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

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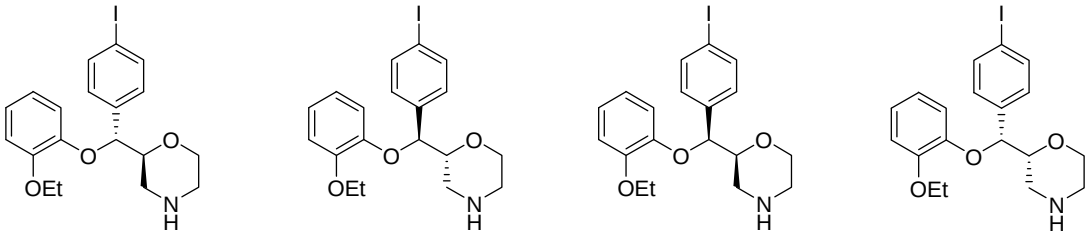
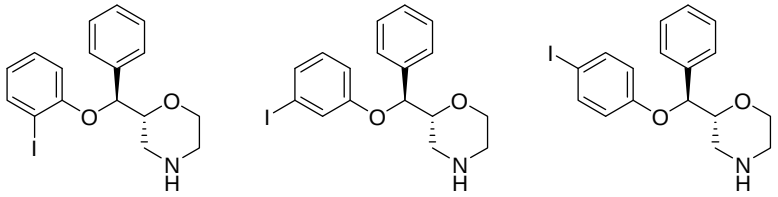
Abstract

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 (2*R*,3*S*)-stereoisomer, which was identified as being as potent as the more studied (2*S*,3*S*)-stereoisomer. Therefore, a new series of iodoanalogues based on the (2*R*,3*S*)-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.

R. Bischoff, D. J. Hamilton, N. K. Jobson and A. Sutherland, *J. Labelled Compds. Radiopharm*., 2007, **50**, 323.

N. K. Jobson, R. Spike, A. R. Crawford, D. Dewar, S. L. Pimlott and A. Sutherland, *Org. Biomol. Chem*., 2008, **6**, 2369.

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Abbreviations

aq.	aqueous
Boc	*tert*-butoxycarbonyl
br	broad
^{o}C	degrees Celsius
cat.	catalytic
$CDCl_3$	deuterated chloroform
CI	chemical ionisation
COMT	catechol *O*-methyl transferase
d	doublet
DA	dopamine
DAT	dopamine transporter
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCM	dichloromethane
dd	doublet of doublets
DIBAL-H	diisobutylaluminium hydride
DMF	*N*,*N*'-dimethylformamide
DMSO	dimethyl sulfoxide
dq	doublet of quartets
dt	doublet of triplets
EDCI	1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride
e.e.	enantiomeric excess
E.I.	electron impact
eq.	equivalents
Et	ethyl
Et_2O	diethyl ether
EtOH	ethanol
FAB	fast atom bombardment
g	gram(s)
h	hour(s)
HCl	hydrochloric acid
5-HT	serotonin
Hz	hertz
IR	infrared
J	NMR spectra coupling constant

K_i	inhibition constant
µL	microlitre
L	litre or ligand
lit.	literature
µM	micromolar
M	molar
m	multiplet
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitors
Me	methyl
MeOH	methanol
mg	milligram
MHz	megahertz
mL	millilitre
mM	millimolar
mol	mole(s)
MOM	methyoxymethyl
mp	melting point
Ms	methanesulfonyl
NA	noradrenaline
NARI	noradrenaline reuptake inhibitor
NAT	noradrenaline transporter
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ph	phenyl
PPTS	pyridinium *p*-toluenesulfonate
q	quartet
quin.	quintet
ROESY	rotational frame nuclear Overhauser effect spectroscopy
RT	room temperature
s	singlet
SEM	standard error of mean
SERT	serotonin transporter
SSRI	selective serotonin reuptake inhibitors
t	triplet
T3P	1-propanephosphonic anhydride

TBACl	tetrabutylammonium chloride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TClA	trichloroisocyanuric acid
TEMPO	tetramethylpiperidine *N*-oxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	*p*-toluenesulfonyl

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.[2,3]

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).

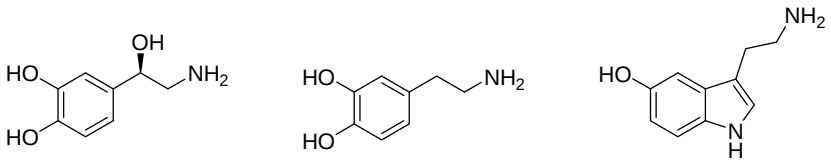


Figure 1

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.

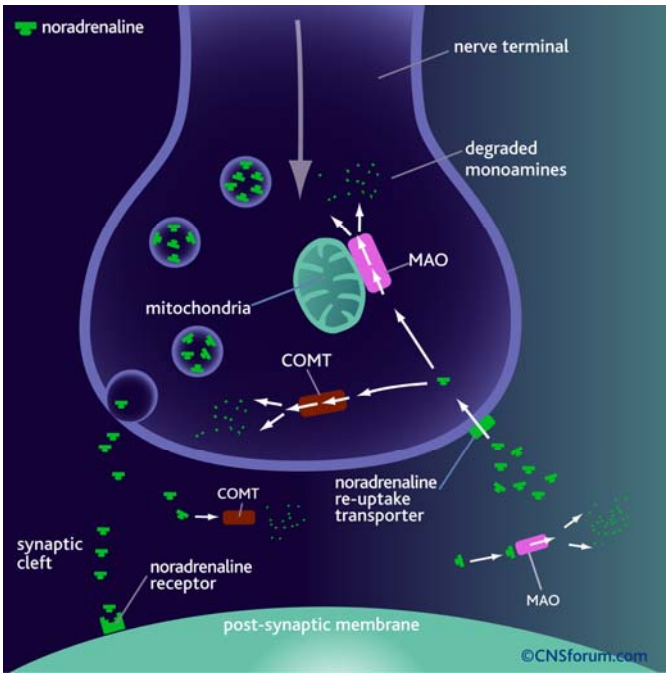


Figure 2

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 noradrenic neurons and its main function is to terminate the action of noradrenaline.[8] 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.[9-12]

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.[13]

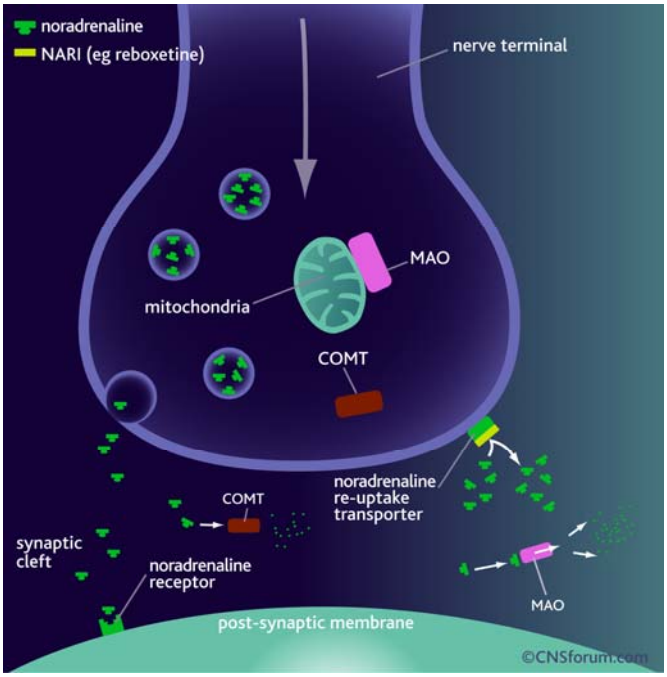


Figure 3

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.[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.[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.

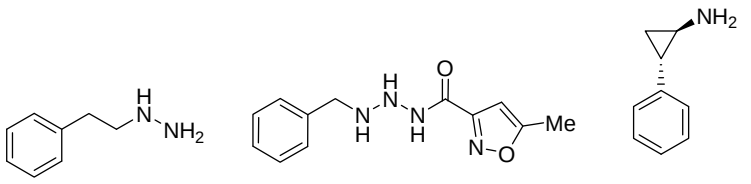
1.3 Clinical Antidepressants

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).[17,18]



Phenelzine Isocarboxazid Tranylcypromine

Figure 4

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.[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.

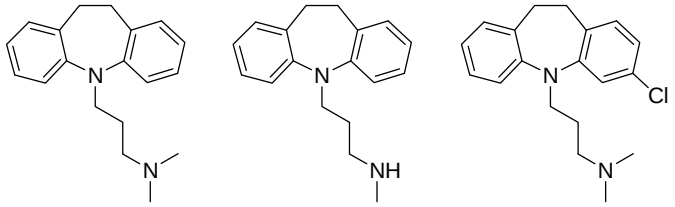


Figure 5

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]

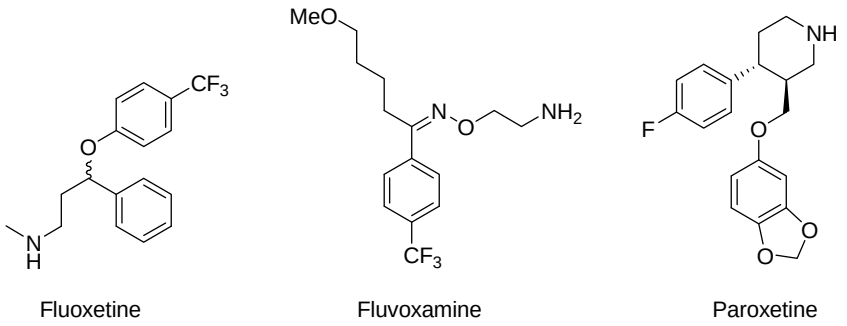


Figure 6

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]

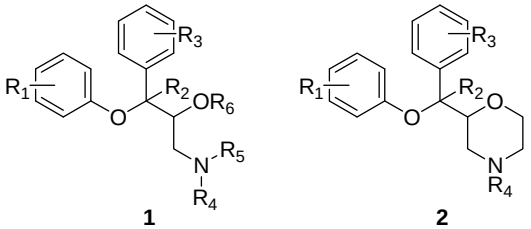
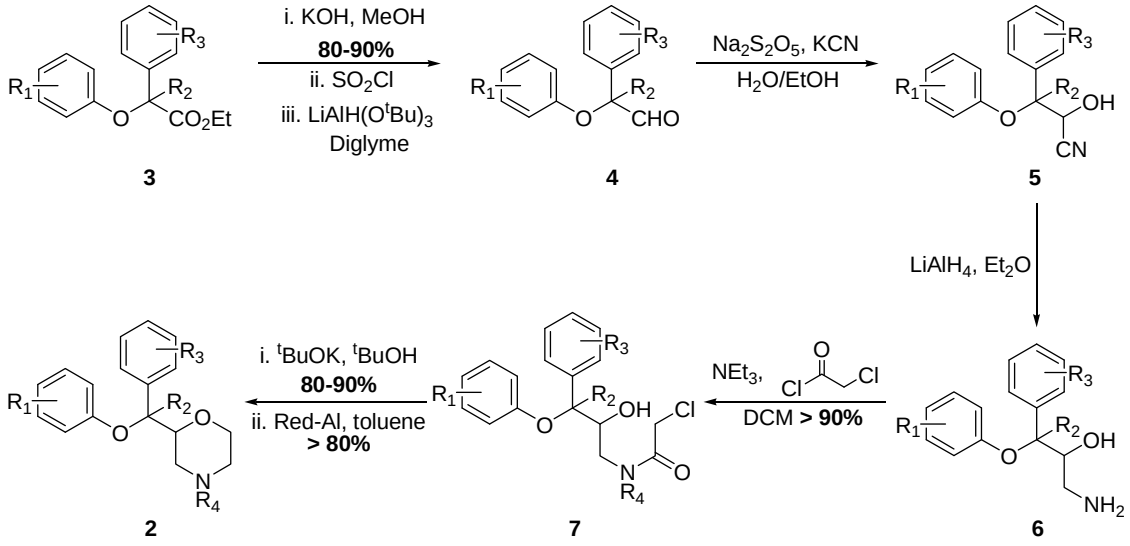


Figure 7

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**.

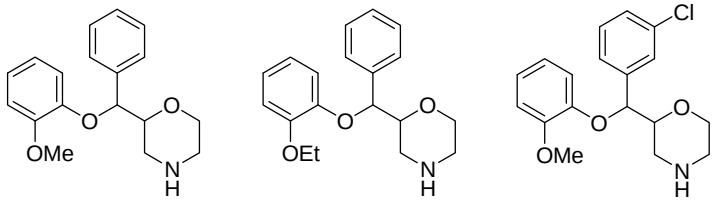


Scheme 1

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-methoxy or 2-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 = 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 CH_2, NH, NMe or S resulted in a significant loss of activity.

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



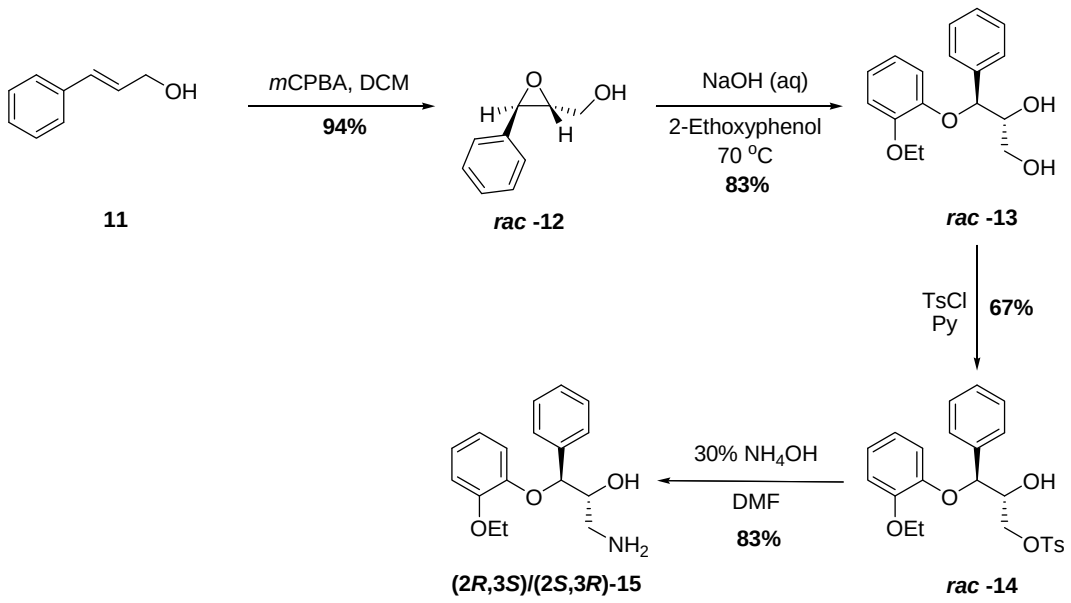
8 **9** **10**

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 ^{o}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*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 ^{o}C, and was therefore not the correct intermediate for the synthesis of **9**.

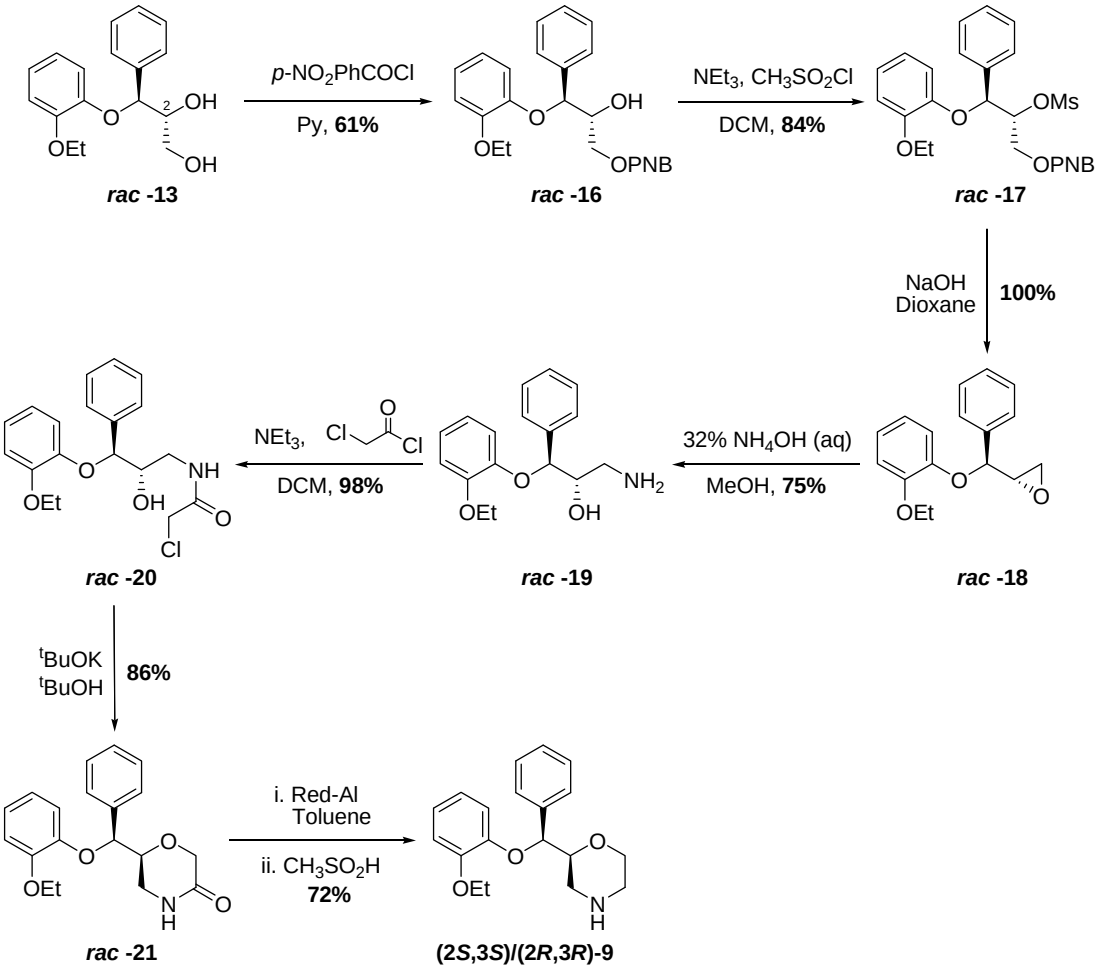


11 ***rac* -12** ***rac* -13**

***rac* -14** **(2*R*,3*S*)/(2*S*,3*R*)-15**

Scheme 2

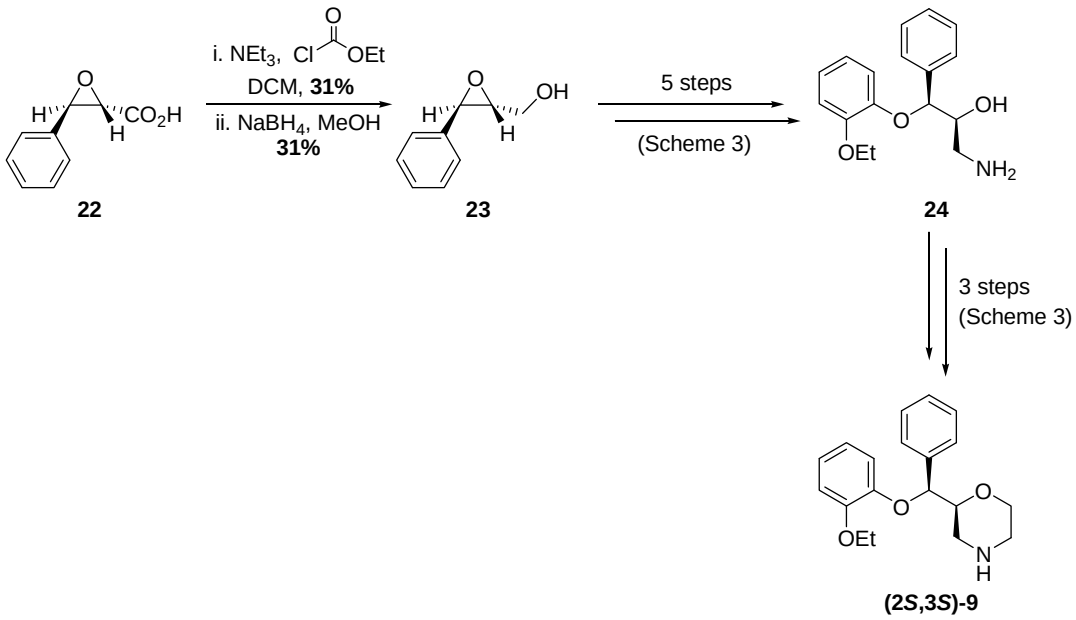
Inversion at the 2-position was required for the correct amino alcohol, and as shown in Scheme 3, primary alcohol **13** was protected as the *p*-nitrobenzoyl ester **16** and the secondary alcohol activated as mesylate **17**.[20] Hydrolysis of the ester under basic conditions, and subsequent displacement 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 ^{o}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.



Scheme 3

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 (2*R*,3*R*)-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 (2*S*,3*S*)-**9** followed those described for the racemic synthesis in Scheme 3.



Scheme 4

The optical rotation of the (2*S*,3*S*)-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

	NAT K_i (nM)	SERT K_i (nM)	Selectivity (SERT/NAT)
(2*S*,3*S*)/(2*R*,3*R*)-**9**	8	1070	130
Desipramine	6	590	98
Imipramine	54	73	1.4

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 (2*S*,3*S*)- and (2*R*,3*R*)-enantiomers, with the (2*S*,3*S*)-isomer reported to be twenty four times more potent than its enantiomer.[20,22]

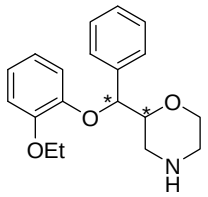


Figure 9

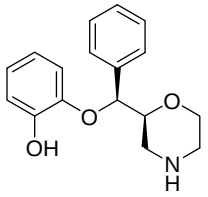
Reboxetine's excellent potency and selectivity make it a potential candidate to become a radiotracer for use in imaging the noradrenaline transporter using single photon emission computed tomography (see Section 1.6).

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

There are two distinct synthetic strategies which have been applied to the synthesis of (2*S*,3*S*)-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 (2*S*,3*S*)-2-(2-morpholin-2-yl-2-phenylmethoxy)phenol **25** (Figure 10).[23]

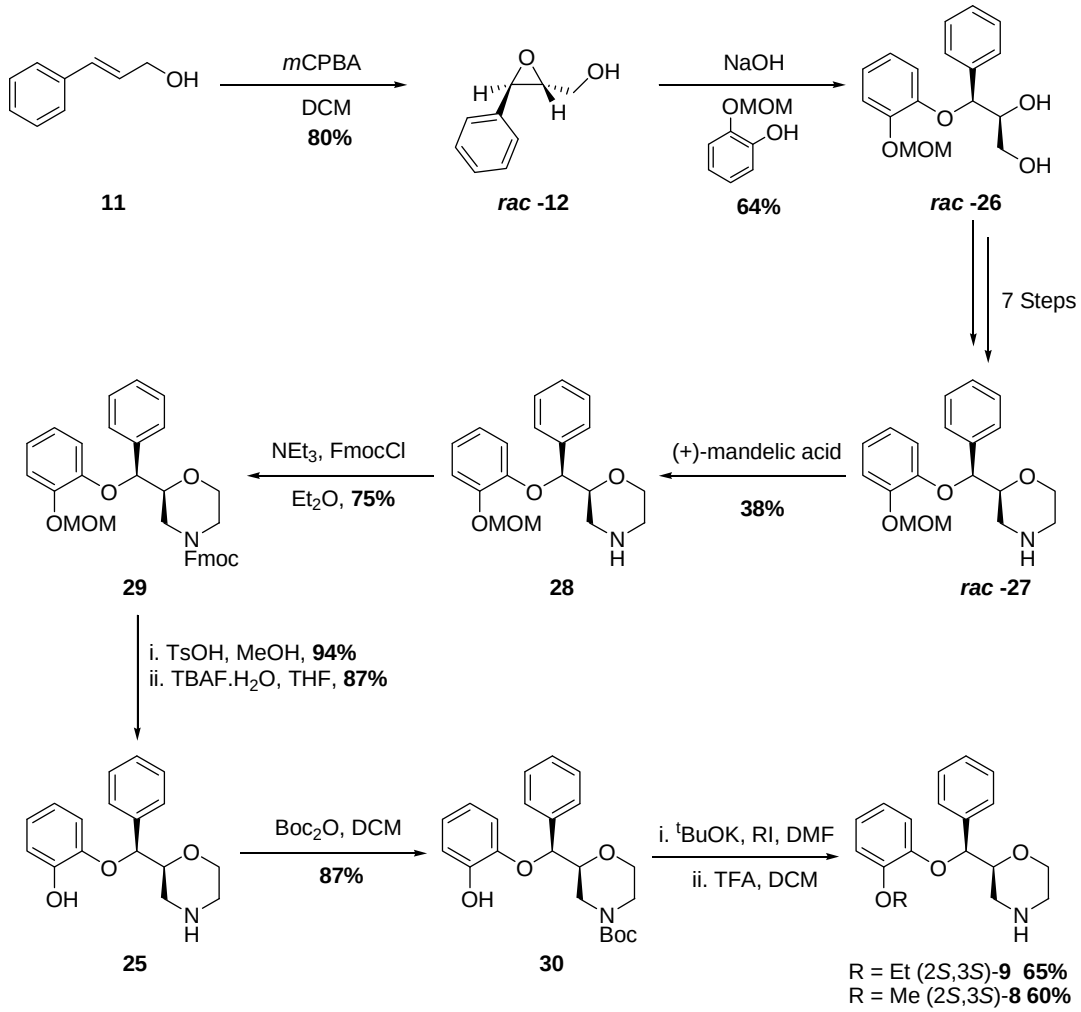


25

Figure 10

The group embarked on a synthesis similar to that described by Melloni and co-workers (Scheme 5).[20] Oxidation of *trans*-cinnamyl alcohol **11** with *m*CPBA 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 (2*S*,3*S*)-**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 (2*S*,3*S*)-reboxetine **9** in a 65% yield over two steps.



Scheme 5

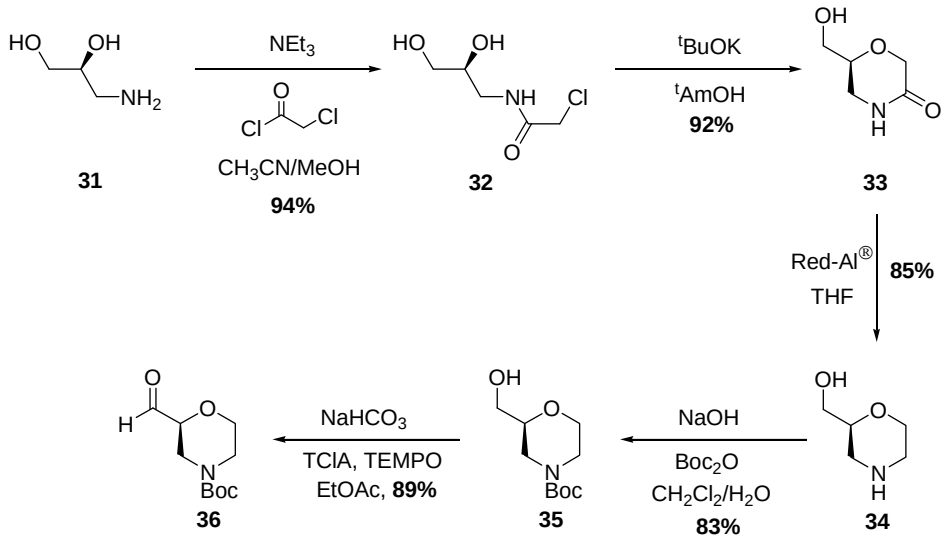
The optical rotation of **9** was comparable to that reported for (2*S*,3*S*)-reboxetine, and therefore the configuration could be assigned. Analysis using chiral HPLC showed the enantiomeric excess to be 98%.

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

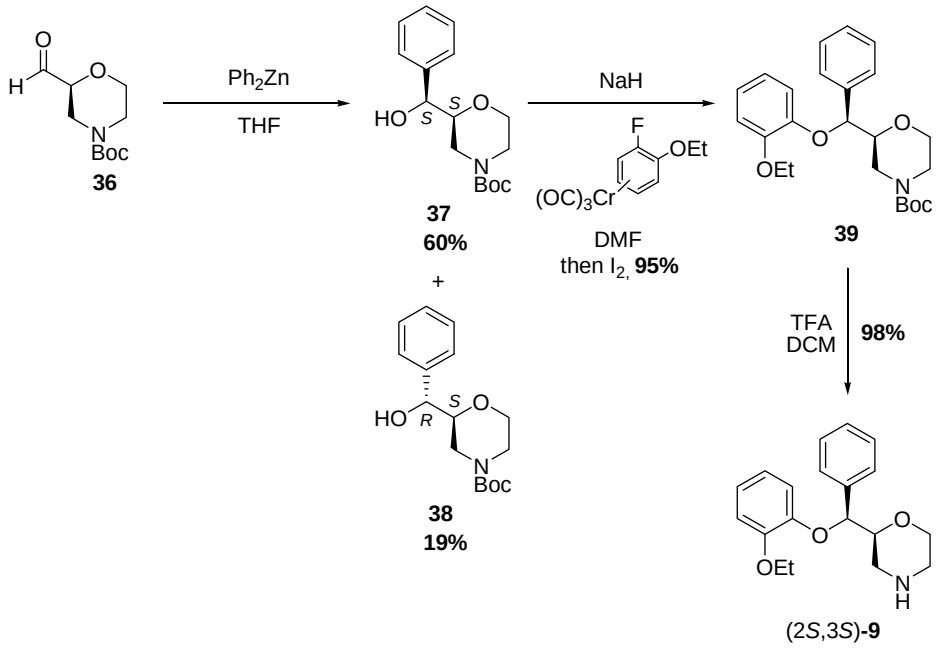
In 2005, the Tamagnan group reported an efficient asymmetric synthesis of (2*S*,3*S*)-reboxetine via a new (*S*)-2-(hydroxymethyl)morpholine intermediate.[24]

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**.



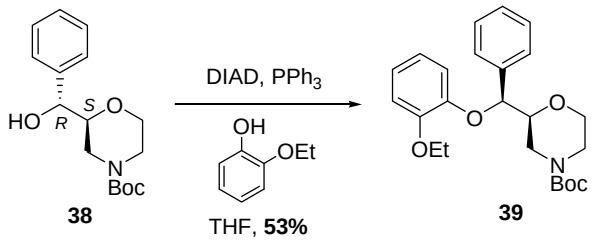
Scheme 6

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 (2*S*,3*S*)-**9** in a 98% yield.



Scheme 7

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 (2*S*,3*S*)-**9**.



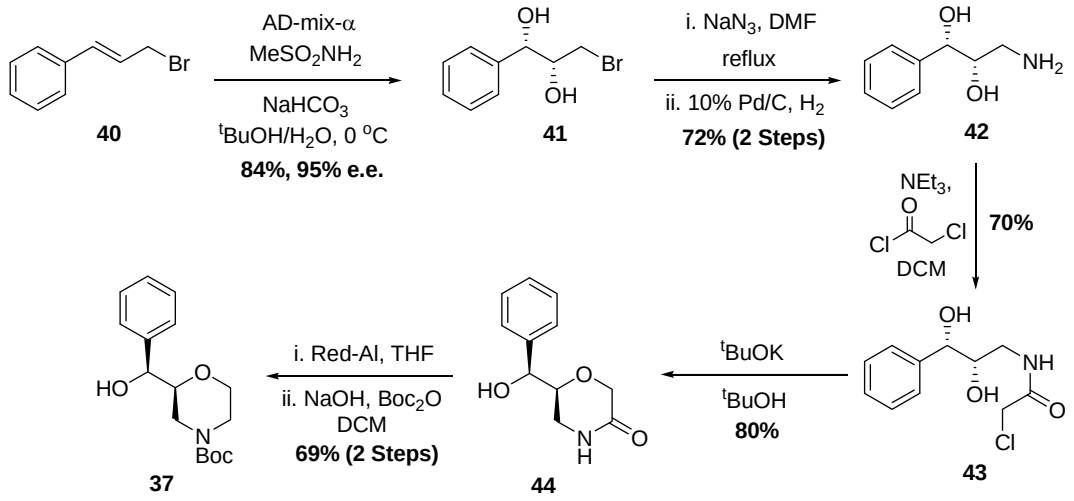
Scheme 8

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

1.4.3 Enantioselective Synthesis

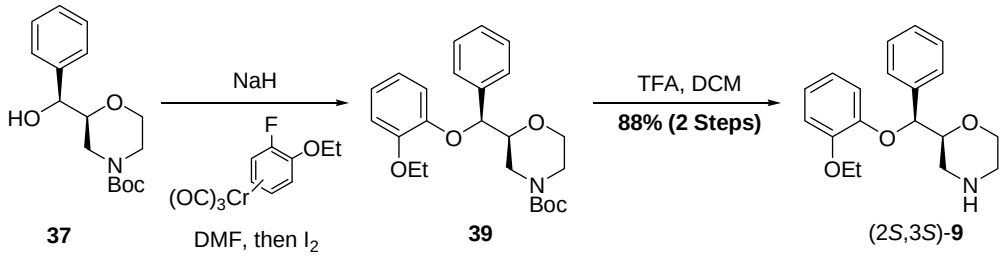
Srinivasan and co-workers reported an efficient enantioselective synthesis of (2*S*,3*S*)-reboxetine.[25] Commercially available *trans*-cinnamyl bromide **40** was subjected to a Sharpless asymmetric dihydroxylation to introduce the desired stereochemistry and gave diol **41** in a good 84% yield (Scheme 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**.



Scheme 9

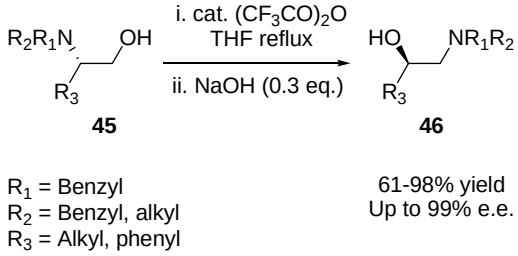
Using chemistry developed by the Tamagnan group, benzyl alcohol **37** underwent a chromium mediated nucleophilic aromatic substitution to introduce the aromatic ring. This gave **39**, which was deprotected using trifluoroacetic acid to give target molecule (2*S*,3*S*)-**9** (Scheme 10).[24] Thus, (2*S*,3*S*)-reboxetine was successfully synthesised in nine linear steps and an overall 21% yield.



Scheme 10

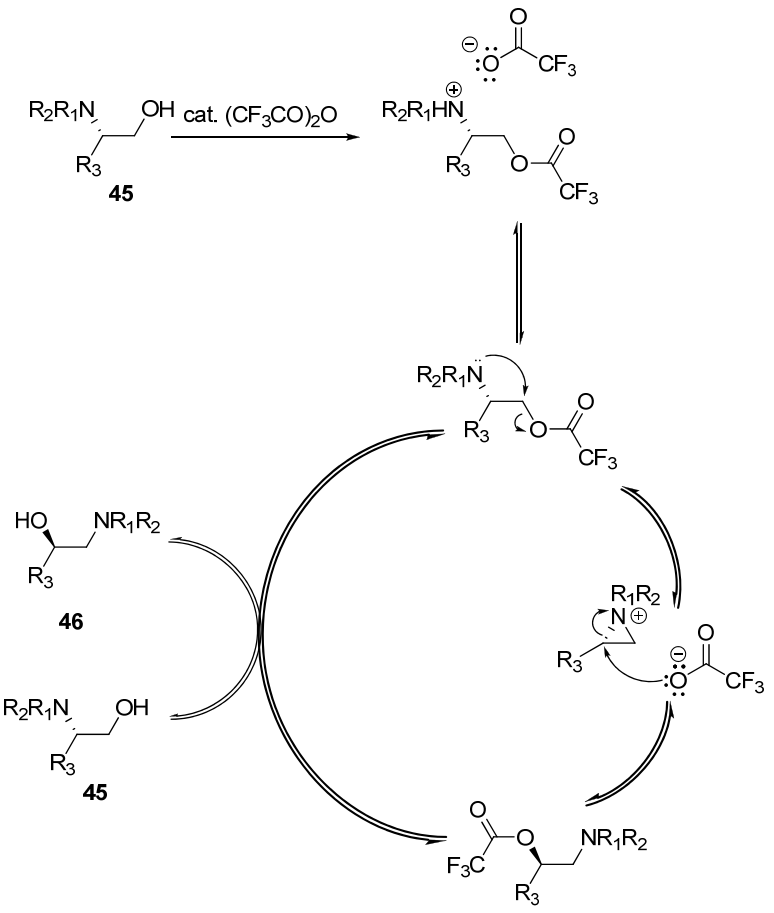
1.4.4 Asymmetric Catalytic Rearrangement

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



Scheme 11

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**.

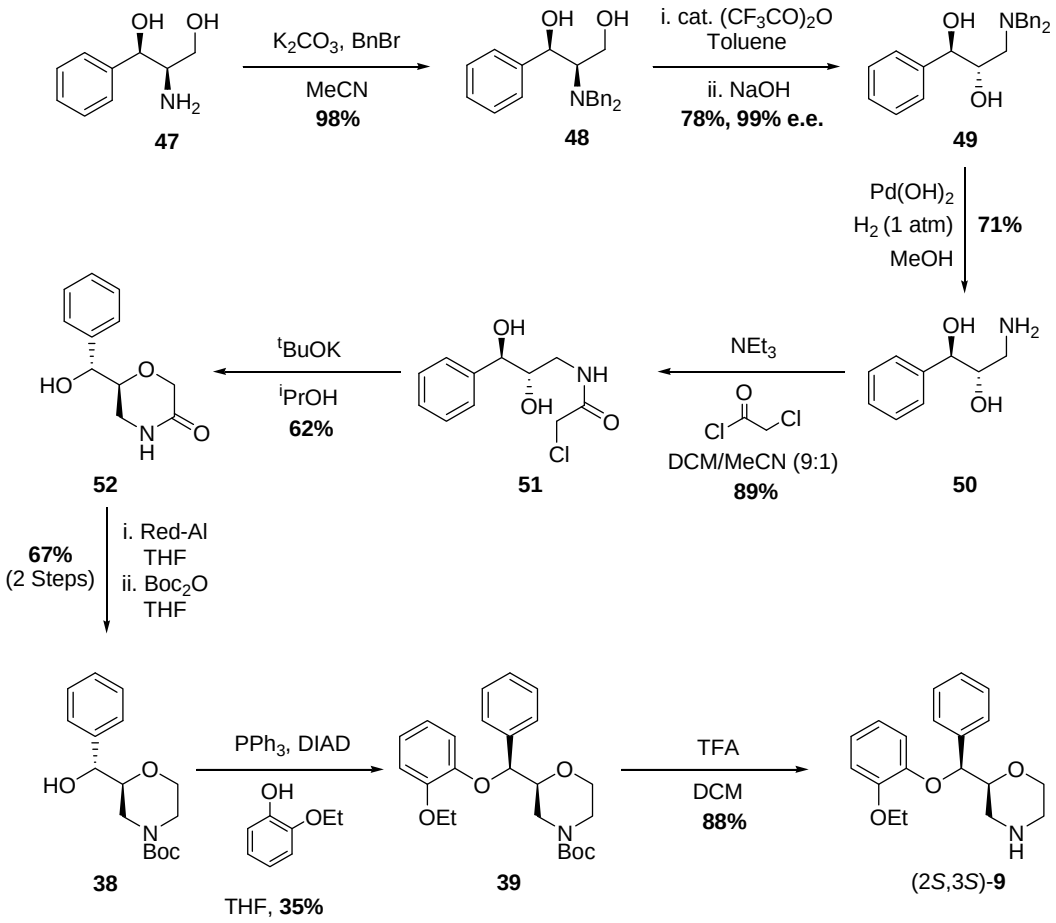


Scheme 12

In 2008, the Cossy group used this chemistry to described two approaches to the synthesis of (2*S*,3*S*)-reboxetine.[27] As shown in Scheme 13, commercially available (1*R*,2*R*)-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.

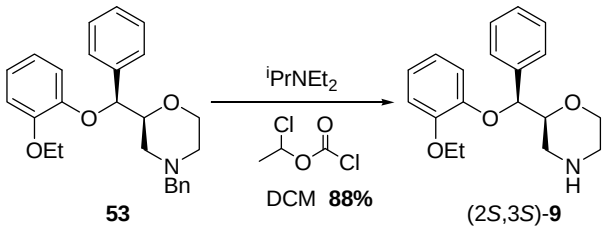
The benzyl protecting groups were removed by hydrogenation and amine **50** acetylated using chloroacetyl chloride to give amide **51**. The morpholine ring was formed by treatment of **51** with potassium *tert*-butoxide to form the morpholinone ring, and reduction of amide **52** was carried out using Red-Al®. 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 (2*S*,3*S*)-**9** in an 88% yield.

Thus, target molecule, (2*S*,3*S*)-reboxetine **9** was synthesised in nine linear steps and a 6.2% overall yield.



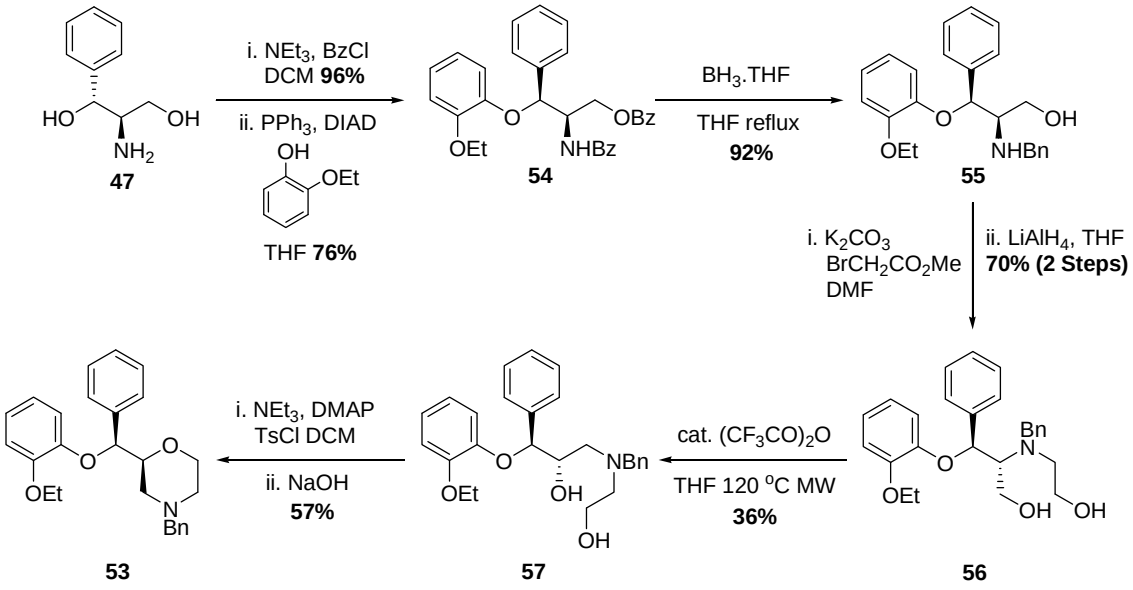
Scheme 13

In the literature, the deprotection of **53** using 1-chloroethylchloroformate is reported to give (2*S*,3*S*)-reboxetine in an 88% yield (Scheme 14).[28] 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.[26]



Scheme 14

As shown in Scheme 15, the amino and primary hydroxyl groups of (1*R*,2*R*)-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 (2*S*,3*S*)-reboxetine was achieved in eight steps and an improved 8.5% overall yield.



Scheme 15

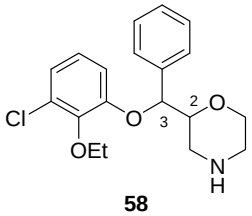
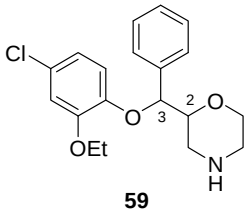
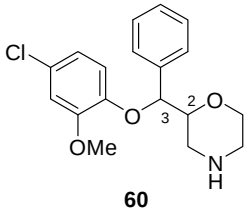
1.5 Synthesis and Evaluation of New Reboxetine Derivatives

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.[29] 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 give in Table 2.

Table 2

		K_i (nM)[a]		
Compound	**Racemate**	**NAT**	**SERT**	**DAT**
 **58**	(2*S*,3*S*/2*R*,3*R*)	275	240	> 10000
	(2*S*,3*R*/2*R*,3*S*)	1490	340	> 10000
 **59**	(2*S*,3*S*/2*R*,3*R*)	15	60	1540
	(2*S*,3*R*/2*R*,3*S*)	390	220	1670
 **60**	(2*S*,3*S*/2*R*,3*R*)	36	28	5050
	(2*S*,3*R*/2*R*,3*S*)	320	85	2200

[a] K_i values are the mean of 3 separate determinations.

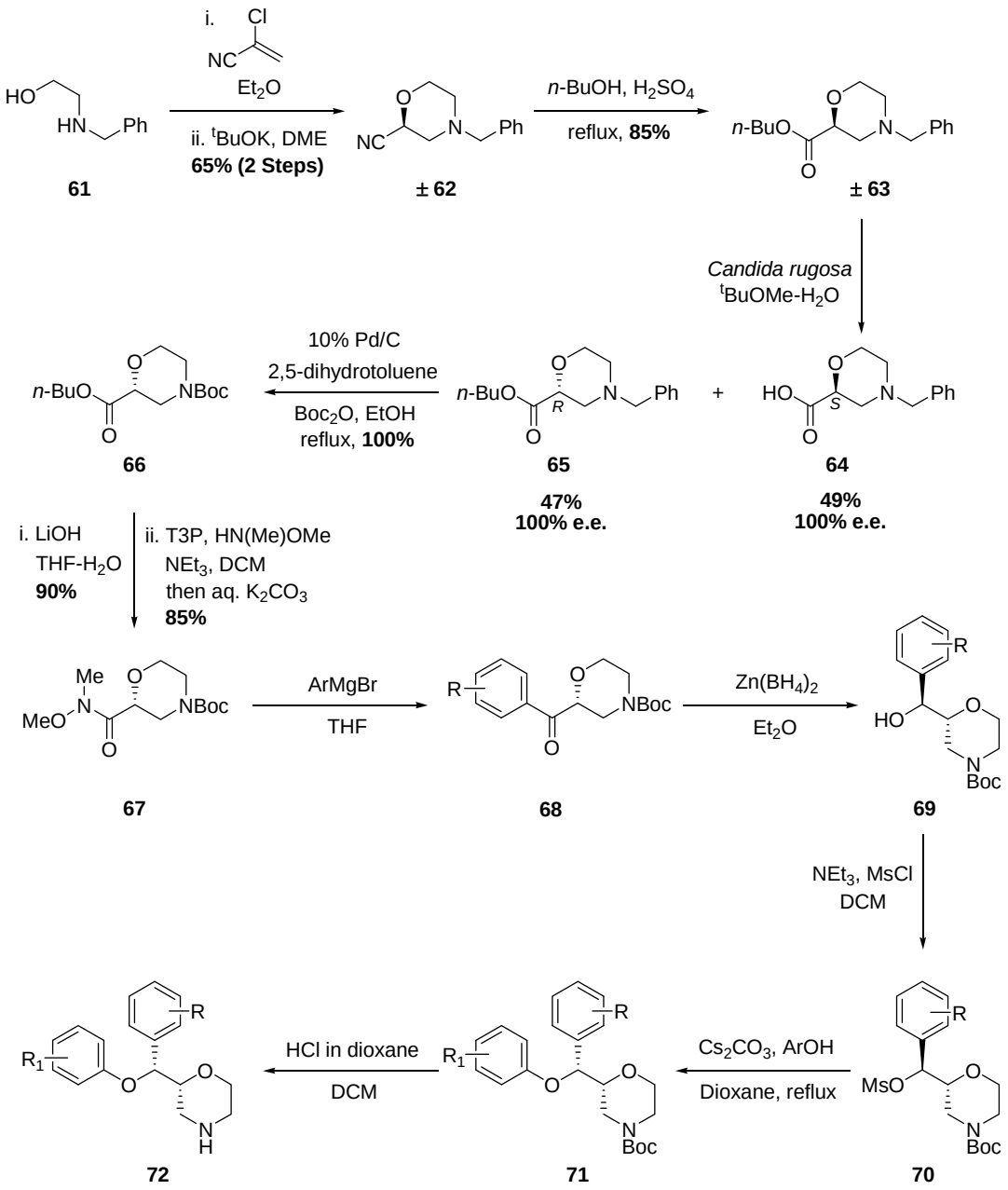
From these results it was concluded that the affinities of the (2*S*,3*S*/2*R*,3*R*)-derivatives were superior to that of the (2*S*,3*R*/2*R*,3*S*)-compounds, and investigation into the latter series was discontinued.

A new stereoselective synthesis to the single enantiomers of the (2*S*,3*S*/2*R*,3*R*)-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 (2*R*,3*S*:2*R*,3*R* 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*,3*R*)-target molecules **72** in a 95% yield.

The (2*S*,3*S*)-enantiomers were prepared using an identical sequence starting from (*S*)-acid **64**.

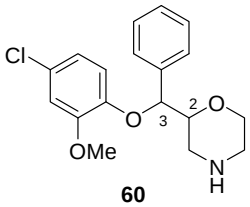
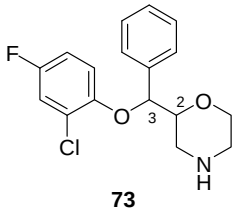
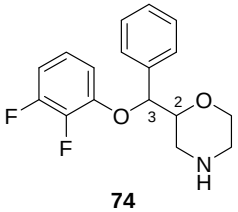


Scheme 16

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 (2*S*,3*S*)-derivatives being selective for the noradrenaline transporter, whilst the (2*R*,3*R*)-derivatives showed better affinity for the serotonin transporter. Both (2*S*,3*S*)- and (2*R*,3*R*)-derivatives showed selectivity against the dopamine transporter.

Table 3

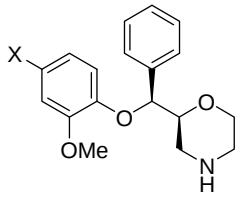
		K_i (nM)[a]		
Compound	**Stereochemistry**	**NAT**	**SERT**	**DAT**
 **60**	(2*S*,3*S*)	8	110	1570
	(2*R*,3*R*)	420	11	1790
 **73**	(2*S*,3*S*)	12	260	1170
	(2*R*,3*R*)	830	20	760
 **74**	(2*S*,3*S*)	10	3390	2600
	(2*R*,3*R*)	130	12	380

[a] 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 (2*S*,3*S*)-compounds showed no significant affinity for other targets, however the (2*R*,3*R*)-compounds showed significant affinity for the H1-histamine receptor. This finding, coupled with the modest affinity for the target monoamine transporters led to the (2*R*,3*R*)-series being discontinued.

The (2*S*,3*S*)-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 CF_3 group lead to an inversion of inhibition profile, with **77** displaying greater affinity for the serotonin transporter.

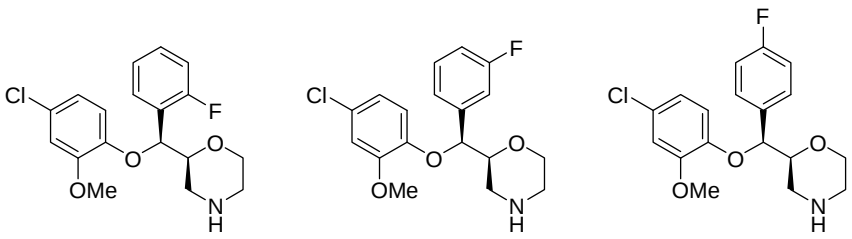
Table 4



X	NAT K_i (nM)[a]	SERT K_i (nM)[a]	DAT K_i (nM)[a]
CN (**75**)	210	110	-
Br (**76**)	12	30	-
CF_3 (**77**)	160	41	-

[a] K_i values are the mean of at least 3 separate determinations.
- Not tested.

Based on lead compound (2*S*,3*S*)-**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.



78 NAT K_i = 22 nM

79 NAT K_i = 9 nM

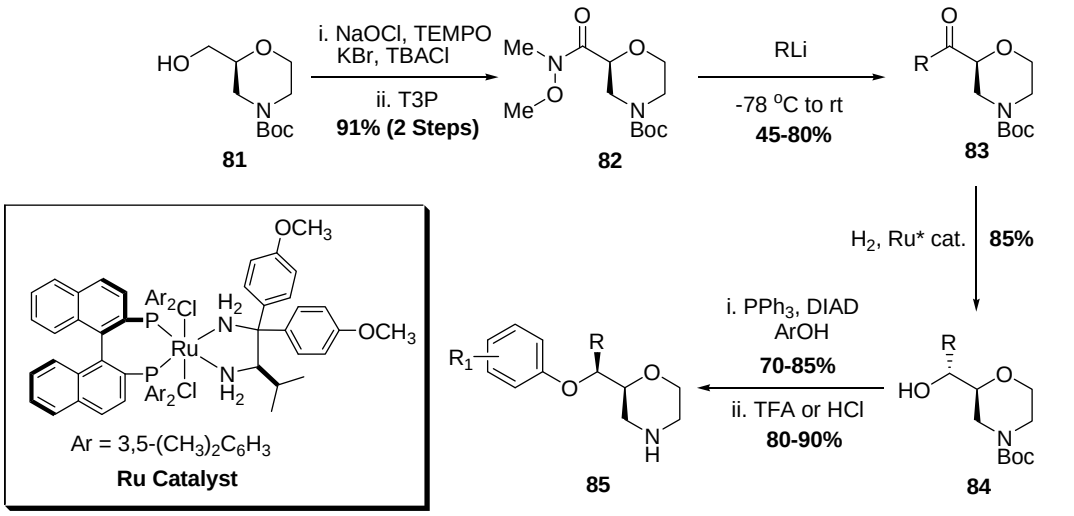
80 NAT K_i = 29 nM

Figure 11

Compound (2*S*,3*S*)-**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 (2*S*,3*S*)-**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.[30] The literature suggests that (2*R*,3*R*)-derivatives of reboxetine are not selective for the noradrenaline transporter,[22] therefore only the (2*S*,3*S*)-, (2*S*,3*R*)- and (2*R*,3*S*)-analogues were synthesised and biologically evaluated.

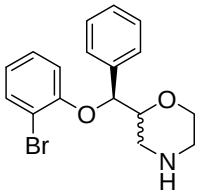
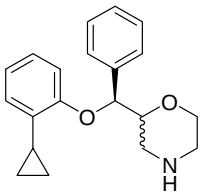
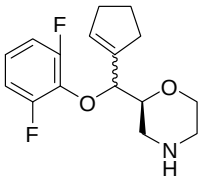
The synthetic strategy involved the synthesis of a late stage intermediate which could be coupled with different groups (Scheme 17). Hydroxymorpholine **81** was oxidised using buffered sodium hypochlorite, and the acid converted to Weinreb amide **82** via a cyclic phosphonic acid anhydride promoted 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.



Scheme 17

As shown in Table 5, the affinity and selectivity of the (2*S*,3*R*)- and (2*R*,3*S*)-derivatives was found to be inferior to that of the (2*S*,3*S*)-derivatives. The (2*S*,3*S*)-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**).

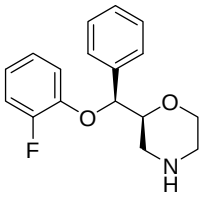
Table 5

Compound	Stereochemistry	NAT K_i (nM)[a]	SERT K_i (nM)[a]
 **86**	(2*S*,3*S*)	3	477
	(2*R*,3*S*)	17	105
 **87**	(2*S*,3*S*)	2	482
	(2*R*,3*S*)	35	75
 **88**	(2*S*,3*S*)	20	3703
	(2*S*,3*R*)	2570	2530

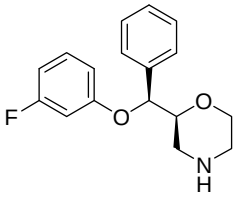
[a] K_i values are the mean of at least 3 separate determinations.

Investigation into the (2*S*,3*R*)- and (2*R*,3*S*)-derivatives was discontinued, and the focus was switched to investigation of the structure activity relationship of substitution on the phenoxy ring.

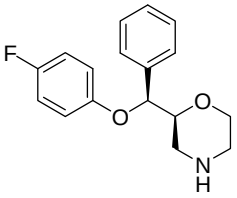
Compounds **89**, **90** and **91** were tested and the results showed that affinity for the noradrenaline transporter decreased as a function of substitution in the order *ortho*, *meta* and *para* (Figure 12). Interestingly, movement of the fluorine from the *ortho* to the *meta* position resulted 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]



89
K_i NAT 7 nM
K_i SERT 6390 nM



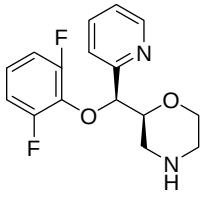
90
K_i NAT 11 nM
K_i SERT 13 nM



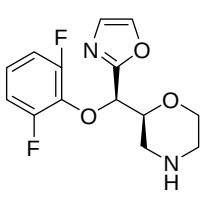
91
K_i NAT 21 nM
K_i SERT 1620 nM

Figure 12

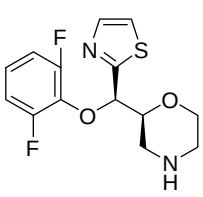
Further investigation revealed that compounds with substitution in the 2- or 2,6-position of the phenoxy ring displayed the best affinity for the noradrenaline transporter. As shown in Figure 13, replacement of the phenyl ring with different heterocyclic systems was examined. 2-Pyridyl rings were found 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.



92
NAT K_i 6 nM
SERT K_i 8980 nM



93
NAT K_i 9 nM
SERT K_i >10000 nM



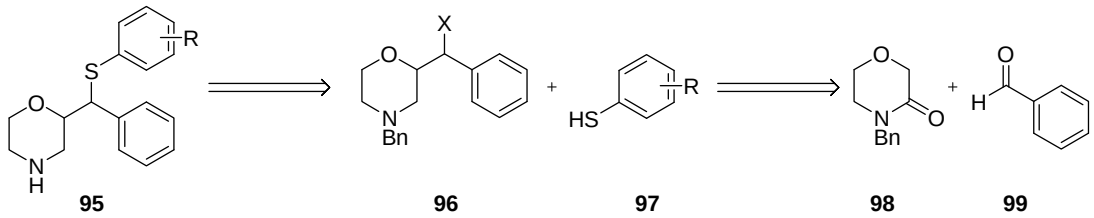
94
NAT K_i 19 nM
SERT K_i >10000 nM

Figure 13

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.[31] 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 **96** which could be made from an aldol condensation between **98** and benzaldehyde **99**. This strategy would allow the rapid generation of analogues by introduction of a variety of thiophenols at a late stage.

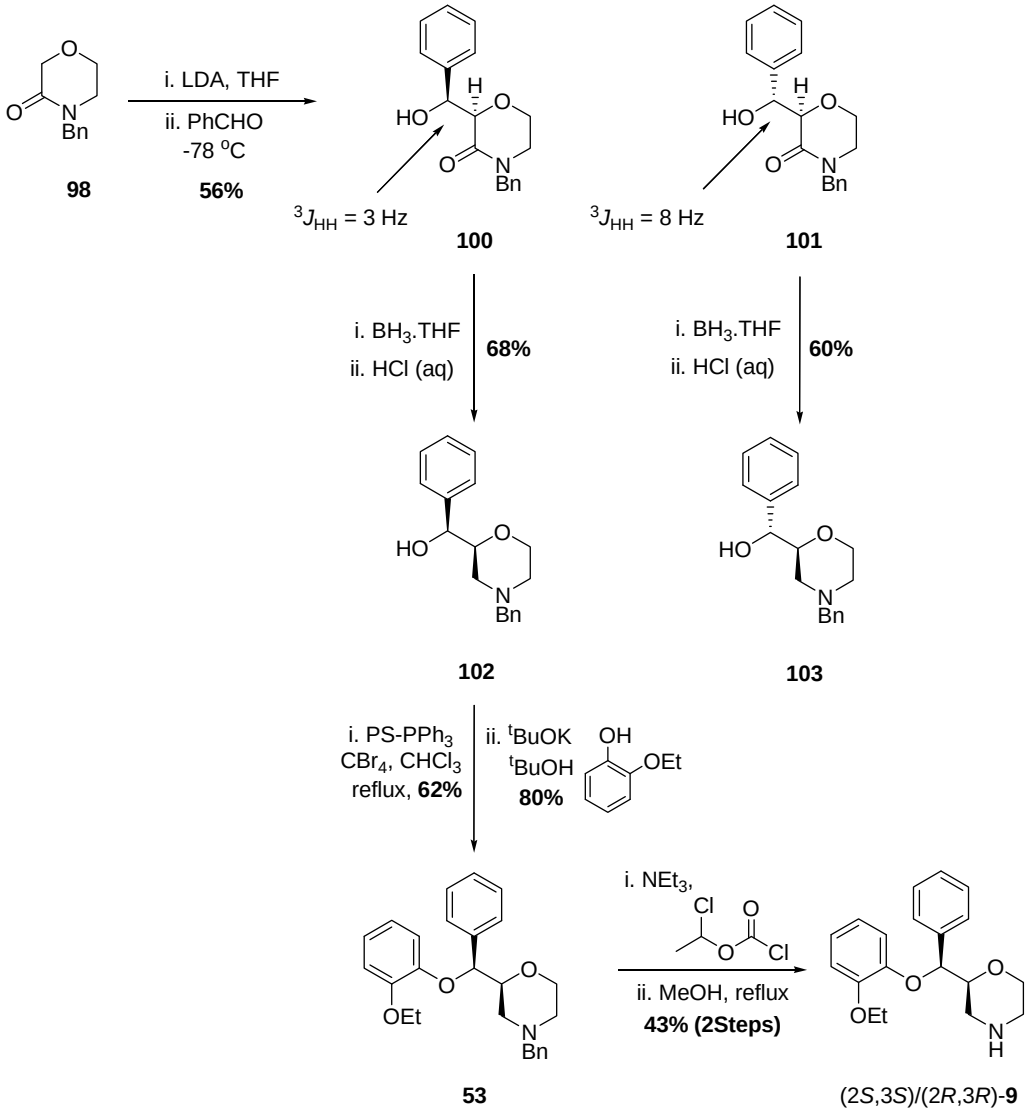


95 **96** **97** **98** **99**

Scheme 18

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 **98** which underwent an aldol condensation reaction to give a 2.2:1 diastereomeric mixture of benzyl alcohols **100** and **101**. 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 (2*S*,3*S*)/(2*R*,3*R*)-**53**, which was deprotected in two steps to give racemic **9**.

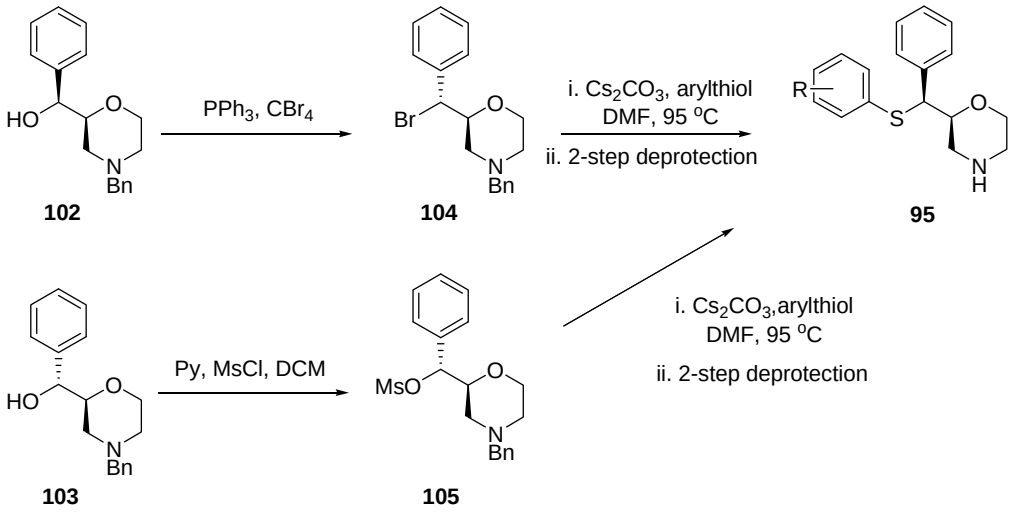


Scheme 19

The target compound was compared to an authentic sample of (2*S*,3*S*/2*R*,3*R*)-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 (2*S*,3*S*/2*R*,3*R*)-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.

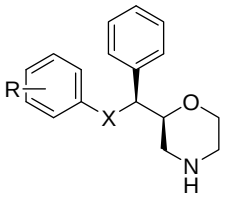


Scheme 20

The target compounds were tested as (2*S*,3*S*/2*R*,3*R*)-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.[19,32] Interestingly, the thio-methoxy analogue **107** displayed excellent inhibition of both the noradrenaline and serotonin transporters.

Table 6



			K_i (nM)[a]		
Compound	**X**	**R**	**NAT**	**SERT**	**DAT**
106	S	H	1.76	36	522.1
107	S	2-OMe	10.7	1.2	>200
108	S	2-Me	8.3	0.2	226.9
109	S	3-Me	108.6	3.2	>200
110	S	4-Me	364.3	>100	>200
(2*S*,3*S*)/(2*R*,3*R*)-**9**	O	2-OEt	1.9	>100	>200

[a] K_i values are the mean of 3 separate determinations.

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]

Figure 14

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]

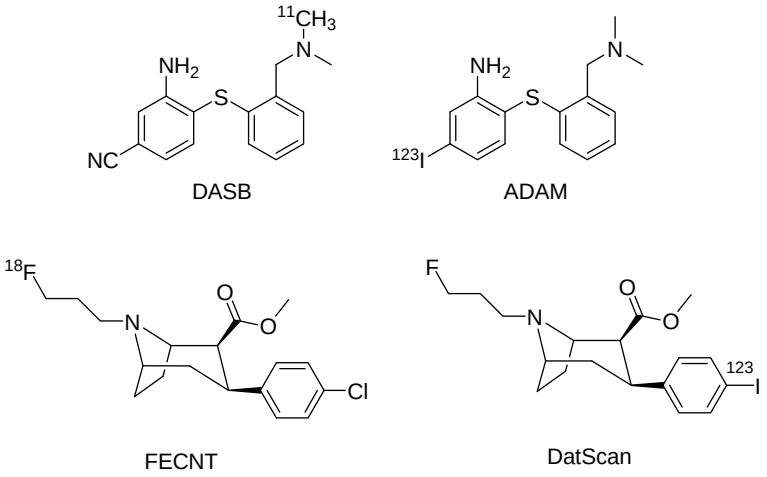
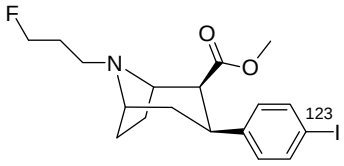


Figure 15

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.[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.[42]



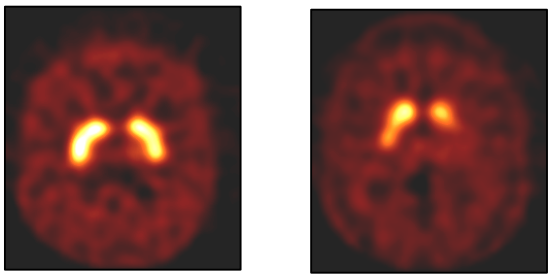


Figure 16

SPECT can also be used to monitor disease progression and evaluate the effectiveness of treatment.[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.[42]

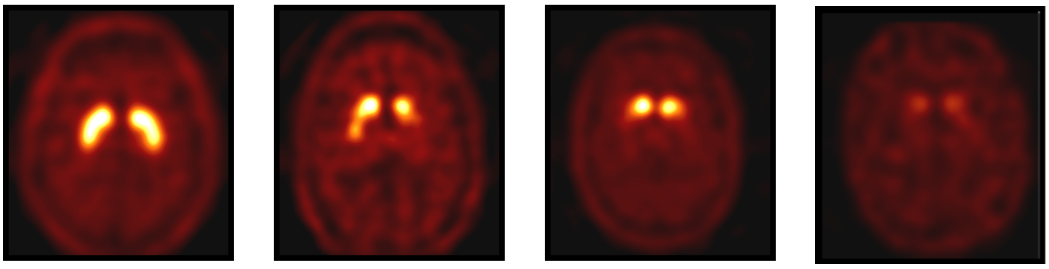
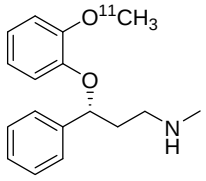


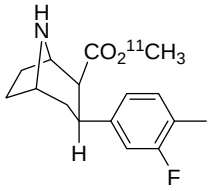
Figure 17

1.6.4 Radiotracers for the Noradrenaline Transporter

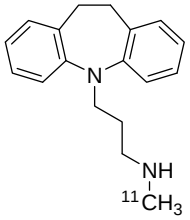
Imaging of the noradrenaline transporter has been hampered by the lack of a suitable ligand. Selected examples of potential radiotracers for the noradrenaline transporter using PET are shown in Figure 18.



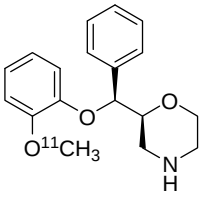
111



112



113



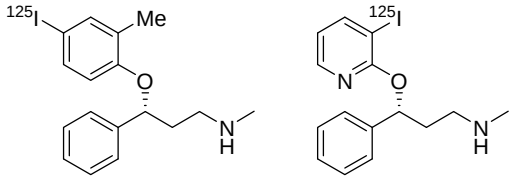
114

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.[45] Nortropane derivative **112** was shown to have good uptake *in vivo*, however it also suffered from non-specific binding in brain tissue.[46]

The tricyclic antidepressant desimpramine **113** was radiolabelled with ^{11}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}C-MeNER **114**.[48-50]

A SPECT radiotracer for the noradrenaline transporter has proved just as elusive to develop. Radiolabelled ^{123}I-tomoxetine (**115**) displayed moderate affinity for the serotonin transporter, however recently a pyridine analogue of nisoxetine labelled with ^{125}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]



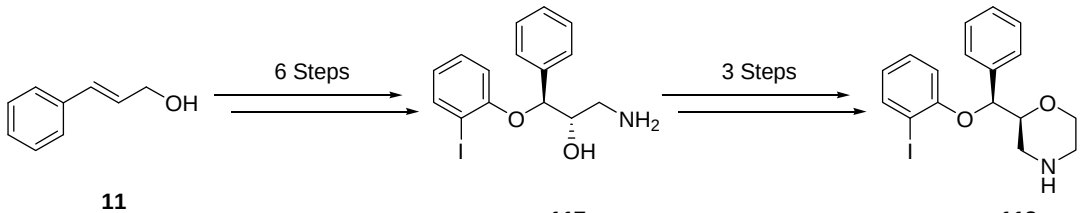
115 **116**

Figure 19

1.7 SPECT Studies

Saji and co-workers reported the synthesis and radioiodination of (2*S*,3*S*)-2-(α-(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 (2*S*,3*S*)/(2*R*,3*R*)-**118** in nine steps (Scheme 21).[20]



11 ***rac* -117** ***rac* -118**

Scheme 21

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 (2*S*,3*S*)/(2*R*,3*R*)-reboxetine. (2*S*,3*S*)-**118** was shown to be almost two and a half times as potent as reboxetine, and twenty times more potent than (2*R*,3*R*)-**118**.

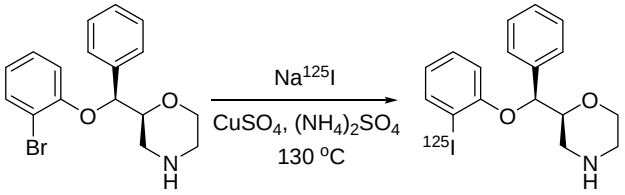
Table 7

Compound	NAT K_i (nM)[a]
(2*S*,3*S*)/(2*R*,3*R*)-**118**	10.4
(2*S*,3*S*)-**118**	4.22
(2*R*,3*R*)-**118**	80.4
(2*S*,3*S*)/(2*R*,3*R*)-**9**	11.6

[a] K_i values are the mean of 3 separate determinations.

The selectivity of (2*S*,3*S*)-**118** was confirmed using selective binding agents for the noradrenaline, serotonin and dopamine transporters. It was found that the binding of (2*S*,3*S*)-**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 (2*S*,3*S*)-**118** in rats was assessed by radiolabeling bromoanalogue (2*S*,3*S*)-**86**. This was achieved using a halogen exchange reaction to give **119** in a 65% radiochemical yield and >98% radiochemical purity (Scheme 22).



(2*S*,3*S*)-86 **119**

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.

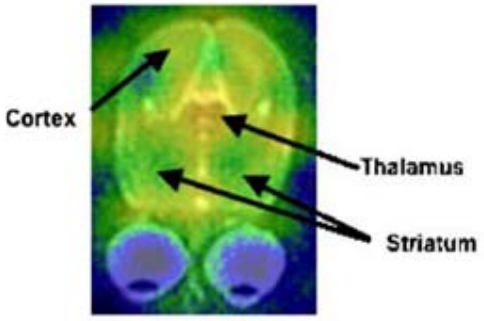
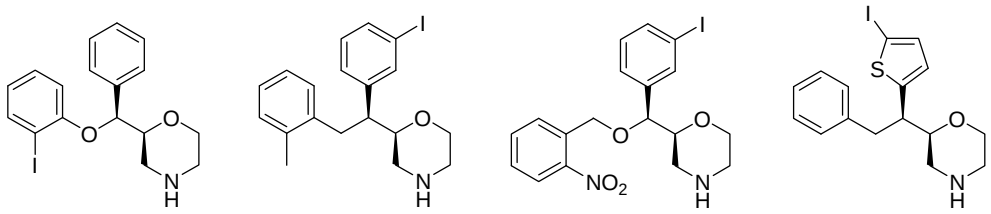


Figure 20

In 2007, the Tamagnan group reported the development of SPECT imaging agents for the noradrenaline transporter.[55] Starting from racemic aminopropanediol, the synthetic sequence reported in their earlier publication was used to synthesise racemic mixtures of different (2*S*,3*S*)/(2*R*,3*R*)-reboxetine analogues. The compounds were then evaluated *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 *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**.



***rac* -118**
NAT K_i = 2.47 nM

***rac* -120**
NAT K_i = 27.6 nM

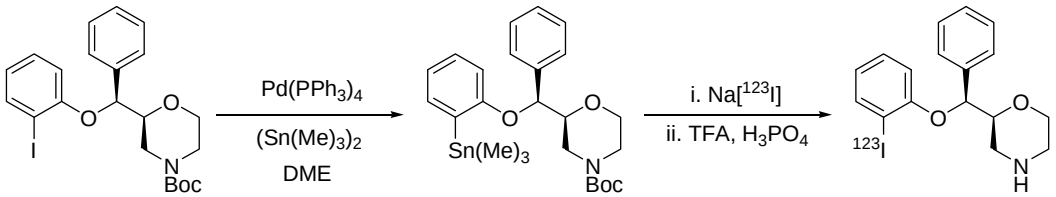
***rac* -121**
NAT K_i = 70.4 nM

***rac* -122**
NAT K_i = 71.9 nM

Figure 21

Racemic **118** was identified as a potential lead, and so the (2*S*,3*S*)-enantiomer was asymmetrically synthesised from (*S*)-3-amino-1,2-propanediol. Enantiopure (2*S*,3*S*)-**118** was then assessed *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.

(2*S*,3*S*)-**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.



123 **124** **125**

Scheme 23

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 *in vivo*.[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.

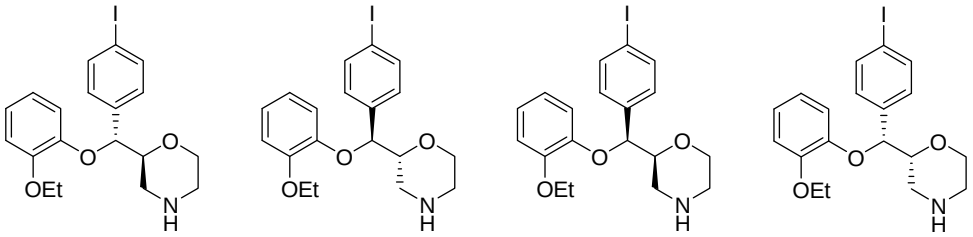
The aims of this research project were:

- 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.



126 **127** **128** **129**

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.

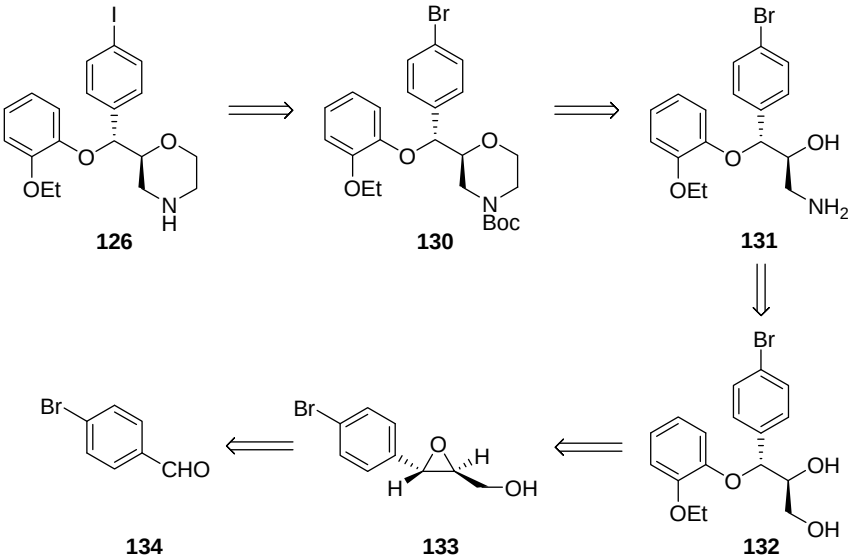
2 Results and Discussion

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

In previously reported studies of reboxetine, only analogues of the (2*S*,3*S*)- and (2*R*,3*R*)-stereoisomers had been tested for their affinity with the noradrenaline transporter.[54,55] The stereoselective synthesis and pharmacology of (2*S*,3*R*)- and (2*R*,3*S*)-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 (2*S*,3*R*)-Iodoreboxetine

The proposed retrosynthetic analysis of (2*S*,3*R*)-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**.



Scheme 24

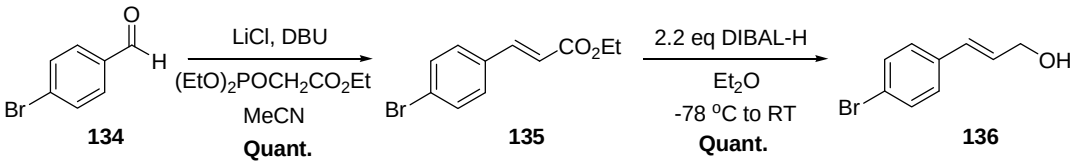
Thus, the important steps in this synthetic strategy were a Sharpless asymmetric epoxidation to introduce the desired stereochemistry, and a copper catalysed halogen exchange reaction to incorporate the key iodine atom. This approach would also allow for the synthesis of the (2*R*,3*S*)-stereoisomer by use of the opposite enantiomer of the chiral ligand, diisopropyl tartrate at the Sharpless asymmetric epoxidation step.

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

As shown in Scheme 25, the synthesis of (2*S*,3*R*)-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.[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.[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.



Scheme 25

In 1980, Sharpless described the first practical method for the asymmetric epoxidation of primary allylic alcohols with good yields and excellent enantioselectivities.[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.[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.[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.

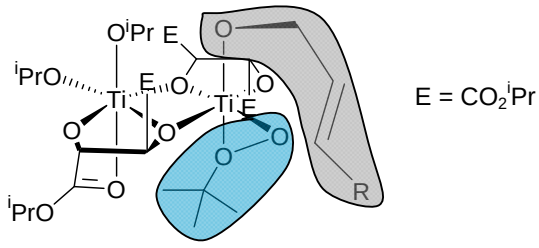


Figure 23

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.

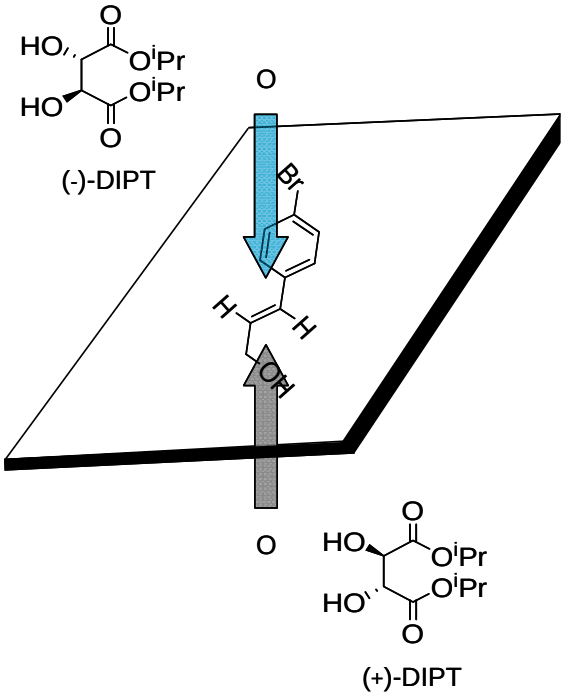
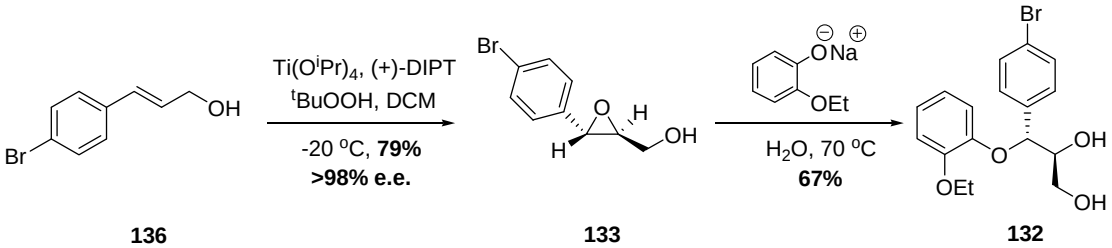


Figure 24

Thus, allylic alcohol **136** underwent a Sharpless asymmetric epoxidation using the (+)-enantiomer of diisopropyl tartrate to confer (2*S*,3*S*)-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.[61] 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.[63]

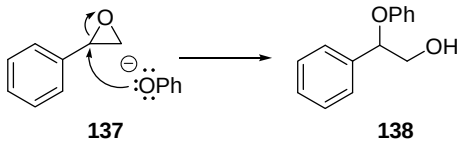
With the desired stereochemistry established, the remainder of the reboxetine backbone was synthesised using the same synthetic sequence as that described by Mellioni and co-workers.[20] Epoxide **133** was regioselectively ring-opened using the sodium salt of 2-ethoxyphenol to give diol **132**.[20,64]



136 **133** **132**

Scheme 26

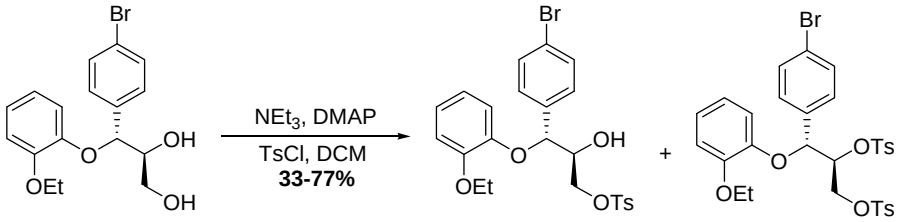
The regioselectivity of the epoxide opening can be rationalised by examining the electronic influences of the phenyl and hydroxyl groups. Guss reported the opening of epoxide **137** with phenol to give predominantly primary alcohol **138**.[64] This suggests that the aromatic group exerts an electron 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).



137 **138**

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%.



132 **139** **140**

Scheme 28

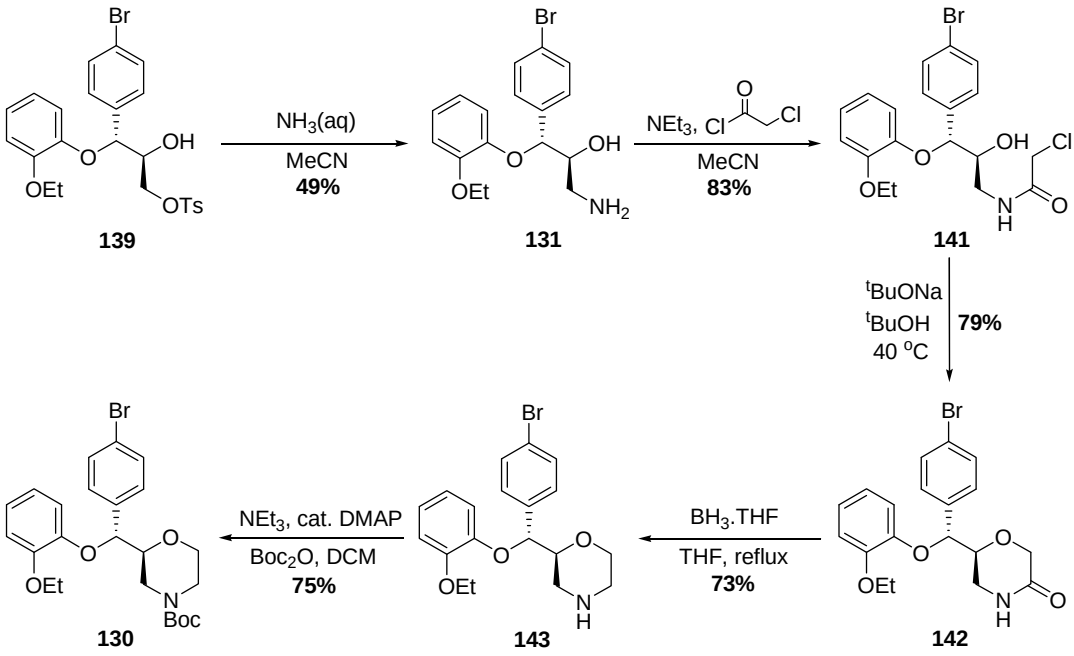
Displacement of the tosyl group using an aqueous solution of ammonia proceeded smoothly to give amino alcohol **131**. The reaction was initially carried out using dimethylformamide as the organic solvent, however recovery of the product was poor (33% yield), and this was thought to be due to the difficultly 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 ^{o}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 ^{o}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

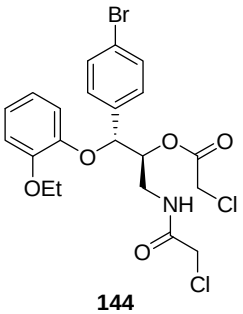
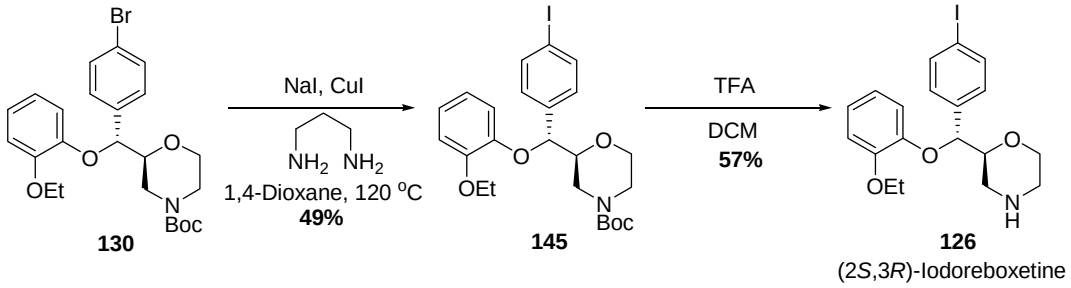


Figure 25

As shown in Scheme 30, the halogen exchange was carried out using conditions described by Kaplars and Buchwald.[65] Reaction of **130** with sodium iodide, catalytic amounts of copper iodide and 1,3-diaminopropane in dioxane at 130 ^{o}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 ^{o}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, (2*S*,3*R*)-iodoreboxetine **126**, in a 57% yield.



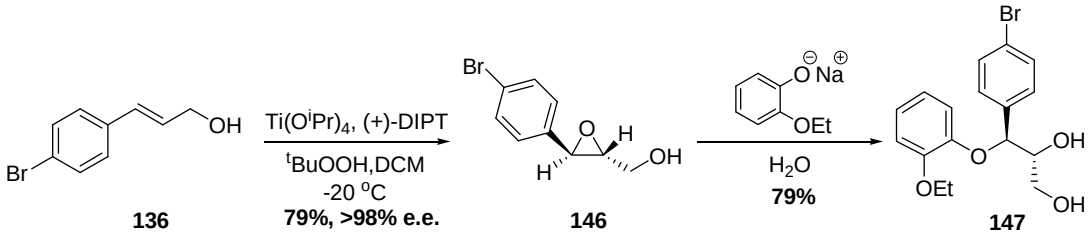
Scheme 30

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

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

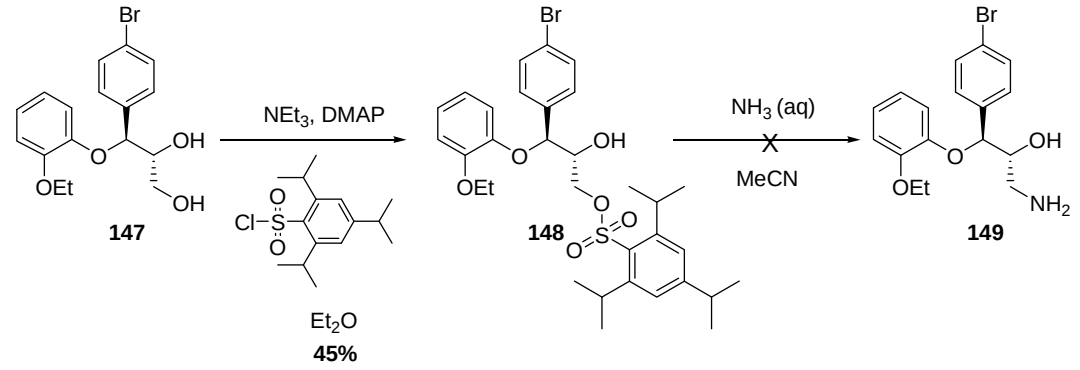
Initial attempts at the epoxidation of allylic alcohol **136** proved to be low yielding. This was overcome by using a fresh bottle of titanium isopropoxide, and commercially available anhydrous *tert*-butyl hydroperoxide in place of drying the aqueous solution. This gave chiral epoxide **146** in a 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

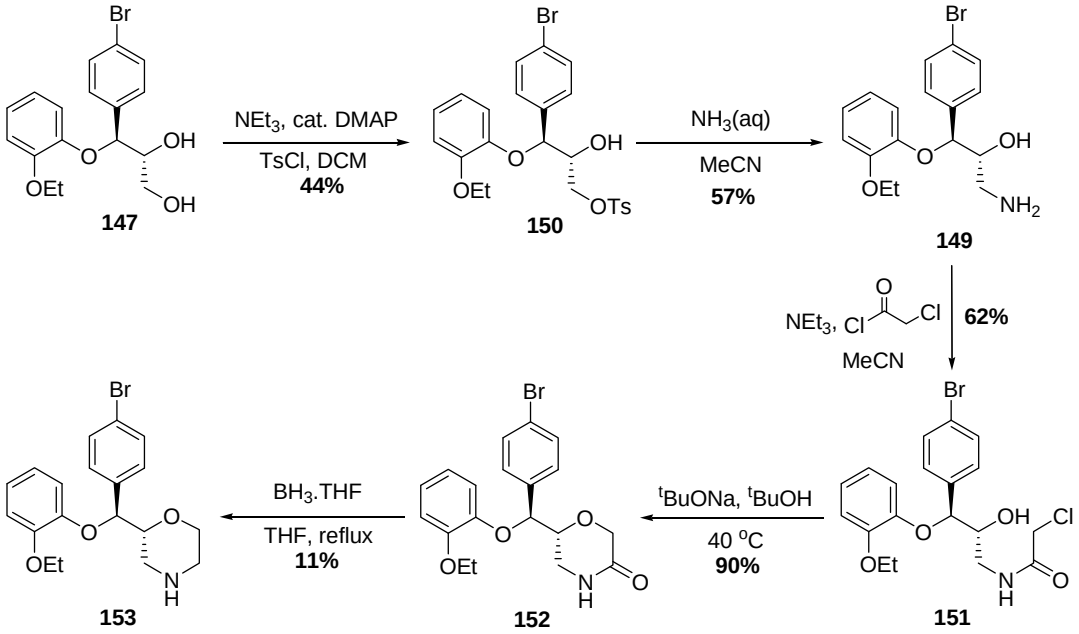
In a bid to increase the selectivity of the tosylation, 2,4,6-triisopropyl benzenesulfonyl chloride was used in place of *p*-toluenesulfonyl chloride to activate the primary alcohol, with the view that the increase in steric bulk around the electrophilic sulfur would discourage nucleophilic attack by 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

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.

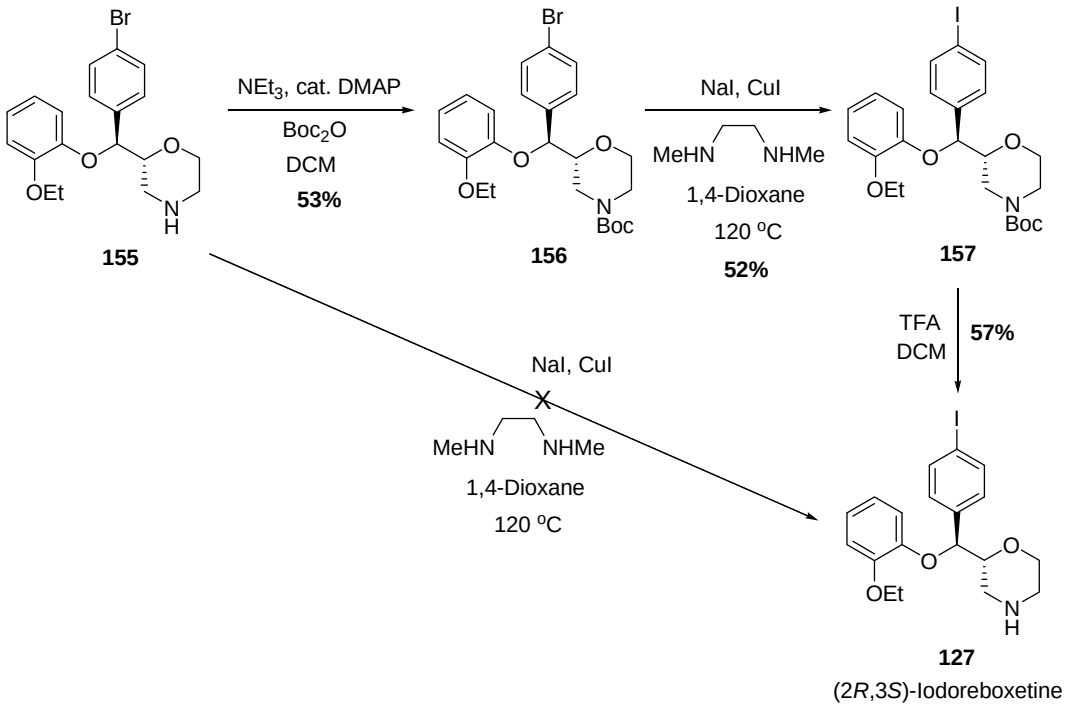


Scheme 33

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'*-dimethylethylenediamine to have a greater conversion rate and recovery than the previously used ligand, 1,3-diaminopropane.[65] 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.[66]

The halogen exchange reaction was carried out using conditions described by Buchwald, this time using *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, (2*R*,3*S*)-iodoreboxetine **127**, in a 57% yield.

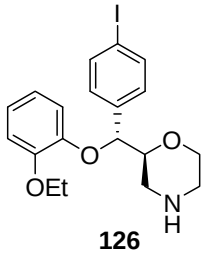
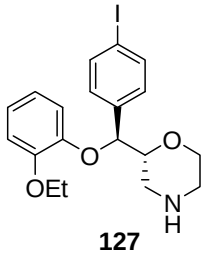


Scheme 34

2.1.4 Biological Evaluation

Both (2*S*,3*R*)- and (2*R*,3*S*)-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 *in vitro* using homogenised rat brain with a [^{3}H]nisoxetine displacement assay. Calculated K_i values for iodo-analogues **126** and **127**, plus the parent compound, racemic (2*S*,3*S*)/(2*R*,3*R*)-reboxetine, are give in Table 8.

Table 8

Compound	NAT (K_i/nM)[a]
(2*S*,3*S*)/(2*R*,3*R*)-**9**	6.9 ± 1.6
 **126** (2*S*,3*R*)-Iodoreboxetine	320.8 ± 9.0
 **127** (2*R*,3*S*)-Iodoreboxetine	58.2 ± 9.4

[a] K_i values are the mean of 3 separate determinations.

From the results shown in Table 8, it can be seen that both (2*S*,3*R*)- and (2*R*,3*S*)-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 (2*R*,3*S*)-iodoreboxetine compound is the more potent of the two compounds with a K_i value of only 58.2 nM, suggesting that (3*S*)-stereochemistry is required for potency.

Although not as potent as the parent compound, racemic reboxetine, the (2*R*,3*S*)-iodoanalogue has similar levels of affinity compared with racemic mixtures of (2*S*,3*S*)- and (2*R*,3*R*)-iodoreboxetine analogues reported in the literature.[54,55]

Therefore the development of more potent iodo-analogues using the (2*R*,3*S*)- 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 (2*S*,3*R*)- and (2*R*,3*S*)-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 (2*R*,3*S*)-stereochemistry to have similar levels of potency compared with the more studied (2*S*,3*S*)- and (2*R*,3*R*)-iodoreboxetine analogues. Therefore, the (2*R*,3*S*)-scaffold was identified as a potential lead for the development of a novel imaging agent for the noradrenaline transporter.

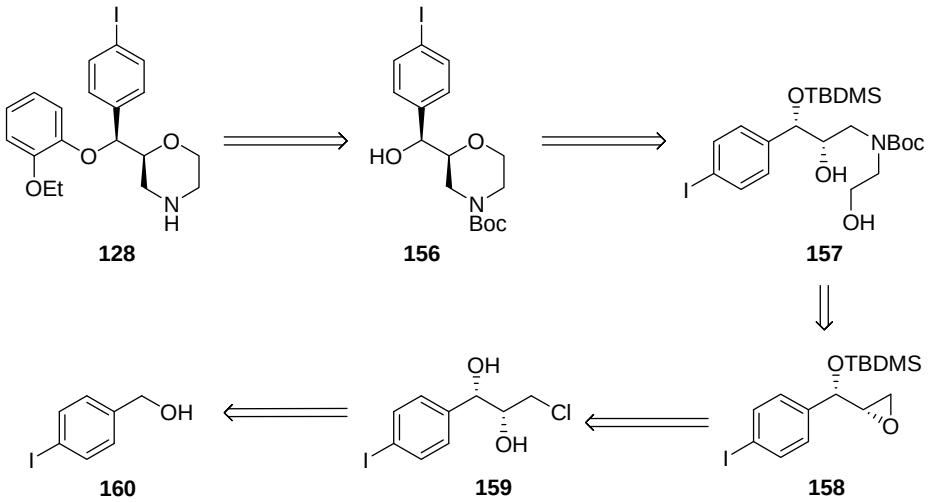
Although a successful synthesis of the target molecules was developed, there were several drawbacks associated with this strategy. The introduction of the second aromatic ring occurred early during the synthetic sequence. Ideally it would be incorporated towards the end of the synthesis, allowing for 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 (2*S*,3*S*)- and (2*R*,3*R*)-Iodoreboxetine

A new synthetic strategy was required for the synthesis of (2*S*,3*S*)- and (2*R*,3*R*)-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 (2*S*,3*S*)-Iodoreboxetine

The proposed retrosynthetic analysis of (2*S*,3*S*)-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

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.[24,31] This strategy would also allow for the synthesis of the (2*R*,3*R*)-stereoisomer by use of AD-mix-β at the asymmetric dihydroxylation step.

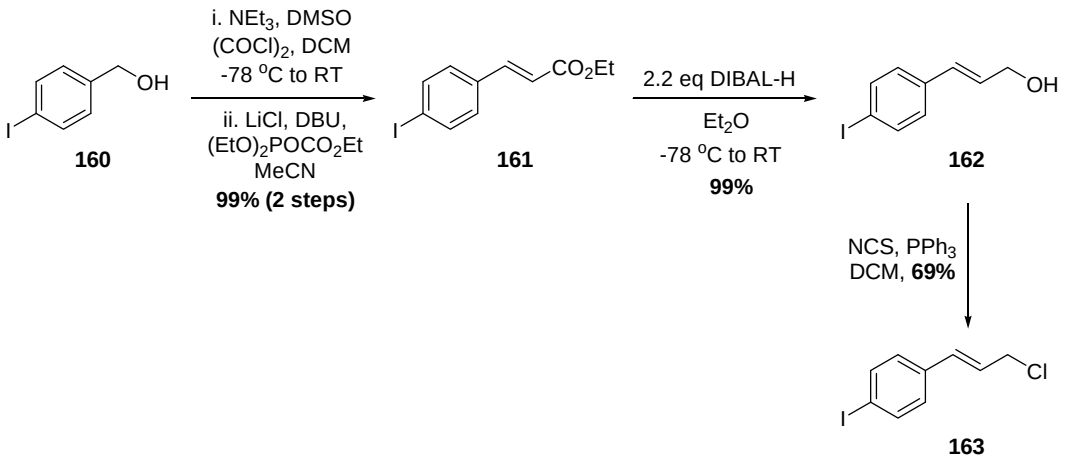
2.2.2 Synthesis of (2*S*,3*S*)-Iodoreboxetine

As shown in Scheme 36, the synthesis of (2*S*,3*S*)-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 *in vacuo* before the addition of the Horner-Wadsworth-Emmons solution. This transformation gave exclusively the *E*-alkene **161** in an excellent 99% yield over two steps.

Reduction of the α,β-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}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.



Scheme 36

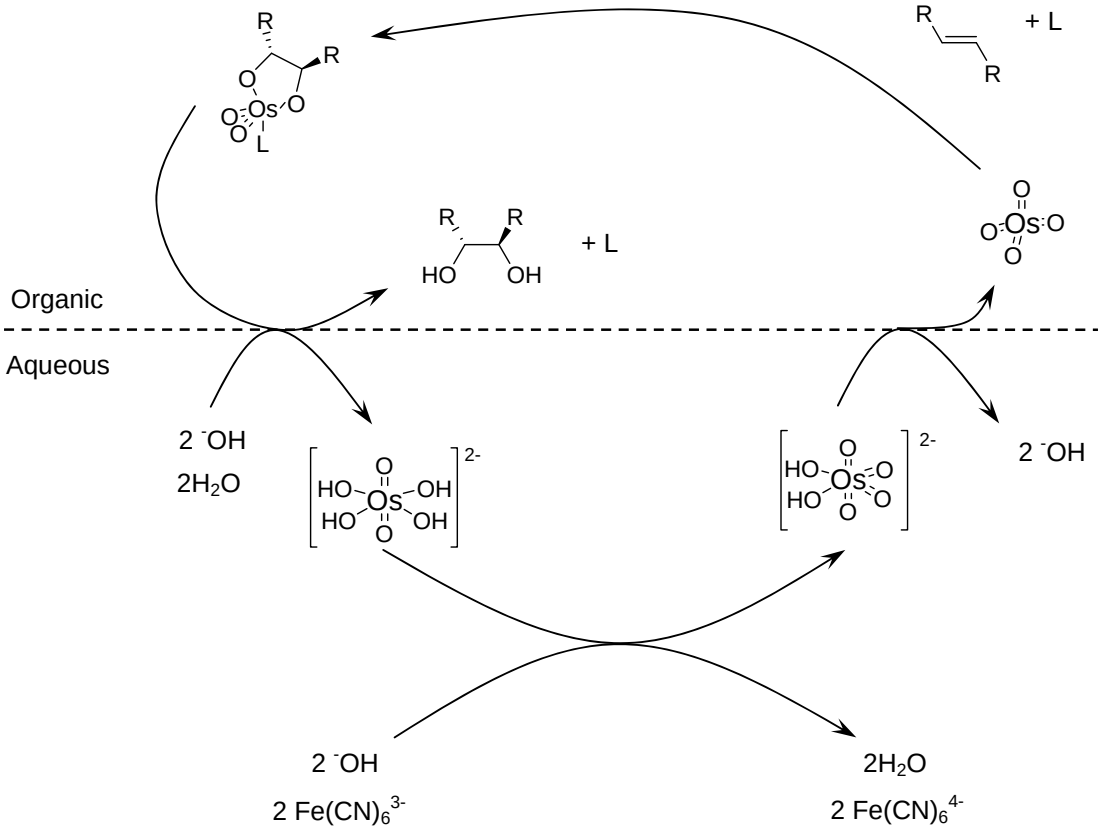
In 1988, Sharpless reported a chiral version of the *syn* dihydroxylation of alkenes by osmium tetroxide. It proved to be an extremely powerful transformation, capable of converting all types of alkenes into *trans* 1,2-diols with excellent enantioselectivity.[67]

The Sharpless asymmetric dihydroxylation is carried out using catalytic amounts of osmium in the form of non-volatile $K_2OsO_2(OH)_4$, 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.

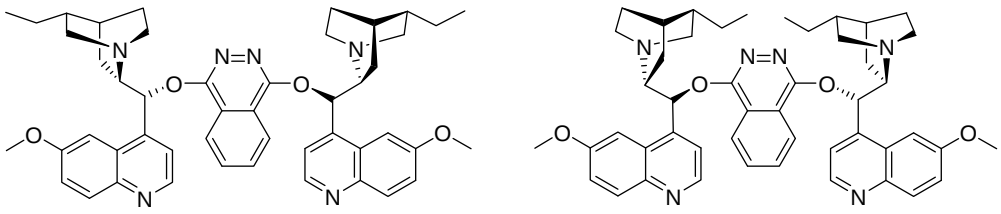
The reaction is carried out in biphasic conditions to eliminate a second, less enantiomerically selective, catalytic cycle in which a second molecule of alkene joins onto the osmium under heterogeneous conditions.

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.



Scheme 37

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 $(DHQ)_2PHAL$ whilst AD-mix-β contains $(DHQD)_2PHAL$.



$(DHQ)_2PHAL$ $(DHQD)_2PHAL$

Figure 26

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.

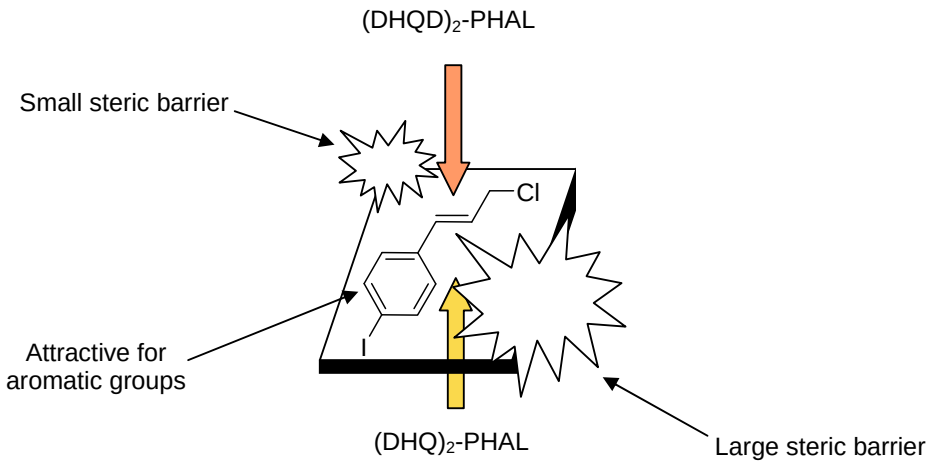
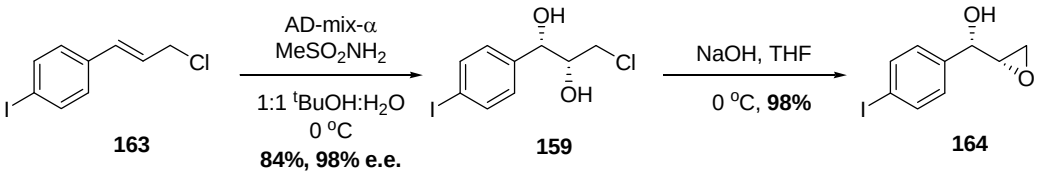


Figure 27

Allylic chloride **163** was subjected to a Sharpless asymmetric dihydroxylation using AD-mix-α to install the desired (2*R*,3*S*) 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.



Scheme 38

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).

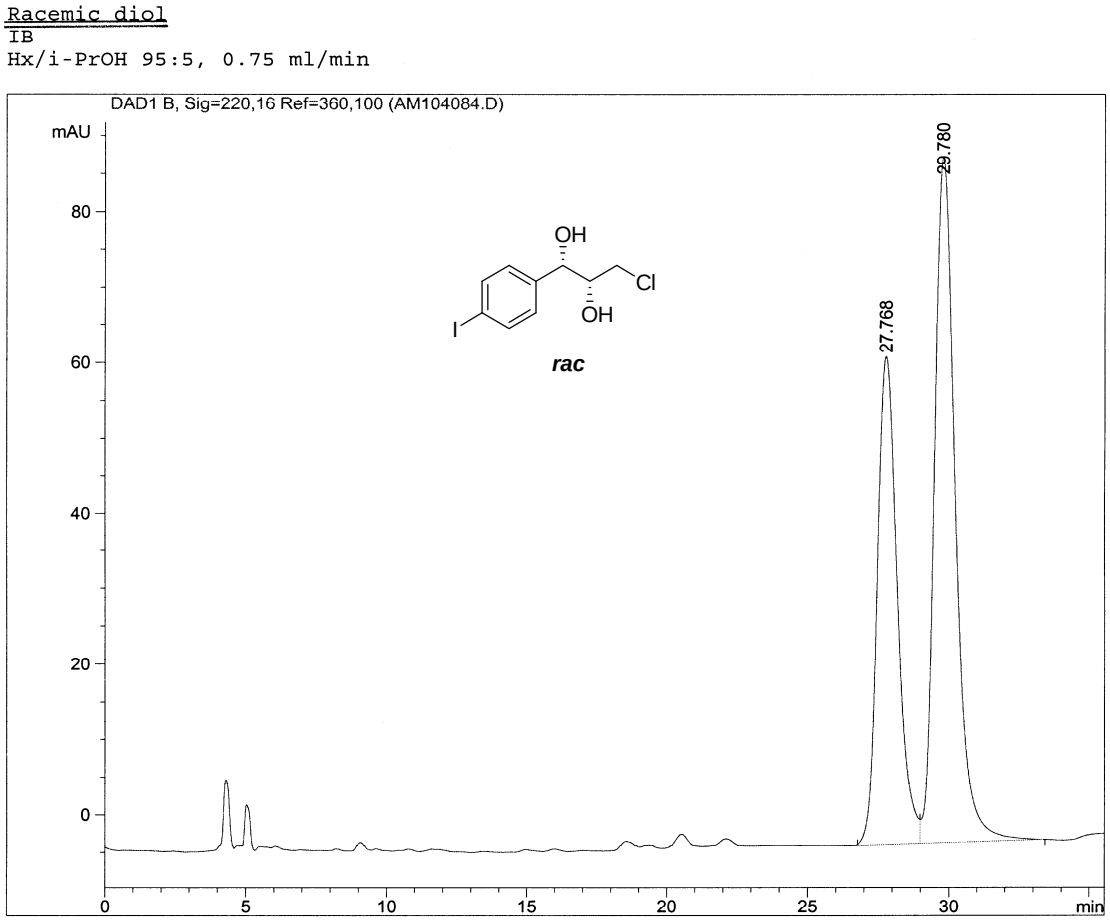


Figure 28

The (2*R*,3*S*)-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.

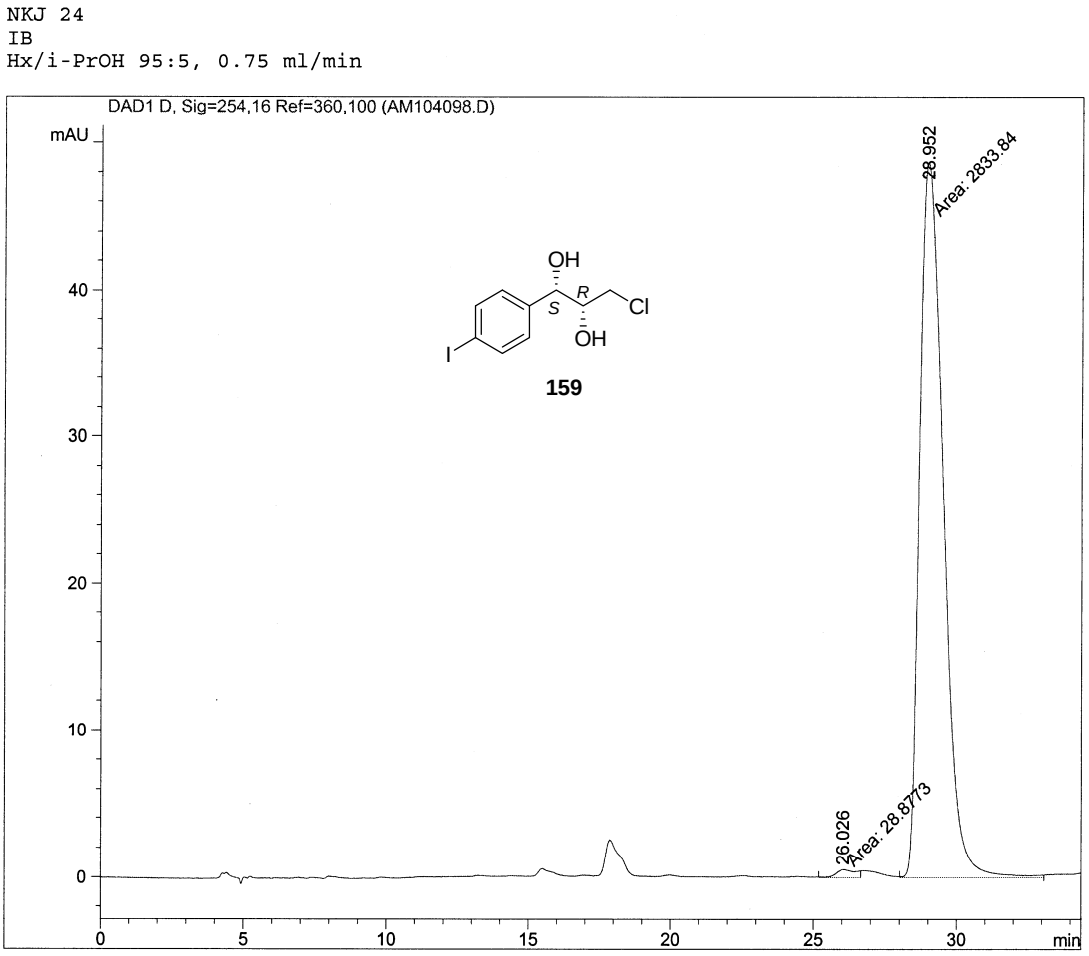
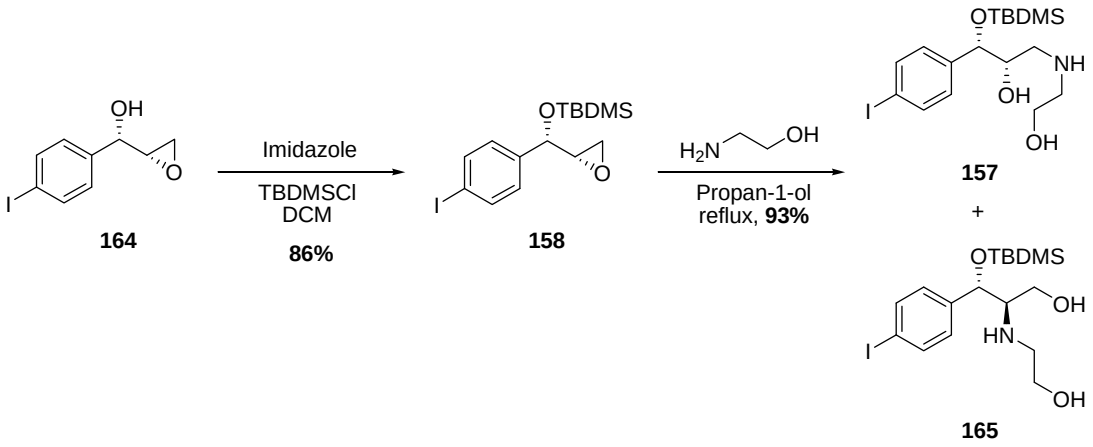


Figure 29

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**.

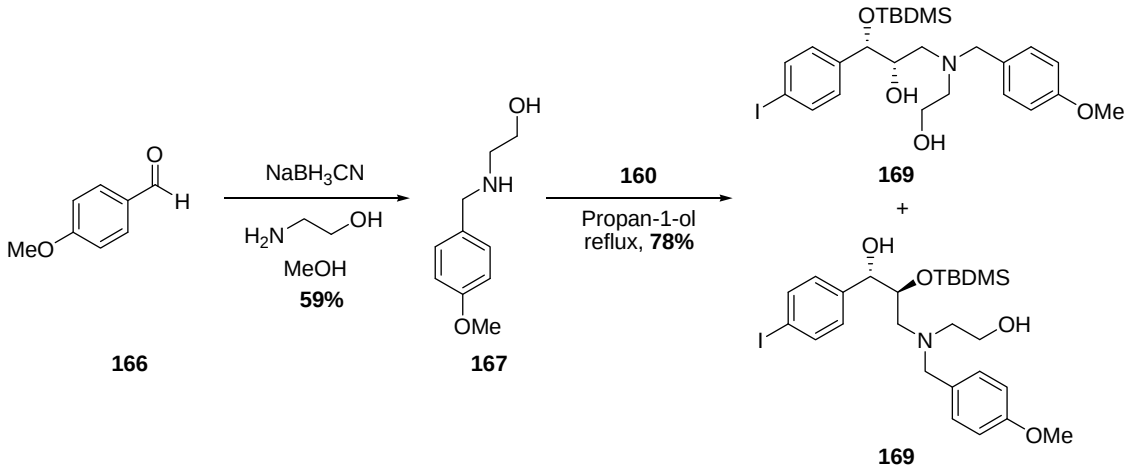


Scheme 39

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.

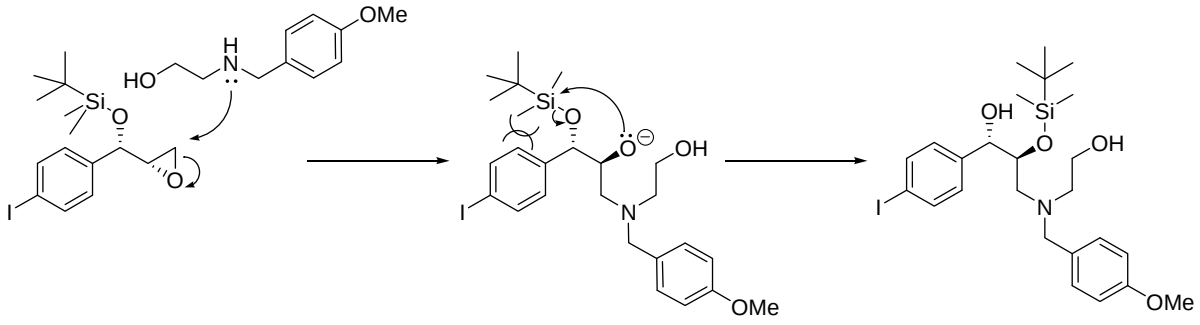
As shown in Scheme 40, the *p*-methoxybenzyl *N*-protected analogue was prepared according to the literature by reaction of ethanolamine with 4-methoxybenzaldehyde **166** followed by *in situ* imine reduction using sodium cyanoborohydride to give **167** in a good 59% yield.[69]

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**.



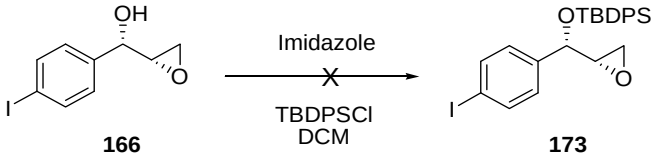
Scheme 40

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**.



Scheme 41

In order to prevent the silyl migration occurring, protection of the secondary alcohol as the *tert*-butyldiphenylsilyl 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).

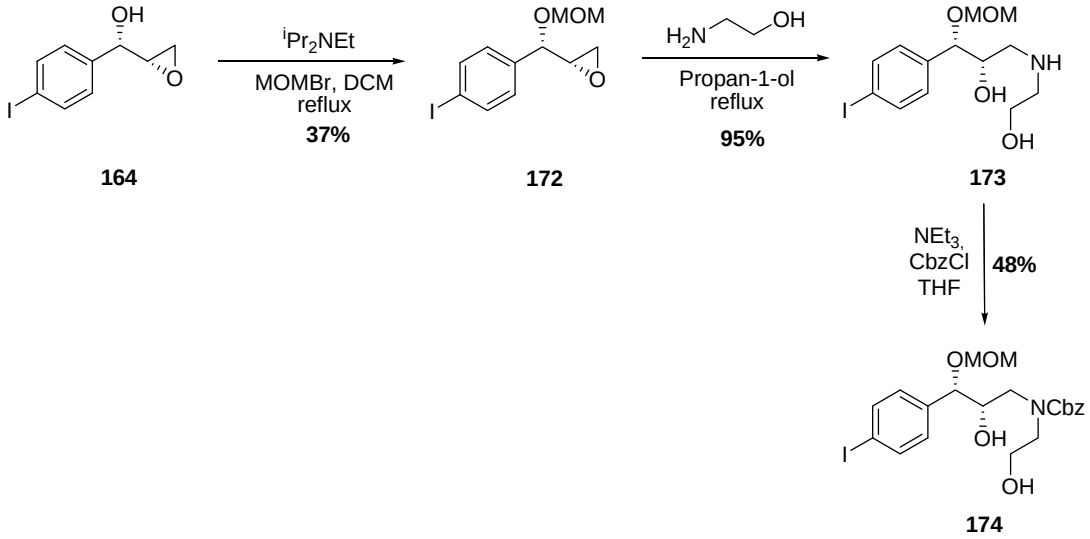


Scheme 42

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.



Scheme 43

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).

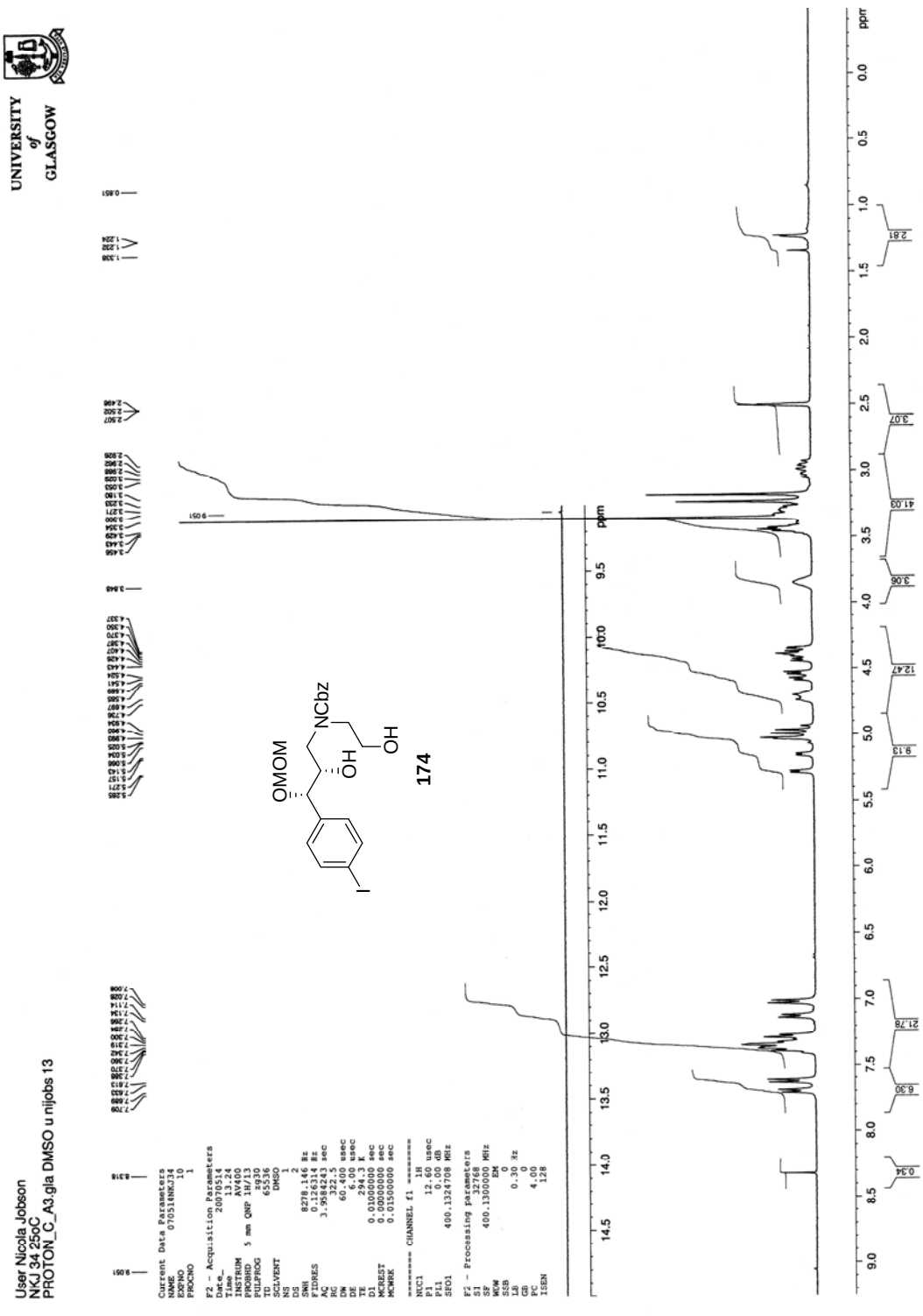

User Nicola Jobson
NKJ 34 25oC
PROTON_C_A3.gla DMSO u nijobs 13
UNIVERSITY of GLASGOW
OMOM
NCbz
OH
OH
I
174
ppm

Figure 30

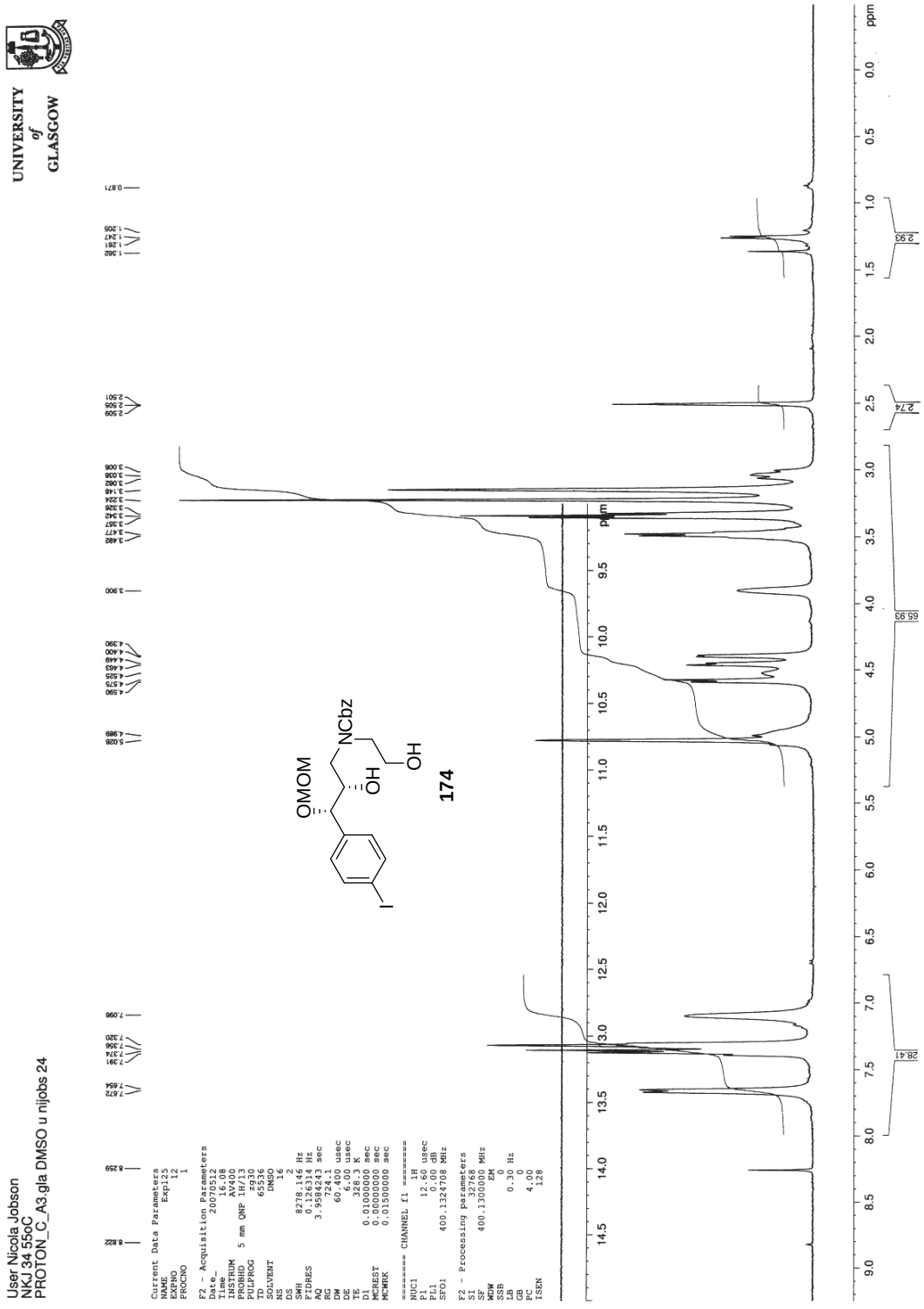

UNIVERSITY of GLASGOW
User Nicola Jobson
NKJ 34 55oC
PROTON_C_A3.gla DMSO u nijobs 24
OMOM
NCbz
OH
OH
I
174
ppm
2.93
2.74
65.93
28.41

Figure 31

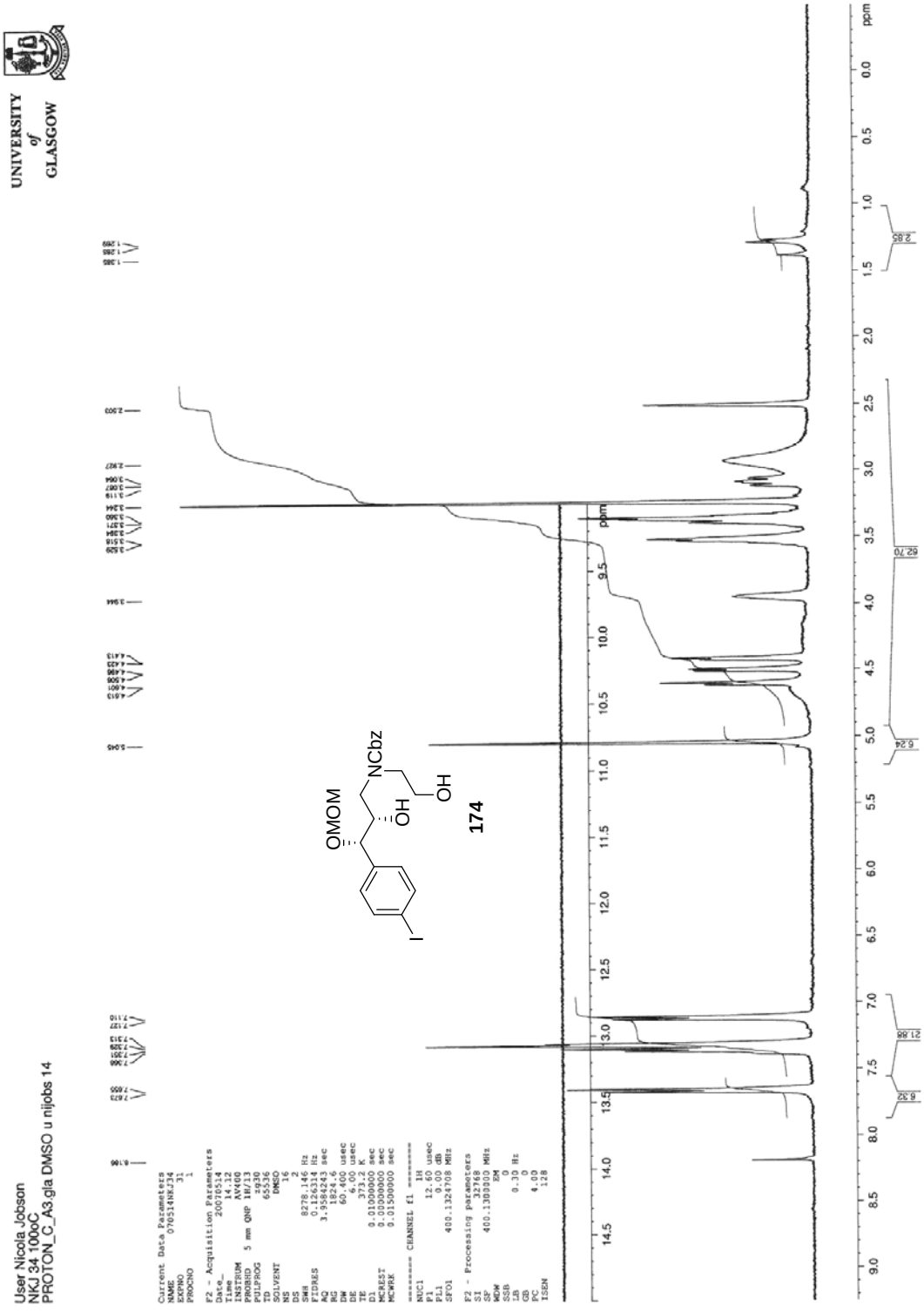
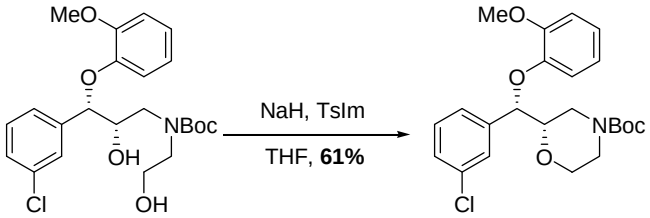

User Nicola Jobson
NKJ 34 100oC
PROTON_C_A3.gla DMSO u nijobs 14
UNIVERSITY of GLASGOW
OMOM
NCbz
OH
OH
I
174
ppm

Figure 32

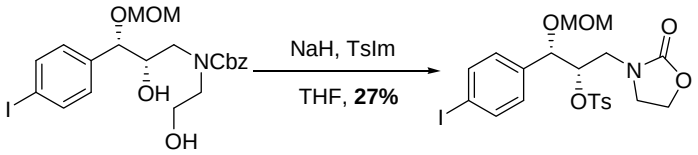
The Harding group described a one-pot procedure for the formation of a morpholine ring by reaction of diol **175** with sodium hydride and tosyl imidazole to affect ring closure (Scheme 44).[70]



175 **176**

Scheme 44

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



174 **177**

Scheme 45

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.[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.

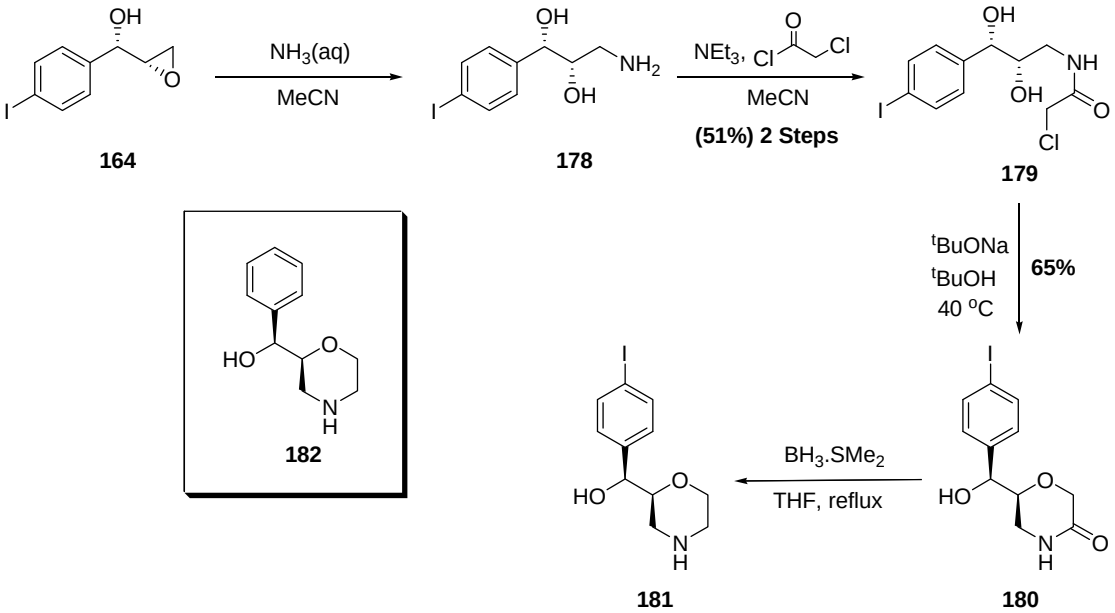
Effecting ring closure by splitting the sequence into selective tosylation of the primary alcohol followed by treatment with base and displacement of the tosyl group by the resultant alkoxide was an alternative option. Unfortunately the initial tosylation of diol **176** yielded a complex crude mixture 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 (2*S*,3*R*)- and (2*R*,3*S*)-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 ^{1}H 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.



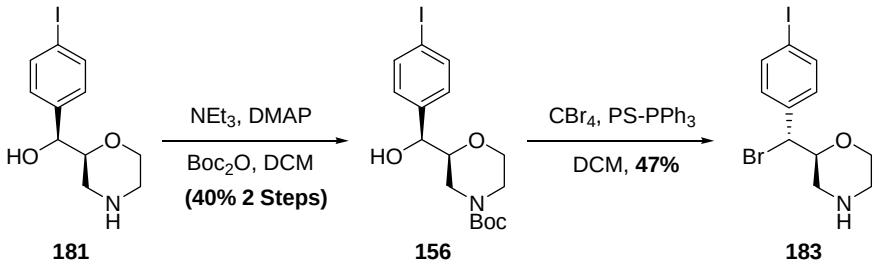
Scheme 46

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 (2*S*,3*S*)-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**.



181 **156** **183**

Scheme 47

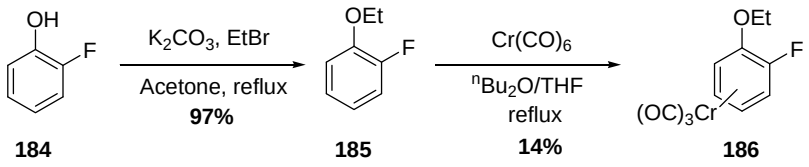
Insertion of the phenoxy ring using epimer **183** was attempted using 2-ethoxyphenol, however this give a complex crude reaction mixture. It was proposed that the unprotected amine may have been deprotonated by the base, and the resultant nucleophilic amine displaced the halogen. It was therefore concluded 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_N2 mechanism. The stability of the benzyl cation could allow a S_N1 reaction to occur and produce a mixture of compounds with (2*S*,3*S*)- and (2*S*,3*R*)- 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.

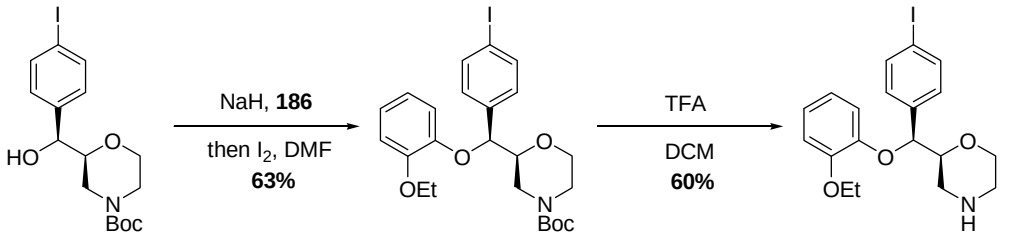
As shown in Scheme 48, chromium complex **186** was prepared according to the literature from the alkylation of commercially available 2-fluorophenol **184** with bromoethane in an excellent 97% yield.[24] The chromium complex was formed by reaction of **185** with chromium hexacarbonyl in a mixture 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.[24]



Scheme 48

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, (2*S*,3*S*)-iodoreboxetine **128**, in a good 60% yield.



156 **187** **128**

(2*S*,3*S*)-Iodoreboxetine

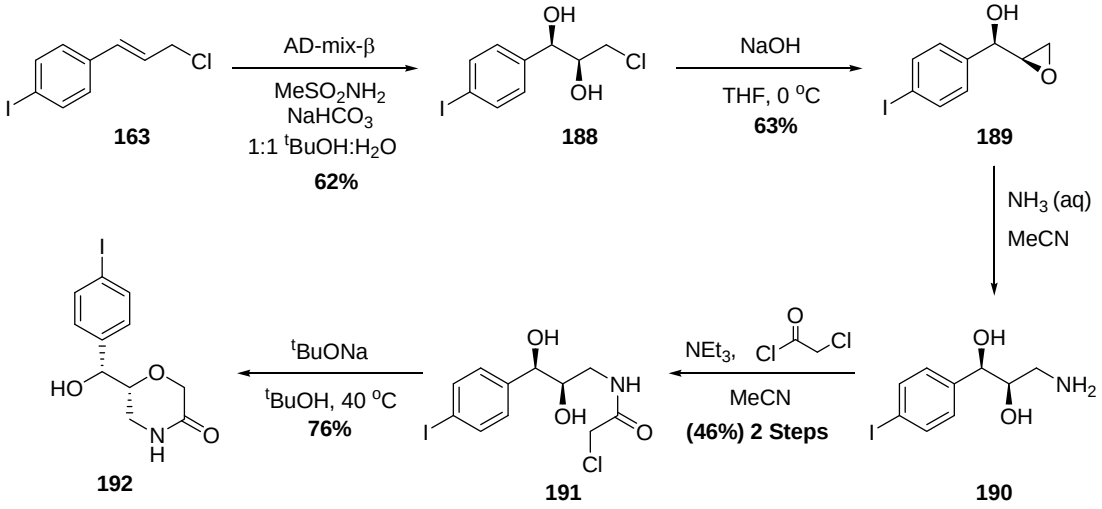
Scheme 49

2.2.3 Synthesis of (2*R*,3*R*)-Iodoreboxetine

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



Scheme 50

The enantiomeric excess of the (2*S*,3*R*)-diol **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).

NKJ 46
IB
Hx/i-PrOH 95:5, 0.75 ml/min

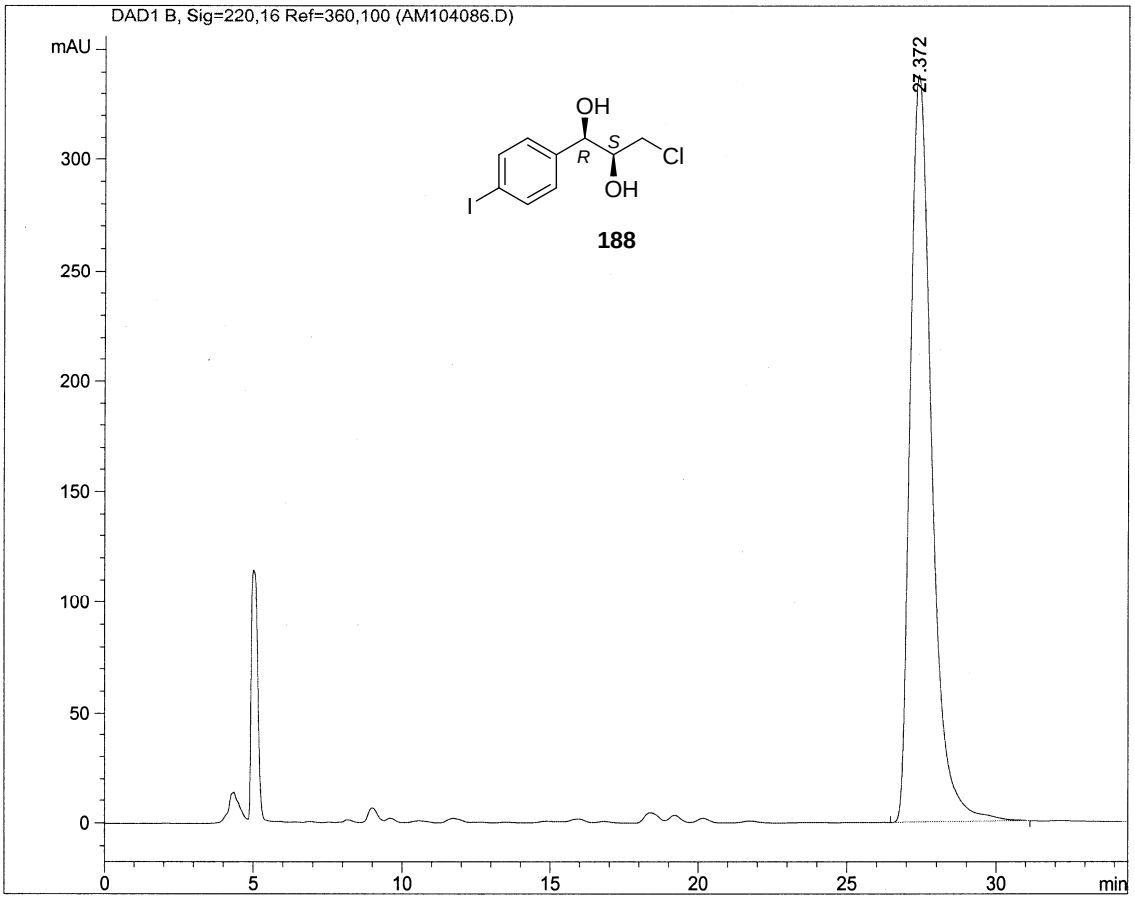
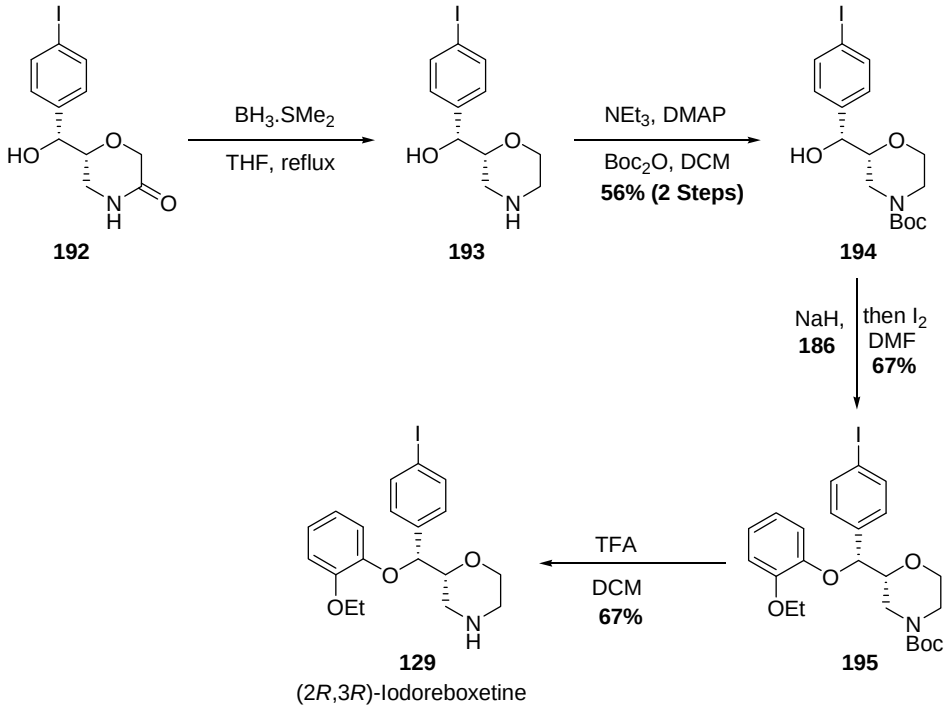


Figure 33

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, (2*R*,3*R*)-iodoreboxetine **129**, in a good 67% yield.

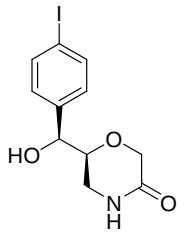
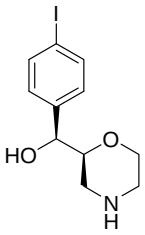


Scheme 51

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

Compound	NAT K_i (nM)[a]
 **180**	>1000
 **181**	>10000

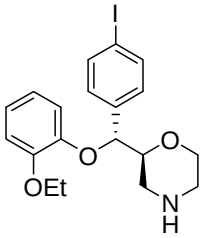
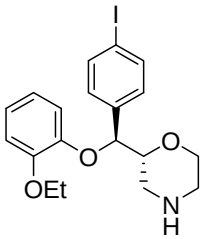
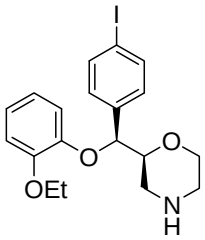
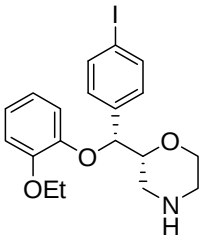
[a] K_i values are the mean of 3 separate determinations.

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

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

Table 10

Compound	NAT K_i (nM)[a]	SERT K_i (nM)[b]	DAT K_i (nM)[b]
 **126** (2*S*,3*R*)-Iodoreboxetine	320.8 ± 9.0	-	-
 **127** (2*R*,3*S*)-Iodoreboxetine	58.2 ± 9.4	-	-
 **128** (2*S*,3*S*)-Iodoreboxetine	53.8 ± 2.7	2793 ± 480	1457 ± 150
 **129** (2*R*,3*R*)-Iodoreboxetine	64.0 ± 2.4	646 ± 142	716 ± 20

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

As expected, (2*S*,3*S*)-iodoreboxetine **128** has higher affinity with a K_i value of 53.8 nM, but surprisingly, (2*R*,3*R*)-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 (2*R*,3*R*)-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 (2*S*,3*S*)- and (2*R*,3*S*)-iodoanalogues and explain the similar levels of potency.

Of most interest is the comparison of the (2*R*,3*S*)- and (2*S*,3*S*)-iodoanalogues. Previously untested (2*R*,3*S*)-iodoreboxetine shows comparable potency to the much more studied (2*S*,3*S*)-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

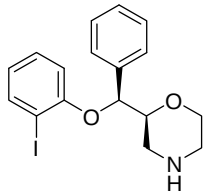
A new 12-step stereoselective route for the synthesis of iodinated analogues of (2*S*,3*S*)- and (2*R*,3*R*)-iodoreboxetine was developed from 4-iodobenzyl alcohol. The key steps in this synthetic sequence involved a Sharpless asymmetric dihydroxylation to establish the desired stereochemistry and a 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 (2*R*,3*S*)-stereochemistry was found to be as potent as the more investigated (2*S*,3*S*)-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 (2*R*,3*S*)- and (2*S*,3*S*)-derivatives, was not good enough to warrant radiolabeling and further development of more potent analogues was required.

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

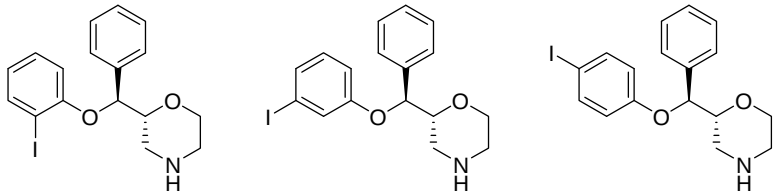
The groups of Saji and Tamagnan reported the synthesis and activity of (2*S*,3*S*)-iodoanalogue **118**, replacing the ethoxy group with an iodine atom (Figure 34).[54,55] This derivative was found to have excellent affinity for the noradrenaline transporter with a K_i value of 0.84 nM.



(2*S*,3*S*)-118

Figure 34

The results of the previous studies suggest that a (2*R*,3*S*)-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 (2*S*,3*S*)- and (2*R*,3*R*)-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.

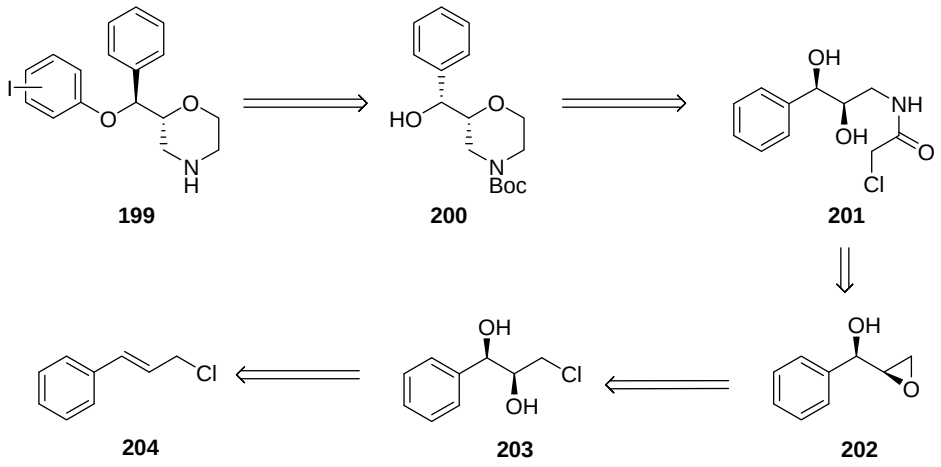


196 **197** **198**

Figure 35

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

The proposed retrosynthetic analysis of (2*R*,3*S*)-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**.



199 **200** **201** **202** **203** **204**

Scheme 52

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.

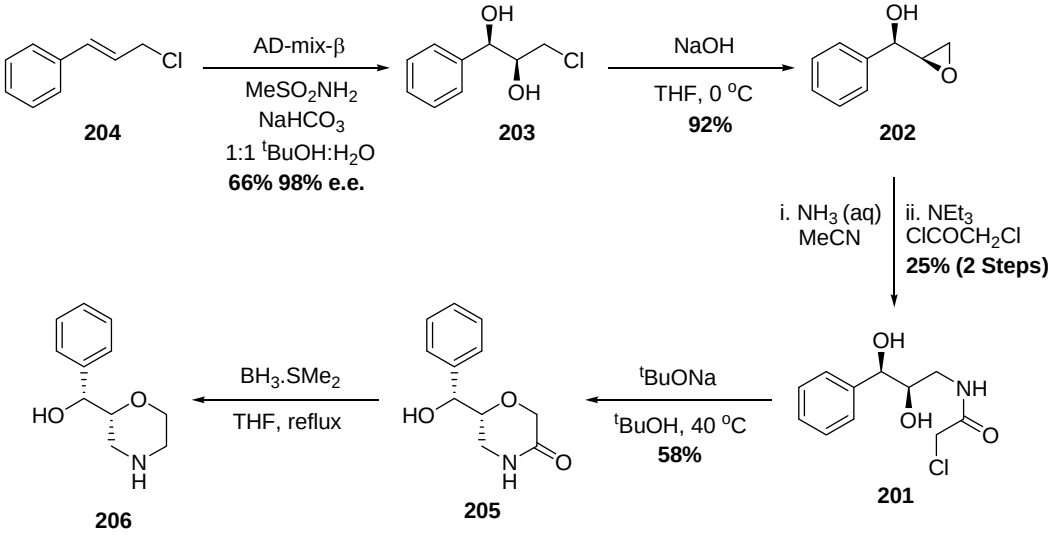
2.3.2 Synthesis of (2*R*,3*S*)-Iodoreboxetine Analogues

As shown in Scheme 53, the synthesis of (2*R*,3*S*)-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 (2*S*,3*R*)-stereochemistry and give diol **203** in a 66% yield, and excellent 98% enantiomeric excess.[73] 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.

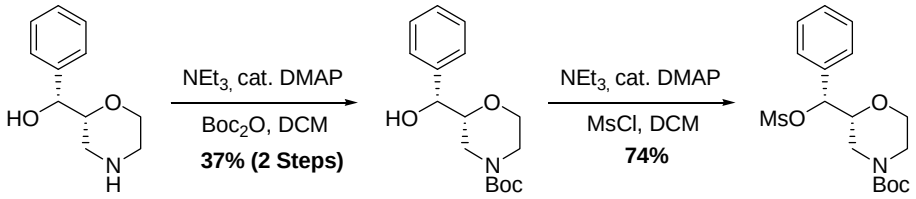


Scheme 53

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]

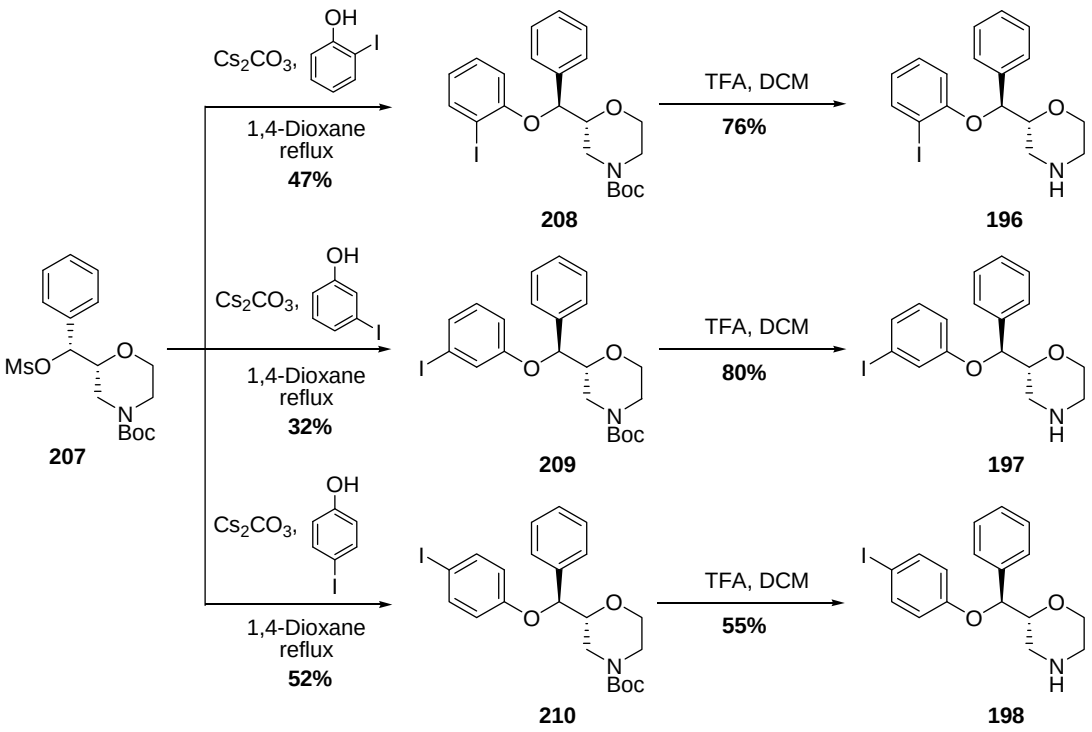
Thus, secondary alcohol **202** was activated as the mesylate to give **209** in a good 74% yield.[29] Isolation of the mesylate intermediate proved successful compared with the 2-step Mitsunobu approach where the deprotection was a problem. Concerns over the stereochemical outcome of the reaction were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



206 **200** **207**

Scheme 54

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.

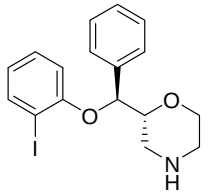
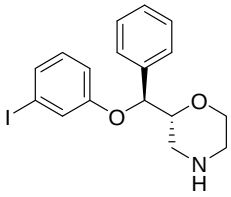
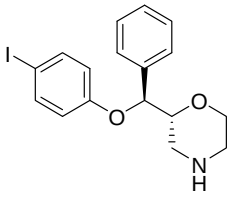


Scheme 55

2.3.3 Biological Evaluation

The three (2*R*,3*S*)-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}H]nisoxetine, [^{3}H]citalopram and [^{3}H]WIN-35,428 displacement assays. The calculated K_i values for the three compounds are given in Table 11.

Table 11

Compound	NAT K_i (nM)[a]	SERT K_i (nM)[b]	DAT K_i (nM)[b]
 **196**	8.4 ± 1.7[b]	51.5 ± 8.4	525.9 ± 125.5
 **197**	1700 ± 500	154.0 ± 12.0	1900 ± 600
 **198**	1100 ± 200	34.5 ± 1.7	2100 ± 300

[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]

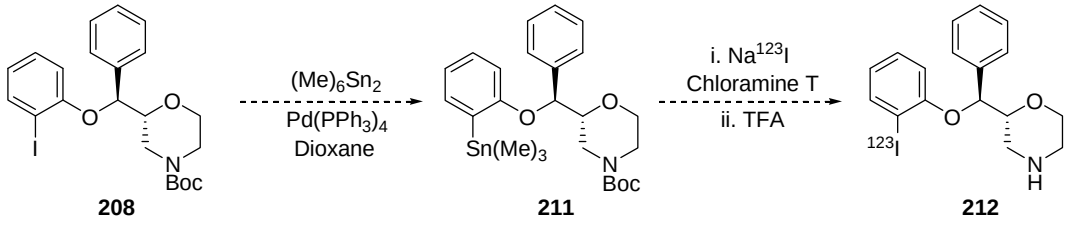
Substitution in the *meta* or *para* position of the phenoxy ring appears to decrease affinity, with K_i values falling into the micromolar range. Interestingly, **198** displayed promising affinity for the serotonin transporter with 30- and 60-fold selectivity over the noradrenaline and dopamine transporters.

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 (2*R*,3*S*)-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

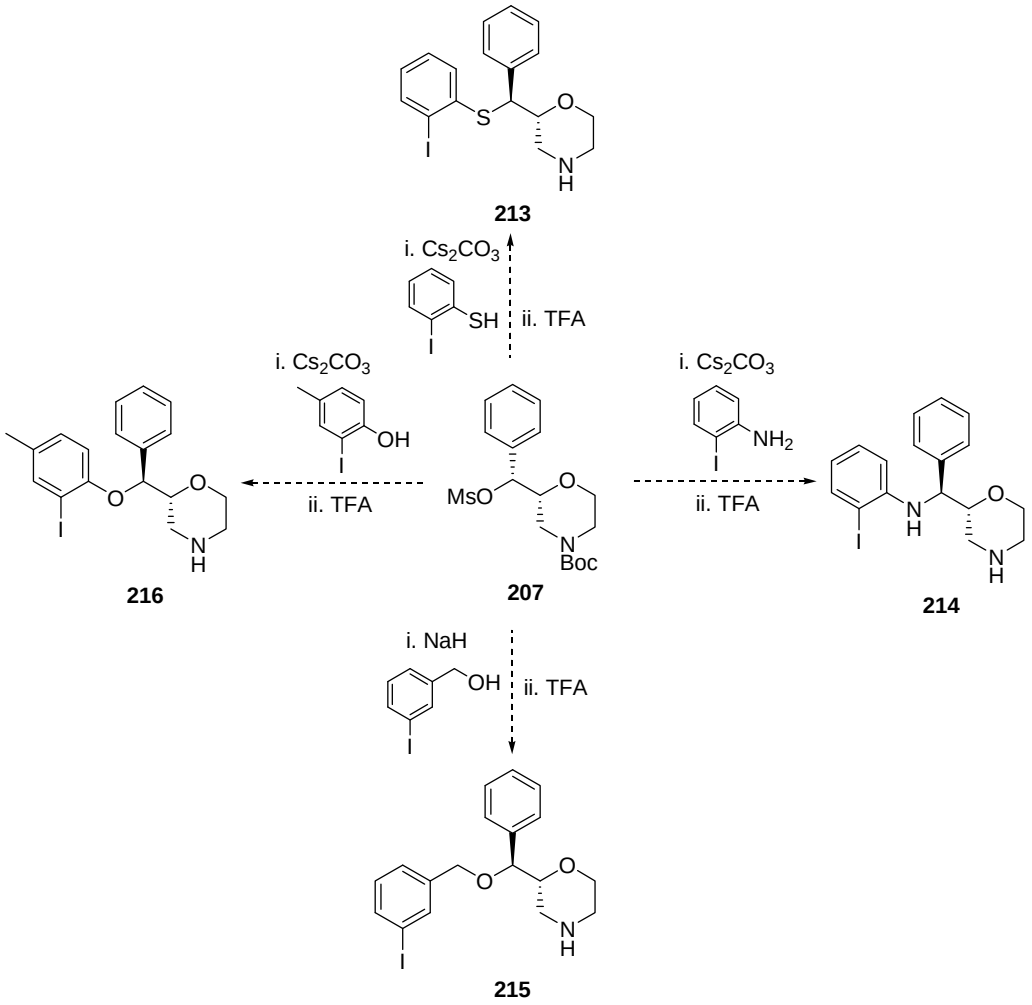
Future work for this project includes the radiolabeling of **196** (Scheme 56). Radiosynthesis would require conversion of Boc-protected **208** into tin precursor **211** by treatment with hexamethylditin and a palladium(0)-catalyst. Electrophilic iododestannylation of **211** using sodium [^{123}I]-iodide 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.[74]



208 **211** **212**

Scheme 56

The synthesis and biological evaluation of iodoanalogues of reboxetine based on the (2*R*,3*S*)-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.


213
i. Cs2CO3
ii. TFA
SH
I
i. Cs2CO3
ii. TFA
OH
I
i. Cs2CO3
ii. TFA
NH2
I
MsO
Boc
O
N
H
S
216
207
214
i. NaH
ii. TFA
OH
I
215

Scheme 57

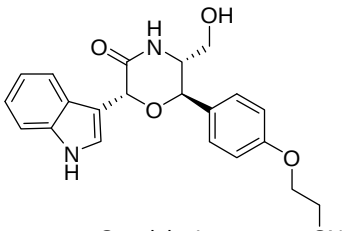
2.4 A New Synthetic Approach for the Total Synthesis of Oxazinin-3

2.4.1 Introduction

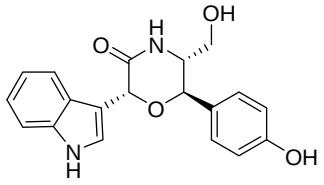
Algal blooms are caused by the proliferation of phytoplankton and cyanobacteria during periods of nutrient abundance in the ocean (Figure 36). Some species of microalgae can produce potent toxins that can contaminate edible shellfish, which if consumed, can pose a serious threat to human health. Therefore,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

Figure 36

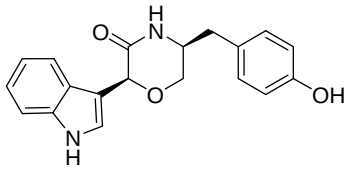
Algal blooms are also a rich source of novel biologically active compounds, which include brevetoxins, saxitoxin and okadaic acid.[75] In 2001, the Fattorusso group isolated and characterised a family of novel marine toxins isolated from the edible muscle *Mytilus Galloprovincialis*. These compounds, 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*.[76]



Oxazinin-1



Oxazinin-2



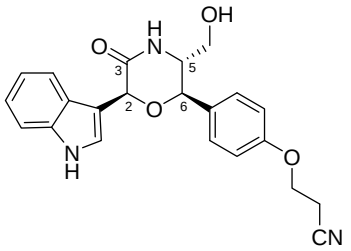
Oxazinin-3

Figure 37

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.

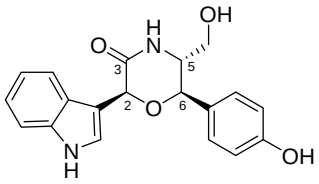
The relative stereochemistry of oxazinin-1 was assigned by examination of NMR spectroscopic data. The coupling constant of 9.2 Hz between H-5 and H-6 in the ^{1}H NMR spectrum suggested a *trans*-diaxial relationship between the two protons. An intense cross peak in the ROESY spectrum between H-2 and H-6 suggested a *cis*-relationship. Thus, the relative stereochemistry was ascertained to be 2*S*,5*R*,6*R*/2*R*,5*S*,6*S* (Figure 38).



217

Figure 38

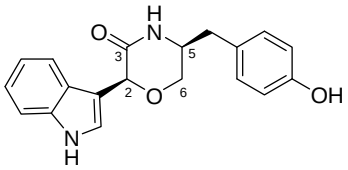
According to the spectroscopic data, the structure of oxazinin-2 was identical to that of oxazinin-1 with the exception of the absence of the cyanide group and associated methylene signals. Thus, the structure and relative stereochemistry of oxazinin-2 was determined to be **218** (Figure 39).



218

Figure 39

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 2*S*,5*S*/2*R*,5*R* (Figure 40).



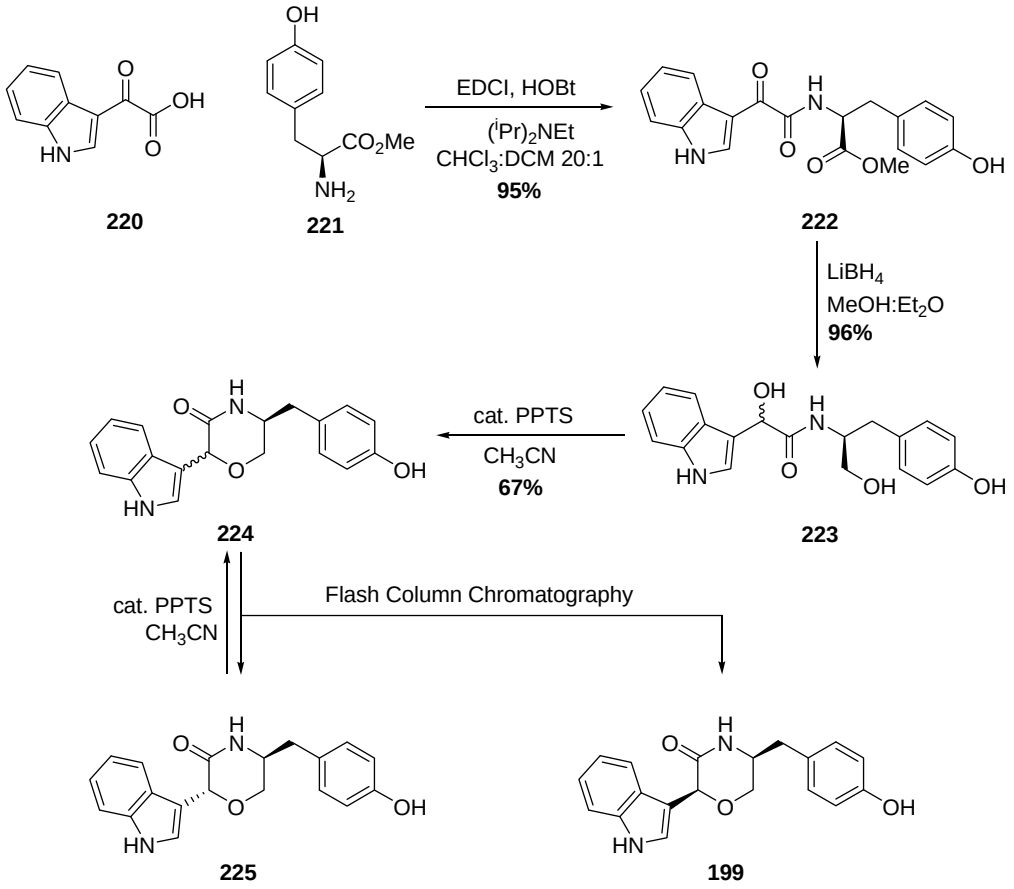
219

Figure 40

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 2*S*,5*R*,6*R*.[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.



Scheme 58

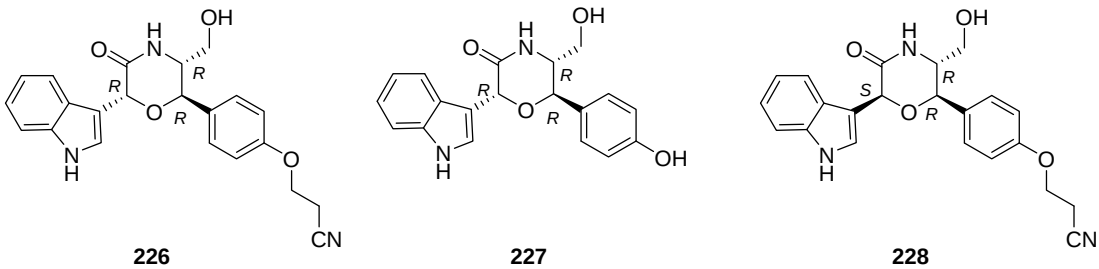
The *cis*-isomer was found to have identical ^{1}H NMR spectra to that reported for oxazinin-3, and comparison of the optical rotation values for the natural and synthetic material established the absolute stereochemistry of oxazinin-3 as 2*S*,5*S*. This synthetic approach gave target molecule oxazinin-3 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*.[80] 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 **226** and -2 **227** to be 2*R*,5*R*,6*R* (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 **228** to be 2*S*,5*R*,6*R*.



226
Oxazinin-1

227
Oxazinin-2

228
Oxazinin-4

Figure 41

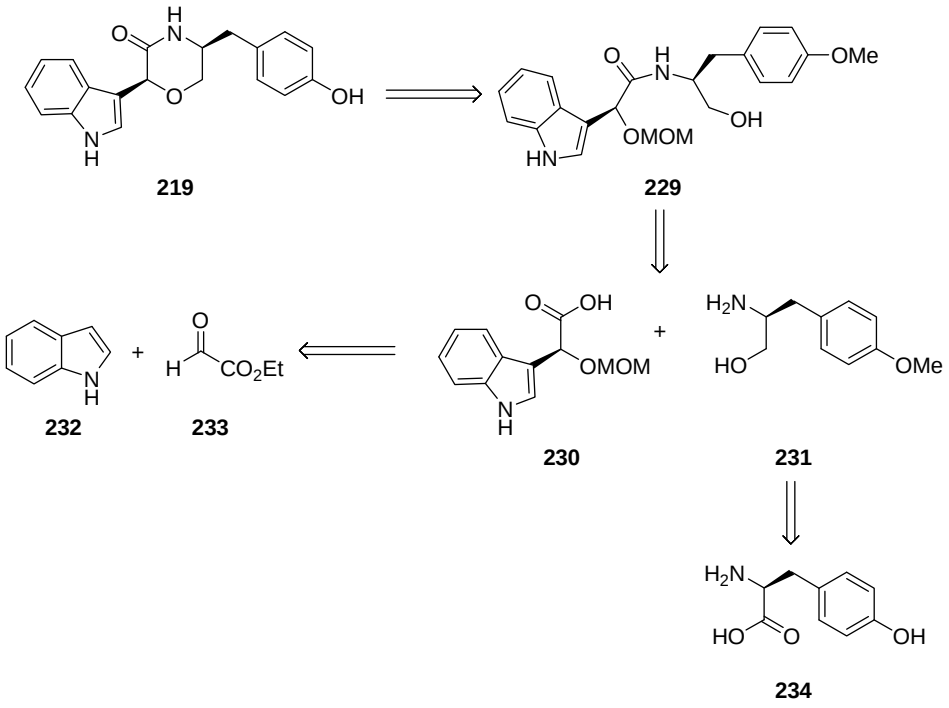
2.4.5 Proposed Research

The published synthesis of oxazinin-2 is relatively long, consisting of 14 steps.[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**.



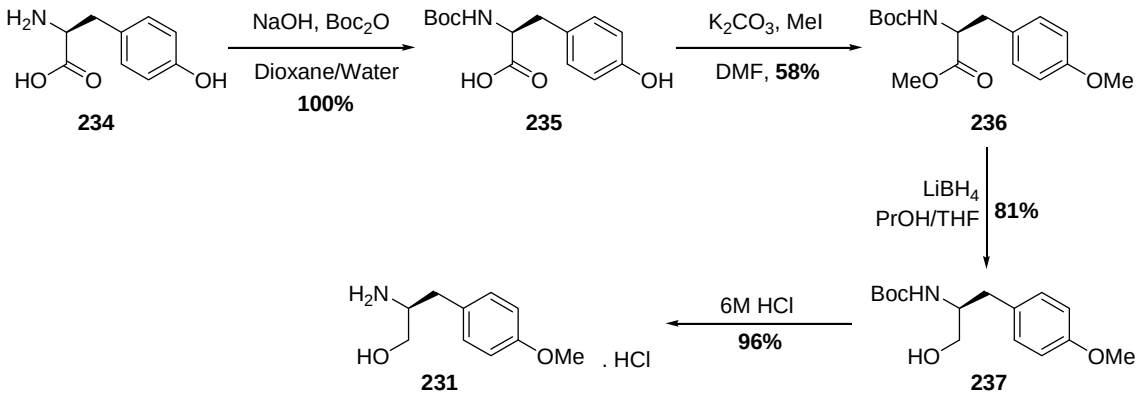
Scheme 59

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

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]

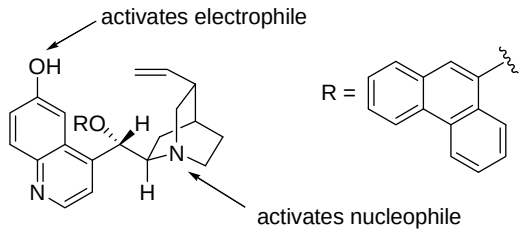


Figure 42

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).[81]

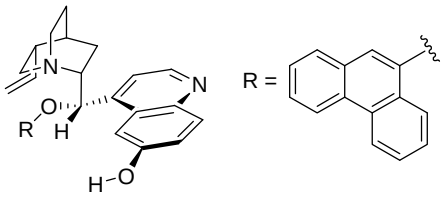


Figure 43

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.[81]

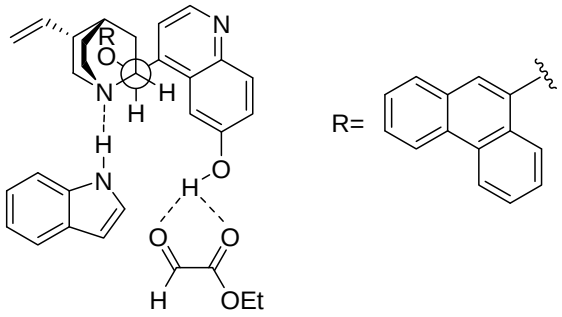
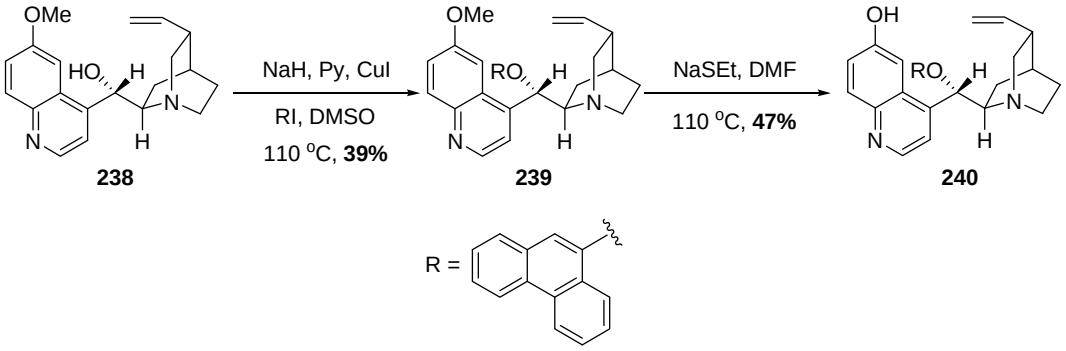


Figure 44

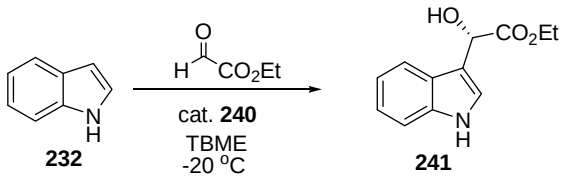
The Deng group report the enantioselective reaction of indole with ethyl glyoxylate to proceed in an 85% yield and good 93% enantiomeric excess.[83] The cinchona alkaloid catalyst required to induce the desired (*S*)-stereochemistry was reported to be easily synthesised from commercially available quinidine over two steps in a 60% overall yield.[82]

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).



Scheme 61

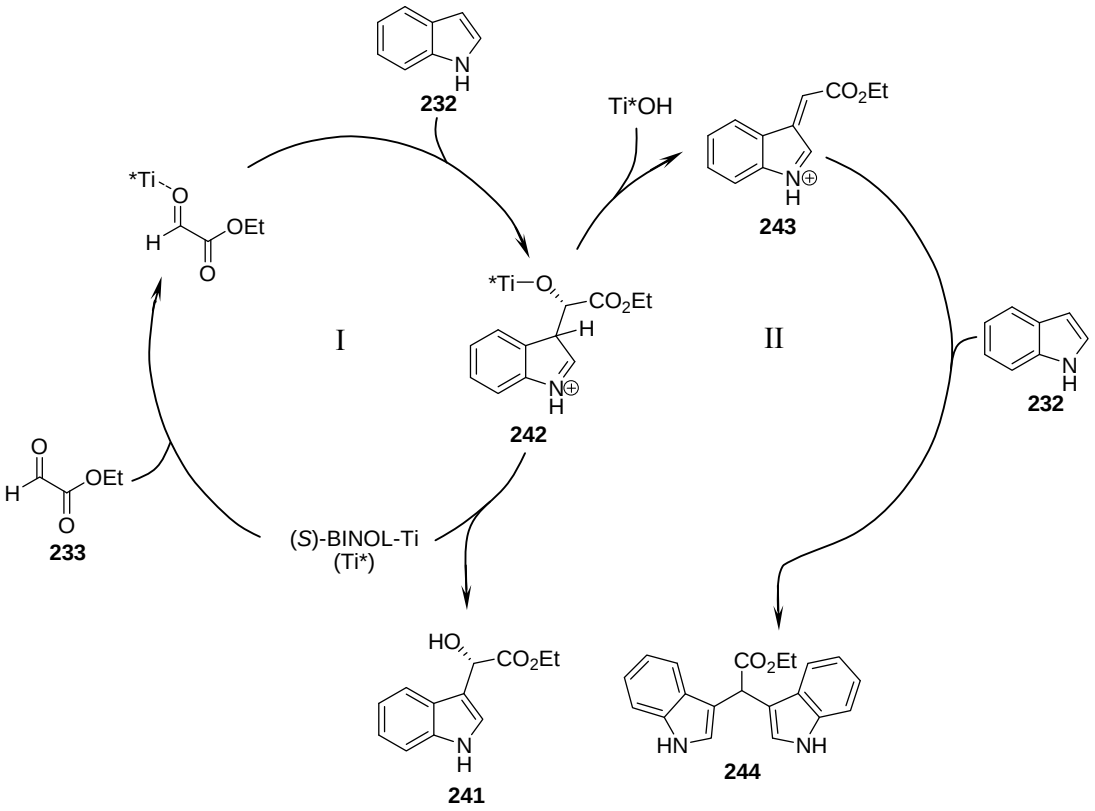
The asymmetric Friedel-Crafts reaction was attempted using indole and ethyl glyoxylate under conditions described by Deng (Scheme 62). The crude reaction mixture showed formation of the target molecule **241**, however purification of the crude reaction mixture using silica gel proved difficult, and gave **241** with a significant amount of impurities present.



Scheme 62

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.[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.



Scheme 63

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.[85,86] 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.

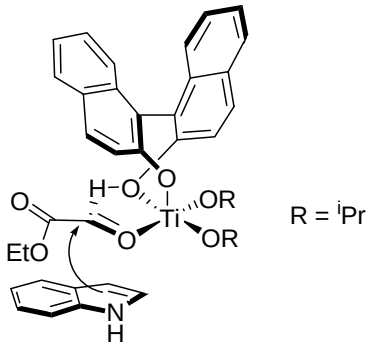
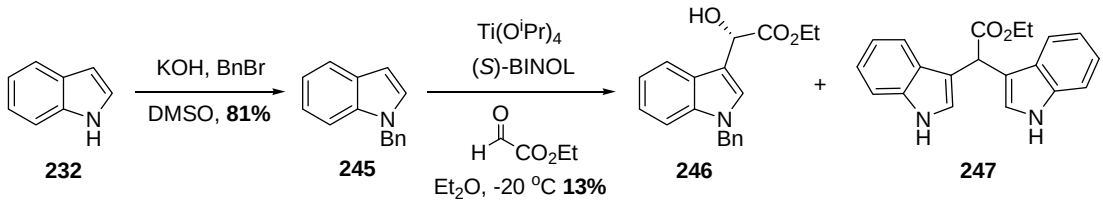


Figure 45

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.[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.[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).[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.

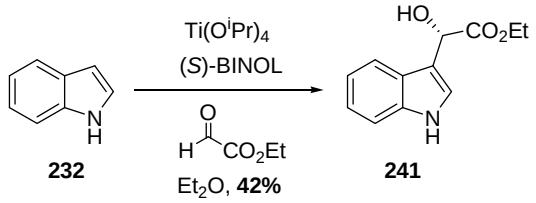


Scheme 64

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.



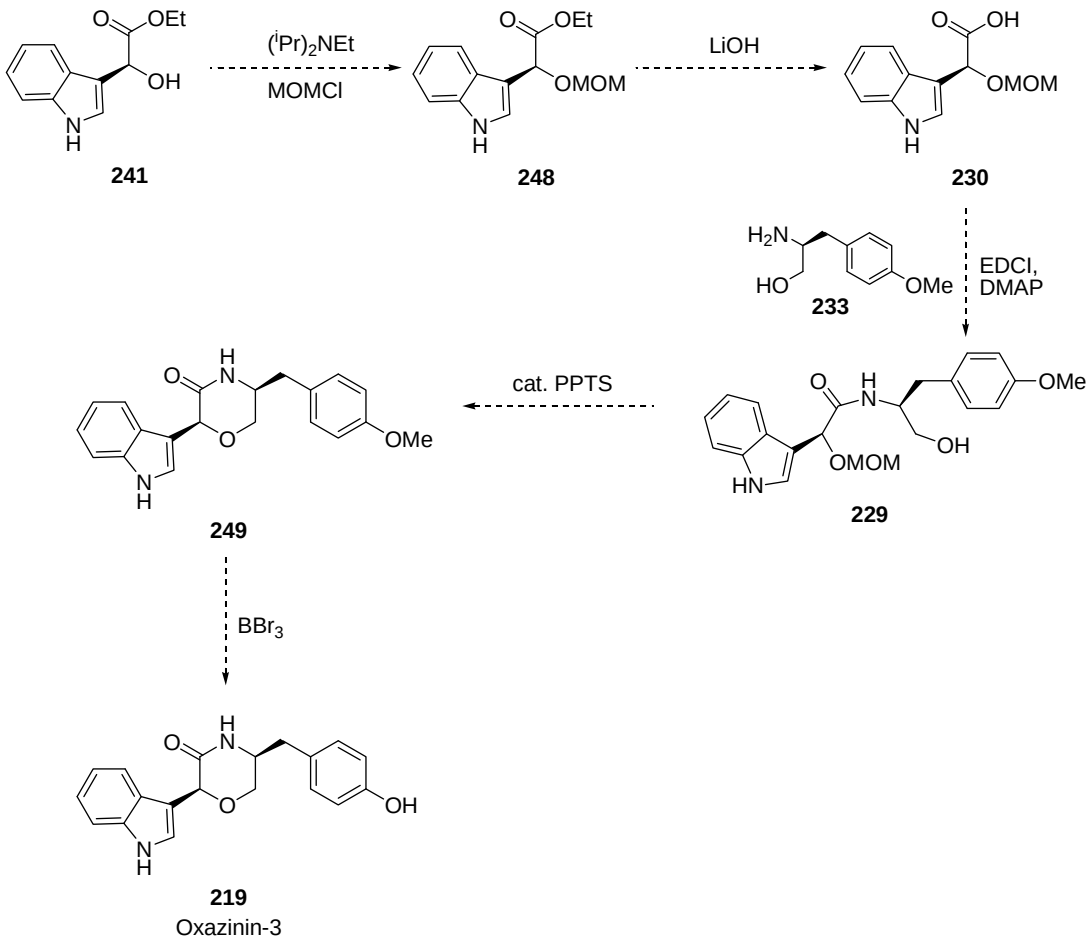
232 241

Scheme 65

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.[79] Deprotection of **249** would give target molecule oxazinin-3 **219**.



Scheme 66

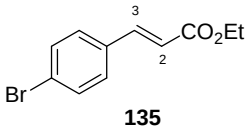
Once the methodology has been satisfactorily developed for this relatively simple system, it would then be applied to the more complex natural products from this family.

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 ^{o}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 $KMnO_4$. ^{1}H NMR and ^{13}C 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. $[\alpha]_D$ values are given in units 10^{-1}degcm^{2}g^{-1}.

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

Ethyl (*E*)-4-bromocinnamate 135[90]

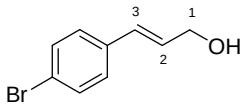


135

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 ($MgSO_4$). 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, $CDCl_3$) 1.33 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 4.27 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 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, $CDCl_3$) 14.3 (CH_3), 60.7 (CH_2), 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^+. $C_{11}H_{11}O_2{}^{79}Br$ requires 253.9942), 211 (88%), 209 (89), 183 (23), 181 (21), 102 (100).

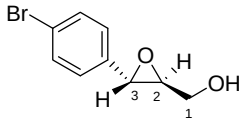
(2*E*)-3-(4-Bromophenyl)prop-2-en-1-ol 136[91]



136

Ethyl (*E*)-4-bromocinnamate **135** (7.0 g, 27.5 mmol) was dissolved in diethyl ether (120 mL) and the solution cooled to -78 ^oC. 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 ^oC, 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 recrystalised using ethyl acetate-petroleum ether (40-60) to give (2*E*)-3-(4-bromophenyl)prop-2-en-1-ol **136** as a colourless solid (5.8 g, 100%). mp 63-65 ^oC (from ethyl acetate), lit.[91] 63-65 ^oC; δ_H (400 MHz, $CDCl_3$) 1.48 (1H, t, *J* 6.0 Hz, OH), 4.33 (2H, dt, *J* 6.0, 1.6 Hz, 1-H_2), 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); δ_C (100 MHz, $CDCl_3$) 63.6 (CH_2), 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^+. $C_9H_9O^{79}Br$ requires 211.9837), 171 (50%), 169 (51), 133 (100), 115 (46), 83 (80).

(2*S*,3*S*)-[3-(4-Bromophenyl)oxiranyl]methanol 133[63]

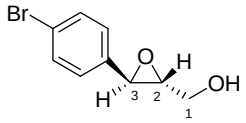


133

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 ^oC 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 ^oC for 0.5 h. A solution of (2*E*)-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

0.25 h. 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 ($MgSO_4$) 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 (2*S*,3*S*)-[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); $[\alpha]_D^{22}$ -38.6 (*c* 1.0, $CHCl_3$), lit.[63] $[\alpha]_D^{25}$ -35.2 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 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*H), 3.91 (1H, d, *J* 2.2 Hz, 3-H), 4.05 (1H, ddd, *J* 12.8, 5.0, 2.2 Hz, 1-H*H*), 7.14-7.18 (2H, m, 2 x Ar), 7.46-7.50 (2H, m, 2 x Ar); δ_C (100 MHz, $CDCl_3$) 54.9 (CH), 61.0 (CH_2), 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^+. $C_9H_9O_2{}^{79}Br$ requires 227.9786), 212 (10%), 210 (10), 187 (25), 185 (34), 89 (75), 83 (100).

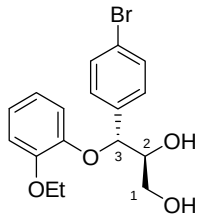
(2*R*,3*R*)-[3-(4-Bromophenyl)oxiranyl]methanol 146[63]



146

The reaction was carried out as described above using (2*E*)-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 (2*R*,3*R*)-[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 hexane/ethyl acetate); $[\alpha]_D^{22}$ +31.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 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-*H*H), 3.91 (1H, d, *J* 2.2 Hz, 3-H), 4.05 (1H, ddd, *J* 12.8, 5.0, 2.2 Hz, 1-H*H*), 7.14-7.19 (2H, m, 2 x Ar), 7.46-7.51 (2H, m, 2 x Ar); δ_C (100 MHz, $CDCl_3$) 55.1 (CH), 61.1 (CH_2), 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^+. $C_9H_9O_2{}^{79}Br$ requires 227.9786), 186 (26%), 185 (38), 171 (13), 169 (16), 91 (87), 83 (100), 81 (64).

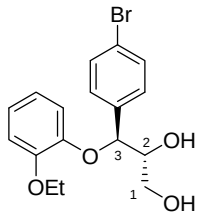
(2*S*,3*R*)-3-(4-Bromophenyl)-3-(2-ethoxyphenoxy)propane-1,2-diol 132



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 ^{o}C until the solid had dissolved. After 1 h of stirring, (2*S*,3*S*)-[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 ($MgSO_4$) and the filtrate concentrated *in vacuo*. The solid was recrystalised from diethyl ether to give (2*S*,3*R*)-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propane-1,2-diol **132** as a colourless solid (1.50 g, 67%). mp 77-78 ^{o}C (from diethyl ether); ν_{max} /cm^{-1} (NaCl) 3345 (OH), 2943 (CH), 1500 (C=C), 1246, 732; $[\alpha]_D^{22}$ -57.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.51 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 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, OCH_2CH_3), 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_C (100 MHz, $CDCl_3$) 14.8 (CH_3), 62.1 (CH_2), 64.2 (CH_2), 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^+. $C_{17}H_{19}O_4{}^{79}Br$ requires 366.0467), 171 (11%), 169 (11), 138 (100), 110 (50), 83 (58), 47 (12).

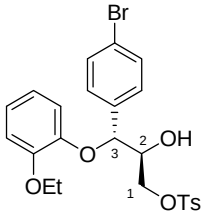
(2*R*,3*S*)-3-(4-Bromo-phenyl)-3-(2-ethoxyphenoxy)propane-1,2-diol 147



147

The reaction was carried out as described above using (2*R*,3*R*)-[3-(4-bromophenyl)oxiranyl]methanol **146** (3.38 g, 14.8 mmol). This gave (2*R*,3*S*)-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propane-1,2-diol **147** as a colourless solid (4.31 g, 79%). mp 76-78 ^{o}C (from diethyl ether); ν_{max} /cm^{-1} (KBr) 3345 (OH), 2943 (CH), 1500 (C=C), 1246, 732; $[\alpha]_D^{25}$ +64.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.50 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 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-*H*H), 3.84-3.88 (1H, m, 2-H), 3.94 (1H, dt, *J* 11.8, 3.4 Hz, 1-H*H*), 4.11 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 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); δ_C (100 MHz, $CDCl_3$) 14.8 (CH_3), 62.2 (CH_2), 64.3 (CH_2), 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^+. $C_{17}H_{19}O_4{}^{79}Br$ requires 366.0467), 171 (15%), 169 (15), 138 (100), 110 (71), 91 (13), 81 (9).

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

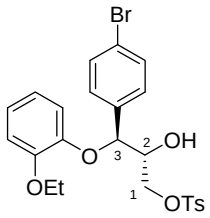


139

(2*S*,3*R*)-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

(30 mL). The aqueous phase was extracted with dichloromethane (30 mL) and the combined organic layers dried ($MgSO_4$) 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 (2*S*,3*R*)-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); $[\alpha]_D^{25}$ -27.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.42 (3H, s, Ar-CH_3), 2.44 (3H, s, Ar-CH_3), 3.07 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 4.44 (1H, dd, *J* 11.2, 2.6 Hz, 1-*H*H), 4.59 (2H, dd, *J* 11.2, 4.6 Hz, 1-H*H*), 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, $CDCl_3$) 14.9 (CH_3), 21.7 (CH_3), 21.8 (CH_3), 64.2 (CH_2), 67.3 (CH_2), 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^+. $C_{31}H_{30}O_8{}^{79}BrS_2Na$ 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 (2*S*,3*R*)-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; $[\alpha]_D^{22}$ -84.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 2.44 (3H, s, Ar-CH_3), 4.05 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 4.09-4.13 (1H, m, 2-H), 4.18-4.21 (2H, m, 1-H_2), 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, $CDCl_3$) 14.8 (CH_3), 21.8 (CH_3), 64.4 (CH_2), 70.3 (CH_2), 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^+. $C_{24}H_{25}O_6{}^{81}BrS$ requires 522.0538), 384 (10%), 382 (9), 213 (19), 211 (20), 155 (67), 138 (100), 91 (78).

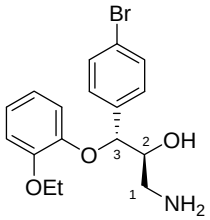
(2*R*,3*S*)-3-(4-Bromophenyl)-3-(2-ethoxyphenoxy)-1-(toluenesulfonyloxy)propan-2-ol 150



150

The reaction was carried out as described above using (2*R*,3*S*)-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propane-1,2-diol **147** (3.26 g, 8.88 mmol). This gave (2*R*,3*S*)-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; $[\alpha]_D^{22}$ +71.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.43 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.45 (3H, s, Ar-CH_3), 3.20 (1H, d, *J* 6.0 Hz, OH), 4.05 (2H, dq, *J* 7.0, 1.6 Hz, OCH_2CH_3), 4.10-4.15 (1H, m, 2-H), 4.21-4.22 (2H, m, 1-H_2), 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); δ_C (100 MHz, $CDCl_3$) 14.8 (CH_3), 21.7 (CH_3), 64.2 (CH_2), 70.3 (CH_2), 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^+. $C_{24}H_{25}O_6{}^{81}BrS$ requires 522.0538), 384 (3%), 382 (3), 213 (11), 211 (11), 155 (67), 138 (100), 91 (78).

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

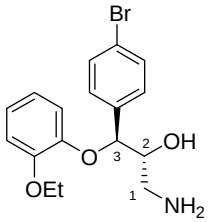


131

(2*S*,3*R*)-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 ($MgSO_4$) and the filtrate concentrated *in vacuo*. Purification was carried

out by flash column chromatography and elution with 90:10 ethyl acetate-methanol gave (2*S*,3*R*)-1-amino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol **131** as a colourless oil (0.22 g, 49%). mp 60-62 ^{o}C (from diethyl ether); ν_{max} /cm^{-1} (NaCl) 3338, 3303, 2901 (CH), 2115, 1593 (C=C); $[\alpha]_D^{22}$ -68.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.47 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.92 (1H, dd, *J* 12.8, 4.6 Hz, 1-*H*H), 3.03 (1H, dd, *J* 12.8, 5.6 Hz, 1-H*H*), 3.99 (1H, m, 2-H), 4.06 (2H, q, *J* 7.0 Hz, OCH_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); δ_C (100 MHz, $CDCl_3$) 14.7 (CH_3), 42.3 (CH_2), 64.3 (CH_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); *m/z* (EI) 366.0699 (M^+. $C_{17}H_{21}O_3N^{79}Br$ requires 366.0705), 367 (3%), 365 (3), 230 (9), 228 (9), 138 (100), 171 (12), 110 (77).

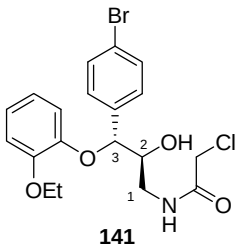
(2*R*,3*S*)-1-Amino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol 149



149

The reaction was carried out as described above using (2*R*,3*S*)-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)-1-(toluenesulfonyloxy)propan-2-ol **150** (2.42 g, 4.6 mmol). This gave (2*R*,3*S*)-1-amino-3-(4-bromo-phenyl)-3-(2-ethoxyphenoxy)propan-2-ol **149** as a colourless oil (0.97 g, 57%). ν_{max} /cm^{-1} (NaCl) 3338, 3303, 2901 (CH), 2115, 1593 (C=C); $[\alpha]_D^{22}$ +71.5 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.48 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.34 (2H, br s, NH_2), 2.81 (1H, dd, *J* 12.8, 4.6 Hz, 1-*H*H), 2.94 (1H, dd, *J* 12.8, 5.6 Hz, 1-H*H*), 3.80-3.84 (1H, m, 2-H), 4.10 (2H, q, *J* 7.0 Hz, OCH_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); δ_C (100 MHz, $CDCl_3$) 14.9 (CH_3), 42.3 (CH_2), 64.3 (CH_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); *m/z* (FAB^+) 368.0685 (MH^+. $C_{17}H_{21}O_3N^{81}Br$ requires 368.0686), 368 (99%), 366 (100), 230 (15), 228 (12), 170 (29), 139 (38).

(2*S*,3*R*)-1-Chloroacetylamino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol 141

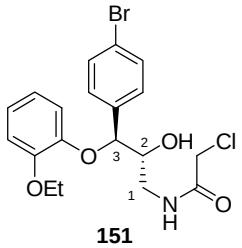


141

(2*S*,3*R*)-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 ^{o}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 ^{o}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 (2*S*,3*R*)-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), 1739 (CO), 1667 (CO), 1651 (C=C), 1595; $[\alpha]_D^{25}$ -58.5 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.47 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 3.75 (1H, dt, *J* 14.4, 5.6 Hz, 1-*H*H), 3.92 (1H, d, *J* 15.0 Hz, NHCOC*H*H), 4.01 (1H, d, *J* 15.0 Hz, NHCOCH*H*), 4.01-4.04 (1H, m, 1-H*H*), 4.03 (1H, d, *J* 18.4 Hz, OCOC*H*H), 4.08 (1H, d, *J* 18.4 Hz, OCOH*H*), 4.11 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 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, $CDCl_3$) 14.9 (CH_3), 39.4 (CH_2), 40.7 (CH_2), 42.6 (CH_2), 64.4 (CH_2), 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^+. $C_{21}H_{22}O_5NCl_2{}^{79}BrNa$ 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 (2*S*,3*R*)-1-chloroacetylamino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol **141** as a colourless oil (0.15 g, 83%). ν_{max}/cm^{-1} (NaCl) 3423 (OH), 3020 (CH), 1660 (CO), 1215, 770; $[\alpha]_D^{22}$ -105.4 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.51 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 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, CH_2Cl), 4.12 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 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, $CDCl_3$) 14.9 (CH_3), 41.9 (CH_2),

42.6 (CH_2), 64.5 (CH_2), 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^+. $C_{19}H_{22}O_4N^{35}Cl^{81}Br$ requires 444.0400), 306 (100%), 304 (74), 226 (62), 228 (23), 192 (19), 139 (80).

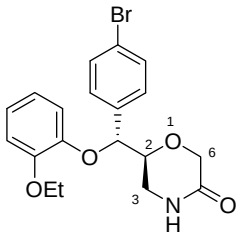
(2*R*,3*S*)-1-Chloroacetylamino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol 151



151

The reaction was carried out as described above using (2*R*,3*S*)-1-amino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol **149** (1.50 g, 4.10 mmol). This gave (2*R*,3*S*)-1-chloroacetylamino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol **151** as a colourless oil (1.11 g, 62%). ν_{max}/cm^{-1} (NaCl) 3423 (OH), 3020 (CH), 1660 (CO), 1215, 770; $[\alpha]_D^{22}$ +114.6 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.51 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 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*), 3.98-4.01 (1H, m, 2-H), 4.03 (2H, s, CH_2Cl), 4.14 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 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); δ_C (100 MHz, $CDCl_3$) 14.8 (CH_3), 41.7 (CH_2), 42.6 (CH_2), 64.5 (CH_2), 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^+. $C_{19}H_{22}O_4N^{35}Cl^{79}Br$ requires 442.0421), 444 (64%), 442 (49), 364 (9), 304 (100), 306 (100), 226 (19), 139 (18).

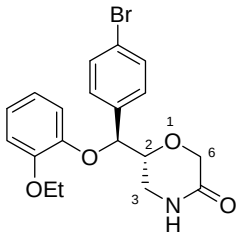
(2*S*,3*R*)-2-[(4-Bromobenzyl)-(2-ethoxyphenoxy)]morpholin-5-one 142



142

A solution of (2*S*,3*R*)-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 ^{o}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 ($MgSO_4$), and the filtrate concentrated *in vacuo*. Purification was carried out by dry flash chromatography and elution with 100% ethyl acetate gave (2*S*,3*R*)-2-[(4-bromobenzyl)-(2-ethoxyphenoxy)]morpholin-5-one **142** as a colourless oil (0.25 g, 79%). ν_{max}/cm^{-1} (NaCl) 3410 (NH), 3019 (CH), 2400, 1679 (CO), 1500, 1216; $[\alpha]_D^{25}$ -79.5 (*c* 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.46 (3H, t, *J* 7.0 Hz, OCH_2CH_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_2CH_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); δ_C (100 MHz, $CDCl_3$) 15.1 (CH_3), 43.9 (CH_2), 64.3 (CH_2), 67.8 (CH_2), 76.0 (CH), 81.5 (CH), 113.6 (CH), 118.4 (CH), 120.7 (CH), 122.4 (C), 123.2 (CH), 129.0 (2 x CH), 131.6 (2 x CH), 137.3 (C), 146.5 (C), 149.9 (C), 168.5 (C); *m/z* (EI) 407.0562 (M^+. $C_{19}H_{20}O_4N^{81}Br$ requires 407.0558), 269 (73%), 267 (73), 171 (86), 169 (87), 138 (100).

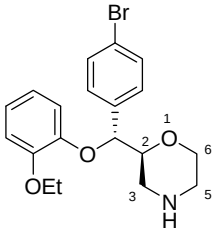
(2*R*,3*S*)-2-[(4-Bromobenzyl)-(2-ethoxyphenoxy)]morpholin-5-one 152



152

The reaction was carried out as described above using (2*R*,3*S*)-1-chloroacetylamino-3-(4-bromophenyl)-3-(2-ethoxyphenoxy)propan-2-ol **151** (1.07 g, 2.42 mmol). This gave (2*S*,3*R*)-2-[(4-bromobenzyl)-(2-ethoxyphenoxy)]morpholin-5-one **152** as a colourless oil (0.89 g, 90%). ν_{max}/cm^{-1} (NaCl) 3410 (NH), 3019 (CH), 2400, 1679 (CO), 1500, 1216; $[\alpha]_D^{22}$ +80.0 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.46 (3H, t, *J* 7.0 Hz, OCH_2CH_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_2CH_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); δ_C (100 MHz, $CDCl_3$) 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^+. $C_{19}H_{20}O_4N^{81}Br$ requires 407.0558), 269 (60%), 267 (60), 171 (83), 169 (84), 138 (100), 110 (60), 102 (29).

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

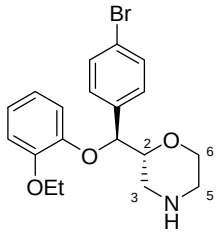


143

(2*S*,3*R*)-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 ^oC. 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 ($MgSO_4$), and the filtrate concentrated *in vacuo* to give (2*S*,3*R*)-2-[(4-bromophenyl)-(2-ethoxyphenoxy)methyl]morpholine **143** as a colourless oil (0.12 g, 73%). ν_{max}/cm^{-1} (NaCl) 3413 (NH), 2925 (CH), 2345, 1638, 1593; $[\alpha]_D^{25}$ -67.5 (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.45 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.81-2.94 (3H, m, 5-H_2, 3-*H*H), 3.37 (1H, br d, *J* 12.4 Hz, 3-H*H*), 3.53 (1H, td, *J* 11.2, 2.8 Hz, 6-*H*H) 3.75-3.80 (1H, m, 2-H), 3.86 (1H, br d, *J* 11.2 Hz, 6-H*H*), 4.05 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 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); δ_C (100 MHz, $CDCl_3$) 15.1 (CH_3), 44.6 (CH_2), 46.4 (CH_2), 64.4 (CH_2), 66.5 (CH_2), 78.1 (CH), 82.2 (CH), 113.7 (CH), 118.1 (CH), 120.7 (CH), 122.1 (C), 122.8 (CH), 129.1 (2 x CH), 131.5 (2 x CH), 137.5 (C), 146.9 (C), 149.9 (C); *m/z* (EI) 393.0756 (M^+. $C_{19}H_{22}O_3N^{81}Br$ requires 393.0765), 255 (86%), 253 (86), 171 (26), 169 (27), 86 (99), 84 (100).

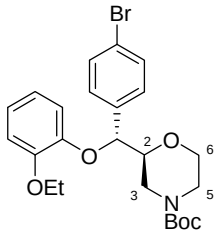
(2*R*,3*S*)-2-[(4-Bromophenyl)-(2-ethoxyphenoxy)methyl]morpholine 153



153

The reaction was carried out as described above using (2*R*,3*S*)-2-[(4-bromobenzyl)-(2-ethoxyphenoxy)]morpholin-5-one **152** (0.85 g, 2.1 mmol). This gave (2*R*,3*S*)-2-[(4-bromophenyl)-(2-ethoxyphenoxy)methyl]morpholine **153** as a colourless oil (0.09 g, 11%). ν_{max}/cm^{-1} (NaCl) 3413 (NH), 2925 (CH), 2345, 1638, 1593; $[\alpha]_D^{22}$ +46.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.45 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.98 (1H, br s, NH), 2.81-2.94 (3H, m, 5-H_2, 3-*H*H), 3.36 (1H, br d, *J* 12.4 Hz, 3-H*H*), 3.53 (1H, td, *J* 11.2, 2.4 Hz, 6-*H*H) 3.75-3.80 (1H, m, 2-H), 3.86 (1H, br d, *J* 11.2 Hz, 6-H*H*), 4.05 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 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); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 44.8 (CH_2), 46.8 (CH_2), 64.5 (CH_2), 66.5 (CH_2), 78.4 (CH), 81.2 (CH), 112.9 (CH), 116.7 (CH), 119.8 (CH), 120.8 (C), 121.4 (CH), 128.1 (2 x CH), 130.3 (2 x CH), 137.1 (C), 146.3 (C), 148.8 (C); *m/z* (EI) 391.0785 (M^+. $C_{19}H_{22}O_3N^{79}Br$ requires 391.0783), 255 (73%), 253 (70), 171 (28), 169 (28), 110 (27), 85 (27).

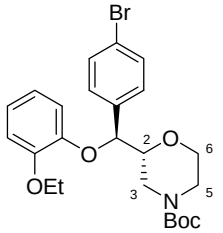
(2*S*,3*R*)-2-[(4-Bromophenyl)-(2-ethoxyphenoxy)methyl]-*N*-*tert*-butoxycarbonylmorpholine 130



130

(2*S*,3*R*)-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 (2*S*,3*R*)-2-[(4-bromophenyl)-(2-ethoxyphenoxy)methyl]-*N*-*tert*-butoxycarbonylmorpholine **130** as a colourless oil (0.13 g, 75%). ν_{max}/cm^{-1} (NaCl) 2925 (CH), 1695 (CO), 1500 (C=C), 1259, 1106; $[\alpha]_D^{24}$ -34.8 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.44-1.47 (12H, m, OCH_2CH_3, $C(CH_3)_3$), 2.94-3.00 (2H, m, 3-*H*H, 5-*H*H), 3.46 (1H, td, *J* 11.6, 2.8 Hz, 5-H*H*), 3.71-3.74 (1H, m, 2-H), 3.86 (2H, dd, *J* 11.6, 2.8 Hz, 6-H_2), 3.97-4.06 (2H, m, OCH_2CH_3), 4.34 (1H, d, *J* 13.2 Hz, 3-H*H*), 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_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 27.4 (3 x CH_3), 42.2 (CH_2), 46.1 (CH_2), 63.4 (CH_2), 65.7 (CH_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^+. $C_{24}H_{30}O_5N^{79}Br$ requires 491.1307), 300 (80%), 298 (90), 256 (94), 254 (99), 138.0 (89), 57 (100).

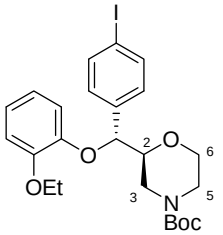
(2*R*,3*S*)-2-[(4-Bromophenyl)-(2-ethoxyphenoxy)methyl]-*N*-*tert*-butoxycarbonylmorpholine 156



156

The reaction was carried out as described above using (2*R*,3*S*)-2-[(4-bromophenyl)-(2-ethoxyphenoxy)methyl]morpholine **155** (0.06 g, 0.18 mmol). This gave (2*R*,3*S*)-2-[(4-bromophenyl)-(2-ethoxyphenoxy)methyl]-*N*-*tert*-butoxycarbonylmorpholine **156** as a colourless oil (0.04g, 53%). ν_{max}/cm^{-1} (NaCl) 2925 (CH), 1695 (CO), 1500 (C=C), 1259, 1106; $[\alpha]_D^{26}$ +38.8 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.44-1.47 (12H, m, OCH_2CH_3, $(CH_3)_3$), 2.94-3.00 (2H, m, 3-*H*H, 5-*H*H), 3.46 (1H, td, *J* 11.6, 2.8 Hz, 5-H*H*), 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_2CH_3), 4.34 (1H, d, *J* 13.2 Hz, 3-H*H*), 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_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^+. $C_{24}H_{30}O_5N^{81}Br$ requires 493.1291), 300 (57%), 298 (60), 256 (65), 254 (68), 169 (46), 138 (70).

(2*S*,3*R*)-2-[(4-Iodophenyl)-(2-ethoxyphenoxy)methyl]-*N*-*tert*-butoxycarbonylmorpholine 145

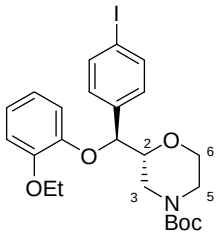


145

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*S*,3*R*)-2-[(4-bromophenyl)-(2-ethoxyphenoxy)methyl]-*N*-*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 ^{o}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 ($MgSO_4$) 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 (2*S*,3*R*)-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; $[\alpha]_D^{25}$ -37.1 (*c* 2.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.44-1.47 (12H, m, OCH_2CH_3, $(CH_3)_3$), 2.90-3.01 (2H, m, 3-*H*H, 5-*H*H), 3.46 (1H, td, *J* 11.6, 2.4 Hz, 5-H*H*), 3.70-3.74 (1H, m, 2-H), 3.86 (2H, dd, *J* 11.6, 2.4 Hz, 6-H_2), 4.05-4.11 (2H, m, OCH_2CH_3), 4.42 (1H, br d, *J* 13.2 Hz, 3-H*H*), 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, $CDCl_3$) 14.0 (CH_3), 27.4 (3 x CH_3), 42.3 (CH_2), 44.1 (CH_2), 63.4 (CH_2), 65.8 (CH_2), 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^+. $C_{24}H_{30}O_5NI$ requires 539.1169), 346 (93%), 302 (94), 217 (44), 138 (73), 57 (100).

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

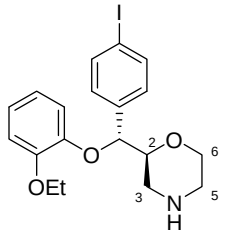


157

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 (2*R*,3*S*)-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 ^{o}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% $NH_{3\ (aq)}$ in 20 mL water) followed by water (2 x 20 mL). The organic fractions were combined, dried ($MgSO_4$) and the filtrate

concentrated *in vacuo* to give (2*R*,3*S*)-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; $[\alpha]_D^{22}$ +43.2 (*c* 2.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.44-1.47 (12H, m, OCH_2CH_3, $(CH_3)_3$), 2.90-3.01 (2H, m, 3-*H*H, 5-*H*H), 3.46 (1H, td, *J* 11.6, 2.4 Hz, 5-H*H*), 3.70-3.74 (1H, m, 2-H), 3.86 (2H, dd, *J* 11.6, 2.4 Hz, 6-H_2), 4.05-4.11 (2H, m, OCH_2CH_3), 4.42 (1H, br d, *J* 13.2 Hz, 3-H*H*), 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, $CDCl_3$) 14.0 (CH_3), 27.3 (3 x CH_3), 42.3 (CH_2), 44.1 (CH_2), 63.4 (CH_2), 65.8 (CH_2), 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^+. $C_{24}H_{30}O_5NI$ requires 539.1169), 346 (93%), 302 (94), 217 (44), 138 (73), 57 (100).

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

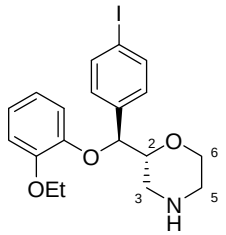


126

Trifluroacetic acid (1 mL, 0.06 mmol) was added to a solution of (2*S*,3*R*)-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 ($MgSO_4$) and the filtrate concentrated *in vacuo* to give (2*S*,3*R*)-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; $[\alpha]_D^{23}$ -38.0 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.45 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.93 (1H, br s, NH), 2.78-2.94 (3H, m, 3-*H*H, 5-H_2,), 3.37 (1H, br d, *J* 11.6 Hz, 3-H*H*), 3.53 (1H, br t, *J* 12.4 Hz, 6-*H*H), 3.77 (1H, m, 2-H), 3.87 (1H, br d, *J* 12.4 Hz, 6-H*H*), 4.06 (2H, qd, *J* 7.0, 2.0 Hz, OCH_2CH_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* 8.4 Hz, 2 x Ar H), 7.65 (2H, d, *J* 8.4 Hz, 2 x Ar H); δ_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^+. $C_{19}H_{22}O_3NI$ requires 439.0644), 301 (99%), 220 (96), 138 (61), 85 (77), 56 (100).

(2*R*,3*S*)-2-[(4-Iodophenyl)-(2-ethoxyphenoxy)methyl]morpholine 127

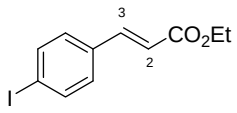


127

The reaction was carried out as described above using (2*R*,3*S*)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)-methyl]-*N*-*tert*-butoxycarbonylmorpholine **157** (0.02 g, 0.04 mmol). This gave (2*R*,3*S*)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)methyl]morpholine **127** as a colourless oil (0.01 g, 57%). ν_{max}/cm^{-1} (NaCl) 3421 (NH), 2084 (CH), 1639 (C=C), 1500, 1255; $[\alpha]_D^{22}$ +38.3 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.45 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.78-2.94 (3H, m, 3-*H*H, 5-H_2,), 3.37 (1H, br d, *J* 11.6 Hz, 3-H*H*), 3.53 (1H, br t, *J* 12.4 Hz, 6-*H*H), 3.76 (1H, m, 2-H), 3.87 (1H, br d, *J* 12.4 Hz, 6-H*H*), 4.06 (2H, qd, *J* 7.0, 2.0 Hz, OCH_2CH_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); δ_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^+. $C_{19}H_{22}O_3NI$ requires 439.0644), 301 (99%), 220 (96), 138 (61), 85 (77), 56 (100).

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

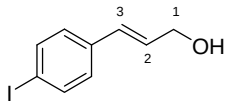
Ethyl (*E*)-3-(4-iodophenyl)acrylate 161[92]



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 ^{o}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 a further 0.25 h before triethylamine (10.4 mL, 75.0 mmol) was added. The reaction mixture was allowed to stir at -78 ^{o}C for 0.5 h before being allowed to warm to room temperature and then stirred for a further 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-diazobicyclo[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 ($MgSO_4$) 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%). δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 4.24 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 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); δ_C (100 MHz, $CDCl_3$) 14.4 (CH_3), 60.8 (CH_2), 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^+. $C_{11}H_{11}O_2I$ requires 301.9804), 302 (100%), 256 (79), 230 (23), 130 (95), 102 (94).

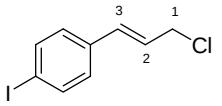
(2*E*)-3-(4-Iodophenyl)prop-2-en-1-ol 162[93]



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 ^{o}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 ^{o}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 (2*E*)-3-(4-iodophenyl)prop-2-en-1-ol **162** as a white powder (5.12 g, 99%). δ_H (400 MHz, $CDCl_3$) 1.57 (1H, t, *J* 5.6 Hz, OH), 4.32 (2H, td, *J* 5.6, 1.2 Hz, 1-H_2), 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); δ_C (100 MHz, $CDCl_3$) 63.5 (CH_2), 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^+. C_9H_9OI requires 259.9698), 260 (70%), 204 (14), 133 (60), 84 (74), 49 (100).

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

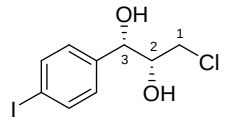


163

(2*E*)-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 ^{o}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 (2*E*)-1-chloro-3-(4-iodophenyl)prop-2-ene **163** as a white solid (3.40 g, 69%). ν_{max} /cm^{-1} 3018 (CH), 1704, 1485, 1302, 1006; δ_H (400 MHz, $CDCl_3$) 4.23 (2H, dd, *J* 7.1, 1.0 Hz, 1-H_2), 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); δ_C (100 MHz, $CDCl_3$) 45.2 (CH_2), 93.8 (C), 125.8 (CH), 128.5 (2 x CH), 133.0 (CH),

135.4 (C), 137.8 (2 x CH); *m/z* (EI) 277.9364 (M^+. $C_9H_8{}^{35}ClI$ requires 277.9359), 243 (66%), 231 (59), 116 (100), 89 (59).

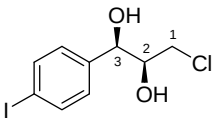
(2*R*,3*S*)-1-Chloro-3-(4-iodophenyl)propane-2,3-diol 159



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 hydrogencarbonate (2.25 g, 26.8 mmol) were added and the bright orange solution cooled to 0 ^oC. (2*E*)-1-Chloro-3-(4-iodophenyl)prop-2-ene **163** (2.5 g, 8.94 mmol) was added and the solution stirred vigorously at 0 ^oC 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 ($MgSO_4$) 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 (2*R*,3*S*)-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; ν_{max} /cm^{-1} 3527 (OH), 3419 (OH), 2961 (CH), 1585 (C=C), 1090; $[\alpha]_D{}^{26}$ -4.5 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 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-*H*H), 3.58 (1H, dd, *J* 11.6, 4.0 Hz, 1-H*H*), 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); δ_C (100 MHz, $CDCl_3$) 46.0 (CH_2), 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^+. $C_9H_{10}O_2{}^{37}ClI$ requires 313.9383), 276 (41%), 233 (98), 231 (22), 106 (100).

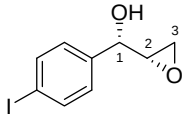
(2*S*,3*R*)-1-Chloro-3-(4-iodophenyl)propane-2,3-diol 188



188

The reaction was carried out as described above, using (2*E*)-1-chloro-3-(4-iodophenyl)prop-2-ene **163** (2.3 g, 8.08 mmol) and AD-mix-β (11.3 g). This gave (2*S*,3*R*)-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; $[\alpha]_D^{22}$ +10.1 (*c* 1.0, $CHCl_3$); δ_H (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-*H*H), 3.60 (1H, dd, *J* 11.6, 5.4 Hz, 1-H*H*), 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); δ_C (100 MHz, $CDCl_3$) 44.6 (CH_2), 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^+. $C_9H_{10}O_2{}^{35}ClI$ requires 311.9414), 276 (13%), 233 (100), 231 (7), 106 (16), 78 (78).

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

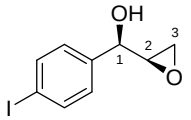


164

(2*R*,3*S*)-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 ^oC 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 (1*S*,2*S*)-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; $[\alpha]_D^{26}$ +6.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.55 (1H, d, *J* 5.2 Hz, OH), 2.83 (1H, dd, *J* 4.4, 2.8 Hz, 3-*H*H), 2.87 (1H, dd, *J* 4.4, 4.0 Hz, 3-H*H*), 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); δ_C (100 MHz, $CDCl_3$) 45.4 (CH_2), 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^+. $C_9H_9O_2I$ requires 275.9647), 233 (89%), 142 (23), 105 (32), 83 (98), 78 (78).

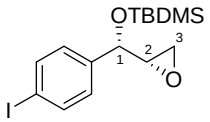
(1*R*,2*R*)-2,3-Epoxy-1-(4-iodophenyl)propan-1-ol 189



189

The reaction was carried out as described above using (2*S*,3*R*)-1-chloro-3-(4-iodophenyl)propane-2,3-diol **188** (0.92 g, 2.95 mmol). This gave (1*R*,2*R*)-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; $[\alpha]_D^{25}$ -2.7 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.80 (1H, dd, *J* 4.6, 2.8 Hz, 3-*H*H), 2.85 (1H, t, *J* 4.6, 4.0 Hz, 3-H*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, $CDCl_3$) 45.5 (CH_2), 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^+. $C_9H_9O_2I$ requires 275.9647), 276 (40%), 233 (100), 203 (5), 105 (15), 78 (81).

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

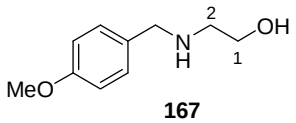


158

(1*S*,2*S*)-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 ($MgSO_4$) and the filtrate concentrated *in vacuo* to give (1*S*,2*S*)-1-(*tert*-Butyldimethylsilyoxy)-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; $[\alpha]_D^{26}$ +5.5 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.00 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.92 (9H, s, $C(CH_3)$), 2.63 (1H, dd, *J* 4.8, 2.8 Hz, 3-*H*H), 2.75 (1H, dd, *J* 4.8, 4.0 Hz, 3-H*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, $CDCl_3$) -4.92 (CH_3), -4.71 (CH_3), 18.3 (C),

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^+. $C_{15}H_{24}O_2ISi$ requires 391.0590), 391 (71%), 361 (100), 333 (55), 259 (80), 235 (49).

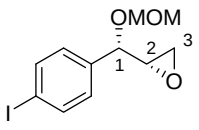
2-(4-Methoxyphenylamino)ethanol 167[69]



167

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%). δ_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); δ_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).

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

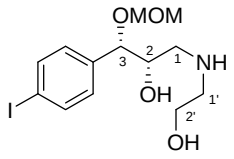


172

(1*S*,2*S*)-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 ^oC 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 ^oC 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 ($MgSO_4$) 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 **(**1*S*,2*S*)-2,3-epoxy-1-(4-iodophenyl)-1-(methoxymethoxy)propane **172** (0.82 g, 37%). ν_{max} /cm^{-1} 2948 (CH), 2891, 1587 (C=C), 1484, 1397; $[\alpha]_D^{26}$ +59.8 (*c* 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.63 (1H, dd, *J* 4.6, 2.8 Hz, 3-*H*H), 2.76 (1H, t, *J* 4.6 Hz, 3-H*H*), 3.16-3.20 (1H, m, 2-H), 3.37 (3H, s, OCH_3), 4.31 (1H, d, *J* 6.4 Hz, 1-H), 4.60 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.73 (1H, d, *J* 6.8 Hz, OCH*H*O), 7.13 (2H, d, *J* 8.4 Hz, 2 x Ar H), 7.70 (2H, d, *J* 8.4 Hz, 2 x Ar H); δ_C (100 MHz, $CDCl_3$) 44.1 (CH_2), 54.9 (CH_3), 55.5 (CH), 78.3 (CH), 94.0 (C), 94.2 (CH_2), 129.0 (2 x CH), 137.4 (C), 137.6 (2 x CH); *m/z* (EI) 319.9908 (M^+. $C_{11}H_{13}O_3I$ requires 319.9909), 277 (43%), 231 (6), 83 (100), 45 (93).

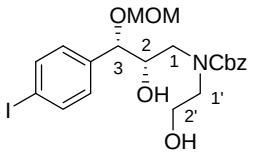
(2*S*,3*S*)-1-(2'-Hydroxyethylamino)-3-(4-iodophenyl)-3-methoxymethoxypropan-2-ol 173



173

(1*S*,2*S*)-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 ($MgSO_4$) and the filtrate concentrated *in vacuo* to give (2*S*,3*S*)-1-(2'-hydroxyethylamino)-3-(4-iodophenyl)-3-methoxymethoxy-propan-2-ol **173** (0.93 g, 95%). ν_{max}/cm^{-1} (NaCl) 3387 (NH/OH), 2883 (CH), 1637 (C=C), 1443, 1148; $[\alpha]_D^{27}$ +86.9 (*c* 0.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.46-2.56 (2H, m, 1-H_2), 2.64-2.73 (2H, m, 1'-H_2), 3.25 (3H, br s, 2 x OH, NH), 3.34 (3H, s, OCH_3), 3.60 (2H, t, *J* 5.0 Hz, 2'-H_2), 3.87 (1H, m, 2-H), 4.48 (1H, d, *J* 6.4 Hz, 3-H), 4.53 (1H, d, *J* 6.6 Hz, OC*H*HO), 4.58 (1H, d, *J* 6.6 Hz, OCH*H*O), 7.07 (2H, d, *J* 8.0 Hz, 2 x Ar H), 7.68 (2H, d, *J* 8.0 Hz, 2 x Ar H); δ_C (100 MHz, $CDCl_3$) 50.8 (CH_2), 51.1 (CH_2), 55.9 (CH_3), 60.7 (CH_2), 73.1 (CH), 79.6 (CH), 94.0 (C), 94.6 (CH_2), 129.5 (2 x CH), 137.5 (2 x CH), 137.9 (C); *m/z* (CI) 382.0522 (MH^+. $C_{13}H_{21}O_4NI$ requires 382.0515), 382 (100%), 350 (15), 256 (45), 224 (6), 74 (41).

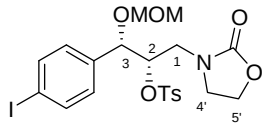
(2*S*,3*S*)-1-(2'-Hydroxyethyl-*N*-benzyloxycarbonylamino)-3-(4-iodophenyl)-3-methoxymethoxypropan2-ol 174



174

(2*S*,3*S*)-1-(2-Hydroxyethylamino)-3-(4-iodophenyl)-3-methoxymethoxy-propan-2-ol **173** (0.1 g, 0.26 mmol) was dissolved in tetrahydrofuran (3 mL). The solution was cooled to 0 ^{o}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 ($MgSO_4$) 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 (2*S*,3*S*)-1-(2'-hydroxyethyl-*N*-benzyloxycarbonylamino)-3-(4-iodophenyl)-3-methoxymethoxypropan2-ol **174** (0.06 g, 48%). ν_{max}/cm^{-1} (NaCl) 3403 (NH/OH), 2931 (CH), 2247, 1687 (CO), 1479; $[\alpha]_D^{27}$ +77.5 (*c* 1.1, $CHCl_3$); Due to the presence of rotomers, the ^{1}H NMR spectrum was recorded at 100 ^{o}C, δ_H (400 MHz, DMSO) 3.10-3.16 (1H, m, 1-*H*H), 3.28 (3H, s, OCH_3), 3.40-3.43 (3H, m, 1-H*H*, 1'-H_2), 3.56-3.57 (2H, m, 2'-H_2), 3.98 (1H, m, 2-H), 4.46 (1H, d, *J* 4.0 Hz, 3-H), 4.54 (2H, d, *J* 4.0 Hz, OC*H*HO), 4.64 (1H, d, *J* 4.8 Hz, OCH*H*O), 5.08 (2H, s, CH_2Ph), 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); δ_C (100 MHz, $CDCl_3$) 50.8 (CH_2), 51.0 (CH_2), 55.2 (CH_3), 59.2 (CH_2), 66.1 (CH_2), 72.1 (CH), 79.7 (CH), 93.0 (C), 95.0 (CH_2), 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* (CI) 516.0888 (MH^+. $C_{21}H_{27}O_6NI$ requires 516.0883), 516 (100%), 454 (56), 408 (24), 238 (23), 183 (17).

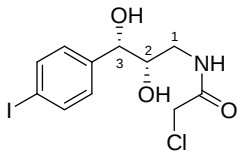
(2*S*,3*S*)-3-(4-Iodophenyl)-3-methoxymethoxy-1-(2'-oxazolidinone)-2-toluenesulfonyloxypropane 177



177

A solution of (2*S*,3*S*)-1-(2'-hydroxyethyl-*N*-benzyloxycarbonylamino)-3-(4-iodophenyl)-3-methoxymethoxypropan2-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 ^{o}C. The solution was stirred at 0 ^{o}C for 0.25 h and then allowed to warm to room temperature over 1 h. The reaction mixture was cooled to 0 ^{o}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 ^{o}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 ^{o}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 ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out using flash column chromatography and elution with 50:50 ethyl acetate-petroleum ether (40-60) gave (2*S*,3*S*)-3-(4-iodophenyl)-3-methoxymethoxy-1-(2'-oxazolidinone)-2-toluenesulfonyloxypropane **177** (0.03 g, 27%). ν_{max}/cm^{-1} (NaCl) 3448, 2926 (CH), 1750 (CO), 1597 (C=C), 1483; $[\alpha]_D^{27}$ +65.3 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CHCl_3$) 2.47 (3H, s, ArC*H*$_3$), 3.25 (3H, s, OCH_3), 3.35 (1H, dd, *J* 15.0, 8.6 Hz, 1-*H*H), 3.50 (1H, dd, *J* 15.0, 3.0 Hz, 1-H*H*), 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, OC*H*HO), 4.49 (1H, d, *J* 6.8 Hz, OCH*H*O), 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); δ_C (100 MHz, $CDCl_3$) 21.8 (CH_3), 45.3 (CH_2), 45.9 (CH_2), 56.1 (CH_3), 62.1 (CH_2), 74.9 (CH), 81.2 (CH), 94.5 (C), 94.7 (CH_2), 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^+. $C_{21}H_{25}O_7NIS$ requires 562.0397), 562 (24%), 436 (31), 374 (28), 220 (67), 130 (100).

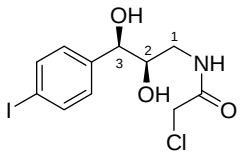
(2*S*,3*S*)-1-Chloroacetylamino-3-(4-iodophenyl)propane-2,3-diol 179



179

(1*S*,2*S*)-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 ($MgSO_4$) and the filtrate concentrated *in vacuo*. The crude material (1.89 g) was dissolved in acetonitrile (130 mL) and the mixture cooled to -10 ^oC 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 ^oC 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 (2*S*,3*S*)-1-chloroacetylamino-3-(4-iodophenyl)propane-2,3-diol **179** as a white solid (1.35 g, 51%). ν_{max}/cm^{-1} (KBr) 3349 (NH/OH), 2922 (CH), 1696 (CO), 1553, 1484; $[\alpha]_D^{24}$ -6.6 (*c* 1.0, MeOH); δ_H (400 MHz, $CDCl_3$) 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*H), 3.47 (1H, ddd, *J* 14.0, 6.4, 4.4 Hz, 1-H*H*), 3.78-3.83 (1H, m, 2-H), 4.07 (2H, s, CH_2Cl), 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); δ_C (100 MHz, $CDCl_3$) 42.4 (CH_2), 42.5 (CH_2), 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^+. $C_{11}H_{14}O_3N^{37}ClI$ requires 371.9681), 370 (14%), 352 (14), 154 (100), 136 (71), 107 (21).

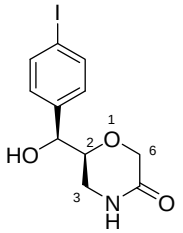
(2*R*,3*R*)-1-Chloroacetylamino-3-(4-iodophenyl)propane-2,3-diol 191



191

The reactions were carried out as described using (1*R*,2*R*)-2,3-epoxy-1-(4-iodophenyl)propan-1-ol **189** (0.46 g, 1.65 mmol). This gave (2*R*,3*R*)-1-chloroacetylamino-3-(4-iodophenyl)propane-2,3-diol **191** as a white solid (0.19 g, 46%). ν_{max}/cm^{-1} (KBr) 3348 (NH/OH), 2923 (CH), 1696 (CO), 1554, 1484; $[\alpha]_D^{21}$ +3.1 (*c* 1.0, MeOH); δ_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-*H*H), 3.43-3.49 (1H, m, 1-H*H*), 3.77-3.83 (1H, m, 2-H), 4.07 (2H, s, CH_2Cl), 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); δ_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^+. $C_{11}H_{14}O_3N^{35}ClI$ requires 369.9707), 352 (34%), 176 (10), 107 (5), 75 (100).

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

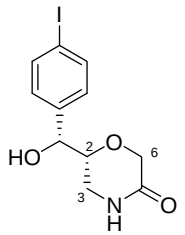


180

Sodium *tert*-butoxide (0.60 g, 6.21 mmol) was dissolved in *tert*-butanol (30 mL). (2*S*,3*S*)-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 ^oC 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 (2*S*,3*S*)-2-[α-hydroxy-(4-iodophenyl)methyl]morpholine-5-one **180** as a white solid (0.44 g, 65%). ν_{max}/cm^{-1} (NaCl) 3321 (NH/OH), 2876 (CH), 1671 (CO), 1589, 1482; $[\alpha]_D^{22}$ +21.5 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.93 (1H, dt, *J* 11.6, 3.4 Hz, 3-*H*H), 3.34 (1H, t, *J* 11.6 Hz, 3-H*H*), 3.76 (1H, ddd, *J* 11.6, 7.2, 3.4 Hz, 2-H), 4.22 (1H, d, *J* 16.8 Hz, 6-*H*H), 4.38 (1H,

d, *J* 16.8 Hz, 6-H*H*), 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); δ_C (100 MHz, $CDCl_3$) 42.2 (CH_2), 66.9 (CH_2), 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* (CI) 333.9937 (MH^+. $C_{11}H_{13}O_3NI$ requires 333.9940), 316 (19%), 208 (53), 155 (3), 101 (7).

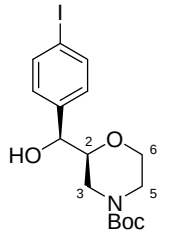
(2*R*,3*R*)-2-[α-Hydroxy-(4-iodophenyl)methyl]morpholine-5-one 192



192

The reaction was carried out as described above using (2*R*,3*R*)-1-chloroacetylamino-3-(4-iodophenyl)propane-2,3-diol **191** (0.18 g, 0.47 mmol). This gave (2*R*,3*R*)-2-[α-hydroxy-(4-iodophenyl)methyl]morpholine-5-one **192** as a white solid (0.12 g, 76%). ν_{max}/cm^{-1} (NaCl) 3375 (NH/OH), 2880 (CH), 1663 (CO), 1483, 1118; $[\alpha]_D^{24}$ -19.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.90 (1H, d, *J* 11.8 Hz, 3-*H*H), 3.10 (1H, br s, OH), 3.31 (1H, t, *J* 11.8 Hz, 3-H*H*), 3.64-3.69 (1H, m, 2-H), 4.20 (1H, d, *J* 16.8 Hz, 6-*H*H), 4.35 (1H, d, *J* 16.8 Hz, 6-H*H*), 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); δ_C (100 MHz, $CDCl_3$) 42.9 (CH_2), 67.7 (CH_2), 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* (CI) 333.9942 (MH^+. $C_{11}H_{13}O_3NI$ requires 333.9940), 316 (6%), 208 (100), 190 (15), 113 (9).

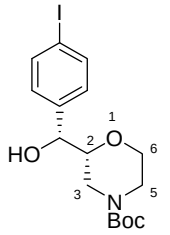
(2*S*,3*S*)-2-[α-Hydroxy-(4-iodophenyl)methyl]-*N*-*tert*-butoxycarbonylmorpholine 156



156

(2*S*,3*S*)-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 ^{o}C. Borane.dimethyl sulfide complex (1.39 mL, 2.77 mmol) was added dropwise and the reaction mixture stirred at 0 ^{o}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 ($MgSO_4$) 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 (2*S*,3*S*)-2-[α-hydroxy-(4-iodophenyl)methyl]-*N*-*tert*-butoxycarbonylmorpholine **156** as a colourless oil (0.15 g, 40%). ν_{max}/cm^{-1} (NaCl) 3434 (OH), 2976 (CH), 2863, 1686 (CO), 1480, 1454; $[\alpha]_D^{27}$ +27.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, 3 x CH_3), 2.60-2.76 (1H, m, 3-*H*H), 2.94 (1H, t, *J* 11.4 Hz, 5-*H*H), 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-*H*H), 3.56-3.66 (1H, m, 3-H*H*), 3.78 (1H, br d, *J* 11.4 Hz, 5-H*H*), 3.92 (1H, br dd, *J* 11.4, 2.0 Hz, 6-H*H*), 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); δ_C (100 MHz, $CDCl_3$) 28.3 (3 x CH_3), 43.7 (CH_2), 44.3 (CH_2), 66.4 (CH_2), 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^+. $C_{16}H_{22}O_4NI$ requires 419.0594), 233 (24%), 187 (58), 130 (91), 86 (53), 57 (100).

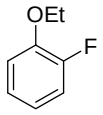
(2*R*,3*R*)-2-[α-Hydroxy-(4-iodophenyl)methyl]-*N*-*tert*-butoxycarbonylmorpholine 194



194

This reaction was carried out as described above using (2*R*,3*R*)-2-[α-hydroxy-(4-iodophenyl)methyl]morpholine-5-one **192** (0.11 g, 0.32 mmol). This gave (2*R*,3*R*)-2-[α-hydroxy-(4-iodophenyl)methyl]-*N*-*tert*-butoxycarbonylmorpholine **194** as a colourless oil (0.05 g, 56%). ν_{max} /cm^{-1} (NaCl) ν_{max}/cm^{-1} (NaCl) 3422 (OH), 2975 (CH), 2863, 1687 (CO), 1481, 1421; $[\alpha]_D^{25}$ -20.8 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, $C(CH_3)_3$), 2.68-2.83 (1H, m, 3-*H*H), 2.96 (1H, t, *J* 11.2 Hz, 5-*H*H), 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-*H*H), 3.58-3.69 (1H, m, 3-H*H*), 3.80 (1H, br d, *J* 11.2 Hz, 5-H*H*), 3.95 (1H, br dd, *J* 11.6, 2.0 Hz, 6-H*H*), 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); δ_C (100 MHz, $CDCl_3$) 28.3 (3 x CH_3), 43.8 (CH_2), 44.3 (CH_2), 66.4 (CH_2), 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$^+$. $C_{16}H_{23}O_4NI$ requires 420.0672), 346 (50%), 302 (30), 217 (31), 130 (22).

1-Ethoxy-2-fluorobenzene 185[24]

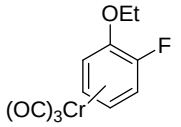


185

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 ^oC 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%). δ_H (400 MHz, $CDCl_3$) 1.40 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 4.04 (2H, d, *J* 7.2 Hz, OCH_2CH_3), 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); δ_C (100 MHz, $CDCl_3$) 14.8 (CH_3), 64.7 (CH_2), 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^+. C_8H_9OF requires 140.0637), 112 (100%), 92 (12), 83 (10), 64 (17), 57 (6).

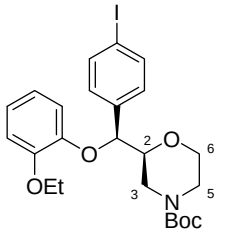
η^6-(1-Ethoxy-2-fluorobenzene)tricarbonylchromium 186[24]



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 ^oC 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 η^6-(1-ethoxy-2-fluorobenzene)tricarbonylchromium **186** as a green solid (0.14 g, 14%). mp 76-77 ^oC, lit.[24] 75-77 ^oC (from diethyl ether); δ_H (400 MHz, $CDCl_3$) 1.47 (3H, t, *J* 6.8 Hz, OCH_2CH_3), 4.00-4.10 (2H, m, OCH_2CH_3), 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_C (100 MHz, $CDCl_3$) 14.6 (CH_3), 66.9 (CH_2), 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^+. $C_{11}H_9O_4FCr$ requires 275.9890) 220 (11%), 192 (100), 164 (20), 143 (28).

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

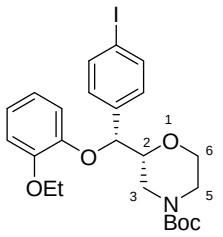


187

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 (2*S*,3*S*)-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 η^6-(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 ^{o}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 (2*S*,3*S*)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)methyl]-*N*-*tert*-butoxycarbonylmorpholine **187** as a colourless oil (0.04 g, 63%). ν_{max}/cm^{-1} (NaCl) 2977 (CH), 1695 (CO), 1591 (C=C), 1500, 1478; $[\alpha]_D^{22}$ +78.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.42-1.44 (12H, m, 3 x C*H*$_3$, OCH$_2$C*H*$_3$), 2.76-2.98 (2H, br m, 5-H$_2$), 3.52 (1H, td, *J* 11.6, 2.4 Hz, 6-*H*H), 3.78-3.85 (3H, m, 2-H, 3-H$_2$), 3.92-3.98 (1H, m, 6-H*H*), 4.05 (2H, q, *J* 6.8 Hz, OC*H*$_2$CH$_3$), 5.09-5.15 (1H, br m, 2-CH), 6.69-6.79 (2H, m, 2 x Ar H), 6.83-6.91 (2H, m, 2 x Ar H), 7.16 (2H, d, *J* 8.2 Hz, 2 x Ar H), 7.64 (2H, d, *J* 8.2 Hz, 2 x Ar H); δ_C (100 MHz, $CDCl_3$) 15.0 (CH_3), 28.3 (3 x CH_3), 46.5 (CH_2), 47.2 (CH_2), 64.4 (CH_2), 66.7 (CH_2), 77.4 (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 (M^+. $C_{24}H_{30}O_5NI$ requires 539.1169), 402 (18%), 346 (100), 302 (90), 217 (39), 176 (25).

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

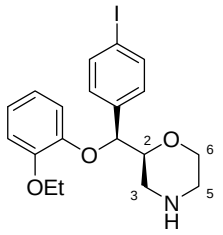


195

The reaction was carried out as described above using (2*R*,3*R*)-2-[α-hydroxy-(4-iodophenyl)methyl]-*N*-*tert*-butoxycarbonylmorpholine **194** (0.04 g, 0.11 mmol). This gave (2*R*,3*R*)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)methyl]-*N*-*tert*-butoxycarbonylmorpholine **195** as a colourless oil (0.04 g, 67%). ν_{max}/cm^{-1} (NaCl) 2977 (CH), 1695 (CO), 1590 (C=C), 1500, 1479; $[\alpha]_D^{26}$ -68.4 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.42-1.44 (12H, m, 3 x C*H*$_3$, OCH$_2$C*H*$_3$), 2.76-2.98 (2H, br m, 5-H$_2$), 3.52 (1H, t, *J* 10.4 Hz, 6-*H*H), 3.77-3.85 (3H, m, 2-H, 3-H$_2$), 3.94 (1H, d, *J* 10.4 Hz, 6-H*H*), 4.05 (2H, q, *J* 6.8 Hz, OC*H*$_2$CH$_3$), 5.09-5.15 (1H, br m, 2-CH), 6.70-6.76 (2H, m, 2 x Ar H), 6.83-6.90 (2H, m, 2 x Ar H),

7.16 (2H, d, *J* 8.0 Hz, 2 x Ar H), 7.64 (2H, d, *J* 8.0 Hz, 2 x Ar H); δ_C (100 MHz, $CDCl_3$) 15.1 (CH_3), 28.4 (3 x CH_3), 46.5 (CH_2), 47.2 (CH_2), 64.5 (CH_2), 66.8 (CH_2), 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^+. $C_{24}H_{30}O_5NI$ requires 539.1169), 402 (19%), 346 (100), 302 (88), 217 (38), 176 (5).

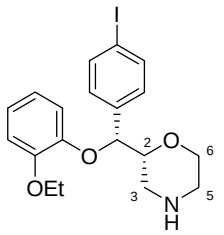
(2*S*,3*S*)-2-[(4-Iodophenyl)-(2-ethoxyphenoxy)methyl]morpholine 128



128

Trifluoroacetic acid (1.0 mL, 0.06 mmol) was added to a solution of (2*S*,3*S*)-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 hydrogencarbonate solution (10 mL). The organic layer was removed, dried ($MgSO_4$) and the filtrate concentrated *in vacuo* to give (2*S*,3*S*)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)methyl]morpholine **128** as a colourless oil (0.01 g, 60%). ν_{max}/cm^{-1} (NaCl) 3422 (NH), 2923 (CH), 1637 (C=C), 1591, 1252; $[\alpha]_D^{22}$ +54.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.68-2.76 (1H, m, 5-*H*H), 2.83-2.86 (3H, m, 3-H_2, 5-H*H*), 3.62-3.68 (1H, m, 6-*H*H), 3.90 (1H, ddd, *J* 10.0, 5.2, 2.4 Hz, 2-H), 3.97 (1H, m, 6-H*H*), 4.04 (2H, qd, *J* 7.0, 1.6 Hz, OCH_2CH_3), 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); δ_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^+. $C_{19}H_{22}O_3NI$ requires 439.0644), 301 (100%), 217 (42), 175 (28), 138 (15), 110 (22).

(2*R*,3*R*)-2-[(4-Iodophenyl)-(2-ethoxyphenoxy)methyl]morpholine 129

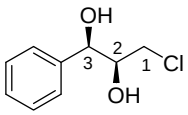


129

The reaction was carried out as described above using (2*R*,3*R*)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)methyl]-*N*-*tert*-butoxycarbonylmorpholine **197** (0.02 g, 0.04 mmol). This gave (2*R*,3*R*)-2-[(4-iodophenyl)-(2-ethoxyphenoxy)methyl]morpholine **129** as a colourless oil (0.01 g, 67%). ν_{max}/cm^{-1} (NaCl) 3422 (NH), 2923 (CH), 1637 (C=C), 1591, 1252; $[\alpha]_D^{26}$ -44.3 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, t, *J* 7.0 Hz, OCH_2CH_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_2CH_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); δ_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^+. $C_{19}H_{22}O_3NI$ requires 439.0644), 301 (100%), 217 (42), 175 (28), 138 (15), 110 (22).

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

(2*S*,3*R*)-1-Chloro-3-phenylpropane-2,3-diol 203[73]

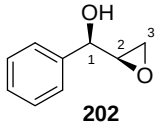


203

AD-mix-β (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 hydrogencarbonate (7.06 g, 84.0 mmol) were added and the bright orange solution cooled to 0 ^oC. Cinnamyl chloride **204** (3.90 mL, 28.0 mmol) was added and the solution stirred vigorously at 0 ^oC 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 (2*S*,3*R*)-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); δ_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-*H*H), 3.55 (1H, dd, *J* 11.6, 3.8 Hz, 1-H*H*), 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); δ_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).

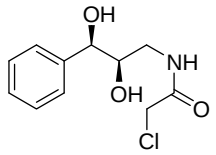
(1*R*,2*R*)-2,3-Epoxy-1-phenylpropan-1-ol 202



202

(2*S*,3*R*)-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 ^oC 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 (1*R*,2*R*)-2,3-epoxy-1-phenylpropan-1-ol **202** as a yellow oil (2.10 g, 92%). ν_{max}/cm^{-1} (NaCl) 3422 (OH), 3031 (CH), 1603 (C=C), 1255, 1046; $[\alpha]_D^{22}$ -13.1 (*c* 1.0, $CHCl_3$); δ_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); δ_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^+. $C_9H_{11}O_2$ requires 151.0759), 133 (100%), 107 (57), 105 (11), 79 (9).

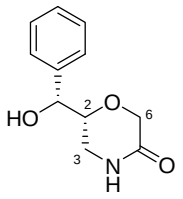
(2*R*,3*R*)-1-Chloroacetylamino-3-phenylpropane-2,3-diol 201



201

(1*R*,2*R*)-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 ($MgSO_4$) and the filtrate concentrated *in vacuo*. The crude material (2.13 g) was dissolved in acetonitrile (250 mL) and the mixture cooled to -10 ^oC. 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 ^oC 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 ($MgSO_4$) 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 (2*R*,3*R*)-1-chloroacetylamino-3-phenylpropane-2,3-diol **201** as a yellow oil (0.85 g, 25%). ν_{max}/cm^{-1} (NaCl) 3410 (NH/OH), 1654 (CO), 1543 (C=C), 1493, 1263, 1084; $[\alpha]_D^{21}$ -22.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.99 (1H, br s, OH), 3.24-3.31 (1H, m, 1-*H*H), 3.40-3.46 (1H, m, 1-H*H*), 3.83-3.93 (1H, m, 2-H), 4.03 (2H, s, CH_2Cl), 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_C (100 MHz, $CDCl_3$) 42.4 (CH_2), 42.5 (CH_2), 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^+. $C_{11}H_{14}O_3N^{35}Cl$ requires 244.0740) 246 (23%), 244 (67), 228 (34), 226 (100), 210 (23), 208 (19), 136 (21).

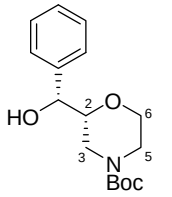
(2*R*,3*R*)-2-[α-Hydroxyphenylmethyl]morpholine-5-one 205



205

Sodium *tert*-butoxide (1.00 g, 10.4 mmol) was dissolved in *tert*-butanol (20 mL). (2*R*,3*R*)-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 ^{o}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 ($MgSO_4$), and the filtrate concentrated *in vacuo* to give (2*R*,3*R*)-2-[α-hydroxyphenylmethyl]morpholine-5-one **205** as a colourless oil (0.42 g, 58%). ν_{max}/cm^{-1} (NaCl) 3370 (NH/OH), 2883 (CH), 1663 (CO), 1495, 1119; $[\alpha]_D^{24}$ +22.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.81 (1H, d, *J* 11.8 Hz, 3-H*H*), 3.03 (1H, br s, OH), 3.23 (1H, t, *J* 11.8 Hz, 3-H*H*), 3.72-3.77 (1H, m, 2-H), 4.15 (1H, d, *J* 16.6 Hz, 6-*H*H), 4.30 (1H, d, *J* 16.6 Hz, 6-H*H*), 4.58 (1H, d, *J* 7.6 Hz, 2-CH), 7.08 (1H, br s, NH), 7.31-7.35 (5H, m, 5 x Ar H); δ_C (100 MHz, $CDCl_3$) 42.9 (CH_2), 67.5 (CH_2), 75.0 (CH), 77.1 (CH), 126.8 (2 x CH), 128.8 (3 x CH), 138.6 (C), 169.0 (C); *m/z* (CI) 208.0973 (MH^+. $C_{11}H_{14}O_3N$ requires 208.0974) 208 (100%), 190 (12), 133 (1), 101 (3), 69 (2).

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

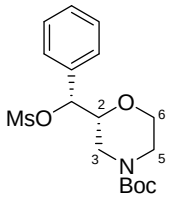


200

(2*R*,3*R*)-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 ^{o}C. Borane.dimethyl sulfide complex (3.0 mL, 6.0 mmol) was added dropwise and the reaction mixture stirred at 0 ^{o}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 *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 *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 *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 *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-(α-hydroxyphenylmethyl)-*N*-*tert*-butoxycarbonylmorpholine **200** as a white solid (0.21 g, 37%). ν_{max}/cm^{-1} (KBr) 3438 (OH), 2972 (CH), 1702 (CO), 1431, 1113; $[\alpha]_D^{28}$ -42.5 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, 3 x CH_3), 2.61-2.81 (1H, br m, 3-*H*H), 2.93-2.97 (1H, m, 5-*H*H), 3.00 (1H, s, OH), 3.47 (1H, m, 2-H), 3.56 (1H, td, *J* 11.6, 2.8 Hz, 6-*H*H), 3.61-3.69 (1H, br m, 3-H*H*), 3.81 (1H, br d, *J* 11.6 Hz, 5-H*H*), 3.97 (1H, dd, *J* 11.6, 1.6 Hz, 6-H*H*), 4.53 (1H, dd, *J* 7.4, 2.2 Hz, 2-CH), 7.31-7.36 (5H, m, 5 x Ar H); δ_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^+. $C_{16}H_{24}O_4N$ requires 294.1705), 276 (12%), 238 (40), 220 (100), 176 (12), 136 (4).

(2*R*,3*R*)-2-(α-Methanesulfonyloxyphenylmethyl)-*N*-*tert*-butoxycarbonylmorpholine 207



207

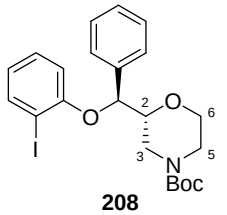
(2*R*,3*R*)-2-(α-Hydroxyphenylmethyl)-*N*-*tert*-butoxycarbonylmorpholine **200** (0.19 g, 0.64 mmol) was dissolved in dichloromethane (4 mL) and triethylamine (0.13 mL, 0.96 mmol), dimethylaminopyridine (0.02 g, 0.13 mmol) and methanesulfonyl chloride (0.07 mL, 0.96 mmol) added sequentially and the 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 *in vacuo*. Purification was carried out by flash column chromatography and elution with 40:60 ethyl acetate-petroleum ether

(40-60) gave (2*R*,3*R*)-2-(α-methanesulfonyloxyphenylmethyl)-*N*-*tert*-butoxycarbonylmorpholine **207** as a white solid (0.18 g, 74%). ν_{max}/cm^{-1} (KBr) 2986 (CH), 2865, 1698 (CO), 1476 (C=C), 1410; $[\alpha]_D^{21}$ -64.2 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, 3 x CH_3), 2.51-2.69 (1H, br m, 3-*H*H), 2.85 (3H, s, SO_2CH_3), 2.93-3.00 (1H, m, 5-*H*H), 3.40-3.50 (1H, br m, 3-H*H*), 3.55 (1H, td, *J* 11.6, 2.8 Hz, 6-*H*H), 3.72-3.85 (2H, m, 2-H, 5-H*H*), 3.98 (1H, d, *J* 11.6 Hz, 6-H*H*), 5.42 (1H, d, *J* 7.6 Hz, 2-CH), 7.35-7.43 (5H, m, 5 x Ar H); δ_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^+. $C_{17}H_{26}O_6NS$ 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*.

(2*R*,3*S*)-2-[(2-Iodophenoxy)phenylmethyl]-*N*-*tert*-butoxycarbonylmorpholine 208

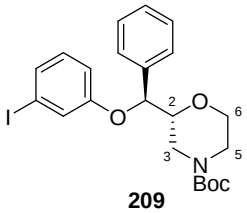


208

The reaction was carried out according to general procedure 1 using (2*R*,3*R*)-2-(α-methanesulfonyloxyphenylmethyl)-*N*-*tert*-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 (2*R*,3*S*)-2-[(2-iodophenoxy)phenylmethyl]-*N*-*tert*-butoxycarbonylmorpholine **208** as a colourless oil (0.05 g, 47%). ν_{max}/cm^{-1} (NaCl) 2974 (CH), 2860 (CH), 1694 (CO), 1470 (C=C), 1243; $[\alpha]_D^{22}$ -79.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, 3 x CH_3), 2.91-3.06 (1H, br m, 3-*H*H), 3.07-3.30 (1H, br m, 5-*H*H), 3.48 (1H, t, *J* 10.8 Hz, 5-*H*H), 3.70-3.73 (1H, m, 2-H), 3.87-3.90 (2H, m, 3-H*H*, 6-H*H*), 4.20-4.47 (1H, br m, 6-H*H*),

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); δ_C (100 MHz, $CDCl_3$) 28.4 (3 x CH_3), 43.0 (CH_2), 46.3 (CH_2), 66.8 (CH_2), 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^+. $C_{22}H_{26}O_4NI$ requires 495.0907) 439 (6%), 422 (5), 309 (25), 220 (100), 176 (84).

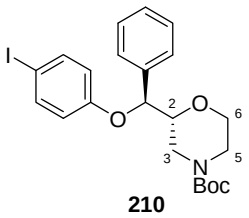
(2*R*,3*S*)-2-[(3-Iodophenoxy)phenylmethyl]-*N*-*tert*-butoxycarbonylmorpholine 209



209

The reaction was carried out according to general procedure 1 using (2*R*,3*R*)-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 (2*R*,3*S*)-2-[(3-iodophenoxy)phenylmethyl]-*N*-*tert*-butoxycarbonylmorpholine **209** as a colourless oil (0.016 g, 32%). ν_{max}/cm^{-1} (NaCl) 2974 (CH), 2860 (CH), 1696 (CO), 1581 (C=C), 1470; $[\alpha]_D^{23}$ -34.3 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, 3 x CH_3), 2.98 (2H, m, 3-*H*H, 5-*H*H), 3.46 (1H, td, *J* 11.6, 2.8 Hz, 6-*H*H), 3.61-3.70 (1H, m, 2-H), 3.80-3.89 (2H, m, 3-H*H*, 5-H*H*), 3.99-4.29 (1H, br m, 6-H*H*), 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); δ_C (100 MHz, $CDCl_3$) 27.0 (3 x CH_3), 43.5 (CH_2), 43.8 (CH_2), 65.4 (CH_2), 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^+. $C_{22}H_{27}O_4NI$ requires 496.0985), 440 (8%), 309 (14), 220 (100), 176 (62).

(2*R*,3*S*)-2-[(4-Iodophenoxy)phenylmethyl]-*N*-*tert*-butoxycarbonylmorpholine 210



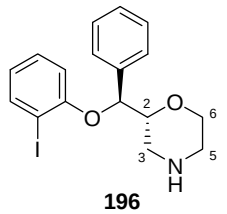
210

The reaction was carried out according to general procedure 1 using (2*R*,3*R*)-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 (2*R*,3*S*)-2-[(4-iodophenoxy)phenylmethyl]-*N*-*tert*-butoxycarbonylmorpholine **210** as a colourless oil (0.026 g, 52%). ν_{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-*H*H, 5-*H*H), 3.46 (1H, td, *J* 11.6, 2.8 Hz, 5-*H*H), 3.60-3.72 (1H, m, 2-H), 3.74-3.91 (2H, m, 3-H*H*, 6-H*H*), 4.01-4.32 (1H, br m, 6-H*H*), 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$^+$. $C_{22}H_{27}O_4NI$ 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*.

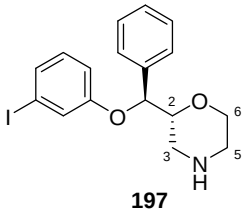
(2*R*,3*S*)-2-[(2-Iodophenoxy)phenylmethyl]morpholine 196



196

The reaction was carried out according to general procedure 2 using (2*R*,3*S*)-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 (2*R*,3*S*)-2-[(2-iodophenoxy)phenylmethyl]morpholine **196** as a colourless oil (0.03 g, 76%). ν_{max}/cm^{-1} (NaCl) 3855 (NH), 2853 (CH), 1638, 1579 (C=C), 1469; $[\alpha]_D^{24}$ -105.5 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.28 (1H, br s, NH), 2.79-2.85 (1H, m, 5-*H*H), 2.95 (1H, td, *J* 11.4, 3.4 Hz, 5-H*H*), 3.09 (1H, dd, *J* 12.4, 10.0 Hz, 3-*H*H), 3.30 (1H, dd, *J* 12.4, 1.6 Hz, 3-H*H*), 3.58 (1H, td, *J* 11.4, 2.3 Hz, 6-*H*H), 3.76-3.82 (1H, m, 2-H), 3.90 (1H, dd, *J* 11.4, 2.3 Hz, 6-H*H*), 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_C (100 MHz, $CDCl_3$) 45.4 (CH_2), 46.5 (CH_2), 67.9 (CH_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* (CI) 396.0462 (MH^+. $C_{17}H_{19}O_2NI$ requires 396.0461), 268 (36%), 176 (100), 113 (16), 85 (36).

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

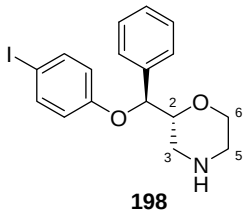


197

The reaction was carried out according to general procedure 2 using (2*R*,3*S*)-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 (2*R*,3*S*)-2-[(3-iodophenoxy)phenylmethyl]morpholine **197** as a white solid (0.01 g, 80%). ν_{max}/cm^{-1} (KBr) 3426 (NH), 2958 (CH), 1583 (C=C), 1470, 1239; $[\alpha]_D^{25}$ -19.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 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); δ_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^+. $C_{17}H_{19}O_2NI$ requires 396.0461), 338 (8%), 288 (11), 177 (90), 119 (14).

(2*R*,3*S*)-2-[(4-Iodophenoxy)phenylmethyl]morpholine 198



198

The reaction was carried out according to general procedure 2 using (2*R*,3*S*)-2-[(4-iodophenoxy)phenylmethyl]-*N*-*tert*-butoxycarbonylmorpholine **210** (0.02 g, 0.04 mmol). Purification was carried out by flash column chromatography and elution with 90 : 10 ethyl acetate-methanol gave (2*R*,3*S*)-2-[(4-iodophenoxy)phenylmethyl]morpholine **198** as a colourless oil (0.009 g, 55%). ν_{max}/cm^{-1} (NaCl) 3423 (NH), 2955 (CH), 1638 (C=C), 1483, 1237; $[\alpha]_D^{25}$ +17.0 (*c* 0.9, $CHCl_3$); δ_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); δ_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^+. $C_{17}H_{19}O_2NI$ 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

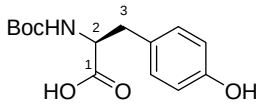
Transporter Assay	Radioligand	Binding Buffer and Incubation Conditions
Noradrenaline Transporter (NAT) *Modified from*: ref [94]	1.2 nM [^{3}H]nisoxetine (71.0 Ci/mmol, GE Healthcare)	50 mM Tris-HCl, pH 7.4 300 mM NaCl 5 mM KCl Incubation: 4 hours at 4 °C
Serotonin Transporter (SERT) *Modified from*: ref [95]	0.4 nM [^{3}H]citalopram (83.0 Ci/mmol, GE Healthcare)	50 mM Tris-HCl, pH 7.4 120 mM NaCl 5 mM KCl Incubation: 2 hours at RTP
Dopamine Transporter (DAT) *Modified from*: refs [96-98]	4.7 nM [^{3}H]WIN-35,428 (85.9 Ci/mmol, Perkin-Elmer)	25 mM NaH_2PO4 25 mM Na_2HPO4 50 mM NaCl pH 7.70 Incubation: 2 hours at 4 °C

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 [^{3}H] 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 [^{3}H]nisoxetine (1.7 nM) and [^{3}H]citalopram (2.1 nM) binding to the NAT and SERT, respectively, were determined under the same assay conditions. A K_d estimation for [^{3}H]WIN-35,428 (5.0 nM) binding to the high

affinity site on the DAT was selected by a review of published literature.[97,98] Data is presented as mean ± SEM for three independent competition experiments with [^{3}H]nisoxetine and two independent competition experiments with [^{3}H]citalopram and [^{3}H]WIN-35,428.

3.4 Steps Towards Oxazinin-3

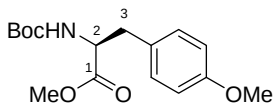
(2*S*)-*tert*-Butoxycarbonylamino-3-(4-hydroxyphenyl)propionic acid 235[99]



235

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-*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 *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 *in vacuo* to give (2*S*)-*tert*-butoxycarbonylamino-3-(4-hydroxyphenyl)propionic acid **235** as a white solid (7.72 g, 100%). mp 138-139 ^{o}C, lit.[99] 137-138 ^{o}C; δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, 3 x CH_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); δ_C (100 MHz, $CDCl_3$) 27.6 (3 x CH_3), 37.3 (CH_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); *m/z* (FAB) 275 (5%), 231 (9), 192 (100), 180 (8), 57 (25).

Methyl (2*S*)-*tert*-butoxycarbonylamino-3-(4-methoxyphenyl)propanoate 236[100]

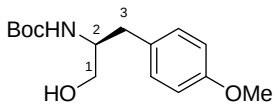


236

(2*S*)-*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 ($MgSO_4$) 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 (2*S*)-*tert*-butoxycarbonylamino-3-(4-methoxyphenyl)propanoate **236** as a white solid (1.90 g, 58%). $[\alpha]_D^{25}$ +50.3 (*c* 1.8, $CHCl_3$), lit.[100] $[\alpha]_D^{25}$ +59.2 (*c* 1.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, 3 x CH_3), 2.96-3.08 (2H, m, 3-H_2), 3.70 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 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); δ_C (100 MHz, $CDCl_3$) 28.3 (3 x CH_3), 37.4 (CH_2), 52.1 (CH_3), 54.6 (CH), 55.2 (CH_3), 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).

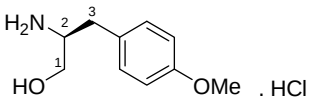
(2*S*)-*N*-*tert*-Butoxycarbonyl-3-(4-methoxyphenyl)propan-1-ol 237[100]



237

Methyl (2*S*)-*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 ^oC. Lithium borohydride (0.51 g, 23.3 mmol) was added and the reaction mixture stirred at 0 ^oC 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 ($MgSO_4$) 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 (2*S*)-*N*-*tert*-butoxycarbonyl-3-(4-methoxyphenyl)propan-1-ol **237** as a white solid (1.06 g, 81%). $[\alpha]_D^{24}$ -21.3 (*c* 1.0, $CHCl_3$), lit.[100] $[\alpha]_D^{20}$ -22.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, 3 x CH_3), 2.52 (1H, br s, OH), 2.77 (2H, d, *J* 6.8 Hz, 3-H_2), 3.51-3.56 (1H, m, 1-H*H*), 3.61-3.68 (1H, m, 1-H*H*), 3.78-3.88 (4H, m, 2-H, OCH_3), 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); δ_C (100 MHz, $CDCl_3$) 28.4 (3 x CH_3), 36.5 (CH_2), 53.9 (CH), 55.3 (CH_3), 64.4 (CH_2), 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).

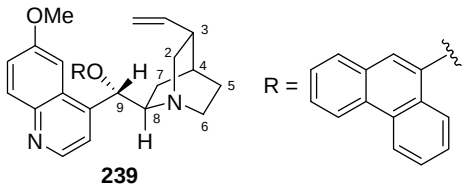
(2*S*)-2-Amino-3-(4-methoxyphenyl)propan-1-ol hydrochloride 231[101]



233

(2*S*)-*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 (2*S*)-2-amino-3-(4-methoxyphenyl)propan-1-ol hydrochloride **231** as a white solid (0.76 g, 96%). mp 223-225 ^{o}C; δ_H (400 MHz, D_2O) 2.75 (1H, dd, *J* 14.4, 7.4 Hz, 3-*H*H), 2.86 (1H, dd, *J* 14.4, 6.4 Hz, 3-H*H*), 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); δ_C (100 MHz, D_2O) 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]

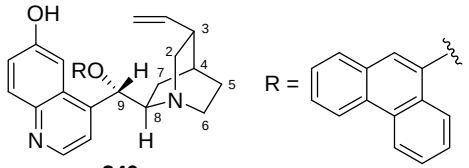


239

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 ^{o}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 ($MgSO_4$) 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 ($MgSO_4$) and the filtrate concentrated *in vacuo* to give quinidine 9-*O*-(9'-phenanthryl) ether **239** as a white foam (1.20 g, 39%). $[\alpha]_D^{23}$ -311.0 (*c* 0.9, EtOH); δ_H (400 MHz, $CDCl_3$) 1.50-1.60 (3H, m, 5-H_2, 7-*H*H), 1.91-1.98 (1H, br m, 7-H*H*), 2.30-2.36 (1H, m, 4-H), 2.41-2.51 (1H, m, 3-H), 2.77-2.85 (1H, m, 6-*H*H), 2.96-3.05 (2H, m, 2-H_2), 3.32-3.38 (2H, m, 8-H, 6-H*H*), 4.02 (3H, s, OCH_3), 5.11 (1H, d, *J* 17.2 Hz, 3-CHC*H*H), 5.18 (1H, d, *J* 10.2 Hz, 3-CHCH*H*), 6.16 (1H, ddd, *J* 17.2, 10.2, 6.4 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, *J* 9.2 Hz, 1 x Ar H), 8.50 (1H, d, *J* 7.6 Hz, 1 x Ar H), 8.60 (1H, d, *J* 4.4 Hz, 1 x Ar H), 8.65-8.75 (2H, m, 2 x Ar H); δ_C (100 MHz, $CDCl_3$) 22.1 (CH_2), 26.5 (CH_2), 27.8 (CH), 39.6 (CH), 50.0 (CH_2), 50.3 (CH_2), 55.8 (CH_3), 60.5 (CH), 78.8 (CH), 100.8 (CH), 104.9 (CH), 114.8 (CH_2), 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).

(9*S*)-6'-Hydroxycinchonan-9-*O*-(9'-phenanthryl) ether 240[82]

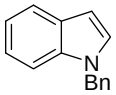


240

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 ^oC 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 ($MgSO_4$) and the filtrate concentrated *in vacuo*. Purification was carried out using flash column chromatography and elution with 95:5 ethyl acetate-methanol gave (9*S*)-6'-hydroxycinchonan-9-*O*-(9'-phenanthryl) ether **241** (0.23 g, 47%). $[\alpha]_D^{25}$ -220.7 (*c* 1.0,

$CHCl_3$), lit.[82] $[\alpha]_D^{25}$ -304.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.34-1.53 (3H, m, 5-H_2, 7-*H*H), 1.94-2.01 (1H, br m, 7-H*H*), 2.28-2.30 (1H, m, 4-H), 2.65-2.70 (2H, m, 6-H_2), 2.98-3.04 (2H, m, 2-H_2), 3.32-3.36 (1H, m, 3-H), 3.53-3.58 (2H, m, 8-H_2), 5.12 (1H, d, *J* 17.2 Hz, 3-CHC*H*H), 5.26 (1H, d, *J* 10.4 Hz, 3-CHCH*H*), 6.17-6.22 (1H, m, 3-CH), 6.29-6.36 (1H, br m, 9-H), 6.50 (1H, d, *J* 7.6 Hz, 1 x Ar H), 6.62 (1H, 1 x Ar H), 6.78 (1H, t, *J* 7.2 Hz, 1 x Ar H), 7.19 (1H, t, *J* 7.6 Hz, 1 x Ar H), 7.25 (1H, m, 1 x Ar H), 7.36 (1H, d, *J* 4.4 Hz, 1 x Ar CH), 7.68-7.71 (2H, m, 2 x Ar H), 7.76 (1H, d, *J* 8.6 Hz, 1 x Ar H), 8.19 (1H, 1 x Ar H), 8.37 (1H, d, *J* 8.6 Hz, 1 x Ar H), 8.46 (1H, d *J* 4.4 Hz, 1 x Ar H), 8.60-8.70 (2H, m, 2 x Ar H); δ_C (100 MHz, $CDCl_3$) 20.3 (CH_2), 25.8 (CH_2), 27.5 (CH), 38.9 (CH), 49.6 (CH_2), 49.8 (CH_2), 59.2 (CH), 105.1 (CH), 106.3 (CH), 115.4 (CH_2), 117.5 (CH), 121.9 (CH), 122.7 (CH), 122.9 (CH), 123.5 (CH), 124.3 (CH), 124.5 (CH), 126.1 (C), 126.3 (CH), 126.5 (C), 126.6 (C), 127.2 (CH), 127.3 (CH), 127.4 (CH), 131.5 (C), 131.9 (CH), 131.9 (CH), 139.5 (CH), 142.4 (C), 143.8 (C), 146.7 (CH), 149.6 (C), 157.1 (C); *m/z* (FAB^+) 487 (MH^+, 100%), 351 (5), 293 (98), 253 (6), 185 (20).

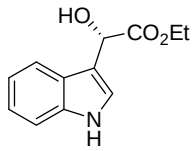
1-Benzylindole 245[89]



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 ($MgSO_4$) 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%). δ_H (400 MHz, $CDCl_3$) 5.31 (2H, s, CH_2Ph), 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).

Ethyl 3-indolyl-2-hydroxyacetate 241[84]



241

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 ^{o}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_H (400 MHz, $CDCl_3$) 1.21 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 3.36 (1H, br s, OH), 4.12-4.16 (1H, dq, *J* 10.8, 7.2 Hz, C*H*HCH_3), 4.29 (1H, dq, *J* 10.8, 7.2 Hz, CH*H*CH_3), 5.46 (1H, s, 2-H), 7.11-7.22 (3H, m, NHC*H*, 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_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 62.1 (CH_2), 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^+, 13%), 202 (100), 146 (8), 103 (41), 81 (10).

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