td>T3P</td>
<td>1-propanephosphonic anhydride</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Name</td>
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<td>TBDPS</td>
<td>tert-butyldiphenylsilyl</td>
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<td>tetramethylpiperidine N-oxide</td>
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<tr>
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<td>trifluoroacetic acid</td>
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<td>tetrahydrofuran</td>
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<td>thin layer chromatography</td>
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<td>Ts</td>
<td>p-toluenesulfonyl</td>
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1 Introduction

1.1 Clinical Depression

Clinical depression is a debilitating mental disorder that affects three hundred and forty million people worldwide. The World Health Organisation predicts that by the year 2020, depression will be one of the leading causes of death and disability in developed countries.¹

Emotional symptoms of depression include misery, apathy and pessimism, low self-esteem, feelings of guilt and inadequacy, indecisiveness and a loss of motivation. Biological symptoms include retardation of thought, loss of appetite, sleep disturbances and loss of libido.² Extreme cases of depression can lead to suicide and eight hundred and fifty thousand people worldwide commit suicide each year.¹

There are two different types of depression, unipolar and bipolar. Unipolar depression accounts for seventy five percent of all cases. Patients experience mood swings in one direction and exhibit signs of anxiety and agitation. Unipolar depression is also known as reactive depression and can be brought on by stressful life events such as the death of a partner. Patients suffering from bipolar depression alternate between feelings of melancholia and mania. It is thought that this type of depression has a strong hereditary tendency.²³

1.2 Aetiology of Depression

The aetiology of depression is multi-factorial, and includes biological, psychological and social factors. The widely accepted theory of the biological effects underlying depression is the monoamine hypothesis.

1.2.1 The Monoamine Hypothesis

First suggested by Schildkraut in 1965, the hypothesis states that depression is caused by a functional deficit of monoamine neurotransmitters at certain sites of the brain.⁴ ⁵ The neurotransmitters it refers to are noradrenaline (NA), dopamine (DA) and serotonin (5-HT) (Figure 1).
The hypothesis originally grew out of associations between clinical effects of various drugs that alleviate symptoms of depression and their known neurochemical effects on monoaminergic transmission in the brain.

1.2.2 Chemical Neurotransmission

Chemical communication between neurons takes place at specialised junctions called synapses. When an action potential occurs in the pre-synaptic terminal it initiates a chain of events which convert the electrical signal into a chemical signal. The chemical signal is then converted back into an electric signal at the post-synaptic membrane.\(^6\)

For example, the monoamine neurotransmitter noradrenaline is released from storage in synaptic vesicles into the synaptic cleft when an action potential arrives at the noradrenic nerve terminal (Figure 2).\(^7\) Noradrenaline molecules then diffuse a short distance across the synaptic cleft and bind to specific receptors on the post-synaptic membrane. This either propagates or inhibits the nerve impulse depending on the receptor.
The action of noradrenaline can be terminated either by degradation in the synaptic cleft by the enzymes monoamine oxidase A (MOA) or catechol O-methyl transferase (COMT). However, the vast majority of released noradrenaline is quickly recaptured and taken back up into the nerve terminal by noradrenaline reuptake transporters.

The noradrenaline reuptake transporter is a 12-membrane spanning protein situated on the pre-synaptic terminal of noradrenergic neurons and its main function is to terminate the action of noradrenaline. Changes in the noradrenaline reuptake transporter have been implicated in a number of neuropsychiatric and neurodegenerative disorders such as clinical depression, attention-deficit/hyperactivity disorder and Alzheimer’s disease.

As depression is thought to be caused by a functional deficit of neurotransmitters, increasing their concentration in the synaptic cleft would amplify the signal and facilitate normal neurotransmission.

There are two medicinal approaches which could be modified in order to increase neurotransmitter concentration in the synaptic cleft. The first would be to interfere with the metabolism of the neurotransmitters by irreversibly binding to the enzymes responsible for their elimination.
The second approach would be to block the reuptake transporter binding sites, and stop the reuptake process from occurring. Figure 3 shows the effect of blocking the noradrenaline transporter with a noradrenaline reuptake inhibitor.\textsuperscript{13}

In its simplest form, the monoamine hypothesis does not fully explain the aetiology of depression. The compounds which block the degradation and reuptake of monoamine neurotransmitters have an immediate pharmacological effect, however the desired antidepressant effect can take weeks to develop.\textsuperscript{14}

Recent observations suggest that neurogenesis, the process by which new neurons proliferate and survive in the adult brain, may play a major role. The rate of neurogenesis was found to rapidly decrease during stress, whereas antidepressant compounds were shown to increase the process.\textsuperscript{15,16} These findings suggest that the biological aspects of depression are extremely complex and still not fully understood. However, the manipulation of monoamine neurotransmission remains the most effective treatment for depression.
1.3 Clinical Antidepressants

Antidepressants have been used successfully in the treatment of clinical depression since the 1950’s. There are two main classes of antidepressants, monoamine oxidase inhibitors (MAOI) and monoamine re-uptake inhibitors (MARI).

1.3.1 Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOI) were the first generation of antidepressant compounds and have been in clinical use for the past five decades.

MAOI compounds (Figure 4) are long lasting antidepressants which cause the irreversible inhibition of the enzyme monoamine oxidase A. MAOI increase the quantity of neurotransmitters in cystolic stores and the synaptic cleft. Unfortunately, MAOI compounds are not very specific, and this lack of selectivity leads to a range of side effects such as hypotension, tremors, insomnia, weight gain and atropine-like side effects including dry mouth, blurred vision and urinary retention. MAOI drugs were largely superseded by tricyclic antidepressants (TCA).\textsuperscript{17,18}

1.3.2 Tricyclic Antidepressants

Tricyclic antidepressants (Figure 5) are the most widely used antidepressants and act by blocking the reuptake of amine neurotransmitters into nerve terminals by competing for the binding site of the transport protein. TCAs have been shown to inhibit both serotonin and noradrenaline reuptake.\textsuperscript{17,18}

Tricyclic antidepressants have an improved side effect profile compared with monoamine oxidase inhibitors, however they can still produce effects such as sedation, confusion, motor in-coordination and atropine-type effects as mentioned previously.
1.3.3 Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (Figure 6) show a high degree of selectivity for inhibiting serotonin reuptake. The increase in selectivity results in a decrease in the number of unwanted side effects. Selective serotonin reuptake inhibitors are as effective for treating moderate depression as MAOI and TCA.17,18

1.3.4 Reboxetine - A Selective Noradrenaline Reuptake Inhibitor

Reboxetine is the first of a new generation of antidepressants called selective noradrenaline reuptake inhibitors (NARI). It was first synthesised by Melloni and co-workers in 1984 when they reported the synthesis and biological evaluation of various α-aryloxybenzyl derivatives of ethanolamine 1 and morpholine 2 (Figure 7).19
The derivatives were synthesised as a mixture of stereoisomers according to the general conditions outlined in Scheme 1. Ester 3 was hydrolysed to the carboxylic acid using potassium hydroxide with yields ranging from 80 to 90%. The acid was converted to the acid chloride which was then reduced to aldehyde 4. The aldehyde was immediately transformed into the cyanohydrin, which in turn was reduced to the amino alcohol using lithium aluminium hydride to give the target ethanolamine derivatives. The morpholine compounds were obtained by acetylation of amine 6 using chloroacetyl chloride to give amide 7. The amide then underwent a ring closing reaction followed by reduction with Red-Al to give target morpholine compounds 2.

Sixty different derivatives were synthesised and screened for potential antidepressant activity based on their antagonism to reserpine. From this substantial screening effort, the morpholine derivatives were found to be more active than the ethanolamine derivatives.
Of the morpholine compounds, the best activity was observed when $R_1 = 2\text{-methoxy}$ or $2\text{-ethoxy}$. Substitution in the 3- or 5-positions led to a loss of activity with these substituents. $R_2 = H$ was deemed essential for potency since a loss of activity was observed when $R_2 = \text{Me}$. Activity was best if $R_3 = H$, with the exception of 3-Cl which showed affinity comparable to that of the two best compounds. Interestingly, replacement of the oxygen in the morpholine ring with $\text{CH}_2$, $\text{NH}$, $\text{NMe}$ or $\text{S}$ resulted in a significant loss of activity.

The initial screening pointed to three potential candidates, 8, 9, and 10 (Figure 8).

Further *in vitro* evaluation found reboxetine 9 to be a potent selective noradrenaline reuptake inhibitor, indicating a possible therapeutic use as a potent antidepressant agent.

In 1985 the Melloni group described the regio- and stereospecific synthesis of 9, and the assignment of its relative and absolute stereochemistry.\(^{20}\) The strategy adopted was to synthesise and assign the correct configuration of the amino alcohol intermediates. Particular interest was given to the amino alcohol with a melting point of 105-107 °C which was known to be a key intermediate in the synthesis of 9.

The synthesis shown in Scheme 2 is racemic, however only one enantiomer is shown for clarity. Commercially available *trans*-cinnamyl alcohol 11 was oxidised to epoxide 12 using $m\text{CPBA}$. The epoxide was then regiospecifically opened using 2-ethoxyphenol to produce diol 13, and the primary alcohol was selectively activated as tosylate 14. The tosyl group was displaced using an aqueous solution of ammonia to produce amino alcohol 15. The melting point of this amino alcohol was found to be 115-117 °C, and was therefore not the correct intermediate for the synthesis of 9.
Inversion at the 2-position was required for the correct amino alcohol, and as shown in Scheme 3, primary alcohol 13 was protected as the \( p \)-nitrobenzoyl ester 16 and the secondary alcohol activated as mesylate 17.\(^{20}\) Hydrolysis of the ester under basic conditions, and subsequent displacement of the mesylate by the primary alkoxide provided the required inversion of configuration to give epoxide 18. Epoxide 18 was regioselectively opened using an aqueous solution of ammonia to give amino alcohol 19. Amino alcohol 19 was found to have a melting point of 105-107 °C, and identical spectroscopic data to that of the intermediate amino alcohol in the synthesis of 9. The amine was subsequently acetylated using chloroacetyl chloride to give amide 20, which then underwent a ring closing reaction with potassium tert-butoxide to give morpholinone ring 21. The amide was reduced to the amine using Red-Al to give 9, the salt of which was generated by treatment with methanesulfonic acid.
The separation of the (+)- and (-)-enantiomers of 9 was achieved by crystallising the L (+) and D (-) mandelic acid salts from absolute ethanol. The optical rotations of the enantiomers separated from the racemate were compared to that of enantiomers synthesised from optically pure epoxides of known absolute configuration.

Treatment of (2R,3R)-glycidic acid 22 with ethyl chloroformate generated the mixed anhydride, which was reduced with sodium borohydride to give epoxide 23 (Scheme 4). The eight step sequence required to convert epoxide 23 into the morpholine derivative (2S,3S)-9 followed those described for the racemic synthesis in Scheme 3.
The optical rotation of the (2S,3S)-methanesulfonic acid salt obtained by this method was found to be identical to the (+)-enantiomer obtained by resolution of racemic mixture. This confirmed that the reactions proceeded without racemisation, and the enantiomers from both methods were optically pure isomers.

Reboxetine is a potent noradrenaline reuptake inhibitor which displays excellent selectivity for the noradrenaline transporter versus the serotonin transporter, in comparison to tricyclic antidepressants despramine and imipramine (Table 1).21

Table 1

<table>
<thead>
<tr>
<th></th>
<th>NAT $K_i$ (nM)</th>
<th>SERT $K_i$ (nM)</th>
<th>Selectivity (SERT/NAT)</th>
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<tr>
<td>(2S,3S)/(2R,3R)-9</td>
<td>8</td>
<td>1070</td>
<td>130</td>
</tr>
<tr>
<td>Desipramine</td>
<td>6</td>
<td>590</td>
<td>98</td>
</tr>
<tr>
<td>Imipramine</td>
<td>54</td>
<td>73</td>
<td>1.4</td>
</tr>
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</table>

Reboxetine was developed by Pharmacia and Upjohn and was approved for clinical use in Europe and South America in 1998.
Reboxetine contains two chiral centres and therefore can exist as four stereoisomers (Figure 9). It is marketed as racemic mixture of (2S,3S)- and (2R,3R)-enantiomers, with the (2S,3S)-isomer reported to be twenty four times more potent than its enantiomer.\textsuperscript{20,22}

Reboxetine’s excellent potency and selectivity make it a potential candidate to become a radiotracer for use in imaging the noradrenaline transporter using single photon emission computed tomography (see Section 1.6).

### 1.4 Literature Preparations of (2S,3S)-Reboxetine

There are two distinct synthetic strategies which have been applied to the synthesis of (2S,3S)-reboxetine. As demonstrated by Melloni, one approach is to introduce the phenoxy domain early with closure of the morpholine ring occurring at late in the synthetic sequence. An alternative approach is to build the chiral moiety first and introduce the phenyl and phenoxy groups at a later stage.

#### 1.4.1 Optical Resolution

In 2004, Kumar and co-workers reported the chiral synthesis of reboxetine via the intermediate (2S,3S)-2-(2-morpholin-2-yl-2-phenylmethoxy)phenol \textsuperscript{25} (Figure 10).\textsuperscript{23}
The group embarked on a synthesis similar to that described by Melloni and co-workers (Scheme 5). Oxidation of trans-cinnamyl alcohol 11 with mCPBA gave epoxide 12, which was regioselectively opened using a MOM-protected phenol to give diol 26. The diol underwent seven transformations, similar to that described previously for the racemic synthesis of reboxetine, to give amine 27. The resolution of 27 was carried out using (+)-mandelic acid to give (2S,3S)-28 in 38% yield. Attempts at the removal of the MOM group using excess p-toluenesulfonic acid yielded only starting material. However, carbamate protection of the amine allowed the MOM group to be removed using catalytic amounts of p-toluenesulfonic acid. The Fmoc protecting group was removed using TBAF to give target molecule 25 in an 87% yield.

In order to establish the configuration of the chiral centres, phenol 25 was converted into reboxetine by protection of the amine followed by alkylation using ethyl iodide. Removal of the Boc group using trifluoroacetic acid gave (2S,3S)-reboxetine 9 in a 65% yield over two steps.

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**Scheme 5**

---
The optical rotation of 9 was comparable to that reported for (2S,3S)-reboxetine, and therefore the configuration could be assigned. Analysis using chiral HPLC showed the enantiomeric excess to be 98%.

The synthetic utility of 25 was proved by the synthesis of methoxy derivative 8, which was tested for affinity with the noradrenaline transporter. Methoxy derivative 8 was found to have a $K_i$ of 12 nM with 100-fold selectivity over other biogenic receptors and transporters.

1.4.2 Use of the Chiral Pool

In 2005, the Tamagnan group reported an efficient asymmetric synthesis of (2S,3S)-reboxetine via a new (S)-2-(hydroxymethyl)morpholine intermediate.24

As shown in Scheme 6, commercially available (S)-3-amino-1,2-propanediol (31) was acetylated with chloroacetyl chloride to give amide 32. Treatment of 32 with potassium tert-butoxide gave morpholinone 33. Reduction of the amide was carried out using Red-Al®, and the resultant amine 34 was Boc protected under standard conditions. The alcohol was oxidised using TEMPO to give aldehyde 36.

The phenyl ring was introduced using a zinc reagent to give diastereoisomers 37 and 38 in a 3:1 ratio (Scheme 7). The diastereoisomers were separated using flash column chromatography, and the major diastereomer 37 was subjected to a chromium mediated aromatic nucleophilic substitution. This gave 39, which was deprotected using trifluoroacetic acid to give target molecule (2S,3S)-9 in a 98% yield.
Minor diastereomer 38 underwent a Mitsunobu reaction with 2-ethoxyphenol to give 39 in 53% yield (Scheme 8). Compound 39 was deprotected using trifluoroacetic acid to give target compound (2S,3S)-9.

The synthesis of (2S,3S)-reboxetine was achieved in eight linear steps with a 30% overall yield and excellent 99% enantiomeric excess. It was envisioned that (2R,3R)-reboxetine could be made using the same sequence, starting from (R)-3-amino-1,2-propanediol.
1.4.3 Enantioselective Synthesis

Srinivasan and co-workers reported an efficient enantioselective synthesis of (2S,3S)-reboxetine. Commercially available trans-cinnamyl bromide 40 was subjected to a Sharpless asymmetric dihydroxylation to introduce the desired stereochemistry and gave diol 41 in a good 84% yield (Scheme 9). The enantiomeric excess was determined by conversion of diol 41 to the epoxide, followed by conversion of the secondary alcohol to the (S)-Mosher’s ester. The enantiomeric purity of the diol was estimated to be 95%.

The nucleophilic displacement of the bromide using sodium azide gave the azido alcohol, which was hydrogenated to give amine 42. The amine was acetylated with chloroacetyl chloride to give amide 43, and ring closure was effected by treatment with potassium tert-butoxide to give morpholinone 44. Reduction of the amide was carried out using Red-Al to give the amine, which was subsequently Boc protected under standard conditions to give structural intermediate, benzyl alcohol 37.

Using chemistry developed by the Tamagnan group, benzyl alcohol 37 underwent a chromium mediated nucleophilic aromatic substitution to introduce the aromatic ring. This gave 39, which was deprotected using trifluoroacetic acid to give target molecule (2S,3S)-9 (Scheme 10). Thus, (2S,3S)-reboxetine was successfully synthesised in nine linear steps and an overall 21% yield.
1.4.4 Asymmetric Catalytic Rearrangement

Cossy and co-workers reported the highly enantioselective rearrangement of β-amino alcohols using catalytic amounts of trifluoroacetic anhydride (Scheme 11).\textsuperscript{26}

The postulated mechanism for the rearrangement is shown in Scheme 12. The primary alcohol 45 is esterified using trifluoroacetic anhydride to form the ammonium trifluoroacetate ester. In the non-catalytic version of the rearrangement, triethylamine is required to deprotonate the ammonium ion. Under catalytic conditions, triethylamine is not required as the proton can be removed by the other amines in the reaction mixture. Intramolecular nucleophilic attack from the amine then occurs to displace the ester, and form the highly strained aziridinium intermediate. Nucleophilic attack by the trifluoroacetate anion at the most substituted carbon of the three-membered ring followed by intermolecular transesterification occurs between amino alcohol 45 and the rearranged amino ester to give target β-amino alcohol 46. The newly formed amino ester of 45 can then enter the catalytic cycle and undergo the rearrangement process. At the end of the reaction the remaining catalytic quantity of amino ester is saponified by sodium hydroxide to give the desired amino alcohol 46.
In 2008, the Cossy group used this chemistry to described two approaches to the synthesis of (2S,3S)-reboxetine.\textsuperscript{27} As shown in Scheme 13, commercially available (1R,2R)-2-amino-1-phenyl-1,3-propanediol 47 underwent a dibenzylation reaction to give tertiary amine 48. The stereospecific rearrangement of 48 was carried out by treatment with trifluoroacetic anhydride in refluxing toluene followed by saponification with sodium hydroxide to give rearrangement product 49 in a 78\% yield and excellent 99\% enantiomeric excess.

The benzyl protecting groups were removed by hydrogenation and amine 50 acetylated using chloroacetyl chloride to give amide 51. The morpholine ring was formed by treatment of 51 with potassium tert-butoxide to form the morpholinone ring, and reduction of amide 52 was carried out using Red-Al\textsuperscript{®}. The amine was Boc protected before undergoing a Mitsunobu reaction with 2-ethoxyphenol to invert the stereochemistry at the 3-position, and deprotection using trifluoroacetic acid gave (2S,3S)-9 in an 88\% yield.
Thus, target molecule, (2S,3S)-reboxetine 9 was synthesised in nine linear steps and a 6.2% overall yield.

In the literature, the deprotection of 53 using 1-chloroethylchloroformate is reported to give (2S,3S)-reboxetine in an 88% yield (Scheme 14). A second, more efficient synthesis of Reboxetine was envisioned by formation of the morpholine ring using the rearrangement of an amino diol containing a hydroxyethyl chain on the amine.
As shown in Scheme 15, the amino and primary hydroxyl groups of (1R,2R)-2-amino-1-phenyl-1,3-propanediol 47 were benzyl protected followed by treatment with 2-ethoxyphenol under Mitsunobu conditions to install the phenoxy moiety and provide inversion of configuration at the C-3 position. Compound 54 was reduced using borane.tetrahydrofuran to yield amino alcohol 55 which was then alkylated using methyl bromoacetate. The ester group was then reduced using lithium aluminium hydride to give rearrangement substrate 56 in a 70% yield over two steps. Diol 56 underwent a trifluoroacetic anhydride catalysed rearrangement to give diol 57. Selective tosylation of the primary alcohol followed by treatment with base, and displacement by the resultant secondary alkoxide anion gave N-benzyl-reboxetine 53. The formal synthesis of (2S,3S)-reboxetine was achieved in eight steps and an improved 8.5% overall yield.

1.5 Synthesis and Evaluation of New Reboxetine Derivatives

The development of more potent and selective reuptake inhibitors for the noradrenaline transporter is still being investigated, using reboxetine as a molecular scaffold.
### 1.5.1 Investigation of Structure Activity Relationships

Fish and co-workers at Pfizer reported the synthesis of reboxetine derivatives in a bid to establish structure-activity relationships for dual serotonin and noradrenaline reuptake inhibition. Initially the group synthesised racemic mixtures of the two diastereoisomers of reboxetine derivatives, introducing chlorine atoms onto the C-3 and C-4 positions of the phenoxy ring. The compounds were then assessed for their affinity with the monoamine reuptake transporters. The calculated $K_i$ values for the noradrenaline, serotonin and dopamine transporters are given in Table 2.

**Table 2**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Racemate</th>
<th>NAT (nM)</th>
<th>SERT (nM)</th>
<th>DAT (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2S,3S/2R,3R)</td>
<td>275</td>
<td>240</td>
<td>&gt; 10000</td>
<td></td>
</tr>
<tr>
<td>(2S,3R/2R,3S)</td>
<td>1490</td>
<td>340</td>
<td>&gt; 10000</td>
<td></td>
</tr>
<tr>
<td>(2S,3S/2R,3R)</td>
<td>15</td>
<td>60</td>
<td>1540</td>
<td></td>
</tr>
<tr>
<td>(2S,3R/2R,3S)</td>
<td>390</td>
<td>220</td>
<td>1670</td>
<td></td>
</tr>
<tr>
<td>(2S,3S/2R,3R)</td>
<td>36</td>
<td>28</td>
<td>5050</td>
<td></td>
</tr>
<tr>
<td>(2S,3R/2R,3S)</td>
<td>320</td>
<td>85</td>
<td>2200</td>
<td></td>
</tr>
</tbody>
</table>

*a $K_i$ values are the mean of 3 separate determinations.*

From these results it was concluded that the affinities of the (2S,3S/2R,3R)-derivatives were superior to that of the (2S,3R/2R,3S)-compounds, and investigation into the latter series was discontinued.
A new stereoselective synthesis to the single enantiomers of the (2S,3S/2R,3R)-analogues was developed to determine the influence of absolute configuration on affinity for monoamine transporters (Scheme 16). Racemic ester 63 was prepared in three steps from commercially available N-benzylethanolamine and chloroacrylonitrile 61 in a 55% yield.

The enzyme *Candida rugosa* was used to resolve 63 by selectively hydrolysing the (S)-ester to the acid whilst leaving the (R)-ester unreacted. The benzyl protecting group of 65 was removed and replaced with a Boc protecting group. Treatment of 66 with base hydrolysed the ester, and activation of the acid with 1-propanephosphonic anhydride (T3P) followed by reaction with HN(Me)OMe gave Weinreb amide 67.

Treatment of 67 with various Grignard reagents gave ketones of general structure 68, and reduction of the ketone using zinc borohydride gave benzylic alcohols 69 in a good diastereoselectivity of (2R,3S:2R,3R 16:1). Activation of the alcohol as the mesylate was carried out under standard conditions, and displacement of the mesylate with a variety of phenols gave 71 with complete inversion of configuration at the 3-position. Boc deprotection using hydrochloric acid gave (2R,3S)-target molecules 72 in a 95% yield.

The (2S,3S)-enantiomers were prepared using an identical sequence starting from (S)-acid 64.
The coupling of 67 with aromatic rings containing different substituents gave a range of molecules which were then tested for their affinity against all three monoamine transporters. Selected examples of enantiomeric pairs and their calculated $K_i$ values are shown in Table 3.
It was found that stereochemistry was important for selectivity, with the (2S,3S)-derivatives being selective for the noradrenaline transporter, whilst the (2R,3R)-derivatives showed better affinity for the serotonin transporter. Both (2S,3S)- and (2R,3R)-derivatives showed selectivity against the dopamine transporter.

Table 3

<table>
<thead>
<tr>
<th>Compound</th>
<th>Stereochemistry</th>
<th>NAT</th>
<th>SERT</th>
<th>DAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>(2S,3S)</td>
<td>8</td>
<td>110</td>
<td>1570</td>
</tr>
<tr>
<td>73</td>
<td>(2S,3S)</td>
<td>12</td>
<td>260</td>
<td>1170</td>
</tr>
<tr>
<td>74</td>
<td>(2S,3S)</td>
<td>10</td>
<td>3390</td>
<td>2600</td>
</tr>
<tr>
<td></td>
<td>(2R,3R)</td>
<td>420</td>
<td>11</td>
<td>1790</td>
</tr>
<tr>
<td></td>
<td>(2S,3S)</td>
<td>12</td>
<td>1170</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2R,3R)</td>
<td>830</td>
<td>20</td>
<td>760</td>
</tr>
<tr>
<td></td>
<td>(2S,3S)</td>
<td>10</td>
<td>3390</td>
<td>2600</td>
</tr>
<tr>
<td></td>
<td>(2R,3R)</td>
<td>130</td>
<td>12</td>
<td>380</td>
</tr>
</tbody>
</table>

$K_i$ values are the mean of at least 3 separate determinations.

The compounds were screened against seventy other receptors, ion channels and enzymes to assess their non-target pharmacological activity. The (2S,3S)-compounds showed no significant affinity for other targets, however the (2R,3R)-compounds showed significant affinity for the H1-histamine receptor. This finding, coupled with the modest affinity for the target monoamine transporters led to the (2R,3R)-series being discontinued.
The (2S,3S)-series was further developed by investigating a broader range of substituents in the para position on the phenoxy ring (Table 4). The cyanide group (75) led to a loss of affinity for both the transporters, however replacement with the larger bromide group (76) gave a dual noradrenaline and serotonin inhibitor. Interestingly, the CF₃ group lead to an inversion of inhibition profile, with 77 displaying greater affinity for the serotonin transporter.

Table 4

<table>
<thead>
<tr>
<th>X</th>
<th>NAT $K_i$ (nM)ᵃ</th>
<th>SERT $K_i$ (nM)ᵃ</th>
<th>DAT $K_i$ (nM)ᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN (75)</td>
<td>210</td>
<td>110</td>
<td>-</td>
</tr>
<tr>
<td>Br (76)</td>
<td>12</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>CF₃ (77)</td>
<td>160</td>
<td>41</td>
<td>-</td>
</tr>
</tbody>
</table>

ᵃ$K_i$ values are the mean of at least 3 separate determinations.
⁻ Not tested.

Based on lead compound (2S,3S)-60, the substituent effect on the phenyl ring was investigated (Figure 11). Compounds with substitution in the ortho (78) or para positions displayed similar levels of affinity with $K_i$ values of 22 and 29 nM respectively. Affinity for the noradrenaline transporter was best when the fluorine atom was in the meta position (79), with a $K_i$ value of 9 nM. Movement of the substituent around the aromatic ring did not have an effect on affinity for the serotonin transporter, which changed only slightly from 70, 58, 62 nM. A similar positional pattern was observed with methyl substitution on the phenyl ring.
Compound (2S,3S)-60 was deemed to be the lead compound due to its affinity for the noradrenaline and serotonin transporters plus its good selectivity and non-interaction with other pharmacological targets. Further tests on this compound showed that it had favourable lipophilicity, good membrane permeation, no significant inhibition of the liver enzyme CYP450 and good metabolic stability. Based on these results, compound (2S,3S)-60 was selected as a candidate for further evaluation in pre-clinical disease models.

Also working at Pfizer, Barta and co-workers synthesised and tested morpholine derivatives in the search for selective noradrenaline reuptake inhibitors. The literature suggests that (2R,3R)-derivatives of reboxetine are not selective for the noradrenaline transporter, therefore only the (2S,3S)-, (2S,3R)- and (2R,3S)-analogues were synthesised and biologically evaluated.

The synthetic strategy involved the synthesis of a late stage intermediate which could be coupled with different groups (Scheme 17). Hydroxymorpholine 81 was oxidised using buffered sodium hypochlorite, and the acid converted to Weinreb amide 82 via a cyclic phosphonic acid anhydride promoted amidation. Amide 82 was treated with various organometallic reagents to give functionalised ketones of general structure 83 in moderate to good yields. The ketone was reduced using hydrogen and a chiral ruthenium catalyst to give the alcohol. Mitsunobu coupling of substituted phenols with the secondary alcohols followed by Boc deprotection gave the target molecules 85. Separation of the enantiomers was carried out using chiral preparatory HPLC, and the molecules assessed for their affinity for all three monoamine transporters.
As shown in Table 5, the affinity and selectivity of the (2S,3R)- and (2R,3S)-derivatives was found to be inferior to that of the (2S,3S)-derivatives. The (2S,3S)-series demonstrated that potency can be achieved with large (86) or bulky (87) substituents on the phenoxy ring. Good affinity was also achieved with 2,6-disubstituted systems, and non-aromatic groups (88).

Table 5

<table>
<thead>
<tr>
<th>Compound</th>
<th>Stereochemistry</th>
<th>NAT $K_i$ (nM)$^a$</th>
<th>SERT $K_i$ (nM)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(2S,3S)</td>
<td>3</td>
<td>477</td>
</tr>
<tr>
<td>86</td>
<td>(2R,3S)</td>
<td>17</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>(2S,3S)</td>
<td>2</td>
<td>482</td>
</tr>
<tr>
<td>87</td>
<td>(2R,3S)</td>
<td>35</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>(2S,3S)</td>
<td>20</td>
<td>3703</td>
</tr>
<tr>
<td>88</td>
<td>(2S,3R)</td>
<td>2570</td>
<td>2530</td>
</tr>
</tbody>
</table>

$^a K_i$ values are the mean of at least 3 separate determinations.
Investigation into the (2S,3R)- and (2R,3S)-derivatives was discontinued, and the focus was switched to investigation of the structure activity relationship of substitution on the phenoxy ring.

Compounds 89, 90 and 91 were tested and the results showed that affinity for the noradrenaline transporter decreased as a function of substitution in the order ortho, meta and para (Figure 12). Interestingly, movement of the fluorine from the ortho to the meta position resulted in a 500-fold increase in affinity for the serotonin reuptake transporter. This result is similar to that described by Fish and co-workers, who described a compound which displayed dual affinity for the noradrenaline and serotonin transporters when bromide substitution was in the meta position (76).29

Further investigation revealed that compounds with substitution in the 2- or 2,6-position of the phenoxy ring displayed the best affinity for the noradrenaline transporter. As shown in Figure 13, replacement of the phenyl ring with different heterocyclic systems was examined. 2-Pyridyl rings were found to be potent and selective inhibitors, however a 3-pyridyl derivative was weaker in comparison with a $K_i$ value of 114 nM for the noradrenaline transporter. Replacement with oxazole or thiazole rings also retained potency and selectivity.
1.5.2 Thioether Linkage

Boot and co-workers at Lilly reported the synthesis and structure activity relationships of reboxetine analogues with a sulfur atom in the linker domain. This required the development of a flexible and stereoselective synthesis to arylthiomethyl morpholine derivatives. The proposed retrosynthetic analysis is shown in Scheme 18.

Cleavage of the thioether linkage would lead back to activated phenylmethyl morpholine which could be made from an aldol condensation between benzaldehyde.

This strategy would allow the rapid generation of analogues by introduction of a variety of thiophenols at a late stage.

The reaction strategy was validated by first carrying out the synthesis of reboxetine using the proposed transformations (Scheme 19). The synthesis started with the morpholine moiety in the form of N-benzyl protected morpholinone which underwent an aldol condensation reaction to give a 2.2:1 diastereomeric mixture of benzyl alcohols and . The aldol products were separated by chromatography, and the relative stereochemistry assigned based on the coupling constants in the \(^1\)H NMR spectrum between the hydrogen at the C-2 position of the morpholinone ring and the benzylic hydrogen. The enantiomers with a coupling constant of 3 Hz were assigned cis-stereochemistry, and the enantiomeric mixture with the 8 Hz coupling constant was assigned trans-stereochemistry. This assignment was later confirmed by X-ray crystallography.
The morpholinone rings were reduced under mild conditions using borane·tetrahydrofuran to give morpholine benzyl alcohols 102 and 103 in good yields. 

Cis-benzyl alcohol 102 was converted to the bromo epimer, followed by a second inversion of configuration via bromine displacement with 2-ethoxyphenol. This gave \((2S,3S)/(2R,3R)-53\), which was deprotected in two steps to give racemic 9.

\[
\text{Scheme 19}
\]

The target compound was compared to an authentic sample of \((2S,3S)/(2R,3R)-\text{reboxetine}\) and this confirmed the assignment of the relative stereochemistry of benzylic alcohol 100 to be correct.
The double inversion strategy was successfully employed to synthesise a range of (2S,3S/2R,3R)-arylthiomethyl morpholine derivatives (Scheme 20). Mesylation of minor diastereoisomer 103 followed by displacement with phenylthiols gave target molecules 95 in yields comparable with those of the double inversion approach.

As shown in general Scheme 20, both the threo product and erythro product of the key aldol condensation could be used as starting material for the synthesis of the target molecules.

The target compounds were tested as (2S,3S/2R,3R)-racemates for reuptake inhibition at the noradrenaline, serotonin and dopamine transporters. From the results given in Table 6, it can be seen that the introduction of a sulfur atom into the linker domain of reboxetine does not dramatically affect potency. Compounds 106 to 110 displayed excellent nanomolar activity for both the noradrenaline and serotonin transporters with excellent selectivity over the dopamine transporter. Movement of the substituent on the thiophenyl ring resulted in a decrease in potency in the order ortho, meta, para.

The methoxy analogue of reboxetine is reported to display poor serotonin uptake inhibition. Interestingly, the thio-methoxy analogue 107 displayed excellent inhibition of both the noradrenaline and serotonin transporters.
Compound 107 was separated into its two enantiomers using chiral HPLC, and the optically active compounds were re-tested against noradrenaline and dopamine transporters. One isomer was shown to inhibit only noradrenaline reuptake with a $K_i$ value of 1.7 nM, whilst the second isomer was shown to effectively inhibit both noradrenaline and serotonin reuptake with $K_i$ values of 24.6 and 1.5 nM respectively. This result raised the possibility of a selective dual action antidepressant which may show more potency and quicker onset of action compared with currently available antidepressants. The assignment of the absolute configuration of the two isomers was not reported.

1.6 Single Photon Emission Computed Tomography

Single photon emission computed tomography (SPECT) is a non-invasive radionuclide imaging technique that can be used to image the abundance, distribution and function of brain receptors in vivo. This information can be used to diagnose neurological diseases and monitor disease progression.33
1.6.1 Radiotracers

SPECT imaging requires a radiotracer, an appropriate radionuclide attached to an organic molecule. The organic molecule controls the distribution of the tracer by displaying high affinity and selectivity for the desired receptor.

A widely used radionuclide is $^{123}$I since it has excellent physical properties for SPECT. The half life of the isotope is 13.2 hours, which means it can be generated in a cyclotron offsite or bought from a commercial source.\(^{34}\)

The organic molecule is usually a radiolabelled drug with established affinity and selectivity for the receptor to be imaged. The desired characteristics of a radiotracer are affinity and selectivity for receptor with low non-specific binding to brain tissue, rapid passage through the blood brain barrier, and the generation of only a few radioactive metabolites in vivo.

1.6.2 SPECT Imaging

A SPECT image can be generated by injecting a patient with an appropriate radiotracer, which travels to, and binds to the receptor of interest. The radioisotope decay can be detected by a gamma camera which produces a picture of the distribution of the radioactive tracer. In SPECT imaging, the gamma camera can rotate around the patient to generate images from different angles, and these images are mathematically reconstructed using algorithms to generate a three-dimensional image. An example of a SPECT imaging suite is shown in Figure 14.\(^{35}\)
Positron emission tomography (PET) is a similar, more sensitive imaging technique which utilises the isotopes $^{11}$C and $^{18}$F. These radioisotopes have short half lives (20 and 110 minutes respectively), and therefore need to be generated by an on-site cyclotron and used immediately.

1.6.3 Radiotracers for the Serotonin and Dopamine Transporters

PET and SPECT radiotracers for both the serotonin and dopamine reuptake transporters have been successfully developed, and some examples of tracers currently used in clinical research studies are shown in Figure 15. DASB and ADAM can be used to image the serotonin receptor, whilst FECNT and DatScan can be used to image the dopamine transporter.  

36-39
One clinical application of SPECT imaging is the diagnosis of Parkinson’s disease. Parkinson’s disease is thought to be caused by a decrease in the number of dopamine receptors in the brain.\textsuperscript{40,41} The change in receptor density can be imaged using SPECT, and Parkinson’s disease is routinely diagnosed using DatScan (Figure 16). The image on the left is that of a normal brain, and the image on the right is the brain of a patient displaying early symptoms of Parkinson’s disease. The intense yellow spots are concentrated areas of radiotracer binding and represent abundance of dopamine receptors. From Figure 16, it can be seen that even in the early stages of Parkinson’s disease, receptor density is reduced by around half compared with the normal level.\textsuperscript{42}
SPECT can also be used to monitor disease progression and evaluate the effectiveness of treatment.\textsuperscript{43,44} The images shown in Figure 17 from left to right are, that of a normal brain, that of someone displaying mild Parkinson’s symptoms, that of a patient with moderate disease progression and that of a patient with severe Parkinson’s disease.\textsuperscript{42}

1.6.4 Radiotracers for the Noradrenaline Transporter

Imaging of the noradrenaline transporter has been hampered by the lack of a suitable ligand. Selected examples of potential radiotracers for the noradrenaline transporter using PET are shown in Figure 18.

Nisoxetine 111 displayed excellent selectivity for the noradrenaline transporter, but suffered from non-specific binding in mouse brain, rendering it unsuitable for development into a radioligand.\textsuperscript{45} Nortropane derivative 112 was shown to have good uptake \textit{in vivo}, however it also suffered from non-specific binding in brain tissue.\textsuperscript{46}
The tricyclic antidepressant desipramine 113 was radiolabelled with $^{11}\text{C}$ in a moderate yield and high specific activity for a PET study, however no in vivo data was reported.$^{47}$ The most promising lead for an imaging agent for the noradrenaline transporter is $^{11}\text{C}$-MeNER 114.$^{48-50}$

A SPECT radiotracer for the noradrenaline transporter has proved just as elusive to develop. Radiolabelled $^{123}\text{I}$-tomoxetine (115) displayed moderate affinity for the serotonin transporter, however recently a pyridine analogue of nisoxetine labelled with $^{125}\text{I}$ 116 was shown to have high, and selective binding for the noradrenaline transporter in rat brain and is currently undergoing further evaluation (Figure 19).$^{51-53}$

![Figure 19](image_url)

1.7 SPECT Studies

Saji and co-workers reported the synthesis and radioiodination of (2S,3S)-2-($\alpha$-(2-iodophenoxy)benzyl)morpholine 118 for imaging of brain noradrenaline transporter using SPECT.$^{54}$

Starting from commercially available trans-cinnamyl alcohol 11, the group utilised the racemic synthetic route developed by Melloni and co-workers to synthesise (2S,3S)/(2R,3R)-118 in nine steps (Scheme 21).$^{20}$

![Scheme 21](image_url)
The enantiomers were separated using chiral HPLC, and the compounds assessed using a \[^{3}H\]-nisoxetine inhibition binding assay with homogenised rat brain. The calculated $K_i$ values are given in Table 7. Racemic 118 exhibited similar affinity compared to the parent compound (2S,3S)/(2R,3R)-reboxetine. (2S,3S)-118 was shown to be almost two and a half times as potent as reboxetine, and twenty times more potent than (2R,3R)-118.

Table 7

<table>
<thead>
<tr>
<th>Compound</th>
<th>NAT $K_i$ (nM)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2S,3S)/(2R,3R)-118</td>
<td>10.4</td>
</tr>
<tr>
<td>(2S,3S)-118</td>
<td>4.22</td>
</tr>
<tr>
<td>(2R,3R)-118</td>
<td>80.4</td>
</tr>
<tr>
<td>(2S,3S)/(2R,3R)-9</td>
<td>11.6</td>
</tr>
</tbody>
</table>

$^a$ $K_i$ values are the mean of 3 separate determinations.

The selectivity of (2S,3S)-118 was confirmed using selective binding agents for the noradrenaline, serotonin and dopamine transporters. It was found that the binding of (2S,3S)-118 was inhibited by selective noradrenaline binding agents nisoxetine and desipramine. The selectivity ratios for noradrenaline over serotonin and dopamine were found to be 25, and more than 1000 respectively.

The biodistribution of (2S,3S)-118 in rats was assessed by radiolabeling bromoanalogue (2S,3S)-86. This was achieved using a halogen exchange reaction to give 119 in a 65% radiochemical yield and >98% radiochemical purity (Scheme 22).
The regional distribution of 119 in rat brain was found to correlate well with established noradrenaline transporter expression. Accumulation was observed in noradrenaline transporter rich areas such as the thalamus and cortex, whilst little was seen in noradrenaline transporter poor areas such as the striatum.

A SPECT imaging study in the common marmoset revealed rapid and high uptake of 119 into the brain (Figure 20). Accumulation was observed in noradrenaline transporter regions, and displacement of the radioligand using nisoxetine suggested that binding of 119 was selective and reversible. It was concluded that 119 was a potential imaging agent for the noradrenaline transporter.

In 2007, the Tamagnan group reported the development of SPECT imaging agents for the noradrenaline transporter. Starting from racemic aminopropanediol, the synthetic sequence reported in their earlier publication was used to synthesise racemic mixtures of different (2S,3S)/(2R,3R)-reboxetine analogues. The compounds were then evaluated \textit{in vitro} for affinity with the noradrenaline, dopamine and serotonin transporters.

The structures of selected racemic analogues and their calculated $K_i$ values for the noradrenaline transporter are shown in Figure 21. All analogues were found to have selectivity for the noradrenaline transporter over the dopamine and serotonin transporters, the only exception being compound 121 which was slightly more active at the dopamine transporter.

The introduction of iodine at the \textit{meta} position of the phenyl ring 120 led to a decrease in potency, as did changing the phenoxy moiety for either a benzyoxy 124 or heterocyclic group 125.
Racemic 118 was identified as a potential lead, and so the (2S,3S)-enantiomer was asymmetrically synthesised from (S)-3-amino-1,2-propanediol. Enantiopure (2S,3S)-118 was then assessed \textit{in vitro} against all three monoamine transporters and displayed excellent affinity for the noradrenaline transporter with a $K_i$ value of 0.84 nM, and good selectivity versus the serotonin and dopamine transporters, with $K_i$ values of 40.4 and 228 nM respectively.

(2S,3S)-123 was radiolabelled, first by conversion to tin precursor 124 followed by iodo-destannylation using radioactive sodium iodide (Scheme 23). The radiolabelled compound was deprotected, purified by HPLC, and then used to evaluate regional brain uptake in female baboons.

It was found that highest uptake of 125 took place in the locus coeruleus (brain stem) and thalamus, whilst lowest uptake was observed in the cerebellum and striatum. These results were consistent with established distribution of noradrenaline transporters in baboon brain and suggest specific binding \textit{in vivo}.\textsuperscript{56}

In agreement with the findings of Saji, it was concluded that 125 was a promising agent for imaging the noradrenaline transporter in vivo using SPECT.
1.8 Proposed Research

Although many compounds are being successfully used to treat clinical depression, their interaction with the noradrenaline transporter in the brain is not well understood. This project planned to address this problem by synthesising and testing iodinated analogues of reboxetine, with a view to developing a new imaging agent for the noradrenaline transporter. At the time this research was first undertaken, there were no literature reports of the stereochemical requirements of the noradrenaline transporter, nor were there any reported SPECT studies using reboxetine as an imaging agent.

The aims of this research project were:

- To selectively synthesise iodinated analogues of the four stereoisomers of reboxetine (Figure 22).

- To assess the stereoisomers in competition binding assays using \(^{3}H\)-ligands for noradrenaline, serotonin and dopamine reuptake transporters.

- To develop some understanding of how the different stereoisomers of a reboxetine analogue bind to the noradrenaline reuptake transporter.

- To re-synthesise efficient binders incorporating the radiolabelled iodine for use in brain tissue imaging using SPECT.

![Figure 22]

Imaging of the noradrenaline transporter using SPECT would help elucidate how antidepressant compounds interact with the receptor. This information could lead to the development of more efficient, faster acting compounds for the treatment of clinical depression.
2 Results and Discussion

2.1 The Stereoselective Synthesis of (2S,3R)- and (2R,3S)-Iodoreboxetine

In previously reported studies of reboxetine, only analogues of the (2S,3S)- and (2R,3R)-stereoisomers had been tested for their affinity with the noradrenaline transporter.\textsuperscript{54,55} The stereoselective synthesis and pharmacology of (2S,3R)- and (2R,3S)-reboxetine analogues had never been reported in the literature, and so the first aim of this project was to synthesise and test these two stereoisomers to gain a greater understanding of the stereochemical demands of the receptor.

2.1.1 Retrosynthetic Analysis of (2S,3R)-Iodoreboxetine

The proposed retrosynthetic analysis of (2S,3R)-iodoreboxetine is shown in Scheme 24. Halogen exchange and disconnection of the morpholine ring would lead back to amino alcohol 131. Functional group interconversion of the amine to a primary alcohol would give diol 132, and disconnection of the aromatic moiety at the ether linkage would lead to chiral epoxide 133. The epoxide could be prepared from the asymmetric epoxidation of the corresponding $E$-allylic alcohol, which could be made from 4-bromobenzaldehyde 134.
Thus, the important steps in this synthetic strategy were a Sharpless asymmetric epoxidation to introduce the desired stereochemistry, and a copper catalysed halogen exchange reaction to incorporate the key iodine atom. This approach would also allow for the synthesis of the (2R,3S)-stereoisomer by use of the opposite enantiomer of the chiral ligand, diisopropyl tartrate at the Sharpless asymmetric epoxidation step.

2.1.2 Synthesis of (2S,3R)-Iodoreboxetine

As shown in Scheme 25, the synthesis of (2S,3R)-iodoreboxetine began from commercially available 4-bromobenzaldehyde 134.

The Horner-Wadsworth-Emmons reaction is a modification of the Wittig reaction, which employs a phosphonate stabilised carbanion in place of a stabilised phosphonium ylide for the generation of E-alkenes. Typical Horner-Wadsworth-Emmons conditions include the use of high temperatures and sodium hydride, or an alkoxide base to deprotonate the phosphonate and generate the reactive species.\textsuperscript{57,58} In 1984, Masamune and Roush described a milder Horner-Wadsworth-Emmons procedure using lithium chloride as a Lewis acid to increase the acidity of phosphonate, which could then be deprotonated at ambient temperatures using a weaker amine base such as 1,8-diazabicyclo[5.4.0]undec-7-ene.\textsuperscript{59} Thus, aldehyde 134 was subjected to a Horner-Wadsworth-Emmons reaction with triethyl phosphonoacetate under Masamune-Roush conditions to give exclusively E-alkene 135 in an excellent quantitative yield.

The α,β-unsaturated ester was then reduced directly to the alcohol using 2.2 equivalents of DIBAL-H to give allylic alcohol 136 in a quantitative yield.
In 1980, Sharpless described the first practical method for the asymmetric epoxidation of primary allylic alcohols with good yields and excellent enantioselectivities.\textsuperscript{60} The procedure employs titanium isopropoxide, a chiral tartrate ligand, and tert-butyl hydroperoxide as the oxidant.

The catalytic complex formed between titanium isopropoxide and diisopropyl tartrate is extremely water sensitive, requiring only one equivalent of water to destroy it, therefore the reaction must be carried out under strictly anhydrous conditions.

Initially the reaction was carried out using stoichiometric quantities of the reagents, however the addition of activated molecular sieves to the reaction mixture proved to be a key modification, allowing the reaction to proceed under catalytic conditions.\textsuperscript{61} The molecular sieves protect the active catalyst from trace water in the reaction medium, or that generated during the titanium catalysed decomposition of tert-butyl hydroperoxide.\textsuperscript{62}

As shown in Figure 23, the tert-butyl hydroperoxide (highlighted in blue) and the alkene (highlighted in grey) coordinate to the titanium complex in such a manner that only one face of the alkene is presented to the bound oxidant.

The stereochemical outcome of the reaction can be predicted by using the model shown in Figure 24. Use of the (−)-enantiomer of the chiral ligand diisopropyl tartrate results in the oxygen atom being delivered to the top face of the alkene. Conversely, use of the (+)-enantiomer of diisopropyl tartrate results in delivery of the oxygen to the bottom face of the alkene.
Thus, allylic alcohol 136 underwent a Sharpless asymmetric epoxidation using the (+)-enantiomer of diisopropyl tartrate to confer (2S,3S)-stereochemistry in epoxide 133 (Scheme 26). The 70% aqueous solution of the stoichiometric oxidant, tert-butyl hydroperoxide, was dried by distillation using Dean-Stark apparatus and 4Å activated molecular sieves were added to the reaction mixture. Even with these precautions in place, the reaction proved to be capricious, and much optimisation was required to synthesise known chiral epoxide 133 in 79% yield.

With the desired stereochemistry established, the remainder of the reboxetine backbone was synthesised using the same synthetic sequence as that described by Mellioni and co-workers. Epoxide 133 was regioselectively ring-opened using the sodium salt of 2-ethoxyphenol to give diol 132.
The regioselectivity of the epoxide opening can be rationalised by examining the electronic influences of the phenyl and hydroxyl groups. Guss reported the opening of epoxide 137 with phenol to give predominantly primary alcohol 138. This suggests that the aromatic group exerts an electron withdrawing effect, decreasing the electron density on the non-terminal carbon atom, and encouraging nucleophilic attack at the more sterically hindered carbon atom (Scheme 27).

![Scheme 27]

Exploiting the difference in the reactivities of the primary and secondary alcohols to selectively activate the primary alcohol as the tosylate was attempted. Reaction of diol 132 with p-toluenesulfonyl chloride gave a mixture of desired mono-tosylate 139 and di-tosylated analogue 140 (Scheme 28). Considerable optimisation was carried out, including decreasing the equivalents of p-toluenesulfonyl chloride used, and lowering the reaction temperature. Careful monitoring of reaction progress using thin layer chromatography revealed that di-tosylated analogue 140 was being formed before all of the diol starting material had been consumed. It was therefore concluded that formation of the di-tosylated compound was unavoidable. Separation of the mono- and di-tosylated compounds using silica gel proved to be difficult, and the isolated yields for this transformation proved to be variable, ranging from 35% to 77%.

![Scheme 28]
Displacement of the tosyl group using an aqueous solution of ammonia proceeded smoothly to give amino alcohol 131. The reaction was initially carried out using dimethylformamide as the organic solvent, however recovery of the product was poor (33% yield), and this was thought to be due to the difficulty of extracting 131 from the organic solvent. Reaction of 141 with aqueous ammonia solution using acetonitrile as the organic solvent saw an improvement in the isolation of the product, and gave desired amine 131 in a modest 49% yield (Scheme 29).

The initial strategy for the formation of the morpholinone ring was to treat amino alcohol 131 with 2.2 equivalents of triethylamine and chloroacetyl chloride to effect acetylation and intramolecular cyclisation in one step. However, this reaction produced two products, acetylation at the amine (141) plus acetylation at both the amine and alcohol functionalities, with no cyclised product observed (Figure 25).

The transformation was therefore split into two steps, acetylation followed by cyclisation. Treatment of the amino alcohol with 1.1 equivalents of chloroacetyl chloride gave amide 141 in a good 83% yield.

Ring closure was first attempted using potassium tert-butoxide in tert-butanol but the reaction was low yielding, giving morpholinone 142 in a poor 13% yield. The transformation was then attempted using a solution of sodium ethoxide in ethanol, but this was also low yielding, giving amide 142 in a poor 23% yield. Experimentally, the main problem associated with using tert-butanol as the solvent was its high melting point (23-26 °C) as it had a tendency to solidify in syringes and needles and whilst stirring. The original experimental procedure was re-examined, and using glassware and syringes directly from the oven, plus heating the reaction mixture to 40 °C instead of stirring at room temperature gave morpholinone 142 in a good 79% yield.
In literature preparations of reboxetine, the amide functionality was reduced using hydride reagents such as lithium aluminium hydride or Red-Al®. These harsh reagents were not suitable for the reduction of amide 142 because of the potential to cleave the relatively weak carbon-bromine bond. Borane.tetrahydrofuran is a mild, highly chemoselective reagent for the reduction of amides in the presence of other more reactive functional groups. Therefore, reduction of the amide to the amine was carried out under mild conditions using borane.tetrahydrofuran to give morpholine 143 in a 73% yield. The morpholine nitrogen was Boc protected under standard conditions to give 130 in a 75% yield.

Scheme 29

Figure 25
As shown in Scheme 30, the halogen exchange was carried out using conditions described by Kaplars and Buchwald. Reaction of 130 with sodium iodide, catalytic amounts of copper iodide and 1,3-diaminopropane in dioxane at 130 °C for 48 hours gave iodo-compound 145 as a three to one mixture with bromo-starting material 130.

Chromatographic separation of the two halo-compounds using silica gel proved to be difficult. Conversion of the remaining starting material was attempted by repeating the reaction using the mixture of material and a combination of the higher boiling point solvents diglyme and m-xylene. Complete conversion was achieved after heating the bromo/iodo mixture to 140 °C for 48 hours to give iodide 145 in a 49% yield.

Removal of the Boc group using trifluoroacetic acid proceeded smoothly to give the first target molecule, (2S,3R)-iodoreboxetine 126, in a 57% yield.

2.1.3 Synthesis of (2R,3S)-Iodoreboxetine

Having successfully developed an asymmetric synthetic route to the first target molecule, work then began on the synthesis of its enantiomer (2R,3S)-iodoreboxetine 127. The synthetic strategy applied here was the same as that used for the (2S,3R)-stereoisomer, this time employing the (-)-enantiomer of diisopropyl tartrate at the asymmetric epoxidation step to introduce the desired (2R,3R)-stereochemistry.

Initial attempts at the epoxidation of allylic alcohol 136 proved to be low yielding. This was overcome by using a fresh bottle of titanium isopropoxide, and commercially available anhydrous tert-butyl hydroperoxide in place of drying the aqueous solution. This gave chiral epoxide 146 in a good 79% yield (Scheme 31).
As described previously, the epoxide was opened regioselectively using the sodium salt of 2-ethoxyphenol to give diol 147 in a 79% yield.

![Scheme 31](image)

In a bid to increase the selectivity of the tosylation, 2,4,6-triisopropyl benzenesulfonyl chloride was used in place of \( p \)-toluenesulfonyl chloride to activate the primary alcohol, with the view that the increase in steric bulk around the electrophilic sulfur would discourage nucleophilic attack by the secondary alcohol. As predicted, the crude reaction mixture showed selective activation of the primary alcohol and no trace of addition at the secondary position to give 148 in a modest 45% yield (Scheme 33). Unfortunately, the increase in steric bulk eventually proved problematic, and displacement of the sulfonyl group using an aqueous solution of ammonia gave a crude reaction mixture full of different products that proved difficult to purify.

![Scheme 32](image)

This approach was subsequently abandoned, and the problematic \( p \)-toluenesulfonyl chloride protocol re-employed. As seen previously, the di-tosylate side product proved to be an issue and 150 was isolated in a fair 44% yield (Scheme 33). Displacement of the tosyl group using an aqueous solution of ammonia gave amino alcohol 149, which underwent acetylation with chloroacetyl chloride to give amide 151 in a 62% yield.
Intramolecular ring closure was carried out using sodium tert-butoxide to give 154 in an excellent 90% yield. Reduction of the amide to the amine under mild conditions using borane.tetrahydrofuran did not give the desired morpholine moiety but a complex mixture of products. A longer reaction time and substantial purification were required to isolate morpholine 155 in a poor 11% yield. The reason for poor conversion is unknown, but there may have been a problem with either the borane reagent or the solvent.

In a bid to preserve atom economy, the halogen exchange reaction was attempted without protection of the morpholine nitrogen. However, after twenty four hours only trace amounts of the desired iodo-compound 127 had formed, and the bromo-starting material was recovered (Scheme 34). It was thought that perhaps the unprotected nitrogen could be co-ordinating with the copper iodide, preventing the formation of the catalytic complex. The morpholine nitrogen was subsequently Boc protected under standard conditions to give 156 in a 53% yield.

A ligand screen carried out by Buchwald showed the diamine ligand N,N'-dimethylethlyenediamine to have a greater conversion rate and recovery than the previously used ligand, 1,3-diaminopropane. Research carried out in the Sutherland research group by L. Stevenson also showed that an efficient halogen exchange reaction could be carried out using this ligand.
The halogen exchange reaction was carried out using conditions described by Buchwald, this time using \(\text{N,N'}\)-dimethylethylenediamine as the ligand. The change of ligand gave a cleaner crude material and desired iodo-compound 155 in a 52\% yield at a lower reaction temperature after 24 hours. The Boc protecting group was removed under standard conditions to give the second target molecule, \((2R,3S)\)-iodoreboxetine 127, in a 57\% yield.

![Scheme 34](image)

### 2.1.4 Biological Evaluation

Both \((2S,3R)\) and \((2R,3S)\)-iodoreboxetine were assayed for affinity with the noradrenaline transporter by our collaborators at the Division of Clinical Neuroscience at the University of Glasgow. The compounds were tested \textit{in vitro} using homogenised rat brain with a \[^{3}H\]\textit{nisoxetine} displacement assay. Calculated \(K_i\) values for iodo-analogues 126 and 127, plus the parent compound, racemic \((2S,3S)/(2R,3R)\)-reboxetine, are give in Table 8.
From the results shown in Table 8, it can be seen that both (2S,3S)- and (2R,3R)-iodoreboxetine have substantial affinity for the noradrenaline transporter, with \( K_i \) values of 320.8 and 58.2 nM respectively. These results are encouraging since it appears that nanomolar affinity can still be achieved even with the introduction of a large iodine atom onto the phenyl ring and alternative stereochemistry at the chiral centres.

The (2R,3S)-iodoreboxetine compound is the more potent of the two compounds with a \( K_i \) value of only 58.2 nM, suggesting that (3S)-stereochemistry is required for potency.

Although not as potent as the parent compound, racemic reboxetine, the (2R,3S)-idoanalogue has similar levels of affinity compared with racemic mixtures of (2S,3S)- and (2R,3R)-iodoreboxetine analogues reported in the literature.\(^{54,55}\)

Therefore the development of more potent iodo-analogues using the (2R,3S)- scaffold may yield novel compounds which can act as SPECT imaging agents for the noradrenaline transporter.
2.1.5 Conclusions

A new 12-step stereoselective synthesis of (2S,3R)- and (2R,3S)-iodoreboxetine was developed from 4-bromobenzaldehyde. The key steps involved a Sharpless asymmetric epoxidation to establish the desired stereochemistry, and a copper catalysed halogen exchange reaction to introduce the key iodine atom. Biological evaluation of these molecules revealed the (2R,3S)-stereochemistry to have similar levels of potency compared with the more studied (2S,3S)- and (2R,3R)-iodoreboxetine analogues. Therefore, the (2R,3S)-scaffold was identified as a potential lead for the development of a novel imaging agent for the noradrenaline transporter.

Although a successful synthesis of the target molecules was developed, there were several drawbacks associated with this strategy. The introduction of the second aromatic ring occurred early during the synthetic sequence. Ideally it would be incorporated towards the end of the synthesis, allowing for the rapid generation of analogues via a common structural intermediate. The activation of the primary hydroxyl as the tosylate proved to be non-selective, and resulted in a significant loss of material at a relatively early stage. The halogen exchange to introduce the iodine atom required the use of a protecting group and this added an extra two steps to the synthesis. Therefore a new synthetic route to the new reboxetine analogues had to be developed to overcome these problems.
2.2 The Stereoselective Synthesis of (2S,3S)- and (2R,3R)-Iodoreboxetine

A new synthetic strategy was required for the synthesis of (2S,3S)- and (2R,3R)-iodoreboxetine. Introduction of the phenoxy ring at a late stage intermediate would allow the rapid generation of different derivatives. Also, having the crucial iodine atom present in the starting material would negate the need for an inefficient halogen exchange.

2.2.1 Retrosynthetic Analysis of (2S,3S)-Iodoreboxetine

The proposed retrosynthetic analysis of (2S,3S)-iodoreboxetine is shown in Scheme 35. Disconnection of the aromatic moiety at the ether linkage would lead back to iodobenzyl alcohol 156. Disconnection of the morpholine ring would give diol 157, which could be made by opening a protected chiral epoxide using ethanolamine. Diol 159 could be made from the asymmetric dihydroxylation of the corresponding E-allylic chloride, which could be synthesised from 4-iodobenzyl alcohol 160.

![Scheme 35](image)

Thus, the key steps in this synthetic strategy were a Sharpless asymmetric dihydroxylation to establish the desired stereochemistry, and the introduction of the second aromatic ring late in the sequence using either a 2-step Mitsunobu procedure or a chromium mediated nucleophilic aromatic substitution. This strategy would also allow for the synthesis of the (2R,3R)-stereoisomer by use of AD-mix-β at the asymmetric dihydroxylation step.
2.2.2 Synthesis of (2S,3S)-Iodoreboxetine

As shown in Scheme 36, the synthesis of (2S,3S)-iodoreboxetine began from commercially available 4-iodobenzyl alcohol 160 which was subjected to a one-pot Swern oxidation/Horner-Wadsworth-Emmons reaction under Masamune-Roush conditions.\(^{59}\) Initially the Horner-Wadsworth-Emmons phosphonoacetate solution was added directly to the Swern reaction mixture when the oxidation was complete. However, it appeared that not all of the aldehyde generated during the oxidation was being converted to the alkene. This was attributed to solubility problems of the lithium chloride complex in dichloromethane, and was overcome by concentrating the Swern reaction mixture \textit{in vacuo} before the addition of the Horner-Wadsworth-Emmons solution. This transformation gave exclusively the \textit{E}-alkene 161 in an excellent 99% yield over two steps.

Reduction of the \(\alpha,\beta\)-unsaturated ester directly to the alcohol was carried out using 2.2 equivalents of DIBAL-H to give allylic alcohol 162 in an excellent 99% yield.

The conversion of allylic alcohol 161 into the allylic chloride was attempted under different conditions. Chlorination of allylic alcohol using hydrochloric acid gave a complex reaction mixture by \(^1\text{H} NMR spectroscopy. Treatment of 162 with caesium carbonate and trimethylsilyl chloride gave solely the desired allylic chloride 163 in a fair 48% yield. The low yield achieved was attributed to the decomposition of the unstable allylic chloride on silica gel during purification.

In a bid to increase the yield, the transformation was attempted using triphenylphosphine and \(N\)-chlorosuccinimide which gave 163 in a good 69% yield. This protocol gave crude material which could be easily purified using dry loaded flash column chromatography, and became the preferred method for the generation of the allylic chloride.
In 1988, Sharpless reported a chiral version of the syn dihydroxylation of alkenes by osmium tetroxide. It proved to be an extremely powerful transformation, capable of converting all types of alkenes into trans 1,2-diols with excellent enantioselectivity. The Sharpless asymmetric dihydroxylation is carried out using catalytic amounts of osmium in the form of non-volatile K$_2$OsO$_2$(OH)$_4$, a chiral cinchona alkaloid ligand, and stoichiometric amounts of potassium ferricyanide and potassium carbonate. These reagents are commercially available in the form of a pre-mixed powder called AD-mix.

The catalytic cycle for the asymmetric dihydroxylation is shown in Scheme 37. The active osmium species (OsO$_4$) forms a complex with the chiral ligand (L) and then undergoes concerted addition to the alkene to form an osmate ester. Hydrolysis of the osmate ester releases the diol and the ligand. This process is greatly increased by the addition of methanesulfonamide, allowing the reaction to be carried out at 0 °C which increases the enantioselectivity of the reaction. Inorganic co-oxidant potassium ferricyanide reoxidises the osmate into the active osmium species in the aqueous layer.

The reaction is carried out in biphasic conditions to eliminate a second, less enantiomERICally selective, catalytic cycle in which a second molecule of alkene joins onto the osmium under heterogeneous conditions.

The reaction mixture can be buffered with three equivalents of sodium hydrogencarbonate to decrease the pH of the aqueous layer from 12 to 10. This addition is required if either the substrate or product of the reaction are base sensitive.
The chiral ligands are based on the cinchona alkaloids dihydroquinine (DHQ) and dihydroquinidine (DHQD) joined together by a phthalazine bridge (Figure 26). AD-mix-α contains (DHQ)$_2$PHAL whilst AD-mix-β contains (DHQD)$_2$PHAL.
A detailed reaction mechanism remains elusive; however it is thought that the chiral ligands form an “enzyme-like” binding pocket with the active osmium species at the bottom. Steric effects only allow the alkene substrate to approach the osmium in a specific way, leading to high enantioselectivity in the oxidation.68

The stereochemical outcome of the reaction can be predicted using the simple pneumonic shown in Figure 27. Thus, it can be predicted that the use of AD-mix-α will install the oxygen atoms on the bottom face of the alkene, whilst AD-mix-β will deliver the oxygen atoms on the top face.

Allylic chloride 163 was subjected to a Sharpless asymmetric dihydroxylation using AD-mix-α to install the desired (2R,3S) stereochemistry (Scheme 38). Initial experiments produced diol 159 with significant amounts of epoxide 164 also being formed. Buffering the reaction mixture with three equivalents of sodium hydrogencarbonate prevented epoxide formation, and gave diol 159 in a good 84% yield and in an excellent 98% enantiomeric excess. Deprotonation of the alcohol using sodium hydroxide, and internal displacement of the chlorine atom proceeded smoothly to give epoxide 164 cleanly in an excellent 98% yield.
The enantiomeric excess of the asymmetric dihydroxylation was established using chiral high performance liquid chromatography (HPLC). A racemic mixture of the diol was analysed using a CHIRALPAK IB column and separation was seen using 95:5 hexane:isopropanol at a flow rate of 0.75 mL (Figure 28).
The (2R,3S)-diol 159 generated from the Sharpless asymmetric dihydroxylation using AD-mix-α was then analysed (Figure 29). It was found to have a retention time of 29.0 minutes and an enantiomeric excess of 98% as calculated.

As shown in Scheme 39, the secondary alcohol was protected as the tert-butyldimethylsilyl ether under standard conditions to give 158 in 86% yield.

Subsequent opening of epoxide 158 using ethanolamine gave a mixture of two products by $^1$H NMR spectroscopy. It was hypothesised that perhaps epoxide opening was not occurring regiospecifically, and that as well as desired product 157, nucleophilic attack was also occurring at the more hindered end of the epoxide to give 165.
To test this theory, the epoxide opening was attempted using bulkier amino alcohol 169 since the increased steric bulk around the nucleophilic nitrogen should discourage attack at the more hindered end of the epoxide.

As shown in Scheme 40, the $p$-methoxybenzyl $N$-protected analogue was prepared according to the literature by reaction of ethanolamine with 4-methoxybenzaldehyde 166 followed by *in situ* imine reduction using sodium cyanoborohydride to give 167 in a good 59% yield.  

Amino alcohol 167 was then used to open silyl protected epoxide 158 and again two compounds were observed by $^1$H NMR spectroscopy. This ruled out the steric hindrance theory and suggested that a silyl migration was taking place to give 169.
One possible mechanism for the formation of 169 is shown in Scheme 41. Nucleophilic attack at the least hindered end of the epoxide would give 170 which could then undergo the silyl rearrangement to release the steric clash between the bulky silyl and phenyl groups to give 169.

In order to prevent the silyl migration occurring, protection of the secondary alcohol as the tert-butylidiphenylsilyl ether was attempted in the hope that the protecting group would be too bulky to migrate. However, due to steric hindrance the protecting group was too bulky and only starting material was recovered (Scheme 43).

Since the silyl protecting groups were proving to be problematic, the reaction between unprotected epoxide 164 and ethanolamine was attempted. This yielded a crude material which appeared complex by $^1$H NMR spectroscopy, suggesting that significant side reactions were taking place. Opening of epoxide 164 using the bulkier amino alcohol 167 also produced a complex crude reaction mixture which proved difficult to purify. It was concluded that protection of the secondary alcohol was necessary, and the silyl protection strategy was abandoned in favour of the methoxymethyl (MOM) group.
Treatment of the secondary alcohol with chloromethylmethyl ether and Hünig’s base also proved to be tricky, and after much optimisation, epoxide 172 was synthesised in only a modest 37% yield (Scheme 43).

Opening of MOM protected epoxide 172 using ethanolamine proceeded smoothly, and produced only desired amino alcohol 173 in an excellent 95% yield. The nitrogen of the amino alcohol was protected with a Cbz group under standard conditions to give 174 in a moderate 48% yield.

Due to the carbamate functionality, the $^1$H NMR spectrum of 174 appeared broad and showed evidence of rotamers (Figure 30). A series of high temperature NMR spectroscopy experiments were carried out to achieve signal coalescence (Figure 31) and multiplicity (Figure 32).
The Harding group described a one-pot procedure for the formation of a morpholine ring by reaction of diol 175 with sodium hydride and tosyl imidazole to affect ring closure (Scheme 44).\textsuperscript{70}

![Scheme 44](image)

Ring closure of 174 was attempted under these conditions, however the main compound isolated was not the expected morpholine but oxazolidinone 177 (Scheme 45).

![Scheme 45](image)

This one-pot ring closure procedure was developed by the Myers group, who reported the formation of oxazolidinones when the reaction is carried out in the presence of N-carbamoyl protecting groups.\textsuperscript{71} To avoid this, Myers used tosyl protected amines to carry out the cyclisation. This would not be appropriate for amine 174, as the reaction conditions required to remove the tosyl protecting group could cleave the key carbon-iodine bond.

Effecting ring closure by splitting the sequence into selective tosylation of the primary alcohol followed by treatment with base and displacement of the tosyl group by the resultant alkoxide was an alternative option. Unfortunately the initial tosylation of diol 176 yielded a complex crude mixture which was difficult to purify.

At this point the new synthetic strategy for the formation of the morpholine ring was abandoned, and the approach used for the synthesis of the (2S,3R)- and (2R,3S)-iodoanalogues employed.
Epoxide 164 was regioselectively opened using an aqueous solution of ammonia to give amine 178, which was acetylated in its crude form using chloroacetyl chloride. This gave amide 179 in a reasonable 51% yield over two steps (Scheme 46). Formation of the morpholinone ring was carried out using sodium tert-butoxide to give 180 in a 65% yield.

The reduction of amide 180 proved to be problematic, and attempts were made using several different hydride reducing agents. Treatment of 180 with borane.tetrahydrofuran or lithium aluminium hydride resulted in significant side reactions and a complex crude material which was difficult to purify.

Treatment of 180 with Red-Al® resulted in the successful reduction of the amide to the amine. However, it also cleaved the key carbon-iodine bond on the phenyl ring to give amine 182. It was thought that perhaps the reaction was being left for too long, and reaction progress was monitored carefully by 1H NMR spectroscopy. This showed de-iodinated 182 was being formed even in the presence of the amide starting material, and suggested that selective reduction of the amide using Red-Al® was not possible for this substrate. Successful reduction of amide 180 was achieved using borane.dimethyl sulfide complex which gave amine 181 cleanly, with no cleavage of the carbon-iodine bond.

Scheme 46
The morpholine nitrogen was Boc protected under standard conditions to give key intermediate, benzyl alcohol 156 in a 40% yield over two steps (Scheme 47).

As demonstrated by Boot and co-workers, the second aromatic ring could be introduced using a 2-step Mitsunobu procedure. Conversion of benzyl alcohol 156 to the bromo epimer followed by displacement using 2-ethoxyphenol would result in overall retention of configuration and the desired (2S,3S)-stereochemistry.

Formation of the bromo epimer was attempted by treatment of 156 with carbon tetrabromide and triphenylphosphine. This gave the desired compound in a poor 17% yield, and it was proposed that the benzyl halogen was decomposing on the silica gel during purification.

The transformation was attempted again using polymer supported triphenylphosphine, which could be filtered out from the reaction mixture and negate the need for column chromatography. This reaction yielded amine 183, the bromo epimer with cleavage of the Boc protecting group, in a 47% yield. As the Boc group is acid sensitive, it was thought that perhaps it had been cleaved by residual hydrogen bromide from the decomposition of the carbon tetrabromide. The reaction was repeated using freshly obtained reagents, however the major product isolated was deprotected amine 183.

Insertion of the phenoxy ring using epimer 183 was attempted using 2-ethoxyphenol, however this gave a complex crude reaction mixture. It was proposed that the unprotected amine may have been deprotonated by the base, and the resultant nucleophilic amine displaced the halogen. It was therefore concluded that a protecting group on the nitrogen was essential.
There were also mechanistic concerns as to whether the displacement of the bromine would proceed exclusively by a $S_N^2$ mechanism. The stability of the benzyl cation could allow a $S_N^1$ reaction to occur and produce a mixture of compounds with (2S,3S)- and (2S,3R)- configuration.

In order to be absolutely sure of the stereochemical outcome of the reaction, the Mitsunobu reaction was abandoned in favour of a synthetic strategy which would not involve the established stereocentres. Using chemistry developed by Tamagnan and co-workers, the second phenyl ring was introduced into the molecule using a chromium mediated nucleophilic aromatic substitution.

As shown in Scheme 48, chromium complex 186 was prepared according to the literature from the alkylation of commercially available 2-fluorophenol 184 with bromoethane in an excellent 97% yield. The chromium complex was formed by reaction of 185 with chromium hexacarbonyl in a mixture of refluxing dibutyl ether and tetrahydrofuran.

The reaction was monitored by $^1$H NMR spectroscopy and seemed to have proceeded very cleanly, however on full scale work-up the chromium complex appeared to have decomposed. It was thought perhaps the complexes were decomposing in solution and/or were light sensitive. The reasonable 47% yield reported in the literature could not be replicated, and chromium complex 186 was isolated in a poor 14% yield.

Protected morpholine 156 underwent a chromium mediated nucleophilic aromatic substitution reaction using sodium hydride and organometallic complex 186 to give the protected target molecule 187 in a good 63% yield (Scheme 49). Treatment of 187 with trifluoroacetic acid gave the third target molecule, (2S,3S)-iodoreboxetine 128, in a good 60% yield.
2.2.3 Synthesis of (2R,3R)-Iodoreboxetine

With (2S,3S)-iodoreboxetine in hand, work then began on the synthesis of its enantiomer (2R,3R)-iodoreboxetine. The synthetic approach used for the synthesis of (2S,3S)-iodoanalogue was employed, this time using AD-mix-β at the asymmetric dihydroxylation step to introduce the desired (2R,3R)-stereochemistry.

As shown in Scheme 50, allylic chloride 163 underwent a Sharpless asymmetric dihydroxylation to give diol 188 in a good 62% yield and excellent 98% enantiomeric excess. Treatment of the diol with sodium hydroxide gave epoxide 189 cleanly in a moderate 63% yield.

Epoxide 189 was regioselectively opened using an aqueous solution of ammonia to give amine 190, which was acetylated in its crude form using chloroacetyl chloride to give amide 191 in a reasonable 46% yield over two steps. Formation of the morpholinone ring was carried out using sodium tert-butoxide to give 192 in a good 76% yield.
The enantiomeric excess of the (2S,3R)-dial 188 generated from the Sharpless asymmetric dihydroxylation of 163 using AD-mix-β was established as described previously using chiral HPLC. It was found to have a retention time of 27.4 minutes and an enantiomeric excess of 98% (Figure 33).

Scheme 50
As shown in Scheme 51, reduction of the amide to the amine using borane-dimethyl sulfide complex proceeded smoothly to give amine 193 which was subsequently Boc-protected under standard conditions to give intermediate 194 in a modest 56% yield over two steps.

Protected morpholine 194 then underwent a chromium mediated nucleophilic aromatic substitution reaction using sodium hydride and chromium complex 186 to give the protected target molecule 195 in 67% yield. Treatment of 195 with trifluoroacetic acid gave the fourth target molecule, (2R,3R)-iodoreboxetine 129, in a good 67% yield.
2.2.4 Biological Evaluation

Synthetic intermediates amide 180 and amine 181 contain the hydrogen bond donating and accepting groups found in reboxetine. The intermediates were sent to the Division of Clinical Neuroscience at the University of Glasgow for in vitro evaluation to investigate the importance of the phenoxy moiety. The compounds were assessed using a [$^3$H]nisoxetine displacement assay for affinity with the noradrenaline transporter. The calculated $K_i$ values for amide 180 and amine 181 are given in Table 9.
Table 9

<table>
<thead>
<tr>
<th>Compound</th>
<th>NAT $K_i$ (nM)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="180" alt="Compound" /></td>
<td>$&gt;1000$</td>
</tr>
<tr>
<td><img src="181" alt="Compound" /></td>
<td>$&gt;10000$</td>
</tr>
</tbody>
</table>

$^a$ $K_i$ values are the mean of 3 separate determinations.

From Table 9 it can be seen that neither intermediate 180 nor 181 show affinity for the noradrenaline transporter with $K_i$ values of $>1000$ and $>10000$ nM respectively. This suggests that a large aromatic or lipophilic moiety at the C-3 position is essential for efficient binding to take place.

Target compounds (2S,3S)-iodoreboxetine 128 and (2R,3R)-iodoreboxetine 129 were tested for affinity with the noradrenaline, serotonin and dopamine transporters using the radioligands $[^3H]$nisoxetine, $[^3H]$citalopram and $[^3H]$WIN-35,428 respectively in the displacement assays.

The calculated $K_i$ values for (2S,3S)- and (2R,3R)-iodoreboxetine are given in Table 10. The $K_i$ values for (2S,3R)- and (2R,3S)-iodoreboxetine from the previous study are given for comparison. Racemic (2S,3S)/(2R,3R)-reboxetine has a $K_i$ value of $6.9 \pm 1.6$ for the noradrenaline transporter.
Table 10

<table>
<thead>
<tr>
<th>Compound</th>
<th>NAT $K_i$ (nM)$^a$</th>
<th>SERT $K_i$ (nM)$^b$</th>
<th>DAT $K_i$ (nM)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td>320.8 ± 9.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><img src="image2.png" alt="Image" /></td>
<td>58.2 ± 9.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><img src="image3.png" alt="Image" /></td>
<td>53.8 ± 2.7</td>
<td>2793 ± 480</td>
<td>1457 ± 150</td>
</tr>
<tr>
<td><img src="image4.png" alt="Image" /></td>
<td>64.0 ± 2.4</td>
<td>646 ± 142</td>
<td>716 ± 20</td>
</tr>
</tbody>
</table>

$^a$ $K_i$ values are the mean of 3 separate determinations.

$^b$ $K_i$ values are the mean of 2 separate determinations.

- Not tested.
From Table 10 it can be seen that (2S,3S)-iodoreboxetine has high affinity and excellent selectivity for the noradrenaline transporter versus the serotonin and dopamine transporters, exhibiting 50- and 30-fold selectivity respectively.

According to the literature, (2S,3S)-reboxetine analogues generally have higher affinity for the noradrenaline transporter than their (2R,3R)-enantiomers. In fact, in some cases the (2S,3S)-compounds have been found to be 100-fold more potent.29,31,54

As expected, (2S,3S)-iodoreboxetine 128 has higher affinity with a $K_i$ value of 53.8 nM, but surprisingly, (2R,3R)-iodoreboxetine 129 displays similar potency with a $K_i$ value of 64.0 nM. From the results of the previous study, it was concluded that (S)-stereochemistry at the C-3 position was essential for affinity.72 The results from this study strongly suggest that (2R,3R)-iodoreboxetine may be binding in a different manner compared to the other three analogues. The addition of the large iodine atom to the phenyl ring makes both rings of similar size compared with the parent compound, and may allow these moieties to alternate binding pockets. This would give a similar three dimensional shape at the C-3 position as with the (2S,3S)- and (2R,3S)-iodoanalogues and explain the similar levels of potency.

Of most interest is the comparison of the (2R,3S)- and (2S,3S)-iodoanalogues. Previously untested (2R,3S)-iodoreboxetine shows comparable potency to the much more studied (2S,3S)-stereochemistry, suggesting that this could be a potential novel scaffold for the synthesis of more potent inhibitors.

Although the results of the initial biological testing of the iodo-compounds were interesting, a more potent inhibitor with a calculated $K_i$ value of 10 nM or less was required to warrant radiolabeling.

2.2.5 Conclusions

A new 12-step stereoselective route for the synthesis of iodinated analogues of (2S,3S)- and (2R,3R)-iodoreboxetine was developed from 4-iodobenzyl alcohol. The key steps in this synthetic sequence involved a Sharpless asymmetric dihydroxylation to establish the desired stereochemistry and a chromium-mediated nucleophilic aromatic substitution to introduce the phenoxy ring.
For the first time all four possible stereoisomers of iodoreboxetine were biologically evaluated, and this generated valuable insight into the stereochemical demands of the noradrenaline transporter. The previously unstudied (2R,3S)-stereochemistry was found to be as potent as the more investigated (2S,3S)-stereochemistry, and may be a potential lead for the development of a novel agent for the imaging of the noradrenaline transporter using SPECT.

Initially we intended to re-synthesise and radiolabel efficient binders for imaging of the noradrenaline transporter using SPECT. Unfortunately, the affinity of the best compounds, the (2R,3S)- and (2S,3S)-derivatives, was not good enough to warrant radiolabeling and further development of more potent analogues was required.

### 2.3 Synthesis of (2R,3S)-Iodoanalogues

The groups of Saji and Tamagnan reported the synthesis and activity of (2S,3S)-iodoanalogue 118, replacing the ethoxy group with an iodine atom (Figure 34).\(^{54,55}\) This derivative was found to have excellent affinity for the noradrenaline transporter with a \(K_i\) value of 0.84 nM.

![Figure 34](image)

The results of the previous studies suggest that a (2R,3S)-stereoisomer of 118 should be just as potent. Not only would this represent the development of a novel SPECT ligand for the noradrenaline transporter, using chemistry developed for the synthesis of the (2S,3S)- and (2R,3R)-compounds, the synthesis of meta and para analogues would also be possible (Figure 35). The testing of these three compounds would allow the evaluation of the structure activity relationship at this part of the molecule.
2.3.1 Retrosynthetic Analysis of (2R,3S)-Iodoreboxetine

The proposed retrosynthetic analysis of (2R,3S)-iodoreboxetine analogue is shown in Scheme 52. Disconnection of the aromatic moiety at the ether linkage would give benzyl alcohol intermediate 200. Disconnection of the morpholine ring would lead back to amide 201, which could be made by regioselectively opening the chiral epoxide generated from diol 203. The stereochemistry could be introduced using an asymmetric dihydroxylation of the corresponding commercially available E-allylic chloride 204.

This synthetic strategy would generate a key intermediate, benzyl alcohol 200, which could be coupled with phenolic compounds containing an iodine atom in either the ortho, meta or para position. Intermediate 200 could also be used to generate new analogues with different electron demands on the second aromatic ring.
2.3.2 Synthesis of (2R,3S)-Iodoreboxetine Analogues

As shown in Scheme 53, the synthesis of (2R,3S)-iodoreboxetine analogues began from commercially available trans-cinnamyl chloride.

 Allylic chloride 204 was subjected to a Sharpless asymmetric dihydroxylation using AD-mix-β to introduce the desired (2S,3R)-stereochemistry and give diol 203 in a 66% yield, and excellent 98% enantiomeric excess. Treatment of the diol with sodium hydroxide gave chiral epoxide 202 cleanly in an excellent 92% yield.

Previous epoxide openings using aqueous ammonia solution yielded a crude material which showed only one product by $^1$H NMR spectroscopy. This transformation however, showed more than one product, suggesting that the epoxide opening was not occurring regiospecifically. The material was acetylated in its crude form using chloroacetyl chloride to give amide 201 in a disappointing 25% yield over two steps.

Ring closure was carried out by treatment of 201 with sodium tert-butoxide to give amide 205 in a 58% yield, and reduction to the amine was carried out successfully using borane.dimethyl sulfide.
As shown in Scheme 54, Boc-protection of amine 206 was carried out under standard conditions to give key intermediate benzyl alcohol 200 in a 37% yield over two steps.

In order to achieve the desired stereochemistry, inversion of configuration at the C-3 position was required. Recently, Fish and co-workers reported the activation of a benzylic alcohol as the mesylate followed by displacement using various phenolic nucleophiles to successfully synthesise different morpholine derivatives. The complete inversion of stereochemistry at the 2-position was confirmed by X-ray crystallography.29

Thus, secondary alcohol 202 was activated as the mesylate to give 209 in a good 74% yield.29 Isolation of the mesylate intermediate proved successful compared with the 2-step Mitsunobu approach where the deprotection was a problem. Concerns over the stereochemical outcome of the reaction were also admonished using this approach.

As shown in Scheme 55, displacement of the mesylate group was carried out using phenolic nucleophiles with iodo substituents in the ortho, meta and para positions. This gave 208, 209 and 210 in 47%, 32% and 52% yields respectively. The Boc protecting groups were removed under standard conditions using trifluoroacetic acid to yield target molecules 196, 197 and 198 in moderate yields.
2.3.3 Biological Evaluation

The three (2R,3S)-iodoreboxetine analogues were sent to the Division of Clinical Neuroscience at the University of Glasgow for in vitro evaluation against noradrenaline, serotonin and dopamine transporters using a $[^3]$Hnisoxetine, $[^3]$Hcitalopram and $[^3]$HWIN-35,428 displacement assays. The calculated $K_i$ values for the three compounds are given in Table 11.
Table 11

<table>
<thead>
<tr>
<th>Compound</th>
<th>NAT $K_i$ (nM)$^a$</th>
<th>SERT $K_i$ (nM)$^b$</th>
<th>DAT $K_i$ (nM)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Compound 196" /></td>
<td>8.4 ± 1.7$^b$</td>
<td>51.5 ± 8.4</td>
<td>525.9 ± 125.5</td>
</tr>
<tr>
<td><img src="image" alt="Compound 197" /></td>
<td>1700 ± 500</td>
<td>154.0 ± 12.0</td>
<td>1900 ± 600</td>
</tr>
<tr>
<td><img src="image" alt="Compound 198" /></td>
<td>1100 ± 200</td>
<td>34.5 ± 1.7</td>
<td>2100 ± 300</td>
</tr>
</tbody>
</table>

$^a K_i$ values are the mean of 3 separate determinations.

$^b K_i$ values are the mean of 5 separate determinations.

From the results shown in Table 11, it can be seen that substitution on the phenoxy ring has a dramatic effect on potency. *Ortho*-analogue 196 has excellent potency and good selectivity for the noradrenaline transporter with a $K_i$ value of only 8.4 nM. Although not as potent as the (2$S$,3$S$)-derivative synthesised by Tamagnan and Saji, ortho analogue 196 is still a suitable candidate for a radiolabeling study.$^{54,55}$

Substitution in the *meta* or *para* position of the phenoxy ring appears to decrease affinity, with $K_i$ values falling into the micromolar range. Interestingly, 198 displayed promising affinity for the serotonin transporter with 30- and 60-fold selectivity over the noradrenaline and dopamine transporters.
2.3.4 Conclusions

An eight step synthesis to key intermediate 207 was developed from trans-cinnamyl chloride using a Sharpless asymmetric dihydroxylation to introduce the desired stereochemistry. Treatment of 207 with various iodophenols allowed the rapid generation of three (2R,3S)-iodoreboxetine derivatives. Biological evaluation of these molecules revealed structure activity relationships for substitution on the phenoxy ring and ortho substituted analogue 196 was identified as a suitable candidate for radiolabeling.

2.3.5 Future Work

Future work for this project includes the radiolabeling of 196 (Scheme 56). Radiosynthesis would require conversion of Boc-protected 208 into tin precursor 211 by treatment with hexamethylditin and a palladium(0)-catalyst. Electrophilic iododestannylation of 211 using sodium $^{123}$I-iodide and chloramine-T followed by deprotection using trifluoroacetic acid would yield the desired radiolabelled iodoreboxetine 212, which could then be used for in vivo animal and human imaging studies.\(^7^4\)

The synthesis and biological evaluation of iodoanalogues of reboxetine based on the (2R,3S)-backbone are on-going in the Sutherland group. As shown in Scheme 57, different compounds could be generated by following the established synthetic route to the mesylate intermediate, which could then be coupled with aromatic rings containing different ether linkages (213) or (214), or different steric (215) and electronic requirements (216). The most potent of the compounds could then be radioiodinated using an iododestannylation reaction and used for SPECT imaging of the noradrenaline transporter.
Scheme 57
2.4 A New Synthetic Approach for the Total Synthesis of Oxazinin-3

2.4.1 Introduction

Algal blooms are caused by the proliferation of phytoplankton and cyanobacteria during periods of nutrient abundance in the ocean (Figure 36). Some species of microalgae can produce potent toxins that can contaminate edible shellfish, which if consumed, can pose a serious threat to human health. Therefore, the isolation and characterisation of marine toxins is important to deduce mechanism of action and evaluate the risk of ingestion.

Figure 36

Algal blooms are also a rich source of novel biologically active compounds, which include brevetoxins, saxitoxin and okadaic acid. In 2001, the Fattorusso group isolated and characterised a family of novel marine toxins isolated from the edible muscle *Mytilus Galloprovincialis*. These compounds, called oxazinins, are indole derived 3-oxomorpholines, which contain unique structural features unseen in previously reported natural products (Figure 37). The three novel marine toxins were biologically evaluated and oxazinin-1 was shown to be a potent cytotoxin against cell lines *in vitro*.
2.4.2 Structural and Stereochemical Elucidation

The structures and relative stereochemistry of the oxazinin family were established using a variety of spectroscopic techniques including mass spectrometry, ultraviolet and infrared spectrometry and extensive 1D and 2D NMR experiments.

The relative stereochemistry of oxazinin-1 was assigned by examination of NMR spectroscopic data. The coupling constant of 9.2 Hz between H-5 and H-6 in the $^1$H NMR spectrum suggested a trans-diaxial relationship between the two protons. An intense cross peak in the ROESY spectrum between H-2 and H-6 suggested a cis-relationship. Thus, the relative stereochemistry was ascertained to be 2S,5R,6R/2R,5S,6S (Figure 38).
According to the spectroscopic data, the structure of oxazinin-2 was identical to that of oxazinin-1 with the exception of the absence of the cyanide group and associated methylene signals. Thus, the structure and relative stereochemistry of oxazinin-2 was determined to be 218 (Figure 39).

![Figure 39](image)

The NMR data for oxazinin-3 suggested a cis-relationship between H-2 and H-5 and difference NOE experiments confirmed this assignment. Therefore the relative stereochemistry of oxazinin-3 was determined to be 2S,5S/2R,5R (Figure 40).

![Figure 40](image)

With the relative stereochemistry of the oxazinin compounds established, the group determined the absolute stereochemistry of oxazinin-1 using a NMR shift correlation reagent for β-chiral primary alcohols.77 The observed NMR spectroscopic data allowed the assignment of the absolute stereochemistry 2S,5R,6R.78

### 2.4.3 Synthesis of Oxazinin-3

In 2004, the Couladouros group reported the first synthesis of oxazinin-3 (Scheme 58).79 Coupling of 3-indoleglyoxylic acid 220 and tyrosine methyl ester 221 followed by simultaneous reduction of the keto and ester functionalities using lithium borohydride gave diol 223. The mixture was treated with pyridinium p-toluenesulfonate to form the morpholinone ring system and gave 219 and 225 in a 1:1 ratio. The diastereoisomers were separated using column chromatography, and the undesired isomer 225 was equilibrated by repeated exposure to PPTS in refluxing acetonitrile.
The cis-isomer was found to have identical $^1$H NMR spectra to that reported for oxazinin-3, and comparison of the optical rotation values for the natural and synthetic material established the absolute stereochemistry of oxazinin-3 as $2S, 5S$. This synthetic approach gave target molecule oxazinin-3 in three steps and a 61% overall yield.

### 2.4.4 Isolation and Characterisation of Oxazinin-4

In 2006, the Fattorusso group reported the isolation of a fourth toxin from the digestive glands of *Mytilus Galloprovincialis*. Initial structural studies suggested that the new toxin, oxazinin-4, was a diastereoisomer of oxazinin-1. The coupling constant between H-5 and H-6 in the $^1$H NMR spectrum suggested a *trans*-relationship and ROESY experiments showed an intense correlation between H-2 and H-6, which suggested a *cis*-relationship. This arrangement would mean that oxazinin-4 and oxazinin-1 had the same relative stereochemistry.
This finding led to the re-examination of the absolute stereochemistry of oxazinin-1. Using more natural material and a 700 MHz instrument, the ROESY experiments were repeated and this time no correlation was seen between H-2 and H-6. This suggested that the ROE correlation seen previously was actually an artifact of the machine, possibly due to the paucity of material and subsequent low signal to noise ratio. The new NMR data pointed towards a *trans*-relationship and reassignment of the absolute stereochemistry of oxazinin-1 \text{226} and -2 \text{227} to be \(2R,5R,6R\) (Figure 41).

A synthetic study was carried out to verify the proposed stereochemistry and oxazinin-2 was synthesised using a similar approach to that described for the synthesis of oxazinin-3. This confirmed the reassignment of the absolute stereochemistry of oxazinin-1 and -2 and established the absolute stereochemistry of oxazinin-4 \text{228} to be \(2S,5R,6R\).

\[\begin{align*}
\text{Oxazinin-1} & & \text{Oxazinin-2} & & \text{Oxazinin-4} \\
\text{226} & & \text{227} & & \text{228}
\end{align*}\]

\text*Figure 41*

### 2.4.5 Proposed Research

The published synthesis of oxazinin-2 is relatively long, consisting of 14 steps.\textsuperscript{80} The key reaction in the synthetic sequence was carried out as a racemic mixture giving a 1:1 ratio of diastereoisomers in a combined 50% yield. Moreover, there is no reported synthesis of the biologically important oxazinin-1.

The aim of this project was to devise a new efficient, stereoselective synthesis of these marine natural products, which would initially lead to a total synthesis of oxazinin-3. This approach would then be applied to the other members of this family of natural products.
2.4.6 Retrosynthesis of Oxazinin-3

The proposed retrosynthesis of oxazinin-3 is shown in Scheme 59. Disconnection of the morpholinone ring of 219 would give amide 229, which could be further disconnected to give two key fragments 230 and 231. Carboxylic acid fragment 230 could be synthesised from indole 232 and ethyl glyoxylate 233 via an asymmetric Friedel-Crafts acylation. The amino alcohol fragment 231 could be synthesised from commercially available L-tyrosine 234.

Thus, the key steps in this synthetic sequence include an organocatalysed asymmetric Friedel-Crafts acylation to introduce the desired stereochemistry into 230, and an EDCI-mediated coupling of the fragments 230 and 231. Simultaneous acid-mediated MOM deprotection and morpholinone ring formation, followed by deprotection of the methyl ether would give 219.

The spectroscopic data of the synthetic material would then be compared to that of the natural product published in the literature to confirm the stereochemical outcome of the ring forming reaction.
2.4.7 Steps Towards Oxazinin-3

The synthesis of oxazinin-3 began from commercially available L-tyrosine 234. The amino acid was Boc protected under standard conditions to give 235 in an excellent quantitative yield (Scheme 60). The hydroxyl and acid functionalities were simultaneously protected as the methyl ether and methyl ester to give 236 in a 58% yield. Reduction of the ester was carried out using lithium borohydride to give amine 237 in an 81% yield. Boc deprotection using hydrochloric acid gave amino alcohol fragment 231 as the hydrochloride salt in a 96% yield.

![Scheme 60](image)

Work then began on the synthesis of the carboxylic acid fragment. Deng and co-workers reported an enantioselective version of the Friedel-Crafts reaction between indole and various carbonyl compounds using base-acid bifunctional cinchona alkaloids as catalysts (Figure 42).81,82

![Figure 42](image)
The active conformer of the flexible catalyst was found to be gauche-open with the transition state organised and stabilised by co-operative hydrogen bonding networks (Figure 43). \(^8^1\)

![Figure 43](image1)

Mechanistic studies showed that the substituents of the two bond forming carbons are staggered rather than eclipsed. The alternative transition state generating the other stereoisomers are relatively disfavoured due to either loss of hydrogen bonding interactions between the catalyst and substrate, or unfavourable eclipsed interactions between substituents of bond forming carbons. Using the model reported for predicting enantioselectivity for a Michael addition, the proposed transition state for the Friedel-Crafts acylation is shown in Figure 44. \(^8^1\)

![Figure 44](image2)

The Deng group report the enantioselective reaction of indole with ethyl glyoxylate to proceed in an 85% yield and good 93% enantiomeric excess. \(^8^3\) The cinchona alkaloid catalyst required to induce the desired (S)-stereochemistry was reported to be easily synthesised from commercially available quinidine over two steps in a 60% overall yield. \(^8^2\)

Thus, quinidine 238 underwent a nucleophilic aromatic substitution reaction with 9-iodophenanthrene to give 239 in a 39% yield. Cleavage of the methyl ether was carried out using sodium ethanethiolate to give desired catalyst 240 in a 47% yield (Scheme 61).
The asymmetric Friedel-Crafts reaction was attempted using indole and ethyl glyoxylate under conditions described by Deng (Scheme 62). The crude reaction mixture showed formation of the target molecule 241, however purification of the crude reaction mixture using silica gel proved difficult, and gave 241 with a significant amount of impurities present.

Since the Deng protocol required a catalyst which was proving low yielding and complicated to synthesise, it was abandoned in favour of a procedure described by Xiao and co-workers.

The Xiao group carried out the same transformation using a (S)-BINOL-titanium(IV) catalytic system.\textsuperscript{84} The postulated mechanism for the transformation is shown in Scheme 64. The titanium and chiral ligand coordinate to form the catalytic complex which then coordinates to ethyl glyoxylate. The activated electrophile then undergoes attack from indole 232 to form intermediate 242 which can follow either pathway I or II. Pathway I involves the release of the titanium catalyst and formation of the desired compound 241. In pathway II, the indolium cation reacts with another equivalent of indole to give bis-indole by-product 244. It was found that formation of the bis-indole could be prevented by carrying out the reaction at low temperatures.
The structure of the active catalytic complex is unknown, however the high enantioselectivity was rationalised based on a transition state previously reported by Corey and Ding. Coordination of ethyl glyoxylate to the (S)-BINOL-titanium(IV) complex results in a hydrogen bonding interaction between the aldehyde proton and an oxygen atom from (S)-BINOL to form a five-membered ring (Figure 45).

The ring makes the coordination bond between the titanium and ethyl glyoxylate less flexible and presents the Si face of the aldehyde for attack from the indole derivative. Attack is less likely to occur at the Re face as it is blocked by the naphthyl subunit.
The reaction of indole with ethyl glyoxylate using this catalytic system was reported to proceed in a 72% yield and a modest 84% enantiomeric excess.\textsuperscript{84} Better enantioselectivity was achieved using protected indoles, with the benzyl group showing the best enantiomeric excess (91%). Protection of the indole nitrogen would discourage potential side reactions in subsequent transformations.

There are numerous examples of high yielding indole protection procedures in the literature, however the protection of indole proved to be problematic.\textsuperscript{87,88} Many different procedures were tried and successful protection was eventually achieved using potassium hydroxide and benzyl bromide in dimethyl sulfoxide to give 245 in 81% yield (Scheme 64).\textsuperscript{89} The Friedel-Crafts reaction was then attempted and 246 was isolated in a poor 13% yield. The poor yield was attributed to the significant quantity of a bisindole side product 247 which was also isolated. This suggested that the reaction mixture was not being kept cold enough.

\begin{equation}
\text{N}\text{H} \quad 232 \quad \text{KOH, BnBr} \quad \text{DMSO, 81\%}
\end{equation}

\begin{equation}
\text{N}\text{H} \quad 245 \quad \text{Ti(O\text{Pr})}_4 \quad \text{(S)-BINOL} \quad \text{Et}_2\text{O, -20 \textdegree C 13\%}
\end{equation}

\begin{equation}
\text{HO} \quad \text{CO}_2\text{Et} \quad \text{251} \quad \text{CO}_2\text{Et} \quad \text{252}
\end{equation}

\textbf{Scheme 64}

Benzyl protection of the indole was repeated however, purification of the crude material proved difficult. It was thought that the excess benzyl bromide from the reaction was being hydrolysed to benzyl alcohol on the silica gel and this was difficult to separate from indole 245. The quantity of benzyl bromide used in the reaction was reduced from 2 to 1.2 equivalents in a bid to reduce the excess and ease purification.
Unfortunately the crude reaction mixture still proved difficult to purify and the indole protection strategy was abandoned.

The (S)-BINOL-titanium(IV) catalysed asymmetric Friedel-Crafts reaction was then attempted using indole and ethyl glyoxylate (Scheme 66). The reaction was monitored by mini-workup and $^1$H NMR spectroscopy and seemed to proceed smoothly. However, on full scale workup, the crude reaction mixture appeared to have decomposed and significant side products were observed in the $^1$H NMR spectrum of the crude material. Further investigation suggested that the crude material was decomposing during the workup procedure and so the crude reaction mixture was applied directly to the silica gel. Exhaustive purification using a diethyl ether/petroleum ether solvent system led to the isolation of 243 in a modest 42% yield.

![Scheme 65](image_url)

2.4.8 Conclusions and Future Work

The first key fragment in the synthesis of oxazinin-3 was prepared from L-tyrosine in four steps and 45% overall yield.

Future work for this project includes the optimisation of the asymmetric Friedel-Crafts acylation using the (S)-BINOL-titanium (IV) catalytic system. As shown in Scheme 66, protection of the secondary alcohol as the MOM ether followed by ester hydrolysis to the acid would give second key fragment 230. An EDCI-mediated coupling of 230 and 231 would give amide 229 which could then be subjected to a simultaneous acid-mediated deprotection of the MOM ether and morpholinone ring formation. Deprotection of 249 would give target molecule oxazinin-3 219.
Once the methodology has been satisfactorily developed for this relatively simple system, it would then be applied to the more complex natural products from this family.
3 Experimental

All reactions were performed under an inert atmosphere unless otherwise noted. Reagents and starting materials were obtained from commercial sources and used as received. All solvents were of reagent grade and were dried and distilled immediately before use. Lithium chloride was oven dried (100 °C) for at least 12 h before use. Brine refers to a saturated solution of sodium chloride. Flash column chromatography was carried out using Fisher Matrex silica 60. Macherey-Nagel aluminium backed plates pre-coated with silica gel 60 (UV 254) were used for thin layer chromatography and were visualised by staining with KMnO₄. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to tetramethylsilane (δ_H 0.00 & δ_C 0.00) or residual chloroform (δ_H 7.28 & δ_C 77.2) as standard. Infrared spectra were recorded using sodium chloride plates on a JASCO FTIR 410 spectrometer and mass spectra were obtained using a JEOL JMS-700 spectrometer. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using an AA series Automatic polarimeter. [α]D values are given in units 10⁻¹degcm²g⁻¹.

3.1 Synthesis of (2S,3R)- and (2R,3S)-Iodoreboxetine

Ethyl (E)-4-bromocinnamate 135⁹⁰

![Chemical Structure](image)

Lithium chloride (2.70 g, 65 mmol) was dissolved in acetonitrile (40 mL). 1,8-Diazobicyclo[5.4.0]undec-7-ene (9.7 mL, 65 mmol) and triethyl phosphonoacetate (12.9 mL, 65 mmol) were added sequentially with stirring. A solution of 4-bromobenzaldehyde 134 (10.0 g, 54 mmol) in acetonitrile (60 mL) was added and the mixture was allowed to stir at room temperature for 18 h. The reaction mixture was concentrated in vacuo and the resulting residue dissolved in ethyl acetate (150 mL). The solution was then washed with water (4 x 100 mL) and the organic layer dried (MgSO₄). The filtrate was concentrated in vacuo to give ethyl (E)-4-bromocinnamate 135 as a yellow oil (13.7 g, 100%). δ_H (400 MHz, CDCl₃) 1.33 (3H, t, J 7.2 Hz, OCH₂CH₃), 4.27 (2H, q, J 7.2 Hz, OCH₂CH₃), 6.42 (1H, d, J 16.0 Hz, 2-H), 7.36-7.40 (2H, m, 2 x Ar H), 7.49-7.53 (2H, m, 2 x Ar H), 7.61 (1H, d, J 16.0 Hz, 3-H); δ_C (100 MHz, CDCl₃) 14.3 (CH₃), 60.7 (CH₂), 119.0 (CH), 124.5
(C), 129.5 (2 x CH), 132.2 (2 x CH), 133.4 (C), 143.2 (CH), 166.8 (C); m/z (EI) 253.9939 (M+. C11H11O279Br requires 253.9942), 211 (88%), 209 (89), 183 (23), 181 (21), 102 (100).

(2E)-3-(4-Bromophenyl)prop-2-en-1-ol 13691

Ethyl (E)-4-bromocinnamate 135 (7.0 g, 27.5 mmol) was dissolved in diethyl ether (120 mL) and the solution cooled to -78 °C. DIBAL-H (60.4 mL, 60.4 mmol, 1 M in hexanes) was added to the solution dropwise. After 1 h, the reaction mixture was allowed to warm to room temperature and left to stir for 18 h. The yellow solution was cooled to 0 °C, before the reaction was quenched using a saturated solution of ammonium chloride (30 mL). The white solution was filtered through a pad of Celite® using diethyl ether and the filtrate concentrated in vacuo. The white solid was recrystallised using ethyl acetate-petroleum ether (40-60) to give (2E)-3-(4-bromophenyl)prop-2-en-1-ol 136 as a colourless solid (5.8 g, 100%). mp 63-65 °C (from ethyl acetate), lit.91 63-65 °C; δH (400 MHz, CDCl3) 1.48 (1H, t, J 6.0 Hz, OH), 4.33 (2H, dt, J 6.0, 1.6 Hz, 1-H2), 6.36 (1H, dt, J 16.0, 1.6 Hz, 2-H), 6.56 (1H, d, J 16.0 Hz, 3-H), 7.23-7.28 (2H, m, 2 x Ar H), 7.42-7.47 (2H, m, 2 x Ar H); δC (100 MHz, CDCl3) 63.6 (CH2), 121.5 (C), 128.0 (2 x CH), 129.3 (CH), 129.8 (CH), 131.7 (2 x CH), 136.0 (C); m/z (EI) 211.9840 (M+. C9H9O79Br requires 211.9837), 171 (50%), 169 (51), 133 (100), 115 (46), 83 (80).

(2S,3S)-[3-(4-Bromophenyl)oxiranyl]methanol 13363

Dichloromethane (150 mL) and activated 4 Å molecular sieves (3.0 g) were added to a round-bottomed flask and the solvent cooled to -20 °C using an acetone/ice bath. (+)-Diisopropyl tartrate (0.18 mL, 0.8 mmol) and titanium isopropoxide (0.2 mL, 0.7 mmol) were added sequentially with stirring. Anhydrous tert-butyl hydroperoxide solution (3.2 mL, 35 mmol, 5.5 M in hexanes) was added dropwise and the mixture was stirred at -20 °C for 0.5 h. A solution of (2E)-3-(4-bromophenyl)prop-2-en-1-ol 136 (3.0 g, 14 mmol) dissolved in dichloromethane (10 mL) was added to the mixture dropwise over a period of
The mixture was left to stir at -20 °C for 2.5 h. The flask was allowed to warm to 0 °C and the reaction quenched using distilled water (15 mL). The mixture was left to stir for 0.5 h while allowing it to warm to room temperature. A solution of 30% sodium hydroxide saturated with sodium chloride (75 mL) was added and the mixture stirred for 0.3 h. Dichloromethane (100 mL) was added to the mixture and left to stir for a further 0.25 h. The mixture was transferred to a separating funnel and the water layer removed. The organic layer was dried (MgSO₄) and filtered through a pad of Celite® that was then washed with diethyl ether. The yellow solution was concentrated in vacuo. Purification was carried out by flash column chromatography and elution with 60:40 ethyl acetate-petroleum ether (40-60) gave (2S,3S)-[3-(4-bromophenyl)oxiranyl]methanol 133 as a colourless solid (2.55 g, 79%). mp 61-62 °C (from petroleum ether/ethyl acetate) lit. 63 67-68 °C (from hexane/ethyl acetate); [α]D²² -38.6 (c 1.0, CHCl₃), lit. 63 [α]D²⁵ -35.2 (c 1.0, CHCl₃); δH (400 MHz, CDCl₃) 1.74 (1H, dd, J 7.8, 5.0 Hz, OH), 3.17 (1H, dt, J 3.6, 2.2 Hz, 2-H), 3.81 (1H, ddd, J 12.8, 7.8, 3.6 Hz, 1-H), 3.91 (1H, d, J 2.2 Hz, 3-H), 4.05 (1H, ddd, J 12.8, 5.0, 2.2 Hz, 1-HH), 7.14-7.18 (2H, m, 2 x Ar), 7.46-7.50 (2H, m, 2 x Ar); δC (100 MHz, CDCl₃) 54.9 (CH), 61.0 (CH₂), 62.4 (CH), 122.0 (C), 127.4 (2 x CH), 131.7 (2 x CH), 134.9 (C); m/z (EI) 227.9787 (M⁺, C₉H₉O₂₇₉Br requires 227.9786), 212 (10%), 210 (10%), 187 (25), 185 (34), 89 (75), 83 (100).

(2R,3R)-[3-(4-Bromophenyl)oxiranyl]methanol 146

The reaction was carried out as described above using (2E)-3-(4-bromophenyl)prop-2-en-1-ol 136 (4.17 g, 19.6 mmol) and (-)-diisopropyl tartrate (0.5 mL, 2.4 mmol). This gave (2R,3R)-[3-(4-bromophenyl)oxiranyl]methanol 146 (3.56 g, 79%) as a colourless solid. mp 61-62 °C (from petroleum ether/ethyl acetate) lit. 63 67-68 °C (from hexene/ethyl acetate); [α]D²² +31.7 (c 1.0, CHCl₃); δH (400 MHz, CDCl₃) 1.86 (1H, dd, J 7.8, 5.0 Hz, OH), 3.18 (1H, dt, J 3.6, 2.2 Hz, 2-H), 4.06 (1H, ddd, J 12.8, 7.8, 3.6 Hz, 1-HH), 3.91 (1H, d, J 2.2 Hz, 3-H), 4.05 (1H, ddd, J 12.8, 5.0, 2.2 Hz, 1-HH), 7.14-7.19 (2H, m, 2 x Ar), 7.46-7.51 (2H, m, 2 x Ar); δC (100 MHz, CDCl₃) 55.1 (CH), 61.1 (CH₂), 62.7 (CH), 122.2 (C), 127.4 (2 x CH), 131.4 (2 x CH), 135.5 (C); m/z (EI) 227.9778 (M⁺, C₉H₉O₂₇₉Br requires 227.9786), 212 (10%), 210 (10), 187 (25), 185 (34), 89 (75), 83 (100).
(2S,3R)-3-(4-Bromophenyl)-3-(2-ethoxyphenoxy)propane-1,2-diol 132

2-Ethoxyphenol (1.10 g, 7.9 mmol) was added to an aqueous sodium hydroxide solution (0.30 g, 6.6 mmol in 70 mL water) and the mixture heated to 70 °C until the solid had dissolved. After 1 h of stirring, (2S,3S)-[3-(4-bromophenyl)oxiranyl]methanol 133 (1.50 g, 6.6 mmol) was added and the mixture left to stir for 4 h. The flask was then allowed to cool to room temperature and acidified to pH 2-3 using 2 M hydrochloric acid. The bulk solvent was decanted and the remaining solid suspended in water, and then extracted using dichloromethane (2 x 100 mL) followed by ethyl acetate (3 x 100 mL). The organic layers were combined, dried (MgSO₄) and the filtrate concentrated \textit{in vacuo}. The solid was recrystalised from diethyl ether to give (2S,3R)-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propane-1,2-diol 132 as a colourless solid (1.50 g, 67%). mp 77-78 °C (from diethyl ether); ν\textsubscript{max} /cm\textsuperscript{-1} (NaCl) 3345 (OH), 2943 (CH), 1500 (C=C), 1246, 732; [α]D\textsubscript{22} -57.0 (c 1.0, CHCl₃); δ\textsubscript{H} (400 MHz, CDCl₃) 1.51 (3H, t, J 7.2 Hz, OCH₂CH₃), 3.13 (1H, dd, J 10.0, 3.4 Hz, 1-OH), 3.26 (1H, d, J 8.0 Hz, 2-OH), 3.65 (1H, ddd, J 11.8, 10.0, 4.3, Hz, 1-H/H), 3.84-3.89 (1H, m, 2-H), 3.95 (1H, dt, J 11.8, 3.4 Hz, 1-H/H), 4.11 (2H, q, J 7.2 Hz, OCH₂CH₃), 5.22 (1H, d, J 4.3 Hz, 3-H), 6.59 (1H, dd, J 8.0, 1.6 Hz, 1 x Ar H), 6.71-6.75 (1H, m, 1 x Ar H), 6.87-6.93 (2H, m, 2 x Ar H), 7.27-7.31 (2H, m, 2 x Ar H), 7.49-7.52 (2H, m, 2 x Ar H); δ\textsubscript{C} (100 MHz, CDCl₃) 14.8 (CH₃), 62.1 (CH₂), 64.2 (CH₂), 74.2 (CH), 85.6 (CH), 112.5 (CH), 116.4 (CH), 120.8 (CH), 122.2 (C), 122.8 (CH), 128.2 (2 x CH), 131.9 (2 x CH), 137.1 (C), 146.8 (C), 149.2 (C); m/z (EI) 366.0465 (M⁺). C₁₇H₁₈O₄⁷⁹Br requires 366.0467, 171 (11%), 169 (11), 138 (100), 110 (50), 83 (58), 47 (12).
The reaction was carried out as described above using \((2R,3R)\)-[3-(4-bromophenyl)oxiranyl]methanol 146 (3.38 g, 14.8 mmol). This gave \((2R,3S)\)-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propane-1,2-diol 147 as a colourless solid (4.31 g, 79%). mp 76-78 °C (from diethyl ether); \(\nu_{\text{max}}/\text{cm}^{-1}\) (KBr) 3345 (OH), 2943 (CH), 1500 (C=C), 1246, 732; \([\alpha]_D^{25} +64.6\) (c 1.0, CHCl₃); \(\delta_H\) (400 MHz, CDCl₃) 1.50 (3H, t, \(J 7.0\) Hz, OCH₂CH₃), 3.18 (1H, dd, \(J 9.6, 3.6\) Hz, 1-OH), 3.34 (1H, d, \(J 8.0\) Hz, 2-OH), 3.66 (1H, ddd, \(J 11.8, 10.0, 4.3\) Hz, 1-HH), 3.84-3.88 (1H, m, 2-H), 3.94 (1H, dt, \(J 11.8, 3.4\) Hz, 1-HH), 4.11 (2H, q, \(J 7.0\) Hz, OCH₂CH₃), 5.21 (1H, d, \(J 4.3\) Hz, 3-H), 6.60 (1H, dd, \(J 8.0, 1.6\) Hz, 1 x Ar H), 6.71-6.75 (1H, m, 1 x Ar H), 6.88-6.95 (2H, m, 2 x Ar H), 7.27-7.31 (2H, m, 2 x Ar H), 7.49-7.52 (2H, m, 2 x Ar H); \(\delta_C\) (100 MHz, CDCl₃) 14.8 (CH₃), 62.2 (CH₂), 64.3 (CH₂), 74.2 (CH), 85.5 (CH), 112.6 (CH), 116.5 (CH), 120.8 (CH), 122.2 (C), 122.8 (CH), 128.0 (2 x CH), 131.9 (2 x CH), 137.1 (C), 146.8 (C), 149.2 (C); \(m/z\) (EI) 366.0465 (M⁺). \(\text{C}_{17}\text{H}_{19}\text{O}_4^{79}\)Br requires 366.0467, 171 (15%), 169 (15), 138 (100), 110 (71), 91 (13), 81 (9).

\((2S,3R)\)-3-(4-Bromophenyl)-3-(2-ethoxyphenoxy)-1-(toluenesulfonyloxy)propan-2-ol 139

\((2S,3R)\)-3-(4-Bromophenyl)-3-(2-ethoxyphenoxy)propane-1,2-diol 132 (0.55 g, 1.49 mmol) was dissolved in dichloromethane (50 mL) and triethylamine (0.31 mL, 2.24 mmol), 4-dimethylaminopyridine (4.00 mg, 0.04 mmol) and \(p\)-toluenesulfonyl chloride (0.34 g, 1.79 mmol) added sequentially with stirring. The reaction mixture was stirred for 3 h before being diluted with diethyl ether (20 mL) and washed with 2 M hydrochloric acid
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(30 mL). The aqueous phase was extracted with dichloromethane (30 mL) and the combined organic layers dried (MgSO₄) and the filtrate concentrated in vacuo. Purification was carried out by flash column chromatography and elution with 40:60 diethyl ether-petroleum ether (40-60) gave (2S,3R)-3-(4-bromophenyl)-1,2-(ditoluenesulfonyloxy)-3-(2-ethoxyphenoxy)propane 140 as a minor impurity. 

ν_max/cm⁻¹ (KBr) 3038 (CH), 2981 (CH), 2919 (CH), 2872 (CH), 1597 (C=C); [α]D²⁵ -27.6 (c 1.0, CHCl₃); δ_H (400 MHz, CDCl₃) 1.37 (3H, t, J 7.0 Hz, OCH₂CH₃), 2.42 (3H, s, Ar-CH₃), 2.44 (3H, s, Ar-CH₃), 3.07 (2H, q, J 7.0 Hz, OCH₂CH₃), 4.44 (1H, dd, J 11.2, 2.6 Hz, 1-HH), 4.59 (2H, dd, J 11.2, 4.6 Hz, 1-HH), 4.71-4.75 (1H, m, 2-H), 5.25 (1H, d, J 6.8 Hz, 3-H), 6.54 (1H, dd, J 8.2, 1.4 Hz, 1 x Ar), 6.67 (1H, td, J 7.6, 1.6 Hz, 1 x Ar H), 6.79 (1H, dd, J 8.2, 1.4 Hz, 1 x Ar H), 6.86-6.90 (1H, m, 1 x Ar H), 7.06 (2H, d, J 8.4 Hz, 2 x Ar H), 7.17 (2H, d, J 8.0 Hz, 2 x Ar H), 7.24-7.26 (4H, m, 4 x Ar H), 7.43 (2H, d, J 8.4 Hz, 2 x Ar H), 7.64 (2H, d, J 8.4 Hz, 2 x Ar); δ_C (100 MHz, CDCl₃) 14.9 (CH₃), 21.7 (CH₃), 21.8 (CH₃), 64.2 (CH₂), 67.3 (CH₂), 78.5 (CH), 80.4 (CH), 113.4 (CH), 117.4 (CH), 120.6 (CH), 122.7 (C), 123.1 (CH), 127.7 (2 x CH), 128.0 (2 x CH), 128.8 (2 x CH), 129.7 (2 x CH), 129.8 (2 x CH), 131.5 (2 x CH), 132.2 (C), 132.6 (C), 135.4 (C), 145.0 (C), 145.0 (C), 146.4 (C), 149.5 (C); m/z (FAB⁺) 697.0536 (MNa⁺. C₃₁H₃₀O₈S₂Na requires 697.0541), 482 (8%), 368 (6), 366 (6), 329 (88), 307 (38), 154 (100). Further elution with 40:60 diethyl ether-petroleum ether (40-60) gave (2S,3R)-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)-1-(toluenesulfonyloxy)propan-2-ol 139 as a colourless oil (0.60 g, 77%). 

ν_max/cm⁻¹ (NaCl) 3438 (OH), 2979 (CH), 1498, 1249; [α]D²² -84.0 (c 1.0, CHCl₃); δ_H (400 MHz, CDCl₃) 1.42 (3H, t, J 7.2 Hz, OCH₂CH₃), 2.44 (3H, s, Ar-CH₃), 4.05 (2H, q, J 7.2 Hz, OCH₂CH₃), 4.09-4.13 (1H, m, 2-H), 4.18-4.21 (2H, m, 1-H₂), 4.97 (1H, d, J 5.2 Hz, 3-H), 6.68-6.97 (4H, m, 4 x Ar), 7.25 (2H, d, J 8.0 Hz, 2 x Ar), 7.29 (2H, d, J 8.0 Hz, 2 x Ar), 7.45 (2H, d, J 8.0 Hz, 2 x Ar), 7.73 (2H, d, J 8.0, 2 x Ar); δ_C (100 MHz, CDCl₃) 14.8 (CH₃), 21.8 (CH₃), 64.4 (CH₂), 70.3 (CH₂), 72.2 (CH), 83.2 (CH), 113.3 (CH), 119.1 (CH), 121.0 (CH), 123.3 (C), 123.7 (CH), 128.0 (2 x CH), 128.9 (2 x CH), 129.9 (2 x CH), 131.7 (2 x CH), 132.6 (C), 136.3 (C), 145.0 (C), 146.9 (C), 150.0 (C); m/z (EI) 522.0538 (M⁺. C₂₄H₂₅O₆Br requires 522.0538), 384 (10%), 382 (9), 213 (19), 211 (20), 155 (67), 138 (100), 91 (78).
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(2R,3S)-3-(4-Bromophenyl)-3-(2-ethoxyphenoxy)-1-(toluenesulfonyloxy)propan-2-ol 150

The reaction was carried out as described above using (2R,3S)-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propane-1,2-diol 147 (3.26 g, 8.88 mmol). This gave (2R,3S)-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)-1-(toluenesulfonyloxy)propan-2-ol 150 as a colourless oil (2.42 g, 44%). ν max /cm⁻¹ (NaCl) 3433 (OH), 3020 (CH), 1653 (C=C), 1215, 754; [α]D° +71.8 (c 1.0, CHCl₃); δH (400 MHz, CDCl₃) 1.43 (3H, t, J 7.0 Hz, OCH₂CH₃), 2.45 (3H, s, Ar-CH₃), 3.20 (1H, d, J 6.0 Hz, OH), 4.05 (2H, dq, J 7.0, 1.6 Hz, OCH₂CH₃), 4.10-4.15 (1H, m, 2-H), 4.21-4.22 (2H, m, 1-H₂), 4.98 (1H, d, J 5.6 Hz, 3-H), 6.68-6.97 (4H, m, 4 x Ar), 7.25 (2H, d, J 8.2 Hz, 2 x Ar), 7.30 (2H, d, J 8.2 Hz, 2 x Ar), 7.45 (2H, d, J 8.4 Hz, 2 x Ar), 7.73 (2H, d, J 8.4 Hz, 2 x Ar); δC (100 MHz, CDCl₃) 14.8 (CH₃), 21.7 (CH₃), 64.2 (CH₂), 70.3 (CH₂), 72.2 (CH), 83.2 (CH), 113.4 (CH), 119.2 (CH), 121.0 (CH), 122.4 (C), 123.7 (CH), 128.0 (2 x CH), 128.9 (2 x CH), 129.9 (2 x CH), 131.7 (2 x CH), 132.7 (C), 136.3 (C), 145.0 (C), 146.9 (C), 150.0 (C); m/z (EI) 522.0537 (M⁺). C₂₄H₂₅O₆Br⁻S requires 522.0538, 384 (3%), 382 (3), 213 (11), 211 (11), 155 (67), 138 (100), 91 (78).

(2S,3R)-1-Amino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol 131

(2S,3R)-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)-1-(toluenesulfonyloxy)propan-2-ol (0.64 g, 1.23 mmol) 139 was dissolved in acetonitrile (40 mL) and 25% ammonia solution (50 mL) was added. The reaction mixture was left to stir for 96 h in a sealed round bottomed flask. The acetonitrile was removed in vacuo and the aqueous solution diluted with distilled water (100 mL). The aqueous solution was then extracted with ethyl acetate (3 x 100 mL), dried (MgSO₄) and the filtrate concentrated in vacuo. Purification was carried
out by flash column chromatography and elution with 90:10 ethyl acetate-methanol gave (2S,3R)-1-amino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol 131 as a colourless oil (0.22 g, 49%). mp 60-62 °C (from diethyl ether); \( \nu_{\text{max}} / \text{cm}^{-1} (\text{NaCl}) \) 3338, 3303, 2901 (CH), 2115, 1593 (C=C); [\( \alpha \)]\text{D}\text{22} -68.8 (c 1.0, CHCl3); \( \delta_{\text{H}} \) (400 MHz, CDCl3) 1.47 (3H, t, J 7.0 Hz, OCH\text{2CH}_3), 2.92 (1H, dd, J 12.8, 4.6 Hz, 1-HH), 3.03 (1H, dd, J 12.8, 5.6 Hz, 1-HH), 3.99 (1H, m, 2-H), 4.06 (2H, q, J 7.0 Hz, OCH\text{2CH}_3), 5.11 (1H, d, J 4.6 Hz, 3-H), 6.63 (1H, dd, J 8.0, 1.4 Hz, 1 x Ar H), 6.72 (1H, dt, J 8.0, 1.4 Hz, 1 x Ar H), 6.85-6.93 (2H, m, 2 x Ar H), 7.27 (2H, d, J 8.2 Hz, 2 x Ar H), 7.47 (2H, d, J 8.2 Hz, 2 x Ar H); \( \delta_{\text{C}} \) (100 MHz, CDCl3) 14.7 (CH\text{3}), 42.3 (CH\text{2}), 64.3 (CH\text{2}), 74.4 (CH), 84.5 (CH), 113.2 (CH), 117.7 (CH), 120.9 (CH), 121.9 (C), 122.8 (CH), 128.7 (2 x CH), 131.5 (2 x CH), 137.8 (C), 147.2 (C), 149.7 (C); \text{m/z} (\text{EI}) 366.0699 (M+ C\text{17H21O3N79Br requires 366.0705}, 367 (3%), 365 (3), 230 (9), 228 (9), 138 (100), 171 (12), 110 (77).

(2R,3S)-1-Amino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol 149

The reaction was carried out as described above using (2R,3S)-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)-1-(toluenesulfonyloxy)propan-2-ol 150 (2.42 g, 4.6 mmol). This gave (2R,3S)-1-amino-3-(4-bromo-phenyloxy)-3-(2-ethoxyphenoxy)propan-2-ol 149 as a colourless oil (0.97 g, 57%). \( \nu_{\text{max}} / \text{cm}^{-1} (\text{NaCl}) \) 3338, 3303, 2901 (CH), 2115, 1593 (C=C); [\( \alpha \)]\text{D}\text{22} +71.5 (c 1.1, CHCl3); \( \delta_{\text{H}} \) (400 MHz, CDCl3) 1.48 (3H, t, J 7.0 Hz, OCH\text{2CH}_3), 2.34 (2H, br s, NH\text{2}), 2.81 (1H, dd, J 12.8, 4.6 Hz, 1-HH), 2.94 (1H, dd, J 12.8, 5.6 Hz, 1-HH), 3.80-3.84 (1H, m, 2-H), 4.10 (2H, q, J 7.0 Hz, OCH\text{2CH}_3), 5.08 (1H, d, J 4.4 Hz, 3-H), 6.66-6.75 (2H, m, 2 x Ar H), 6.86-6.93 (2H, m, 2 x Ar H), 7.29 (2H, d, J 8.4 Hz, 2 x Ar H), 7.47 (2H, d, J 8.4 Hz, 2 x Ar H); \( \delta_{\text{C}} \) (100 MHz, CDCl3) 14.9 (CH\text{3}), 42.3 (CH\text{2}), 64.3 (CH\text{2}), 74.4 (CH), 84.7 (CH), 113.2 (CH), 117.7 (CH), 120.9 (CH), 121.9 (C), 122.7 (CH), 128.7 (2 x CH), 131.6 (2 x CH), 137.6 (C), 147.3 (C), 149.7 (C); \text{m/z} (\text{FAB}^+) \text{368.0685 (MH}^+) \text{, C}_{17}\text{H}_{21}\text{O}_{3}\text{N}^{79}\text{Br requires 368.0705}, 367 (3%), 365 (3), 230 (9), 228 (9), 138 (100), 171 (12), 110 (77).
(2S,3R)-1-Chloroacetylamino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol 141

(2S,3R)-1-Amino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol 131 (0.15 g, 0.42 mmol) was dissolved in acetonitrile (6.5 mL) and the mixture cooled to -10 °C using an acetone/ice bath. Triethylamine (0.07 mL, 0.50 mmol) and chloroacetyl chloride (0.04 mL, 0.46 mmol) were added sequentially and the solution was allowed to stir at -10 °C for 1 h. The reaction mixture was then warmed to room temperature and left to stir for 18 h. The reaction mixture was concentrated in vacuo and purification was carried out by flash column chromatography. Elution with 40:60 ethyl acetate-petroleum ether (40-60) gave (2S,3R)-1-chloroacetylamino-2-chloroacetylhydroxy-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propane 144 as a white solid (0.03 g, 11%).

ν_max/cm⁻¹ (KBr) 3302 (NH), 2978 (CH), 2978 (CH), 1739 (CO), 1667 (CO), 1651 (C=C), 1595; [α]_D²⁵ -58.5 (c 1.0, CHCl₃); δ_H (400 MHz, CDCl₃) 1.47 (3H, t, J 7.0 Hz, OCH₂C_H₃), 3.75 (1H, dt, J 14.4, 5.6 Hz, 1-H_H), 3.92 (1H, d, J 15.0 Hz, NHCOC_HH), 4.01 (1H, d, J 15.0 Hz, NHCOC_HH), 4.01-4.04 (1H, m, 1-H_H), 4.03 (1H, d, J 18.4 Hz, OCOH₃), 4.08 (1H, d, J 18.4 Hz, COOH), 4.11 (2H, q, J 7.0 Hz, OCH₂C_H₃), 5.22 (1H, d, J 6.4 Hz, 3-H), 5.29 (1H, m, 2-H), 6.65 (1H, dd, J 7.6, 1.6 Hz, 1 x Ar), 6.73 (1H, dt, J 7.6, 1.6 Hz, 1 x Ar), 6.88-6.97 (2H, m, 2 x Ar), 7.32 (2H, d, J 8.4 Hz, 2 x Ar), 7.49 (2H, d, J 8.4 Hz, 2 x Ar); δ_C (100 MHz, CDCl₃) 14.9 (CH₃), 39.4 (CH₂), 40.7 (CH₂), 42.6 (CH₂), 64.4 (CH₂), 76.1 (CH), 81.1 (CH), 113.6 (CH), 118.7 (CH), 120.9 (CH), 122.7 (C), 123.6 (CH), 128.8 (2 x CH), 131.9 (2 x CH) 136.2 (C), 146.6 (C), 149.7 (C), 166.7 (C), 167.0 (C); m/z (FAB⁺) 541.9916 (MNa⁺. C₂₁H₂₂O₅NCl₂BrNa requires 541.9934), 384 (46), 382 (100), 107 (90), 541 (70), 383 (47), 169 (18). Further elution with 50:50 ethyl acetate-petroleum ether (40-60) gave (2S,3R)-1-chloroacetylamino-2-chloroacetylhydroxy-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propane 141 as a colourless oil (0.15 g, 83%). ν_max/cm⁻¹ (NaCl) 3423 (OH), 3020 (CH), 1660 (CO), 1215, 770; [α]_D²² -105.4 (c 1.0, CHCl₃); δ_H (400 MHz, CDCl₃) 1.51 (3H, t, J 7.1 Hz, OCH₂C_H₃), 3.35 (1H, ddd, J 14.0, 7.4, 4.2 Hz, 1-H_H), 3.73 (1H, ddd, J 14.0, 7.2, 3.6 Hz, 1-H_H), 3.98-4.00 (1H, m, 2-H), 4.03 (2H, s, CH₂Cl), 4.12 (2H, q, J 7.1 Hz, OCH₂C_H₃), 4.97 (1H, d, J 5.2 Hz, 3-H), 6.73-7.00 (4H, m, 4 x Ar_H), 7.18 (1H, br s, NH), 7.33 (2H, d, J 8.4 Hz, 2 x Ar_H), 7.52 (2H, d, J 8.4 Hz, 2 x Ar_H); δ_C (100 MHz, CDCl₃) 14.9 (CH₃), 41.9 (CH₂),
42.6 (CH₂), 64.5 (CH₂), 73.1 (CH), 85.2 (CH), 113.4 (CH), 119.5 (CH), 121.2 (CH), 122.3 (C), 123.8 (CH), 128.8 (2 x CH), 131.8 (2 x CH) 137.0 (C), 147.2 (C), 149.9 (C), 166.9 (C); m/z (CI) 444.0399 (MH⁺. C₁₉H₂₂O₄N³Cl⁸¹Br requires 444.0400), 306 (100%), 304 (74), 226 (62), 228 (23), 192 (19), 139 (80).

(2R,3S)-1-Chloroacetylamino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol

The reaction was carried out as described above using (2R,3S)-1-amino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol 149 (1.50 g, 4.10 mmol). This gave (2R,3S)-1-chloroacetylamino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol 151 as a colourless oil (1.11 g, 62%). νmax/cm⁻¹ (NaCl) 3423 (OH), 3020 (CH), 1660 (CO), 1215, 770; [α]D²² +114.6 (c 1.1, CHCl₃); δH (400 MHz, CDCl₃) 1.51 (3H, t, J 7.1 Hz, OCH₂C₃H₃), 3.35 (1H, ddd, J 14.0, 7.4, 4.2 Hz, 1-H), 3.73 (1H, ddd, J 14.0, 7.2, 3.6 Hz, 1-HH), 3.98-4.01 (1H, m, 2-H), 4.03 (2H, s, CH₂Cl), 4.14 (2H, q, J 7.1 Hz, OCH₂CH₃), 4.97 (1H, d, J 5.2 Hz, 3-H), 6.73-7.00 (4H, m, 4 x Ar H), 7.17 (1H, br s, NH), 7.33 (2H, d, J 8.4 Hz, 2 x Ar H), 7.52 (2H, d, J 8.4 Hz, 2 x Ar H); δc (100 MHz, CDCl₃) 14.8 (CH₃), 41.7 (CH₂), 42.6 (CH₂), 64.5 (CH₂), 73.1 (CH), 85.4 (CH), 113.4 (CH), 119.6 (CH), 121.2 (CH), 122.4 (C), 123.9 (CH), 128.7 (2 x CH), 131.8 (2 x CH), 136.9 (C), 147.3 (C), 150.0 (C), 166.9 (C); m/z (CI) 442.0425 (MH⁺. C₁₉H₂₂O₄N³Cl⁸¹Br requires 442.0421), 444 (64%), 442 (49), 364 (9), 304 (100), 306 (100), 226 (19), 139 (18).
A solution of (2S,3R)-1-chloroacetylamino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol 141 (0.35 g, 0.79 mmol) in tert-butanol (4 mL) was added dropwise to a solution of potassium tert-butoxide (0.19 g, 2.0 mmol) in tert-butanol (1.0 mL) and the reaction mixture stirred at 40 °C for 3 h. The solution was acidified to pH 2-3 by the addition of 2 M hydrochloric acid and then concentrated in vacuo. The residue was suspended in water (50 mL) and the aqueous solution extracted with ethyl acetate (3 x 50 mL), dried (MgSO4), and the filtrate concentrated in vacuo. Purification was carried out by dry flash chromatography and elution with 100% ethyl acetate gave (2S,3R)-2-[(4-bromobenzyl)-(2-ethoxyphenoxy)]morpholin-5-one 142 as a colourless oil (0.25 g, 79%).

\[ \text{\nu}_{\text{max}}/\text{cm}^{-1} (\text{NaCl}) 3410 (\text{NH}), 3019 (\text{CH}), 2400, 1679 (\text{CO}), 1500, 1216; [\alpha]_D^{25} -79.5 (c 0.6, \text{CHCl}_3); \delta^H (400 \text{ MHz, CDCl}_3) 1.46 (3H, t, J 7.0 Hz, OCH}_2\text{CH}_3), 3.66-3.80 (2H, m, 3-H_2), 3.99-4.02 (1H, m, 2-H), 4.04-4.29 (4H, m, 6-H_2, OCH}_2\text{CH}_3), 5.04 (1H, d, J 7.6 Hz, 2-CH), 6.27 (1H, br s, NH), 6.64-6.94 (4H, m, 4 x Ar H), 7.29-7.32 (2H, m, 2 x Ar H), 7.46-7.51 (2H, m, 2 x Ar H); \delta^C (100 \text{ MHz, CDCl}_3) 15.1 (\text{CH}_3), 43.9 (\text{CH}_2), 64.3 (\text{CH}_2), 67.8 (\text{CH}_2), 76.0 (\text{CH}), 81.5 (\text{CH}), 113.6 (\text{CH}), 118.4 (\text{CH}), 120.7 (\text{CH}), 122.4 (C), 123.2 (\text{CH}), 129.0 (2 x \text{CH}), 131.6 (2 x \text{CH}), 137.3 (C), 146.5 (C), 149.9 (C), 168.5 (C); m/z (EI) 407.0562 (M^+). C_{19}H_{26}O_\text{N^81}Br requires 407.0558, 269 (73%), 267 (73), 171 (86), 169 (87), 138 (100).
(2R,3S)-2-[(4-Bromobenzyl)-(2-ethoxyphenoxy)]morpholin-5-one 152

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\text{OEt} & \quad \text{N} \\
\text{HO} & \quad \text{1, 2, 3, 6} \\
\end{align*}
\]

The reaction was carried out as described above using (2R,3S)-1-chloroacetylamino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol 151 (1.07 g, 2.42 mmol). This gave (2S,3R)-2-[(4-bromobenzyl)-(2-ethoxyphenoxy)]morpholin-5-one 152 as a colourless oil (0.89 g, 90%). \( \nu_{\text{max}}/\text{cm}^{-1} \) (NaCl) 3410 (NH), 3019 (CH), 2400, 1679 (CO), 1500, 1216; \( \alpha_{\text{D}} \)^22 +80.0 (c 0.9, CHCl3); \( \delta_{\text{H}} \) (400 MHz, CDCl3) 1.46 (3H, t, \( J \) 7.0 Hz, OCH\(_2\)CH\(_3\)), 3.66-3.79 (2H, m, 3-H\(_2\)), 3.98-4.02 (1H, m, 2-H), 4.03-4.29 (4H, m, 6-H\(_2\), OCH\(_2\)CH\(_3\)), 5.05 (1H, d, \( J \) 7.2 Hz, 2-CH), 6.50 (1H, br s, NH), 6.64-6.93 (4H, m, 4 x Ar H), 7.30 (2H, m, 2 x Ar H), 7.48 (2H, m, 2 x Ar H); \( \delta_{\text{C}} \) (100 MHz, CDCl3) 15.0 (CH\(_3\)), 43.8 (CH\(_2\)), 64.2 (CH\(_2\)), 67.7 (CH\(_2\)), 75.9 (CH), 81.5 (CH), 113.5 (CH), 118.4 (CH), 120.7 (CH), 122.4 (C), 123.2 (CH), 129.0 (2 x CH), 131.6 (2 x CH), 137.2 (C), 146.5 (C), 149.9 (C), 168.5 (C); \( m/z \) (EI) 407.0561 (M\(^+\). \( C_{19}H_{20}O_4N_8\)\( ^{35}\)Br requires 407.0558), 269 (60%), 267 (60), 171 (83), 169 (84), 138 (100), 110 (60), 102 (29).

(2S,3R)-2-[(4-Bromophenyl)-(2-ethoxyphenoxy)methyl]morpholine 143

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\text{OEt} & \quad \text{N} \\
\text{HO} & \quad \text{1, 2, 5, 6} \\
\end{align*}
\]

(2S,3R)-2-[(4-Bromobenzyl)-(2-ethoxyphenoxy)]morpholin-5-one 142 (0.20 g, 0.5 mmol) was dissolved in THF (0.5 mL) and the solution cooled to 0 °C. Borane.tetrahydrofuran complex (1.10 mL, 1.1 mmol) was added to the solution dropwise with stirring. After 0.5 h, the solution was heated under reflux for 4 h. After cooling in an ice bath, the excess borane was destroyed by the addition of distilled water (1 mL) and the solution was concentrated in vacuo. The residue was dissolved in 6 M hydrochloric acid (5 mL) and allowed to stir for 0.25 h. The solution was then concentrated in vacuo and the residue
dissolved in 2 M sodium hydroxide (5 mL). The aqueous solution was extracted using chloroform (3 x 5 mL) and the organic layers combined, dried (MgSO₄), and the filtrate concentrated *in vacuo* to give (2S,3R)-2-[(4-bromophenyl)-(2-ethoxyphenoxy)methyl]morpholine 143 as a colourless oil (0.12 g, 73%).

\[ \nu_{\text{max}} / \text{cm}^{-1} (\text{NaCl}) 3413 (\text{NH}), 2925 (\text{CH}), 2345, 1638, 1593; [\alpha]_D^{25} -67.5 (c 0.2, \text{CHCl}_3); \delta_\text{H} (400 \text{ MHz, CDCl}_3) 1.45 (3H, t, J 7.0 Hz, OCH₂CH₃), 2.81-2.94 (3H, m, 5-H₂, 3-HH), 3.37 (1H, br d, J 12.4 Hz, 3-HH), 3.53 (1H, td, J 11.2, 2.8 Hz, 6-HH) 3.75-3.80 (1H, m, 2-H), 3.86 (1H, br d, J 11.2 Hz, 6-HH), 4.05 (2H, q, J 7.0 Hz, OCH₂CH₃), 4.98 (1H, d, J 6.8 Hz, 2-CH), 6.64-6.89 (4H, m, 4 x Ar H), 7.29 (2H, d, J 8.4 Hz, 2 x Ar H), 7.45 (2H, d, J 8.4 Hz, 2 x Ar H); \delta_\text{C} (100 \text{ MHz, CDCl}_3) 15.1 (\text{CH}_3), 44.6 (\text{CH}_2), 46.4 (\text{CH}_2), 64.4 (\text{CH}_2), 66.5 (\text{CH}_2), 78.1 (\text{CH}), 82.2 (\text{CH}), 113.7 (\text{CH}), 118.1 (\text{CH}), 120.7 (\text{CH}), 122.1 (\text{C}), 122.8 (\text{CH}), 129.1 (2 x \text{CH}), 131.5 (2 x \text{CH}), 137.5 (\text{C}), 146.9 (\text{C}), 149.9 (\text{C}); m/z (EI) 393.0756 (M⁺. C₁₉H₂₂O₃N₈ºBr requires 393.0765), 255 (86%), 253 (86), 171 (26), 169 (27), 86 (99), 84 (100).

\[ (2R,3S)-2-[(4-Bromophenyl)-(2-ethoxyphenoxy)methyl]morpholine 153 \]

\[ \text{Br} \]

\[ \text{O} \]

\[ \text{O} \]

\[ \text{N} \]

\[ \text{H} \]

\[ \text{OEt} \]

\[ \text{2} \]

\[ \text{3} \]

\[ \text{5} \]

\[ \text{6} \]

The reaction was carried out as described above using (2R,3S)-2-[(4-bromobenzyl)-(2-ethoxyphenoxy)]morpholin-5-one 152 (0.85 g, 2.1 mmol). This gave (2R,3S)-2-[(4-bromophenyl)-(2-ethoxyphenoxy)methyl]morpholine 153 as a colourless oil (0.09 g, 11%).

\[ \nu_{\text{max}} / \text{cm}^{-1} (\text{NaCl}) 3413 (\text{NH}), 2925 (\text{CH}), 2345, 1638, 1593; [\alpha]_D^{22} +46.8 (c 1.0, \text{CHCl}_3); \delta_\text{H} (400 \text{ MHz, CDCl}_3) 1.45 (3H, t, J 7.0 Hz, OCH₂CH₃), 1.98 (1H, br s, NH), 2.81-2.94 (3H, m, 5-H₂, 3-HH), 3.36 (1H, br d, J 12.4 Hz, 3-HH), 3.53 (1H, td, J 11.2, 2.4 Hz, 6-HH) 3.75-3.80 (1H, m, 2-H), 3.86 (1H, br d, J 11.2 Hz, 6-HH), 4.05 (2H, q, J 7.0 Hz, OCH₂CH₃), 4.98 (1H, d, J 6.8 Hz, 2-CH), 6.64-6.89 (4H, m, 4 x Ar H), 7.29 (2H, d, J 8.4 Hz, 2 x Ar H), 7.45 (2H, d, J 8.4 Hz, 2 x Ar H); \delta_\text{C} (100 \text{ MHz, CDCl}_3) 14.0 (\text{CH}_3), 44.8 (\text{CH}_2), 46.8 (\text{CH}_2), 64.5 (\text{CH}_2), 66.5 (\text{CH}_2), 78.4 (\text{CH}), 81.2 (\text{CH}), 112.9 (\text{CH}), 116.7 (\text{CH}), 119.8 (\text{CH}), 120.8 (\text{C}), 121.4 (\text{CH}), 128.1 (2 x CH), 130.3 (2 x CH), 137.1 (\text{C}), 146.3 (\text{C}), 148.8 (\text{C}); m/z (EI) 391.0785 (M⁺. C₁₉H₂₂O₃N₇ºBr requires 391.0783), 255 (73%), 253 (70), 171 (28), 169 (28), 110 (27), 85 (27).
(2S,3R)-2-[(4-Bromophenyl)-(2-ethoxyphenoxy)methyl]-N-tert-butoxycarbonylmorpholine 130

(2S,3R)-2-[(4-Bromophenyl)-(2-ethoxyphenoxy)methyl]morpholine 143 (0.14 g, 0.4 mmol) was dissolved in dichloromethane (3 mL). Triethylamine (55 μL, 0.4 mmol), dimethylaminopyridine (10 mg, 0.07 mmol) and di-tert-butyl dicarbonate (90 mg, 0.4 mmol) were added sequentially with stirring and the reaction mixture allowed to stir at room temperature for 18 h. Purification was carried out using flash column chromatography and elution with 20:80 ethyl acetate-petroleum ether (40-60) gave (2S,3R)-2-[(4-bromophenyl)-(2-ethoxyphenoxy)methyl]-N-tert-butoxycarbonylmorpholine 130 as a colourless oil (0.13 g, 75%). ν\textsubscript{max}/cm\textsuperscript{-1} (NaCl) 2925 (CH), 1695 (CO), 1500 (C=C), 1259, 1106; [α]\textsubscript{D}\textsuperscript{24} -34.8 (c 0.5, CHCl\textsubscript{3}); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 1.44-1.47 (12H, m, OCH\textsubscript{2}CH\textsubscript{3}, C(CH\textsubscript{3})\textsubscript{3}), 2.94-3.00 (2H, m, 3-HH, 5-HH), 3.46 (1H, td, J 11.6, 2.8 Hz, 5-HH), 3.71-3.74 (1H, m, 2-H), 3.86 (2H, dd, J 11.6, 2.8 Hz, 6-H\textsubscript{2}), 3.97-4.06 (2H, m, OCH\textsubscript{2}CH\textsubscript{3}), 4.34 (1H, d, J 13.2 Hz, 3-HH), 5.02 (1H, br m, 2-CH), 6.70-6.91 (4H, m, 4 x Ar H), 7.30 (2H, d, J 8.4 Hz, 2 x Ar H), 7.45 (2H, d, J 8.4 Hz, 2 x Ar H); δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 14.0 (CH\textsubscript{3}), 27.4 (3 x CH\textsubscript{3}), 42.2 (CH\textsubscript{2}), 46.1 (CH\textsubscript{2}), 63.4 (CH\textsubscript{2}), 65.7 (CH\textsubscript{2}), 78.1 (CH), 79.0 (C), 81.7 (CH), 113.9 (CH), 117.2 (CH), 120.7 (CH), 121.0 (C), 121.6 (CH), 129.2 (2 x CH), 130.3 (2 x CH), 136.6 (C), 146.1 (C), 148.9 (C), 153.8 (C); m/z (EI) 491.1302 (M\textsuperscript{+}). C\textsubscript{24}H\textsubscript{30}O\textsubscript{5}N\textsubscript{79}Br requires 491.1307, 300 (80%), 298 (90), 256 (94), 254 (99), 138.0 (89), 57 (100).
(2\textit{R},3\textit{S})-2-[(4-Bromophenyl)-(2-ethoxyphenoxy)methyl]-\textit{N}-\textit{tert}-butoxycarbonylmorpholine 156

The reaction was carried out as described above using (2\textit{R},3\textit{S})-2-[(4-bromophenyl)-(2-ethoxyphenoxy)methyl]morpholine 155 (0.06 g, 0.18 mmol). This gave (2\textit{R},3\textit{S})-2-[(4-bromophenyl)-(2-ethoxyphenoxy)methyl]-\textit{N}-\textit{tert}-butoxycarbonylmorpholine 156 as a colourless oil (0.04 g, 53%). \(\nu_{\text{max}}/\text{cm}^{-1}\) (NaCl) 2925 (CH), 1695 (CO), 1500 (C=C), 1259, 1106; \([\alpha]_{D}^{26}\) +38.8 (c 1.1, CHCl\(_3\)); \(\delta_H\) (400 MHz, CDCl\(_3\)) 1.44-1.47 (12H, m, OCH\(_2\)CH\(_3\), (CH\(_3\))\(_3\)), 2.94-3.00 (2H, m, 3-HH, 5-HH), 3.46 (1H, td, \(J\ 11.6, 2.8\) Hz, 5-HH), 3.71-3.74 (1H, m, 2-H), 3.86 (2H, dd, \(J\ 11.6, 2.8\) Hz, 6-H\(_2\)), 4.03-4.12 (2H, m, OCH\(_2\)CH\(_3\)), 4.34 (1H, d, \(J\ 13.2\) Hz, 3-HH), 5.02 (1H, br m, 2-CH), 6.70-6.91 (4H, m, 4 x Ar H), 7.30 (2H, d, \(J\ 8.4\) Hz, 2 x Ar H), 7.45 (2H, d, \(J\ 8.4\) Hz, 2 x Ar H); \(\delta_C\) (100 MHz, CDCl\(_3\)) 14.0 (CH\(_3\)), 27.4 (3 x CH\(_3\)), 42.1 (CH\(_2\)), 46.1 (CH\(_2\)), 63.4 (CH\(_2\)), 65.7 (CH\(_2\)), 78.2 (CH), 79.0 (C), 81.8 (CH), 114.0 (CH), 117.2 (CH), 120.7 (CH), 121.0 (C), 121.7 (CH), 129.2 (2 x CH), 130.3 (2 x CH), 136.6 (C), 146.1 (C), 148.9 (C), 153.8 (C); \(m/z\) (EI) 493.1297 (M\(^+\). C\(_{24}\)H\(_{30}\)O\(_5\)N\(_8\)Br requires 493.1291), 300 (57%), 298 (60), 256 (65), 254 (68), 169 (46), 138 (70).

(2\textit{S},3\textit{R})-2-[(4-Iodophenyl)-(2-ethoxyphenoxy)methyl]-\textit{N}-\textit{tert}-butoxycarbonylmorpholine 145

A Schlenk tube was charged with copper iodide (1.0 mg, 10 mol\%), sodium iodide (0.01 g, 0.14 mmol) and the tube evacuated and back filled with argon. 1,3-Diaminopropane (0.50 mg, 10 mol\%) and (2\textit{S},3\textit{R})-2-[(4-bromophenyl)-(2-ethoxyphenoxy)methyl]-\textit{N}-\textit{tert}-butoxycarbonylmorpholine 130 (0.03 g, 0.07 mmol) dissolved in dioxane (1 mL) were
added under argon. The Schlenk tube was sealed using a Teflon valve and the reaction mixture stirred at 130 °C for 48 h. The resulting suspension was cooled to room temperature and diluted with 25% aqueous ammonia solution (2 mL) and poured onto water (20 mL). The aqueous solution was washed with dichloromethane (3 x 15 mL) and the organic layers combined, dried (MgSO₄) and the filtrate concentrated in vacuo. Purification was carried out using column chromatography and elution with 20:80 ethyl acetate-petroleum ether (40-60) gave (2S,3R)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)methyl]-N-tert-butoxycarbonylmorpholine 145 as a colourless oil (0.02 g, 49%). ν_max/cm⁻¹ (NaCl) 2976 (CH), 2357, 1695 (CO), 1502 (C=C), 1254; [α]D²⁵ -37.1 (c 2.5, CHCl₃); δ_H (400 MHz, CDCl₃) 1.44-1.47 (12H, m, OCH₂CH₃, (CH₃)₃), 2.90-3.01 (2H, m, 3-HH, 5-HH), 3.46 (1H, td, J 11.6, 2.4 Hz, 5-HH), 3.70-3.74 (1H, m, 2-H), 3.86 (2H, dd, J 11.6, 2.4 Hz, 6-H₂), 4.05-4.11 (2H, m, OCH₂CH₃), 4.42 (1H, br d, J 13.2 Hz, 3-HH), 5.00 (1H, br m, 2-CH), 6.70-6.88 (4H, m, 4 x Ar H), 7.16 (2H, d, J 8.2 Hz, 2 x Ar H), 7.65 (2H, d, J 8.2 Hz, 2 x Ar H); δ_C (100 MHz, CDCl₃) 14.0 (CH₃), 27.4 (3 x CH₃), 42.3 (CH₂), 44.1 (CH₂), 63.4 (CH₂), 65.8 (CH₂), 77.2 (C), 78.1 (CH), 80.7 (CH), 112.9 (CH), 117.1 (CH), 119.7 (CH), 121.6 (CH), 128.4 (2 x CH), 130.4 (C), 136.3 (2 x CH), 137.3 (C), 146.1 (C), 148.9 (C), 153.8 (C); m/z (EI) 539.1166 (M⁺). C₂₄H₃₆O₅NI requires 539.1169, 346 (93%), 302 (94), 217 (44), 138 (73), 57 (100).

(2R,3S)-2-[(4-Iodophenyl)-(2-ethoxyphenoxy)methyl]-N-tert-butoxycarbonylmorpholine 157

A Schlenk tube was charged with copper iodide (0.01 g, 0.05 mmol), sodium iodide (0.027 g, 0.18 mmol) and the tube evacuated and back filled with argon. N,N’-Dimethylethylenediamine (0.01 mL, 0.10 mmol) and a solution of (2R,3S)-2-[(4-bromophenyl)-(2-ethoxyphenoxy)methyl]-N-tert-butoxycarbonylmorpholine 156 in butan-1-ol (0.04 g, 0.09 mmol in 3 mL) were added under argon. The Schlenk tube was sealed using a Teflon valve and the reaction mixture stirred at 120 °C for 24 h. The resulting suspension was concentrated in vacuo and the crude material dissolved in diethyl ether (20 mL), and washed with ammonia solution (1 mL of 30% NH₃(aq) in 20 mL water) followed by water (2 x 20 mL). The organic fractions were combined, dried (MgSO₄) and the filtrate
concentrated in vacuo to give (2R,3S)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)methyl]-N-tert-butoxycarbonylmorpholine 157 as a colourless oil (0.03 g, 52%). ν max/cm⁻¹ (NaCl) 2976 (CH), 2357, 1695 (CO), 1502 (C=C), 1254; [α]D²² +43.2 (c 2.2, CHCl₃); δH (400 MHz, CDCl₃) 1.44-1.47 (12H, m, OCH₂C₃H₃, (C₃H₇)₃), 2.90-3.01 (2H, m, 3-H₂, 5-H₂), 3.46 (1H, td, J 11.6, 2.4 Hz, 5-HH), 3.70-3.74 (1H, m, 2-H), 3.86 (2H, dd, J 11.6, 2.4 Hz, 6-H₂), 4.05-4.11 (2H, m, OCH₂CH₃), 4.42 (1H, br d, J 13.2 Hz, 3-HH), 5.00 (1H, br m, 2-CH), 6.70-6.88 (4H, m, 4 x Ar H), 7.16 (2H, d, J 8.2 Hz, 2 x Ar H), 7.65 (2H, d, J 8.2 Hz, 2 x Ar H); δC (100 MHz, CDCl₃) 14.0 (CH₃), 27.3 (3 x CH₃), 42.3 (CH₂), 44.1 (CH₂), 63.4 (CH₂), 65.8 (CH₂), 78.1 (CH), 80.7 (CH), 112.9 (CH), 117.1 (CH), 119.7 (CH), 121.6 (CH), 128.4 (2 x CH), 130.4 (C), 136.3 (2 x CH), 137.3 (C), 146.0 (C), 148.9 (C), 153.8 (C); m/z (EI) 539.1166 (M⁺ C₂₄H₃₀O₅NI requires 539.1169), 346 (93%), 302 (94), 217 (44), 138 (73), 57 (100).

(2S,3R)-2-[(4-Iodophenyl)-(2-ethoxyphenoxy)methyl]morpholine 126

Trifluoroacetic acid (1 mL, 0.06 mmol) was added to a solution of (2S,3R)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)methyl]-N-tert-butoxycarbonylmorpholine 145 (0.02 g, 0.04 mmol) in dichloromethane (5 mL) and the reaction mixture allowed to stir at room temperature for 4 h. The reaction mixture was concentrated in vacuo and the crude material redissolved in dichloromethane (10 mL) and washed with a saturated sodium hydrogen carbonate solution (10 mL). The organic layer was separated, dried (MgSO₄) and the filtrate concentrated in vacuo to give (2S,3R)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)methyl]morpholine 126 as a colourless oil (0.01 g, 57%). ν max/cm⁻¹ (NaCl) 3421 (NH), 2084 (CH), 1639 (C=C), 1500, 1255; [α]D²³ -38.0 (c 0.9, CHCl₃); δH (400 MHz, CDCl₃) 1.45 (3H, t, J 7.0 Hz, OCH₂CH₃), 1.93 (1H, br s, NH), 2.78-2.94 (3H, m, 3-HH, 5-H₂), 3.37 (1H, br d, J 11.6 Hz, 3-HH), 3.53 (1H, br t, J 12.4 Hz, 6-HH), 3.77 (1H, m, 2-H), 3.87 (1H, br d, J 12.4 Hz, 6-HH), 4.06 (2H, qd, J 7.0, 2.0 Hz, OCH₂CH₃), 4.97 (1H, d, J 7.0 Hz, 2-CH), 6.64-6.73 (2H, m, 2 x Ar H), 6.84-6.89 (2H, m, 2 x Ar H), 7.16 (2H, d, J 8.4 Hz, 2 x Ar H), 7.65 (2H, d, J 8.4 Hz, 2 x Ar H); δC (100 MHz, CDCl₃) 14.0 (CH₃), 45.0 (CH₂), 47.9 (CH₂), 64.5 (CH₂), 67.8 (CH₂), 77.3 (CH), 82.3 (CH), 113.7 (CH), 117.6 (CH), 120.8 (CH), 122.4 (CH), 129.3 (2 x CH), 130.3 (C), 136.3 (2 x CH), 137.8
(2R,3S)-2-[(4-Iodophenyl)-(2-ethoxyphenoxy)methyl]morpholine 127

\[ \text{O} \quad \text{O} \quad \text{N} \quad \text{O} \quad \text{Et} \]

\[ ^1 \]

\[ 2 \quad 3 \quad 5 \quad 6 \]

The reaction was carried out as described above using (2R,3S)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)-methyl]-N-tert-butoxycarbonylmorpholine 157 (0.02 g, 0.04 mmol). This gave (2R,3S)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)methyl]morpholine 127 as a colourless oil (0.01 g, 57%). \( \nu_{\text{max}}/\text{cm}^{-1} \) (NaCl) 3421 (NH), 2084 (CH), 1639 (C=C), 1500, 1255; \( [\alpha]_{D}^{22} +38.3 \) (c 0.9, CHCl\(_3\)); \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 1.45 (3H, t, \( J 7.0 \) Hz, OCH\(_2\)CH\(_3\)), 2.78-2.94 (3H, m, 3-\( HH\), 5-\( H_2\)), 3.37 (1H, br d, \( J 11.6 \) Hz, 3-\( HH\)), 3.53 (1H, br t, \( J 12.4 \) Hz, 6-\( HH\)), 3.76 (1H, m, 2-\( H\)), 3.87 (1H, br d, \( J 12.4 \) Hz, 6-\( HH\)), 4.06 (2H, qd, \( J 7.0, 2.0 \) Hz, OCH\(_2\)CH\(_3\)), 4.97 (1H, d, \( J 7.0 \) Hz, 2-\( CH\)), 6.64-6.73 (2H, m, 2 x Ar \( H\)), 6.84-6.89 (2H, m, 2 x Ar \( H\)), 7.16 (2H, d, \( J 8.2 \) Hz, 2 x Ar \( H\)), 7.65 (2H, d, \( J 8.2 \) Hz, 2 x Ar \( H\)); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 14.0 (CH\(_3\)), 45.0 (CH\(_2\)), 47.9 (CH\(_2\)), 64.5 (CH\(_2\)), 67.8 (CH\(_2\)), 77.3 (CH), 82.3 (CH), 113.7 (CH), 117.6 (CH), 120.8 (CH), 122.4 (CH), 129.3 (2 x CH), 130.3 (C), 136.3 (2 x CH), 137.8 (C), 146.3 (C), 148.7 (C); \( m/z \) (EI) 439.0642 (M\(^+\). \( \text{C}_{19}\text{H}_{22}\text{O}_3\text{NI} \) requires 439.0644), 301 (99%), 220 (96), 138 (61), 85 (77), 56 (100).
3.2 Synthesis of (2S,3S)- and (2R,3R)-Iodoreboxetine

Ethyl (E)-3-(4-iodophenyl)acrylate 161

Dimethyl sulfoxide (2.50 mL, 37.5 mmol) was added to a stirred mixture of oxalyl chloride (1.57 mL, 18.0 mmol) in dichloromethane (80 mL) at -78 °C. This mixture was stirred for 0.25 h before 4-iodobenzyl alcohol 160 (3.5 g, 15.0 mmol) was added. The mixture was stirred for another 0.25 h before triethylamine (10.4 mL, 75.0 mmol) was added. The reaction mixture was allowed to stir at -78 °C for 0.5 h before being allowed to warm to room temperature and then stirred for another 1.5 h. Meanwhile, a solution of lithium chloride (1.58 g, 37.5 mmol), triethyl phosphonoacetate (7.43 mL, 37.5 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (5.60 mL, 37.5 mmol) in acetonitrile (60 mL) was prepared and stirred for 0.5 h. The aldehyde mixture was concentrated in vacuo and the phosphonate ester mixture added to the residue. The reaction mixture was then allowed to stir at room temperature for 67 h. The reaction mixture was quenched with saturated ammonium chloride solution (100 mL) and the organic solvent removed in vacuo. Diethyl ether (100 mL) was added and the solution filtered to remove the white precipitate. The organic layer was removed and the aqueous layer extracted further with diethyl ether (3 x 100 mL). The organic fractions were combined, dried (MgSO₄) and the filtrate concentrated in vacuo. Purification was carried out using flash column chromatography and elution with 10:90 ethyl acetate-petroleum ether (40-60) gave ethyl (E)-3-(4-iodophenyl)acrylate 161 as a yellow oil (4.46 g, 99%). δH (400 MHz, CDCl₃) 1.31 (3H, t, J 7.2 Hz, OCH₂CH₃), 4.24 (2H, q, J 7.2 Hz, OCH₂CH₃), 6.40 (1H, d, J 16.0 Hz, 2-H), 7.20 (2H, d, J 8.4 Hz, 2 x Ar H), 7.55 (1H, d, J 16.0 Hz, 3-H), 7.67 (2H, d, J 8.4 Hz, 2 x Ar H); δC (100 MHz, CDCl₃) 14.4 (CH₃), 60.8 (CH₂), 96.5 (C), 119.5 (CH), 129.5 (2 x CH), 134.2 (C), 138.4 (2 x CH), 143.3 (CH), 166.6 (C); m/z (EI) 301.9802 (M⁺. C₁₁H₁₁O₂I requires 301.9804), 302 (100%), 256 (79), 230 (23), 130 (95), 102 (94).
(2E)-3-(4-Iodophenyl)prop-2-en-1-ol 162

Ethyl (E)-3-(4-iodophenyl)acrylate 161 (6.0 g, 19.9 mmol) was dissolved in diethyl ether (100 mL) and the solution cooled to -78 °C. DIBAL-H (43.7 mL, 43.7 mmol, 1 M in hexanes) was added to the solution dropwise and after 1 h the reaction mixture was allowed to warm to room temperature and stirred for 18 h. The yellow solution was cooled to 0 °C and the reaction was quenched using saturated ammonium chloride solution (30 mL). The white solution was left to stir vigorously for 2 h before being filtered through a pad of Celite® using diethyl ether and the filtrate concentrated in vacuo to give (2E)-3-(4-iodophenyl)prop-2-en-1-ol 162 as a white powder (5.12 g, 99%). δH (400 MHz, CDCl3) 1.57 (1H, t, J 5.6 Hz, OH), 4.32 (2H, td, J 5.6, 1.2 Hz, 1-H2), 6.37 (1H, dt, J 15.8, 5.6 Hz, 2-H), 6.55 (1H, d, J 15.8 Hz, 3-H), 7.12 (2H, d, J 8.4 Hz, 2 x Ar H), 7.64 (2H, d, J 8.4 Hz 2 x Ar H); δC (100 MHz, CDCl3) 63.5 (CH2), 93.0 (C), 128.2 (2 x CH), 129.5 (CH), 130.0 (CH), 137.4 (C), 137.7 (2 x CH); m/z (EI) 259.9696 (M+). C9H9OI requires 259.9698, 260 (70%), 204 (14), 133 (60), 84 (74), 49 (100).

(2E)-1-Chloro-3-(4-iodophenyl)prop-2-ene 163

(2E)-3-(4-Iodophenyl)prop-2-en-1-ol 162 (4.62 g, 17.8 mmol) was dissolved in dichloromethane (300 mL) and the solution cooled to 0 °C. N-Chlorosuccinimide (4.03 g, 30.2 mmol) and triphenylphosphine (9.33 g, 35.6 mmol) were added sequentially with stirring and the reaction mixture left to stir for 4 h after which it was concentrated in vacuo. Purification was carried out using flash column chromatography and elution with 50:50 ethyl acetate-petroleum ether (40-60) gave (2E)-1-chloro-3-(4-iodophenyl)prop-2-ene 163 as a white solid (3.40 g, 69%). νmax /cm⁻¹ 3018 (CH), 1704, 1485, 1302, 1006; δH (400 MHz, CDCl3) 4.23 (2H, dd, J 7.1, 1.0 Hz, 1-H2), 6.33 (1H, dt, J 15.6, 7.1 Hz, 2-H), 6.59 (1H, d, J 15.6 Hz, 3-H), 7.13 (2H, d, J 8.4 Hz, 2 x Ar H), 7.67 (2H, d, J 8.4 Hz, 2 x Ar H); δC (100 MHz, CDCl3) 45.2 (CH2), 93.8 (C), 125.8 (CH), 128.5 (2 x CH), 133.0 (CH),
(2R,3S)-1-Chloro-3-(4-iodophenyl)propane-2,3-diol 159

AD-mix-α (12.5 g) was dissolved in a mixture of water (80 mL) and tert-butanol (80 mL). Methanesulfonamide (0.85 g, 8.94 mmol) and sodium hydrogen carbonate (2.25 g, 26.8 mmol) were added and the bright orange solution cooled to 0 °C. (2E)-1-Chloro-3-(4-iodophenyl)prop-2-ene 163 (2.5 g, 8.94 mmol) was added and the solution stirred vigorously at 0 °C for 120 h. Sodium sulfite (12.0 g, 0.1 mol) was added and the solution left to stir for 2 h at which point it changed colour from an opaque yellow to colourless. The reaction mixture was concentrated in vacuo and the residue dissolved in water (250 mL). The aqueous solution was extracted with ethyl acetate (3 x 250 mL) and the organic fractions combined, washed with 2 M potassium hydroxide (500 mL), dried (MgSO₄) and the filtrate concentrated in vacuo. Purification was carried out using flash column chromatography and elution with 40:60 ethyl acetate-petroleum ether (40-60) gave (2R,3S)-1-chloro-3-(4-iodophenyl)propane-2,3-diol 159 as a colourless oil (2.38 g, 84%). 98% ee determined by HPLC analysis using CHIRALPAK IB column (5% iPrOH/hexane at 0.75 mL/min), retention time: $t_{2S,3R} = 27.8$ min, and $t_{2R,3S} = 29.8$ min; $\nu_{\text{max}}$ /cm⁻¹ 3527 (OH), 3419 (OH), 2961 (CH), 1585 (C=C), 1090; $[\alpha]_D^{26}$ -4.5 (c 1.0, CHCl₃); $\delta_H$ (400 MHz, CDCl₃) 2.93 (1H, d, $J$ 5.2 Hz, 2-OH), 3.01 (1H, d, $J$ 3.4 Hz, 3-OH), 3.39 (1H, dd, $J$ 11.6, 5.6 Hz, 1-HH), 3.58 (1H, dd, $J$ 11.6, 4.0 Hz, 1-HH), 3.82-3.88 (1H, m, 2-H), 4.70 (1H, dd, $J$ 6.4, 3.4 Hz, 3-H), 7.13 (2H, d, $J$ 8.4 Hz, 2 x Ar H), 7.71 (2H, d, $J$ 8.4 Hz, 2 x Ar H); $\delta_C$ (100 MHz, CDCl₃) 46.0 (CH₂), 74.1 (CH), 75.3 (CH), 94.2 (C), 128.6 (2 x CH), 137.8 (2 x CH), 139.5 (C); $m/z$ (EI) 313.9387 (M⁺, C₉H₁₀O₂⁺Cl requires 313.9383), 276 (41%), 233 (98), 231 (22), 106 (100).
(2S,3R)-1-Chloro-3-(4-iodophenyl)propane-2,3-diol 188

The reaction was carried out as described above, using (2E)-1-chloro-3-(4-iodophenyl)prop-2-ene 163 (2.3 g, 8.08 mmol) and AD-mix-β (11.3 g). This gave (2S,3R)-1-chloro-3-(4-iodophenyl)propane-2,3-diol 188 as a colourless oil (1.57 g, 62%). 98% ee determined by HPLC analysis using CHIRALPAK IB column (5% iPrOH/hexane at 0.75 mL/min), retention time: t_{2S,3R} = 27.8 min, and t_{2R,3S} = 29.8 min; ν_{max}/cm^{-1} 3530 (OH), 3410 (OH), 2960 (CH), 1585 (C=C), 1100; [α]_D^{22} +10.1 (c 1.0, CHCl_3); δH (400 MHz, CDCl_3) 2.70 (1H, d, J 5.4 Hz, 2-OH), 2.73 (1H, d, J 3.4 Hz, 3-OH), 3.41 (1H, dd, J 11.6, 4.0 Hz, 1-HH), 3.60 (1H, dd, J 11.6, 5.4 Hz, 1-HH), 3.83-3.89 (1H, m, 2-H), 4.73 (1H, dd, J 6.4, 3.4 Hz, 3-H), 7.16 (2H, d, J 8.4 Hz, 2 x Ar H), 7.72 (2H, d, J 8.4 Hz, 2 x Ar H); δC (100 MHz, CDCl_3) 44.6 (CH2), 72.8 (CH), 73.9 (CH), 92.7 (C), 127.2 (2 x CH), 136.4 (2 x CH), 138.1 (C); m/z (EI) 311.9412 (M^+ C_9H_10O_2Cl requires 311.9414), 276 (13%), 233 (100), 231 (7), 106 (16), 78 (78).

(1S,2S)-2,3-Epoxy-1-(4-iodophenyl)propan-1-ol 164

(2R,3S)-1-Chloro-3-(4-iodophenyl)propane-2,3-diol 159 (1.85 g, 5.92 mmol) and sodium hydroxide (0.47 g, 11.8 mmol) were suspended in tetrahydrofuran (120 mL). The mixture was cooled to 0 °C and left to stir for 18 h. The reaction mixture was poured onto water (200 mL) and the aqueous solution extracted using dichloromethane (2 x 200 mL). The organic fractions were combined, dried (MgSO_4) and the filtrate concentrated in vacuo to give (1S,2S)-2,3-epoxy-1-(4-iodophenyl)propan-1-ol 164 as a colourless oil (1.59 g, 98%). ν_{max}/cm^{-1} 3424 (OH), 3022 (CH), 1639 (C=C), 1216, 758; [α]_D^{26} +6.1 (c 1.0, CHCl_3); δH (400 MHz, CDCl_3) 2.55 (1H, d, J 5.2 Hz, OH), 2.83 (1H, dd, J 4.4, 2.8 Hz, 3-HH), 2.87 (1H, dd, J 4.4, 4.0 Hz, 3-HH), 3.17-3.20 (1H, m, 2-H), 4.45 (1H, t, J 5.2 Hz, 1-H), 7.17 (2H, d, J 8.4 Hz, 2 x Ar H), 7.72 (2H, d, J 8.4 Hz, 2 x Ar H); δC (100 MHz, CDCl_3) 45.4 (CH2), 55.7 (CH), 73.8 (CH), 93.9 (C), 128.2 (2 x CH), 137.8 (2 x CH), 139.7 (C); m/z (EI)
275.9650 (M⁺, C₈H₉O₂I requires 275.9647), 233 (89%), 142 (23), 105 (32), 83 (98), 78 (78).

**(1R,2R)-2,3-Epoxy-1-(4-iodophenyl)propan-1-ol 189**

![Image of compound 189](image1.png)

The reaction was carried out as described above using (2S,3R)-1-chloro-3-(4-iodophenyl)propane-2,3-diol 188 (0.92 g, 2.95 mmol). This gave (1R,2R)-2,3-epoxy-1-(4-iodophenyl)propan-1-ol 189 as a colourless oil (0.51 g, 63%). ν_max /cm⁻¹ 3409 (OH), 2994 (CH), 1588 (C=C), 1484, 1254; [α]D_25 -2.7 (c 1.1, CHCl₃); δ_H (400 MHz, CDCl₃) 2.80 (1H, dd, J 4.6, 2.8 Hz, 3-H), 2.85 (1H, t, J 4.6, 4.0 Hz, 3-H), 2.95 (1H, br d, J 4.8 Hz, OH), 3.15-3.18 (1H, m, 2-H), 4.41 (1H, t, J 5.0 Hz, 1-H), 7.15 (2H, d, J 8.2 Hz, 2 x Ar H), 7.70 (2H, d, J 8.2 Hz, 2 x Ar H); δ_C (100 MHz, CDCl₃) 45.5 (CH₂), 55.9 (CH), 73.9 (CH), 93.9 (C), 128.3 (2 x CH), 137.7 (2 x CH), 139.7 (C); m/z (EI) 275.9651 (M⁺, C₈H₉O₂I requires 275.9647), 276 (40%), 233 (100), 203 (5), 105 (15), 78 (81).

**(1S,2S)-1-(tert-Butyldimethylsilyloxy)-2,3-epoxy-1-(4-iodophenyl)propane 158**

(1S,2S)-2,3-Epoxy-1-(4-iodophenyl)propan-1-ol 164 (1.46 g, 5.29 mmol) was dissolved in dichloromethane. Imidazole and tert-butyldimethylsilyl chloride were added sequentially and the reaction mixture allowed to stir at room temperature for 24 h. The reaction mixture was diluted with dichloromethane (200 mL) and washed with 1 M hydrochloric acid (200 mL). The aqueous layer was then extracted with dichloromethane (2 x 200 mL) and the organic fractions combined, dried (MgSO₄) and the filtrate concentrated in vacuo to give (1S,2S)-1-(tert-Butyldimethylsilyloxy)-2,3-epoxy-1-(4-iodophenyl)propane 158 as a colourless oil (1.78 g, 86%). ν_max /cm⁻¹ (NaCl) 3020 (CH), 1611 (C=C), 1422, 1216, 758; [α]D_26 +5.5 (c 1.1, CHCl₃); δ_H (400 MHz, CDCl₃) 0.00 (3H, s, SiCH₃), 0.12 (3H, s, SiCH₃), 0.92 (9H, s, C(CH₃)), 2.63 (1H, dd, J 4.8, 2.8 Hz, 3-H), 2.75 (1H, dd, J 4.8, 4.0 Hz, 3-H), 3.04-3.07 (1H, m, 2-H), 4.35 (1H, d, J 6.4 Hz, 1-H), 7.12 (2H, d, J 8.2 Hz, 2 x Ar H), 7.68 (2H, d, J 8.2 Hz, 2 x Ar H); δ_C (100 MHz, CDCl₃) -4.92 (CH₃), -4.71 (CH₃), 18.3 (C),
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25.8 (3 x CH$_3$), 45.1 (CH$_2$), 56.6 (CH), 76.0 (CH), 93.3 (C), 128.2 (2 x CH), 137.4 (2 x CH), 140.6 (C); m/z (CI) 391.0591 (MH$^+$. C$_{15}$H$_{24}$O$_2$Si requires 391.0590), 391 (71%), 361 (100), 333 (55), 259 (80), 235 (49).

2-(4-Methoxyphenylamino)ethanol 167$^{69}$

![Chemical structure](image)

Glacial acetic acid was added dropwise to a stirred solution of ethanolamine (5.3 mL, 88.2 mmol) in methanol (10 mL) until pH 6 was achieved. 4-Methoxybenzaldehyde (1.79 mL, 14.7 mmol) and cyanoborohydride (0.56 g, 8.82 mmol) were then added and the reaction mixture stirred at room temperature for 68 h. The reaction mixture was acidified to pH 2 with concentrated hydrochloric acid and the solvent removed _in vacuo_. The residue was dissolved in water (50 mL) and the aqueous solution extracted with diethyl ether (3 x 50 mL). The aqueous layer was adjusted to pH 11 using sodium hydroxide pellets and the solution saturated with sodium chloride. The aqueous solution was then extracted with diethyl ether (3 x 50 mL) and the organic portions combined, dried (MgSO$_4$), and the filtrate concentrated _in vacuo_. Purification was carried out using flash column chromatography and elution with 20:80 methanol-ethyl acetate gave 2-(4-methoxyphenylamino)ethanol 167 as a yellow oil (1.56 g, 59%). $\delta$H (400 MHz, CDCl$_3$) 2.74 (2H, t, $J$ 5.2 Hz, 2-H$_2$), 3.64 (2H, t, $J$ 5.2 Hz, 1-H$_2$), 3.72 (2H, s, 2-NHCH$_2$), 3.76 (3H, s, OCH$_3$), 6.85 (2H, d, $J$ 8.6 Hz, 2 x Ar H), 7.23 (2H, d, $J$ 8.6 Hz, 2 x Ar H); $\delta$C (100 MHz, CDCl$_3$) 50.4 (CH$_2$), 51.4 (CH$_2$), 55.3 (CH$_3$), 60.1 (CH$_2$), 114.1 (2 x CH), 129.5 (2 x CH), 131.5 (C), 158.9 (C); m/z (CI) 302 (MH$^+$, 34%), 182 (91), 163 (10), 150 (45), 121 (100).

(1S,2S)-2,3-Epoxy-1-(4-iodophenyl)-1-(methoxymethoxy)propane 172

![Chemical structure](image)

(1S,2S)-2,3-Epoxy-1-(4-iodophenyl)propan-1-ol 164 (1.91 g, 6.92 mmol) was dissolved in dichloromethane (60 mL). _N,N_-Diisopropylethylamine (3.61 mL, 20.8 mmol) was added and the solution cooled to 0 °C and stirred for 0.25 h before bromomethyl methyl ether (1.13 mL, 13.8 mmol) was added. The reaction mixture was stirred at 0 °C for 0.25 h
before being heated under reflux for 8 h. The reaction mixture was quenched with water (100 mL) and the aqueous layer extracted with dichloromethane (3 x 100 mL). The organic fractions were combined, washed with brine (300 mL), dried (MgSO₄) and the filtrate concentrated in vacuo. Purification was carried out using flash column chromatography and elution with 20:80 diethyl ether-petroleum ether (40-60) gave (1S,2S)-2,3-epoxy-1-(4-iodophenyl)-1-(methoxymethoxy)propane 172 (0.82 g, 37%). νmax /cm⁻¹ 2948 (CH), 2891, 1587 (C=C), 1484, 1397; [α]D 26 +59.8 (c 1.4, CHCl₃); δH (400 MHz, CDCl₃) 2.63 (1H, dd, J 4.6, 2.8 Hz, 3-H), 2.76 (1H, t, J 4.6 Hz, 3-H), 3.16-3.20 (1H, m, 2-H), 3.37 (3H, s, OCH₃), 4.31 (1H, d, J 6.4 Hz, 1-H), 4.60 (1H, d, J 6.8 Hz, OCHHO), 4.73 (1H, d, J 6.8 Hz, OCHHO), 7.13 (2H, d, J 8.4 Hz, 2 x Ar H), 7.70 (2H, d, J 8.4 Hz, 2 x Ar H); δC (100 MHz, CDCl₃) 44.1 (CH₂), 54.9 (CH₃), 55.5 (CH), 78.3 (CH), 94.0 (C), 94.2 (CH₂), 129.0 (2 x CH), 137.4 (C), 137.6 (2 x CH); m/z (EI) 319.9908 (M⁺. C₁₁H₁₃O₃I requires 319.9909), 277 (43%), 231 (6), 83 (100), 45 (93).

(2S,3S)-1-(2’-Hydroxyethylamino)-3-(4-iodophenyl)-3-methoxymethoxypropan-2-ol 173

(1S,2S)-2,3-Epoxy-1-(4-iodophenyl)-1-(methoxymethoxy)propane 172 (0.82 g, 2.58 mmol) was dissolved in propan-1-ol (50 mL) and ethanolamine (0.47 mL, 7.74 mmol) was added with stirring. The reaction mixture was heated under reflux for 20 h before being cooled to room temperature and partitioned between ethyl acetate (100 mL) and a 1:1 mixture of brine and sodium hydrogencarbonate (100 mL). The organic layer was removed and the aqueous layer washed with dichloromethane (2 x 100 mL). The organic fractions were combined, dried (MgSO₄) and the filtrate concentrated in vacuo to give (2S,3S)-1-(2’-hydroxyethylamino)-3-(4-iodophenyl)-3-methoxymethoxy-propan-2-ol 173 (0.93 g, 95%). νmax/cm⁻¹ (NaCl) 3387 (NH/OH), 2883 (CH), 1637 (C=C), 1443, 1148; [α]D 27 +86.9 (c 0.8, CHCl₃); δH (400 MHz, CDCl₃) 2.46-2.56 (2H, m, 1-H₂), 2.64-2.73 (2H, m, 1’-H₂), 3.25 (3H, br s, 2 x OOH, NH), 3.34 (3H, s, OCH₃), 3.60 (2H, t, J 5.0 Hz, 2’-H₂), 3.87 (1H, m, 2-H), 4.48 (1H, d, J 6.4 Hz, 3-H), 4.53 (1H, d, J 6.6 Hz, OCHHO), 4.58 (1H, d, J 6.6 Hz, OCHHO), 7.07 (2H, d, J 8.0 Hz, 2 x Ar H), 7.68 (2H, d, J 8.0 Hz, 2 x Ar H); δC (100 MHz, CDCl₃) 50.8 (CH₂), 51.1 (CH₂), 55.9 (CH₃), 60.7 (CH₂), 73.1 (CH), 79.6 (CH), 94.0 (C), 94.6 (CH₂), 129.5 (2 x CH), 137.5 (2 x CH), 137.9 (C); m/z (CI) 382.0522 (MH⁺. C₁₃H₁₄O₄NI requires 382.0515), 382 (100%), 350 (15), 256 (45), 224 (6), 74 (41).
(2S,3S)-1-(2’-Hydroxyethyl-N-benzyloxycarbonylamino)-3-(4-iodophenyl)-3-methoxymethoxypropan-2-ol 174

(2S,3S)-1-(2-Hydroxyethylamino)-3-(4-iodophenyl)-3-methoxymethoxypropan-2-ol 173 (0.1 g, 0.26 mmol) was dissolved in tetrahydrofuran (3 mL). The solution was cooled to 0 °C before triethylamine (71 μL, 0.51 mmol) and benzyl chloroformate (44 μL, 0.31 mmol) were added sequentially. The reaction mixture was left to stir for 5 h before being poured onto water (10 mL) and the aqueous solution extracted with ethyl acetate (3 x 10 mL). The organic fractions were combined, dried (MgSO₄) and the filtrate concentrated in vacuo. Purification was carried out using flash column chromatography and elution with 80:20 ethyl acetate: petroleum ether (40-60) gave (2S,3S)-1-(2’-hydroxyethyl-N-benzyloxycarbonylamino)-3-(4-iodophenyl)-3-methoxymethoxypropan-2-ol 174 (0.06 g, 48%). ν_max/cm⁻¹ (NaCl) 3403 (NH/OH), 2931 (CH), 2247, 1687 (CO), 1479; [α]_D²⁷ +77.5 (c 1.1, CHCl₃); Due to the presence of rotomers, the ¹H NMR spectrum was recorded at 100 °C, δH (400 MHz, DMSO) 3.10-3.16 (1H, m, 1-HH); 3.28 (3H, s, OCH₃), 3.40-3.43 (3H, m, 1-HH, 1’-H₂), 3.56-3.57 (2H, m, 2’-H₂), 3.98 (1H, m, 2-H), 4.46 (1H, d, J 4.0 Hz, 3-H), 4.54 (2H, d, J 4.0 Hz, OCH₂), 4.64 (1H, d, J 4.8 Hz, OCH₂), 5.08 (2H, s, CH₂Ph), 7.15 (2H, d, J 7.0 Hz, 2 x Ar H), 7.35-7.41 (5H, m, 5 x Ar H), 7.79 (2H, d, J 7.0 Hz, 2 x Ar H); δC (100 MHz, CDCl₃) 50.8 (CH₂), 51.0 (CH₂), 55.2 (CH₃), 59.2 (CH₂), 66.1 (CH₂), 72.1 (CH), 79.7 (CH), 93.0 (C), 95.0 (CH₂), 127.2 (2 x CH), 127.4 (1 x CH), 127.6 (2 x CH), 129.8 (2 x CH), 136.7 (2 x CH), 137.1 (C), 139.1 (C), 155.7 (C); m/z (Cl) 516.0888 (MH⁺). C₂₁H₂₇O₆NI requires 516.0883, 516 (100%), 454 (56), 408 (24), 238 (23), 183 (17).
A solution of (2S,3S)-1-(2'-hydroxyethyl-N-benzyloxycarbonylamino)-3-(4-iodophenyl)-3-methoxymethoxypropan-2-ol 174 (0.1 g, 0.21 mmol) in tetrahydrofuran (2 mL) was added dropwise to a solution of sodium hydride (60% in mineral oil) (12.7 mg, 0.53 mmol) in tetrahydrofuran (3 mL) at 0 °C. The solution was stirred at 0 °C for 0.25 h and then allowed to warm to room temperature over 1 h. The reaction mixture was cooled to 0 °C and 1-(p-toluenesulfonyl)imidazole (0.05 g, 0.21 mmol) added in one portion. The reaction mixture was allowed to stir at 0 °C for 0.25 h before being allowed to warm to room temperature and stirred for 24 h. The reaction mixture was cooled to 0 °C quenched by careful dropwise addition of saturated ammonium chloride solution (5 mL). The aqueous solution was extracted with ethyl acetate (3 x 10 mL) and the organic fractions combined, dried (MgSO₄) and concentrated in vacuo. Purification was carried out using flash column chromatography and elution with 50:50 ethyl acetate-petroleum ether (40-60) gave (2S,3S)-3-(4-iodophenyl)-3-methoxymethoxy-1-(2'-oxazolidinone)-2-toluenesulfonyloxypropane 177 (0.03 g, 27%). \( \nu_{\text{max}} \text{cm}^{-1} \) (NaCl) 3448, 2926 (CH), 1750 (CO), 1597 (C=C), 1483; [\( \alpha \)]\text{D}²⁷ +65.3 (c 1.2, CHCl₃); \( \delta \)H (400 MHz, CHCl₃) 2.47 (3H, s, ArCH₃), 3.25 (3H, s, OCH₃), 3.35 (1H, dd, \( J \) 15.0, 8.6 Hz, 1'-H), 3.50 (1H, dd, \( J \) 15.0, 3.0 Hz, 1-HH), 3.57-3.62 (2H, m, 4'-H 2), 4.16-4.25 (2H, m, 5'-H 2), 4.41 (1H, d, \( J \) 6.8 Hz, OCHHO), 4.49 (1H, d, \( J \) 6.8 Hz, OCHHO), 4.70 (1H, d, \( J \) 4.8 Hz, 3-H), 5.00 (1H, ddd, \( J \) 8.6, 4.8, 3.0 Hz, 2-H), 6.95 (2H, d, \( J \) 7.8 Hz, 2 x Ar H), 7.29 (2H, d, \( J \) 7.8 Hz, 2 x Ar H), 7.65 (2H, d, \( J \) 8.4 Hz, 2 x Ar H), 7.63 (2H, d, \( J \) 8.4 Hz, 2 x Ar H); \( \delta \)C (100 MHz, CDCl₃) 21.8 (CH₃), 45.3 (CH₂), 45.9 (CH₂), 56.1 (CH₃), 62.1 (CH₂), 74.9 (CH), 81.2 (CH), 94.5 (C), 94.7 (CH₂), 127.6 (2 x CH), 129.3 (2 x CH), 129.8 (2 x CH), 133.5 (C), 135.7 (C), 137.6 (2 x CH), 145.0 (C), 158.5 (C); \( m/z \) (CI) 562.0399 (MH⁺). C₂₁H₂₉O₇NIS requires 562.0397, 562 (24%), 436 (31), 374 (28), 220 (67), 130 (100).
(2S,3S)-1-Chloroacetylamino-3-(4-iodophenyl)propane-2,3-diol 179

(1S,2S)-2,3-Epoxy-1-(4-iodophenyl)propan-1-ol 164 (1.98 g, 7.2 mmol) was dissolved in acetonitrile (25 mL) and ammonia solution (25 mL) added with stirring. The reaction mixture was stirred at room temperature for 24 h before being concentrated in vacuo. The residue was dissolved in water (50 mL) acidified to pH 2 before being extracted with ethyl acetate (50 mL). The pH of aqueous layer was made basic (pH 13) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried (MgSO₄) and the filtrate concentrated in vacuo. The crude material (1.89 g) was dissolved in acetonitrile (130 mL) and the mixture cooled to -10 °C using an acetone/ice bath. Triethylamine (1.08 mL, 7.74 mmol) and chloroacetyl chloride (0.54 mL, 7.10 mmol) were added dropwise sequentially and the solution stirred at -10 °C for 1 h. The reaction mixture was allowed to warm to room temperature and left to stir for 18 h and then concentrated in vacuo. Purification was carried out by flash column chromatography and elution with 90:10 ethyl acetate-petroleum ether (40-60) gave (2S,3S)-1-chloroacetylamino-3-(4-iodophenyl)propane-2,3-diol 179 as a white solid (1.35 g, 51%). νₘₚₑₓ/ cm⁻¹ (KBr) 3349 (NH/OH), 2922 (CH), 1696 (CO), 1553, 1484; [α]D²⁴ -6.6 (c 1.0, MeOH); δH (400 MHz, CDCl3) 2.92 (1H, d, J 4.0 Hz, 2-OH), 3.14 (1H, d, J 4.0 Hz, 3-OH), 3.30 (1H, ddd, J 14.0, 6.8, 5.2 Hz, 1-H), 3.47 (1H, ddd, J 14.0, 6.4, 4.4 Hz, 1-HH), 3.78-3.83 (1H, m, 2-H), 4.07 (2H, s, CH₂Cl), 4.53 (1H, d, J 4.0 Hz, 3-H), 6.93-6.98 (1H, br m, NH), 7.13 (2H, d, J 8.4 Hz, 2 x Ar H), 7.71 (2H, d, J 8.4 Hz, 2 x Ar H); δC (100 MHz, CDCl3) 42.4 (CH₂), 42.5 (CH₂), 74.5 (CH), 74.5 (CH), 94.0 (C), 128.6 (2 x CH), 137.8 (2 x CH), 139.7 (C), 167.4 (C); m/z (FAB⁺) 371.9681 (MH⁺. C₁₁H₁₄O₃N₃Cl requires 371.9681), 370 (14%), 352 (14), 154 (100), 136 (71), 107 (21).
**(2R,3R)-1-Chloroacetylamino-3-(4-iodophenyl)propane-2,3-diol 191**

![Chemical Structure](image)

The reactions were carried out as described using (1R,2R)-2,3-epoxy-1-(4-iodophenyl)propan-1-ol 189 (0.46 g, 1.65 mmol). This gave (2R,3R)-1-chloroacetylamino-3-(4-iodophenyl)propane-2,3-diol 191 as a white solid (0.19 g, 46%). $\nu_{\text{max}}$/cm$^{-1}$ (KBr) 3348 (NH/OH), 2923 (CH), 1696 (CO), 1554, 1484; $\left[\alpha\right]_D^{21}$ +3.1 (c 1.0, MeOH); $\delta_H$ (400 MHz, CDCl$_3$) 2.95 (1H, d, $J$ 4.0 Hz, 2-OH), 3.15 (1H, d, $J$ 4.0 Hz, 3-OH), 3.27-3.34 (1H, m, 1-HH), 3.43-3.49 (1H, m, 1-HH), 3.77-3.83 (1H, m, 2-H), 4.07 (2H, s, CH$_2$Cl), 4.52-4.45 (1H, m, 3-H), 6.91-6.99 (1H, br m, NH), 7.12 (2H, d, $J$ 8.4 Hz, 2 x Ar H), 7.71 (2H, d, $J$ 8.4 Hz, 2 x Ar H); $\delta_C$ (100 MHz, CDCl$_3$) 41.9 (CH$_2$), 42.0 (CH$_2$), 74.0 (CH), 74.1 (CH), 93.5 (C), 128.1 (2 x CH), 137.4 (2 x CH), 139.1 (C), 166.9 (C); m/z (FAB$^+$) 369.9713 (MH$^+$). C$_{11}$H$_{14}$O$_3$N$_3$S$_2$I requires 369.9707, 352 (34%), 176 (10), 107 (5), 75 (100).

**(2S,3S)-2-[\alpha-Hydroxy-(4-iodophenyl)methyl]morpholine-5-one 180**

![Chemical Structure](image)

Sodium tert-butoxide (0.60 g, 6.21 mmol) was dissolved in tert-butanol (30 mL). (2S,3S)-1-Chloroacetylamino-3-(4-iodophenyl)propane-2,3-diol 179 (0.77 g, 2.07 mmol) dissolved in tert-butanol (10 mL) was added dropwise to the basic solution and the reaction mixture heated to 40 °C for 3 h. The solution was acidified with drops of 2 M hydrochloric acid and then concentrated in vacuo. The residue was suspended in water (200 mL) and the aqueous solution extracted with ethyl acetate (3 x 200 mL). The organic portions were combined, dried (MgSO$_4$), and the filtrate concentrated in vacuo. Purification was carried out by dry flash chromatography and elution with 10:90 methanol-ethyl acetate gave (2S,3S)-2-[\alpha-hydroxy-(4-iodophenyl)methyl]morpholine-5-one 180 as a white solid (0.44 g, 65%). $\nu_{\text{max}}$/cm$^{-1}$ (NaCl) 3321 (NH/OH), 2876 (CH), 1671 (CO), 1589, 1482; $\left[\alpha\right]_D^{22}$ +21.5 (c 1.0, CHCl$_3$); $\delta_H$ (400 MHz, CDCl$_3$) 2.93 (1H, dt, $J$ 11.6, 3.4 Hz, 3-HH), 3.34 (1H, t, $J$ 11.6 Hz, 3-HH), 3.76 (1H, ddd, $J$ 11.6, 7.2, 3.4 Hz, 2-H), 4.22 (1H, d, $J$ 16.8 Hz, 6-HH), 4.38 (1H,
d, J 16.8 Hz, 6-HH), 4.59 (1H, d, J 7.2 Hz, 2-CH), 6.03 (1H, br s, NH), 7.11 (2H, d, J 8.4 Hz, 2 x Ar H), 7.72 (2H, d, J 8.4 Hz, 2 x Ar H); δC (100 MHz, CDCl3) 42.2 (CH2), 66.9 (CH2), 73.7 (CH), 76.8 (CH), 93.7 (C), 128.0 (2 x CH), 137.2 (2 x CH), 137.7 (C), 167.9 (C); m/z (Cl) 333.9937 (MH+. C11H13O3NI requires 333.9940), 316 (19%), 208 (53), 155 (3), 101 (7).

(2R,3R)-2-[α-Hydroxy-(4-iodophenyl)methyl]morpholine-5-one 192

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{C} & \quad \text{N} \\
\text{O} & \quad \text{HO}
\end{align*}
\]

192

The reaction was carried out as described above using (2R,3R)-1-chloroacetylamino-3-(4-iodophenyl)propane-2,3-diol 191 (0.18 g, 0.47 mmol). This gave (2R,3R)-2-[α-hydroxy-(4-iodophenyl)methyl]morpholine-5-one 192 as a white solid (0.12 g, 76%). νmax/cm⁻¹ (NaCl) 3375 (NH/OH), 2880 (CH), 1663 (CO), 1483, 1118; [α]D²⁴ -19.6 (c 1.0, CHCl₃); δH (400 MHz, CDCl₃) 2.90 (1H, d, J 11.8 Hz, 3-HH), 3.10 (1H, br s, OH), 3.31 (1H, t, J 11.8 Hz, 3-HH), 3.64-3.69 (1H, m, 2-H), 4.20 (1H, d, J 16.8 Hz, 6-HH), 4.35 (1H, d, J 16.8 Hz, 6-HH), 4.58 (1H, d, J 7.2 Hz, 2-CH), 6.70 (1H, br s, NH), 7.10 (2H, d, J 8.2 Hz, 2 x Ar H), 7.71 (2H, d, J 8.2 Hz, 2 x Ar H); δC (100 MHz, CDCl₃) 42.9 (CH₂), 67.7 (CH₂), 74.4 (CH), 76.9 (CH), 94.5 (C), 128.7 (2 x CH), 137.9 (2 x CH), 138.3 (C), 168.6 (C); m/z (Cl) 333.9942 (MH⁺. C11H13O3NI requires 333.9940), 316 (6%), 208 (100), 190 (15), 113 (9).
(2S,3S)-2-[α-Hydroxy-(4-iodophenyl)methyl]-N-tert-butoxycarbonylmorpholine 156

(2S,3S)-2-[α-Hydroxy-(4-iodophenyl)methyl]morpholine-5-one 180 (0.29 g, 0.86 mmol) was dissolved in tetrahydrofuran and the solution cooled to 0 °C. Borane.dimethyl sulfide complex (1.39 mL, 2.77 mmol) was added dropwise and the reaction mixture stirred at 0 °C for 0.2 h, allowed to warm to room temperature and stirred for 0.5 h before being heated under reflux for 18 h. The reaction mixture was quenched by the careful addition of water (10 mL) and the organic solvent removed in vacuo. The residue was dissolved in 6 M hydrochloric acid (10 mL) and the mixture stirred for 1 h before the solution was concentrated in vacuo. The residue was dissolved in 1 M sodium hydroxide solution (20 mL) and the aqueous solution extracted with ethyl acetate (3 x 20 mL). The organic portions were combined, dried (MgSO₄) and the filtrate concentrated in vacuo. The crude material (0.28 g) was dissolved in dichloromethane (10 mL) and triethylamine (0.13 mL, 0.95 mmol), dimethylaminopyridine (0.01 g, 0.09 mmol) and di-tert-butyl dicarbonate (0.21 g, 0.95 mmol) added sequentially and the reaction mixture stirred at room temperature for 18 h. The reaction mixture was concentrated in vacuo and purification carried out using flash column chromatography. Elution with 30:70 ethyl acetate-petroleum ether (40-60) gave (2S,3S)-2-[α-hydroxy-(4-iodophenyl)methyl]-N-tert-butoxycarbonylmorpholine 156 as a colourless oil (0.15 g, 40%). νmax/cm⁻¹ (NaCl) 3434 (OH), 2976 (CH), 2863, 1686 (CO), 1480, 1454; [α]D²⁷ +27.8 (c 1.0, CHCl₃); δH (400 MHz, CDCl₃) 1.40 (9H, s, 3 x CH₃), 2.60-2.76 (1H, m, 3-HH), 2.94 (1H, t, J 11.4 Hz, 5-HH), 3.40 (1H, ddd, J 10.0, 7.2, 2.6 Hz, 2-H), 3.50 (1H, td, J 11.4, 2.8 Hz, 6-HH), 3.56-3.66 (1H, m, 3-HH), 3.78 (1H, br d, J 11.4 Hz, 5-HH), 3.92 (1H, br dd, J 11.4, 2.0 Hz, 6-HH), 4.46 (1H, d, J 7.2 Hz, 2-CH), 7.08 (2H, d, J 8.2 Hz, 2 x Ar H), 7.66 (2H, d, J 8.2 Hz, 2 x Ar H); δC (100 MHz, CDCl₃) 28.3 (3 x CH₃), 43.7 (CH₂), 44.3 (CH₂), 66.4 (CH₂), 74.6 (CH), 79.0 (CH), 80.3 (C), 94.0 (C), 128.8 (2 x CH), 137.6 (2 x CH), 139.0 (C), 154.6 (C); m/z (EI) 419.0598 (M⁺). C₁₆H₂₂O₄NI requires 419.0594, 233 (24%), 187 (58), 130 (91), 86 (53), 57 (100).
(2R,3R)-2-[α-Hydroxy-(4-iodophenyl)methyl]-N-tert-butoxycarbonylmorpholine 194

This reaction was carried out as described above using (2R,3R)-2-[α-hydroxy-(4-iodophenyl)methyl]morpholine-5-one 192 (0.11 g, 0.32 mmol). This gave (2R,3R)-2-[α-hydroxy-(4-iodophenyl)methyl]-N-tert-butoxycarbonylmorpholine 194 as a colourless oil (0.05 g, 56%). νmax /cm⁻¹ (NaCl) νmax/cm⁻¹ (NaCl) 3422 (OH), 2975 (CH), 2863, 1687 (CO), 1481, 1421; [α]D [25] -20.8 (c 0.9, CHCl₃); δH (400 MHz, CDCl₃) 1.40 (9H, s, C(CH₃)₃), 2.68-2.83 (1H, m, 3-HH), 2.96 (1H, t, J 11.2 Hz, 5-HH), 3.06 (1H, br s, OH), 3.41 (1H, ddd, J 10.0, 7.2, 2.6 Hz, 2-H), 3.53 (1H, td, J 11.6, 2.6 Hz, 6-HH), 3.58-3.69 (1H, m, 3-HH), 3.80 (1H, br d, J 11.2 Hz, 5-HH), 3.95 (1H, br dd, J 11.6, 2.0 Hz, 6-HH), 4.49 (1H, d, J 7.2 Hz, 2-CH), 7.11 (2H, d, J 8.0 Hz, 2 x Ar H), 7.69 (2H, d, J 8.0 Hz, 2 x Ar H); δC (100 MHz, CDCl₃) 28.3 (3 x CH₃), 43.8 (CH₂), 44.3 (CH₂), 66.4 (CH₂), 74.6 (CH), 79.0 (CH), 80.3 (C), 94.0 (C), 128.8 (2 x CH), 137.6 (2 x CH), 139.0 (C), 154.7 (C); m/z (FAB⁺) 420.0660 (MH⁺. C₁₆H₂₃O₄NI requires 420.0672), 346 (50%), 302 (30), 217 (31), 130 (22).

1-Ethoxy-2-fluorobenzene 185²⁴

2-Fluorophenol (4.0 mL, 44.6 mmol), bromoethane (5.0 mL, 66.9 mmol) and potassium carbonate (12.3 g, 89.2 mmol) were dissolved in acetone (90 mL) and the reaction mixture stirred at 55 °C for 18 h. The reaction mixture was filtered and concentrated under reduced pressure to give 1-ethoxy-2-fluorobenzene 185 as a yellow oil (6.06 g, 97%). δH (400 MHz, CDCl₃) 1.40 (3H, t, J 7.2 Hz, OCH₂CH₃), 4.04 (2H, d, J 7.2 Hz, OCH₂CH₃), 6.80-6.86 (1H, m, 1 x Ar H), 6.90 (1H, dt, J 8.2, 1.6 Hz, 1 x Ar H), 6.98-7.06 (2H, m, 2 x Ar H); δC (100 MHz, CDCl₃) 14.8 (CH₃), 64.7 (CH₂), 114.7 (CH), 116.3 (d, J 18.0 Hz, CH), 120.9 (d, J 7.0 Hz, CH), 124.3 (d, J 3.0 Hz, CH), 147.0 (d, J 11.0 Hz, C), 152.7 (d, J 243 Hz, C);
m/z (EI) 140.0634 (M⁺, C₇H₈OF requires 140.0637), 112 (100%), 92 (12), 83 (10), 64 (17), 57 (6).

η⁶-(1-Ethoxy-2-fluorobenzene)tricarbonylchromium 186

1-Ethoxy-2-fluorobenzene 185 (0.50 g, 3.57 mmol) was dissolved in a mixture of dibutyl ether (25 mL) and tetrahydrofuran (25 mL). Chromium hexacarbonyl (1.18 g, 5.36 mmol) was added and the reaction mixture heated to 145 °C for 42 h in the dark. The reaction mixture was cooled to room temperature and the solution filtered and concentrated in vacuo. Purification was carried out by flash column chromatography and elution with 15:85 diethyl ether/petroleum ether (40-60) gave η⁶-(1-ethoxy-2-fluorobenzene)tricarbonylchromium 186 as a green solid (0.14 g, 14%). mp 76-77 °C, lit. 75-77 °C (from diethyl ether); δₜ (400 MHz, CDCl₃) 1.47 (3H, t, J 6.8 Hz, OCH₂CH₃), 4.00-4.10 (2H, m, OCH₂CH₃), 5.00-5.07 (2H, m, 2 x Ar H), 5.25-5.27 (1H, m, 1 x Ar H), 5.60-5.62 (1H, m, 1 x Ar H); δ₵ (100 MHz, CDCl₃) 14.6 (CH₃), 66.9 (CH₂), 78.1 (CH), 82.4 (d, J 18.0 Hz, CH), 85.4 (d, J 5.0 Hz, CH), 88.8 (CH), 131.2 (d, J 8.1 Hz, C), 134.8 (d, J 263 Hz, C), 232.2 (C); m/z (EI) 275.9889 (M⁺, C₁₁H₉O₄FCr requires 275.9890) 220 (11%), 192 (100), 164 (20), 143 (28).

(2S,3S)-2-[(4-Iodophenyl)-(2-ethoxyphenoxy)methyl]-N-tert-butoxycarbonylmorpholine 187

Sodium hydride (0.02 g, 0.8 mmol, 60% dispersion in mineral oil) was washed once with petroleum ether (40-60) and then dissolved in N,N-dimethylformamide (2 mL). A solution of (2S,3S)-2-[α-hydroxy-(4-iodophenyl)methyl]-N-tert-butoxycarbonylmorpholine 156 in N,N-dimethylformamide (0.05 g, 0.13 mmol in 1.5 mL) was added to the basic solution dropwise and the reaction mixture stirred for 1.5 h. A solution of η⁶-(1-ethoxy-2-
fluorobenzene)tricarbonylchromium \(186\) in \(N,N\)-dimethylformamide (0.05 g, 0.20 mmol in 1.5 mL) was added to the reaction mixture and left to stir for 3.5 h. The reaction mixture was cooled to 0 °C and an iodine solution (0.20 g, 0.79 mmol in 0.6 mL of tetrahydrofuran) was added and the mixture stirred for 0.5 h. Sodium thiosulfate solution (10% w/v, 20 mL) was added and the solution extracted with ethyl acetate (3 x 20 mL). The organic portions were combined and washed with water (2 x 40 mL) before being dried (MgSO\(_4\)) and the filtrate concentrated in vacuo. Purification was carried out by flash column chromatography and elution with 30:70 ethyl acetate-petroleum ether (40-60) gave (2S,3S)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)methyl]-\(N\)-tert-butoxycarbonylmorpholine \(187\) as a colourless oil (0.04 g, 63%).

\[
\begin{align*}
\text{ν}_{\text{max/cm}}^\text{-1} \text{ (NaCl)} & = 2977 \text{ (CH)}, 1695 \text{ (CO)}, 1591 \text{ (C=C), } 1500, 1478; \ \left[\alpha\right]_D^{22} & = +78.6 \text{ (c } 1.0, \text{ CHCl}_3) ; \ \delta_H (400 \text{ MHz, CDCl}_3) & = 1.42-1.44 \text{ (12H, m, 3 x } CH_3, \text{ OCH}_2CH_3), 2.76-2.98 \text{ (2H, br m, 5-H}_2\text{), } 3.52 \text{ (1H, td, } J = 11.6, 2.4 \text{ Hz, 6-}HH\text{), } 3.78-3.85 \text{ (3H, m, 2-H, 3-H), } 3.92-3.98 \text{ (1H, m, 6-}HH\text{), } 4.05 \text{ (2H, q, } J = 6.8 \text{ Hz, OCH}_2CH_3), 5.09-5.15 \text{ (1H, br m, 2-CH), } 6.69-6.79 \text{ (2H, m, 2 x Ar H), } 6.83-6.91 \text{ (2H, m, 2 x Ar H), } 7.16 \text{ (2H, d, } J = 8.2 \text{ Hz, 2 x Ar H), } 7.64 \text{ (2H, d, } J = 8.2 \text{ Hz, 2 x Ar H); } \delta_C (100 \text{ MHz, CDCl}_3) & = 15.0 \text{ (CH}_3), 28.3 \text{ (3 x } CH_3), 46.5 \text{ (CH}_2), 47.2 \text{ (CH}_2), 64.4 \text{ (CH}_2), 66.7 \text{ (CH}_2), 77.4 \text{ (CH), 79.9 (C), 82.2 (CH), 93.9 (C), 113.9 (CH), 118.8 (CH), 120.7 (CH), 122.9 (CH), 127.4 (C), 129.4 (2 x CH), 137.3 (2 x CH), 147.3 (C), 150.1 (C), 154.8 (C); m/z (EI) & = 539.1168 \text{ (M}^+\text{). C}_{24}H_{30}O_NI \text{ requires 539.1169), 402 (18%), 346 (100), 302 (90), 217 (39), 176 (25).}
\end{align*}
\]

(2R,3R)-2-[(4-Iodophenyl)-(2-ethoxyphenoxy)methyl]-\(N\)-tert-butoxycarbonylmorpholine \(195\)

The reaction was carried out as described above using (2R,3R)-2-\([\alpha\text{-hydroxy-(4-iodophenyl)methyl]}-N\text{-tert-butoxycarbonylmorpholine }194\) (0.04 g, 0.11 mmol). This gave (2R,3R)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)methyl]-\(N\)-tert-butoxycarbonylmorpholine \(195\) as a colourless oil (0.04 g, 67%).

\[
\begin{align*}
\text{ν}_{\text{max/cm}}^\text{-1} \text{ (NaCl)} & = 2977 \text{ (CH), 1695 \text{ (CO)}, 1590 \text{ (C=C), } 1500, 1479; \ \left[\alpha\right]_D^{26} & = -68.4 \text{ (c } 1.1, \text{ CHCl}_3) ; \ \delta_H (400 \text{ MHz, CDCl}_3) & = 1.42-1.44 \text{ (12H, m, 3 x } CH_3, \text{ OCH}_2CH_3), 2.76-2.98 \text{ (2H, br m, 5-H}_2\text{), } 3.52 \text{ (1H, t, } J = 10.4 \text{ Hz, 6-}HH\text{), } 3.77-3.85 \text{ (3H, m, 2-H, 3-H), } 3.94 \text{ (1H, d, } J = 10.4 \text{ Hz, 6-}HH\text{), } 4.05 \text{ (2H, q, } J = 6.8 \text{ Hz, OCH}_2CH_3), 5.09-5.15 \text{ (1H, br m, 2-CH), 6.70-6.76 \text{ (2H, m, 2 x Ar H), } 6.83-6.90 \text{ (2H, m, 2 x Ar H),}
\end{align*}
\]
7.16 (2H, d, J 8.0 Hz, 2 x Ar H), 7.64 (2H, d, J 8.0 Hz, 2 x Ar H); δc (100 MHz, CDCl3) 15.1 (CH3), 28.4 (3 x CH3), 46.5 (CH2), 47.2 (CH2), 64.5 (CH2), 66.8 (CH2), 77.4 (CH), 80.1 (C), 82.0 (CH), 93.9 (C), 113.9 (CH), 118.8 (CH), 120.8 (CH), 122.9 (CH), 127.4 (C), 129.4 (2 x CH), 137.3 (2 x CH), 147.3 (C), 150.1 (C), 154.8 (C); m/z (EI) 539.1166 (M+.
C24H30O5NI requires 539.1169), 402 (19%), 346 (100), 302 (88), 217 (38), 176 (5).

(2S,3S)-2-[(4-Iodophenyl)-(2-ethoxyphenoxy)methyl]morpholine 128

Trifluoroacetic acid (1.0 mL, 0.06 mmol) was added to a solution of (2S,3S)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)methyl]-N-tert-butoxycarbonylmorpholine 187 (0.02 g, 0.04 mmol) in dichloromethane (5 mL). The reaction mixture was allowed to stir at room temperature for 4 h. The reaction mixture was concentrated in vacuo and the crude material dissolved in dichloromethane (10 mL) and washed with saturated sodium hydrogen carbonate solution (10 mL). The organic layer was removed, dried (MgSO4) and the filtrate concentrated in vacuo to give (2S,3S)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)methyl]morpholine 128 as a colourless oil (0.01 g, 60%). νmax/cm⁻¹ (NaCl) 3422 (NH), 2923 (CH), 1637 (C=C), 1591, 1252; [α]D²² +54.6 (c 1.0, CHCl3); δH (400 MHz, CDCl3) 1.42 (3H, t, J 7.0 Hz, OCH₂CH₃), 2.68-2.76 (1H, m, 5-HH), 2.83-2.86 (3H, m, 3-H₂, 5-HH), 3.62-3.68 (1H, m, 6-HH), 3.90 (1H, ddd, J 10.0, 5.2, 2.4 Hz, 2-H), 3.97 (1H, m, 6-HH), 4.04 (2H, qd, J 7.0, 1.6 Hz, OCH₂CH₃), 5.08 (1H, d, J 5.2 Hz, 2-CH), 6.70-6.76 (2H, m, 2 x Ar H), 6.82-6.89 (2H, m, 2 x Ar H), 7.14 (2H, d, J 8.4 Hz, 2 x Ar H), 7.64 (2H, d, J 8.4 Hz, 2 x Ar H); δc (100 MHz, CDCl3) 15.0 (CH3), 45.4 (CH2), 46.9 (CH2), 64.5 (CH2), 67.7 (CH2), 78.5 (CH), 82.5 (CH), 93.7 (C), 114.0 (CH), 118.3 (CH), 120.8 (CH), 122.7 (CH), 129.3 (2 x CH), 137.3 (2 x CH), 137.7 (C), 147.7 (C), 150.0 (C); m/z (EI) 439.0643 (M⁺. C₁₉H₂₂O₅NI requires 439.0644), 301 (100%), 217 (42), 175 (28), 138 (15), 110 (22).
(2R,3R)-2-[(4-Iodophenyl)-(2-ethoxyphenoxy)methyl]morpholine 129

The reaction was carried out as described above using (2R,3R)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)methyl]-N-tert-butoxy carbonylmorpholine 197 (0.02 g, 0.04 mmol). This gave (2R,3R)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)methyl]morpholine 129 as a colourless oil (0.01 g, 67%). $\nu_{\text{max}}$/cm$^{-1}$ (NaCl) 3422 (NH), 2923 (CH), 1637 (C=C), 1591, 1252; $[\alpha]_D^{26} -44.3$ (c 1.2, CHCl$_3$); $\delta_H$ (400 MHz, CDCl$_3$) 1.42 (3H, t, $J$ 7.0 Hz, OCH$_2$CH$_3$), 2.82-2.88 (1H, m, 5-H/H), 2.93-2.99 (3H, m, 3-H$_2$, 5-H/H), 3.70-3.76 (1H, m, 2-H), 4.00-4.09 (4H, m, 6-H$_2$, OCH$_2$CH$_3$), 5.08 (1H, d, $J$ 4.8 Hz, 2-CH), 6.71-6.73 (2H, m, 2 x Ar H), 6.83-6.91 (2H, m, 2 x Ar H), 7.12 (2H, d, $J$ 8.2 Hz, 2 x Ar H), 7.65 (2H, d, $J$ 8.2 Hz, 2 x Ar H); $\delta_C$ (100 MHz, CDCl$_3$) 15.0 (CH$_3$), 45.4 (CH$_2$), 46.9 (CH$_2$), 64.5 (CH$_2$), 67.7 (CH$_2$), 78.5 (CH), 82.5 (CH), 93.7 (C), 114.0 (CH), 118.3 (CH), 120.8 (CH), 122.7 (CH), 129.3 (2 x CH), 137.3 (2 x CH), 137.7 (C), 147.7 (C), 150.0 (C); m/z (EI) 439.0643 (M$^+$. C$_{19}$H$_{22}$O$_3$NI requires 439.0644), 301 (100%), 217 (42), 175 (28), 138 (15), 110 (22).

3.3 Synthesis of (2R,3S)-Iodoanalogues

(2S,3R)-1-Chloro-3-phenylpropane-2,3-diol 203

AD-mix-$\beta$ (11.3 g) was dissolved in a mixture of water (140 mL) and tert-butanol (140 mL). Methanesulfonamide (2.66 g, 28.0 mmol) and sodium hydrgencarbonate (7.06 g, 84.0 mmol) were added and the bright orange solution cooled to 0 °C. Cinnamyl chloride 204 (3.90 mL, 28.0 mmol) was added and the solution stirred vigorously at 0 °C for 96 h. Sodium sulfite (35.0 g, 0.3 mol) was added and the solution left to stir for 1 h before being concentrated in vacuo. The residue was dissolved in water (250 mL) and the aqueous solution extracted with ethyl acetate (3 x 250 mL). The combined organic fractions were washed with 2 M potassium hydroxide (250 mL), dried (MgSO$_4$) and the filtrate
concentrated in vacuo. Purification was carried out by flash column chromatography and elution with 30:70 ethyl acetate-petroleum ether (40-60) gave (2S,3R)-1-chloro-3-phenylpropane-2,3-diol 203 as a colourless oil (3.46 g, 66%). $[\alpha]_D^{24} -2.6$ ($c$ 1.0, EtOH), lit. 73 $[\alpha]_D -3.0$ ($c$ 1.0, EtOH); $\delta_H$ (400 MHz, CDCl$_3$) 2.95-2.98 (2H, m, 2 x OH), 3.38 (1H, dd, $J$ 11.6, 5.6 Hz, 1-HH), 3.55 (1H, dd, $J$ 11.6, 3.8 Hz, 1-HH), 3.86-3.91 (1H, m, 2-H), 4.72 (1H, dd, $J$ 6.8, 3.4 Hz, 3-H), 7.30-7.38 (5H, m, 5 x Ar H); $\delta_C$ (100 MHz, CDCl$_3$) 44.2 (CH$_2$), 74.8 (CH), 75.5 (CH), 126.7 (2 x CH), 128.5 (CH), 128.8 (2 x CH), 139.8 (C); $m/z$ (EI) 150 (33%), 107 (100), 105 (32), 79 (98), 77 (89).

**(1R,2R)-2,3-Epoxy-1-phenylpropan-1-ol 202**

(2S,3R)-1-Chloro-3-phenylpropane-2,3-diol 203 (2.82 g, 15.1 mmol) and pulverised sodium hydroxide (1.21 g, 30.2 mmol) were dissolved in tetrahydrofuran (300 mL). The mixture was cooled to 0 °C and left to stir for 24 h. The reaction mixture was poured onto water (300 mL) and the aqueous solution extracted using dichloromethane (3 x 300 mL). The organic fractions were combined, dried (MgSO$_4$) and the filtrate concentrated in vacuo to give (1R,2R)-2,3-epoxy-1-phenylpropan-1-ol 202 as a yellow oil (2.10 g, 92%). $\nu_{\text{max}}$ cm$^{-1}$ (NaCl) 3422 (OH), 3031 (CH), 1603 (C=O), 1255, 1046; $[\alpha]_D^{22} -13.1$ ($c$ 1.0, CHCl$_3$); $\delta_H$ (400 MHz, CDCl$_3$) 2.75 (1H, d, $J$ 5.0 Hz, OH), 2.81-2.86 (2H, m, 3-H$_2$), 3.20-3.23 (1H, m, 2-H), 4.45 (1H, t, $J$ 5.0 Hz, 1-H), 7.30-7.43 (5H, m, 5 x Ar H); $\delta_C$ (100 MHz, CDCl$_3$) 45.5 (CH$_2$), 56.1 (CH), 74.6 (CH), 126.3 (2 x CH), 128.3 (CH), 128.7 (2 x CH), 140.1 (C); $m/z$ (CI) 151.0758 (MH$^+$ C$_9$H$_{11}$O$_2$ requires 151.0759), 133 (100%), 107 (57), 105 (11), 79 (9).
(2R,3R)-1-Chloroacetylamino-3-phenylpropane-2,3-diol 201

![Chemical Structure](image)

(1R,2R)-2,3-Epoxy-1-phenylpropan-1-ol 202 (2.09 g, 13.9 mmol) was dissolved in acetonitrile (200 mL) and ammonia solution (200 mL) added with stirring. The reaction mixture was stirred at room temperature for 22 h before being concentrated in vacuo. The residue was dissolved in water (250 mL) and extracted with ethyl acetate (250 mL). The pH of aqueous layer was adjusted to pH 12 and extracted with ethyl acetate (2 x 250 mL). The combined organic layers were dried (MgSO₄) and the filtrate concentrated in vacuo. The crude material (2.13 g) was dissolved in acetonitrile (250 mL) and the mixture cooled to -10 °C. Triethylamine (2.13 mL, 15.3 mmol) and chloroacetyl chloride (1.07 mL, 14.0 mmol) were added sequentially and the solution stirred at -10 °C for 1 h. The reaction mixture was allowed to warm to room temperature and left to stir for 18 h before being concentrated in vacuo. The residue was dissolved in saturated ammonium chloride solution and extracted with ethyl acetate (200 mL). The organic fraction was filtered to remove the brown triethylamine salt, dried (MgSO₄) and the filtrate concentrated in vacuo. Purification was carried out by flash column chromatography and elution with 90:10 ethyl acetate-petroleum ether (40-60) gave (2R,3R)-1-chloroacetylamino-3-phenylpropane-2,3-diol 201 as a yellow oil (0.85 g, 25%). ν\textsubscript{max}/cm\textsuperscript{-1} (NaCl) 3410 (NH/OH), 1654 (CO), 1543 (C=C), 1493, 1263, 1084; [α]\textsubscript{D}\textsuperscript{21} -22.6 (c 1.0, CHCl₃); δ\textsubscript{H} (400 MHz, CDCl₃) 2.99 (1H, br s, OH), 3.24-3.31 (1H, m, 1-HH), 3.40-3.46 (1H, m, 1-HH), 3.83-3.93 (1H, m, 2-H), 4.03 (2H, s, CH₂Cl), 4.55 (1H, d, J 6.4 Hz, 3-H), 6.95 (1H, br s, NH), 7.30-7.42 (5H, m, 5 x Ar H); δ\textsubscript{C} (100 MHz, CDCl₃) 42.4 (CH₂), 42.5 (CH₂), 74.5 (CH), 75.4 (CH), 126.6 (2 x CH), 128.5 (CH), 128.8 (2 x CH), 140.0 (C), 167.1 (C); m/z (CI) 244.0729 (MH\textsuperscript{+}. C\textsubscript{11}H\textsubscript{14}O\textsubscript{3}N\textsuperscript{25}Cl requires 244.0740) 246 (23%), 244 (67), 228 (34), 226 (100), 210 (23), 208 (19), 136 (21).
(2R,3R)-2-[α-Hydroxyphenylmethyl]morpholine-5-one 205

\[
\begin{align*}
\text{(2R,3R)-2-[α-Hydroxyphenylmethyl]morpholine-5-one 205}
\end{align*}
\]

Sodium tert-butoxide (1.00 g, 10.4 mmol) was dissolved in tert-butanol (20 mL). (2R,3R)-1-chloroacetylamino-3-phenylpropane-2,3-diol 201 (0.85 g, 3.48 mmol) dissolved in tert-butanol (30 mL) was added dropwise to the basic solution and the reaction mixture heated to 40 °C and allowed to stir for 5 h. The solution was acidified to pH 1 with hydrochloric acid and the solution concentrated in vacuo. The residue was suspended in water (200 mL) and the aqueous solution extracted with ethyl acetate (3 x 200 mL). The organic portions were combined, dried (MgSO₄), and the filtrate concentrated in vacuo to give (2R,3R)-2-[α-hydroxyphenylmethyl]morpholine-5-one 205 as a colourless oil (0.42 g, 58%).

\(\nu_{\text{max}}/\text{cm}^{-1} (\text{NaCl}) 3370 (\text{NH/OH}), 2883 (\text{CH}), 1663 (\text{CO}), 1495, 1119; [\alpha]_D^{24} +22.3 (c 1.0, \text{CHCl}_3)\)

\(\delta_H (400 \text{ MHz, CDCl}_3) 2.81 (1\text{H, d, } J 11.8 \text{ Hz, 3-HH}), 3.03 (1\text{H, br s, OH}), 3.23 (1\text{H, t, } J 11.8 \text{ Hz, 3-HH}), 3.72-3.77 (1\text{H, m, 2-H}), 4.15 (1\text{H, d, } J 16.6 \text{ Hz, 6-HH}), 4.30 (1\text{H, d, } J 16.6 \text{ Hz, 6-HH}), 4.58 (1\text{H, d, } J 7.6 \text{ Hz, 2-CH}), 7.08 (1\text{H, br s, NH}), 7.31-7.35 (5\text{H, m, 5 x Ar H}); \delta_C (100 \text{ MHz, CDCl}_3) 42.9 (\text{CH}_2), 67.5 (\text{CH}_2), 75.0 (\text{CH}), 77.1 (\text{CH}), 126.8 (2 \text{x CH}), 128.8 (3 \text{x CH}), 138.6 (\text{C}), 169.0 (\text{C}); m/z (\text{Cl}) 208.0973 (\text{MH}^+)\). C₁₁H₁₄O₃N requires 208.0974. 208 (100%), 190 (12), 133 (1), 101 (3), 69 (2).

(2R,3R)-2-(α-Hydroxyphenylmethyl)-N-tert-butoxycarbonylmorpholine 200

(2R,3R)-2-[α-Hydroxyphenylmethyl]morpholine-5-one 205 (0.39 g, 1.87 mmol) was dissolved in tetrahydrofuran (25 mL) and the solution cooled to 0 °C. Borane.dimethyl sulfide complex (3.0 mL, 6.0 mmol) was added dropwise and the reaction mixture stirred at 0 °C for 0.2 h, allowed to warm to room temperature and stirred for 0.5 h before being heated under reflux for 18 h. The reaction mixture was quenched by the careful addition of
water (20 mL) and the organic solvent removed \textit{in vacuo}. The residue was dissolved in 5 M hydrochloric acid (20 mL) and the mixture stirred for 1 h before the solution was concentrated \textit{in vacuo}. The residue was dissolved in 1 M sodium hydroxide solution (50 mL) and the aqueous solution extracted with ethyl acetate (3 x 50 mL). The organic portions were combined, dried (MgSO$_4$) and the filtrate concentrated \textit{in vacuo}. The crude material (0.24 g, 1.24 mmol) was dissolved in dichloromethane (25 mL) and triethylamine (0.19 mL, 1.36 mmol), dimethylaminopyridine (0.03 g, 0.25 mmol) and di-tert-butyl dicarbonate (0.30 g, 1.36 mmol) added sequentially and the reaction mixture stirred at room temperature for 18 h. The reaction mixture was concentrated \textit{in vacuo}. Purification was carried out by flash column chromatography and elution with 20:80 ethyl acetate-petroleum ether (40-60) gave (2$R$,3$R$)-2-(\alpha-hydroxyphenylmethyl)-N-tert-butoxycarbonylmorpholine 200 as a white solid (0.21 g, 37\%). $\nu_{\max}$/cm$^{-1}$ (KBr) 3438 (OH), 2972 (CH), 1702 (CO), 1431, 1113; $\left[\alpha\right]_D^{28}$ -42.5 ($c$ 1.0, CHCl$_3$); $\delta_H$ (400 MHz, CDCl$_3$) 1.39 (9H, s, 3 x CH$_3$), 2.61-2.81 (1H, br m, 3-\textit{H})H, 2.93-2.97 (1H, m, 5-\textit{H}), 3.00 (1H, s, OH), 3.47 (1H, m, 2-H), 3.56 (1H, td, $J$ 11.6, 2.8 Hz, 6-\textit{H}), 3.61-3.69 (1H, br m, 3-\textit{H}), 3.81 (1H, br d, $J$ 11.6 Hz, 5-\textit{H}), 3.97 (1H, d, $J$ 11.6, 1.6 Hz, 6-\textit{H}), 4.53 (1H, dd, $J$ 7.4, 2.2 Hz, 2-CH), 7.31-7.36 (5H, m, 5 x Ar H); $\delta_C$ (100 MHz, CDCl$_3$) 28.3 (3 x CH$_3$), 43.5 (CH$_2$), 44.8 (CH$_2$), 66.4 (CH$_2$), 75.3 (CH), 79.3 (CH), 80.1 (C), 126.9 (3 x CH), 128.4 (CH), 128.6 (CH), 139.2 (C), 154.7 (C); $m/z$ (CI) 294.1708 (MH$^+$. C$_{16}$H$_{24}$O$_4$N requires 294.1705), 276 (12%), 238 (40), 220 (100), 176 (12), 136 (4).

(2$R$,3$R$)-2-(\alpha-Methanesulfonyloxyphenylmethyl)-N-tert-butoxycarbonylmorpholine 207

(2$R$,3$R$)-2-(\alpha-Hydroxyphenylmethyl)-N-tert-butoxycarbonylmorpholine 200 (0.19 g, 0.64 mmol) was dissolved in dichloromethane (4 mL) and triethylamine (0.13 mL, 0.96 mmol), dimethylaminopyridine (0.02 g, 0.13 mmol) and methanesulfonyl chloride (0.07 mL, 0.96 mmol) added sequentially and the reaction mixture stirred at room temperature for 18 h. The reaction mixture was acidified to pH 1 with hydrochloric acid and the organic layer separated, dried (MgSO$_4$) and the filtrate concentrated \textit{in vacuo}. Purification was carried out by flash column chromatography and elution with 40:60 ethyl acetate-petroleum ether
(40-60) gave \((2R,3R)-2-(\alpha\text{-methanesulfonyloxyphenylmethyl})-N\text{-}t\text{ert}-\text{butoxycarbonylmorpholine} \, 207\) as a white solid (0.18 g, 74%). \(\nu_{\text{max}}/\text{cm}^{-1}\) (KBr) 2986 (CH), 2865, 1698 (CO), 1476 (C=C), 1410; \([\alpha]_D^{21}\) -64.2 (c 1.0, CHCl\(_3\)); \(\delta_H\) (400 MHz, CDCl\(_3\)) 1.39 (9H, s, 3 x CH\(_3\)), 2.51-2.69 (1H, br m, 3-\(HH\)), 2.85 (3H, s, SO\(_2\)CH\(_3\)), 2.93-3.00 (1H, m, 5-\(HH\)), 3.40-3.50 (1H, br m, 3-\(HH\)), 3.55 (1H, td, \(J = 11.6\) Hz, 6-\(HH\)), 3.72-3.85 (2H, m, 2-\(H\), 5-\(HH\)), 3.98 (1H, d, \(J = 11.6\) Hz, 6-\(HH\)), 5.42 (1H, d, \(J = 7.6\) Hz, 2-\(CH\)), 7.35-7.43 (5H, m, 5 x Ar \(H\)); \(\delta_C\) (100 MHz, CDCl\(_3\)) 28.2 (3 x CH\(_3\)), 39.1 (CH\(_3\)), 43.4 (CH\(_2\)), 44.1 (CH\(_2\)), 66.3 (CH\(_2\)), 76.6 (CH), 80.3 (C), 84.4 (CH), 127.5 (3 x CH), 129.1 (CH), 129.8 (CH), 134.4 (C), 154.5 (C); \(m/z\) (EI) 371.1402 (M\(^+\), C\(_{17}\)H\(_{26}\)O\(_6\)NS requires 371.1403), 243 (3%), 219 (9), 202 (11), 174 (26), 130 (100).

**General procedure 1: Nucleophilic displacement of the mesylate**

Cesium carbonate (1.2 eq.) and the iodophenol (1.2 eq.) were dissolved in dioxane and the solution heated under reflux for 1 h. The mesylate (1 eq.) was then added and the reaction heated under reflux for a further 24 h. The reaction mixture was concentrated *in vacuo* and the residue dissolved in water (10 mL). The aqueous solution was extracted with ethyl acetate (3 x 10 mL) and the organic fractions combined, dried (MgSO\(_4\)) and the filtrate concentrated *in vacuo*.

\((2R,3S)-2\text{-[2-Iodophenoxy)phenylmethyl]-}\text{N\text{-}t\text{ert}-butoxycarbonylmorpholine} \, 208\)

The reaction was carried out according to general procedure 1 using \((2R,3R)-2-(\alpha\text{-methanesulfonyloxyphenylmethyl})-N\text{-}t\text{ert}-\text{butoxycarbonylmorpholine} \, 207\) (0.08 g, 0.22 mmol) and 2-iodophenol (0.06 g, 0.26 mmol). Purification was carried out by flash column chromatography and elution with 10:90 ethyl acetate-petroleum ether (40-60) gave \((2R,3S)-2\text{-[2-Iodophenoxy)phenylmethyl]-}\text{N\text{-}t\text{ert}-butoxycarbonylmorpholine} \, 208\) as a colourless oil (0.05 g, 47%). \(\nu_{\text{max}}/\text{cm}^{-1}\) (NaCl) 2974 (CH), 2860 (CH), 1694 (CO), 1470 (C=C), 1243; \([\alpha]_D^{22}\) -79.6 (c 1.0, CHCl\(_3\)); \(\delta_H\) (400 MHz, CDCl\(_3\)) 1.44 (9H, s, 3 x CH\(_3\)), 2.91-3.06 (1H, br m, 3-\(HH\)), 3.07-3.30 (1H, br m, 5-\(HH\)), 3.55 (1H, td, \(J = 11.6\) Hz, 6-\(HH\)), 3.76-3.85 (2H, m, 2-\(H\), 5-\(HH\)), 4.20-4.47 (1H, br m, 6-\(HH\)), 5.42 (1H, d, \(J = 7.6\) Hz, 2-\(CH\)), 7.35-7.43 (5H, m, 5 x Ar \(H\)); \(\delta_C\) (100 MHz, CDCl\(_3\)) 28.2 (3 x CH\(_3\)), 39.1 (CH\(_3\)), 43.4 (CH\(_2\)), 44.1 (CH\(_2\)), 66.3 (CH\(_2\)), 76.6 (CH), 80.3 (C), 84.4 (CH), 127.5 (3 x CH), 129.1 (CH), 129.8 (CH), 134.4 (C), 154.5 (C); \(m/z\) (EI) 371.1402 (M\(^+\), C\(_{17}\)H\(_{26}\)O\(_6\)NS requires 371.1403), 243 (3%), 219 (9), 202 (11), 174 (26), 130 (100).
5.13-5.26 (1H, br m, 2-CH), 6.55 (1H, d, J 8.0 Hz, 1 x Ar H), 6.62 (1H, t, J 8.0 Hz, 1 x Ar H), 7.06 (1H, t, J 8.0 Hz, 1 x Ar H), 7.25-7.39 (5H, m, 5 x Ar H), 7.74 (1H, d, J 8.0 Hz, 1 x Ar H); δC (100 MHz, CDCl3) 28.4 (3 x CH3), 43.0 (CH2), 46.3 (CH2), 66.8 (CH2), 77.5 (C), 78.6 (CH), 81.2 (CH), 86.9 (C), 113.3 (CH), 122.7 (CH), 126.8 (CH), 128.3 (2 x CH), 128.8 (2 x CH), 129.2 (CH), 137.2 (C), 139.4 (CH), 154.8 (C), 155.8 (C); m/z (EI) 495.0903 (M+). C22H26O4NI requires 495.0907 439 (6%), 422 (5), 309 (25), 220 (100), 176 (84).

(2R,3S)-2-[(3-Iodophenoxy)phenylmethyl]-N-tert-butoxycarbonylmorpholine 209

The reaction was carried out according to general procedure 1 using (2R,3R)-2-(α-methanesulfonyloxyphenylmethyl)-N-tert-butoxycarbonylmorpholine 207 (0.04 g, 0.10 mmol) and 3-iodophenol (0.03 g, 0.12 mmol). Purification was carried out by flash column chromatography and elution with 10:90 ethyl acetate-petroleum ether (40-60) gave (2R,3S)-2-[(3-iodophenoxy)phenylmethyl]-N-tert-butoxycarbonylmorpholine 209 as a colourless oil (0.016 g, 32%). νmax/cm⁻¹ (NaCl) 2974 (CH), 2860 (CH), 1696 (CO), 1581 (C=C), 1470; [α]D²³ -34.3 (c 1.1, CHCl3); δH (400 MHz, CDCl3) 1.43 (9H, s, 3 x CH3), 2.98 (2H, m, 3-HH, 5-HH), 3.46 (1H, td, J 11.6, 2.8 Hz, 6-HH), 3.61-3.70 (1H, m, 2-H), 3.80-3.89 (2H, m, 3-HH, 5-HH), 3.99-4.29 (1H, br m, 6-HH), 5.08 (1H, d, J 5.6 Hz, 2-CH), 6.76 (1H, dd, J 8.0, 2.0 Hz, 1 x Ar H), 6.86 (1H, t, J 8.0 Hz, 1 x Ar H), 7.24-7.35 (6H, m, 6 x Ar H); δC (100 MHz, CDCl3) 27.0 (3 x CH3), 43.5 (CH2), 43.8 (CH2), 65.4 (CH2), 77.0 (CH), 78.7 (C), 79.3 (CH), 92.8 (C), 113.7 (CH), 124.2 (CH), 125.5 (2 x CH), 126.9 (CH), 127.2 (2 x CH), 128.9 (CH), 129.3 (CH), 136.0 (C), 153.4 (C), 156.8 (C); m/z (FAB+) 496.0985 (MH+). C22H27O4NI requires 496.0985, 440 (8%), 309 (14), 220 (100), 176 (62).
The reaction was carried out according to general procedure 1 using (2R,3R)-2-(α-methanesulfonyloxyphenylmethyl)-N-tert-butoxycarbonylmorpholine 207 (0.04 g, 0.10 mmol) and 4-iodophenol (0.03 g, 0.13 mmol). Purification was carried out by flash column chromatography and elution with 10:90 ethyl acetate-petroleum ether (40-60) gave (2R,3S)-2-[(4-iodophenoxy)phenylmethyl]-N-tert-butoxycarbonylmorpholine 210 as a colourless oil (0.026 g, 52%). ν_{\text{max}} /cm^{-1} (NaCl) 2973 (CH), 2860 (CH), 1696 (CO), 1581 (C=C), 1484; [\alpha]_D^{23} -17.7 (c 0.9, CHCl_3); δ_H (400 MHz, CDCl_3) 1.43 (9H, s, 3 x CH_3), 2.96-3.02 (2H, m, 3-HH, 5-HH), 3.46 (1H, td, J 11.6, 2.8 Hz, 5-HH), 3.60-3.72 (1H, m, 2-H), 3.74-3.91 (2H, m, 3-HH, 6-HH), 4.01-4.32 (1H, br m, 6-HH), 5.06 (1H, d, J 6.0 Hz, 2-CH), 6.61 (2H, d, J 8.8 Hz, 2 x Ar H), 7.29-7.34 (5H, m, 5 x Ar H), 7.43 (2H, d, J 8.8 Hz, 2 x Ar H); δ_C (100 MHz, CDCl_3) 28.4 (3 x CH_3), 43.7 (CH_2), 43.9 (CH_2), 66.8 (CH_2), 78.5 (CH), 80.2 (C), 80.7 (CH), 83.5 (C), 118.3 (2 x CH), 126.9 (2 x CH), 128.3 (CH), 128.6 (2 x CH), 137.4 (C), 138.2 (2 x CH), 154.8 (C), 157.5 (C); m/z (FAB\(^+\)) 496.0984 (MH\(^+\). C_{22}H_{27}O_{4}NI requires 496.0985), 440 (10%), 309 (24), 220 (100), 176 (98).

**General procedure 2: Deprotection of the morpholine nitrogen**

Trifluoroacetic acid (1 mL) was added to a solution of the protected morpholine compound (1 eq.) in dichloromethane (5 mL). The reaction mixture was allowed to stir at room temperature for 4 h. The reaction mixture was concentrated *in vacuo* and the residue dissolved in saturated sodium hydrogencarbonate (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, dried (MgSO_4) and the filtrate concentrated *in vacuo.*
(2R,3S)-2-[(2-Iodophenoxy)phenylmethyl]morpholine 196

The reaction was carried out according to general procedure 2 using (2R,3S)-2-[(2-iodophenoxy)phenylmethyl]-N-tert-butoxycarbonylmorpholine 208 (0.04 g, 0.09 mmol). Purification was carried out by flash column chromatography and elution with 90:10 ethyl acetate-methanol gave (2R,3S)-2-[(2-iodophenoxy)phenylmethyl]morpholine 196 as a colourless oil (0.03 g, 76%). ν\textsubscript{max}/cm\textsuperscript{-1} (NaCl) 3855 (NH), 2853 (CH), 1638, 1579 (C=C), 1469; [α]\textsubscript{D}\textsuperscript{24} -105.5 (c 0.9, CHCl\textsubscript{3}); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 2.28 (1H, br s, NH), 2.79-2.85 (1H, m, 5-HH), 2.95 (1H, td, J 11.4, 3.4 Hz, 5-HH), 3.09 (1H, dd, J 12.4, 10.0 Hz, 3-HH), 3.30 (1H, dd, J 12.4, 1.6 Hz, 3-HH), 3.58 (1H, td, J 11.4, 2.3 Hz, 6-HH), 3.76-3.82 (1H, m, 2-H), 3.90 (1H, dd, J 11.4, 2.3 Hz, 6-HH), 5.20 (1H, d, J 5.6 Hz, 2-CH), 6.55-6.65 (2H, m, 2 x Ar H), 7.04-7.09 (1H, m, 1 x Ar H), 7.25-7.38 (5H, m, 5 x Ar H), 7.73 (1H, d, J 10.4, 1.6 Hz, 1 x Ar H); δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 45.4 (CH\textsubscript{2}), 46.5 (CH\textsubscript{2}), 67.9 (CH\textsubscript{2}), 79.6 (CH), 81.4 (CH), 86.6 (C), 113.1 (CH), 122.2 (CH), 126.5 (2 x CH), 127.8 (CH), 128.2 (2 x CH), 128.8 (CH), 137.2 (C), 139.0 (CH), 155.6 (C); m/z (Cl) 396.0462 (MH\textsuperscript{+}. C\textsubscript{17}H\textsubscript{19}O\textsubscript{2}NI requires 396.0461), 268 (36%), 176 (100), 113 (16), 85 (36).

(2R,3S)-2-[(3-Iodophenoxy)phenylmethyl]morpholine 197

The reaction was carried out according to general procedure 2 using (2R,3S)-2-[(3-iodophenoxy)phenylmethyl]-N-tert-butoxycarbonylmorpholine 209 (0.02 g, 0.03 mmol). Purification was carried out by flash column chromatography and elution with 90:10 ethyl acetate-methanol gave (2R,3S)-2-[(3-iodophenoxy)phenylmethyl]morpholine 197 as a white solid (0.01 g, 80%). ν\textsubscript{max}/cm\textsuperscript{-1} (KBr) 3426 (NH), 2958 (CH), 1583 (C=C), 1470, 1239; [α]\textsubscript{D}\textsuperscript{25} -19.7 (c 1.0, CHCl\textsubscript{3}); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 1.89 (1H, br s, NH), 2.76-2.83
(1H, m, 5-\(H_H\)), 2.86-2.94 (2H, m, 3-\(H_H\), 5-\(H_H\)), 3.12 (1H, dd, \(J 12.4, 1.6\) Hz, 3-\(H_H\)), 3.56 (1H, td, \(J 11.4, 2.8\) Hz, 6-\(H_H\)), 3.73 (1H, m, 2-H), 3.88 (1H, dd, \(J 11.4, 2.0\) Hz, 6-\(H_H\)), 5.07 (1H, d, \(J 6.0\) Hz, 2-\(CH\)), 6.76 (1H, ddd, \(J 8.4, 2.4, 0.8\) Hz, 1 x Ar H), 6.86 (1H, t, \(J 8.0\) Hz, 1 x Ar H), 7.20 (1H, ddd, \(J 7.6, 1.4, 0.8\) Hz, 1 x Ar H), 7.25-7.30 (5H, m, 5 x Ar H), 7.34 (1H, d, \(J 4.4\) Hz, 1 x Ar H); \(\delta_C\) (100 MHz, CDCl\(_3\)) 43.7 (CH\(_2\)), 44.8 (CH\(_2\)), 66.3 (CH\(_2\)), 77.7 (CH), 79.1 (CH), 92.1 (C), 113.0 (CH), 123.6 (CH), 124.8 (2 x CH), 126.1 (CH), 126.5 (2 x CH), 128.2 (CH), 128.5 (CH), 135.7 (C), 156.3 (C); \(m/z\) (FAB\(^+\)) 396.0449 (MH\(^+\). \(\text{C}_{17}\text{H}_{19}\text{O}_2\text{NI}\) requires 396.0461), 338 (8%), 288 (11), 177 (90), 119 (14).

\textbf{(2R,3S)-2-[(4-Iodophenoxy)phenylmethyl]morpholine 198}

![Chemical Structure](image)

The reaction was carried out according to general procedure 2 using (2R,3S)-2-[(4-iodophenoxy)phenylmethyl]-\(N\)-\(\text{ tert\text{-}butyloxycarbonyl}\)morpholine 210 (0.02 g, 0.04 mmol). Purification was carried out by flash column chromatography and elution with 90 : 10 ethyl acetate-methanol gave (2R,3S)-2-[(4-iodophenoxy)phenylmethyl]morpholine 198 as a colourless oil (0.009 g, 55%). \(\nu_{\text{max}}/\text{cm}^{-1}\) (NaCl) 3423 (NH), 2955 (CH), 1638 (C=C), 1483, 1237; \([\alpha]_{D}^{25} +17.0\) (c 0.9, CHCl\(_3\)); \(\delta_H\) (400 MHz, CDCl\(_3\)) 1.83 (1H, br s, NH), 2.80 (1H, m, 5-\(H_H\)), 2.86-2.94 (2H, m, 3-\(H_H\), 5-\(H_H\)), 3.13 (1H, d, \(J 12.0\) Hz, 3-\(H_H\)), 3.56 (1H, td, \(J 11.2, 2.2\) Hz, 6-\(H_H\)), 3.71-3.76 (1H, m, 2-H), 3.89 (1H, dd, \(J 11.2, 2.2\) Hz, 6-\(H_H\)), 5.05 (1H, d, \(J 6.0\) Hz, 2-\(CH\)), 6.61 (2H, d, \(J 8.8\) Hz, 2 x Ar H), 7.29-7.33 (5H, m, 5 x Ar H), 7.43 (2H, d, \(J 8.8\), 2 x Ar H); \(\delta_C\) (100 MHz, CDCl\(_3\)) 45.7 (CH\(_2\)), 46.8 (CH\(_2\)), 68.4 (CH\(_2\)), 79.8 (CH), 81.1 (CH), 83.3 (C), 118.4 (2 x CH), 126.9 (2 x CH), 128.1 (CH), 128.5 (2 x CH), 137.8 (C), 138.1 (2 x CH), 157.7 (C); \(m/z\) (CI) 396.0456 (MH\(^+\). \(\text{C}_{17}\text{H}_{19}\text{O}_2\text{NI}\) requires 396.0461) 338 (6%), 282 (3), 270 (9), 176 (100).
3.3.1 Radioligand binding methodology

Whole brains, excluding the cerebellum, were obtained from male adult Sprague-Dawley rats and homogenised using a Polytron in ice-cold binding buffer (1 g :10 mL volumes) for the relevant transporter (see Table 12). Homogenates were centrifuged at 25,400 g for 15 minutes at 4 °C and the resulting pellet was washed (3x) by centrifugation and resuspension. Final resuspension was stored in aliquots at -50 °C until use.

Table 12

<table>
<thead>
<tr>
<th>Transporter Assay</th>
<th>Radioligand</th>
<th>Binding Buffer and Incubation Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noradrenaline Transporter (NAT)</td>
<td>1.2 nM [3H]nisoxetine (71.0 Ci/mmol, GE Healthcare)</td>
<td>50 mM Tris-HCl, pH 7.4</td>
</tr>
<tr>
<td>Modified from: ref 94</td>
<td></td>
<td>300 mM NaCl</td>
</tr>
<tr>
<td>Serotonin Transporter (SERT)</td>
<td>0.4 nM [3H]citalopram (83.0 Ci/mmol, GE Healthcare)</td>
<td>50 mM Tris-HCl, pH 7.4</td>
</tr>
<tr>
<td>Modified from: ref 95</td>
<td></td>
<td>120 mM NaCl</td>
</tr>
<tr>
<td>Dopamine Transporter (DAT)</td>
<td>4.7 nM [3H]WIN-35,428 (85.9 Ci/mmol, Perkin-Elmer)</td>
<td>25 mM NaH2PO4</td>
</tr>
<tr>
<td>Modified from: refs 96-98</td>
<td></td>
<td>25 mM Na2HPO4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mM NaCl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pH 7.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incubation: 2 hours at 4 °C</td>
</tr>
</tbody>
</table>

For determination of $K_i$ values, triplicate aliquots of membrane suspensions (750-850 µg of protein) were incubated in 0.5 mL volumes as detailed in Table 1 in the presence or absence of 12-20 concentrations of the competitor (range 1 pM - 300 µM). Non-specific binding was defined in the presence of 10 µM reboxetine (Tocris), 20 µM fluoxetine (Tocris), and 30 µM nomifensine (Sigma-Aldrich) for NAT, SERT, and DAT assays, respectively. Reactions were terminated by rapid vacuum filtration through Whatman GF/B glass fibre filters pre-soaked in 0.5% polyethylenimine in relevant binding buffer using a 24-well Brandel cell harvester. Filters received three rapid washes in ice-cold binding buffer and [3H] counts were determined by liquid scintillation analysis. $K_i$ values were derived from nonlinear regression analysis using GraphPad Prism Version 4 (GraphPad Software Inc.) and $K_d$ values for [3H]nisoxetine (1.7 nM) and [3H]citalopram (2.1 nM) binding to the NAT and SERT, respectively, were determined under the same assay conditions. A $K_d$ estimation for [3H]WIN-35,428 (5.0 nM) binding to the high
affinity site on the DAT was selected by a review of published literature.\textsuperscript{97,98} Data is presented as mean ± SEM for three independent competition experiments with [\textsuperscript{3}H]nisoxetine and two independent competition experiments with [\textsuperscript{3}H]citalopram and [\textsuperscript{3}H]WIN-35,428.

### 3.4 Steps Towards Oxazinin-3

(2S)-\textit{tert}-Butoxycarbonylamino-3-(4-hydroxyphenyl)propionic acid 235\textsuperscript{99}

\begin{center}
\textbf{235}
\end{center}

L-Tyrosine 234 (5.0 g, 27.6 mmol) and potassium hydroxide (1.7 g, 30.4 mmol) were dissolved in a mixture of dioxane (75 mL) and water (75 mL). Di-\textit{tert}-butyl dicarbonate (6.63 g, 30.4 mmol) was added and the reaction mixture stirred at room temperature for 18 h. The crude reaction mixture was concentrated \textit{in vacuo} and the residue dissolved in water (100 mL). The aqueous solution was extracted with ethyl acetate (3 x 100 mL) and the organic fractions combined, dried and the filtrate concentrated \textit{in vacuo} to give (2S)-\textit{tert}-butoxycarbonylamino-3-(4-hydroxyphenyl)propionic acid 235 as a white solid (7.72 g, 100%). mp 138-139 °C, lit.\textsuperscript{99} 137-138 °C; \(\delta_H\) (400 MHz, CDCl\textsubscript{3}) 1.22 (9H, s, 3 x CH\textsubscript{3}), 2.64 (1H, dd, \(J\) 13.8, 4.8 Hz, 3-\(H_H\)), 2.94 (1H, dd, \(J\) 13.8, 4.8 Hz, 3-\(H_H\)), 3.98-4.01 (1H, m, 2-H), 6.69 (2H, d, \(J\) 8.2 Hz, 2 x Ar H), 7.00 (2H, d, \(J\) 8.2 Hz, 2 x Ar H); \(\delta_C\) (100 MHz, CDCl\textsubscript{3}) 27.6 (3 x CH\textsubscript{3}), 37.3 (CH\textsubscript{2}), 57.4 (CH), 80.9 (C), 115.5 (2 x CH), 130.6 (2 x CH), 154.7 (C), 156.1 (C), 157.3 (C), 179.2 (C); \textit{m/z} (FAB) 275 (5%), 231 (9), 192 (100), 180 (8), 57 (25).

Methyl (2S)-\textit{tert}-butoxycarbonylamino-3-(4-methoxyphenyl)propanoate 236\textsuperscript{100}

\begin{center}
\textbf{236}
\end{center}

(2S)-\textit{tert}-Butoxycarbonylamino-3-(4-hydroxyphenyl)propionic acid 235 (3.0 g, 10.7 mmol) was dissolved in \(N,N\)-dimethylformamide (53 mL) and potassium carbonate (8.86 g, 64.2 mmol) and methyl iodide (4.66 mL, 74.9 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 18 h before being diluted with ethyl
acetate (200 mL) and the organic layer washed with water (100 mL). The organic layer was dried (MgSO₄) and the filtrate concentrated in vacuo. Purification was carried by flash column chromatography and elution with 30:70 ethyl acetate-petroleum ether (40-60) gave methyl (2S)-tert-butoxycarbonylamino-3-(4-methoxyphenyl)propanoate 236 as a white solid (1.90 g, 58%). \[\alpha\]D²⁵ +50.3 (c 1.8, CHCl₃), lit.¹⁰⁰ \[\alpha\]D²⁵ +59.2 (c 1.8, CHCl₃); δH (400 MHz, CDCl₃) 1.42 (9H, s, 3 x CH₃), 2.96-3.08 (2H, m, 3-H₂), 3.70 (3H, s, OCH₃), 3.77 (3H, s, OCH₃), 4.53 (1H, dd, J 8.0, 6.0 Hz, 2-H), 5.04 (1H, d, J 8.0 Hz, NH), 6.82 (2H, d, J 8.6 Hz, 2 x Ar H), 7.03 (2H, d, J 8.6 Hz, 2 x Ar H); δC (100 MHz, CDCl₃) 28.3 (3 x CH₃), 37.4 (CH₂), 52.1 (CH₃), 54.6 (CH), 55.2 (CH₃), 79.8 (C), 114.0 (2 x CH), 128.0 (C), 130.3 (2 x CH), 155.1 (C), 158.6 (C), 172.5 (C); m/z (CI) 310 (MH⁺, 4%), 284 (19), 254 (100), 210 (51), 192 (12).

(2S)-N-tert-Butoxycarbonyl-3-(4-methoxyphenyl)propan-1-ol 237¹⁰⁰

Methyl (2S)-tert-butoxycarbonylamino-3-(4-methoxyphenyl)propanoate 236 (1.44 g, 4.66 mmol) was dissolved in a mixture of tetrahydrofuran (4.66 mL) and propanol (41 mL) and the solution cooled to 0 °C. Lithium borohydride (0.51 g, 23.3 mmol) was added and the reaction mixture stirred at 0 °C for 0.3 h before being allowed to warm to room temperature and stirred for 20 h. The reaction mixture was quenched with 0.5 M hydrochloric acid (80 mL) and then extracted with ethyl acetate (3 x 120 mL). The organic fractions were combined, dried (MgSO₄) and the filtrate concentrated in vacuo. Purification was carried out by flash column chromatography and elution with 50:50 ethyl acetate-petroleum ether (40-60) gave (2S)-N-tert-butoxycarbonyl-3-(4-methoxyphenyl)propan-1-ol 237 as a white solid (1.06 g, 81%). \[\alpha\]D²⁴ -21.3 (c 1.0, CHCl₃), lit.¹⁰⁰ \[\alpha\]D²⁰ -22.9 (c 1.0, CHCl₃); δH (400 MHz, CDCl₃) 1.42 (9H, s, 3 x CH₃), 2.52 (1H, br s, OH), 2.77 (2H, d, J 6.8 Hz, 3-H₂), 3.51-3.56 (1H, m, 1-HH), 3.61-3.68 (1H, m, 1-HH), 3.78-3.88 (4H, m, 2-H, OCH₃), 4.76 (1H, d, J 8.0 Hz, NH), 6.84 (2H, d, J 8.6 Hz, 2 x Ar H), 7.12 (2H, d, J 8.6 Hz, 2 x Ar H); δC (100 MHz, CDCl₃) 28.4 (3 x CH₃), 36.5 (CH₂), 53.9 (CH), 55.3 (CH₃), 64.4 (CH₂), 79.7 (C), 114.0 (2 x CH), 129.8 (C), 130.3 (2 x CH), 156.3 (C), 158.3 (C); m/z (CI) 282 (MH⁺, 69%), 226 (100), 208 (41), 182 (58), 121 (12).
(2S)-2-Amino-3-(4-methoxyphenyl)propan-1-ol hydrochloride 231\(^{101}\)

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \\
\text{HO} & \quad \text{OMe} \\
\text{233} & \quad \text{HCl}
\end{align*}
\]

(2S)-N-tert-Butoxycarbonyl-3-(4-methoxyphenyl)propan-1-ol 237 (1.02 g, 3.63 mmol) was dissolved in 6 M hydrochloric acid (70 mL) and the mixture stirred at room temperature for 20 h. The reaction mixture was concentrated in vacuo to give (2S)-2-amino-3-(4-methoxyphenyl)propan-1-ol hydrochloride 231 as a white solid (0.76 g, 96%). mp 223-225 °C; \(\delta_H\) (400 MHz, D\(_2\)O) 2.75 (1H, dd, \(J 14.4, 7.4\) Hz, 3-HH), 2.86 (1H, dd, \(J 14.4, 6.4\) Hz, 3-HH), 3.43-3.55 (3H, m, 1-H\(_2\), 2-H), 3.72 (3H, s, OCH\(_3\)), 6.89 (2H, d, \(J 8.6\) Hz, 2 x Ar H), 7.13 (2H, d, \(J 8.6\) Hz, 2 x Ar H); \(\delta_C\) (100 MHz, D\(_2\)O) 33.8 (CH\(_2\)), 54.4 (CH), 55.3 (CH\(_3\)), 60.5 (CH\(_2\)), 114.5 (2 x CH), 127.9 (C), 130.5 (2 x CH), 158.0 (C); \(m/z\) (CI) 182 (MH\(^+\), 100%), 164 (3), 150 (2), 121 (5), 85 (13).

Quinidine 9-O-(9’-phenanthryl) ether 239\(^{82}\)

\[
\begin{align*}
\text{OMe} & \quad \text{RO} \\
\text{H} & \quad \text{H} \\
\text{239} & \quad \text{R} = \quad \text{9’-phenanthryl}
\end{align*}
\]

Quinidine 238 (2.0 g, 6.2 mmol) was dissolved in dimethyl sulfoxide (20 mL) and sodium hydride (0.4 g, 7.71 mmol, 60% dispersion in mineral oil) was added portion-wise to yield a cloudy yellow solution of the sodium alkoxide. Pyridine (1.0 mL, 12.3 mmol) and copper iodide (1.17 g, 6.17 mmol) were added and the solution turned dark orange/brown. After 0.5 h, 9-iodophenanthrene (1.56 g, 5.14 mmol) was added and the solution heated to 120 °C for 70 h. The reaction mixture was cooled to room temperature and water (20 mL), dichloromethane (20 mL) and diethyl ether (20 mL) were added followed by ethylenediaminetetraacetate disodium salt dihydrate (3.0 g) and concentrated aqueous ammonia solution (3 mL, 25%). The solution was stirred vigorously for 1 h before the aqueous and organic phases were separated and the aqueous layer washed with dichloromethane (2 x 20 mL). The combined organic layers were washed with aqueous ammonia solution (20 mL, 5%) followed by 1 M hydrochloric acid (2 x 20 mL) and water (3 x 20 mL) to remove the excess quinidine. The organic layer was then washed with
ammonium hydroxide solution (20 mL), dried (MgSO₄) and the filtrate concentrated in vacuo. The residue was dissolved in diethyl ether (20 mL) and treated with ethereal hydrochloric acid until no further precipitates were generated. The solid was collected and dissolved in dichloromethane and basified to pH 13 using aqueous ammonium hydroxide solution. The organic was washed with brine, dried (MgSO₄) and the filtrate concentrated in vacuo to give quinidine 9-O-(9'-phenanthryl) ether 239 as a white foam (1.20 g, 39%).

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[\alpha]_D^{23} -311.0 \text{ (c 0.9, EtOH);} \delta_H (400 MHz, CDCl₃) 1.50-1.60 (3H, m, 5-H₂, 7-HH), 1.91-1.98 (1H, br m, 7-HH), 2.30-2.36 (1H, m, 4-H), 2.41-2.51 (1H, m, 3-H), 2.77-2.85 (1H, m, 6-HH), 2.96-3.05 (2H, m, 2-H₂), 3.32-3.38 (2H, m, 8-H, 6-HH), 4.02 (3H, s, OCH₃), 5.11 (1H, d, \text{J} 17.2 \text{ Hz, 3-CHCHH}), 5.18 (1H, d, \text{J} 10.2 \text{ Hz, 3-CHCHH}), 6.16 (1H, ddd, \text{J} 17.2, 10.2, 6.4 \text{ Hz, 3-CH}), 6.36-6.37 (1H, br m, 9-H), 6.66 (1H, s, 1 x Ar H), 7.34-7.48 (5H, m, 5 x Ar H), 7.52-7.56 (1H, br m, 1 x Ar H), 7.69-7.74 (2H, m, 2 x Ar H), 8.07 (1H, d, \text{J} 9.2 \text{ Hz, 1 x Ar H}), 8.50 (1H, d, \text{J} 7.6 \text{ Hz, 1 x Ar H}), 8.60 (1H, d, \text{J} 4.4 \text{ Hz, 1 x Ar H}), 8.65-8.75 (2H, m, 2 x Ar H); \delta_C (100 MHz, CDCl₃) 22.1 (CH₂), 26.5 (CH₂), 27.8 (CH), 39.6 (CH), 50.0 (CH₂), 50.3 (CH₂), 55.8 (CH₃), 60.5 (CH), 78.8 (CH), 100.8 (CH), 104.9 (CH), 114.8 (CH₂), 118.2 (CH), 121.9 (CH), 122.4 (CH), 122.7 (CH), 122.8 (CH), 124.6 (CH), 126.4 (C), 126.5 (CH), 126.6 (C), 126.7 (C), 126.9 (CH), 127.3 (CH), 127.5 (CH), 131.5 (C), 132.2 (CH), 132.3 (C), 140.3 (CH), 143.7 (C), 144.8 (C), 147.8 (CH), 150.4 (C), 158.2 (C); m/z (FAB⁺) 501 (MH⁺, 100%), 307 (25), 213 (4), 173 (8), 139 (8).

(9S)-6'-Hydroxycinchonan-9-O-(9'-phenanthryl) ether 240

Quinidine 9-O-(9'-phenanthryl) ether 239 (0.50 g, 1.0 mmol) was dissolved in N,N'-dimethylformamide (7 mL) and sodium ethanethiolate (0.34g, 4.0 mmol) was added with stirring. The reaction mixture was heated to 110 °C for 5 h before being cooled to room temperature. Saturated ammonium chloride solution (10 mL) and water (10 mL) were added with stirring and the aqueous layer extracted with ethyl acetate (2 x 40 mL). The combined organic layers were washed with brine (4 x 10 mL) and then dried (MgSO₄) and the filtrate concentrated in vacuo. Purification was carried out using flash column chromatography and elution with 95:5 ethyl acetate-methanol gave (9S)-6'-hydroxycinchonan-9-O-(9'-phenanthryl) ether 241 (0.23 g, 47%). [\alpha]_D^{25} -220.7 (c 1.0,
1-Benzylindole 245

Potassium hydroxide (0.38 g, 6.84 mmol) was dissolved in dimethyl sulfoxide and the solution allowed to stir for 0.2 h before indole 232 (0.2 g, 1.71 mmol) was added and the reaction mixture was allowed to stir for 0.75 h. Benzyl bromide (0.4 mL, 3.42 mmol) was added and the reaction mixture stirred for 1.5 h. The reaction mixture was diluted with water (10 mL) and the aqueous solution extracted with diethyl ether (3 x 10 mL). Each diethyl ether layer was then washed with water (3 x 10 mL) and the combined organic layers dried (MgSO₄) and the filtrate concentrated in vacuo. Purification was carried out using flash column chromatography and elution with 100% petroleum ether (40-60) gave 1-benzylindole 245 as a colourless oil (0.29 g, 81%). δH (400 MHz, CDCl₃) 5.31 (2H, s, CH₂Ph), 6.55 (1H, d, J 3.2 Hz, 3-H), 7.09-7.18 (4H, m, 2-H, 3 x Ar H), 7.23-7.30 (5H, m, 5 x Ar H), 7.65 (1H, d, J 7.6 Hz, 1 x Ar H).
Titanium tetraisopropoxide (0.13 mL, 0.43 mmol) and (S)-BINOL (0.24 g, 0.85 mmol) were dissolved in diethyl ether (9 mL) and the solution stirred at room temperature for 1 h. The solution was cooled to -20 °C and indole 232 (0.5 g, 4.27 mmol) and ethyl glyoxylate (1.3 mL, 6.4 mmol) were added and the reaction mixture stirred for 96 h. Purification was carried out using flash column chromatography and elution with 20:80 diethyl ether-petroleum ether (40-60) gave ethyl 3-indolyl-2-hydroxyacetate 241 as a colourless oil (0.4 g, 42%).

δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 1.21 (3H, t, J 7.2 Hz, OCH<sub>2</sub>C<sub>H</sub><sub>3</sub>), 3.36 (1H, br s, OH), 4.12-4.16 (1H, dq, J 10.8, 7.2 Hz, CHHCH<sub>2</sub>), 4.29 (1H, dq, J 10.8, 7.2 Hz, CHHCH<sub>2</sub>), 5.46 (1H, s, 2-H), 7.11-7.22 (3H, m, NHCH, 2 x Ar H), 7.33 (1H, d, J 8.2 Hz, 1 x Ar H), 7.71 (1H, d, J 8.2 Hz, 1 x Ar H), 8.26 (1H, br s, NH); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 14.1 (CH<sub>3</sub>), 62.1 (CH<sub>2</sub>), 67.3 (CH), 111.4 (CH), 113.8 (C), 119.4 (1 x CH), 120.1 (1 x CH), 122.5 (1 x CH), 123.3 (1 x CH), 125.3 (C), 136.4 (C), 174.1 (C); m/z (CI) 219 (MH<sup>+</sup>, 13%), 202 (100), 146 (8), 103 (41), 81 (10).
4 References


42 Images obtained from a Neurofocus SPECT scanner at the Southern General Hospital.


