Synthesis of Selective A_3 and M_1 Receptor Agonists

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School of Chemistry

Contents

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Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
ACh	acetylcholinesterase
AD	Alzheimer's disease
AIBN	2,2'-azobisisobutyronitrile
Å	Ångstrom(s)
aq	aqueous
Ar	aryl
B:	base
Boc	*tert*-butoxycarbonyl
Bp	boiling point
Br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
^{13}C NMR	carbon nuclear magnetic resonance
cat.	catalytic
Cbz	carbobenzyloxy
CI	chemical ionisation
d	doublet
dd	double doublet
ddq	double double quartet
δ	chemical shift
DCM	dichloromethane
DIBAL-H	di-*iso*-butylaluminium hydride
DIPA	di-*iso*-propylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
EI	electron impact ionisation
eq	equivalent(s)

Et	ethyl
ES	electrospray
exp.	experiment
g	gram(s)
h	hour(s)
^{1}H NMR	Proton nuclear magnetic resonance
Hz	Hertz
i-Pr	*iso*-propyl
IR	infrared
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium di-*iso*-propylamide
Lit.	literature
m	multiplet
M	molarity
M^+	molecular ion
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
MHz	megaHertz
mmol	millimole(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
Ns	2-nitrobenzene sulfonyl
Tf	trifluorosulfonyl
P	protective group
petrol	petroleum ether (40-60 ^{o}C)
Ph	phenyl
ppm	parts per million
q	quartet
qn	quintet
R	alkyl group

R_f	retention factor
RM	reaction mixture
RT	room temperature
s	singlet
sat.	saturated aqueous solution
t	triplet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
tert	tertiary
Tf	triflate
THF	tetrahydrofuran
TLC	thin layer chromatography
TM	target molecule
TMP	2,2,6,6-tetramethylpiperidine
TPAP	tetrapropylammonium perruthenate
UV	ultraviolet
X	leaving group

Abstract

The University of Manchester
Stephen Snee
Doctor of Philosophy
Synthesis of Selective A_3 and M_1 Receptor Agonists
September 2010

Detailed within this thesis is the synthesis of three A_1 agonists which were designed by Muscagen using computational studies. The agonists are derived from condensation of the modified adenosine: (4*S*,6*R*)-6-(6-chloro-9*H*-purin-9-yl)-*N*,2,2-trimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxamide with novel heterocyclic primary amines.

The amines 5-(aminomethyl)-*N*,*N*-diethyl-7-methyloxazolo[4,5-b]pyridin-2-amine, 5-(1-aminoethyl)-*N*,*N*,7-trimethyloxazolo[4,5-b]pyridin-2-amine and 5-(1-aminoethyl)-*N*,*N*-diethyl-7-methyloxazolo[4,5-b]pyridin-2-amine were prepared from 2-amino-6-((*tert*-butyldiphenylsilyloxy)methyl)-4-methylpyridin-3-ol which was available from 2,4-lutidine.

The dimethylaminooxazole functionality was introduced by treating a 1,2-hydroxyaminopyridine with phosgene iminium chloride whereas the diethylamino-oxazoles were prepared by displacement of chloride from a 2-chloro-oxazole with diethylamine.

Using chemistry developed by Ellman it was possible to introduce a methyl appendage into the scaffold.

Also detailed within this thesis is the synthesis of the novel M_1 agonist; (+/-) (3a*S*,7*R*,7a*R*)-3-benzyl-7-(furan-2-yl)hexahydrooxazolo[4,5-c]pyridin-2(3*H*)-one. Cyclobutanecarboxylic acid was elaborated to *tert*-butyl(4-cyanato-2-cyclobutylbut-2-enyloxy)dimethylsilane which underwent a [3,3]-sigmatropic rearrangement to afford *tert*-butyl(2-cyclobutyl-2-isocyanatobut-3-enyloxy)dimethyl silane which was treated with sodium benzalkoxide. This yielded the Cbz protected amine with the required quaternary centre installed. Ozonolysis of the olefin moiety gave an aldehyde to which (1-(furan-2-yl)vinyl)lithium was introduced with excellent diastereoselectivity. The resulting alkoxide underwent *in situ* cyclisation to form the oxazolidinone with concurrent loss of benzyl alcohol. Hydroboration was used to install the stereochemistry of the furan bearing carbon and the resulting alcohol was subjected to an intramolecular Fukuyama-Mitsunobu reaction to furnish the piperidine ring.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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This thesis would not have been possible without the help and support given by a great number of people.

First and foremost I would like to thank my supervisor, Professor Thomas for his extensive guidance and encouragement.

It is impossible to overstate my gratitude to Muscagen for giving me the opportunity to work on such interesting and rewarding projects. Particular thanks go to Dr. Robin Davies.

I would also like to thank the entire staff of the analytical department at Manchester. Special thanks go to Gareth and Val in Mass Spec.

I owe my deepest gratitude to Alan Lee who initially took me under his wing when I was an undergraduate student, and has been a valued friend ever since. The practical skills and theoretical insights I gained from his diligent tuition will be invaluable for years to come.

Sincere thanks go also to Anthony Green who has on so many occasions taken the time to explain some of the complexities of organic chemistry in a way that was easy to understand. His contribution to my years in Manchester has been of great value on both an academic and personal level.

I would like to thank my mum, dad, brother, sister and nana Gabrielli for their unwavering love and support. They have been a constant source of motivation throughout my student years.

Finally it is with mixed emotions that I hand the Muscagen baton to Erica Burnell.

Preface

This thesis describes the research carried out by the author between September 2006 and September 2009. Two separate projects are discussed. Initially efforts focused on the synthesis of novel A_3 agonists; accordingly this body of work is presented first. The second chapter discusses the synthesis of a novel M_1 agonist.

Chapter 1: Approaches toward novel A_3 agonists

1.1 Introduction

Adenosine (Figure 1.0) is a ubiquitous neurotransmitter present in all cell types which exerts its actions through binding to four distinct G-protein-coupled receptors: A_1, A_2, A_{2B}, and A_3. Each of these subtypes has a unique tissue distribution, ligand affinity and signal transduction mechanism.[1,2]

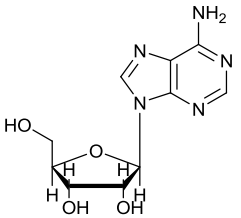


Figure 1.0

Adenosine, the indigenous adenosine receptor ligand, is produced by tissues when there is an imbalance between oxygen supply and demand. This has the effect of increasing oxygen supply by causing vasodilatation, and decreasing the energy demand of the tissue by a negative feedback mechanism thus preventing ischemia.[3]

The A_3 receptors are currently being investigated as potential targets to treat inflammatory and neurodegenerative disease, asthma and cardiac ischemia. It has been shown that A_3 receptor agonists reduce hypoxic heart damage, protect blood eosinophils, HL-60 and U-937 from apoptosis, and promote protective mechanisms in astroglial cultures.[4]

It has been demonstrated that adenosine *N6* benzyl derivatives are potent agonists at the A_3 receptor subtype. Additionally derivatives modified at the 5' position had enhanced affinity and selectivity for the A_3 receptor subtype.[5,6]

Muscagen have identified a novel structural motif as a potential scaffold for a source of selective A_3 agonists (Figure 1.1). It is anticipated that molecules designed around this platform will show promise for development into therapeutic agents to prevent cardiac ischemia.

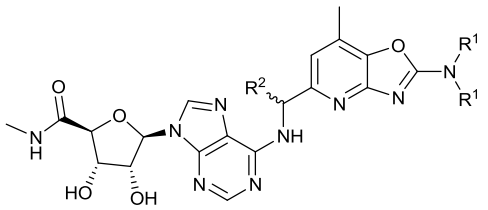


Figure 1.1

Uncertainties in the molecular modelling calculations meant that it was necessary to synthesise and biologically evaluate several compounds to establish proof of principle. These compounds will differ at the C2 substituent on the oxazole ring (R^1), and the presence or absence of a methyl group on the carbon atom adjacent to the pyridine (R^2) giving rise to a small group novel compounds **1.01-104**. (Figure 1.2)

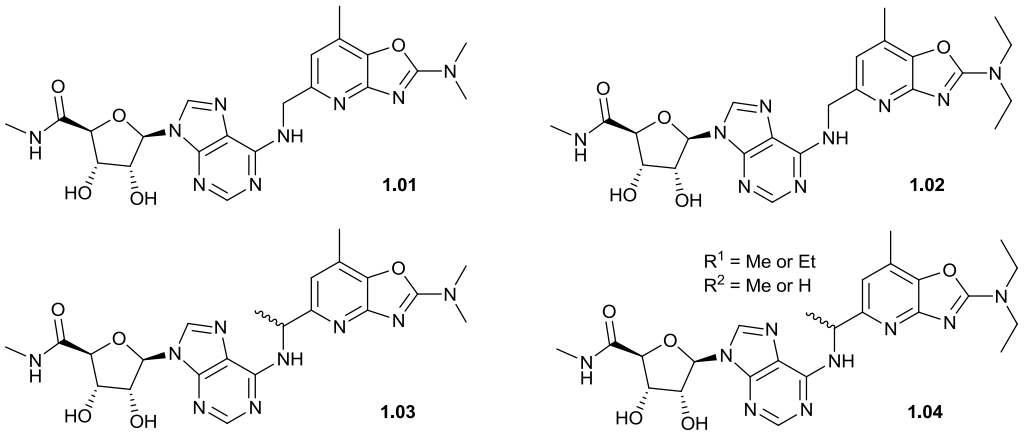


Figure 1.2

1.1.1 Previous work

Previous work in the group has led to the synthesis of compound **1.01**.[7] Disconnection of the nitrogen-purine bond *via* nucleophilic aromatic substitution gives two fragments of approximately equal size and complexity. (Figure 1.3)

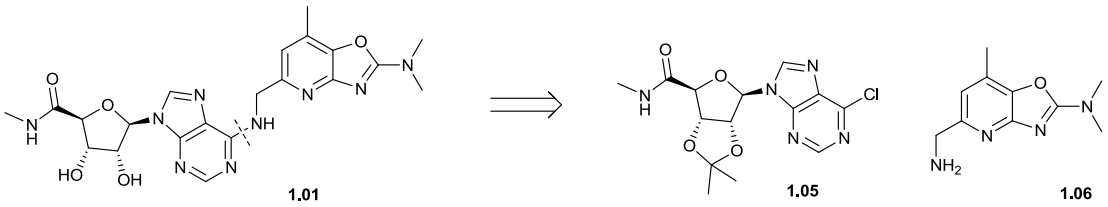
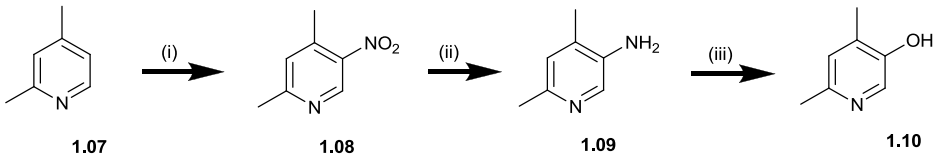


Figure 1.3

A sample of the chloropurine **1.05** was provided by Muscagen and so the synthetic efforts were focused on the amine **1.06**.

1.1.1.1 Synthesis of the amine 1.06

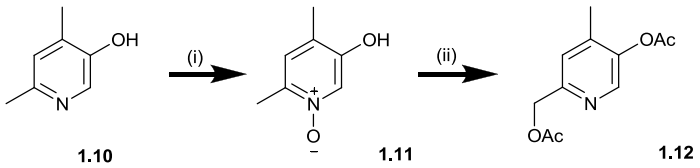
Nitration of 2,4-lutidine **1.07** gave a mixture of starting material, 3- and 5-nitro-2,4-lutidine (5:2:3) which were separated by fractional vacuum distillation to give a modest (20 %) yield of the desired 5-nitro-2,4-lutidine **1.08**. The nitrated product was subjected to palladium catalysed hydrogenation to give the corresponding aromatic amine **1.09** in quantitative yield. A Sandmeyer-type reaction using water as a nucleophile furnished the required hydroxypyridine functionality **1.10**. (Figure 1.4)



Reagents and conditions: (i) fuming H_2SO_4, KNO_3, 100 °C, 8 h, 120 °C, 16 h (20 %). (ii) 10 % Pd/C (2 mol %), H_2, EtOAc, 16 h (99 %). (iii) a) $NaNO_2$, H_2SO_4, H_2O, 0 °C, 15 mins b) Δ (40 %).

Figure 1.4

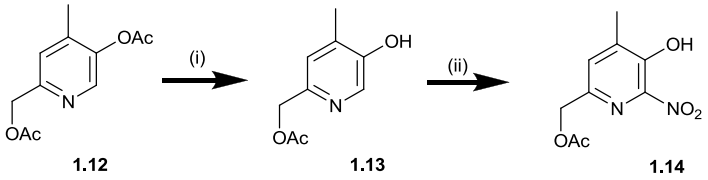
5-Hydroxy-2,4-lutidine **1.10** was further functionalised by selective oxidation of the 2-methyl position. Treatment with *m*-CPBA in dichloromethane gave the pyridine *N*-oxide **1.11** in 88 % yield which when heated to reflux in neat acetic anhydride afforded bis-acetylated pyridine **1.12** in 77 % yield. (Figure 1.5)



Reagents and conditions: (i) *m*-CPBA, DCM, rt, 16 h, 88 %. (ii) Ac_2O, Δ, 2.5 h, 77 %.

Figure 1.5

Selective deprotection of the aromatic hydroxyl group was achieved by treating bis-acetate **1.12** with pyrrolidine in dichloromethane. This gave the corresponding hydroxypyridine **1.13** in 71 % yield. Directed nitration using ceric ammonium nitrate as a mild, non acidic nitrating agent afforded nitration exclusively at the C6 position to give **1.14**. (Figure 1.6)



Reagents and conditions: (i) Pyrrolidine, DCM, rt, 16 h, 71 %. (ii) CAN, $NaHCO_3$, MeCN, rt, 5 h, 45 %.

Figure 1.6

It was anticipated that hydrogenation of nitropyridine **1.14** with palladium on carbon and molecular hydrogen would lead to reduction of the nitro group to the corresponding amine **1.15**. However, none of the desired product was isolated and NMR analysis showed a complex mixture of products with complete loss of starting material.

One possible explanation for this result is that upon reduction to the amine the now electron rich aromatic system spontaneously eliminated the acetyl group as shown leading decomposition. (Figure 1.7)

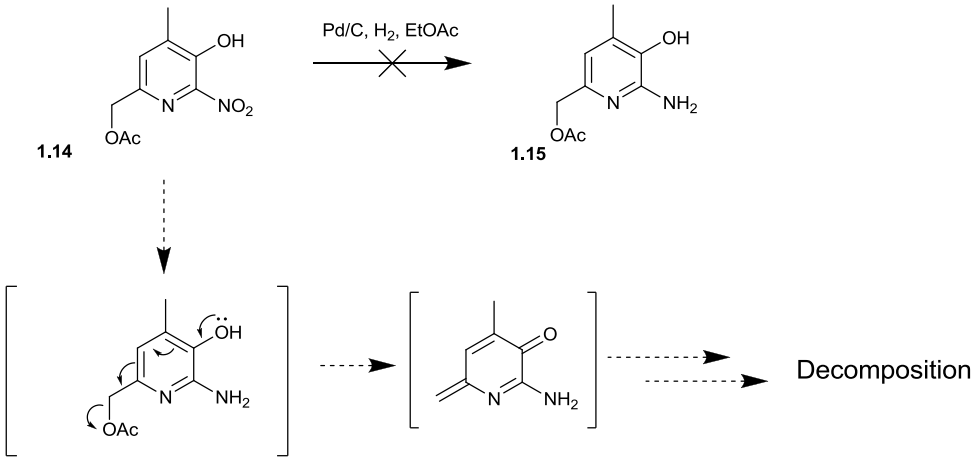
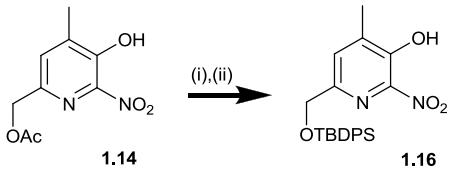


Figure 1.7

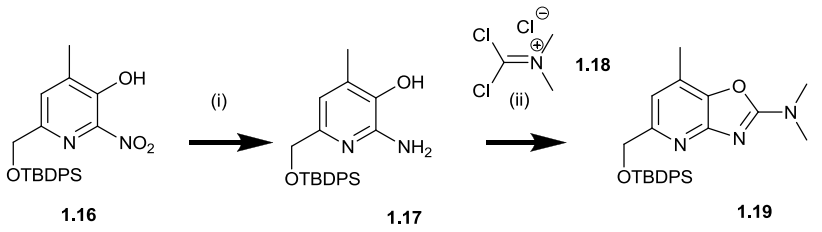
Thus the use of a protecting group that represented a poorer leaving group was expected to avoid this problem. A TBDPS group was chosen as an alternative due to its robust nature. This also eliminated the possibility of palladium based side reactions occurring at the aromatic acetate position. The acetate group was removed upon treatment with aqueous sodium hydroxide and methanol. The resulting hydroxypyridine was subsequently treated with *tert*-butyl(chloro)diphenylsilane in the presence of imidazole and catalytic DMAP to afford silyl ether **1.16**. (Figure 1.8)



Reagents and conditions: (i) 2M $NaOH_{(aq)}$, MeOH, 3 h, 99 %. (ii) TBDPSCl, imidazole, DMAP, DMF, 85 %.

Figure 1.8

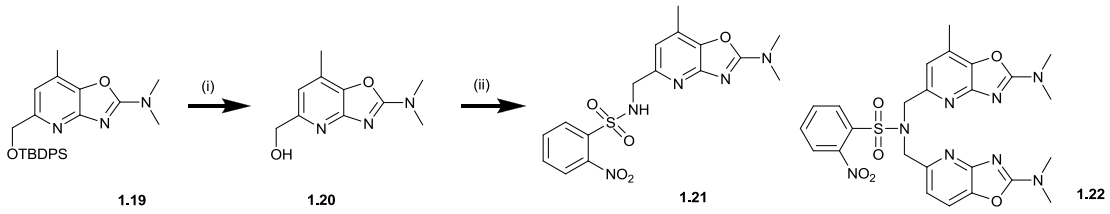
The palladium catalysed hydrogenation of the nitro group to the aromatic amine was then found to proceed in quantitative yield and the resulting amino hydroxypyridine was treated with commercially available phosgene iminium chloride **1.18** and refluxed in dichloromethane to furnish the oxazole ring with the 2-*N,N*-dimethyl amine functionality in one high yielding step. (Figure 1.9)



Reagents and conditions: (i) 10 % Pd/C (2 mol %), H_2, EtOAc, 16 h, 99 %. (ii) **1.18**, NEt_3, DCM, reflux 30 min, 85 %.

Figure 1.9

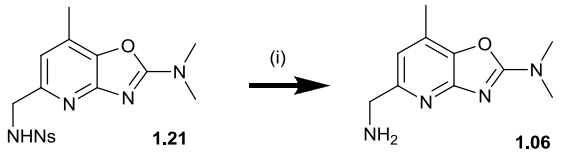
At this point TBAF mediated silicon de-protection was effected to give the primary alcohol **1.20** which was treated with 2-nitrobenzenesulfonamide under Mitsunobu conditions to furnish the sulfonamide **1.21** in modest yield. A large quantity of the tertiary sulfonamide **1.22** was also isolated; however given the proximity to the end of the synthesis it was decided that the low yield was acceptable and the reaction could be optimised in later synthetic studies (Figure 1.10)



Reagents and conditions: (i) TBAF, THF, 1 hour, rt, 90 %. (ii) 2-nitrobenzenesulfonamide, PPh_3, DIAD, THF, 30 %.

Figure 1.10

De-protection of the required sulfonamide with sodium thiophenolate proceeded in high yield to give the key amine **1.06** in 85 % after purification by silica gel chromatography. (Figure 1.11)

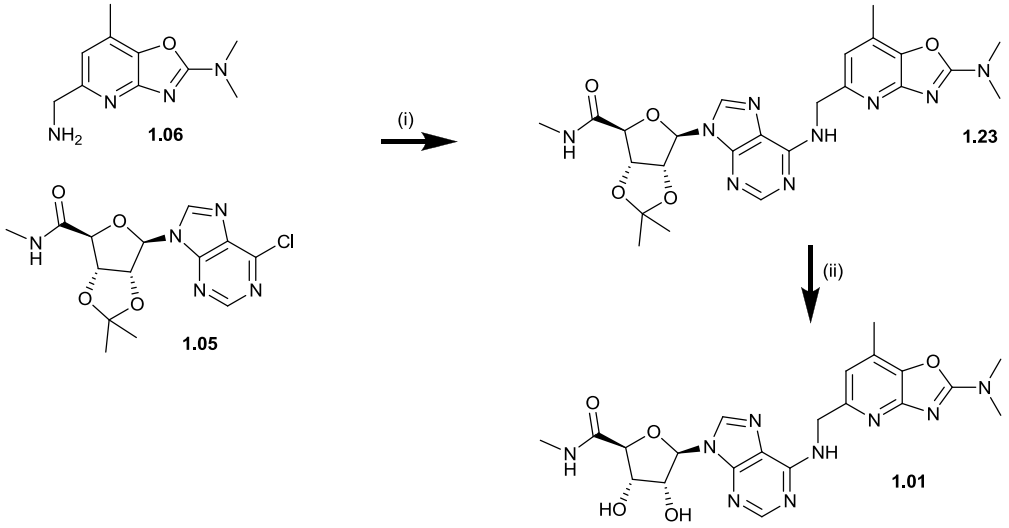


Reagents and conditions: (i) PhSH, K_2CO_3, MeCN, 16 hours, 85 %.

Figure 1.11

1.1.1.2 Condensation of the amine and chloropurine

The coupling of the primary amine and chloropurine fragment proceeded *via* nucleophilic aromatic substitution and subsequent treatment with warm aqueous hydrochloric acid liberated the diol to afford agonist **1.01**. (Figure 1.12)



Reagents and conditions: (i) EtOH, 80 ºC, 16 hours, 80 %, (ii) 1M HCl, 65 ºC, 1 hour, 90 %.

Figure 1.12

This completed the total synthesis of the first target, and concludes the previous work on these molecules.

1.2 Results and discussion

1.2.1 Approaches toward ethyl A_3 agonists

At this point in time attention turned to the synthesis of the diethyl derivative **1.02**. (Figure 1.13)

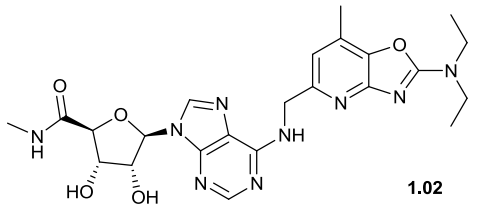


Figure 1.13

This involved designing a synthesis that would furnish the oxazole ring with an *N,N*-diethyl moiety instead of an *N,N*-dimethyl group at C2. However, it was possible that biological evaluation of these primary candidates would result in a demand for more analogues, diversified at the C2 position. For this reason it was considered important to have a convergent synthesis which would allow late stage modification at this position. This precluded the use of the phosgene iminium salt based cyclisations which had been used to great effect in the previous synthesis because only the dimethyl phosgene salt is commercially available. A more general cyclisation approach was required.

1.2.1 Retrosynthetic analysis

Access to target compound **1.02** would be *via* the nucleophilic aromatic substitution of chloropurine **1.05** and primary amine **1.24** (Figure 1.14). Chloropurine **1.05** has previously been prepared from commercially available inosine **1.25** in three steps. Therefore the focus of synthetic studies will be on the hitherto unknown amine **1.24**.

Known hydroxypyridine **1.17** is expected to cyclise on to carbon disulfide to give a 2-thio-oxazole which would be susceptible to nucleophilic attack at the sulfur bearing carbon atom with diethylamine giving access to the amine **1.24**. The aminohydroxypyridine will be derived from directed nitration of pyridine **1.13** using ceric ammonium nitrate (CAN) followed by palladium catalysed reduction of the nitro group. Acetic anhydride mediated rearrangement of *N*-oxide **1.11** will facilitate procurement of pyridine **1.13**. The *N*-oxide is accessible from commercially available 2,4-lutidine. (Figure 1.14)

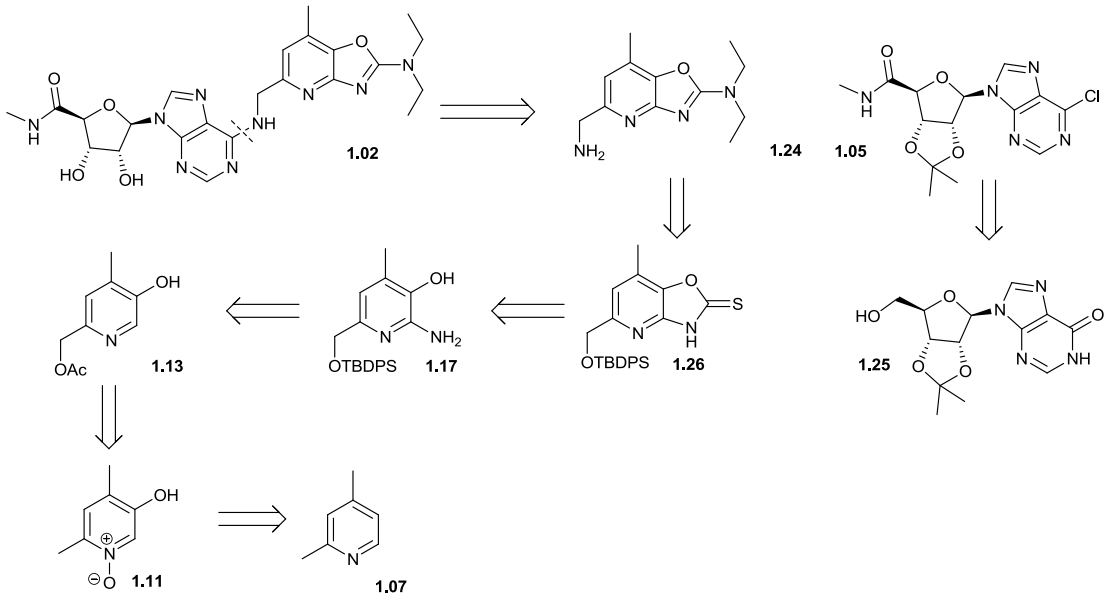


Figure 1.14

1.2.2 Synthetic approaches toward novel A_3 agonists

1.2.3 Nitration of 2,4-lutidine

As the intended route towards agonist **1.02** utilises a common intermediate from the synthesis of agonist **1.01**, the first several steps of this synthesis parallel those of the previous synthesis.

The first step called for the nitration of 2,4-lutidine. Pyridines are generally poor substrates for conventional nitration reactions because under the strongly acidic conditions of typical nitrating mixtures they exist predominantly as a pyridinium salt which is inert towards electrophilic attack. (Figure 1.15)

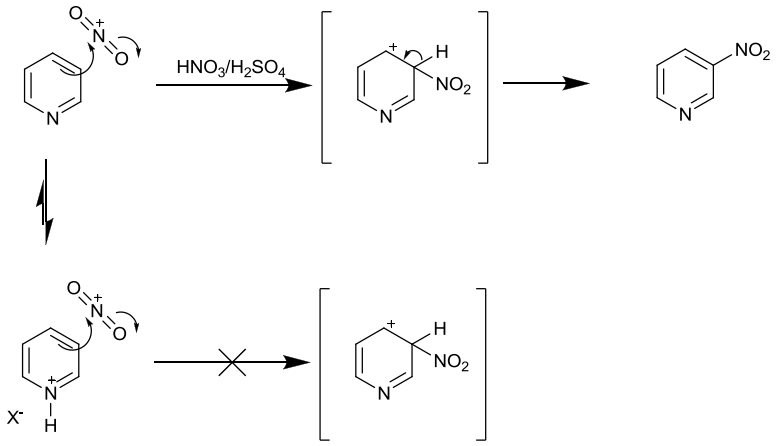
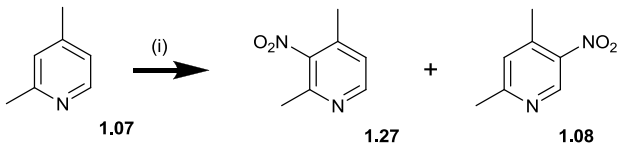


Figure 1.15

Nevertheless the nitro-lutidine **1.08** was prepared by heating 2,4-lutidine with a mixture of fuming sulphuric acid (20 % oleum) and potassium nitrate at 100 ºC for 8 hours followed by heating at 120 ºC for a further 16 hours.[8] It was important not to heat at too high a temperature initially, as this resulted in lower yields. One possible explanation for this could be that at higher temperatures volatile anhydrous nitric acid is driven from solution. The required 5-nitrolutidine **1.08** was isolated in a modest 20 % yield from a crude mixture of starting material (52 %), 3-nitrolutidine **1.27** (21 %) and 5-nitrolutidine (27 %) by fractional vacuum distillation. Nevertheless it was possible to generate the required product in multi-gram quantities. (Figure 1.16)

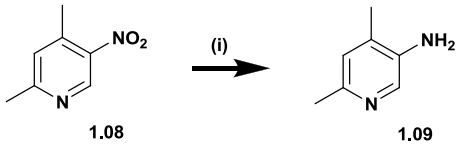


Reagents and conditions: (i) Fuming H_2SO_4, KNO_3, 100 °C 8 hours, then 120 °C 16 hours, 20 % **1.08**.

Figure 1.16

1.2.4 Formation of the hydroxypyridine moiety

Following the preparation of nitropyridine **1.08** it was necessary to effect reduction of the nitro group. There are many examples reported in the literature for the reduction of aromatic nitro groups to the corresponding aniline. Catalytic hydrogenation using nickel,[9,10] platinum oxide[11] and palladium[8,12] are mild and commonly used methods. A palladium catalysed hydrogenation in methanol worked well in this instance being experimentally convenient, extremely high yielding and proceeding without the formation of any detectable by-products. (Figure 1.17)

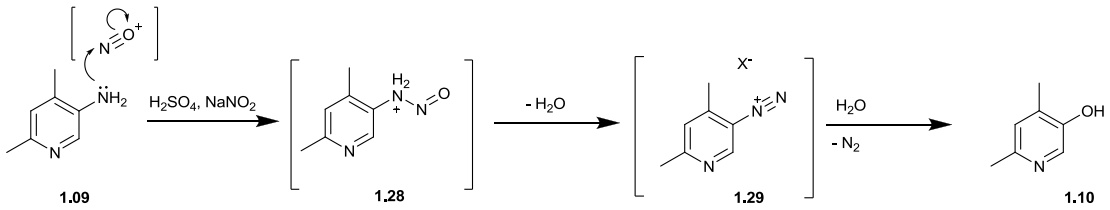


Reagents and conditions: (i) 10% Pd/C, 2 mol %, MeOH, rt, 2 hours, 99 %.

Figure 1.17

A Sandmeyer-type reaction using water as a nucleophile[8] furnished the required hydroxypyridine functionality. Spontaneous dehydration of *N*-nitroso compound **1.28** leads to the unstable diazonium salt **1.29** which decomposes in the presence of water to give the required hydroxypyridine **1.10**. However it was found that to obtain a high yield the diazonium salt intermediate required heating rapidly to point at which N_2 was evolved, and immediately after effervescence ceased, poured directly onto ice. This was easily achieved when performing the reaction on milligram quantities of starting material. However

when scaled to synthetically useful quantities, the time required to heat the larger volume of liquid increased and led to significant decomposition of product giving lower yields of 40 %. Once isolated and purified, hydroxypyridine **1.10** was stable to storage in the freezer with no detectable decomposition after several months. (Figure 1.18)

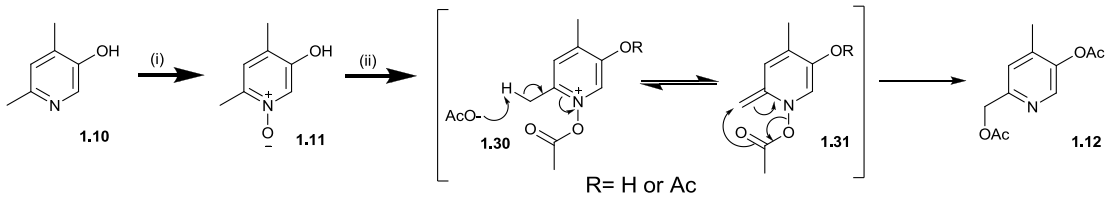


Reagents and conditions: 4.8 % $H_2SO_{4\,(aq)}$, $NaNO_2$, 0 °C, 20 mins, then Δ, 40-80 % yield.

Figure 1.18

1.2.5 Methyl activation

5-Hydroxy-2,4-lutidine **1.10** was further functionalised by selective oxidation of the 2-methyl group. Treatment with *m*-CPBA in dichloromethane gave the pyridine *N*-oxide **1.11** in excellent yield.[13] When refluxed in neat acetic anhydride bis-ester **1.12** was generated as the major product and was isolated in 77 % yield after silica gel chromatography.[14,15,16] (Figure 1.19) The regiochemistry of the bis acetate has previously been established by x-ray crystallography.



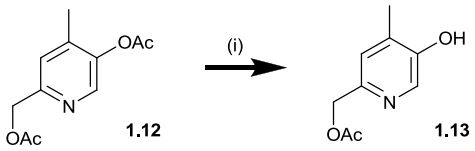
Reagents and conditions: (i) *m*-CPBA, DCM, 16 hours, 88 %; (ii) Ac_2O, Δ, 77 %.

Figure 1.19

1.2.6 Selective deacetylation

Månson has shown that aromatic acetates are more susceptible to aminolysis with pyrrolidine than aliphatic acetates and that this discrimination can be exploited to liberate phenols from acetyl-phenols in the presence of aliphatic acetates.[17]

Unmasking of the hydroxyl group was achieved by treating bis-acetate **1.12** with pyrrolidine in dichloromethane to give the corresponding hydroxylutidine **1.13** in 71 % yield after silica chromatography. (Figure 1.20)



Reagents and conditions: pyrrolidine, DCM, rt, 1 hours, 71 %.

Figure 1.20

1.2.7 Directed nitration

Ceric ammonium nitrate (CAN) has been shown by Ganguly *et al.* to be a mild, non-acidic nitrating agent capable of nitrating 6-hydroxycoumarin(s) exclusively at the ortho position.[18] (Figure 1.21)

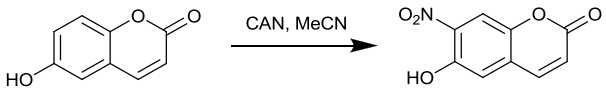


Figure 1.21

This exclusivity was further demonstrated by Biehl who showed that CAN/$NaHCO_3$ in MeCN also reacts with a wide variety of electron rich phenols to

give the *ortho* nitrated product.[19] Moreover, where more than one ortho position was available the substitution occurs solely at the less hindered carbon atom.[20]

In the first step of Ganguly's proposed mechanism an electron rich phenol **1.32** is oxidised by CAN **1.33** to give a phenolic radical cation species **1.34**. A second molecule of $Ce(NO_3)_6^{-2}$ then forms a complex **1.35** with **1.34** from which a NO_2 radical is transferred *via* a tight ion radical pair **1.36** yielding the Wheland intermediate **1.37** which furnishes the nitrophenol **1.38** after proton loss. (Figure 1.22)

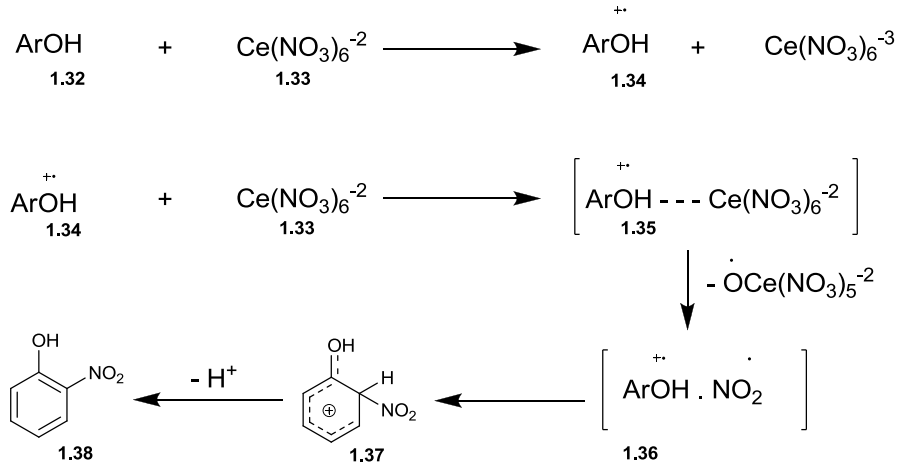
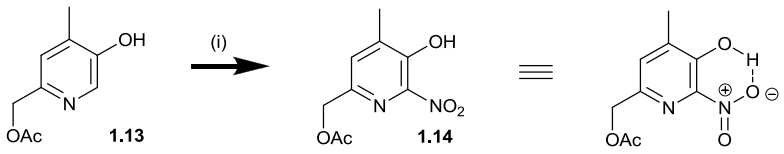


Figure 1.22

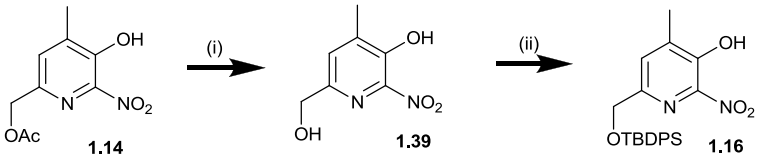
When hydroxypyridine **1.13** was treated with CAN/$NaHCO_3$ at room temperature in MeCN the required nitro pyridine **1.14** was generated in a fair yield after purification. The low yield was likely to be due to the solubility of the nitropyridine in water; as TLC studies showed the reaction proceeded with complete consumption of starting material and without the production of any other detectable products. The ^1H NMR spectrum showed a very sharp singlet at 10.19 ppm suggesting hydrogen bonding between the nitro and hydroxyl groups. (Figure 1.23)



Reagents and conditions: CAN, $NaHCO_3$, MeCN, rt, 16 hours, 45 %.

Figure 1.23

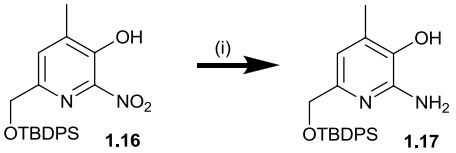
It has been demonstrated previously that acetate **1.14** is unstable to the conditions required to reduce the nitro group. For this reason the acetate group was removed and replaced with a more robust bulky silyl group.[7] The primary alcohol **1.39** was liberated in quantitative yield upon warming with 2M NaOH in methanol.[21] Subsequent treatment of the alcohol with tert-butyldiphenylchlorosilane, imidazole and catalytic *N,N*-dimethylaminiopyridine in dimethylformamide gave the silyl ether **1.16** in 85 % yield. (Figure 1.24)



Reagents and conditions: (i) NaOH, MeOH, rt, 3 hours, 99 %; (ii) TBDPSCl, DMAP, DMF, rt, 16 hours, 85 %.

Figure 1.24

Reduction of the nitro group was then achieved by stirring in methanol under an atmosphere of hydrogen in the presence of catalytic palladium to give known aniline **1.17** in quantitative yield. (Figure 1.25)



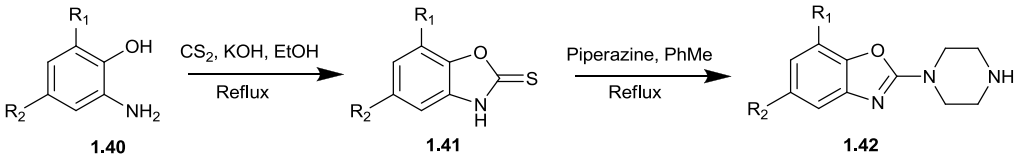
Reagents and conditions: (i) Pd/C, MeOH, H_2, rt, 16 hours, 99 %.

Figure 1.25

1.2.8 Cyclisation studies

The next part of the synthesis called for the formation of the oxazole ring in a way which either directly furnished the diethylamino moiety, or gave easy access to it.

Yoshida *et al.* have recently reported the synthesis of a series of benzoxazole-2-thiones, from the corresponding *o*-amino phenols.[22,23] When *o*-amino phenols **1.40** were treated with carbon disulfide and potassium hydroxide in ethanol, benzoxazole-2-thiones **1.41** were produced in high yield. These were used to alkylate a variety of amines to yield 2-aminooxazoles. (Figure 1.26)

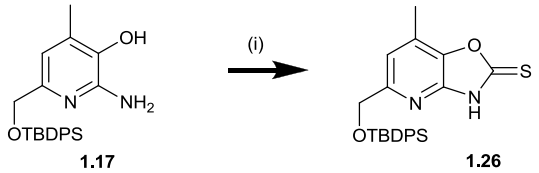


R= H, Me, Cl

Figure 1.26

It was expected that benzoxazole-2-thione **1.26** would give access to the 2-diethylaminooxazole **1.24** *via* nucleophilic substitution of sulfur with diethyl amine. This methodology should allow the diversification of the 2-oxazole position at a relatively late stage in the synthesis by treating the 2-mercaptobenzoxazole with a variety of amines.

Benzoxazole-2-thione **1.26** was prepared in 85 % yield by refluxing aminophenol **1.17** with potassium hydroxide and carbon disulfide in ethanol for 16 hours as prescribed by Yoshida (Figure 1.27)



Reagents and conditions: CS_2, KOH, EtOH, 80 ºC, 3 hours, 85 %.

Figure 1.27

1.2.9 Thione/thiol tautomerism

In order to study the equilibrium between 2-thiooxazoles **1.43** and their thione tautomers **1.44** (Figure 1.28) Kjellin and Sandstrom prepared a series of these compounds and their N- and S-methyl derivatives.[24]

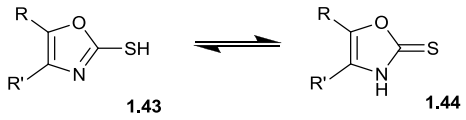
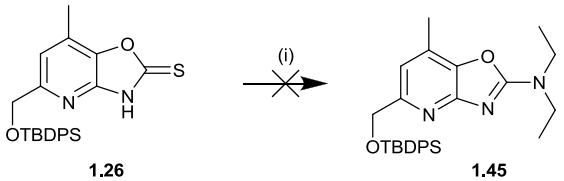


Figure 1.28

The position of the thione to thiol equilibrium has been determined for a series of oxazoline-2-thiones by measuring the acidity constants of the tautomers and these methyl derivatives. The thione: thiol ratio was found to be 10^5-10^7. This high thione: thiol ratio has been rationalised in terms of the difference in π-electronic energy of the two forms as well as the differences in solvation energies of the two tautomers.[25] In light of these data it is reasonable to assume that the related compounds prepared for this project exist predominantly as the thione tautomer.

1.2.10 Introduction of diethylamine

Despite strong literature precedent illustrating the direct coupling of benzoxazole-2-thiones with a variety of amines to give the corresponding 2-amino benzoxazoles this was not successful with diethylamine. On each occasion the coupling was attempted only un-reacted starting material was recovered from the reaction mixture. (Figure 1.29)



Reagents and conditions: Diethylamine, toluene, Δ.

Figure 1.29

With the benefit of hindsight it is perhaps significant that this methodology has only been used successfully with high boiling amines (>100 ºC). As these reactions are conducted in refluxing toluene, it is possible that diethylamine (bp 55 °C) is driven from the reaction mixture before reacting in the desired way.

Conveniently Yoshida has also reported the synthesis of a range of 2-aminobenzoxazoles **1.48** from 2-chlorobenzoxazole **1.47**.[22,23] The higher reactivity of the 2-chlorobenzoxazoles relative to benzoxazole-2-thiones means that they react rapidly with amines even at mild temperatures. Furthermore 2-chlorobenzoxazoles were conveniently prepared by the chlorination of the benzoxazole-2-thiones. (Figure 1.30)

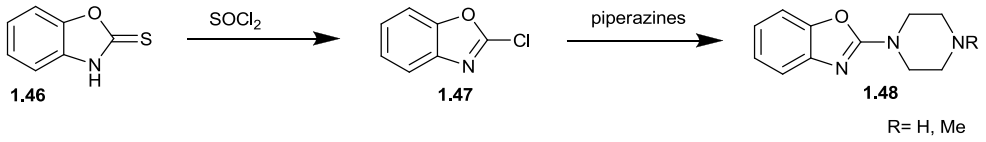
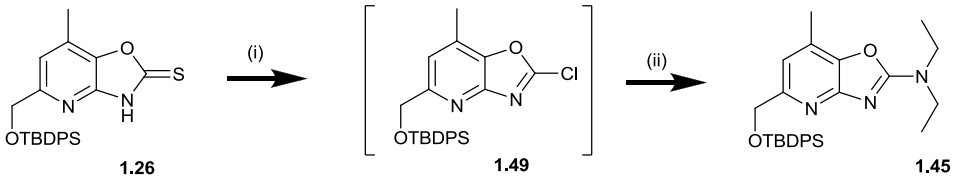


Figure 1.30

It was decided to synthesise 2-chlorobenzoxazole **1.49** to investigate its reactivity towards diethylamine. After stirring a solution of thione **1.26** with thionyl chloride and solid sodium bicarbonate for three hours, the reaction mixture was treated with an excess of diethylamine and further stirred at room temperature for 1 hour to give the desired compound **1.45** in 70 % overall yield as indicated by the clear presence of the diethyl moiety in the ^{1}H NMR. (Figure 1.31)



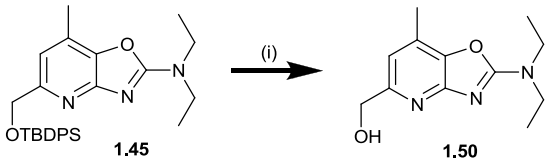
Reagents and conditions: (i) $SOCl_2$, C_6H_6, 50 ºC, 3 hours; (ii) $HNEt_2$, rt, 1 hour, 70 %.

Figure 1.31

It is anticipated that this methodology would allow the introduction of a range of amine substituent's at the C2 position by varying the amine component.

1.2.11 Conversion to the primary amine

The next requirement was to convert the protected primary alcohol to the corresponding primary amine. The silyl group was removed upon treatment with TBAF in tetrahydrofuran at room temperature to liberate the primary alcohol **1.50** in excellent yield. (Figure 1.32)

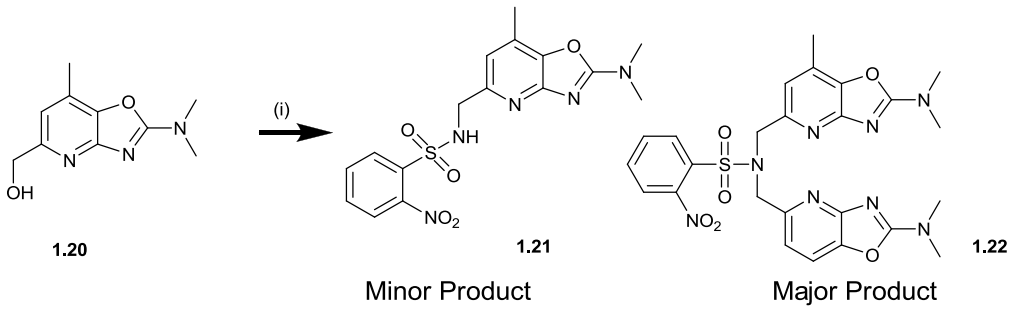


Reagents and conditions: (i) TBAF, THF, 93 %.

Figure 1.32

Fukuyama has shown that 2-nitrobenzenesulfonamide acts as a highly efficient nucleophile component in Mitsunobu reactions to give *N*-nosyl protected secondary amines from primary alcohols.[26, 27]

In a previous route to related amine **1.06**, A. Lee showed that the alcohol **1.20** underwent a Mitsunobu reaction with 2-nitrobenzenesulfonamide to furnish the benzoxazole **1.21** with protected amine functionality in the desired position. However it was found that when the alcohol and 2-nitrobenzenesulfonamide were treated with triphenylphosphine and DIAD in tetrahydrofuran, the major product showed no sulfonamide proton in the ^{1}H NMR and the protons associated with the nitro-aromatic integrated to exactly one half of what would be expected. Suspicions that the major product had undergone double alkylation were confirmed by mass spec analysis which clearly showed that the major product was disubstituted sulfonamide **1.22**. The desired compound was also isolated albeit in low (30 %) yield. (Figure 1.33)

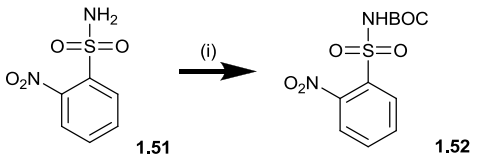


Reagents and conditions: (i) TBAF, THF, 1 hour, rt, 90 %. (ii) 2-nitobenzenesulfonamide, PPh_3, DIAD, THF, 30 % **1.21**, 50 % **1.22**.

Figure 1.33

It has been shown by Fukuyama that sulfonamide **1.52** is exclusively susceptible to mono alkylation under Mitsunobu conditions,[28] and that post-alkylation the 2-nitrobenzenesulfonamide and BOC groups can be removed easily, to yield the primary amine. Due to the iterative nature of the removal of the amine protecting groups, this methodology facilitates the controlled elaboration of the amine.

In an effort to avoid double alkylation, compound **1.52** was prepared in excellent yield by treatment of 2-nitrobenzenesulfonamide with di-*tert*-butyl carbonate, triethylamine and DMAP in dichloromethane using the conditions described by Fukayama (Figure 1.34). This reaction was characterised by the rapid evolution of gas and profuse effervescence upon the addition of DMAP.



Reagents and conditions: (i) BOC_2O, NEt_3, DMAP, DCM, rt, 98 %.

Figure 1.34

When sulfonamide **1.52** and alcohol **1.50** were treated with diisopropyl azodicarboxylate and triphenylphosphine they underwent a Fukuyama-Mitsunobu reaction affecting alkylation of the sulfonamide (Figure 1.35). The desired mono alkylated product **1.53** was isolated in excellent (97 %) yield as indicated by the 1:1 ratio of nitro-aromatic to benzoxazole protons in the ^{1}H NMR spectrum.

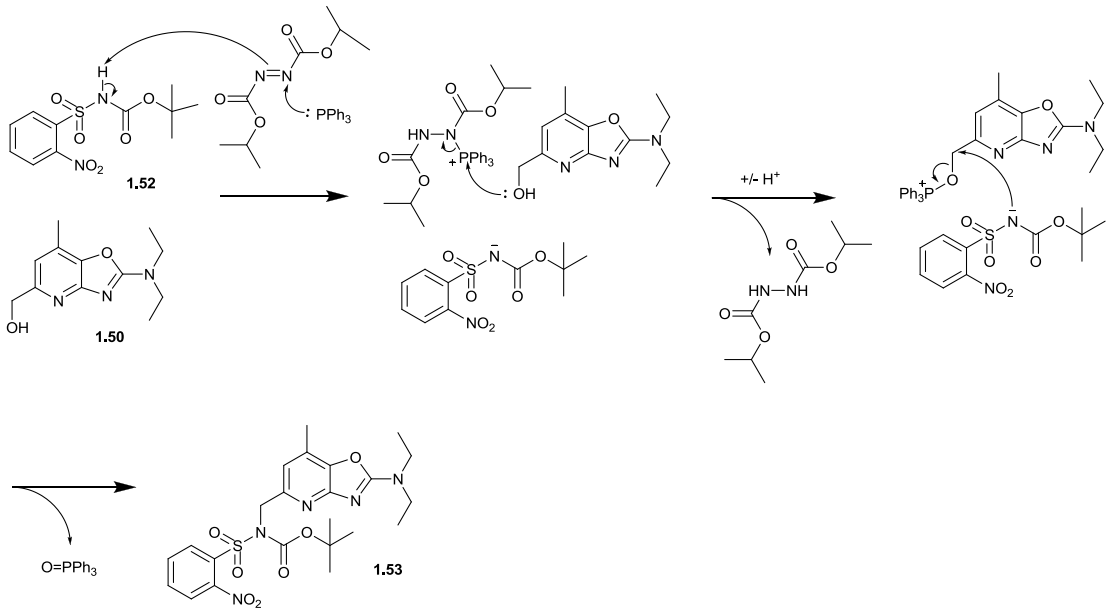
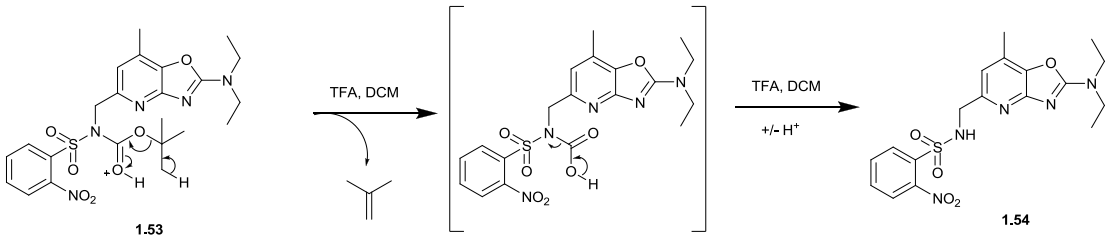


Figure 1.35

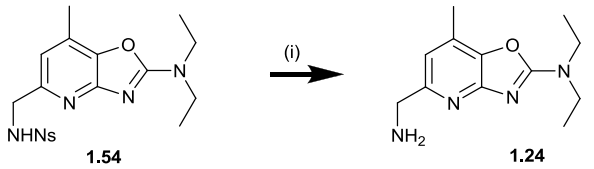
Trifluoroacetic acid mediated removal of the BOC moiety preceded in 79 % yield (Figure 1.36) This gave the sulfonamide **1.54** as indicated by the presence of the characteristic sulfonamide proton which was a broad triplet at 6.41 ppm in the ^{1}H NMR.



Reagents and conditions: TFA, DCM, room temperature, 16 hours, 79 %

Figure 1.36

Thiophenol mediated removal of the 2-nitrobenzensulfonamide group produced the key primary amine in 85 % yield.[26, 27] (Figure 1.37)



Reagents and conditions: (i) PhSH, K_2CO_3, MeCN, rt, 2 hours, 85 %.

Figure 1.37

1.2.12 Chloropurine

The sample of chloropurine initially provided by Muscagen had been used for the synthesis of **1.01** and as such it was necessary to synthesise more of this essential intermediate from commercially available material. Chloropurine **1.05** could be prepared in three steps from commercially available inosine **1.25**. (Figure 1.38)

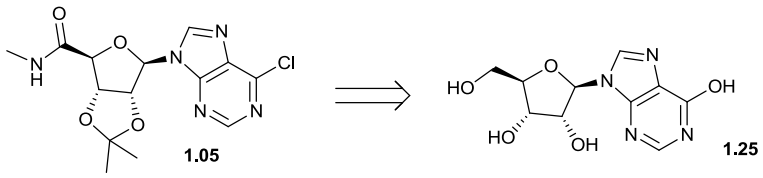
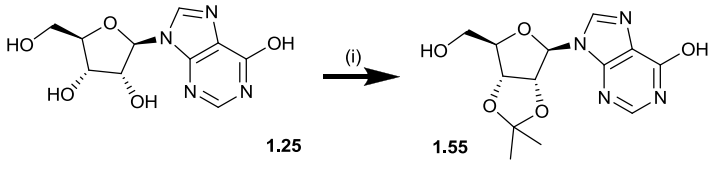


Figure 1.38

In the first step inosine was treated with phoshoryl chloride in water and acetone protecting the 1,2-diol as an acetonide **1.55** which was isolated in 70 % yield after recrystallisation from water.[29] (Figure 1.39)

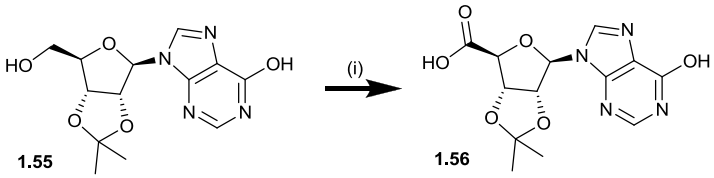


Reagents and conditions: (i) $POCl_3$, H_2O, acetone, 15 °C, 30 mins, 70 %.

Figure 1.39

Secondly the primary alcohol was subjected to permanganate-mediated oxidation to give the corresponding carboxylic acid **1.56** in 40 % yield after

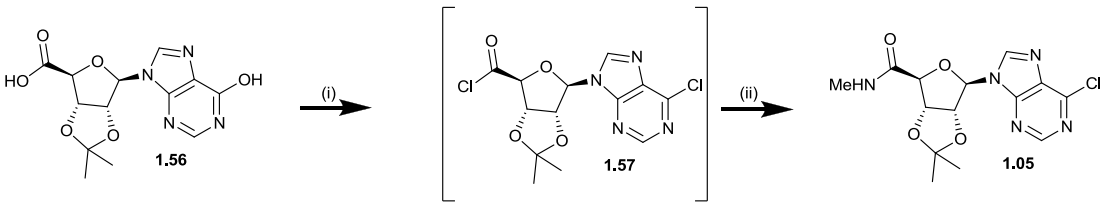
recrystallisation from glacial acetic acid.[30] Higher yields have been reported using chromium mediated oxidation conditions,[31] however it was desirable to avoid chromium residues in the final compound which could interfere with biological testing. (Figure 1.40)



Reagents and conditions: (i) $KMnO_4$, KOH, H_2O, 3 days, 41 %.

Figure 1.40

In the final manipulation the purine **1.56** was treated with thionyl chloride in dimethylformamide to convert the acid and hydroxypurine moieties to the corresponding acid chloride and iminoyl chloride. The crude reaction residue was then immediately treated with methyl amine in tetrahydrofuran which reacted only with the acid chloride.[31] Favourable comparison of ^1H NMR data with that recorded in the literature confirmed the successful preparation of chloropurine **1.05**. (Figure 1.41)



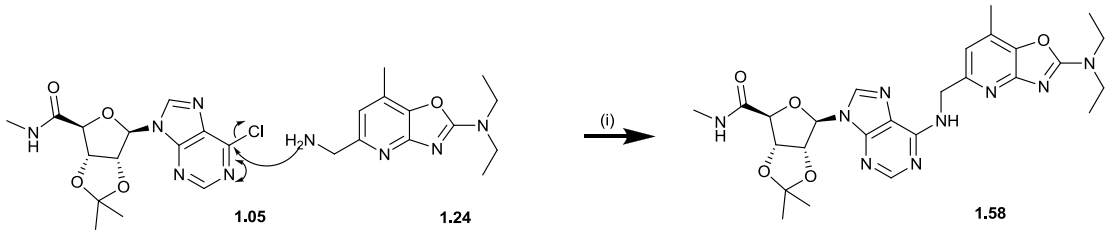
Reagents and conditions: (i) $SOCl_2$, DMF, Δ, 18 hours, (ii) 2 M $MeNH_2$, THF, 0 ºC, 15 mins, 61 % over two steps.

Figure 1.41

In summary chloropurine **1.05** was readily prepared in three steps from commercially available inosine **25** in 17 % overall yield.

It was then possible to attempt the coupling of amine **1.24** and the chloropurine **1.05**.

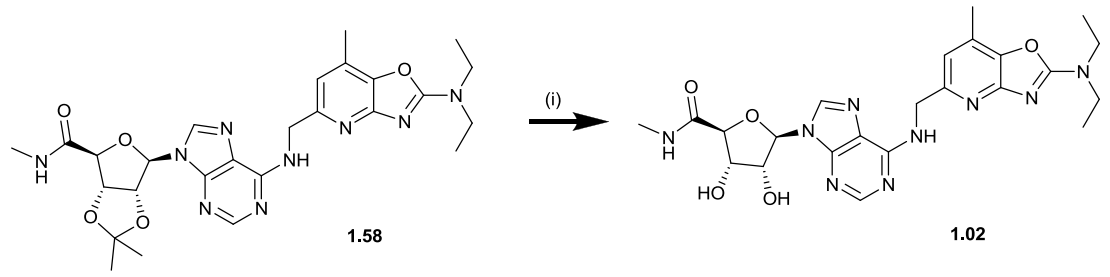
The amine **1.24** and chloropurine **1.05** were refluxed in ethanol along with triethylamine to affect a nucleophilic aromatic substitution to give the acetonide **1.58** in acceptable yield. (Figure 1.42)



Reagents and conditions: (i) EtOH, NEt_3, Δ, 16 hours, 55 %.

Figure 1.42

The acetonide protecting group was subsequently removed by heating in aqueous 1M hydrochloric acid for one hour to give a single compound in excellent yield with no observed decomposition. ^1H NMR analysis of **1.02** showed the absence of the two methyl groups from the acetonide and the presence of two doublets at 5.8 and 5.6 ppm corresponding to each of the alcohol groups. (Figure 1.43)



Reagents and conditions: (i) 1M HCl, 65 ºC, 1 hour, 84 %.

Figure 1.43

This completed the total synthesis of the second member of this new family of A_3 agonists. The next challenge was the introduction of a methyl group on the carbon bridge between the purine and the oxazolopyridine.

1.2.13 Methyl Analogues

The second pair of compounds **1.03** and **1.04** (Figure 1.44) are structurally identical to the two compounds now prepared (**1.01** and **1.02**), except for the introduction of a methyl group between the aromatic amine and the pyridine ring. Muscagen initially want to test the compounds as a mixture of diastereoisomers at the methyl position, however the final route should preferably allow access to both epimers selectively.

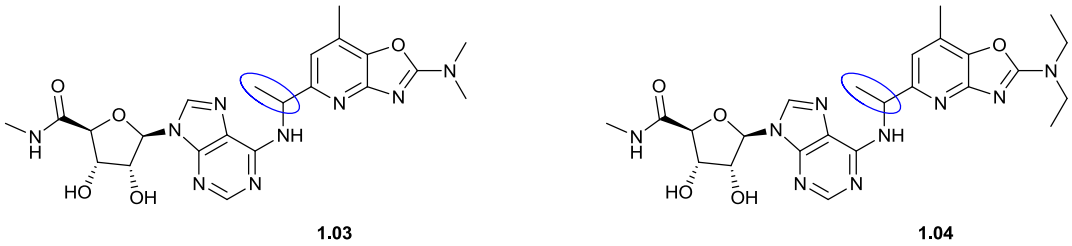


Figure 1.44

Due to the more straightforward synthesis of the *N,N*-dimethyl oxazole ring relative to if the diethyl analogue, it was decided to focus efforts initially on the synthesis of **1.03**.

1.2.14 Retrosynthetic analysis

` It was expected that **1.03** would come from the nucleophilic aromatic substitution of chloropurine **1.05** and racemic primary amine **1.59**. Synthetic efforts will focus on the primary amine. The amine **1.59** was expected to be available from the addition of a nucleophilic methyl group to an imine of type **1.60**. The imine was anticipated to be prepared from the aldehyde derived from known alcohol **1.20**. (Figure 1.45)

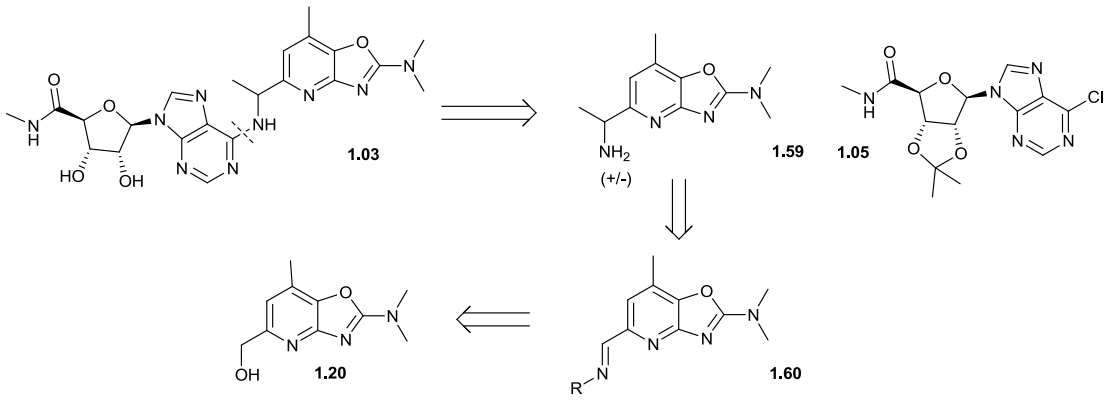


Figure 1.45

In 1997, Ellman reported that aldehydes condense with optically pure *tert*-butanesulfinamide **1.61** at room temperature in the presence of a suitable desiccant, to form chiral sulfinimines **1.63**.[32]

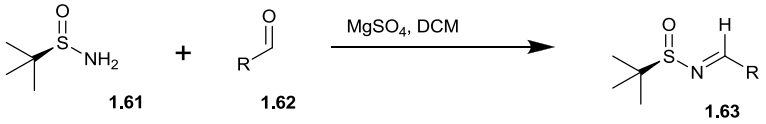


Figure 1.46

These sulfinimines undergo nucleophilic addition reactions with Grignard reagents, to give the branched amine adducts in high yields and excellent diastereoselectivity. Furthermore, the residual *tert*-butyl sulfinamide **1.65** are easily cleaved by subsequent treatment with acid to give the chiral amine **1.66** (Figure 1.47).

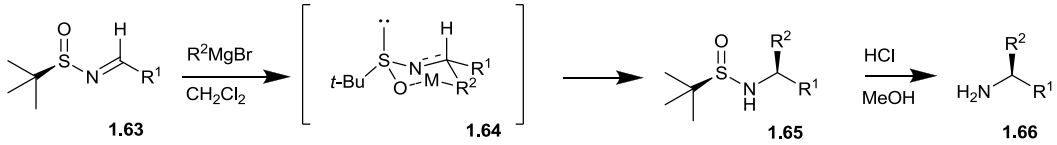


Figure 1.47

1.2.15 Synthesis of *tert*-butylsulfinimine

Catalytic asymmetric oxidation of *tert*-butyl disulfide produces optically active *tert*-butanethiosulfinate **1.68** or **1.69** in 89-91 % ee which upon treatment with lithium amide in liquid ammonia gives the corresponding *tert*-

butylsulfinamide **1.61** or **1.70** with complete inversion at sulphur. The required enantiomerically pure sulfinamide is obtained in 72-78 % yield after a single recrystallisation. Since both antipodes of the chiral ligand are available, both enantiomers of *tert*-butylsulfonamide is available. [33,34] (Figure 1.48)

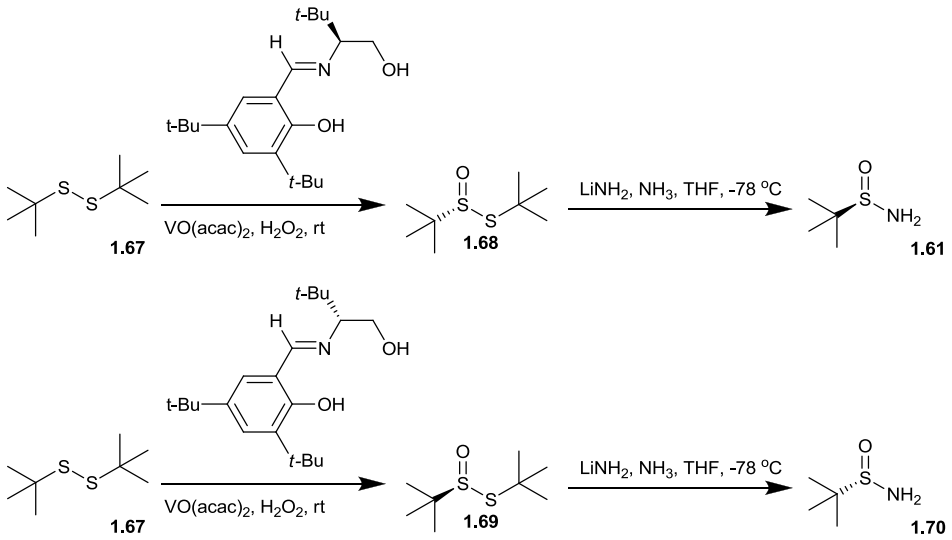


Figure 1.48

Due to the ease of synthesis and high demand; both enantiomers of *tert*-butylsulfinamide are commercially available in addition to the racemic material.

Muscagen wished to test the target compound as a mixture of epimers at the methyl position. For this reason it was necessary to prepare the racemic primary amine **1.59**, which required the use of racemic *tert*-butylsulfinamide. However this methodology should allow access to either enantiomer of the amine.

Ellman's methodology also allows the introduction of a wide array of nucleophiles onto the so formed *tert*-butylsulfinamide, not limited to Grignard reagents, making the synthesis of **1.71** and **1.72** from a common aldehyde intermediate possible. (Figure 1.49)

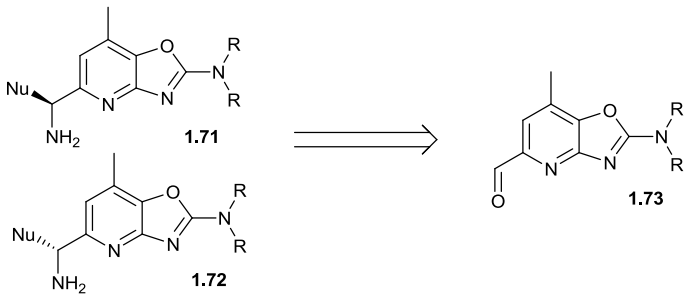


Figure 1.49

To allow the utilisation of Ellman's chemistry it was first necessary to oxidise known alcohol **1.20** to the corresponding aldehyde. Several methods have been developed which allow the mild and selective oxidation of primary alcohols to aldehydes. Many of the most commonly employed modern methods exploit the redox chemistry of sulphur including the Swern,[35,36,37] Parikh-Doering[38] and Corey–Kim reactions.[39] However these reactions are not without drawbacks.

The Swern reaction is characterised by the evolution of dimethyl sulfide, an unpleasant and toxic gas, along with carbon monoxide. The reagents and intermediates are highly intolerant of water and as such the reaction must be carried out under an inert atmosphere. In addition carefully controlled temperature parameters (typically less than – 25 °C) must be observed to prevent side reactions becoming prevalent. Whilst the Parikh-Doering and Corey-Kim reactions each avoid some of these issues (particularly the temperature at which they can be successfully carried out), neither represents an ideal alternative.

In 1983 James Martin and Daniel Dess reported the synthesis of periodinane reagent **1.74** in two steps from 2-iodobenzoic acid. In the first step 2-iodobenzoic acid **1.75** is oxidised under acidic conditions to IBX **1.76** with potassium bromate. IBX is itself an oxidising agent, and had been known for some time; however its synthetic utility is severely limited by its insolubility in most common solvents. In a second step Dess and Martin overcame this problem by per-acetylating IBX using a mixture of acetic anhydride and acetic acid to afford the soluble periodinane **1.74**.[40] (Figure 1.50)

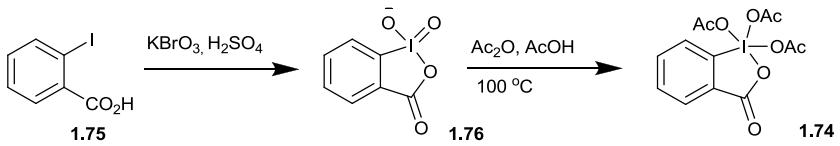


Figure 1.50

Dess and Martin went on to demonstrate the new periodinane held synthetic utility through its ability to selectively oxidise primary and secondary alcohols to the corresponding aldehydes and ketones. The oxidations proceeded in excellent yield, used modest equivalents of periodinane, were experimentally simple to carry out and work-up and avoided the use of, or production of toxic intermediates or by-products. Furthermore, it was later found that traces of water in the reaction actually improved the efficiency of the reagent.[41] The Dess-Martin periodinane is now one reagent of choice for many oxidations involving complex, fragile or valuable alcohol substrates.

Although the intricacies of the mechanism of the oxidation is not fully understood it is known that in the first step of the oxidation a primary or secondary alcohol attacks the periodinane **1.74** at iodine causing the displacement of an acetate. The oxidation itself proceeds *via* a five or six membered transition state involving one of the oxygen atoms on either of the acetate ligands.[42] (Figure 1.51)

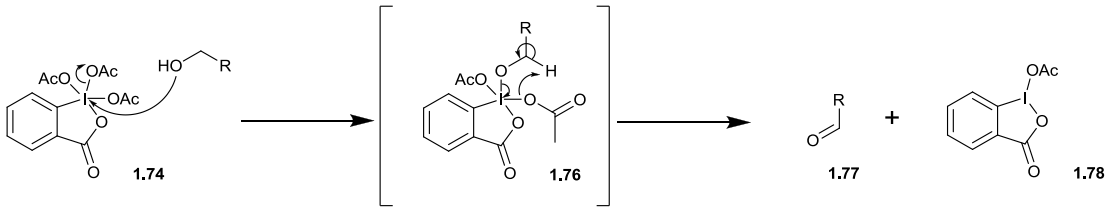
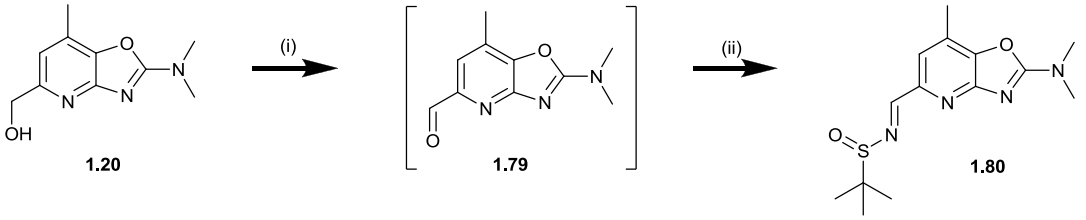


Figure 1.51

In 1999 Frigero reported a refined synthesis of IBX from 2-iodobenzoic acid in which carcinogenic potassium bromate was replaced with environmentally and physiologically benign Oxone™.[43]

Due to the reliability and experimental simplicity it was decided to use a Dess-Martin mediated oxidation in the production of aldehyde **1.79**.

Alcohol **1.20** was oxidised by way of the Dess-Martin periodinane and the crude product was immediately dissolved in dichloromethane and stirred at room temperature with anhydrous copper sulphate and racemic *tert*-butyl sulfinamide for 16 hours. This gave sulfinimine **1.80** in 90 % yield over the two steps (Figure 1.52). The proton residing on the unsaturated carbon between the sulfinimine nitrogen and the aromatic system displayed a characteristic chemical shift at 8.57 ppm.

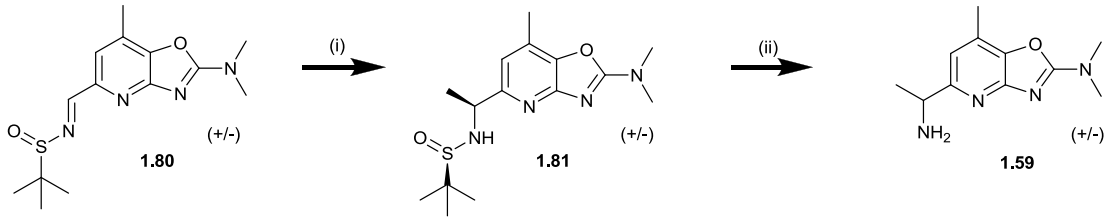


Reagents and conditions: (i) Dess-Martin Periodinane, DCM, rt, 20 mins; (ii) *tert*-butylsulfinimine, anhydrous $CuSO_4$, DCM, 16 hours (90 % over two steps).

Figure 1.52

1.2.16 Addition of methyl group to sulfinimine 1.80

Sulfinimine **1.80** was treated with 6.3 eq of methylmagnesium bromide at -78 °C and was stirred at this temperature for one hour to yield methyl adduct **1.81** in 76 % yield. Only one diastereoisomer was visible by NMR. Liberation of the required primary amine was effected by stirring at room temperature with dry HCl in methanol to give **1.59** in 83 %. (Figure 1.53) The ^{1}H NMR spectrum of **1.59** showed the absence of the *tert*-butyl group and the expected broad singlet corresponding to the primary amine at 3.01 ppm.

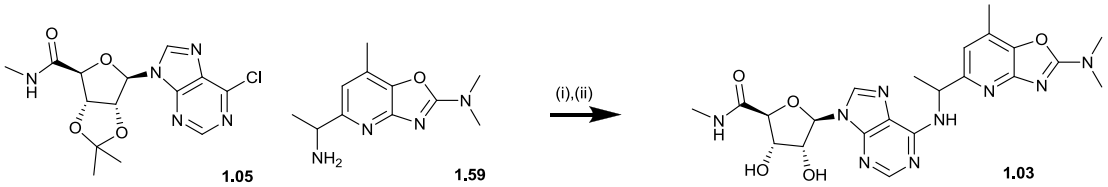


Reagents and conditions: a) MeMgBr, THF, - 78 °C, 1 hour (76 %). b) HCl in dioxane, MeOH, 30 mins, rt (83 %).

Figure 1.53

The next challenge was to join together the primary amine and chloropurine. Primary amine **1.59** and chloropurine **1.05** were refluxed in ethanol along with triethylamine to affect a nucleophilic aromatic substitution.

The acetonide protecting group on the subsequent adduct was removed by warming at 65 ºC in 1M aqueous hydrochloric acid for one hour to give a 4:6 mixture of diastereoisomers in excellent yield. (Figure 1.54) Although it is not known at this time which of the diastereoisomers is the major isomer it is thought that the slight enrichment is due to kinetic resolution in the coupling step. The presence of two broad doublets in the ^{1}H NMR corresponding to each of the hydroxyl groups, integrating to one proton relative to the five methyl groups on the molecule confirmed the successful coupling and deprotection.



Reagents and conditions: (i) EtOH, NEt_3, Δ, 16 hours, 78 %; (ii) 1M HCl, 65 ºC, 1 hour, 90 %.

Figure 1.54

This completed the total synthesis of the third A_3 agonist. Following this successful synthesis of the methyl bearing agonist **1.03** efforts turned to the preparation of the more synthetically challenging diethyl analogue **1.04**.

1.2.17 Synthesis of methyl diethyl agonist 1.04

It was hoped that by using a combination of the Yoshida chemistry used to prepare **1.02**, and the Ellman chemistry used to prepare **1.03** the synthesis of **1.04** would be expedient. (Figure 1.55)

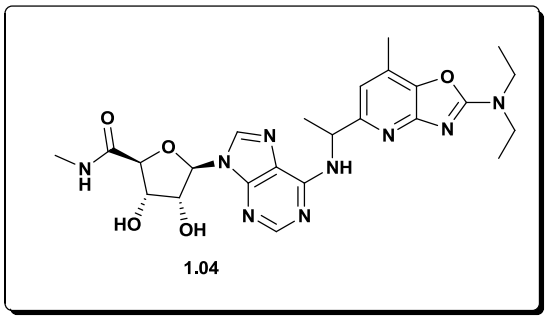


Figure 1.55

It was expected that **1.04** would come from the nucleophilic aromatic substitution of chloropurine **1.05** and racemic primary amine **1.82**. The amine was expected to be available from addition of methylmagnesium bromide to sulfinimine **1.83**. Sulfinimine **1.83** was anticipated to be prepared from condensation of racemic *tert*-butylsulfinamide and the aldehyde derived from known alcohol **1.50**. (Figure 1.56)

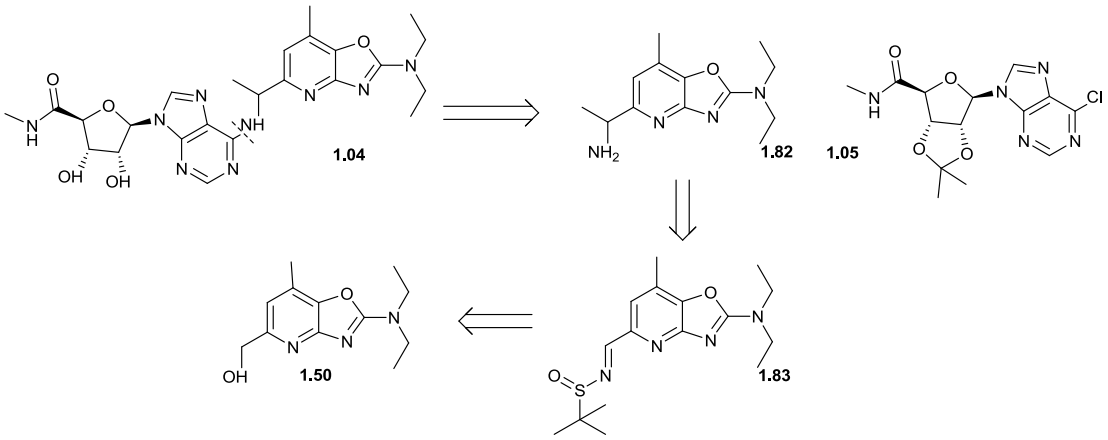
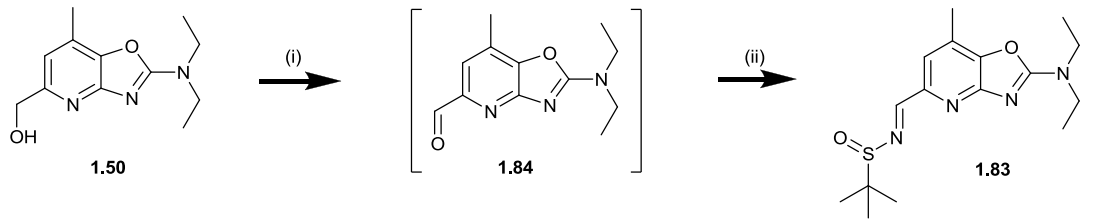


Figure 1.56

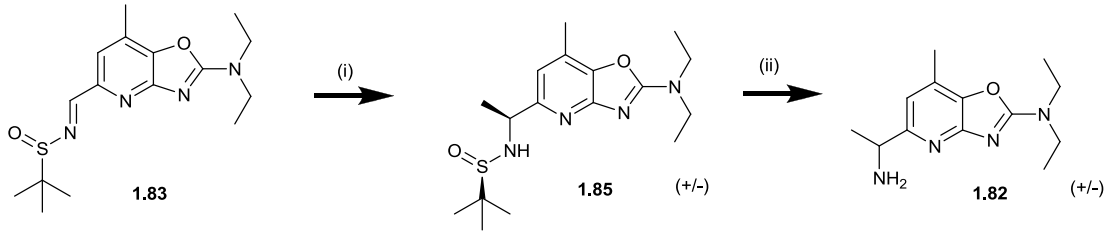
Alcohol **1.50** was oxidised upon treatment with Dess-Martin periodinane and the crude aldehyde **1.84** was immediately dissolved in dichloromethane and stirred at room temperature with anhydrous copper sulphate and racemic *tert*-butyl sulfinamide **1.83** for 16 hours. This gave sulfinimine **1.83** in 90 % yield over the two steps. (Figure 1.57)



Reagents and conditions: (i) Dess-Martin periodinane, DCM, rt, 20 mins. (ii) *tert*-butylsulfinimine, anhydrous $CuSO_4$, DCM, 16 hours (90 % over two steps).

Figure 1.57

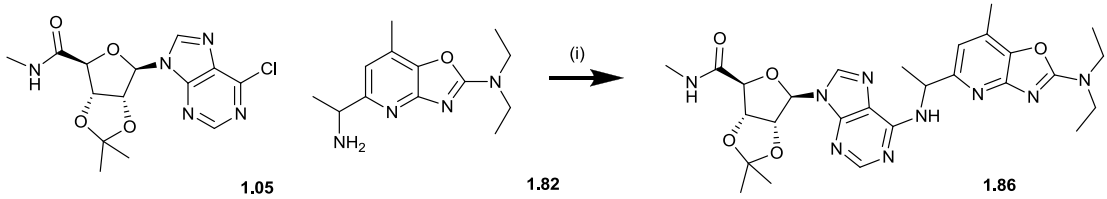
Sulfinimide **1.83** was treated with 6.3 eq of methylmagnesium bromide at -78 °C and was stirred at this temperature for one hour to yield **1.85** in 76 % yield. Again only one diastereoisomer was visible by NMR as indicated by a single doublet at 1.43 ppm representing the new methyl group. Sulfinamide **1.85** was stirred at room temperature with dry hydrogen chloride in methanol to give the amine **1.82** in 82 %. (Figure 1.58)



Reagents and conditions: (i) MeMgBr, THF, - 78 °C, 1 hour (76 %). (ii) HCl in dioxane, MeOH, 30 mins, rt (82 %).

Figure 1.58

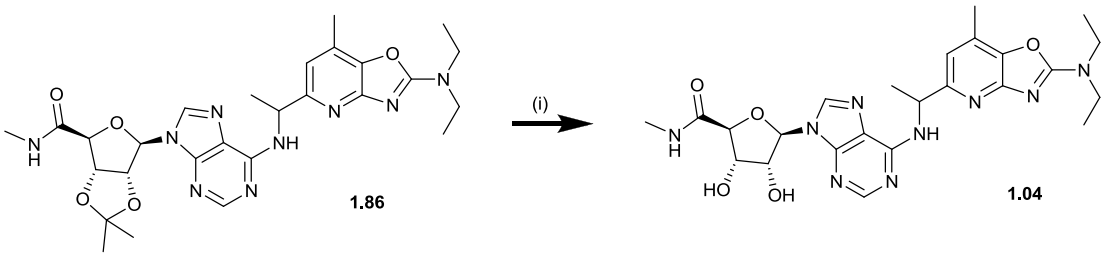
Upon refluxing in ethanol with triethylamine, amine **1.82** and chloropurine **1.05** underwent nucleophilic aromatic substitution to give acetonide **1.86**. (Figure 1.59)



Reagents and conditions: NEt_3, EtOH, Δ, 16 hours, 82 %.

Figure 1.59

The acetonide protecting group was subsequently removed by warming at 65 ^{O}C in 1M aqueous HCl for one hour to give the required diols **1.04** as a 4:6 mixture, in excellent yield with no observed decomposition. (Figure 1.60)



Reagents and conditions: 1M HCl, 65 ^{o}C, 1 hour, 92 %.

Figure 1.60

This completed the total synthesis of the final A_3 agonist.

1.3 Conclusions and Future work

A new family of potential A_3 agonists have been identified by Muscagen using advanced computational design. To allow initial investigations into the biological activity of this new platform a total of four novel compounds were required for biological testing. One of these had already been prepared from the coupling of known chloropurine **1.05** and novel amine **1.06**. (Figure 1.61)

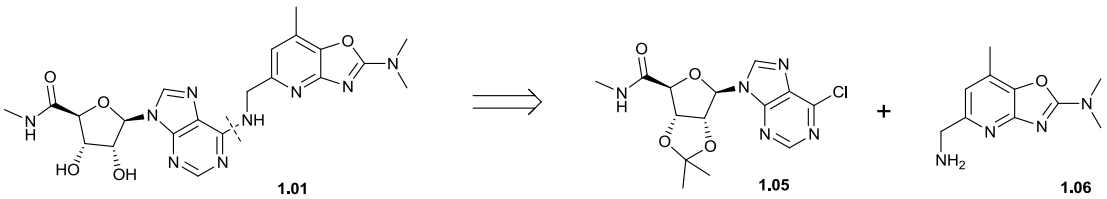


Figure 1.61

Recent efforts have focused on the completion of the total synthesis of the remaining synthetic targets which required the preparation of three novel primary amines (Figure 1.62) and their subsequent alkylation with purine **1.05**.

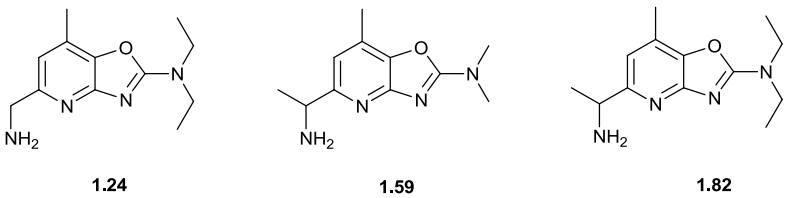


Figure 1.62

Each of the amines was prepared from the common intermediate 2-amino-6-((*tert*-butyldiphenylsilyloxy)methyl)-4-methylpyridin-3-ol (**1.17**) which was in turn prepared from commercially available 2,4-lutidine (**1.07**). (Figure 1.63)

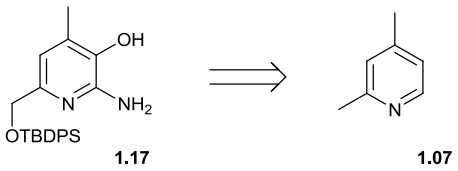


Figure 1.63

Using chemistry established by Yoshida *et al.* it was possible to introduce diethylamine onto the oxazole ring by displacing the chlorine on readily prepared 2-chlorobenzoxoles. It is expected that this method has the scope to introduce a varied selection of amines at this position, potentially aiding in lead optimisation.

It has also been demonstrated that the introduction of a methyl group next to the pyridine ring can be achieved by treating the corresponding Ellman sulfinimine with methylmagnesium bromide. It is expected that this methodology could be extended to a wide variety of nucleophiles and that the adducts could be prepared selectively in either enantiomeric form by using optically active sulfinimine.

1.3.1 Future Work

Should initial tests show that the methyl substituted compounds **1.03** and **1.04** are indeed biologically active the synthesis could be applied to prepare a variety of optically pure materials **1.87** and **1.88** to help distinguish the active enantiomer as part of a full structure-activity relationship study, similarly the amine at the 2 position of the benzoxazole could be varied systematically. (Figure 1.64)

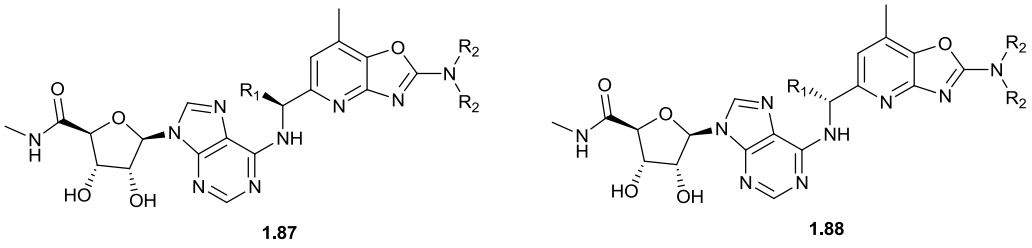


Figure 1.64

Chapter 2: Approaches towards novel M_1 Agonists

Advanced computational studies performed by Muscagen have resulted in the recent discovery of a family of novel M_1 receptor agonists. It is believed that these compounds will show potential for development of therapeutic agents involved in the treatment of Alzheimer's disease.

The targets of interest all contain the core 3-benzyl-3a-cyclobutylhexahydrooxazolo[4,5-c]pyridin-2(3*H*)-one platform with various pendant groups *syn* to the oxazole ring at the C-7 position (Figure 2.01).

The three contiguous stereocenters including a quaternary carbon, and the *cis*-fused 4,5-pyridyloxazolidinone ring system mean that these targets represent a formidable synthetic challenge.

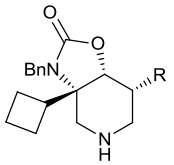


Figure 2.01

2.1 Introduction

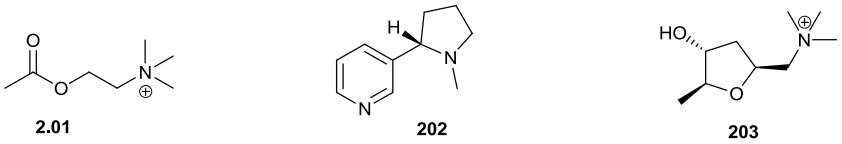
2.1.1 Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia. In 2006 an estimated 26.6 million people were living with Alzheimer's disease, this figure is expected to quadruple by 2050.[44]

One of the distinct characteristics of the condition is a reduced level of the neurotransmitter acetylcholine. In addition to this, insoluble protein plaques form in the brain.[45]

Acetylcholine (**2.01**) is a ubiquitous neurotransmitter released from neurons across the synapse. Once it has diffused across the synapse acetylcholine ligates receptors and elicits a cellular response. The nature of this response depends on the exact cell type involved.

Acetylcholine receptors are classically subdivided into two groups. Those that are also sensitive to nicotine (**2.02**) are termed nicotinic receptors. Those which are also sensitive to muscarine (**2.03**) are termed muscarinic receptors. (Figure 2.02)



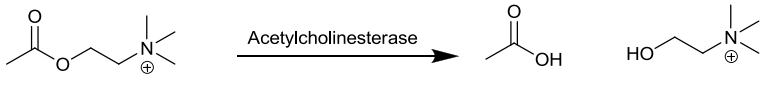
2.01 202 203

Figure 2.02

2.1.1.1 Different Strategies for treating Alzheimer's disease

2.1.1.2 Inhibition of acetylcholinesterase

One of the primary effects of AD is a large reduction of acetylcholine.[46] After effecting the required response in the body acetylcholine is rapidly hydrolysed by the enzyme acetylcholinesterase to acetic acid (**2.05**) and choline (**2.06**) (Figure 2.03). Attempts to maintain higher levels of this essential neurotransmitter in the brain have led to efforts in inhibiting the enzyme acetylcholinesterase.



2.01 2.05 2.06

Figure 2.03

Current treatments for AD are based on this anti-cholinesterase strategy. The most popular anticholinesterase drugs in use are Aricept **2.07** (Pfizer), Cognex **2.08** (Parke-Davis), Exelon **2.09** (Novartis) and Reminyl **2.10** (Janssen)

(Figure 2.04). However the anti-cholinesterase strategy represents a less than ideal solution due to the fact that it is self-limiting. Raising the acetylcholine levels indiscriminately can activate an auto-inhibition feedback system *via* pre synaptic M_2 receptors leading to an overall decrease in levels of acetylcholine.

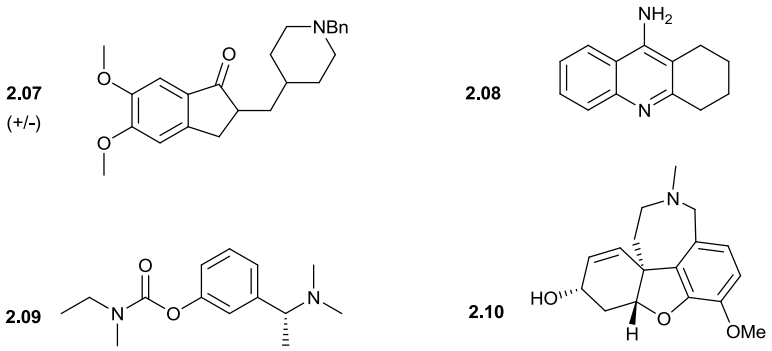


Figure 2.04

2.1.1.3 Muscarinic strategy

Another approach exploits the fact that muscarinic receptors are involved in memory function. Classical muscarinic antagonists have been shown to cause memory impairment in man and animals. Furthermore, muscarinic agonists are able to reverse memory deficits suggesting that muscarinic receptors are involved in higher cognitive function including memory.[47,48]

Muscarinic receptors (of which there are five distinct types) are expressed throughout the brain and peripheral tissues. It is activation of the peripherally expressed receptors by non-selective agonists that is responsible for the unwanted side-effects of typical muscarinic agonists.

M_1 receptors are a notable exception to this rule and are almost exclusively expressed in the central nervous system. Because of this locality; specific M_1 receptor agonists should allow for selective activation of brain muscarinic receptors. A selective M_1 agonist could give the benefits of muscarinic agonism, with few side effects.

The development of selective M_1 agonists represents a formidable task as all five of the receptor subtypes are predicted to have almost identical agonist binding cavities. It is hoped that substrates can be developed which can

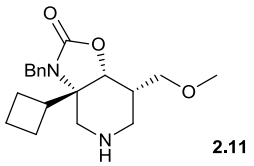
distinguish between the subtle conformational changes conferred by different amino acid residues at non-binding portions of the receptor.

Classical muscarinic agonists are characterised by having low bioavailability and low selectivity causing a high incidence of side effects limiting their application and dosage. The main goal of this project is to design and make a potent, biologically available M_1 agonist with reduced side effects.

2.1.2 Previous work

Compounds of based on the general scaffold illustrated in Figure 2.01 have represented targets of interest to Muscagen for a number of years. Indeed a number of compounds with this general structure have been successfully prepared.[49] The total synthesis of previous targets will be briefly presented in the following pages.

Muscagen initially required access to a methyl ether **2.11**. (Figure 2.05) To simplify the synthesis and therefore expedite the biological testing Muscagen required the compounds to be prepared as a racemic mixture.

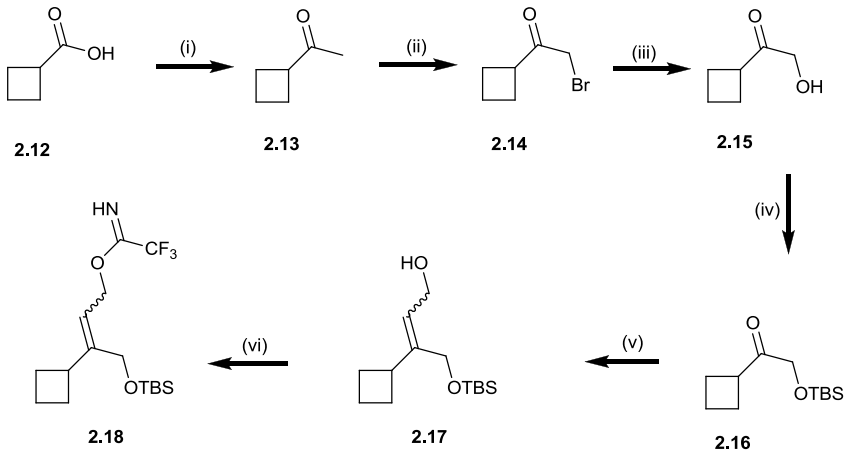


2.11

Figure 2.05

2.1.2.1 Synthesis of agonist (2.11)[49]

Addition of two equivalents of methyl lithium to cyclobutanecarboxylic acid (**2.12**) gave ketone **2.13** upon aqueous workup.[51] Treatment of the resulting cyclobutylmethyl ketone with elemental bromine gave the expected α-bromoketone[52] **2.14** which was hydrolysed with potassium formate and methanol to afford hydroxyketone **2.15**. This was protected as its silyl ether **2.16** using TBSCl and imidazole. The silyl ether **2.16** was then subjected to a Horner-Wadsworth-Emmons reaction and the crude ester was reduced directly with DIBAL-H to afford the allyic alcohol as a 3:1 mixture of geometric isomers **2.17**. Treatment of the alcohol with trifluoroacetonitrile and NaH at –78 ºC gave the trifluoroacetimidate **2.18**. (Figure 2.06)

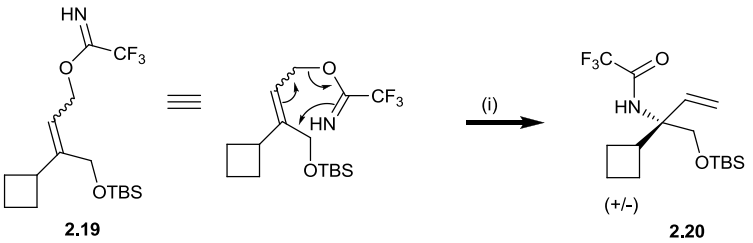


Reagents and conditions: (i) MeLi, Et_2O, reflux, (50 %); (ii) Br_2, MeOH, rt, (80 %); (iii) HCO_2K, MeOH, reflux, (80 %); (iv) TBSCl, imidazole, DMAP, DCM, (85 %); (v) NaH, triethyl phosphonoacetate, THF then DIBAL-H, THF, (70 %); (vi) CF_3CN, NaH, -78 ºC, (88 %).

Figure 2.06

2.1.2.2 [3,3]-Sigmatropic rearrangement

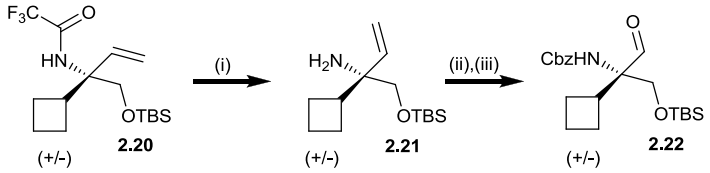
When trifluoroacetimidate **2.19** was heated in xylene it underwent a smooth [3,3]-sigmatropic rearrangement to give **2.20** in 91 % yield. (Figure 2.07)



Reagents and conditions: (i) Xylene, Δ, 91 %;

Figure 2.07

The resulting trifluoroacetamide was reduced to the corresponding primary amine **2.21** with sodium borohydride and was protected by treatment with benzyl chloroformate. Ozonolysis followed by reduction with triphenylphosphine gave the required aldehyde **2.22**. (Figure 2.08) Due to the potential instability of the aldehyde it was considered prudent to store bulk material as the olefin and only liberate the aldehyde immediately before it was required.



Reagents and conditions: (i) $NaBH_4$, EtOH, 0 °C, 80 %, (ii) CbzCl, NEt_3, DCM, rt, 83 %, (iii) O_3, -78 °C then PPh_3, 75 %.

Figure 2.08

2.1.2.3 Chelation-controlled Grignard addition to aldehyde 2.22

When aldehyde **2.22** was treated with isopropenyl magnesium bromide at –78 °C, cyclic carbamate **2.26** was formed in 66 % yield. Only one diastereoisomer was recovered from the reaction mixture, which is consistent with the reaction proceeding *via* chelation control. The relative diastereoselectivity of the reaction is best rationalised by Cram's model. The cyclobutyl group is more sterically demanding than the CH_2OTBS group, so it is reasonable to expect nucleophilic

attack adjacent to the CH_2OTBS group. The formation of the required oxazolidinone can be rationalised if it is assumed that dianion **2.24** exists in equilibrium with isocyanate **2.25** which would be highly reactive to nucleophilic attack by the alkoxide. (Figure 2.09)

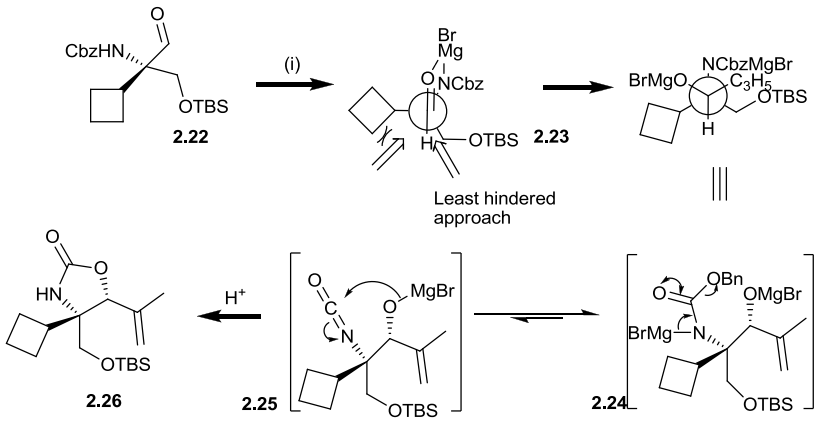
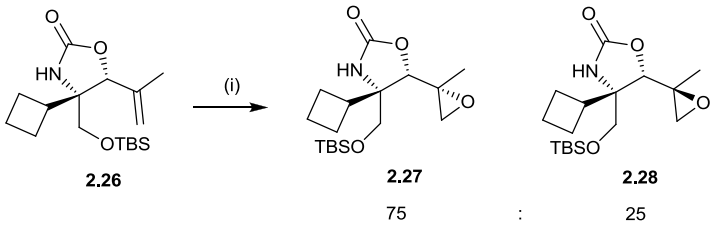


Figure 2.09

2.1.2.4 Introduction of oxygen

The next synthetic challenge was the introduction of the oxygen atom that would bear the methyl ether. Olefin **2.26** was epoxidised using *m*-CPBA to afford an inconsequential 3:1 inseparable mixture of diastereomeric epoxides **2.27** and **2.28**. A crystal was grown from the mixture of epoxides and subjected to X-Ray analysis, which was able to determine the major diastereoisomer present. (Figure 2.10)

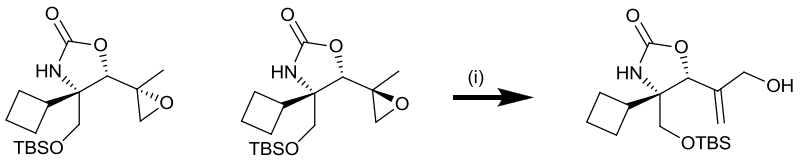


Reagents and conditions: *m*-CPBA, DCM, rt, 75 %

Figure 2.10

Upon treatment with the sterically hindered amide base derived from tetramethylpiperidine and *n*-BuLi the epoxides opened to give the required allyl

alcohol in 67 % yield. (Figure 2.11) Deprotonation of the carbamate in the reaction mixture is thought to protect the system as when the reaction was attempted on the protected carbamate a complex mixture of products was produced.



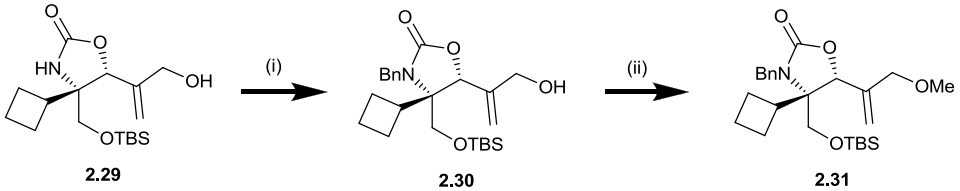
2.27 : **2.28** — **2.29**

75 : 25

Reagents and conditions: TMP, BuLi, THF, 0 ºC, 67 %.

Figure 2.11

Selective benzylation of the carbamate moiety proceeded in 80 % yield, with 18 % recovered starting material. When alcohol **2.29** was treated with sodium hydride and benzyl bromide. The methyl ether **2.31** was then furnished in 90 % yield by treating the resultant alcohol with an excess of methyl iodide and sodium hydride. (Figure 2.12)



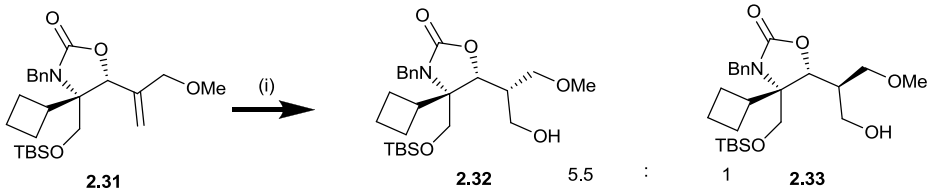
2.29 — **2.30** — **2.31**

Reagents and conditions: (i) BnBr, NaH, THF, Δ, 80 %; (ii) MeI, NaH, THF, rt, 90%.

Figure 2.12

2.1.2.5 Hydroboration Studies

The 1,1-disubstituted olefin **2.31** was treated at 0 ºC with borane tetrahydrofuran complex and oxidised with alkaline hydrogen peroxide. The alcohols **2.32** and **2.33** were obtained in 95 % yield as an inseparable (5.5:1) mixture of diastereomers (Figure 2.13). The major component was confirmed to be the desired compound by nOe studies later in the synthesis.

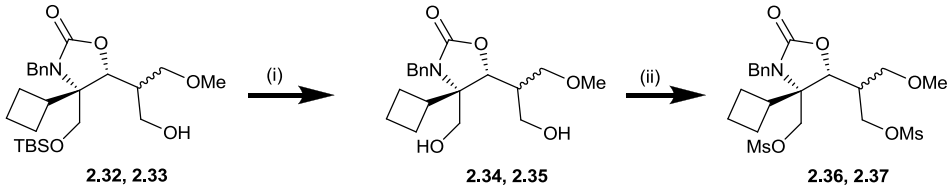


Reagents and conditions: (i) BH_3.THF, THF, 0 ºC then EtOH, NaOAc, H_2O_2 95 %.

Figure 2.13

2.1.2.6 Ring closure to form the piperidine

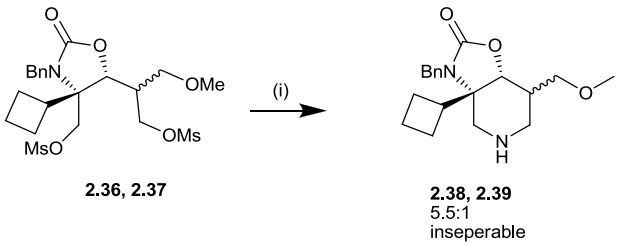
Upon treatment of silyl ethers **2.32** and **2.33** with tetrabutylammonium fluoride, the diols **2.34** and **2.35** were liberated in 90 %. Bis-mesylation of the diols proceeded smoothly upon treatment with methanesulfonyl chloride to give activated diols **2.36** and **2.37**. (Figure 2.14)



Reagents and conditions: (i) TBAF, THF, rt, 90 %; (ii) MsCl, NEt_3, DCM, rt, 80 %.

Figure 2.14

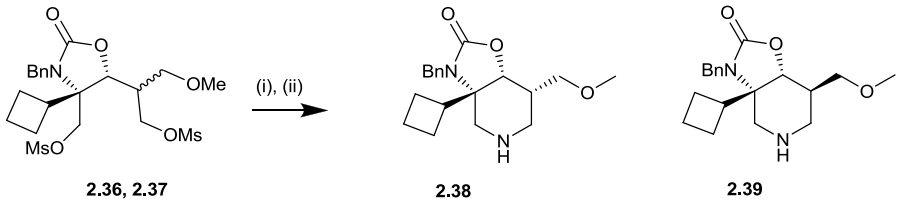
The final step of the synthesis was the displacement of the activated diol with a nucleophilic amine to give the required piperidine. When mesylates **2.36** and **2.37** were treated with anhydrous ammonia in a sealed tube and stirred for 48 hours the required piperidines were indeed isolated in a 40 % yield as a 5.5:1 mixture of diastereomers. The low yield is best explained by the poor nucleophilicity of ammonia. Unfortunately the diastereomers remained inseparable by silica gel chromatography. (Figure 2.15)



Reagents and conditions: (i) NH_3, THF, rt, 40 %

Figure 2.15

However when bis-mesylates **2.36** and **2.37** were treated with benzylamine the cyclisations proceeded far more efficiently to give the piperidines in 62 % as a 5.5:1 mixture of diastereoisomers. Fortunately, these benzyl derivatives were readily separated by silica gel chromatography allowing the efficient removal of the undesired diastereoisomer before selective benzyl deprotection to give the required piperidine **2.38** in 71 %. (Figure 2.16)



Reagents and conditions: (i) $BnNH_2$, Δ, 62 %; (ii)10% Pd/C, HCO_2H, MeOH, rt, 71 %.

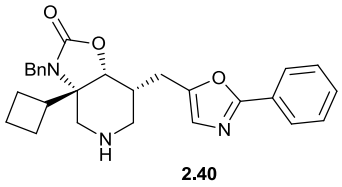
Figure 2.16

Piperidine **2.38** was found to be a 50 % agonist of the M_1 muscarinic receptor with a potency of 10^{-7} molar. The synthesis was completed in 21 steps and 0.3 % overall yield.

2.1.2.7 Synthesis of second generation agonist

The next target earmarked for synthesis took into account the fact that Muscagen anticipate the most valuable piperidines to have a pendant aromatic

heterocycle at the C-7 position. Molecule **2.40** was chosen as the target. (Figure 2.17)



2.40

Figure 2.17

2.1.2.8 Retrosynthesis

Piperidine **2.40** was expected to be available from olefin **2.41** after hydroboration and double displacement of the corresponding bis-mesylate. Olefin **2.41** could come from known alcohol **2.30** ozazole **2.42** (Figure 2.18).

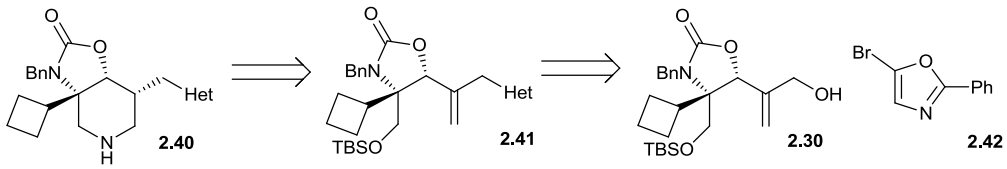
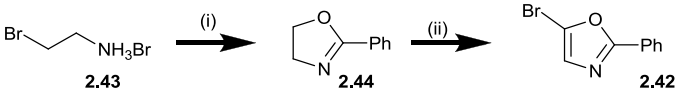


Figure 2.18

2.1.2.9 Synthesis of 5-bromo-2-phenyloxazole

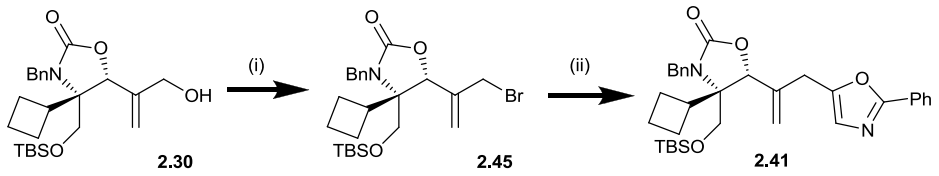
Oxazole **2.42** was prepared from ammonium bromide **2.43**. Treatment of aminobromide with benzoyl bromide and triethylamine afforded the desired 4,5-dihydro-oxazole **2.44** in 36 % yield after purification by distillation. The required oxazole was obtained in 45 % yield when **2.44** was subjected to bromination with *N*-bromosuccinimide in carbon tetrachloride. (Figure 2.19)



Reagents and conditions: (i) PhCOCl, NEt_3, C_6H_5, 36 %; (ii) NBS, AIBN, CCl_4, 45 %.

Figure 2.19

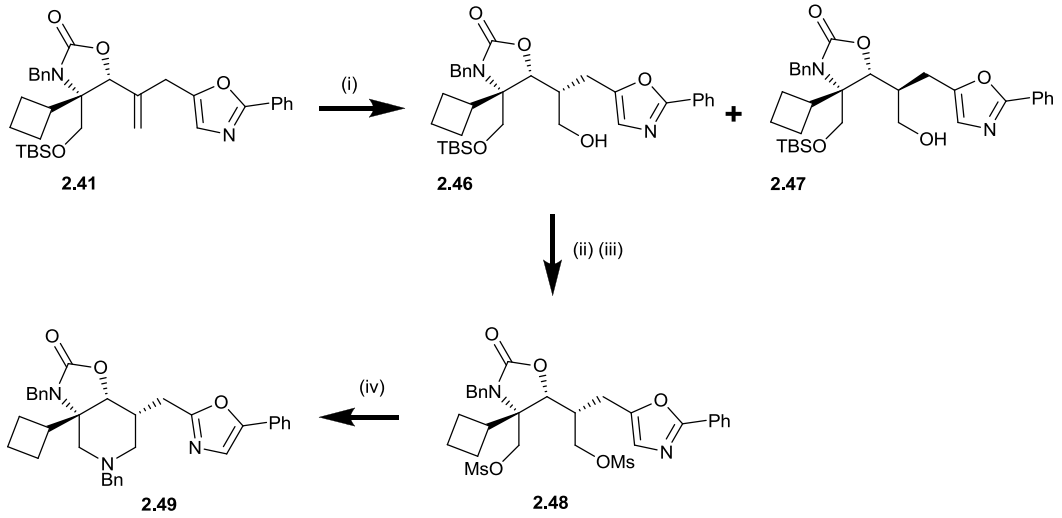
With the oxazole **2.42** in hand, known alcohol **2.30** was subjected to Appel conditions yielding allyl bromide **2.45** quantitatively. The bromide was displaced by an organocopper species derived from the oxazole to give the heteroaromatic **2.41**. (Figure 2.20)



Reagents and conditions: (i) CBr_4, PPh_3, MeCN, 100 %; (ii) **2.42**, *n*-BuLi, CuCN, LiCl, -18 °C to -40 °C, 80 %.

Figure 2.20

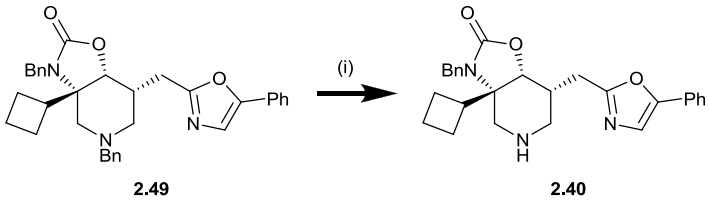
The next step was to form a primary alcohol from the 1,1-disubstituted olefin and simultaneously set the stereochemistry at the adjacent carbon. Hydroboration followed by oxidative workup led to the isolation of alcohols **2.46** and **2.47** as a 9:1 mixture of diastereomers which were separated by silica gel chromatography. After removal of the TBS group the diol was treated with methanesulfonyl chloride and triethylamine to afford bis-mesylate **2.48**. Treatment with benzylamine afforded the protected piperidine **2.49**. (Figure 2.21)



Reagents and conditions: (i) BH_3.THF, THF, -20 °C to rt, 16 hours then EtOH, NaOAc (sat), H_2O_2, 60 °C, 50 %; (ii) TBAF, THF, rt, 83 %; (iii) MsCl, NEt_3, THF, 0 °C; (iv) $BnNH_2$, 90 °C, 81 % (2 steps).

Figure 2.21

Finally benzylamine **2.49** was subjected to transfer hydrogenation conditions to remove selectively the benzyl protecting group leaving the benzylcarbamate intact. (Figure 2.22)



Reagents and conditions: (i) HCO_2H, 10% Pd/C, MeOH, rt, 54 %.

Figure 2.22

This gave the required second generation piperidine in 0.15 % yield over 22 steps.

2.1.2.10 Approaches towards third generation M_1 agonist

Following the biological testing of compounds **2.11** and **2.40** and further computational refinements by Muscagen it was thought that another desirable candidate for testing against M_1 agonism would have an aromatic heterocycle directly attatched at C-7. Compounds without a methylene spacer between the heterocycle and the piperidine ring were expected to represent a greater synthetic challenge due to the enhanced acidity of the C7 proton. This may make the molecule fragile with respect to elimination.

Muscagen wished to test heteroaromatic piperidine **2.50** (Figure 2.23)

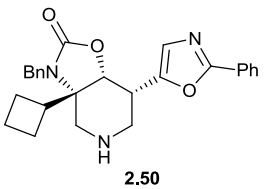


Figure 2.23

2.1.2.12 Retrosynthesis of 2.50

It was thought that piperidine **2.50** would be accessible *via* the 1,1 disubstituted olefin **2.51** which was in turn expected to be derived from palladium-mediated coupling of the enol triflate **2.52** derived from known carbamate **2.26**. (Figure 2.24)

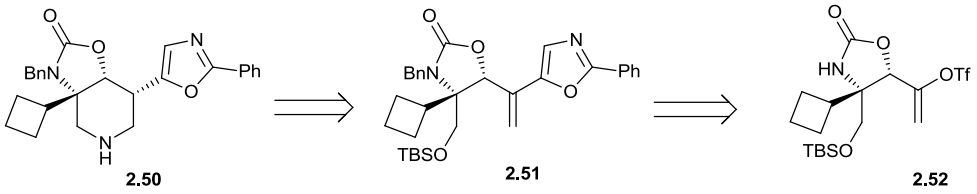
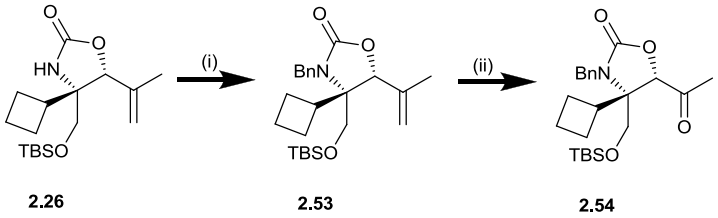


Figure 2.24

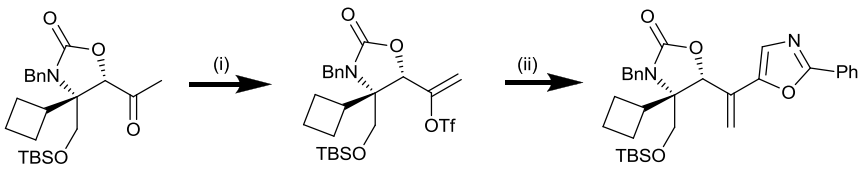
Known carbamate **2.26** was first elaborated to it's *N*-benzyl derivative and ozonolysis of the resulting olefin gave the methyl ketone **2.54** in 85 % over the two steps. (Figure 2.25)



Reagent and conditions: (i) BnBr, NaH, THF, Δ, 79 %; (ii) O_3, PPh_3, DCM, -78 °C, 93 %.

Figure 2.25

The ketone was deprotonated with potassium hexamethyldisilazide to give the potassium enolate which was quenched with phenyl triflimide to afford enol triflate **2.52** in 71 % yield. The heterocyclic bromide **2.42** was treated with an excess of butyl lithium at -18 °C affording the corresponding organolithium species followed by zinc chloride and the reaction mixture was stirred at room temperature for one hour. The resulting organozinc species was added to a stirred solution of triflate **2.52** and $PdCl_2(PPh_3)$ and stirred for 48 hours at room temperature. The desired 1,1 disubstituted olefin was isolated from the reaction mixture in a modest 38 % yield. (Figure 2.26)



Reagents and conditions: (i) KHMDS, $PhN(Tf)_2$, THF, - 78 °C, 71 %; **2.42**, *n*-BuLi, ZnCl, $PdCl_2(PPh_3)_2$, - 18 °C to rt, 38 %.

Figure 2.26

A lack of material meant that synthetic studies towards this target agonist were suspended. Muscagen were keen to prioritise the synthesis of a furan bearing derivative.

Furan containing molecules are often metabolised by the liver rapidly; typically by hydroxylation of the ring. This can lead to rapid deactivation and short drug half-lives. Nevertheless some extremely successful drugs do contain furan rings, such as GSK's blockbuster Zantac. (Figure 2.27)

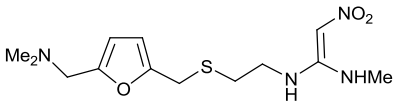
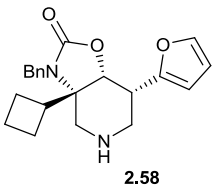


Figure 2.27

The chemistry of furan has been extensively studied and many furan-bearing intermediates are available from standard chemical suppliers. This is in contrast to more exotic heterocycles which were also considered to satisfy the molecular modelling studies. As such, the furan analogue **2.58** was tentatively considered for synthesis.

It was considered that furan **2.58** would serve as a valuable probe to refine Muscagen's model of the M_1 receptor. The synthesis was approached with the consideration that it should be amenable to the introduction of a variety of heterocycles.

2.1.2.13 Towards agonist 2.28[50]



2.58

Figure 2.28

2.1.2.14 Retrosynthetic analysis

Piperidine **2.58** was expected to be available *via* a double displacement reaction of a derivative of diol **2.59** by analogy with the successful synthesis of **2.11**. Hydroboration of **2.60** was expected to proceed with high regio- and stereo-selectivity to give the diol **2.59**. Addition of 2-lithiofuran to aldehyde **2.61** followed by oxidation of the resulting secondary alcohol, and a one carbon Wittig reaction should give olefin **2.60**. Addition of propenylmagnesium bromide into aldehyde **2.22** was anticipated to proceed with a high degree of chelation control, and subsequent ozonolysis of the olefin would give the aldehyde **2.61**. Allyl cyanate **2.62** would undergo a [3,3]-sigmatropic rearrangement to give access to aldehyde **2.22**. The allyl cyanate is expected to be available from the dehydration of allyl carbamate **2.63**. Elaboration of silyl ether **2.16** is anticipated to yield carbamate **2.53**. The silyl ether itself is expected to be derived from methyl ketone **2.13** which is commercially available. (Figure 2.29)

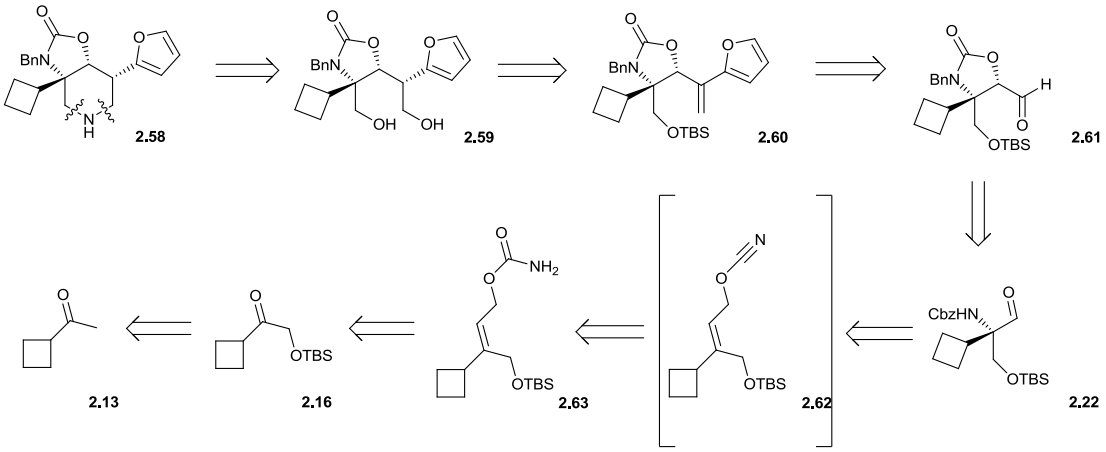
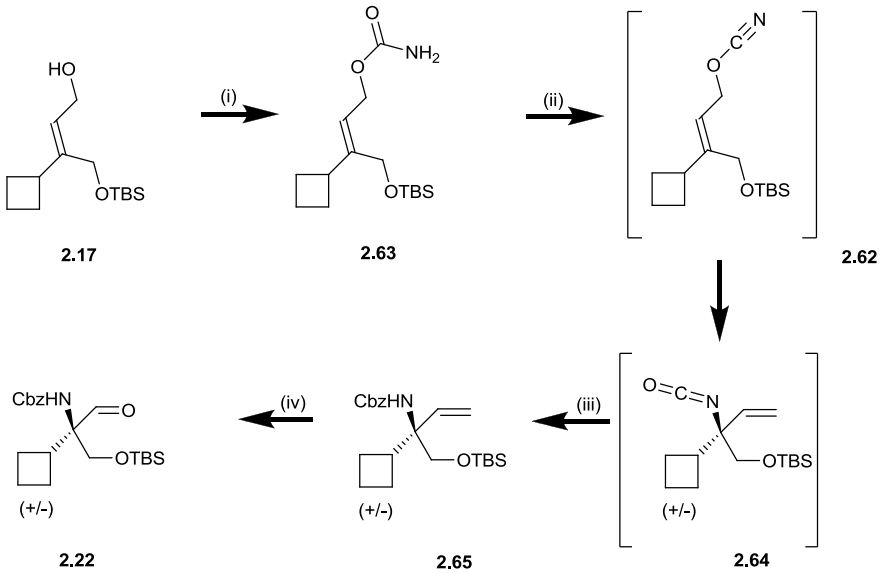


Figure 2.29

The approach was very similar to the approach used by in the early generation synthesis. One key difference being the replacement of the [3,3] sigmatropic rearrangement precursor from trifluoroacetimidate **2.18** to allyl carbamate **2.63**. This eliminated the need to handle trifluoroacetonitrile which is an extremely toxic gas.

2.1.2.15 Modified synthesis of aldehyde 2.22

The allylic alcohols **2.17** were treated with trichloroacetyl isocyanate, and were subsequently hydrolysed upon treatment with methanolic potassium carbonate to afford carbamate **2.63**. Treatment of carbamate **2.63** with triphenylphosphine, carbon tetrabromide and triethylamine afforded allyl isocyanate **2.64** *via* the unstable intermediate allyl cyanate **2.62** which underwent spontaneous [3,3]-sigmatropic rearrangement. Allyl isocyanate **2.64** was immediately treated with freshly prepared sodium benzalkoxide and 4 Å molecular sieves to afford racemic olefin **2.65**. Treatment with ozone followed by triphenylphosphine gave aldehyde **2.22** in 8 % overall yield from commercially available cyclobutanecarboxylic acid without the use of the toxic gas trifluoroacetonitrile. (Figure 2.30)

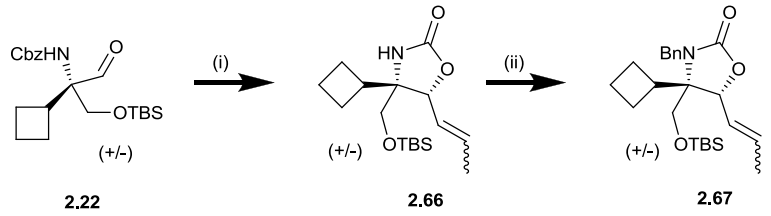


Regents and conditions: (i) trichloroacetyl isocyanate, DCM, 0 °C, then K_2CO_3, MeOH, H_2O, 97 %; (ii) PPh_3, NEt_3, CBr_4, DCM, -10 °C (iii) BnONa, 4 Å molecular seives, THF, 80 % over two steps; (iv) O_3, DCM, -78 °C, then PPh_3, 75 %.

Figure 2.30

2.1.2.16 Oxazolidonone Formation

Chelation controlled addition of 1-propenyl magnesium bromide to aldehyde **2.22** and spontaneous cyclisation of the resulting alkoxide onto the carbamate gave vinyl carbamate **2.66** as a mixture of geometric isomers. Benzyl protection of the carbamate was facilitated by sodium hydride mediated deprotonation followed by treatment of the resulting anion with benzyl chloride in tetrahydrofuran. (Figure 2.31)

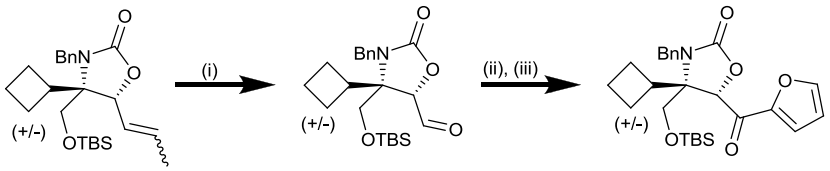


2.22 **2.66** **2.67**

Reagents and conditions: (i) 1-propenyl magnesiumbromide, THF, -78 ºC then rt 16 hours. (ii) BnBr, NaH, THF, 70 %.

Figure 2.31

The olefin was then subjected to treatment with ozone and reductive workup which liberated aldehyde **2.61**. Freshly prepared 2-lithiofuran was added to a stirred solution of the aldehyde at -78 ºC to give the corresponding secondary alcohol as an inconsequential mixture of diastereoisomers. The alcohol was oxidised to the ketone upon subjecting to Ley oxidation conditions.[53] (Figure 2.32)

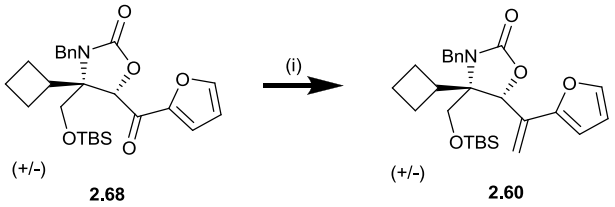


2.67 **2.61** **2.68**

Reagents and conditions: (i) O_3, DCM, PPh_3 -78 °C; 70 % (ii) *n*-BuLi, furan, THF, -78 °C then **2.61** 60 %; (iii) TPAP, NMO, 4 Å molecular sieves, DCM, 85 %.

Figure 2.32

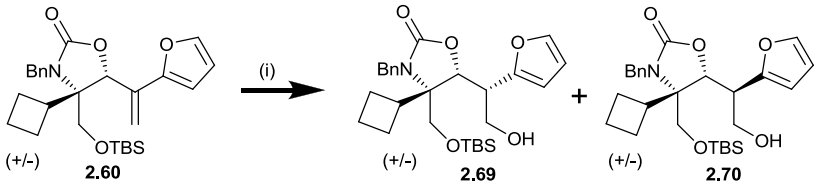
The resulting ketone **2.68** was subjected to a one carbon Wittig reaction to give key intermediate **2.60** in 23 % overall yield from commercially available cyclobutanecarboxylic acid. (Figure 2.33)



Reagents and conditions: (i) Methyltriphenylphosphonium bromide, THF*, n*-BuLi, rt, 1 hour, then ketone **2.68**, rt, 15 mins, 72 %.

Figure 2.33

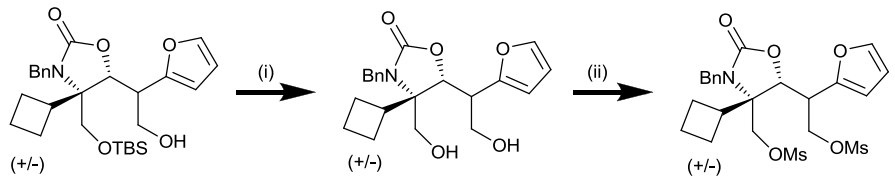
Vinyl furan **2.60** was subjected to hydroboration conditions using sodium perborate as a mild oxidant. The reaction proceeded to give alcohols **2.69** and **2.70** in 60 % yield as an inseparable (2:1) mixture of epimers. Attempts to improve selectivity using 9-BBN gave poor yields and were not pursued. The stereochemistry at the newly formed centre was not determined at this stage, however by analogy with the hydroboration of closely related olefin **2.31** it was considered plausible that the major product was the required epimer. (Figure 2.34)



Reagents and conditions: (i) BH_3.THF, THF 0 °C to rt, then $NaBO_3.4H_2O$, H_2O, 0 °C to rt 60 %, 2:1 (**2.69**:**2.70**).

Figure 2.34

The silyl ethers were treated with tetrabutylammonium fluoride in tetrahydrofuran to liberate the corresponding diols, which became separable at this point. The major diastereoisomer was treated with mesyl chloride and triethylamine to afford bis-mesylate **2.72**. (Figure 2.35)



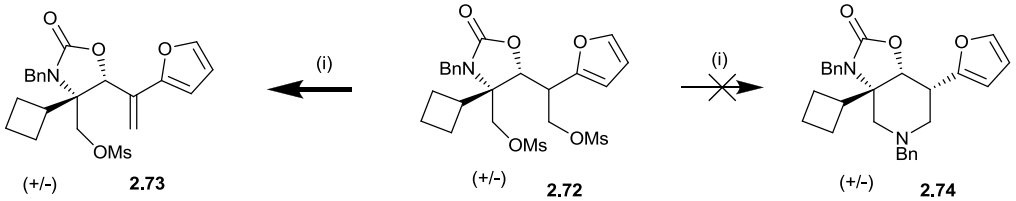
Reagents and conditions: (i) TBAF, THF, rt, 81 %, (ii) MsCl, NEt_3, THF 0 ºC-rt

Figure 2.35

2.1.2.17 Cyclisation attempts

The final stage of the synthesis was to convert mesylate **2.72** to the piperidine. This was expected to be achieved by double displacement of the mesylate with benzylamine.

However, all attempts to displace mesylate **2.72** with benzylamine led to an elimination reaction and reintroduction of the olefin. The required cyclic product was never observed. (Figure 2.36) This was a departure from the behaviour of the one carbon homologues **248**, **236** and **237** which were manipulated successfully in this way for the synthesis of the parent piperidines. (Figure 2.36)



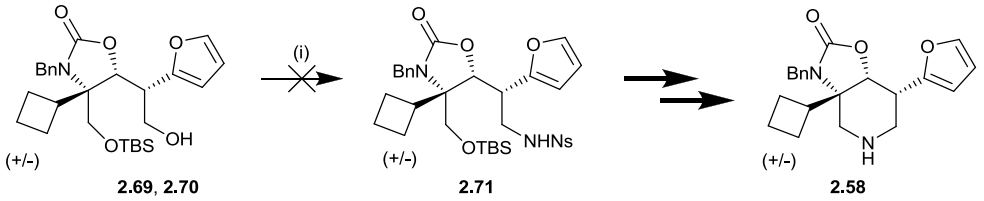
Reagents and conditions: $BnNH_2$, 80 ºC, 18 hours, olefin **2.73** obtained in 87 % from diol **2.71**.

Figure 2.36

This phenomenon can be rationalised by considering the effect of the furan group on enhancing the acidity of the adjacent proton by stabilising the resulting carbocation. Significantly the isolated product retained the neopentylic

mesylate despite the rather forcing reaction conditions. This illustrates the hindered nature of this position. The second attempt to furnish the nitrogen functionality was *via* a Fukuyama-Mitsunobu reaction on the primary alcohol.

However after treatment with triphenylphosphine, diisopropyl azodicarboxylate, and 2-nitrobenzenesulfonyl chloride only starting material was recovered from the reaction mixture. (Figure 2.37)



Reagents and conditions: PPh_3, DIAD, $NsNH_2$, THF, rt.

Figure 2.37

2.2 Results and discussion

2.2.1 Retrosynthetic analysis

The required piperidine **2.58** was expected to be available from an alcohol derived from the oxidation of the olefin **2.60**. Olefin **2.60** has been shown to be available from quaternary aldehyde **2.22**.[49,50] The aldehyde has been prepared from commercially available cyclobutanecarboxylic acid. (Figure 2.38)

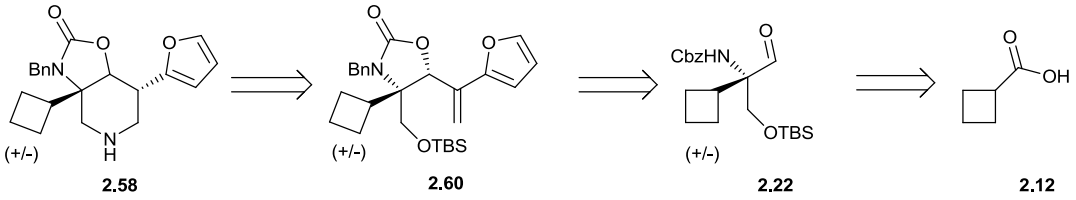


Figure 2.38

A review of the established chemistry up to this point gave cause for optimism. Commercially available cyclobutanecarboxylic acid could be elaborated to quaternary aldehyde **2.22** in eleven linear steps and 8 % overall yield. In a further six steps the aldehyde has been transformed into the key intermediate olefin **2.60** in 23 % yield. (Figure 2.39)

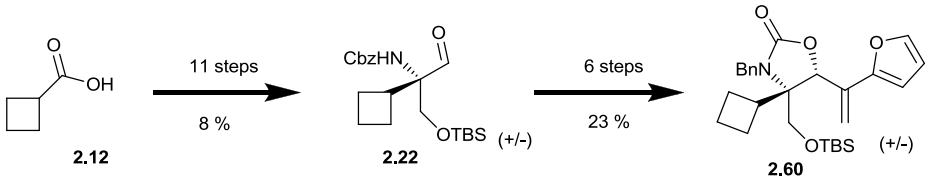


Figure 2.39

Studies into the chemical behaviour of the late stage intermediates were still in the preliminary stages, however it was clear that the end game strategy developed for the early targets was ineffective towards the synthesis of **2.58**. Therefore, it was necessary to develop a new synthetic approach towards the construction of the furan bearing piperidine.

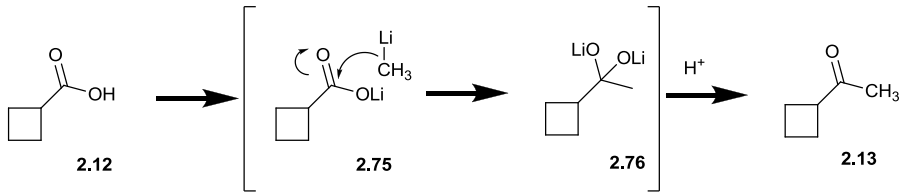
It was considered that the previously identified olefin **2.60** held great potential as a versatile late stage intermediate towards the required piperidine,

as such access to large quantities of this key intermediate was strategically important. However, at this stage supplies of advanced material were depleted and it was necessary to bring material through from commercially available materials.

This was an excellent opportunity to refine the overall synthesis. Reducing the total number of steps to the key olefin **2.60** would be of huge benefit. Larger amounts of advanced materials would be available in less time and at a more viable cost. It was decided to develop a new route to the olefin **2.60**, and bring material through the established procedure at the same time.

2.2.2 Established Route:[49,50]

In the first step of the established synthesis of aldehyde **2.22**, cyclobutyl carboxylic acid is treated with two equivalents of methyl lithium to give the corresponding bis-lithiated ketohydrate **2.76** which collapses to the ketone upon aqueous workup.[51] (Figure 2.40)



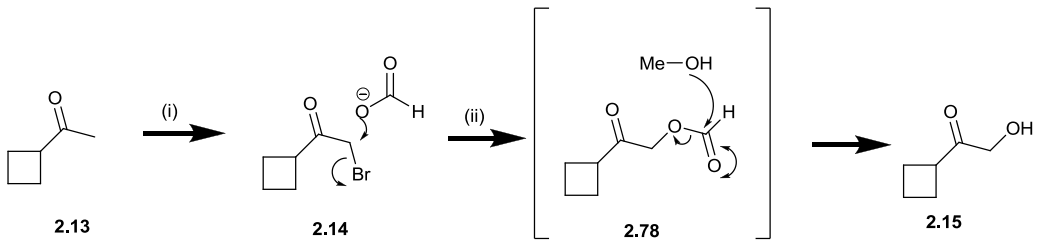
Reagents and conditions: MeLi, Et_2O, Δ, 2 hours, 60 %.

Figure 2.40

The ketone is commercially available, although it is more expensive than the acid. However for future synthetic studies it was considered cost efficient to simply buy the ketone rather than persisting with the methylation of the acid which uses two equivalents of methyllithium and proceeds only in modest yield.

As prescribed by the previously established synthesis methyl ketone **2.13** was treated with elemental bromine to afford the bromoketone[52] as a mobile

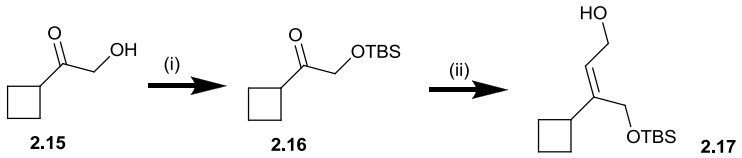
orange oil which was found to be volatile and lachrymatory. For this reason it was used immediately after preparation, without purification. Treatment with potassium formate in refluxing methanol afforded the primary alcohol *via* the transesterification of the intermediate formate ester.[49] (Figure 2.41)



Reagents and conditions: (i) Br_2, methanol, 0 °C to rt, 16 hours, 80 %; (ii) HCO_2K, MeOH, Δ, 16 hours, 70 %.

Figure 2.41

The alcohol was next protected as it's *tert*-butyldimethylsilyl ether and the ketone was subjected to a Horner Wadsworth Emmons reaction the product of which was reduced directly without isolation to give the allylic alcohol **2.17** as a 3:1 mixture of geometric isomers.[49] (Figure 2.42)

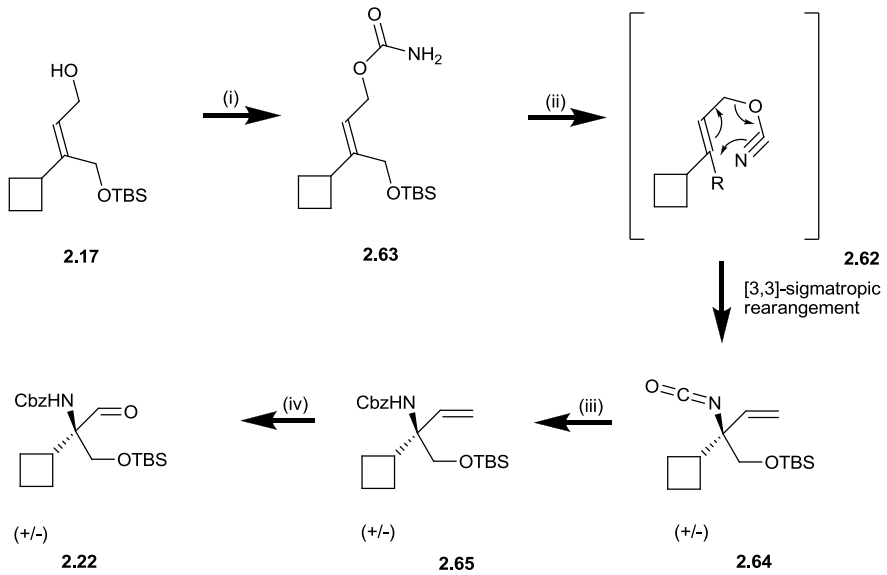


Reagents and conditions: (i) TBSCl, imidazole, DCM, rt, 85 %; (ii) NaH, triethyl phosphonoacetate, THF then DIBAL-H, THF, (70 %);

Figure 2.42

The allylic alcohol **2.17** was treated with trichloroacetyl isocyanate, the resulting carbamate was hydrolysed *in situ* upon treatment with methanolic potassium carbonate to afford carbamate **2.63**. Treatment of the carbamate with triphenylphosphine, carbon tetrabromide, and triethylamine afforded allyl isocyanate **2.64** *via* the unstable intermediate allyl cyanate **2.62** which undergoes spontaneous [3,3] sigmatropic rearrangement. The allyl isocyanate **2.64** was immediately treated with freshly prepared sodium benzalkoxide and 4 Å molecular sieves to afford olefin **2.65**. Treatment with ozone followed by

triphenylphosphine gave aldehyde **2.22** as indicated by a sharp singlet at 9.62 ppm. (Figure 2.43)



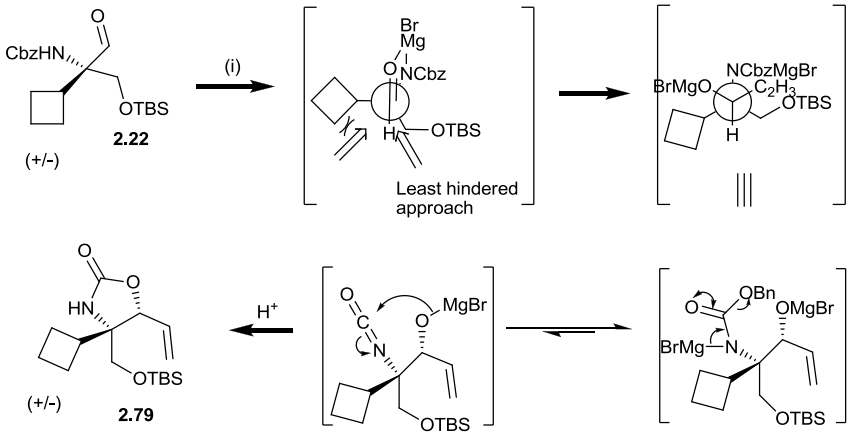
2.17 **2.63** **2.62** **2.64** **2.65** **2.22**

(+/-) (+/-) (+/-)

Figure 2.43

Regents and conditions: (i) trichloroacetyl isocyanate, DCM, 0 °C, then K_2CO_3, MeOH, H_2O, 97 %; (ii) PPh_3, NEt_3, CBr_4, DCM, -10 °C (iii) BnONa, 4 Å molecular sieves, THF, 80 % over two steps; (iv) O_3, DCM, -78 °C, then PPh_3, 75 %.

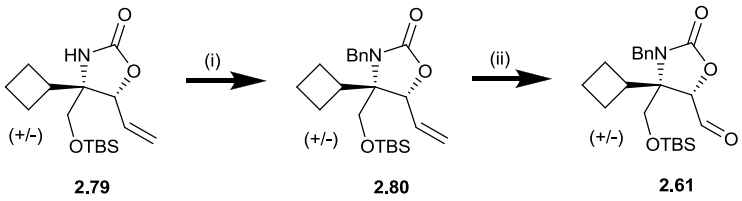
In the previous synthesis (Figure 2.31) the aldehyde was then treated with 1-propenylmagnesium bromide to afford the olefin **2.66** as a mixture of *cis* and *trans* isomers. This mixture of compounds could be avoided by treating the aldehyde with vinyl magnesium bromide instead. When the aldehyde was treated with vinylmagnesium bromide the addition and subsequent cyclisation took place as expected to give the carbamate **2.79** in excellent yield. Only one diastereoisomer was observed in the NMR suggesting that the reaction proceeded with the expected high degree of chelation control. (Figure 2.44)



Reagents and conditions: Vinylmagnesium bromide, THF, -78 ºC, 2 hours then room temperature 16 hours, 91 %.

Figure 2.44

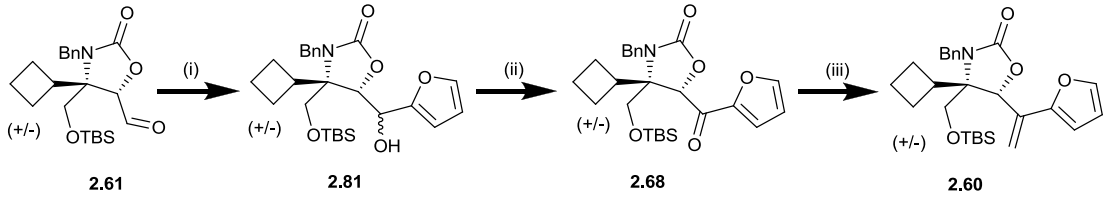
The carbamate was deprotonated with sodium hydride and alkylated with benzyl bromide to give the *N*-benzyl carbamate in 70 % yield. The olefin underwent smooth ozonolysis to give the aldehyde **2.61** as a thick colourless oil which was used immediately in the next step. (Figure 2.45)



Reagents and conditions: (i) BnBr, NaH, THF, 70 %; (ii) O_3, DCM PPh_3 -78 °C, then PPh_3, rt, 1 hour, 70 %.

Figure 2.45

The aldehyde was treated at -78 ºC with a suspension of freshly prepared ortho-lithiated furan to afford an inconsequential epimeric mixture of secondary alcohols. The alcohols were subjected to Ley oxidation[53] conditions to give ketone **2.81** in 85 % which underwent a one carbon Wittig reaction with methyltriphenylphosphonium bromide to afford the required key olefin **2.60**. (Figure 2.46)



Reagents and conditions: (i) BuLi, furan, THF, -78 °C then **2.61** 60 %; (ii) TPAP, NMO, 4 Å molecular sieves, DCM, 85 %; (iii) methyltriphenylphosphonium bromide, THF, *n*-BuLi, room temp, 1 hour, then ketone **2.68**, rt, 15 mins, 72 %.

Figure 2.46

At the same time as material was being advanced through this route, investigations were ongoing into the development of a new, shorter route to the key olefin. This work will be presented in the following chapter.

2.2.3 New approaches to olefin 2.60

2.2.3.1 Addition of nitrile 2.84 to aldehyde 2.22

It was decided to investigate the possibility of direct introduction of the nitrogen bearing furan moiety *via* the addition of lithiated 2-(furan-2-yl)acetonitrile to aldehyde **2.22**. Amine **2.82** should be accessible *via* reduction of a nitrile group which could come from addition of furan **2.84** to known aldehyde **2.22**. This route potentially represents a saving of four steps and eliminates the need for the problematic introduction of the amine later in the synthesis. (Figure 2.47)

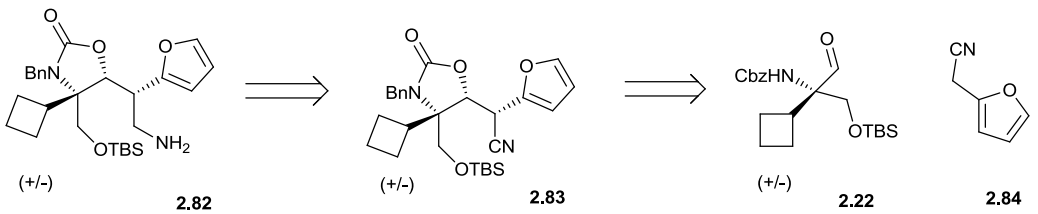
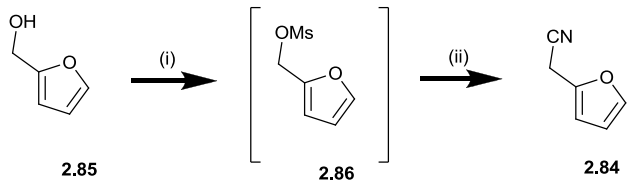


Figure 2.47

Furfuryl alcohol **2.85** was treated with methanesulfonyl chloride and triethylamine in dichloromethane followed by potassium cyanide in DMSO.[54,55] The reaction mixture was warmed to room temperature overnight. This yielded the required nitrile **2.84** in acceptable yield. (Figure 2.48)



Reagents and conditions: (i) MsCl, NEt_3, DCM 0 °C; (ii) KCN, 18-crown-6, DMSO, rt, 40 % overall.

Figure 2.48

Attempts to isolate intermediate mesylate **2.86**, resulted in a complex mixture of products from which the required compound could not be isolated. Presumably this is due to the highly reactive nature of the species caused by having a leaving group conjugated to an electron rich furan. (Figure 2.49)

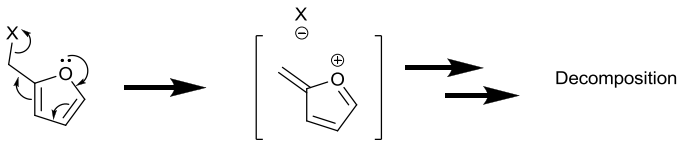
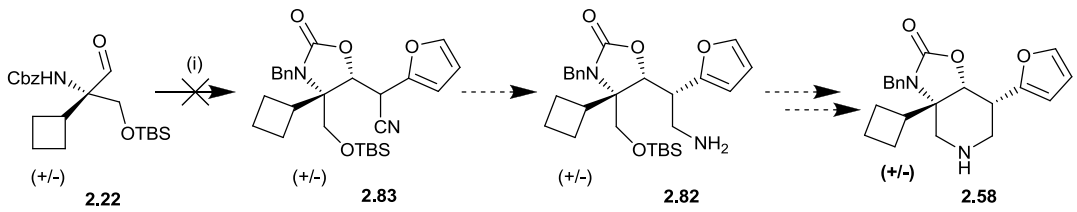


Figure 2.49

Unfortunately attempts to add lithiated **2.84** into aldehyde **2.22** gave a complex mixture of products. (Figure 2.50) As such, research in this area was discontinued.



Reagents and conditions: (i) nitrile **2.84**, LDA, THF, -78 °C then aldehyde **2.22**, -78 °C to rt.

Figure 2.50

2.2.3.2 Addition of Vinylfuran to aldehyde 2.22

A retrosynthetic analysis of the key olefin **2.60** indicated that it should be available from the addition of an organometallic species such as **2.87** to quaternary aldehyde **2.22**, followed by benzyl protection of the carbamate (Figure 2.51). If successful this would make the key olefin available in just two synthetic steps from the aldehyde. This is in contrast to the six steps previously required. It is hoped that this would give access to large amounts of the key olefin in a shorter amount of time.

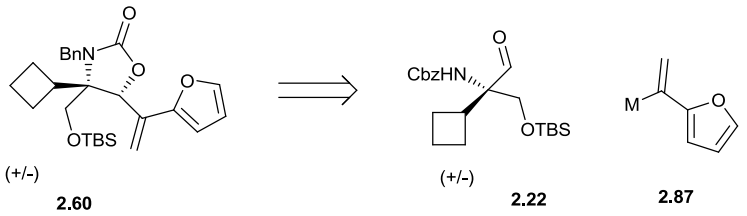
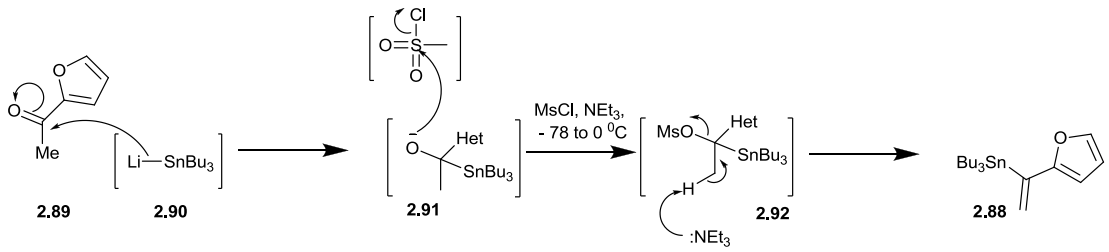


Figure 2.51

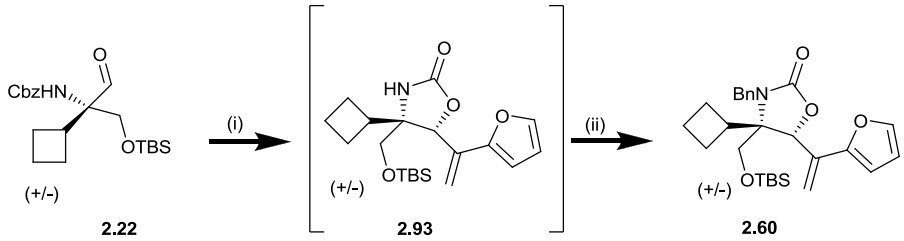
It can be envisaged that organometallic species **2.87** can be derived from several sources including the corresponding vinyl iodide or the tosyl hydrozone.[56] We opted instead to prepare the vinyl stannane **2.88** from which the vinyl lithium could be formed i*n situ* upon treatment with butyllithium. Darwish has shown that a wide range of vinyl stannanes can be prepared in a single synthetic step from the corresponding ketones by treatment with lithium tributyltin followed by activation and elimination of the subsequent alcohol.[57] Commercially available acetyl furan **2.89** was treated with freshly prepared tributyltin lithium at – 78 ºC as described by Darwish. A large excess of mesyl chloride and triethylamine were added to afford the olefin. (Figure 2.52) The polar by products of the reaction were removed by partitioning the crude reaction mixture between acetonitrile and pentane.



Reagents and conditions: DIPA, *n*-BuLi, THF, 0 ºC, 30 mins then Bu_3SnH, 30 mins, 0 ºC then acetyl furan, room temperature, 1 hour, then MsCl, NEt_3, 16 hours, room temperature, 55 %.

Figure 2.52

Vinyl stannane **2.88** was treated with butyl lithium to affect tin-lithium exchange, aldehyde **2.22** was added drop-wise to the blood red solution and the reaction mixture was stirred at room temperature overnight to yield cyclic carbamate **2.60** in excellent yield (Figure 2.53).[58] Only a single diastereoisomer was detected by NMR which suggests that the modified addition remains mediated by chelation control. A crystal structure of a later intermediate confirmed the relative stereochemistry of the newly formed centre.



Reagents and conditions: (i) vinyl stannane **2.88**, THF, *n*-BuLi, -78 ºC, 10 minutes then aldehyde **2.22**, -78 ºC to rt, 16 hours; (ii) NaH, THF, BnBr, Δ, 6 hours, 78 % over two step.

Figure 2.53

This provided the key olefin in only two steps and almost 80 % overall yield from the quaternary aldehyde.

2.2.4 Introduction of nitrogen to olefin 2.60

2.2.4.1 Mitsunobu of 2.97

It was hoped that it would be possible to introduce the nitrogen functionality directly at the neopentylic position where elimination is mechanistically impossible. An intramolecular cyclisation reaction onto the activated primary alcohol may then out-compete the elimination reaction. In addition the vinyl furan should be less sterically congested allowing for increased reactivity at the neopentylic position. (Figure 2.54)

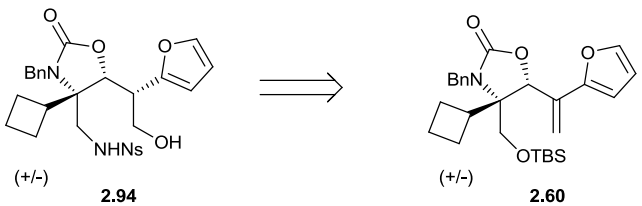
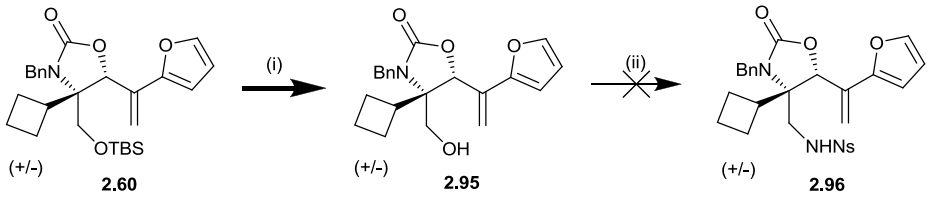


Figure 2.54

Silyl ether **2.60** was treated with tetra-butylammonium fluoride to liberate the neopentylic alcohol **2.95**. However, treatment with 2-nitrobenzenesulfonamide under Mitsunobu conditions did not result in nosylation of the alcohol, instead only starting material was recovered from the reaction mixture. (Figure 2.55) It was suspected that steric interactions were responsible for the lack of desired reactivity. Indeed it was shown subsequently that neopently alcohol itself fails to react under the same conditions.

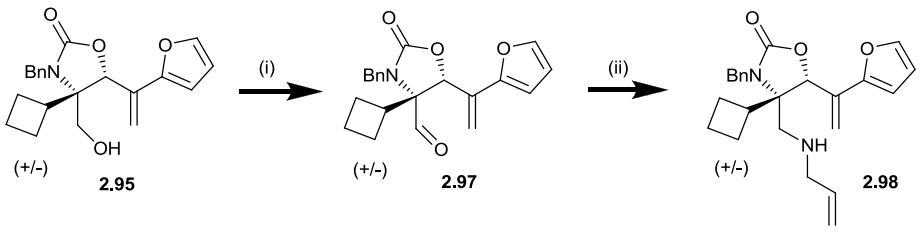


Reagents and conditions: (i) TBAF, THF, rt, 1 hour, 99 %; (ii) PPh_3, DIAD, NH_2Ns, THF, rt, 16 hours.

Figure 2.55

2.2.4.2 Reductive amination of 2.97

The required amine could also be introduced through a reductive amination reaction. The hindered primary alcohol **2.95** was treated with Dess-Martin periodinane in dichloromethane to afford the corresponding aldehyde in quantitative yield. The crude aldehyde was used without further purification. As such it was prepared as needed and used directly. The aldehyde was refluxed in dichloromethane with allylamine and oven dried magnesium sulphate to afford the corresponding imine. The imine was stable to TLC analysis and the progression of the reaction was monitored in this way. When all starting aldehyde had been consumed the reaction mixture was filtered through cotton wool and the solvent was removed under reduced pressure and the residue was immediately taken up in methanol. Addition of sodium cyanoborohydride and acetic acid afforded allylic amine **2.98** in good yield. (Figure 2.56)



Reagents and conditions: (i) Dess-Martin periodinane, DCM, 30 mins, 80 %; (ii) allylamine, $MgSO_4$, DCM, Δ then $NaCNBH_4$, AcOH, MeOH, 70 % yield.

Figure 2.56

An X-ray crystal structure of amine **2.98** confirmed the relative stereochemistry of the oxazolinone confirming that the earlier Grignard addition had proceeded with the expected chelation-control (Figure 2.57).

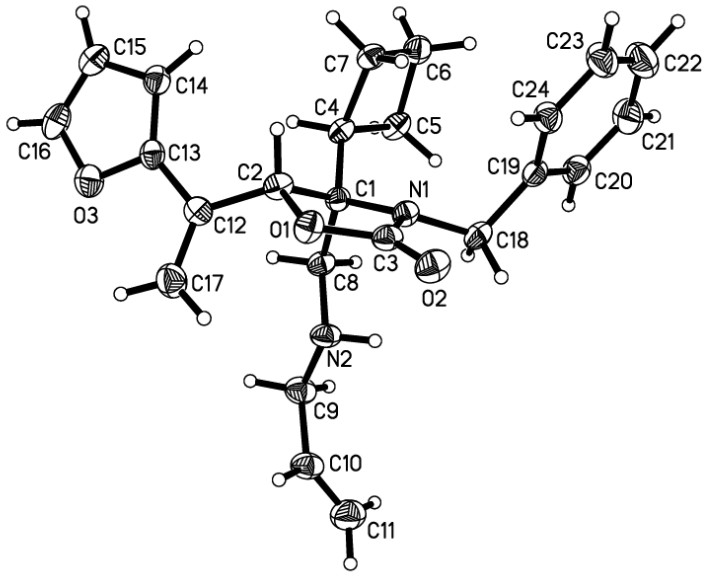


Figure 2.57

2.2.5 Deallylation of 2.98

Guibé has shown that *N,N'*-dimethylbarbituric acid is a powerful allyl group scavenger in the palladium catalysed deallylation of allylamines.[59] In Guibé's proposed catalytic cycle allylammonium species **2.104** is formed together with the carbanion **2.102** and **2.103** in an acid-base equilibrium between the starting amine and dimethylbarbituric acid, or its mono allyl derivative. The allylammonium species reacts with the palladium catalyst to give π-allyl palladium (II) complex **2.106** and the deallylated amine **2.107**. Carbanion **2.102** or **2.103** then traps the allyl group, to give allylated species **2.100** or **2.105** with simultaneous regeneration of the palladium(0) catalyst.(Figure 2.58)

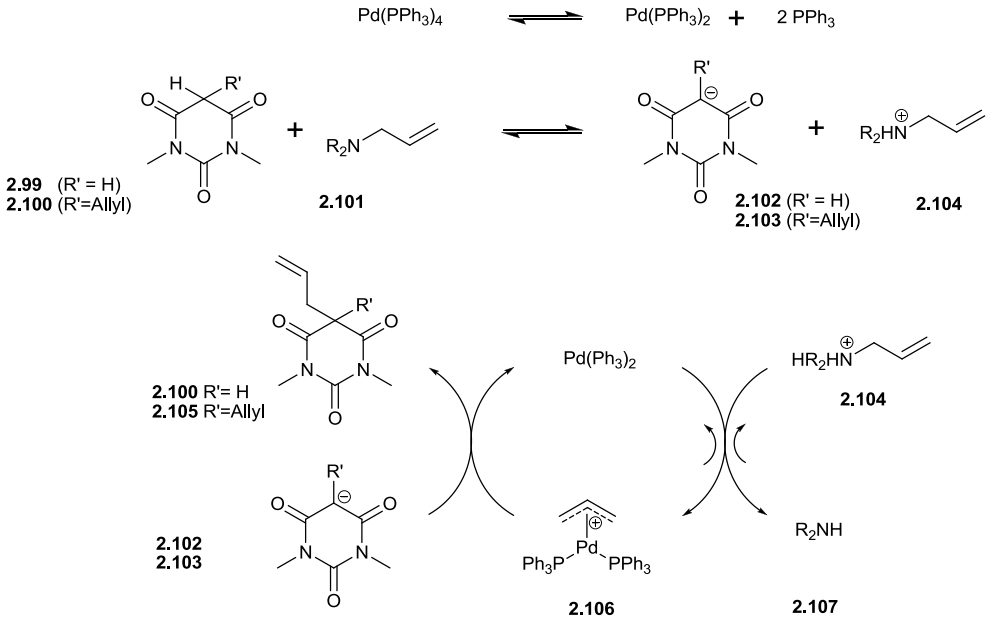
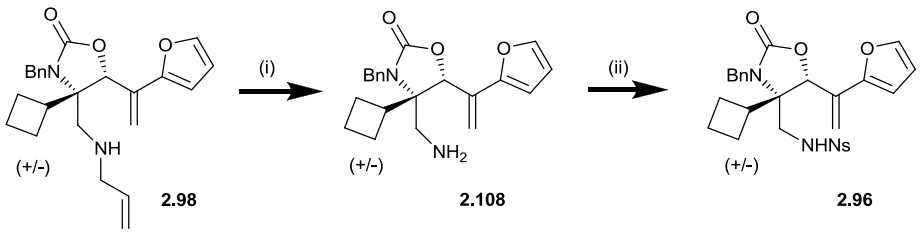


Figure 2.58

The allylamine **2.98** was treated with palladium tetrakistriphenylphosphine and dimethylbarbituric acid to afford the primary amine **2.108** in 65 % yield. The low yield is thought to be due to the partial solubility of the amine in water. The neopentylic amine was immediately treated with nosyl chloride in the presence of triethylamine to afford the required sulfonamide **2.96** in excellent yield. (Figure 2.59)

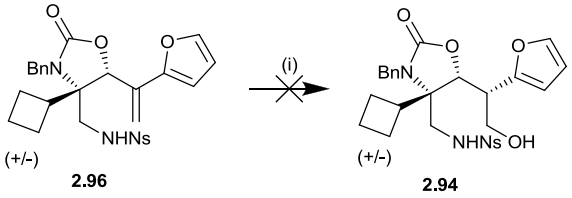


Reagents and conditions: *N-N'*-dimethylbarbituric acid, DCM, $Pd(PPh_3)_4$, 35 °C, 65 %; (ii) 2-NsCl, NEt_3, DCM, rt, 2 hours, 87 %.

Figure 2.59

2.2.6 Hydroboration attempt of 2.96

The next synthetic challenge was the introduction of oxygen to the olefin to afford an alcohol. Although it was possible to form two diastereoisomers in this step, related olefin **2.31** has previously been shown to undergo smooth hydroboration affording predominantly the required alcohol.[49] Hydroboration attempts on the sulfonamide led to complex mixtures, with complete consumption of starting material. The required alcohol **2.94** was not isolated. (Figure 2.60) It is possible that the sulfonamide is not compatible with the oxidising conditions of the hydroboration workup.

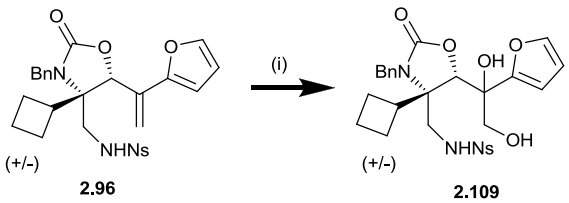


Reagents and conditions: BH_3, THF, 0 °C, 3 hours, then NaOH, H_2O_2.

Figure 2.60

2.2.7 Dihydroxylation of 2.96

Fortunately, when subjected to Upjohn dihydroxylation conditions the olefin was smoothly transformed to the corresponding diol.[60,61] Only one diastereoisomer was visible by NMR. (Figure 2.61)

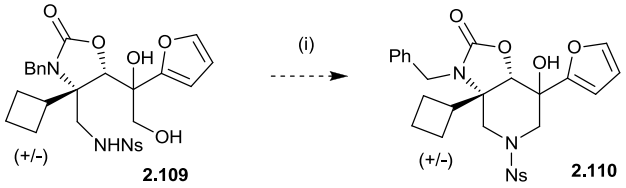


Reagents and conditions: (i) OsO_4, NMO, THF, H_2O, 16 hours, rt, 64 %.

Figure 2.61

2.2.8 Cyclisation Studies

It was expected that under Fukuyama modified Mitsunobu conditions[26,27,28] the sulfonamide would cyclise onto the activated primary alcohol. The hope was that the intramolecular cyclisation would occur more rapidly than the elimination reaction. When sulfonamide **2.109** was treated with triphenylphosphine and diisopropyl azodicarboxylate in tetrahydrofuran a single product was obtained in good yield. (Figure 2.62)



Reagents and conditions: (i) PPh_3, DIAD, THF, rt, 16 hours, 73 %.

Figure 2.62

NMR analysis of the single product, however was not consistent with the expected product. A portion of the ^1H spectrum is shown below. In this region of the spectrum one would expect to see three signals corresponding to CH_2 groups in the molecule; two on the piperidine ring and one on the benzyl group. These would be expected to appear as AB systems. However, the NMR spectrum obtained contains only two straightforward AB systems. One appearing at 3.65 (1H) & 3.85 (1H) ppm and the other at 4.15 (1H) & 4.45 (1H) ppm . The remaining signal between 4.3 and 4.45 (2H) appears as an ABX system. Furthermore a 1H triplet can be seen at 2.65 ppm. (Figure 2.63) These data are incompatible with the isolated product having the structure of required sulphonamide **2.110**.

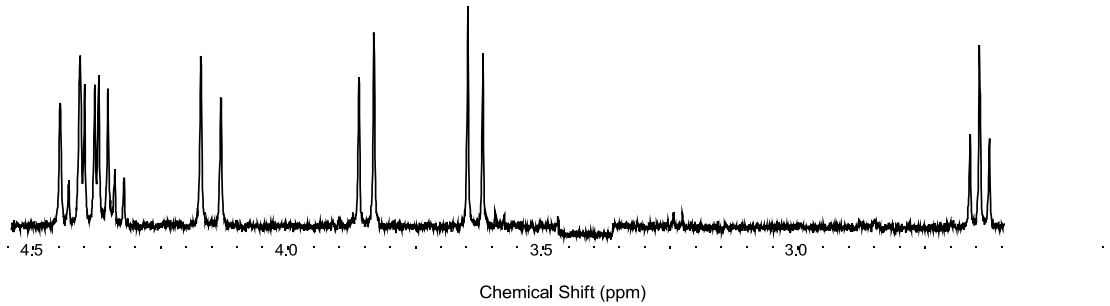


Figure 2.63

To facilitate the structural elucidation of the Mitsunobu product it was decided to perform a D_2O shake and obtain a further proton NMR. The relevant portion of this second spectrum is shown in Figure 2.64. The loss of the one proton triplet signal as well as the simplification of the ABX system into a standard AB system (4.35 & 4.4 PPM) suggests that the triplet is derived from an exchangeable proton adjacent to a CH_2 group.

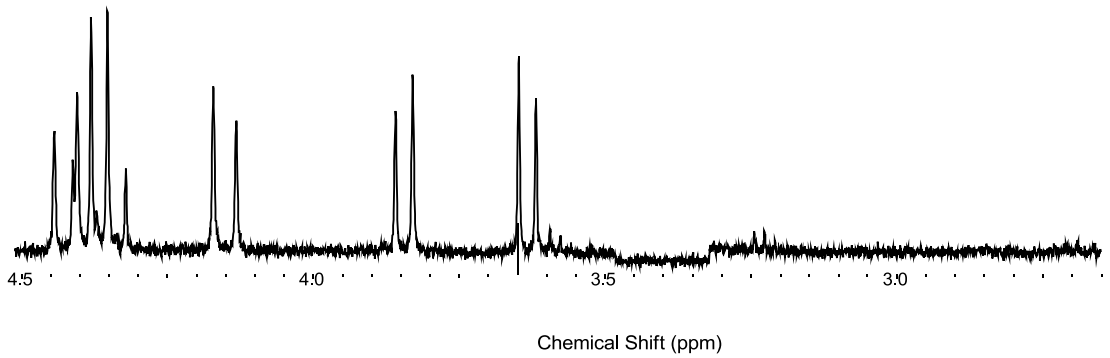
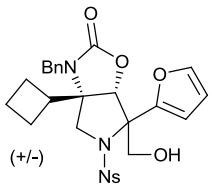


Figure 2.64

In light of this data, combined with supporting evidence from IR spectroscopy and mass spectrometry the structure of the Mitsunobu product was assigned as primary alcohol **2.111**. (Figure 2.65) The alcohol appeared to be a single diastereoisomer from the NMR data however due to a lack of material no attempts were made to identify which diastereoisomer it was.



2.111

Figure 2.65

Upon treatment with triphenylphosphine and diisopropyl azodicarboxylate primary alcohols are initially activated as the phosphonium salt. The driving force of the reaction is the thermodynamically favoured formation of the strong phosphorus oxygen double bond. Under the reaction conditions it believed that the tertiary alcohol reacts to form the epoxide **2.113** rather than the sulfonamide. Once the epoxide is formed it is highly reactive towards nucleophilic attack at the more hindered position where the carbonium ion is efficiently stabilised by the heterocyclic ring. (Figure 2.66)

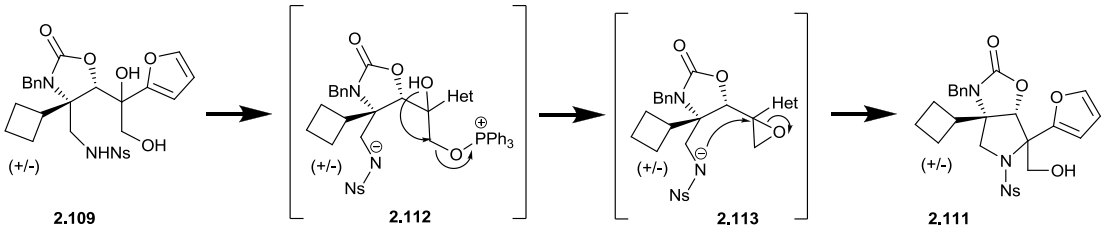
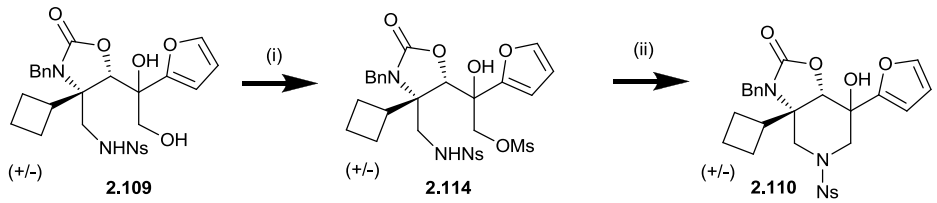


Figure 2.66

It was hoped that if the primary alcohol was activated less strongly, the cyclisation may procede to give the thermodynamically favoured cyclic sulfonamide. It was decided to mesylate the primary alcohol,[62] and attempt the *in situ* cyclisation by gently warming with potassium carbonate in dimethylformamide.[63] Under these reaction conditions the piperidine derivative was isolated in good yield. (Figure 2.67). Only one diastereoisomer was detected by NMR, however the relative stereochemistry was not determined at this stage.



Reagents and conditions: (i) MsCl, NEt_3, DCM, 0 °C, 2 hours (ii) DMF, K_2CO_3, 45 °C, 1.5 hours, 42 % over two steps.

Figure 2.67

2.2.9 Reduction of Benzylic alcohol

The final major transformation was the reduction of the tertiary alcohol. Benzylic tertiary alcohols are commonly reduced to the corresponding hydrogen bearing centre upon treatment with triethylsilane and BF_3 etherate.

The reaction typically proceeds under S_N1 conditions, and it was expected that upon deoxygenation there would be a very large preference for the bulky triethylsilane to deliver a hydride from the less crowded exo face, giving the required stereochemical outcome in the product.

During the total synthesis of methoxy ether **2.11**, diastereoisomers **2.115** and **2.116** were isolated. Comparison of the *J* value between the highlighted protons illustrates the small coupling constant in the required compound **2.115** and the larger coupling constant in the epimer **2.116**. (Figure 2.68)

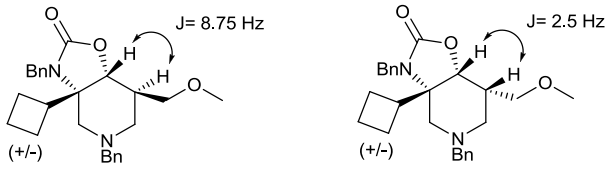
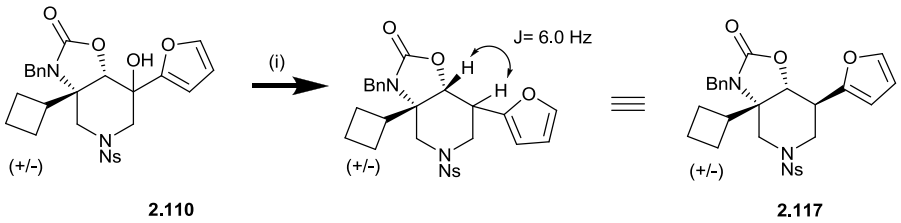


Figure 2.68

When tertiary alcohol **2.110** was treated at 0 ºC with triethylsilane and boron trifluoride etherate the des-hydroxy compound was produced in acceptable yield. Only one diastereoisomer was detected by NMR. However the coupling constant was significantly larger than would be expected for the required *syn* compound, indeed it was more consistent with what would be expected for the opposite diastereoisomer. As such the structure of **2.117** was tentatively assigned to be the wrong diastereoisomer and efforts focused on alternative routes towards the required diastereoisomer. (Figure 2.69)

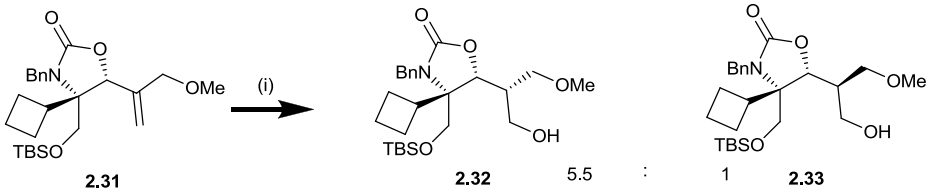


Reagents and conditions: (i) $HSiEt_3$, DCM, $BF_3.OEt_2$, 0 ºC to rt, 2 hours, 32 %.

Figure 2.69

2.2.10 Hydroboration of olefin 2.60

It had previously been shown that olefin **2.31** undergoes smooth hydroboration/ oxidation to give a 5.5:1 diasteromeric mixture of alcohols from which the major compound was shown to be the required epimer. (Figure 2.70)

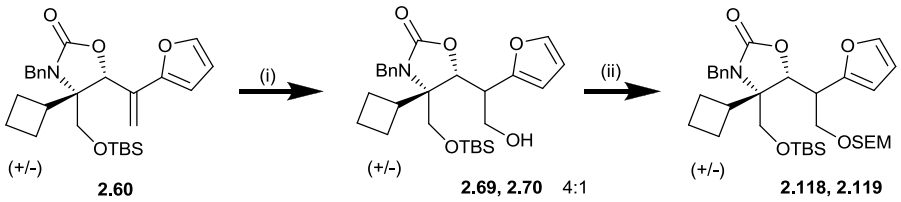


Reagents and conditions: (i) BH_3.THF, THF, 0 ºC then EtOH, NaOAc, H_2O_2, 95 %.

Figure 2.70

However on the furan bearing system these intermediates were shown to be prone to elimination at the activated primary alcohol stage. Nonetheless, hydroboration of the olefin at this stage would give the required alcohol functionality, and set the required stereochemistry. For this reason it was decided to revisit the hydroboration products as a route towards piperidine **2.58**.

When treated with borane tetrahydrofuran complex followed by oxidative workup with basic hydrogen peroxide in water, the alcohols **2.69** and **2.70** were obtained as an inseparable 4:1 mixture in fair yield. The mixture of alcohols was directly treated with 2-(trimethylsilyl)ethoxymethyl chloride to give the still inseparable corresponding silyl ethers as a viscous yellow oil. (Figure 2.71)



Reagents and conditions: (i) BH_3.THF, THF 0 °C to rt, then NaOH, H_2O_2, H_2O, 0 °C to rt 65 %; (ii) SEMCl, DMAP, TBAI, *i*-$PrNEt_2$, DCM, rt, 16 hours, 99 %; 4:1 diastereomers.

Figure 2.71

Treatment of the mixture of **2.118** and **2.119** with TBAF afforded selective de-silation to liberate the neopentylic alcohols which became separable at this

point. The major epimer **2.120** was isolated and used from this point on although the stereochemistry remained unconfirmed at this point. (Figure 2.72)

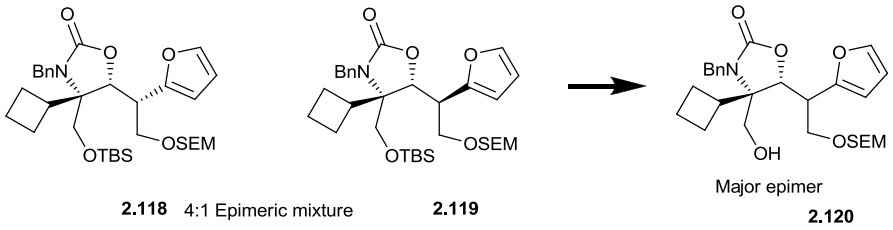
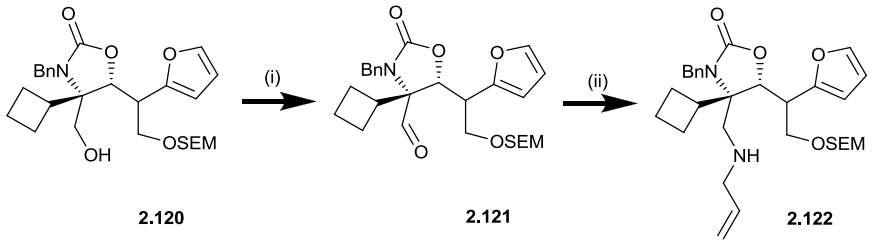


Figure 2.72

The alcohol was treated with Dess-Martin periodinane and the crude aldehyde was immediately subjected to reductive amination conditions with allylamine. It was found that during a one pot reductive amination reaction the aldehyde was reduced to the alcohol even using the mild reducing agent sodium cyanoborohydride. This can be explained by the slow rate of formation of the imine due to the relatively hindered nature of the aldehyde.

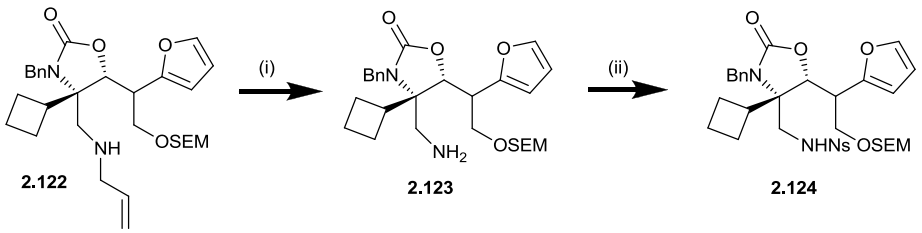
However the imine was successfully pre-formed by refluxing the aldehyde with allylamine and anhydrous magnesium sulfate in dichloromethane. The subsequent addition of cyanoborohydride produced the amine **2.22** in good yield. (Figure 2.73)



Reagents and conditions: (i) DMP, DCM, rt, 1 hour; (ii) allylamine, DCM, Δ, then $NaCNBH_3$, MeOH, AcOH, 73 % overall.

Figure 2.73

The allylamine was shown to be amenable to deallylation upon treatment with *N,N'*-dimethylbarbituric acid under palladium catalysis.[59] The crude primary amine **2.123** was highly reactive towards nosyl chloride, and the required sulfonamide **2.124** was formed. (Figure 2.74)

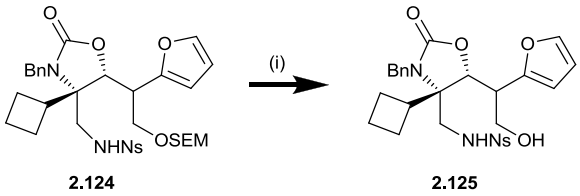


Reagents and conditions: $Pd(PPh_3)_4$, *N,N'*-dimethylbarbituric acid, DCM, 35 ºC, 90 %; (ii) nosyl chloride, NEt_3, DCM, 60 %.

Figure 2.74

Several methods exist for the removal of SEM groups. Due to the 'robust' nature of the SEM ether common methods of removal tend to be rather forcing. TBAF in HMPA,[64] TBAF in refluxing THF,[65] and HCl in dioxane[66] are commonly used methods. We had success following the procedure established by Hoffmann in which SEM ethers are removed mildly upon treatment with magnesium bromide in diethyl ether using nitromethane as a co-solvent, to give the corresponding alcohols.[67]

When silyl ether **2.124** was treated at room temperature with magnesium bromide and nitromethane in diethyl ether the primary alcohol **2.125** was isolated in good yield. (Figure 2.75)

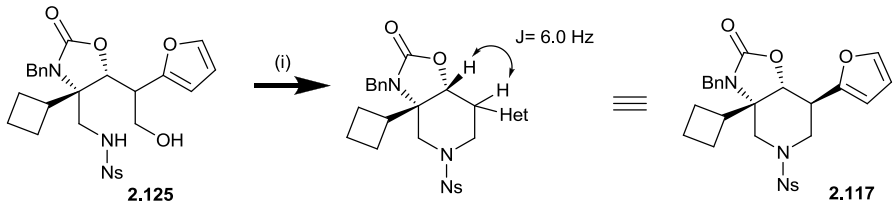


Reagents and conditions: $MgBr_2$, Et_2O, $MeNO_2$, 2 hours, rt, 77 %.

Figure 2.75

The penultimate step was the formation of the six membered piperidine ring. It was expected that given the absence of nucleophilic neighbouring groups a sulfonamide-based Mitsunobu reaction would give access to the piperidine.[26,68,69]

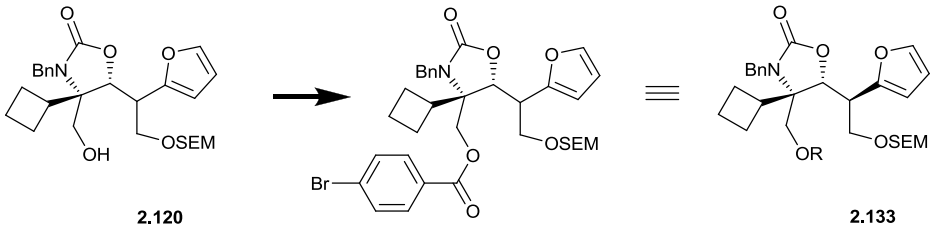
When alcohol **2.125** was treated with triphenylphosphine and diisopropyl azodicarboxylate in tetrahydrofuran a single product was formed and isolated in good yield. Disappointingly however NMR studies on the product showed a coupling constant of 6 Hz for the proton at the foot of the furan. All further data obtained was consistent with the product being identical to known piperidine **2.117**. (Figure 2.76)



Reagents and conditions: PPh_3, DIAD, THF, rt, 2 hours, 73 %.

Figure 2.76

To conclusively establish stereochemistry of the piperidine **2.117** the para-brombenzoate derivative of alcohol **2.120** was prepared upon treatment of the neopentylic alcohol **2.120** with *p*-bromobenzoyl chloride in dichloromethane in the presence of triethylamine(Figure 2.77). As expected this material was highly crystalline. A single high purity crystal was grown and subjected to X-ray analysis; which confirmed that the alcohol **2.120** was of the opposite configuration to that required to form the desired piperidine, and as such that piperidine **2.117** was correctly assigned. (Figure 2.78)



Reagents and conditions: *p*-bromobenzoyl chloride, NEt_3, DMAP, DCM, 80 %

Figure 2.77

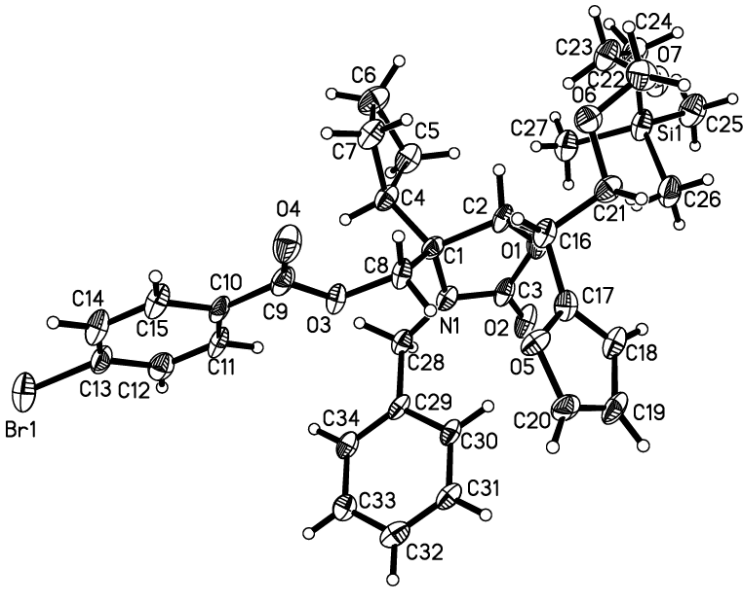
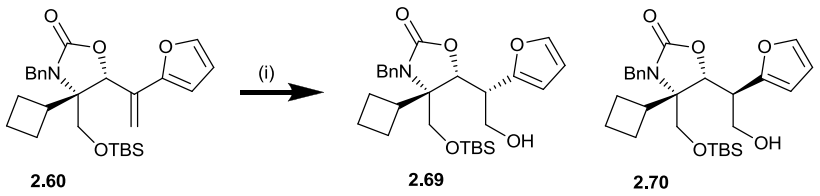


Figure 2.78

This was an interesting result as it means that the selectivity of the hydroboration is inverted upon replacement of the CH_2OMe group for a 2-furanyl group. (Figure 2.85)

2.2.11 Optimised hydroboration

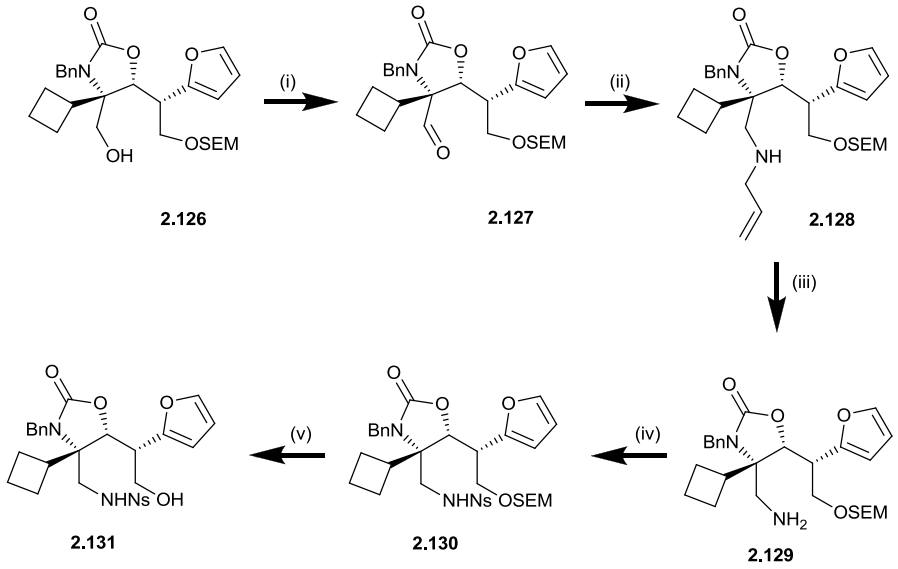
It was expected that the selectivity of the hydroboration step could be optimised to give increased amounts of the desired epimer. We were pleased to discover that upon treatment with borane in tetrahydrofuran at 40 ºC the diastereoselectivity of the hydroboration could be reduced to give almost equal amounts of alcohols **2.69** and **2.70**. Although the overall yield of the reaction was slightly diminished at the higher temperature, it still gave access to larger amounts of the required alcohol that was otherwise possible and it was considered an acceptable result. (Figure 2.79)



Reagents and conditions: (i) BH_3.THF, THF 40 ºC, then NaOH, H_2O_2, H_2O, 0 °C to rt 65 % 1:1 diastereomers.

Figure 2.79

With sufficient material now available the previously neglected neopentylic alcohol **2.126** was subjected to Dess-Martin mediated oxidation. The aldehyde **2.127** underwent reductive amination with allylamine and palladium catalysed deallylation to give the primary amine **2.129**. The amine was treated with 2-nitrobenzenesulfonyl chloride to afford the sulfonamide. Finaly the SEM group was removed upon treatment with magnesium bromide in diethyl ether and nitromethane to give what was expected to be the correct precursor to piperidine **2.58**. (Figure 2.80)

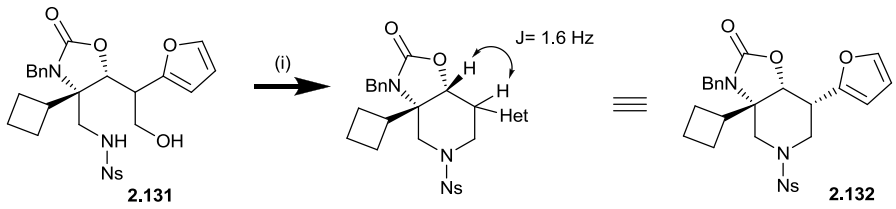


Reagents and conditions: (i) DMP, DCM, rt, 1 hour (ii) allylamine, DCM, Δ, then $NaCNBH_3$, 70 % overall; (iii) $Pd(PPh_3)_4$, *N,N'*-dimethylbarbituric acid, DCM, 35 ºC, 79 %; (iv) nosyl chloride, NEt_3, DCM, 70 %; v) $MgBr_2$, Et_2O, $MeNO_2$, 90 %.

Figure 2.80

When subjected to the Fukuyama-Mitsunobu conditions the alcohol **2.131** underwent smooth cyclisation to give a single compound. NMR analysis showed

that the coupling between the highlighted protons was found to be 1.6 Hz which is significantly smaller than the 6 Hz observed for the wrong diastereoisomer and is consistent with the expected *cis* axial/equatorial relationships between the protons at C7 and C7a. (Figure 2.81)



Reagents and conditions: PPh_3, DIAD, THF, rt, 2 hours, 80 %.

Figure 2.81

Furthermore, piperidine **2.132** was found to be a solid and as such a single crystal was grown and subjected to X-ray analysis. This confirmed that **2.132** was indeed the required configuration. (Figure 2.82)

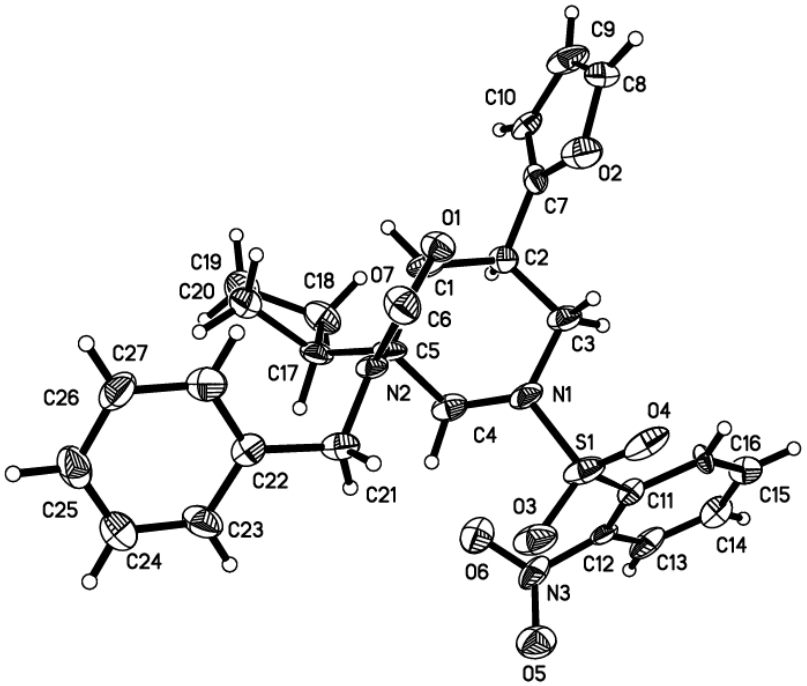
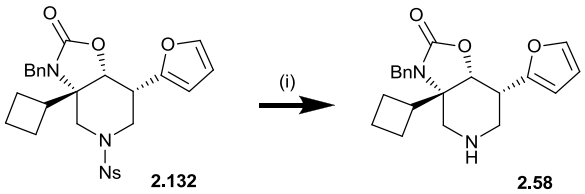


Figure 1.28

All that remained was the removal of the sulfonamide group. Thus, treatment with potassium carbonate and thiophenol in acetonitrile afforded clean deprotection to give the required piperidine in good yield. (Figure 2.83)



Reagents and conditions: PhSH, K_2CO_3, MeCN, rt, 86 %

Figure 2.83

2.3 Conclusions and future work

The total synthesis of a novel M_1 agonist has been discussed in this thesis. Similar compounds have been prepared by Muscagen in the past, however this was the first time an aromatic heterocycle was joined directly to the piperidine ring. This greatly enhanced the acidity of the adjacent proton and meant a new synthetic approach was necessary.

The key intermediate olefin **2.60** was prepared expediently upon the addition of vinyl lithium **2.87** to the aldehyde **2.22**, followed by benzyl protection. The aldehyde had previously been prepared from cyclobutanecarboxylic acid. (Figure 2.84)

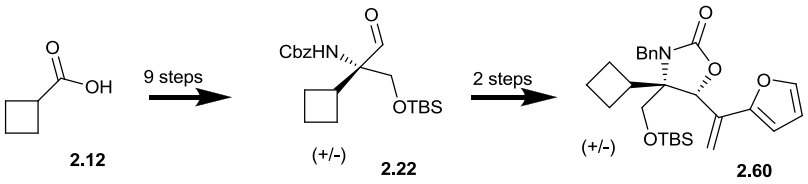
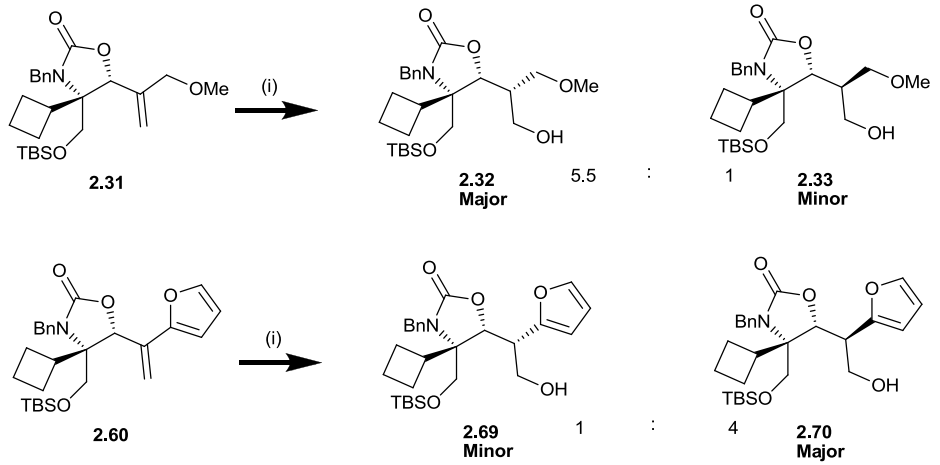


Figure 2.84

The stereochemical preference of the hydroboration was shown to be inverted upon replacement of the methoxy ether with a 2-furanyl moiety. (Figure 2.85) However, it was shown that by performing the hydroboration at elevated temperature the selectivity of the reaction could be optimised giving access to either diastereoisomer at this position.



Reagents and conditions: (i) BH_3.THF, THF, 0 °C then oxidation

Figure 2.85

The amine was introduced *via* a reductive amination reaction at the neopentylic centre. The allyl group was then removed and the amine was protected as the 2-nitrobenzene sulfonamide. The piperidine ring was then furnished using an intramolecular Fukuyama-Mitsunobu reaction. (Figure 2.86)

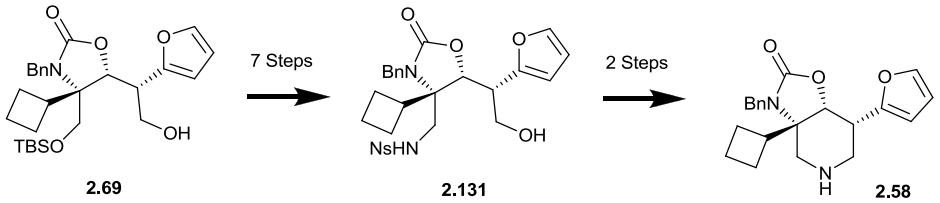


Figure 2.86

2.3.1 Future work

One possible avenue for future studies could be to prepare a small library of compounds with varying heterocyclic groups in place of the furan and compare their biological activity with that predicted by the Muscagen computer model. In the longer term, it will also become important to establish a tin free route to the required vinyl lithium species. Possibly *via* the environmentally benign tosyl hydrazones, as in the Shapiro reaction. (Figure 2.87)

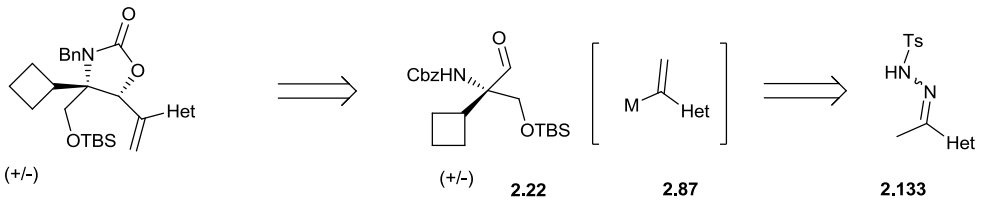


Figure 2.87

Chapter 3: Experimental procedures

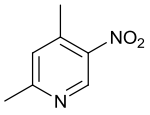
3.1 General Experimental:

Flash column chromatography was performed using Merck silica (60H; 40-60 μ, 230-240 mesh). Light petroleum (petrol) was redistilled before use and refers to the fraction boiling between 40 and 60 ºC. Tetrahydrofuran was dried over sodium-benzophenone and was distilled prior to use. Dichloromethane was dried over calcium hydride and was distilled before use. Ether refers to diethyl ether. Reaction under non aqueous conditions were carried out under an atmosphere of nitrogen.

Electron impact (EI) or chemical ionisation using ammonia (CI) mass spectra were recorded using a Fisons VG Trio 200 spectrometer and high resolution mass spectra on a Kratos Concept IS spectrometer. Infra-red spectra were measured using a Genesis FTIR spectrometer on sodium chloride plates, either neat, or as evaporated films. Nuclear magnetic resonance spectra were recorded in deuterated chloroform unless otherwise stated on either a Varian Unity 500 (500 MHz), Varian INOVA 300 (300 MHz). Coupling constants (*J*) are given in Hertz (Hz) and chemical shifts are relative to tetramethylsilane.

3.2 Approaches towards A3 agonists

2,4-Dimethyl-5-nitropyridine (1.08)[8]



2,4-Lutidine (25 g, 233.3 mmol) was added drop-wise to fuming H_2SO_4.20 % SO_3 (250g) at 0 °C. KNO_3 (42.5 g, 420 mmol) was added in portions with stirring, using an external ice bath to maintain the temperature at 0 °C. The reaction mixture was slowly warmed to 100 °C for 8 h and further heated to 120 °C for 8 h. The resultant slurry was poured slowly onto ice (510 g) before being neutralised (K_2CO_3) and filtered to remove the insoluble precipitate. The filtrate was extracted with dichloromethane (3 X 200 mL), washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was subjected to vacuum distillation (79-81 ºC 3.73 mm Hg [lit. 44 ºC 0.17 mm Hg])[8] to give 5-nitro 2,4-lutidine as a mobile, pale yellow oil (14.8 g, 21 %) R_f 0.60 (Et_2O);

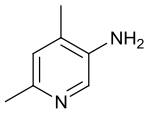
ν_{max}/cm^{-1} 2930, 1610, 1557, 1519, 1346, 838;

δ_H NMR 300 MHz 2.62 (3H, s, 4-C*H*$_3$); 2.63 (3H, s, 2-C*H*$_3$), 7.16 (1H, s, 3-*H*), 9.09 (1H, s, 6-*H*);

δ_C (75 MHz, $CDCl_3$) 20.5, 24.5, 126.9, 143.6, 145.9, 150.3, 163.5;

m/z (ESI) 153 ([M+H]$^+$, 100%).

4,6-Dimethylpyridin-3-amine (1.09)[8]



2,4-Dimethyl-5-nitropyridine (0.5 g, 3.28 mmol) was added to a stirred suspension of 10 % Pd/C (70 mg, 0.066 mmol) in MeOH (53 mL). The reaction mixture was stirred under an atmosphere of hydrogen for 16 h before filtration

through Celite. The solvent was removed under reduced pressure to yield a cream coloured waxy solid (0.43 g, 100%) which was sufficiently pure for use without further purification. R_f 0.1 (Et_2O) Blue under UV, M.p. 62-64 °C (lit. m.p. 66-68 °C);[8]

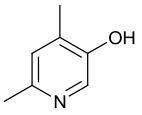
ν_{max}/cm^{-1} 3375, 3338, 3209, 1651, 1612, 1505, 1448, 1242, 668;

δ_H NMR 300 MHz 2.07 (3H, s, 4-C*H*$_3$); 2.33 (3H, s, 2-C*H*$_3$), 3.41 (2H, br s, N*H*$_2$), 6.76 (1H, s, 3-*H*), 7.85 (1H, s, 6-*H*);

δ_C NMR 75 MHz 16.5, 22.8, 124.3, 131.4, 135.6, 138.7, 147.8;

m/z (ESI) 123 ([M+H]$^+$, 100%).

4,6-Dimethylpyridin-3-ol (1.10)[8]



4,6-Dimethylpyridin-3-amine (3.0 g, 8.19 mmol) was dissolved in 4.8 % aq H_2SO_4 (48 mL) at 0 °C. To this was added drop wise a solution of $NaNO_2$ (1.86 g, 27.0 mmol) in water (17.2 ml). The reaction mixture was stirred at 0 °C for 20 mins before being placed in a preheated oil bath (130 °C) until N_2 evolution ceased and before the reaction mixture began to boil. The dark red reaction mixture was immediately poured onto ice (110 g) and neutralized (K_2CO_3). The aqueous residue was extracted with dichloromethane (5 x 30 mL) and the combined organics were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by silica-gel chromatography (100 % Et_2O) to give a white solid (1.16 g, 39 %). R_f 0.61 (10% MeOH/Et_2O), M.p. 146-148 °C (lit. m.p. 144-146 °C);[8]

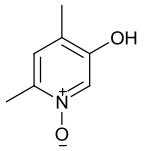
ν_{max}/cm^{-1} 2922, 2618, 2554, 1612, 1504, 1462, 1423, 1295, 1219, 946;

δ_H NMR 300 MHz 2.32 (3H, s, 4-C*H*$_3$), 2.49 (3H, s, 2-C*H*$_3$), 7.01 (1H, s, 3-*H*), 8.11 (1H, s, 6-*H*);

δ_C NMR 75 MHz 16.1, 22.1, 126.5, 134.0, 137.2, 147.8, 152.4;

m/z (ESI) 124 ([M+H]$^+$, 100%).

5-Hydroxy-2,4-dimethylpyridine 1-oxide (1.11)[13]



Commercially available 77 % pure *m*-CPBA (4.0 g, 18 mmol) was added to a stirred solution of 4,6-dimethylpyridin-3-ol (2.0 g, 16.24 mmol) in dichloromethane (30 mL). The reaction mixture was stirred at room temperature for 16 hours and then the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (10 % MeOH/ Et_2O) to afford product as a pale yellow solid (1.99 g, 88 %). R_f 0.55 (10% MeOH/Et_2O). M.p. 227-229 °C (lit m.p. 229 °C);[13]

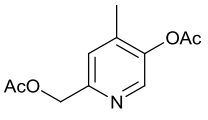
ν_{max}/cm^{-1} 3390, 2161, 2921, 1514, 1491, 1434, 1310, 1189, 1105, 879, 844;

δ_H (300 MHz, CD_3OD)2.25 (3H, s, 4-C*H*$_3$), 2.43 (3H, s, 2-C*H*$_3$), 7.26 (1H, s, 3-*H*), 7.89 (1H, s, 6-*H*);

δ_C (75 MHz, CD_3OD) 13.9, 15.4, 126.1, 127.7, 131.1, 140.2, 153.0;

m/z (ESI+) 418 ([3M+H]$^+$, 8%), 279 ([2M+H]$^+$, 22%), 162 ([M+Na]$^+$, 25%), 140 ([M+H]$^+$, 100%).

(5-Acetoxy-4-methylpyridin-2-yl)methyl acetate (1.12)[7]

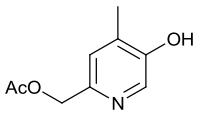


5-Hydroxy-2,4-dimethylpyridine-1-oxide (1.98 g, 14.23 mmol) was refluxed in acetic anhydride (35.6 ml) for 2.5 hours. The black reaction mixture was filtered through Celite and the excess acetic anhydride removed by vacuum distillation. Purification was by silica-gel chromatography (25 → 60 % Et_2O/ petrol) afforded product as a pale yellow oil (2.46 g, 77 %). R_f 0.11 (50% Et_2O/Petrol);

ν_{max}/cm^{-1} 1760, 1747, 1609, 1486, 1440, 1371, 1268, 1232, 1218, 1194, 1135, 1048, 1013, 892;

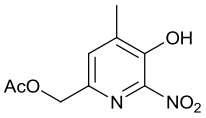
δ_H (300 MHz, $CDCl_3$) 2.16 (3H, s, CH_2OCOCH_3), 2.23 (3H, s, $COCH_3$), 2.36 (3H, s, 4-CH_3), 5.18 (2H, s, 2-CH_2), 7.16 (1H, s, 3-*H*), 8.28 (1H, s, 6-*H*);
δ_C (75 MHz, $CDCl_3$) 16.2, 20.9, 21.2, 66.6, 124.6, 140.5, 143.5, 146.2, 153.2, 169.0, 170.9;
m/z (ESI+) 224 ($[M+H]^+$, 100%).

(5-Hydroxy-4-methylpyridin-2-yl)methyl acetate (1.13)[7]



To a stirred solution of bis-acetate **1.12** (2.46 g, 11.0 mmol) in dichloromethane (31.0 mL) was added pyrolidine (0.92 mL, 11.0 mmol) at room temperature. The reaction mixture was stirred for 16 hours and was then concentrated under reduced pressure. The residue was purified by silica gel chromatography (50→100% Et_2O/ Petrol) to give a pale yellow oil (1.16 g, 71 %) R_f 0.23 (Et_2O);
ν_{max}/cm^{-1} 3028, 2959, 1746, 1611, 1505, 1455, 1378, 1362, 1293, 1229, 1032, 879;
δ_H (300 MHz, $CDCl_3$) 2.10 (3H, s, $OCOCH_3$), 2.34 (3H, s, 4-CH_3), 5.16 (2H, s, 2-CH_2), 7.25 (1H, s, 3-*H*), 8.16 (1H, s, 6-*H*);
δ_C (75 MHz, $CDCl_3$) 16.2, 21.1, 65.9, 126.4, 134.7, 137.2, 145.4, 154.0, 171.1;
m/z (ESI+) 204 ($[M+Na]^+$, 25%), 182 ($[M+H]^+$, 100%);
HRMS (ESI+) found 204.0627, $C_9H_{11}NO_3Na$ ($[M+Na]^+$) requires 204.0631 (-1.8 ppm).

(5-Hydroxy-4-methyl-6-nitropyridin-2-yl)methyl acetate (1.14)[7]



To a stirred solution of hydroxypyridine **1.13** (480 mg, 2.6 mmol) and $NaHCO_3$ (356 mg, 4.2 mmol) in MeCN (30.2 mL) was added ceric ammonium nitrate (1.6 g, 2.9 mmol) in one portion. The orange reaction mixture was stirred at reflux for 5 hours over which time the reaction mixture assumed a pale yellow coloration. The mixture was filtered through Celite and the clear yellow filtrate was evaporated to dryness. The oily residue was taken up in dichloromethane and extracted between water (50 ml) and dichloromethane (4 x 50 ml). The combined organics were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by silica gel chromatography (10→20 % Et_2O/ Petrol) yielded a yellow solid (265 mg, 45 %); R_f 0.65 (Et_2O); M.p. 84-87.0 °C (Lit. 84-87 °C)[7]

ν_{max}/cm^{-1} 3297, 2962, 1744, 1573, 1543, 1482, 1440, 1410, 1380, 1356, 1322, 1229, 1049, 917, 773 ;

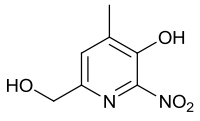
δ_H (300 MHz, $CDCl_3$) 2.16 (3H, s, OCOC*H*$_3$), 2.44 (3H, s, 4-C*H*$_3$), 5.16 (2H, s, 2-C*H*$_2$), 7.55 (1H, s, 3-*H*), 10.19 (1H, bs, 5-O*H*);

δ_C (75 MHz, $CDCl_3$) 16.2, 21.1, 65.9, 131.6, 141.2, 142.6, 146.3, 149.6, 170.8

m/z (ESI+) 227 ([M+H]$^+$, 100 %), 244 ([M+NH_4]$^+$, 95 %);

HRMS (ESI+) found 249.0489, $C_9H_{10}N_2O_5Na$ ([M+Na]$^+$) requires 249.0482 (+2.8 ppm).

6-(Hydroxymethyl)-4-methyl-2-nitropyridin-3-ol (1.39)[7]



To a stirred solution of acetate **1.14** (860 mg, 3.8 mmol) in methanol (3.8 mL) was added 2 M NaOH (3.82 mL, 7.6 mmol) at room temperature. The reaction

mixture was stirred at room temperature for three hours was then evaporated to dryness under reduced pressure. The residue was taken up in water and 2M hydrochloric acid was added until the solution was pH 5. This was then extracted with dichloromethane (8 x 50 ml). The combined organics were dried over Na_2SO_4 and the solvent was removed under reduced pressure to give product as a pale oil (706 mg, 99%). R_f 0.52 (Et_2O);

ν_{max}/cm^{-1} 3321, 2473, 1535, 1478, 1362, 1307, 1257, 1200, 1089;

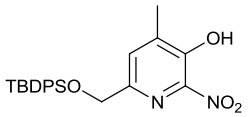
δ_H (300 MHz, CD_3OD) 2.45 (1H, s, 4-C*H*$_3$), 4.63 (2H, s, 6-C*H*$_2$), 7.74 (1H, s, 5-*H*);

δ_C (75 MHz, CD_3OD) 15.0, 63.6, 129.7, 142.5, 147.8, 151.3;

m/z (ESI+) 207 ([M+Na]$^+$, 100%), 185 ([M+H]$^+$, 32%);

HRMS (ESI+) found 207.0380, $C_7H_8N_2O_4Na$ ([M+Na]$^+$) requires 207.0376 (+1.8 ppm).

6-(*tert*-Butyldiphenylsilyloxymethyl)-4-methyl-2-nitropyridin-3-ol (1.16)[7]



To a stirred solution of nitro pyridine **1.39** (113 mg, 0.613 mmol) and imidazole (210 mg, 3.07 mmol) in DMF (2.4 mL) was added TBDPSCl (156 mg, 0.613 mmol). The reaction mixture was stirred at room temperature for 16 hours before being extracted between water (20 mL) and dichloromethane (4 x 20 mL), the combined organics were dried over Na_2SO_4 and solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (10 % Et_2O/Petrol) to give yellow solid (230 mg, 89 %). R_f 0.63 (20 % Et_2O/Petrol); M.p. 84-86 °C;

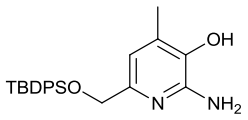
ν_{max}/cm^{-1} 3434, 2930, 2857, 1651, 1538, 1236, 1113, 823, 701 ;

δ_H (300 MHz, $CDCl_3$) 1.18 (9H, s, SiC(C*H*$_3$)$_3$); 2.49 (3H, s, 4-C*H*$_3$), 4.85 (2H, s, 6-C*H*$_2$), 7.51-7.39 (6H, m, 6 x SiPh*H*), 7.72-7.68 (4H, m, 4 x SiPh*H*), 7.83 (1H, s, 5-*H*), 10.47 (1H, s, 3-O*H*),

δ_C (75 MHz, $CDCl_3$) 16.5, 19.6, 27.2, 66.1, 128.1, 130.0, 130.2, 133.0, 135.8, 142.1, 149.0, 151.5;

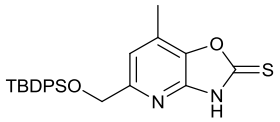
m/z (ESI+) 867 ([2M+Na]$^+$, 57%), 445 ([M+Na]$^+$, 75%), 423 ([M+H]$^+$, 100%);
HRMS (ESI+) found 423.1746, $C_{23}H_{27}N_2O_4Si$ ([M+H]$^+$) requires 423.1735 (+2.7 ppm).

2-Amino-6-(*tert*-butyldiphenylsilyloxymethyl)-4-methylpyridin-3-ol (1.17)[7]



To a stirred suspension of 10 % Pd/C (5.0 mg) in EtOAc (0.88 mL) was added nitropyridine **1.16** (100 mg, 0.24 mmol). The reaction mixture was stirred at room temperature under balloon of H_2 for 16 hours and then filtered through Celite. Clear colourless solution was concentrated under reduced pressure yield a brown foam (95 mg, 100 %) which was used without further purification. R_f 0.21 (Et_2O) ; M.p. 131-133 °C;
ν_{max}/cm^{-1} 3350, 3070, 2930, 2857, 2361, 1623, 1519, 1475, 1427, 1227, 1167, 1112, 1051, 822, 740, 702 ;
δ_H (300 MHz, $CDCl_3$) 1.13 (9H, s, SiC(C*H*$_3$)$_3$), 2.18 (3H, s, 4-C*H*$_3$), 4.64 (2H, s, 6-C*H*$_2$), 5.02 (3H, bs, 2-N*H*$_2$ and 3-O*H*), 6.71 (1H, s, 5-*H*), 7.47-7.35 (6H, m, 6 x SiPh*H*), 7.72-7.69 (4H, m, 4 x SiPh*H*);
δ_C (75 MHz, $CDCl_3$) 16.1, 19.6, 27.2, 65.7, 128.0, 130.0, 133.1, 133.4, 133.6, 135.1, 135.8, 137.2, 149.1;
m/z (ESI+) 415 ([M+Na]$^+$, 7%), 393 ([M+H]$^+$, 100%);
HRMS (ESI+) found 393.1999, $C_{23}H_{29}N_2O_2Si$ ([M+H]$^+$) requires 393.1993 (+1.6 ppm).

5-(*tert*-Butyldiphenylsilyloxymethyl)-7-methyloxazolo[4,5-b]pyridine-2(3*H*)-thione (1.26)



To a solution of aminopyridine **1.17** (200 mg, 0.509 mmol) and potassium hydroxide (65 mg, 1.16 mmol) in ethanol (1.42 mL) was added carbon disulfide (0.468 mL, 7.7 mmol) at room temperature. The reaction mixture was then warmed at reflux for 3 hours. The reaction mixture was concentrated to a thick oil under reduced pressure and subsequently extracted between 5M HCl (10 mL) and EtOAc (4 x 15 mL). The combined organics were dried over $MgSO_4$ and then the solvent was removed under reduced pressure to yield a yellow solid (184 mg, 83 %); R_f 0.37 (50 % Et_2O/Petrol); M.p. 166.4-168.2 °C

ν_{max}/cm^{-1} 3070.4, 2930.3, 2857.1, 1654.1, 1613.3, 1487.8, 1448.8, 1427.4, 1391.4, 1378.0, 1288.7, 1268.5, 1180.4, 1114.4 ;

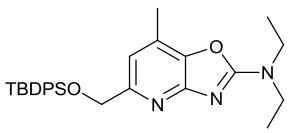
δ_H NMR 300 MHz 1.20 (9H, s, 3 x C*H*$_3$, 2.53 (3H, s, Ar-C*H*$_3$), 5.19 (2H, s, Ar-C*H*$_2$), 7.51-7.36 (7H, m, Ar-*H*), 7.77-7.71 (4H, m, Ar-*H*);

δ_C NMR 75 MHz 15.3, 19.6, 27.3, 66.5, 117.7, 128.1, 130.2, 130.8, 133.2, 135.9, 140.8, 145.7, 156.6, 181.1;

m/z (ESI-) 433 ([M-H]$^-$, 100 %);

HRMS (ESI+) found 435.1550, $C_{24}H_{27}O_2N_2S_1Si_1$ ([M+H]$^+$) requires 435.1557 (-1.6 ppm).

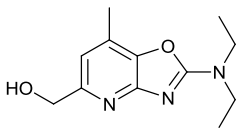
(2-(Diethylamino)-7-methyloxazolo[4,5-b]pyridin-5-yl-(*tert*-butyldiphenylsiloxy) methanol (1.45)



To a stirred suspension containing thione **1.26** (50.0 mg, 0.1 mmol) and Na_2CO_3 (18.0 mg, 0.15 mmol) in benzene (0.13 mL) was added thionyl chloride (12.6 μL, 0.15 mmol) at 0 °C. The reaction mixture was warmed to 50 °C for 3 hours then

allowed to cool to room temperature. Diethylamine (66 μL, 0.55 mmol) was then added drop-wise and the reaction mixture further stirred at room temperature for 1 hour. The mixture was extracted between water (10 mL) and Et_2O (4 x 15 mL). The combined organics were dried over Na_2SO_4 before solvent was removed under reduced pressure. Purification was by silica gel chromatography (Et_2O → 10 % MeOH/ Et_2O) to yield a pale oil which solidified upon storage (37 mg, 70 %).
R_f 0.38 (50 % Et_2O/ Petrol); Mp 90.3-91.6 °C;
ν_{max}/cm^{-1} 3067.1, 2958.9, 2928.6, 2889.9, 2855.3, 2355.1, 1564.9, 1460.8, 1445.1, 1426.7, 1389.1, 1361.0, 1138.3, 1111.8, 1081.9;
δ_H NMR 300 MHz 1.19 (9H, s, 3 x C*H*$_3$), 1.33 (6H, t, *J* 7.10 Hz, NCH_2CH_3), 2.49 (1H, s, Pyr-C*H*$_3$), 3.65 (4H, q, *J* 7.10 Hz, NCH_2CH_3), 4.92 (2H, s, Pyr-C*H*$_2$), 7.13 (1H, s, Pyr-*H*), 7.47-7.35 (6H, m, 6xSi-Ar-*H*), 7.79-7.74 (4H, m, 4xSi-Ar-*H*);
δ_C NMR 75 MHz 13.7, 15.3, 19.6, 27.2, 43.2, 67.0, 113.7, 126.5, 128.0, 129.9, 133.8, 135.8, 140.0, 155.5, 157.8, 163.9;
m/z (ESI+) 474 ($[M+H]^+$, 100 %), 947 ($[2M+H]^+$, 24 %);
HRMS (ESI+) found 474.2567, $C_{28}H_{36}O_2N_3Si_1$ ($[M+H]^+$) requires 474.2571 (-0.9 ppm).

(2-(Diethylamino)-7-methyloxazolo[4,5-b]pyridine-5-yl)methanol (1.50)



To a stirred solution of silyl ether **1.45** (303 mg, 0.64 mmol) in tetrahydrofuran (10.7 mL) was added 1.0 M TBAF in tetrahydrofuran (0.8 mL, 0.77 mmol). The reaction mixture was stirred for 1 hour at room temperature and the solvent was removed under reduced pressure. The oily residue was extracted between water (20 mL) and Et_2O (4 x 20 mL). The combined organics were dried over Na_2SO_4 and the solvent removed under reduced pressure. Purification was by silica gel chromatography (Et_2O→ 10 % MeOH) to yield a pale oil (139 mg, 93 %).
R_f 0.45 (10 % MeOH/Et_2O);
ν_{max}/cm^{-1} 3309, 2974, 2934, 2360, 2340, 1650, 1636, 1569, 1448, 1388, 1363;

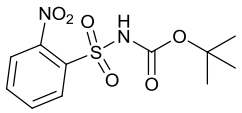
δ_H (500 MHz, $CDCl_3$) 1.23 (6H, t, *J* 7.25 Hz, NCH_2CH_3), 2.32 (3H, s, Ar-CH_3), 3.55 (4H, q, *J* 7.25 Hz, NCH_2CH_3), 4.61 (2H, s, Ar-CH_2), 6.57 (1H, s, O*H)*;

δ_C (125 MHz, $CDCl_3$) 13.4, 14.7, 43.0, 64.1, 113.7, 126.8, 139.8, 153.7, 157.3, 163.6;

m/z (ESI+) 236.2 ($[M+H]^+$, 100%);

HRMS (ESI+) found 236.1396, $C_{12}H_{18}O_2N_3$ ($[M+H]^+$) requires 236.1394 (+1.0 ppm).

N-tert-Butoxycarbonyl-2-nitrobenzenesulfomide (1.52) [28]

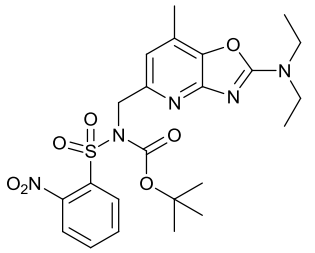


To a stirred solution of 2-nitrobenzenesulfonamide (2.08 g, 9.4 mmol), triethylamine (2.15 mL, 15.4 mmol) and di-*tert*-butyldicarbonate (2.69 g, 12.4 mmol) in dichloromethane (20 mL) was added DMAP (126 mg, 1.03 mmol). After the vigorous effervescence ceased the reaction mixture was stirred for a further 2 hours at room temperature before being extracted between 1 M HCl (50 mL) and Et_2O (4 x 50 mL). The combined organics were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by triturating with 40 % Et_2O/ Petrol to yield a bright white solid (3.05 g, 98 %). R_f 0.79 (Et_2O); ν_{max}/cm^{-1} 3246, 1775, 1545, 1452, 1430, 1356, 1239, 1182, 1145, 1119, 1055, 915, 734;

δ_H (300 MHz, $CDCl_3$) 1.46 (9H, s, $C(CH_3)_3$), 7.67 (1H, s, N*H*), 7.94-7.79 (3H, m, Ar-*H*), 8.42-8.35 (1H, m, Ar-*H*);

m/z (ESI+) 320 ($[M+NH_4]$, 100 %).

***tert*-Butyl (2-(diethylamino)-7-methyloxazolo[4,5-b]pyridin-5-yl)methyl(2-nitrophenylsulfonyl)carbamate (1.53)**



To a stirred solution of primary alcohol **1.50** (20.3 mg, 0.087 mmol), sulfonamide **1.52** (39 mg, 0.13 mmol) and triphenylphosphine (29 mg, 0.11 mmol) in tetrahydrofuran (2.2 mL) was added DIAD (22 μL, 0.11 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 hours and then evaporated to dryness. The residue was purified by silica gel chromatography (Et_2O) to yield a pale oil (44 mg, 98 %). R_f 0.24 (Et_2O);

ν_{max}/cm^{-1} 2979.8, 1735.1, 1639.5, 1565.1, 1543.7, 1364.8, 1149.2, 1123;

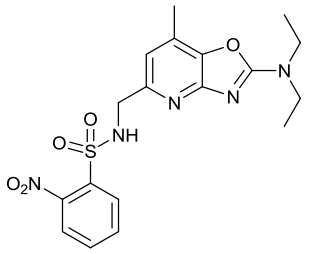
δ_H (300 MHz, $CDCl_3$) 1.30 (9H, s, $C(CH_3)_3$), 1.33 (6H, t, *J* 7.20 Hz, NCH_2CH_3), 2.44 (3H, s, Pyr-CH_3), 3.67 (4H, q, *J* 7.20 Hz, NCH_2CH_3), 5.11 (2H, s, Pyr-CH_2), 6.87 (1H, s, Pyr-*H*), 7.84-7.76 (3H, m, Ar-*H*), 8.60-8.52 (1H, m, Ar-*H*),

δ_C (75 MHz, $CDCl_3$) 13.7, 15.1, 28.3, 43.2, 52.5, 85.2, 114.1, 124.6, 126.6, 132.1, 133.7, 133.9, 134.3, 140.1, 148.1, 150.8, 151.7, 158.1, 163.9;

m/z (ESI+) 520 ($[M+H]^+$, 100%), 542 ($[M+Na]^+$, 78%), 1061 ($[2M+Na]^+$, 80 %);

HRMS (ESI+) found 520.1860, $C_{23}H_{30}O_7N_5S_1$ ($[M+H]^+$) requires 520.1860 (-0.1 ppm).

***N*-(2-Diethylamino-7-methyl-oxazolo[4,5-*b*]pyridin-5-ylmethyl)-2-nitrobenzenesulfonamide (1.54)**



Sulfonamide **1.53** (102 mg, 0.2 mmol, 1.0) was dissolved in trifluoroacetic acid (0.51 mL) and stirred at room temperature for 1 hour. The reaction mixture was then diluted with ethyl acetate and extracted between sat. $NaHCO_3$ (5 mL) and Et_2O (5 x 50 mL). The combined organics were dried over $MgSO_4$ and solvent removed under reduced pressure. The residue was purified by silica gel chromatography (Et_2O → 10 % MeOH/Et_2O) to yield pale oil (64.4 mg, 79 %). R_f 0.1 (Et_2O);

ν_{max}/cm^{-1} 2978, 2360, 1640, 1568, 1540, 1445, 1393, 1363, 1207, 1167;

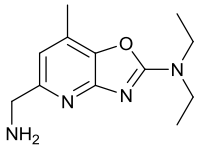
δ_H (300 MHz, $CDCl_3$) 1.32 (6H, t, *J* 7.20 Hz, NCH_2CH_3), 2.39 (3H, s, Pyr-C*H*$_3$), 3.64 (4H, q, *J* 7.20 Hz, NCH_2CH_3), 4.38 (2H, d, *J* 2.70 Hz, Pyr-C*H*$_2$), 6.41 (1H, brt, *J* 2.70 Hz, N*H*), 6.72 (1H, s, Pyr-*H*), 7.71-7.63 (2H, m, Ar-*H*), 7.87-7.82 (1H, m, Ar-*H*), 8.13-8.06 (1H, m, Ar-*H*);

δ_C (75 MHz, $CDCl_3$) 13.6, 14.8, 43.3, 48.7, 125.5, 128.7, 128.8, 131.1, 132.3, 132.6, 133.4, 134.1, 140.3, 149.4, 158.2, 164.0;

m/z (ESI+) 420 ([M+H]$^+$, 100 %), 442 ([M+Na]$^+$, 37 %), 839 ([2M+H]$^+$, 30 %);

HRMS (ESI+) found 420.1330, $C_{18}H_{22}O_5N_5S_1$ ([M+H]$^+$) requires 420.1336 (-1.5 ppm).

5-(Aminomethyl)-*N,N*-diethyl-7-methyloxazolo[4,5-b]pyridin-2-amine (1.24)



To a stirred suspension containing the sulfonamide **1.54** (23.5 mg, 0.084 mmol) and K_2CO_3 (31 mg, 0.34 mmol) in MeCN (0.95 mL) was added thiophenol (17 µL, 0.25 mmol) in one portion at room temperature. The reaction mixture was stirred for 16 hours at room temperature and the opaque yellow solution was then evaporated to dryness. Purification was by silica gel chromatography (10 % MeOH/ DCM with 1 % NEt_3) to yield a pale yellow oil (11.8 mg, 85 %). R_f 0.1 (10 % MeOH/ Et_2O);

ν_{max}/cm^{-1} 3357, 2970, 1652, 1570, 1447, 1393, 1075;

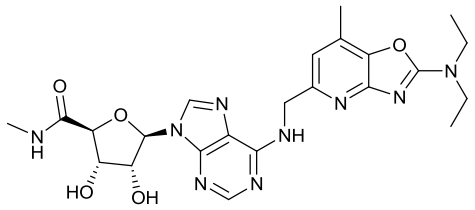
δ_H (300 MHz, $CDCl_3$) 1.29 (6H, t, *J* 7.20 Hz, NCH_2CH_3), 2.38 (3H, s, Pyr-C*H*$_3$), 3.62 (4H, q, *J* 7.20 Hz, NCH_2CH_3), 4.22 (2H, s, Pyr-C*H*$_2$), 5.28 (2H, brs, N*H*$_2$), 6.77 (1H, s, Pyr-*H*);

δ_C (75 MHz, $CDCl_3$) 13.4, 14.7, 43.0, 52.3, 113.7, 126.2, 157.9, 160.5, 163.6;

m/z (ESI+) 235 ([M+H$^+$], 100 %), 257 ([M+Na], 52 %);

HRMS (ESI+) found 235.1558, $C_{12}H_{19}O_1N_4$ ([M+H]$^+$) requires 235.1553 (+2.0 ppm).

(2S,3S,4R,5R)-5-(6-((2-(Diethylamino)-7-methyloxazolo[4,5-b]pyridine-5-yl)methylamino)-9H-purin-9-yl)-tetrahydro-3,4-dihydroxy-N-methylfuran-2-carboxamide (1.02)



To a stirred solution of the primary amine **1.24** (11.5 mg, 0.049 mmol) and triethylamine (13.7 µL, 0.1 mmol) in ethanol (0.5 mL) was added chloropurine **1.05** (17.4 mg, 0.049 mmol). The reaction mixture was heated to reflux, and stirred at this temperature for 16 hours. The liquid was distilled from the

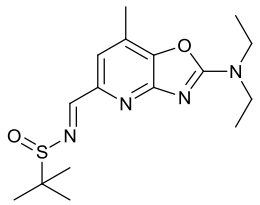
reaction mixture under reduced pressure to yield a colourless oil. (15.0 mg, 55 %). R_f 0.41 (10 % MeOH/ Et_2O) which was immediately dissolved in 1M HCl (1.5 mL). The reaction mixture was stirred at 65 °C for 1 hour and then sat. $NaHCO_3$ was added to pH 7. The water was removed under reduced pressure and the white solid was purified by silica gel chromatography (0→20 % MeOH/DCM) to yield a white solid (11.6 mg, 46 %). R_f 0.1 (20 % MeOH/DCM);

δ_H (NMR 500 MHz, DMSO) 1.23 (6H, t, *J* 6.9 Hz, $N(CH_2CH_3)_2$), 2.33 (3H, s, $ArCH_3$), 2.73 (3H, d, *J* 4.4 Hz, $NHCH_3$), 3.57 (4H, q, *J* 6.9 Hz, $N(CH_2CH_3)_2$), 4.16 (1H, m, *H*3'), 4.33 (1H, s, *H*4'), 4.62 (1H, m, *H*2'), 4.74 (2H, d, *J* 4.7 Hz, $NHCH_2$), 5.61 (1H, d, *J* 6.3 Hz, O*H* 2'),), 5.78 (1H, d, *J* 4.4 Hz, O*H* 3'), 6.00 (1H, d, *J* 7.5 Hz, *H*1'), 6.76 (1H, s, *H*6"), 8.30 (1H, s, *H*2), 8.42 (1H, br s, $NHCH_2$), 8.47 (1H, s, *H*8), 8.96 (1H, m, N*H*CO);

m/z (ESI+) 512 ($[M+H]^+$, 100%), 534 ($[M+H^+]$, 85 %);

HRMS (ESI+) found 512.2373, $C_{23}H_{30}O_5N_9$ ($[M+H]^+$) requires 512.2364 (+ 1.7 ppm).

(+/-) 2-Methyl-propane-2-sulfinic acid 1-(2-diethylamino-7-methyl-oxazolo[4,5-*b*]pyridin-5-yl)-meth-(E)-ylideneamide (1.83)



To a stirred solution of primary alcohol **1.50** (116 mg, 0.5 mmol) dissolved in dichloromethane (3.5 mL) was added Dess-Martin periodinane (315 mg, 0.74 mmol) in one portion at room temperature. This solution was stirred at room temperature for 20 minutes over which time a white precipitate formed. TLC showed loss of starting material and development of a single product (R_f 0.5 10 % MeOH).

The reaction mixture was then concentrated to an oil under reduced pressure and was immediately dissolved in fresh dichloromethane (1.24 mL). To this solution was added anhydrous copper sulphate (158 mg, 0.99 mmol) and (+/-) 2-methyl-2-propyl sulfinamide (66 mg, 0.54 mmol), and the solution was stirred at room

temperature for 16 hours. The reaction mixture was filtered to remove insoluble material and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography (0.5→2 % MeOH/ DCM) to yield a pale oil (150 mg, 90 %). R_f 0.57 (10 % MeOH/ Et_2O);

ν_{max}/cm^{-1} 3434, 2971, 2361, 1647, 1600, 1553, 1450, 1393 ,1210, 1138, 1084, 872, 769;

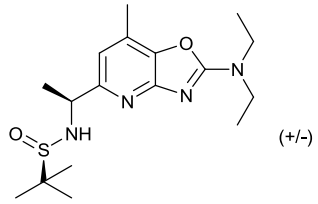
δ_H (NMR 500 MHz $CDCl_3$) 1.21 (9H, s, C(C*H*$_3$)$_3$), 1.24 (6H, t, *J* 7.25 Hz, NCH_2CH_3), 2.40 (3H, s, Ar-C*H*$_3$), 3.58 (4H, q, *J* 7.15 Hz, NCH_2CH_3), 7.45 (1H, s, Py-*H*), 8.56 (1H, s, Ar-C*H*N);

δ_C (NMR 75 MHz $CDCl_3$)13.6, 14.8, 22.9, 43.5, 58.1, 118.8, 126.5, 142.7, 147.7, 158.9, 164.2;

m/z (ESI+) 337 ($[M+H]^+$, 100 %);

HRMS (ESI+) found 337.1704, $C_{16}H_{25}O_2N_4S_1$, ($[M+H]^+$) requires 337.1693 (+3.3 ppm).

(+/-) (R)-N-((R)-1-(2-(diethylamino)-7-methyloxazolo[4,5-b]pyridin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (1.85)



(+/-)

To a stirred solution of the sulfinimine **1.83** (150 mg, 0.45 mmol) in tetrahydrofuran (4.45 mL) was added 3M ethereal solution of MeMgBr (0.53 mL, 1.6 mmol) dropwise at -78 ºC. The reaction mixture was stirred at -78 °C for 1 hour then sat. NH_4Cl (5 mL) was added. The solution was extracted with ethyl acetate (6 x 5 mL) and the combined organics were dried over Na_2SO_4 and concentrated to a thick oil under reduced pressure. Purification of the residue was by silica gel chromatography (0→4 % MeOH/ DCM). This yielded a pale oil (119 mg, 76 %). R_f 0.1 (EtOAC);

ν_{max}/cm^{-1} 2974, 1654, 1565, 1388, 1069;

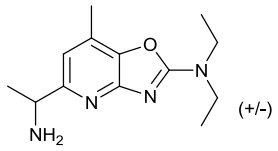
δ_H (NMR 500 MHz $CDCl_3$) 1.15 (9H, s, $C(CH_3)_3$), 1.22 (6H, t, *J* 7.25 Hz, NCH_2CH_3), 1.43 (3H, d, *J* 6.60 Hz, $ArCHCH_3$), 2.31 (3H, s, Ar-CH_3), 3.55 (4H, q, *J* 7.25 Hz, 2xNCH_2CH_3), 4.40 (1H, qn, *J* 6.70 Hz, ArCHN), 4.49 (1H, d, *J* 6.95 Hz, NH), 6.62 (1H, s, Py-*H*);

δ_C NMR (125 MHz $CDCl_3$) 12.4, 13.7, 21.7, 22.9, 42.0, 54.6, 55.4, 113.7, 125.4, 138.9, 156.0, 156.9, 162.6;

m/z (ESI+) 375 ($[M+Na]^+$, 100 %);

HRMS (ESI+) Found 375.1834, $C_{17}H_{28}O_2N_4Na_1S_1$ ($[M+Na)^+$) requires 375.1825 (+2.4 ppm).

(+/-) 5-(1-Aminoethyl)-*N,N*-diethyl-7-methylozolo[4,5-b]pyridine-2-amine (1.82)



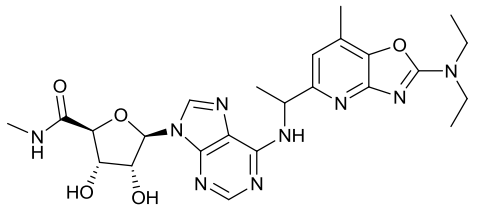
To a stirred solution of sulfinamide **1.85** (110 mg, 0.313 mmol) in MeOH (3.1 mL) was added 4 M HCl in dioxane (0.47 mL, 1.88 mmol) drop wise at room temperature. The reaction mixture was stirred for 30 minutes and then sat. $NaHCO_3$ was added until the solution was strongly alkaline (pH 9-10). The solvent was reaction mixture was then evaporated to dryness under reduced pressure and the residue was subjected to silica gel chromatography (0→3 % MeOH/ DCM + 0.5 % NEt_3). This yielded a pale oil (64 mg, 82 %). R_f 0.2 (10 %/ MeOH/ DCM); ν_{max}/cm^{-1} 3356, 2973, 1652, 1565, 1447, 1386, 1081;

δ_H (NMR 500 MHz $CDCl_3$) 1.21 (6H, t, *J* 7.10 Hz, NCH_2CH_3), 1.41 (3H, d, *J* 6.60 Hz, Pyr-CH-CH_3), 2.32 (3H, s, Pyr-CH_3), 3.12 (2H, brs, NH_2), 3.55 (4H, q, *J* 7.15 Hz, NCH_2CH_3), 4.08 (1H, brq, *J* 6.30 Hz, Pyr-CH-NH_2), 6.61 (1H, s, Pyr-*H*);

δ_C (NMR 75 MHz $CDCl_3$) 13.4, 14.8, 24.7, 42.8, 52.3, 113.7, 126.2, 139.5, 157.9, 160.5, 163.6;

m/z (ESI+) 249 ($[M+H]^+$, 100 %); HRMS (ESI+) found 249.7105, $C_{13}H_{21}O_1N_4$, ($[M+H]^+$), requires 249.1710 (-2.0 ppm).

(2S,3S,4R,5R)-5-(6-(1-(2-(Diethylamino)-7-methyloxazolo[4,5-b]pyridine-5-yl)-tetrahydro-3,4-dihydroxy-N-methylfuran-2-carboxamide (1.04)

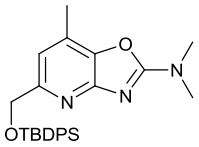


To a stirred solution of primary amine **1.82** (64 mg, 0.258 mmol) and triethylamine (72 µL, 0.52 mmol) in ethanol (2.6 mL) was added chloropurine **1.05** (92 mg, 0.258 mmol) in one portion at room temperature. The reaction mixture was stirred at reflux for 16 hours and evaporated to dryness under reduced pressure to yield a pale oil (120 mg, 82 %). R_f 0.25 (10 % MeOH/ Et_2O). This oil was immediatly dissolved in 1 M HCl (1.5 mL) and the reaction mixture was stirred at 65 °C for 1 hour and was then neutralised by the addition of sat. $NaHCO_3$. Water was removed under reduced pressure and the residue was purified by silica gel chromatography (DCM→ 20 % MeOH/ DCM). This gave a white solid (80 mg, 60 %). R_f 0.58 (20 % MeOH/ DCM); M.p. 143-146 °C;

δ_H (NMR 500 MHz DMSO) 1.28 (6H, t, *J* 7.1, $N(CH_2C\mathit{H}_3)_2$), 1.60 (3H, d, *J* 6.9, Pyr-CH-$C\mathit{H}_3$), 2.39 (3H, s, Pyr-$C\mathit{H}_3$), 2.77 (1.2H, d, *J* 4.5 Hz, $NHC\mathit{H}_3^{min}$), 2.78 (1.8H, d, *J* 4.4 Hz, $NHC\mathit{H}_3^{maj}$), 3.62 (4H, q, *J* 7.1 Hz, $N(C\mathit{H}_2CH_3)_2$), 4.21 (1H, s, *H*3'), 4.38 (1H, s, *H*4'), 4.66 (1H, m, *H*2'), 5.51 (1H, m, $NC\mathit{H}CH_3$), 5.64 (1H, d, *J* 6.0 Hz, 2'O*H*), 5.81 (1H, s, 3'O*H*), 6.04 (1H, d, *J* 7.6, *H*1'), 6.95 (1H, s, Pyr-*H*), 8.10 (1H, d, *J* 6.9 Hz, ArN*H*), 8.35 (1H, s, *H*2), 8.53 (1H, s, *H*8), 8.95 (0.4H, q, *J* 4.5 Hz, $N\mathit{H}CO^{min}$), 8.97 (0.6H, q, *J* 4.4 Hz, $N\mathit{H}CO^{maj}$);

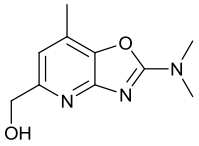
m/z (ESI+) 526 ($[M+H]^+$, 100 %); HRMS (ESI+) Found 526.2532, $C_{24}H_{32}O_5N_9$, ($[M+H]^+$), requires 526.2521, (+2.1 ppm).

5-((*tert*-Butyldiphenylsilyloxy)methyl)-N,N,7-trimethyloxazolo[4,5-b]pyridin-2-amine (1.19)[7]



To a stirred solution of amino phenol **1.17** (400 mg, 1.01 mmol) and triethylamine (0.68 mL, 4.8 mmol) in dichloromethane (10.7 mL) was added phosgeneiminium chloride (265 mg, 1.62 mmol) in one portion at room temperature. The reaction mixture was heated at reflux for 2 hours and then poured onto sat. $NaHCO_3$ (30 mL). The organic layer was removed and the aqueous layer extracted with ether (4 x 30 mL). The combined organics were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (100 % Et_2O) to yield a pale oil (363 mg, 80 %). R_f 0.16 (Et_2O);
ν_{max}/cm^{-1} 3070, 2931, 2892, 2857, 1680, 1571, 1428, 1387, 1285, 1190, 1140, 1111, 1088, 703;
δ_H (NMR 500 MHz $CDCl_3$) 1.05 (9H, s, C(CH_3)$_3$), 2.35 (3H, s, Ar-CH_3), 3.13 (6H, s, N(CH_3)$_2$), 4.78 (2H, s, Ar-CH_2), 7.01(1H, s, Py-*H*),7.26-7.53 (6H, m, 6 of Si-Ar-*H*), 7.63 (4H, dd, *J* 6.60 Hz, 1.42 Hz, 4 x Si-Ar-*H*);
δ_C (NMR 125 MHz $CDCl_3$) 15.0, 19.4, 27.0, 37.4, 66.8, 113.7, 126.5, 127.7, 129.7, 133.5, 135.5, 140.0, 155.3, 157.4, 164.4;
m/z (ESI+) 446 ($[M+H]^+$, 100 %), 891 ($[2M+H^+]$, 67 %;
HRMS (ESI+) found 446.2255, $C_{26}H_{32}O_2N_3Si$, ($[M+H]^+$), requires 446.2258 (-0.7 ppm).

(2-(Dimethylamino)-7-methyloxazolo[4,5-b]pyridine-5-yl)methanol (1.20)[7]



To a stirred solution of silyl ether **1.19** (360 mg, 0.81 mmol) in tetrahydrofuran (13.5 mL) was added 1.0 M tetrahydrofuran solution of TBAF (0.97 mL, 0.97 mmol). The reaction mixture was stirred at room temperature for 1 hour and the

solvent was removed under reduced pressure. The residue was extracted between water (20 mL) and Et_2O (6 x 20 mL). The combined organics were dried over Na_2SO_4 and the solvent was once again removed under reduced pressure. The residue was purified by silica gel chromatography (Et_2O→ 15% MeOH/ Et_2O) to yield a white waxy solid (159 mg, 89 %). R_f 0.24 (10 % MeOH/ Et_2O);

ν_{max}/cm^{-1} 3234, 2925, 2873, 1661, 1643, 1573, 1402, 1382, 1367, 1276, 1238, 1183, 1135, 1064, 895, 836, 777, 726;

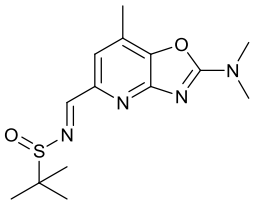
δ_H (NMR 500 MHz $CDCl_3$) 2.33 (3H, s, Ar-C*H*$_3$), 3.17 (6H, s, N(C*H*$_3$)$_2$), 3.74 (1H, brs, O*H*), 4.62 (2H, s, Ar-C*H*$_2$), 6.58 (1H, s, Py-*H*);

δ_C NMR (75 MHz $CDCl_3$) 15.0, 37.4, 64.4, 114.2, 127.3, 140.4, 154.1, 157.5, 164.6;

m/z (ESI+) 208 ([M+H$^+$], 100 %), 230 ([M+Na$^+$], 13 %) 437 ([2M+Na$^+$], 30 %);

HRMS (ESI+) found 208.1066, $C_{10}H_{14}O_2N_3$ ([M+H]$^+$), requires 208.1081 (-7.0 ppm).

(+/-) 2-Methyl-propane-2-sulfinic acid 1-(2-dimethylamino-7-methyl-oxazolo[4,5-*b*]pyridin-5-yl)-meth-(E)-ylideneamide (1.80)



To a stirred solution of primary alcohol **1.20** (130 mg, 0.63 mmol) in dichloromethane (4.5 mL) was added Dess-Martin periodinane (399 mg, 0.94 mmol). This solution was stirred until TLC analysis showed loss of starting material and development of a new product *Ca* 20 mins (R_f 0.36 10 % MeOH/Et_2O).

The reaction mixture was then concentrated to an oil under reduced pressure before being dissolved in fresh dichloromethane (1.6 mL). Anhydrous copper sulphate (200 mg, 1.25 mmol) and (+/-) 2-methyl-2-propyl sulfinamide (84 mg, 0.69 mmol) were then added and the solution stirred at room temperature for 16 hours.

The reaction mixture was filtered and the filtrate evaporated to dryness under reduced pressure. The oily residue was purified by silica gel chromatography

(0.5→2 % MeOH/ DCM) to yield a pale oil (135 mg, 70 %). R_f 0.43 (10 % MeOH/ Et_2O); ν_{max}/cm^{-1} 2927, 1664, 1560, 1558, 1430, 1393, 1285, 1188, 1138, 1085, 891, 772, 732;

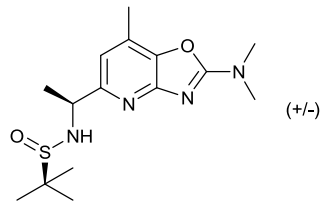
δ_H (NMR 500 MHz $CDCl_3$) 1.21 (9H, s, $C(CH_3)_3$), 2.40 (3H, s, Ar-C*H*$_3$), 3.21 (6H, s, $N(CH_3)_2$), 7.47 (1H, s, Pyr-*H*), 8.57 (1H, s, ArC*H*N),

δ_C NMR 125 MHz $CDCl_3$ 14.7, 22.1, 22.7, 57.8, 118.7, 126.4, 142.7, 147.6, 158.6, 164.0;

m/z (ESI+) 331 ([M+Na]$^+$, 100 %);

HRMS (ESI+) found 331.1195, $C_{14}H_{20}O_2N_4Na_1S_1$ ([M+Na]$^+$), requires 331.1199 (-1.3 ppm).

(+/-) 2-Methyl-propane-2-sulfinic acid [1-(2-dimethylamino-7-methyl-oxazolo[4,5-*b*]pyridin-5-yl)-ethyl]-amide (1.81)



To a stirred solution of sulfinimine **1.80** (132 mg, 0.43 mmol) in tetrahydrofuran (4.3 mL) at was added 3M ethereal solution of MeMgBr (0.51 mL, 1.6 mmol) dropwise at – 78 ºC. The reaction mixture was stirred at -78 °C for 1 hour and then being sat. NH_4Cl (5 mL) was added. The solution was extracted with EtOAc (6 x 5 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue was by silica gel chromatography (0→4 % MeOH/ DCM). This yielded a pale oil (119 mg, 76 %). R_f 0.1 (EtOAC);

ν_{max}/cm^{-1} 3234, 2927, 1667, 1570, 1430, 1389, 1290, 1190, 1145, 1063, 894;

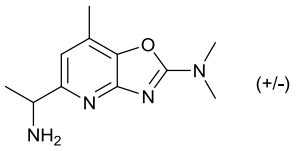
δ_H (NMR 500 MHz $CDCl_3$) 1.16 (9H, s, $C(CH_3)_3$), 1.42 (3H, d, *J* 6.60 Hz, ArCHC*H*$_3$), 2.31 (3H, s, Ar-C*H*$_3$), 3.16 (6H, s, $N(CH_3)_2$), 4.42 (1H, qn, *J* 6.65 Hz, ArC*H*N), 4.51 (1H, d, *J* 6.30 Hz, N*H*), 6.64 (1H, s, Pyr-*H*);

δ_C (NMR 75 MHz $CDCl_3$) 15.0, 22.4, 23.0, 24.2, 37.7, 56.4, 115.2, 126.9, 140.4, 157.4, 158.0, 164.7;

m/z (ESI+) 325 ([M+H]$^+$, 100 %);

HRMS (ESI+) Found 325.1691, $C_{15}H_{25}O_2N_4S_1$, ($[M+H]^+$), requires 325.1693 (-0.5 ppm).

(+/-) 5-(1-Aminoethyl)-*N,N*,7-trimethlyoxazolo[4,5-b]pyridine-2-amine (1.59)



To a stirred solution of **1.81** (132 mg, 0.407 mmol) in MeOH (4.1 mL) was added 4 M HCl in dioxane (0.61 mL, 2.4 mmol) drop wise at room temperature. The reaction mixture was stirred at room temperature for 30 minutes and was quenched by the addition of sat. $NaHCO_3$ until basic before being evaporated to dryness under reduced pressure. Purification was by silica gel chromatography (DCM→3 % MeOH/ DCM + 0.5 % NEt_3). This yielded a pale waxy solid (74 mg, 83 %). R_f 0.3 (10 %/ MeOH/ DCM);

ν_{max}/cm^{-1} 3365, 2920, 2361, 1659, 1571, 1430, 1392, 1286, 896;

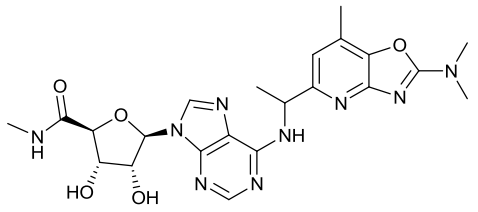
δ_H (NMR 300z $CDCl_3$)1.49 (3H, d, *J* 6.60 Hz, Ar-CH_2-C*H*$_3$), 2.41 (3H, s, Ar-C*H*$_3$), 3.01 (2H, brs, N*H*$_2$), 3.27 (6H, s, NC*H*$_3$), 4.15 (1H, d, *J* 6.75 Hz, Ar-CH_2-C*H*-NH_2), 6.72 (1H, s, Pyr-*H*);

δ_C (MR 75 MHz $CDCl_3$) 15.0, 22.4, 29.9, 37.7, 52.4, 114.4, 126.8, 157.9, 159.8, 164.6;

m/z (ESI+) 221 ($[M+H]^+$, 100 %), 441 ($[2M+H]^+$, 16 %);

HRMS (ESI+) found 221.1397, $C_{11}H_{17}O_1N_4$, ($[M+H]^+$) requires 221.1397 (+0.1 ppm).

(2S,3S,4R,5R)-5-(6-(1-(2-(Dimethylamino)-7-methyloxazolo[4,5-b]pyridine-5-yl)-tetrahydro-3,4-dihydroxy-N-methylfuran-2-carboxamide (1.04)



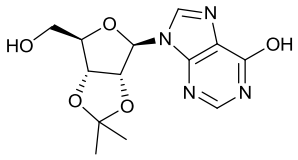
To a stirred solution of primary amine **1.59** (69 mg, 0.313 mmol) and triethylamine (87 µL, 0.626 mmol) in ethanol (3.1 mL) was added chloropurine **1.05** (111 mg, 0.313 mmol) in one portion at room temperature. The reaction mixture was stirred at reflux for 16 hours before being evaporated to dryness under reduced pressure to give a pale oil (R_f 0.38 (20 % MeOH/ Et_2O)) which was immediately dissolved in a stirred solution of 1 M HCl (1.5 mL) and the reaction mixture stirred at 65 °C for 1 hour. sat. $NaHCO_3$ was added until the reaction mixture was neutral. The water was removed under reduced pressure to give an oily residue which was subjected to silica gel chromatography (DCM→ 20 % MeOH/ DCM). This gave a white solid (77 mg, 50 %). R_f 0.6 (20 % MeOH/ DCM); Mp 171-173 °C;

δ_H (NMR 500 MHz DMSO) 1.55 (3H, d, *J* 6.9, Pyr-CH-C*H*$_3$), 2.35 (3H, s, Pyr-C*H*$_3$), 2.71 (1.2H, d, *J* 4.3 Hz, NHC*H*$_3^{min}$), 2.72 (1.8H, d, *J* 4.5 Hz, NHC*H*$_3^{maj}$), 3.17 (6H, s, N(C*H*$_3$)$_2$), 4.16 (1H, m, *H*3'), 4.32 (1H, s, *H*4'), 4.61 (1H, m, *H*2'), 5.47 (1H, m, NC*H*CH$_3$), 5.54 (1H, br s, 2'O*H*), 5.72 (1H, s, 3'O*H*), 5.98 (1H, d, *J* 7.3, *H*1'), 6.91 (1H, s, Pyr-*H*), 8.10 (1H, m, ArN*H*), 8.29 (1H, s, *H*2), 8.46 (1H, s, *H*8), 8.86 (0.4H, q, *J* 4.4 Hz, N*H*CO^{min}), 8.88 (0.6H, q, *J* 4.6 Hz, N*H*CO^{maj});

m/z (ESI+) 498 ([M+H]$^+$, 100 %), 995 (2M+H]$^+$, 17 %);

HRMS (ESI+) found 498.2206, $C_{22}H_{28}O_5N_9$, ([M+H]$^+$), requires 498.2208 (-0.4 ppm).

9-((3aR,4R,6R,6aR)-Tetrahydro-4-(hydroxymethyl)-2,2-dimethylfuro[3,4-d][1,3]dioxol-6-yl)-9H-purin-6-ol (1.55)[29]



To a stirred solution of acetone (82 mL) and water (1.34 mL) at was added $POCl_3$ (14.0 ml, 150 mmol) 15 °C. Inosine (10 g, 37.3 mmol) was then added portion wise keeping the temp below 15 °C. After stirring for 30 minutes the reaction mixture was added to 2.5 M NaOH keeping the pH above 9.

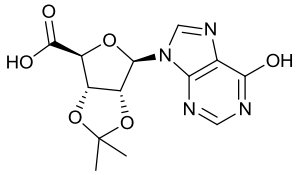
The mixture was cooled to 10 °C and the precipitate removed by filtration, washed with 50 % aqueous acetone and discarded.

The pH was then further adjusted to neutral and cooled, the precipitate was collected and re-crystallised from water to yield a white powder (7.97 g, 69 %) R_f 0.63 (20 % MeOH/ Et_2O);

δ_H (NMR 300 MHz DMSO) 1.35 (3H, s, C*H*$_3$), 1.56 (3H, s, C*H*$_3$), 3.57 (1H, d, *J* 4.40 Hz, C*H*$_2$), 4.26 (1H, m, *H*3'), 4.96 (1H, dd, *J* 2.50 Hz, 3.65 Hz, *H*4'), 5.16 (1H, s, O*H*), 5.30 (1H, dd, *J* 4.20 Hz, 3.20 Hz *H*2'), 6.14 (1H, d, *J* 2.95 Hz, *H*1'), 8.13 (1H, s, Ar-*H*), 8.35 (1H, s, Ar-*H*), 12.48 (1H, s, Ar-O*H*),

δ_C (NMR 75 MHz DMSO) 25.8, 27.7, 62.1, 82.0, 84.5, 87.4, 90.3, 113.8, 125.2, 139.5, 146.8, 148.5, 157.2; *m/z* (ESI+) 331 ($[M+Na]^+$, 100 %).

(3aS,4S,6R,6aR)-Tetrahydro-6-(6-hydroxy-9H-purin-9-yl)-2,2-dimethylfuro[3,4-d][1,3]dioxole-carboxylic acid (1.56)[30,31]



Method 1:

To a stirred solution of acetonide **1.55** (1.36 g, 4.41 mmol) and KOH (0.74 g, 13.26 mmol) in water (288 mL) was added a solution of $KMnO_4$ (2.1 g, 13.26 mmol) in water (58 mL). The deep purple reaction mixture was stirred at room temperature for 3 days and then 30 % H_2O_2 (10 ml) was added.

The reaction mixture was concentrated under reduced pressure until an approximate volume of 20 mL had been reached, at this point the solution was adjusted to pH 4 using concentrated hydrochloric acid. The precipitate thus formed was isolated by filtration and purified by re-crystallisation from glacial acetic acid. This gave white crystals (573 mg, 41 %).

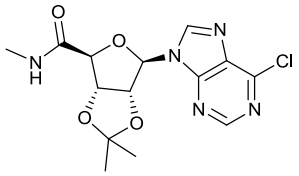
Method 2:

To a stirred solution of CrO_3 (550 mg, 5.5 mmol) in glacial acetic acid (18 mL) was added acetonide **1.55** (1.54 g, 5.0 mmol). The reaction mixture was stirred at room temperature for 48 hours and the solid was removed by filtration, and re-crystallised from glacial acetic acid several times to removed residual chromium compounds. This gave fine white needle shaped crystals (475 mg, 30 %). R_f 0.1 (20 % MeOH/ Et_2O).

δ_H (NMR 500 MHz solvent) 1.38 (3H, s, C*H*$_3$), 1.60 (3H, s, C*H*$_3$), 4.66 (1H, d, *J* 1.6 Hz, *H4'*), 5.35 (1H, dd, J 2.4 Hz, 3.8 Hz, *H3'*), 5.46 (1H, dd, 1.8 Hz, 4.0 Hz, *H2'*), 6.4 (1H, d, 2.5 Hz, *H1'*), 8.01 (1H, s, Ar-*H*), 8.25 (1H, s, Ar-*H*), 12.4 (1H, brs, O*H*), 12.6 (1H, brs, CO_2*H*);

δ_C (NMR 75 MHz DMSO) 171.5, 157.3, 148.7, 146.3, 140.5, 125.0, 113.4, 90.4, 86.1, 84.4, 84.2, 27.1, 25.6; *m/z* (ESI-) 321 ([M-H]$^-$, 100 %).

(3aS, 4S, 6R, 6aR)-6-(6-Chloro-9H-purin-9-yl)-tetrahydro-N,2,2-trimethylfuro[3,4-d][1,3]dioxole-4-carboxamide (1.05)[31]



To a stirred solution of acid **1.56** (1.42 g, 4.4 mmol) in DMF (0.34 mL, 4.4 mmol) and chloroform (56.5 mL) was added thionyl chloride (0.65 mL, 8.8 mmol). The reaction mixture was heated to reflux for 18 hours. The solvent was then removed under reduced pressure to leave a thick oil which was dissolved in fresh chloroform (43.4 mL) and cooled to 0 °C. A solution of 2 M $MeNH_2$ in tetrahydrofuran (11 mL, 22 mmol) was then added and the reaction mixture was

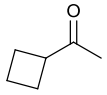
stirred at 0 °C for 15 minutes. The reaction mixture was then extracted with 0.1 M HCl (3 x 80 mL), 0.5 M $NaHCO_3$ (135 mL), water (2 x 75 mL) and then dried over $MgSO_4$. The solvent was then removed under reduced pressure and the residue purified by silica gel chromatography (2% MeOH/ DCM). This gave a pale yellow solid (772 mg, 61%). R_f 0.76 (20 % MeOH/ Et_2O);

δ_H (NMR 300 MHz $CDCl_3$) 1.34 (3H, s, C*H*$_3$), 1.57 (3H, s, C*H*$_3$), 2.46 (3H, d, *J* 5.05 Hz, NC*H*$_3$), 4.69 (1H, d, *J* 1.60 Hz, *H*4'), 5.35 (1H, dd, *J* 2.35 Hz, 3.80 Hz, *H*3'), 5.44 (1H, dd, *J* 1.90 Hz, 4.40 Hz, *H*2'), 6.14 (1H, d, *J* 2.50 Hz, *H*1'), 6.26 (1H, brs, N*H*), 8.16 (1H, s, Ar-*H*), 8.69 (1H, s, Ar-*H*);

δ_C NMR 75 MHz solvent: 24.9, 25.1, 26.5, 30.7, 55.0, 83.3, 83.4, 86.8, 90.2, 112.8, 131.2, 147.0, 149.0, 151.3, 168.7; *m/z* (ESI+) 376 ($[M+Na]^+$, 100 %).

3.3 Approaches towards M_3 Agonists

1-Cyclobutylmethyl ketone (2.13)[51]



At 0 °C a solution of methyl lithium (13.1 mL, 20.1 mmol) was added drop wise to a stirred solution of cyclobutylcarboxylic acid (1.0 g, 9.98 mmol) in diethyl ether (10 mL). A precipitate formed immediately and the resulting mixture was allowed to warm to room temperature and was then refluxed for 2 hours. The solution was cooled to 0 °C and acetone (0.1 mL) and then water (50 mL) were added. The two phases were separated and the aqueous layer was washed with ether (3 x 50 mL), the combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude ketone. The residue was distilled to afford pure ketone (590 mg, 60 %). R*f* 0.46 (20 % Et_2O/ Petrol);

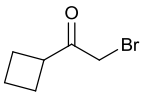
IR υ_{max} (neat/cm^{-1}) 3350, 2950, 2929, 2859, 1470, 1358, 1253, 1100, 1076, 1000, 940, 920, 838, 778;

δH (300 MHz, $CDCl_3$) 1.73-2.28 (6H, m, C*H*$_2$ C*H*$_2$ C*H*$_2$), 2.06 (s, 3H, C*H*$_3$), 3.24 (1H, m, C*H*CO);

δC (75 MHz, $CDCl_3$) 17.5, 24.2, 26.9, 46.1, 210;

m/z (CI) 116 ($M+NH_4^+$, 100%);

2-Bromo-1-cyclobutylethanone (2.14)[52]



To a stirred solution of cyclobutylethanone (10 mL, 91.9 mmol) in methanol (62 mL) at 0 °C was added drop wise elemental bromine (4.7 mL, 91.9 mmol). The reaction mixture was allowed to warm to room temperature and stirring was continued for 1 hour. Water (20 mL) was added and the methanol was removed under reduced pressure. Diethyl ether (50 mL) was added and the two phases separated, the aqueous layer was further extracted with diethyl ether (2 x 50 mL). The organic extracts were combined, dried over $MgSO_4$ and evaporated under reduced pressure to afford crude bromoketone. Purification by silica gel

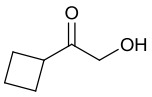
chromatography (10 % Et_20/ petrol) gave a mobile pale orange oil (12.3 g, 80 %). R_f 0.53 (20 % Et_2O/ petrol); IR υ_{max} (neat/cm^{-1}) 2985, 2940, 2863, 1710, 1701, 1393, 1345, 1250, 1175, 1113, 1067, 985, 732;

δH (300 MHz, $CDCl_3$) 1.81-2.38 (6H, m, C*H*$_2$ C*H*$_2$ C*H*$_2$), 3.61 (1H, m, C*H*CO), 3.24 (1H, m, C*H*), 3.91 (1H, s, C*H*$_2$Br);

δC (75 MHz, $CDCl_3$) 17.9, 25.0, 32.7, 42.9, 203;

m/z (CI) 194 ($M+NH_4^+$, 50%), 196 ($M+NH_4^+$, 50%),

1-Cyclobutyl-2-hydroxyethanone (2.15)[49]



Potassium formate (37.7 g, 448 mmol) was added to a stirred solution of bromoketone **2.14** (31.7 g, 179 mmol) in methanol (400 mL). The heterogeneous mixture was heated at reflux for 16 hours. The solvent was removed and diethyl ether (200 mL) was added causing a precipitate to form. This was removed by vacuum filtration and discarded; the filtrate was concentrated under vacuum and the residue purified by silica gel chromatography (10 % Et_2O/ Petrol) to give the alcohol as a pale oil (14.3 g, 70 %). R_f 0.25 (25 % Et_2O/ Pertol);

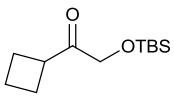
IR υ_{max} (neat/cm^{-1}) 3425, 2983, 2955, 2860, 1709, 1460, 1440, 1351, 1270, 1250, 1199, 1075, 1032, 982, 910;

δH (300 MHz, $CDCl_3$) 1.80-2.38 (6H, m, C*H*$_2$ C*H*$_2$ C*H*$_2$), 3.30 (1H, m, C*H*CO);

δC (75 MHz, $CDCl_3$) 18.5, 24.7, 41.4, 66.0, 212;

m/z (CI) 132 ($M+NH_4^+$, 100 %).

2-(*tert*-Butyldimethylsilyloxy)-1-cyclobutylethanone (2.16)[49]



To a stirred solution of alcohol **2.15** (1.0 g, 8.8 mmol) and imidazole (665 mg, 9.7 mmol) in dichloromethane (45 ml) was added *tert*-butyldimethylsilyl chloride (1.4

g, 9.7 mmol) and stirring was continued at room temperature for 16 hours. The reaction mixture was extracted between water (15 ml) and diethyl ether (3 x 15 ml). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification was by silica gel chromatography (0→ 20 % Et_2O/ Petrol) which gave a pale oil (1.7 g, 85 %) Rf 0.2 (10 % Et_2O/ petrol);

IR υ_{max} (neat/cm^{-1}) 2951, 2859, 1712, 1471, 1434, 1390, 1360, 1344, 1258, 1171, 1108, 1048, 1007, 939, 912, 841, 778, 736;

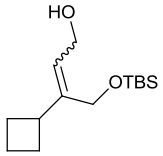
δH (300 MHz, $CDCl_3$) 0.05 (6H, s, SiCH_3), 0.91 (9H, s, SiC(CH_3)$_3$), 1.7-2.36 (6H, m, CH_2 CH_2 CH_2), 3.49 (1H, m, CHCO), 4.2 (2H, s, CH_2OSi);

δC (75 MHz, $CDCl_3$) -5.0, 18.2, 18.3, 24.2, 25.7, 41.6, 67.8, 211.4;

m/z (ESI+) 251 ($M+Na^+$, 100 %);

HRMS (ESI+) found 229.1621, $C_{12}H_{25}O_2Si$ ($[M+H]^+$), requires 229.1624 (-1.2 ppm).

4-(*tert*-Butyldimethylsilyloxy)-3-cyclobutylbut-2-en-1-ol (2.17)[49]



To a stirred suspension of a 60 % dispersion of sodium hydride in mineral oil (2.75 g, 69 mmol) in tetrahydrofuran was added triethylphosphonoacetate (13.7 mL, 68.7 mmol) dropwise at room temperature. The reaction mixture was stirred at this temperature for 1 hour and then a solution of ketone **2.16** (14.3 g, 62.5 mmol) in tetrahydrofuran (40 mL) was added dropwise. The reaction mixture was stirred at room temperature for 2.5 hours then saturated ammonium chloride solution (100 mL) and ether (150 mL) were added. The layers were seperated and the aqueous phase further extracted with diethyl ether (3 x 150 mL). The combined organics were dried over magnesium sulfate and the solvent was removed under reduced pressure to give a very mobile oil (18.7 g, 100 %) R_f 0.63 (25 % EtOAc/ petrol) which was immediately taken up in fresh tetrahydrofuran (45 mL). The stirred solution was cooled to -78 °C and 1 M solution of DIBAL-H in hexanes (162 mL, 162 mmol) was added dropwise, Stirring was continued at -

78 ºC for 3 hours and then the reaction mixture was warmed to 0 ºC and stirred for a further 1 hour. Water (5 mL) was added dropwise over a period of 10 minutes and then saturated Rochelle salt (160 mL) was added and the reaction mixture was stirred at room temperature for 16 hours. The organic phase was separated and the aqueous was extracted with ether (3 x 200 ml). The combined organics were dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography (10 % Et_2O/ Petrol) to afford the allylic alcohol (14.4 g, 89 %) as a mixture of Z and E geometric isomers (75/25).

Z isomer: R_f 0.42 (20 % EtOAc/Petrol);

IR υ_{max} (neat/cm^{-1}) 3359, 2955, 2932, 2885, 2859, 1471, 1389, 1361, 1253, 1087, 1007;

δH (300 MHz, $CDCl_3$) 0.09 (6H, s, SiC*H*$_3$), 0.91 (9H, s, SiC(C*H*$_3$)$_3$), 1.68-1.76 (1H, m, O*H*), 1.84-2.13 (6H, m, C*H*$_2$ C*H*$_2$ C*H*$_2$), 3.04 (1H, m, *c*-Bu), 4.14 (2H, s, C*H*$_2$OSi), 4.20 (2H, dd, *J* 7.0 Hz, 6.25 Hz, C*H*$_2$OH), 5.54 (1H, t, *J* 7 Hz, =C*H*);

δC (75 MHz, $CDCl_3$) -5.4, 17.8, 18.3, 25.9, 27.5, 39.9, 58.8, 60.3, 123.6, 145.9;

m/z (ESI+) 279 ($M+Na^+$, 100 %); HRMS (ESI+) found 279.1747, $C_{14}H_{28}O_2Na_1Si$ ($[M+Na]^+$), requires 279.1751 (-1.4 ppm).

E isomer: R_f 0.38 (20 % EtOAc/Petrol);

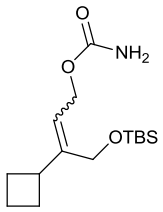
IR υ_{max} (neat/cm^{-1}) 3335, 2955, 2932, 2885, 2859, 1471, 1254, 1087, 1006, 838, 776;

δH (300 MHz, $CDCl_3$) 0.07 (6H, s, SiC*H*$_3$), 0.91 (9H, s, SiC(C*H*$_3$)$_3$), 1.80-2.11 (6H, m, C*H*$_2$ C*H*$_2$ C*H*$_2$), 2.24 (1H, brs, O*H*), 3.31 (1H, m, *c*-Bu), 4.12 (2H, s, C*H*$_2$OSi), 4.16 (2H, dd, *J* 6.25 Hz, 3 Hz, C*H*$_2$OH), 5.57 (1H, t, *J* 6.25, =C*H*);

δC (75 MHz, $CDCl_3$) -5.4, 18.3, 19.2, 25.8, 28.0, 35.9, 58.8, 64.3, 122.8, 143.3;

m/z (CI+) 257 ($M+H^+$, 100 %); HRMS (ESI+) found 257.1927, $C_{14}H_{29}O_2Si$ ($[M+H]^+$), requires 257.1937 (-3.9 ppm).

4-(*tert*-Butyldimethylsilyloxy)-3-cyclobutylbut-2-enyl carbamate (2.63)[50]



To a stirred solution of allyl alcohol **2.17** (200 mg, 0.8 mmol) in dichloromethane (5 mL) was added trichloroacetyl isocyanate (190 μL, 1.6 mmol) at 0 ºC. The reaction mixture was stirred at this temperature for one hour and then the solvent was removed by evaporation under reduced pressure. The residue was immediately taken up in methanol (5 mL) and water (2.7 mL) and the solution was cooled to 0 ºC. Potassium carbonate (330 mg, 1.7 mmol) was added to the stirred solution and the reaction mixture was warmed to room temperature for three hours. The solvent was removed under reduced pressure and the product was subjected to silica chromatography (20 % Et_2O/petrol) to give the title compound as a 3:1 mixture of geometric isomers as a colourless oil (170 mg, 70 %);

Z isomer: R_f 0.20 (20 % EtOAc/Petrol);

IR υ_{max} (neat/cm^{-1}) 3344, 2928, 2856, 1717, 1471, 1400, 1329, 1252, 836, 775;

δH (300 MHz, $CDCl_3$) 0.07 (6H, s, SiCH_3), 0.92 (9H, s, SiC(CH_3)$_3$), 1.67-2.09 (6H, m, CH_2 CH_2 CH_2), 3.34 (1H, m, *c*-Bu), 4.17 (2H, s, CH_2OSi), 4.60 (2H, d, *J* 7.0 Hz, CH_2OCO, 4.8 (2H, bs, NH_2), 5.53 (1H, dt, *J* 7.0 Hz, 1.6 Hz, =C*H*);

δC (75 MHz, $CDCl_3$) -5.4, 18.2, 19.2, 25.8, 27.6, 39.3, 59.8, 61.5, 118.0, 147.4, 156.9;

m/z (ESI+) 322 ($M+Na^+$, 100 %); HRMS (ESI+) found 322.1815, $C_{15}H_{29}N_1O_3Na_1Si$ ($[M+Na]^+$), requires 322.1809 (-1.4 ppm).

E isomer: R_f 0.20 (20 % EtOAc/Petrol);

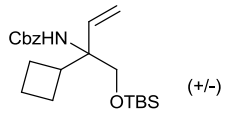
IR υ_{max} (neat/cm^{-1}) 3344, 2928, 2856, 1717, 1471, 1400, 1329, 1253, 1052, 836, 775;

δH (300 MHz, $CDCl_3$) 0.06 (6H, s, SiCH_3), 0.89 (9H, s, SiC(CH_3)$_3$), 1.67-2.09 (6H, m, CH_2 CH_2 CH_2), 3.11 (1H, m, *c*-Bu), 4.15 (2H, s, CH_2OSi), 4.67 (2H, d, *J* 7.0 Hz, CH_2OCO, 4.8 (2H, bs, NH_2), 5.33 (1H, t, *J* 7.0 Hz);

δC (75 MHz, $CDCl_3$) -5.4, 18.3, 19.2, 25.9, 27.9, 35.8, 60.4, 61.3, 117.5, 145.5, 157;

m/z (ESI+) 322 ($M+Na^+$, 100 %); HRMS (ESI+) found 322.1815, $C_{15}H_{29}N_1O_3Na_1Si$ ($[M+Na]^+$), requires 322.1809 (-1.4 ppm).

(+/-) Benzyl 1-(*tert*-butyldimethylsilyloxy)-2-cyclobutylbut-3-en-2-ylcarbamate (2.65)[50]



To a stirred solution of allyl carbamate (12.75 g, 42.6 mmol) and triphenylphosphine (27.94 g, 106.5 mmol) in dichloromethane (536 mL) was added a solution of carbon tetrabromide (39.6 g, 119 mmol) in dichloromethane (93 mL) at -10 ºC. The reaction mixture was stirred at -10 °C for 1 hour then the reaction mixture was washed with sat $NaHCO_{3\ (aq)}$, brine and then dried over $MgSO_4$. Concentration under reduced pressure gave a thick oil which was immediately dissolved in fresh tetrahydrofuran (180 mL) and powdered molecular sieves (22 g) were added. The resulting suspension was treated at 0 °C with a solution of BnONa (freshly prepared from benzyl alcohol (8.8 mL, 85 mmol) and NaH (3.4 g, 85 mmol) in (THF 375 mL)). The reaction mixture was stirred at room temperature for 1 hour and diluted with EtOAc. The organic layer was washed with sat $NH_4Cl_{\ (aq)}$, brine and dried over $MgSO_4$. The solvent was stripped under reduced pressure and the product was purified by silica gel chromatography (0-10 % Et_2O/petrol). This gave a colourless oil, (13.75 g, 83 %) R_f 0.65 (20 % Et_2O/petrol); IR (neat) υ_{max} 3360, 3090, 3067, 3033, 2952, 2933, 2887, 2858, 1733, 1498, 1470, 1400, 1250, 1100, 1005, 778;

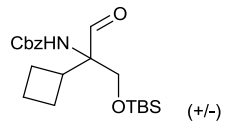
δH (500 MHz, $CDCl_3$) 0.00 (3H, s SiCH_3), 0.01 (3H, s, SiCH_3), 0.87 (9H, s, SiC(CH_3)$_3$), 1.6-1.97 (6H, m, CH_2 CH_2 CH_2), 2.87-2.96 (1H, m, *c*-Bu), 3.67 (1H, d, J= 9.46 Hz, CH_ACH$_B$OSi), 3.78 (1H, d, J= 9.46 Hz, CH$_A$CH_BOSi), 4.89 (1H, brs, N*H*), 5.04 (2H, s, CH_2OCO), 5.08 (1H, d, J= 16.71 Hz, CH_AH$_B$=CH), 5.22 (1H, d, J= 11.0 Hz, CH$_A$$H_B$=CH), 5.88 (1H, dd, J=17.7, 11 Hz, CH$_A$H$_B$=C*H*), 7.25-7.4 (m, 5H, Ar-*H*);

δC (75 MHz, $CDCl_3$) -5.3, 17.8, 18.5, 23.3, 23.4, 26.1, 40.6, 61.3, 64.6, 66.5, 114.8, 128.3, 128.4, 128.7, 137.1, 137.6, 142.2;

m/z (ES+) 412 ($M+Na^+$, 100 %);

HRMS (ESI+) found 412.2274, $C_{22}H_{35}O_3N_1Na_1Si_1$ ($[M+Na]^+$), requires 412.2278 (-1.1 ppm).

(+/-) Benzyl 1-(*tert*-butyldimethylsilyloxy)-2-cyclobutyl-3-oxopropan-2-ylcarbamate (2.22)[49]



A mixture of ozone and oxygen was bubbled through a solution of alkene **2.65** (500 mg, 1.28 mmol, 1.0 eq) in dichloromethane (14.1 mL) at -78 °C until the reaction mixture assumed a pale blue colour. Triphenylphosphine (404 mg, 1.5 mmol, 1.2 eq) was then added and the solution allowed to warm to room temperature, stirring was continued for two hours. The reaction mixture was concentrated under reduced pressure and the resulting residue subjected to silica gel chromatography (0→3 % Et_2O/ Petrol). This gave a very pale mobile oil (408 mg, 81 %). R*f* = 0.25 (10 % Et_2O/ Petrol);

IR (neat/ cm^{-1}) 3401, 3350, 2961, 2853, 1718, 1506, 1380, 1253, 1106, 1008, 835, 781, 740, 692;

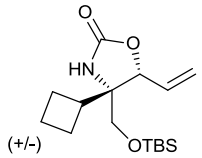
δH (300 MHz, $CDCl_3$) 0.01 (6H, s, 2xSiCH_3), 0.85 (9H, s, SiC(CH_3)$_3$, 1.62-2.16 (6H, m, CH_2 CH_2 CH_2), 2.88-3.05 (1H, m, *c-Bu*), 3.95 (1H, d, *J* 10.5 Hz, CH_ACH_BOSi), 4.05 (1H, d, *J* 10.5 Hz, 1H, CH_ACH_BOSi), 5.10 (2H, s, ArCH_2O), 5.46 (1H, brs, N*H*), 7.3-7.4 (5H, m, Ar-*H*), 9.62 (1H, s, *H*CO);

δC (75 MHz, $CDCl_3$) -5.4, -5.4, 18.3, 18.7, 23.4, 24.1, 26.0, 37.6, 61.6, 67.1, 67.7, 128.4, 128.8, 155.8, 200.8;

m/z (ES^-) 390 ($M\text{-}H^+$, 100 %),

HRMS (ESI+) found 392.2234, $C_{21}H_{34}O_4N_1Si_1$ ($[M+H]^+$), requires 392.2252 (-4.5 ppm).

(+/-) (4S,5R)-4-((*tert*-Butyldimethylsilyloxy)methyl)-4-cyclobutyl-5-vinyloxazolidin-2-one (2.79)



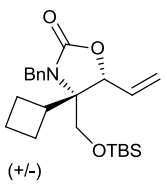
To a stirred solution of aldehyde **2.22** (3.6 g, 9.2 mmol) in tetrahydrofuran (92 mL) was added a 0.7 M solution of vinyl magnesium bromide in tetrahydrofuran (26.3 mL, 20.24 mmol) at -78 ºC. The solution was stirred for 2 hours at this temperature then for 16 hours at room temperature. Saturated NH_4Cl (50 mL) was added and the solvent was removed under reduced pressure. The aqueous residue was extracted with diethyl ether (3 x 50 mL) and dried over $MgSO_4$. Solvent was removed under vacuum and the residue was subjected to silica gel chromatography (25 % Et_2O/ Petrol) to give a clear oil (2.6 g, 91 %). R_f 0.6 (25 % Et_2O/ Petrol);

IR (neat/ cm^{-1}) 3210, 2950, 2930, 2857, 1749, 1471, 1463, 1428, 1369, 1290, 1256, 1108, 1070, 1023, 989, 953, 939, 896, 838;

δH (300 MHz, $CDCl_3$) 0.01 (3H, s, SiC*H*$_3$), 0.00 (3H, s, SiC*H*$_3$), 0.84 (9H, s, SiC(C*H*$_3$)$_3$), 1.67-2.10 (6H, m, C*H*$_2$ C*H*$_2$ C*H*$_2$), 2.44-2.55 (1H, m, *c-Bu*), 2.36 (1H, d, *J* 10.5 Hz, C*H*$_A$H$_B$OSi), 2.39 (1H, d, *J* 10.5 Hz, CH$_A$*H*$_B$OSi), 4.51 (1H, d, *J* 7.0 Hz, C*H*OCO), 5.27 (1H, d, *J* 10.5 Hz, CHCHC*H*$_A$H$_B$), 5.34 (1H, d, *J* 17.0, CHCHCH$_A$*H*$_B$), 5.95 (1H, ddd, *J*, 17.0, 10.5, 6.0, CHC*H*CH$_A$H$_B$), 6.42 (1H, s, N*H*);

m/z (ES^-) 310 ($M\text{-}H^+$, 100 %), Accurate mass (ES+) found 334.1812, $C_{16}H_{29}O_3N_1Na_1Si_1$ requires 334.1809 (+0.9 ppm).

(4S,5R)-3-Benzyl-4-((*tert*-butyldimethylsilyloxy)methyl)-4-cyclobutyl-5-vinyloxazolidin-2-one (2.80)



To a stirred solution of crude carbamate **2.79** (615 mg, 1.97 mmol) in tetrahydrofuran (15 mL) was added a 60 % by mass dispersion of sodium hydride in paraffin oil (120 mg, 3 mmol) and benzyl bromide (0.47 mL, 4 mmol) at 0 ºC. The reaction mixture was heated to reflux and held at this temperature for 6 hours. Sat. NH_4Cl (50 mL) was added and the tetrahydrofuran was removed under reduced pressure. The aqueous residue was extracted with diethyl ether (3 x 50 mL). The combined organics were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude benzyl carbamate was purified by silica gel chromatography (0 → 40 % Et_2O/ Petrol) to give a thick oil (670 mg, 86 %). R_f 0.25 (15 % Et_2O/ Petrol)

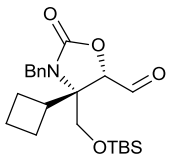
IR (neat/ cm^{-1}) 2929, 1752, 1402, 1252, 1107, 838, 777, 701;

δH (300 MHz, $CDCl_3$) 0.00 (6H, s, 2 x SiCH_3), 0.87 (9H, s, SiC(CH_3)$_3$), 1.29-1.87 (6H, m, CH_2 CH_2 CH_2), 2.52 (1H, m, *c*-Bu), 3.49 (2H, s, CH_2OSi), 4.03 (1H, d, *J* 15.8 Hz, CH_AH$_B$Ph), 4.65 (1H, d, *J* 15.8 Hz, CH$_A$$H_B$Ph), 4.82 (1H, d, *J* 7.6 Hz, C*H*OCO), 5.36 (1H, d, *J*, 10.5 Hz, CHCHCH_AH$_B$), 5.48 (1H, d, *J* 16.0 Hz, CHCHCH$_A$$H_B$), 6.04 (1H, ddd, *J* 18.0 Hz, 9.8 Hz, 7.6 Hz, CHC*H*CH$_A$H$_B$), 7.2-7.35 (5H, m, Ar-H);

δC (125 MHz, $CDCl_3$) 5.8, 17.5, 18.0, 22.6, 25.7, 38.2, 45.3, 61.7, 67.8, 79.8, 120.8, 127.3, 127.8, 128.4, 132.6, 138.5, 156.0;

m/z (ES^+) 424 ($M+Na^+$, 100 %), Accurate mass (ES+) found 424.2281, $C_{23}H_{35}O_3N_1Na_1Si_1$ requires 424.2278 (+0.6 ppm).

(+/-)(4S,5S)-3-Benzyl-4-((*tert*-butyldimethylsilyloxy)methyl)-4-cyclobutyl-2-oxooxazolidine-5-carbaldehyde (2.61)



A mixture of O_2 and O_3 were bubbled through a stirred solution of olefin **2.80** (1.87 g, 4.65 mmol) in dichloromethane (50 mL) at -78 ºC until the solution assumed a pale blue colouration. Triphenylphosphine (1.36 g, 5.56 mmol) was added immediately and reaction mixture was stirred at room temperature for

three hours. The solvent was removed under reduced pressure and the product purified by silica gel chromatography (25 → 100 % Et_2O/ Petrol) to give the aldehyde as a pale oil (1.7 g, 90 %). R_f 0.1 (20 % Et_2O/ Petrol).

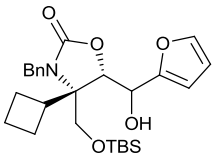
IR (neat/ cm^{-1}) 2929, 2853, 2357, 1755, 1738, 1405, 1101, 837;

δH (300 MHz, $CDCl_3$) 0.00 (3H, s, SiCH_3), 0.01 (3H, s, SiCH_3), 0.89 (9H, s, SiC(CH_3)$_3$), 1.20-2.06 (6H, m, CH_2 CH_2 CH_2), 2.39 (1H, m, *c*-Bu), 3.42 (1H, d, *J* 11.0 Hz, CH_AH$_B$OSi), 3.49 (1H, d, *J* 11.0 Hz, CH$_A$$H_B$OSi), 3.94 (1H, d, *J* 15.5 Hz, CH_AH$_B$Ph), 4.65 (1H, d, *J* 1 Hz, C*H*OCO), 4.71 (1H, d, *J* 15.5 Hz, CH$_A$$H_B$Ph), 7.26-7.38 (5H, m, Ar-H), 9.82 (1H, d, *J* 1.0 Hz, C*H*O);

δC (125 MHz, $CDCl_3$) 5.8, 17.3, 17.9, 22.5, 25.6, 37.0, 44.9, 59.3, 72.6, 78.6, 127.8, 128.2, 128.6, 137.5, 157.9, 199.9;

m/z (ES^-) 402 ($M\text{-}H^+$, 100 %), Accurate mass (ES+) found 404.2258, $C_{23}H_{34}O_4N_1Si_1$ requires 404.2252 (+1.6 ppm).

(+/-) (4S,5S)-3-Benzyl-4-((*tert*-butyldimethylsilyloxy)methyl)-4-cyclobutyl-5-(furan-2-yl(hydroxy)methyl)oxazolidin-2-one (2.81)



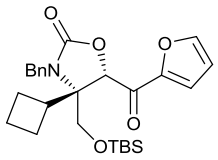
To a stirred solution of furan (85 µl, 1.2 mmol) in tetrahydrofuran (2.4 mL) ºC was added dropwise a 1.6 M solution of BuLi in hexanes (730 µl, 1.2 mmol) at -78. The reaction mixture was warmed to room temperature and stirred for 1.5 hours. The solution was re-cooled to -78 ºC and a solution of aldehyde **2.61** (157 mg, 0.39 mmol) in tetrahydrofuran (1.2 mL) was added. The mixture was stirred at this temperature for 5 hours and then sat. NH_4Cl (5 mL) was added. The solvent was removed under reduced pressure and the remaining liquid extracted with ether (3 x 5 mL). The combined organics were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was subjected to silica gel chromatography (20 % Et_2O/ Petrol) to give the required alcohol (110 mg, 60 %) as an inseparable mixture of diastereoisomers.

Isomer 1: R_f 0.52 (50 % Et_2O/ Petrol);

IR (neat/ cm^{-1}) 3385, 2956, 2857, 2351, 2335, 1727, 1411, 1256, 1106, 838;
δH (300 MHz, $CDCl_3$) -0.01 (3H, s, SiC*H*$_3$), 0.00 (3H, s, SiC*H*$_3$), 0.83 (9H, s, SiC(C*H*$_3$)$_3$), 1.54-2.16 (6H, m, C*H*$_2$ C*H*$_2$ C*H*$_2$), 2.70 (1H, m, *c*-Bu), 3.46 (1H, d, *J* 4.5 Hz, O*H*), 3.58 (1H, d, *J* 11.4 Hz, C*H*$_A$H$_B$OSi), 3.66 (1H, d, *J* 11.4 Hz, CH$_A$*H*$_B$OSi), 4.33 (1H, d, *J* 16.0 Hz, C*H*$_A$H$_B$Ph), 4.42 (1H, d, *J* 16.0 Hz, CH$_A$*H*$_B$Ph), 4.67 (1H, d, *J* 8.8 Hz, COOC*H*), 5.07 (1H, dd, *J* 8.8 Hz, 4.5 Hz, C*H*OH), 6.34 (1H, dd, *J* 3.2 Hz, 1.5 Hz, Fur-*H*), 6.38 (1H, d, *J* 3.2 Hz, Fur-*H*), 7.21-7.32 (5H, m, Ar-H), 7.4 (1H, d, *J* 1.5 Hz, Fur-*H*);
δC (125 MHz, $CDCl_3$) -6.0, 17.5, 18.0, 23.2, 23.3, 25.7, 39.4, 45.4, 62.3, 66.0, 68.1, 78.0, 108.7, 110.5, 127.5, 127.6, 127.8, 128.5, 128.6, 138.5, 142.5, 152.8, 158.2;
m/z (ES^-) 470.3 ($M\text{-}H^+$, 100 %), Accurate mass (ES+) found 472.2505, $C_{26}H_{38}O_5N_1Si_1$ requires 472.2514 (-1.9 ppm).

Isomer 2: R_f 0.37 (50 % Et_2O/ Petrol);
IR (neat/ cm^{-1}) 3375, 2956, 2852, 2366, 2325, 1741, 1403, 1258, 1095, 838;
δH (300 MHz, $CDCl_3$) 0.00 (3H, s, SiC*H*$_3$), 0.01 (3H, s, SiC*H*$_3$), 0.85 (9H, s, SiC(C*H*$_3$)$_3$), 1.38-1.82 (6H, m, C*H*$_2$ C*H*$_2$ C*H*$_2$), 2.29 (1H, m, *c*-Bu), 3.22 (1H, d, *J* 4.5 Hz, O*H*), 3.64 (1H, d, *J* 11.4 Hz, C*H*$_A$H$_B$OSi), 3.66 (1H, d, *J* 11.4 Hz, CH$_A$*H*$_B$OSi), 4.13 (1H, d, *J* 16.0 Hz, C*H*$_A$H$_B$Ph), 4.57 (1H, d, *J* 16.0 Hz, CH$_A$*H*$_B$Ph), 4.69 (1H, d, *J* 4.5 Hz, COOC*H*), 5.12 (1H, t, 4.5 Hz, C*H*OH), 6.34 (1H, dd, *J* 3.2 Hz, 1.6 Hz, Fur-*H*), 6.40 (1H, d, *J* 3.2 Hz, Fur-*H*), 7.18-7.30 (5H, m, Ar-H), 7.36 (1H, d, *J* 1Hz, Fur-*H*);
δC (125 MHz, $CDCl_3$) -5.9, 17.3, 18.0, 22.9, 23.0, 25.7, 39.2, 45.3, 61.7, 66.2, 67.4, 78.7, 108.3, 110.7, 127.4, 127.5, 128.5, 138.1, 142.3, 152.7, 158.4;
m/z (ES^-) 470.4 ($M\text{-}H^+$, 100 %), Accurate mass (ES+) found 494.2327, $C_{26}H_{37}O_5N_1Na_1Si_1$ requires 494.2333 (-1.3 ppm).

(+/-) (4S,5S)-3-Benzyl-4-((*tert*-butyldimethylsilyloxy)methyl)-4-cyclobutyl-5-(furan-2-carbonyl)oxazolidin-2-one (2.68)



To a stirred solution of epimeric alcohol **2.81** (1.37 g, 2.9 mmol), NMO (512 mg, 4.4 mmol) and 4 Å molecular sieves (1.4 g) in dichloromethane (29 mL) was added TPAP (102 mg, 0.29 mmol). The reaction mixture was stirred for 2 hours at room temperature and then filtered through Celite ®. The solvent was removed under reduced pressure and the crude residue purified upon subjection to silica gel chromatography (0 → 20 % Et_2O/ Petrol). This gave ketone as a clear, colourless oil (1.21 g, 85 %). R_f 0.47 (50 % Et_2O/ Petrol);

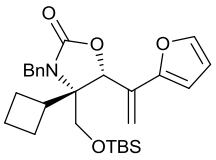
IR (neat/ cm^{-1}) 2929, 2853, 1754, 1664, 1463, 1409, 1254, 1104, 838, 777;

δH (300 MHz, $CDCl_3$) 0.00 (3H, s, SiCH_3), 0.09 (3H, s, SiCH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 1.51-2.44 (6H, m, CH_2CH_2CH_2), 2.72 (1H, m, *c*-Bu), 3.77 (1H, d, *J* 11.4 Hz, CH_AH$_B$OSi), 3.97 (1H, d, *J* 11.4 Hz, CH$_A$$H_B$OSi), 4.42 (1H, d, *J* 15.8 Hz, CH_AH$_B$Ph), 5.02 (1H, d, *J* 15.8 Hz, CH$_A$$H_B$Ph), 5.35 (1H, s, COOC*H*), 6.80 (1H, dd, *J* 3.5 Hz, 2.0 Hz, Fur-*H*), 7.50-7.63 (5H, m, Ar-H), 7.89 (1H, d, *J* 2.0 Hz, Fur-*H*), 7.95 (1H, d, *J* 3.5 Hz, Fur-*H*));

δC (125 MHz, $CDCl_3$) -6.2, 17.2, 18.0, 22.7, 25.5, 38.6, 45.1, 59.9, 71.7, 78.0, 112.6, 122.3, 127.6, 128.0, 128.5, 137.8, 147.0, 150.6, 157.8, 184.1;

m/z (ES^+) 492 ($M+H^+$, 100 %), Accurate mass (ES+) found 492.2175, $C_{26}H_{35}O_5N_1Na_1Si_1$ requires 492.2117 (-0.3 ppm).

(+/-) (4S,5R)-3-Benzyl-4-((*tert*-butyldimethylsilyloxy)methyl)-4-cyclobutyl-5-(1-(furan-2-yl)vinyl)oxazolidin-2-one (2.60)



Method 1: Via Wittig

To a stirred solution of methyltriphenylphosphonium bromide (126 mg, 0.35 mmol) in tetrahydrofuran (1.25 mL) was added a 1.6 M solution of BuLi in hexanes (221 µl, 0.35 mmol). The reaction mixture was stirred at room temperature for 1 hour before the drop wise addition of a solution of ketone **2.68** (111 mg, 0.24 mmol) in tetrahydrofuran (1.2 mL). The reaction mixture was stirred at room temperature for 15 minutes and quenched by the addition of sat. NH_4Cl (5 mL). The solvent was removed under reduced pressure and the remaining liquid was extracted with ether (3 x 5 mL). The combined organics were dried over $MgSO_4$ and the solvent removed under reduced pressure to give crude olefin **2.60**. Subjection to silica gel chromatography (15 % Et_2O/ Petrol) gave analytically pure product as a yellow oil (80 mg, 72 %).

Method 2:

To a stirred solution of vinyl stannane **2.88** (6.2 g, 16.2 mmol) in tetrahydrofuran (125 mL) was added 1.6 M solution of nBuLi in hexanes (10.1 mL, 16.2 mmol) dropwise at – 78 ºC. The reaction mixture was stirred at this temperature for 10 minutes over which time the solution developed a deep blood red coloration. A solution of aldehyde **2.22** (2.9g, 7.4 mmol) in tetrahydrofuran was then added drop wise and stirring was continued at this temperature for 20 minutes. The reaction mixture was allowed to warm to room temperature and stirring was continued for 16 hours. Sat. NH_4Cl (50 mL) was added and the organic layer removed. The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the organic extracts were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure to yield a yellow oil which was used without further purification. R_f 0.35 (50 % Et_2O/ Petrol).

To a stirred solution of crude carbamate in tetrahydrofuran (25 mL) was added a 60 % by mass dispersion of sodium hydride in paraffin oil (422 mg, 10.5 mmol)

and benzyl bromide (1.4 mL, 15 mmol) at 0 ºC. The reaction mixture was heated to reflux and held at this temperature for 6 hours. Sat. NH_4Cl (50 mL) was added and solvent was removed under reduced pressure The aqueous residue was extracted with diethyl ether (3 x 50 mL) and the combined organics were dried over Na_2SO_4 and solvent removed under reduced pressure. The residue was purified by silica gel chromatography (20 % Et_2O/ Petrol) to give a thick pale oil (2.7 g, 78 % over two steps). R_f 0.24 (20 % Et_2O/ Petrol);

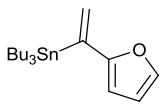
IR (neat/ cm^{-1}) 2928, 2852, 2361, 1754, 1254, 1107, 837;

m/z (ES^+) 49 ($M+Na^+$, 100 %), Accurate mass (ES+) found 490.2379, $C_{27}H_{37}O_4N_1Na_1Si_1$ requires 490.2384 (-1.0 ppm).

δH (300 MHz, $CDCl_3$) 0.00 (3H, s, SiC*H*$_3$), 0.05 (3H, s, SiC*H*$_3$), 0.99 (9H, s, SiC(C*H*$_3$)$_3$), 1.77-2.24 (6H, m, C*H*$_2$ C*H*$_2$ C*H*$_2$), 3.11 (1H, qn, *J* 9 Hz, *c*-Bu), 3.54 (1H, d, *J* 11.0 Hz, C*H*$_A$H$_B$OSi), 3.69 (1H, d, *J* 11.0 Hz, CH$_A$*H*$_B$OSi), 4.60 (1H, d, *J* 15.8 Hz, C*H*$_A$H$_B$Ph), 4.85 (1H, d, *J* 15.8 Hz, CH$_A$*H*$_B$Ph), 5.59 (1H, d, *J* 1 Hz, =*H*$_A$H$_B$) 5.70 (1H, s, COOC*H*), 5.99 (1H, d, *J* 1 Hz, =H$_A$*H*$_B$), 6.61 (1H, dd, *J* 3.5 Hz, 2.0 Hz, Fur-*H*), 6.63 (1H, d, *J* 3.5 Hz, Fur-*H*), 7.41-7.54 (5H, m, Ar-H), 7.59 (1H, d, *J* 1.5 Hz, Fur-*H*);

δC (125 MHz, $CDCl_3$) -6.2, -6.0, 17.0, 18.0, 22.7, 22.9, 25.8, 37.8, 45.8, 62.7, 68.5, 76.0, 106.9, 111.5, 114.6, 127.0, 127.2, 128.3, 132.9, 138.6, 142.1, 152.1, 158.8.

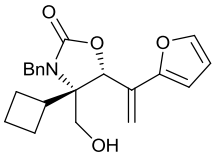
Tributyl(1-(furan-2-yl)vinyl)stannane (2.88)



A 1.6 M solution of nBuLi in hexanes (31.2 mL, 50 mmol) was added drop wise to a solution of DIPA (7.1 mL, 50 mmol) in tetrahydrofuran (244 mL) at 0 ºC and stirred for 30 minutes. Bu_3SnH (12.2 mL) was then added drop wise with care and the solution was stirred for a further 30 minutes over which time the solution attained a dark yellow coloration. A solution of acetyl furan (5.0 g, 45.4 mmol) in tetrahydrofuran (9.1 mL) was added to the mixture and the solution was warmed to room temperature and stirred until loss of acetyl furan by TLC (*ca* 1 hour). Mesyl chloride (14.8 mL, 182 mmol) and NEt_3 (47 mL, 340.5 mmol)

were then added and the reaction mixture allowed to stir at room temperature overnight. The thick pale brown mixture was extracted between MeCN (500 mL) and pentane (3 x 500 mL). The pentane extractions were combined and evaporated under reduced pressure to give crude vinyl stannane which was purified by silica gel chromatography (100 % pentane) to give a very mobile yellow oil (8.4 g, 59 %) which was used immediately. R_f 0.95 (pentane);
δH (300 MHz, $CDCl_3$) 0.8-1.5 (27H, m, Bu), 5.22 (1H, d, *J* 2.5 Hz, =CH_AH$_B$), 6.15 (1H, d, *J* 3.5 Hz, Fur-*H*), 6.19 (1H, d, *J* 2.5 Hz, =CH$_A$$H_B$), 6.28 (1H, dd, *J* 3.5 Hz, 1.8 Hz, Fur-H), 7.27 (1H, d, *J* 1.8 Hz, Fur-*H*);
δC (125 MHz, $CDCl_3$) 10.1, 13.7, 27.5, 28.9, 106.0, 111.2, 122.6, 139.8, 141.4, 158.6.

(+/-) (4S,5R)-3-Benzyl-4-cyclobutyl-5-(1-(furan-2-yl)vinyl)-4-(hydroxymethyl)oxazolidin-2-one (2.95)



To a stirred solution of silyl ether **2.93** (108 mg, 0.23 mmol) in tetrahydrofuran (2.3 mL) was added drop wise a 1 M solution of TBAF in tetrahydrofuran (0.24 mL, 0.24 mmol) at room temperature. The yellow solution was stirred at room temperature for 1 hour and then a saturated solution of NH_4Cl (5 mL) was added. The solvent was removed under reduced pressure and the remaining liquid was extracted with ether (4 x 5 mL). The combined organics were dried over Na_2SO_4 and solvent removed under reduced pressure. The residue was purified by silica gel chromatography (50 % Et_2O/ Petrol) to give the primary alcohol (82 mg, 100 %) as a thick oil. R_f 0.12 (50 % Et_2O/ Petrol);

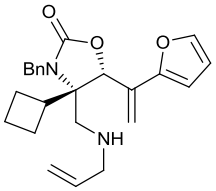
IR (neat/ cm^{-1}) 3427, 2945, 2361, 1750, 1495, 1434, 1408, 1357, 1289, 1149, 1063, 1017, 918, 884, 808, 744, 703;
δH (300 MHz, $CDCl_3$) 1.26 (1H, brs, O*H*), 1.53-1.98 (6H, m, CH_2 CH_2 CH_2), 2.75 (1H, qn, *J* 9 Hz, *c*-Bu), 3.29 (1H, dd, *J* 12.5 Hz, 4.0 Hz, CH_AH$_B$OH), 3.34 (1H, dd, *J* 12.5 Hz, 2.5 Hz, CH$_A$$H_B$OSH), 4.45 (1H, d, *J* 16.5 Hz, CH_AH$_B$Ph), 4.49 (1H, d, *J*

16.5 Hz, CH_AH_BPh), 5.32 (1H, s, COOC*H*), 5.39 (1H, s, $=H_AH_B$) 5.73 (1H, s, $=H_AH_B$), 6.34 (1H, dd, *J* 3.5 Hz, 2.0 Hz, Fur-*H*), 6.41 (1H, d, *J* 3.5 Hz, Fur-*H*), 7.17-7.32 (5H, m, Ar-H), 7.33 (1H, d, *J* 1.5 Hz, Fur-*H*);

δC (125 MHz, $CDCl_3$) 17.1, 22.9, 38.2, 45.6, 61.8, 68.7, 76.1, 107.4, 111.6, 114.2, 127.6, 128.7, 133.6, 138.4, 142.5, 151.6, 158.8;

m/z (ES^+) 371 ($M+NH_4^+$, 100 %), Accurate mass (ES+) found 376.1529, $C_{21}H_{23}O_4N_1Na_1$ requires 376.1519 (+2.6 ppm).

(+/-)(4S,5R)-4-((Allylamino)methyl)-3-benzyl-4-cyclobutyl-5-(1-(furan-2-yl)vinyl)oxazolidin-2-one (2.98)



To a stirred solution of primary alcohol **2.95** (39 mg, 0.11 mmol) in dichloromethane (1.1 mL) was added Dess-Martin periodinane (70 mg, 0.17 mmol) at room temperature. The initially clear solution was stirred at room temperature for 2 hours over which time a white precipitate appeared. The solvent was removed under reduced pressure and residue (31 mg, 80 %) R_f 0.46 (50 % Et_2O/ Petrol) was taken up in dry dichloromethane (0.3 mL). To this stirred solution was added allylamine (12 µl, 1.52 mmol) and oven dried $MgSO_4$ (44 mg, 0.36 mmol). The mixture was stirred at reflux for 16 hours before being filtered through Celite ® and the solvent was removed under reduced pressure. The crude residue was immediately dissolved in methanol (0.6 mL) and acetic acid (6.2 µl, 0.106 mmol) and a 1 M solution of $NaCNBH_3$ in tetrahydrofuran (122 µl, 0.122 mmol) were added. The reaction mixture was stirred at room temperature for 1 hour and then a saturated solution of $NaHCO_3$ (5 mL) was added. The aqueous mixture was extracted with ether (5 x 5 mL) and the combined organics were dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude residue purified by silica gel chromatography (20 % Et_2O/ Petrol) to give allylamine **2.98** (25 mg, 56 %) as a white foam. R_f 0.51 (50 % Et_2O/ Petrol);

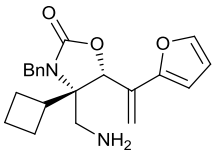
IR (neat/ cm^{-1}) 3343, 2945, 2359, 2341, 1744, 1643, 1495, 1455, 1403, 1359, 1287, 1148, 1060, 1017, 918, 805, 744, 703, 668;

δH (300 MHz, $CDCl_3$) 1.47-1.95 (6H, m, C*H*$_2$ C*H*$_2$ C*H*$_2$), 2.23 (1H, d, *J* 13.5 Hz, C*H*$_A$H$_B$C-cBu), 2.37 (1H, d, *J* 13.5 Hz, CH$_A$*H*$_B$C-cBu), 2.72 (3H, m, *c*-Bu and NHC*H*$_2$CHCH$_2$), 4.41 (1H, d, *J* 15.8 Hz, C*H*$_A$H$_B$Ph), 4.54 (1H, d, *J* 15.8 Hz, CH$_A$*H*$_B$Ph), 4.86 (1H, dd, *J* 16.5 Hz, 1.6 Hz NHCH$_2$CHC*H*$_A$H$_B$), 4.87 (1H, dd, *J* 10 Hz, 1.6 Hz NHCH$_2$CHCH$_A$*H*$_B$), 5.28 (1H, s, COOC*H*), 5.38 (1H, s, =*H*$_A$H$_B$), 5.52 (1H, ddt, *J* 16.5 Hz, 10 Hz, 6.0 Hz, C*H*=H$_A$H$_B$), 5.70 (1H, s, =H$_A$*H*$_B$), 6.33 (1H, dd, *J* 3.5 Hz, 1.5 Hz, Fur-*H*), 6.37 (1H, d, *J* 3.5 Hz, Fur-*H*), 7.14-7.32 (6H, m, Ar-H, Fur-*H*);

δC (125 MHz, $CDCl_3$) 17.1, 23.2, 23.4, 39.9, 46.0, 50.0, 53.0, 68.5, 76.9, 107.3, 111.8, 114.3, 115.9, 127.5, 127.8, 128.7, 134.1, 136.7, 138.9, 142.4, 152.2, 159.1.

m/z (ES^+) 393 ($M+H^+$, 100 %), Accurate mass (ES+) found 393.2170, $C_{24}H_{29}O_3N_2$ requires 393.2173 (-0.7 ppm).

(+/-) (4S,5R)-4-(Aminomethyl)-3-benzyl-4-cyclobutyl-5-(1-(furan-2-yl)vinyl)oxazolidin-2-one (2.108)

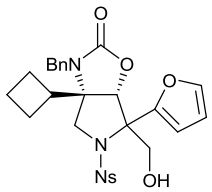


To a stirred solution of allylamine **2.98** (82 mg, 0.23 mmol), and 1,3-dimethylbarbituric acid (99 mg, 0.69 mmol) in dichloromethane (0.5 mL) was added $Pd(PPh_3)_4$ (2.5 mg, 1 mol %) at room temperature. The reaction mixture was warmed to 35 ºC and held at this temperature for 2 hours at which point TLC analysis showed complete loss of starting material. Saturated $NaHCO_3$ (5 mL) and ether (5 mL) were added to the reaction mixture and the organic layer separated. The aqueous layer was further extracted with ether (3 x 5 mL) and the combined organics dried over Na_2SO_4. Solvent was removed under reduced pressure and the crude residue purified by silica gel chromatography (70 % Et_2O/ Petrol) to give primary amine **2.108** (48 mg, 74 %) as a white foam. R_f 0.31 (Et_2O)

IR (neat/ cm^{-1}) 3407, 2943, 2867, 2360, 2342, 1739, 1622, 1495, 1404, 1359, 1286, 1163, 1061, 1018, 913, 807, 704;

δH (500 MHz, $CDCl_3$) 0.77 (2H, br s, NH_2), 1.47-1.99 (6H, m, CH_2 CH_2 CH_2), 2.51 (2H, s, CH_2N), 2.74 (1H, qn, *J* 8.8 Hz, *c*-Bu), 4.43 (1H, d, *J* 15.9 Hz, CH_AH$_B$Ph), 4.50 (1H, d, *J* 16.0 Hz, CH$_A$$H_B$Ph), 5.29 (1H, s, Fur-CC$H_AH_B$), 5.41 (1H, s, Fur-CC$H_AH_B$), 5.72 (1H, s, COOC*H*), 6.34 (1H, dd, *J* 3.2 Hz, 1.9 Hz, Fur-*H*), 6.40 (1H, d, *J* 3.2 Hz, Fur-*H*), 7.16-7.34 (6H, m, Ar-*H* + Fur-*H*);
δC (125 MHz, $CDCl_3$) 15.3, 17.0, 23.0, 23.1, 30.3, 39.4, 42.7, 45.6, 65.9, 69.2, 76.7, 107.3, 111.6, 114.2, 127.5, 127.6, 128.6, 133.9, 138.7, 142.4, 151.8, 159.1;
m/z (ES^+) 375 ($M+Na^+$, 100 %), Accurate mass (ES+) found 353.1857, $C_{21}H_{25}O_3N_2$ requires 353.1860 (-0.7 ppm).

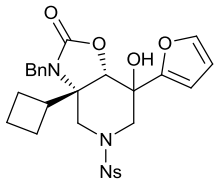
(+/-) (3aS,6aS)-3-Benzyl-3a-cyclobutyl-6-(furan-2-yl)-6-(hydroxymethyl)-5-(2-nitrophenylsulfonyl)hexahydro-2*H*-pyrrolo[3,4-d]oxazol-2-one (2.111)



To a stirred solution of diol **2.109** (4 mg, 7 μmol) and triphenylphosphine (2.3 mg, 9.1 μmol) in tetrahydrofuran (70 μL) was added DIAD (1.8 μL, 9.1 μmol) at room temperature. The solution was stirred for 16 hours and then the solvent was removed under reduced pressure. The residue was immediately subjected to silica gel chromatography (5-10 % Et_2O/petrol) and the solvent was removed to give primary alcohol **2.111** (2.8 mg) as a pale oil. Rf 0.43 (Et_2O);
IR (neat/ cm^{-1}) 3343, 2954, 2356, 1741, 1543, 1410, 1359, 1163, 1067, 985, 911, 851, 733, 668;
δH (400 MHz, $CDCl_3$) 1.19-1.70 (6H, m, CH_2 CH_2 CH_2), 2.55 (1H, m, *c*-Bu), 3.79 (1H, t, *J* 7.5 Hz, O*H*), 3.63 (1H, d, *J* 11.9 Hz, *c*-BuCCH_AH$_B$N), 3.85 (1H, d, *J* 11.9 Hz, *c*-BuCCH$_A$$H_B$N), 4.15 (1H, d, *J* 15.6 Hz, CH_AH$_B$Ph), 4.35 (1H, dd, *J* 12.6 Hz, 7.3 Hz, CH_AH$_B$OH), 4.42 (1H, dd, *J* 12.6 Hz, 7.5 Hz, CH_AH$_B$OH), 4.43 (1H, d, *J* 15.6 Hz, CH$_A$$H_B$Ph), 5.03 (1H, s, COOC*H*), 6.18 (1H, dd, *J* 3.3 Hz, 1.8 Hz, Fur-*H*), 6.40 (1H, dd, *J* 3.5 Hz, 0.8 Hz, Fur-*H*), 7.06 (1H, dd, *J* 1.8 Hz, 0.8 Hz, Fur-*H*), 7.19-7.29 (5H, m, Ar-*H*), 7.42-7.60 (3H, m, Ns-*H*), 7.67 (1H, dd, 8.1 Hz, 1.3 Hz, Ns-*H*);

m/z (ES^+) 576 ($M+Na^+$, 100 %), Accurate mass (ES+) found 554.1599, $C_{27}H_{28}O_8N_3S_1$ requires 554.1592 (+1.3 ppm).

(3aS,7aS)-3-Benzyl-3a-cyclobutyl-7-(furan-2-yl)-7-hydroxy-5-(2-nitrophenylsulfonyl)hexahydrooxazolo[4,5-c]pyridin-2(3H)-one (2.110)



To a stirred solution of diol **2.109** (34 mg, 0.06 mmol) in pyridine (0.5 mL) was added methanesulfonyl chloride (4.8 μL, 0.063 mmol) at 0 ºC and the reaction mixture was allowed to stir at this temperature for 2 hours then water (5 mL) was added and the mixture extracted with ethyl acetate (4 x 5 mL). Removal of the solvent under reduced pressure gave a pale yellow oil which was immediately dissolved in DMF (0.4 mL) and K_2CO_3 (10 mg, 0.07 mmol) was added. The reaction mixture was warmed to 45 ºC for 1.5 hours before being poured onto ethyl acetate (10 mL) and washed with saturated $NaHCO_3$ (3 mL) and water (2 x 3 mL). Solvent was removed under reduced pressure and the crude residue was purified by silica gel chromatography to give piperidine **2.110** (14 mg, 42 %) as a yellow syrup. R_f 0.58 (Et_2O);

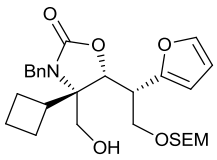
IR (neat/ cm^{-1}) 3312, 2935, 2852, 1741, 1493, 1447, 1429, 1403, 1349, 1245, 1217, 1173, 1150, 1064, 1026, 995, 959, 907, 840, 814;

δH (400 MHz, $CDCl_3$) 1.41-1.89 (6H, m, C*H*$_2$ C*H*$_2$ C*H*$_2$), 2.54 (1H, m, *c*-Bu), 3.30 (1H, d, *J* 12.9 Hz, *c*-BuCC*H*$_A$H$_B$N), 3.49 (1H, d, *J* 12.6 Hz, Fur-CHC*H*$_A$H$_B$), 3.59 (1H, d, *J* 12.9 Hz, *c*-BuCCH$_A$*H*$_B$N), 3.60 (1H, dd, *J* 12.6 Hz, 1.5 Hz, Fur-CHCH$_A$*H*$_B$), 3.79 (1H, d, *J* 1.5 Hz, O*H*), 4.23 (1H, d, *J* 15.6 Hz, C*H*$_A$H$_B$Ph), 4.41 (1H, d, *J* 15.6 Hz, CH$_A$*H*$_B$Ph), 4.86 (1H, s, COOC*H*), 6.24 (1H, dd, *J* 3.3 Hz, 1.8 Hz, Fur-*H*), 6.39 (1H, dd, *J* 3.3 Hz, 0.8 Hz, Fur-*H*), 7.19-7.34 (6H, m, Ar-*H* + Fur-*H*), 7.56-7.68 (3H, m, Ns-*H*), 7.77 (1H, m, Ns-*H*);

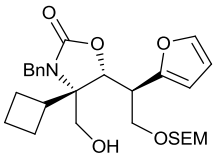
δC (125 MHz, $CDCl_3$) 17.3, 22.8, 22.9, 30.3, 31.0, 41.1, 45.1, 46.2, 49.1, 64.1, 70.7, 75.0, 108.7, 110.9, 124.4, 127.9, 128.4, 128.7, 130.9, 131.0, 131.9, 134.0, 137.1, 143.1, 148.2, 152.5, 157.4;

m/z (ES^+) 576 ($M+Na^+$, 100 %), Accurate mass (ES+) found 554.1586, $C_{27}H_{28}O_8N_3S_1$ requires 554.1592 (-1.0 ppm).

(+/-) (4S,5R)-3-Benzyl-4-cyclobutyl-5-(1-(furan-2-yl)-2-((2-(trimethylsilyl)ethoxy)methoxy)ethyl)-4-(hydroxymethyl)oxazolidin-2-one (2.120), (2.126)



2.120



2.126

To a stirred solution of olefin **2.60** (85 mg, 0.18 mmol) in tetrahydrofuran (2.2 mL) was added a 1M solution of BH_3.THF (0.54 mL,0.54 mmol) at 0 ºC and the solution was warmed to 35 ºC and allowed to hydroborate for 3 hours. A 3 M solution of NaOH (0.5 mL) was then added and the solution stirred for 30 minutes before a 30 % solution of H_2O_2 (0.54 mL) was added and stirred for a final 30 minutes. The reaction mixture was poured onto water (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organics were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude residue was subjected to silica gel chromatography to give primary alcohols as an inseparable mixture of isomers 1:1, (60 mg, 65 %) R_f 0.24 (40 % EtOAc/ Petrol). Which was used immediately in the next step.

To a stirred solution of primary alcohols **2.69** and **2.70** (706 mg, 1.45 mmol) in dichloromethane (15 mL) was added SEM chloride (0.8 mL, 4.36 mmol), DMAP (18 mg, 0.015 mmol), TBAI (54 mg, 0.015 mmol) and *i*-$PrNEt_2$ (1.5 mL, 8.7 mmol). The reaction mixture was stirred at room temperature for 16 hours. Sat NH_4Cl (50 mL) was added and the organic phase removed, the aqueous layer was extracted with diethyl ether (3 x 15 mL), the organics were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude residue purified by silica gel chromatography. (20 % Et_2O/ Petrol) to give an inseparable mixture of diastereoisomers of title compound as a yellow oil (889 mg, 99 %). R_f 0.80 (50 % Et_2O/ Petrol). Which was used immediately in the next step.

To a stirred solution of TBS ether (369 mg, 0.58 mmol) in tetrahydrofuran (6 mL) was added a 1 M solution of TBAF in tetrahydrofuran (0.87 mL, 8.7 mmol). The orange solution was stirred for 16 hours until complete loss of starting material by TLC. Saturated NH_4Cl (5 mL) was added and solvent was removed under reduced pressure. The aqueous mixture was extracted with ether (3 x 5 mL) and the combined organics were dried over Na_2SO_4. The crude residue was subjected to silica gel chromatography to give the target compounds as yellow oil.

2.120 (127 mg, 43 %) R_f 0.84 (Et_2O).

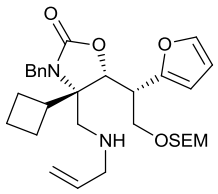
IR (neat/ cm^{-1}) 3431, 2952, 2351, 1723, 1411, 1248, 1058, 835, 703;
δH (500 MHz, $CDCl_3$) 0.00 (9H, s, $Si(CH_3)_3$), 0.90-0.95 (2H, m, OCH_2CH_2Si), 1.06 (1H, br s, O*H*), 1.68-2.03 (6H, m, CH_2 CH_2 CH_2), 2.96 (1H, qn, *J* 8.8 Hz, *c*-Bu), 3.41 (1H, d, *J* 12.0 Hz, CH_AH_BOH), 3.45 (1H, dd, *J* 9.8 Hz, 5.7 Hz, Fur-C*H*), 3.49 (1H, d, *J* 12.0 Hz, CH_AH_BOH), 3.59 (2H, dd, *J* 9.5 Hz, 7.6 Hz, OCH_2H_2Si), 3.67 (1H, dd, *J* 9.6 Hz, 5.7 Hz, CH_AH_BOSEM), 3.86 (1H, t, *J* 9.8 Hz, CH_AH_BOSEM), 4.15 (1H, d, *J* 16.1 Hz, CH_AH_BPh), 4.49 (1H, d, *J* 16.1 Hz, CH_AH_BPh), 4.69 (2H, s, OCH_2O), 5.00 (1H, s, COOC*H*), 6.39 (1H, dd, *J* 2.8 Hz, 1.9 Hz, Fur-*H*), 6.43 (1H, d, *J* 3.0 Hz, Fur-*H*), 6.94-6.99 (2H, m, Ar-*H*), 7.17-7.22 (3H, m, Ar-*H*), 7.33 (1H, m, Fur-*H*);
δC (125 MHz, $CDCl_3$) 0.01, 19.0, 19.5, 24.2, 24.7, 40.1, 41.2, 46.4, 63.6, 66.9, 67.8, 69.9, 76.5, 96.4, 110.5, 112.6, 128.6, 128.7, 130.0, 139.5, 142.9, 152.0, 156.0;
m/z (ES^+) 524.3 ($M+Na^+$, 100 %), Accurate mass (ES+) found 524.2421, $C_{27}H_{39}O_6N_1Si_1Na_1$ requires 524.2444 (-2.3 ppm).

2.126 (106 mg, 36 %) %) R_f 0.53 (Et_2O)

IR (neat/ cm^{-1}) 3425, 2951, 1739, 1496, 1410, 1359, 1248, 1148, 1063, 916, 859, 835, 733;
δH (500 MHz, $CDCl_3$) 0.00 (9H, s, $Si(CH_3)_3$), 0.86-0.92 (2H, m, OCH_2CH_2Si), 1.45-1.85 (7H, m, CH_2 CH_2 CH_2 + O*H*), 2.16 (1H, qn, *J* 9.1 Hz, *c*-Bu), 3.36 (1H, dd, *J* 12.8 Hz, 2.2 Hz, CH_AH_BOH), 3.48 (2H, t, *J* 8.5 Hz, OCH_2H_2Si), 3.52 (1H, dd, *J* 13.0 Hz, 6.9 Hz, CH_AH_BOH), 3.90 (1H, ddd, *J* 10.7 Hz, 7.3 Hz, 3.8 Hz, Fur-C*H*), 3.93 (1H, dd, *J* 9.1 Hz, 5.7 Hz, CH_AH_BOSEM), 3.98 (1H, t, *J* 9.1 Hz, 7.0 Hz, CH_AH_BOSEM), 4.42 (1H, d, *J* 15.8 Hz, CH_AH_BPh), 4.55 (1H, d, *J* 15.8 Hz, CH_AH_BPh), 4.61 (1H, d, *J* 6.8 Hz, OCH_AH_BO), 4.64 (1H, d, *J* 6.7 Hz, OCH_AH_BO),

4.73 (1H, d, *J* 10.1 COOC*H*), 6.28 (1H, d, *J* 3.4, Fur-*H*), 6.34 (1H, dd, *J* 3.2 Hz, 1.9 Hz, Fur-*H*), 7.27-7.38 (4H, m, Ar-*H* + Fur-*H*), 7.42-7.46 (2H, m, Ar-*H*);
δC (125 MHz, $CDCl_3$) 0.01, 18.7, 19.4, 23.9, 24.3, 40.0, 40.8, 46.6, 61.5, 66.4, 69.2, 70.2, 78.2, 96.3, 109.9, 112.2, 129.2, 129.3, 130.4, 139.8, 142.8, 154.1, 160.2;
m/z (ES^+) 524 ($M+Na^+$, 100 %), Accurate mass (ES+) found 524.2400, $C_{27}H_{39}O_6N_1Si_1Na_1$ requires 524.2444 (+2.1 ppm).

(+/-) (4S,5R)-4-((Allylamino)methyl)-3-benzyl-4-cyclobutyl-5-((R)-1-(furan-2-yl)-2-((2-(trimethylsilyl)ethoxy)methoxy)ethyl)oxazolidin-2-one (2.128)



To a stirred solution of primary alcohol **2.126** (189 mg, 0.365 mmol) dissolved in dichloromethane (3.6 mL) was added Dess-Martin periodinane (185 mg, 0.44 mmol) at room temperature. The reaction mixture was stirred at this temperature for 2 hours. $NaHCO_3$ (1 mL) and freshly prepared saturated $Na_2S_2O_3$ (1 mL) were then added and stirring was continued for a further 20 minutes. Ether (5 mL) was added and the organic layer separated. The remaining aqueous portion was further extracted with ether (4 x 5 mL) before the organics were combined and dried over Na_2SO_4. Removal of solvent under reduced pressure gave aldehyde a thick dark yellow oil which was immediately dissolved in dichloromethane (1.5 ml). To this solution were added allylamine (35 μL, 0.48 mmol) and oven dried $MgSO_4$ (114 mg). The reaction mixture was refluxed for 16 hours at which point TLC analysis showed complete loss of starting material. Solvent was removed under reduced pressure and the crude residue was immediately dissolved in anhydrous methanol (2.2 mL). Glacial acetic acid (27 μL, 0.48 mmol) and a 1 M solution of sodium cyanoborohydride in tetrahydrofuran (0.44 mL, 0.44 mmol) were added at room temperature. The reaction mixture was stirred for 1 hour before saturated $NaHCO_3$ (5 mL) was added. The aqueous mixture was extracted with ether (5 x 5 mL) and the

combined organics were dried over Na_2SO_4. Removal of solvent gave crude allylamine which was purified by silica gel chromatography (50 % Et_2O/ Petrol) to give the allylamine **2.128** (137 mg, 70 %). R_f 0.27 (50 % Et_2O/ Petrol).

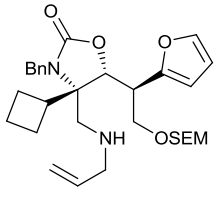
IR (neat/ cm^{-1}) 2951, 1744, 1407, 1248, 1111, 1062, 1033, 834, 707.

δH (500 MHz, $CDCl_3$) 0.00 (9H, s, $Si(CH_3)_3$), 0.86-0.92 (2H, m, OCH_2CH_2Si), 1.38-1.83 (6H, m, CH_2 CH_2 CH_2), 2.17 (1H, qn, *J* 8.7, c-Bu), 2.46 (1H, d, *J* 13.6 Hz, *c*-BuCCH_AH_BN), 2.54 (1H, d, *J* 13.6 Hz, *c*-BuCCH_AH_BN), 2.83 (1H, m, dd, *J* 13.9 Hz, 6.3 Hz, NC$H_AH_B$allyl), 2.90 (1H, dd, *J* 13.9 Hz, 6.0 Hz, NC$H_AH_B$allyl), 3.47 (2H, t, *J* 8.5 Hz, OCH_2CH_2Si), 3.94 (1H, dd, *J* 9.5 Hz, 3.9 Hz, CH_AH_BOSEM), 3.97 (1H, dd, *J* 9.5, 7.3, CH_AH_BOSEM), 4.19 (1H, ddd, *J* 11.0, 7.3 Hz, 4.0 Hz, Fur-C*H*), 4.39 (1H, d, *J* 15.8 Hz, CH_AH_BPh), 4.46 (1H, d, *J* 15.8 Hz, CH_AH_BPh), 4.60 (1H, d, *J* 6.8 Hz, OCH_AH_BO), 4.63 (1H, d, *J* 6.8 Hz, OCH_AH_BO), 4.65 (1H, d, *J* 11.0 COOC*H*), 5.02 (1H, d, *J* 10.1 Hz, $NCH_2CHCH_AH_B$), 5.03 (1H, d, *J* 17.6 Hz, $NCH_2CHCH_AH_B$), 5.66 (1H, ddt, *J* 17.6 Hz, 10.1 Hz, 6.3 Hz, NCH_2CHCH_2), 6.22 (1H, dd, *J* 3.2 Hz, Fur-*H*), 6.32 (1H, dd, *J* 3.2 Hz, 1.8 Hz, Fur-*H*), 7.26-7.36 (4H, m, Ar-*H* + Fur-*H*), 7.42-7.45 (2H, m, Ar-*H*);

δC (125 MHz, $CDCl_3$) 0.0, 2.4, 18.3, 19.4, 24.0, 24.4, 40.4, 41.8, 46.6, 49.8, 53.7, 66.3, 69.3, 78.2, 96.3, 110.0, 112.1, 117.5, 129.1, 129.4, 130.1, 138.0, 139.7, 142.6, 154.4, 160.0.

m/z (ES^+) 541 ($M+H^+$, 100 %), Accurate mass (ES+) found 541.3089, $C_{30}H_{45}O_5N_2Si_1$ requires 541.3092 (-0.6 ppm).

(+/-) (4S,5R)-4-((Allylamino)methyl)-3-benzyl-4-cyclobutyl-5-((S)-1-(furan-2-yl)-2-((2-(trimethylsilyl)ethoxy)methoxy)ethyl)oxazolidin-2-one (2.122)



To a stirred solution of primary alcohol **1.20** (421 mg, 0.81 mmol) dissolved in dichloromethane (8.0 mL) was added Dess-Martin periodinane (420 mg, 1 mmol) at room temperature. The reaction mixture was stirred at this temperature for 2 hours before being quenched by the addition of saturated $NaHCO_3$ (2 mL) and

freshly prepared saturated $Na_2S_2O_3$ (2 mL) and stirred for a further 20 minutes. Ether (15 mL) was added and the organic layer separated. The remaining aqueous portion was further extracted with ether (4 x 15 mL) before the organics were combined and dried over Na_2SO_4. Removal of solvent under reduced pressure gave a thick yellow oil which was immediately dissolved in fresh dichloromethane (3.2 mL). To this solution were added allylamine (80 μL, 1.1 mmol) and oven dried $MgSO_4$ (253 mg). The reaction mixture was refluxed for 16 hours at which point TLC analysis showed complete loss of starting material. Solvent was removed under reduced pressure and the crude residue was immediately dissolved in anhydrous methanol (4.9 mL). Glacial acetic acid (61 μL, 1.1 mmol) and a 1 M solution of sodium cyanoborohydride in tetrahydrofuran (1 mL, 1 mmol) were added at room temperature. The reaction mixture was stirred for 1 hour before saturated $NaHCO_3$ (10 mL) was added. The aqueous mixture was extracted with ether (5 x 15 mL) and the combined organics were dried over Na_2SO_4. Removal of solvent gave crude allylamine which was purified by silica gel chromatography (50 % Et_2O/ Petrol) to give the allylamine (333 mg, 73 %); R_f 0.95 (Et_2O).

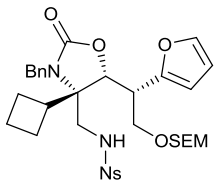
IR (neat/ cm^{-1}); 3335, 2950, 1752, 1496, 1402, 1248, 1156, 1029, 918, 859, 836, 758.7, 702;

δH (300 MHz, $CDCl_3$) δH (500 MHz, $CDCl_3$) 0.00 (9H, s, $Si(CH_3)_3$), 0.90-0.95 (2H, m, OCH_2CH_2Si), 1.67-2.02 (6H, m, CH_2 CH_2 CH_2), 2.51 (1H, d, *J* 12.7 Hz, *c*-$BuCCH_AH_BN$), 2.59 (1H, d, *J* 12.8 Hz, *c*-$BuCCH_AH_BN$), 2.81-2.90 (2H, m, *c*-Bu + NCH_AH_Ballyl), 2.93 (1H, dd, *J* 14.2 Hz, 6.0 Hz, NCH_AH_Ballyl), 3.56-3.61 (2H, m, OCH_2CH_2Si), 3.62-3.69 (2H, m, Fur-CH + CH_AH_BOSEM), 3.86 (1H, m, CH_AH_BOSEM), 4.17 (1H, d, *J* 16.0 Hz, CH_AH_BPh), 4.45 (1H, d, *J* 16.0 Hz, CH_AH_BPh), 4.69 (2H, s, OCH_2O), 4.94-5.00 (3H, m, COOCH + NCH_2CHCH_2), 5.63 (1H, ddt, *J* 17.8 Hz, 9.8 Hz, 6.0 Hz, NCH_2CHCH_2), 6.36 (1H, dd, *J* 3.3 Hz, 1.6 Hz, Fur-*H*), 6.38 (1H, d, *J* 3.3 Hz, Fur-*H*), 6.89-6.93 (2H, m, Ar-*H*), 7.13-7.19 (3H, m, Ar-*H*), 7.31 (1H, m, Fur-*H*);

δC (125 MHz, $CDCl_3$) 0.0, 18.8, 19.5, 24.5, 25, 40.8, 41.8, 46.4, 51.7, 54.3, 66.8, 67.1, 69.9, 77.2, 78.1, 96.2, 110.3, 112.5, 117.3, 128.3, 128.5, 129.7, 137.9, 139.6, 142.6, 152.3, 160.0.

m/z (ES^-) 563 ($M+Na^+$, 100 %), Accurate mass (ES+) found 563.2906, $C_{30}H_{44}O_5N_2Na_1Si_1$ requires 563.2912 (-1.0 ppm);

(+/-) N-(((4S,5R)-3-Benzyl-4-cyclobutyl-5-((R)-1-(furan-2-yl)-2-((2-(trimethylsilyl)ethoxy)methoxy)ethyl)-2-oxooxazolidin-4-yl)methyl)-2-nitrobenzenesulfonamide (2.130)



To a stirred solution of the allylamine **2.128** (22 mg, 0.04 mmol), and 1,3-dimethylbarbituric acid (19 mg, 0.12 mmol) in dichloromethane (0.1 mL) was added $Pd(PPh_3)_4$ (0.5 mg, 0.45 μmol) at room temperature. The reaction mixture was warmed to 35 ºC and held at this temperature for 2 hours at which point TLC analysis showed complete loss of starting material. Saturated $NaHCO_3$ (5 mL) and ether (5 mL) were added to the reaction mixture and the organic layer separated. The aqueous layer was further extracted with ether (3 x 5 mL) and the combined organics dried over Na_2SO_4. Solvent was removed under reduced pressure to give a yellow oil (16 mg, 79 %). R_f 0.24 (Et_2O) which was immediately taken up in dichloromethane (0.1 mL). To this stirred solution was added 2-nitrobenzenesulfonyl chloride (8 mg, 0.035 mmol) and triethylamine (4.5 μL, 0.032 mmol). The colorless solution was stirred at room temperature for 2 hours at which point TLC analysis showed complete loss of starting material. Saturated NH_4Cl (5 mL) was added and the mixture was extracted with ether (4 x 5 mL). The combined organics were dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield an oil which was subjected to silica gel chromatography (0→ 100 % Et_2O/ Petrol). This gave the sulfonamide **2.131** as a white foam (15 mg, 70 %). R_f 0.65 (Et_2O).

IR (neat/ cm^{-1}) 2949, 1746, 1541, 1405, 1360, 1248, 1172, 1110, 1062, 916, 853, 836, 732, 705, 656;

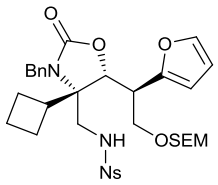
δH (400 MHz, $CDCl_3$) 0.00 (9H, s, $Si(CH_3)_3$), 0.87-0.92 (2H, m, OCH_2CH_2Si), 1.31-1.84 (6H, m, CH_2 CH_2 CH_2), 2.19 (1H, qn, *J* 9.1 Hz, *c*-Bu), 3.02 (1H, dd, *J* 14.2 Hz, 6.0 Hz, *c*-$BuCCH_AH_BN$), 3.27 (1H, dd, *J* 14.0 Hz, 6.9 Hz, *c*-$BuCCH_AH_BN$), 3.48-3.53 (2H, m, OCH_2CH_2Si), 3.56 (1H, ddd, *J* 10.4 Hz, 6.3 Hz, 4.4 Hz, Fur-CH), 3.91 (1H, dd, *J* 9.6 Hz, 4.4 Hz, CH_AH_BOSEM), 3.96 (1H, dd, *J* 9.6 Hz, 6.6 Hz, CH_AH_BOSEM), 4.24 (1H, d, *J* 16.1 Hz, CH_AH_BPh), 4.58 (1H, d, *J* 16.1 Hz, CH_AH_BPh), 4.63 (1H, d, *J* 6.8 Hz, OCH_AH_BO), 4.66 (1H, d, *J* 6.8 Hz, OCH_AH_BO),

4.77 (1H, d, *J* 10.1 Hz, COOC*H*), 5.43 (1H, br t, *J* 6.2, N*H*), 6.29 (1H, d, *J* 3.2 Hz, Fur-*H*), 6.34 (1H, dd, *J* 3.2 Hz, 1.9 Hz, Fur-*H*), 7.23-7.35 (6H, m, Ar-*H* + Fur-*H*), 7.72-7.79 (2H, m, Ns-*H*), 7.85 (1H, dd, *J* 7.6 Hz, 1.6 Hz, Ns-*H*), 7.95 (1H, dd, *J* 7.3 Hz, 1.6 Hz, Ns-*H*);

δC (125 MHz, $CDCl_3$) 0.0, 18.0, 19.4, 23.8, 24.1, 24.2, 40.3, 40.47, 44.46, 46.7, 66.7, 67.3, 68.8, 78.0, 96.3, 110.0, 112.5, 126.8, 129.0, 129.1, 130.2, 132.4, 134.1, 134.2, 135.3, 139.2, 143.1, 153.1, 159.3;

m/z (ES^+) 708 ($M+Na^+$, 100 %), Accurate mass (ES+) found 708.2389, $C_{33}H_{43}O_9N_3Na_1S_1Si_1$ requires 708.2381 (+1.1 ppm);

(+/-) N-(((4S,5R)-3-Benzyl-4-cyclobutyl-5-((S)-1-(furan-2-yl)-2-((2-(trimethylsilyl)ethoxy)methoxy)ethyl)-2-oxooxazolidin-4-yl)methyl)-2-nitrobenzenesulfonamide (2.124)



To a stirred solution of the allylamine **2.122** (41 mg, 0.076 mmol), and 1,3-dimethylbarbituric acid (35 mg, 0.23 mmol) in dichloromethane (0.2 mL) was added $Pd(PPh_3)_4$ (1 mg, 0.86 μmol) at room temperature. The reaction mixture was warmed to 35 ºC and held at this temperature for 2 hours at which point TLC analysis showed complete loss of starting material. Saturated $NaHCO_3$ (5 mL) and ether (5 mL) were added to the reaction mixture and the organic layer separated. The aqueous layer was further extracted with ether (3 x 5 mL) and the combined organics dried over Na_2SO_4. Solvent was removed under reduced pressure to yield a yellow oil (34 mg, 90 %). R_f 0.38 (Et_2O) which was immediately taken up in dichloromethane (0.2 mL). To this stirred solution was added 2-nitrobenzenesulfonyl chloride (17 mg, 74 μmol) and triethylamine (10 μL, 68 μmol). The colorless solution was stirred at room temperature for 2 hours at which point TLC analysis showed complete loss of starting material. Saturated NH_4Cl (5 mL) was added and the mixture was extracted with ether (4 x 5 mL). The combined organics were dried over $MgSO_4$ and the solvent was removed under reduced pressure giving a crude oil which was subjected to silica gel

chromatography (0→ 100 % Et_2O/ Petrol). This gave the sulfonamide **2.124** as a clear oil (28 mg, 60 %). R_f 0.7 (Et_2O);

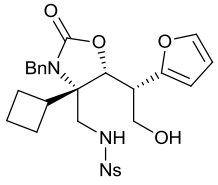
IR (neat/ cm^{-1}) 3323, 2950, 1747, 1541, 1408, 1361, 1249, 1174, 1058, 836, 732;

δH (400 MHz, $CDCl_3$) 0.00 (9H, s, Si(C*H*$_3$)$_3$), 0.89-0.97 (2H, m, OCH$_2$C*H*$_2$Si), 1.72-2.14 (6H, m, C*H*$_2$ C*H*$_2$ C*H*$_2$), 2.80 (1H, dd, *J* 13.6 Hz, 5.2 Hz, *c*-BuCC*H*$_A$H$_B$N), 2.85 (1H, dd, *J* 13.6 Hz, 6.6 Hz, *c*-BuCCH$_A$*H*$_B$N), 2.99 (1H, qn, *J* 8.4 Hz, *c*-Bu), 3.39 (1H, ddd, *J* 10.2 Hz, 5.4 Hz, 0.9 Hz, Fur-C*H*), 3.58-3.63 (2H, m, OC*H*$_2$CH$_2$Si), 3.65 (1H, dd, *J* 9.8 Hz, 5.5 Hz, C*H*$_A$H$_B$OSEM), 3.87 (1H, t, *J* 9.9 Hz, CH$_A$*H*$_B$OSEM), 3.96 (1H, d, *J* 16.1 Hz, C*H*$_A$H$_B$Ph), 4.54 (1H, d, *J* 16.1 Hz, CH$_A$*H*$_B$Ph), 4.70 (2H, s, OC*H*$_2$O), 5.07 (1H, d, *J* 1.1 Hz, COOC*H*), 5.12 (1H, br t, *J* 6.1, N*H*), 6.33 (1H, dd, *J* 3.3 Hz, 1.8 Hz, Fur-*H*), 6.40 (1H, dd, *J* 3.3 Hz, 0.7 Hz, Fur-*H*), 6.90-6.94 (2H, m, Ar-*H*), 7.13 (1H, dd, *J* 1.8, 0.7 Hz, Fur-*H*), 7.14-7.19 (3H, m, Ar-*H*), 7.58-7.72 (3H, m, Ns-*H*), 7.79 (1H, dd, *J* 8.0 Hz, 1.3 Hz, Ns-*H*);

δC (125 MHz, $CDCl_3$) 0.00, 18.9, 19.5, 24.3, 24.9, 40.8, 41.3, 46.2, 46.8, 66.8, 77.0, 69.6, 76.3, 96.4, 111.0, 112.8, 126.7, 128.7, 128.9, 130.1, 132.6, 133.8, 134.0, 135.2, 139.1, 142.9, 149.4, 151.1, 159.2;

m/z (ES^+) 708 ($M+Na^+$, 100 %), Accurate mass (ES+) found 708.2384, $C_{33}H_{43}O_9N_3Na_1S_1Si_1$ requires 708.2381 (+1.1 ppm);

(+/-) N-(((4S,5R)-3-Benzyl-4-cyclobutyl-5-((R)-1-(furan-2-yl)-2-hydroxyethyl)-2-oxooxazolidin-4-yl)methyl)-2-nitrobenzenesulfonamide (2.131)



To a stirred solution of protected alcohol **2.130** (15 mg, 21 μmol) dissolved in anhydrous diethyl ether (0.4 mL) was added $MeNO_2$ (34 μL, 0.61 mmol) and $MgBr_2$ (56 mg, 0.3 mmol) at room temperature. The reaction mixture was stirred at this temperature for 2 hours and dichloromethane (5 mL) then water (5 mL) were added. The organics were separated and the aqueous layer further extracted with dichloromethane (4 x 5 mL). The combined organics were dried

over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by filtration through a very short pad of silica to give a pale oil (9 mg, 75 %). R_f 0.16 (Et_2O)

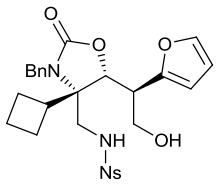
IR (neat/ cm^{-1}) 3336, 2915, 1739, 1540, 1410, 1359, 1171, 1067, 911, 853, 731;

δH (400 MHz, $CDCl_3$) 1.22-1.76 (6H, m, C*H*$_2$ C*H*$_2$ C*H*$_2$), 2.09 (1H, qn, *J* 8.6 Hz, *c*-Bu), 2.97 (1H, d, *J* 13.9 Hz, *c*-BuCC*H*$_A$H$_B$N), 3.22 (1H, d, *J* 13.9 Hz, *c*-BuCCH$_A$*H*$_B$N), 3.49 (1H, dt, *J* 10.4 Hz, 5.4, Fur-C*H*), 3.95 (2H, m, C*H*$_2$OH), 4.18 (1H, d, *J* 16.1 Hz, C*H*$_A$H$_B$Ph), 4.52 (1H, d, *J* 16.1 Hz, CH$_A$*H*$_B$Ph), 5.75 (1H, d, *J* 10.4 Hz, COOC*H*), 5.42 (1H, br s, N*H*), 6.26 (1H, d, *J* 3.3 Hz, Fur-*H*), 6.30 (1H, dd, *J* 3.3 Hz, 2.2 Hz, Fur-*H*), 7.16-7.30 (6H, m, Ar-*H* + Fur-*H*), 7.64-7.72 (2H, m, Ns-*H*), 7.78 (1H, dd, *J* 7.9 Hz, 0.9 Hz, Ns-*H*), 7.88 (1H, dd, *J* 7.6 Hz, 1.2 Hz, Ns-*H*);

δC (125 MHz, $CDCl_3$) 15.3, 16.7, 22.6, 22.7, 38.9, 41.0, 43.0, 45.4, 63.7, 65.9, 67.5, 109.0, 111.1, 125.4, 127.6, 127.8, 128.9, 131.0, 132.8, 132.9, 134.0, 137.7, 142.3, 148.1, 151.3, 157.9;

m/z (ES^+) 578 ($M+H^+$, 100 %), Accurate mass (ES+) found 578.1580, $C_{27}H_{29}O_8N_3Na_1S_1$ requires 578.1568 (+2.2 ppm);

(+/-) N-(((4S,5R)-3-Benzyl-4-cyclobutyl-5-((S)-1-(furan-2-yl)-2-hydroxyethyl)-2-oxooxazolidin-4-yl)methyl)-2-nitrobenzenesulfonamide (2.125)



To a stirred solution of protected alcohol **2.122** (72 mg, 0.1 mmol) dissolved in anhydrous diethyl ether (2 mL) was added $MeNO_2$ (162 μL, 2.9 mmol) and $MgBr_2$ (270 mg, 1.45 mmol) at room temperature. The reaction mixture was stirred at this temperature for 2 hours and then dichloromethane (10 mL) and water (10 mL) were added. The organics were separated and the aqueous layer further extracted with dichloromethane (4 x 10 mL). The combined organics were dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude residue

was purified by filtration through a very short pad of silica to give a clear oil. (45 mg, 77 %). R_f 0.3 (Et_2O);

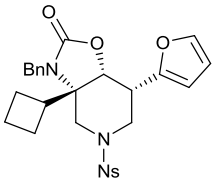
IR (neat/ cm^{-1}); 3340, 2910, 1740, 1550, 1410, 1330, 1153, 1070, 910, 853, 730;

δH (400 MHz, $CDCl_3$) 1.79-2.24 (6H, m, C*H*$_2$ C*H*$_2$ C*H*$_2$), 2.90 (1H, dd, *J* 13.6 Hz, 6.3 Hz, *c*-BuCC*H*$_A$H$_B$N), 2.99 (1H, dd, *J* 13.6 Hz, 8.1 Hz, *c*-BuCCH$_A$*H*$_B$N), 3.09 (1H, m, *c*-Bu), 3.44 (1H, ddd, *J* 9.3 Hz, 5.8 Hz, 1.3 Hz, Fur-C*H*), 3.94 (1H, m, C*H*$_A$H$_B$OH), 4.07 (1H, m, CH$_A$*H*$_B$OH), 4.07 (1H, d, *J* 16.1 Hz, C*H*$_A$H$_B$Ph), 4.64 (1H, d, *J* 16.1 Hz, CH$_A$*H*$_B$Ph), 5.20 (1H, m, *J* 6.1, N*H*), 5.22 (1H, d, *J* 1.3 Hz, COOC*H*), 6.46 (1H, dd, *J* 3.3 Hz, 2.0 Hz, Fur-*H*), 6.52 (1H, dd, *J* 3.3 Hz, 0.7 Hz, Fur-*H*), 7.01-7.05 (2H, m, Ar-*H*), 7.24-7.31 (4H, m, Ar-*H* + Fur-*H*), 7.71-7.84 (3H, m, Ns-*H*), 7.91 (1H, dd, *J* 8.0 Hz, 1.3 Hz, Ns-H);

δC (125 MHz, $CDCl_3$) 17.6, 22.6, 23.5, 30.4, 39.7, 42.2, 44.7, 45.6, 63.3, 65.4, 74.7, 109.6, 111.5, 125.2, 127.1, 127.5, 128.9, 131.2, 132.5, 133.0, 134.4, 137.8, 141.7, 148.1, 150.2, 158.2;

m/z (ES^+) 578 ($M+Na^+$, 100 %), Accurate mass (ES+) found 578.1566, $C_{27}H_{29}O_8N_3Na_1S_1$ requires 578.1568 (-0.3 ppm).

(+/-) (3aS,7R,7aR)-3-Benzyl-3a-cyclobutyl-7-(furan-2-yl)-5-(2-nitrophenylsulfonyl)hexahydrooxazolo[4,5-c]pyridin-2(3H)-one (2.132)



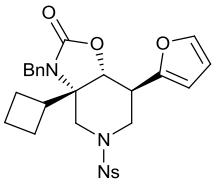
To a stirred solution of sulfonamide **2.131** (9 mg, 16 μmol) dissolved in tetrahydrofuran (0.16 mL) was added triphenylphosphine (5.5 mg, 21 μmol) and DIAD (4 μL, 21 μmol) at room temperature. The reaction mixture was stirred for two hours and the solvent was removed under reduced pressure. The reaction residue was subjected to silica gel chromatography (0→ 50 % Et_2O/ Petrol) to give (7 mg, 80 %) a pale oil. R_f 0.48 (Et_2O).

IR (neat/ cm^{-1}) 2949, 1741, 1538, 1370, 1160, 1050, 813, 732;

δH (500 MHz, $CDCl_3$) 1.04-1.89 (6H, m, C*H*$_2$ C*H*$_2$ C*H*$_2$), 2.50 (1H, qn, *J* 8.8 Hz, *c*-Bu), 3.25 (1H, d, *J* 14.5 Hz, *c*-BuCC*H*$_A$H$_B$N), 3.38 (1H, dd, *J* 12.3 Hz, 5.7 Hz, Fur-C*H*), 3.55 (1H, dd, *J* 10.7 Hz, 5.9 Hz, Fur-CHC*H*$_A$H$_B$), 3.66 (1H, d, *J* 11.0 Hz, Fur-

CHCH$_A$*H*$_B$), 3.68 (1H, d, *J* 14.6 Hz, *c*-BuCCH$_A$*H*$_B$N), 3.95 (1H, d, *J* 16.1 Hz, C*H*$_A$H$_B$Ph), 4.75 (1H, d, *J* 16.1 Hz, CH$_A$*H*$_B$Ph), 4.85 (1H, s, COOC*H*), 6.37 (1H, m, Fur-*H*), 6.39 (1H, d, *J* 3.2 Hz, Fur-*H*), 7.25-7.39 (6H, m, Ar-*H* + Fur-*H*), 7.66-7.77 (3H, m, Ns-*H*), 8.00 (1H, d, *J* 7.4 Hz, Ns-*H*);
m/z (ES$^+$) 560 (M+Na$^+$), 100 %), Accurate mass (ES+) found 560.1454, $C_{27}H_{27}O_7N_3Na_1S_1$ requires 560.1462 (-1.4 ppm).

(+/-) (3aS,7S,7aR)-3-Benzyl-3a-cyclobutyl-7-(furan-2-yl)-5-(2-nitrophenylsulfonyl)hexahydrooxazolo[4,5-c]pyridin-2(3H)-one (2.117)



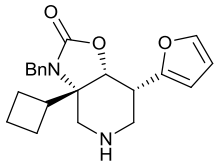
Method 1: To a stirred solution of tertiary alcohol **2.125** (13 mg, 23 μmol) in dichloromethane (0.2 ml) was added triethylsilane (9 μL, 60 μmol) and $BF_3.Et_2O$ (8.3 μL, 65 μmol) at 0 ºC. The reaction mixture was stirred at this temperature for 15 minutes and then warmed to room temperature and stirred for a further 2 hours. The reaction was quenched by the addition of saturated $NaHCO_3$ (5 mL) and the aqueous solution was extracted with dichloromethane (3 x 5 mL). The combined organics were dried over $MgSO_4$ and the solvent removed under reduced pressure the crude residue was purified to give piperidine (4.0 mg, 32 %). R_f 0.53 (Et_2O);
Method 2: To a stirred solution of sulfonamide **2.125** (31 mg, 55 μmol) dissolved in tetrahydrofuran (0.5 mL) was added triphenylphosphine (19 mg, 72 μmol) and DIAD (14 μL, 72 μmol) at room temperature. The reaction mixture was stirred for two hours and the solvent was removed under reduced pressure. The reaction mixture was subjected to silica gel chromatography (0→ 50 % Et_2O/ Petrol) to give the piperidine (22 mg, 73 %) as a pale oil.
IR (neat/ cm^{-1}) 2919, 1744, 1543, 1458, 1405, 1360, 1166, 1060, 909, 851, 732;
δH (500 MHz, $CDCl_3$) 1.29-1.76 (6H, m, C*H*$_2$ C*H*$_2$ C*H*$_2$), 2.22 (1H, m, *c*-Bu), 3.04 (1H, d, *J* 14.2 Hz, *c*-BuCC*H*$_A$H$_B$N), 3.33-3.41 (2H, m, Fur-C*H* + Fur-CHC*H*$_A$H$_B$), 3.63 (1H, d, *J* 14.2 Hz, *c*-BuCCH$_A$*H*$_B$N),4.69 (1H, m, Fur-CHCH$_A$*H*$_B$), 4.10 (1H, d, *J* 15.5 Hz, C*H*$_A$H$_B$Ph), 4.62 (1H, d, *J* 15.5 Hz, CH$_A$*H*$_B$Ph), 4.79 (1H, d, *J* 6.0 Hz,

COOC*H*), 6.10 (1H, d, *J* 3.2 Hz, Fur-*H*), 6.23 (1H, dd, *J* 3.2 Hz, 1.9 Hz, Fur-*H*), 7.20-7.29 (4H, m, Ar-*H* + Fur-*H*), 7.32-7.36 (2H, m, Ar-*H*), 7.59-7.71 (3H, m, Ns-*H*), 7.90 (1H, dd, *J* 7.6 Hz, 1.6 Hz, Ns-H);

δC (125 MHz, $CDCl_3$) 17.1, 22.6, 30.5, 38.7, 40.4, 43.0, 44.2,63.4, 74.1, 107.8, 110.9, 124.4, 124.5, 126.5, 228.2, 128.8, 131.4, 131.8, 131.9, 134.1, 137.0, 142.5, 150.9, 157.3;

m/z (ES^+) 537 ($M+NH_4^+$, 100 %), Accurate mass (ES+) found 538.1642, $C_{27}H_{28}O_7N_3S_1$ requires 560.1462 (-1.0 ppm).

(+/-) (3aS,7R,7aR)-3-Benzyl-3a-cyclobutyl-7-(furan-2-yl)hexahydrooxazolo[4,5-c]pyridin-2(3H)-one (2.58)



To a stirred solution of sulfonamide **2.132** (44 mg, 82 μmol) in acetonitrile (1.7 mL) was added potassium carbonate (45 mg,) and thiophenol (25 μl, 245 μmol). The reaction mixture was stirred at room temperature for 2 hours and the solvent was removed under reduced pressure. The residue was immediately subjected to silica gel chromatography (100% petrol → 10 % MeOH/ Et_2O) to give the piperidine (25 mg, 86 %) as a pale oil. R_f 0.38 (10 % MeOH/ Et_2O);

IR (neat/ cm^{-1}) 2931, 1742, 1408, 1164, 1013, 705;

δH (500 MHz, $CDCl_3$) 1.52-1.95 (6H, m, C*H*$_2$ C*H*$_2$ C*H*$_2$), 2.34 (1H, d, *J* 14.5 Hz, *c*-BuCC*H*$_A$H$_B$N), 2.62 (1H, qn, *J* 8.8 Hz, *c*-Bu), 2.64 (1H, d, *J* 14.5 Hz, *c*-BuCCH$_A$*H*$_B$N), 3.02 (1H, t, *J* 12 Hz, Fur-CHC*H*$_A$H$_B$), 3.12 (1H, dd, *J* 12 Hz, 6.3 Hz, Fur-CHCH$_A$*H*$_B$), 3.16 (1H, ddd, *J* 12.0 Hz, 6.3 Hz, 2 Hz, Fur-C*H*), 4.14 (1H, d, *J* 15.5 Hz, C*H*$_A$H$_B$Ph), 4.41 (1H, d, *J* 15.5 Hz, CH$_A$*H*$_B$Ph), 4.78 (1H, d, *J* 2 Hz, COOC*H*), 6.19 (1H, d, *J* 3.2 Hz, Fur-*H*), 6.27 (1H, dd, *J* 3.2 Hz, 2.0 Hz, Fur-*H*), 7.18-7.34 (6H, m, Ar-*H* + Fur-*H*);

δC (125 MHz, $CDCl_3$) 15.5, 17.6, 22.3, 22.9, 35.5, 38.5, 41.7, 44.7, 64.0, 65.9, 74.9, 106.9, 110.5, 130.0, 128.8, 138.2, 141.6, 152.2, 158.7;

m/z (ES^+) 353 ($M+H^+$, 100 %), Accurate mass (ES+) found 353.1860 $C_{21}H_{25}O_3N_2$ requires 353.1860 (0.1 ppm).

Chapter 4: References

1. L. Chenard, M.P. DeNinno, K. DiRico, C. Eller, J. Etienne, R. Hill, S. Kennedy, D. Knight, J. Kong, H. Masamune J. Oleynek, J. Tickner, W. Tracy *Bioorganic & Medicinal Chemistry Letters*. **2006**, 16, 2525-2257.

2. M. Abbracchio, G. Burnstock, J. Daly, B. Fredholm K. Harden, K. Jacobson, P. Leff, M. Williams, *Pharmacological Reviews*, **1994**, 46, 143-156.

3. W. Flameng, K. Mubagwa,; *Cardiovascular Research*, **2001**, 52, 25-39.

4. P. Baraldi, P. Borea, *Trends in Pharmacological Sciences*, **2000**, 21, 456-459.

5. C. Gallo-Rodriguez, A.P. Ijerman, K.A. Jacobson, N. Melman, M.E. Olah, G.L. Stilles, A.H. VanBergen, P.J. VanGalen, *Molecular Pharmacology*, **1994**, 34, 1101-1111.

6. P.G. Baraldi, P.A. Borea, B. Cacciari, S. Merighi, R. Romagnoi, G. Spallo, K. Varani, *Medicinal Research Reviews*, **2000**, 20, 103-128.

7. A. T. L. Lee, E. J. Thomas, unpublished work.

8. T. Lin, M. Liu, A.C. Sartorelli, Y. Wang, *Journal of Medicinal Chemistry,* **1992**, 35, 3667-3671.

9. S. R. Natarajan, S. J. O'Keef, E. A. O'Neil, J.E. Thompson, D. D. Wisnoski, *Bioorganic & Medicinal Chemistry Letters*, **2006**, 16, 4400-4404.

10. Murray Raney. *US Pat*., 1 628 190, 1927.

11. B. S. J. Blagg, G. Shen, M. Wang, T. Welch, *Journal of Organic Chemistry*, **2006**, 71, 7618-7631.

12. A. Straub, *Synthetic Communications*, **1993**, 23, 365-372.

13. M. Hamana, H. Nagano, Y. Nawata, *Chemical & Pharmaceutical Bulletin*, **1987**, 35, 4068-4077.

14. E. Blanz, F. French, *Cancer Research*, **1968**, 28, 2419-2422.

15. K.C. Agrawal, B.A. Booth, A.J. Lin, A.C. Sartorelli, R. Wheaton, *Journal of Medicinal Chemsirty*, **1974**, 17, 631-635.

16. P.L. Pacini, V.J. Traynelis, *Journal of the American Chemical Society*, **1964**, 86, 4917-4922.

17. P. Månson, *Tetrahedron Letters*, **1982**, 23, 1845-1846.

18. R. Chakravarty, M. Datta, P. De, N.C. Ganguly, *Synthetic Communications*, **2003**, 33, 647-659.

19. E. Biehl, U.N. Rao, R. Sathunuru, *Archive for Organic Chemistry*, **2003**, 15, 124-133.

20. E. Biehl, R. Sathunuru, *Archive for Organic Chemistry*, **2004**, 14, 89-95.

21. T.H. Chan, M. Lalonde, *Synthesis*, **1985**, 817-845.

22. M. Ishikawa, F.Konno, T. Nizato, Y.sato, T.Soneda, K. Suzuki, M. Yamada, S. Yoshida, *Journal of Medicinal Chemsitry*, **1998**, 41, 3015-3021.

23. T. Ito, K. Kawano, H. Marakami, Y. Sato, S. Shiokawa, H. Suzuki, S Yoshida, *Journal of Medicinal Chemistry*, **2005**, 48, 7075-7079.

24. K. Gunnar, J. Sandstrom, *Acta Chemica Scandinavica*, **1969**, 23, 2888.

25. M.J. Dewar, I.J. Turchi, *Chemical Reviews*, **1975**, 75, 389-437.

26. T. Kan, T. Fukuyama, *Chemical Communications*, **2004**, 353–359

27. M. Cheung, T. Fukuyama, C. Jow, *Tetrahedron Letters*, **1995**, 36, 6373-6374.

28. M. Cheung, T. Fukuyama, T. Kan, *Synlett, **1999**,* 8, 1301-1303.

29. T. Kato, M. Yoshikawa, *Bulletin of the Chemical Society of Japan*, **1967**, 40, 2849-2853.

30. D. G. Allen, C. Chan, C. M. Cook, R. P. C. Cousins, B. Cox, H. J. Dyke, F. Ellis, J. V. Geden, H. Hobbs, S. E. Keeling, A. J. Redgrave, S. Swanson, D. Bays; Brit. UK. Pat Appl., 2203149, 1998.

31. J.W. Daly, S. Kusachi, R.A. Olsson, W. Padgett, R.D. Thompson, D. Ukena, *Journal of Medicinal Chemistry*, **1986**, 29, 1683-1689.

32. D.A. Cogan, J.A. Ellman, G. Liu, *Journal of the American Chemical Society*, **1997**, 119, 9913-9914.

33. J. Ellman, T.D. Owens, T.P. Tang, *Accounts of Chemical Research*, **2002**, 35, 984-995.

34. B.J. Backes, D.A. Cogan, J.A. Ellman, K. Kim, G. Liu, *Journal of the American Chemical Society,* **1998**, 120, 9011-8019.

35. K. Omura, D. Swern, *Tetrahedron*, **1978**, 34, 1651-1668.

36. D.S. Brownfield, A.J. Mancuso, D. Swern, *Journal of Organic Chemistry*, **1979**, 44, 4148-4150.

37. S. Huang, D. Swern, A.J. Mancuso, *Journal of Organic Chemistry*, **1978**, 43, 2480-2482.

38. W.E. Doering, J.R. Parikh, *Journal of the American Chemical Society*, **1967**, 89, 5505-5507.

39. E.J. Corey, C.U. Kim, *Journal of the American Chemical Society*, **1972**, 94, 7586-7587.

40. D.B. Dess, J.C. Martin, *Journal of Organic Chemistry*, **1983**, 48, 4155-4156.

41. S.D. Meyer, S.L. Schreiber, *Journal of Organic Chemistry*, **1994**, 59, 7549-7552.

42. D.B. Dess, J.C. Martin, *Journal of the American Chemical Society*, **1991**, 7277-7286.

43. M. Frigerio, M. Santagostino, S. Sputore, *Journal of Organic Chemistry,* **1999**, 64, 4537-4538.

44. H. Arrighi, R. Brookmeyer, E. Johnson, K. Zielgler-Graham, *Alzheimer's & Dementia*, **2007**, 3, 186-191.

45. J. Corey-Bloom, L.A. Hanson, L.J. Thal, P. Tiraboschi, *Neurology*, **2004**, 62, 1984-1989.

46. D.M. Quinn, *Chemical Reviews*, **1987**, 87, 955-979.

47. F. Barzaghi, M. M'Harzi, C. Oberlander, A.M. Palou, *Pharmacology, Biochemistry & Behaviour*, **1995**, 51, 119-124.

48. A.M. Fisher, *Neuroscience Intelligence Unit*, Muscarinic Agonists and the Treatment of Alzheimer's Disease, **1996**, Springer.

49. M.G.P. Buffat, Ph.D. Thesis, University of Manchester, 2003.

50. X. Moreau, E. J. Thomas, unpublished work.

51. H. Langhals, G. Range, C. Rüchardt, E. Witsuba, *Chimische Berichte*, **1981**, 114, 3813-3830.

52. G. Braunlich, B.A. Briggs, W. Bullock, A. Concepcion, M. Es-Sayed, R. Fischer, M.F. Fitzgerald, B. Fugmann, R. Henning, K.H. Schlemmer, S.Schneider, M.Sperzel, G. Sturton, *PCT. Int. Appl.*, PCT/EP00/04012, WO 00/69843, **200**.

53. W.P. Griffith, S.V. Ley, P. Marsden, J. Norman, *Synthesis*, **1994**, 7, 639-666.

54. G. Arena, R. Cali, E. Maccarone, A. Passerini, *Journal of the Chemical Society, Perkin Transactions 2*, **2002**, 12, 1961-2164.

55. *U.S. Pat. Appl. Publ*. 208153883, **2008**.

56. *R*.L. Buswell, L.A. Capuano, M.F. Lipton, K.J. Kolonko, R.H. Shapiro, *Tetrahedron Letters*, **1975**, 16, 1811-1814.

57. *J*.M. Chong, A. Darwish, *Journal of Organic Chemistry*, **2007**, 72, 1507-1509.

58. A.J. Barlow, B.J. Compton, R.T. Weavers, *Journal of Organic Chemistry*, **2005**, 7, 2470-2475.

59. F. Garro-Helion, F. Guibe, A. Merzouk, *Journal of Organic Chemistry*, **1993**, 58, 6109-6113.

60. D.Y. Cha, R.C. Kelly, V. VanRheenen, *Tetrahedron Letters*, **1976**, 1973-1976.

61. A.S. ElAzas, K. Kadota, K. Ogasawara, M. Takeuchi, T. Tanlguchi, *Synthesis*, **1999**, 8, 1325-1330.

62. Y. Furukawa, H. Itoh, H. Takeshiba, M. Tsuda, *Bioorganic & Medicinal Chemistry*, **2004**, 12, 3561-3567.

63. M. Hideki, K. Hirosato, Y. Kohichi, Y. Kohichiro, M. Nobuaki, N. Shin-Ichiro, T. Takahiro, I. Yoshimasa, *Journal of Medicinal Chemistry*, **2004**, 8, 1930-1938.

64. M. Hashimoto, T. Kan, H. Shirahama, M. Yanagiya, *Tetrahedron Letters*, **1988**, 29, 5417-5418.

65. S. Ito, N. Hosoda, M. Asam, C. Zhang, *Tetrahedron*, **2008**, 64, 9879-9884.

66. K.K. Moffet, R. Shetty, *Tetrahedron Letters*, **2006**, 47, 8021-8024.

67. F.F. Fleming, O.W. Steward, Q. Wang, *Organic Letters*, **2000**, 2, 1477-1479.

68. T. Fukuyama, T. Kan, H. Kobayashi, *Synlett*, **2002**, 5, 697-699.

69. A. Fujiwara, T. Fukuyama, T. Kan, H. Kobayashi, *Tetrahedron*, **2002**, 58, 6267-6276.

Appendix

Crystal data and structure refinement for 2.89

Identification code	s3081
Empirical formula	C24 H28 N2 O3
Formula weight	392.48
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 11.874(3) A alpha = 90 deg. b = 18.239(4) A beta = 94.881(4) deg. c = 9.829(2) A gamma = 90 deg.
Volume	2120.8(9) A^3
Z, Calculated density	4, 1.229 Mg/m^3
Absorption coefficient	0.081 mm^-1
F(000)	840
Crystal size	0.55 x 0.30 x 0.20 mm
Theta range for data collection	1.72 to 26.50 deg.
Limiting indices	-14<=h<=14, -15<=k<=22, -12<=l<=12
Reflections collected / unique	12048 / 4328 [R(int) = 0.0726]
Completeness to theta = 26.50	98.3 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4328 / 0 / 266
Goodness-of-fit on F^2	0.928
Final R indices [I>2sigma(I)]	R1 = 0.0534, wR2 = 0.0905
R indices (all data)	R1 = 0.1041, wR2 = 0.1032
Largest diff. peak and hole	0.207 and -0.174 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for s3081.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	3756(1)	950(1)	-618(1)	26(1)
O(2)	5111(1)	1644(1)	-1422(1)	31(1)
O(3)	821(1)	-5(1)	1954(2)	34(1)
N(1)	4969(1)	1515(1)	898(2)	21(1)
N(2)	2979(2)	2357(1)	1067(2)	27(1)
C(1)	4098(2)	1237(1)	1750(2)	21(1)
C(2)	3506(2)	686(1)	713(2)	22(1)
C(3)	4662(2)	1400(1)	-454(2)	24(1)
C(4)	4552(2)	816(1)	3022(2)	22(1)
C(5)	5286(2)	1207(1)	4185(2)	26(1)
C(6)	6143(2)	572(1)	4202(2)	30(1)
C(7)	5503(2)	248(1)	2908(2)	25(1)
C(8)	3340(2)	1857(1)	2178(2)	24(1)
C(9)	2133(2)	2879(1)	1487(2)	30(1)
C(10)	1796(2)	3402(1)	365(2)	31(1)
C(11)	1954(2)	4111(1)	443(2)	42(1)
C(12)	2259(2)	572(1)	753(2)	25(1)
C(13)	1937(2)	-1(1)	1684(2)	24(1)
C(14)	2477(2)	-565(1)	2333(2)	27(1)
C(15)	1670(2)	-948(1)	3061(2)	32(1)
C(16)	695(2)	-591(1)	2802(2)	36(1)
C(17)	1500(2)	961(1)	-8(2)	35(1)
C(18)	5761(2)	2110(1)	1289(2)	25(1)
C(19)	6939(2)	1868(1)	1792(2)	24(1)
C(20)	7530(2)	2233(1)	2868(2)	30(1)
C(21)	8619(2)	2027(1)	3315(2)	39(1)
C(22)	9131(2)	1443(1)	2698(3)	44(1)
C(23)	8549(2)	1084(1)	1620(2)	37(1)
C(24)	7466(2)	1295(1)	1171(2)	29(1)

Table 3. Bond lengths [A] and angles [deg] for s3081.

O(1)-C(3)	1.352(2)
O(1)-C(2)	1.448(2)
O(2)-C(3)	1.214(2)
O(3)-C(16)	1.371(2)
O(3)-C(13)	1.373(2)
N(1)-C(3)	1.364(2)
N(1)-C(18)	1.466(2)
N(1)-C(1)	1.475(2)
N(2)-C(8)	1.458(2)
N(2)-C(9)	1.468(2)
N(2)-H(2N)	0.90(2)
C(1)-C(4)	1.526(3)
C(1)-C(8)	1.528(2)
C(1)-C(2)	1.556(3)
C(2)-C(12)	1.499(3)
C(2)-H(2)	1.0000
C(4)-C(7)	1.543(3)
C(4)-C(5)	1.550(2)
C(4)-H(4)	1.0000
C(5)-C(6)	1.541(3)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(7)	1.542(3)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.487(3)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.308(3)
C(10)-H(10)	0.9500
C(11)-H(11A)	0.9500
C(11)-H(11B)	0.9500
C(12)-C(17)	1.327(3)
C(12)-C(13)	1.461(3)
C(13)-C(14)	1.344(3)
C(14)-C(15)	1.426(3)
C(14)-H(14)	0.9500
C(15)-C(16)	1.334(3)
C(15)-H(15)	0.9500
C(16)-H(16)	0.9500
C(17)-H(17A)	0.9500
C(17)-H(17B)	0.9500
C(18)-C(19)	1.508(3)
C(18)-H(18A)	0.9900
C(18)-H(18B)	0.9900
C(19)-C(24)	1.386(3)
C(19)-C(20)	1.389(3)
C(20)-C(21)	1.382(3)
C(20)-H(20)	0.9500
C(21)-C(22)	1.390(3)
C(21)-H(21)	0.9500
C(22)-C(23)	1.380(3)
C(22)-H(22)	0.9500

C(23)-C(24)	1.379(3)
C(23)-H(23)	0.9500
C(24)-H(24)	0.9500

C(3)-O(1)-C(2)	108.43(14)
C(16)-O(3)-C(13)	106.20(16)
C(3)-N(1)-C(18)	118.83(16)
C(3)-N(1)-C(1)	111.00(15)
C(18)-N(1)-C(1)	124.78(15)
C(8)-N(2)-C(9)	111.01(16)
C(8)-N(2)-H(2N)	100.9(13)
C(9)-N(2)-H(2N)	107.9(14)
N(1)-C(1)-C(4)	114.99(15)
N(1)-C(1)-C(8)	111.12(15)
C(4)-C(1)-C(8)	108.77(16)
N(1)-C(1)-C(2)	98.60(15)
C(4)-C(1)-C(2)	108.70(15)
C(8)-C(1)-C(2)	114.52(15)
O(1)-C(2)-C(12)	110.38(15)
O(1)-C(2)-C(1)	105.13(15)
C(12)-C(2)-C(1)	117.70(16)
O(1)-C(2)-H(2)	107.7
C(12)-C(2)-H(2)	107.7
C(1)-C(2)-H(2)	107.7
O(2)-C(3)-O(1)	121.85(18)
O(2)-C(3)-N(1)	127.45(19)
O(1)-C(3)-N(1)	110.70(17)
C(1)-C(4)-C(7)	119.19(16)
C(1)-C(4)-C(5)	120.69(16)
C(7)-C(4)-C(5)	89.64(14)
C(1)-C(4)-H(4)	108.6
C(7)-C(4)-H(4)	108.6
C(5)-C(4)-H(4)	108.6
C(6)-C(5)-C(4)	89.52(14)
C(6)-C(5)-H(5A)	113.7
C(4)-C(5)-H(5A)	113.7
C(6)-C(5)-H(5B)	113.7
C(4)-C(5)-H(5B)	113.7
H(5A)-C(5)-H(5B)	111.0
C(5)-C(6)-C(7)	90.01(14)
C(5)-C(6)-H(6A)	113.6
C(7)-C(6)-H(6A)	113.6
C(5)-C(6)-H(6B)	113.6
C(7)-C(6)-H(6B)	113.6
H(6A)-C(6)-H(6B)	110.9
C(6)-C(7)-C(4)	89.73(15)
C(6)-C(7)-H(7A)	113.7
C(4)-C(7)-H(7A)	113.7
C(6)-C(7)-H(7B)	113.7
C(4)-C(7)-H(7B)	113.7
H(7A)-C(7)-H(7B)	110.9
N(2)-C(8)-C(1)	113.48(16)
N(2)-C(8)-H(8A)	108.9
C(1)-C(8)-H(8A)	108.9
N(2)-C(8)-H(8B)	108.9
C(1)-C(8)-H(8B)	108.9
H(8A)-C(8)-H(8B)	107.7
N(2)-C(9)-C(10)	110.79(17)
N(2)-C(9)-H(9A)	109.5
C(10)-C(9)-H(9A)	109.5
N(2)-C(9)-H(9B)	109.5

C(10)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	108.1
C(11)-C(10)-C(9)	124.3(2)
C(11)-C(10)-H(10)	117.9
C(9)-C(10)-H(10)	117.9
C(10)-C(11)-H(11A)	120.0
C(10)-C(11)-H(11B)	120.0
H(11A)-C(11)-H(11B)	120.0
C(17)-C(12)-C(13)	122.28(18)
C(17)-C(12)-C(2)	122.42(18)
C(13)-C(12)-C(2)	115.31(17)
C(14)-C(13)-O(3)	109.50(17)
C(14)-C(13)-C(12)	134.78(18)
O(3)-C(13)-C(12)	115.67(17)
C(13)-C(14)-C(15)	107.37(18)
C(13)-C(14)-H(14)	126.3
C(15)-C(14)-H(14)	126.3
C(16)-C(15)-C(14)	105.97(19)
C(16)-C(15)-H(15)	127.0
C(14)-C(15)-H(15)	127.0
C(15)-C(16)-O(3)	110.96(19)
C(15)-C(16)-H(16)	124.5
O(3)-C(16)-H(16)	124.5
C(12)-C(17)-H(17A)	120.0
C(12)-C(17)-H(17B)	120.0
H(17A)-C(17)-H(17B)	120.0
N(1)-C(18)-C(19)	115.20(16)
N(1)-C(18)-H(18A)	108.5
C(19)-C(18)-H(18A)	108.5
N(1)-C(18)-H(18B)	108.5
C(19)-C(18)-H(18B)	108.5
H(18A)-C(18)-H(18B)	107.5
C(24)-C(19)-C(20)	118.60(18)
C(24)-C(19)-C(18)	121.11(18)
C(20)-C(19)-C(18)	120.26(18)
C(21)-C(20)-C(19)	120.7(2)
C(21)-C(20)-H(20)	119.7
C(19)-C(20)-H(20)	119.7
C(20)-C(21)-C(22)	120.2(2)
C(20)-C(21)-H(21)	119.9
C(22)-C(21)-H(21)	119.9
C(23)-C(22)-C(21)	119.3(2)
C(23)-C(22)-H(22)	120.3
C(21)-C(22)-H(22)	120.3
C(24)-C(23)-C(22)	120.4(2)
C(24)-C(23)-H(23)	119.8
C(22)-C(23)-H(23)	119.8
C(23)-C(24)-C(19)	120.9(2)
C(23)-C(24)-H(24)	119.6
C(19)-C(24)-H(24)	119.6

Symmetry transformations used to generate equivalent atoms:

Crystal data and structure refinement for 2.132

Identification code	s3255m
Empirical formula	C30 H30 N3 O7 S
Formula weight	576.63
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 13.818(2) A alpha = 76.010(4) deg. b = 14.714(2) A beta = 82.840(4) deg. c = 14.863(3) A gamma = 70.291(3) deg.
Volume	2757.3(8) A^3
Z, Calculated density	4, 1.389 Mg/m^3
Absorption coefficient	0.171 mm^-1
F(000)	1212
Crystal size	0.22 x 0.18 x 0.04 mm
Theta range for data collection	1.41 to 25.03 deg.
Limiting indices	-16<=h<=16, -17<=k<=17, -17<=l<=17
Reflections collected / unique	20144 / 9704 [R(int) = 0.1125]
Completeness to theta = 25.00	99.4 %
Absorption correction	None
Max. and min. transmission	0.9932 and 0.9633
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9704 / 37 / 738
Goodness-of-fit on F^2	0.820
Final R indices [I>2sigma(I)]	R1 = 0.0668, wR2 = 0.1249
R indices (all data)	R1 = 0.2054, wR2 = 0.2176
Largest diff. peak and hole	0.380 and -0.366 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for s3255m.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	7702(3)	2435(3)	2072(2)	27(1)
C(2)	8532(3)	2881(3)	2144(3)	24(1)
C(3)	8104(3)	3989(3)	2109(3)	29(1)
C(4)	6870(3)	3411(3)	3317(3)	28(1)
C(5)	6797(3)	2645(3)	2818(2)	23(1)
C(6)	6180(3)	3231(3)	1309(3)	30(1)
C(7)	9414(3)	2645(3)	1450(3)	26(1)
C(8)	10206(3)	2847(3)	72(3)	43(1)
C(9)	10795(3)	2055(3)	614(3)	42(1)
C(10)	10296(3)	1916(3)	1509(3)	27(1)
C(17)	6753(3)	1710(3)	3530(3)	28(1)
C(18)	7757(3)	1030(3)	4014(3)	37(1)
C(19)	7457(3)	132(3)	3945(3)	40(2)
C(20)	6654(3)	828(3)	3222(3)	36(1)
C(21)	4826(3)	3468(3)	2547(3)	30(1)
C(22)	4148(3)	2837(3)	2617(3)	26(1)
C(23)	3404(3)	2825(3)	3340(3)	37(1)
C(24)	2725(3)	2322(3)	3394(3)	44(2)
C(25)	2774(3)	1792(3)	2740(3)	41(2)
C(26)	3517(3)	1763(3)	2021(3)	39(1)
C(27)	4204(3)	2297(3)	1964(3)	38(1)
C(28)	7160(3)	1019(3)	9126(3)	29(1)
C(29)	7568(3)	1437(3)	9787(2)	24(1)
C(30)	8174(3)	2112(3)	9272(3)	29(1)
C(31)	6536(3)	2854(3)	8406(3)	31(1)
C(32)	6500(3)	1835(3)	8363(2)	24(1)
C(33)	7915(3)	723(3)	7700(3)	30(1)
C(34)	8194(3)	645(3)	10524(2)	28(1)
C(35)	8431(4)	-665(3)	11668(3)	61(2)
C(36)	9254(3)	-399(4)	11600(3)	59(2)
C(37)	9113(3)	465(3)	10845(3)	41(1)
C(38)	7820(2)	4603(2)	8502(2)	24(1)
C(40)	8269(3)	5872(2)	8957(2)	28(1)
C(41)	7526(3)	5893(3)	9677(3)	29(1)
C(42)	6913(3)	5313(3)	9793(3)	28(1)
C(43)	7076(3)	4640(3)	9228(3)	29(1)
C(44)	5381(3)	1873(3)	8430(3)	26(1)
C(45)	5065(3)	952(3)	8428(3)	34(1)
C(46)	4180(3)	1303(3)	9150(3)	47(2)
C(47)	4782(3)	1928(3)	9378(3)	34(1)
C(48)	6803(3)	2052(3)	6572(2)	25(1)
C(49)	5999(3)	1744(3)	6222(3)	28(1)
C(50)	5060(3)	2429(3)	5952(3)	32(1)
C(51)	4306(3)	2128(3)	5672(3)	43(2)
C(52)	4496(3)	1157(3)	5669(3)	40(1)
C(53)	5442(3)	472(3)	5916(3)	37(1)
C(54)	6188(3)	766(3)	6189(3)	28(1)
C(55)	9641(3)	3147(3)	4429(3)	40(1)
C(56)	10147(3)	2386(3)	3982(3)	51(2)
C(57)	10333(3)	1420(3)	4438(3)	60(2)

C(58)	10020(3)	1212(3)	5348(3)	54(2)
C(59)	9528(3)	1955(3)	5816(3)	45(2)
C(60)	9339(3)	2927(3)	5358(3)	40(2)
N(1)	7089(2)	4228(2)	2636(2)	29(1)
N(2)	5907(2)	3058(2)	2227(2)	22(1)
N(4)	7595(2)	2820(2)	8477(2)	27(1)
N(5)	7067(2)	1526(2)	7525(2)	25(1)
O(1)	7235(2)	2892(2)	1177(2)	27(1)
O(2)	9312(2)	3242(2)	582(2)	41(1)
O(3)	5569(2)	5451(2)	3211(2)	42(1)
O(4)	6664(2)	5986(2)	1849(2)	39(1)
O(7)	5622(2)	3601(2)	652(2)	33(1)
O(8)	8010(2)	411(2)	8639(2)	33(1)
O(9)	7726(2)	-24(2)	11012(2)	51(1)
O(10)	9154(2)	3198(2)	7796(2)	32(1)
O(11)	7479(2)	4073(2)	7034(2)	36(1)
O(14)	8503(2)	296(2)	7160(2)	36(1)
S(1)	6559(1)	5362(1)	2746(1)	34(1)
S(2)	8055(1)	3651(1)	7854(1)	28(1)
C(11)	7327(2)	5559(2)	3555(2)	18(1)
C(12)	7265(3)	5343(3)	4520(2)	24(2)
C(13)	7904(3)	5585(3)	5009(2)	35(2)
C(14)	8605(3)	6043(4)	4533(3)	31(2)
C(15)	8667(3)	6259(3)	3569(3)	26(2)
C(16)	8028(2)	6017(2)	3079(2)	19(2)
N(3)	6494(4)	4952(3)	5019(3)	33(1)
O(5)	5821(4)	5480(3)	5467(3)	45(1)
O(6)	6580(3)	4095(3)	5032(3)	38(1)
C(11S)	7417(4)	5670(4)	3380(3)	18(1)
C(12S)	8179(5)	6117(4)	3118(4)	24(2)
C(13S)	8754(5)	6184(6)	3789(5)	35(2)
C(14S)	8568(6)	5803(6)	4721(5)	31(2)
C(15S)	7806(6)	5356(6)	4982(3)	26(2)
C(16S)	7231(5)	5289(4)	4312(3)	19(2)
N(3S)	8324(6)	6515(4)	2168(5)	33(1)
O(5S)	7979(6)	7414(5)	1904(5)	45(1)
O(6S)	8876(5)	5942(5)	1699(4)	38(1)
C(39)	8370(1)	5250(1)	8376(1)	23(1)
N(6)	9063(1)	5421(2)	7520(1)	28(1)
O(12)	8985(2)	5135(2)	6835(1)	21(1)
O(13)	9707(2)	5789(3)	7626(2)	63(1)
C(39S)	8402(1)	5198(1)	8429(1)	23(1)
N(6S)	9244(1)	5182(2)	7667(1)	28(1)
O(12S)	10093(1)	5144(3)	7857(2)	21(1)
O(13S)	8958(2)	5277(2)	6889(1)	63(1)

Table 3. Bond lengths [A] and angles [deg] for s3255m.

C(1)-O(1)	1.459(4)
C(1)-C(2)	1.525(6)
C(1)-C(5)	1.563(5)
C(1)-H(1)	1.0000
C(2)-C(7)	1.498(5)
C(2)-C(3)	1.526(5)
C(2)-H(2)	1.0000
C(3)-N(1)	1.494(5)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-N(1)	1.464(5)
C(4)-C(5)	1.526(6)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-N(2)	1.469(4)
C(5)-C(17)	1.535(5)
C(6)-O(7)	1.222(4)
C(6)-N(2)	1.356(5)
C(6)-O(1)	1.377(4)
C(7)-C(10)	1.321(5)
C(7)-O(2)	1.368(4)
C(8)-C(9)	1.318(5)
C(8)-O(2)	1.390(5)
C(8)-H(8)	0.9500
C(9)-C(10)	1.422(6)
C(9)-H(9)	0.9500
C(10)-H(10)	0.9500
C(17)-C(20)	1.527(6)
C(17)-C(18)	1.551(5)
C(17)-H(17)	1.0000
C(18)-C(19)	1.540(6)
C(18)-H(18A)	0.9900
C(18)-H(18B)	0.9900
C(19)-C(20)	1.560(5)
C(19)-H(19A)	0.9900
C(19)-H(19B)	0.9900
C(20)-H(20A)	0.9900
C(20)-H(20B)	0.9900
C(21)-N(2)	1.475(4)
C(21)-C(22)	1.505(6)
C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900
C(22)-C(27)	1.375(6)
C(22)-C(23)	1.393(5)
C(23)-C(24)	1.362(7)
C(23)-H(23)	0.9500
C(24)-C(25)	1.368(7)
C(24)-H(24)	0.9500
C(25)-C(26)	1.384(6)
C(25)-H(25)	0.9500
C(26)-C(27)	1.406(6)
C(26)-H(26)	0.9500
C(27)-H(27)	0.9500
C(28)-O(8)	1.447(4)
C(28)-C(29)	1.525(6)
C(28)-C(32)	1.556(5)
C(28)-H(28)	1.0000

C(29)-C(34)	1.498(5)
C(29)-C(30)	1.518(5)
C(29)-H(29)	1.0000
C(30)-N(4)	1.483(4)
C(30)-H(30A)	0.9900
C(30)-H(30B)	0.9900
C(31)-N(4)	1.463(5)
C(31)-C(32)	1.534(6)
C(31)-H(31A)	0.9900
C(31)-H(31B)	0.9900
C(32)-N(5)	1.472(5)
C(32)-C(44)	1.520(5)
C(33)-O(14)	1.199(4)
C(33)-N(5)	1.352(4)
C(33)-O(8)	1.367(4)
C(34)-C(37)	1.331(6)
C(34)-O(9)	1.372(5)
C(35)-C(36)	1.307(7)
C(35)-O(9)	1.400(5)
C(35)-H(35)	0.9500
C(36)-C(37)	1.452(6)
C(36)-H(36)	0.9500
C(37)-H(37)	0.9500
C(38)-C(39S)	1.354(2)
C(38)-C(39)	1.372(2)
C(38)-C(43)	1.393(5)
C(38)-S(2)	1.805(3)
C(40)-C(39S)	1.360(3)
C(40)-C(39)	1.368(3)
C(40)-C(41)	1.386(5)
C(40)-H(40)	0.9500
C(41)-C(42)	1.362(6)
C(41)-H(41)	0.9500
C(42)-C(43)	1.393(6)
C(42)-H(42)	0.9500
C(43)-H(43)	0.9500
C(44)-C(47)	1.547(5)
C(44)-C(45)	1.558(6)
C(44)-H(44)	1.0000
C(45)-C(46)	1.559(5)
C(45)-H(45A)	0.9900
C(45)-H(45B)	0.9900
C(46)-C(47)	1.546(7)
C(46)-H(46A)	0.9900
C(46)-H(46B)	0.9900
C(47)-H(47A)	0.9900
C(47)-H(47B)	0.9900
C(48)-N(5)	1.464(4)
C(48)-C(49)	1.520(6)
C(48)-H(48A)	0.9900
C(48)-H(48B)	0.9900
C(49)-C(50)	1.383(5)
C(49)-C(54)	1.385(5)
C(50)-C(51)	1.402(6)
C(50)-H(50)	0.9500
C(51)-C(52)	1.364(6)
C(51)-H(51)	0.9500
C(52)-C(53)	1.382(5)
C(52)-H(52)	0.9500
C(53)-C(54)	1.380(6)
C(53)-H(53)	0.9500

C(54)-H(54)	0.9500
C(55)-C(56)	1.379(6)
C(55)-C(60)	1.383(6)
C(55)-H(55)	0.9500
C(56)-C(57)	1.370(6)
C(56)-H(56)	0.9500
C(57)-C(58)	1.361(6)
C(57)-H(57)	0.9500
C(58)-C(59)	1.374(6)
C(58)-H(58)	0.9500
C(59)-C(60)	1.378(6)
C(59)-H(59)	0.9500
C(60)-H(60)	0.9500
N(1)-S(1)	1.621(3)
N(4)-S(2)	1.608(3)
O(3)-S(1)	1.433(3)
O(4)-S(1)	1.446(3)
O(10)-S(2)	1.438(3)
O(11)-S(2)	1.432(3)
S(1)-C(11S)	1.830(6)
S(1)-C(11)	1.830(3)
C(11)-C(12)	1.3900
C(11)-C(16)	1.3900
C(12)-C(13)	1.3900
C(12)-N(3)	1.424(6)
C(13)-C(14)	1.3900
C(13)-H(13)	0.9500
C(14)-C(15)	1.3900
C(14)-H(14)	0.9500
C(15)-C(16)	1.3900
C(15)-H(15)	0.9500
C(16)-H(16)	0.9500
N(3)-O(6)	1.222(6)
N(3)-O(5)	1.233(6)
C(11S)-C(12S)	1.3900
C(11S)-C(16S)	1.3900
C(12S)-C(13S)	1.3900
C(12S)-N(3S)	1.409(8)
C(13S)-C(14S)	1.3900
C(13S)-H(13S)	0.9500
C(14S)-C(15S)	1.3900
C(14S)-H(14S)	0.9500
C(15S)-C(16S)	1.3900
C(15S)-H(15S)	0.9500
C(16S)-H(16S)	0.9500
N(3S)-O(6S)	1.223(8)
N(3S)-O(5S)	1.226(7)
C(39)-N(6)	1.5184
N(6)-O(12)	1.2210
N(6)-O(13)	1.2297
C(39S)-N(6S)	1.5183
N(6S)-O(12S)	1.2210
N(6S)-O(13S)	1.2297

O(1)-C(1)-C(2)	108.7(3)
O(1)-C(1)-C(5)	105.6(3)
C(2)-C(1)-C(5)	113.3(3)
O(1)-C(1)-H(1)	109.7
C(2)-C(1)-H(1)	109.7
C(5)-C(1)-H(1)	109.7
C(7)-C(2)-C(1)	113.0(3)

C(7)-C(2)-C(3)	111.2(3)
C(1)-C(2)-C(3)	112.9(3)
C(7)-C(2)-H(2)	106.4
C(1)-C(2)-H(2)	106.4
C(3)-C(2)-H(2)	106.4
N(1)-C(3)-C(2)	109.9(3)
N(1)-C(3)-H(3A)	109.7
C(2)-C(3)-H(3A)	109.7
N(1)-C(3)-H(3B)	109.7
C(2)-C(3)-H(3B)	109.7
H(3A)-C(3)-H(3B)	108.2
N(1)-C(4)-C(5)	109.4(3)
N(1)-C(4)-H(4A)	109.8
C(5)-C(4)-H(4A)	109.8
N(1)-C(4)-H(4B)	109.8
C(5)-C(4)-H(4B)	109.8
H(4A)-C(4)-H(4B)	108.2
N(2)-C(5)-C(4)	110.7(3)
N(2)-C(5)-C(17)	111.9(3)
C(4)-C(5)-C(17)	109.8(3)
N(2)-C(5)-C(1)	100.9(3)
C(4)-C(5)-C(1)	110.5(3)
C(17)-C(5)-C(1)	112.9(3)
O(7)-C(6)-N(2)	128.4(4)
O(7)-C(6)-O(1)	121.3(3)
N(2)-C(6)-O(1)	110.3(3)
C(10)-C(7)-O(2)	111.4(3)
C(10)-C(7)-C(2)	131.1(3)
O(2)-C(7)-C(2)	117.4(3)
C(9)-C(8)-O(2)	108.3(4)
C(9)-C(8)-H(8)	125.8
O(2)-C(8)-H(8)	125.8
C(8)-C(9)-C(10)	109.1(3)
C(8)-C(9)-H(9)	125.4
C(10)-C(9)-H(9)	125.4
C(7)-C(10)-C(9)	105.2(3)
C(7)-C(10)-H(10)	127.4
C(9)-C(10)-H(10)	127.4
C(20)-C(17)-C(5)	121.0(3)
C(20)-C(17)-C(18)	89.7(3)
C(5)-C(17)-C(18)	117.9(3)
C(20)-C(17)-H(17)	108.9
C(5)-C(17)-H(17)	108.9
C(18)-C(17)-H(17)	108.9
C(19)-C(18)-C(17)	88.5(3)
C(19)-C(18)-H(18A)	113.9
C(17)-C(18)-H(18A)	113.9
C(19)-C(18)-H(18B)	113.9
C(17)-C(18)-H(18B)	113.9
H(18A)-C(18)-H(18B)	111.1
C(18)-C(19)-C(20)	88.9(3)
C(18)-C(19)-H(19A)	113.8
C(20)-C(19)-H(19A)	113.8
C(18)-C(19)-H(19B)	113.8
C(20)-C(19)-H(19B)	113.8
H(19A)-C(19)-H(19B)	111.1
C(17)-C(20)-C(19)	88.6(3)
C(17)-C(20)-H(20A)	113.9
C(19)-C(20)-H(20A)	113.9
C(17)-C(20)-H(20B)	113.9
C(19)-C(20)-H(20B)	113.9

H(20A)-C(20)-H(20B)	111.1
N(2)-C(21)-C(22)	116.8(3)
N(2)-C(21)-H(21A)	108.1
C(22)-C(21)-H(21A)	108.1
N(2)-C(21)-H(21B)	108.1
C(22)-C(21)-H(21B)	108.1
H(21A)-C(21)-H(21B)	107.3
C(27)-C(22)-C(23)	118.1(4)
C(27)-C(22)-C(21)	122.2(4)
C(23)-C(22)-C(21)	119.6(4)
C(24)-C(23)-C(22)	121.7(4)
C(24)-C(23)-H(23)	119.2
C(22)-C(23)-H(23)	119.2
C(23)-C(24)-C(25)	120.3(4)
C(23)-C(24)-H(24)	119.9
C(25)-C(24)-H(24)	119.9
C(24)-C(25)-C(26)	120.1(5)
C(24)-C(25)-H(25)	120.0
C(26)-C(25)-H(25)	120.0
C(25)-C(26)-C(27)	119.2(4)
C(25)-C(26)-H(26)	120.4
C(27)-C(26)-H(26)	120.4
C(22)-C(27)-C(26)	120.7(4)
C(22)-C(27)-H(27)	119.7
C(26)-C(27)-H(27)	119.7
O(8)-C(28)-C(29)	110.0(3)
O(8)-C(28)-C(32)	106.0(3)
C(29)-C(28)-C(32)	112.9(3)
O(8)-C(28)-H(28)	109.3
C(29)-C(28)-H(28)	109.3
C(32)-C(28)-H(28)	109.3
C(34)-C(29)-C(30)	110.6(3)
C(34)-C(29)-C(28)	112.5(3)
C(30)-C(29)-C(28)	111.9(3)
C(34)-C(29)-H(29)	107.2
C(30)-C(29)-H(29)	107.2
C(28)-C(29)-H(29)	107.2
N(4)-C(30)-C(29)	110.1(3)
N(4)-C(30)-H(30A)	109.6
C(29)-C(30)-H(30A)	109.6
N(4)-C(30)-H(30B)	109.6
C(29)-C(30)-H(30B)	109.6
H(30A)-C(30)-H(30B)	108.2
N(4)-C(31)-C(32)	110.7(3)
N(4)-C(31)-H(31A)	109.5
C(32)-C(31)-H(31A)	109.5
N(4)-C(31)-H(31B)	109.5
C(32)-C(31)-H(31B)	109.5
H(31A)-C(31)-H(31B)	108.1
N(5)-C(32)-C(44)	113.3(3)
N(5)-C(32)-C(31)	110.6(3)
C(44)-C(32)-C(31)	108.6(3)
N(5)-C(32)-C(28)	100.1(3)
C(44)-C(32)-C(28)	113.5(3)
C(31)-C(32)-C(28)	110.5(3)
O(14)-C(33)-N(5)	128.6(4)
O(14)-C(33)-O(8)	122.1(3)
N(5)-C(33)-O(8)	109.2(3)
C(37)-C(34)-O(9)	111.2(3)
C(37)-C(34)-C(29)	133.5(4)
O(9)-C(34)-C(29)	115.2(3)

C(36)-C(35)-O(9)	110.7(4)
C(36)-C(35)-H(35)	124.6
O(9)-C(35)-H(35)	124.6
C(35)-C(36)-C(37)	107.1(4)
C(35)-C(36)-H(36)	126.5
C(37)-C(36)-H(36)	126.5
C(34)-C(37)-C(36)	105.9(4)
C(34)-C(37)-H(37)	127.1
C(36)-C(37)-H(37)	127.1
C(39S)-C(38)-C(39)	4.1
C(39S)-C(38)-C(43)	116.2(3)
C(39)-C(38)-C(43)	117.2(3)
C(39S)-C(38)-S(2)	125.4(2)
C(39)-C(38)-S(2)	124.9(2)
C(43)-C(38)-S(2)	117.7(2)
C(39S)-C(40)-C(39)	4.1
C(39S)-C(40)-C(41)	116.8(3)
C(39)-C(40)-C(41)	118.0(3)
C(39S)-C(40)-H(40)	122.0
C(39)-C(40)-H(40)	121.0
C(41)-C(40)-H(40)	121.0
C(42)-C(41)-C(40)	120.6(4)
C(42)-C(41)-H(41)	119.7
C(40)-C(41)-H(41)	119.7
C(41)-C(42)-C(43)	120.1(4)
C(41)-C(42)-H(42)	119.9
C(43)-C(42)-H(42)	119.9
C(42)-C(43)-C(38)	120.2(4)
C(42)-C(43)-H(43)	119.9
C(38)-C(43)-H(43)	119.9
C(32)-C(44)-C(47)	118.0(3)
C(32)-C(44)-C(45)	122.1(3)
C(47)-C(44)-C(45)	88.2(3)
C(32)-C(44)-H(44)	108.9
C(47)-C(44)-H(44)	108.9
C(45)-C(44)-H(44)	108.9
C(44)-C(45)-C(46)	87.7(3)
C(44)-C(45)-H(45A)	114.0
C(46)-C(45)-H(45A)	114.0
C(44)-C(45)-H(45B)	114.0
C(46)-C(45)-H(45B)	114.0
H(45A)-C(45)-H(45B)	111.2
C(47)-C(46)-C(45)	88.2(3)
C(47)-C(46)-H(46A)	113.9
C(45)-C(46)-H(46A)	113.9
C(47)-C(46)-H(46B)	113.9
C(45)-C(46)-H(46B)	113.9
H(46A)-C(46)-H(46B)	111.1
C(46)-C(47)-C(44)	88.5(3)
C(46)-C(47)-H(47A)	113.9
C(44)-C(47)-H(47A)	113.9
C(46)-C(47)-H(47B)	113.9
C(44)-C(47)-H(47B)	113.9
H(47A)-C(47)-H(47B)	111.1
N(5)-C(48)-C(49)	112.0(3)
N(5)-C(48)-H(48A)	109.2
C(49)-C(48)-H(48A)	109.2
N(5)-C(48)-H(48B)	109.2
C(49)-C(48)-H(48B)	109.2
H(48A)-C(48)-H(48B)	107.9
C(50)-C(49)-C(54)	119.0(4)

C(50)-C(49)-C(48)	120.6(4)
C(54)-C(49)-C(48)	120.3(3)
C(49)-C(50)-C(51)	120.1(4)
C(49)-C(50)-H(50)	120.0
C(51)-C(50)-H(50)	120.0
C(52)-C(51)-C(50)	120.0(4)
C(52)-C(51)-H(51)	120.0
C(50)-C(51)-H(51)	120.0
C(51)-C(52)-C(53)	120.2(4)
C(51)-C(52)-H(52)	119.9
C(53)-C(52)-H(52)	119.9
C(54)-C(53)-C(52)	120.0(4)
C(54)-C(53)-H(53)	120.0
C(52)-C(53)-H(53)	120.0
C(53)-C(54)-C(49)	120.6(4)
C(53)-C(54)-H(54)	119.7
C(49)-C(54)-H(54)	119.7
C(56)-C(55)-C(60)	119.2(4)
C(56)-C(55)-H(55)	120.4
C(60)-C(55)-H(55)	120.4
C(57)-C(56)-C(55)	120.9(4)
C(57)-C(56)-H(56)	119.5
C(55)-C(56)-H(56)	119.5
C(58)-C(57)-C(56)	119.3(4)
C(58)-C(57)-H(57)	120.3
C(56)-C(57)-H(57)	120.3
C(57)-C(58)-C(59)	121.0(4)
C(57)-C(58)-H(58)	119.5
C(59)-C(58)-H(58)	119.5
C(58)-C(59)-C(60)	119.7(4)
C(58)-C(59)-H(59)	120.1
C(60)-C(59)-H(59)	120.1
C(59)-C(60)-C(55)	119.7(4)
C(59)-C(60)-H(60)	120.1
C(55)-C(60)-H(60)	120.1
C(4)-N(1)-C(3)	116.7(3)
C(4)-N(1)-S(1)	121.2(2)
C(3)-N(1)-S(1)	116.9(3)
C(6)-N(2)-C(5)	112.8(3)
C(6)-N(2)-C(21)	120.2(3)
C(5)-N(2)-C(21)	125.6(3)
C(31)-N(4)-C(30)	117.5(3)
C(31)-N(4)-S(2)	122.0(2)
C(30)-N(4)-S(2)	119.3(3)
C(33)-N(5)-C(48)	121.2(3)
C(33)-N(5)-C(32)	114.0(3)
C(48)-N(5)-C(32)	124.8(3)
C(6)-O(1)-C(1)	109.5(3)
C(7)-O(2)-C(8)	105.9(3)
C(33)-O(8)-C(28)	110.6(3)
C(34)-O(9)-C(35)	105.1(4)
O(3)-S(1)-O(4)	121.00(16)
O(3)-S(1)-N(1)	108.18(18)
O(4)-S(1)-N(1)	106.97(16)
O(3)-S(1)-C(11S)	113.0(2)
O(4)-S(1)-C(11S)	98.5(2)
N(1)-S(1)-C(11S)	108.3(2)
O(3)-S(1)-C(11)	105.43(16)
O(4)-S(1)-C(11)	108.04(17)
N(1)-S(1)-C(11)	106.39(15)
C(11S)-S(1)-C(11)	9.68(19)

O(11)-S(2)-O(10)	120.92(16)
O(11)-S(2)-N(4)	107.24(18)
O(10)-S(2)-N(4)	106.45(15)
O(11)-S(2)-C(38)	108.12(15)
O(10)-S(2)-C(38)	106.09(15)
N(4)-S(2)-C(38)	107.37(15)
C(12)-C(11)-C(16)	120.0
C(12)-C(11)-S(1)	129.05(15)
C(16)-C(11)-S(1)	110.92(15)
C(11)-C(12)-C(13)	120.0
C(11)-C(12)-N(3)	120.9(3)
C(13)-C(12)-N(3)	118.9(3)
C(12)-C(13)-C(14)	120.0
C(12)-C(13)-H(13)	120.0
C(14)-C(13)-H(13)	120.0
C(15)-C(14)-C(13)	120.0
C(15)-C(14)-H(14)	120.0
C(13)-C(14)-H(14)	120.0
C(14)-C(15)-C(16)	120.0
C(14)-C(15)-H(15)	120.0
C(16)-C(15)-H(15)	120.0
C(15)-C(16)-C(11)	120.0
C(15)-C(16)-H(16)	120.0
C(11)-C(16)-H(16)	120.0
O(6)-N(3)-O(5)	124.1(5)
O(6)-N(3)-C(12)	118.2(4)
O(5)-N(3)-C(12)	117.5(4)
C(12S)-C(11S)-C(16S)	120.0
C(12S)-C(11S)-S(1)	134.4(3)
C(16S)-C(11S)-S(1)	105.5(3)
C(13S)-C(12S)-C(11S)	120.0
C(13S)-C(12S)-N(3S)	121.9(5)
C(11S)-C(12S)-N(3S)	118.1(5)
C(12S)-C(13S)-C(14S)	120.0
C(12S)-C(13S)-H(13S)	120.0
C(14S)-C(13S)-H(13S)	120.0
C(15S)-C(14S)-C(13S)	120.0
C(15S)-C(14S)-H(14S)	120.0
C(13S)-C(14S)-H(14S)	120.0
C(14S)-C(15S)-C(16S)	120.0
C(14S)-C(15S)-H(15S)	120.0
C(16S)-C(15S)-H(15S)	120.0
C(15S)-C(16S)-C(11S)	120.0
C(15S)-C(16S)-H(16S)	120.0
C(11S)-C(16S)-H(16S)	120.0
O(6S)-N(3S)-O(5S)	125.3(7)
O(6S)-N(3S)-C(12S)	116.7(6)
O(5S)-N(3S)-C(12S)	117.5(6)
C(40)-C(39)-C(38)	123.6(2)
C(40)-C(39)-N(6)	113.27(17)
C(38)-C(39)-N(6)	122.81(17)
O(12)-N(6)-O(13)	126.6
O(12)-N(6)-C(39)	119.2
O(13)-N(6)-C(39)	114.0
C(38)-C(39S)-C(40)	125.7(2)
C(38)-C(39S)-N(6S)	119.25(17)
C(40)-C(39S)-N(6S)	114.98(18)
O(12S)-N(6S)-O(13S)	126.6
O(12S)-N(6S)-C(39S)	119.2
O(13S)-N(6S)-C(39S)	114.0

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for s3255m.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(1)	31(2)	29(2)	19(2)	-13(2)	-6(2)	-1(2)
C(2)	17(2)	31(2)	27(2)	-13(2)	-3(2)	-8(2)
C(3)	23(2)	34(2)	35(2)	-22(2)	0(2)	-7(2)
C(4)	26(2)	31(2)	27(2)	-15(2)	-7(2)	-3(2)
C(5)	14(2)	35(2)	23(2)	-19(2)	-1(2)	-3(2)
C(6)	36(2)	26(2)	34(2)	-9(2)	-3(2)	-14(2)
C(7)	36(2)	36(2)	19(2)	-11(2)	2(2)	-26(2)
C(8)	50(3)	45(2)	42(2)	-28(2)	23(2)	-23(2)
C(9)	20(2)	42(2)	70(3)	-37(2)	-2(2)	1(2)
C(10)	30(2)	15(2)	34(2)	-9(2)	-7(2)	0(2)
C(17)	27(2)	37(2)	21(2)	-13(2)	10(2)	-10(2)
C(18)	32(2)	51(3)	25(2)	-4(2)	0(2)	-13(2)
C(19)	43(3)	40(3)	34(3)	-3(2)	-1(2)	-15(2)
C(20)	39(2)	42(2)	34(2)	-14(2)	10(2)	-19(2)
C(21)	25(2)	34(2)	29(2)	-16(2)	-2(2)	-3(2)
C(22)	22(2)	26(2)	28(2)	-7(2)	-10(2)	-3(2)
C(23)	31(2)	56(3)	29(2)	-19(2)	7(2)	-16(2)
C(24)	44(3)	47(3)	44(3)	-11(2)	13(2)	-22(2)
C(25)	21(2)	30(2)	66(3)	0(2)	-2(2)	-6(2)
C(26)	37(2)	33(2)	55(3)	-23(2)	-8(2)	-10(2)
C(27)	35(3)	39(2)	38(3)	-14(2)	3(2)	-8(2)
C(28)	30(2)	24(2)	29(2)	-6(2)	-4(2)	-2(2)
C(29)	28(2)	25(2)	19(2)	-10(2)	-4(2)	-3(2)
C(30)	26(2)	33(2)	27(2)	-18(2)	-10(2)	1(2)
C(31)	44(2)	25(2)	26(2)	-12(2)	0(2)	-9(2)
C(32)	32(2)	24(2)	18(2)	-8(2)	-6(2)	-8(2)
C(33)	39(2)	31(2)	29(2)	-13(2)	-12(2)	-13(2)
C(34)	37(2)	29(2)	18(2)	-18(2)	9(2)	-8(2)
C(35)	85(4)	37(3)	29(3)	-4(2)	-28(3)	27(3)
C(36)	26(3)	104(4)	31(2)	-34(2)	-10(2)	14(3)
C(37)	27(2)	75(3)	23(2)	-21(2)	-4(2)	-11(2)
C(38)	30(2)	26(2)	17(2)	-11(2)	-1(2)	-6(2)
C(40)	24(2)	38(2)	28(2)	-9(2)	-3(2)	-17(2)
C(41)	31(2)	26(2)	33(2)	-10(2)	-4(2)	-9(2)
C(42)	31(2)	32(2)	18(2)	-10(2)	7(2)	-5(2)
C(43)	41(2)	21(2)	29(2)	-6(2)	-8(2)	-13(2)
C(44)	33(2)	22(2)	23(2)	-11(2)	-3(2)	-7(2)
C(45)	33(2)	38(2)	36(2)	-9(2)	-6(2)	-16(2)
C(46)	52(3)	64(3)	34(3)	-12(2)	-3(2)	-27(2)
C(47)	37(2)	36(2)	32(2)	-14(2)	-8(2)	-7(2)
C(48)	34(2)	19(2)	22(2)	-4(2)	-3(2)	-7(2)
C(49)	40(2)	30(2)	16(2)	-7(2)	2(2)	-14(2)
C(50)	48(3)	23(2)	28(2)	-11(2)	-6(2)	-9(2)
C(51)	39(3)	45(3)	44(3)	-24(2)	-12(2)	4(2)
C(52)	45(3)	47(2)	44(2)	-35(2)	-3(2)	-19(2)
C(53)	51(3)	30(2)	37(2)	-18(2)	5(2)	-16(2)
C(54)	36(2)	26(2)	27(2)	-18(2)	5(2)	-10(2)
C(55)	32(2)	67(3)	29(2)	-20(2)	3(2)	-21(2)
C(56)	23(2)	89(3)	59(3)	-49(2)	2(2)	-20(2)

C(57)	33(3)	75(3)	92(3)	-70(2)	-2(2)	-5(2)
C(58)	34(3)	57(3)	78(3)	-30(3)	-11(3)	-11(2)
C(59)	43(3)	51(3)	42(3)	-13(2)	-7(2)	-13(2)
C(60)	32(2)	41(3)	42(3)	-17(2)	-2(2)	-1(2)
N(1)	33(2)	29(2)	33(2)	-22(1)	-1(2)	-9(2)
N(2)	21(2)	27(2)	20(2)	-14(1)	-1(1)	-5(1)
N(4)	27(2)	35(2)	22(2)	-14(1)	-11(2)	-6(2)
N(5)	32(2)	26(2)	19(2)	-13(1)	-2(2)	-7(1)
O(1)	25(1)	38(1)	22(1)	-11(1)	-1(1)	-11(1)
O(2)	39(2)	44(2)	42(2)	-20(1)	1(2)	-9(1)
O(3)	31(2)	49(2)	57(2)	-36(1)	-5(1)	-6(1)
O(4)	44(2)	29(1)	43(2)	-22(1)	-16(1)	3(1)
O(7)	31(2)	44(2)	29(2)	-9(1)	-3(1)	-17(1)
O(8)	36(2)	29(1)	30(2)	-17(1)	-11(1)	3(1)
O(9)	63(2)	51(2)	39(2)	-10(2)	-10(2)	-16(2)
O(10)	35(2)	38(2)	29(2)	-18(1)	5(1)	-14(1)
O(11)	53(2)	37(2)	23(1)	-11(1)	-3(1)	-18(1)
O(14)	38(2)	37(2)	34(2)	-26(1)	0(1)	0(1)
S(1)	28(1)	36(1)	43(1)	-26(1)	-9(1)	-1(1)
S(2)	39(1)	31(1)	20(1)	-14(1)	-1(1)	-13(1)
C(11)	31(2)	16(2)	7(2)	-1(2)	-7(2)	-5(2)
C(12)	36(3)	14(3)	21(3)	-9(2)	6(3)	-4(2)
C(13)	57(4)	23(3)	26(3)	-13(2)	-13(3)	-6(3)
C(14)	34(3)	26(3)	33(3)	-7(2)	-12(2)	-5(2)
C(15)	18(3)	39(3)	32(3)	-22(2)	-7(2)	-11(2)
C(16)	22(3)	29(3)	15(3)	-5(2)	1(2)	-19(2)
N(3)	53(3)	25(2)	28(2)	-13(2)	-7(2)	-14(2)
O(5)	56(3)	45(2)	32(2)	-15(2)	4(2)	-13(2)
O(6)	62(3)	38(2)	19(2)	-8(2)	-3(2)	-21(2)
C(11S)	31(2)	16(2)	7(2)	-1(2)	-7(2)	-5(2)
C(12S)	36(3)	14(3)	21(3)	-9(2)	6(3)	-4(2)
C(13S)	57(4)	23(3)	26(3)	-13(2)	-13(3)	-6(3)
C(14S)	34(3)	26(3)	33(3)	-7(2)	-12(2)	-5(2)
C(15S)	18(3)	39(3)	32(3)	-22(2)	-7(2)	-11(2)
C(16S)	22(3)	29(3)	15(3)	-5(2)	1(2)	-19(2)
N(3S)	53(3)	25(2)	28(2)	-13(2)	-7(2)	-14(2)
O(5S)	56(3)	45(2)	32(2)	-15(2)	4(2)	-13(2)
O(6S)	62(3)	38(2)	19(2)	-8(2)	-3(2)	-21(2)
C(39)	23(2)	30(2)	18(2)	-8(2)	-6(2)	-9(2)
N(6)	23(2)	33(2)	28(2)	-11(2)	-6(2)	-3(2)
O(12)	32(2)	18(2)	7(2)	-1(2)	-1(2)	-3(2)
O(13)	36(2)	128(3)	65(3)	-67(2)	11(2)	-49(2)
C(39S)	23(2)	30(2)	18(2)	-8(2)	-6(2)	-9(2)
N(6S)	23(2)	33(2)	28(2)	-11(2)	-6(2)	-3(2)
O(12S)	32(2)	18(2)	7(2)	-1(2)	-1(2)	-3(2)
O(13S)	36(2)	128(3)	65(3)	-67(2)	11(2)	-49(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for s3255m.

	x	y	z	U(eq)
H(1)	8017	1706	2123	32
H(2)	8820	2564	2770	28
H(3A)	8593	4195	2383	35
H(3B)	8020	4355	1455	35
H(4A)	6213	3663	3667	33
H(4B)	7424	3101	3764	33
H(8)	10365	3103	-558	51
H(9)	11448	1643	435	51
H(10)	10545	1408	2037	32
H(17)	6200	1901	4015	34
H(18A)	8393	1079	3647	44
H(18B)	7778	1094	4658	44
H(19A)	7146	-166	4529	48
H(19B)	8018	-378	3691	48
H(20A)	6893	802	2570	44
H(20B)	5962	752	3354	44
H(21A)	4515	4107	2120	35
H(21B)	4821	3608	3167	35
H(23)	3370	3176	3809	45
H(24)	2215	2340	3887	53
H(25)	2298	1444	2779	49
H(26)	3561	1388	1571	47
H(27)	4713	2284	1470	45
H(28)	6738	607	9490	35
H(29)	6958	1849	10108	29
H(30A)	8298	2479	9699	35
H(30B)	8849	1712	9044	35
H(31A)	6245	3341	7841	37
H(31B)	6112	3071	8951	37
H(35)	8326	-1218	12103	73
H(36)	9835	-712	11973	70
H(37)	9580	827	10625	49
H(40)	8696	6278	8870	34
H(41)	7444	6315	10093	35
H(42)	6373	5368	10260	34
H(43)	6678	4205	9339	35
H(44)	4997	2441	7947	31
H(45A)	5589	313	8670	41
H(45B)	4825	959	7825	41
H(46A)	3511	1700	8872	57
H(46B)	4102	767	9674	57
H(47A)	5218	1595	9919	41
H(47B)	4349	2605	9431	41
H(48A)	7432	1918	6160	30
H(48B)	6538	2772	6547	30
H(50)	4926	3106	5957	39
H(51)	3662	2599	5485	52
H(52)	3977	950	5497	48
H(53)	5579	-200	5897	44
H(54)	6838	293	6357	34
H(55)	9500	3815	4104	48
H(56)	10369	2534	3348	62

H(57)	10678	901	4123	73
H(58)	10142	543	5664	64
H(59)	9319	1799	6452	54
H(60)	9004	3443	5678	48
H(13)	7861	5437	5668	42
H(14)	9041	6208	4868	38
H(15)	9146	6573	3244	31
H(16)	8070	6165	2420	23
H(13S)	9274	6489	3610	42
H(14S)	8961	5849	5179	38
H(15S)	7679	5096	5619	31
H(16S)	6711	4984	4490	23

Table 6. Torsion angles [deg] for s3255m.

O(1)-C(1)-C(2)-C(7)	-65.0(4)
C(5)-C(1)-C(2)-C(7)	177.9(3)
O(1)-C(1)-C(2)-C(3)	62.2(4)
C(5)-C(1)-C(2)-C(3)	-54.8(4)
C(7)-C(2)-C(3)-N(1)	166.8(3)
C(1)-C(2)-C(3)-N(1)	38.5(4)
N(1)-C(4)-C(5)-N(2)	-65.7(4)
N(1)-C(4)-C(5)-C(17)	170.3(3)
N(1)-C(4)-C(5)-C(1)	45.2(4)
O(1)-C(1)-C(5)-N(2)	8.9(4)
C(2)-C(1)-C(5)-N(2)	127.8(3)
O(1)-C(1)-C(5)-C(4)	-108.2(3)
C(2)-C(1)-C(5)-C(4)	10.7(4)
O(1)-C(1)-C(5)-C(17)	128.5(3)
C(2)-C(1)-C(5)-C(17)	-112.6(4)
C(1)-C(2)-C(7)-C(10)	-92.3(5)
C(3)-C(2)-C(7)-C(10)	139.5(5)
C(1)-C(2)-C(7)-O(2)	84.7(4)
C(3)-C(2)-C(7)-O(2)	-43.5(5)
O(2)-C(8)-C(9)-C(10)	-0.6(6)
O(2)-C(7)-C(10)-C(9)	-0.1(5)
C(2)-C(7)-C(10)-C(9)	177.0(4)
C(8)-C(9)-C(10)-C(7)	0.4(5)
N(2)-C(5)-C(17)-C(20)	55.4(4)
C(4)-C(5)-C(17)-C(20)	178.7(3)
C(1)-C(5)-C(17)-C(20)	-57.6(5)
N(2)-C(5)-C(17)-C(18)	163.5(3)
C(4)-C(5)-C(17)-C(18)	-73.3(4)
C(1)-C(5)-C(17)-C(18)	50.5(5)
C(20)-C(17)-C(18)-C(19)	-15.8(3)
C(5)-C(17)-C(18)-C(19)	-141.2(4)
C(17)-C(18)-C(19)-C(20)	15.5(3)
C(5)-C(17)-C(20)-C(19)	138.4(3)
C(18)-C(17)-C(20)-C(19)	15.6(3)
C(18)-C(19)-C(20)-C(17)	-15.7(3)
N(2)-C(21)-C(22)-C(27)	-39.9(5)
N(2)-C(21)-C(22)-C(23)	142.9(3)
C(27)-C(22)-C(23)-C(24)	-2.1(5)
C(21)-C(22)-C(23)-C(24)	175.2(3)
C(22)-C(23)-C(24)-C(25)	1.5(6)
C(23)-C(24)-C(25)-C(26)	0.1(6)
C(24)-C(25)-C(26)-C(27)	-1.1(6)
C(23)-C(22)-C(27)-C(26)	1.1(5)
C(21)-C(22)-C(27)-C(26)	-176.1(3)
C(25)-C(26)-C(27)-C(22)	0.4(6)
O(8)-C(28)-C(29)-C(34)	-62.4(4)
C(32)-C(28)-C(29)-C(34)	179.4(3)
O(8)-C(28)-C(29)-C(30)	62.9(4)
C(32)-C(28)-C(29)-C(30)	-55.3(4)
C(34)-C(29)-C(30)-N(4)	173.5(3)
C(28)-C(29)-C(30)-N(4)	47.3(4)
N(4)-C(31)-C(32)-N(5)	-63.0(4)
N(4)-C(31)-C(32)-C(44)	172.0(3)
N(4)-C(31)-C(32)-C(28)	46.9(4)
O(8)-C(28)-C(32)-N(5)	2.8(4)
C(29)-C(28)-C(32)-N(5)	123.3(3)
O(8)-C(28)-C(32)-C(44)	123.9(3)

C(29)-C(28)-C(32)-C(44)	-115.6(4)
O(8)-C(28)-C(32)-C(31)	-113.8(3)
C(29)-C(28)-C(32)-C(31)	6.7(4)
C(30)-C(29)-C(34)-C(37)	5.3(6)
C(28)-C(29)-C(34)-C(37)	131.2(5)
C(30)-C(29)-C(34)-O(9)	-178.1(3)
C(28)-C(29)-C(34)-O(9)	-52.1(4)
O(9)-C(35)-C(36)-C(37)	-0.9(5)
O(9)-C(34)-C(37)-C(36)	0.5(5)
C(29)-C(34)-C(37)-C(36)	177.2(4)
C(35)-C(36)-C(37)-C(34)	0.3(5)
C(39S)-C(40)-C(41)-C(42)	-4.9(5)
C(39)-C(40)-C(41)-C(42)	-0.4(5)
C(40)-C(41)-C(42)-C(43)	4.6(5)
C(41)-C(42)-C(43)-C(38)	-4.4(5)
C(39S)-C(38)-C(43)-C(42)	4.4(4)
C(39)-C(38)-C(43)-C(42)	0.0(4)
S(2)-C(38)-C(43)-C(42)	175.5(3)
N(5)-C(32)-C(44)-C(47)	164.9(3)
C(31)-C(32)-C(44)-C(47)	-71.7(4)
C(28)-C(32)-C(44)-C(47)	51.6(4)
N(5)-C(32)-C(44)-C(45)	57.9(4)
C(31)-C(32)-C(44)-C(45)	-178.8(3)
C(28)-C(32)-C(44)-C(45)	-55.5(5)
C(32)-C(44)-C(45)-C(46)	142.5(3)
C(47)-C(44)-C(45)-C(46)	20.1(3)
C(44)-C(45)-C(46)-C(47)	-20.1(3)
C(45)-C(46)-C(47)-C(44)	20.3(3)
C(32)-C(44)-C(47)-C(46)	-146.2(3)
C(45)-C(44)-C(47)-C(46)	-20.3(3)
N(5)-C(48)-C(49)-C(50)	119.6(4)
N(5)-C(48)-C(49)-C(54)	-58.8(4)
C(54)-C(49)-C(50)-C(51)	1.5(6)
C(48)-C(49)-C(50)-C(51)	-176.9(3)
C(49)-C(50)-C(51)-C(52)	0.2(6)
C(50)-C(51)-C(52)-C(53)	-1.8(6)
C(51)-C(52)-C(53)-C(54)	1.7(6)
C(52)-C(53)-C(54)-C(49)	0.1(6)
C(50)-C(49)-C(54)-C(53)	-1.7(6)
C(48)-C(49)-C(54)-C(53)	176.8(3)
C(60)-C(55)-C(56)-C(57)	1.5(7)
C(55)-C(56)-C(57)-C(58)	-0.5(7)
C(56)-C(57)-C(58)-C(59)	-0.6(7)
C(57)-C(58)-C(59)-C(60)	0.6(7)
C(58)-C(59)-C(60)-C(55)	0.4(7)
C(56)-C(55)-C(60)-C(59)	-1.4(7)
C(5)-C(4)-N(1)-C(3)	-65.0(4)
C(5)-C(4)-N(1)-S(1)	141.4(3)
C(2)-C(3)-N(1)-C(4)	20.4(5)
C(2)-C(3)-N(1)-S(1)	175.2(3)
O(7)-C(6)-N(2)-C(5)	-177.1(4)
O(1)-C(6)-N(2)-C(5)	4.9(5)
O(7)-C(6)-N(2)-C(21)	-9.8(7)
O(1)-C(6)-N(2)-C(21)	172.3(3)
C(4)-C(5)-N(2)-C(6)	108.4(4)
C(17)-C(5)-N(2)-C(6)	-128.9(3)
C(1)-C(5)-N(2)-C(6)	-8.6(4)
C(4)-C(5)-N(2)-C(21)	-58.1(5)
C(17)-C(5)-N(2)-C(21)	64.6(5)
C(1)-C(5)-N(2)-C(21)	-175.1(3)
C(22)-C(21)-N(2)-C(6)	89.6(4)

C(22)-C(21)-N(2)-C(5)	-104.8(4)
C(32)-C(31)-N(4)-C(30)	-57.8(4)
C(32)-C(31)-N(4)-S(2)	134.4(3)
C(29)-C(30)-N(4)-C(31)	8.7(4)
C(29)-C(30)-N(4)-S(2)	176.9(2)
O(14)-C(33)-N(5)-C(48)	-5.7(7)
O(8)-C(33)-N(5)-C(48)	176.7(3)
O(14)-C(33)-N(5)-C(32)	177.9(4)
O(8)-C(33)-N(5)-C(32)	0.2(5)
C(49)-C(48)-N(5)-C(33)	98.2(4)
C(49)-C(48)-N(5)-C(32)	-85.7(4)
C(44)-C(32)-N(5)-C(33)	-123.2(4)
C(31)-C(32)-N(5)-C(33)	114.6(4)
C(28)-C(32)-N(5)-C(33)	-2.0(4)
C(44)-C(32)-N(5)-C(48)	60.5(5)
C(31)-C(32)-N(5)-C(48)	-61.7(5)
C(28)-C(32)-N(5)-C(48)	-178.2(4)
O(7)-C(6)-O(1)-C(1)	-176.5(4)
N(2)-C(6)-O(1)-C(1)	1.6(4)
C(2)-C(1)-O(1)-C(6)	-128.8(3)
C(5)-C(1)-O(1)-C(6)	-6.9(4)
C(10)-C(7)-O(2)-C(8)	-0.2(5)
C(2)-C(7)-O(2)-C(8)	-177.8(4)
C(9)-C(8)-O(2)-C(7)	0.5(5)
O(14)-C(33)-O(8)-C(28)	-176.0(4)
N(5)-C(33)-O(8)-C(28)	1.9(5)
C(29)-C(28)-O(8)-C(33)	-125.4(3)
C(32)-C(28)-O(8)-C(33)	-3.0(4)
C(37)-C(34)-O(9)-C(35)	-1.0(4)
C(29)-C(34)-O(9)-C(35)	-178.4(3)
C(36)-C(35)-O(9)-C(34)	1.2(5)
C(4)-N(1)-S(1)-O(3)	-30.4(3)
C(3)-N(1)-S(1)-O(3)	176.0(3)
C(4)-N(1)-S(1)-O(4)	-162.3(3)
C(3)-N(1)-S(1)-O(4)	44.2(3)
C(4)-N(1)-S(1)-C(11S)	92.4(3)
C(3)-N(1)-S(1)-C(11S)	-61.2(3)
C(4)-N(1)-S(1)-C(11)	82.4(3)
C(3)-N(1)-S(1)-C(11)	-71.1(3)
C(31)-N(4)-S(2)-O(11)	-25.2(3)
C(30)-N(4)-S(2)-O(11)	167.2(3)
C(31)-N(4)-S(2)-O(10)	-155.9(3)
C(30)-N(4)-S(2)-O(10)	36.4(3)
C(31)-N(4)-S(2)-C(38)	90.8(3)
C(30)-N(4)-S(2)-C(38)	-76.9(3)
C(39S)-C(38)-S(2)-O(11)	-92.6(2)
C(39)-C(38)-S(2)-O(11)	-87.7(2)
C(43)-C(38)-S(2)-O(11)	97.2(3)
C(39S)-C(38)-S(2)-O(10)	38.5(3)
C(39)-C(38)-S(2)-O(10)	43.4(3)
C(43)-C(38)-S(2)-O(10)	-131.7(2)
C(39S)-C(38)-S(2)-N(4)	152.0(2)
C(39)-C(38)-S(2)-N(4)	156.9(2)
C(43)-C(38)-S(2)-N(4)	-18.2(3)
O(3)-S(1)-C(11)-C(12)	30.6(2)
O(4)-S(1)-C(11)-C(12)	161.24(19)
N(1)-S(1)-C(11)-C(12)	-84.2(2)
C(11S)-S(1)-C(11)-C(12)	172.7(11)
O(3)-S(1)-C(11)-C(16)	-147.37(16)
O(4)-S(1)-C(11)-C(16)	-16.68(17)
N(1)-S(1)-C(11)-C(16)	97.88(17)

C(11S)-S(1)-C(11)-C(16)	-5.2(11)
C(16)-C(11)-C(12)-C(13)	0.0
S(1)-C(11)-C(12)-C(13)	-177.76(18)
C(16)-C(11)-C(12)-N(3)	174.6(3)
S(1)-C(11)-C(12)-N(3)	-3.2(3)
C(11)-C(12)-C(13)-C(14)	0.0
N(3)-C(12)-C(13)-C(14)	-174.7(3)
C(12)-C(13)-C(14)-C(15)	0.0
C(13)-C(14)-C(15)-C(16)	0.0
C(14)-C(15)-C(16)-C(11)	0.0
C(12)-C(11)-C(16)-C(15)	0.0
S(1)-C(11)-C(16)-C(15)	178.14(15)
C(11)-C(12)-N(3)-O(6)	72.4(5)
C(13)-C(12)-N(3)-O(6)	-113.0(4)
C(11)-C(12)-N(3)-O(5)	-112.6(5)
C(13)-C(12)-N(3)-O(5)	62.0(5)
O(3)-S(1)-C(11S)-C(12S)	-145.5(3)
O(4)-S(1)-C(11S)-C(12S)	-16.5(4)
N(1)-S(1)-C(11S)-C(12S)	94.6(4)
C(11)-S(1)-C(11S)-C(12S)	174.5(13)
O(3)-S(1)-C(11S)-C(16S)	38.5(3)
O(4)-S(1)-C(11S)-C(16S)	167.5(2)
N(1)-S(1)-C(11S)-C(16S)	-81.4(2)
C(11)-S(1)-C(11S)-C(16S)	-1.4(10)
C(16S)-C(11S)-C(12S)-C(13S)	0.0
S(1)-C(11S)-C(12S)-C(13S)	-175.5(4)
C(16S)-C(11S)-C(12S)-N(3S)	-178.4(5)
S(1)-C(11S)-C(12S)-N(3S)	6.0(6)
C(11S)-C(12S)-C(13S)-C(14S)	0.0
N(3S)-C(12S)-C(13S)-C(14S)	178.4(5)
C(12S)-C(13S)-C(14S)-C(15S)	0.0
C(13S)-C(14S)-C(15S)-C(16S)	0.0
C(14S)-C(15S)-C(16S)-C(11S)	0.0
C(12S)-C(11S)-C(16S)-C(15S)	0.0
S(1)-C(11S)-C(16S)-C(15S)	176.7(3)
C(13S)-C(12S)-N(3S)-O(6S)	97.3(8)
C(11S)-C(12S)-N(3S)-O(6S)	-84.3(9)
C(13S)-C(12S)-N(3S)-O(5S)	-75.4(9)
C(11S)-C(12S)-N(3S)-O(5S)	103.0(9)
C(39S)-C(40)-C(39)-C(38)	70.0(2)
C(41)-C(40)-C(39)-C(38)	-4.2(4)
C(39S)-C(40)-C(39)-N(6)	-116.25(8)
C(41)-C(40)-C(39)-N(6)	169.5(2)
C(39S)-C(38)-C(39)-C(40)	-73.2(2)
C(43)-C(38)-C(39)-C(40)	4.4(3)
S(2)-C(38)-C(39)-C(40)	-170.7(2)
C(39S)-C(38)-C(39)-N(6)	113.70(10)
C(43)-C(38)-C(39)-N(6)	-168.8(2)
S(2)-C(38)-C(39)-N(6)	16.2(3)
C(40)-C(39)-N(6)-O(12)	-158.88(18)
C(38)-C(39)-N(6)-O(12)	14.89(18)
C(40)-C(39)-N(6)-O(13)	25.89(18)
C(38)-C(39)-N(6)-O(13)	-160.35(18)
C(39)-C(38)-C(39S)-C(40)	99.3(2)
C(43)-C(38)-C(39S)-C(40)	-5.1(3)
S(2)-C(38)-C(39S)-C(40)	-175.4(2)
C(39)-C(38)-C(39S)-N(6S)	-76.87(9)
C(43)-C(38)-C(39S)-N(6S)	178.7(2)
S(2)-C(38)-C(39S)-N(6S)	8.4(3)
C(39)-C(40)-C(39S)-C(38)	-102.4(2)
C(41)-C(40)-C(39S)-C(38)	5.4(4)

C(39)-C(40)-C(39S)-N(6S)	73.89(9)
C(41)-C(40)-C(39S)-N(6S)	-178.3(2)
C(38)-C(39S)-N(6S)-O(12S)	-134.07(18)
C(40)-C(39S)-N(6S)-O(12S)	49.36(17)
C(38)-C(39S)-N(6S)-O(13S)	50.68(18)
C(40)-C(39S)-N(6S)-O(13S)	-125.88(17)

Symmetry transformations used to generate equivalent atoms:

Crystal data and structure refinement for 2.133

Identification code	s3197bm
Empirical formula	C34 H42 Br N O7 Si
Formula weight	684.69
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 15.520(9) A alpha = 90 deg. b = 9.854(5) A beta = 95.522(9) deg. c = 21.836(12) A gamma = 90 deg.
Volume	3324(3) A^3
Z, Calculated density	4, 1.368 Mg/m^3
Absorption coefficient	1.321 mm^-1
F(000)	1432
Crystal size	0.28 x 0.20 x 0.05 mm
Theta range for data collection	1.87 to 23.26 deg.
Limiting indices	-17<=h<=17, -10<=k<=10, -24<=l<=24
Reflections collected / unique	19351 / 4764 [R(int) = 0.1769]
Completeness to theta = 23.26	99.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4764 / 0 / 400
Goodness-of-fit on F^2	0.935
Final R indices [I>2sigma(I)]	R1 = 0.0637, wR2 = 0.1242
R indices (all data)	R1 = 0.1183, wR2 = 0.1429
Largest diff. peak and hole	1.257 and -0.544 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for s3197bm.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Br(1)	3914(1)	-4061(1)	410(1)	44(1)
Si(1)	12072(1)	2544(2)	2632(1)	36(1)
O(1)	9439(3)	2720(4)	1783(2)	28(1)
O(2)	8762(3)	2628(4)	2649(2)	34(1)
O(3)	7063(2)	714(4)	627(2)	27(1)
O(4)	7022(3)	376(4)	-397(2)	40(1)
O(5)	7761(2)	4933(4)	622(2)	29(1)
O(6)	10572(3)	3513(4)	483(2)	30(1)
O(7)	11826(3)	3688(4)	1162(2)	33(1)
N(1)	8182(3)	1646(4)	1748(2)	23(1)
C(1)	8453(4)	1398(5)	1127(3)	23(1)
C(2)	9232(4)	2389(5)	1138(2)	24(1)
C(3)	8769(4)	2349(5)	2111(3)	26(2)
C(4)	8749(4)	-87(5)	1064(3)	26(1)
C(5)	9560(4)	-625(5)	1454(3)	31(2)
C(6)	9798(4)	-1402(6)	879(3)	39(2)
C(7)	9164(4)	-491(6)	479(3)	33(2)
C(8)	7747(4)	1690(5)	608(3)	26(1)
C(9)	6757(4)	116(6)	90(3)	29(2)
C(10)	6080(4)	-880(5)	185(3)	25(1)
C(11)	5858(4)	-1244(5)	769(3)	30(2)
C(12)	5218(4)	-2177(6)	833(3)	31(2)
C(13)	4786(4)	-2772(6)	318(3)	32(2)
C(14)	4988(4)	-2428(6)	-268(3)	35(2)
C(15)	5633(4)	-1500(6)	-327(3)	33(2)
C(16)	9128(4)	3734(5)	773(3)	24(1)
C(17)	8505(4)	4741(5)	989(3)	25(1)
C(18)	8560(4)	5640(5)	1461(3)	29(2)
C(19)	7780(4)	6417(6)	1382(3)	35(2)
C(20)	7309(4)	5948(6)	874(3)	31(2)
C(21)	10017(4)	4386(6)	789(3)	28(2)
C(22)	11446(4)	3918(6)	564(3)	37(2)
C(23)	11978(4)	2277(6)	1299(3)	36(2)
C(24)	12562(4)	2190(6)	1893(3)	38(2)
C(25)	12959(4)	2855(7)	3249(3)	47(2)
C(26)	11306(4)	4009(6)	2558(3)	40(2)
C(27)	11435(4)	1025(6)	2831(3)	43(2)
C(28)	7444(3)	1024(6)	1997(3)	25(1)
C(29)	6620(4)	1853(5)	1931(2)	22(1)
C(30)	6634(4)	3264(5)	1837(3)	26(2)
C(31)	5879(4)	4004(6)	1808(3)	28(1)
C(32)	5107(4)	3373(6)	1868(3)	33(2)
C(33)	5090(4)	1978(6)	1968(3)	28(2)
C(34)	5840(4)	1232(5)	1996(2)	25(1)

Table 3. Bond lengths [A] and angles [deg] for s3197bm.

Br(1)-C(13)	1.881(6)
Si(1)-C(25)	1.856(6)
Si(1)-C(26)	1.867(6)
Si(1)-C(27)	1.868(6)
Si(1)-C(24)	1.883(7)
O(1)-C(3)	1.368(7)
O(1)-C(2)	1.452(6)
O(2)-C(3)	1.206(6)
O(3)-C(9)	1.357(7)
O(3)-C(8)	1.436(6)
O(4)-C(9)	1.203(7)
O(5)-C(17)	1.355(7)
O(5)-C(20)	1.368(7)
O(6)-C(22)	1.408(7)
O(6)-C(21)	1.429(6)
O(7)-C(22)	1.398(7)
O(7)-C(23)	1.437(7)
N(1)-C(3)	1.342(7)
N(1)-C(28)	1.450(7)
N(1)-C(1)	1.477(7)
C(1)-C(8)	1.527(8)
C(1)-C(4)	1.544(7)
C(1)-C(2)	1.552(8)
C(2)-C(16)	1.547(7)
C(2)-H(2)	1.0000
C(4)-C(7)	1.539(8)
C(4)-C(5)	1.544(8)
C(4)-H(4)	1.0000
C(5)-C(6)	1.545(8)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(7)	1.540(8)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.467(8)
C(10)-C(11)	1.399(8)
C(10)-C(15)	1.399(8)
C(11)-C(12)	1.370(8)
C(11)-H(11)	0.9500
C(12)-C(13)	1.384(8)
C(12)-H(12)	0.9500
C(13)-C(14)	1.387(8)
C(14)-C(15)	1.371(8)
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500
C(16)-C(17)	1.493(8)
C(16)-C(21)	1.520(8)
C(16)-H(16)	1.0000
C(17)-C(18)	1.355(8)
C(18)-C(19)	1.430(8)
C(18)-H(18)	0.9500
C(19)-C(20)	1.348(9)
C(19)-H(19)	0.9500

C(20)-H(20)	0.9500
C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900
C(22)-H(22A)	0.9900
C(22)-H(22B)	0.9900
C(23)-C(24)	1.511(8)
C(23)-H(23A)	0.9900
C(23)-H(23B)	0.9900
C(24)-H(24A)	0.9900
C(24)-H(24B)	0.9900
C(25)-H(25A)	0.9800
C(25)-H(25B)	0.9800
C(25)-H(25C)	0.9800
C(26)-H(26A)	0.9800
C(26)-H(26B)	0.9800
C(26)-H(26C)	0.9800
C(27)-H(27A)	0.9800
C(27)-H(27B)	0.9800
C(27)-H(27C)	0.9800
C(28)-C(29)	1.513(8)
C(28)-H(28A)	0.9900
C(28)-H(28B)	0.9900
C(29)-C(34)	1.376(7)
C(29)-C(30)	1.405(8)
C(30)-C(31)	1.376(8)
C(30)-H(30)	0.9500
C(31)-C(32)	1.367(8)
C(31)-H(31)	0.9500
C(32)-C(33)	1.392(8)
C(32)-H(32)	0.9500
C(33)-C(34)	1.372(8)
C(33)-H(33)	0.9500
C(34)-H(34)	0.9500

C(25)-Si(1)-C(26)	110.9(3)
C(25)-Si(1)-C(27)	109.6(3)
C(26)-Si(1)-C(27)	107.0(3)
C(25)-Si(1)-C(24)	108.7(3)
C(26)-Si(1)-C(24)	112.0(3)
C(27)-Si(1)-C(24)	108.5(3)
C(3)-O(1)-C(2)	109.8(4)
C(9)-O(3)-C(8)	117.7(5)
C(17)-O(5)-C(20)	107.7(5)
C(22)-O(6)-C(21)	112.7(4)
C(22)-O(7)-C(23)	113.4(5)
C(3)-N(1)-C(28)	120.8(5)
C(3)-N(1)-C(1)	113.0(5)
C(28)-N(1)-C(1)	125.4(5)
N(1)-C(1)-C(8)	113.7(5)
N(1)-C(1)-C(4)	110.6(4)
C(8)-C(1)-C(4)	108.1(5)
N(1)-C(1)-C(2)	99.9(4)
C(8)-C(1)-C(2)	113.2(4)
C(4)-C(1)-C(2)	111.1(5)
O(1)-C(2)-C(16)	108.0(4)
O(1)-C(2)-C(1)	104.8(4)
C(16)-C(2)-C(1)	119.3(5)
O(1)-C(2)-H(2)	108.1
C(16)-C(2)-H(2)	108.1
C(1)-C(2)-H(2)	108.1
O(2)-C(3)-N(1)	128.6(6)

O(2)-C(3)-O(1)	121.7(5)
N(1)-C(3)-O(1)	109.6(5)
C(7)-C(4)-C(5)	89.1(4)
C(7)-C(4)-C(1)	118.1(5)
C(5)-C(4)-C(1)	120.7(5)
C(7)-C(4)-H(4)	109.1
C(5)-C(4)-H(4)	109.1
C(1)-C(4)-H(4)	109.1
C(4)-C(5)-C(6)	88.2(5)
C(4)-C(5)-H(5A)	114.0
C(6)-C(5)-H(5A)	114.0
C(4)-C(5)-H(5B)	114.0
C(6)-C(5)-H(5B)	114.0
H(5A)-C(5)-H(5B)	111.2
C(7)-C(6)-C(5)	89.0(4)
C(7)-C(6)-H(6A)	113.8
C(5)-C(6)-H(6A)	113.8
C(7)-C(6)-H(6B)	113.8
C(5)-C(6)-H(6B)	113.8
H(6A)-C(6)-H(6B)	111.0
C(4)-C(7)-C(6)	88.5(4)
C(4)-C(7)-H(7A)	113.9
C(6)-C(7)-H(7A)	113.9
C(4)-C(7)-H(7B)	113.9
C(6)-C(7)-H(7B)	113.9
H(7A)-C(7)-H(7B)	111.1
O(3)-C(8)-C(1)	109.4(4)
O(3)-C(8)-H(8A)	109.8
C(1)-C(8)-H(8A)	109.8
O(3)-C(8)-H(8B)	109.8
C(1)-C(8)-H(8B)	109.8
H(8A)-C(8)-H(8B)	108.2
O(4)-C(9)-O(3)	123.3(6)
O(4)-C(9)-C(10)	125.3(6)
O(3)-C(9)-C(10)	111.3(6)
C(11)-C(10)-C(15)	118.1(5)
C(11)-C(10)-C(9)	122.9(5)
C(15)-C(10)-C(9)	119.0(6)
C(12)-C(11)-C(10)	120.7(5)
C(12)-C(11)-H(11)	119.7
C(10)-C(11)-H(11)	119.7
C(11)-C(12)-C(13)	120.0(6)
C(11)-C(12)-H(12)	120.0
C(13)-C(12)-H(12)	120.0
C(12)-C(13)-C(14)	120.7(6)
C(12)-C(13)-Br(1)	119.7(5)
C(14)-C(13)-Br(1)	119.5(4)
C(15)-C(14)-C(13)	118.9(6)
C(15)-C(14)-H(14)	120.6
C(13)-C(14)-H(14)	120.6
C(14)-C(15)-C(10)	121.7(6)
C(14)-C(15)-H(15)	119.2
C(10)-C(15)-H(15)	119.2
C(17)-C(16)-C(21)	109.0(4)
C(17)-C(16)-C(2)	116.4(5)
C(21)-C(16)-C(2)	107.5(5)
C(17)-C(16)-H(16)	107.9
C(21)-C(16)-H(16)	107.9
C(2)-C(16)-H(16)	107.9
C(18)-C(17)-O(5)	110.3(5)
C(18)-C(17)-C(16)	132.8(5)

O(5)-C(17)-C(16)	116.6(5)
C(17)-C(18)-C(19)	105.5(5)
C(17)-C(18)-H(18)	127.2
C(19)-C(18)-H(18)	127.2
C(20)-C(19)-C(18)	107.5(5)
C(20)-C(19)-H(19)	126.2
C(18)-C(19)-H(19)	126.2
C(19)-C(20)-O(5)	108.9(5)
C(19)-C(20)-H(20)	125.5
O(5)-C(20)-H(20)	125.5
O(6)-C(21)-C(16)	108.8(4)
O(6)-C(21)-H(21A)	109.9
C(16)-C(21)-H(21A)	109.9
O(6)-C(21)-H(21B)	109.9
C(16)-C(21)-H(21B)	109.9
H(21A)-C(21)-H(21B)	108.3
O(7)-C(22)-O(6)	112.8(5)
O(7)-C(22)-H(22A)	109.0
O(6)-C(22)-H(22A)	109.0
O(7)-C(22)-H(22B)	109.0
O(6)-C(22)-H(22B)	109.0
H(22A)-C(22)-H(22B)	107.8
O(7)-C(23)-C(24)	107.8(5)
O(7)-C(23)-H(23A)	110.1
C(24)-C(23)-H(23A)	110.1
O(7)-C(23)-H(23B)	110.1
C(24)-C(23)-H(23B)	110.1
H(23A)-C(23)-H(23B)	108.5
C(23)-C(24)-Si(1)	117.9(5)
C(23)-C(24)-H(24A)	107.8
Si(1)-C(24)-H(24A)	107.8
C(23)-C(24)-H(24B)	107.8
Si(1)-C(24)-H(24B)	107.8
H(24A)-C(24)-H(24B)	107.2
Si(1)-C(25)-H(25A)	109.5
Si(1)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
Si(1)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5
Si(1)-C(26)-H(26A)	109.5
Si(1)-C(26)-H(26B)	109.5
H(26A)-C(26)-H(26B)	109.5
Si(1)-C(26)-H(26C)	109.5
H(26A)-C(26)-H(26C)	109.5
H(26B)-C(26)-H(26C)	109.5
Si(1)-C(27)-H(27A)	109.5
Si(1)-C(27)-H(27B)	109.5
H(27A)-C(27)-H(27B)	109.5
Si(1)-C(27)-H(27C)	109.5
H(27A)-C(27)-H(27C)	109.5
H(27B)-C(27)-H(27C)	109.5
N(1)-C(28)-C(29)	115.3(5)
N(1)-C(28)-H(28A)	108.4
C(29)-C(28)-H(28A)	108.5
N(1)-C(28)-H(28B)	108.5
C(29)-C(28)-H(28B)	108.5
H(28A)-C(28)-H(28B)	107.5
C(34)-C(29)-C(30)	118.7(5)
C(34)-C(29)-C(28)	119.7(5)
C(30)-C(29)-C(28)	121.5(5)

C(31)-C(30)-C(29)	120.4(6)
C(31)-C(30)-H(30)	119.8
C(29)-C(30)-H(30)	119.8
C(32)-C(31)-C(30)	120.3(5)
C(32)-C(31)-H(31)	119.9
C(30)-C(31)-H(31)	119.9
C(31)-C(32)-C(33)	119.6(6)
C(31)-C(32)-H(32)	120.2
C(33)-C(32)-H(32)	120.2
C(34)-C(33)-C(32)	120.5(6)
C(34)-C(33)-H(33)	119.8
C(32)-C(33)-H(33)	119.8
C(33)-C(34)-C(29)	120.5(5)
C(33)-C(34)-H(34)	119.7
C(29)-C(34)-H(34)	119.7

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for s3255m [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)