Flexible Access to an Array of Optically-enriched Conformationally-locked Bicyclic Morpholines and Approaching Bridged Bicyclic Piperazines

Thesis submitted to the University of Strathclyde in fulfilment of the requirements for the degree of Doctor of Philosophy

By

Rachael E. B. Dunn

2014

Department of Pure and Applied Chemistry
University of Strathclyde
Thomas Graham Building
295 Cathedral Street
Glasgow
G1 1XL

Declaration of Copyright

This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

Signed:

Date:

Acknowledgments

First and foremost I would like to thank Billy for giving me the opportunity to carry out my PhD in his group, and for supporting and challenging me throughout my PhD. Also, a final apology for the train situation that occurred when we were both coming back from Macclesfield one Friday night. It was just temporary memory loss that I encountered when you asked what train I was getting and I said I did not know when in fact I did!!

I would also like to thank my supervisor at AstraZeneca, Scott Lamont, who no matter what chemical I would ask for would always send it to me without any fuss! Thanks for making my three month placement down in Alderley Park so enjoyable and for all the visits to Strathclyde which meant Goldie and I could get a free lunch!

A special thanks goes to my work wife, Laura G (or Goldie). We definitely managed to keep each other (semi-) sane during the 3.5 year we worked together doing our PhDs. We first properly met back in final year of Undergrad when we both got the opportunity to do a project in Billy's group. During those 6 months we became great friends, even though the Chief used to try and put us in competition with each other by making us race to see who could get the correct mechanism first! We then started our PhD at the same time and did similar projects (well for the first half), which meant we were always there for each other during all the peaks and troughs! I will never forgot the time the retro-hetro workshop got cancelled and we sat in Billy's office and told him that we could not get money back for flights and accommodation and his response was 'are you thinking what I am thinking?' and we both thought probably not! But he was, and he got a trip to Nottingham where we got the legendary photo of Spanky van Dykes!

I also want to thank Laura P (LPats) for being my councillor from the day you started! Your office was always available when I needed a wee 5/30 min to calm down about something or have a rant, or when I would just wanted a chat.

Having been able to work in Billy's group has meant I have had the opportunity to work with a brilliant bunch of people over the years. So a big thanks goes to: the Chief, Linsey, Alison, Tina, Calum (Laura P was my councillor, and I was definitely Calum's), Natalie, Malky, Marc, Murali, Andy, Muddster, Philippa (everyone thought I was the posh one until they met Philippa), Scott, Tim (Kerr group honorary member), Olivia, Gayle, Jenny D, Jen C, Kirsty and Rory.

A massive thanks also goes to my family! My mum and dad have encouraged and supported me throughout my whole life, especially the last 8.5 years while I have been at university! Also, mum thanks for doing a lot of the wedding planning it made having a wedding during my PhD a lot easier!

Last but certainly not least, I would like to say a big thanks to my amazing husband, Pete (or poor Pete as Billy and the rest of the group would sometimes say). You have been my rock during the last 3.5 years, I honestly don't know how I would have got through it without you! You kept saying to me it would be worth it, and it was definitely all worth it in the end!

Abstract

Over recent years, bridged heterocycles have emerged as desirable targets within the pharmaceutical industry. More specifically, pharmaceutical partners have become interested in exploring the bioactivity of bridged morpholines, as well as bridged piperazines. Despite the interest in these types of compounds, there is a lack of routes into these scaffolds which allow for diversification surrounding the core scaffold. Consequently, the focus of this study was to develop preparative access into these synthetically challenging, strained bicyclic 6,5-systems. The aim was for the developed routes to be practically accessible, robust, and indeed flexible, to allow a diverse array of compounds to be obtained.

Initially, work focused on the synthesis of the bridged morpholine scaffold, with, in the first instance, a racemic route being targeted. The initial proposed bridged morpholine precursor, an α,β-unsaturated ester, was synthesised, however, the key final step to deliver the desired bridged morpholine proved to be unsuccessful. Following on from this, an alternative epoxide derivative was also prepared, but unfortunately did not deliver the corresponding bridged morpholine moiety. Following a series of computational studies, whereby the final (cyclisation) step for a variety of substrates was investigated, an alternative aldehyde precursor was explored. A successful synthesis to this compound was developed, and pleasingly this compound reacted to form the first bridged morpholine product within this programme. It was then shown that the route developed was sufficiently flexible to allow a further ten novel bridged morpholine compounds to be synthesised.

Having developed a racemic synthesis, it was then decided to explore the possibility of performing the route asymmetrically. In this regard, the original racemic route was utilised with optically pure starting material, however, it was found that many steps in the racemic synthesis caused the original stereogenic center to epimerise. Through an

extensive optimisation study, a route was established to deliver a key bridged morpholine scaffold without any appreciable loss in chirality. In addition, a key intermediate towards another further bridged morpholine scaffold was also obtained with an elevated enantiomeric ratio.

The final part of this study focused on utilising the developed bridged morpholine synthesis to allow a range of bridged piperazines to be obtained. Although no bridged piperazines were synthesised, several key intermediates towards the desired piperazine series were obtained, which will allow for further research in this area to be continued.

Abbreviations

Ac	Acetyl
AcOH	Acetic acid
Aloc	Allyloxycarbonyl
Ar	Aryl
BBN	Borabicyclo[3.3.1]nonane
Bn	Benzyl
Boc	Butyloxycarbonyl
Bu	Butyl
n-BuLi	*n*-Butyllithium
Bz	Benzoyl
Cat	Catalytic
Cbz	Carboxybenzyl
cm^{-1}	Reciprocal centimeters
Cp	Cyclopentadienyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
er	Enantiomeric ratio
Et	Ethyl
Et_3N	Triethylamine
Et_2O	Diethyl ether

EtOH	Ethanol
Eq	Equivalent
Fmoc	Fluorenylmethyloxycarbonyl
FTIR	Fourier transform infrared
g	Grams
h	Hour
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
IBX	2-Iodoxybenzoic acid
i-Pr	Isopropyl alcohol
J	Coupling constant
KHMDS	Potassium hexamethyldisilazane
LDA	Lithium diisopropylamide
M	Molar
Me	Methyl
MeCN	Acetonitrile
MeO	Methoxy
MeOH	Methanol
Mg	Milligram
MHz	Megahertz
Min	Minute
Mp	Melting point
mL	Millilitre
mmol	Millimole
mol	Moles
MsCl	Methanesulfonyl chloride
MWI	Microwave irradiation
NMM	*N*-Methylmorpholine
NMR	Nuclear magnetic resonance;

	s – singlet
	bs – broad singlet
	d – doublet
	bd – broad doublet
	dd – doublet of doublets
	t – triplet
	q – quartet
	m – multiplet
NOB	Natural bonding order
nOe	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
Nu	Nucleophile
[O]	Oxidation
PDC	Pyridinium dichromate
Pd_2dba_3	Tris(dibenzylideneacetone)dipalladium
$Pd(OAc)_2$	Palladium acetate
PG	Protecting group
Ph	Phenyl
Phth	Phthalimide
PPh_3	Triphenylphosphine
PPL	Pig pancreatic lipase
ppm	Part per million
p-TsOH	*Para*-toluenesulfonic acid
rt	Room temperautre
TBAF	*Tetra*-*n*-butylammonium fluoride
TBDMS	*Tert*-butyldimethylsilyl
TBDPS	*Tert*-butyldiphenylsilyl
t-Bu	*Tert*-butyl
TCCA	Trichloroisocyanuric acid

TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxidanyl
TFA	Trifluoroacetic acid
Tf_2NPh	*N*-Phenyl-bis(trifluoromethylsulfonamide)
TfOH	Triflic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TLC	Thin layer chromatography
Ts	Tosyl
vs	Versus
μm	Micrometres
μL	Microlitres
°C	Degree Celsius
2D	Two-dimensional
3D	Three-dimensional

Table of Contents

Introduction

Table of Contents

1. Introduction

1.1 3D vs 2D Molecules in the Drug Discovery Process

For over a decade, drug design has been largely governed by a set of guidelines introduced by Lipinski, which assess the physical properties of compounds in order to identify whether or not they would be a good candidate for a drug.[1] The properties which are covered by Lipinski's rules, also known as the "Rule of Five", include how many hydrogen bond donors and acceptors the compound bears, the lipophilicity of the compound, and the overall molecular weight of the compound. In addition to the "Rule of Five", properties such as the number of rotatable bonds (less than 10), and the polar surface area of a compound have been shown to play a key role in the success of candidates as they progress through the drug discovery process.[2] Not only have the properties described played a key role in drug design, but they are also regularly used in absorption, distribution, metabolism, and excretion (ADME) prediction models.[3-5] As a consequence, these properties are continually being analysed as a compound progresses from a hit, through to a lead, and finally to a drug candidate. Although many successful drugs fall within the parameters that have been described, there is one feature of a molecule that is overlooked when using these descriptors; that is how structurally complex the molecule is (i.e. how saturated is the compound, and does the compound contain stereocentres?).

Many compounds tested in the drug discovery process have a high degree of unsaturation due to the rise in parallel synthesis being employed within the pharmaceutical industry, which tends to create sp^2 rich compounds.[6] This parallel synthesis protocol predominantly leads to sp^2 rich compounds due to their ease of preparation through reactions such as amide couplings, and sp^2-sp^2 metal-mediated cross couplings.[6] These compounds, which contain greater unsaturation, are largely two-dimensional, and therefore lack in chiral centres, and as a result, possess lowered levels of structural complexity.[6] Studies have shown that highly active compounds, on average, are more complex than the inactive compounds,[7] though it was also

shown that part of this is simply due to larger and more complex compounds having a greater affinity for targets.[8] As a result, there have been a number of attempts to address this issue by synthesising a range of more complex molecules, through what is commonly referred to as diversity-orientated synthesis.[9-12] It was believed that the benefits of this approach would be that the molecules accessed would resemble natural products, and could also allow additional areas of chemical space to be explored.[9,11] Since many drugs are derived from natural products, creating more complex, and consequently more drug-like libraries, would offer an increased chance of discovering a biologically active compound.[6]

Lovering *et al.* explained that increasing the saturation of a compound should be used as an approach to improving clinical success.[6] By increasing the saturation in a compound, the three-dimensionality is increased, as well as the ability to install chirality, which, in turn, allows a larger variety of compounds to be screened for biological activity. An example of this is illustrated with dimethyl pyridine, which has five possible isomers, each of which are unsaturated, and therefore relatively planar (**Figure 1**). In contrast, for the saturated version, dimethylpiperidine, 34 isomers are now available for biological testing, therefore a larger area of chemical space will be covered simply by increasing the saturation of the compound.[6]

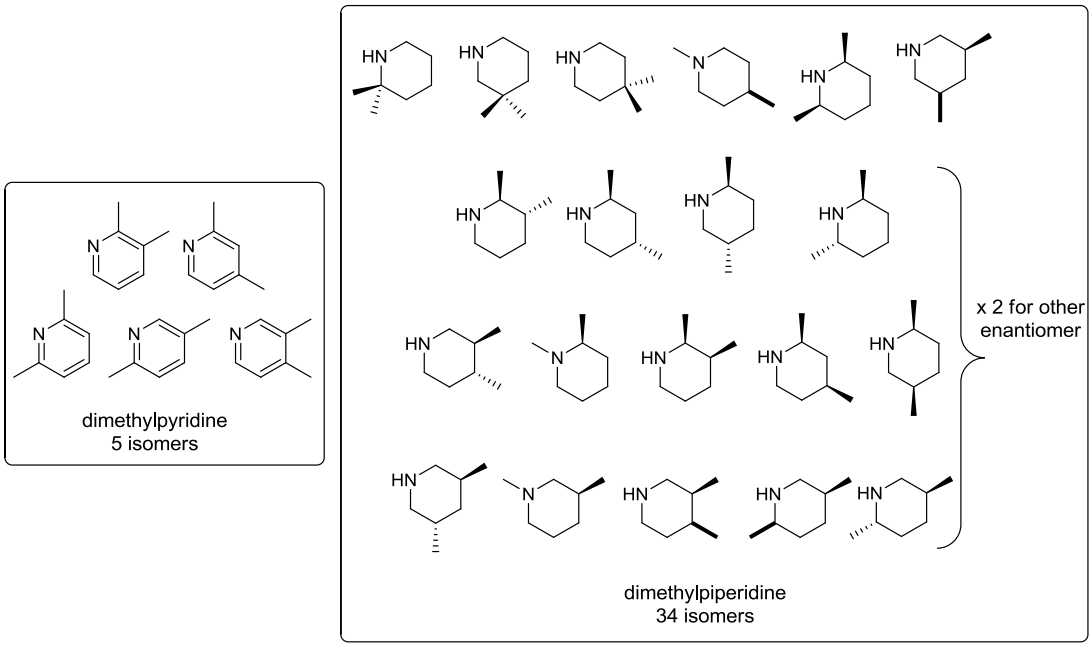


Figure 1

Furthermore, over recent years complex natural products, which have three-dimensional structures, have been used to understand protein function.[13] Within these natural products there are a number of functional groups at stereogenic centres that have been shown to act as potential sites for protein binding. These chiral functional centres can also be crucial for differentiating between closely related proteins, which a planar molecule would not be as likely to do.[9] Therefore by increasing the sp^3 character, a compound can be designed to complement the desired protein target, and, in turn, this should reduce the chance of undesired proteins being inhibited. This sp^3 functionality would also allow additional protein-ligand interactions that would not be possible by having a flat substituent, such as an aromatic ring. Having said this, π-π interactions are favourable; however, by increasing the saturation, the compound could better position these types of functional groups.[6] It has been shown that as drug candidates progress through the discovery process, those compounds which are highly saturated, as well as having stereogenic centres, are more likely to succeed.[6] Indeed, saturation of a compound also increases its solubility and lowers its melting point, without significantly increasing the molecular weight, which are also important considerations when designing new potential drug entities.[6]

In conclusion, it has been discussed how more complex molecules have the potential capacity to allow the exploration of a greater area of chemical space, and, in turn, make the chances of discovering a drug candidate more probable. Increasing the complexity, i.e. making a compound three-dimensional, allows greater potential for identifying a compound which is better suited for a particular target, and consequently reduce the number of off-target effects. Another descriptor for complexity is the presence of stereogenic centres; and it has been shown that the proportion of such molecules increase as drug candidates are transitioned through the discovery process.[6] Finally, as also discussed, the pharmaceutical industry tend to make drug libraries through parallel synthesis, which leads to highly unsaturated compounds, and therefore limit the chances of finding drug-like candidates. This has led to a movement of creating more complex sp^3-rich compounds for drug libraries, in order to discover more biologically active compounds at the start of any discovery process.[6]

1.2 Bridge Containing Compounds

Having discussed that there is an increase in interest for three-dimensional molecules for drug libraries, it is proposed that one way of creating a more three-dimensional compound is by incorporating a bridge, as shown in **Figure 2**.

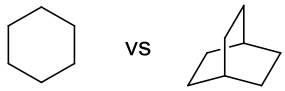
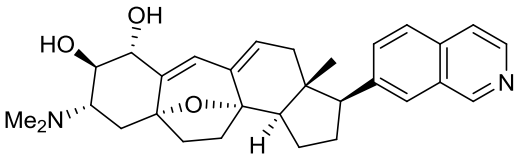


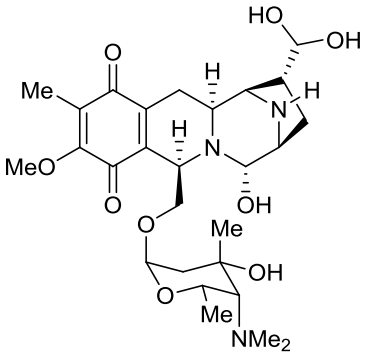
Figure 2

It has been shown that drug targets which contain a bridge will often have similar physicochemical properties to their unbridged counterpart, however, the more rigid bridged structure can enhance the potency and target selectivity.[14] This has resulted in a rise in popularity for such structure types within medicinal chemistry programmes.

Bridge containing compounds are found extensively within natural product systems and are being increasingly investigated within the pharmaceutical industry due to the movement towards synthesising more sp^3-rich compounds.[15-19] Two examples of natural products which contain a bridging unit are Cortistatin A and (-)-Lemonomycin (**Figure 3**). Both compounds are known to have biological properties: Cortistatin A is a compound known to inhibit the proliferation of human umbilical vein endothelial cells, and (-)-Lemonomycin has antibiotic properties, as well as being cytotoxic.[20,21]



Cortistatin A



(-)-Lemonomycin

Figure 3

As mentioned above, compounds which contain bridged units are becoming increasingly popular as potential bioactive species. Indeed, the more three-dimensional a compound is, the more selective and potent a drug it could be. An example of this was shown by medical chemists employed at the pharmaceutical company, Pfizer. During attempts to discover biologically active compounds for the GPR119 receptor, two potential drug candidates, **1** and **2** (**Figure 4**) were compared. Compound **1**, which has a more two-dimensional structure, was found to be only weakly active, however, a subtle change to the piperidine framework, more specifically installation of a bridge moiety, resulted in a significant increase in agonist selectivity.[17]

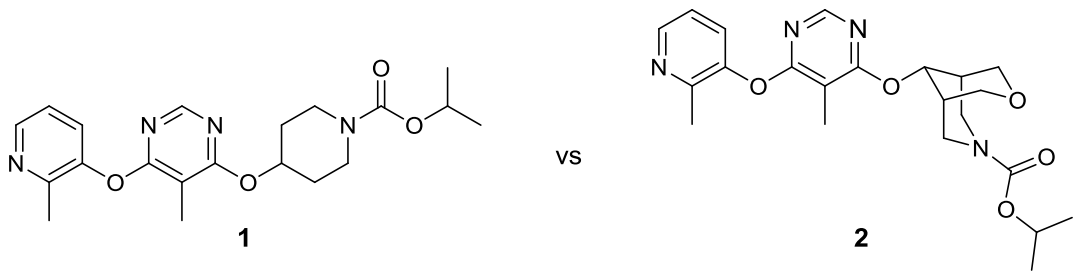


Figure 4

Interestingly, it was also found that an isomer of **2**, compound **3** (**Figure 5**), was an antagonist to the same receptor, illustrating the diverse properties of such bridged compounds.

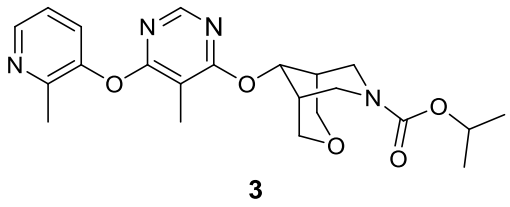


Figure 5

In addition to the bridged core above, Park *et al.* also showed that when a piperidine ring was replaced with a bridged piperidine, the compound was also found to possess elevated levels of activity against the GPR119 receptor (**Figure 6**).[18]

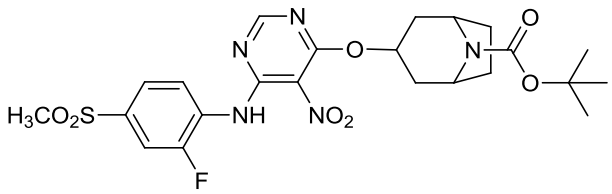
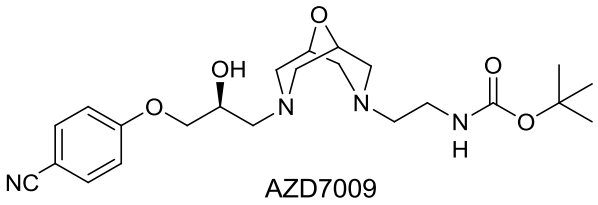


Figure 6

An alternative bridged heterocycle, known as an oxabispidine, was incorporated into a drug candidate by AstraZeneca (**Figure 7**).[22] AZD7009 acts as an atrial repolarisation delaying agent, and thus can be used in the treatment against cardiac

arrhythmia. Indeed, it is the bridging functionality that is key to the activity of this compound.[22]



AZD7009

Figure 7

Having illustrated that bridged compounds are becoming increasingly popular within the drug discovery process, there is now a requirement for robust and diverse routes into these types of moieties. In particular, AstraZeneca have become interested in two specific types of bridged heterocycles; bridged morpholines, and bridged piperazines (**Figure 8**).

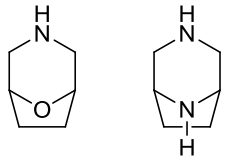


Figure 8

These types of compounds remain a challenge to synthesise due to their strained [3.2.1] ring system. To date, there are a lack of practically accessible and flexible routes (*vide infra*) into these substrates, which allow for diversification when starting from the same initial starting materials.

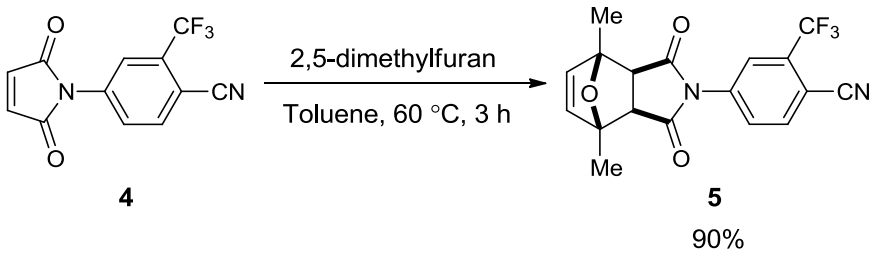
1.3 Synthesis of Bridged Heterocycles

As previously discussed, there are a lack of methods leading to the synthesis of bridged morpholine and piperazine type compounds which allow for significant diversification, with the majority of the syntheses being developed for specific

compounds to test their biological activity. The following section will present a brief discussion of some examples of routes used to successfully synthesise these types of bridged compounds.

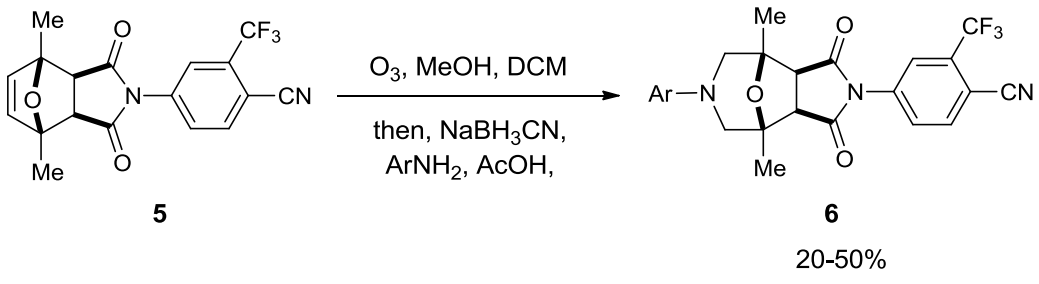
1.3.1 Synthesis of Bridged Morpholines

Bridged morpholines have been approached by a medicinal chemistry group at the Bristol-Myers Squibb company in order to assess their effectiveness as antagonists of the androgen receptor.[23] Their synthesis began with an intermolecular Diels-Alder reaction to synthesise bridged compound **5**, as shown in **Scheme 1**. Within this reaction 2,5-dimethylfuran was used in combination with **4** to form the bridged product in an excellent yield of 90%.[23]



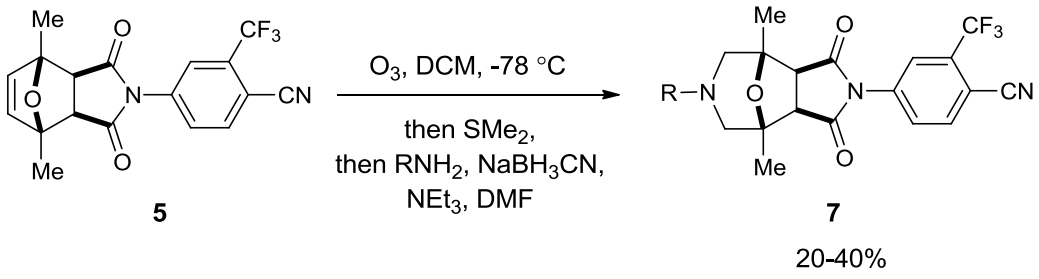
Scheme 1

Following on from this, compound **5** then underwent ozonolysis, and subsequent reductive amination to provide bridged morpholine **6** in poor to moderate yields depending on the aryl amine utilised (**Scheme 2**).



Scheme 2

It was only possible to synthesise aromatic amine analogues *via* the reaction sequence shown in **Scheme 2**. The reason was that when an aliphatic amine was employed, the amine became protonated by the acetic acid, and consequently this prohibited the desired reductive amination reaction from occurring. In order to synthesise aliphatic substrates, the conditions were altered. In this alternative approach, the ozonolysis was still performed, however, within this reaction, the ozonide was subsequently reduced with dimethylsulfide to give the dialdehyde intermediate. This dialdehyde intermediate was then subjected to reductive amination conditions to deliver the desired *N*-alkyl products in poor to moderate yields (**Scheme 3**).[23]

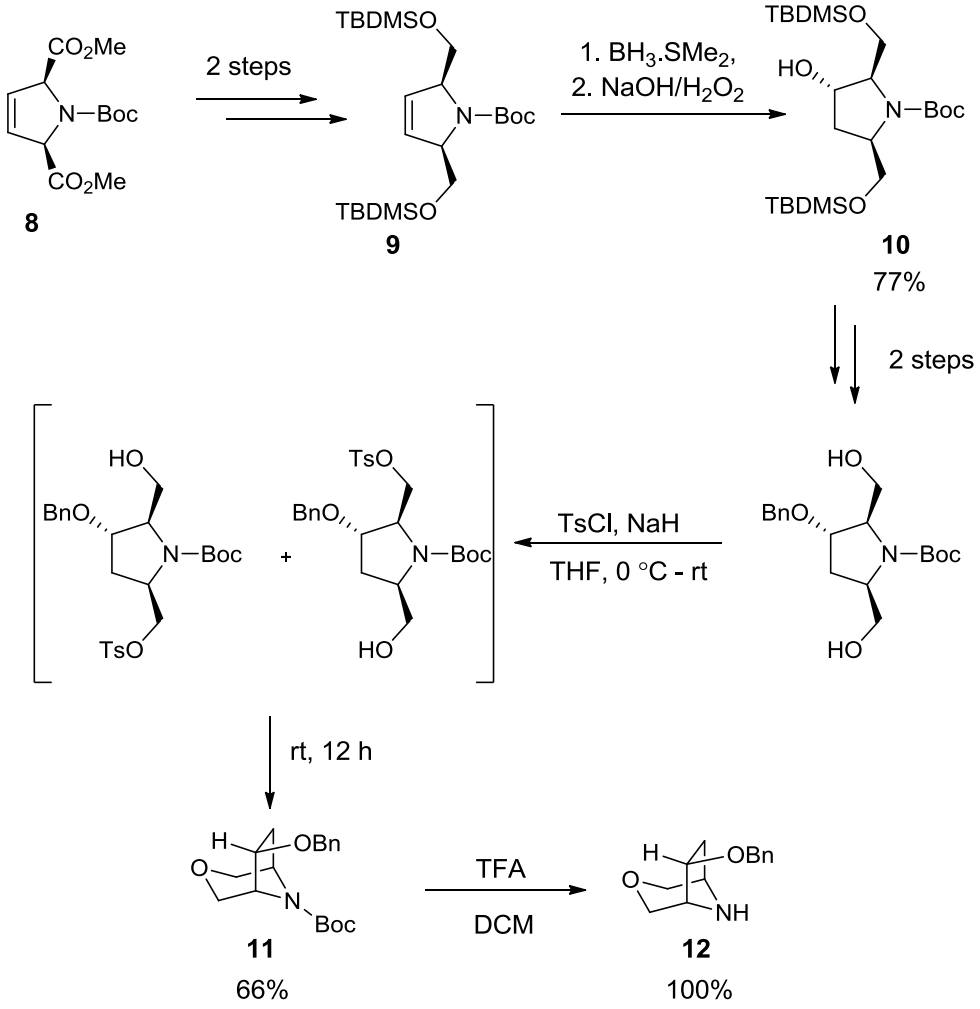


Scheme 3

From this route several bridged morpholines were made *via* derivatisation of the nitrogen on the morpholine ring, and such bridged morpholine compounds were found to act as antagonists of the androgen receptor, highlighting the importance of the synthesis of these types of structural motifs.[23]

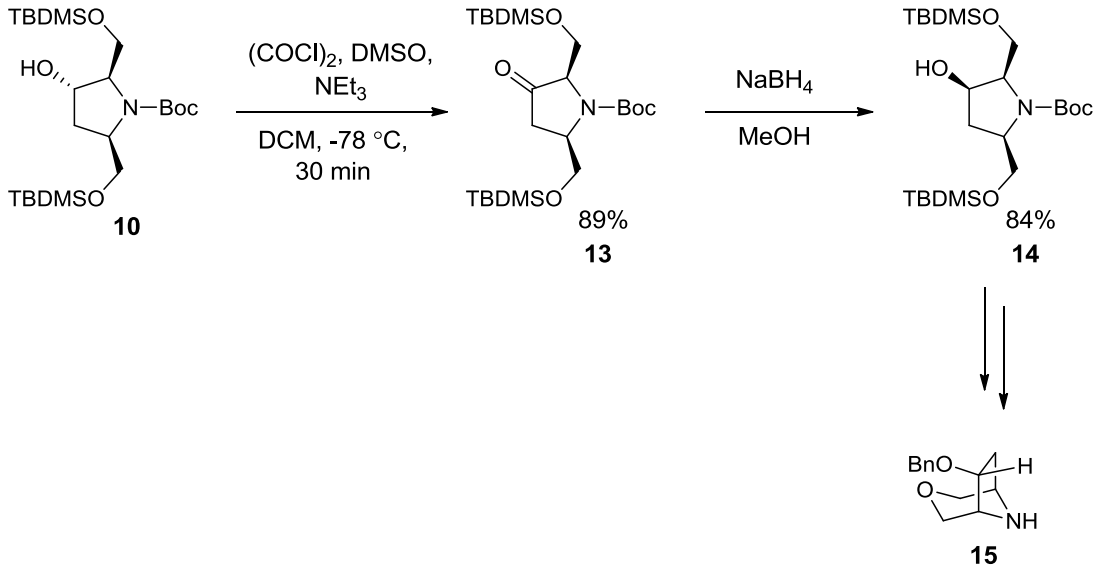
An alternative way to synthesising bridged morpholine compounds was illustrated by a group of medicinal chemists at Wyeth Research (**Scheme 4**).[24] This route involved an eight step synthesis to construct bridged morpholine **12**, which was to be utilised in the synthesis of an active metabolite of a potent kinase inhibitor. The route began with compound **8**, and, following a series of routine transformations, compound **9** was isolated. Following, what turned out to be a stereoselective hydroboration-oxidation reaction, alcohol **10** was obtained in good yield. After a benzylation reaction, and subsequent deprotection, the key cyclisation occurred *via* activated

(tosylated) intermediates to provide bridged morpholine **11**. The free bridged morpholine core was then synthesised *via* the removal of the Boc group. It was deduced from NMR studies that compound **12** had an *exo* conformation, which led to the realisation that the hydroboration reaction must have been stereoselective.[24]



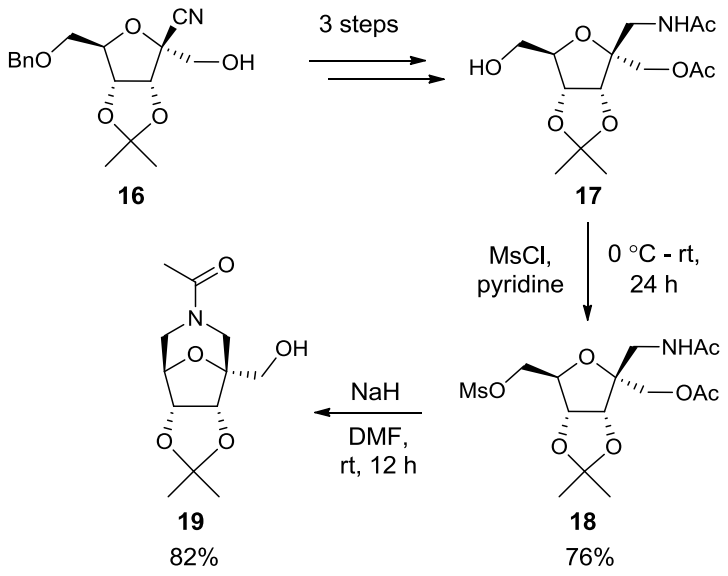
Scheme 4

In addition to the *exo*-bridged morpholine being synthesised, it was also shown that the *endo*-adduct could be accessed from intermediate **10** (**Scheme 5**).[24] This was achieved by oxidising the secondary alcohol to its corresponding ketone, followed by a stereoselective reduction of the ketone, using sodium borohydride, to synthesis the *cis*-alcohol **14**. Following the same synthetic steps described previously for the *exo*-product, *endo*-bridged morpholine **15** was isolated.[24]



Scheme 5

Fuentes *et al.* demonstrated that bridged morpholine adducts could be obtained when starting from a sugar derivative, as shown in **Scheme 6**.[25] Starting from compound **16**, and following routine transformations, tetrahydrofuran derivative **17** could be accessed. Initial mesylation of intermediate **17** was performed, followed by an intramolecular nucleophilic substitution reaction by the acetyl-protected nitrogen to produce bridged morpholine **19** in good overall yield.[25]

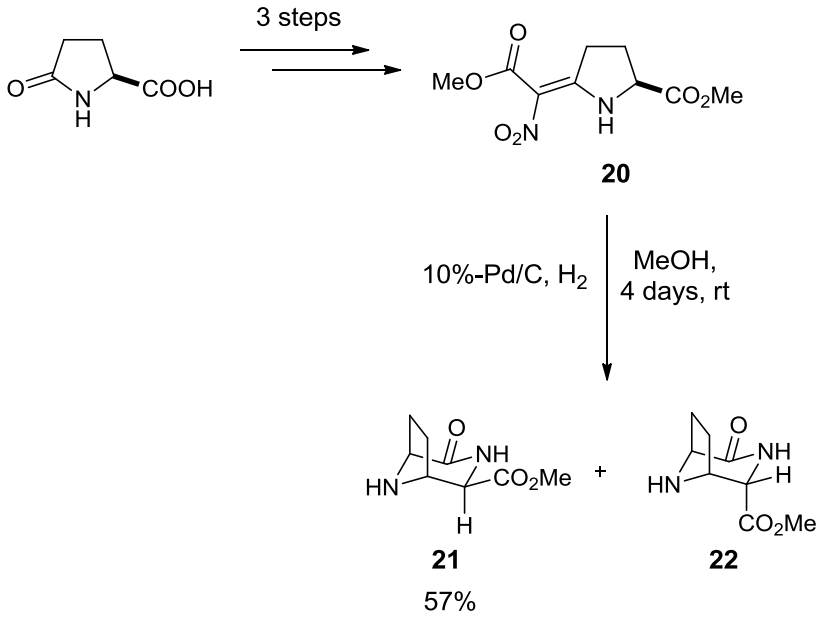


Scheme 6

As has been illustrated, routes have been developed to allow access into the bridged morpholine scaffold, however, there appears to be a lack more generalised methods to approach these compounds, and which allow for more diverse libraries of compounds to be synthesised, rather than the specific compounds shown.

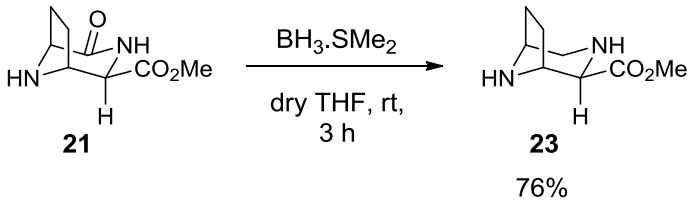
1.3.2 Synthesis of Bridged Piperazines

Jordis *et al.* developed a five step synthesis to a range of bridged piperazine motifs starting from commercially available pyroglutamic acid (**Scheme 7**).[26] From intermediate **20**, the key palladium-mediated reaction to install the bridged unit was performed. Hydrogenation of both the olefin and the nitro group under these conditions resulted in a diamino compound, which subsequently underwent a cyclisation reaction to produce both the equatorial (**21**) and axial (**22**) diastereomers of the bridged compound. Following a crystallisation procedure, the equatorial diastereomer was selectivity obtained in a 57% yield.



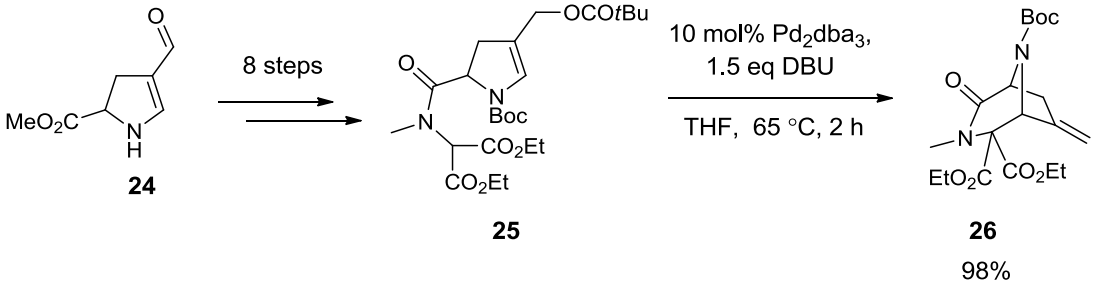
Scheme 7

Following on from this, compound **21** was subsequently transformed into the bridged piperazine core (**23**) *via* a reduction reaction, as illustrated in **Scheme 8**.



Scheme 8

Wipf *et al.* have also developed a novel pathway using palladium for the formation of alternative bridged piperazine adducts (**Scheme 9**).[27] The route involved an eight step sequence starting from the commercially available aldehyde **24** to access the key intermediate **25**. From intermediate **25**, an intramolecular palladium-catalysed allylic alkylation reaction was performed in order to construct the piperazine-type bridged compound **26**.[27]

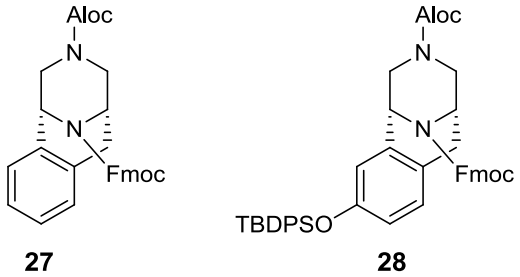


Scheme 9

In addition to compound **26** being synthesised, an aromatic ring could also be incorporated into the amide moiety. The palladium-catalysed allylic alkylation reaction was shown to be successful with an unsubstituted aryl ring, as well as the ring being dimethoxy substituted, with both reactions giving excellent yields (**Scheme 10**).[27]

Scheme 10

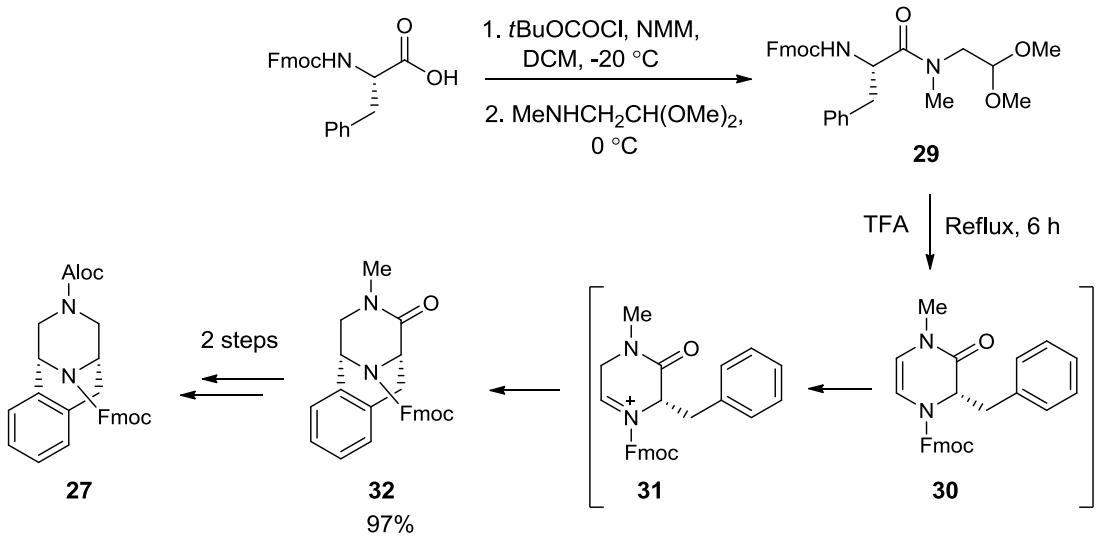
In addition to the routes above, Opatz has developed a short synthesis of the two chiral bridged piperazine motifs shown in **Figure 9**.[28] It was proposed that these two scaffolds could be utilised in the design and synthesis of drug-like molecules.



27 **28**

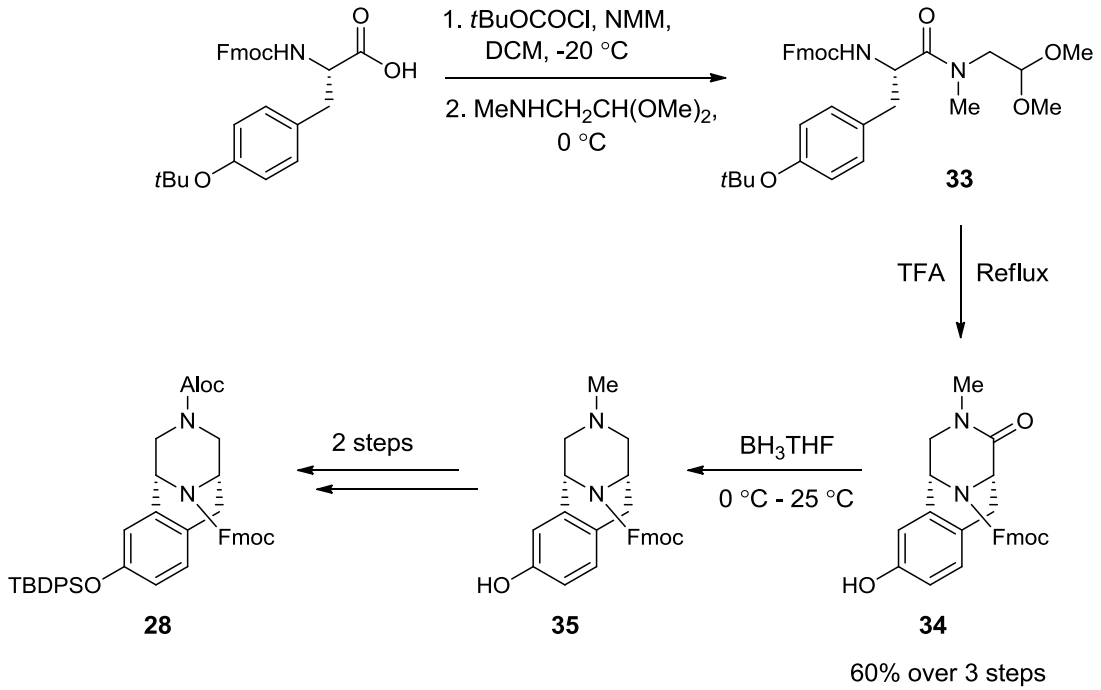
Figure 9

The route to these novel scaffolds began with the condensation of Fmoc-L-phenylalanine and commercially available *N*-(methylamino)acetaldehyde dimethyl acetal to produce amide **29** (**Scheme 11**).[28] Following this amide formation, the key reaction to synthesise the restricted piperazine proceeded with the cyclisation of **29** to produce **30**, which, under acidic conditions formed iminium ion **31**. This iminium ion then proceeded to take part in an intramolecular Friedel-Crafts reaction with the phenyl ring, to produce the bridged intermediate **32** in an excellent yield of 97%. After this cyclisation, reduction of the tertiary amide was performed, followed by a protecting group switch to form the bridged piperazine **27**.[28]



Scheme 11

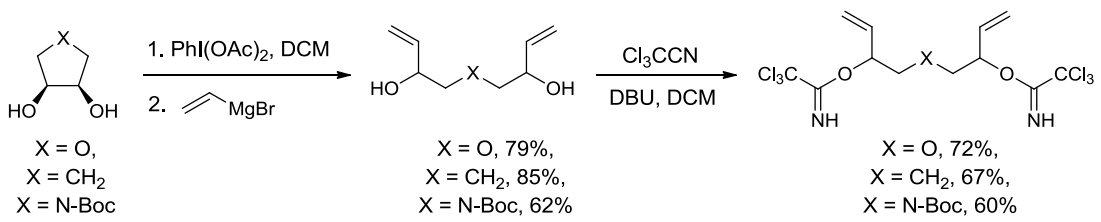
As previously mentioned, in addition to bridged piperazine **27**, the substituted aryl moiety **28** was also synthesised.[28] A very similar approach to that described previously was employed to synthesis **28**, with the route now starting with Fmoc-L-tyrosine *tert*-butyl ether (**Scheme 12**). It was discovered that under the cyclisation conditions the *tert*-butyl group was cleaved with the free phenol product **34** being obtained. Following the reduction of the amide, the hydroxyl group was reprotected, and a protecting group switch on the nitrogen was performed, with the desired bridged piperazine **28** being obtained.[28]



Scheme 12

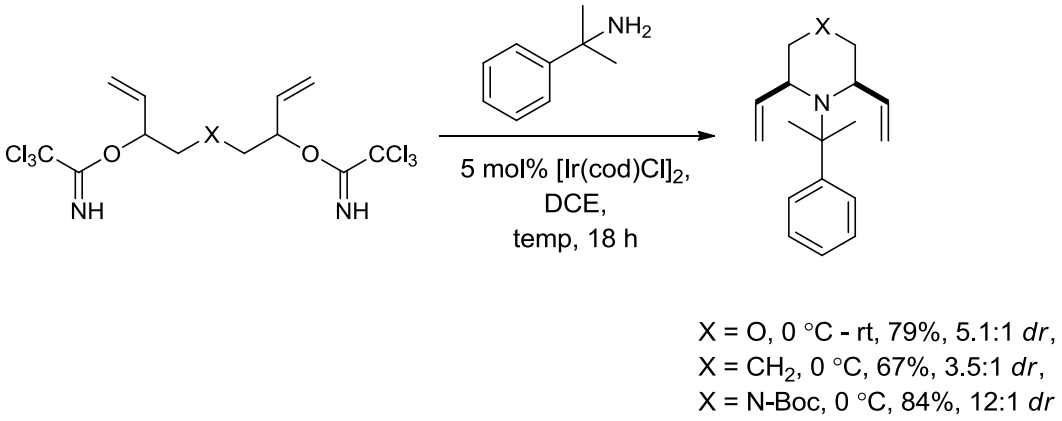
1.3.3 Synthetic Route which Allows Access to Both Bridged Morpholines and Bridged Piperazines

Brawn *et al.* developed a process in which several different bridged heterocycles could be synthesised when utilising a ring closing metathesis reaction as the key transformation (**Scheme 13**).[29] The synthetic sequence began with a cyclic diol, which underwent an oxidative cleavage, followed by addition of vinylmagnesium bromide to afford the bis-allylic alcohol in good overall yield. The diol intermediates were then converted to the desired bisimidate by employing trichloroacetonitrile as the reagent.[29]



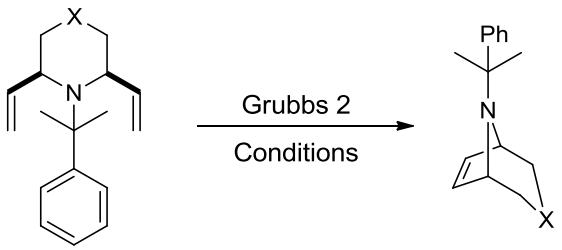
Scheme 13

Following the formation of the bisimidates, an iridium-catalysed bis-amination reaction was employed, which led to the synthesis of the *cis*-2,6-divinyl heterocycles in moderate to good *dr* (**Scheme 14**).



Scheme 14

These heterocycles then underwent a ring closing metathesis reaction using Grubbs 2nd generation catalyst to deliver the desired bridged compounds in moderate to high overall yield, as shown in **Scheme 15**, **Table 1**. This synthetic route appears to be the most diverse to date, as a short synthesis has been employed to access not just one bridged heterocycle, but three.



Scheme 15

X	*Solvent*	*Temperature (°C)*	*Yield (%)*
O	Toluene	120	79
CH_2	Xylenes	150	34
N-Boc	Toluene	120	82

Table 1

1.4 Conclusion

In conclusion, as has been described, the pharmaceutical industry tend to build their drug libraries through parallel synthesis, which generally lead to highly unsaturated compounds, and therefore limit the chances of finding drug-like candidates. This has led to a movement towards creating more complex sp^3-rich (more three-dimensional) compounds for drug libraries, in order to discover more biologically active compounds at the onset of any discovery programme. This is due to the complexity a three-dimensional molecule will possess. For example, the structure can become chiral, and therefore can be better designed to fit certain targets and lower the risk of off-target effects.

In this regard, one way of creating a three-dimensional compound whilst installing conformational restriction is by incorporating a bridge. Consequently, pharmaceutical partners have become increasingly interested in the biological activity displayed by the bridged morpholine and bridged piperazine compounds. To date, there appears to be a lack of synthetic routes towards these compounds which allows for diversification at various stages along the synthetic route. Most of the routes that have been described have been established to allow the synthesis of particular substrates for biological testing, rather than creating a generalised route into the desired scaffolds.

2. References

1. C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, *Adv. Drug Delivery Rev.*, 1997, **23**, 3.
2. D. F. Veber, S. R. Johnson, H.-Y. Cheng, B. R. Smith, K. W. Ward and K. D. Kopple, *J. Med. Chem.*, 2002, **45**, 2615.
3. M. P. Gleeson, *J. Med. Chem.*, 2008, **51**, 817.
4. Y. C. Martin, *J. Med. Chem.*, 2005, **48**, 3164.
5. H. Pajouhesh and G. R. Lenz, *NeuroRx*, 2005, **2**, 541.
6. F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752.
7. P. Selzer, H.-J. Roth, P. Ertl and A. Schuffenhauer, *Curr. Opin. Chem. Biol*, 2005, **9**, 310.
8. P. J. Hajduk, *J. Med. Chem.*, 2006, **49**, 6972.
9. P. Arya, R. Joseph, Z. Gan and B. Rakic, *Chem. Biol.*, 2005, **12**, 163.
10. D. Morton, S. Leach, C. Cordier, S. Warriner and A. Nelson, *Angew. Chem. Int. Ed.*, 2009, **48**, 104.
11. M. D. Burke and S. L. Schreiber, *Angew. Chem. Int. Ed.*, 2004, **43**, 46.
12. S. L. Schreiber, *Science*, 2000, **287**, 1964.
13. J. R. Peterson and T. J. Mitchison, *Chem. Biol.*, 2002, **9**, 1275.
14. A. Zask, J. C. Verheijen, D. J. Richard, J. Kaplan, K. Curran, L. Toral-Barza, J. Lucas, I. Hollander and K. Yu, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2644.
15. A. Zask, J. Kaplan, J. C. Verheijean, D. J. Richard, K. Curran, N. Brooijmans, E. M. Bennet, L. Toral-Barza, I. Hollander, S. Ayral-Kaloustain and K. Yu, *J. Med. Chem.*, 2009, **52**, 7942.
16. K. J. Curran, J. C. Verheijean, J. Kaplan, D. J. Richard, L. Toral-Barza, I. Hollander, J. Lucas, S. Ayral-Kaloustain, K. Yu and A. Zask, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1440.
17. K. F. McClure, E. Darout, C. R. W. Guimaraes, M. P. DeNinno, V. Mascitti, M. J. Munchhof, R. P. Robinson, J. Kohrt, A. R. Harris, D. E. Moore, B. Li, L. Samp, B. A. Lefker, K. Futatsugi, D. Kung, P. D. Bonin, P. Cornelius, R. Wang, E. Salter, S. Hornby, A. S. Kalgutkar and Y. Chen, *J. Med. Chem.*, 2011, **54**, 1948.

18. Z. Yang, Y. Fang, T.-A. N. Pham, J. Lee and H. Park, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 1519.
19. E. Darout, R. P. Robinson, K. F. McClure, M. Corbett, B. Li, A. Shavnya, M. P. Andrews, C. S. Jones, Q. Li, M. L. Minich, V. Mascitti, C. R. W. Guimaraes, M. J. Munchhof, Q. B. Bahnck, C. Cai, D. A. Price, S. Liras, P. D. Bonin, P. Cornelius, R. Wang, V. Bagdasarian, C. P. Sobota, S. Hornby, V. M. Masterson, R. M. Joseph, A. S. Kalgutkar and Y. Chen, *J. Med. Chem.*, 2013, **56**, 301.
20. S. Aoki, Y. Watanabe, M. Sanagawa, A. Setiawan, N. Kotoku and M. Kobayashi, *J. Am. Chem. Soc.*, 2006, **128**, 3148.
21. H. A. Whaley, E. L. Patterson, M. Dann, A. J. Shay and J. N. Porter, *Antimicrob. Agents Chemother.*, 1964, **8**, 83.
22. A. Bjoere, D. Cladingboel, G. Ensor, A. Herring, J. Kajanus, R. Lundqvist, C. Olsson, C.-G. Sigfridsson and G. Strandlund, 2006, PCT Int. Appl., Application: WO 2006-SE2688 20060612.
23. H.-Y. Xiao, A. Balog, R. M. Attar, D. Fairfax, L. B. Fleming, C. L. Holst, G. S. Martin, L. M. Rossiter, J. Chen, M.-E. Cvjic, J. Dell-John, J. Geng, M. N. Gottardis, W.-C. Han, A. Nation, M. Obermeier, C. A. Rizzo, L. Schweizer, T. S. Jr., W. Shan, A. Gavai, M. E. Salvati and G. Vite, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 4491.
24. Z. Chen, A. M. Venkatesan, O. D. Santos, E. D. Santos, C. M. Dehnhardt, S. Ayral-Kaloustian, J. Ashcroft, L. A. McDonald and T. S. Mansour, *J. Org. Chem.*, 2010, **75**, 1643.
25. F. J. Sayago, J. Fuentes, M. Angulo, C. Gasch and M. A. Pradera, *Tetrahedron*, 2007, **63**, 4695.
26. S. Pichlmair, K. Mereiter and U. Jordis, *Tetrahedron Lett.*, 2004, **45**, 1481.
27. G. H. C. Woo, S.-H. Kim and P. Wipf, *Tetrahedron*, 2006, **62**, 10507.
28. T. Opatz, *Eur. J. Org. Chem.*, 2004, 4113.
29. R. A. Brawn, C. R. W. Guimaraes, K. F. McClure and S. Liras, *Org. Lett.*, 2012, **14**, 4802.

Chapter One:

Bridged Morpholines - Racemic Synthesis

Table of Contents

1. Proposed Work

As discussed in the introductory section, bridged heterocycles have emerged as desirable targets within the pharmaceutical industry. More specifically, collaborative partners within AstraZeneca have become interested in exploring the bioactivity of bridged morpholines (**Figure 1**) and, as previously illustrated, there are a lack of routes into these types of scaffolds which allow for desired levels of diversification.

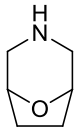


Figure 1

In addition to bridged morpholines, AstraZeneca has also been interested in the bridged hetereocycle, oxabispidine (**Figure 2**), due to their increasingly popular therapeutic properties.[1-6]

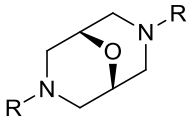
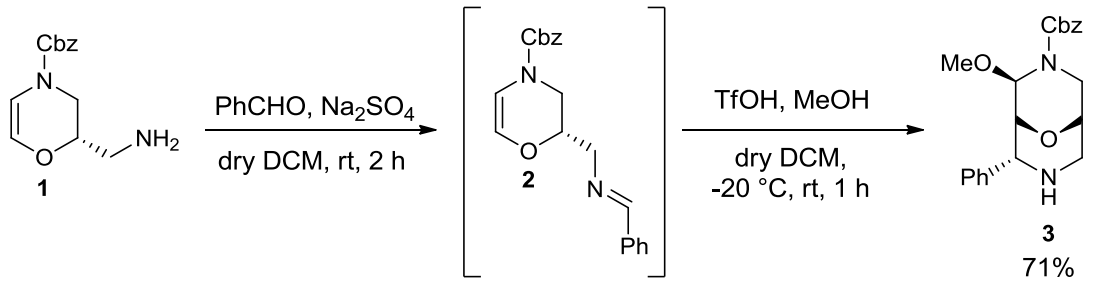


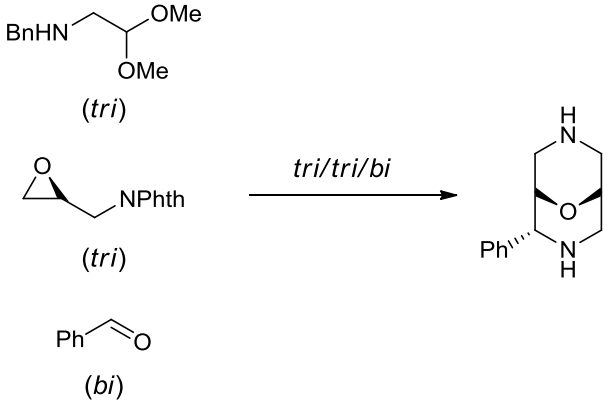
Figure 2

Due to AstraZeneca's interest in the oxabispidine scaffold, a collaborative programme between AstraZeneca and the University of Strathclyde was initiated. Consequently, a route towards a range of optically-enriched oxabispidine units has been developed.[7] The synthesis towards the chiral oxabispidine unit occurs *via* the condensation of amine **1** with an aldehyde, such as benzaldehyde, to deliver oxazine imine **2**, which then undergoes an intramolecular Mannich-type reaction to form the oxabispidine scaffold (**Scheme 1**).



Scheme 1

In relation to that described above, MacLellan and Nelson recently disclosed an article describing 'a conceptual framework for analysing and planning synthetic approaches to diverse lead-like scaffolds', which highlighted the applicability of our oxabispidine synthesis for allowing the exploration of chemical space.[8,9] These authors stated that synthetic approaches to fragments are more powerful if more bonds are formed to individual building blocks, or if more building blocks are utilised.[8] They have classified these synthetic approaches according to the number of new bonds that are formed to each building block in the conversion into the fragment.[8] As a result, our oxabispidine synthesis has been deemed powerful due to the fact that three building blocks are employed. In addition to this, they explain that the more tri-connective compounds utilised, the more complex the fragment will become, and within the oxabispidine synthesis the building blocks consist of two tri-connective and one bi-connective compound (**Scheme 2**).[8]



Scheme 2

Following on from this, and as highlighted in the introductory section, due to their potential biological activity and driven by the lack of flexible methods for their preparation, we propose to develop a synthesis into the synthetically more challenging, strained bicyclic 6,5-system and, in particular, bridged morpholines (**Figure 3**). We aimed for this system to be practically accessible, robust, and indeed flexible to allow a diverse array of compounds to be obtained.

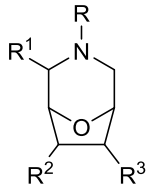
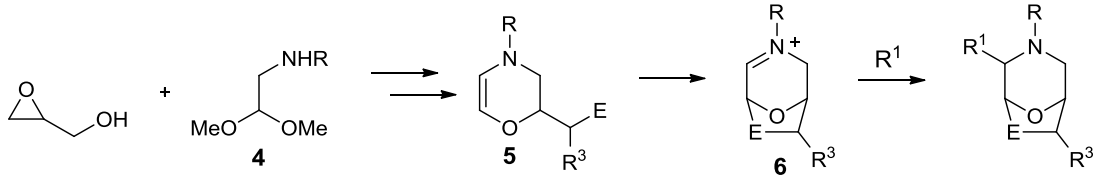


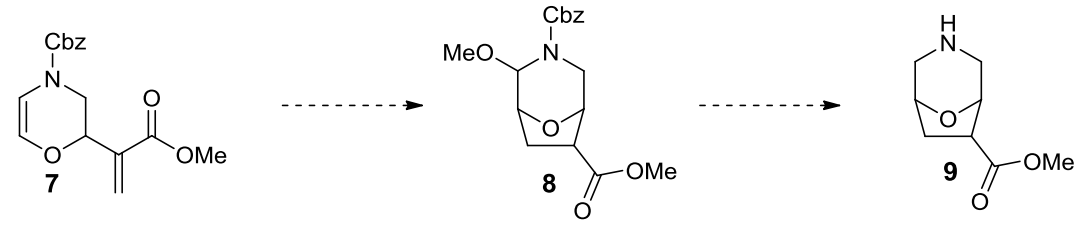
Figure 3

With the oxabispidine synthesis in mind, a general approach towards these bridged morpholine targets was proposed as outlined in **Scheme 3**. As shown, the key oxazine **5**, which would bear a pendant electrophilic unit, could undergo a cyclisation process *via* the iminium ion **6**, followed by trapping with an appropriate nucleophile (R^1) to form a variety of bridged morpholine motifs. The synthesis would utilise commercially available glycidol, and amine acetal **4**.



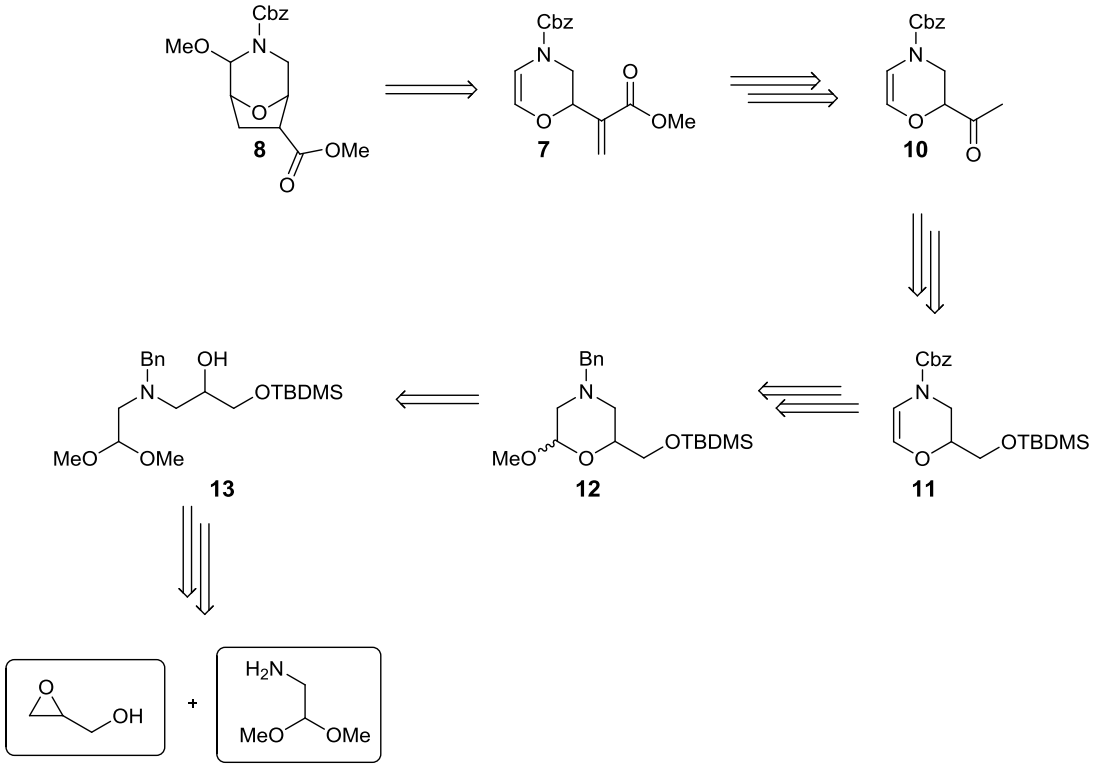
Scheme 3

According to this proposed strategy, the first target would be the α,β-unsaturated ester **7**, which it is anticipated to cyclise to form bridged morpholine **8**. This could then undergo a reduction process to produce the free bridged morpholine core **9** (**Scheme 4**).



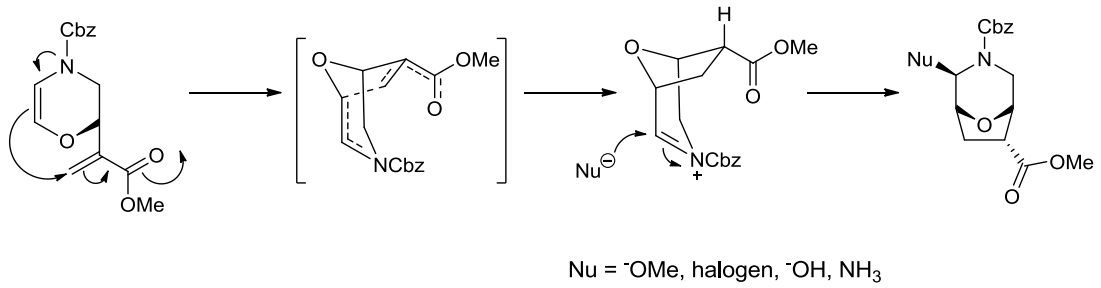
Scheme 4

Scheme **5** outlines the proposed retrosynthetic route into this new bridged morpholine compound. As previously discussed, bridged morpholine **8** could be accessed *via* the cyclisation of the α,β-unsaturated ester **7**. This ester could be obtained in a few steps from ketone **10**, which, in turn, could be accessed from intermediate **11**. This protected alcohol intermediate could be obtained from morpholine derivative **12**, which could be accessed *via* the cyclisation of amine alkyl chain **13**. Finally, the amine alkyl chain could ultimately be synthesised *via* the two commercially available starting materials, glycidol and 2,2-dimethoxyethylamine.



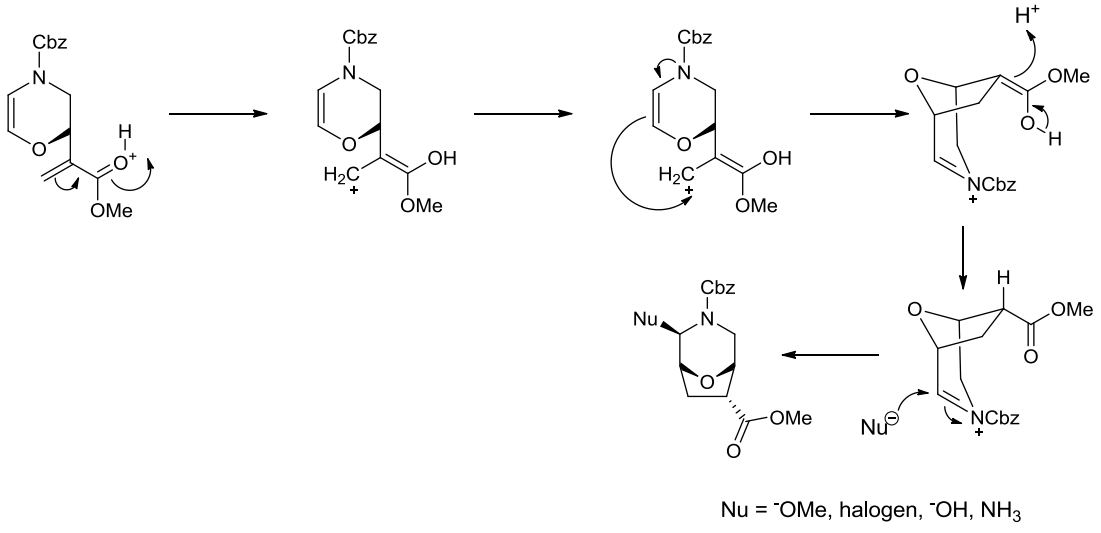
Scheme 5

With respect to the mechanism of the key cyclisation reaction, construction of the desired product could take place *via* a 5-*endo*-trig process, followed by nucleophilic attack onto the iminium ion to deliver the desired bridged morpholine (**Scheme 6**).



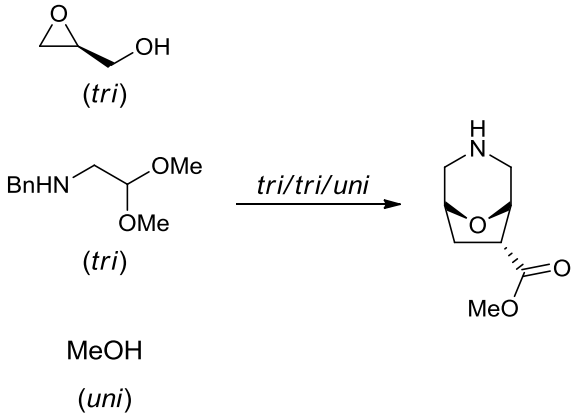
Scheme 6

Alternatively, this cyclisation could also be considered as a cyclisation onto a stabilised cation followed by a (re-)protonation step. The (re-)protonation step should take place on the less hindered face and, after nucleophilic attack onto the iminium ion has taken place, a single diastereomer of the desired product could be delivered (**Scheme 7**).



Scheme 7

The route proposed will further underpin the concepts described by MacLellan and Nelson for approaching diverse lead-like scaffolds. In a similar fashion to the oxabispidine synthesis, three different building blocks would be utilised. The building blocks being employed consist of one uni-connective and two tri-connective compounds, making this a potentially powerful synthetic approach to diverse lead-like scaffolds (**Scheme 8**).



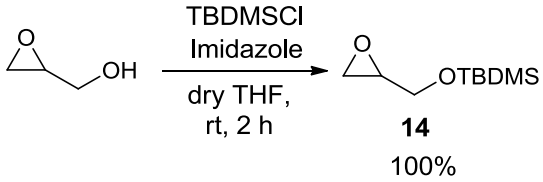
Scheme 8

2. Results and Discussion

2.1 Synthesis of α,β*-Unsaturated Ester Substrate* ***7***

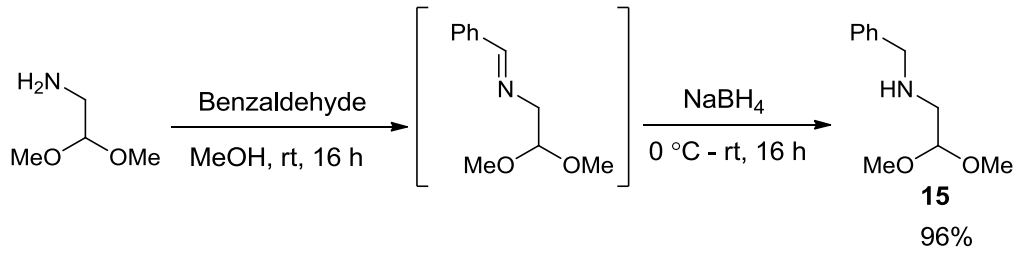
In order to establish a synthetic route to a variety of bridged morpholine motifs, the proposed route would start by using commercially available glycidol. As discussed in the previous section, although the asymmetric bridged morpholine was the desired end point, it was decided to initiate the route development by using racemic glycidol.

The first step in the proposed synthesis was to protect the hydroxyl moiety of glycidol. An acid-stable protecting group was required due to acidic media being used latter in the synthesis, therefore it was decided that glycidol would be protected as the TBDMS-ether, which was achieved in quantitative yield (**Scheme 9**).



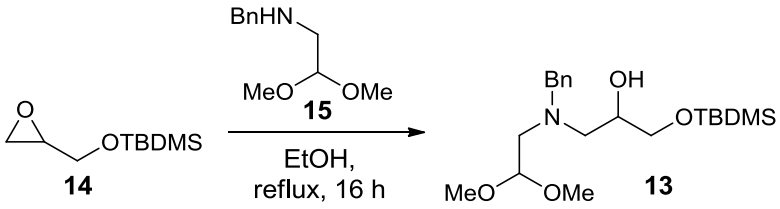
Scheme 9

The next stage in the synthesis involved opening the previously protected epoxide with the benzyl protected amine acetal **15**. Before this reaction could be performed, the amine itself required protection. This was achieved *via* a reductive amination reaction, with the benzyl-protected amine being produced in an excellent yield of 96% (**Scheme 10**).



Scheme 10

With the protected amine **15** in hand, the epoxide was regioselectivity opened under neutral conditions to provide the functionalised amine alkyl chain **13** in high yields on a variety of scales (**Scheme 11**, **Table 1**). No impurities were observed in the NMR analysis of **13**, therefore it was decided that no purification was needed at this stage, and **13** would be taken through the subsequent step in crude form.

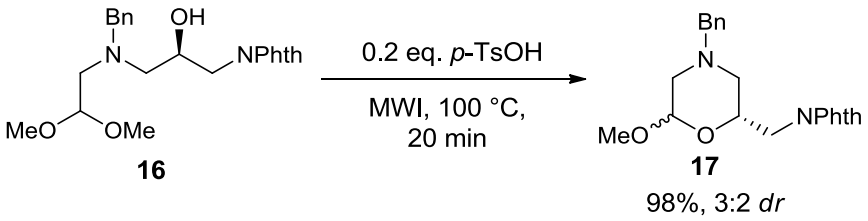


Scheme 11

Entry	*Scale (mmol)*	*Yield (%)*
1	2.7	98
2	22.8	95

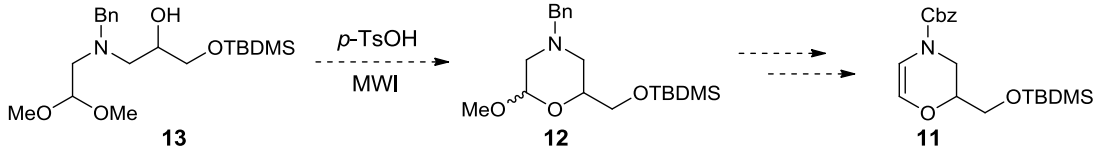
Table 1

During the route development towards the oxabispidine moiety, it was discovered that the cyclisation to form morpholine intermediate **17** occurred in high yields when performing the reaction under microwave irradiation, as illustrated in **Scheme 12**. It was also revealed by ^{1}H NMR analysis that a 3:2 mixture of diastereomers was obtained.[7]



Scheme 12

As the cyclisation of **16** gave an excellent yield under microwave irradiation, it was decided that initial attempts to close alkyl chain **13** would be carried out under the same conditions. Furthermore and as stated above, this cyclisation will also produce a mixture of diastereomers. However, such a stereoisomeric mixture would not pose a problem as **12** would ultimately undergo an elimination reaction to lose one stereogenic centre, as shown in **Scheme 13**.

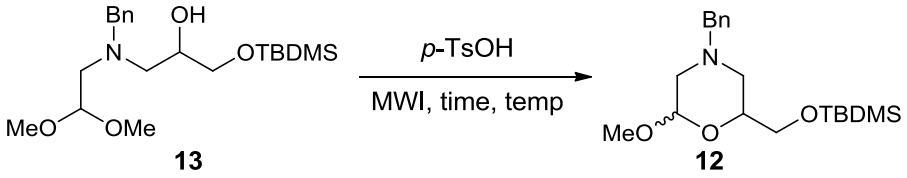


Scheme 13

When utilising the same reaction conditions that were employed to synthesise morpholine derivative **17** the reaction did not proceed to completion after the 20 min reaction time (**Scheme 14**, **Table 2**). In order to enhance the conversion, the reaction time had to be increased from 20 min to 40 min (**Table 2**, **Entry 1**). In this case, despite full conversion of starting material only 50% yield was obtained. Unfortunately, it was discovered that when this reaction was repeated, a total of 0.3 eq. of acid had to be employed, as well as a reaction time of 5.5 h in order for the reaction to proceed more effectively (**Entry 2**). In an attempt to improve this less than reliable process, it was decided to utilise recrystallised *p*-toluenesulfonic acid. This modification produced the desired product in a 60% yield with a 1 h reaction time (**Entry 3**). In an effort to reduce the reaction time, a higher reaction temperature was employed, however, it was found that when the temperature was increased to

115 °C, the same reaction time (1 h) was required for the reaction to proceed to completion (**Entry 4**).

As with morpholine derivative **17**, this reaction also produced a 3:2 ratio of diastereomers. At this stage in the synthesis, the NMR complexity was greatly increased due to the presence of a six membered ring, as well as diastereomers, therefore in order to help deduce whether or not the desired product was obtained, 2D NMR was utilised.



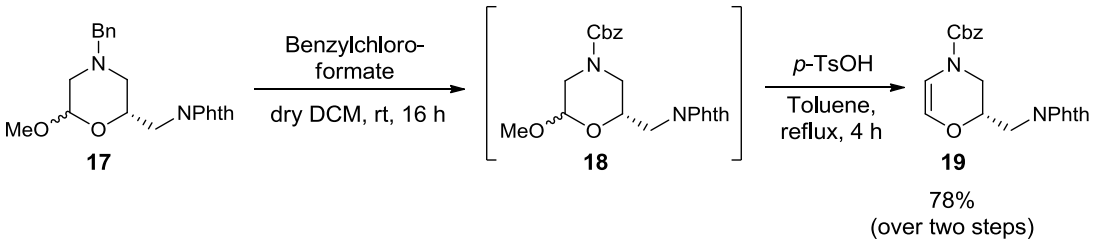
Scheme 14

Entry	*Eq. of acid*	*Time*	*Temp (°C)*	*Yield (%)*	*dr*
1	0.2	40 min	100	50	3:2
2	0.2 + 0.1	5.5 h	100	68	3:2
3	0.2[a]	1 h	100	60	3:2
4	0.2[a]	1 h	115	60	3:2

[a] Recrystallised acid was employed

Table 2

With the cyclised intermediate now in hand, attention turned to the elimination reaction to remove the newly formed stereogenic centre, and consequently install a double bond (see **Scheme 13**). Within the oxabispidine synthesis, when the elimination on morpholine **17** was investigated, it was found that a protecting group switch on the amine was required. When the amine was benzyl protected the nitrogen was too basic and became protonated under the reaction conditions, which prevented the elimination from occurring. However, it was found that when the amine was carboxybenzyl protected, the basicity of the nitrogen decreased, and the elimination could take place (**Scheme 15**).[7]

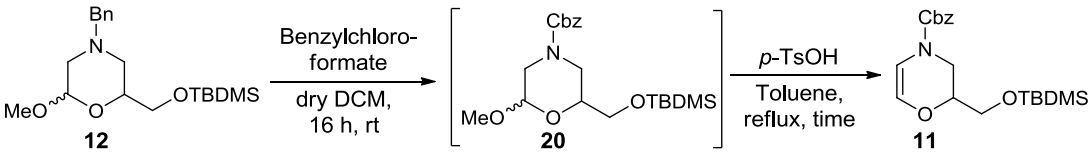


Scheme 15

With this result in mind, it was decided to perform the same protecting group switch in an attempt to avoid such issues with this desired elimination. As such, morpholine **12** was treated with benzylchloroformate with the protecting group switch occurring smoothly (**Scheme 16**). As benzyl chloride was the only expected by-product from this transformation it was decided not to isolate **20**, as it was anticipated that benzyl chloride would not have any adverse effect on the elimination step. Since the elimination reaction should only require a catalytic amount of acid, it was decided to start with 0.2 eq. of *p*-toluenesulfonic acid. However, after 24 h no product was detected, with only starting material being observed by TLC analysis. In an attempt to promote the reaction, a further 0.2 eq. of *p*-toluenesulfonic acid was added to the reaction mixture. Unfortunately, after an additional 3 h, an undesirable by-product **21** (see **Figure 4**) was produced in a 71% yield (**Table 3**, **Entry 1**).

Due to the success of using recrystallised *p*-toluenesulfonic acid when performing the ring closing reaction (*vide supra*), it was decided to attempt to effect this transformation using the same technique, however, with 0.2 eq. of recrystallised acid and a reaction time of 24 h, no product was detected by TLC analysis. On addition of a further 0.1 eq. of recrystallised acid, both the desired product **11**, and **21** were observed by TLC analysis after a further 6 h (**Entry 2**). Frustratingly, a very poor yield of only 5% of the desired eliminated product was obtained, along with a 65% yield of the undesired bridged morpholine **21**. In a final attempt to synthesise **11**, a reaction was performed using 0.2 eq. of acid with careful monitoring of the reaction. However, during a one week time frame, no product was observed by TLC analysis, and after 7 days complete decomposition of the starting material had occurred.

On introduction of the double bond in oxazine **11**, a stereogenic centre was removed, therefore diastereomers were no longer observed, however, due to the change in the amine protecting group to the carboxybenzyl group, rotamers were now observed in the NMR analysis.

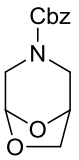


Scheme 16

Entry	*Eq. of acid*	*Time*	*Yield 11 (%)*	*Yield 21 (%)*
1	0.2 + 0.2	27 h	-	71
2[a]	0.2 + 0.1	30 h	5	65
3[a]	0.2	7 d	-	-

[a] Recrystallised acid

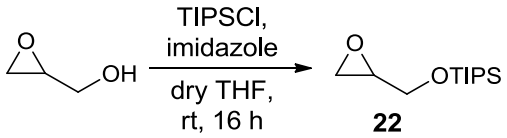
Table 3



21

Figure 4

As it appeared to be the lability of the TBDMS group under the strongly acidic conditions that was causing the formation of the undesired bridged morpholine **21**, it was decided that a more acid-stable protecting group should be employed. As such, it was decided to use the bulkier silyl group, TIPS. Consequently, the new synthetic sequence began with the formation of the TIPS protected glycidol **22**, which was achieved in excellent yields on a variety of scales (**Scheme 17**, **Table 4**).

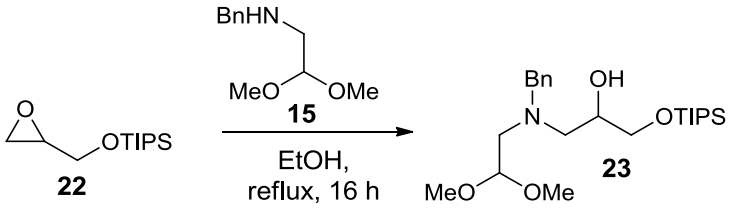


Scheme 17

Entry	*Scale (mmol)*	*Yield (%)*
1	13.5	87
2	29.7	88
3	110.7	97

Table 4

The protected epoxide was then regioselectivity opened under neutral conditions, with the previously used benzyl protected amine acetal **15**, to give the functionalised amine **23** in excellent yields (**Scheme 18**, **Table 5**). No impurities were observed in the NMR analysis of **23**, therefore it was decided that no purification was needed at this stage, and **23** would be taken through the subsequent step in crude form.

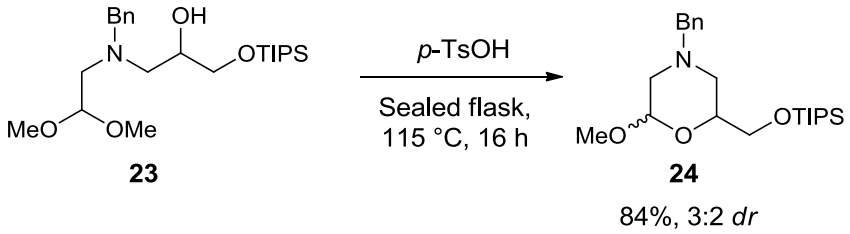


Scheme 18

Entry	*Scale (mmol)*	*Yield (%)*
1	10.8	90
2	104.6	100

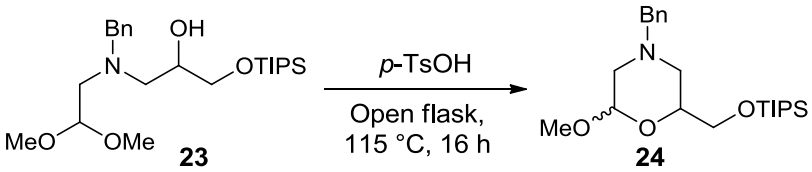
Table 5

The next step in the synthesis involved the ring closure of **23** to deliver the cyclised morpholine derivative **24** (**Scheme 19**). For the previous cyclisation reaction of compound **13** microwave irradiation was utilised. However, a disadvantage with this technique is that the scale of the reaction is limited to the small size of the microwave tubes. In order to allow the reaction to be scaled up, it was decided to test the reaction in a sealed, one neck, round bottom flask, which would be placed into a pre-heated oil bath. Pleasingly, this technique resulted in an excellent yield of the desired cyclised product **24** (**Scheme 19**). As with cyclisation of **13**, this cyclisation reaction also produced a 3:2 mixture of diastereomers.



Scheme 19

Due to the discovery that microwave irradiation was not necessary for the success of the reaction, it was decided to investigate if, indeed, the sealed flask was essential, or whether the reaction could be performed under air. Pleasingly, when the reaction was performed in an open flask excellent yields of **24** were again obtained (**Scheme 20**, **Table 6**).

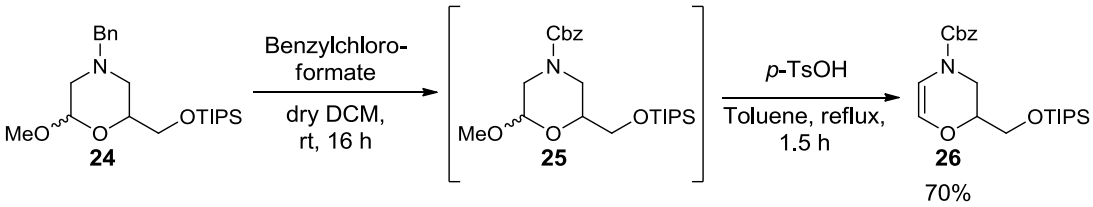


Scheme 20

Entry	*Scale (mmol)*	*Yield (%)*	*dr*
1	3.40	83	3:2
2	105.0	87	3:2

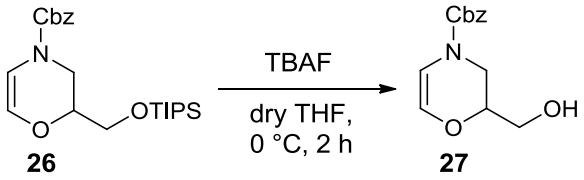
Table 6

At this stage, it was now hoped that with the more acid-stable TIPS group in place, the elimination reaction to form **26** would occur without complication. The initial protecting group switch occurred successfully, and to great delight the elimination reaction delivered only the desired product (**26**) in a high 70% yield (**Scheme 21**).



Scheme 21

With the eliminated product now in hand, the next stage in the synthesis involved the removal of the TIPS protecting group. The deprotection of **26** was effected using TBAF to produce alcohol **27** in excellent yields (**Scheme 22**, **Table 7**).



Scheme 22

Entry	*Scale (mmol)*	*Yield (%)*
1	1.1	95
2	14.1	82

Table 7

In order to introduce the extra carbon unit required to synthesise the key bridged morpholine precursor (**Figure 5**), an oxidation of the alcohol had to be performed.

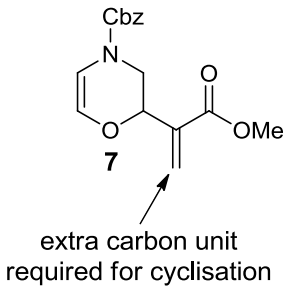
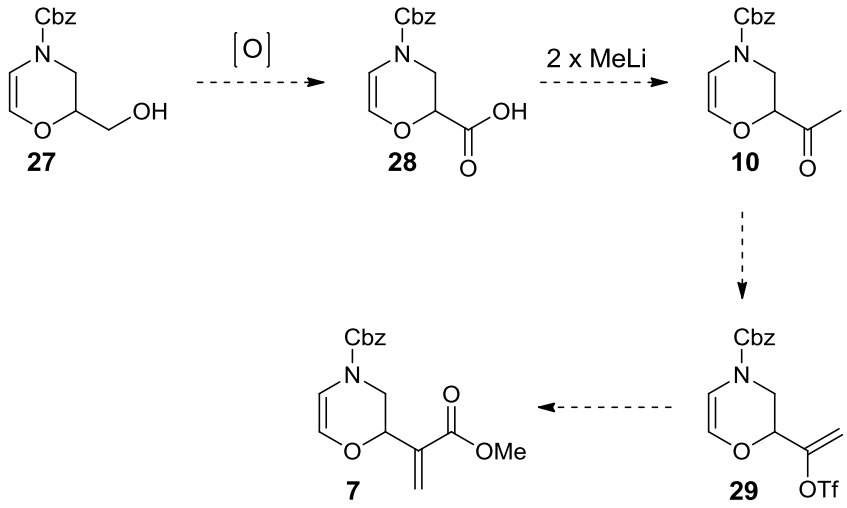


Figure 5

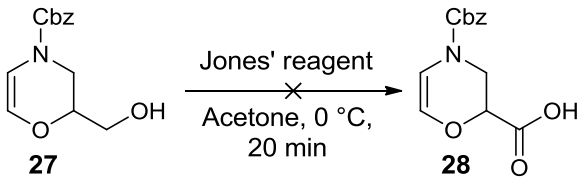
To keep the number of steps in the synthesis to a minimum, initial attempts began by trying to oxidise the alcohol to the corresponding carboxylic acid, which would subsequently be reacted with 2 eq. of methyllithium to introduce the methyl group (**Scheme 23**). Following on from this, formation of enol triflate **29** would take place, followed by a palladium-catalysed carbonylation reaction to obtain bridged morpholine precursor **7** (**Scheme 23**).



Scheme 23

Oxidation of the alcohol to the corresponding acid was first attempted using the well-known chromium based oxidant, Jones' reagent.[10] Under these conditions the

reaction appeared to be unsuccessful as only degradation products were observed (**Scheme 24**).

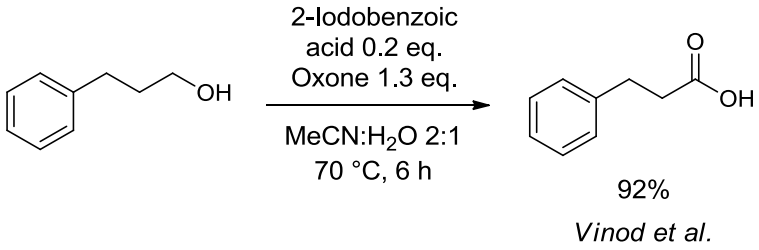


Scheme 24

The next set of oxidation conditions investigated involved the use of pyridinium dichromate in DMF, which is known to produce the carboxylic acid over the corresponding aldehyde.[11] Unfortunately, as with the previous oxidation reaction, only degradation products were observed (**Scheme 25**).

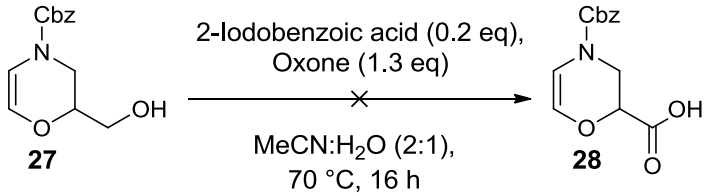
Scheme 25

Following the unsuccessful attempts using both Jones' reagent and PDC, it was decided to investigate an oxidation procedure that was developed by Vinod *et al.*[12] This method involved the use of catalytic 2-iodobenzoic acid with oxone to (re-) generate IBX *in situ*, with alcohols being oxidised to their corresponding carboxylic acid (**Scheme 26**).



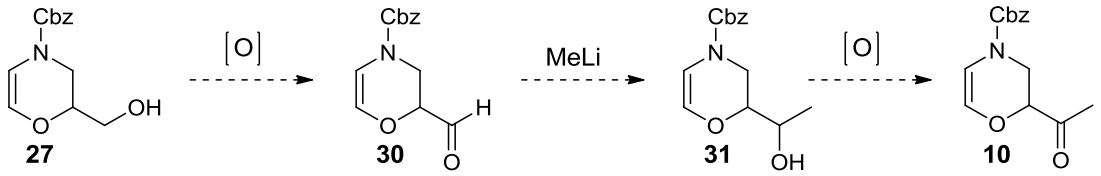
Scheme 26

Again, under this oxidation technique, neither the starting alcohol nor the carboxylic acid were obtained from the reaction mixture, with only degradation products being observed (**Scheme 27**).



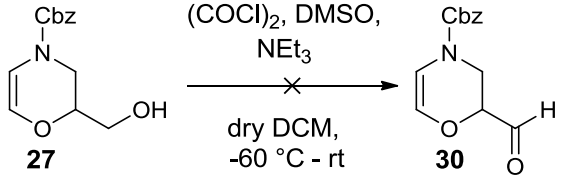
Scheme 27

Due to the lack of oxidation conditions which can be utilised to form a carboxylic acid in the presence of a double bond, attention turned to synthesising the aldehyde and introducing the methyl group in a more step-wise fashion, as detailed in **Scheme 28**.



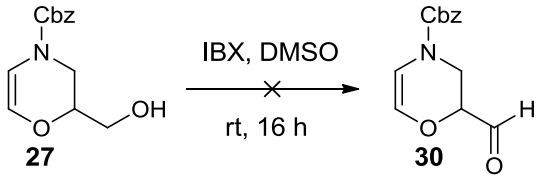
Scheme 28

Preliminary, Swern conditions were employed to synthesise the desired aldehyde.[13] Disappointingly, the oxidation of alcohol **27** was unsuccessful under these conditions. When the reaction was performed it was monitored by ^{1}H NMR, which showed the initial formation of the aldehyde, 9.62 ppm, however, this diagnostic signal disappeared during the course of the reaction.



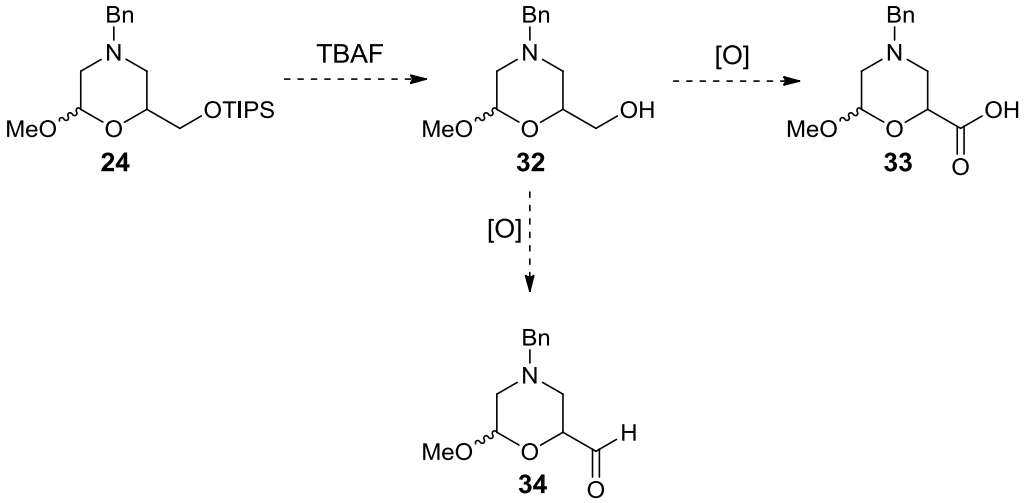
Scheme 29

The next set of conditions that were investigated involved using IBX as the oxidant (**Scheme 30**). However, the reaction was again unsuccessful as the aldehyde was not isolated, and the starting alcohol was also not recovered from the reaction mixture.



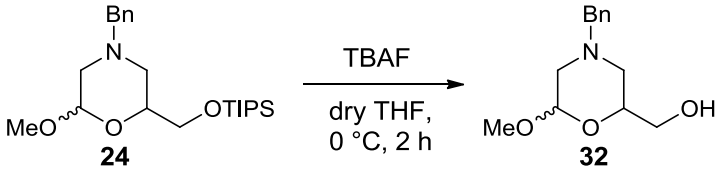
Scheme 30

As previously mentioned, a wider range of oxidation conditions are available for compounds without an olefin present, therefore it was decided that the modified route shown in **Scheme 31** would be explored. This alternative route involved the alcohol deprotection of **24**, following which an oxidation to the carboxylic acid (or aldehyde) would then be investigated, prior to the installation of the double bond.



Scheme 31

In order to examine the oxidation of alcohol **32**, morpholine derivative **24** had to initially undergo a deprotection. The removal of the TIPS group was effected using TBAF, with the alcohol being obtained in excellent yields (**Scheme 32**, **Table 8**).

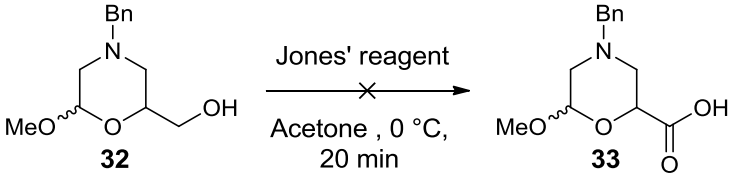


Scheme 32

Entry	*Scale (mmol)*	*Yield (%)*
1	33.0	99
2	91.0	90

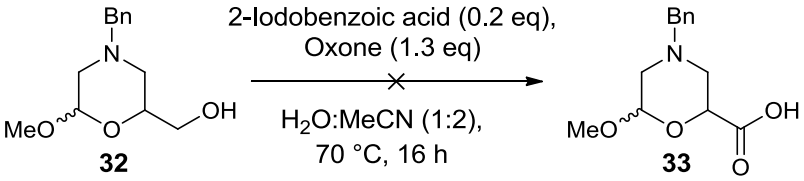
Table 8

As with the previous attempts to synthesise a carboxylic acid, it was decided to start with Jones' reagent.[10] Unfortunately, when Jones' reagent was employed the reaction was unsuccessful with only degradation products being obtained from the reaction mixture.



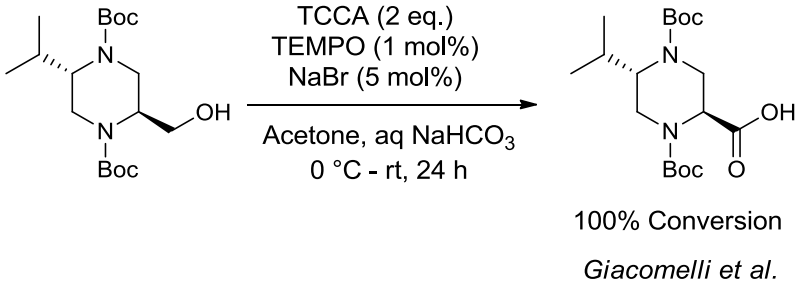
Scheme 33

Despite the initial failure to produce the acid, the conditions previously discussed by Vinod *et al.*, were utilised on substrate **32** (**Scheme 34**).[12] Unfortunately, the reaction was unsuccessful with neither the acid nor the alcohol being recovered from the reaction mixture.



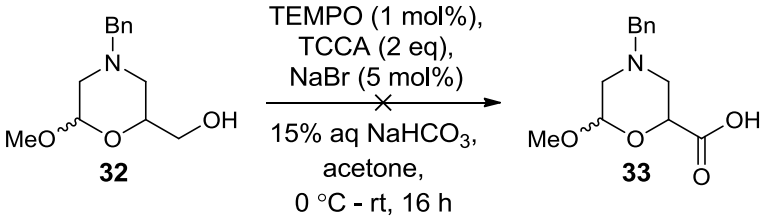
Scheme 34

The final attempt to synthesise acid **33** utilised conditions developed by Giacomelli *et al*., which involved the use of catalytic TEMPO, in addition to trichloroisocyanuric acid (TCCA) to synthesise the carboxylic acid over the aldehyde (**Scheme 35**).[14]



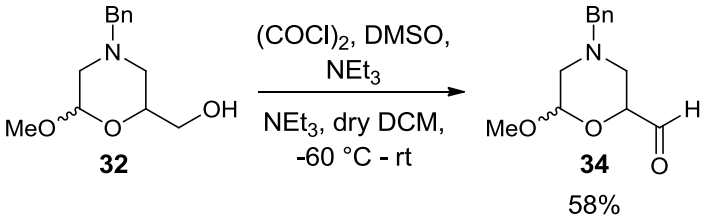
Scheme 35

When this method was applied to substrate **32**, frustratingly, the acid was not formed and the starting material was also not recovered from the reaction (**Scheme 36**).



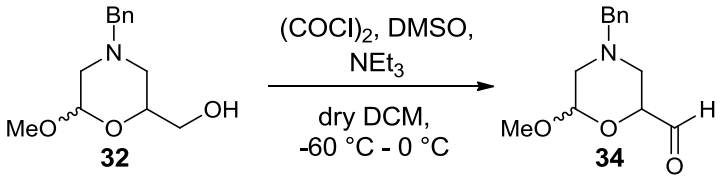
Scheme 36

As the synthesis of the carboxylic acid proved to be difficult, attempts to synthesise aldehyde **34** were initiated. The first reaction that was tested employed standard Swern conditions.[13] Pleasingly, the aldehyde was synthesised under these conditions with a moderate yield of 58% being achieved (**Scheme 37**).



Scheme 37

The initial reaction for forming the aldehyde involved warming the reaction mixture to ambient temperature, working up the reaction, and subsequently purifying the resultant oil by column chromatography. In an attempt to improve the yield, the reaction was warmed to 0 °C, and a small amount of toluene was added to allow DCM to be removed *in vacuo* to leave a slurry, which was subsequently purified by column chromatography. It was found that the yield significantly increased when using this new technique (**Scheme 38**, **Table 9**). Due to the sensitive nature of the aldehyde, it was also necessary to synthesise and react it in the subsequent step on the same day.



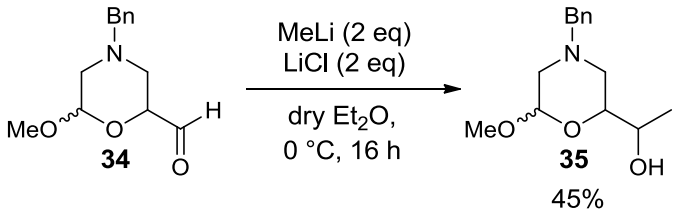
Scheme 38

Entry	*Scale (mmol)*	*Yield (%)*
1	4.2	94
2	18.7	82
3	84.3	98

Table 9

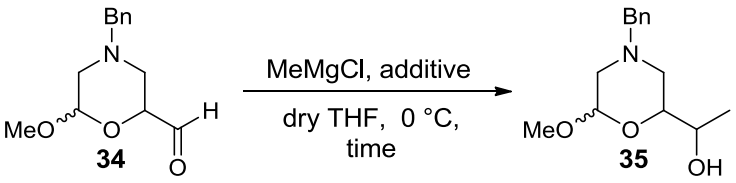
With the aldehyde finally synthesised, efforts turned towards introducing the methyl group. The initial reaction was performed using methyllithium, however, even

though the secondary alcohol was formed, it was found that the reaction did not go to completion, even with up to 6 eq. of methyllithium. Initially, it was believed this would not pose a problem, as it was thought that excess aldehyde could be removed *via* column chromatography. However, it was discovered that on purifying alcohol **35** that the aldehyde co-eluted. As a result, efforts were made to push the reaction to completion. It was found that when reacting Methyllithium (2 eq.) with lithium chloride (2 eq.), followed by addition of the aldehyde, and leaving the reaction to stir at 0 °C for 16 h, only trace amounts of aldehyde was present, however, a poor yield of 45% of the desired secondary alcohol was obtained (**Scheme 39**).



Scheme 39

Due to the poor yields obtained when using methyllithium, an alternative methylating reagent was sought. Methylmagnesium chloride was investigated, and was found to improve the yield to 58% (**Table 10**, **Entry 1**). With no additive present the reaction took 16 h to proceed to completion, yet it was pleasing to discover that, on the addition of lithium chloride, the reaction time was reduced to 2 h and the yield also improved further (**Entry 2-4**).

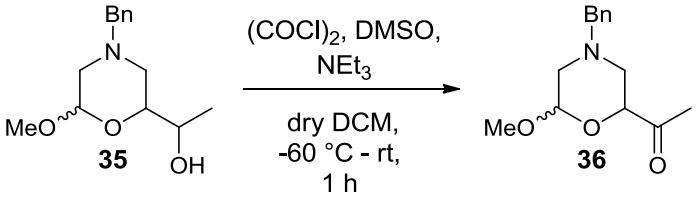


Scheme 40

Entry	*Scale (mmol)*	*Additive*	*Time (h)*	*Yield (%)*
1	0.75	None	16	58
2	3.2	LiCl	2	85
3	14.9	LiCl	2	89
4	40.4	LiCl	2	93

Table 10

With the secondary alcohol now in hand, attention turned to the oxidation step. Utilising Swern conditions, the secondary alcohol was converted into the desired methyl ketone in good yields on a variety of scales (**Scheme 41**, **Table 11**).



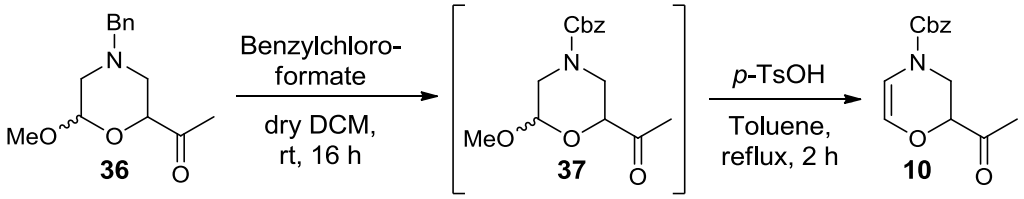
Scheme 41

Entry	*Scale (mmol)*	*Yield (%)*
1	2.8	73
2	13.0	74
3	37.4	75

Table 11

With the ketone functionality having been successfully embedded within the molecule prior to the double bond installation, work could now begin on the elimination reaction to install the olefin. The protecting group switch on ketone **36** occurred smoothly, and to great delight the elimination was able to occur (**Scheme 42**, **Table 12**). As mentioned previously, introduction of the double bond removed a stereogenic centre, therefore diastereomers were no longer observed. However, due

to the change in the amine protecting group to the carboxybenzyl group, rotamers were now observed by NMR analysis.

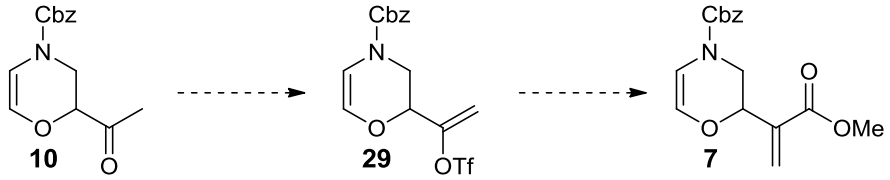


Scheme 42

Entry	*Scale (mmol)*	*Yield (%)*
1	2.0	61
2	9.7	65

Table 12

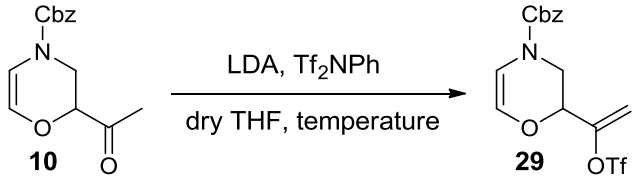
With the olefin now in place, and the ketone functionality present within the molecule, work could now be initiated on forming enol triflate **29**. The enol triflate is necessary for a palladium-catalysed carbonylation reaction to take place, which would produce the desired bridged morpholine precursor **7** (**Scheme 43**).



Scheme 43

Initial efforts involved the use of the base, LDA. It was envisaged that due to the bulky nature of LDA, as well as the reaction being performed at low temperatures, the deprotonation would occur at the less hindered carbon and exclusively form isomer **29**. Unfortunately, when the reaction was carried out at -78 °C, warmed to room temperature and stirred at room temperature for 1 h, only 30% of starting material was recovered with none of the desired compound being obtained (**Table**

13, **Entry 1**). Subsequently, the reaction was carried out under alternative conditions (-78 °C, warmed to 0 °C, and stirred for 1 h at 0 °C), however, only 28% of starting material was recovered from this reaction, with again no product being obtained (**Entry 2**).

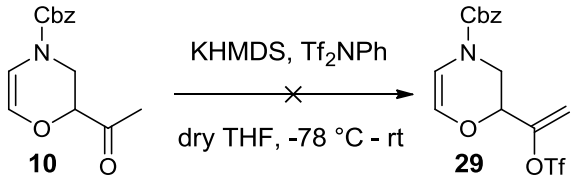


Scheme 44

Entry	*Temperature*	*Yield 29 (%)*	*Recovered ketone 10 (%)*
1	-78 °C – rt	-	30
2	-78 °C – 0 °C	-	28

Table 13

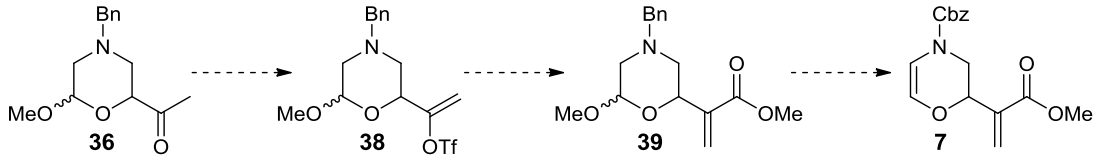
As the use of LDA was proving to be unsuccessful, an alternative base was sought. The next base to be investigated was KHMDS. Disappointingly, the reaction was unsuccessful as no enol triflate was obtained, and only 39% of the starting material was recovered from the reaction mixture.



Scheme 45

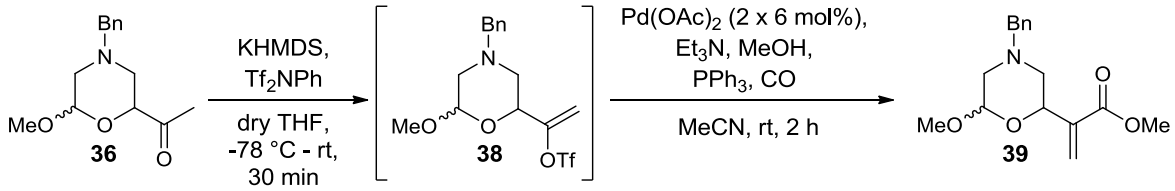
Previously, when attempting to install the ketone functionality it was shown that the oxidation was only successful in the absence of the double bond, therefore it was decided to use the same approach with installing the enol triflate functionality. It was

proposed that ketone **36** would be transformed into enol triflate **38**, which would then undergo a palladium-catalysed carbonylation to install the α,β-unsaturated ester functionality, with the final step being the elimination reaction (**Scheme 46**).



Scheme 46

Pleasingly, it was found that the enol triflate could be successfully embedded in the absence of the double bond when using KHMDS as the base. Having said this, when the reaction was initially performed with the electrophile as an internal quench the reaction was unsuccessful. On changing to an external quench, the desired product was obtained. However, it was found that even after purifying *via* column chromatography, **38** could not be obtained in a satisfactory purity to determine an accurate yield. It was believed that the by-product from the triflating reagent was remaining in the product, which was co-eluting with the enol triflate. It was therefore decided to take the mixture through the subsequent step with the intention of gaining access to a pure cross-coupled product. When using standard palladium-catalysed carbonylation conditions, α,β-unsaturated ester **39** was successfully isolated with no impurities (**Scheme 47**). It should be noted that the quality of the KHMDS solution is essential for the reaction outcome. When KHMDS has begun to even minimally hydrolyse, very poor yields were obtained.

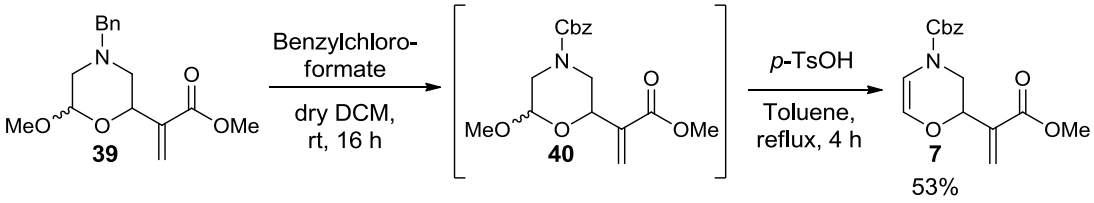


Scheme 47

Entry	*Scale (mmol)*	*Yield (%)*
1	2.11	43
2	3.83	40

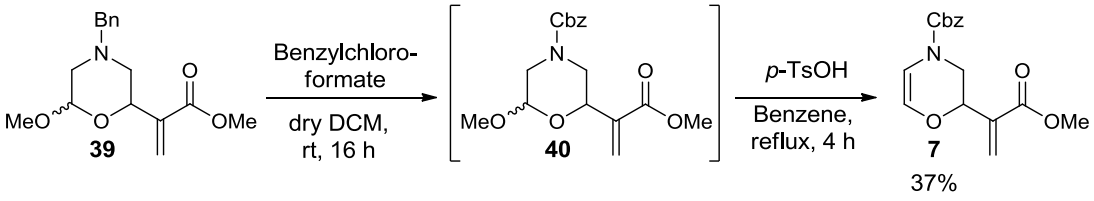
Table 14

The final stage towards the synthesis of the targeted bridged morpholine precursor was the installation of the double bond. As before, when carrying out the elimination of methanol to install the double bond, the protecting group exchange had to initially be performed. It was found that the protecting switch on **39** was successful with the α,β-unsaturated ester present. The elimination reaction was then carried out, with a moderate yield of 53% being obtained over two steps.



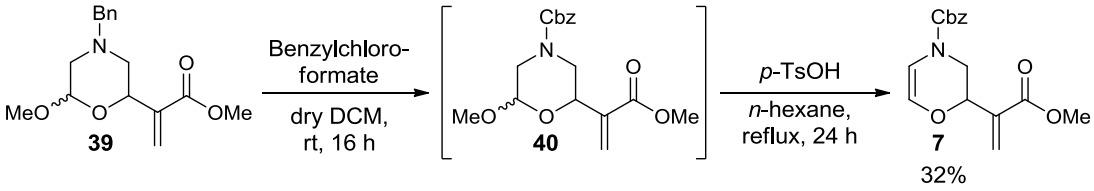
Scheme 48

In an attempt to improve the yield, it was decided to vary the solvent so that the reaction temperature could be decreased (**Scheme 49**). As benzene has a lower boiling point compared to toluene, and is still able to azeotrope methanol, it was hoped that under the milder conditions a higher yield would be obtained. Disappointingly, when utilising benzene as the solvent a lower yield of 37% was obtained.



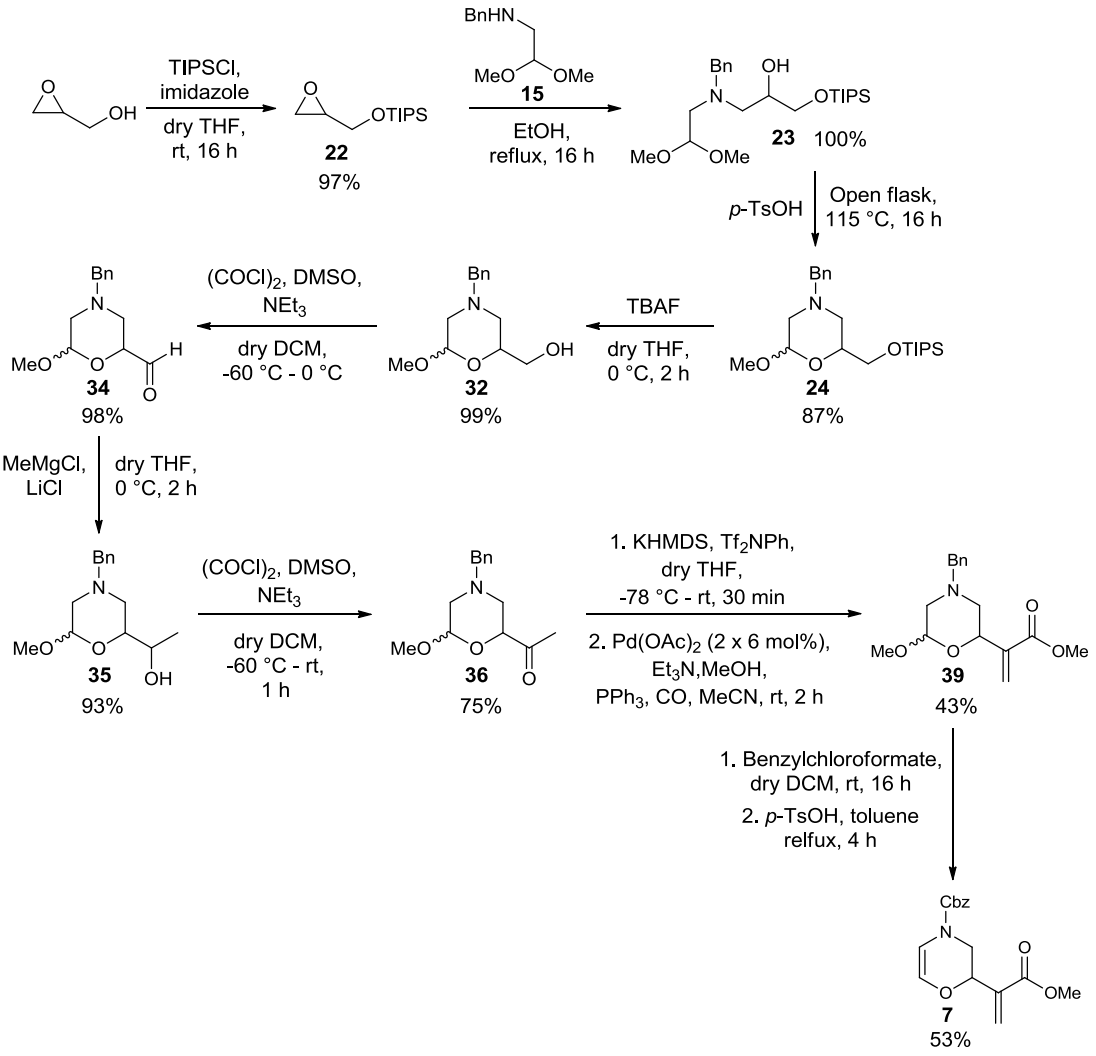
Scheme 49

With benzene failing to improve the yield, it was decided to employ *n*-hexane as the solvent, as it also has a lower boiling point and is able to azeotrope methanol. However, even under these conditions the yield obtained from the reaction was poor (32%). Additionally, a longer reaction time of 20 h was required, as well as an additional 0.2 eq. of *p*-toluenesulfonic acid to enable the reaction to proceed to completion. It was therefore decided that, for future reactions, toluene would be the solvent utilised.



Scheme 50

At this stage in the project it was pleasing to have synthesised α,β-unsaturated ester **7**, which was required for the synthesis of the desired bridged morpholine. The initially proposed route to this key intermediate proved to be unsuccessful. It was discovered that an alternative glycidol protecting group was required, as well as it being shown that the order in which the reactions were performed was crucial when trying to access **7** (**Scheme 51**).



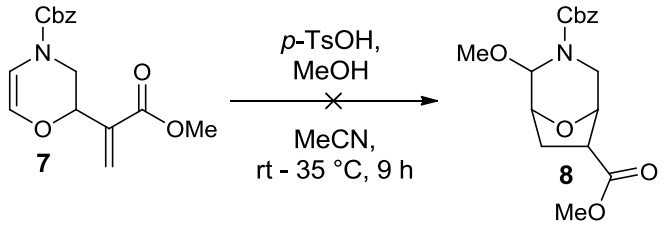
Scheme 51

Having now developed a robust and reproducible route to the α,β-unsaturated ester, attention could turn to the final cyclisation step.

2.2 α,β-Unsaturated Ester Cyclisation

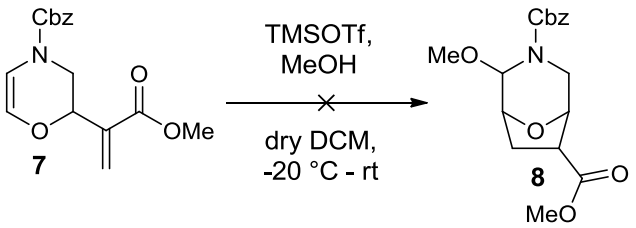
With the bridged morpholine precursor now in hand, efforts could be focused towards the key cyclisation step. In order to give the cyclisation the best chance of occurring, it was decided to carry out the reaction in the presence of an activating reagent. In this regard, the carbonyl portion of an α,β-unsaturated ester could be

activated *via* the use of an acid or Lewis acid. For this reason, the initial reaction performed involved the use of *p*-toluenesulfonic acid (**Scheme 52**). The reaction was primarily carried out at ambient temperature, however, after 3 h only starting material was observed by TLC analysis. It was therefore decided to increase the reaction temperature to 35 °C. After 6 h at this temperature, a new spot was observed by TLC analysis, with no starting material being observed. However, following purification by column chromatography, only degradation products were obtained, with none of the desired product being isolated.



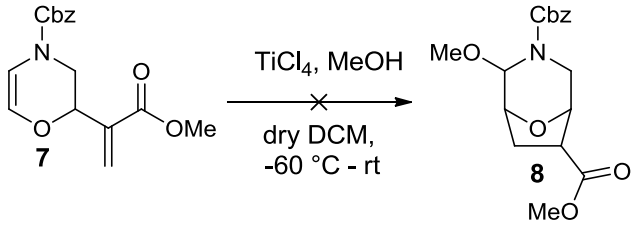
Scheme 52

Despite the initial unsuccessful result, the subsequent reaction involved the use of TMSOTf as an alternative activating reagent (**Scheme 53**). TMSOTf was added to the reaction mixture at -20 °C with the reaction mixture then being slowly warmed to ambient temperature. As the reaction mixture was warmed to ambient temperature the colour changed significantly. The colour of the reaction mixture turned from yellow to dark brown by the time the mixture was at ambient temperature, by which point no starting material was observed by TLC analysis. However, as with the previous reaction, after purification by column chromatography only degradation products were obtained with none of the desired product being isolated.



Scheme 53

An alternative Lewis acid, titanium tetrachloride, was then used to activate α,β-unsaturated ester **7** (**Scheme 54**). The reaction was carried out at -60 °C and after 3 h only starting material was observed by TLC analysis. The reaction temperature was therefore increased to ambient temperature, during which time the starting material was no longer observed by TLC analysis. In addition to this, the reaction mixture turned black in colour as it warmed. As with the previously described reactions, after purification by column chromatography degradation products were obtained, with none of the desired product being isolated.

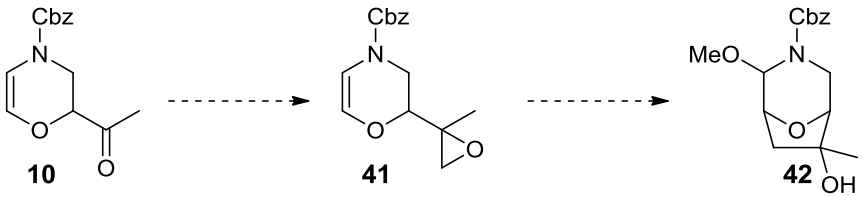


Scheme 54

Whilst developing the synthetic route to the α,β-unsaturated ester **7**, and attempting the cyclisation reaction, the synthesis of an alternative bridged precursor and its cyclisation reaction was being investigated simultaneously.

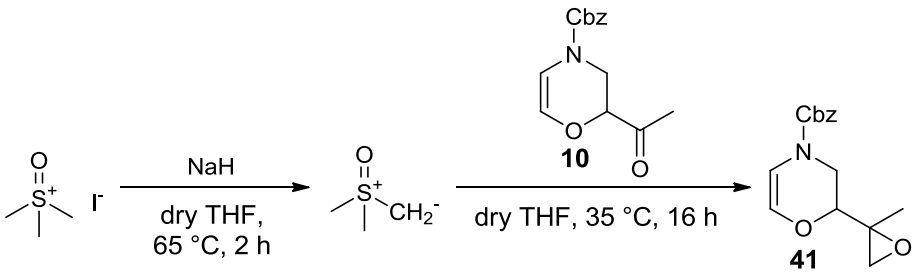
*2.3 Synthesis of Epoxide **41***

It was proposed that epoxide **41** could be accessed *via* ketone **10** (**Scheme 55**), which had previously been synthesised in an alternative route (*vide supra*). It was reasoned that the cyclisation onto the epoxide would allow access into the alternative bridged morpholine **42**.



Scheme 55

Pleasingly, the epoxide was successfully synthesised in moderate yield *via* a Corey Chaykovsky reaction, as shown in **Scheme 56**, **Table 15**.[15]



Scheme 56

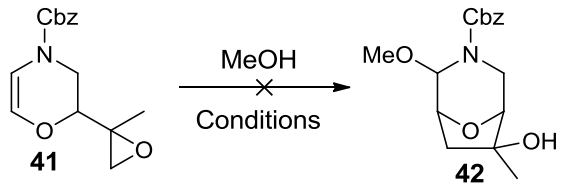
Entry	*Scale (mmol)*	*Yield (%)*
1	0.38	66
2	0.65	53

Table 15

2.4 Epoxide Cyclisation

With the epoxide successfully synthesised, efforts could be made towards establishing a cyclisation protocol to form the bridged morpholine. As methanol is required as the nucleophile in this reaction, it was decided to perform the reaction with methanol as the solvent (**Scheme 57**). In the initial attempt, the reaction mixture was heated to reflux in an oil bath for 26 h. Unfortunately, after this time, only starting material was observed by TLC analysis. In an attempt to promote the cyclisation, the reaction mixture was transferred to a microwave vial and MWI was utilised. Accordingly, the reaction mixture was heated to 70 °C for 30 min, however, after this time, only the epoxide was observed by TLC analysis. The reaction temperature was then increased to 90 °C, and the reaction mixture was irradiated at this temperature for a further 1 h. Again, after this time, only starting material was observed by TLC analysis. The reaction temperature was further increased to 110 °C for 1 h. After 1 h a new spot was observed by TLC analysis, therefore the reaction

was stopped and the mixture was purified. Unfortunately, it was discovered that the desired cyclisation had not occurred, and instead, methanol had opened the epoxide ring which resulted in the formation of alcohol **43** (**Figure 6**) in a 46% yield (along with 30% recovered starting material).



Conditions: thermal, 65 °C, 26 h, then MWI, 70 °C - 110 °C, 2.5 h

Scheme 57

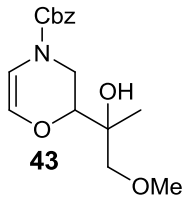
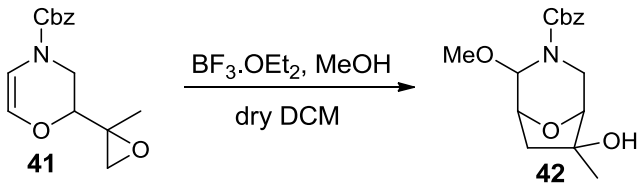


Figure 6

In an attempt to minimise the nucleophilic attack of methanol onto the epoxide, it was decided to use only a slight excess of methanol, as opposed to using it as the solvent. Additionally, it was decided to attempt to activate the epoxide with the Lewis acid, boron trifluoride diethyletherate (**Scheme 58**). Under these conditions it was again discovered that the epoxide was being opened by methanol (60% yield obtained), with none of the desired cyclised product being formed (**Table 16**, **Entry 1**). In an attempt to eradicate the formation of **43**, a reaction was performed whereby the Lewis acid was added at the start of the reaction, and once no starting material was observed by TLC analysis, the reaction would be quenched with methanol. It was hypothesised that in the absence of methanol, only the cyclisation pathway would be able to occur, with methanol merely being added at the end of the reaction to quench the iminium ion formed during the cyclisation. When the reaction was

performed under these conditions, no starting material was observed by TLC analysis after 16 h, after which time methanol was added. Disappointingly, after purification by column chromatography, no product of value was recovered from the reaction mixture (**Entry 2**).

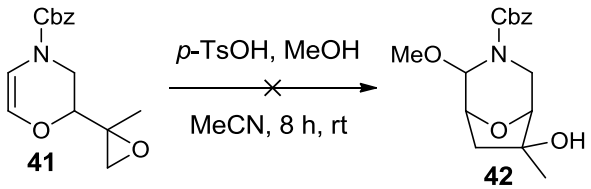


Scheme 58

Entry	*Conditions*	*42 Yield (%)*	*43 Yield (%)*
1	MeOH added at start	-	60
2	MeOH added as a quench	-	-

Table 16

In a final attempt to promote the cyclisation, *p*-toluenesulfonic acid was utilised as an epoxide activator (**Scheme 59**). Both the acid and methanol were added at the start of the reaction, however, after 4 h, only epoxide **41** was observed by TLC analysis. Consequently, a further 0.2 eq. of *p*-toluenesulfonic acid was added. TLC analysis revealed that after a further 4 h no epoxide was present, however, it was found that neither **43** nor the desired product **42** were formed, with only degradation of the starting material being observed.



Scheme 59

At this stage in the project it seemed as though the cyclisation onto both the α,β-unsaturated ester and epoxide would continue to be challenging tasks. With this in mind, it was decided that it would be beneficial to use computational studies to deliver some insight into whether or not the desired cyclisations would indeed be possible or, indeed, fundamentally disfavoured.

2.5 Computational Studies

In collaboration with AstraZeneca, it was decided that computational studies would be utilised to establish how the perceived energy changes during the cyclisation reactions.[16] In order to obtain this information, three sets of calculations were performed. Initially, the low energy conformation of each structure had to be calculated (**A** in **Figure 7**). Following on from this, a structure whereby the distance between the reacting carbon and electrophilic unit was fixed to 2.7 Å was calculated (structure **B**). Finally, a calculation was carried out whereby the distance, in steps of 0.1 Å until 1.4 Å, of the two reacting units was compressed and plotted with how the energy varies (**C**).

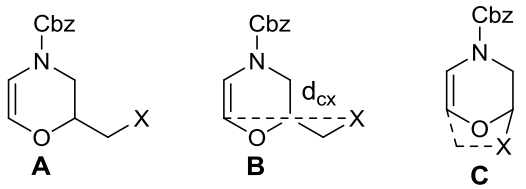


Figure 7

In relation to the epoxide substrate, it was decided to calculate the epoxide with and without the methyl group present (**Figure 8**, **41** and **44**, respectively). The epoxide without the methyl group could be accessed *via* an epoxidation of aldehyde **34**, which would allow access into an alternative bridged morpholine structure (**Scheme 60**). In addition to the α,β-unsaturated ester and epoxides, the calculations for two alternative bridged morpholine precursors were also performed. These alternative

analogues were aldehydes **45** and **46** (again one substrate with the methyl, and one without), as it was reasoned that they could also be potential precursors for bridged morpholines. The calculations on the substrates shown were performed based upon the cyclisation reactions being carried out without any acid activation present.

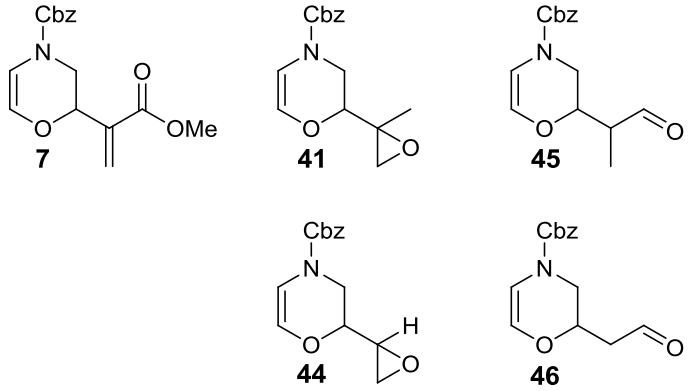
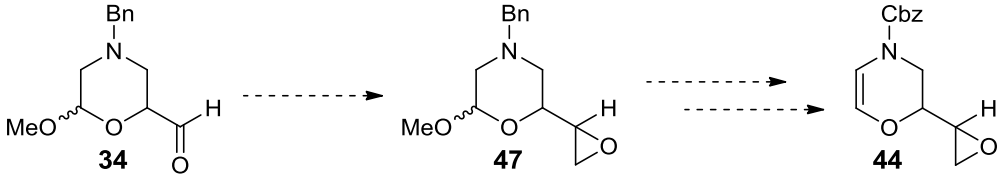


Figure 8



Scheme 60

In addition to the substrates mentioned above, a calculation was also performed for the successful oxabispidine cyclisation, which involves attack onto a protonated imine (**48**) (see **Figure 9**). This would allow a comparison to be made between a reaction that is known to be successful, against those that have so far been unattainable, or yet to be performed experimentally. Finally, in addition to the protonated imine, the calculations were also performed on the unactivated form of the imine (**49**) (**Figure 9**).

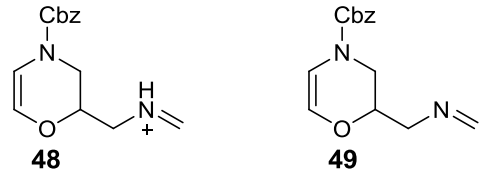


Figure 9

For the majority of the substrates the calculations were performed twice, once with the electrophilic unit over the ring, and the other with the unit facing away from the ring. The reason for doing this was to deduce whether or not the positioning of the reacting unit affected the cyclisation. An example of this is shown in **Figure 10** for the non-methylated aldehyde substrate. For full details on all substrates analysed see the **Appendix** section.

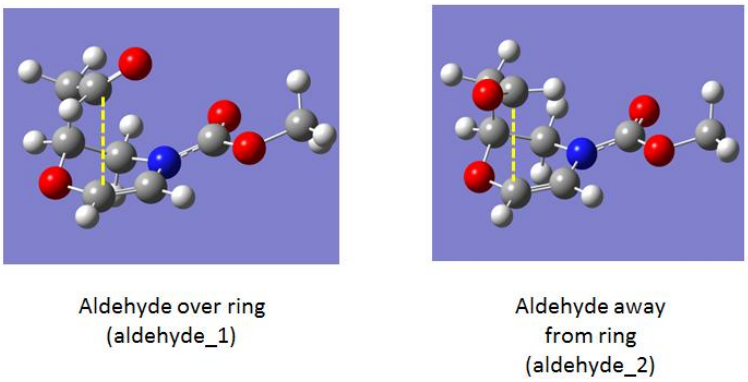


Figure 10

Following the calculations, a plot of energy vs distance was constructed. **Figure 11** shows that the energy required for each of the cyclisations to make the bridged morpholines is significantly higher than that of the protonated oxabispidine precursor (iminium ion). Interestingly, the energy required for the unactivated oxabispidine precursor (imine) to cyclise is similar to that of the other substrates considered as part of this programme of work. This shows that for oxabispidine formation to occur, activation of the imine may be crucial. Due to the significant change in the energy

between the activated and unactivated reactions it was decided to repeat the calculations but this time use the activated form of each individual substrate.

It should also be noted that for each substrate after the energy has decreased the energy starts to increase again. The reason for this increase is that bond formation has occurred, but distance between the atoms is still being decreased, and therefore the atoms are being pushed closer together than their equilibrium bond distance. Indeed, van der Waals repulsion starts to occur, which causes the energy to increase.

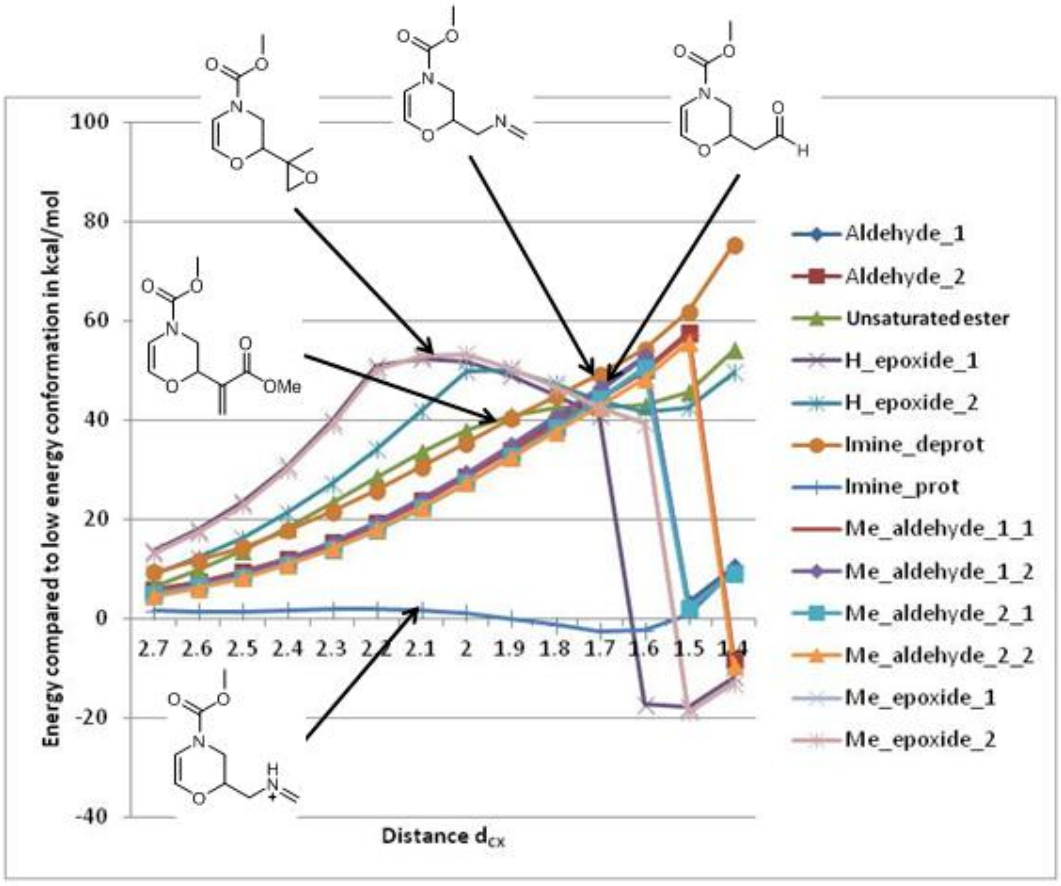


Figure 11

It can be seen from **Figure 12** that for the α,β-unsaturated ester substrate there is a significant drop in energy when the α,β-unsaturated ester is activated. Having said this, the energy is still higher than that calculated for the activated oxabispidine precursor, which requires an equivalent of triflic acid for the reaction to proceed.

Indeed, the same was shown to be true for the epoxide; the energy of the activated substrate drops, but is still appreciably higher than that of the protonated imine.

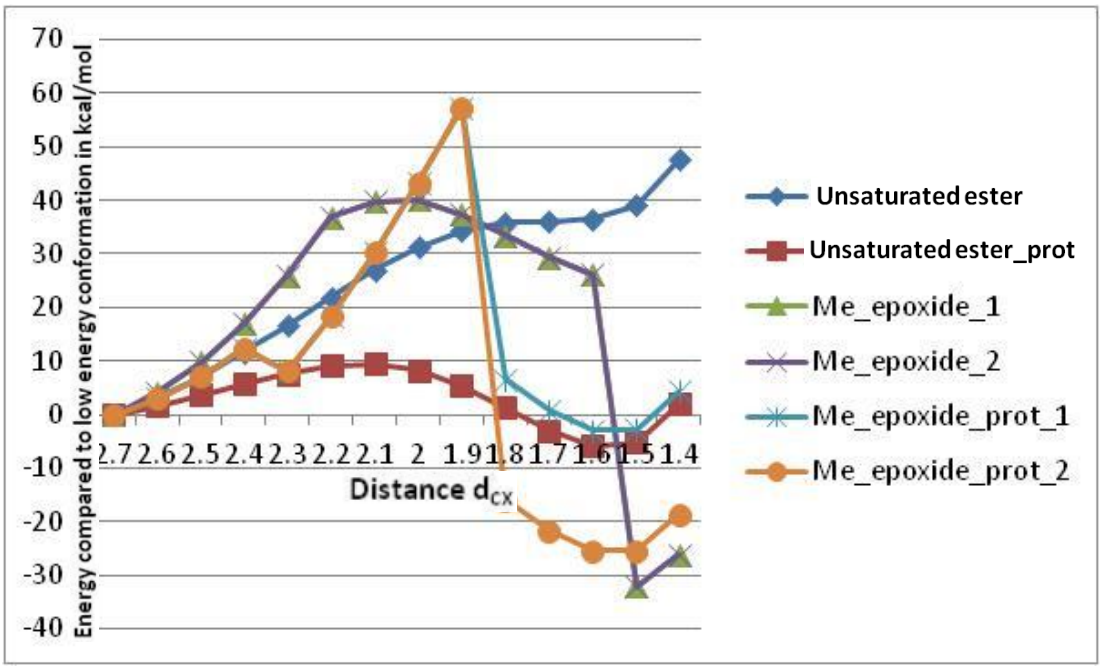
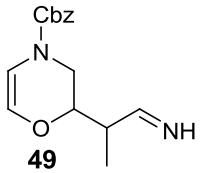


Figure 12

The energies of the non-protonated and the protonated aldehyde were also calculated. In addition to the aldehyde, the protonated and non-protonated version of the imine shown in **Figure 13** were also calculated at this stage, as this substrate could give rise to another possible bridged morpholine structure. Intriguingly, it can be seen from **Figure 14** that there is a significant decrease in energy for both substrates in the activated form. The aldehyde appears to be the most promising substrate to cyclise, as these calculations predict that this substrate should require less energy than that required for the protonated imine for the oxabispidine synthesis. It was for this reason that the aldehyde was the next substrate targeted as part of this synthesis programme.



49

Figure 13

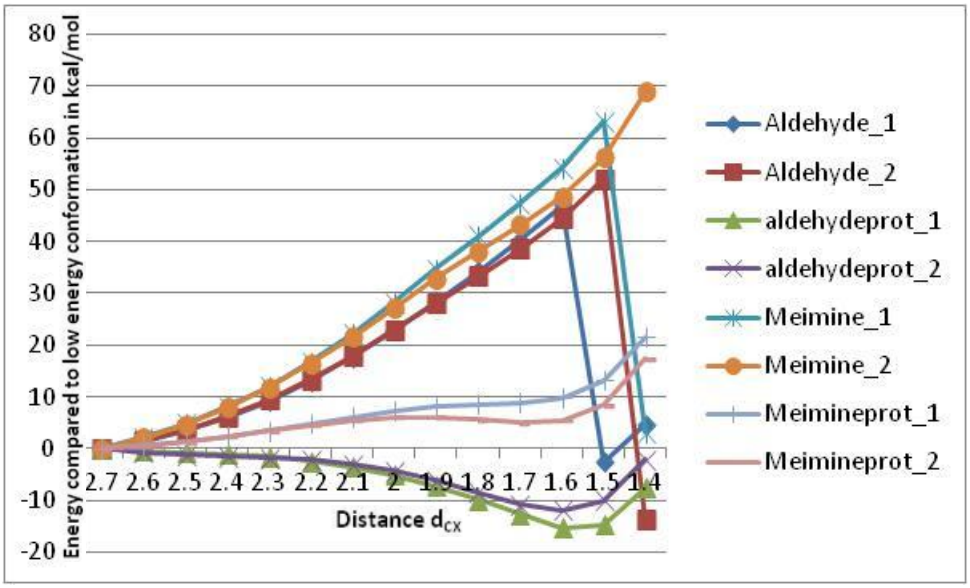
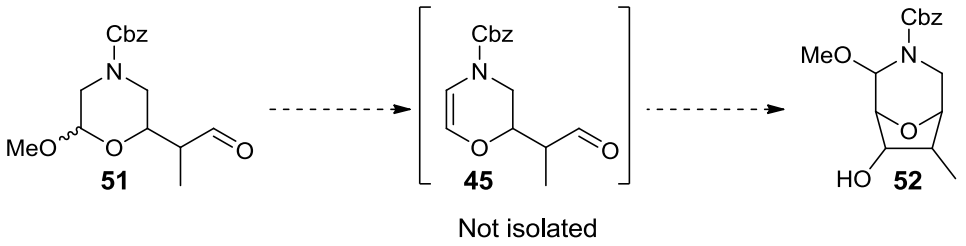


Figure 14

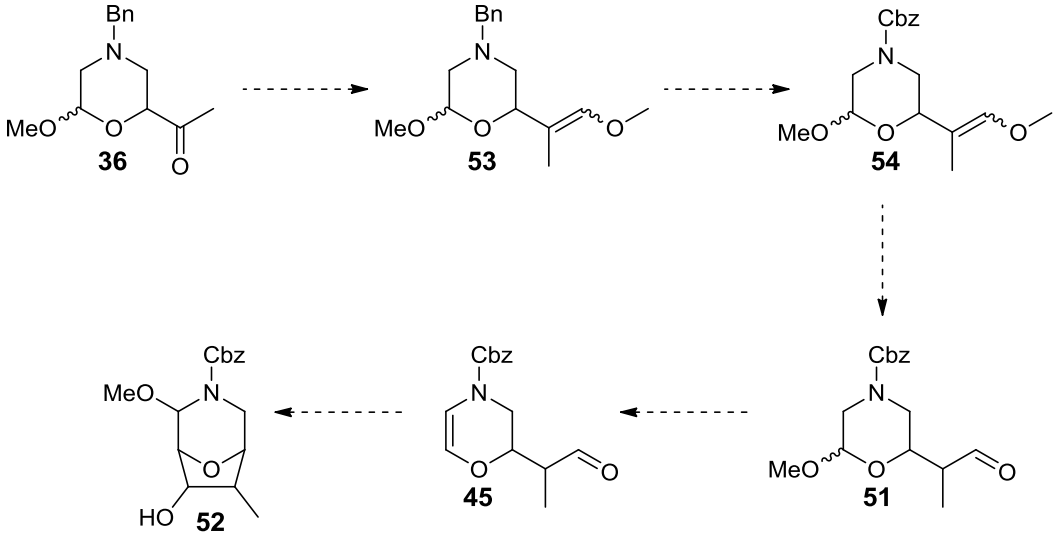
*2.6 Synthesis of Aldehyde **45***

It was decided that the initial attempt at synthesising the desired aldehyde moiety would be prior to the double bond installation i.e. compound **51**. The reason for this choice was that it was envisaged that under the acidic conditions used for the double bond installation, the cyclisation onto the protonated aldehyde may occur within the same reaction pot, as illustrated in **Scheme 61**.



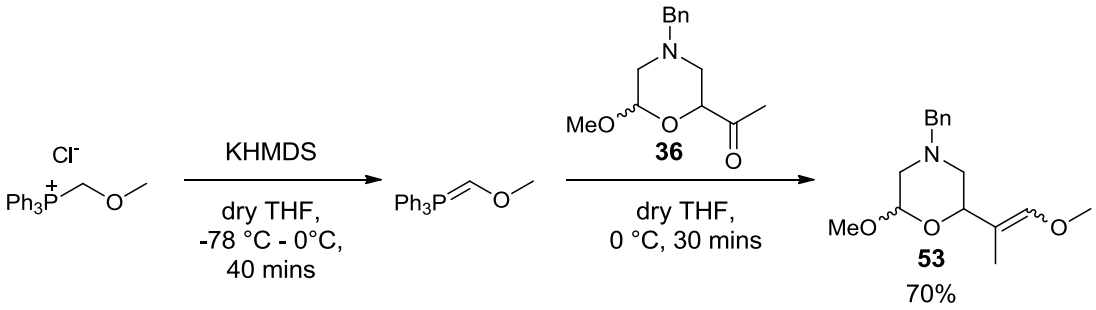
Scheme 61

The proposed synthetic route to the desired aldehyde, which would incorporate the potential for the above one-pot process, is shown in **Scheme 62**. It was thought that the pathway could begin with the previously synthesised ketone **36** with a methoxy Wittig reaction being explored to form enol ether **53**. This enol ether could then undergo a hydrolysis reaction to form aldehyde **51**. As previously mentioned, under acidic conditions the benzyl protected amine would be too basic and therefore would become protonated, which would inhibit the hydrolysis of the enol ether. In order to allow the hydrolysis to occur under acidic conditions, the protecting group exchange would have to be performed first. With the aldehyde and carboxybenzyl functionality in place, the last step would involve the double bond installation to form the bridged morpholine precursor, followed by a cyclisation to deliver the desired target scaffold. At this stage it was not known if the hydrolysis of the enol ether could occur in the presence of the acetal functionality (**54** to **51**).



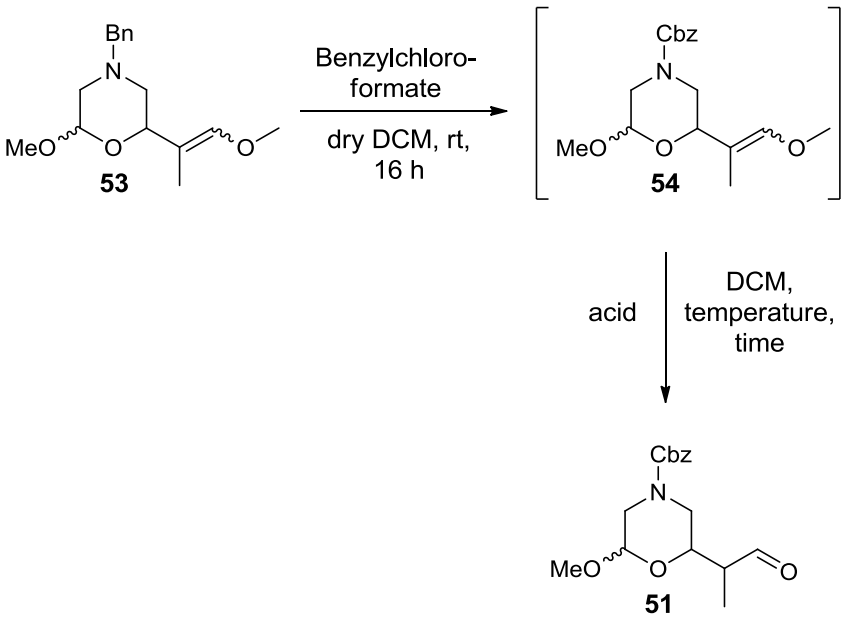
Scheme 62

Pleasingly, the Wittig reaction to form enol ether **53** was successful, with the desired product being obtained in a good yield (**Scheme 63**).



Scheme 63

As mentioned previously, when using catalytic acidic conditions in the presence of the benzyl amine, the nitrogen becomes protonated and inhibits any other reaction from taking place, therefore the amine protecting group has to be switched. In order to hydrolyse the enol ether under acidic conditions, the protecting group switch to the carboxybenzyl group had to be performed initially (**Scheme 64**). This protecting group switch was carried out successfully, and as benzyl chloride was the only by-product it was decided not to isolate **54**. *p*-Toluenesulfonic acid was added to the reaction and after 2 h a new spot appeared by TLC analysis, with no starting material being observed. After purification by column chromatography, it was discovered that the morpholine ring had opened to form **55** (see **Figure 15**) in an 82% yield (**Table 17**, **Entry 1**). In an attempt to suppress the formation of **55**, the reaction mixture was cooled to -20 °C prior to the addition of the *p*-toluenesulfonic acid. After 2 h at -20 °C all starting material had reacted, however, the undesired bisaldehyde **55** had formed and was isolated in a 75% yield (**Entry 2**). The milder trifluoroacetic acid was employed next, however, as in the previous reaction, **55** was observed by TLC analysis (**Entry 3**). Finally, the less acidic oxalic acid was then utilised for the hydrolysis, however, again the undesired intermediate **55** was formed (**Entry 4**).



Scheme 64

Entry	***Acid***	***Temperature (°C)***	***Time (h)***	***Yield 51 (%)***	***Yield 55 (%)***
1	*p*-toluenesulfonic acid	rt	2	-	82
2	*p*-toluenesulfonic acid	-20	2	-	75
3	Trifluoroacetic acid	rt	2	-	N/A[a]
4	Oxalic acid dihydrate	rt	3	-	N/A[a]

[a] Observed by TLC analysis

Table 17

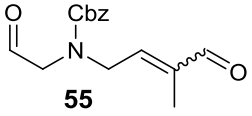
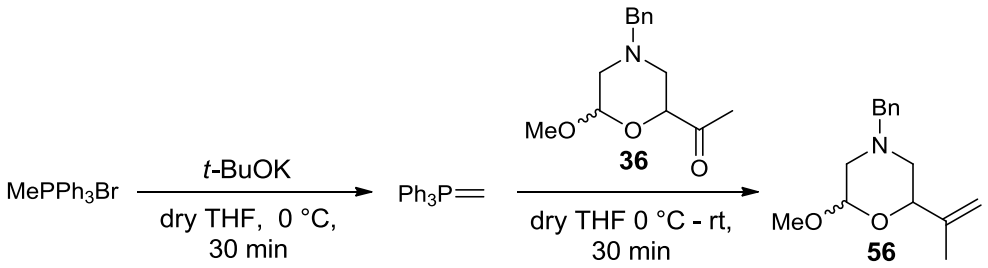


Figure 15

Since the hydrolysis to form aldehyde **51** proved to be unsuccessful, it was envisaged that a more stepwise approach to this intermediate could be employed. In this regard, a standard Wittig reaction could be implemented to form alkene **56**, which could then undergo a hydroboration-oxidation to provide access to intermediate **57**. Finally, oxidation of the alcohol would yield the desired aldehyde **58** (**Scheme 65**).

Scheme 65

The initial step in this new synthetic pathway proved to be successful as alkene **56** was isolated in high yields on a variety of scales (**Scheme 66**, **Table 18**).

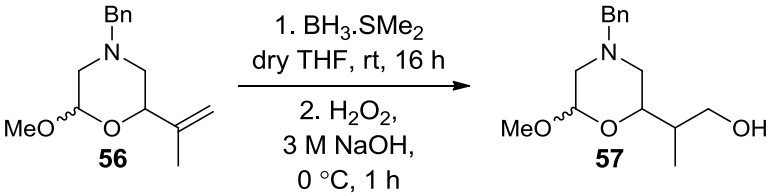


Scheme 66

Entry	*Scale (mmol)*	*Yield (%)*
1	2.0	78
2	28.1	78

Table 18

The next stage in the synthesis was the hydroboration-oxidation sequence.[17] The reaction was performed using borane dimethysulfide complex as the hydroborating reagent and, after oxidation, the desired primary alcohol (**57**) was isolated in moderate yields (**Scheme 67**, **Table 19**).

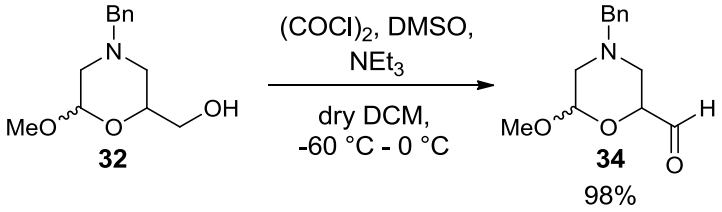


Scheme 67

Entry	*Scale (mmol)*	*Yield (%)*
1	0.4	56
2	1.6	55

Table 19

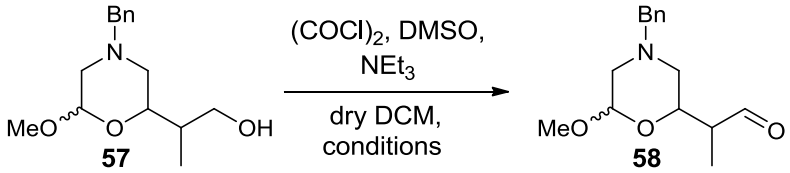
With the alcohol now in hand, the oxidation to the corresponding aldehyde could be investigated. Due to the success of oxidising substrate **32** under Swern conditions (**Scheme 68**), it was decided to use the same approach for the oxidation of **57**.



Scheme 68

As such, the initial reaction involved performing the oxidation at -60 °C, then warming the reaction to 0 °C, and subsequently purifying the resultant slurry *via* column chromatography. Under these conditions, the reaction did not proceed to completion, with only 55% of the desired product being obtained and 31% of the starting alcohol being retrieved (**Scheme 69**, **Table 20**, **Entry 1**). In an attempt to push the reaction to completion, the reaction was left stirring for 16 h at room temperature (**Entry 2**), however, the reaction remained incomplete. Having said this, the desired aldehyde was obtained in a moderate 61% yield from this reaction. In an attempt to drive the reaction to completion, the equivalents of each reagent were

increased. Unfortunately, increasing the equivalents of all the reagents appeared to have a detrimental effect on the reaction, as only 36% of the desired aldehyde was obtained with no starting material being recovered (**Entry 3**).



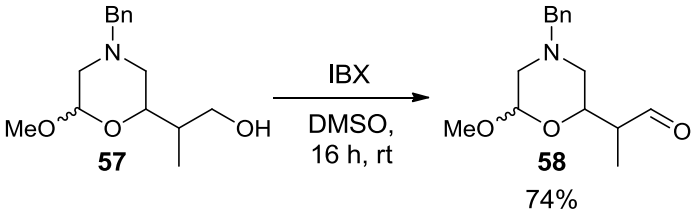
Scheme 69

Entry	***Conditions***	***Yield 58 (%)***	***57 (%* recovered)**
1[a]	-60 °C - 0 °C, 30 min	55	31
2	-60 °C – rt, 16 h	61	33
3[b]	-60 °C – rt, 16 h	36	0

[a] Directly purified by column chromatography; [b] Increased equivalents of all reagents

Table 20

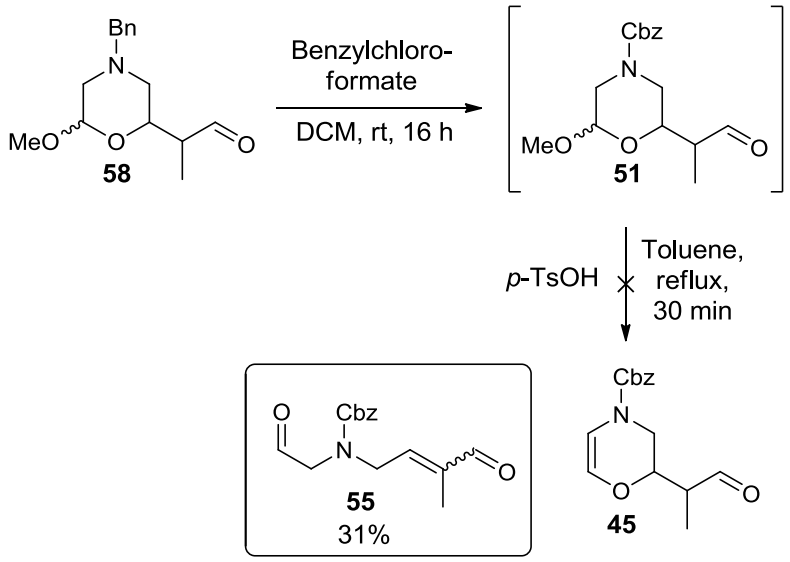
In an attempt to improve the yield of the oxidation step, IBX was investigated as a potential oxidant. Pleasingly, it was found that when employing IBX the reaction progressed to completion after 16 h, with a higher yield of 74% being obtained (**Scheme 70**).



Scheme 70

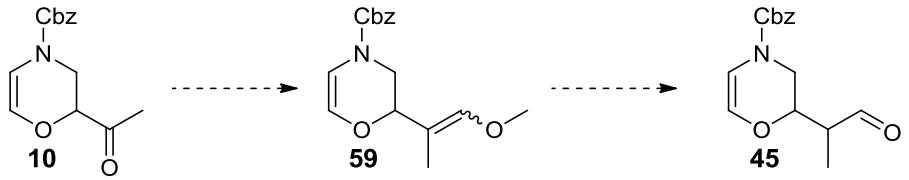
With the desired aldehyde now synthesised, the double bond installation was carried out in an attempt to deliver the requisite cyclisation precursor **45** or the bridged morpholine product **52**. As before, the protecting group switch occurred successfully

with the aldehyde functionality remaining intact, however, when the elimination reaction was attempted, frustratingly, the morpholine ring opened with the allylic bisaldehyde **55** being isolated in a 31% yield (**Scheme 71**).



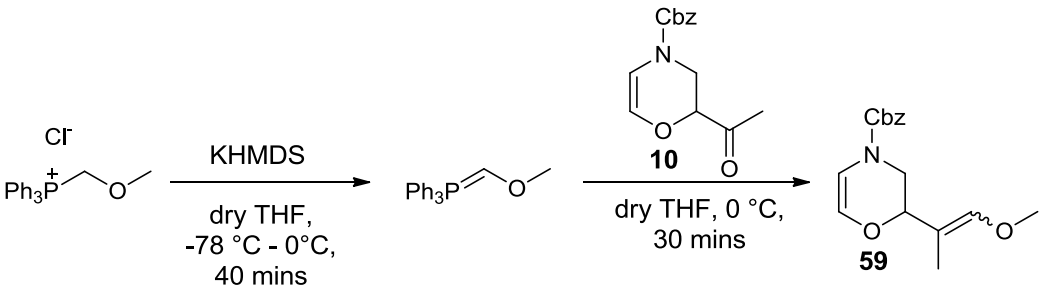
Scheme 71

With the installation of the double bond unable to take place with the aldehyde functionality already embedded within the molecule, it was decided to attempt to synthesise the aldehyde post double bond installation. Indeed, the synthesis of the aldehyde with the double bond already in place (**59** to **45**) could be investigated from a previous intermediate, ketone **10**. Initially, it was decided to carry out the methoxy Wittig reaction to form enol ether **59**, which, in turn, could be hydrolysed to the desired aldehyde **45** (**Scheme 72**).



Scheme 72

The Wittig reaction to form enol ether **59** was successful with the desired product being obtained in moderate to good yields (**Scheme 73**, **Table 21**).

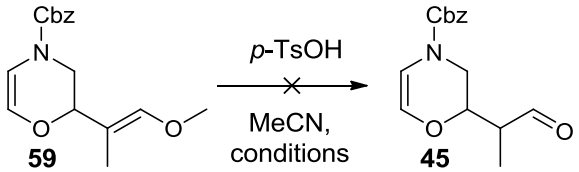


Scheme 73

Entry	*Scale (mmol)*	*Yield (%)*
1	0.90	71
2	1.76	55

Table 21

With the enol ether in hand, the hydrolysis was attempted using *p*-toluenesulfonic acid (**Scheme 74**). When using catalytic amounts of the acid no starting material was observed by TLC analysis after just 30 min. Having said this, following purification *via* column chromatography, none of the desired aldehyde was isolated (**Table 22**, **Entry 1**). It was possible that under these reaction conditions a one-pot process was taking place, i.e. the aldehyde was being formed, and then the desired cyclisation onto the aldehyde was occurring. The reaction was therefore repeated with the addition of methanol to trap the potential iminium ion formed. In addition to adding methanol, the reaction mixture was also cooled to -20 °C. Disappointingly, the reaction was unsuccessful with only degradation of the starting material being observed (**Entry 2**).



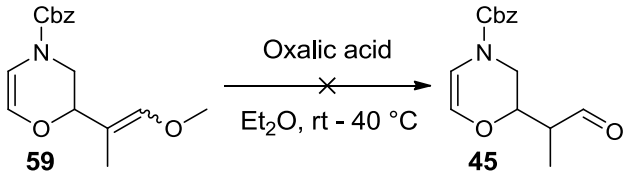
Scheme 74

Entry	*Temperature*	*Time*	*Yield (%)*
1	25 °C	30 min	-
2[a]	-20 °C	2 h	-

[a] Reaction performed with 2 eq. of MeOH

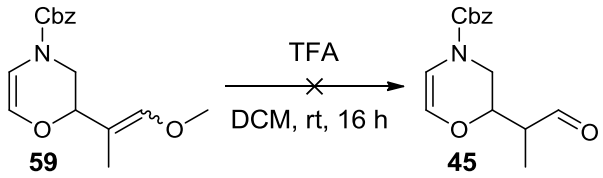
Table 22

Despite the above results, alternative acids where probed in order to facilitate the hydrolysis of **59**. In this regard, the milder oxalic acid was employed (**Scheme 75**). After the reaction had been stirring for 6 h (with 0.1 eq. of acid) the enol ether was the only spot observed by TLC analysis, therefore an additional 0.1 eq. of oxalic acid was added, and the reaction mixture was stirred for a further 16 h. After this time, again, only starting material was observed by TLC analysis. In order to try and promote the hydrolysis, the reaction mixture was heated to 40 °C for a further 16 h. Disappointingly, heating the reaction mixture appeared to have no effect on the hydrolysis as, again, only the enol ether was observed by TLC analysis. The reaction mixture was then stirred for 72 h at ambient temperature, however, only starting material was present. In an attempt to promote the desired reaction, a further 0.3 eq. of oxalic acid was added to the reaction mixture and the reaction was heated to 40 °C for 16 h, however, only the enol ether was present. In a final attempt to initiate the reaction, a further 0.5 eq. of oxalic was added and the reaction was stirred at 40 °C for a further 36 h. After the 36 h all that appeared to be in the reaction mixture was the enol ether. To determine if the enol was degrading under these conditions, the reaction was quenched and purified by column chromatography. An 87% return of the enol ether (**59**) was obtained, showing that the enol ether was too stable to oxalic acid.



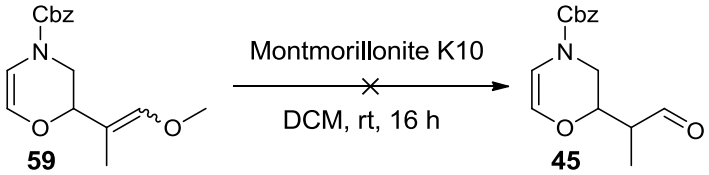
Scheme 75

With oxalic acid proving too mild to induce hydrolysis, the more acidic trifluoroacetic acid was investigated next (**Scheme 76**). Disappointingly, the reaction was unsuccessful as the starting material appeared to degrade under these conditions.



Scheme 76

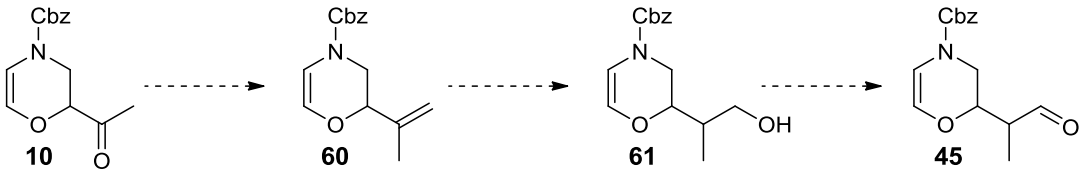
In a final attempt to yield aldehyde **45** *via* this synthetic pathway, the acid clay Montmorillonite K10 was employed (**Scheme 77**).[18] Again, all that appeared to occur was degradation of the starting material.



Scheme 77

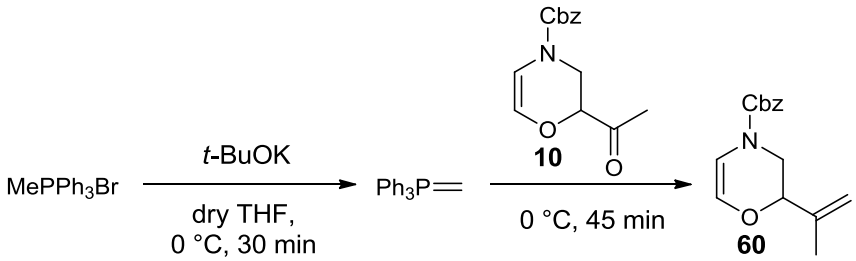
As the acidic conditions employed to hydrolyse the enol ether seemed to be too harsh, an alternative route into the desired aldehyde was required. In this regard, a new route to the same aldehyde intermediate was devised, as shown in **Scheme 78**. This alternative route, with the double bond embedded, involved a standard Wittig reaction on ketone **10**, followed by a hydroboration-oxidation sequence to produce

primary alcohol **61**. This alcohol could then be subjected to oxidation conditions to provide access to the desired aldehyde **45**.



Scheme 78

In order to probe this new route, the initial Wittig reaction to install the requisite double bond for the hydroboration step was performed. The installation of the double bond proved to be successful, with desired product **60** being isolated in good yields (**Scheme 79**, **Table 23**).



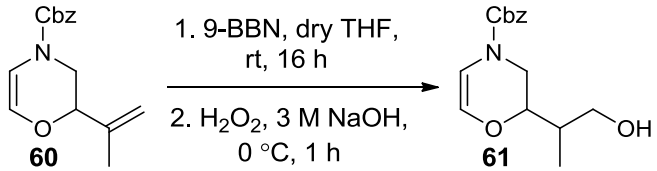
Scheme 79

Entry	*Scale (mmol)*	*Yield (%)*
1	0.77	69
2	11.9	87

Table 23

With the olefin in hand, the hydroboration-oxidation reaction could be investigated.[17] Pleasingly, when using 9-BBN as the hydroborating reagent, the desired primary alcohol was isolated in appreciable yields after oxidation (**Scheme 80**, **Table 24**). However, it is important to note that, depending on the quality of the 9-BBN solution, an impurity was sometimes observed by TLC analysis. It was found that

when the work-up was carried out, the organic phase contained peroxides (determined by the use of starch iodide paper), therefore, if this impurity was observed an alternative work up was carried out which removed this unknown peroxide. The alternative work-up involved mixing the organic layer of the reaction mixture with a saturated aqueous solution of sodium metabisulfite, which successfully removed this impurity (see **Experimental Section** for full details). It should also be noted at this stage that the diastereoselective outcome of this reaction will be discussed later.



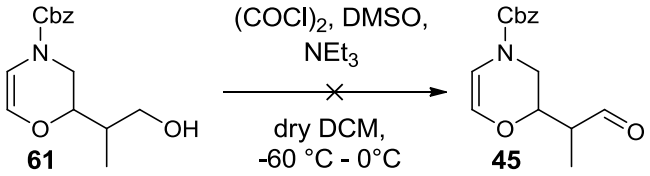
Scheme 80

Entry	*Scale (mmol)*	*Yield (%)*
1	0.41	65
2	4.24	82

Table 24

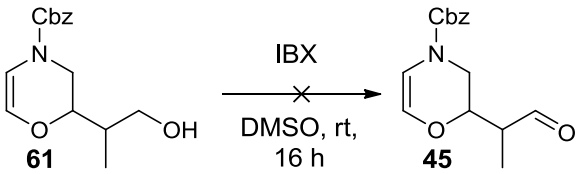
With the hydroboration-oxidation reaction proving successful, efforts turned again, towards introducing the aldehyde functionality. The first oxidation method investigated was the Swern oxidation. The initial reaction investigated involved performing the oxidation at -60 °C, then warming the reaction to 0 °C, and purifying the slurry by column chromatography, as this has shown to be successful previously when synthesising an earlier intermediate aldehyde **34**. Indeed, the ^{1}H NMR of the product from this reaction indicated an aldehyde peak (9.76 ppm), however, the NMR also contained many unidentifiable peaks which did not appear to correlate to the desired product. In addition to this, the olefinic protons did not integrate properly (1.2H instead of 2H). At this stage, it was unclear whether the aldehyde, once

isolated, was unstable, or whether the aldehyde was unstable to the reaction conditions being utilised. It was also possible that the aldehyde was not stable to column chromatography, therefore, it was proposed that a reaction should be performed whereby the aldehyde was not purified by column chromatography. When the oxidation was repeated, the reaction mixture was warmed to 0 °C and was simply worked up rather than purified *via* column chromatography. Unfortunately, the ^{1}H NMR of the material isolated was the same as with the previous reaction, suggesting that the product was not stable to the Swern conditions being employed.



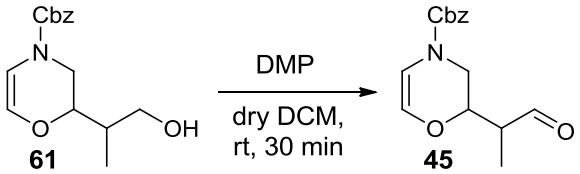
Scheme 81

Due to the unsuccessful Swern reactions, IBX was investigated as an alternative oxidising agent (**Scheme 82**). Unfortunately, this protocol also proved to be unsuccessful as none of the desired aldehyde or the alcohol were obtained from the reaction mixture.



Scheme 82

Despite these unsuccessful results, it was decided to use the milder oxidant DMP to promote the aldehyde formation. Under these alternative oxidation conditions it was pleasing to access aldehyde **45** in a good yield (**Table 25**, **Entry 1**). In an attempt to improve the chemical yield, the reaction temperature was decreased to 0 °C. When performing the oxidation at this lower temperature, the reaction took 5 h to proceed to completion, with a lower yield being obtained (**Entry 2**).



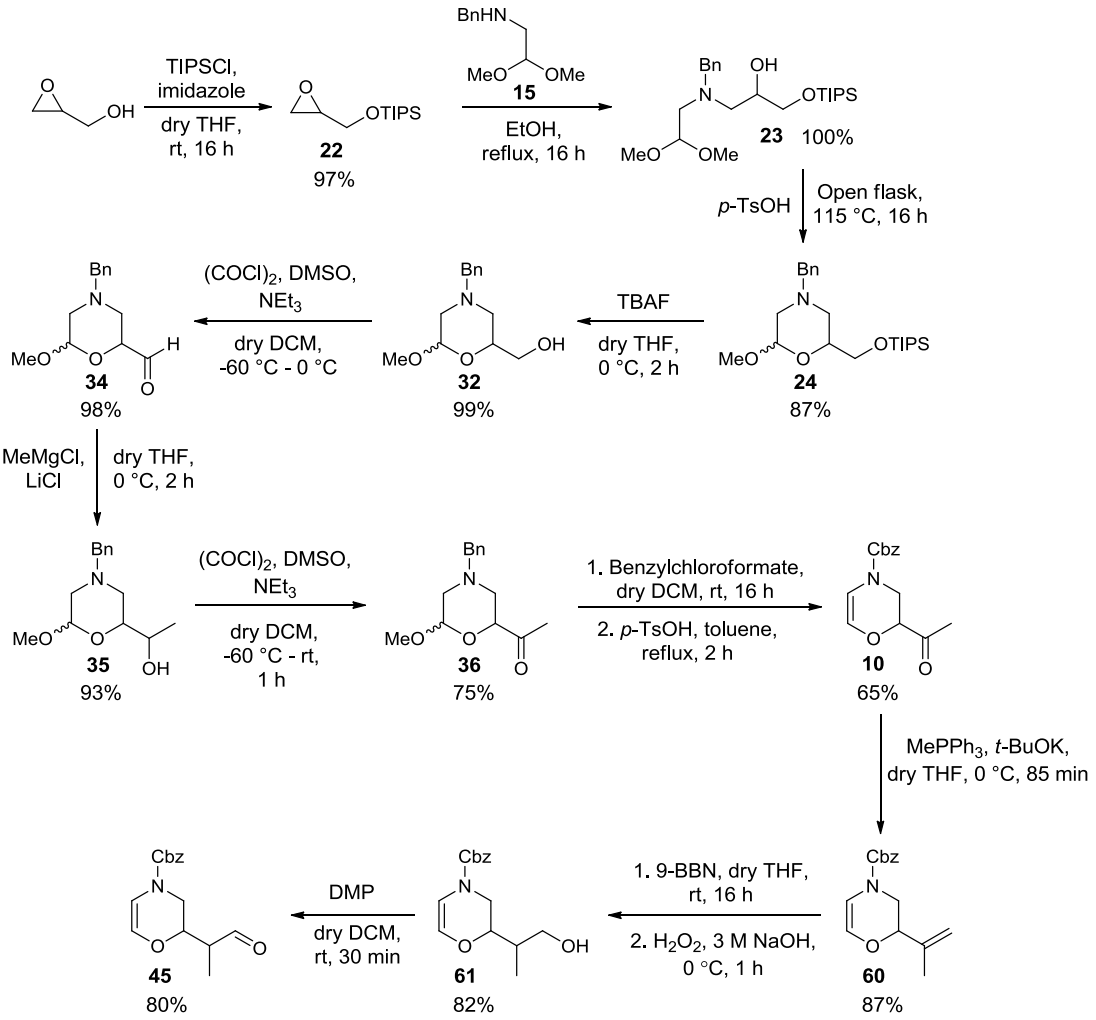
Scheme 83

Entry	*Scale (mmol)*	*Yield (%)*
1	1.01	80
2[a]	0.88	62

[a] Reaction performed at 0 °C for 5 h

Table 25

At this stage in the project we were pleased to have finally synthesised aldehyde **45**, which was required for the synthesis of the desired bridged morpholine. As with the route to the α,β-unsaturated ester **7**, it was discovered that the order in which the reactions were performed was key to being able to isolate aldehyde **45**. As well as having synthesised this key intermediate, a robust and reproducible route to the aldehyde had been developed (**Scheme 84**), therefore attention could turn to the final cyclisation step.

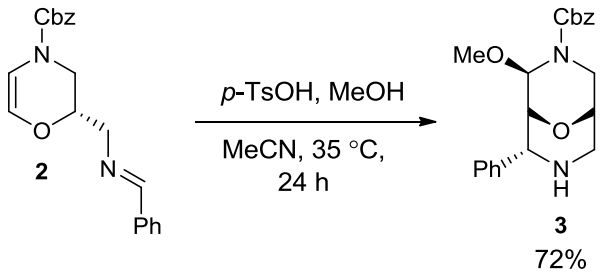


Scheme 84

2.7 Aldehyde Cyclisation

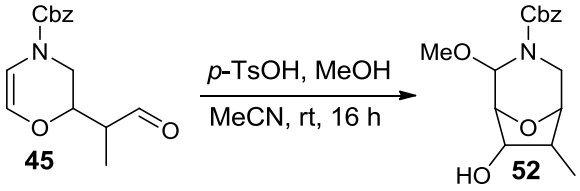
As it was shown in the computational studies, the energy for the cyclisation significantly decreased when the aldehyde was protonated. As such, it was decided to perform the initial reaction under acidic conditions. Within the oxabispidine synthesis, it had been shown that the cyclisation of **2** could occur with a catalytic amount of *p*-toluenesulfonic acid, along with heating the reaction slightly for 24 h (**Scheme 85**).[19] Due to the energy profile of the bridged morpholine cyclisation appearing to be more favourable than the oxabispidine cyclisation (**Computational**

Studies section), it was proposed that the initial reaction investigated should utilise catalytic amounts of *p*-toluenesulfonic acid at ambient temperature.



Scheme 85

It was to great delight, with the use of 0.1 eq. of *p*-toluenesulfonic acid, the reaction proceeded to completion after 16 h at ambient temperature, with good yields of the novel bridged morpholine compound **52** being obtained (**Scheme 86**, **Table 26**). It should be noted that the stereochemical outcome of this reaction will be discussed later.



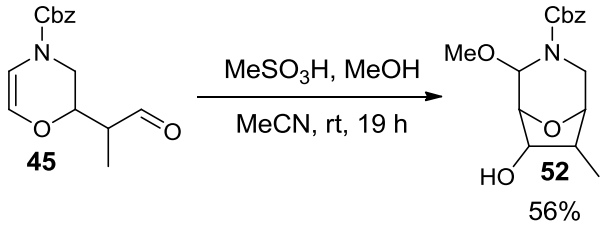
Scheme 86

Entry	*Scale (mmol)*	*Yield (%)*
1	0.45	58
2	0.81	67

Table 26

In an attempt to improve the yield, the milder acid, methanesulfonic acid, was investigated (**Scheme 87**). After 16 h at ambient temperature, with 0.1 eq. of the acid, the reaction had not gone to completion, therefore a further 0.1 eq. of acid was

added to the reaction mixture. After stirring the reaction for an additional 3 h, no starting material was observed by TLC analysis. Whilst the desired product was obtained, this protocol did not deliver any improvement in terms of chemical yield.



Scheme 87

2.8 Relative Stereochemistry

It was revealed through detailed NMR studies that a mixture of diastereomers (7:3) was produced from the cyclisation of the aldehyde, as well as a set of rotamers for each diastereomer being observed. Evidence from NOESY NMR experiments revealed that within the major diastereomer (**52a**) the bridging oxygen, the methoxy group, the methyl group, and the alcohol moiety were all positioned on the same face of the molecule (**Figure 16**). Alternatively, it was identified that the minor diastereomer (**52b**) had the alcohol functionality on the opposite face.

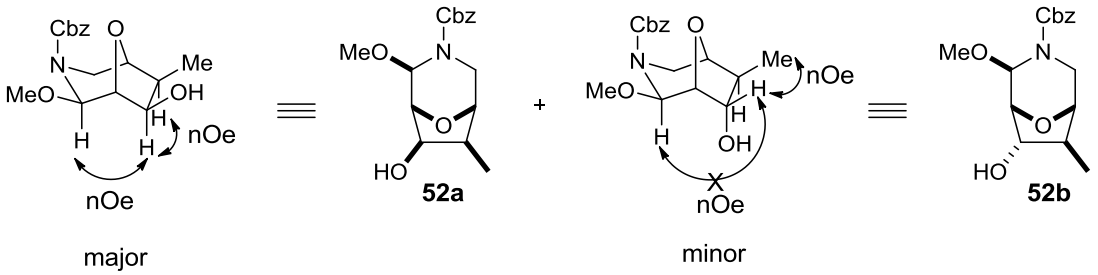
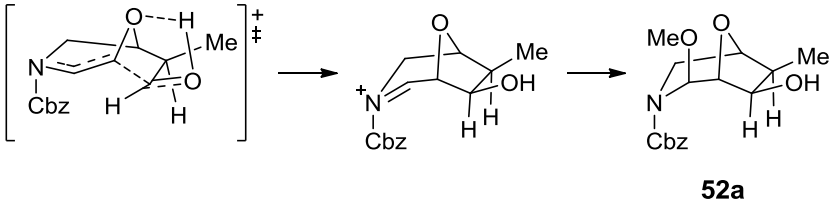


Figure 16

In order to explain the stereochemistry obtained from the cyclisation onto the protonated aldehyde, the transition state depicted in **Figure 17** was proposed. In this model, neighbouring interaction with the bridging morpholine oxygen could lead to

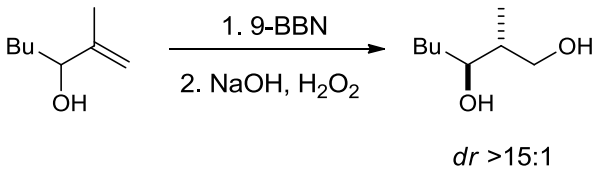
conformational restriction of the activated aldehyde and, in turn, led to the major diastereomer. It was proposed that the stereoselectivity is partially lost due to competing interactions between the methyl group and the activated carbonyl, leading to formation of the minor diastereomer. Following cyclisation, methanol approaches on the least hindered face of the resultant iminium ion.



52a

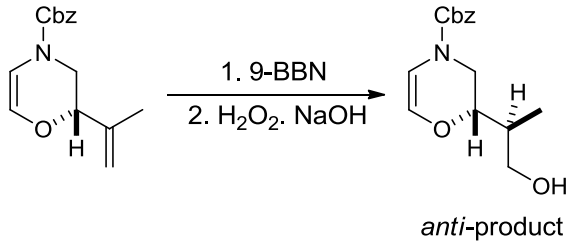
Figure 17

In an attempt to explain the methyl group being set, it was proposed that the hydroboration must proceed in a facially selective manner. Indeed, Still and Barrish showed that the hydroboration of 1,1-disubstituted allylic alcohols and ethers occurred with high levels of diastereoselectivity, whereby the *anti*-product was the major product formed (**Scheme 88**).[20] Within the bridged morpholine synthesis, the *anti*-product was also observed as the major product (**Scheme 89**).



dr >15:1

Scheme 88



anti-product

Scheme 89

The model which Still and Barrish proposed led to the observed diastereoselectivity is shown in **Figure 18**. There are three minimum energy conformations of the starting allylic alcohol that first of all need to be considered (**A1**, **A2** and **A3**). It was proposed that one of the lowest energy conformers would be **A1**, which would be expected to be the most reactive since it would lead to a transition state (**B** or **C**) which has the smallest substituent (H) over the transition state ring. It was then proposed that the borane must approach from the least hindered side of the olefinic π system, leading to the less sterically encumbered transition state, and thus leading to the *anti*-product.[20]

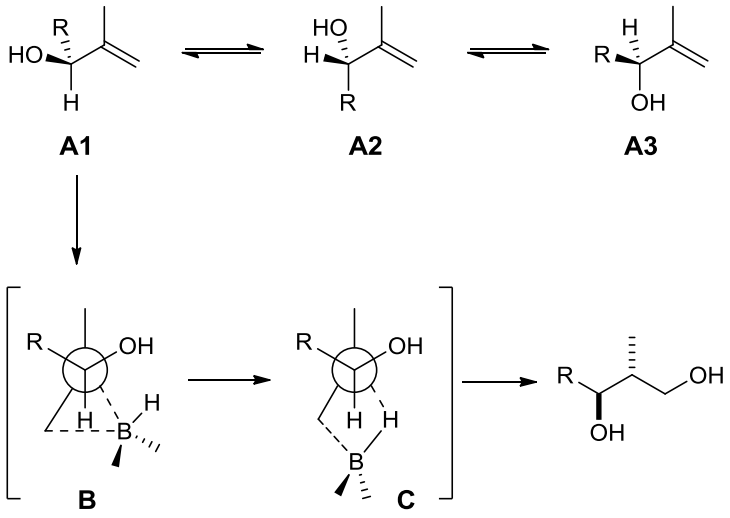


Figure 18

Based on the Still and Barrish model, the transition state which would lead to the observed *anti*-product within the bridged morpholine synthesis is shown in **Figure 19**. As with their model, the transition state shown has the smallest substituent (H) over the transition state ring. The borane would also approach the less hindered side of the olefinic π system, leading to the less sterically encumbered transition state, and thus leading to the observed *anti*-product.

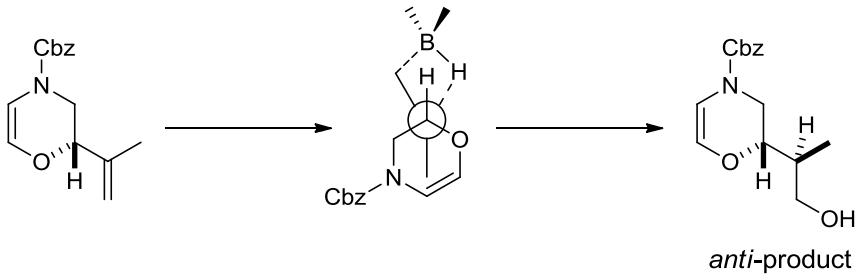
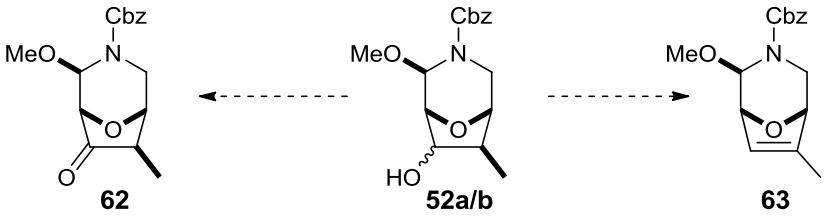


Figure 19

*2.9 Further Functionalisation of Bridged Morpholine **52a** and **52b***

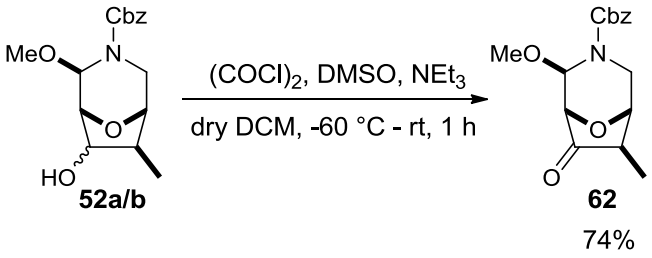
As discussed in the introductory section, there are a lack of generalised routes into the bridged morpholine scaffold which allows for diversification, therefore, we wanted to show that the route developed allowed for a range of bridged morpholines to be synthesised. In this regard, it was decided to further functionalise alcohols **52a** and **52b**, as it was proposed that the alcohol could serve as an intermediate for the synthesis of alternative bridged morpholines. As illustrated in **Scheme 90**, one route could involve oxidation of the alcohol to produce ketone **62**, with another being the elimination of the alcohol functionality to install a double bond (**63**). Ketone **62** would also allow for further functionalisation by reaction through the carbonyl group to allow access to heavier substituted derivatives. In addition, compound **63** would be an intriguing scaffold which could undergo further functionalisation.



Scheme 90

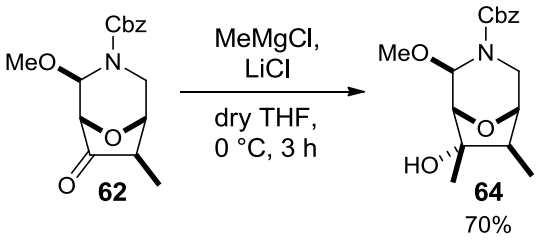
*2.9.1 Oxidation of Bridged Morpholines **52a** and **52b***

The first pathway to be investigated was the oxidation of alcohols **52a** and **52b** to the corresponding ketone. In this regard, the 7:3 mixture of the alcohols successfully underwent oxidation to provide ketone **62** in a moderate yield of 74% under Swern conditions (**Scheme 91**).



Scheme 91

As discussed, to further illustrate that more late stage functionalisation can be performed using this route, ketone **62** underwent an alkylation reaction to produce the tertiary alcohol **64** in a good yield of 70% (**Scheme 92**).



Scheme 92

Again, utilising detailed NMR studies it was shown that only one diastereomer was produced under these reaction conditions. It was deduced that the Grignard must approach from the same face as the bridging oxygen and methoxy group, thereby causing the methyl group to be on the same face (**Figure 20**).

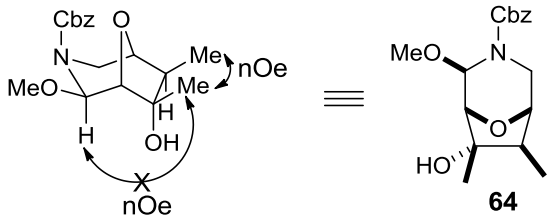
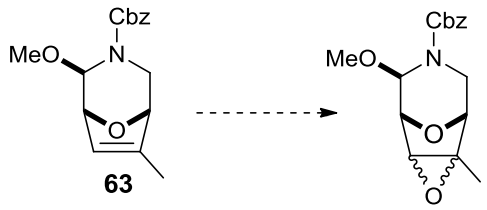


Figure 20

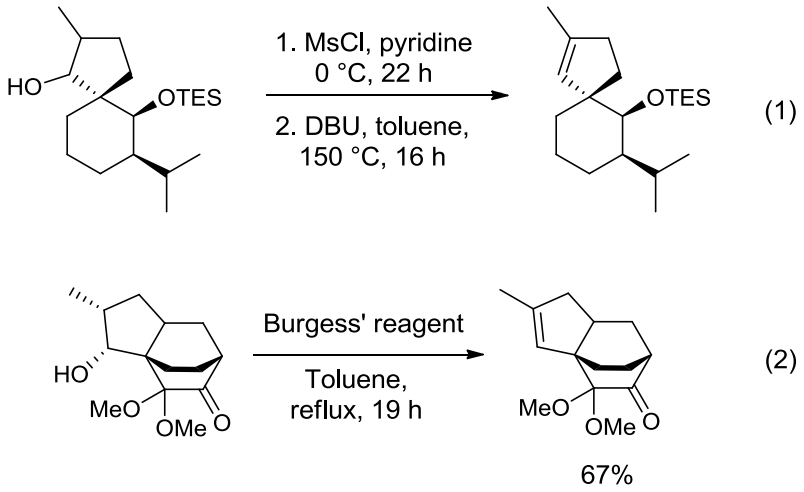
*2.9.2 Elimination of Bridged Morpholine **52a** and **52b***

Attempts were also made to allow access to the eliminated product **63**. When synthesised, this would also allow for further functionalisation, for example, *via* a facially selective epoxidation and subsequent manipulation (**Scheme 93**).



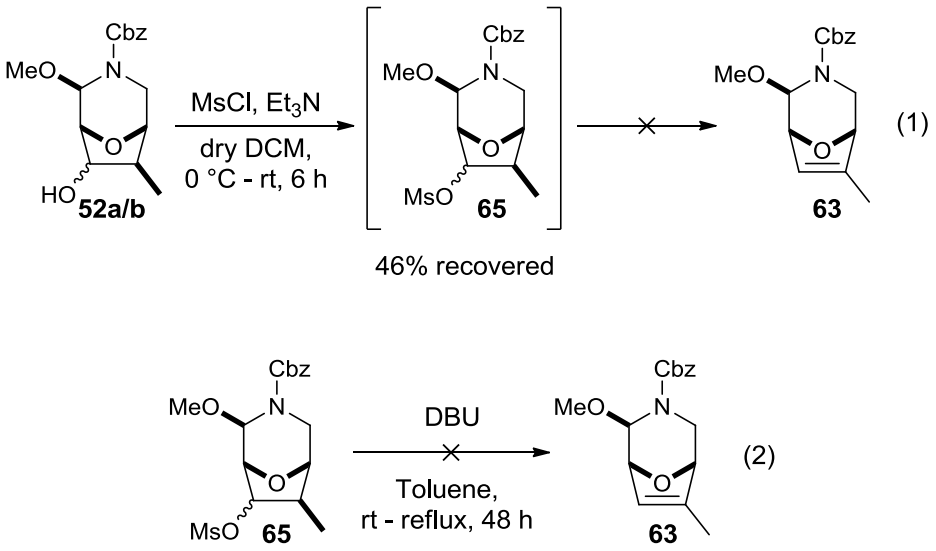
Scheme 93

Upon inspection of the literature, similar elimination processes have been shown to be successful (**Scheme 94**). It should be noted that both examples shown require the elimination of an alcohol in a 5-membered ring system with an adjacent methyl group to the alcohol substituent, which, parallels that found in the ring system within **52a** and **52b**. Kobayashi *et al.* demonstrated that upon activation of the alcohol to the mesylate, the desired elimination could occur using DBU (**Scheme 94**, **eq. 1**).[21] Chen *et al.* also showed the elimination to install the double bond could occur using Burgess' reagent (**Scheme 94**, **eq. 2**).[22]



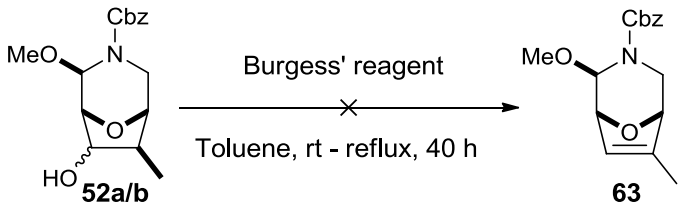
Scheme 94

In relation to substrate **52a** and **52b**, the initial attempt at the elimination reaction involved activation *via* the mesylate intermediate, prior to base-induced elimination. A one-pot mesylation/elimination reaction was carried out initially by using a large excess of triethylamine, however, only the mesylated alcohol **65** was recovered from the reaction mixture (**Scheme 95**, **eq. 1**). The mesylated product was then reacted with DBU in toluene at ambient temperature (**Scheme 95**, **eq. 2**). Unfortunately, after 22 h, only starting material was observed by TLC analysis. As such, the reaction temperature was increased to reflux, however, after a further 26 h only 39% of the mesylated alcohol was recovered, with none of the desired eliminated product being obtained.



Scheme 95

Despite the above results, we investigated the use of Burgess' reagent to carry out the desired transformation (**Scheme 96**). The reaction was initially performed at ambient temperature, however, after 24 h, only the starting material was observed by TLC analysis. In an attempt to promote the elimination the reaction temperature was increased to reflux, however, after a further 16 h only 23% of starting material was recovered. Due to the lack of success in synthesising the eliminated bridged morpholine, efforts now turned towards alternative compounds.



Scheme 96

2.10 Alternative Bridged Morpholines

In order to further expand the bridged morpholine library, the syntheses of new analogues were investigated. It was proposed that the synthetic route for the bridged

morpholines already synthesised could be utilised for the synthesis of **66** (**Figure 21**).

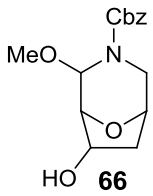
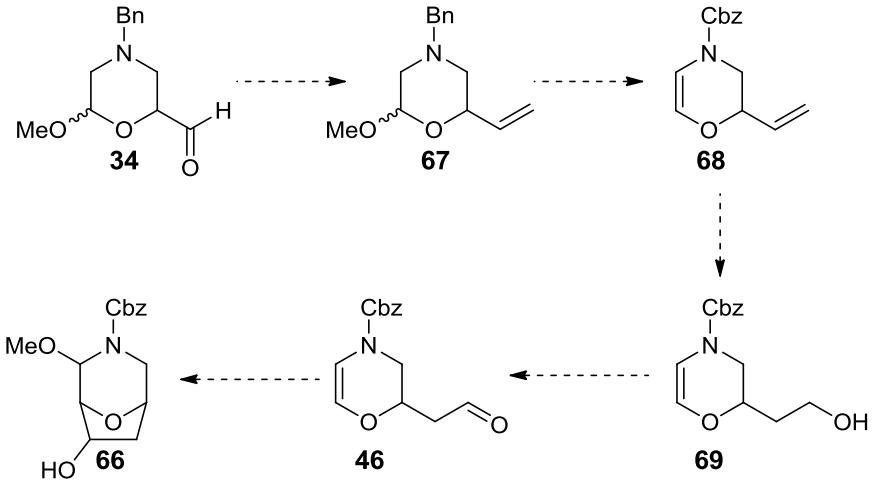


Figure 21

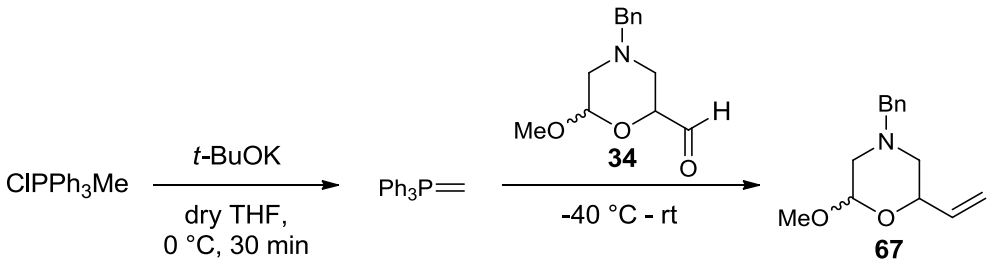
The proposed route to this novel compound is illustrated in **Scheme 97**. Utilising the previously prepared intermediate aldehyde **34** (*vide supra*), a Wittig reaction could be performed to synthesise morpholine derivative **67**. Installation of the double bond in the ring would then be investigated, followed by a hydroboration-oxidation sequence to produce alcohol **70**. Oxidation of the alcohol to the corresponding aldehyde would then be carried out, followed by a cyclisation reaction to produce the new bridged morpholine.



Scheme 97

Research into this route began with the investigation of the Wittig reaction. The initial reaction carried out utilised potassium *t*-butoxide as the base, and performing the reaction at -40 °C (**Scheme 98**). Disappointingly, under these conditions a very

poor yield of 8% was achieved (**Table 27**, **Entry 1**). Due to the sensitive nature of this particular aldehyde, it was decided to perform a reaction utilising a reverse addition process, whereby the pre-formed ylide was added, *via* a cannula, to a solution of the aldehyde. Unfortunately, when performing the reaction in this fashion a poorer yield of 2% was achieved (**Entry 2**). Due to the disappointingly low yields of the previous reactions, alternative reaction conditions were sought. As previously mentioned, aldehyde **34** is very sensitive, therefore, it was proposed that Barbier conditions (addition of the base to a solution containing both phosphonium salt and aldehyde) would be investigated, as this would allow a slow release of ylide into the reaction mixture. In relation to this, it was pleasing to observe that an improved yield of 32% was achieved (**Entry 3**).

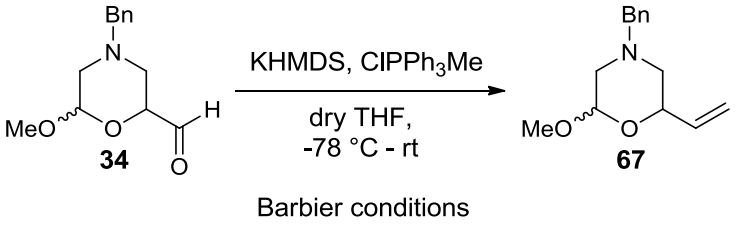


Scheme 98

Entry	***Conditions***	***Yield (%)***
1	Aldehyde added to ylide	8
2	Ylide added to aldehyde	2
3	Barbier conditions	32

Table 27

Since Barbier conditions showed promising results with respect to increasing the yield, it was decided to utilise these conditions with the alternative base KHMDS, in an attempt to improve the yield further (**Scheme 99**). The base was added at -78 °C, with the reaction mixture then being warmed to -50 °C for 50 min before being warmed to ambient temperature. Under these conditions the yield improved significantly, as shown in **Table 28**.

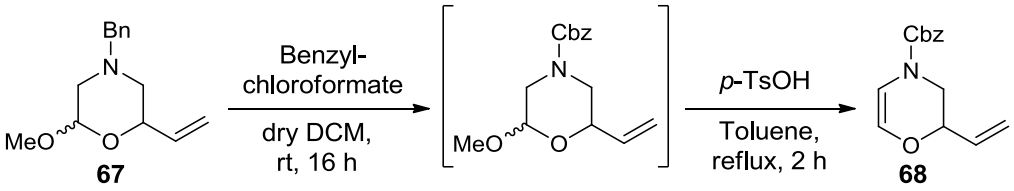


Scheme 99

Entry	*Scale (mmol)*	*Yield (%)*
1	6.5	57
2	19.7	59

Table 28

With the olefin now in hand, the double bond installation could be carried out. As with all previous elimination reactions, the protecting group switch was initially performed. Following the successful protecting group switch, the elimination reaction to install the double bond occurred to produce **68** in moderate yields (**Scheme 100**, **Table 29**).

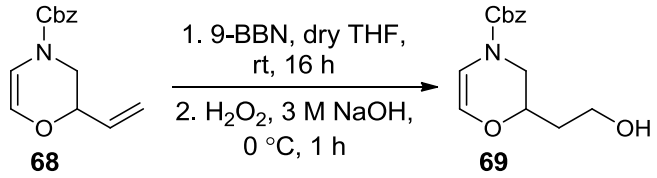


Scheme 100

Entry	*Scale (mmol)*	*Yield (%)*
1	2.7	51
2	10.7	67

Table 29

Following on from the elimination reaction, the hydroboration-oxidation sequence could be investigated. When using 9-BBN as the hydroborating reagent the desired primary alcohol was isolated after oxidation (**Scheme 101**, **Table 30**). As discussed previously, depending on the quality of the 9-BBN solution, an impurity was sometimes observed, and if this impurity was observed an alternative work up was carried out. This alternative work-up involved mixing the organic layer of the reaction mixture with a saturated aqueous solution of sodium metabisulfite, which successfully removed this impurity (see **Experimental Section** for full details).



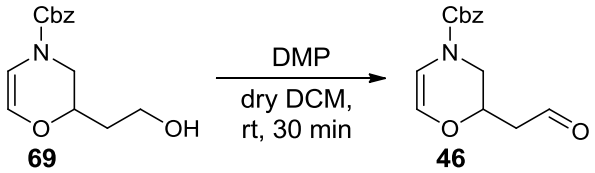
68 **69**

Scheme 101

Entry	*Scale (mmol)*	*Yield (%)*
1	1.4	68
2	6.9	56

Table 30

Pleasingly, utilising DMP as the oxidant, alcohol **69** was transformed to the corresponding aldehyde **46** in good yields (**Table 31**).



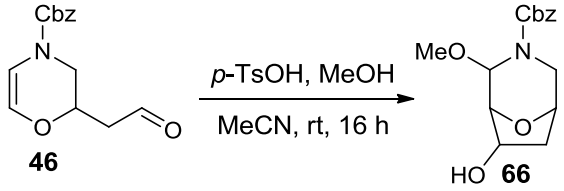
69 **46**

Scheme 102

Entry	*Scale (mmol)*	*Yield (%)*
1	0.29	66
2	4.03	75

Table 31

With the bridged morpholine precursor successfully synthesised, efforts could focus on the final cyclisation step. To great delight, with the use of 0.1 eq. of *p*-toluenesulfonic acid, the desired cyclisation reaction was complete after 16 h, yielding the novel bridged morpholine **66** (**Scheme 103**, **Table 32**).



Scheme 103

Entry	*Scale (mmol)*	*Yield (%)*
1	0.45	71
2	0.67	67

Table 32

Analysis of the NMR data revealed that the cyclisation was a diastereoselective process, whereby the bridged morpholine was obtained as a single diastereomer. It should be noted that although the NMR appears to be a mixture of two compounds, it is in fact a mixture of rotamers that are observed. In order to completely authenticate the relative stereochemistry, NOESY experiments were carried out. It was established through interpretation of the nOe interactions that the bridging oxygen, the methoxy group, and the alcohol were situated on the same face of the molecule (**Figure 22**).

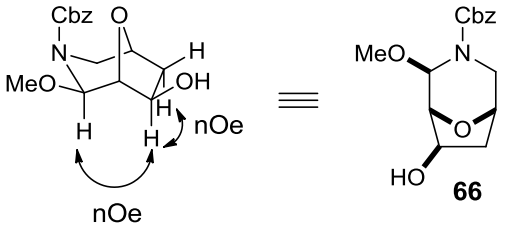


Figure 22

As previously mentioned, the proposed transition state for the cyclisation is shown in **Figure 23**. In this model, neighbouring interaction with the bridging morpholine oxygen leads to conformational restriction of the activated aldehyde, and due to the lack of methyl group within this compound (cf. substrate **45** and products **52a**/**b**; **Figures 16** and **17**), only one diastereomer is observed.

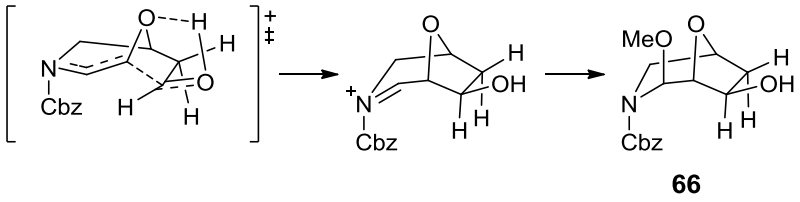
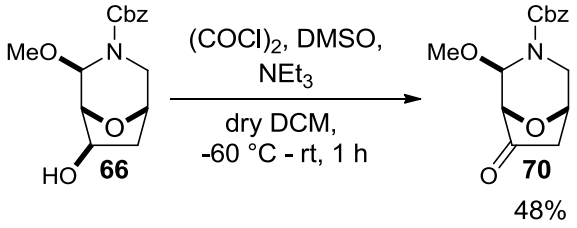


Figure 23

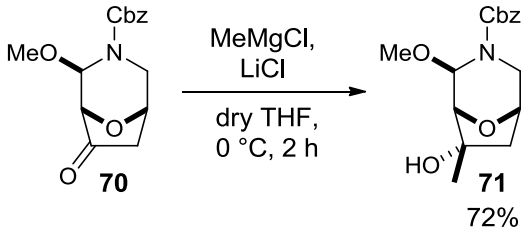
*2.10.1 Further Functionalisation of Alcohol **66***

In order to illustrate the scope for diversity, the alcohol moiety was oxidised to ketone **70** under Swern conditions. Pleasingly, the ketone was isolated in a moderate yield of 48% (**Scheme 104**).



Scheme 104

To further illustrate that more late stage functionalisation can be embedded using this route, ketone **70** underwent an alkylation reaction to produce the tertiary alcohol **71** in a high yield of 72% (**Scheme 105**).



Scheme 105

Again, utilising NMR studies it was shown that only one diastereomer was produced under these reaction conditions. It was deduced that the Grignard must approach from the same face as the bridging oxygen and methoxy group, thereby causing the methyl group to be on the same face (**Figure 24**).

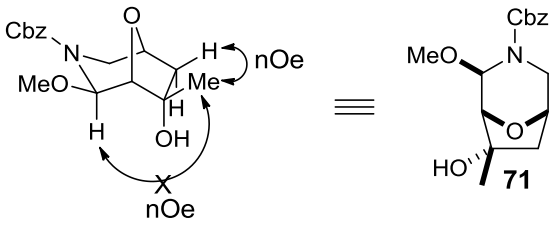
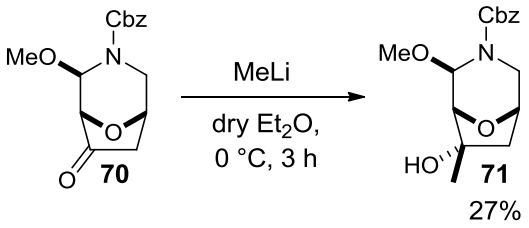


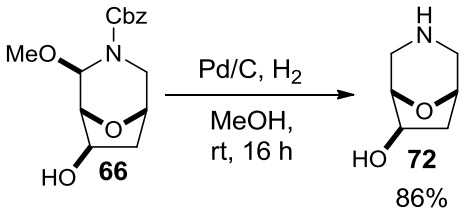
Figure 24

To deduce whether the Grignard was producing only one diastereomer because of chelation control, the reaction was repeated using methyllithium. When the reaction was run with methyllithium, only one diastereomer was obtained. It was established from the NOESY NMR that the diastereomer was the same as when the reaction was performed with methylmagnesium chloride, which implies that the approach of attack is more likely to be due to steric effects.



Scheme 106

To show that the bridged morpholine core could be accessed without protection, alcohol **66** underwent a hydrogenation reaction to remove the carboxybenzyl amine protecting group, as well as the methoxy group. The reaction was successful using an atmospheric pressure of hydrogen, in addition to palladium on charcoal, with a yield of 86% being obtained (**Scheme 107**).



Scheme 107

At this stage in the project seven novel bridged morpholines have been synthesised (**Figure 25**), as well as the stereochemistry for these compounds being determined. A route has been designed which allows for diversification at different stages during the route in order to allow a library of bridged morpholines to be created.

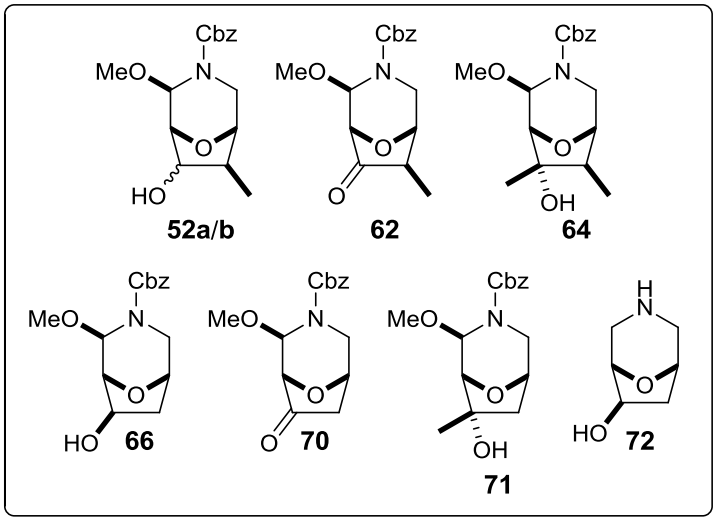
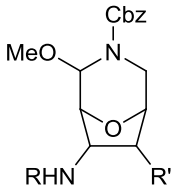


Figure 25

2.11 Amine Functionalised Bridged Morpholines

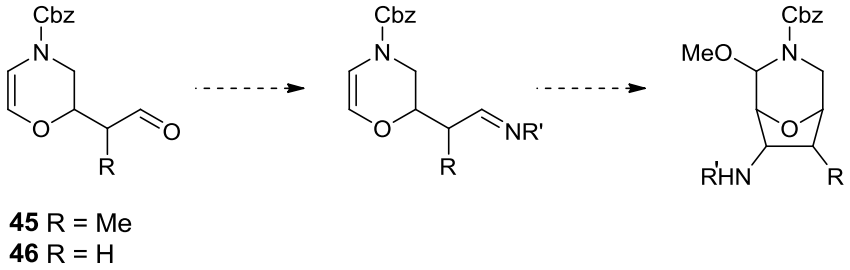
To further illustrate the late stage diversification that could be performed using the developed route, it was proposed that the alternative amine bridged morpholines could be synthesised (**Figure 26**). This would give rise to intriguing morpholine scaffolds decorated with amino functionality, complementary to the oxygenated derivatives already synthesised.



R' = H or Me

Figure 26

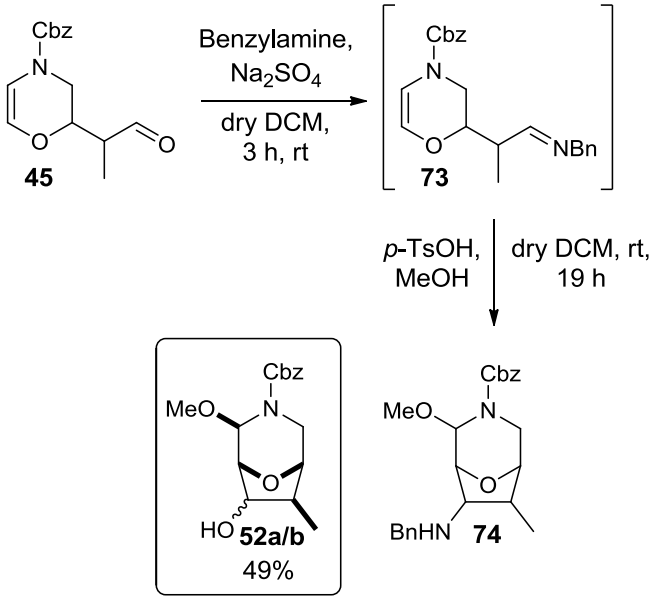
It was proposed that the amines could be accessed by utilising the previously synthesised aldehydes **45** and **46**. The aldehydes could undergo an imine formation, which under acid catalysed conditions were envisaged to cyclise to the desired amine bridged morpholine, as illustrated in **Scheme 108**.



Scheme 108

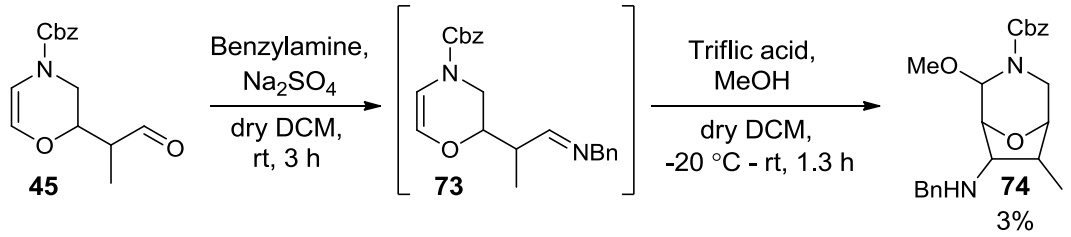
2.11.1 Methyl Bridged Morpholine Amines

With the proposed route in mind, aldehyde **45** was reacted with benzylamine, with the desired imine being formed after 3 h. Following filtration to remove the sodium sulfate, and subsequent addition of *p*-toluenesulfonic acid and methanol, it was discovered that the desired amine **74** was not formed. Instead, hydrolysis of the imine to the aldehyde occurred, which resulted in the formation of the alcohol bridged morpholine (**Scheme 109**).



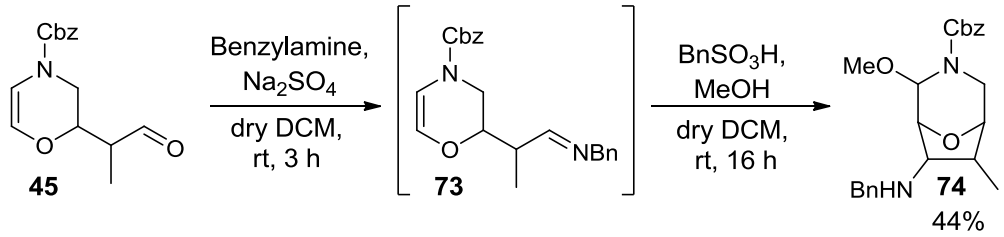
Scheme 109

Due to *p*-toluenesulfonic acid being used in its hydrate form, which was presumably causing the imine to hydrolyse, it was decided to move to a non-hydrated acid, such as triflic acid. Unfortunately, triflic acid appeared to be too acidic, as only a trace amount of the desired amine bridged morpholine was obtained (**Scheme 110**).



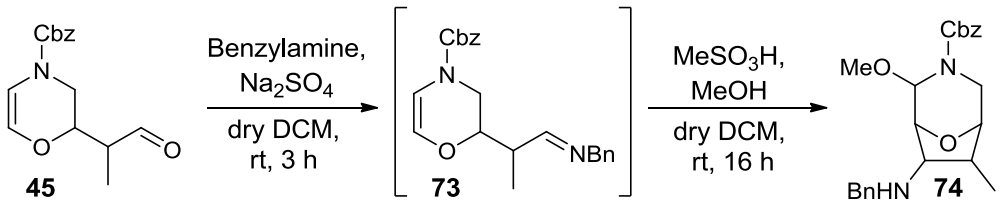
Scheme 110

Due to the disappointing results obtained with *p*-toluenesulfonic acid and triflic acid, it was decided to move to benzenesulfonic acid. Very pleasingly, it was found that when using 1 eq. of benzenesulfonic acid, the benzylamine bridged morpholine was obtained in a 44% yield (**Scheme 111**).



Scheme 111

In an attempt to improve on this yield, the less acidic methanesulfonic acid was utilised (**Scheme 112**). Under the alternative acidic conditions an improved yield of 56% was obtained (**Table 33**, **Entry 1**). This improved yield was obtained when using 1 eq. of methanesulfonic acid. Therefore in a further effort to improve the yield 0.5 eq. of acid was used. Unfortunately, after purification of the reaction mixture by column chromatography, only degradation products were obtained (**Entry 2**).



Scheme 112

Entry	*$MeSO_3H$ (eq.)*	*Yield (%)*
1	1	56
2	0.5	-

Table 33

In order to deduce whether the *E* or *Z* imine was formed, a NOESY NMR was carried out. Interpretation of NOESY spectra concluded that the *E*-imine was formed due to a nOe between the imine proton and the benzylic protons, as illustrated in **Figure 27**.

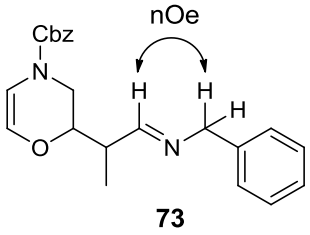


Figure 27

With regards to the stereochemistry, it was revealed that only one diastereomer **74** was produced from the cyclisation reaction, with a mixture of rotamers being observed in the NMR. Through interpretation of the NMR data it was concluded that the amine group was on the opposite side to the methyl group, bridging oxygen and the methoxy group, as shown in **Figure 28**. Indeed, this is opposite to the hydroxyl derivative **52a**/**b**, whereby a 7:3 mixture of diastereomers was obtained, with the major diastereomer having all substituents on the same face of the molecule.

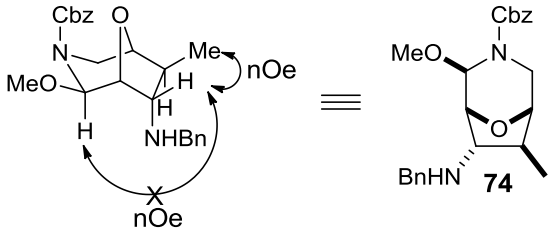
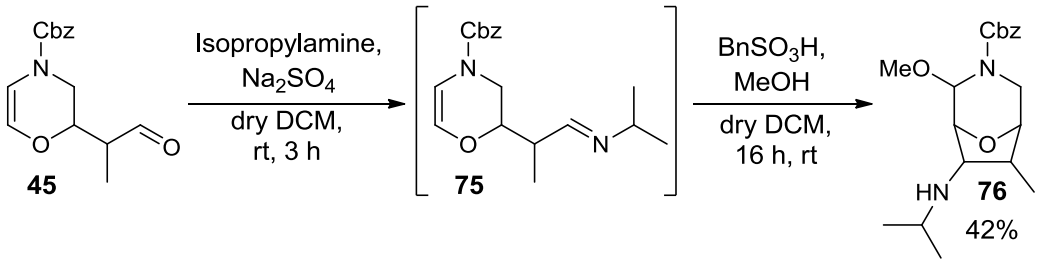


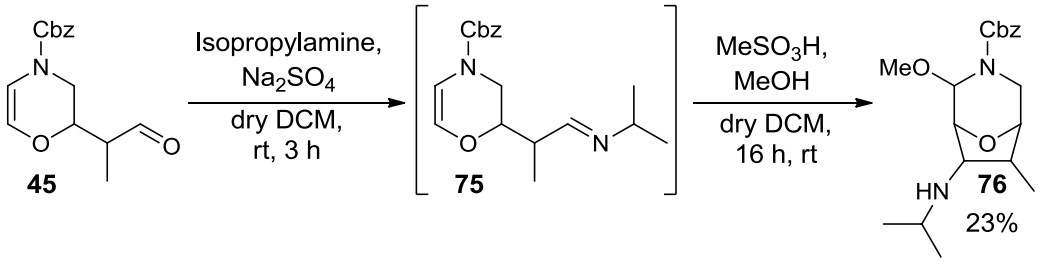
Figure 28

To expand the library of amine bridged morpholines, an investigation into synthesising the isopropyl version began. It was found, by using ^{1}H NMR analysis, that the isopropyl imine had formed after a 3 h reaction time. By utilising benzenesulfonic acid, in addition to methanol, bridged morpholine **76** could be synthesised in a moderate 42% yield (**Scheme 113**).



Scheme 113

In an effort to obtain a higher yield of amine **76**, 1 eq. of methanesulfonic acid was used to promote the cyclisation (the conditions which improved the benzylamine bridged morpholine yield), however, a poorer yield of 23% was obtained (**Scheme 114**). This could indicate that the isopropyl imine is less stable than the benzyl derivative, as it could require the stronger acid to promote a faster reaction before the imine has time to degrade.



Scheme 114

By examining the NMR data of **76**, it was determined that one diastereomer was obtained from the cyclisation reaction, and as with all other bridged morpholines, rotamers were observed. As guided by NOESY spectroscopy, the diastereomer produced has shown to have the amine group on the opposite face to the other functional groups in the molecule, as shown in **Figure 29**. This further reflected that obtained with benzylamine in this series (see **Figure 28**).

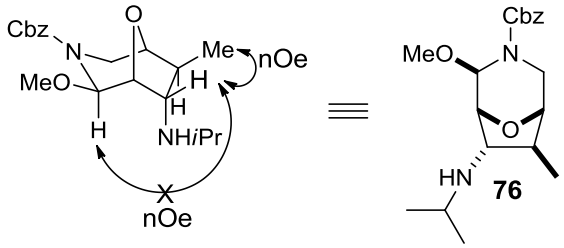
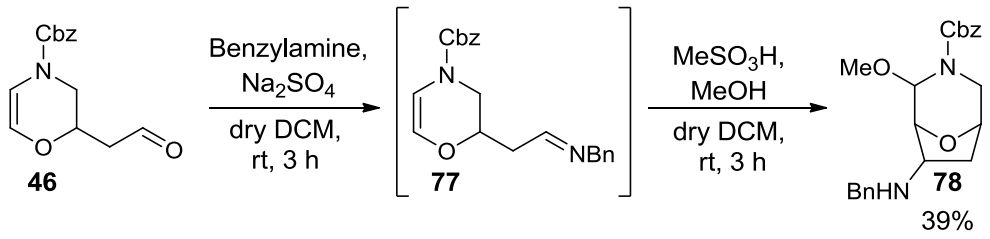


Figure 29

2.11.2 Non-Methylated Bridged Morpholine Amines

Following this, the substrate without the methyl group on the methylene unit was investigated with the amines. Utilising aldehyde **46**, the benzyl imine **77** was successfully synthesised when using benzylamine. On subjecting the imine to methanesulfonic acid, as well as methanol, the desired benzyl amine bridged morpholine was obtained in a moderate 39% yield (**Scheme 115**).



Scheme 115

Again, it was revealed using NOESY NMR that the *E*-imine was produced during the reaction, as an nOe was observed between the benzylic protons and the imine proton as shown in **Figure 30**.

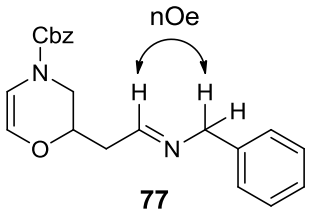


Figure 30

As with the previous amine bridged morpholines, only one diastereomer was produced from the reaction. However, in contrast to the previously synthesised amine compounds (**74** and **76**), it was intriguing to find that the NOESY NMR revealed the amine group to now be on the same face of the molecule as the methyoxy group and bridging oxygen (**Figure 31**). Computational studies to explain the difference in stereochemistry observed with and without the methyl group present on the methylene bridge were carried out and will be discussed in the following section.

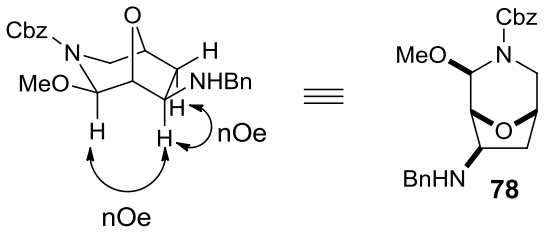
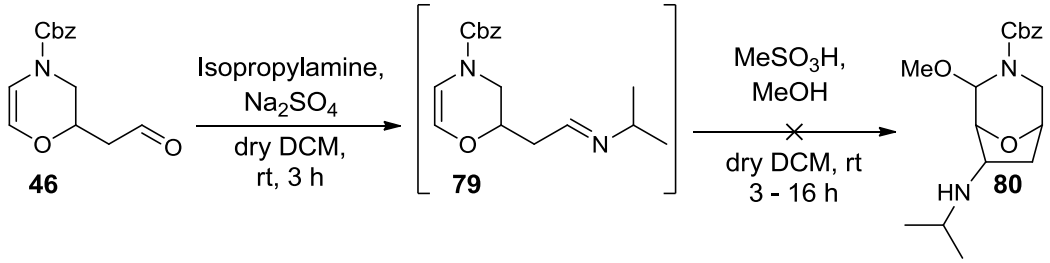


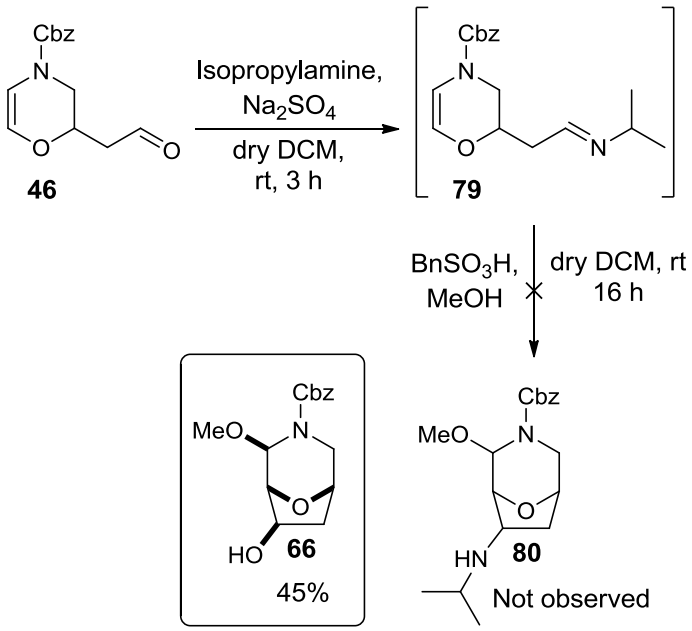
Figure 31

With the benzyl amines being synthesised in a moderate yield, an investigation into the isopropyl amine version was then initiated. As with all the previous amines, it was shown by using ^{1}H NMR analysis that the imine was successfully synthesised after 3 h. However, it was found that when subjecting the imine to methanesulfonic acid, and leaving the reaction to stir for 3 h, the TLC plate showed only a streak, therefore the reaction was stopped. Indeed, none of the desired product was produced, with 45% recovery of the aldehyde being obtained. The reaction was repeated and left stirring for 16 h, however, only degradation products were obtained from the reaction mixture.



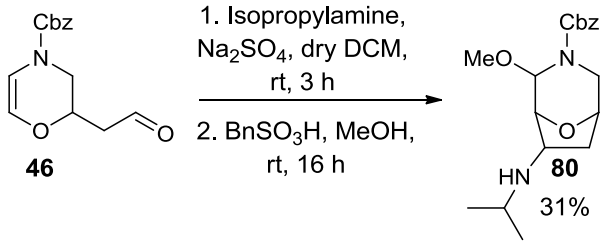
Scheme 116

On moving to benzenesulfonic acid it was found that the imine must have hydrolysed to reform aldehyde **46**, which subsequently cyclised, as alcohol **66** was isolated in a 45% yield.



Scheme 117

In attempts to try and obtain the desired amine **80**, benzenesulfonic acid was dried overnight under high vacuum in an attempt to remove any water which could cause the imine to hydrolyse. When the reaction was carried out using the pre-dried acid, a mixture of the alcohol **66** and amine **80** were obtained, which unfortunately co-eluted when performing column chromatography. The formation of alcohol **66** showed that imine **79** was extremely sensitive to any water present. With this in mind, it was decided that once the imine formation had occurred, the sodium sulfate would not be filtered off, with the acid and methanol being added after the 3 h reaction. Under these alternative reaction conditions it was pleasing to find that amine **80** was isolated in a 31% yield. This reflects that found with the equivalent benzylamine product **78** (see **Figure 31**).



Scheme 118

As with the previous amine bridged morpholine, only one diastereomer was produced from the reaction. NOESY NMR revealed the amine, methyoxy group and bridging oxygen all to be on the same face of the molecule, as shown in **Figure 32**.

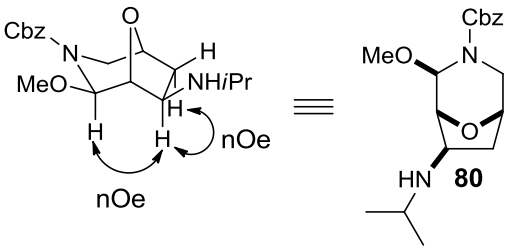


Figure 32

At this stage in the programme it was pleasing to having synthesised a further four novel bridged morpholines *via* late stage diversification (**Figure 33**).

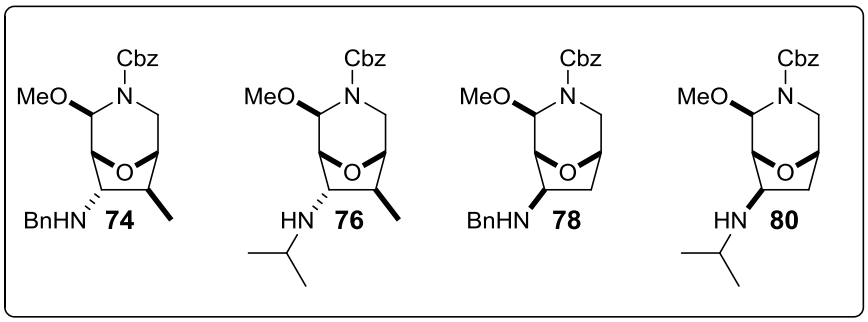
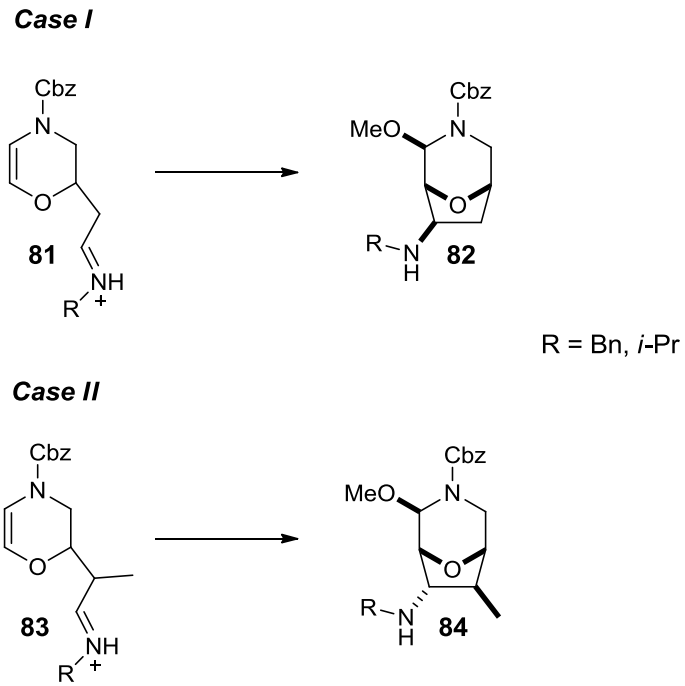


Figure 33

2.12 Computational Studies

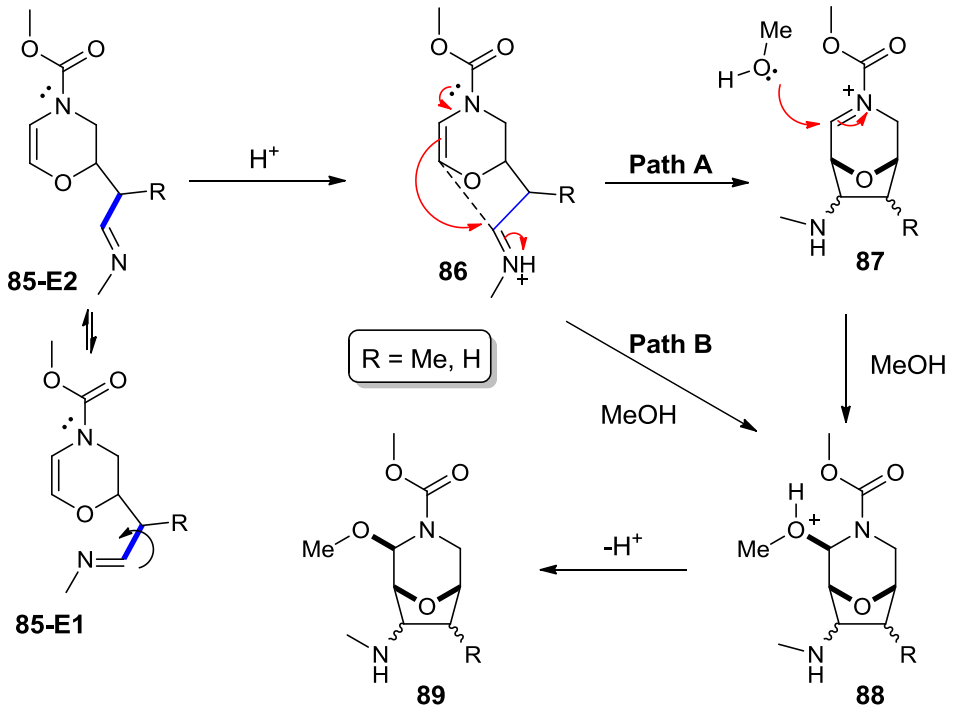
In synthetic efforts towards the amine-substituted bridged morpholines, the diastereoselectivity of the key cyclisation step was found to be dependent on the substitution pattern of the carbon alpha to that holding the nitrogen (**Scheme 119**). In ***Case I***, cyclisation occurred to produce the bridged morpholine with the amine group to be on the same face of the molecule as the methyoxy group and bridging oxygen. Conversely, in ***Case II*** the addition of a methyl group alpha to the iminium ion, as in

83, forced the amine substituent into the opposite configuration, *anti* to all other stereocentres, including the adjacent methyl group.



Scheme 119

Under the acid-catalysed conditions employed it was hypothesised that the most likely reaction mechanism would be based on **Path A** or **B**, as illustrated in **Scheme 120**. In both cases, *in-situ* protonation of **85** would first generate iminium ion **86** prior to cyclisation. Subsequently, cyclisation may proceed in a stepwise manner *via* **Path A**, or a concerted manner *via* **Path B**. In **Path A**, nucleophilic participation of the electron-rich olefin to generate cyclised iminium **87** would occur before nucleophilic addition of methanol to the newly formed iminium ion, generating common intermediate, **88**. Final deprotonation would deliver the morpholine product **89**. Alternatively, the cyclisation from iminium **86** to intermediate **88** could occur in a concerted manner, concomitant with methanol attack (**Path B**).



Scheme 120

2.12.1 Proposed Computational Analysis and Assumptions

To investigate the operative reaction mechanism, and to understand the diastereoselectivity switch, a series of mechanistic density functional theory (DFT) studies were undertaken (see **Appendix** for further information on the methods employed, *vide infra*).[23] In approaching this model, several key assumptions were made:

1) The protonated imine, **86**, exists solely as the *E*-stereoisomer. This is based on experimental evidence observed *via* NOESY NMR (*vide supra*).
2) Diastereoselectivity is based on the conformation of the iminium ion prior to cyclisation from **86** to **87**/**88**, as dictated by rotation about the bold blue bond (**Scheme 120**, structures **85-E1** and **85-E2**). The conformers (and subsequent intermediates derived from them) will henceforth be denoted **E1** and **E2**.

3) As the observed diastereoselectivity switch was common to both *i*-propyl and *n*-benzyl derivatives, calculations were carried out on the truncated *n*-methyl structures shown above in **Scheme 120**.
4) Similarly to assumption 3, further computational cost was saved by truncating the Cbz group, replacing the *O*-benzyl group with an *O*-methyl group. It was assumed that the extended and more remote parts of the carbamate structure would have minimal influence on the energetics of the cyclisation step.
5) The barrier to interconversion between the conformers of iminium **86** (prior to cyclisation) is negligible compared to barriers associated with the cyclisation itself.

2.12.2 Mechanistic Investigations – Case I

First, we considered the case of the lesser substituted morpholine precursor (**86**, R = H, **Scheme 120**). **Figure 34** shows the calculated reaction pathway for the stepwise variant of the proposed mechanism. The blue line denotes the pathway leading to the disfavoured product, **96-E1**, whereas the red line represents the favoured, experimentally observed product, **96-E2**. Firstly, protonation of the imine precursor reverses the relative free energies of conformers (**90→91**). At this key stage, ΔG_{rel}^{o}[**91-E1**, **91-E2**] between the protonated iminium conformers **91-E1** and **91-E2** is 1.5 kcal/mol in favour of **91-E2**. Following assumption 5 (above), Boltzmann analysis of this relative energy difference shows that the equilibrium ratio of **91-E1**:**91-E2** is approximately 8:92, in favour of the pathway leading to the observed diastereomer, **96-E2**. Upon cyclisation, conformer **91-E2** is also slightly more reactive. Specifically, the barrier to cyclisation, $\Delta G^{\ddagger}$[**91→92**], is 0.8 kcal/mol lower in energy for **91-E2** than for **91-E1**. After cyclisation, intermediate **93-E2** (en route to the observed product) is substantially lower in energy than **93-E1** (ΔG_{rel}^{o}[**93-E1**, **93-E2**] = 3.3 kcal/mol). Notably, the reverse reaction (**93→92**) is more accessible for the disfavoured conformer **E1**. From **93**, addition of methanol through transition state **94** to give **95** is calculated to be the rate limiting step. Additionally, the reverse process (**95→94**) is very flat on the potential energy surface (PES). As a result, with our current method, we have not yet been able to resolve the issue of intermediate

95-E2 being higher in energy than the transition state, **94-E2**. However, supplementary calculations of the intrinsic reaction coordinate (IRC) confirm the validity of the transition state connecting **93** and **95**. Work is ongoing to upgrade the accuracy of the current method and fully resolve this issue. Lastly, deprotonation to give product **96** shows that: (i) observed product **96-E2** is 1.2 kcal/mol more thermodynamically stable than **96-E1**, and (ii) the overall reaction is exothermic.

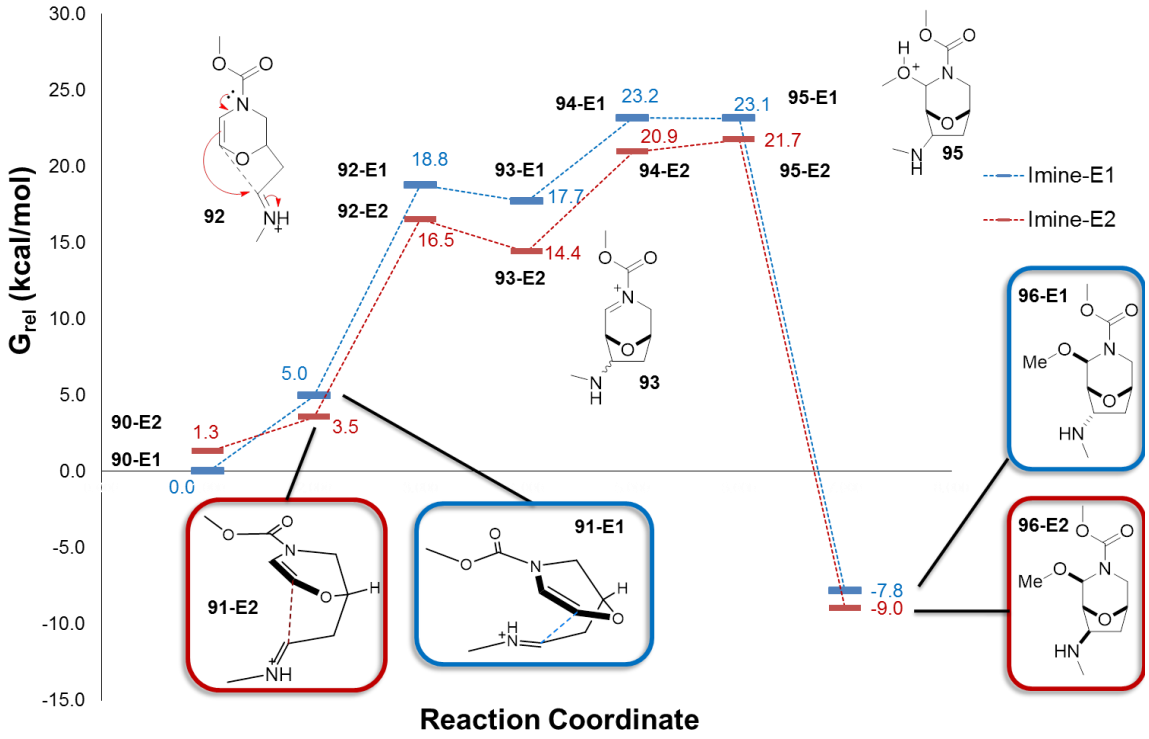


Figure 34

Subsequent analysis of **Path B**, proceeding through simultaneous cyclisation and methanol addition, revealed a significant increase in the free energy barrier to cyclisation (**91→[97]→95**, **Figure 35**). Whereas the stepwise barriers to cyclisation are 13.0 and 13.8 kcal/mol for conformers **E2** and **E1**, respectively, the concerted process possesses barriers of 19.2 and 19.3 kcal/mol, respectively. This is explained most simply as an increase in the negative entropy contribution to $\Delta G^{\ddagger}$[**91→97**] *versus* $\Delta G^{\ddagger}$[**91→92**] due the increased order in the transition state. Additionally, the imaginary frequency associated with the transition state (**91→97**) is dominated by

the carbon-carbon bond forming process, and shows minimal involvement of the methanol molecule.

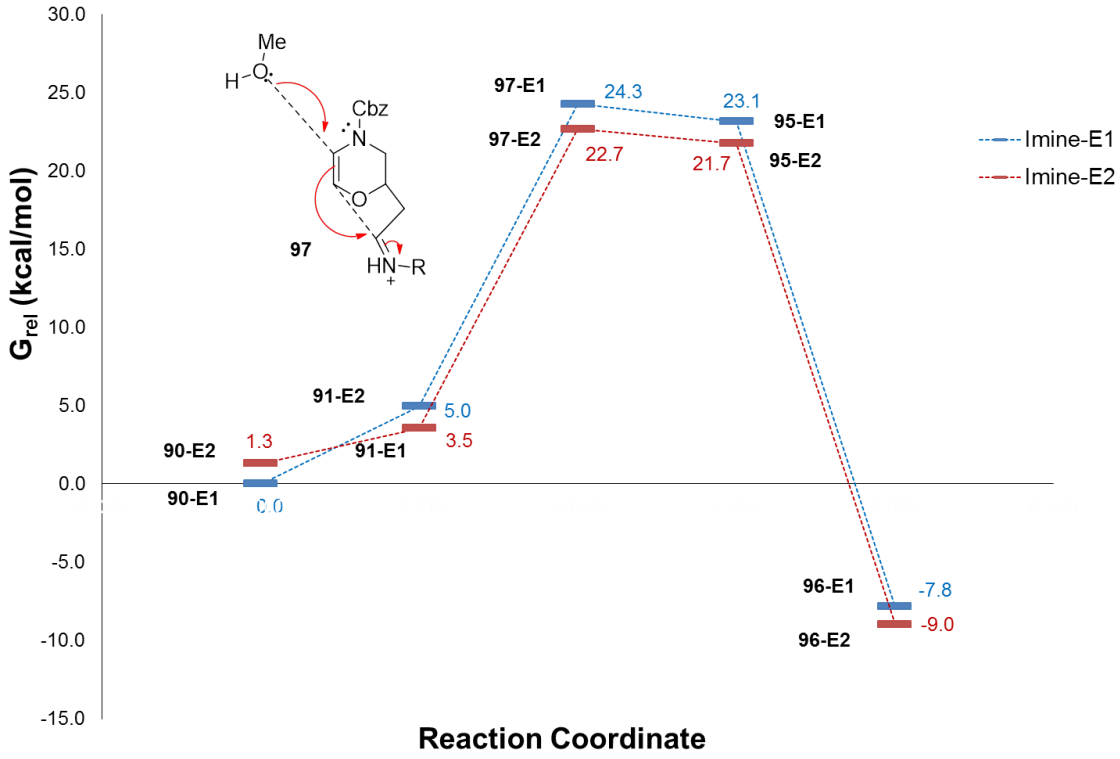


Figure 35

2.12.2.1 Understanding Diastereoselectivity – Case I

To explain the observed diastereoselectivity of the reaction, and assuming the stepwise mechanism (**Path A**), we turned our attention back to the iminium precursors, **91-E1** and **91-E2**, and associated transition states, **92-E1** and **92-E2** (**Figure 34**). It was necessary to understand: (i) why the ground state iminium **91-E2** is thermodynamically more stable than **91-E1**, and (ii) why **91-E2** is also faster reacting than **91-E2**.

In answering question (i), on relative iminium stability, natural bond order (NBO) analysis on each conformer revealed a possible electronic reason behind the energetic differences observed. As expected, it was found that the electron density associated

with the HOMO of the iminium structures **91-E1** and **91-E2** is centred over the electron-rich olefin; the LUMO lies over the C-N iminium double bond (see **Appendix** for all associated diagrams). Of most relevance to question (i) is the differing nature of the HOMO orbitals (**Figure 36**). In **91-E1** the electron density of the HOMO is more localised across the olefin, whereas **91-E2** also benefits from delocalisation into π*-type component of the iminium C-N bond. As a result, the nucleophilic and electrophilic centres of the iminium lie closer together in **91-E2** than in **91-E1** (2.92 *versus* 3.27 Å, respectively). This occurs despite the greater steric encumbrance associated with **91-E2**.

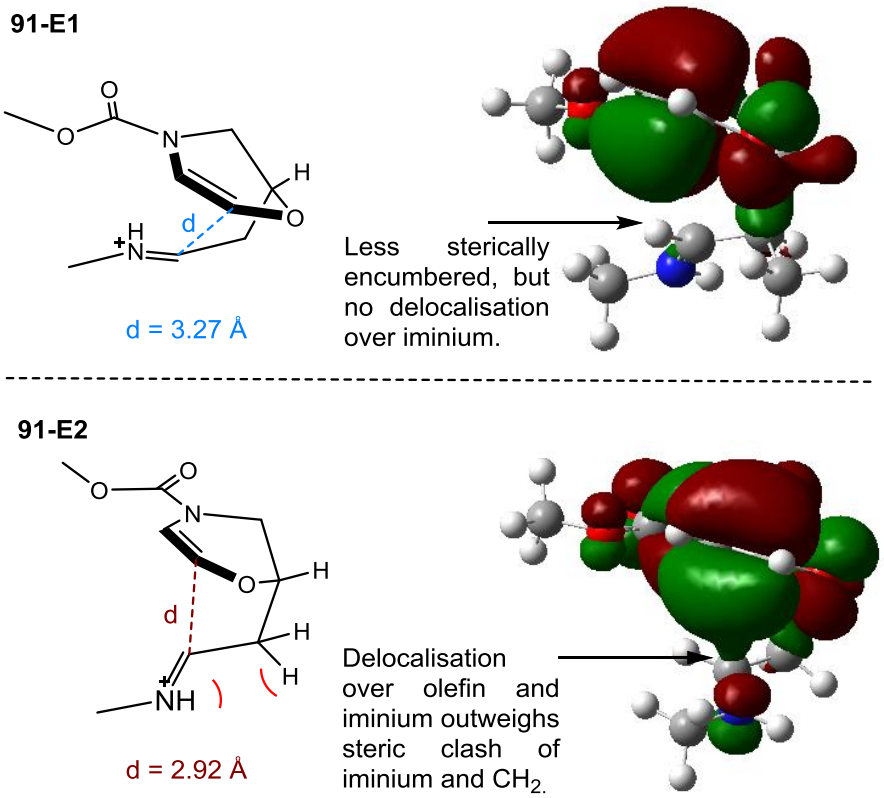


Figure 36

The distance between reacting centres in the iminium precursors also helps to answer question (ii) on why **91-E2** is more reactive. If we compare distance, *d*, as shown in **Figure 36**, with the distance between reacting centres at the transition state, $d^{\ddagger}$, it is clear that the more reactive conformer has distorted least from the ground state to reach the bond forming transition state (**Table 34**).

Entry	*Conformer*	*d (Å)*	*$d^{\ddagger}$ (Å)*	*d - $d^{\ddagger}$(Å)*
1	**E1**	3.27	1.86	1.41
2	**E2**	2.92	1.96	0.96

Table 34

2.12.2.2 Summary – Case I

From the current model of the diastereoselective cyclisation process to form the less highly substituted class of bridged morpholines (**89**, R = H, **Scheme 120**), we can infer the following:

1) The cyclisation and methanol addition steps are more likely to occur in a stepwise rather than concerted manner (**91→92** *versus* **91→97**). However, in lieu of further experimental evidence, the concerted mechanism cannot be rejected.
2) The diastereoselectivity-determining step is that of the stepwise cyclisation (**91→**[**92**]**→93**).
3) The more stable conformer of the iminium precursor to cyclisation, **91-E2**, is also the most reactive. This is due to different levels of HOMO delocalisation and ground state distortion on approaches the transition state.
4) Cyclisation of conformer **91-E1** is more reversible than **91-E2**.
5) The reaction is under thermodynamic control.
6) The methanol addition step (**93→[94]→95**) is rate-limiting.

2.12.3 Mechanistic Investigations – Case II

With the model developed for ***Case I***, investigations turned to ***Case II*** (**83→84**, **Scheme 119**), where the addition of a methyl group alpha to the starting imine forces the amine *anti* (rather than *syn*) to all other stereocentres in the bridged morpholine product. As before, calculations were carried out on the proposed step wise cyclisation and methanol addition mechanism (**Path A**), comparing the energetics of

reactions for available reactant conformers, **E1** and **E2**. The results are displayed below in **Figure 37**. Unlike ***Case I***, on protonation of the imine (**98→99**), **E1** is the more stable conformer, with ΔG_{rel}^{o}[**99-E1**, **99-E2**] = 0.8 kcal/mol. By the simplest approximation, this equates to a distribution for **99-E1**:**99-E2** of 74:26. However, in this case, the most stable iminium is not the most reactive upon cyclisation. Specifically, $\Delta G^{\ddagger}$[**99→100**] is 1.8 kcal/mol lower for conformer **E2** (the disfavoured product not observed experimentally). The faster reactivity of **E2** can be reasoned similarly to ***Case I***, based on HOMO delocalisation and reacting centre proximities (*vide infra*). Additionally, **E2** also provides the more stable cyclised iminium intermediate, **101**. Upon the rate-limiting methanol attack (**101→102**), the barrier is 1.5 kcal/mol lower in energy for **E1**. Again, there exist discrepancies in the energy values of transition state **102** and product **103** due to the flat of this portion of the PES. As in ***Case I***, additional IRC calculation confirm the validity of the transition state obtained, and work is ongoing to solve the energy values associated with **102** and **103**. Final deprotonation again shows that the overall process is exothermic. In this case, the alternative conformer, **E1** not **E2**, give the most stable product, ΔG_{rel}^{o}[**104-E1**, **104-E2**] = 0.7 kcal/mol.

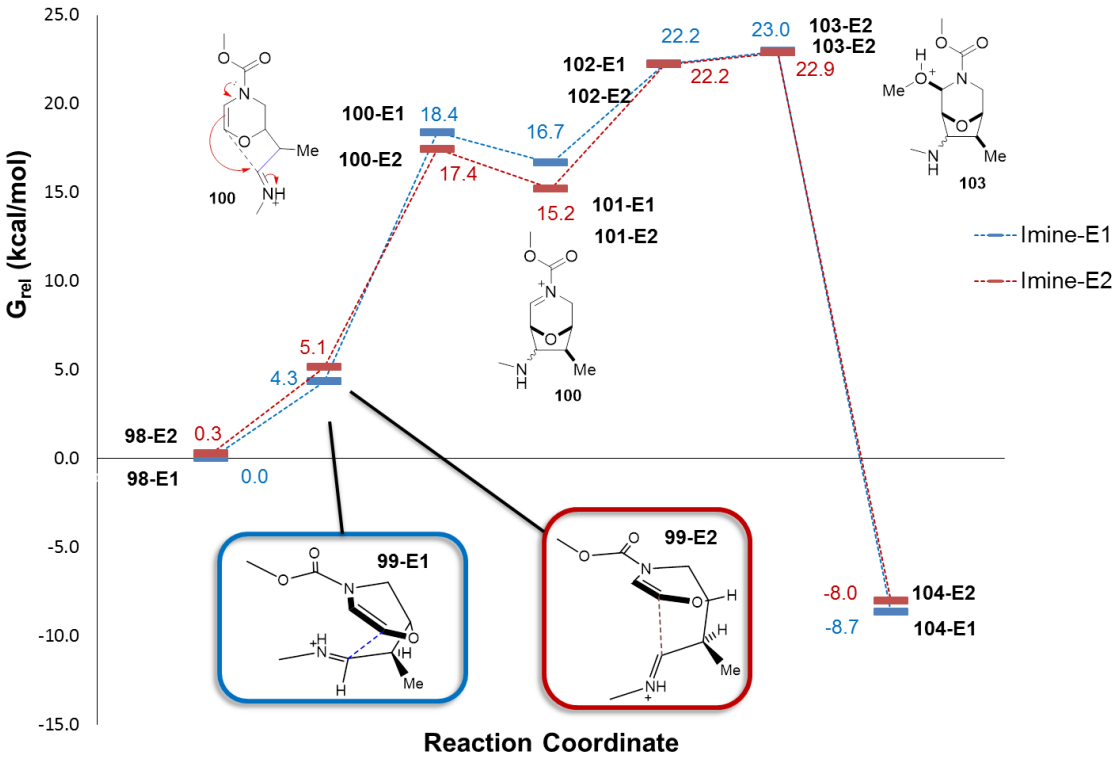


Figure 37

2.12.3.1 Understanding Diastereoselectivity – Case II

To begin to understand the observed diastereoselectivity in ***Case II***, we again have to consider the diastereoselectivity-determining cyclisation step (**99→100→101**). In this case, the key to a simple understanding of the switch in amine configuration (observed in the product) is to consider why **E1** gives the most stable iminium precursor, and not **E2**, as in ***Case I***. NBO analysis on **99-E1** and **E2** again revealed the expected location of the HOMO and LUMO within each molecule. As with ***Case I*** (**91-E2**, **Figure 36**), the same type of extra delocalisation was available to **99-E2**, with no such delocalisation being observed for **99-E1** (**Figure 38**). However, unlike ***Case I***, the compound with this extra delocalisation does not lead the observed product, in fact it leads to the diastereomer with the higher energy (see **Figure 37**). This therefore implies that the steric clash between the iminium ion and the methyl group must now dominate the reaction pathway, and not the favourable HOMO delocalisation as in ***Case I***.

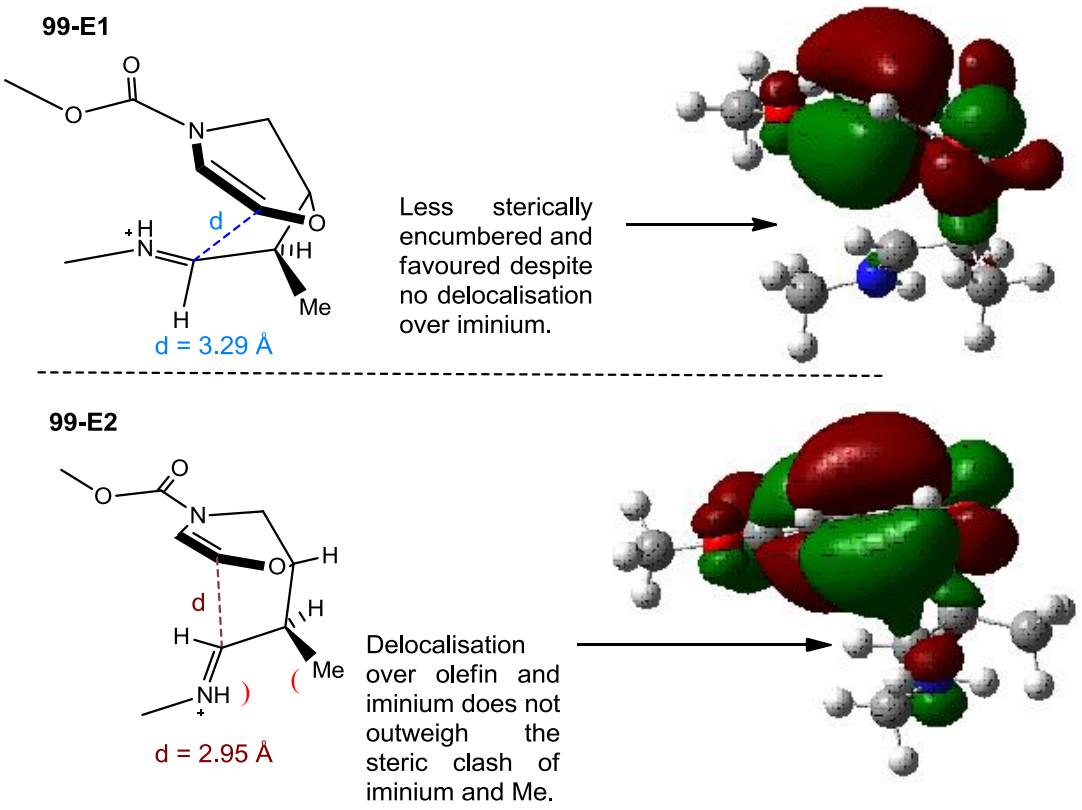


Figure 38

To fully explain the experimentally observed diastereoselectivity for ***Case II***, analysis of the barrier to **99-E1/99-E2** interconversion may have to be investigated. In this manner, Curtin-Hammett analysis of the product distribution can be approached to better explain the output of the current model. Tentatively, the more significant steric clash (iminium/Me (for **99**) *versus* iminium/CH_2 (for **91**)) appears to play a crucial role in the switch of amine configuration between ***Cases I*** and ***II***.

3. Conclusions and Future Work

At the onset of the programme we sought to develop a route which allowed for the synthesis of novel bridged morpholine scaffolds whilst allowing for structural diversification. The two initial oxazine precursors explored within this project were α,β-unsaturated ester **7** and epoxide **41** (**Figure 39**). A successful racemic synthesis was developed to both of these precursors, however, the desired cyclisations to deliver their corresponding bridged morpholines proved to be unsuccessful under a series of acidic and Lewis acid conditions.

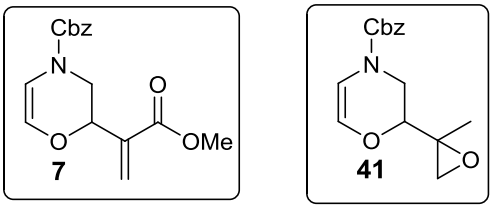


Figure 39

Following a series of computational studies, which focused on the key final cyclisation step, aldehydes **45** and **46** were investigated as potential cyclisation substrates (**Figure 40**).

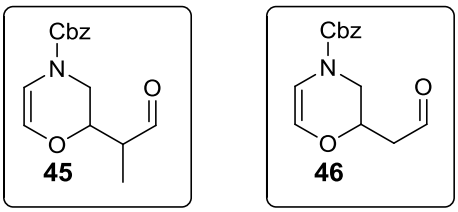
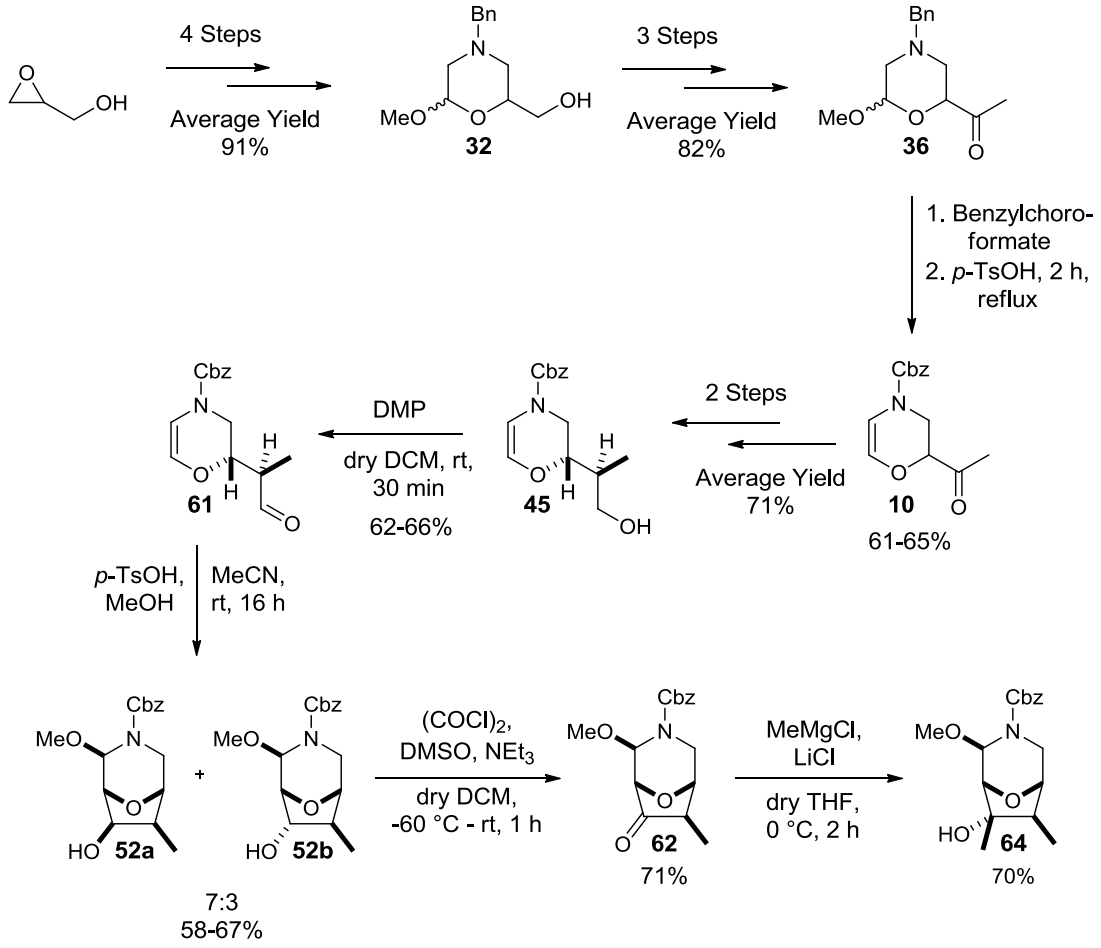


Figure 40

A preparative route was successfully developed towards each of these bridged morpholine precursors, and pleasingly each aldehyde successfully cyclised to provide the desired bridged morpholine (**Scheme 121** and **Scheme 122**).

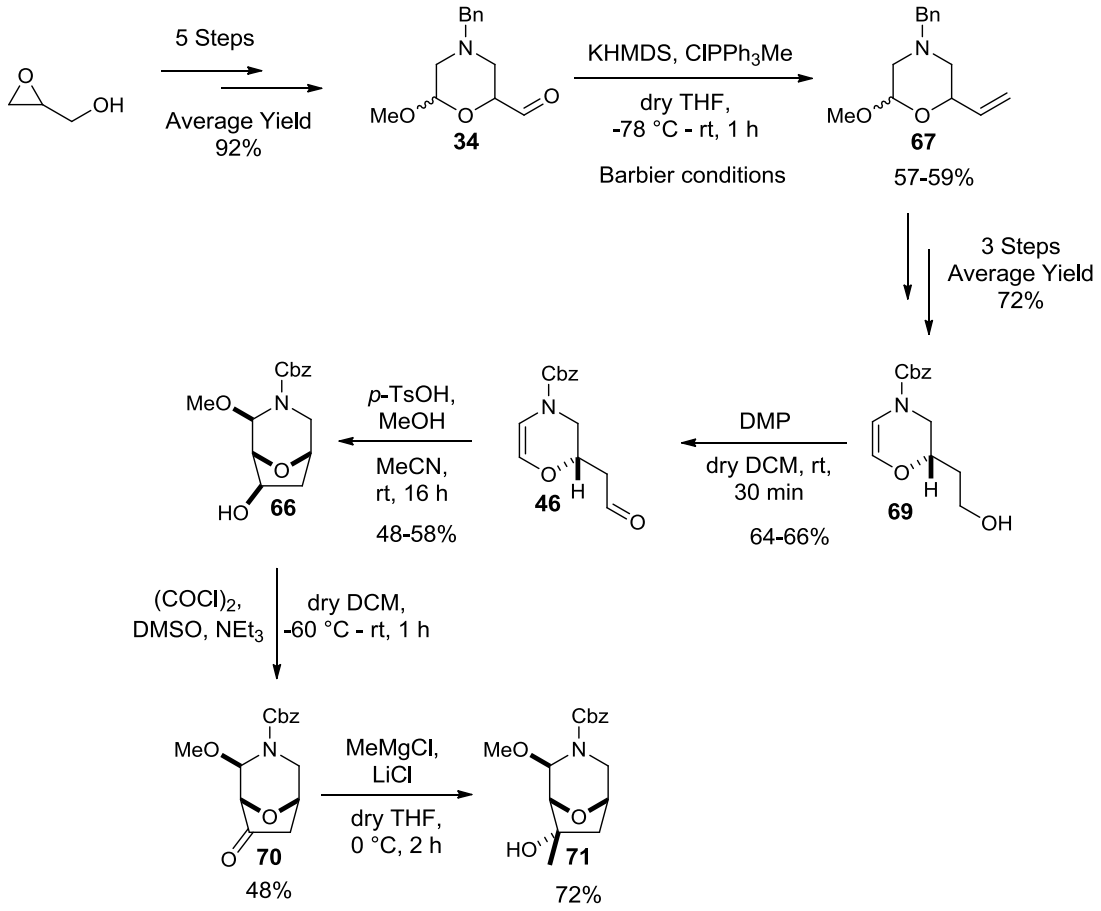
With respect to bridged morpholine **52**, extensive NMR studies revealed that a 7:3 ratio of diastereomers (**52a** and **52b**) was produced when aldehyde **45** was cyclised. Further functionalisation of the alcohol bridged morpholine was also investigated, and it was shown that the 7:3 mixture of **52a** and **52b** could undergo an oxidation reaction to the corresponding ketone derivative (**62**). This ketone substrate was also transformed into its corresponding tertiary alcohol (**64**), which was a facially selective process, producing only one diastereomer.



Scheme 121

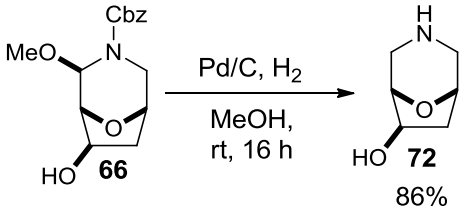
With regards to the cyclisation of aldehyde **46**, it was deduced, again through detailed NMR studies, that the cyclisation was a diastereoselective process, as only one diastereomer was observed (**66**) (**Scheme 122**). It was also shown that **66** could

undergo an oxidation reaction to produce ketone **70**, which subsequently underwent an alkylation reaction to synthesise tertiary alcohol **71**.



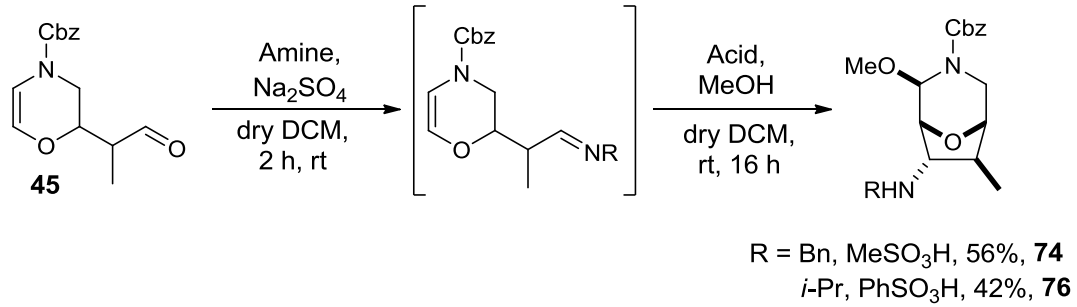
Scheme 122

In the case of bridged morpholine **66**, it was also shown that the free core (**72**) could be accessed readily *via* a hydrogenation reaction (**Scheme 123**).

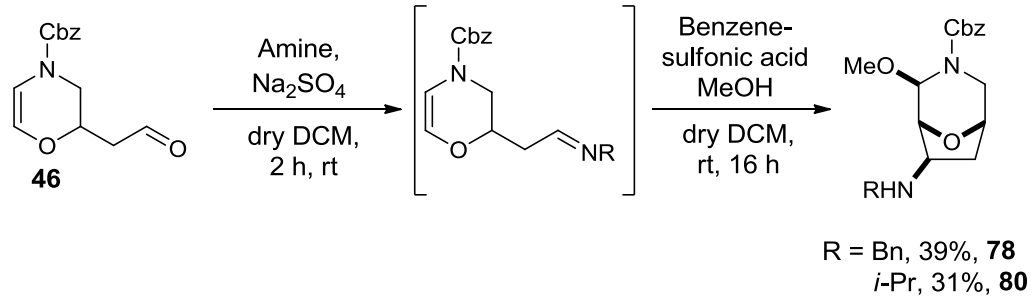


Scheme 123

In addition to the alcohol and ketone bridged morpholines, four further novel bridged morpholines were synthesised. These were the benzyl and isopropyl amine derivatives, with and without the methyl group present on the methylene unit adjacent to the final amine functionality (**Scheme 124** and **Scheme 125**, respectively). The reactions to these new bridged morpholines utilised the aldehyde from the alcohol bridged morpholine synthesis, with all the reactions showing complementary yet intriguing diastereoselectivity. Additionally, a computational study revealed the reaction is likely to progress in a step-wise manner, as well as illustrating that a substituent alpha to the imine is likely to be playing a crucial role in the diastereoselective outcome of the cyclisation process.



Scheme 124



Scheme 125

At this stage, a robust stereoselective racemic route has been developed to allow the synthesis of a range of differentially functionalised bridged morpholine compounds. Work would now begin on the development of an asymmetric variant of this process, and the discussions surrounding this part of the project are detailed in **Chapter Two**.

4. Experimental

4.1 General

All reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. All reactions were carried out under an inert, dry, nitrogen atmosphere unless otherwise stated. All glassware was flame dried and cooled under a blanket of nitrogen.

- Dichloromethane, THF, diethyl ether and toluene were obtained from Innovatic Technology, Pure Solv, SPS-400-5 drying columns.
- Methanol was distilled over calcium hydride before use.
- Benzaldehyde was distilled under nitrogen before use.
- Where specified, *p*-toluenesulfonic acid was recrystallised from diethyl ether.
- Petrol refers to petroleum ether boiling point range 40-60 °C.
- *n*-BuLi was obtained as a 2.5 M solution in hexanes.
- KHMDS was obtained as a 0.5 M solution in toluene.
- MeMgCl was obtained as a 2 M solution in THF.
- MeLi was obtained as a 1.2 M solution in diethyl ether.
- $TiCl_4$ was obtained as a 1 M solution in DCM.
- 9-BBN was obtained as a 0.5 M solution in THF.
- Tetra-*n*-butylammonium fluoride was obtained as a 1 M solution in THF.

Thin layer chromatography was carried out using silica gel 60 F_{254} plates. This was analysed using a Mineralight UVG-25 lamp or developed using vanillin solution.

Flash chromatography was carried out using Zeo Chem silica gel (40-63 µm).

IR spectra were recorded on a Perkin Elmer Spectrometer 1 machine.

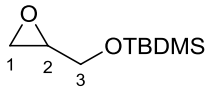
^{1}H and ^{13}C spectra were recorded on a Bruker DPX 400 Spectrometer at 400 MHz and 100 MHz, respectively, or a Bruker 500 Spectrometer at 500 MHz and 125 MHz, respectively. Analysis for compounds **52a** and **52b**, as well as all NOESY spectra, were recorded on a Bruker DPX 600 Spectrometer at 600 MHz. Chemical shifts are reported in ppm and coupling constants are reported in Hz and refer to $^{3}J_{H\text{-}H}$ interactions unless otherwise specified.

n-BuLi, KHMDS, MeMgCl and MeLi were standardised before use using salicylaldehyde phenylhydrazone as an indicator.[24]

High resolution mass spectra were recorded on a Finnigan MAT 90XLT instrument at the EPSRC Mass Spectrometry facility at the University of Swansea, Wales.

Microwave irradiation experiments were performed using a CEM Discover unit.

tert-Butyldimethyl(oxiran-2-ylmethoxy)silane, ***14*** [25]



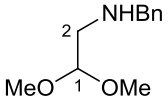
Chemical Formula: $C_9H_{20}O_2Si$
Molecular Weight: 188.34

Scheme 9

Imidazole (2.7 g, 40 mmol) was added to a stirred solution of glycidol (2.0 g, 27.0 mmol) in dry THF (45 mL). *Tert*-butyldimethylsilyl chloride (6.1 g, 40 mmol) was then added during which time a white precipitate formed. The reaction mixture was stirred at ambient temperature for 2 h after which time the precipitate was filtered through a bed of celite and washed with diethyl ether. The filtrate was concentrated *in vacuo* and purified by column chromatography (0-10% diethyl ether in petrol) to yield **14** as a colourless oil (5.1 g, 100% yield).

FTIR (CH_2Cl_2): 1253, 1260, 3048, 3068 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 0.09 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 2.66 (dd, ^2J = 5.2 Hz, J = 2.7 Hz, 1H, H1), 2.79 (dd, ^2J = 5.2 Hz, J = 4.1 Hz, 1H, H1), 3.01-3.12 (m, 1H, H2), 3.67 (dd, ^2J = 11.9 Hz, J = 4.8 Hz, 1H, H3), 3.85 ppm (dd, ^2J = 12.0 Hz, J = 3.3 Hz, 1H, H3).
^{13}C NMR (100 MHz, $CDCl_3$): -5.4, -5.5, 18.4, 25.9, 44.5, 52.4, 64.0 ppm.

N-Benzyl-2,2-dimethoxyethanamine, ***15***



Chemical Formula: $C_{11}H_{17}NO_2$
Molecular Weight: 195.26

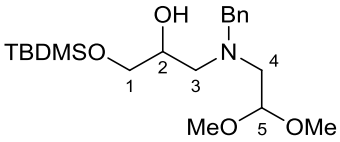
Scheme 10

Benzaldehyde (33 mL, 0.32 mol) was added to a stirred solution of 2,2-dimethoxyethylamine (35 mL, 0.32 mol) in methanol (670 mL) at ambient temperature and stirred for 16 h. The mixture was then cooled to 0 °C and sodium

borohydride (18.2 g, 0.48 mol) was added portionwise. After stirring the mixture for 16 h at ambient temperature, the resultant solution was acidified to pH~9 with 2 M HCl. The methanol was then removed *in vacuo* and water was added. The pH was corrected again to pH~9 and the product was then extracted with ethyl acetate (x 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield **15** as a colourless oil (60.0 g, 96%).

FTIR (CH_2Cl_2): 2837, 3030 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 2.77 (d, *J* = 5.5 Hz, 2H, H2), 3.39 (s, 6H, OCH_3), 3.83 (s, 2H, benzylic CH_2), 4.51 (t, *J* = 5.5 Hz, 1H, H1), 7.28-7.35 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 50.6, 53.9, 54.0, 104.0, 127.0, 128.1, 128.4, 140.1 ppm.
HRMS *m/z* (ESI) calc for $C_{11}H_{18}NO_2$ (M^++H): 196.1332. Found: 196.1327.

5-Benzyl-3-methoxy-10,10,11,11-tetramethyl-2,9-dioxa-5-aza-10-siladodecan-7-ol, ***13***



Chemical Formula: $C_{20}H_{37}NO_4Si$
Molecular Weight: 383.60

General Procedure

Epoxide **14** was added to a stirred solution of amine **15** in ethanol at ambient temperature. The mixture was then heated to reflux and stirred at this temperature for 16 h. The mixture was cooled and concentrated *in vacuo* to yield **13** as a colourless oil.

Scheme 11*, *Table 1

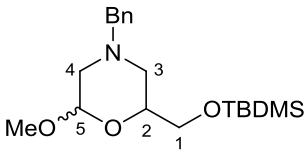
The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of epoxide **14**, (b) amount of amine **15**, (c) volume of ethanol, (d) amount of **13**, and (e) yield.

***Entry 1**:* (a) 500 mg, 2.7 mmol, (b) 517 mg, 2.7 mmol, (c) 15 mL, (d) 1 g, and (e) 98%.

***Entry 2**:* (a) 4.3 g, 22.8 mmol, (b) 4.46 g, 22.8 mmol, (c) 130 mL, (d) 8.35 g, and (e) 95%.

FTIR (CH_2Cl_2): 1262, 2857, 3030, 3452 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 0.07 (s, 6H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 2.58-2.75 (m, 4H, H3, H4), 3.29 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 3.47 (bs, 1H, OH), 3.56-3.74 (m, 4H, benzylic CH_2, H1), 3.80-3.86 (m, 1H, H2), 4.38 (t, *J* = 5.4 Hz, 1H, H5), 7.30-7.41 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): -5.4, 18.3, 26.0, 53.2, 53.9, 56.0, 58.1, 61.4, 65.4, 69.0, 103.5, 127.0, 128.3, 129.1, 138.9 ppm.
HRMS *m/z* (ESI) calc for $C_{20}H_{38}NO_4Si$ (M^++H): 384.2565. Found: 384.2559.

*4-Benzyl-2-(((tert-butyldimethylsilyl)oxy)methyl)-6-methoxymorpholine, **12***



Chemical Formula: $C_{19}H_{33}NO_3Si$
Molecular Weight: 351.56

General Procedure

Compound **13** was added to a microwave vial and *p*-toluenesulfonic acid was added. The vial was sealed and placed into the microwave. The mixture was heated to the desired temperature with the cooling function on for the designated amount of time.

The reaction mixture was then dissolved in DCM and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-30% diethyl ether in petrol) to yield **12** as a pale yellow oil.

Scheme 14, ***Table 2***

The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of substrate **13**, (b) amount of *p*-toluenesulfonic acid, (c) temperature, (d) time, (e) amount of **12**, (f) yield, and (g) *dr*.

Entry 1*:* (a) 1 g, 2.61 mmol, (b) 99 mg, 0.52 mmol, (c) 100 °C, (d) 40 min, (e) 458 mg, (f) 50%, and (g) 3:2.

Entry 2:

Compound **13** (6 g, 15.6 mmol) was added to a microwave vial and *p*-toluenesulfonic acid (593 mg, 3.12 mmol) was added. The vial was sealed and placed into the microwave. The mixture was heated to 100 °C with the cooling function on. After 4 h the reaction had not gone to completion therefore a further quantity of *p*-toluenesulfonic acid (297 mg, 1.56 mmol) was added. After a further 1.5 h the reaction was complete. The reaction mixture was then dissolved in DCM and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-30% diethyl ether in petrol) to yield **12** as a pale yellow oil (3.7 g, 68% yield, 3:2 *dr*).

Entry 3: (a) 500 mg, 1.30 mmol, (b) 49 mg[*], 0.26 mmol, (c) 100 °C, (d) 1 h, (e) 275 mg, (f) 60%, and (g) 3:2.

[*] Recrystallised *p*-toluenesulfonic acid

Entry 4: (a) 603 mg, 1.57 mmol, (b) 60 mg*, 0.31 mmol, (c) 115 °C, (d) 1 h, (e) 332 mg, (f) 60%, and (g) 3:2.

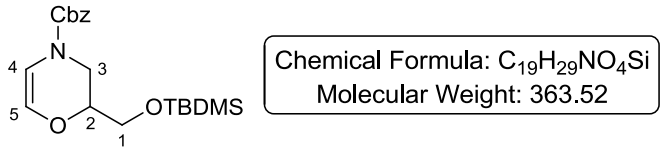
FTIR (CH_2Cl_2): 1260, 2857, 3031 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 0.06 (s, 6H, $SiCH_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.20-1.96 (m, 1.6H, H3, H4), 2.22 (dd, ^2J = 12.0 Hz, J = 2.4 Hz, 0.4H, H4), 2.81-2.90 (m, 2H, H3, H4), 3.42 (s, 1.2H, OCH_3), 3.50 (s, 1.8H, OCH_3), 3.55-3.79 (m, 4.6H, H1, H2, benzylic CH_2), 4.00-4.09 (m, 0.4H, H2), 4.51 (dd, J = 8.3 Hz, J = 2.5 Hz, 0.6H, H5), 4.69 (bd, J = 2.5 Hz, 0.4H, H5), 7.31-7.41 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): -5.4, 18.3, 25.8, 54.8, 55.0, 55.7, 56.3, 56.8, 62.8, 63.4, 64.1, 64.6, 69.2, 74.5, 97.3, 100.4, 127.2, 128.3, 129.2 129.5, 136.8, 137.5 ppm.

HRMS *m/z* (ESI) calc for $C_{19}H_{34}NO_3Si$ (M^++H): 352.2302. Found: 352.2306.

Benzyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-2H-1,4-oxazine-4(3H)-carboxylate, ***11***



Scheme 16, ***Table 3***

Entry 1:

Benzylchloroformate (0.26 mL, 1.79 mmol) was added to a stirred solution of **12** (450 mg, 1.28 mmol) in dry DCM (5 mL). The mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The residual oil was dissolved in toluene (20 mL) and *p*-toluenesulfonic acid (49 mg, 0.25 mmol) was added to the mixture. The mixture was then stirred at reflux for 24 h using a Dean-Stark apparatus. After this time, the reaction had not gone to completion, therefore a further quantity of *p*-toluenesulfonic acid (49 mg, 0.25 mmol) was added, and after a

further 3 h the solution was cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was subsequently purified by column chromatography (0-30% diethyl ether in petrol) to yield **21** as a pale yellow oil (226 mg, 71 % yield).

Entry 2:

Benzylchloroformate (82 µL, 0.60 mmol) was added to a stirred solution of **12** (150 mg, 0.43 mmol) in dry DCM (1.5 mL). The mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The residual oil was then dissolved in toluene (7 mL) and *p*-toluenesulfonic acid[*] (16 mg, 0.09 mmol) was added to the mixture. The mixture was then stirred at reflux for 24 h using a Dean-Stark apparatus. After this time the reaction had not gone to completion, therefore a further quantity of *p*-toluenesulfonic acid[*] (8 mg, 0.04 mmol) was added and after a further 6 h the solution was cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-30% diethyl ether in petrol) to yield **11** as a pale yellow oil (7 mg, 5% yield), as well as **21** as a pale yellow oil (69 mg, 65% yield).

Entry 3:

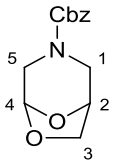
Benzylchloroformate (0.3 mL, 2.34 mmol) was added to a stirred solution of **12** (588 mg, 1.68 mmol) in dry DCM (15 mL). The mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The residual oil was then dissolved in toluene (27 mL) and *p*-toluenesulfonic acid[*] (64 mg, 0.33 mmol) was added to the mixture. The mixture was then stirred at reflux for one week using a Dean-Stark apparatus monitored by TLC analysis. After one week the reaction mixture showed extensive decomposition.

[*] Recrystallised *p*-toluenesulfonic acid

^{1}H NMR (400 MHz, $CDCl_3$): 0.09 (s, 6H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 3.31 (dd, ^{2}J = 13.0 Hz, J = 8.2 Hz, 0.6H, H3), 3.42 (dd, ^{2}J = 12.8 Hz, J = 7.5 Hz, 0.4H, H3), 3.64-3.76 (m, 1H, H3), 3.78-3.86 (m, 1H, H1), 3.93-4.05 (m, 1.4H, H1, H2), 4.10 (bd, J = 14.7 Hz, 0.6H, H2), 5.20-5.24 (m, 2H, benzylic CH_2), 5.92 (d, J = 4.9 Hz, 0.6H, H4), 6.03 (d, J = 4.9 Hz, 0.4H, H4), 6.22 (d, J = 4.9 Hz, 0.6H, H5), 6.33 (d, J = 4.9 Hz, 0.4H, H5), 7.35-7.46 ppm (m, 5H, ArH).

A 3:2 ratio of rotamers were observed in the ^{1}H NMR.

Benzyl 6,8-dioxa-3-azabicyclo[3.2.1]octane-3-carboxylate, ***21***



Chemical Formula: $C_{13}H_{15}NO_4$
Molecular Weight: 249.26

FTIR (CH_2Cl_2): 1702 cm^{-1}.

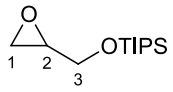
^{1}H NMR (400 MHz, $CDCl_3$): 3.03-3.15 (m, 1H, H1), 3.29-3.44 (m, 1H, H5), 3.80-4.05 (m, 4H, H1, H3, H5), 4.51 (bs, 0.4H, H2), 4.59 (bs, 0.6H, H2), 5.12-5.23 (m, 2H, benzylic CH_2), 5.49 (s, 0.6H, H4), 5.53 (s, 0.4H, H4), 7.31-7.42 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 47.3, 47.8, 48.4, 48.7, 67.3, 67.4, 71.2, 71.4, 98.0, 98.6, 113.1, 127.9, 128.0, 128.1, 128.5, 136.4, 151.5 ppm.

HRMS *m/z* (ESI) calc for $C_{13}H_{16}NO_4$ (M^{+}+H): 250.1074. Found: 250.1073.

A 3:2 ratio of rotamers were observed in the ^{1}H NMR.

Triisopropyl(oxiran-2-ylmethoxy)silane, ***22***



Chemical Formula: $C_{12}H_{26}O_2Si$
Molecular Weight: 230.42

General Procedure

Imidazole was added to a stirred solution of glycidol in dry THF. Triisopropylsilyl chloride was then added during which time a white precipitate formed. The reaction mixture was stirred at ambient temperature for 16 h. The precipitate was filtered through a bed of celite and washed with diethyl ether. The filtrate was concentrated *in vacuo* and purified by column chromatography (0-5% diethyl ether in petrol) to yield **22** as a colourless oil.

Scheme 17, ***Table 4***

The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of imidazole, (b) amount of glycidol, (c) amount of TIPSCl, (d) volume of dry THF, (e) amount of **22**, and (f) yield.

Entry 1: (a) 1.01 g, 14.8 mmol, (b) 1.00 g, 13.5 mmol, (c) 3.2 mL, 14.8 mmol, (d) 25 mL, (e) 2.70 g, and (f) 87%.

Entry 2: (a) 2.20 g, 32.7 mmol, (b) 2.20 g, 29.7 mmol, (c) 7.0 mL, 32.7 mmol, (d) 55 mL, (e) 6.0 g, and (f) 88%.

Entry 3: (a) 8.3 g, 121.7 mmol, (b) 8.2 g, 110.7 mmol, (c) 26.1 mL, 121.7 mmol, (d) 200 mL, (e) 24.1 g, and (f) 97%.

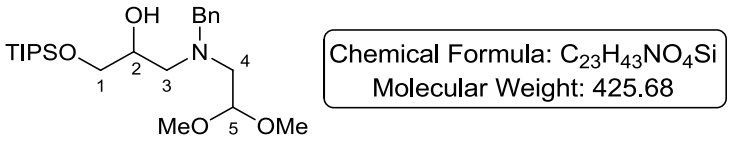
FTIR (CH_2Cl_2): 1260, 1266, 3050, 3061 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.06-1.13 (m, 21H, $Si(CH(CH_3)_2)_3$), 2.69 (dd, ^2J = 5.2 Hz, J = 2.8 Hz, 1H, H1), 2.80 (dd, ^2J = 5.3 Hz, J = 4.2 Hz, 1H, H1), 3.12-3.15 (m,

1H, H2), 3.78 (dd, ^{2}J = 11.7 Hz, J = 4.6 Hz, 1H, H3), 3.93 ppm (dd, ^{2}J = 11.6 Hz, J = 3.3 Hz, 1H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): 11.5, 17.4, 44.0, 52.1, 63.4 ppm.

HRMS *m/z* (ESI) calc for $C_{12}H_{27}O_2Si$ (M^++H): 231.1775. Found: 231.1777.

5-Benzyl-10,10-diisopropyl-3-methoxy-11-methyl-2,9-dioxa-5-aza-10-siladodecan-7-ol, ***23***



General Procedure

Epoxide **22** was added to a stirred solution of amine **15** in ethanol at ambient temperature. The mixture was heated to reflux and stirred at this temperature for 16 h. The mixture was then cooled, and concentrated *in vacuo* to yield **23** as a colourless oil.

Scheme 18, ***Table 5***

The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of epoxide **22**, (b) amount of amine **15**, (c) volume of ethanol, (d) amount of **23**, and (e) yield.

Entry 1: (a) 2.50 g, 10.8 mmol, (b) 2.12 g, 10.8 mmol, (c) 75 mL, (d) 4.16 g, and (e) 90%.

Entry 2: (a) 24.1 g, 104.6 mmol, (b) 20.4 g, 104.6 mmol, (c) 500 mL, (d) 44.5 g, and (e) 100%.

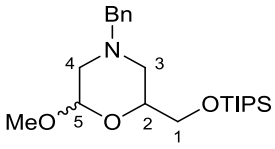
FTIR (CH_2Cl_2): 1267, 2867, 3031, 3452 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 1.04-1.10 (m, 21H, $Si(CH(CH_3)_2)_3$), 2.60-2.70 (m, 2H, H3, H4), 2.73-2.81 (m, 2H, H3, H4), 3.29 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 3.48 (s, 1H, OH), 3.64-3.78 (m, 4H, H1, benzylic CH_2), 3.80-3.86 (m, 1H, H2), 4.38 (t, *J* = 5.5 Hz, 1H, H5), 7.31-7.36 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 11.4, 17.5, 52.7, 53.4, 55.6, 57.8, 60.0, 65.3, 68.7, 102.9, 126.7, 127.8, 128.6, 138.4 ppm.

HRMS *m/z* (ESI) calc for $C_{23}H_{44}NO_4Si$ (M^++H): 426.3034. Found: 426.3033.

4-Benzyl-2-methoxy-6-(((triisopropylsilyl)oxy)methyl)morpholine, ***24***



Chemical Formula: $C_{22}H_{39}NO_3Si$
Molecular Weight: 393.64

Scheme 19

Compound **23** (39.0 g, 92.0 mmol) was added to a one neck round bottom flask and *p*-toluenesulfonic acid (4.4 g, 22.0 mmol) was added. The flask was sealed with a suba seal and placed into an oil bath which had been pre-heated to 115 °C. The reaction mixture was left to stir at this temperature for 16 h. The mixture was then dissolved in DCM and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-20% diethyl ether in petrol) to yield **24** as a pale yellow oil (30.1 g, 84%, 3:2 *dr*).

General Procedure

Substrate **23** was added to a one necked round bottom flask and *p*-toluenesulfonic acid was added. A plug of cotton wool was placed in the neck of the flask and the flask was placed into an oil bath which had been pre-heated to 115 °C. The reaction mixture was left to stir at this temperature for 16 h. The mixture was then dissolved

in DCM and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-20% diethyl ether in petrol) to yield **24** as a pale yellow oil.

Scheme 20, ***Table 6***

The following experiments were carried out using the above **General Procedure**. Data are reported as: (a) amount of substrate **23**, (b) amount of *p*-toluenesulfonic acid, (c) amount of **24**, (d) yield, and (e) *dr*.

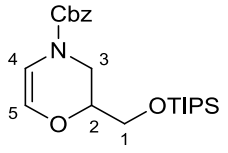
Entry 1: (a) 1.45 g, 3.40 mmol, (b) 259 mg, 1.36 mmol, (c) 1.11 g, (d) 83%, and (e) 3:2.

Entry 2: (a) 44.5 g, 105.0 mmol, (b) 8.4 g, 41.8 mmol, (c) 35.8 g, (d) 87%, and (e) 3:2.

FTIR (CH_2Cl_2): 1270, 2867 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.02-1.09 (m, 21H, $Si(CH(CH_3)_2)_3$), 1.87-2.01 (m, 1.6H, H3, H4), 2.23 (dd, ^2J = 11.7 Hz, J = 2.8 Hz, 0.4H, H4), 2.84-2.97 (m, 2H, H3, H4), 3.42 (s, 1.2H, OCH_3), 3.50 (s, 1.8H, OCH_3), 3.53-3.90 (m, 4.6H, H1, H2, benzylic CH_2), 4.05-4.12 (m, 0.4H, H2), 4.51 (dd, J = 8.5 Hz, J = 2.5 Hz, 0.6H, H5), 4.68 (bd, J = 2.4 Hz, 0.4H, H5), 7.29-7.39 ppm (m, 5H, ArH).
^{13}C NMR (125 MHz, $CDCl_3$): 11.9, 17.9, 55.0, 55.1, 55.2, 55.7, 56.2, 56.8, 62.8, 63.4, 64.7, 65.0, 69.3, 74.5, 97.3, 100.4, 127.2, 128.2, 129.2, 129.5, 136.7, 137.5 ppm.

HRMS *m/z* (ESI) calc for $C_{22}H_{40}NO_3Si$ (M^++H): 394.2772. Found: 394.2771.

Benzyl 2-(((triisopropylsilyl)oxy)methyl)-2H-1,4-oxazine-4(3H)-carboxylate, ***26***



Chemical Formula: $C_{22}H_{35}NO_4Si$
Molecular Weight: 405.60

Scheme 21

Benzylchloroformate (4.2 mL, 28.5 mmol) was added to a stirred solution of **24** (8.00 g, 20.3 mmol) in dry DCM (80 mL). The mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The residual oil was then dissolved in toluene (230 mL) and *p*-toluenesulfonic acid (773 mg, 4.1 mmol) was added to the mixture. The mixture was then stirred at reflux for 1.5 h using a Dean-Stark apparatus. The solution was then cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-20% diethyl ether in petrol) to yield **26** as a pale yellow oil (5.77 g, 70% yield).

FTIR (CH_2Cl_2): 1263, 1665, 1706 cm^{-1}.

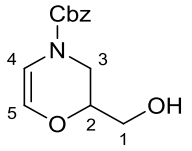
^{1}H NMR (400 MHz, $CDCl_3$): 0.99-1.22 (m, 21H, $Si(CH(CH_3)_2)_3$), 3.35 (dd, ^2J = 12.9 Hz, J = 8.3 Hz, 0.6H, H3), 3.45 (dd, ^2J = 12.9 Hz, J = 7.5 Hz, 0.4H, H3), 3.71 (dd, ^2J = 10.8 Hz, J = 7.5 Hz, 0.4H, H3), 3.80 (dd, ^2J = 10.8 Hz, J = 6.3 Hz, 0.6H, H3), 3.88-4.04 (m, 2H, H1), 4.15 (bd, J = 13.2 Hz, 0.4H, H2), 4.16 (bd, J = 13.2 Hz, 0.6H, H2), 5.14-5.39 (m, 2H, benzylic CH_2) 5.92 (d, J = 5.0 Hz, 0.6H, H4), 6.03 (d, J = 5.0 Hz, 0.4H, H4), 6.22 (d, J = 5.0 Hz, 0.6H, H5), 6.34 (d, J = 5.0 Hz, 0.4H, H5), 7.32-7.46 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 11.9, 17.9, 43.0, 43.5, 62.8, 63.2, 67.5, 67.6, 73.6, 74.3, 105.2, 105.8, 128.0, 126.1, 128.2, 128.6, 129.6, 136.2, 152.2 ppm.

HRMS *m/z* (ESI) calc for $C_{22}H_{39}N_2O_4Si$ (M^++NH_4): 423.2674. Found: 423.2670.

A 3:2 ratio of rotamers was observed in the ^{1}H NMR.

Benzyl 2-(hydroxymethyl)-2H-1,4-oxazine-4(3H)-carboxylate, ***27***



Chemical Formula: $C_{13}H_{15}NO_4$
Molecular Weight: 249.26

General Procedure

Tetra-*n*-butylammonium fluoride was added to a stirred solution of **26** in dry THF at 0 °C. The solution was then allowed to stir at 0 °C for a further 2 h. The reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate solution and the organic layer was separated. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The alcohol was then purified by column chromatography (50-80% diethyl ether in petrol) to yield **27** as a colourless oil.

Scheme 22, ***Table 7***

The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) volume of tetra-*n*-butylammonium fluoride, (b) amount of substrate **26**, (c) volume of dry THF, (d) amount of **27**, and (e) yield.

Entry 1: (a) 1.1 mL, 1.1 mmol, 1 M in THF, (b) 450 mg, 1.1 mmol, (c) 14 mL, (d) 264 mg and, (e) 95%.

Entry 2: (a) 14 mL, 14.1 mmol, 1 M in THF, (b) 5.7 g, 14.1 mmol, (c) 170 mL, (d) 2.9 g and, (e) 82%.

FTIR (CH_2Cl_2): 1666, 1706, 3600 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 3.34 (dd, ^2J = 13.4 Hz, J = 8.6 Hz, 0.6H, H3), 3.41 (dd, ^2J = 13.4 Hz, J = 8.8 Hz, 0.4H, H3), 3.70-3.87 (m, 2H, H1, H3), 3.97-4.13 (m, 2H, H1, H2), 5.22 (s, 2H, benzylic CH_2), 5.95 (d, J = 5.0 Hz, 0.6H, H4), 6.08 (d, J =

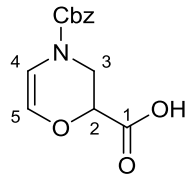
5.0 Hz, 0.4H, H4), 6.25 (d, *J* = 5.0 Hz, 0.6H, H5), 6.38 (d, *J* = 5.0 Hz, 0.4H, H5), 7.31-7.46 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 42.3, 43.0, 62.6, 67.7, 67.8, 73.5, 74.1, 105.5, 106.1, 128.1, 128.2, 128.3, 128.4, 128.6, 129.4, 136.0, 152.0, 152.3 ppm.

HRMS *m/z* (ESI) calc for $C_{13}H_{16}NO_4$ (M^++H): 250.1074. Found: 250.1079.

A 3:2 ratio of rotamers were observed in the ^{1}H NMR.

Attempted synthesis of 4-(benzyloxycarbonyl)-3,4-dihydro-2H-1,4-oxazine-2-carboxylic acid, ***28***



Chemical Formula: $C_{13}H_{13}NO_5$
Molecular Weight: 263.25

Scheme 24

Jones' reagent was prepared by dissolving chromium trioxide (670 mg, 6.6 mmol) in distilled water (1.3 mL). Concentrated sulfuric acid (0.6 mL) was then slowly added and the salts which precipitated were dissolved by adding the minimum quantity of distilled water.[26]

Alcohol **27** (85 mg, 0.34 mmol) was dissolved in acetone (2 mL) and the solution was cooled to 0 °C. Jones' reagent was added dropwise until the orange colour persisted and the reaction was then stirred for 20 min. Isopropyl alcohol (0.5 mL) was then added followed by water (1 mL) and ethyl acetate (10 mL). The organic phase was separated and washed with brine until neutral, dried over Na_2SO_4, and concentrated *in vacuo*. The reaction was unsuccessful as no product was obtained, as well as no starting alcohol being recovered from the reaction.

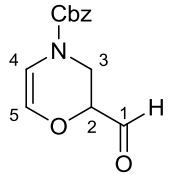
Scheme 25

PDC (1.19 g, 3.16 mmol) was added to a stirred solution of alcohol **27** (225 mg, 0.90 mmol) in DMF (2.4 mL) at ambient temperature. The mixture was stirred for 5.5 h before water was added. The organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The reaction was unsuccessful as no product was obtained, as well as no starting alcohol being recovered from the reaction.

Scheme 27

Alcohol **27** (200 mg, 0.80 mmol) was dissolved in a mixture of acetonitrile:H_2O (2:1, 10 mL). 2-Iodobenzoic acid (40 mg, 0.16 mmol) was added to the solution followed by Oxone (566 mg, 0.92 mmol). The reaction mixture was then heated to 70 °C and stirred at this temperature for 16 h. The mixture was then cooled to 0 °C to precipitate the insoluble hypervalent iodine compounds. The reaction mixture was then filtered and washed with water (2 x 5 mL), followed by DCM (2 x 5 mL). The filtrate was extracted with DCM (2 x 10 mL) and the organic phases were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The reaction was unsuccessful as no product was obtained, as well as no alcohol being recovered from the reaction.

Attempted synthesis of benzyl 2-formyl-2H-1,4-oxazine-4(3H)-carboxylate, ***30***



Chemical Formula: $C_{13}H_{13}NO_4$
Molecular Weight: 247.25

Scheme 29

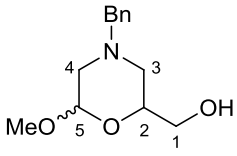
DMSO (0.32 mL, 4.61 mmol) was added slowly to a stirred solution of oxalyl chloride (0.2 mL, 2.61 mmol) in dry DCM (4 mL) at -60 ºC. The mixture was stirred at this temperature for 10 min and then **27** (500 mg, 2.00 mmol), as a solution in dry DCM (2 mL), was added. The reaction mixture was stirred for a further 15 min

before triethylamine (1.4 mL, 10.03 mmol) was added and the mixture being warmed to room temperature. During the reaction an aldehyde peak was observed in the ^{1}H NMR (9.62 ppm) however, the signal disappeared during the course of the reaction. Additionally, none of the starting alcohol was recovered from the reaction mixture.

Scheme 30

Alcohol **27** (200 mg, 0.80 mmol) was dissolved in DMSO (2.5 mL) and IBX (336 mg, 1.20 mmol) was added. The reaction mixture was stirred at ambient temperature for 16 h. Water was then added to precipitate the hypervalent iodine compounds, which were then filtered off. The filtrate was extracted with DCM and the organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The reaction was unsuccessful with no product was obtained, as well as no starting alcohol being recovered from the reaction.

(4-Benzyl-6-methoxymorpholin-2-yl)methanol, ***32***



Chemical Formula: $C_{13}H_{19}NO_3$
Molecular Weight: 237.29

General Procedure

Tetra-*n*-butylammonium fluoride was added to a stirred solution of **24** in dry THF at 0 °C. The solution was then allowed to stir at 0 °C for a further 2 h. The reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The alcohol was then purified by column chromatography (80% diethyl ether in petrol) to yield **32** as a colourless oil.

Scheme 32*, *Table 8

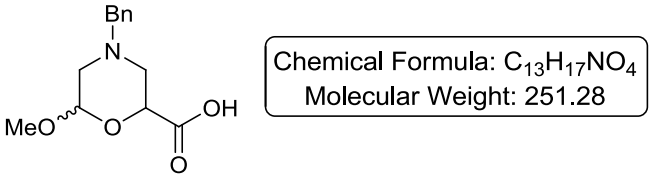
The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of tetra-*n*-butylammonium fluoride, (b) amount of substrate **24**, (c) volume of dry THF, (d) amount of **32**, (e) yield, and (f) *dr*.

Entry 1: (a) 33 mL, 33.0 mmol, 1 M in THF, (b) 13.0 g, 33.0 mmol, (c) 400 mL, (d) 7.73 g, (e) 99%, and (g) 3:2.

Entry 2: (a) 91 mL, 91.0 mmol, 1 M in THF, (b) 35.8 g, 91.0 mmol, (c) 600 mL, (d) 19.3 g, (e) 90%, and (g) 3:2.

FTIR (CH_2Cl_2): 2883, 3031, 3598 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.93-2.03 (m, 1.6H, H3, H4), 2.27 (dd, ^2J = 11.7 Hz, J = 2.9 Hz, 0.4H, H4), 2.72-2.74 (m, 0.6H, H3), 2.75-2.77 (m, 0.4H, H3), 2.85-2.92 (m, 1H, H4), 3.44 (s, 1.2H, OCH_3), 3.49-3.75 (m, 5.8H, OCH_3, H1, benzylic CH_2), 3.76-3.83 (m, 0.6H, H2), 4.06-4.14 (m, 0.4H, H2), 4.57 (dd, J = 8.4 Hz, J = 2.4 Hz, 0.6H, H5), 4.74 (bs, 0.4H, H5), 7.28-7.35 ppm (m, 5H, ArH).
^{13}C NMR (125 MHz, $CDCl_3$): 53.4, 53.6, 55.2, 55.7, 56.5, 56.7, 62.7, 63.3, 63.8, 64.2, 69.0, 74.3, 97.4, 100.6, 127.3, 128.3, 128.4, 129.2, 129.5, 136.7, 137.4 ppm.
HRMS *m/z* (ESI) calc for $C_{13}H_{20}NO_3$ (M^++H): 238.1438. Found: 238.1440.

*Attempted synthesis of 4-benzyl-6-methoxymorpholine-2-carboxylic acid, **33***



Scheme 33

Jones' reagent was prepared by dissolving chromium trioxide (670 mg, 6.6 mmol) in distilled water (1.3 mL). Concentrated sulfuric acid (0.6 mL) was then slowly added

and the salts which precipitated were dissolved by adding the minimum quantity of distilled water.[26]

Alcohol **32** (106 mg, 0.45 mmol) was dissolved in acetone (2.5 mL) and the solution was cooled to 0 °C. Jones reagent was added dropwise until the orange colour persisted and then the reaction was stirred for 20 min. Isopropyl alcohol (1 mL) was added followed by water (1.5 mL) and ethyl acetate (10 mL). The organic phase was separated and washed with brine until neutral, dried over Na_2SO_4, and concentrated *in vacuo*. The reaction was unsuccessful as no product was obtained, as well as no starting alcohol being recovered from the reaction.

Scheme 34

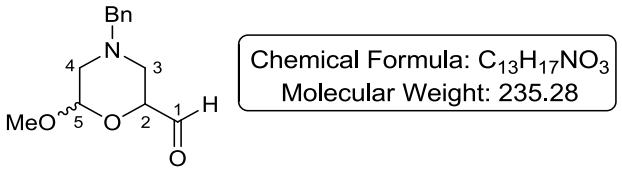
Alcohol **32** (91 mg, 0.38 mmol) was dissolved in a mixture of acetonitrile:H_2O (2:1, 5 mL). 2-Iodobenzoic acid (18 mg, 0.08 mmol) was added to the solution followed by Oxone (271 mg, 0.44 mmol). The reaction mixture was heated to 70 °C and stirred at this temperature for 16 h. The mixture was cooled to 0 °C to precipitate the insoluble hypervalent iodine compounds, which was then filtered and washed with water (2 x 5 mL), followed by DCM (2 x 5 mL). The filtrate was extracted with DCM (2 x 10 mL) and the organic phases were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The reaction was unsuccessful as no product was obtained, as well as no starting alcohol being recovered from the reaction.

Scheme 36

Alcohol **32** (281 mg, 1.18 mmol) was dissolved in acetone (12 mL) and the solution was cooled to 0 °C. 15% aq $NaHCO_3$ (4 mL) was added followed by NaBr (6 mg, 0.06 mmol) and TEMPO (2 mg, 0.01 mmol). TCCA (550 mg, 2.37 mmol) was then added in 4 portions over 20 min. The reaction mixture was warmed to ambient temperature and stirred at this temperature for 16 h. Isopropyl alcohol (0.7 mL) was then added and the mixture was filtered through a bed of celite and washed with diethyl ether. The filtrate was then concentrated *in vacuo*. A saturated aqueous

solution of sodium bicarbonate (4 mL) was added to the residual mixture and this was washed with a mixture of ethyl acetate/1 M HCl and the aqueous phase was extracted with ethyl acetate (x 2). The organic phases were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The reaction was unsuccessful as no product was obtained, as well as no starting alcohol being recovered from the reaction.

4-Benzyl-6-methoxymorpholine-2-carbaldehyde, ***34***



Scheme 37

DMSO (0.68 mL, 9.69 mmol) was added slowly to a stirred solution of oxalyl chloride (0.47 mL, 5.48 mmol) in dry DCM (9 mL) at -60 ºC. The mixture was stirred at this temperature for 10 min and **32** (1.0 g, 4.21 mmol), as a solution in dry DCM (3 mL), was added. The reaction mixture was stirred for a further 15 min before triethylamine (2.9 mL, 21.07 mmol) was added. The mixture was then warmed to ambient temperature and allowed to stir for 1 h. The reaction mixture was quenched with saturated ammonium chloride solution and the organic phase was separated. The organic phase was washed with water (x 2) and brine. The organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (80% ether in petrol) to yield **34** as an off yellow oil (571 mg, 58% yield, 1:1 *dr*).

General Procedure

DMSO was added slowly to a stirred solution of oxalyl chloride in dry DCM at -60 ºC. The mixture was stirred at this temperature for 10 min and then **32**, as a solution in dry DCM, was slowly added. The reaction mixture was stirred for a further 15 min before triethylamine was added. The mixture was then warmed to 0 °C and toluene

was added. The slurry was concentrated *in vacuo* to remove only the DCM before being purified by column chromatography (80% diethyl ether in petrol) to yield **34** as a pale yellow oil.

Scheme 38, ***Table 9***

The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of DMSO, (b) amount of oxalyl chloride, (c) volume of dry DCM, (d) amount of substrate **32**, (e) volume of dry DCM, (f) amount of triethylamine, (g) volume of toluene, (h) amount of **34**, (i) yield, and (k) *dr*.

Entry 1: (a) 0.47 mL, 9.7 mmol, (b) 0.47 mL, 5.5 mmol, (c) 9 mL, (d) 1.0 g, 4.2 mmol, (e) 3 mL, (f) 2.9 mL, 21.1 mmol, (g) 10 mL, (h) 932 mg, (i) 94%, and (j) 1:1

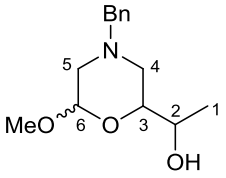
Entry 2: (a) 3.1 mL, 43.0 mmol, (b) 2.1 mL, 24.3 mmol, (c) 40 mL, (d) 4.40 g, 18.7 mmol, (e) 13 mL, (f) 13.0 mL, 93.5 mmol, (g) 10 mL, (h) 3.56 g, (i) 82%, and (j) 1:1

Entry 3: (a) 13.3 mL, 193.9 mmol, (b) 9.0 mL, 109.6 mmol, (c) 180 mL, (d) 19.3 g, 84.3 mmol, (e) 60 mL, (f) 57.0 mL, 421 mmol, (g) 15 mL, (h) 18.8 g, (i) 98%, and (j) 1:1

FTIR (CH_2Cl_2): 1737 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 2.18-2.33 (m, 1.5H, H3, H4), 2.40 (dd, ^2J = 11.7 Hz, J = 3.1 Hz, 0.5H, H4), 2.76-2.83 (m, 1.5H, H3, H4), 2.93-2.98 (m, 0.5H, H4), 3.47-3.60 (m, 5H, OCH_3, benzylic CH_2), 4.09 (dd, J = 8.7 Hz, J = 3.3 Hz, 0.5H, H2), 4.47 (dd, J = 9.7 Hz, J = 3.2 Hz, 0.5H, H2), 4.64 (dd, J = 6.8 Hz, J = 2.5 Hz, 0.5H, H5), 4.82 (apparent t, J = 2.5 Hz, 0.5H, H5), 7.26-7.37 (m, 5H, ArH), 9.65 (s, 0.5H, H1), 9.74 ppm (s, 0.5, H1).
^{13}C NMR (125 MHz, $CDCl_3$): 51.0, 51.1, 55.1, 55.2, 55.9, 56.1, 62.1, 62.4, 73.7, 77.5, 97.1, 99.6, 127.0, 127.9, 128.6, 128.8, 135.8, 136.3, 199.8, 200.2 ppm.

Due to the sensitive nature of the substrate accurate mass spectral details could not be obtained.

1-(4-Benzyl-6-methoxymorpholin-2-yl)ethanol, ***35***



Chemical Formula: $C_{14}H_{21}NO_3$
Molecular Weight: 251.32

Scheme 39

Lithium chloride (40 mg, 0.93 mmol) was placed in a three necked round bottom flask which was flame dried under vacuum and allowed to cool under a blanket of nitrogen. Methyllithium (0.85 mL, 0.93 mmol, 1.1 M in diethyl ether) was added and the resultant mixture was cooled to 0 °C. Aldehyde **34** (110 mg, 0.46 mmol), as a dry diethyl ether solution (0.3 mL), was then slowly added and the mixture was stirred at 0 °C for 16 h. The reaction mixture quenched with a saturated aqueous solution of ammonium chloride and the organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The alcohol was purified by column chromatography (60-80% diethyl ether in petrol) to yield **35** as a colourless oil (52 mg, 45% yield).

Scheme 40, ***Table 10***,

Entry 1:

Aldehyde **34** (177 mg, 0.75 mmol) was dissolved dry THF (0.5 mL) and the resultant mixture was cooled to 0 °C. Methylmagnesium chloride (0.8 mL, 1.50 mmol, 2 M in THF) was then slowly added and the mixture was stirred at 0 °C for 16 h. The reaction mixture then quenched with a saturated aqueous solution of ammonium chloride and the organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The alcohol was purified by column chromatography (60-80% diethyl ether in petrol) to yield **35** as a colourless oil (110 mg, 58% yield).

General Procedure

Lithium chloride was placed in a three necked round bottom flask which was flame dried under vacuum and allowed to cool under a blanket of nitrogen. Methylmagnesium chloride was added and the resultant mixture was cooled to 0 °C. Aldehyde **34**, as a dry THF solution, was slowly added and the mixture was stirred at 0 °C for a further 2 h. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride and the organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant alcohol was purified by column chromatography (60-80% diethyl ether in petrol) to yield **35** as a colourless oil.

Scheme 40, ***Table 10***

Entry 2:

The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of lithium chloride, (b) amount of methylmagnesium chloride, (c) amount of substrate **34**, (d) volume of dry THF (e) amount of **35**, and (f) yield.

Entry 2: (a) 270 mg, 6.4 mmol, (b) 3.2 mL, 6.4 mmol, 2 M in THF, (c) 750 mg, 3.2 mmol, (d) 2.3 mL, (e) 698 mg, and (f) 85%,

Entry 3: (a) 1.26 g, 29.8 mmol, (b) 14.9 mL, 29.8 mmol, 2 M in THF, (c) 3.50 g, 14.9 mmol, (d) 11 mL, (e) 3.31 g, and (f) 89%.

Entry 4: (a) 3.4 g, 80.8 mmol, (b) 27 mL, 80.8 mmol, 3 M in THF, (c) 9.5 g, 40.4 mmol, (d) 27 mL, (e) 9.4 g, and (f) 93%,.

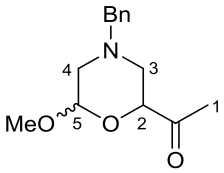
FTIR (CH_2Cl_2): 3032, 3599 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 1.17-1.24 (m, 3H, H1), 1.86-2.31 (m, 2H, H4, H5), 2.75-2.91 (m, 2H, H4, H5), 3.40-3.63 (m, 6H, benzylic CH_2, H2, OCH_3), 3.84-3.97 (m, 1H, H3), 4.52-4.57 (m 0.5H, H6), 4.70-4.77 (m, 0.5H, H6), 7.30-7.37 ppm (m, 5H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): 18.4, 18.5, 52.2, 55.1, 55.6, 56.4, 56.7, 62.9, 63.4, 68.4, 68.5, 71.9, 97.5, 100.6, 127.3, 128.3, 129.2, 129.5, 136.7, 137.5 ppm.

HRMS *m/z* (ESI) calc for $C_{14}H_{22}NO_3$ (M^++H): 252.1594. Found: 252.1595.

1-(4-Benzyl-6-methoxymorpholin-2-yl)ethanone, ***36***



Chemical Formula: $C_{14}H_{19}NO_3$
Molecular Weight: 249.31

General Procedure

DMSO was added slowly to a stirred solution of oxalyl chloride in dry DCM at -60 ^oC. The mixture was stirred at this temperature for 10 min and then **35**, as a solution in dry DCM, was slowly added. The reaction mixture was stirred for a further 15 min before triethylamine was added. The mixture was warmed to ambient temperature and allowed to stir for 1 h. The reaction mixture was quenched with saturated aqueous solution of ammonium chloride, and the organic layer was separated. After washing with water (x 2) and brine, the organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-50% diethyl ether in petrol) to yield **36** as an off yellow oil.

Scheme 41, ***Table 11***

The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of DMSO, (b) amount of oxalyl chloride, (c)

volume of dry DCM, (d) amount of substrate **35**, (e) volume of dry DCM, (f) amount of triethylamine, (g) amount of **36**, (h) yield, and (i) *dr*.

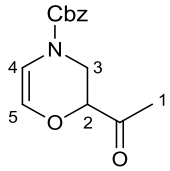
Entry 1: (a) 0.45 mL, 6.42 mmol, (b) 0.30 mL, 3.62 mmol, (c) 6.2 mL, (d) 700 mg, 2.8 mmol, (e) 2 mL, (f) 2.0 mL, 14.0 mmol, (g) 506 mg, (h) 73%, and (i) 1:1.

Entry 2: (a) 2.2 mL, 30.3 mmol, (b) 1.5 mL, 17.0 mmol, (c) 30 mL, (d) 3.3 g, 13.0 mmol, (e) 10 mL, (f) 9.0 mL, 65.9 mmol, (g) 2.42 g, (h) 74%, and (i) 1:1.

Entry 3: (a) 6.1 mL, 86.0 mmol, (b) 4.2 mL, 48.6 mmol, (c) 83 mL, (d) 9.4 g, 37.4 mmol, (e) 28 mL, (f) 26 mL, 187 mmol, (g) 7.0 g, (h) 75%, and (i) 1:1.

FTIR (CH_2Cl_2): 1718, 2828, 3031 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.91-2.04 (m, 1.5H, H3, H4), 2.08-2.15 (m, 0.5H, H4), 2.22 (s, 1.5H, H1), 2.29 (s, 1.5H, H1), 2.83-2.92 (m, 1H, H3), 3.00-3.14 (m, 1H, H4), 3.48 (s, 1.5H, OCH_3), 3.50-3.62 (m, 3.5H, benzylic CH_2, OCH_3), 4.09 (dd, J = 10.5 Hz, J = 2.9 Hz, 0.5H, H2), 4.45 (dd, J = 10.4 Hz, J = 2.9 Hz, 0.5H, H2), 4.56 (dd, J = 8.5 Hz, J = 2.4 Hz, 0.5H, H5), 4.80 (bs, 0.5H, H5), 7.29-7.56 ppm (m, 5H, ArH).
^{13}C NMR (125 MHz, $CDCl_3$): 26.3, 53.0, 53.1, 55.3, 55.5, 56.2, 56.5, 62.5, 63.0, 74.3, 79.2, 97.5, 100.7, 127.4, 128.3, 128.4, 129.1, 129.4, 136.4, 137.0, 207.1, 207.2 ppm.
HRMS *m/z* (ESI) calc for $C_{14}H_{20}NO_3$ (M^++H): 250.1438. Found: 250.1440.

Benzyl 2-acetyl-2H-1,4-oxazine-4(3H)-carboxylate, ***10***



Chemical Formula: $C_{14}H_{15}NO_4$
Molecular Weight: 261.27

General Procedure

Benzylchloroformate was added to a stirred solution of **36** in dry DCM. The mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The resultant oil was then dissolved in toluene and *p*-toluenesulfonic acid was added the mixture. The mixture was then stirred at reflux for 2 h using Dean-Stark apparatus. The solution was then cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The oil was then purified by column chromatography (0-40% diethyl ether in petrol) to yield **10** as a pale yellow oil.

Scheme 42, ***Table 12***

The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of benzylchloroformate, (b) amount of substrate **36**, (c) volume of dry DCM, (d) amount of *p*-toluenesulfonic acid, (e) volume of toluene, (f) amount of **10**, and (g) yield.

Entry 1: (a) 0.4 mL, 2.79 mmol, (b) 497 mg, 2.00 mmol, (c) 11 mL, (d) 152 mg, 0.80 mmol, (e) 32 mL, (f) 318 mg, and (g) 61%.

Entry 2: (a) 1.9 mL, 13.6 mmol, (b) 2.4 g, 9.7 mmol, (c) 54 mL, (d) 739 mg, 3.9 mmol, (e) 160 mL, (f) 1.65 g, and (g) 65%.

FTIR (CH_2Cl_2): 1666, 1710 cm^{-1}.

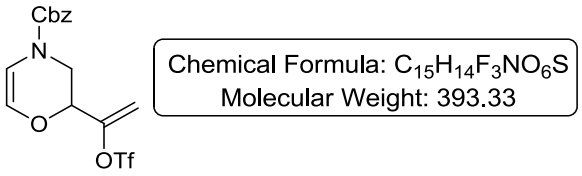
^{1}H NMR (400 MHz, $CDCl_3$): 2.30 (s, 3H, H1), 3.71 (dd, ^2J = 13.2 Hz, J = 6.5 Hz, 0.5H, H3), 3.80 (dd, ^2J = 13.4 Hz, J = 6.3 Hz, 0.5H, H3), 3.95 (bd, ^2J = 13.4 Hz, 0.5H, H3), 4.05 (bd, ^2J = 13.0 Hz, 0.5H, H3), 4.37-4.43 (m, 1H, H2), 5.17-5.26 (m, 2H, benzylic CH_2), 6.01 (d, J = 4.8 Hz, 0.5H, H4), 6.13 (d, J = 4.8 Hz, 0.5H, H4), 6.29 (d, J = 4.8 Hz, 0.5H, H5), 6.43 (d, J = 4.8 Hz, 0.5H, H5), 7.30-7.46 ppm (m, 5H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): 26.2, 41.7, 42.2, 67.9, 78.1, 78.5, 106.5, 107.1, 127.6, 128.2, 128.4, 128.6, 135.7, 135.9, 148.0, 206.4 ppm.

HRMS *m/z* (ESI) calc for $C_{14}H_{16}NO_4$ (M^++H): 262.1074. Found: 262.1079.

A ratio of 1:1 of rotamers was observed in the ^{1}H NMR.

Attempted synthesis of benzyl 2-(1-(((trifluoromethyl)sulfonyl)oxy)vinyl)-2H-1,4-oxazine-4(3H)-carboxylate, ***29***



Scheme 44, ***Table 13***

Entry 1:

n-BuLi (0.47 mL, 1.12 mmol, 2.36 M in hexane) was added to a solution of diisopropylamine (0.16 mL, 1.12 mmol) in dry THF (1.3 mL) at 0 °C. The mixture was stirred for a further 30 min at 0 °C. The reaction mixture was then cooled to -78 °C and **10** (266 mg, 1.02 mmol), as a dry THF (5 mL) solution, was added and stirred for a further 1 h at -78 °C. *N*-Phenyl-bis-trifluoromethane sulfonimide (400 mg, 1.12 mmol), as a dry THF solution (1.3 mL), was then added to the mixture at -78 °C. The mixture was warmed to ambient temperature and stirred at this temperature for a further 1 h. Water was then added and the organic phase was

separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-30% diethyl ether in petrol) to yield the starting ketone (**10**) (80 mg, 30% recovery).

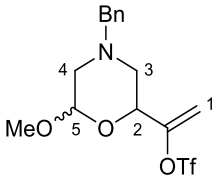
Entry 2:

n-BuLi (0.24 mL, 0.58 mmol, 2.36 M in hexane) was added to a solution of diisopropylamine (80 µL, 0.58 mmol) in dry THF (0.7 mL) at 0 °C. The mixture was stirred for a further 30 min at 0 °C. The reaction mixture was then cooled to -78 °C and **10** (137 mg, 0.52 mmol), as a dry THF (2.6 mL) solution, was added and was allowed to stir for a further 1 h at -78 °C. *N*-Phenyl-bis-trifluoromethane sulfonimide (206 mg, 0.58 mmol), as a dry THF solution (0.7 mL), was added to the mixture at -78 °C and the mixture was warmed to 0 °C and stirred at this temperature for a further 1 h. Water was then added and the organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-30% diethyl ether in petrol) to yield the starting ketone (**10**) (38 mg, 28% recovery).

Scheme 45

KHMDS (0.94 mL, 0.47 mmol, 0.5 M in toluene) was slowly added to a stirred solution of ketone **10** (102 mg, 0.39 mmol) in dry THF (10 mL) at -78 °C. The mixture was allowed to stir at -78 °C for 3 h. *N*-Phenyl-bis-trifluoromethane sulfonimide was then added as a solid in one portion. The reaction mixture was stirred at -78 °C for a further 3 h before being warmed to ambient temperature. Brine was added and the organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-30% diethyl ether in petrol) to yield the starting ketone (**10**) (40 mg, 39% recovery).

1-(4-Benzyl-6-methoxymorpholin-2-yl)vinyl trifluoromethanesulfonate, ***38***



Chemical Formula: $C_{15}H_{18}F_3NO_5S$
Molecular Weight: 381.37

General Procedure

KHMDS was slowly added to a stirred solution of ketone **36** in dry THF at -78 °C. The mixture was allowed to stir at this temperature for 15 min. *N*-Phenyl-*bis*-trifluoromethane sulfonimide was then added as a solid in one portion. The reaction mixture was stirred at -78 °C for a further 15 min before being warmed to ambient temperature. Brine was added and the organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-30% diethyl ether in petrol) to yield **38**, which was used directly in the next step.

The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of KHMDS, (b) amount of substrate **36**, (c) volume of dry THF, (d) amount of *n*-phenyl-*bis*-trifluoromethane sulfonimide, and (e) amount of **38**.

Scheme 47, ***Table 14***

Entry 1: (a) 4.2 mL, 2.11 mmol, 0.5 M in toluene, (b) 552 mg, 2.11 mmol, (c) 55 mL, (d) 754 mg, 2.11 mmol, and (e) 746 mg (crude).

Entry 2: (a) 7.7 mL, 3.83 mmol, 0.5 M in toluene, (b) 1.0 g, 3.83 mmol, (c) 100 mL, (d) 1.4 g, 3.83 mmol, and (e) 1.1 g (crude).

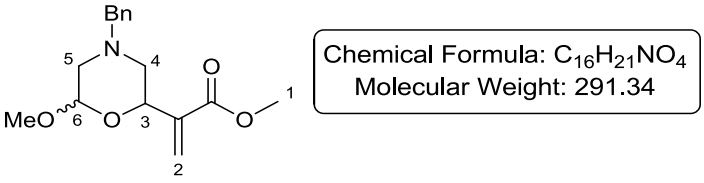
FTIR (CH_2Cl_2): 1423, 1673 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 2.00 (dd, ^{2}J = 11.2 Hz, J = 8.7 Hz, 0.6H, H3), 2.05-2.11 (m, 0.6H, H4), 2.17-2.23 (m, 0.4H, H3), 2.35 (dd, ^{2}J = 11.8 Hz, J = 2.8 Hz, 0.4H, H4), 2.84-3.00 (m, 2H, H3, H4), 3.44 (s, 1H, OCH_3), 3.52-3.66 (m, 4H, OCH_3, benzylic CH_2), 4.29 (d, J = 9.9 Hz, 0.6H, H5), 4.56-4.64 (m, 1H, H2), 4.77 (bs, 0.4H, H5), 5.27-5.35 (m, 2H, H1), 7.29-7.36 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 54.7, 55.2, 55.5, 56.1, 56.5, 62.4, 62.9, 67.6, 72.2, 97.4, 100.7, 105.4, 105.7, 120.0 (q, ^{1}J = 319.4 Hz), 127.5, 128.4, 129.1, 129.3, 136.3, 136.9, 152.5, 153.3 ppm.
^{19}F NMR (376 MHz, $CDCl_3$): -74.0 ppm.

A ratio of 3:2 of rotamers was observed in the ^{1}H NMR.

Due to the sensitive nature of the substrate accurate mass spectral details could not be obtained.

Methyl 2-(4-benzyl-6-methoxymorpholin-2-yl)acrylate, ***39***



General Procedure

Palladium acetate was added to a stirred solution of **38** in MeCN at ambient temperature. Triphenylphosphine was then added followed by triethylamine and methanol. The flask was evacuated and back filled with carbon monoxide (x 3) *via* a three way tap attached to a vacuum manifold and a carbon monoxide balloon. After 15 min, further palladium acetate was added and the flask was evacuated and purged with carbon monoxide (x 3) from a balloon. The reaction mixture turned a deep red colour. The mixture was stirred for a further 2 h at ambient temperature. Brine was then added to the reaction mixture and the organic layer was separated, dried over

Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-40% diethyl ether in petrol) to yield **39** as a pale oil.

Scheme 47, ***Table 14***

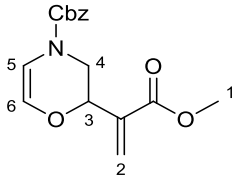
The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of palladium acetate, (b) amount of substrate **38**, (c) volume of MeCN, (d) amount of triphenylphosphine, (e) amount of triethylamine, (f) amount of methanol, (g) amount of palladium acetate, (h) amount of **39**, and (i) yield, and (j) *dr*.

Entry 1: (a) 26 mg, 0.12 mmol, (b) 746 mg, (c) 7.5 mL, (d) 61 mg, 0.23 mmol, (e) 0.55 mL, 3.92 mmol, (f) 3.2 mL, 78.40 mmol, (g) 26 mg, 0.12 mmol, (h) 270 mg, (i) 43% (over two steps), and (j) 1:1.

Entry 2: (a) 38 mg, 0.17 mmol, (b) 1.10 g, (c) 10 mL, (d) 91 mg, 0.35 mmol, (e) 0.81 mL, 5.78 mmol, (f) 4.7 mL, 116 mmol, (g) 38 mg, 0.17 mmol, (h) 435 mg, and (i) 40% (over two steps), and (j) 1:1.

FTIR (CH_2Cl_2): 1606, 1709 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.82 (dd, ^2J = 10.9 Hz, J = 9.9 Hz, 0.5H, H4), 1.89-1.98 (m, 1H, H5), 2.28 (dd, ^2J = 11.7 Hz, J = 2.8 Hz, 0.5H, H4), 2.88-2.93 (m, 1H, H4), 3.03-3.13 (m, 1H, H5), 3.42 (s, 1.5H, OCH_3), 3.50-3.69 (m, 3.5H, benzylic CH_2, OCH_3), 3.77 (s, 3H, H1), 4.56-4.62 (m, 1H, H3), 4.76 (d, J = 2.6 Hz, 0.5H, H6), 4.95 (d, J = 9.6 Hz, 0.5H, H6), 5.96 (apparent t, J = 1.5 Hz, 0.5H, H2), 6.08 (apparent t, J = 1.5 Hz, 0.5H, H2), 6.36 (apparent t, J = 1.5 Hz, 0.5H, H2), 6.38 (apparent t, J = 1.5 Hz, 0.5H, H2), 7.31-7.35 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 51.8, 51.9, 55.2, 56.2, 56.4, 57.8, 62.3, 62.9, 66.4, 71.7, 97.6, 100.8, 126.3, 126.5, 127.2, 128.2, 128.3, 128.5, 129.1, 129.4, 137.3, 128.5, 166.0 ppm.
HRMS *m/z* (ESI) calc for $C_{16}H_{22}NO_4$ (M^++H): 292.1543. Found: 292.1546.

Benzyl 2-(3-methoxy-3-oxoprop-1-en-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, ***7***



Chemical Formula: $C_{16}H_{17}NO_5$
Molecular Weight: 303.31

Scheme 48

Benzylchloroformate (0.23 mL, 1.68 mmol) was added to a stirred solution of **39** (326 mg, 1.12 mmol) in dry DCM (7.5 mL). The mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The resultant oil was then dissolved in toluene (18 mL) and *p*-toluenesulfonic acid (43 mg, 0.22 mmol) was added to the mixture. The mixture was then stirred at reflux for 4 h using a Dean-Stark apparatus. The solution was then cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-30% diethyl ether in petrol) to yield **7** as a pale yellow oil (178 mg, 53% yield).

Scheme 49

Benzylchloroformate (98 µL, 0.69 mmol) was added to a stirred solution of **39** (118 mg, 0.41 mmol) in dry DCM (2.7 mL). The mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The resultant oil was then dissolved in benzene (7 mL) and *p*-toluenesulfonic acid (15 mg, 0.08 mmol) was added to the mixture. The mixture was then stirred at reflux for 4 h using a Dean-Stark apparatus. The solution was then cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-30% diethyl ether in petrol) to yield **7** as a pale yellow oil (45 mg, 37% yield).

Scheme 50

Benzylchloroformate (108 µL, 0.73 mmol) was added to a stirred solution of **39** (125 mg, 0.43 mmol) in dry DCM (2.8 mL). The mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The resultant oil was dissolved in *n*-hexane (7 mL) and *p*-toluenesulfonic acid (16 mg, 0.09 mmol) was added to the mixture. The mixture was then stirred at reflux for 4 h using a Dean-Stark apparatus. *p*-Toluenesulfonic acid (16 mg, 0.09 mmol) was then added and the reaction mixture was stirred at reflux for a further 20 h. The solution was then cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-30% diethyl ether in petrol) to yield **7** as a pale yellow oil (41 mg, 32% yield).

FTIR (CH_2Cl_2): 1666, 1710 cm^{-1}.

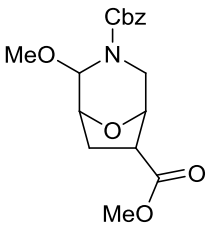
^{1}H NMR (400 MHz, $CDCl_3$): 3.13 (dd, ^2J = 12.9 Hz, J = 8.1 Hz, 0.6H, H4), 3.22 (dd, ^2J = 13.0 Hz, J = 8.1 Hz, 0.4H, H4), 3.79 (s, 1.2H, H1), 3.83 (s, 1.8H, H1), 4.25 (d, ^2J = 12.7 Hz, 0.4H, H4), 4.33 (d, ^2J = 13.5 Hz, 0.6H, H4), 4.79 (t, J = 6.8 Hz, 1H, H3) 5.15-5.32 (m, 2H, benzylic CH_2), 5.97-5.99 (2 x overlapping s, 1H, H2), 6.03 (d, J = 4.8 Hz, 0.6H, H5), 6.16 (d, J = 4.8 Hz, 0.4H, H5), 6.28 (d, J = 4.8 Hz, 0.6H, H6), 6.40 (d, J = 4.8 Hz, 0.4H, H6), 6.47 (s, 1H, H2), 7.35-7.42 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 45.8, 46.4, 52.1, 52.2, 67.6, 67.8, 71.4, 71.8, 105.7, 106.2, 127.7, 127.8, 128.0, 128.1, 128.3, 128.6, 128.7, 129.9, 136.1, 136.7, 137.0, 152.0, 165.4 ppm.

HRMS *m/z* (ESI) calc for $C_{16}H_{21}N_2O_5$ (M^++NH_4): 321.1445. Found: 321.1443.

A ratio of 3:2 of rotamers was observed in the ^{1}H NMR.

Attempted synthesis of 3-benzyl 6-methyl 2-methoxy-8-oxa-3-azabicyclo[3.2.1]octane-3,6-dicarboxylate, ***8***



Chemical Formula: $C_{17}H_{21}NO_6$
Molecular Weight: 335.35

Scheme 52

p-Toluenesulfonic acid (90 mg, 0.47 mmol), followed by methanol (19 µL, 0.47 mmol), were added to a stirred solution of **7** (144 mg, 0.47 mmol) in acetonitrile (3 mL). The reaction mixture was stirred at room temperature for 3 h. TLC analysis after this time showed only starting material to be present. As such, the reaction mixture was heated to 35 °C and stirred at this temperature for 6 h. After this time, the reaction mixture was cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-100% diethyl ether in petrol), to yield only degradation products.

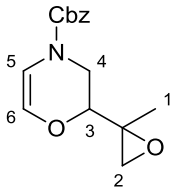
Scheme 53

TMSOTf (114 µL, 0.63 mmol), followed by methanol (25 µL, 0.63 mmol), was added to a stirred solution of **7** (190 mg, 0.63 mmol) in dry DCM (3 mL) at -20 °C. The reaction was warmed to ambient temperature, during which time the reaction mixture turned from yellow in colour to dark brown. The reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-100% diethyl ether in petrol), to yield only degradation products.

Scheme 54

Titanium tetrachloride (333 µL, 0.33 mmol, 1 M in DCM), followed by methanol (13 µL, 0.33 mmol), was added to a stirred solution of **7** (101 mg, 0.33 mmol) in dry DCM (2 mL) at -60 °C. The reaction mixture was stirred at -60 °C for 3 h, after which time, only starting material was observed by TLC analysis. The reaction mixture was therefore warmed to room temperature with darkening to a black colour on warming. The reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-100% diethyl ether in petrol), to yield only degradation products.

Benzyl 2-(2-methyloxiran-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, ***41***



Chemical Formula: $C_{15}H_{17}NO_4$
Molecular Weight: 275.30

General Procedure

Sodium hydride was added to a stirred solution of trimethylsulfoxonium iodide in dry THF and the reaction mixture was heated to 65 °C and stirred at this temperature for 2 h. After this time the reaction mixture was cooled to ambient temperature and **10**, as a dry THF solution, was added. The reaction mixture was subsequently heated to 35 °C and stirred for 16 h. The reaction was then cooled to ambient temperature, quenched with water, and diluted with diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-40% diethyl ether in petrol) to yield **41** as a colourless oil.

Scheme 56, ***Table 15***

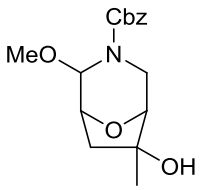
The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of trimethylsulfoxonium iodide, (b) amount of sodium hydride, (c) volume of dry THF, (d) amount of substrate **10**, (e) volume of dry THF, (f) amount of **41**, and (g) yield.

Entry 1: (a) 110 mg, 0.50 mmol, (b) 12 mg, 0.50 mmol, (c) 2.8 mL, (d) 101 mg, 0.38 mmol, (e) 1 mL, (f) 70 mg, and (g) 66%.

Entry 2: (a) 185 mg, 0.84 mmol, (b) 20 mg, 0.84 mmol, (c) 4.7 mL, (d) 169 mg, 0.65 mmol, (e) 1.5 mL, (f) 94 mg, and (g) 53%.

FTIR (CH_2Cl_2): 1236, 1665, 1703 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.35-1.44 (m, 3H, H1), 2.62-2.71 (m, 1H, H2), 2.79-2.92 (m, 1H, H2), 3.09-3.24 (m, 0.6H, H4), 3.31 (dd, ^2J = 12.4 Hz, J = 9.3 Hz, 0.4H, H4), 3.59 (bd, J = 9.6 Hz, 0.4H, H3), 3.67-3.78 (m, 0.6H, H3), 4.13 (apparent t, J = 11.7 Hz, 0.4H, H4), 4.21-4.31 (m, 0.6H, H4), 5.17-5.27 (m, 2H, benzylic CH_2), 5.95-5.97 (m, 0.6H, H5), 6.08-6.10 (m, 0.4H, H5), 6.24-6.26 (m, 0.6H, H6), 6.34-6.39 (m, 0.4H, H6), 7.37-7.40 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 17.1, 17.2, 42.2, 42.4, 42.7, 42.9, 50.6, 52.2, 53.3, 55.5, 55.6, 56.1, 67.8, 75.4, 75.6, 75.8, 76.0, 105.4, 105.6, 106.0, 106.2, 127.0, 127.6, 128.1, 128.3, 128.4, 128.5,128.6, 128.8, 129.6, 129.8, 136.0, 141.0, 151.8, 151.9, 152.2 ppm.
HRMS *m/z* (ESI) calc for $C_{15}H_{21}N_2O_4$ (M^++NH_4): 293.1496. Found: 293.1500.

Attempted synthesis of benzyl 6-hydroxy-2-methoxy-6-methyl-8-oxa-3 azabicyclo[3.2.1]octane-3-carboxylate, ***42***



Chemical Formula: $C_{16}H_{21}NO_5$
Molecular Weight: 307.34

Scheme 57

41 (70 mg, 0.25 mmol) in methanol (1 mL) was heated to reflux for 26 h after which time only starting material was observed by TLC analysis. The reaction mixture was cooled to ambient temperature and the reaction mixture was transferred to a microwave vial and placed in the microwave. The reaction mixture was irradiated at 70 °C for 30 min. Again, after this time only starting material was observed by TLC analysis. As such, the reaction mixture was irradiated at 90 °C for 1 h. Only the starting epoxide was present in the reaction mixture, therefore, the reaction mixture was then irradiated at 110 °C for a further 1 h. Methanol was then removed *in vacuo* and the resultant oil was then purified by column chromatography (0-100% ethyl acetate in petrol), to yield **43** (36 mg, 46%) as well as **41** (21 mg, 30% recovered).

Scheme 58, ***Table 16***

Entry 1:

Boron trifluoride diethyl etherate (9 µL, 0.07 mmol) was added to a stirred solution of **41** (94 mg, 0.34 mmol) and methanol (0.03 mL, 0.68 mmol) in dry DCM (3.4 mL). The solution was stirred at ambient temperature for 16 h. The reaction was then quenched with water and the organics separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-100% ethyl acetate in petrol) to yield **43** as a colourless oil (63 mg, 60% yield).

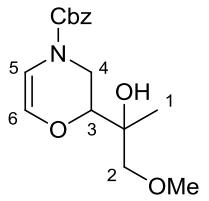
Entry 2:

Boron trifluoride diethyl etherate (11 µL, 0.08 mmol) was added to a stirred solution of **41** (114 mg, 0.41 mmol) in dry DCM (4.1 mL). The resultant solution was stirred at ambient temperature for 16 h. Methanol (33 µL, 0.82 mmol) was added and the reaction mixture was stirred for a further 3 h at this temperature. The reaction was quenched with water and the organic layer separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-100% ethyl acetate in petrol), however only degradation products were obtained.

Scheme 59

p-Toluenesulfonic acid (14 mg, 0.07 mmol) and methanol (29 µL, 0.72 mmol) were added to a stirred solution of **41** (100 mg, 0.36 mmol) in acetonitrile (3.6 mL). After 4 h, a further quantity of *p*-toluenesulfonic acid (14 mg, 0.07 mmol) was added to the reaction mixture and after a further 4 h the reaction was quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-100% ethyl acetate in petrol), however only degradation products were obtained.

Benzyl 2-(2-hydroxy-1-methoxypropan-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, ***43***



Chemical Formula: $C_{16}H_{21}NO_5$
Molecular Weight: 307.34

FTIR (CH_2Cl_2): 1709, 3562 cm^{-1}.

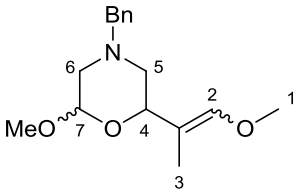
^{1}H NMR (400 MHz, $CDCl_3$): 1.23-1.27 (m, 3H, H1), 3.09-3.30 (m, 1.6H, H2), 3.37-3.43 (m, 4H, MeO, H4), 3.50-3.56 (m, 0.4H, H2), 3.81-3.89 (m, 1H, H4), 4.22-4.44 (m, 1H, H3), 5.21 (s, 2H, benzylic CH_2), 5.94-5.98 (m, 0.6H, H5), 6.06-6.11 (m,

0.4H, H5), 6.24-6.26 (m, 0.6H, H6), 6.35-6.38 (m, 0.4H, H6), 7.31-7.49 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 18.8, 19.3, 20.7, 21.1, 41.3, 41.4, 41.8, 41.9, 59.3, 59.4, 67.6, 67.6, 67.7, 72.0, 72.2, 75.4, 76.2, 76.6, 105.6, 106.2, 128.1, 128.2, 128.3, 128.6, 128.8, 129.3, 129.9, 126.2, 152.1, 152.3 ppm.

HRMS *m/z* (ESI) calc for $C_{16}H_{22}NO_5$ (M^++H): 308.1492. Found: 308.1497.

4-Benzyl-2-methoxy-6-(1-methoxyprop-1-en-2-yl)morpholine, ***53***



Chemical Formula: $C_{16}H_{23}NO_3$
Molecular Weight: 277.36

Scheme 63

KHMDS (3.1 mL, 1.56 mmol, 0.5 M in toluene) was added dropwise to a stirred slurry of methoxymethyltriphenylphosphonium chloride (535 mg, 1.56 mmol) in dry THF (27 mL) at -78 °C. The resultant slurry was warmed to 0 °C and stirred for 40 min, during which time the reaction mixture turned deep red in colour. Ketone **36** (300 mg, 1.20 mmol), as a dry THF (4 mL) solution, was added dropwise and stirred for a further 30 min at 0 °C. The reaction mixture was diluted with diethyl ether and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-30% diethyl ether in petrol) to yield **53** as a colourless oil (234 mg, 70%).

FTIR (CH_2Cl_2): 1635 cm^{-1}.

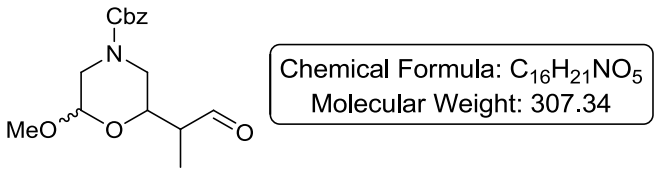
^{1}H NMR (400 MHz, $CDCl_3$):1.54-1.64 (m, 3H, H3), 1.81-1.91 (m, 0.4H, H5), 1.98-2.21 (m, 1.6H, H5, H6), 2.55-2.69 (m, 1H, H5), 2.80-2.88 (m, 1H, H6), 3.38-3.61 (m, 8H, H1, OCH_3, benzylic CH_2), 3.92-3.95 (m, 0.4H, H4), 4.48-4.54 (m, 0.6H, H7),

4.67-4.72 (m, 0.6H, H4), 5.06 (dd, *J* = 10.8 Hz, *J* = 2.4 Hz, 0.4H, H7), 5.77-5.83 (m, 0.6H, H2), 6.07-6.10 (m, 0.4H, H2), 7.28-7.34 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 10.0, 12.9, 54.9, 55.2, 55.4, 56.3, 56.4, 56.7, 59.4, 59.5, 59.6, 70.4, 75.7, 97.5, 100.5, 100.6, 111.6, 111.8, 112.0, 127.1, 127.2, 128.2, 129.2, 129.4, 137.1, 137.6, 137.7, 143.5, 144.6, 145.0 ppm.

HRMS *m/z* (ESI) calc for $C_{16}H_{24}NO_3$ (M^++H): 278.1751. Found: 278.1748.

Attempted synthesis of benzyl 2-methoxy-6-(1-oxopropan-2-yl)morpholine-4-carboxylate, ***51***



Scheme 64**, **Table 17

Entry 1:

Benzylchloroformate (0.12 mL, 0.81 mmol) was added to a stirred solution of **53** (150 mg, 0.54 mmol) in dry DCM (3.6 mL) and the mixture was stirred at ambient temperature for 16 h. *p*-Toluenesulfonic acid (9 mg, 0.05 mmol) was added to the reaction mixture and after 2 h the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-100% diethyl ether in petrol), to yield **55** as a colourless oil (122 mg, 82% yield).

Entry 2:

Benzylchloroformate (0.11 mL, 0.75 mmol) was added to a stirred solution of **53** (138 mg, 0.50 mmol) in dry DCM (3.6 mL) and the mixture was stirred at ambient temperature for 16 h. The reaction mixture was cooled to -20 °C and *p*-

toluenesulfonic acid (8 mg, 0.05 mmol) was added. After 2 h the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-100% diethyl ether in petrol), to yield the undesired bisaldehyde **55** as a colourless oil (102 mg, 75% yield).

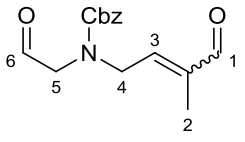
Entry 3:

Benzylchloroformate (0.07 mL, 0.49 mmol) was added to a stirred solution of **53** (91 mg, 0.33 mmol) in dry DCM (2.5 mL) and the mixture was stirred at ambient temperature for 16 h. Trifluoroacetic acid (2.5 µL, 0.03 mmol) was added to the reaction mixture and after 2 h the reaction was stopped as **55** was observed by TLC analysis.

Entry 4:

Benzylchloroformate (0.12 mL, 0.87 mmol) was added to a stirred solution of **53** (161 mg, 0.58 mmol) in dry DCM (3.6 mL) and the mixture was stirred at ambient temperature for 16 h. Oxalic acid dihydrate (7.3 mg, 0.06 mmol) was added to the reaction mixture and after 3 h the reaction was stopped as **55** was observed by TLC analysis.

Benzyl 3-methyl-4-oxobut-2-enyl(2-oxoethyl)carbamate, ***55***



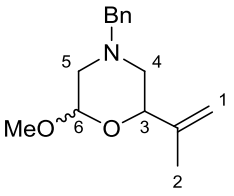
Chemical Formula: $C_{15}H_{17}NO_4$
Molecular Weight: 275.30

FTIR (CH_2Cl_2): 1647, 1683 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 1.68 (s, 1.5H, H2), 1.78 (s, 1.5H, H2), 4.10 (s, 1H, H5), 4.19 (s, 1H, H5), 4.24 (d, *J* = 5.9 Hz, 1H, H4), 4.31 (d, *J* = 5.6 Hz, 1H, H4),

5.15-5.18 (m, 2H, benzylic CH_2), 6.40-6.52 (m, 1H, H3), 7.29-7.41 (m, 5H, ArH), 9.40 (s, 0.5H, H6), 9.44 (s, 0.5H, H6), 9.60 (s, 0.5H, H1), 9.64 ppm (s, 0.5H, H1).
^{13}C NMR (100 MHz, $CDCl_3$): 14.8, 46.2, 46.6, 57.0, 57.5, 67.6, 67.7, 127.6, 127.9, 127.1, 135.3, 139.9, 140.3, 146.9, 147.0, 155.2, 155.5, 193.7, 196.3, 196.4 ppm.
HRMS *m/z* (ESI) calc for $C_{15}H_{18}NO_4$ (M^++H): 276.1230. Found: 276.1234.

4-Benzyl-2-methoxy-6-(prop-1-en-2-yl)morpholine, ***56***



Chemical Formula: $C_{15}H_{21}NO_2$
Molecular Weight: 247.33

General Procedure

Potassium *tert*-butoxide was added portionwise to a stirred slurry of methyltriphenylphosphonium bromide in dry THF at 0 ºC. The resultant yellow slurry was stirred at this temperature for 30 min. A solution of **36** in dry THF was added dropwise, and the resultant slurry was stirred at 0 ºC for a further 30 min. The mixture was then warmed to ambient temperature before being quenched with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-30% diethyl ether in petrol) to yield **56** as a pale yellow oil.

Scheme 66, ***Table 18***

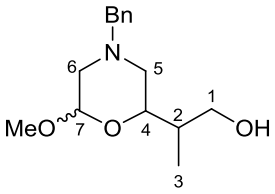
The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of potassium *tert*-butoxide, (b) amount of methyltriphenylphosphonium bromide, (c) volume of dry THF, (d) amount of substrate **36**, (e) volume of dry THF, (f) amount of **56**, (g) yield, and (h) *dr*.

Entry 1: (a) 246 mg, 2.2 mmol, (b) 786 mg, 2.2 mmol, (c) 15 mL, (d) 500 mg, 2.0 mmol, (e) 5 mL, (f) 386 mg, (g) 78%, and (h) 3:2.

Entry 2: (a) 3.5 g, 30.9 mmol, (b) 11.0 g, 30.9 mmol, (c) 250 mL, (d) 7.0 g, 28.1 mmol, (e) 30 mL, (f) 5.4 g, (g) 78%, and (h) 3:2.

FTIR (CH_2Cl_2): 1656 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.75-1.77 (m, 3H, H2), 1.89-2.09 (m, 1.6H, H4, H5), 2.23 (d, ^2J = 11.9 Hz, 0.4H, H5), 2.77-2.92 (m, 2H, H4, H5), 3.41 (s, 1.2H, OCH_3), 3.47-3.62 (m, 3.8H, OCH_3, benzylic CH_2), 4.06 (d, J = 10.4 Hz, 0.6H, H3), 4.41 (d, J = 8.1 Hz, 0.4H, H3), 4.55 (d, J = 2.5 Hz, 0.6H, H6), 4.72 (bs, 0.4H, H6), 4.99 (s, 1H, H1), 5.01 (s, 0.4H, H1), 5.04 (s, 0.6H, H1), 7.23-7.39 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 19.2, 19.3, 55.1, 55.4, 56.3, 56.6, 62.7, 63.3, 71.2, 97.4, 100.4, 111.7, 111.9, 127.2, 128.2, 128.3, 129.2, 129.5, 136.8, 137.3, 142.8, 143.4 ppm.
HRMS *m/z* (ESI) calc for $C_{15}H_{22}NO_2$ (M^++H): 248.1645. Found: 248.1648.

2-(4-Benzyl-6-methoxymorpholin-2-yl)propan-1-ol, ***57***



Chemical Formula: $C_{15}H_{23}NO_3$
Molecular Weight: 265.35

General Procedure

Borane dimethyl sulfide was added to a stirred solution of **56** in dry THF at ambient temperature. The solution was then stirred for 16 h. The reaction mixture was then cooled to 0 °C and water, followed by 3 M NaOH and 30% hydrogen peroxide, were added. The reaction mixture was stirred for a further 1 h. The reaction mixture was diluted with diethyl ether and the organics separated. The aqueous was extracted with diethyl ether (x 2) and the combined extracts were dried over Na_2SO_4, and

concentrated *in vacuo*. The resulting oil was then purified by column chromatography (40-100% diethyl ether in petrol) to yield **57** as a colourless oil.

Scheme 67, ***Table 19***

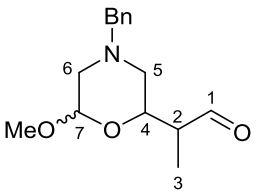
The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of borane dimethyl sulfide, (b) amount of substrate **56**, (c) volume of dry THF, (d) amount of water, (e) amount of 3 M NaOH, (f) amount of 30% hydrogen peroxide, (g) amount of **57**, and (h) yield.

Entry 1: (a) 0.03 mL, 0.4 mmol, 10 M, (b) 100 mg, 0.4 mmol, (c) 4 mL, (d) 0.4 mL, (e) 1.1 mL, (f) 0.8 mL, (g) 60 mg, and (h) 56%.

Entry 2: (a) 0.9 mL, 1.6 mmol, 10 M, (b) 389 mg, 1.6 mmol, (c) 15 mL, (d) 1.5 mL, (e) 4.3 mL, (f) 3 mL, (g) 227 mg, and (h) 55%.

FTIR (CH_2Cl_2): 3424 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 0.88-1.01 (m, 3H, H3), 1.86-2.26 (m, 3H, H2, H5, H6), 2.65-2.91 (m, 2H, H5, H6), 3.40-3.79 (m, 7.6H, H1, H4, OCH_3, benzylic CH_2), 3.91-3.98 (m, 0.2H, H4), 4.11-4.16 (m, 0.2H, H4), 4.82-4.51 (m, 0.6H, H7), 4.66-4.69 (m, 0.4H, H7), 7.22-7.37 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 11.8, 12.1, 13.5, 13.6, 37.9, 38.0, 38.2, 54.5, 54.9, 55.0, 55.1, 55.4, 55.7, 55.8, 56.2, 56.3, 56.4, 62.7, 62.8, 63.3, 63.4, 65.7, 65.9, 66.7, 67.1, 70.6, 73.4, 75.9, 78.4, 97.2, 97.3, 100.7, 127.3, 128.3, 129.1, 129.4, 137.3, 137.4 ppm.
HRMS *m/z* (ESI) calc for $C_{15}H_{24}NO_3$ (M^++H): 266.1751. Found: 266.1754.

2-(4-Benzyl-6-methoxymorpholin-2-yl)propanal, ***58***



Chemical Formula: $C_{15}H_{21}NO_3$
Molecular Weight: 263.33

Scheme 69, Table 20

Entry 1:

DMSO (123 µL, 1.73 mmol) was slowly added to a stirred solution of oxalyl chloride (84 µL, 0.98 mmol) in dry DCM (2 mL) at -60 ºC. The mixture was stirred at this temperature for 10 min and then **57** (200 mg, 0.75 mmol), as a solution in dry DCM (1 mL), was slowly added. The reaction mixture was stirred for a further 15 min before triethylamine (0.53 mL, 3.77 mmol) was added. The mixture was warmed to 0 °C over 30 min, and the slurry was purified directly by column chromatography (80% diethyl ether in petrol) to yield **58** as a yellow oil (110 mg, 55%), as well as the starting alcohol **57** (62 mg, 31% recovered).

Entry 2:

DMSO (123 µL, 1.73 mmol) was slowly added to a stirred solution of oxalyl chloride (84 µL, 0.98 mmol) in dry DCM (2 mL) at -60 ºC. The mixture was stirred at this temperature for 10 min and then **57** (200 mg, 0.75 mmol), as a solution in dry DCM (1 mL), was slowly added. The reaction mixture was stirred for a further 15 min before triethylamine (0.53 mL, 3.77 mmol) was added. The mixture was warmed to ambient temperature and allowed to stir for 16 h. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride and the organic layer was separated. The organic layer was washed with water (x 2) followed by brine. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (80% diethyl ether in petrol) to

yield **58** as a yellow oil (120 mg, 61%), as well as the starting alcohol **57** (66 mg, 33% recovered).

Entry 3:

DMSO (0.3 mL, 4.20 mmol) was slowly added to a stirred solution of oxalyl chloride (0.25 mL, 2.93 mmol) in dry DCM (5 mL) at -60 ºC. The mixture was stirred at this temperature for 10 min and then **57** (338 mg, 1.27 mmol), as a solution in dry DCM (1.5 mL), was added. The reaction mixture was stirred for a further 15 min before triethylamine (1.1 mL, 7.64 mmol) was added. The mixture was warmed to ambient temperature and allowed to stir for 16 h. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride and the organic layer was separated. The organic layer was washed with water (x 2) and brine. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (80% diethyl ether in petrol) to yield **58** as a yellow oil (121 mg, 36%).

Scheme 70

IBX (178 mg, 0.63 mmol) was added to a stirred solution of alcohol **57** (130 mg, 0.49 mmol) in DMSO (1.5 mL) and the reaction mixture was stirred at ambient temperature for 16 h. Following this, water was added and the reaction mixture was filtered. The filtrate was extracted with DCM and the organic layer dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (80% diethyl ether in petrol) to yield **58** as a colourless oil (95 mg, 74%).

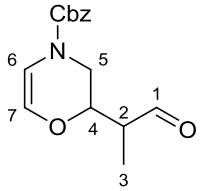
FTIR (CH_2Cl_2): 1724 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.06-1.21 (m, 3H, H3), 1.89-2.11 (m, 1.5H, H5, H6), 2.25-2.28 (m, 0.5H, H6), 2.40-2.49 (m, 0.5H, H2), 2.52-2.61 (m, 0.5H, H2), 2.70-2.93 (m, 2H, H5, H6), 3.37-3.63 (m, 5H, OCH_3, benzylic CH_2), 3.89 (t, J = 8.9 Hz,

0.5H, H4), 4.44-4.88 (m, 0.5H, H4), 4.56-4.63 (m, 0.5H, H7), 4.69 (s, 0.5H, H7), 7.26-7.36 (m, 5H, ArH), 9.74-9.85 ppm (m, 1H, H1).

^{13}C NMR (100 MHz, $CDCl_3$): 10.4, 10.5, 48.8, 49.0, 54.6, 55.1, 55.2, 55.3, 55.5, 56.3, 56.4, 62.6, 63.2, 69.4, 74.7, 97.3, 100.5, 127.4, 128.3, 128.4, 129.1, 129.3, 136.5, 203.5 ppm.

Due to the sensitive nature of the substrate accurate mass spectral details could not be obtained.

Attempted synthesis of benzyl 2-(1-oxopropan-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, ***45***



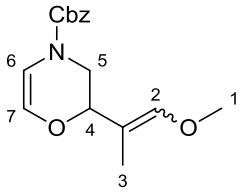
Chemical Formula: $C_{15}H_{17}NO_4$
Molecular Weight: 275.30

Scheme 71

Benzylchloroformate (0.1 mL, 0.67 mmol) was added to a stirred solution of **58** (110 mg, 0.42 mmol) in dry DCM (3 mL). The mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The resultant oil was dissolved in toluene (10 mL) and *p*-toluenesulfonic acid (16 mg, 0.08 mmol) was added to the mixture. The reaction mixture was then stirred at reflux for 30 min using Dean-Stark apparatus. The solution was cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-100% diethyl ether in petrol) to yield **55** as a colourless oil (36 mg, 31%) and none of the desired product.

Data for compound ***55*** *is shown on* ***page 165***

Benzyl 2-(1-methoxyprop-1-en-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, ***59***



Chemical Formula: $C_{16}H_{19}NO_4$
Molecular Weight: 289.33

General Procedure

KHMDS was added dropwise to a stirred slurry of methoxymethyltriphenylphosphonium chloride in dry THF at -78 °C. The resultant slurry was warmed to 0 °C and stirred for 40 min, during which time the reaction mixture turned deep red in colour. Ketone **10**, as a solution in dry THF, was added dropwise and stirred for a further 30 min. The reaction mixture was diluted with diethyl ether and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The oil was purified by column chromatography (0-30% diethyl ether in petrol) to yield **59** as a colourless oil.

Scheme 73, ***Table 21***

The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of KHMDS, (b) amount of methoxymethyltriphenylphosphonium chloride, (c) volume of dry THF, (d) amount of substrate **10**, (e) volume of dry THF, (f) amount of **59**, and (g) yield.

Entry 1: (a) 2.3 mL, 1.17 mmol, 0.5 M in toluene, (b) 401 mg, 1.17 mmol, (c) 28 mL, (d) 250 mg, 0.90 mmol, (e) 2 mL, (f) 195 mg, and (g) 71%.

Entry 2: (a) 4.8 mL, 2.38 mmol, 0.5 M in toluene, (b) 816 mg, 2.38 mmol, (c) 50 mL, (d) 460 mg, 1.76 mmol, (e) 4 mL, (f) 281 mg, and (g) 55%.

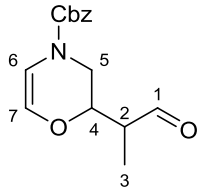
FTIR (CH_2Cl_2): 1665 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 1.54-1.70 (m, 3H, H3), 3.16-3.35 (m, 1H, H5), 3.60 (s, 1.8H, H1), 3.65 (s, 1.2H, H1), 3.93 (t, *J* = 13.0 Hz, 0.4H, H5), 3.96-4.20 (m, 1H, H4, H5), 4.86-4.90 (m, 0.6H, H4), 5.15-5.29 (m, 2H, benzylic CH_2), 5.92-5.99 (m, 1H, H2, H6), 6.10-6.15 (m, 1H, H2, H6), 6.22 (d, *J* = 4.7 Hz, 0.6H, H7), 6.34 (d, *J* = 4.7 Hz, 0.4H, H7), 7.31-7.46 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 9.0, 9.1, 10.3, 43.7, 44.3, 45.1, 45.7, 59.7, 59.8, 67.5, 67.6, 67.7, 70.1, 70.6, 75.4, 75.9, 104.9, 105.5, 109.4, 109.7, 128.1, 128.2, 128.3, 128.6, 129.4, 130.4, 130.5, 136.2, 136.3, 145.0, 145.2, 146.5, 146.7, 152.2

HRMS *m/z* (ESI) calc for $C_{16}H_{20}NO_4$ (M^++H): 290.1387. Found: 290.1391.

Attempted synthesis of benzyl 2-(1-oxopropan-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, ***45***



Chemical Formula: $C_{15}H_{17}NO_4$
Molecular Weight: 275.30

Scheme 74, ***Table 22***

Entry 1:

p-Toluenesulfonic acid (23 mg, 0.07 mmol) was added to a stirred solution of **59** (101 mg, 0.35 mmol) in acetonitrile (3.5 mL). The reaction mixture was stirred at ambient temperature for 30 min. The reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-100% ethyl acetate in petrol), however none of the desired product was obtained.

Entry 2:

p-Toluenesulfonic acid (12 mg, 0.06 mmol) was added to a stirred solution of **59** (84 mg, 0.29 mmol) and methanol (23 µL, 0.58 mmol) in acetonitrile (2.9 mL) at -20 °C. After 2 h the reaction was warmed to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-100% ethyl acetate in petrol), however none of the desired product was obtained.

Scheme 75

Oxalic acid dihydrate (4.4 mg, 0.04 mmol) was added to a stirred solution of **59** (101 mg, 0.35 mmol) in diethyl ether (3.5 mL) at ambient temperature. After 6 h only starting material was observed by TLC analysis, therefore a further quantity of oxalic acid dihydrate (4.4 mg, 0.04 mmol) was added and the reaction was stirred for a further 16 h. Again, starting material was still present therefore the reaction mixture was heated to 40 °C for 16 h, and then stirred for 72 h at ambient temperature. By TLC analysis only enol ether was present in the reaction mixture therefore a further quantity of oxalic acid dihydrate (13.2 mg, 0.11 mmol) was added and the reaction was heated to 40 °C for 16 h. After this time, only starting material was observed by TLC analysis therefore oxalic acid dihydrate (22.0 mg, 0.18 mmol) was added to the reaction mixture and the reaction was stirred at 40 °C for a further 36 h. The reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-30% diethyl ether in petrol) to recover **59** as a colourless oil (88 mg, 87%).

Scheme 76

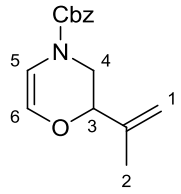
Trifluoroacetic acid (7 µL, 0.06 mmol) was added to a stirred solution of **59** (88 mg, 0.30 mmol) in DCM (3 mL). The reaction mixture was stirred at ambient temperature

for 16 h. After this time, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-100% ethyl acetate in petrol), however none of the desired product was obtained.

Scheme 77

Montmorillonite K10 (300 mg) was added to a stirred solution of **59** (182 mg, 0.63 mmol) in DCM (6.3 mL) and the slurry was stirred at ambient temperature for 16 h. The reaction mixture was filtered, the clay washed with methanol, the filtrate was then concentrated *in vacuo*, and purified by column chromatography (0-100% ethyl acetate in petrol), however none of the desired product was obtained.

Benzyl 2-(prop-1-en-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, ***60***



Chemical Formula: $C_{15}H_{17}NO_3$
Molecular Weight: 259.30

General Procedure

Potassium *tert*-butoxide was added portionwise to a stirred slurry of methyltriphenylphosphonium bromide in dry THF at 0 ºC. The resultant yellow slurry was stirred at this temperature for 30 min. A solution of **10** in dry THF was added dropwise and the resultant mixture was stirred at 0 ºC for a further 45 min. The mixture was then warmed to ambient temperature before being quenched with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-20% diethyl ether in petrol) to yield **60** as a pale yellow oil.

Scheme 79, ***Table 23***

The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of potassium *tert*-butoxide, (b) amount of methyltriphenylphosphonium bromide, (c) volume of dry THF, (d) amount of substrate **10**, (e) volume of dry THF, (f) amount of **60**, and (g) yield.

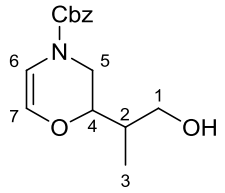
Entry 1: (a) 111 mg, 0.99 mmol, (b) 354 mg, 0.99 mmol, (c) 6 mL, (d) 200 mg, 0.77 mmol, (e) 1.6 mL, (f) 136 mg, and (g) 69%.

Entry 2: (a) 1.7 g, 15.4 mmol, (b) 5.5 g, 15.4 mmol, (c) 100 mL, (d) 3.1 g, 11.9 mmol, (e) 20 mL, (f) 2.7 g, and (g) 87%.

FTIR (CH_2Cl_2): 1665, 1703 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.79-1.82 (m, 3H, H2), 3.17 (dd, ^2J = 13.0 Hz, J = 8.7 Hz, 0.6H, H4), 3.27 (dd, ^2J = 12.8 Hz, J = 8.7 Hz, 0.4H, H4), 4.08 (bd, ^2J = 12.3 Hz, 0.4H, H4), 4.18-4.28 (m, 1.6H, H3, H4), 5.04 (bs, 1H, H1), 5.09 (d, ^2J = 5.6 Hz, 1H, H1), 5.18-5.27 (m, 2H, benzylic CH_2), 6.10 (d, J = 5.0 Hz, 0.6H, H5), 6.12 (d, J = 5.0 Hz, 0.4H, H5), 6.25 (d, J = 4.8 Hz, 0.6H, H6), 6.37 (d, J = 4.8 Hz, 0.4H, H6), 7.32-7.49 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 18.2, 18.3, 44.3, 44.9, 67.2, 75.7, 76.1, 104.7, 105.2, 112.9, 113.2, 127.6, 127.7, 127.8, 128.1, 128.5, 129.6, 135.6, 140.5, 151.4, 151.7 ppm.
HRMS *m/z* (ESI) calc for $C_{15}H_{18}NO_3$ (M^++H): 260.1281. Found: 260.1286.

A 3:2 ratio of rotamers was observed in the ^{1}H NMR.

Benzyl 2-(1-hydroxypropan-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, ***61***



Chemical Formula: $C_{15}H_{19}NO_4$
Molecular Weight: 277.32

General Procedure

9-BBN was added to a stirred solution of **60** in dry THF and the resultant solution was stirred at ambient temperature for 16 h. The reaction mixture was then cooled to 0 °C and water, followed by 3 M NaOH and 30% hydrogen peroxide, were added. The reaction mixture was then stirred for a further 1 h before being diluted with diethyl ether and the organics separated. The aqueous was extracted (x 2) with diethyl ether and the combined extracts were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (40-80% diethyl ether in petrol) to yield **61** as a colourless oil.

Alternative work up if impurity is present:

The organic layer was separated and the aqueous was extracted (x 2) with diethyl ether. The extracts were combined and a saturated aqueous solution of sodium metabisulfite was added and the mixture stirred vigorously for 10 min. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (40-80% diethyl ether in petrol) to yield **61** as a colourless oil.

Scheme 80, ***Table 24***

The following experiments were carried out using the above ***General Procedure***.
Data are reported as: (a) amount of 9-BBN, (b) amount of substrate **60**, (c) volume of

dry THF, (d) amount of water, (e) amount of 3 M NaOH, (f) amount of 30% hydrogen peroxide, (g) amount of **61**, and (h) yield.

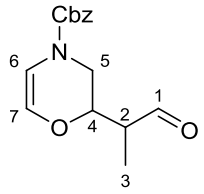
Entry 1: (a) 1 mL, 0.53 mmol, 0.5 M in THF, (b) 106 mg, 0.41 mmol, (c) 4 mL, (d) 0.4 mL, (e) 1.1 mL (f) 0.8 mL, (g) 73 mg, and (h) 65%.

Entry 2: (a) 14.4 mL, 7.2 mmol, 0.5 M in THF, (b) 1.1 g, 4.24 mmol, (c) 42 mL, (d) 4.2 mL, (e) 12 mL, (f) 8.3 mL, (g) 964 mg, and (h) 82%.

FTIR (CH_2Cl_2): 1665, 1694, 3477 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 0.99-1.04 (m, 3H, H3), 1.89-2.01 (m, 2H, H2, OH), 3.22 (dd, ^2J = 13.1 Hz, J = 8.7 Hz, 0.7H, H5), 3.35 (dd, ^2J = 12.7 Hz, J = 8.7 Hz, 0.3H, H5), 3.69-3.76 (m, 2H, H1), 3.81-3.88 (m, 1H, H4), 3.97-4.06 (m, 0.3H, H5), 4.13-4.20 (m, 0.7H, H5), 5.16-5.27 (m, 2H, benzylic CH_2), 5.92-5.95 (m, 0.7H, H6), 6.04-6.06 (m, 0.3H, H6), 6.24-6.26 (m, 0.7H, H7), 6.36-6.38 (m, 0.3H, H7), 7.31-7.45 ppm (m, 5H, ArH).
^{13}C NMR (125 MHz, $CDCl_3$): 13.2, 13.3, 37.2, 37.5, 44.0, 44.5, 65.5, 67.7, 67.8, 76.7, 105.7, 106.2, 128.1, 128.3, 128.6, 128.9, 129.3, 136.1, 152.2 ppm.
HRMS *m/z* (ESI) calc for $C_{15}H_{19}NO_4Na$ (M^++Na): 300.1206. Found: 300.1211.

A 7:3 ratio of rotamers was observed in the ^{1}H NMR.

Benzyl 2-(1-oxopropan-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, ***45***



Chemical Formula: $C_{15}H_{17}NO_4$
Molecular Weight: 275.30

Scheme 81

Attempt 1: with column chromatography

DMSO (59 µL, 0.83 mmol) was slowly added to a stirred solution of oxalyl chloride (40 µL, 0.47 mmol) in dry DCM (0.7 mL) at -60 ºC. The mixture was stirred at this temperature for 10 min and then **61** (101 mg, 0.36 mmol), as a solution in dry DCM (0.3 mL), was slowly added. The reaction mixture was stirred for a further 15 min before triethylamine (0.25 mL, 1.80 mmol) was added. The mixture was then warmed to 0 °C and the slurry was purified by column chromatography (80% diethyl ether in petrol). Unfortunately, neither the starting alcohol nor the desired aldehyde was obtained from the column.

^{1}H NMR showed aldehyde peak at 9.76 ppm and olefinic peaks at 5.94-6.07 ppm, which only integrated to 1.2H.

Attempt 2: without column chromatography

DMSO (0.18 mL, 2.3 mmol) was slowly added to a stirred solution of oxalyl chloride (0.11 mL, 1.3 mmol) in dry DCM (2 mL) at -60 ºC. The mixture was stirred at this temperature for 10 min and **61** (276 mg, 1.0 mmol), as a solution in dry DCM (1 mL), was added. The reaction mixture was stirred for a further 15 min before triethylamine (0.7 mL, 5.0 mmol) was slowly added. The mixture was then warmed to 0 ºC, quenched with a saturated aqueous solution of ammonium chloride, and the organic layer was separated. The organic layer was washed with water (x 2) and

brine, dried over Na_2SO_4, and concentrated *in vacuo*. Unfortunately, neither the starting alcohol nor the desired aldehyde were observed in the crude NMR.

Scheme 82

IBX (54 mg, 0.20 mmol) was added to a stirred solution of alcohol **61** (41 mg, 0.15 mmol) in DMSO (1 mL). The reaction mixture was stirred at ambient temperature for 16 h. After this time, water was added and the reaction mixture was filtered. The filtrate was extracted with DCM and the organic layer dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (80% diethyl ether in petrol), however, neither the starting alcohol nor the desired aldehyde was obtained from the column.

Scheme 83, ***Table 25***

Entry 1:

DMP (471 mg, 1.11 mmol) was added to a stirred solution of alcohol **61** (280 mg, 1.01 mmol) in dry DCM (6.3 mL). The reaction mixture was stirred at ambient temperature for 30 min, during which time a white precipitate formed. The reaction mixture was diluted with diethyl ether and DCM was removed *in vacuo*. The mixture was further diluted with diethyl ether and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate and saturated aqueous solution of sodium bicarbonate was added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography, (60% diethyl ether in petrol) to yield **45** as a colourless oil (222 mg, 80%).

Entry 2:

DMP (412 mg, 0.97 mmol) was added to a stirred solution of alcohol **61** (245 mg, 0.88 mmol) in dry DCM (5.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 h during which time a white precipitate formed. The reaction mixture was

diluted with diethyl ether and DCM was removed *in vacuo*. The mixture was further diluted with diethyl ether and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate and saturated aqueous solution of sodium bicarbonate was added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography, (60% diethyl ether in petrol) to yield **45** as a colourless oil (152 mg, 62%).

FTIR (CH_2Cl_2): 1662, 1699 cm^{-1}.

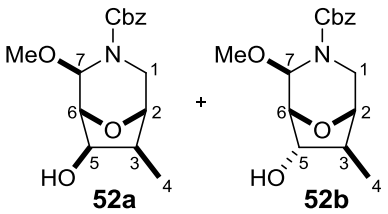
^{1}H NMR (400 MHz, $CDCl_3$): 1.14-1.26 (m, 3H, H3), 2.60-2.72 (m, 1H, H2), 3.34 (dd, ^2J = 12.7 Hz, J = 7.7 Hz, 0.6H, H5), 3.42 (dd, ^2J = 13.0 Hz, J = 7.9 Hz, 0.4H, H5), 3.95-4.20 (m, 2H, H4, H5), 5.17-5.26 (m, 2H, benzylic CH_2), 5.91 (d, J = 5.0 Hz, 0.6H, H6), 6.05 (d, J = 4.8 Hz, 0.4H, H6), 6.27 (d, J = 5.0 Hz, 0.6H, H7), 6.39 (d, J = 4.9 Hz, 0.4H, H7), 7.33-7.44 (m, 5H, ArH), 9.71-9.80 ppm (m, 1H, H1).

^{13}C NMR (100 MHz, $CDCl_3$): 9.7, 42.7, 43.2, 47.1, 47.3, 67.4, 73.2, 73.7, 105.2, 105.8, 127.6, 127.7, 127.8, 127.9, 128.1, 128.8, 135.4, 201.4, 201.6 ppm.

A 3:2 ratio of rotamers was observed in the ^{1}H NMR.

Due to the sensitive nature of the substrate accurate mass spectral details could not be obtained.

*Benzyl 7-hydroxy-2-methoxy-6-methyl-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate, **52a** and **52b***



Chemical Formula: $C_{16}H_{21}NO_5$
Molecular Weight: 307.34

General Procedure

Methanol followed by *p*-toluenesulfonic acid were added to a stirred solution of **45** in acetonitrile at ambient temperature. The reaction mixture was stirred for 16 h before being quenched with a saturated aqueous solution of sodium bicarbonate. The solution was diluted with diethyl ether and the organics were separated. The aqueous layer was extracted with diethyl ether (x 2) and the combined organic extracts were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (100% diethyl ether) to yield **52a** and **52b** as a colourless oil.

Scheme 86**, **Table 26

The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of methanol, (b) amount of *p*-toluenesulfonic acid, (c) amount of substrate **45**, (d) volume of acetonitrile, (e) amount of **52a** and **52b**, and (f) yield.

Entry 1: (a) 36 µL, 0.89 mmol, (b) 9 mg, 0.04 mmol, (c) 124 mg, 0.45 mmol, (d) 4.4 mL, (e) 79 mg, and (f) 58% (7:3).

Entry 2: (a) 65 µL, 1.61 mmol, (b) 15 mg, 0.08 mmol, (c) 222 mg, 0.81 mmol, (d) 8 mL, (e) 166 mg, and (f) 67% (7:3).

Scheme 87

Methanol (45 µL, 1.06 mmol) followed by methanesulfonic acid (4 µL, 0.05 mmol) were added to a stirred solution of **45** (147 mg, 0.53 mmol) in acetonitrile (5.3 mL) at ambient temperature and the reaction mixture was stirred for 16 h. Methanesulfonic acid (4 µL, 0.05 mmol) was added to the reaction and after a further 3 h the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate. The solution was diluted with diethyl ether and the organics were separated. The aqueous layer was extracted with diethyl ether (x 2) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (100% diethyl ether) to yield **52a** and **52b** as a colourless oil (91 mg, 56%, 7:3).

FTIR (CH_2Cl_2): 1679, 3488 cm^{-1}.

52a/b Mixture

^{1}H NMR (400 MHz, $CDCl_3$): 1.10-1.27 (m, 3H, H4), 1.82-2.13 (m, 1.3H, OH, H3), 2.12-2.37 (m, 0.7H, H3), 3.27-4.30 (m, 8H, H1, H2, H5, H6, OCH_3), 4.96-5.27 (m, 3H, H7, benzylic CH_2), 7.30-7.45 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 12.6, 12.7, 14.8, 19.1, 19.2, 29.8, 39.2, 39.4, 43.4, 44.6, 45.2, 45.3, 53.0, 54.8, 55.0, 55.5, 65.4, 67.1, 67.4, 73.2, 73.5, 77.5, 78.0, 79.0, 79.8, 80.0, 80.1, 80.5, 81.1, 81.5, 82.0, 83.8, 84.2, 127.4, 127.5, 127.6, 127.7, 127.8, 128.0, 128.1, 128.2, 135.4, 135.5, 155.3, 155.8 ppm.

Compound 52a *(major diastereomer)*

^{1}H NMR (400 MHz, $CDCl_3$): 1.10 (d, J = 2.2 Hz, 1.5H, H4), 1.12 (d, J = 2.2 Hz, 1.5H, H4), 1.82 (bs, 1H, OH), 2.23-2.37 (m, 1H, H3), 3.29 (s, 1.5H, OCH_3), 3.34 (dd, ^2J = 13.0 Hz, J = 2.3 Hz, 0.5H, H1), 3.40-3.45 (m, 2H, H1, OCH_3), 3.55 (bd, ^2J = 12.1 Hz, 0.5H, H1), 3.63 (bd, ^2J = 12.9 Hz, 0.5H, H1), 3.97 (s, 0.5H, H2), 4.04 (s, 0.5H, H2), 4.14 (d, J = 0.9 Hz, 0.5H, H6), 4.17 (d, J = 7.7 Hz, 0.5H, H5), 4.21-4.25 (m, 1H, H5, H6), 4.98 (d, J = 1.3 Hz, 0.5H, H7), 5.10 (d, J = 1.2 Hz, 0.5H, H7), 5.13-5.27 (m, 2H, carbamate CH_2), 7.31-7.45 ppm (m, 5H, ArH).

A 1:1 ratio of rotamers was observed in ^{1}H NMR.

Compound 52b *(minor diastereomer)*

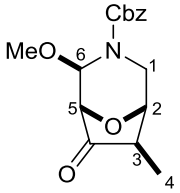
^{1}H NMR (600 MHz, $CDCl_3$): 1.19-1.23 (m, 3H, H4), 1.80-1.85 (m, 0.4H, H3), 1.87-1.92 (m, 0.6H, H3), 3.30 (s, 1.2H, OCH_3), 3.39-3.42 (m, 2.4H, OCH_3, H1), 3.47-3.51 (0.4H, H1), 3.63-3.67 (m, 0.4H, H1), 3.74-3.76 (m, 1H, H1, H2), 3.83 (bs, 0.6H, H2), 3.94-3.98 (m, 1H, H5), 4.15-4.18 (m, 0.6H, H6), 4.23-4.26 (m, 0.4H, H6), 5.14-5.21 (m, 2H, benzylic CH_2), 5.21 (bs, 0.6H, H7), 5.29 (bs, 0.4H, H7), 7.29-7.38 ppm (m, 5H, ArH).

A 3:2 ratio of rotamers was observed in ^{1}H NMR.

HRMS *m/z* (ESI) calc for $C_{16}H_{21}NO_5Na$ (M^++Na): 330.1312. Found: 330.1316.

*Stereochemistry of **52a** and **52b** was elucidated using NOESY spectra which are in the Appendix.*

Benzyl 2-methoxy-6-methyl-7-oxo-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate, ***62***



Chemical Formula: $C_{16}H_{19}NO_5$
Molecular Weight: 305.33

Scheme 91

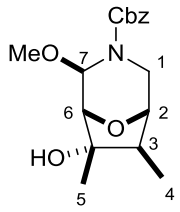
DMSO (60 µL, 0.83 mmol) was slowly added to a stirred solution of oxalyl chloride (40 µL, 0.47 mmol) in dry DCM (1 mL) at -60 ºC. The mixture was stirred at this temperature for 10 min and **52a** and **52b** as a 7:3 mixture (111 mg, 7:3, 0.36 mmol), as a solution in dry DCM (0.5 mL), was added. The reaction mixture was stirred for a further 15 min before triethylamine (252 µL, 1.81 mmol) was slowly added. The

mixture was then warmed to ambient temperature and stirred for 1 h before being quenched with a saturated aqueous solution of ammonium chloride and the organic layer separated. The organic layer was washed with water (x 2) and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (40% diethyl ether in petrol) to yield **62** as a colourless oil (81 mg, 74%).

FTIR (CH_2Cl_2): 1701, 1769 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.24-1.42 (m, 3H, H4), 2.24-2.45 (m, 1H, H3), 3.31 (s, 1.8H, OCH_3), 3.47 (s, 1.2H, OCH_3), 3.62-3.89 (m, 2H, H1), 4.10-4.48 (m, 2H, H2, H5), 5.03-5.33 (m, 3H, benzylic CH_2, H6), 7.30-7.53 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 14.3, 14.4, 43.2, 43.6, 44.3, 55.2, 55.9, 67.5, 67.6, 77.2, 77.5, 78.7, 79.2, 80.2, 80.6, 127.6, 127.9, 128.1, 131.2, 132.2, 135.1, 135.2, 141.3, 154.2, 155.4, 210.1 ppm.
HRMS *m/z* (ESI) calc for $C_{16}H_{23}N_2O_5$ (M^++NH_4): 323.1601. Found: 323.1608.

A 3:2 ratio of rotamers was observed in ^{1}H NMR.

Benzyl 7-hydroxy-2-methoxy-6,7-dimethyl-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate, ***64***



Chemical Formula: $C_{17}H_{23}NO_5$
Molecular Weight: 321.37

Scheme 92

Lithium chloride (15 mg, 0.35 mmol) was placed in a three-necked round bottom flask which was flame-dried under vacuum and allowed to cool under a blanket of nitrogen. Methylmagnesium chloride (117 µL, 0.35 mmol, 3 M in THF) was added and the resultant mixture was cooled to 0 °C. Ketone **62** (62 mg, 0.20 mmol), as a

dry THF (1 mL) solution, was slowly added and the mixture was stirred at 0 °C for a further 3 h. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride and the organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant alcohol was purified by column chromatography (60-80% diethyl ether in petrol) to yield **64** (46 mg, 70%) as a colourless oil.

FTIR (CH_2Cl_2): 1688, 3466 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): 1.09-1.16 (m, 3H, H4), 1.30-1.32 (m, 3H, H5), 1.96-2.12 (m, 1H, H3), 3.28 (s, 1.2H, OCH_3), 3.38-3.41 (m, 2.2H, OCH_3, H1), 3.46-3.49 (m, 0.6H, H1), 3.62-3.65 (m, 0.4H, H1), 3.69-3.71 (m, 0.6H, H6), 3.72-3.75 (m, 0.6H, H1), 3.75-3.78 (m, 0.8H, H2, H6), 3.83-3.85 (m, 0.6H, H2), 5.14-5.21 (m, 2H, benzylic CH_2), 5.27 (bs, 0.6H, H7), 5.34 (bs, 0.4H, H7), 7.28-7.37 ppm (m, 5H, ArH).

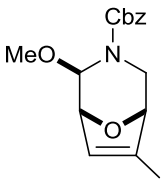
^{13}C NMR (100 MHz, $CDCl_3$): 14.6, 14.7, 24.2, 24.3, 44.9, 45.6, 45.9, 55.0, 55.5, 67.1, 67.2, 79.2, 80.2, 80.5, 81.2, 81.6, 83.5, 84.0, 127.4, 127.5, 127.7, 127.8, 128.1, 135.7, 155.7, 155.9, 212.1, 213.9 ppm.

HRMS *m/z* (ESI) calc for $C_{17}H_{23}NO_5Na$ (M^++Na): 344.1468. Found: 344.1467.

A 3:2 ratio of rotamers was observed in ^{1}H NMR.

*Stereochemistry of **64** was elucidated using a NOESY spectrum which is in the Appendix.*

Attempted synthesis of benzyl 2-methoxy-6-methyl-8-oxa-3-azabicyclo[3.2.1]oct-6-ene-3-carboxylate, ***63***



Chemical Formula: $C_{16}H_{19}NO_4$
Molecular Weight: 289.33

Scheme 95

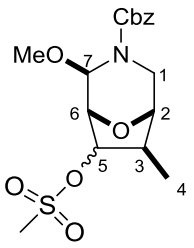
Eq. (1)

Methanesulfonyl chloride (63 µL, 0.82 mmol) followed by triethylamine (0.3 mL, 2.05 mmol) were added to a stirred solution of alcohol **52a** and **52b** (126 mg, 0.41 mmol, 7:3 *dr*) in dry DCM (0.8 mL) at 0 °C. The reaction was then warmed to ambient temperature and stirred for a further 6 h. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (50-80% diethyl ether in petrol) to yield the mesylate intermediate **65** as a pale yellow oil (72 mg, 46%).

Eq. (2)

DBU (42 µL, 0.28 mmol) was added to a stirred solution of **65** (72 mg, 0.19 mmol) in toluene (1 mL), and the reaction mixture was stirred at ambient temperature for 22 h. No product was observed therefore the reaction was heated to reflux for a further 26 h. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (50-80% diethyl ether in petrol) to recover **65** as a pale yellow oil (28 mg, 39% recovery).

Benzyl-2-methoxy-6-methyl-7-((methylsulfonyl)oxy)-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate, ***65***



Chemical Formula: $C_{17}H_{23}NO_7S$
Molecular Weight: 385.43

FTIR (CH_2Cl_2): 1701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 1.03-1.36 (m, 3H, H4), 2.17-2.29 (m, 0.2H, H3), 2.41-2.59 (m, 0.8H, H3), 2.72-4.70 (m, 10H, H1, H2, H6, OCH_3, SCH_3), 4.97-5.34 (m, 4H, H5, H7, benzylic CH_2), 7.26-7.43 ppm (m, 5H, ArH).

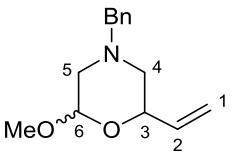
^{13}C NMR (100 MHz, $CDCl_3$): 13.5, 13.7, 18.5, 31.0, 37.1, 37.4, 37.7, 37.8, 37.9, 38.0, 38.9, 39.1, 39.6, 40.2, 40.4, 41.0, 42.5, 44.1, 44.2, 44.6, 44.8, 54.9, 55.0, 55.3, 55.6, 67.0, 67.3, 67.4, 67.5, 76.2, 76.5, 79.5, 79.6, 79.7, 80.0, 80.5, 81.0, 81.2, 81.3, 81.4, 81.6, 81.8, 82.7, 127.3, 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 135.2, 135.3, 135.5, 135.9, 155.1, 155.6 ppm.

HRMS *m/z* (ESI) calc for $C_{17}H_{24}NO_7S$ (M^++H): 386.1268. Found: 386.1268

Scheme 96

Burgess' reagent (141 mg, 0.59 mmol) was added to a stirred solution of **52a** and **52b** (139 mg, 0.45 mmol, 7:3 *dr*) in toluene (4.5 mL) at ambient temperature. The reaction mixture was stirred at this temperature for 24 h. The reaction was then heated to reflux for 16 h. The reaction was then cooled to ambient temperature and water was added. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo* to recover starting alcohol **52a**/**b** (32 mg, 23% recovery).

4-Benzyl-2-methoxy-6-vinylmorpholine, ***67***



Chemical Formula: $C_{14}H_{19}NO_2$
Molecular Weight: 233.31

Scheme 98*,* ***Table 27***

Entry 1:

Potassium *tert*-butoxide (263 mg, 2.34 mmol) was added portionwise to a stirred slurry of methyltriphenylphosphonium bromide (829 mg, 2.34 mmol) in dry THF (17 mL) at 0 ºC. The resultant yellow slurry was stirred at this temperature for 30 min. The solution was then cooled to -40 °C and a solution of **34** (459 mg, 2.0 mmol) in dry THF (3 mL) was added dropwise and the resultant slurry was stirred at 0 ºC for a further 30 min. The mixture was then warmed to ambient temperature before being quenched with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-30% diethyl ether in petrol) to yield **67** as a pale yellow oil (47 mg, 8%, 3:2 *dr*).

Entry 2:

Potassium *tert*-butoxide (210 mg, 1.9 mmol) was added portionwise to a stirred slurry of methyltriphenylphosphonium bromide (679 mg, 1.9 mmol) in dry THF (16 mL) at 0 ºC. The resultant yellow slurry was stirred at this temperature for 30 min before being cooled to -40 °C and transferred, *via* a cannula, to a solution of **34** (440 mg, 1.9 mmol) in dry THF (3 mL) at -40 °C. The resultant slurry was stirred at 0 ºC for a further 30 min. The mixture was then warmed to ambient temperature before being quenched with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was separated, washed with brine,

dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-30% diethyl ether in petrol) to yield **67** as a pale yellow oil (8 mg, 2%, 3:2 *dr*).

Entry 3:

Potassium *tert*-butoxide (183 mg, 1.63 mmol) was added portionwise to a stirred mixture of aldehyde **34** (384 mg, 1.63 mmol) and methyltriphenylphosphonium bromide (582 mg, 1.63 mmol) in dry THF (16 mL) at -40 ºC. The resultant mixture was then stirred at -40 °C for 30 min before being warmed to ambient temperature, quenched with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-30% diethyl ether in petrol) to yield **67** as a pale yellow oil (121 mg, 32%, 3:2 *dr*).

General Procedure

KHMDS was slowly added to a stirred mixture of aldehyde **34** and methyltriphenylphosphonium bromide in dry THF at -78 ºC. The resultant mixture was then warmed to -50 °C and stirred at this temperature for 50 min during which time the reaction mixture turned bright yellow in colour. The reaction was then warmed to ambient temperature and quenched with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-30% diethyl ether in petrol) to yield **67** as a pale yellow oil.

Scheme 99, ***Table 28***

The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of KHMDS, (b) amount of substrate **34**, (c) amount

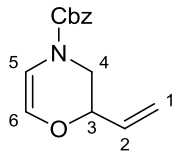
of methyltriphenylphosphonium bromide, (d) volume of dry THF, (e) amount of **67**, (f) yield, and (g) *dr*.

Entry 1: (a) 14.3 mL, 7.15 mmol, 0.5 M in toluene, (b) 1.53 g, 6.50 mmol, (c) 2.56 g, 7.15 mmol, (d) 14.3 mL, (e) 817 mg, (f) 57%, and (g) 3:2.

Entry 2: (a) 39 mL, 19.6 mmol, 0.5 M in toluene, (b) 4.2 g, 17.9 mmol, (c) 7.0 g, 19.7 mmol, (d) 200 mL, (e) 2.5 g, (f) 59%, and (g) 3:2.

FTIR (CH_2Cl_2): 1649 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.89-2.04 (m, 1.6H, H4, H5), 2.26 (dd, ^2J = 11.6 Hz, J = 2.8, 0.4H, H5), 2.70-2.93 (m, 2H, H4, H5), 3.43 (s, 1.2H, OCH_3), 3.53-3.56 (m, 3.8H, OCH_3, benzylic CH_2), 4.12-4.18 (m, 0.6H, H3), 4.46-4.52 (m, 0.4H, H3), 4.52 (dd, J = 8.5 Hz, J = 2.4, 0.6H, H6), 4.73 (bd, J = 2.4 Hz, 0.4H, H6), 5.16-5.21 (m, 1H, H1), 5.30-5.38 (m, 0.4H, H1), 5.61 (dt, J = 7.3 Hz, ^4J = 1.5 Hz, 0.6H, H1), 5.76-5.91 (m, 1H, H2), 7.28-7.36 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 54.6, 54.9, 55.9, 56.0, 56.6, 56.8, 62.1, 62.7, 74.0, 96.9, 99.9, 115.9, 116.2, 126.7, 126.8, 127.7, 127.8, 128.7, 128.9, 135.1, 135.7, 136.3, 136.9 ppm.
HRMS *m/z* (ESI) calc for $C_{14}H_{20}NO_2$ (M^++H): 234.1489. Found: 234.1483.

Benzyl 2-vinyl-2H-1,4-oxazine-4(3H)-carboxylate, ***68***



Chemical Formula: $C_{14}H_{15}NO_3$
Molecular Weight: 245.27

General Procedure

Benzylchloroformate was added to a stirred solution of **67** in dry DCM. The mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The resultant oil was then dissolved in toluene and *p*-toluenesulfonic acid was added to

the mixture. The mixture was then stirred at reflux for 2 h using Dean-Stark apparatus. The solution was then cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-40% diethyl ether in petrol) to yield **68** as a pale yellow oil.

Scheme 100**, **Table 29

The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of benzylchloroformate, (b) amount of substrate **67**, (c) volume of dry DCM, (d) volume of toluene, (e) amount of *p*-toluenesulfonic acid, (f) amount of **68**, and (g) yield.

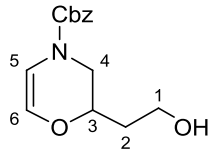
Entry 1: (a) 0.6 mL, 4.4 mmol, (b) 634 mg, 2.7 mmol, (c) 17 mL, (d) 50 mL, (e) 155 mg, 0.8 mmol (f) 340 mg, and (g) 51%.

Entry 2: (a) 2.4 mL, 17.2 mmol, (b) 2.5 g, 10.7 mmol, (c) 70 mL, (d) 200 mL, (e) 814 mg, 4.3 mmol (f) 1.8 g, and (g) 67%.

FTIR (CH_2Cl_2): 1701, 1662 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 3.20-3.33 (m, 1H, H4), 3.97-4.02 (m, 0.4H, H4), 4.08-4.13 (m, 0.6H, H4), 4.35-4.45 (m, 1H, H3), 5.22 (s, 2H, benzylic CH_2), 5.30-5.36 (m, 1H, H1), 5.40-5.47 (m, 1H, H1), 5.82-5.94 (m, 1H, H2), 5.97 (d, J = 5.0 Hz, 0.6H, H5), 6.10 (d, J = 5.0 Hz, 0.4H, H5), 6.24 (d, J = 5.0 Hz, 0.6H, H6), 6.37 (d, J = 5.0 Hz, 0.4H, H6), 7.32-7.45 ppm (m, 5H ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 45.8, 45.5, 67.2, 71.4, 73.1, 73.6, 104.8, 105.3, 117.7, 117.9, 127.5, 127.6, 127.7, 127.8, 128.1, 128.2, 129.1, 129.3, 133.1, 135.6 ppm.
HRMS *m/z* (ESI) calc for $C_{14}H_{19}N_2O_3$ (M^++NH_4): 246.1125. Found: 246.1128.

A ratio of 3:2 of rotamers was observed in the ^{1}H NMR.

Benzyl 2-(2-hydroxyethyl)-2H-1,4-oxazine-4(3H)-carboxylate, ***69***



Chemical Formula: $C_{14}H_{17}NO_4$
Molecular Weight: 263.29

General Procedure

9-BBN was added to a stirred solution of **68** in dry THF and the resultant solution was stirred at ambient temperature for 16 h. The reaction mixture was then cooled to 0 °C and water, followed by 3 M NaOH and 30% hydrogen peroxide, were added. The reaction mixture was then stirred for a further 1 h before being diluted with diethyl ether and the organics separated. The aqueous layer was extracted (x 2) with diethyl ether and the combined extracts were dried over Na_2SO_4, and concentrated *in vacuo*. The oil was then purified by column chromatography (40-80% diethyl ether in petrol) to yield **69** as a colourless oil.

Alternative work up if impurity is present:

The organics were separated and the aqueous layer was extracted (x 2) with diethyl ether. The extracts were combined and a saturated aqueous solution of sodium metabisulfite was added and the mixture stirred vigorously for 10 min. The organic layer were separated, dried over Na_2SO_4, and concentrated *in vacuo*. The oil was then purified by column chromatography (40-80% diethyl ether in petrol) to yield **69** as a colourless oil.

Scheme 101, ***Table 30***

The following experiments were carried out using the above ***General Procedure***.
Data are reported as: (a) amount of 9-BBN, (b) amount of substrate **68**, (c) volume of dry THF, (d) amount of water, (e) amount of 3 M NaOH, (f) amount of 30% hydrogen peroxide, (g) amount of **69**, and (h) yield.

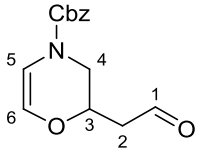
Entry 1: (a) 4.2 mL, 2.1 mmol, 0.5 M in THF, (b) 340 mg, 1.4 mmol, (c) 14 mL, (d) 1.4 mL, (e) 3.7 mL, (f) 2.7 mL, (g) 365 mg, and (h) 68 %.

Entry 2: (a) 21 mL, 13.9 mmol, 0.5 M in THF, (b) 1.7 g, 6.9 mmol, (c) 70 mL, (d) 7 mL, (e) 18 mL, (f) 13 mL, (g) 1.1 g, and (h) 56%.

FTIR (CH_2Cl_2): 1662, 1697, 3414 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.81-1.92 (m, 3H, H2, OH), 3.18 (dd, ^2J = 12.8 Hz, J = 8.3 Hz, 0.6H, H4), 3.26 (dd, ^2J = 13.1 Hz, J = 8.4 Hz, 0.4H, H4), 3.80-3.87 (m, 2H, H1) 4.05-4.16 (m, 2H, H3, H4), 5.20 (s, 2H, benzylic CH_2), 5.88 (d, J = 5.0 Hz, 0.6H, H5), 6.02 (d, J = 5.0 Hz, 0.4H, H5), 6.23 (d, J = 5.0 Hz, 0.6H, H6), 6.36 (d, J = 5.0 Hz, 0.4H, H6), 7.31-7.43 ppm (m, 5H, ArH).
^{13}C NMR (125 MHz, $CDCl_3$): 34.6, 34.7, 45.6, 46.3, 59.4, 67.7, 67.7, 71.7, 72.3, 105.5, 106.0, 128.1, 128.3, 128.6, 129.3, 136.1, 151.9, 152.2 ppm.
HRMS *m/z* (ESI) calc for $C_{14}H_{18}NO_4$ (M^++H): 264.1230. Found: 264.1223.

A ratio of 3:2 of rotamers was observed in the ^{1}H NMR.

Benzyl 2-(2-oxoethyl)-2H-1,4-oxazine-4(3H)-carboxylate, ***46***



Chemical Formula: $C_{14}H_{15}NO_4$
Molecular Weight: 261.27

General Procedure

DMP was added to a stirred solution of alcohol **69** in dry DCM. The reaction mixture was stirred at ambient temperature for 30 min during which time a white precipitate formed. The reaction mixture was diluted with diethyl ether and DCM was removed *in vacuo*. The mixture was further diluted with diethyl ether and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate and saturated aqueous solution of sodium bicarbonate was added. The organic layer was separated, washed with brine,

dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography, (60% diethyl ether in petrol) to yield **46** as a colourless oil.

Scheme 102**, **Table 31

The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of DMP, (b) amount of substrate **69**, (c) volume of dry DCM, (d) amount of **46**, and (e) yield.

Entry 1: (a) 136 mg, 0.32 mmol, (b) 81 mg, 0.29 mmol, (c) 1.8 mL, (d) 53 mg, and (e) 66%.

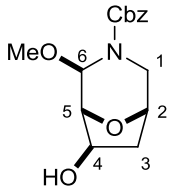
Entry 2: (a) 1.89 g, 4.43 mmol, (b) 1.06 g, 4.03 mmol, (c) 25 mL, (d) 751 mg, and (e) 75%.

FTIR (CH_2Cl_2): 1662, 1697 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 2.67-2.75 (m, 1H, H2), 2.77 (dd, ^2J = 7.7 Hz, J = 2.0 Hz, 0.6H, H2), 2.79 (dd, ^2J = 7.8 Hz, J = 2.1 Hz, 0.4H, H2), 3.26 (dd, ^2J = 13.0 Hz, J = 7.8 Hz, 0.6H, H4), 3.34 (dd, ^2J = 13.3 Hz, J = 8.1 Hz, 0.4H, H4), 3.96-4.07 (m, 1H, H4), 4.43-4.52 (m, 1H, H3), 5.17-5.23 (m, 2H, benzylic CH_2), 5.88 (d, J = 5.2 Hz, 0.6H, H5), 6.01 (d, J = 5.2 Hz, 0.4H, H5), 6.25 (d, J = 5.2 Hz, 0.6H, H6), 6.37 (d, J = 5.2 Hz, 0.4H, H6), 7.32-7.43 (m, 5H, ArH), 9.79-9.82 ppm (m, 1H, H1).
^{13}C NMR (125 MHz, $CDCl_3$): 44.9, 45.6, 45.7, 67.8, 67.9, 68.2, 68.7, 105.6, 106.1, 128.0, 128.1, 128.2, 128.4, 128.6, 129.1, 135.9, 136.0, 151.9, 152.2, 198.5, 198.7 ppm.

A ratio of 3:2 of rotamers was observed in the ^{1}H NMR.

Due to the sensitive nature of the substrate accurate mass spectral details could not be obtained.

Benzyl 7-hydroxy-2-methoxy-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate, ***66***



Chemical Formula: $C_{15}H_{19}NO_5$
Molecular Weight: 293.32

General Procedure

Methanol, followed by *p*-toluenesulfonic acid were added to a stirred solution of **46** in acetonitrile at ambient temperature. The reaction mixture was stirred for 16 h before being quenched with a saturated aqueous solution of sodium bicarbonate. The solution was diluted with diethyl ether and the organics were separated. The aqueous was extracted with diethyl ether (x 2) and the combined organics were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (100% diethyl ether) to yield **66** as a colourless oil.

Scheme 103, Table 32

The following experiments were carried out using the above ***General Procedure***. Data are reported as: (a) amount of methanol, (b) amount of *p*-toluenesulfonic acid, (c) amount of substrate **46**, (d) volume of acetonitrile, (e) amount of **66**, and (f) yield.

Entry 1: (a) 36 µL, 0.89 mmol, (b) 9 mg, 0.045 mmol, (c) 117 mg, 0.45 mmol, (d) 4.3 mL, (e) 73 mg, and (f) 71%.

Entry 2: (a) 54 µL, 1.34 mmol, (b) 13 mg, 0.067 mmol, (c) 175 mg, 0.67 mmol, (d) 6.7 mL, (e) 93 mg, and (f) 67%.

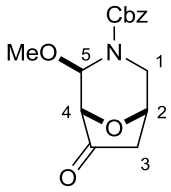
FTIR (CH_2Cl_2): 1697, 3449 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.62 (bs, 1H, OH), 1.86 (dd, ^2J = 7.5 Hz, J = 2.7 Hz, 0.5H, H3), 1.89 (dd, ^2J = 7.1 Hz, J = 2.2 Hz, 0.5H, H3), 2.19, (dd, ^2J = 13.3 Hz, J =

7.4 Hz, 0.5H, H3), 2.26 (dd, ^{2}J = 13.9 Hz, J = 7.7 Hz, 0.5H, H3), 3.29-3.60 (m, 5H, H1, OCH_3), 4.15 (bs, 0.5H, H5), 4.23 (bs, 0.5H, H5), 4.29 (dd, J = 7.5 Hz, J = 2.6 Hz, 0.5H, H4), 4.36 (dd, J = 7.5 Hz, J = 2.5 Hz, 0.5H, H4), 4.57 (d, J = 7.3 Hz, 0.5H, H2), 4.61 (d, J = 7.3 Hz, 0.5H, H2), 4.97 (d, J = 1.4 Hz, 0.5H, H6), 5.10 (d, J = 1.6 Hz, 0.5H, H6), 5.14-5.26 (m, 2H, benzylic CH_2), 7.28-7.50 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 38.4, 38.5, 44.6, 45.3, 54.8, 55.3, 67.2, 67.4, 72.1, 72.3, 74.2, 74.7, 80.9, 81.3, 82.8, 83.2, 127.4, 127.7, 127.9, 128.0, 128.1, 128.2, 135.5, 151.3, 151.8 ppm.
HRMS *m/z* (ESI) calc for $C_{15}H_{19}NO_5Na$ (M^++Na): 316.1155. Found: 316.1159.

A ratio of 1:1 of rotamers was observed in the ^{1}H NMR.

The stereochemistry was elucidated using a NOESY spectrum which is in the Appendix.

Benzyl 2-methoxy-7-oxo-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate, ***70***



Chemical Formula: $C_{15}H_{17}NO_5$
Molecular Weight: 291.30

Scheme 104

DMSO (176 µL, 2.27 mmol) was slowly added to a stirred solution of oxalyl chloride (110 µL, 1.28 mmol) in dry DCM (1.9 mL) at -60 ºC. The mixture was stirred at this temperature for 10 min and **66** (289 mg, 0.99 mmol), as a solution in dry DCM (0.9 mL), was added. The reaction mixture was stirred for a further 15 min before triethylamine (689 µL, 4.93 mmol) was slowly added. The mixture was then warmed to ambient temperature and stirred for a further 1 h before being quenched with a saturated aqueous solution of ammonium chloride and the organic layer was separated. The organic layer was washed with water (x 2) and brine, dried over

Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (40% diethyl ether in petrol) to yield **70** as a colourless oil (137 mg, 48%).

FTIR (CH_2Cl_2): 1707, 1765 cm^{-1}.

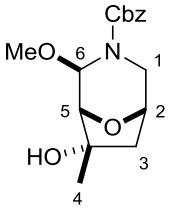
^{1}H NMR (400 MHz, $CDCl_3$): 2.20-2.34 (m, 1H, H3), 2.63-2.73 (m, 1H, H3), 3.30 (s, 1.8H, OCH_3), 3.45 (s, 1.2H, OCH_3), 3.63-3.45 (m, 2H, H1), 4.07 (bs, 0.6H, H4), 4.14 (bs, 0.4H, H4), 4.74 (d, *J* = 7.3 Hz, 0.4H, H2), 4.82 (d, *J* = 7.3 Hz, 0.6H, H2), 5.04-5.27 (m, 3H, H5, benzylic CH_2), 7.31-7.42 ppm (m, 5H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): 39.4, 44.0, 44.8, 55.9, 56.3, 65.8, 68.0, 68.1, 72.8, 73.3, 77.4, 80.7, 81.1, 128.0, 128.1, 128.4, 128.5, 128.6, 135.6, 135.7, 155.5, 155.9, 209.6, 210.3 ppm.

HRMS *m/z* (ESI) calc for $C_{15}H_{17}NO_5Na$ (M^++Na): 314.0999. Found: 314.1001.

HRMS *m/z* (ESI) calc for $C_{15}H_{21}N_2O_5$ (M^++NH_4): 309.1445. Found: 309.1451.

Benzyl 7-hydroxy-2-methoxy-7-methyl-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate, ***71***



Chemical Formula: $C_{16}H_{21}NO_5$
Molecular Weight: 307.34

Scheme 105

Lithium chloride (26 mg, 0.61 mmol) was placed in a three necked round bottom flask which was flame dried under vacuum and allowed to cool under a blanket of nitrogen. Methylmagnesium chloride (204 µL, 0.61 mmol, 3 M in THF) was added and the resultant mixture was cooled to 0 °C. Ketone **70** (137 mg, 0.47 mmol), as a dry THF (2 mL) solution, was slowly added and the mixture was stirred at 0 °C for a further 2 h. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride and the organic layer was separated, dried over

Na_2SO_4, and concentrated *in vacuo*. The resultant alcohol was purified by column chromatography (60-80% diethyl ether in petrol) to yield **71** (105 mg, 72%) as a colourless oil.

Scheme 106

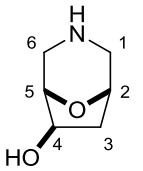
Methyllithium (226 µL, 0.36 mmol) was added to a stirred solution of ketone **70** (81 mg, 0.28 mmol) in dry diethyl ether (2.7 mL) at 0 °C and the reaction mixture was stirred for 3 h. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride and the organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant alcohol was purified by column chromatography (60-80% diethyl ether in petrol) to yield **71** (23 mg, 27%) as a colourless oil.

FTIR (CH_2Cl_2): 1688, 3447 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.42-1.49 (m, 3H, H4), 1.77 (m, 1H, H3), 2.11 (m, 1H, H3), 3.29-3.83 (m, 6H, OCH_3, H1, H5), 4.28 (d, *J* = 7.4 Hz, 0.5H, H2), 4.35 (d, *J* = 7.4 Hz, 0.5H, H2), 5.14-5.23 (m, 2H, benzylic CH_2), 5.29 (s, 0.5H, H6), 5.36 (s, 0.5H, H6), 7.27-7.43 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 30.0, 30.1, 42.5, 42.6, 45.1, 45.7, 55.0, 55.4, 67.1, 67.2, 73.8, 74.2, 77.1, 80.4, 80.7, 81.8, 82.3, 127.3, 127.4, 127.7, 128.0, 128.1, 135.7, 155.8, 156.0 ppm.
HRMS *m/z* (ESI) calc for $C_{16}H_{21}NO_5Na$ (M^++Na): 330.1312. Found: 330.1314.

A ratio of 1:1 of rotamers was observed in the ^{1}H NMR.

The stereochemistry was elucidated using a NOESY spectrum which is in the Appendix.

8-oxa-3-azabicyclo[3.2.1]octan-6-ol, ***72***



Chemical Formula: $C_6H_{11}NO_2$
Molecular Weight: 129.16

Scheme 107

A three necked flask under nitrogen was charged with palladium on charcoal (164 mg, 0.15 mmol) followed by a solution of **66** (452 mg, 1.54 mmol) in methanol (15.4 mL). The flask was evacuated and back filled with hydrogen (x 3) *via* a three way tap attached to a vacuum manifold and a hydrogen balloon. The reaction mixture was then stirred for a 16 h before being filtered through a pad of celite. The celite was washed with additional methanol followed by a 1 M ammonia in methanol solution, and the resultant solution was concentrated *in vacuo* to yield **72** as a yellow gum (171 mg, 86%).

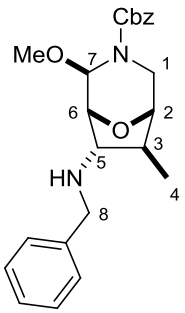
FTIR: 3332 cm^{-1}.

^{1}H NMR (400 MHz, D_2O): 2.19 (dd, ^{2}J = 15.1 Hz, J = 8.3 Hz, 1H, H3), 2.55 (dd, ^{2}J = 14.8 Hz, J = 7.4 Hz, 1H, H3), 3.18 (d, ^{2}J = 13.1 Hz, 1H, H1) 3.36 (bs, 2H, H1, H6), 3.39 (s, 1H, H6), 4.39 (bs, 1H, H5), 4.69 (d, J = 7.9 Hz, 1H, H4), 4.75-4.84 ppm (obscured by solvent peak, 1H, H2).

^{13}C NMR (100 MHz, D_2O): 36.6, 43.7, 46.2, 71.6, 72.3, 78.8 ppm.

HRMS *m/z* (ESI) calc for $C_6H_{12}NO_2$ (M^++H): 130.0863. Found: 130.0860.

Benzyl 7-(benzylamino)-2-methoxy-6-methyl-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate, ***74***



Chemical Formula: $C_{23}H_{28}N_2O_4$
Molecular Weight: 396.48

Scheme 109

Benzylamine (22 µL, 0.19 mmol) was added to a stirred suspension of aldehyde **45** (55 mg, 0.19 mmol) and sodium sulfate (270 mg, 1.90 mmol) in dry DCM (1.9 mL) at ambient temperature. The reaction mixture was then stirred for 3 h before filtering off the sodium sulfate and washing with dry DCM (1.9 mL). Methanol (15 µL, 0.38 mmol) followed by *p*-toluenesulfonic acid (36 mg, 0.19 mmol) were added to the resultant solution and the mixture was stirred for a further 16 h. The reaction had not gone to completion therefore *p*-toluenesulfonic acid (18 mg, 0.09 mmol) was added and the reaction was stirred for a further 3 h. The reaction mixture was then quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated. The aqueous layer was extracted with DCM (x 2) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (50-100% diethyl ether in petrol) to yield alcohol **52a**/**b** as a colourless oil (30 mg, 49%).

Data for compound ***52a*** *and* ***52b*** *is shown on* ***page 183***

Scheme 110

Benzylamine (20 µL, 0.18 mmol) was added to a stirred suspension of aldehyde **45** (51 mg, 0.18 mmol) and sodium sulfate (263 mg, 1.80 mmol) in dry DCM (1.8 mL)

at ambient temperature. The reaction mixture was then stirred for 3 h before filtering off the sodium sulfate and washing with dry DCM (1.8 mL). The reaction mixture was then cooled to -20 °C before adding methanol (15 µL, 0.36 mmol) followed by triflic acid (16 µL, 0.18 mmol). The mixture was then stirred at -20 °C for 20 min before being warmed to ambient temperature and stirred for a further 1 h. The reaction mixture was then quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated. The aqueous layer was extracted with DCM (x 2) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (70% diethyl ether in petrol) to yield **74** as a colourless oil (2 mg, 3%).

Scheme 111

Benzylamine (33 µL, 0.30 mmol) was added to a stirred suspension of aldehyde **45** (82 mg, 0.30 mmol) and sodium sulfate (426 mg, 3.0 mmol) in dry DCM (3 mL) at ambient temperature. The reaction mixture was then stirred for 3 h before filtering off the sodium sulfate and washing with dry DCM (3 mL). Methanol (24 µL, 0.60 mmol) followed by benzenesulfonic acid (47 mg, 0.30 mmol) were added to the resultant solution and the mixture was stirred for a further 16 h. The reaction mixture was then quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated. The aqueous layer was extracted with DCM (x 2) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (70% diethyl ether in petrol) to yield **74** as a colourless oil (52 mg, 44%).

Scheme 112*, *Table 33

Entry 1:

Benzylamine (43 µL, 0.39 mmol) was added to a stirred suspension of aldehyde **45** (109 mg, 0.39 mmol) and sodium sulfate (554 mg, 3.90 mmol) in dry DCM (4 mL) at ambient temperature. The reaction mixture was then stirred for 3 h before filtering

off the sodium sulfate and washing with dry DCM (4 mL). Methanol (32 µL, 0.78 mmol) followed by methanesulfonic acid (25 µL, 0.39 mmol) were added to the resultant solution and the mixture was stirred for a further 16 h. The reaction mixture was then quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated. The aqueous layer was extracted with DCM (x 2) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (70% diethyl ether in petrol) to yield **74** as a colourless oil (88 mg, 56%).

Entry 2:

Benzylamine (45 µL, 0.41 mmol) was added to a stirred suspension of aldehyde **45** (112 mg, 0.41 mmol) and sodium sulfate (582 mg, 4.10 mmol) in dry DCM (4.1 mL) at ambient temperature. The reaction mixture was then stirred for 3 h before filtering off the sodium sulfate and washing with dry DCM (4.1 mL). Methanol (33 µL, 0.82 mmol) followed by methanesulfonic acid (13 µL, 0.21 mmol) were added to the resultant solution and the mixture was stirred for a further 16 h. The reaction mixture was then quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated. The aqueous layer was extracted with DCM (x 2) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (70-100% diethyl ether in petrol) to yield only degradation products.

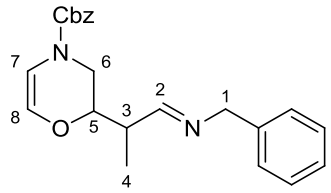
FTIR (CH_2Cl_2): 1697 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.21 (d, *J* = 7.1 Hz, 1.2H, H4), 1.24 (d, *J* = 7.1 Hz, 1.8H, H4), 1.69-1.77 (m, 0.4H, H3), 1.81-1.89 (m, 0.6H, H3), 2.95-3.01 (m, 1H, H5), 3.28 (s, 1.8H, OCH_3), 3.38 (s, 1.2H, OCH_3), 3.40-3.90 (m, 5H, H1, H2, H8), 4.17 (dd, *J* = 6.3 Hz, *J* = 1.1 Hz, 0.6H, H6), 4.24 (bd, *J* = 6.3 Hz, 0.4H, H6), 5.05-5.28 (m, 3H, carbamate CH_2, H7), 7.25-7.45 ppm (m, 10H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 20.4, 42.4, 42.5, 44.9, 45.5, 52.8, 53.1, 54.8, 55.3, 67.1, 67.3, 77.6, 77.9, 80.0, 80.1, 80.4, 80.5, 126.6, 126.7, 127.4, 127.5, 127.6, 127.7, 127.8, 128.0, 128.1, 135.5, 135.8, 139.6, 155.4, 155.7 ppm.

HRMS *m/z* (ESI) calc for $C_{23}H_{29}N_2O_4$ (M^++H): 397.2122. Found: 391.2120.

A ratio of 3:2 of rotamers was observed in the ^1H NMR.

The stereochemistry was elucidated using a NOESY spectrum which is in the Appendix.

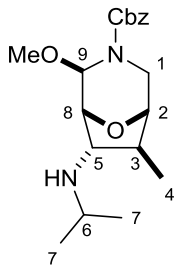
Benzyl 2-(1-(benzylimino)propan-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, ***73***



Chemical Formula: $C_{22}H_{24}N_2O_3$
Molecular Weight: 364.44

^{1}H NMR (400 MHz, $CDCl_3$): 1.22-1.25 (m, 3H, H4), 2.67-2.82 (m, 1H, H3), 3.18-3.37 (m, 1H, H6), 3.95-4.24 (m, 2H, H5, H6), 4.56-4.71 (m, 2H, H1), 5.19-5.24 (m, 2H, carbamate CH_2), 5.92-5.97 (m, 0.6H, H7), 6.06-6.09 (m, 0.4H, H7), 6.24-6.27 (m, 0.6H, H8), 6.36-6.39 (m, 0.4H, H8), 7.21-7.47 (m, 10H, ArH), 7.76-7.84 ppm (m, 1H, H2).

Benzyl 7-(isopropylamino)-2-methoxy-6-methyl-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate, ***76***



Chemical Formula: $C_{19}H_{28}N_2O_4$
Molecular Weight: 348.44

Scheme 113

Isopropylamine (25 µL, 0.29 mmol) was added to a stirred suspension of aldehyde **45** (80 mg, 0.29 mmol) and sodium sulfate (413 mg, 2.90 mmol) in dry DCM (2.9 mL) at ambient temperature. The reaction mixture was then stirred for 3 h before filtering off the sodium sulfate and washing with dry DCM (2.9 mL). Methanol (23 µL, 0.58 mmol) followed by benzenesulfonic acid (46 mg, 0.29 mmol) were added to the resultant solution and the mixture was stirred for a further 16 h. The reaction mixture was then quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated. The aqueous layer was extracted with DCM (x 2) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (70% diethyl ether in petrol) to yield **76** as a colourless oil (42 mg, 42%).

Scheme 114

Isopropylamine (33 µL, 0.39 mmol) was added to a stirred suspension of aldehyde **45** (106 mg, 0.39 mmol) and sodium sulfate (554 mg, 3.90 mmol) in dry DCM (3.9 mL) at ambient temperature. The reaction mixture was then stirred for 3 h before filtering off the sodium sulfate and washing with dry DCM (3.9 mL). Methanol (32 µL, 0.78 mmol) followed by methanesulfonic acid (32 µL, 0.39 mmol) were added to the resultant solution and the mixture was stirred for a further 16 h. The reaction mixture was then quenched with a saturated aqueous solution of sodium bicarbonate

and the organic layer was separated. The aqueous layer was extracted with DCM (x 2) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (70-100% diethyl ether in petrol) to yield **76** as a colourless oil (31 mg, 23%).

FTIR (CH_2Cl_2): 1697 cm^{-1}.

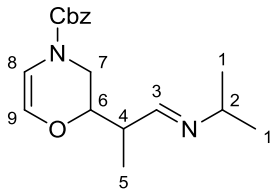
^{1}H NMR (400 MHz, $CDCl_3$): 0.95-1.09 (m, 6H, H7), 1.20-1.27 (m, 3H, H4), 1.59-1.77 (m, 1H, H3), 2.76-2.88 (m, 1H, H6), 2.99-3.07 (m, 1H, H5), 3.31-3.51 (m, 4H, OCH_3, H1), 3.60-3.71 (m, 1H, H1), 3.78-3.86 (m, 1H, H2), 4.17 (d, *J* = 6.1 Hz, 0.6H, H8), 4.26 (d, *J* = 6.1 Hz, 0.4H, H8), 5.11-5.25 (m, 3H, H9, benzylic CH_2), 7.30-7.43 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 20.4, 22.3, 22.5, 22.6, 22.9, 42.6, 42.7, 44.9, 45.5, 46.7, 47.0, 54.8, 55.3, 64.4, 64.5, 67.1, 67.2, 77.7, 77.9, 79.9, 80.2, 80.3, 80.6, 127.4, 127.8, 1279, 128.0, 128.1, 128.2, 135.4, 135.8, 155.3, 155.7 ppm.

HRMS *m/z* (ESI) calc for $C_{19}H_{29}N_2O_4$ (M^++H): 349.2122. Found: 349.2133.

A ratio of 3:2 of rotamers was observed in the ^{1}H NMR.

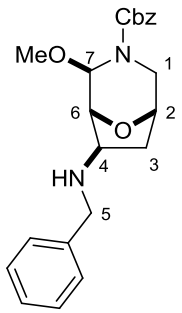
(E)-benzyl 2-(1-(isopropylimino)propan-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, ***75***



Chemical Formula: $C_{18}H_{24}N_2O_3$
Molecular Weight: 316.39

^{1}H NMR (400 MHz, $CDCl_3$): 1.04-1.24 (m, 9H, H1, H5), 2.05-2.68 (m, 1H, H4), 3.13-3.38 (m, 2H, H2, H7), 3.88-4.17 (m, 2H, H6, H7), 5.14-5.25 (m, 2H, benzylic CH_2), 5.87-5.97 (m, 0.6H, H8), 6.01-6.07 (m, 0.4H, H8), 6.19-6.27 (m, 0.6H, H9), 6.31-6.41 (m, 0.4H, H9), 7.30-7.41 (m, 5H, ArH), 7.59-7.64 ppm (m, 1H, H3).

Benzyl 7-(benzylamino)-2-methoxy-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate, ***78***



Chemical Formula: $C_{22}H_{26}N_2O_4$
Molecular Weight: 382.45

Scheme 115

Benzylamine (30 µL, 0.28 mmol) was added to a stirred suspension of aldehyde **46** (72 mg, 0.28 mmol) and sodium sulfate (387 mg, 2.76 mmol) in dry DCM (2.8 mL) at ambient temperature. The reaction mixture was then stirred for 3 h before filtering off the sodium sulfate and washing with dry DCM (2.8 mL). Methanol (22 µL, 0.55 mmol) followed by methanesulfonic acid (27 µL, 0.41 mmol) were added to the resultant solution and the mixture was stirred for a further 3 h. The reaction mixture was then quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated. The aqueous layer was extracted with DCM (x 2) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (10% methanol in diethyl ether) to yield **78** as a colourless oil (41 mg, 39%).

FTIR (CH_2Cl_2): 1697 cm^{-1}.

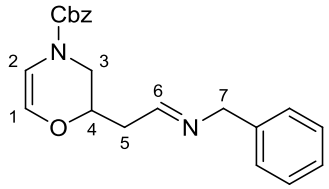
^{1}H NMR (400 MHz, $CDCl_3$): 1.60 (bs, 1H, NH), 1.72-1.83 (m, 1H, H3), 2.04-2.18 (m, 1H, H3), 3.18 (dd, *J* = 8.0 Hz, *J* = 3.8 Hz, 0.5H, H4), 3.26-3.63 (m, 5.5H, H1, H4, OCH_3), 3.75 (s, 1H, H5), 3.77 (s, 1H, H5), 4.16 (d, *J* = 1.3 Hz, 0.5H, H6), 4.23 (d, *J* = 1.3 Hz, 0.5H, H6), 4.45 (d, *J* = 7.1 Hz, 0.5H, H2), 4.52 (d, *J* = 7.1 Hz, 0.5H, H2), 4.87 (d, *J* = 1.4 Hz, 0.5H, H7), 5.01 (d, *J* = 1.4 Hz, 0.5H, H7), 5.11-5.25 (m, 2H carbamate CH_2), 7.17-7.44 ppm (m, 10H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 35.6, 35.8, 44.8, 45.5, 51.5, 51.7, 54.8, 55.3, 58.7, 58.8, 67.1, 67.3, 73.7, 74.3, 79.7, 80.1, 82.2, 82.6, 126.7, 126.8, 127.3, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 135.5, 135.7, 139.0, 139.1 155.3, 155.9 ppm.
HRMS *m/z* (ESI) calc for $C_{22}H_{27}N_2O_4$ (M^++H): 383.1965. Found: 383.1965.

A ratio of 1:1 of rotamers was observed in the ^{1}H NMR.

The stereochemistry was elucidated using a NOESY spectrum which is in the Appendix.

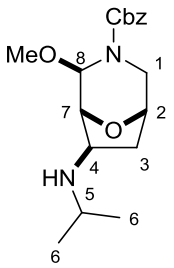
Benzyl 2-(2-(benzylimino)ethyl)-2H-1,4-oxazine-4(3H)-carboxylate, ***77***



Chemical Formula: $C_{21}H_{22}N_2O_3$
Molecular Weight: 350.41

^{1}H NMR (400 MHz, $CDCl_3$): 2.52-2.78 (m, 2H, H5), 3.23-3.34 (m, 1H, H3), 4.05-4.16 (m, 1H, H3), 4.27-4.31 (m, 1H, H4), 4.62 (s, 1H, H7), 6.65 (s, 1H, H7), 5.20-5.23 (m, 2H, carbamate CH_2), 5.93 (d, *J* = 5.0 Hz, 0.6H, H1), 6.06 (d, *J* = 5.0 Hz, 0.4H, H1), 6.27 (d, *J* = 5.0 Hz, 0.6H, H2), 6.39 (d, *J* = 5.0 Hz, 0.4H, H2) 7.22-7.47 (m, 10H, ArH), 7.89 ppm (t, *J* = 4.5 Hz, 1H, H6).

Benzyl 7-(isopropylamino)-2-methoxy-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate, ***80***



Chemical Formula: $C_{18}H_{26}N_2O_4$
Molecular Weight: 334.41

Scheme 116

Attempt 1: 3 h reaction time

Isopropylamine (29 µL, 0.34 mmol) was added to a stirred suspension of aldehyde **46** (89 mg, 0.34 mmol) and sodium sulfate (483 mg, 3.40 mmol) in dry DCM (3.4 mL) at ambient temperature. The reaction mixture was then stirred for 3 h before filtering off the sodium sulfate and washing with dry DCM (3.4 mL). Methanol (28 µL, 0.68 mmol) followed by methanesulfonic acid (22 µL, 0.34 mmol) were added to the resultant solution and the mixture was stirred for a further 3 h. The reaction mixture was then quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated. The aqueous layer was extracted with DCM (x 2) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (50-100% diethyl ether in petrol then 10% methanol in diethyl ether) to yield aldehyde **46** (45% recovery).

Data for compound ***46*** *is shown on* ***page 195***

Attempt 1: 16 h reaction time

Isopropylamine (27 µL, 0.32 mmol) was added to a stirred suspension of aldehyde **46** (83 mg, 0.32 mmol) and sodium sulfate (454 mg, 3.20 mmol) in dry DCM (3.2

mL) at ambient temperature. The reaction mixture was then stirred for 3 h before filtering off the sodium sulfate and washing with dry DCM (3.2 mL). Methanol (26 µL, 0.64 mmol) followed by methanesulfonic acid (21 µL, 0.32 mmol) were added to the resultant solution and the mixture was stirred for a further 16 h. The reaction mixture was then quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated. The aqueous layer was extracted with DCM (x 2) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (50-100% diethyl ether in petrol then 10% methanol in diethyl ether) to yield only degradation products.

Scheme 117

Isopropylamine (28 µL, 0.33 mmol) was added to a stirred suspension of aldehyde **46** (85 mg, 0.33 mmol) and sodium sulfate (469 mg, 3.30 mmol) in dry DCM (3.3 mL) at ambient temperature. The reaction mixture was then stirred for 3 h before filtering off the sodium sulfate and washing with dry DCM (3.3 mL). Methanol (27 µL, 0.66 mmol) followed by benzenesulfonic acid (52 mg, 0.33 mmol) were added to the resultant solution and the mixture was stirred for a further 16 h. The reaction mixture was then quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated. The aqueous layer was extracted with DCM (x 2) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (50-100% diethyl ether in petrol then 10% methanol in diethyl ether) to yield alcohol **66** (41 mg, 45%).

*Data for compound **66** is shown on **page 196***

Scheme 118

Isopropylamine (30 µL, 0.34 mmol) was added to a stirred suspension of aldehyde **46** (90 mg, 0.34 mmol) and sodium sulfate (488 mg, 3.40 mmol) in dry DCM (3.4 mL) at ambient temperature. The reaction mixture was then stirred for 3 h before

methanol (28 µL, 0.68 mmol) followed by benzenesulfonic acid (107 mg, 0.68 mmol) were added and the mixture was stirred for a further 16 h. The reaction mixture was then quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated. The aqueous layer was extracted with DCM (x 2) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (50-100% diethyl ether in petrol then 10% methanol in diethyl ether) to yield amine **80** (35 mg, 31%).

FTIR (CH_2Cl_2): 1701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 1.02-1.09 (m, 6H, H6), 1.64-1.73 (m, 1H, H3), 1.85 (bs, 1H, NH), 2.02-2.13 (m, 1H, H3), 2.79-2.87 (m, 1H, H5), 3.23-3.63 (m, 6H, H1, H4, OCH_3), 4.10 (d, *J* = 1.3 Hz, 0.5H, H7), 4.18 (d, *J* = 1.1 Hz, 0.5H, H7), 4.42 (d, *J* = 7.2 Hz, 0.5H, H2), 4.49 (d, *J* = 7.2 Hz, 0.5H, H2), 4.89 (d, *J* = 1.5 Hz, 0.5H, H8), 5.01 (d, *J* = 1.4 Hz, 0.5H, H8), 5.14-5.23 (m, 2H, carbamate CH_2), 7.31-7.44 ppm (m, 5H, ArH).

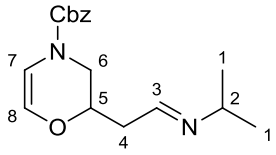
^{13}C NMR (100 MHz, $CDCl_3$): 22.2, 22.3, 22.6, 35.7, 38.9, 44.8, 45.4, 45.7, 45.8, 54.8, 55.3, 56.0, 56.2, 67.1, 67.2, 73.7, 74.3, 80.3, 82.1, 82.6, 127.4, 127.6, 127.8, 127.9, 128.1, 155.3, 155.9 ppm.

HRMS *m/z* (ESI) calc for $C_{18}H_{27}N_2O_4$ (M^++H): 335.1965. Found: 335.1970.

A ratio of 1:1 of rotamers was observed in the ^{1}H NMR.

The stereochemistry was elucidated using a NOESY spectrum which is in the Appendix.

(E)-benzyl 2-(2-(isopropylimino)ethyl)-2H-1,4-oxazine-4(3H)-carboxylate, ***79***



Chemical Formula: $C_{17}H_{22}N_2O_3$
Molecular Weight: 302.37

^{1}H NMR (400 MHz, $CDCl_3$): 1.10-1.18 (m, 6H, H1), 2.41-2.62 (m, 2H, H4), 3.13-3.25 (m, 1H, H2), 3.26-3.37 (m, 1H, H6), 3.98-4.11 (m, 1H, H6), 4.12-4.21 (m, 1H, H5), 5.14-5.20 (m, 2H, benzylic CH_2), 5.87 (d, *J* = 5.0 Hz, 0.6H, H7), 6.00 (d, *J* = 5.0 Hz, 0.4H, H7), 6.21 (d, *J* = 5.0 Hz, 0.6H, H8), 6.33 (d, *J* = 5.0 Hz, 0.4H, H8), 7.28-7.39 (m, 5H, ArH), 7.69-7.75 ppm (m, 1H, H3).

5. References

1. C. Boss, C. Brotschi, B. Heidmann, T. Sifferlen and J. T. Williams, 2013, Int. Appl., WO 2013-050938 A050931.
2. A. Mazurov, L. Miao, Y.-D. Xiao, D. Yohannes, S. R. Akireddy, S. R. Breining, D. Kombo and V. S. Murthy, 2010, PCT Int. Appl., WO 2010-002971 A002971.
3. A. Zask, J. A. Kaplan, J. C. Verheijen, K. J. Curran, D. J. Richard and S. Ayral-Kaloustian, 2009, U.S. Pat. Appl. Publ., US 2008-251712 20081015.
4. M. Furber, L. Alcaraz, J. E. Bent, A. Beyerbach, K. Bowers, M. Braddock, M. V. Caffrey, D. Cladingboel, J. Collington, D. K. Donald, M. Fagura, F. Ince, E. C. Kinchin, C. Laurent, M. Lawson, T. J. Luker, M. M. P. Mortimore, A. D. Pimm, R. J. Riley, N. Roberts, M. Robertson, J. Theaker, P. V. Thorne, R. Weaver, P. Webborn and P. Willis, *J. Med. Chem.*, 2007, **50**, 5882.
5. A. Bjoere, D. Cladingboel, G. Ensor, A. Herring, J. Kajanus, R. Lundqvist, C. Olsson, C.-G. Sigfridsson and G. Strandlund, 2006, PCT Int. Appl., Application: WO 2006-SE2688 20060612.
6. C. Chan, J. N. Hamblin, H. A. Kelly, N. P. King, A. M. Mason, V. K. Patel, S. Senger, G. P. Shah, N. S. Watson, H. E. Weston, C. Whitworth and R. J. Young, 2002, PCT Int. Appl., WO 2002-GB2586 20020606.
7. H. Brice, D. M. Gill, L. Goldie, P. S. Keegan, W. J. Kerr and P. H. Svensson, *Chem. Commun.*, 2012, **48**, 4836.
8. P. MacLellan and A. Nelson, *Chem. Commun.*, 2013, **49**, 2383.
9. M. Dow, M. Fisher, T. James, F. Marchetti and A. Nelson, *Org. Biomol. Chem.*, 2012, **10**, 17.
10. K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39.
11. E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, **20**, 399.
12. A. P. Thottumkara, M. S. Bowsher and T. K. Vinod, *Org. Lett.*, 2005, **7**, 2933.

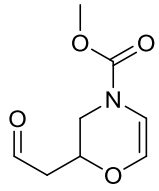
13. A. J. Mancuso and D. Swern, *Synthesis*, 1985, 165.
14. L. D. Luca, G. Giacomelli, S. Masala and A. Porcheddu, *J. Org. Chem.*, 2003, **68**, 4999.
15. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353.
16. Computational studies were carried out by Dr. Andrew Leach, University of Leeds (previously AstraZeneca).
17. H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 1959, **81**, 247.
18. G. Nagendrappa, *Resonance*, 2002, **7(1)**, 64.
19. D. M. Gill and H. Holness, AstraZeneca, Personal communications.
20. W. C. Still and J. C. Barrish, *J. Am. Chem. Soc.*, 1983, **105**, 2487.
21. K. Tamura, A. Nakazaki and S. Kobayashi, *Synlett*, 2009, 2449.
22. G. Y. C. Leung, H. Li, Q.-Y. Toh, A. M.-Y. Ng, R. J. Sum, J. E. Bandow and D. Y.-K. Chen, *Eur. J. Org. Chem.*, 2011, 183.
23. Computational studies were carried out by Marc Reid, University of Strathclyde.
24. B. E. Love and E. G. Jones, *J. Org. Chem.*, 1999, **64**, 3755.
25. A. M. Zaed and A. Sutherland, *Org. Biomol. Chem.*, 2010, **8**, 4394.
26. E. J. Corey and E. Hamanaka, *Org. Synth, Coll. Vol 5.*, 1973, **45**, 28.

6. Appendix

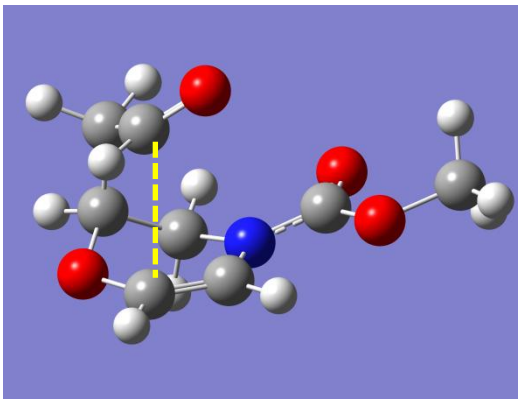
Computational Study Structures for Figure 11

Density functional theory[1,2] (DFT) was employed to calculate the electronic structures and energies for all species involved in cyclisation step. The hybrid functional B3LYP[3-6] was used in conjunction with the 6-31G(d) basis set[7,8] without solvation and was used along with the keyword opt=modredun, using Gaussian 09 quantum chemistry program package.[9]

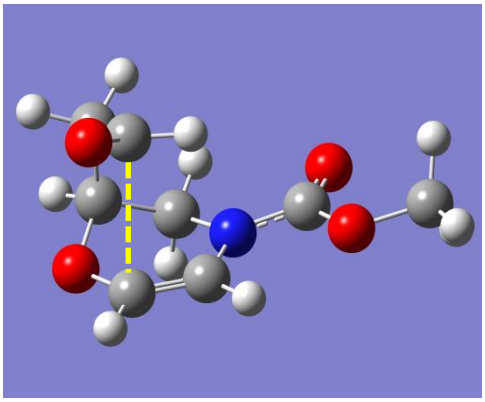
Aldehyde



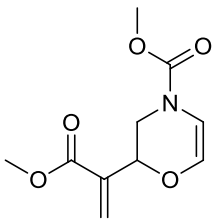
Aldehyde_1

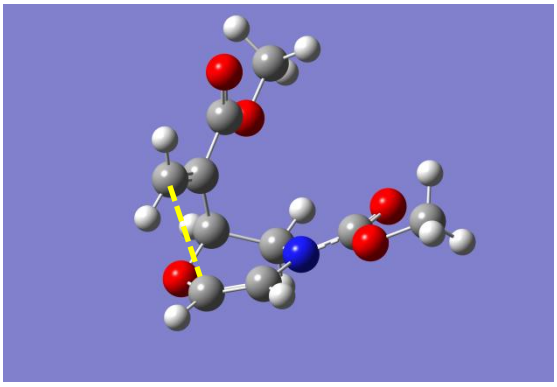


Aldehyde_2

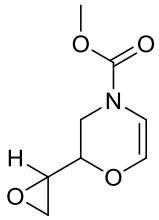


α,β-Unsaturated ester

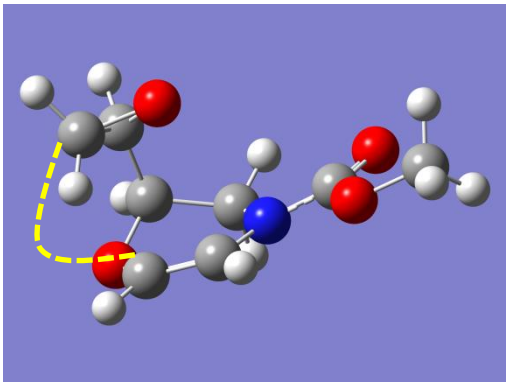




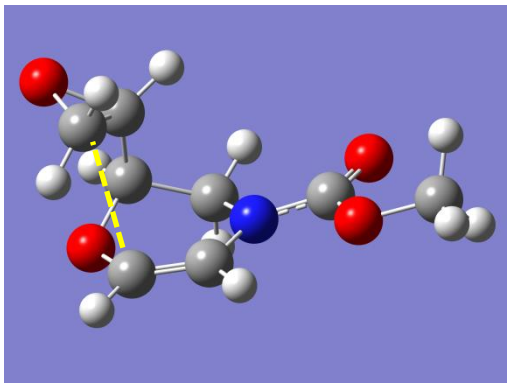
Epoxide



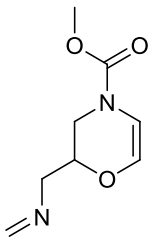
H_Epoxide_1



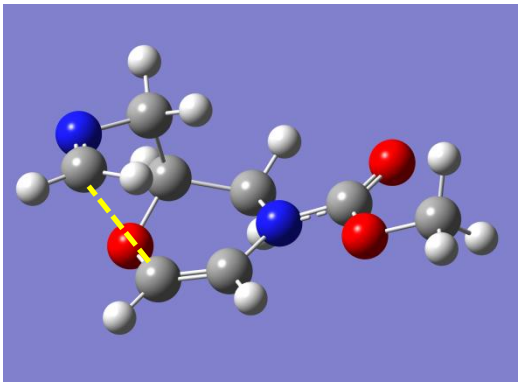
H_Epoxide_2



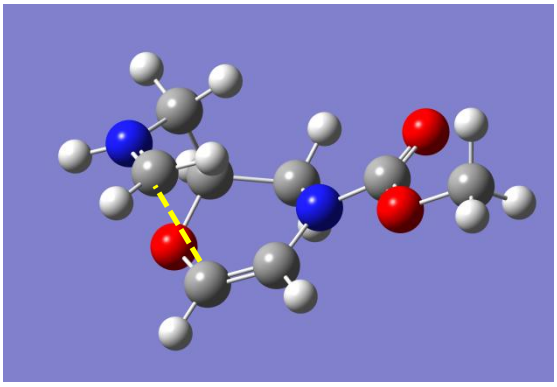
Imine



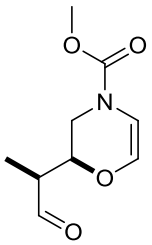
Imine_Deprot

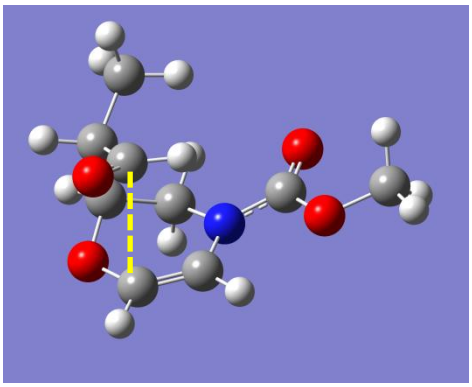


Imine_prot

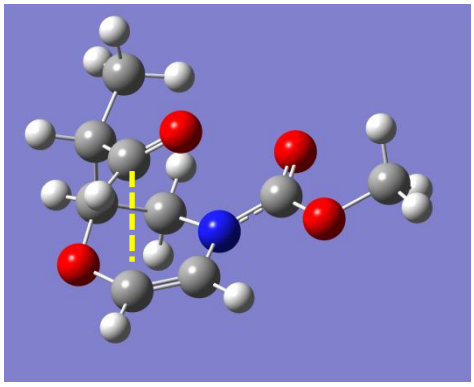


Methyl aldehyde Me_aldehyde_1_1

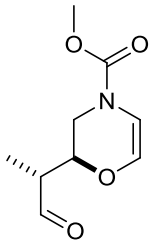


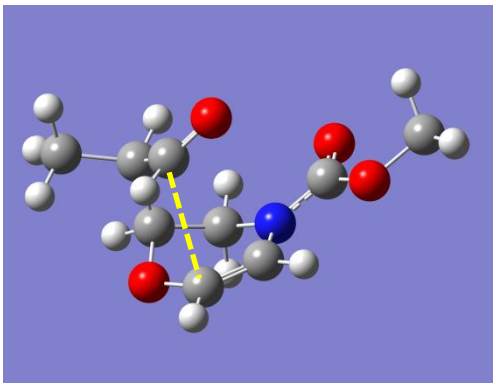


Me_aldehyde_1_2

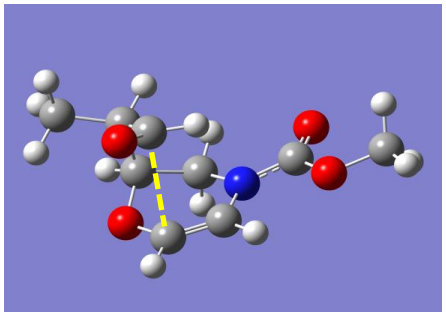


Methyl aldehyde Me_aldehyde_2_1

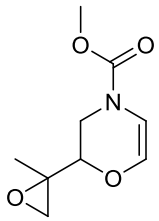


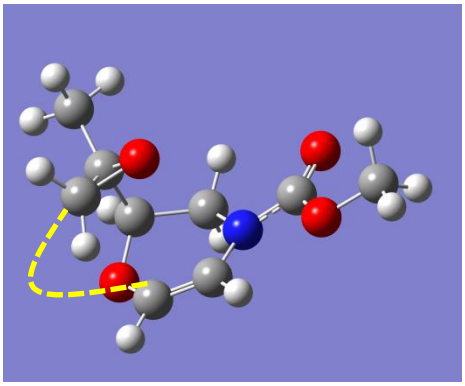


Me_aldehyde_2_2

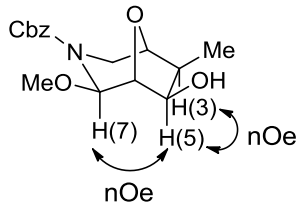


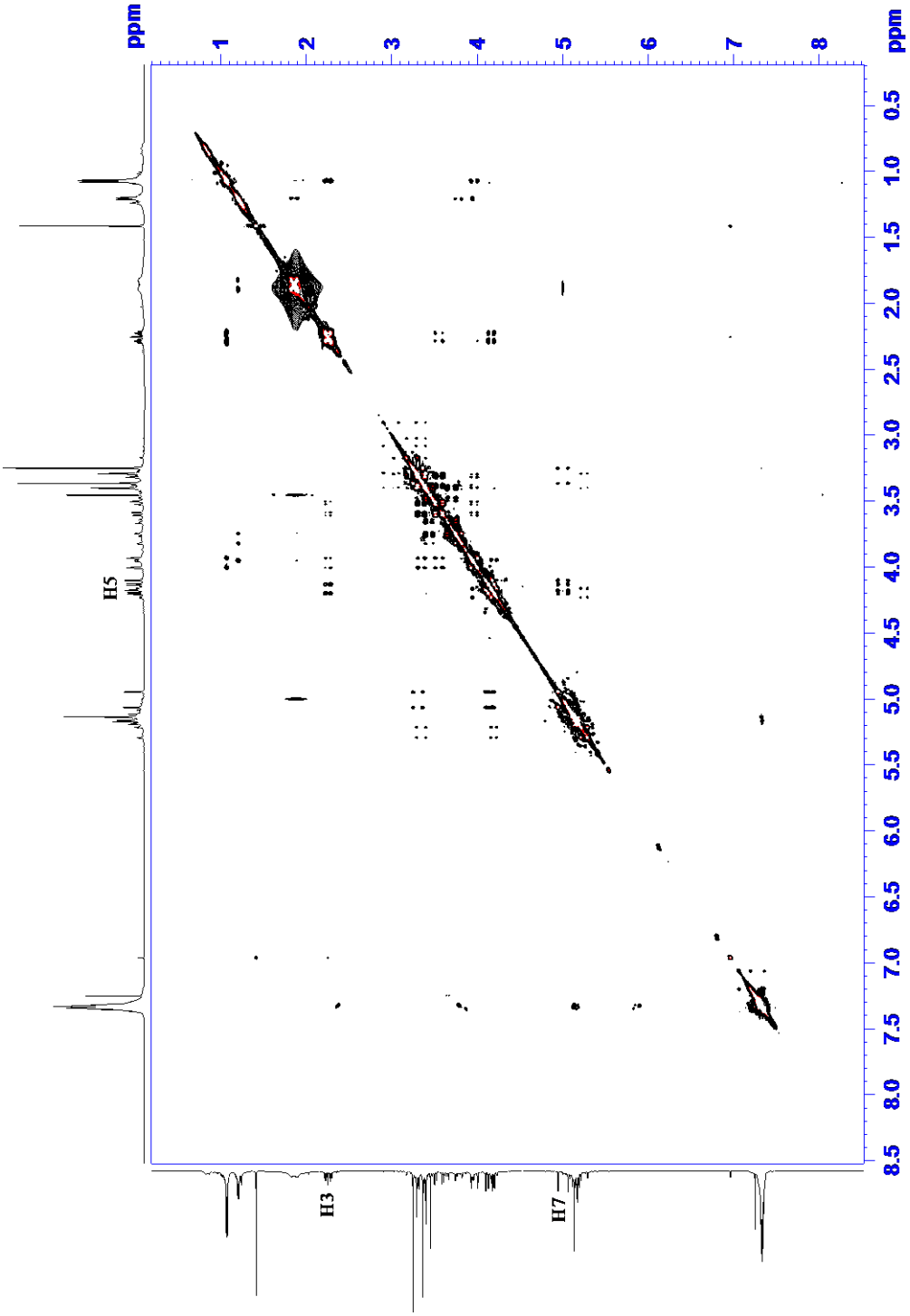
Epoxide Me_epoxide_1



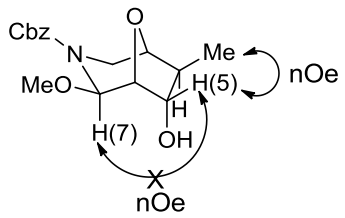


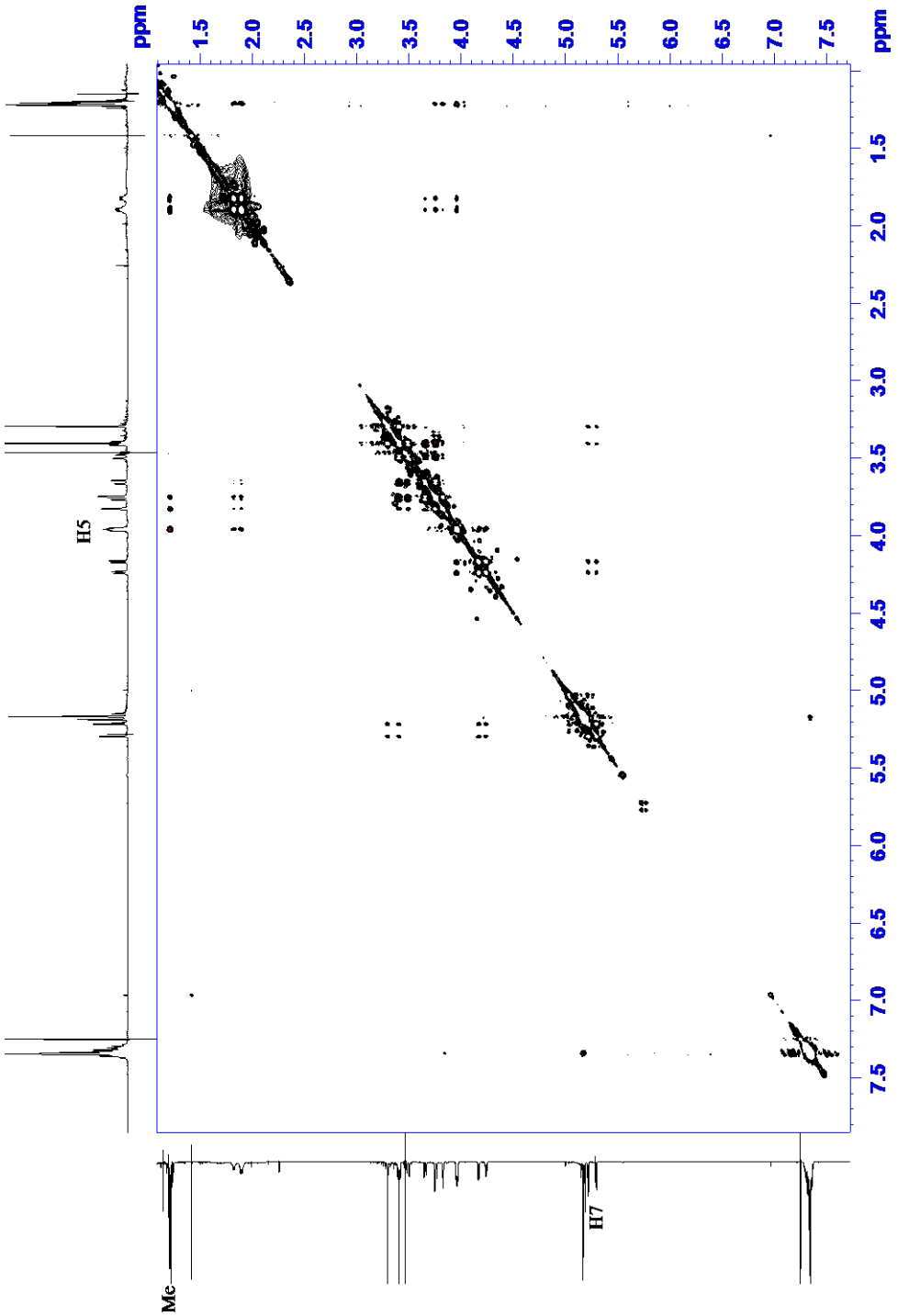
NOESY Spectrum for Compound 52a



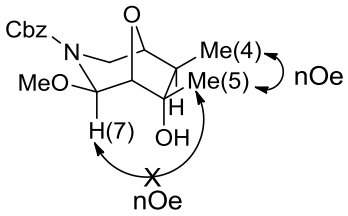


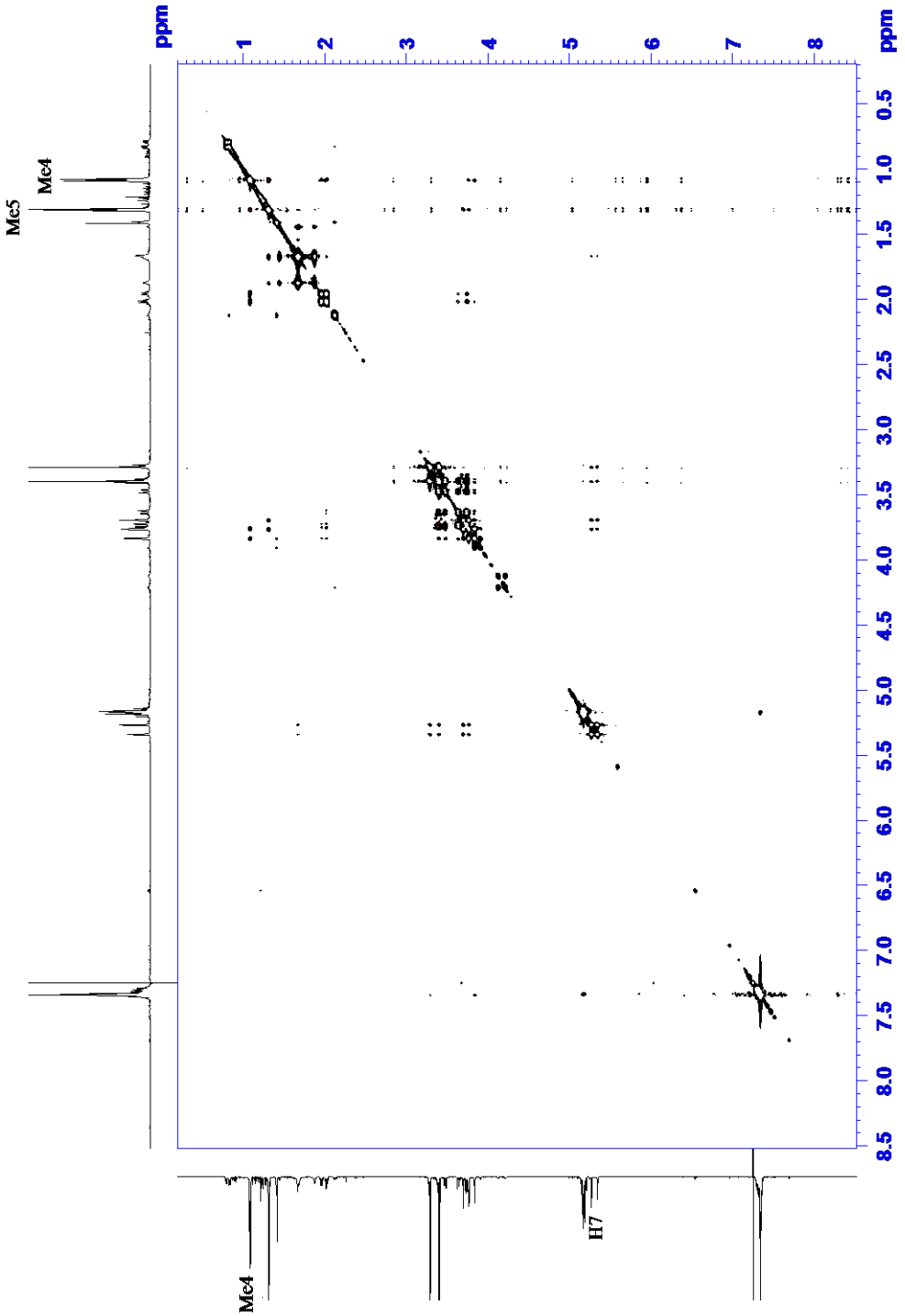
NOESY Spectrum for Compound 52b



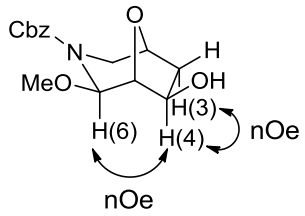


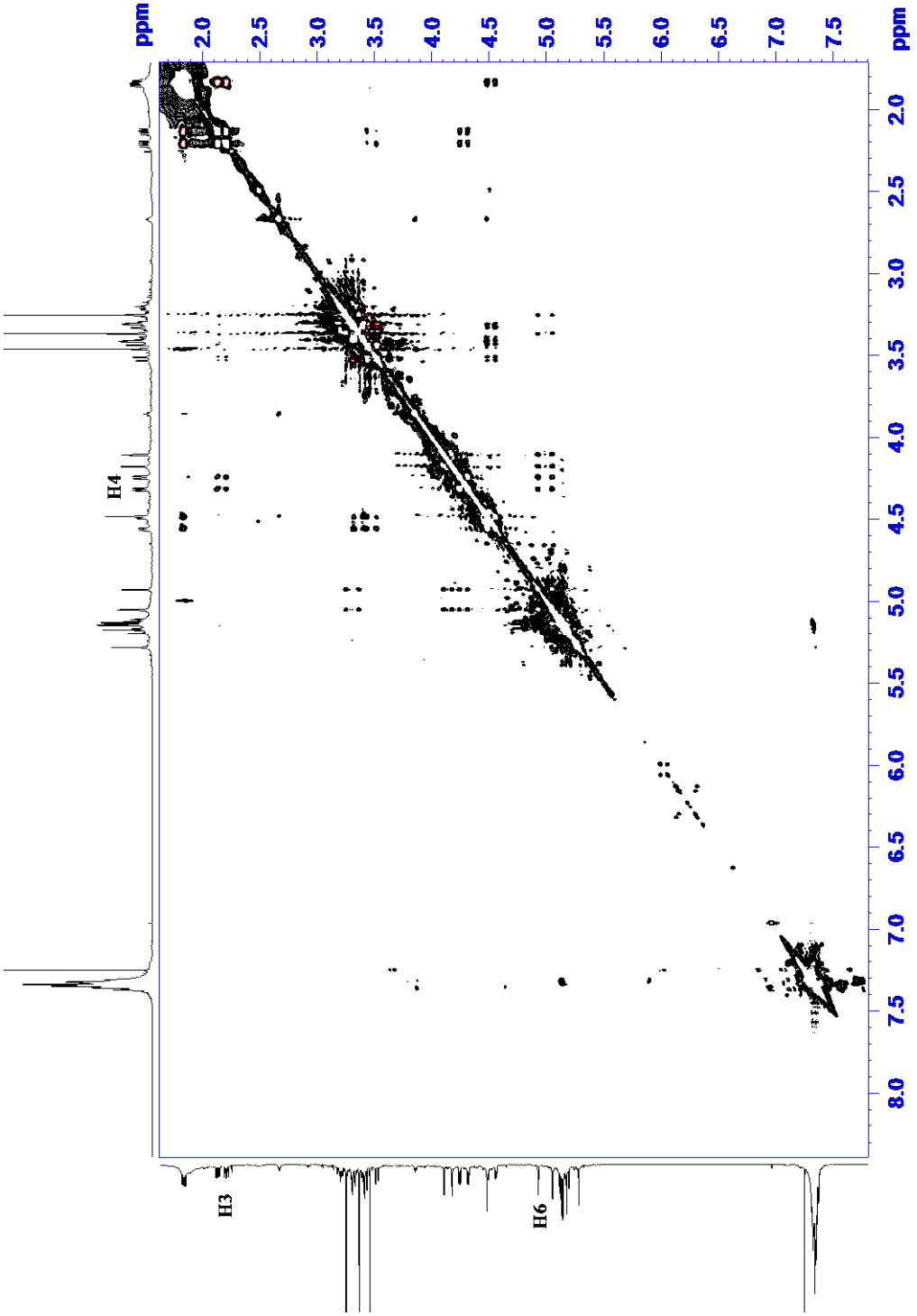
NOESY Spectrum for Compound 64



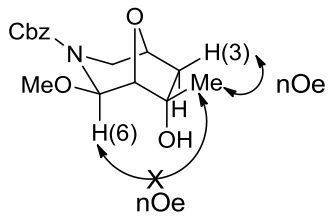


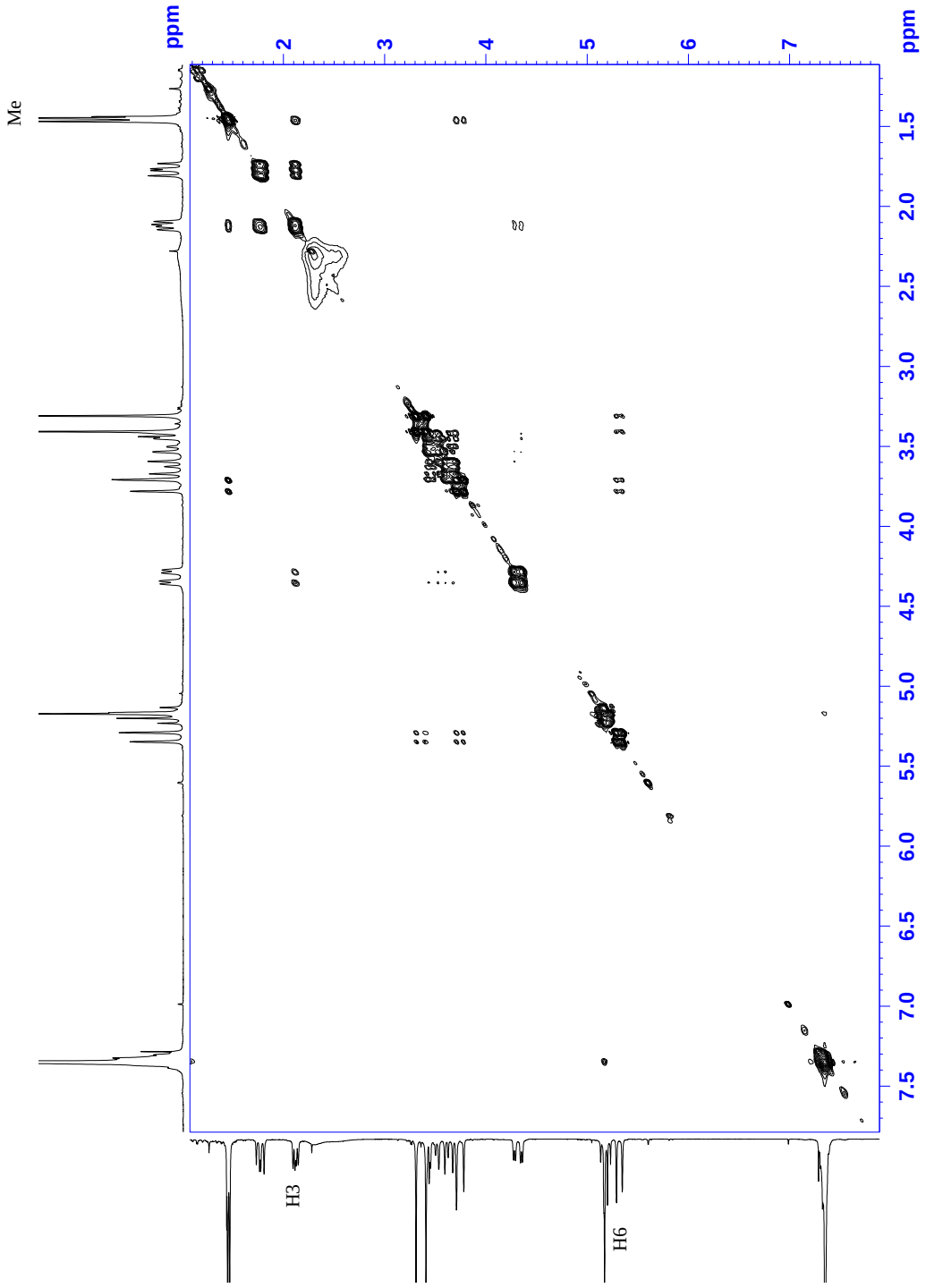
NOESY Spectrum for Compound 66



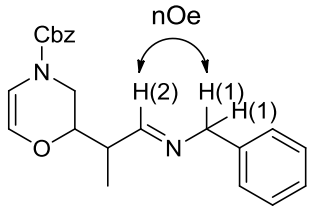


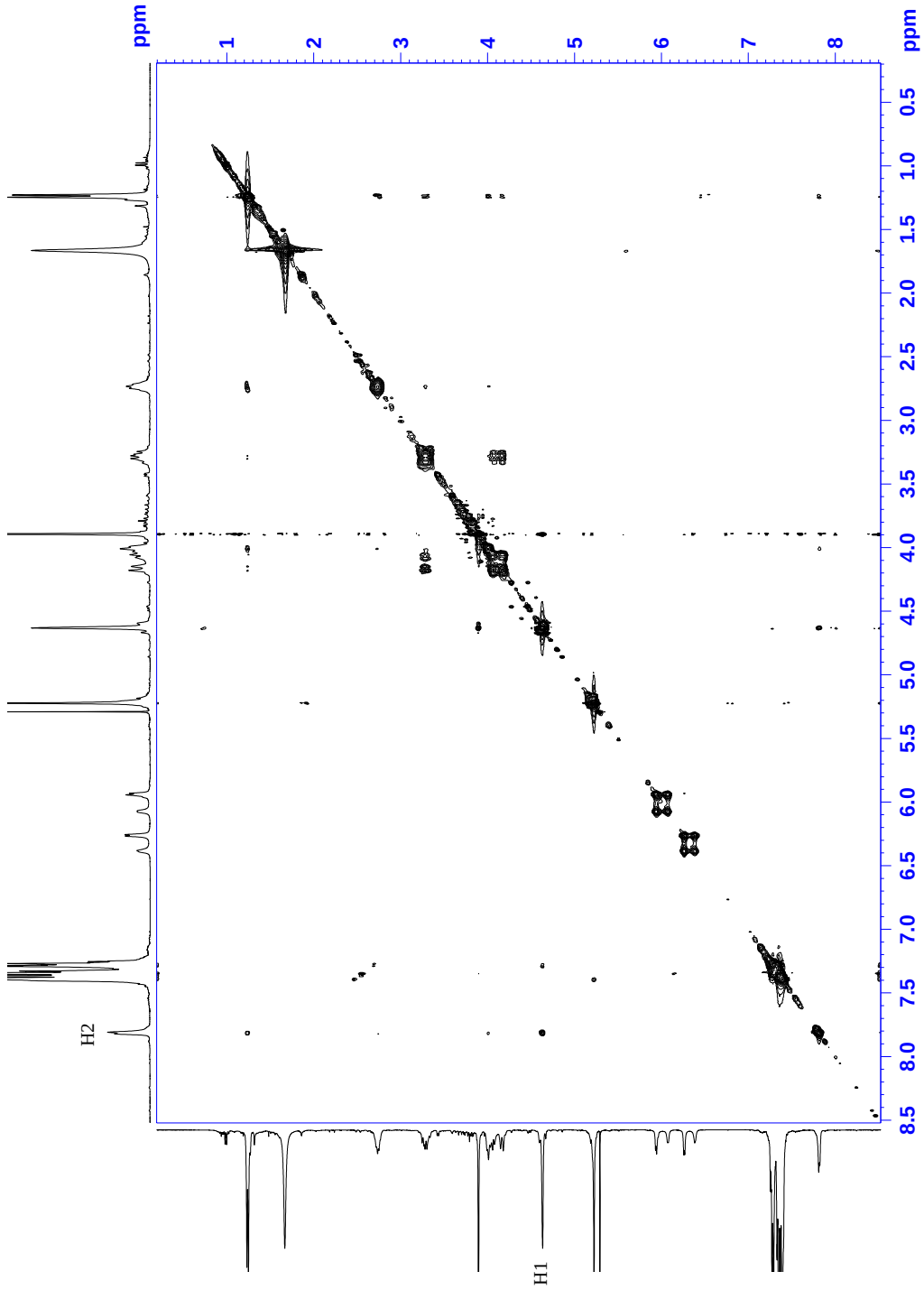
NOESY Spectrum for Compound 71



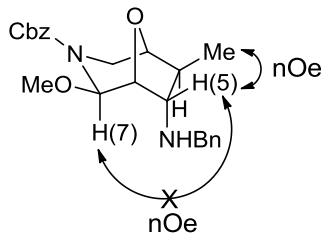


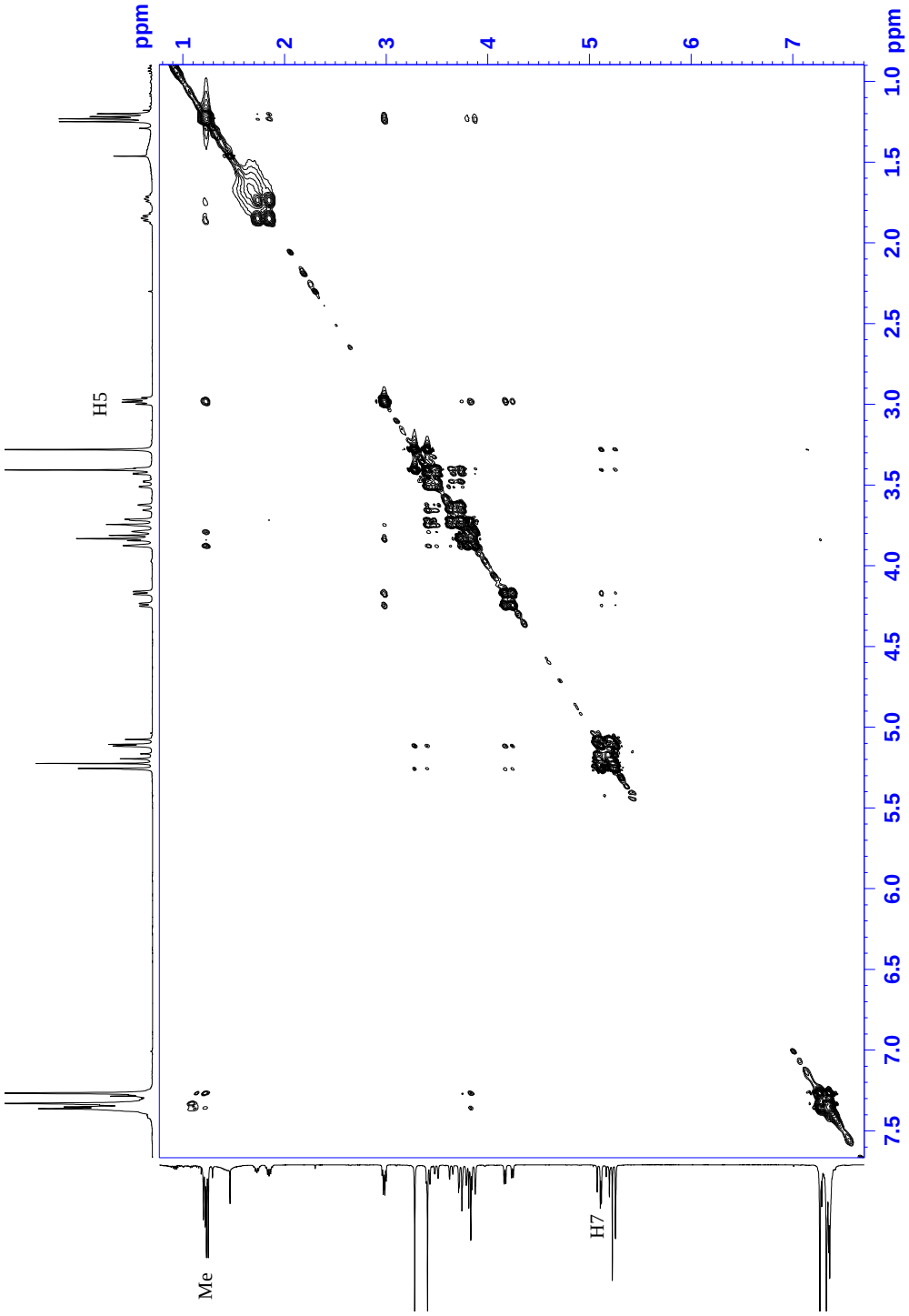
NOESY Spectrum for Compound 73



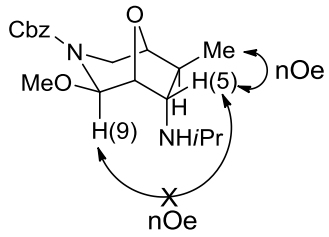


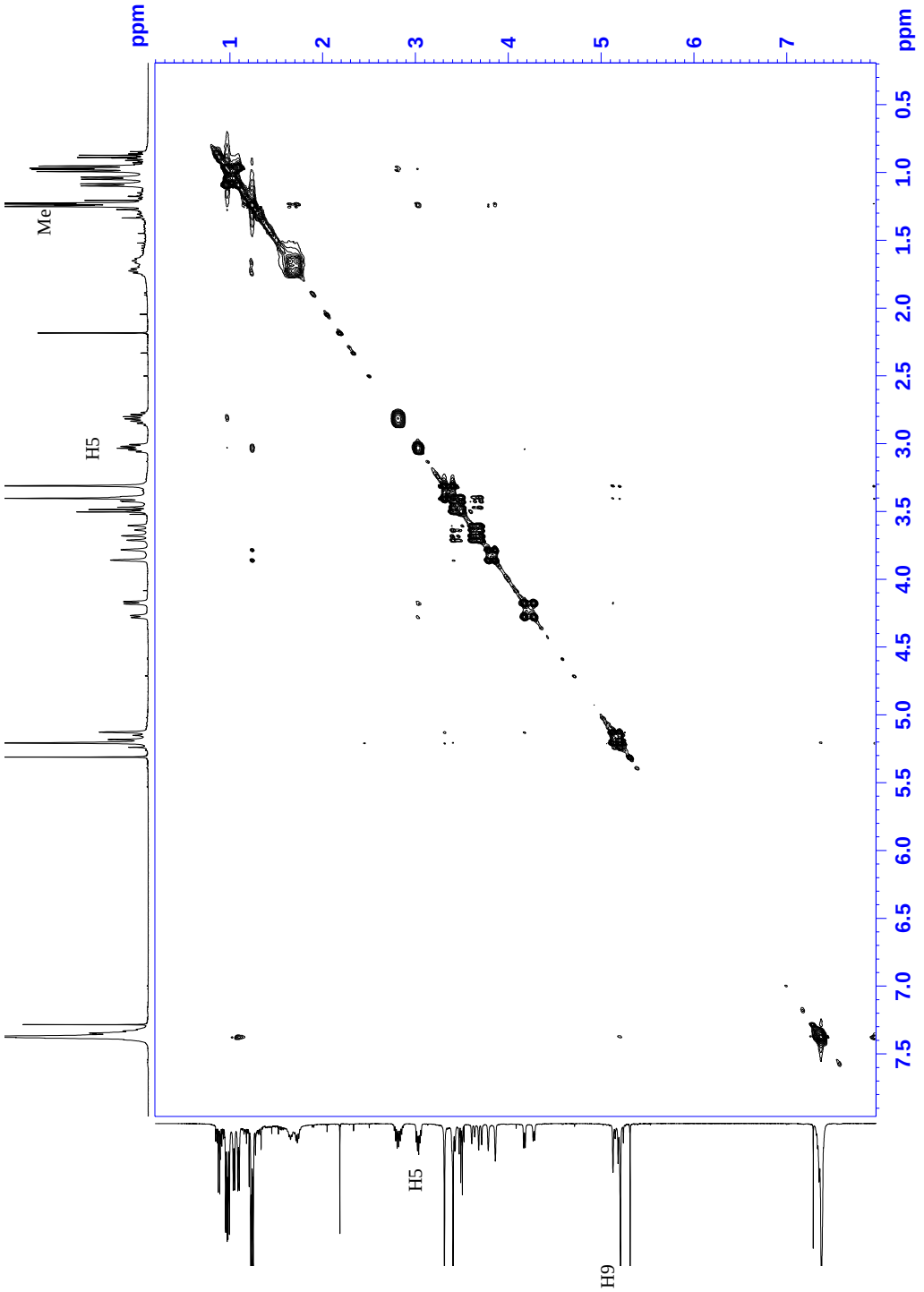
NOESY Spectrum for Compound 74



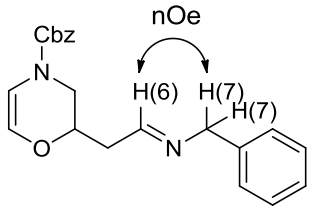


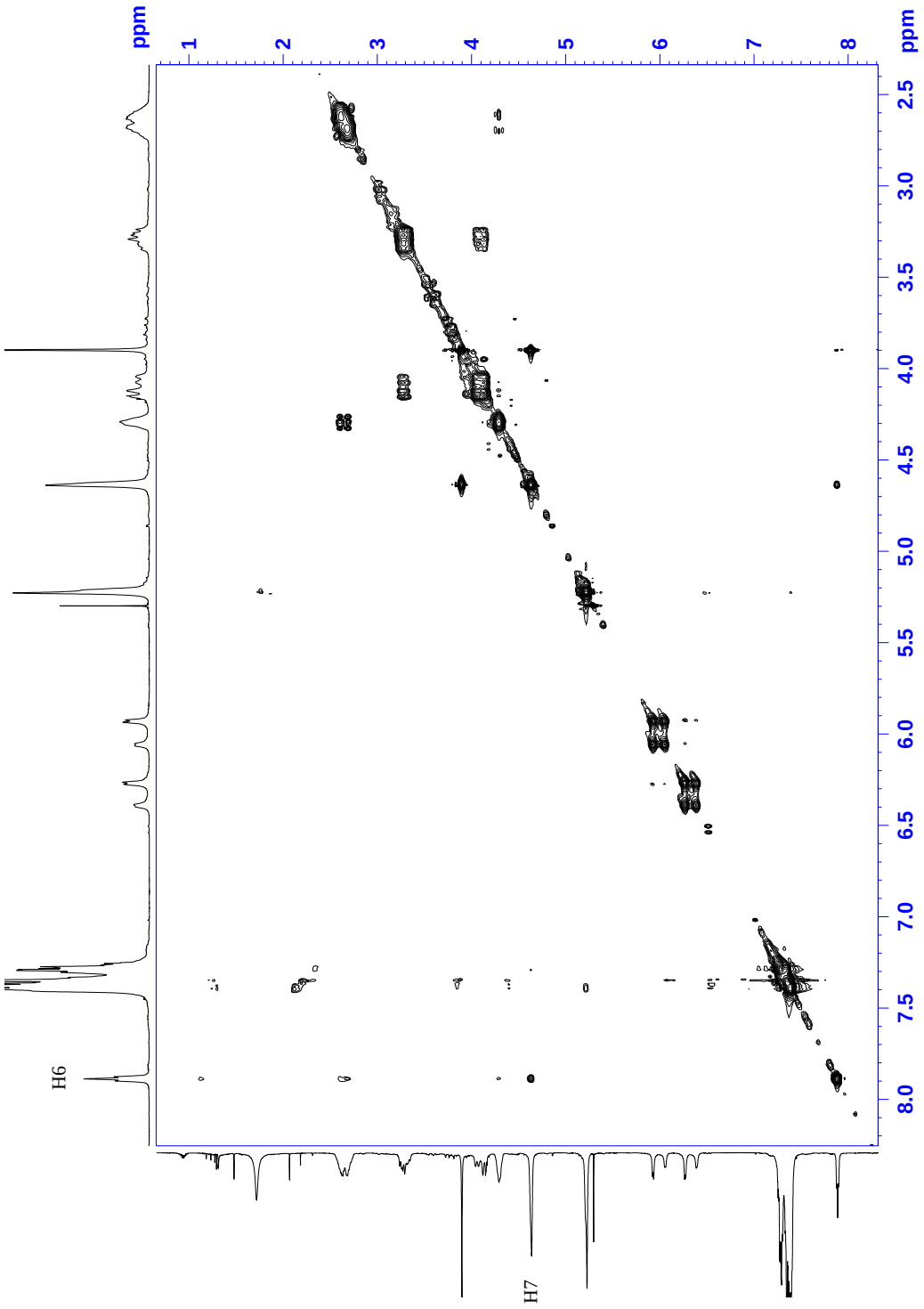
NOESY Spectrum for Compound 76



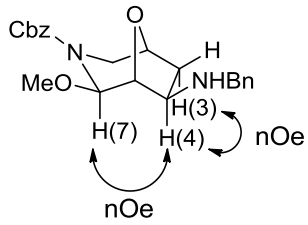


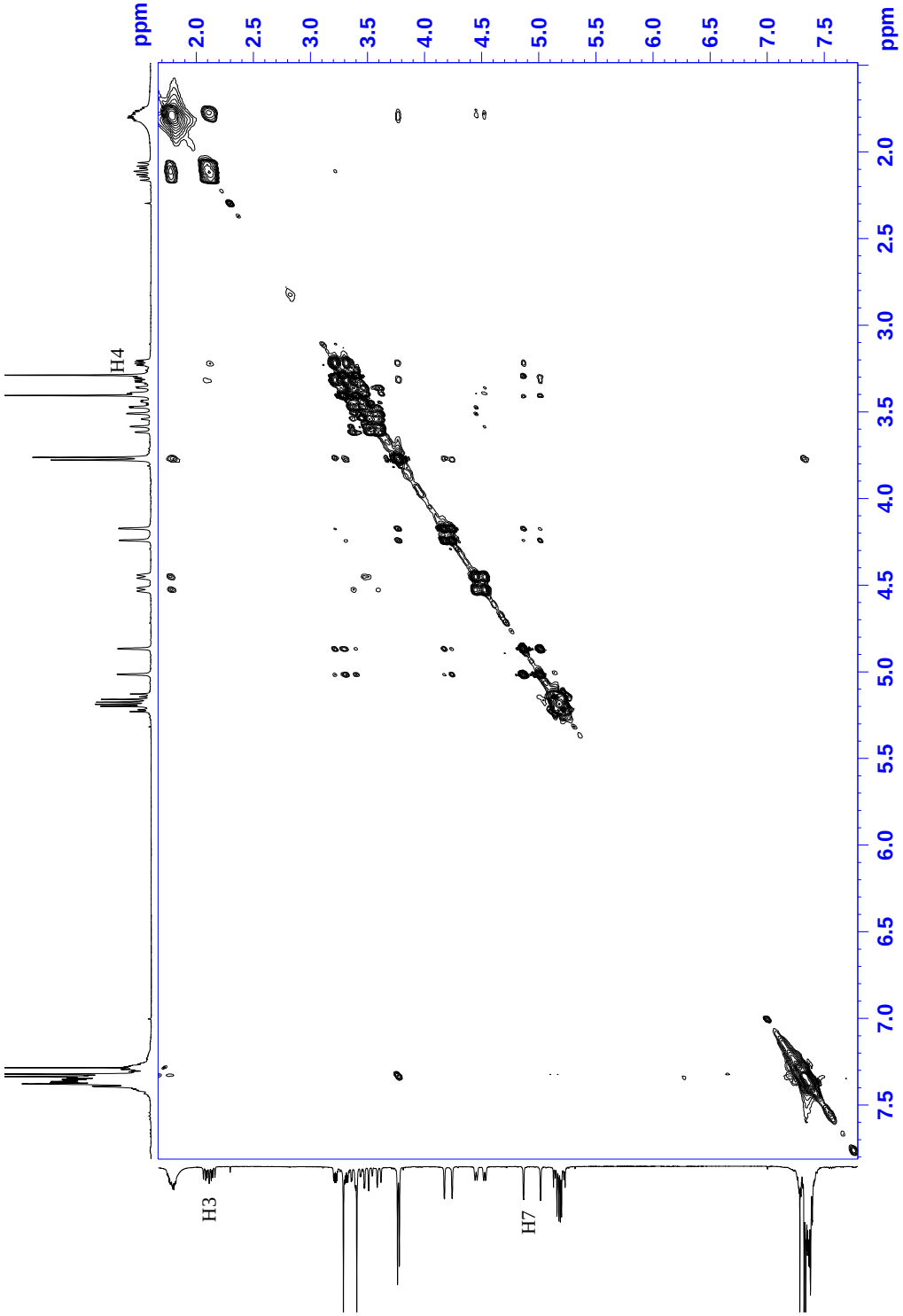
NOESY Spectrum for Compound 77



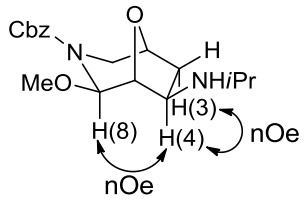


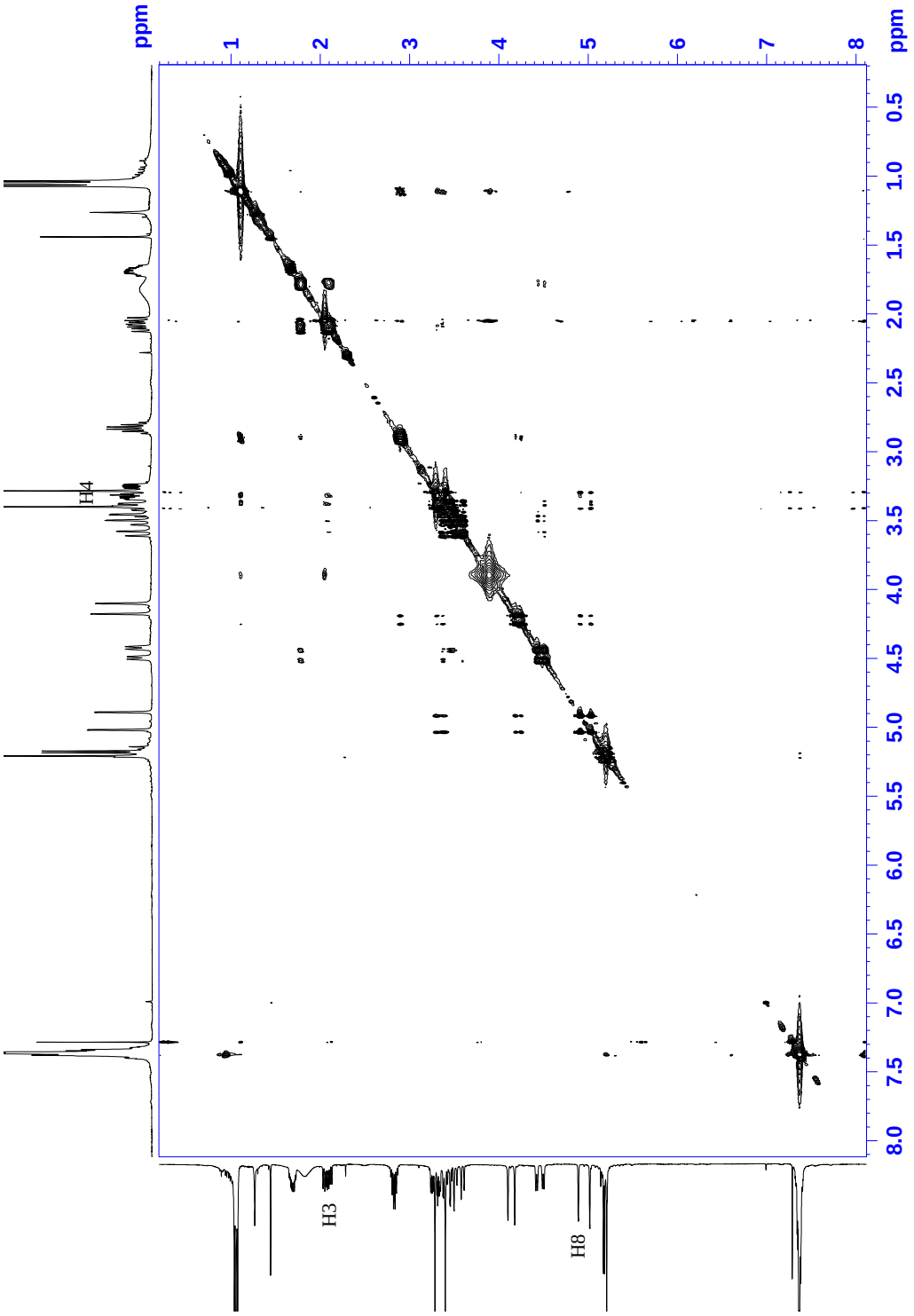
NOESY Spectrum for Compound 78





NOESY Spectrum for Compound 80



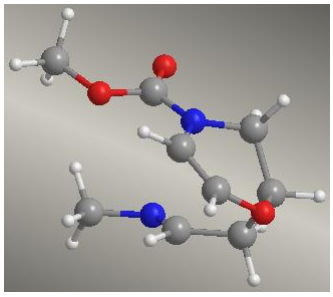


Computational Details for Section 2.12 in Results and Discussion

Density functional theory[1,2] (DFT) was employed to calculate the electronic structures and energies for all species involved in bridged morpholine syntheses. All structures thus far have been optimised with the hybrid meta-GGA exchange correlation functional M06.[10] The M06 density functional was used in conjunction with the 6-311G(*d*,*p*)[11] basis set for main group non-metal atoms. All calculations were run in conjunction with the polarisable continuum model (PCM) for DCM solvation (ε = 8.93), employing the Gaussian keyword scrf=(solvent=dichloromethane).[12] The participating transition states (TS) are located at the same level of theory, using the Berny algorithm[13] through the Gaussian keyword opt=(ts,calcfc,noeigentest). Harmonic vibrational frequencies are calculated at the same level of theory to characterise respective minima (reactants, intermediates, and products with no imaginary frequency) and first order saddle points (TSs with one imaginary frequency). All calculations using the M06 functional have been performed using Gaussian 09 quantum chemistry program package.[9] Natural bond order (NBO) calculations were performed using the keyword pop=nbo, utilising NBO version 3 though Gaussian.[14] All coordinates provided are listed in Cartesian (xyz) format, with charge and multiplicity of each system given at the top of the coordinate list (e.g. 0 1 = neutral singlet; 1 1 = 1+ charged singlet).

Optimised Coordinates from Figure 34

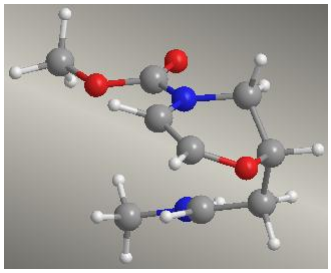
E1 Reactant – non protonated ***(90-E1)***



0 1

C	1.11237300	-0.77628000	1.27475500
C	0.60038400	-1.48844900	-0.96669500
C	1.88162300	-1.28360200	-1.27191100
C	2.24208300	0.03849300	0.66258100
H	-0.06854800	-2.02226100	-1.62506000
H	0.65219300	-0.22861800	2.09946600
H	1.51117000	-1.72327200	1.65951500
H	2.32890000	-1.67307700	-2.17770500
H	3.07738400	0.05180500	1.37065100
N	0.10191300	-1.04559800	0.26976100
O	2.76820400	-0.60744900	-0.50138400
C	-1.21802500	-0.82244800	0.54216600
O	-1.65269700	-0.48713700	1.61842900
O	-1.97250000	-1.03016500	-0.54770700
C	1.86961900	1.49069600	0.37230100
H	1.78162900	2.01927800	1.32876600
C	0.60080700	1.71175800	-0.38569000
H	0.54724600	1.30459300	-1.41120600
N	-0.36310000	2.34737100	0.12603400
H	2.70757400	1.93429500	-0.18075000
C	-1.54850600	2.52572900	-0.67799600
H	-2.41812300	2.14513800	-0.13012000
H	-1.72725000	3.59461100	-0.83699300
H	-1.49538700	2.02432800	-1.65780900
C	-3.37624800	-0.89038500	-0.35167900
H	-3.83759000	-1.15001200	-1.30288100
H	-3.72826700	-1.56244900	0.43422100
H	-3.63133600	0.13816300	-0.08235300

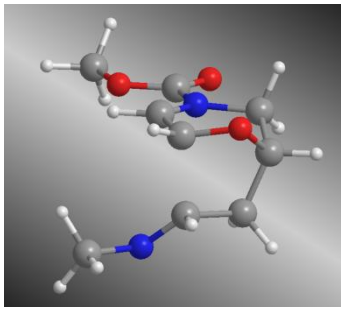
E1 Reactant – protonated ***(91-E1)***



1 1

C	1.13839900	-0.81451400	1.26733100
C	0.61262500	-1.47592900	-0.98144100
C	1.89590200	-1.27968300	-1.28195100
C	2.26707100	0.00988100	0.67387900
H	-0.05805400	-2.02686500	-1.62348200
H	0.70088400	-0.31396100	2.13337300
H	1.52275800	-1.79212100	1.58043800
H	2.35523400	-1.68421000	-2.17400400
H	3.10885200	0.03977400	1.37085100
N	0.12136800	-0.98787900	0.24744200
O	2.77574200	-0.58507500	-0.51400400
C	-1.20720500	-0.81008100	0.54702300
O	-1.61566300	-0.43611000	1.61953500
O	-1.97020000	-1.06494100	-0.51859700
C	1.84809300	1.46301300	0.41475000
H	1.73926800	1.98536300	1.37159200
C	0.62422700	1.60475400	-0.39406800
H	0.56809200	1.15386500	-1.38610900
N	-0.38965000	2.28263900	-0.00260600
H	-0.34779000	2.71944000	0.91841200
H	2.66137200	1.94477500	-0.14361000
C	-1.61872100	2.48383300	-0.76174700
H	-2.46623000	2.20399800	-0.13493400
H	-1.70653500	3.53652700	-1.03319300
H	-1.59213600	1.86518400	-1.65837200
C	-3.38106700	-1.01313300	-0.29549200
H	-3.84092800	-1.17494100	-1.26793400
H	-3.68510800	-1.79753200	0.40067100
H	-3.67668800	-0.04245300	0.10728000

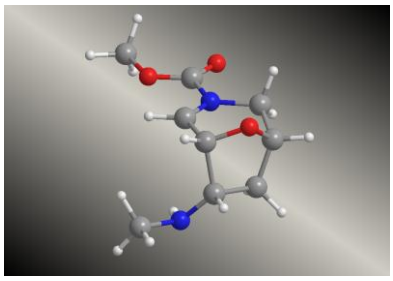
E1 Transition state – stepwise cyclisation ***(92-E1)***



1 1

C	0.38536400	-1.92583700	-0.21309400
C	0.00765600	0.13500700	0.99952800
H	0.33915500	1.12951800	1.28004200
H	0.81486800	-2.09048300	-1.20251400
H	0.76889400	-2.68994400	0.46744400
N	0.82562000	-0.59449100	0.25669900
C	2.14046700	-0.16956400	-0.11814000
O	2.85036200	-0.86913000	-0.77294100
O	2.39684600	1.02515400	0.35730200
N	-2.02300200	1.55699400	-0.80760400
H	-1.19786000	1.73459100	-1.36880900
C	-1.31330000	-0.27537200	1.24192400
H	-1.83160000	0.18186500	2.07941300
C	-1.12962000	-1.92899000	-0.24920100
H	-1.48830100	-2.92962500	-0.48813000
C	-1.69742100	-0.84891900	-1.17866100
H	-0.94930300	-0.50233800	-1.90033500
H	-2.54706200	-1.22650500	-1.75187600
O	-1.60268300	-1.60925400	1.06200300
C	-2.15919100	0.30154200	-0.30741700
H	-3.14357800	0.14687400	0.14543600
C	-2.53010900	2.68415100	-0.05591100
H	-2.53827000	3.57552900	-0.68334400
H	-3.55523700	2.47707500	0.26230700
H	-1.92544400	2.89167600	0.83978500
C	3.70314800	1.54994400	0.05431700
H	3.74475500	2.52322500	0.53538900
H	4.47054600	0.88732500	0.45597600
H	3.82194800	1.64777300	-1.02542600

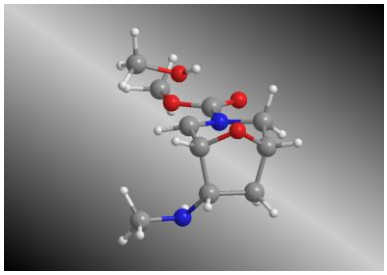
E1 Cyclised iminium – stepwise cyclisation ***(93-E1)***



1 1

C	0.40366100	-1.87051200	-0.20948200
C	0.02552100	0.29875500	0.81373700
H	0.38440900	1.30191100	1.02956400
H	0.77034100	-2.03773500	-1.22393400
H	0.89192900	-2.58194500	0.46036500
N	0.83112600	-0.50523800	0.19441200
C	2.21290700	-0.14894800	-0.13182700
O	2.90700700	-0.92642400	-0.70025600
O	2.48027500	1.05244600	0.28984800
N	-2.22963000	1.44139600	-0.86670600
H	-1.38009000	1.60966700	-1.39512800
C	-2.25170500	0.19174800	-0.21511300
H	-3.25575400	0.01707200	0.19407900
C	-1.34872900	-0.10602500	1.09663900
H	-1.74130500	0.38443700	1.98816200
C	-1.10613300	-1.94623700	-0.11976200
H	-1.42489400	-2.98391800	-0.21649900
C	-1.81309300	-0.98911700	-1.08708300
H	-1.14051500	-0.64777300	-1.88257800
H	-2.67283600	-1.45772700	-1.56749500
O	-1.46493200	-1.49439500	1.19122000
C	3.82291000	1.52415800	0.03606500
H	3.86655100	2.51855500	0.47014700
H	4.53963500	0.85726500	0.51539500
H	3.99919600	1.55985100	-1.03910000
C	-2.63575300	2.57837500	-0.06714100
H	-2.67409500	3.47499900	-0.68807400
H	-3.64042700	2.40199300	0.33044300
H	-1.96892800	2.78404700	0.78802000

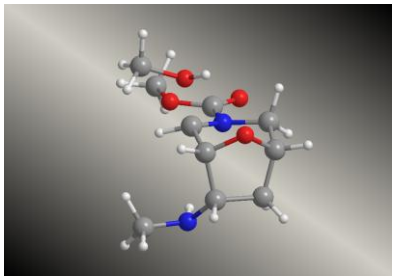
*E1 Transition state – stepwise MeOH attack (**94-E1**)*



1 1

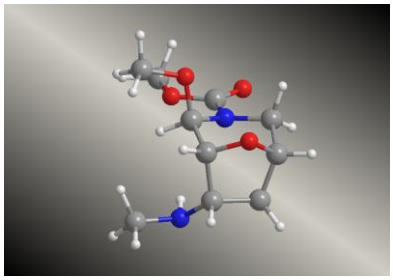
C	0.03919300	-1.93908300	0.65776800
H	0.25754000	-2.76662100	-0.01888200
H	0.54711800	-2.12653400	1.61042300
N	0.59246400	-0.70574700	0.05780400
C	1.91059400	-0.79191700	-0.45881700
O	2.47991000	-1.83616700	-0.56443400
O	2.36867500	0.40199400	-0.78126800
N	-2.06693900	0.55484400	-1.83524900
H	-1.17908800	0.24185000	-2.21519200
C	-2.33037000	0.01255100	-0.53514300
H	-3.34880800	0.30742600	-0.24971500
C	-1.44619800	0.45661600	0.66598700
H	-1.74517000	1.41910300	1.08794600
C	-1.44931500	-1.76137600	0.85713700
H	-1.84428600	-2.59111400	1.44376300
C	-2.19370800	-1.51593700	-0.45663600
H	-1.63369100	-1.89886400	-1.31600600
H	-3.17072500	-2.00025100	-0.45930800
O	-1.64095400	-0.55563200	1.62348000
C	3.68910100	0.42629400	-1.34996900
H	3.89298100	1.47032200	-1.57268300
H	4.41107800	0.03842800	-0.63015200
H	3.71421600	-0.17342000	-2.26075500
C	-2.24302300	1.98915700	-1.94589300
H	-2.06923600	2.30412800	-2.97690400
H	-3.27656300	2.24623900	-1.68975100
H	-1.58380400	2.59085200	-1.29504500
C	0.00723400	0.47972500	0.29060800
H	0.37961300	1.30746500	-0.30851600
C	1.00550800	2.47176800	1.92540900
H	0.09742600	3.04973800	1.73369400
H	1.39729600	2.69777800	2.91631100
H	1.76146400	2.68260100	1.17043700
H	0.17124800	0.75876900	2.57353800
O	0.74344500	1.05625900	1.84674800

E1 Product – stepwise MeOH attack ***(95-E1)***



```
1 1
 C                 -0.02037000   -1.96688600    0.49000400
 H                  0.19401400   -2.73913800   -0.25039900
 H                  0.45863700   -2.25758900    1.43302900
 N                  0.56077900   -0.69953400    0.00804400
 C                  1.86926000   -0.75875500   -0.48655000
 O                  2.42880000   -1.79156600   -0.71873700
 O                  2.37018400    0.45897000   -0.65594400
 N                 -1.84908600    0.72894900   -1.84651100
 H                 -0.92814300    0.41242700   -2.13487900
 C                 -2.27039300    0.11852500   -0.61558500
 H                 -3.29818700    0.44895700   -0.41876200
 C                 -1.47740300    0.44675200    0.67127500
 H                 -1.80958400    1.36599500    1.16226000
 C                 -1.51040500   -1.78662200    0.67330400
 H                 -1.93108300   -2.65612400    1.17910800
 C                 -2.21839300   -1.41894500   -0.62949900
 H                 -1.66923600   -1.78080300   -1.50400100
 H                 -3.22107700   -1.84631700   -0.66817700
 O                 -1.71504400   -0.64437200    1.53585700
 C                  3.69693200    0.50830800   -1.20037100
 H                  3.95823900    1.56257900   -1.24540000
 H                  4.38828000   -0.03136400   -0.55164400
 H                  3.71089800    0.06848600   -2.19874800
 C                 -1.97077200    2.17289300   -1.88112100
 H                 -1.67775000    2.54530200   -2.86504500
 H                 -3.01825800    2.44988500   -1.71945100
 H                 -1.36964800    2.71190300   -1.12648600
 C                  0.01666000    0.49613100    0.43597200
 H                  0.38703200    1.35519500   -0.12177200
 C                  0.92148200    2.17412200    2.21965100
 H                  0.04024600    2.79828000    2.06537400
 H                  1.24133100    2.19003800    3.25832600
 H                  1.73823000    2.45954000    1.56051300
 H                  0.02100600    0.35997100    2.54262000
 O                  0.61401200    0.78493500    1.89011300
```

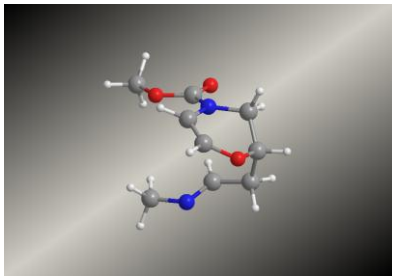
E1 Final Product ***(96-E1)***



0 1

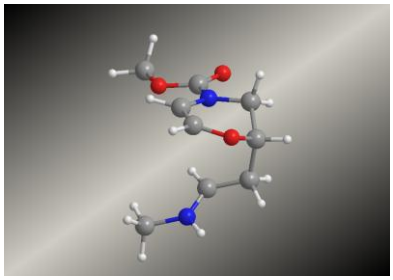
C	0.03484700	-2.02111700	0.37810500
H	0.38454800	-2.74114100	-0.36534500
H	0.38004100	-2.35107500	1.36782100
N	0.59555100	-0.71172800	0.04747000
C	1.88631400	-0.67892700	-0.41049700
O	2.53941200	-1.65725200	-0.68308600
O	2.32956100	0.57944700	-0.55205700
N	-1.68486800	0.96087000	-1.76527600
H	-0.70818500	0.75865000	-1.96151100
C	-2.17142100	0.13508700	-0.68442700
H	-3.23621300	0.37222100	-0.55308700
C	-1.52091300	0.27973300	0.71113700
H	-1.94451300	1.09424000	1.30720900
C	-1.47491700	-1.91859700	0.37294300
H	-1.91524600	-2.87184800	0.67413600
C	-2.01919100	-1.37336300	-0.94991700
H	-1.32990300	-1.55524300	-1.78098600
H	-2.97638700	-1.83195700	-1.20600500
O	-1.84747600	-0.94046600	1.34876500
C	3.66112900	0.70130400	-1.04352200
H	3.86851700	1.76920600	-1.08162900
H	4.36701900	0.20514500	-0.37375200
H	3.74923500	0.26587300	-2.04164000
C	-1.89992000	2.38044200	-1.56518700
H	-1.53613900	2.93840000	-2.43181000
H	-2.97538300	2.57184200	-1.47516200
H	-1.41661200	2.80474400	-0.66620600
C	-0.00669600	0.45302500	0.65036300
H	0.24150300	1.32780400	0.03463200
C	0.58060400	1.97666200	2.33647500
H	-0.41917900	2.43298700	2.38592500
H	1.02426700	2.01411800	3.33231700
H	1.19978400	2.56870800	1.64552600
O	0.53463400	0.62800100	1.94154900

*E2 Reactant – non protonated (**90-E2**)*



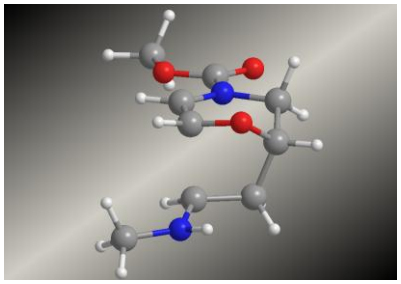
```
0 1
 C                 -0.82770400   -1.68268000   -0.60548400
 C                 -0.23292400   -0.71664800    1.51594000
 C                 -1.53000500   -0.48934000    1.71602500
 C                 -2.06488900   -0.79662500   -0.57623600
 H                  0.49691400   -0.62822200    2.30668600
 H                 -0.44265100   -1.77188900   -1.62279900
 H                 -1.09088400   -2.68313600   -0.24112800
 H                 -1.92759800   -0.24182800    2.69226100
 H                 -2.88950600   -1.34706000   -1.04254600
 N                  0.20731200   -1.12061500    0.24222500
 O                 -2.49507600   -0.56889100    0.76922700
 C                  1.45267300   -0.87975500   -0.26062300
 O                  1.81564000   -1.18201800   -1.37499400
 O                  2.22240600   -0.25058900    0.63815500
 C                 -1.92120600    0.53042400   -1.32255300
 H                 -1.87269900    0.29998200   -2.39437200
 C                 -0.73474800    1.35153200   -0.93017500
 H                  0.22491900    1.10336500   -1.42117900
 N                 -0.81601500    2.27740000   -0.07754300
 H                 -2.83014600    1.11241900   -1.13892400
 C                  3.53348100    0.07782500    0.18678400
 H                  4.03988800    0.52574000    1.03991000
 H                  4.06808600   -0.81518300   -0.14362700
 H                  3.48593400    0.79419600   -0.63811300
 C                  0.40520300    2.95844300    0.27764400
 H                  1.27316300    2.64480800   -0.32572400
 H                  0.27391900    4.04051000    0.17679900
 H                  0.62852700    2.76172600    1.33295500
```

E2 Reactant – protonated ***(91-E2)***



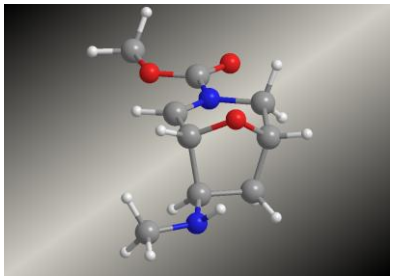
```
1 1
 C                  0.28829800   -1.90654600   -0.32621500
 C                  0.14787000   -0.22489700    1.38611400
 C                 -1.07358500   -0.68535500    1.68043800
 C                 -1.22430300   -1.77396600   -0.37045400
 H                  0.63711600    0.51097600    2.00734200
 H                  0.70194700   -2.03127000   -1.32836500
 H                  0.54225900   -2.79477900    0.26536500
 H                 -1.61204900   -0.37257700    2.56530500
 H                 -1.64514100   -2.71333000   -0.73655900
 N                  0.85192000   -0.71740100    0.28103100
 O                 -1.75912700   -1.58757000    0.92821500
 C                  2.03487400   -0.20060300   -0.19152300
 O                  2.68623400   -0.70454600   -1.07175800
 O                  2.34484500    0.93339700    0.44186000
 C                 -1.75409800   -0.66630800   -1.30957800
 H                 -1.26994100   -0.79260600   -2.28538600
 C                 -1.50540700    0.71210700   -0.85017800
 H                 -0.50100600    1.13118600   -0.85544800
 N                 -2.45253800    1.48979100   -0.47360100
 H                 -3.40365700    1.12240600   -0.47337700
 H                 -2.82962200   -0.81956000   -1.44020300
 C                  3.59248600    1.52078900    0.06676500
 H                  3.69168700    2.41810500    0.67375100
 H                  4.41615600    0.83365300    0.27079800
 H                  3.59184700    1.77893300   -0.99404800
 C                 -2.27251600    2.83907100    0.04283000
 H                 -1.22022000    3.11105600   -0.02597200
 H                 -2.87930500    3.53442000   -0.53716900
 H                 -2.59307600    2.86065400    1.08622900
```

E2 Transition state – stepwise cyclisation ***(92-E2)***



```
1 1
 C                  0.58887700   -1.81612800    0.04790200
 C                  0.16773600    0.40140500    0.90393400
 C                 -0.92179200   -1.81709400   -0.08804700
 H                  0.48736700    1.42564300    1.05466600
 H                  1.06945100   -2.15487700   -0.87169800
 H                  0.90638200   -2.46619200    0.86733800
 H                 -1.27326700   -2.84312200   -0.19512000
 N                  1.02641400   -0.43686500    0.31538400
 O                 -1.49441200   -1.29367000    1.10900000
 C                  2.33612100   -0.06779900   -0.08438300
 O                  3.07587200   -0.84987600   -0.60348300
 O                  2.57660000    1.19401300    0.20021800
 N                 -3.11877800    0.70027400   -0.52246700
 H                 -3.70106100   -0.09629100   -0.28390100
 C                 -1.42691500   -0.90824000   -1.21841100
 H                 -0.67696100   -0.79255400   -2.00477200
 H                 -2.31653300   -1.34439000   -1.67922200
 C                 -1.79949200    0.45002400   -0.65093500
 H                 -1.23238700    1.31581600   -0.98978800
 C                 -1.14911000    0.02966400    1.14750800
 H                 -1.74610800    0.63532800    1.82082100
 C                 -3.59904700    1.99510500   -0.09371600
 H                 -4.64960100    2.10477800   -0.36340000
 H                 -3.50165800    2.12991300    0.99219500
 H                 -3.02391000    2.77685800   -0.59525100
 C                  3.88095300    1.67505400   -0.16457700
 H                  3.89736300    2.72254600    0.12407600
 H                  4.64911300    1.11679800    0.37224100
 H                  4.02990500    1.57020800   -1.24012200
```

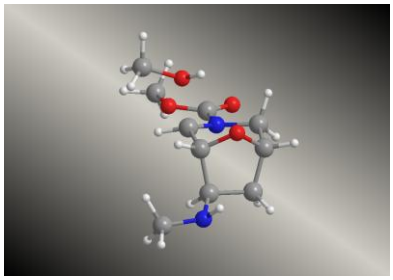
E2 Cyclised iminium – stepwise cyclisation ***(93-E2)***



1 1

C	-0.58305700	-1.73405000	-0.08858900
C	-0.21644000	0.61621200	-0.55422000
C	0.93148400	-1.76744000	-0.10574300
H	-0.59024100	1.63647400	-0.56489300
H	-0.98898900	-2.13739700	0.84138900
H	-1.01388400	-2.28817600	-0.92569100
H	1.26532700	-2.79674600	-0.23833800
N	-1.03538100	-0.32637300	-0.19824500
O	1.36405200	-1.00901800	-1.23731200
C	-2.44529300	-0.08321300	0.09112700
O	-3.15012800	-0.98113700	0.41943700
O	-2.72971700	1.17581100	-0.08022000
N	3.34546600	0.50155000	0.43780800
H	3.72560600	-0.20810700	-0.18357500
C	1.57368900	-1.06927800	1.09841900
H	0.90499100	-1.03296500	1.96185700
H	2.48548700	-1.58249000	1.40957600
C	1.94382200	0.34038000	0.59879700
H	1.56335700	1.13888400	1.24420300
C	1.18592200	0.31360000	-0.81689500
H	1.62593600	1.01661000	-1.52570400
C	-4.10396000	1.55116100	0.15842100
H	-4.14743400	2.62024200	-0.02733300
H	-4.75429000	1.01060900	-0.52975500
H	-4.37213100	1.32448300	1.19057500
C	3.79404800	1.83267300	0.08958100
H	4.88364800	1.84734500	0.02969400
H	3.39901600	2.20469000	-0.87132100
H	3.48807600	2.53478500	0.87175800

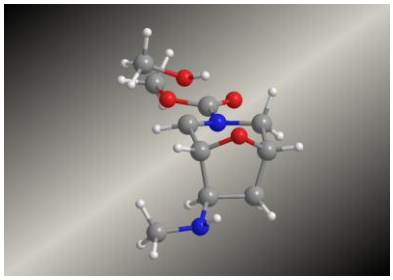
*E2 Transition state – stepwise MeOH attack (**94-E2**)*



1 1

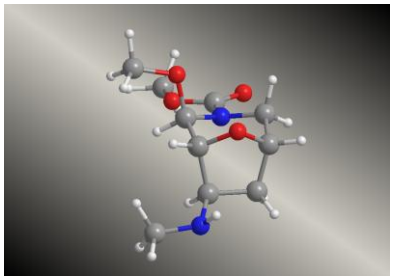
C	-0.38281600	-1.66476200	-1.01463400
C	1.12110700	-1.56851800	-1.15362800
H	-0.67884200	-2.63317100	-0.60891000
H	-0.87514600	-1.53273900	-1.98490800
H	1.45524700	-2.22195400	-1.96044500
N	-0.85920100	-0.61441900	-0.09174800
O	1.45287400	-0.21631100	-1.51810900
C	-2.19566900	-0.72311600	0.35243300
O	-2.84924700	-1.70676500	0.16861400
O	-2.58029700	0.38110800	0.96697600
N	3.40864000	-0.03762800	0.92456400
H	3.87768900	-0.05892100	0.02170000
C	1.85904300	-1.79031600	0.16331500
H	1.31954700	-2.46764900	0.82885500
H	2.85069400	-2.21389500	-0.01209500
C	2.01981500	-0.38093500	0.76250200
H	1.53069800	-0.29202300	1.74090000
C	1.28581300	0.48074100	-0.30107300
H	1.70794900	1.48488500	-0.39711400
C	-3.91757900	0.36291800	1.49172200
H	-4.05971100	1.33074300	1.96558700
H	-4.63497700	0.22330300	0.68183800
H	-4.02291600	-0.44090900	2.22163200
C	3.64399600	1.21761800	1.60938200
H	4.71833500	1.39780700	1.68619000
H	3.18969000	2.09994500	1.12618100
H	3.24249800	1.15486300	2.62668600
C	-0.18112200	0.55144200	-0.00451900
H	-0.50366900	1.21791100	0.79226600
H	-0.20472900	1.32524000	-2.11945200
C	-0.89950400	2.93978200	-1.12537500
H	0.06215200	3.37090400	-0.83865900
H	-1.27064300	3.40228500	-2.03849400
H	-1.62994900	3.05473000	-0.32609400
O	-0.77814200	1.51869900	-1.35699700

E2 Product – stepwise MeOH attack ***(95-E2)***



```
1 1
 C                 -0.38564600   -1.67689400   -0.98974900
 C                  1.11708900   -1.58758900   -1.14396100
 H                 -0.67581500   -2.63636700   -0.55912300
 H                 -0.88233100   -1.57678300   -1.96292900
 H                  1.44475000   -2.25806400   -1.93949000
 N                 -0.85311600   -0.60746100   -0.08791500
 O                  1.45281300   -0.24202000   -1.54059100
 C                 -2.17080800   -0.70860200    0.37659600
 O                 -2.82630900   -1.70315900    0.25412700
 O                 -2.56157200    0.42200000    0.95022100
 N                  3.36814600   -0.01008200    0.98478800
 H                  3.87716200   -0.03462600    0.10402000
 C                  1.86639100   -1.77949100    0.16898900
 H                  1.35285300   -2.47042400    0.84089900
 H                  2.86961700   -2.17294100   -0.01279100
 C                  1.98865100   -0.36271200    0.75820000
 H                  1.45410800   -0.26914200    1.71259000
 C                  1.29276900    0.48312200   -0.33446500
 H                  1.74081700    1.47438800   -0.45277700
 C                 -3.88791300    0.40989700    1.49682300
 H                 -4.03213900    1.39174000    1.94091000
 H                 -4.61921200    0.23740200    0.70555400
 H                 -3.97639000   -0.36936900    2.25519400
 C                  3.55950700    1.25581700    1.66420600
 H                  4.62733600    1.44679800    1.79102400
 H                  3.12217700    2.12895000    1.14930600
 H                  3.10974300    1.20166000    2.66169500
 C                 -0.18915000    0.59952500   -0.08757400
 H                 -0.48300400    1.25923100    0.72726000
 H                 -0.17661600    1.17832400   -2.13359300
 C                 -0.88550200    2.86734700   -1.22238800
 H                 -1.24844500    3.25079800   -2.17308600
 H                 -1.63077100    3.00922700   -0.44252000
 H                  0.06985500    3.31824500   -0.95155300
 O                 -0.73758700    1.42458400   -1.37110200
```

E2 Final Product ***(96-E2)***

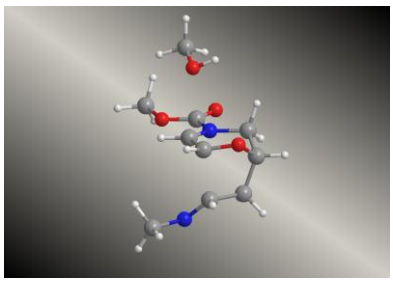


0 1

C	0.44145800	-1.68537600	0.96825000
C	-1.07209300	-1.71323200	0.98417700
H	0.84401300	-2.60873100	0.54553800
H	0.82226200	-1.58180600	1.99392000
H	-1.42275700	-2.50796700	1.64699800
N	0.88783100	-0.56713800	0.13859800
O	-1.53905900	-0.46845800	1.50795500
C	2.17505800	-0.61095800	-0.32812400
O	2.89712200	-1.57606800	-0.24774000
O	2.53162400	0.54219100	-0.91272400
N	-3.30295200	-0.02816500	-1.01577100
H	-3.80255000	-0.19271600	-0.14372100
C	-1.67330800	-1.77295800	-0.42050200
H	-1.02377900	-2.29429600	-1.12810300
H	-2.64036400	-2.28352300	-0.41218100
C	-1.89214200	-0.29539000	-0.79298900
H	-1.35250900	-0.01894400	-1.70865700
C	-1.30088500	0.42635700	0.43295700
H	-1.80831900	1.36968500	0.66051000
C	3.84867700	0.56522200	-1.45418500
H	3.96953900	1.54920300	-1.90388100
H	4.59337200	0.41883900	-0.66825000
H	3.97171600	-0.21215700	-2.21175500
C	-3.57476200	1.30948800	-1.50388300
H	-4.65315400	1.45130000	-1.61236600
H	-3.19187800	2.12475000	-0.86537100
H	-3.12306600	1.43192800	-2.49528300
C	0.19375900	0.68867800	0.28954400
H	0.36481800	1.29592700	-0.61086800
C	0.63212300	2.75485600	1.32365000
H	-0.40617100	3.11198100	1.26715300
H	1.08951600	3.17280800	2.22162600
H	1.17697300	3.12251300	0.44110500
O	0.71417400	1.35461000	1.41881100

Optimised Coordinates from Figure 35

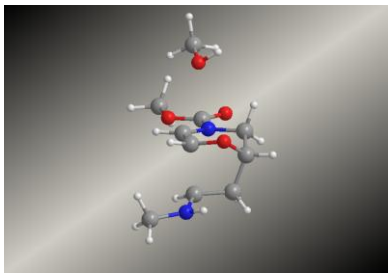
E1 Transition State – concerted cyclisation ***(97-E1)***



1 1

C	-0.17196500	-1.19928000	1.41576800
C	0.14793500	-0.06514500	-0.69069800
H	-0.10237600	0.74701900	-1.36471500
H	-0.32855600	-0.83768500	2.43338500
H	-0.84080500	-2.04709700	1.23630700
N	-0.49846600	-0.11209000	0.48013600
C	-1.59292200	0.72294800	0.79800700
O	-2.22328000	0.57973100	1.80514300
O	-1.79860500	1.61555900	-0.14920200
N	2.77193700	1.46363700	-0.11208600
H	2.19801900	2.06232200	0.47093100
C	1.23046400	-0.88968400	-0.94996400
H	1.58565300	-0.98246200	-1.97011700
C	1.27330900	-1.59273400	1.17927100
H	1.52864700	-2.44802100	1.80426300
C	2.23453800	-0.41069300	1.37562900
H	1.78162900	0.37629400	1.98864600
H	3.14580600	-0.73207600	1.88697800
O	1.41060400	-2.00969500	-0.17890600
C	2.61403200	0.13768600	0.02352100
H	3.36189700	-0.44077100	-0.52353800
C	3.21817900	2.02439500	-1.36973200
H	3.53958300	3.05531600	-1.22359700
H	4.06444100	1.44459800	-1.74512700
H	2.41949600	2.00520500	-2.12462500
C	-2.94883000	2.45642700	0.03429700
H	-2.95432200	3.13496000	-0.81465900
H	-3.85411800	1.84562800	0.04326400
H	-2.86634600	3.00976700	0.97050700
C	-3.02030900	-1.30974700	-1.32684200
H	-3.81403700	-1.94706400	-1.73314700
H	-3.17041300	-1.22697100	-0.23899300
H	-3.12864100	-0.31338400	-1.76360900
H	-1.64877500	-2.68857400	-1.37216800
O	-1.73092800	-1.77595200	-1.66102000

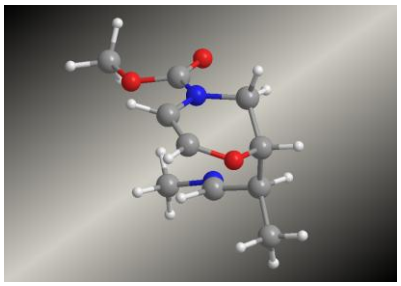
E2 Transition State – concerted cyclisation ***(97-E2)***



```
1 1
 C                  0.31215800    0.79929200    1.53850900
 C                 -0.06117800   -0.03623000   -0.68851100
 C                 -1.18203600    1.04806500    1.47029600
 H                  0.21715900   -0.68787200   -1.50798600
 H                  0.58706800    0.31029100    2.47483300
 H                  0.86196700    1.74122400    1.45419400
 H                 -1.46291800    1.76527600    2.24149400
 N                  0.68357600   -0.08059400    0.42519500
 O                 -1.50365000    1.63140600    0.21079300
 C                  1.86897800   -0.83262200    0.54680900
 O                  2.55580500   -0.77664700    1.52582200
 O                  2.09007300   -1.55047200   -0.53802600
 N                 -3.57927600   -0.60240400   -0.27636600
 H                 -4.06465600    0.23066600    0.04104800
 C                 -2.01451200   -0.23881000    1.55370400
 H                 -1.50014300   -1.00898600    2.13381600
 H                 -2.96289300   -0.03182600    2.05607800
 C                 -2.31715400   -0.75668800    0.16131200
 H                 -1.86753600   -1.70068600   -0.14264300
 C                 -1.24338500    0.68043600   -0.73422100
 H                 -1.71787000    0.85269600   -1.69374400
 C                 -4.01692700   -1.16266500   -1.53594200
 H                 -5.10522700   -1.21965900   -1.55383700
 H                 -3.68311700   -0.55875000   -2.39023100
 H                 -3.61082000   -2.17121400   -1.64096500
 C                  3.31744300   -2.29538700   -0.54346500
 H                  3.31006500   -2.86826200   -1.46711000
 H                  4.16700000   -1.60914600   -0.52546200
 H                  3.35934800   -2.95890900    0.32112300
 C                  2.86418800    1.80132700   -1.17827000
 H                  3.55097700    2.47179700   -1.70847500
 H                  3.24397900    1.65616800   -0.15582200
 H                  2.88218400    0.83398900   -1.68957700
 H                  1.50840700    3.14466000   -0.81750200
 O                  1.53170400    2.26436400   -1.20013200
```

Optimised Coordinates from Figure 37

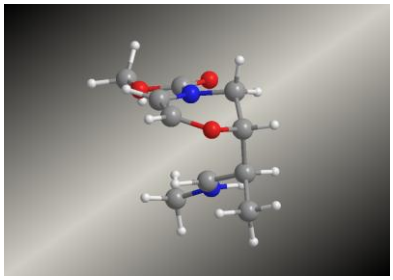
E1 Reactant – non protonated ***(98-E1)***



0 1

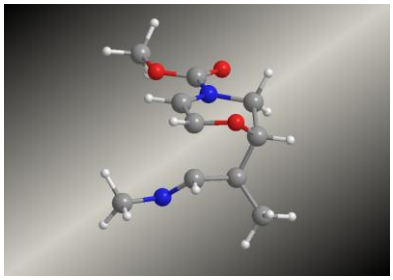
C	0.58805400	-1.16835600	1.28190300
C	-0.02358100	-1.64689100	-0.99703300
C	1.27544700	-1.76356000	-1.27083300
C	1.90572100	-0.65070300	0.72331700
H	-0.78455400	-1.96385000	-1.69404300
H	0.25790300	-0.54735300	2.11695500
H	0.72440100	-2.19602900	1.64109500
H	1.63381100	-2.21434600	-2.18763600
H	2.69761300	-0.87473900	1.44850300
N	-0.43109800	-1.14526700	0.24899500
O	2.28242100	-1.37680300	-0.45006700
C	-1.66228100	-0.61175200	0.50733100
O	-2.03110100	-0.22139300	1.58938200
O	-2.41247300	-0.58055200	-0.60505400
C	1.93375400	0.86608500	0.49744000
H	1.86541700	1.31634200	1.49804100
C	3.23851900	1.29487500	-0.16374600
H	3.29301100	0.93007200	-1.19437800
H	3.31910100	2.38542100	-0.18380300
H	4.10182600	0.89578500	0.37859900
C	0.77184300	1.40804900	-0.28048000
H	0.68200400	1.07347200	-1.33204400
N	-0.03369000	2.23615400	0.22836600
C	-1.09471500	2.74153700	-0.60969600
H	-2.05838100	2.57809400	-0.11421300
H	-0.98605200	3.82539500	-0.72391200
H	-1.12284600	2.28020600	-1.60973400
C	-3.74063100	-0.09684600	-0.43053100
H	-4.22727300	-0.20561100	-1.39819800
H	-4.27158200	-0.67879300	0.32605500
H	-3.73444100	0.95506900	-0.13294400

E1 Reactant – protonated ***(99-E1)***



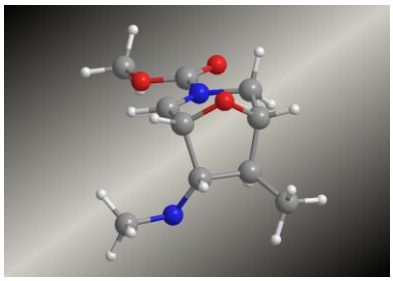
```
1  1
 C                  0.59152800   -1.17992000    1.28201500
 C                 -0.00794800   -1.64521200   -0.99955100
 C                  1.29055000   -1.79836900   -1.25538100
 C                  1.91988300   -0.68650800    0.73718900
 H                 -0.77452500   -1.97373600   -1.68487300
 H                  0.27276100   -0.57986900    2.13646300
 H                  0.69169500   -2.22320200    1.60270500
 H                  1.65529300   -2.28680300   -2.14897800
 H                  2.71276900   -0.88618100    1.46594800
 N                 -0.40249400   -1.07894600    0.22892600
 O                  2.29587300   -1.39982200   -0.43204600
 C                 -1.65648300   -0.59259000    0.50366200
 O                 -1.99493600   -0.16423500    1.58067500
 O                 -2.42728400   -0.61835100   -0.58644300
 C                  1.93123700    0.83729900    0.50478100
 H                  1.86502300    1.29846600    1.49998500
 C                  3.22474100    1.28860200   -0.17826500
 H                  3.30637100    0.86639200   -1.18248000
 H                  3.27348000    2.37725700   -0.24875400
 H                  4.07944800    0.94162900    0.40796500
 C                  0.79371300    1.31606300   -0.31272600
 H                  0.69562200    0.98609900   -1.34957500
 N                 -0.05210500    2.18247000    0.10521100
 H                  0.02385600    2.50160200    1.07192300
 C                 -1.13580100    2.75624600   -0.68468300
 H                 -2.07925700    2.60366700   -0.15931700
 H                 -0.96323800    3.82676600   -0.80197100
 H                 -1.16214500    2.27277700   -1.66021100
 C                 -3.78757400   -0.22723100   -0.38630800
 H                 -4.26214400   -0.29710900   -1.36258500
 H                 -4.27761700   -0.89909800    0.32115500
 H                 -3.84750000    0.79565600   -0.00825400
```

E1 Transition state – stepwise cyclisation ***(100-E1)***



```
1 1
 C                  0.35652700   -1.88652500    0.07817500
 C                  0.37236500    0.30387700    1.10338000
 C                 -0.94652500    0.09389000    1.52163000
 C                 -1.14250200   -1.69361600    0.19502100
 H                  0.84919500    1.26834100    1.24412100
 H                  0.64439400   -2.19773500   -0.92766400
 H                  0.71665000   -2.63240400    0.79118800
 H                 -1.31737800    0.69661000    2.34477900
 H                 -1.64265000   -2.65966600    0.10189700
 N                  1.00861700   -0.59125700    0.35882100
 O                 -1.43208000   -1.19222700    1.50201900
 C                  2.30692900   -0.37132600   -0.19437800
 O                  2.84942400   -1.20590600   -0.85223600
 O                  2.75707900    0.81676500    0.13412200
 C                 -3.02485300   -1.07720400   -1.40244100
 H                 -3.74010800   -1.33158600   -0.61256800
 H                 -3.45035300   -0.27005600   -2.00521500
 H                 -2.89709100   -1.95299300   -2.04402600
 C                 -1.69719500   -0.65481900   -0.79359000
 H                 -0.96629500   -0.47978600   -1.59547500
 H                 -0.87403400    1.78501400   -1.35810500
 N                 -1.62896800    1.79566400   -0.68196200
 C                 -1.87398500    0.64129000   -0.01678100
 H                 -2.80871200    0.68820000    0.55428400
 C                 -1.89074000    3.06826400   -0.04609900
 H                 -1.88829900    3.86383200   -0.79129600
 H                 -2.87521400    3.04068200    0.42758300
 H                 -1.14057300    3.30471400    0.72290000
 C                  4.07070100    1.14282300   -0.35537800
 H                  4.28254200    2.13991600    0.02084100
 H                  4.79684800    0.42408700    0.02623400
 H                  4.07380500    1.13300500   -1.44596800
```

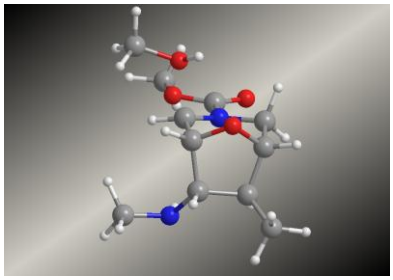
E1 Cyclised iminium – stepwise cyclisation ***(101-E1)***



1 1

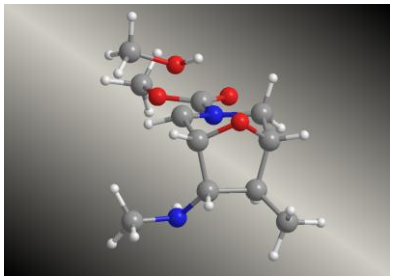
C	0.40608300	-1.80603100	0.06694100
C	0.39048400	0.48570000	0.86338500
C	-0.99058100	0.29422300	1.29878900
C	-1.08551000	-1.68213100	0.29791100
H	0.88561900	1.45034900	0.93789600
H	0.64487400	-2.11513600	-0.95265600
H	0.87208600	-2.50799200	0.76244000
H	-1.23264600	0.92343100	2.15616000
H	-1.52814000	-2.67877900	0.35327200
N	1.03350200	-0.47697800	0.28219200
O	-1.26122600	-1.05028700	1.57033900
C	2.41336700	-0.34033300	-0.18834000
O	2.95017500	-1.25383600	-0.72364600
O	2.86486900	0.85000700	0.07902600
C	-3.12623600	-1.31545500	-1.19051100
H	-3.75339500	-1.58624400	-0.33323500
H	-3.65791800	-0.56165200	-1.77861000
H	-2.99433100	-2.20505000	-1.81235700
N	-1.87352600	1.70376400	-0.76940500
H	-1.06138900	1.70097300	-1.37748100
C	-1.97340700	0.55788300	0.04680500
H	-2.94913900	0.56721100	0.55497200
C	-1.79585300	-0.76729600	-0.71387300
H	-1.14480000	-0.58441700	-1.58083000
C	-2.08917300	2.97688200	-0.11352200
H	-1.32602500	3.22809400	0.64261500
H	-2.10564400	3.77806900	-0.85453400
H	-3.06217900	2.96401500	0.38784600
C	4.22383300	1.11472000	-0.33642000
H	4.42731000	2.13504400	-0.02550600
H	4.89749200	0.41410300	0.15702400
H	4.29980800	1.01442000	-1.41927300

*E1 Transition state – stepwise MeOH attack (**102-E1**)*



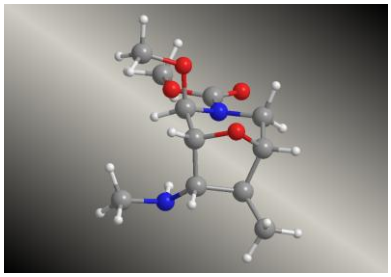
```
1 1
 C                  0.04839800   -1.70099800   -0.92116700
 C                  1.04627700    0.91391500   -0.60177000
 C                  1.46574800   -1.21143800   -1.11423700
 H                  0.02197600   -2.63788600   -0.36227200
 H                 -0.45125300   -1.85900000   -1.88321000
 H                  1.14454700    1.96584600   -0.88094900
 H                  1.98838500   -1.86037400   -1.82034500
 N                 -0.71155400   -0.69169100   -0.15250000
 O                  1.39946600    0.10389800   -1.69956100
 C                 -1.96873800   -1.10399200    0.35883200
 O                 -2.32544100   -2.24264400    0.31103300
 O                 -2.62937500   -0.08160700    0.86461400
 C                  3.68443100   -1.40567600    0.11796400
 H                  4.16021900   -0.89214100   -0.72603600
 H                  4.20945100   -1.11432900    1.03318100
 H                  3.81151300   -2.48310900   -0.02124500
 N                  1.73660400    0.75393900    1.88440800
 H                  0.94167400    0.21976100    2.22137600
 C                  2.03956200    0.47888800    0.51094000
 H                  2.97277700    1.00629700    0.26277400
 C                  2.22137500   -1.02130100    0.20725200
 H                  1.73786500   -1.60409000    1.00209600
 C                  1.63364300    2.16116200    2.21746800
 H                  0.83936100    2.70675600    1.67800100
 H                  1.44876800    2.27521000    3.28760700
 H                  2.58343400    2.65685700    1.98961800
 C                 -3.90886700   -0.39440500    1.44091200
 H                 -4.29143400    0.54438400    1.83255800
 H                 -4.57557900   -0.79055700    0.67382400
 H                 -3.78895600   -1.12559200    2.24137200
 C                 -0.37281600    0.60578100   -0.22546300
 H                 -0.88213700    1.26160200    0.47681900
 H                 -0.65791600    1.04997600   -2.45370600
 C                 -1.66437500    2.59501600   -1.65608900
 H                 -0.81454100    3.25932100   -1.48047200
 H                 -2.14551900    2.83677400   -2.60294500
 H                 -2.38673100    2.67511700   -0.84468400
 O                 -1.24328500    1.21681800   -1.69540600
```

*E1 Product – stepwise MeOH attack (**103-E1**)*



```
1 1
 C                  0.06476200   -1.72629800   -0.87898500
 C                  1.06219200    0.90559600   -0.64706200
 C                  1.48611300   -1.24650900   -1.05843100
 H                  0.02997000   -2.64716000   -0.29439200
 H                 -0.40941200   -1.91982200   -1.84917400
 H                  1.18846500    1.94321600   -0.97120700
 H                  2.03039600   -1.92147800   -1.72247600
 N                 -0.69935800   -0.69619100   -0.15008200
 O                  1.43702000    0.04616000   -1.70410600
 C                 -1.93353300   -1.08642100    0.38447200
 O                 -2.27817100   -2.23127500    0.44902900
 O                 -2.62957000   -0.03385000    0.79518600
 C                  3.66391700   -1.38620600    0.25099200
 H                  4.16905000   -0.90404000   -0.59458100
 H                  4.15847300   -1.06174600    1.17207200
 H                  3.79393600   -2.46800700    0.15495200
 N                  1.64569900    0.84701900    1.85865300
 H                  0.82885200    0.33621000    2.17921500
 C                  2.00535800    0.51132600    0.51052100
 H                  2.95261100    1.02392700    0.28499700
 C                  2.19936200   -0.99888600    0.27623300
 H                  1.68644600   -1.54778700    1.07637000
 C                  1.54212000    2.26911800    2.12125400
 H                  0.77246900    2.79498600    1.52885200
 H                  1.32102100    2.43641600    3.17751800
 H                  2.50328300    2.74709500    1.90275800
 C                 -3.88912700   -0.33118300    1.41490800
 H                 -4.33863100    0.63152000    1.64532500
 H                 -4.52198900   -0.89585700    0.72889600
 H                 -3.73171400   -0.90671400    2.32853800
 C                 -0.39509700    0.63440400   -0.34842900
 H                 -0.86525100    1.29510200    0.37887100
 H                 -0.55503200    0.89468300   -2.44899600
 C                 -1.68052000    2.44466500   -1.72606000
 H                 -0.88206900    3.16581000   -1.54636900
 H                 -2.12993200    2.58669300   -2.70573800
 H                 -2.43820800    2.48086300   -0.94619900
 O                 -1.14683000    1.08679700   -1.69457300
```

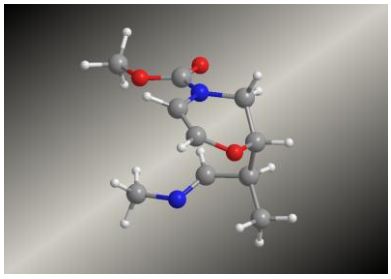
*E1 Final Product (**104-E1**)*



0 1

C	0.08821400	-1.74317800	-0.89819000
C	1.09757800	0.85980100	-0.75114200
C	1.53642200	-1.31018700	-0.95382400
H	-0.02252600	-2.67159200	-0.33329900
H	-0.28883000	-1.91126700	-1.91652000
H	1.28158600	1.86080800	-1.15349400
H	2.13000400	-2.05111300	-1.49822000
N	-0.68835600	-0.70120600	-0.22854100
O	1.60303600	-0.08068400	-1.68250500
C	-1.89119000	-1.06266100	0.31767800
O	-2.28775300	-2.20000300	0.40444800
O	-2.56572500	0.00180800	0.77857100
C	3.57225300	-1.36305300	0.56401700
H	4.15239800	-0.93808400	-0.26453200
H	3.98867800	-0.97765100	1.50112800
H	3.70797200	-2.44928800	0.55140300
N	1.38987000	0.97346700	1.80675900
H	0.50143600	0.52027100	2.00415100
C	1.90608300	0.54994800	0.52599500
H	2.88288900	1.04128000	0.39673700
C	2.11349400	-0.97566600	0.42859200
H	1.52527700	-1.46641200	1.21481700
C	1.28701500	2.41244400	1.95539600
H	0.62958500	2.91114500	1.22011900
H	0.91459000	2.65784400	2.95329400
H	2.28335900	2.85780700	1.85432000
C	-3.81652500	-0.29297500	1.39363400
H	-4.21089500	0.66050500	1.74032300
H	-4.50472000	-0.74342400	0.67459100
H	-3.68395500	-0.97469200	2.23663300
C	-0.40532500	0.67137400	-0.57233100
H	-0.76475100	1.31279300	0.24336600
C	-1.46880200	2.35068200	-1.82223900
H	-0.59761900	3.02254800	-1.82540300
H	-2.01779400	2.49802100	-2.75339300
H	-2.11757800	2.62463700	-0.97651300
O	-1.10143200	0.99523900	-1.75583200

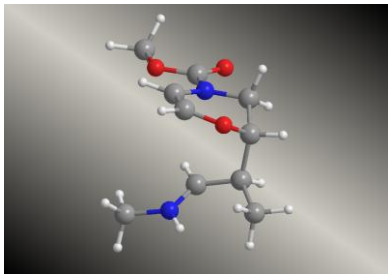
E2 Reactant – non protonated ***(98-E2)***



0 1

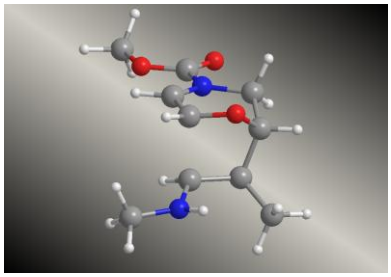
C	-0.33837800	-1.77767800	-0.66117100
C	0.31246200	-0.93410100	1.49667700
C	-0.97441700	-0.96587200	1.83835200
C	-1.70132000	-1.14463200	-0.41518000
H	1.09796900	-0.79142700	2.22353500
H	-0.05779000	-1.69060000	-1.71246900
H	-0.38672100	-2.84216600	-0.40080800
H	-1.29869500	-0.88726400	2.86832700
H	-2.46121900	-1.79853100	-0.86132400
N	0.67504300	-1.13198900	0.15265800
O	-2.00993400	-1.13474300	0.98089100
C	1.81449100	-0.64803200	-0.42123100
O	2.10421300	-0.77232000	-1.58977000
O	2.57030700	-0.00384300	0.47851600
C	-1.89841400	0.24728300	-1.03989800
H	-1.81201300	0.07656300	-2.12437400
C	-3.28680100	0.77935700	-0.72766000
H	-3.39404200	0.97311400	0.34132800
H	-3.46855800	1.71756800	-1.25916300
H	-4.05240400	0.05688800	-1.02929000
C	-0.81046800	1.21276700	-0.66064600
H	0.12661700	1.14130300	-1.24349700
N	-0.93793200	2.05599200	0.26744400
C	3.76079300	0.58385900	-0.03835500
H	4.27192200	1.02326900	0.81644600
H	4.39498900	-0.16870100	-0.51147400
H	3.51847100	1.36084900	-0.76864900
C	0.20804000	2.87363000	0.57985300
H	1.04328300	2.74127300	-0.12788200
H	-0.07748600	3.92995300	0.60172400
H	0.56327900	2.61766400	1.58531400

E2 Reactant –protonated ***(99-E2)***



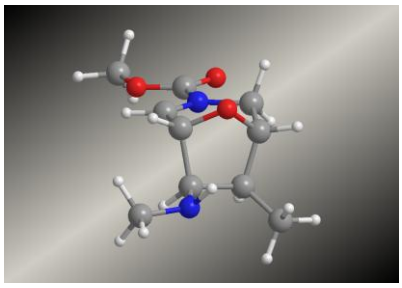
```
1  1
 C                  0.33308600   -1.80010300   -0.21459000
 C                  0.54149200   -0.02944200    1.40807700
 C                 -0.65020700   -0.38578100    1.89804200
 C                 -1.16103700   -1.60522400   -0.02259500
 H                  1.15057400    0.71658900    1.89654900
 H                  0.57120700   -1.97710000   -1.26529300
 H                  0.63860900   -2.68561800    0.35690500
 H                 -1.04538700    0.02867700    2.81608100
 H                 -1.65171300   -2.55958700   -0.23485200
 N                  1.05424400   -0.63002700    0.25287800
 O                 -1.47634800   -1.30414800    1.32508200
 C                  2.27324000   -0.32812800   -0.31010600
 O                  2.76251900   -0.95077500   -1.21902900
 O                  2.81970700    0.74022200    0.27284400
 C                 -1.84400600   -0.57221200   -0.96461400
 H                 -1.47066900   -0.80816500   -1.97293300
 C                 -3.35379100   -0.73442100   -0.91314300
 H                 -3.73293200   -0.59086000    0.10397400
 H                 -3.86347400   -0.04369800   -1.59029800
 H                 -3.62460300   -1.74694300   -1.21873900
 C                 -1.38405600    0.80892700   -0.69715700
 H                 -0.34415700    1.07351400   -0.87697400
 N                 -2.15410300    1.75112200   -0.29525400
 H                 -3.13804400    1.53833300   -0.13352100
 C                  4.10981700    1.11085900   -0.21663400
 H                  4.41756100    1.96793300    0.37853900
 H                  4.81799400    0.28951700   -0.09074100
 H                  4.05703300    1.38370000   -1.27258300
 C                 -1.71514900    3.10068800    0.03420000
 H                 -0.66330800    3.20769600   -0.22750800
 H                 -2.31547700    3.82346600   -0.51795200
 H                 -1.84756600    3.26151800    1.10591700
```

*E2 Transition state – stepwise cyclisation (**100-E2**)*



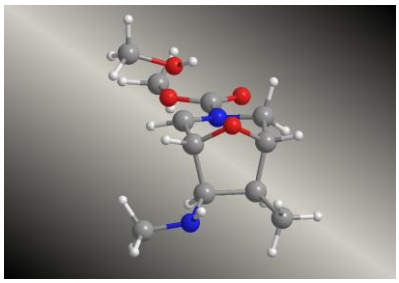
```
1  1
 C                  0.63177800   -1.74154700    0.34030800
 C                  0.46898600    0.59190600    0.93526300
 C                 -0.84808400    0.37202200    1.32361500
 C                 -0.88097400   -1.63883600    0.35963700
 H                  0.88009300    1.59462100    0.92451000
 H                  0.97971800   -2.22337600   -0.57541800
 H                  0.99112800   -2.32101000    1.19482600
 H                 -1.33896100    1.11614800    1.94145800
 H                 -1.30106300   -2.64293800    0.44767100
 N                  1.20014400   -0.38609200    0.39328100
 O                 -1.29228900   -0.90752600    1.51171600
 C                  2.50120500   -0.19430200   -0.13718400
 O                  3.12721400   -1.10008300   -0.60183400
 O                  2.87238800    1.06305300   -0.02785200
 C                 -1.48611500   -0.88608700   -0.83972300
 H                 -0.80614400   -0.96059300   -1.69597100
 C                 -2.82748500   -1.49536600   -1.22127900
 H                 -3.49459300   -1.56446600   -0.35439200
 H                 -3.32925600   -0.92378800   -2.00443700
 H                 -2.67080300   -2.51239200   -1.58955100
 C                 -1.57491600    0.60389900   -0.47597900
 H                 -0.88282000    1.25749100   -1.00726400
 N                 -2.79528000    1.16283500   -0.33727300
 H                 -3.50826400    0.59658600    0.10937400
 C                 -2.93753600    2.59363600   -0.17845900
 H                 -3.97269600    2.88190600   -0.36194300
 H                 -2.65646100    2.92425600    0.83118100
 H                 -2.29839600    3.10344400   -0.90292500
 C                  4.18773000    1.36708300   -0.52178600
 H                  4.31573200    2.43603100   -0.37384000
 H                  4.93625500    0.80898900    0.04248600
 H                  4.25644200    1.11388500   -1.58054400
```

E2 Cyclised iminium – stepwise cyclisation ***(101-E2)***



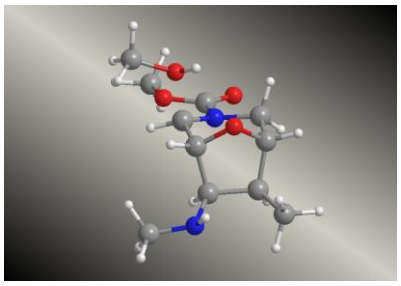
```
1 1
 C                  0.66842400   -1.60637400    0.48294000
 C                  0.50603000    0.80943200    0.52860500
 C                 -0.89915800    0.67848700    0.89818400
 C                 -0.84145600   -1.50161200    0.53904300
 H                  0.95448700    1.78073300    0.34004200
 H                  1.00898700   -2.20503000   -0.36458000
 H                  1.08348600   -2.03200200    1.39986600
 H                 -1.23691800    1.52577300    1.49715800
 H                 -1.26102200   -2.46148700    0.84719800
 N                  1.23283600   -0.24544400    0.31809300
 O                 -1.16370200   -0.53503000    1.54175500
 C                  2.63508600   -0.17317200   -0.07933700
 O                  3.25696600   -1.16923800   -0.25838300
 O                  3.01139300    1.06964100   -0.17618700
 C                 -1.47367300   -0.96482400   -0.76106400
 H                 -0.74192300   -1.01696100   -1.57598000
 C                 -2.70430200   -1.75334300   -1.16751500
 H                 -3.42968300   -1.81076200   -0.34972200
 H                 -3.20219200   -1.30163500   -2.02782300
 H                 -2.41809200   -2.77585500   -1.43097400
 C                 -1.74213100    0.53826500   -0.45738400
 H                 -1.35115000    1.18603300   -1.24960900
 N                 -3.10642000    0.86099900   -0.24381600
 H                 -3.49669300    0.34576400    0.54049600
 C                 -3.40938100    2.27475600   -0.17133600
 H                 -4.48389200    2.41234600   -0.03870100
 H                 -2.89639000    2.80138900    0.65155900
 H                 -3.11802300    2.75679000   -1.10983400
 C                  4.38514800    1.28482900   -0.56719100
 H                  4.50040400    2.36253900   -0.63418400
 H                  5.05013900    0.86950300    0.19042100
 H                  4.56879500    0.81232000   -1.53243200
```

*E2 Transition state – stepwise MeOH attack (**102-E2**)*



```
1 1
 C                  0.63177800   -1.74154700    0.34030800
 C                  0.46898600    0.59190600    0.93526300
 C                 -0.84808400    0.37202200    1.32361500
 C                 -0.88097400   -1.63883600    0.35963700
 H                  0.88009300    1.59462100    0.92451000
 H                  0.97971800   -2.22337600   -0.57541800
 H                  0.99112800   -2.32101000    1.19482600
 H                 -1.33896100    1.11614800    1.94145800
 H                 -1.30106300   -2.64293800    0.44767100
 N                  1.20014400   -0.38609200    0.39328100
 O                 -1.29228900   -0.90752600    1.51171600
 C                  2.50120500   -0.19430200   -0.13718400
 O                  3.12721400   -1.10008300   -0.60183400
 O                  2.87238800    1.06305300   -0.02785200
 C                 -1.48611500   -0.88608700   -0.83972300
 H                 -0.80614400   -0.96059300   -1.69597100
 C                 -2.82748500   -1.49536600   -1.22127900
 H                 -3.49459300   -1.56446600   -0.35439200
 H                 -3.32925600   -0.92378800   -2.00443700
 H                 -2.67080300   -2.51239200   -1.58955100
 C                 -1.57491600    0.60389900   -0.47597900
 H                 -0.88282000    1.25749100   -1.00726400
 N                 -2.79528000    1.16283500   -0.33727300
 H                 -3.50826400    0.59658600    0.10937400
 C                 -2.93753600    2.59363600   -0.17845900
 H                 -3.97269600    2.88190600   -0.36194300
 H                 -2.65646100    2.92425600    0.83118100
 H                 -2.29839600    3.10344400   -0.90292500
 C                  4.18773000    1.36708300   -0.52178600
 H                  4.31573200    2.43603100   -0.37384000
 H                  4.93625500    0.80898900    0.04248600
 H                  4.25644200    1.11388500   -1.58054400
```

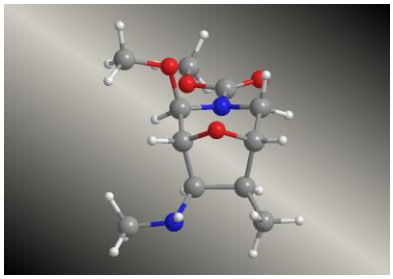
*E2 Product – stepwise MeOH attack (**103-E2**)*



1 1

C	0.30910500	-1.69453500	0.81844400
C	-0.99561400	0.75348300	0.40925700
C	-1.15327600	-1.37388200	1.04293800
H	0.41953600	-2.63192400	0.27073700
H	0.83063900	-1.80174600	1.77766600
H	-1.29621800	1.78663600	0.60747800
H	-1.55865000	-2.04969300	1.79975200
N	0.95067000	-0.62376300	0.03361000
O	-1.25984200	-0.03193800	1.55839500
C	2.23693500	-0.88904800	-0.44901000
O	2.71990100	-1.98497400	-0.43794000
O	2.81295200	0.21670200	-0.90391300
C	-1.99936000	-1.34101400	-0.23148600
H	-1.60635100	-2.05454000	-0.96354500
C	-3.44427700	-1.68891000	0.08239600
H	-3.82753600	-1.07328300	0.90489300
H	-4.09069300	-1.54172300	-0.78405600
H	-3.51491400	-2.73509000	0.39363800
C	-1.78937900	0.10932800	-0.75526100
H	-1.16354300	0.09138000	-1.65756200
N	-3.00650600	0.79319300	-1.10576900
H	-3.59020700	0.93432500	-0.28608800
C	-2.78829700	2.04729000	-1.80024900
H	-3.74837200	2.52233600	-2.01318000
H	-2.16752300	2.77601100	-1.24899500
H	-2.29262900	1.85042700	-2.75719000
C	4.12209700	0.04398500	-1.46401200
H	4.43862900	1.03373800	-1.78381900
H	4.80497300	-0.35050600	-0.70999400
H	4.08125600	-0.63721400	-2.31533800
C	0.48956600	0.66922300	0.16741700
H	0.88894500	1.35551100	-0.57769900
C	1.52520600	2.65975400	1.52905500
H	0.66263800	3.28862300	1.30623600
H	1.92592600	2.87291200	2.51723000
H	2.29995800	2.75751000	0.77129200
H	0.52428100	1.02238500	2.24873100
O	1.13879700	1.25319400	1.52195600

*E2 Final Product (**104-E2**)*

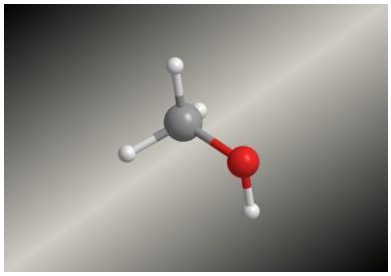


0 1

C	-0.37918700	-1.60525100	-1.01173000
C	1.00614600	0.75167800	-0.50094800
C	1.11733000	-1.38664200	-1.06987100
H	-0.61210800	-2.58324500	-0.58458200
H	-0.79781000	-1.56475100	-2.02715500
H	1.35967600	1.76498200	-0.71966000
H	1.56952900	-2.11125400	-1.75440000
N	-0.98552500	-0.57620300	-0.16855400
O	1.36680200	-0.08130600	-1.59017600
C	-2.22870600	-0.83346900	0.34440800
O	-2.77785900	-1.90837500	0.29611100
O	-2.75681600	0.24948900	0.93401900
C	1.79070200	-1.37703100	0.31025900
H	1.20507400	-1.97682000	1.01657900
C	3.20025100	-1.93519800	0.23042800
H	3.76897400	-1.45083900	-0.57277700
H	3.74731900	-1.78740400	1.16361400
H	3.16725200	-3.00667600	0.00870000
C	1.70816900	0.12260600	0.71819200
H	1.08298800	0.23256000	1.61447800
N	2.99594100	0.71218100	1.03245800
H	3.55792200	0.76730800	0.18619400
C	2.88174700	2.02559900	1.63554500
H	3.87661500	2.45151500	1.78917800
H	2.29165100	2.75327900	1.04966200
H	2.40329200	1.93438700	2.61757400
C	-4.03363100	0.05040500	1.53277700
H	-4.31925800	1.01258400	1.95417400
H	-4.76627300	-0.26509000	0.78653800
H	-3.97979500	-0.70364000	2.32154400
C	-0.50809100	0.77522300	-0.33191600
H	-0.75412800	1.34875200	0.57417300
C	-1.27757100	2.74527000	-1.35579900
H	-0.30251400	3.25287700	-1.33147100
H	-1.81933900	3.08545300	-2.23944500
H	-1.84383600	3.03312900	-0.45700900
O	-1.15351500	1.34792900	-1.44636800

Optimised Structures Relevant to All Calculations

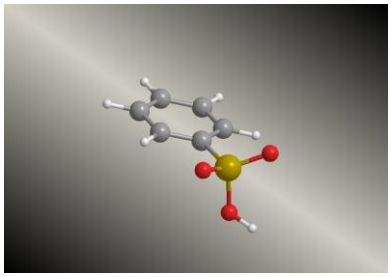
Methanol



0 1

C	0.65652100	-0.01934800	0.00000000
H	1.08838900	0.98453700	-0.00000200
H	1.02890800	-0.54471100	-0.89062500
H	1.02890800	-0.54470800	0.89062700
O	-0.74469500	0.12229100	0.00000000
H	-1.12776900	-0.75735800	0.00000000

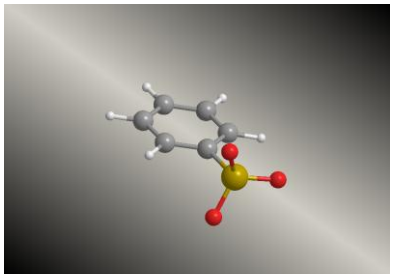
Benzenesulfonic Acid



0 1

S	1.45705300	0.04661400	-0.12025700
O	1.91963000	1.39018200	-0.37731000
O	1.95248100	-1.04352200	-0.93270600
O	1.75092300	-0.32302100	1.42439500
H	2.63089400	-0.72081500	1.50667400
C	-0.30625900	0.02282900	-0.06063900
C	-0.99675700	1.22374700	-0.00778300
C	-0.95409300	-1.20598900	-0.06664400
C	-2.38261300	1.18885100	0.03823400
H	-0.45571300	2.16344500	-0.00893500
C	-2.33768500	-1.22387000	-0.01873700
H	-0.38222600	-2.12678800	-0.11762700
C	-3.04777500	-0.02962500	0.03387500
H	-2.94295200	2.11663500	0.07627700
H	-2.86402400	-2.17214800	-0.02604900
H	-4.13201000	-0.05092700	0.06890100

Benzenesulfonate



```
-1 1
 S                  1.52680800    0.00340100    0.00104800
 O                  1.94259200    1.41473800   -0.06494900
 O                  1.90652700   -0.77957400   -1.18893500
 O                  1.88454100   -0.65799000    1.26922100
 C                 -0.27040800    0.02026400   -0.01125700
 C                 -0.97170100    1.21562200   -0.00754200
 C                 -0.94895800   -1.19396700   -0.00718500
 C                 -2.36162500    1.19840300    0.00027100
 H                 -0.42099200    2.15046100   -0.01202000
 C                 -2.33429100   -1.20660100   -0.00054400
 H                 -0.38835400   -2.12475900   -0.01027100
 C                 -3.04329500   -0.00971800    0.00409100
 H                 -2.91243000    2.13434400    0.00376400
 H                 -2.86580900   -2.15361900    0.00154100
 H                 -4.12894200   -0.02226100    0.01052100
```

Method for Generating G_{rel} Graphs

Each horizontal point on **Figures 34** and **35** is the sum of the free energy of the morpholine fragment, methanol, and (depending on the charge of the system) either benzenesulfonic acid or benzenesulfonate. This is summarised in **Equations 1** to **3**, below.

For points involving iminium or oxonium (1+) charged intermediates:

$$rel = G\ morpholine\ fragment + G\ MeOH + G(benzenesulfonate) \quad (1)$$

For uncharged starting materials:

$$G_{rel} = G(morpholine\ fragment) + G(MeOH) + G(benzenesulfonic\ acid) \quad (2)$$

For uncharged products:

$$rel = G\ morpholine\ fragment + G(benzenesulfonic\ acid) \quad (3)$$

Computational References

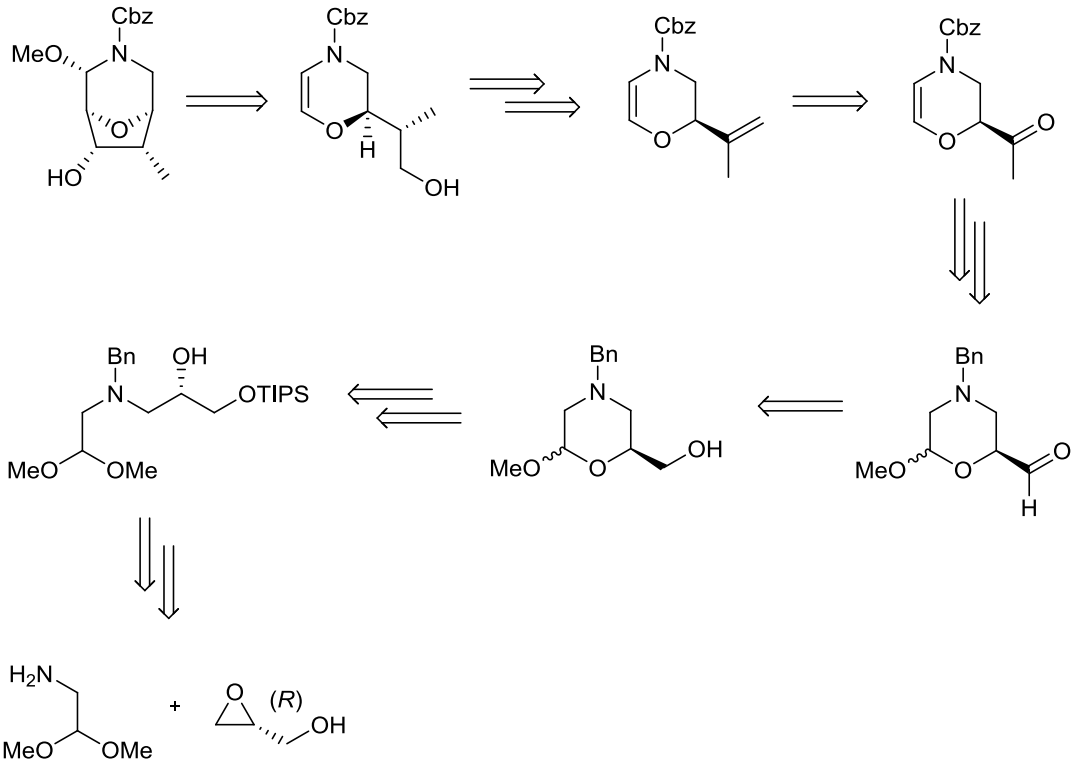
1. W. Kohn and L. J. Sham, *Phys. Rev*., 1965, **140**, 1133.
2. R. G. Parr and W. T. Yang, *Density Functional Theory of Atoms and Molecules*, Oxford University Press, New York, 1989.
3. A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.
4. C. Lee, W. Yang and R.G. Parr, *Phys. Rev. B*, 1988, **37**, 785.
5. S. H. Vosko, L. Wilk and M. Nusair, *Can. J. Phys*., 1980, **58**, 1200.
6. P. J. Stephens, F. J. Devlin, C. F. Chabalowski and M. J. Frisch, *J. Phys. Chem.*, 1994, **98**, 11623.
7. M. J. Frisch, J. A. Pople and J. S. Binkley, *J. Chem. Phys.*, 1984, **80**, 3265.
8. R. Ditchfield, W. J. Hehre and J. A. Pople, *J. Chem. Phys.*, 1971, **54**, 724.
9. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, GAUSSIAN (A.02 ed.), Gaussian, Inc., Wallingford, CT, 2009.
10. Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc.*, 2008, **120**, 215.
11. A. D. McLean and G. S. Chandler, *J. Chem. Phys.*, 1980, **72**, 5639.
12. S. Miertuš, E. Scrocco, and J. Tomasi, *Chem. Phys.*, 1981, **55**, 117.
13. H. B. Schlegel, *J. Comp. Chem.*, 1982, **3**, 214.
14. J. P. Foster and F. Weinhold, *J. Am. Chem. Soc.*, 1980, **102**, 7211.

Chapter Two:
Bridged Morpholines - Asymmetric Synthesis

Table of Contents

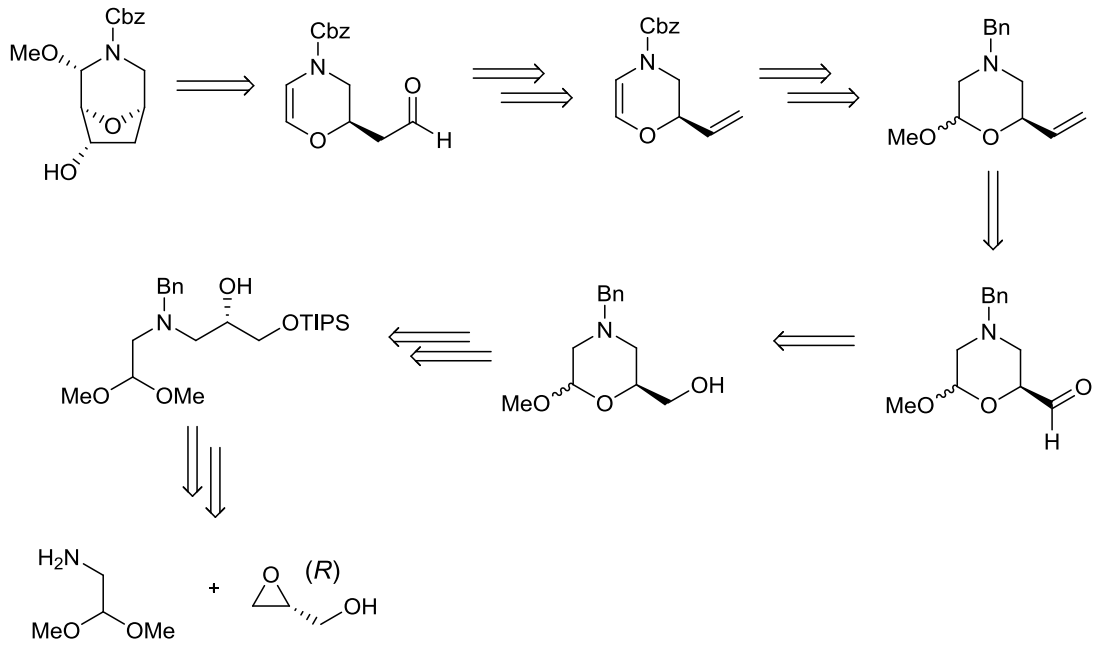
1. Proposed Work

Having developed a robust racemic synthesis into a range of bridged morpholines (**Chapter 1**),[1] it was now proposed that the route developed would be carried out asymmetrically. Indeed, compounds in their enantiomerically pure form would be the ultimate target within any pharmaceutical drug programme. In order to achieve this, the originally developed synthesis is amenable in the sense that the key substrate, glycidol, is available in both enantiomeric forms. Indeed, the initial stereogenic centre in glycidol will control the instalment of further centres along the reaction sequence. It is envisaged that both enantiomers of the final bridged morpholine core could be accessed *via* this approach. Of course, careful assessment of the enantiomeric ratio of key compounds would be required throughout. At the outset, it was proposed that the route shown in **Scheme 1**, leading to the synthesis of the methylated bridged morpholine, would be explored initially.



Scheme 1

In addition to the synthesis shown in **Scheme 1**, it was proposed that the asymmetric synthesis to the non-methylated bridged morpholine would also be investigated (**Scheme 2**).

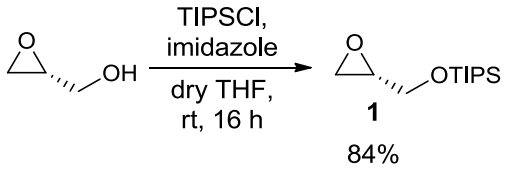


Scheme 2

2. Results and Discussion

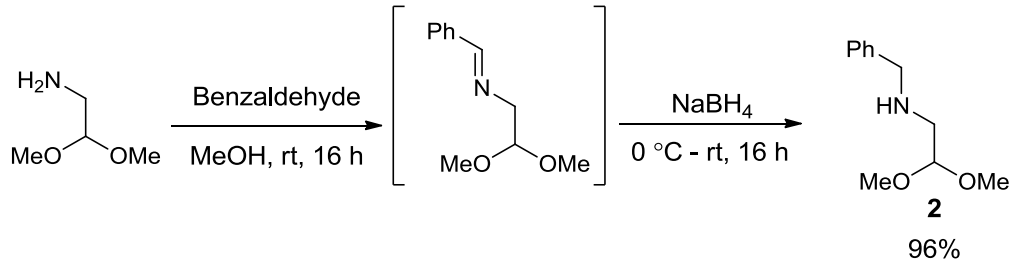
2.1 Methylated Bridged Morpholine

The investigation into the asymmetric synthesis began with TIPS protection of the commercially available (*R*)-glycidol (obtained with a >99:1 *er*), which was achieved in an 84% yield (**Scheme 3**).



Scheme 3

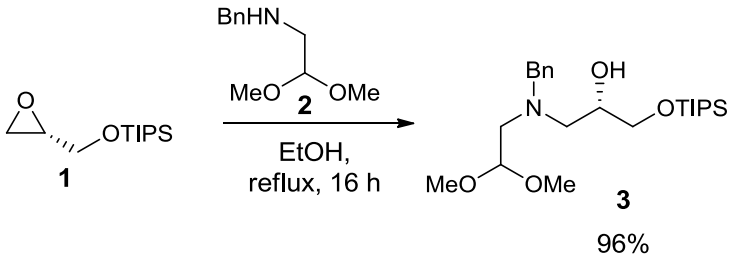
The next stage in the synthesis involved opening the previously protected epoxide with benzyl protected amine acetal **2**. However, before this reaction could be performed, the amine itself required protection. This was achieved *via* a reductive amination reaction, with the benzyl-protected amine being produced in a high 96% yield (**Scheme 4**).



Scheme 4

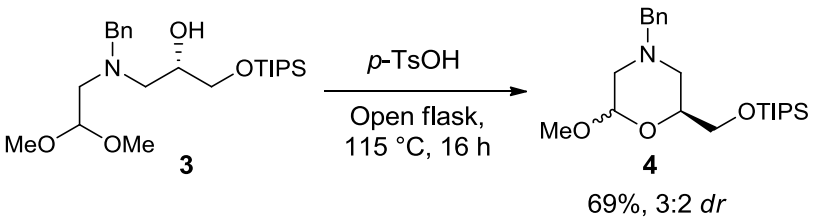
With the protected amine **2** in hand, the epoxide was regioselectivity opened under neutral conditions to give the functionalised amine alkyl chain **3** in a high yield (**Scheme 5**). No impurities were observed in the NMR analysis of **3**, therefore it was

decided that no purification was needed at this stage and **3** would be taken through the subsequent step in crude form.



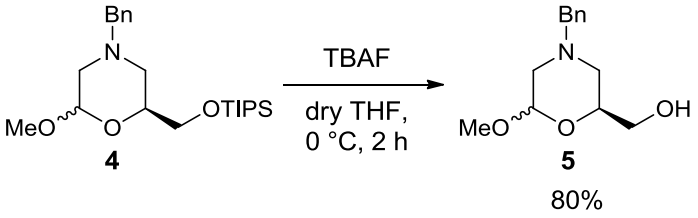
Scheme 5

In order to deduce whether any epimerisation had occurred during the first two steps of the synthesis, the amine alkyl chain was analysed using chiral HPLC analysis. It was pleasing to find that no epimerisation had occurred during the initial synthesis, as **3** was obtained with an *er* of >99:1. Following on from this, **3** was subjected to catalytic acidic conditions, which caused a ring closure reaction to occur, and produced morpholine derivative **4** in a good 69% yield (**Scheme 6**). As with the racemic route, this reaction produced a 3:2 mixture of diastereomers. As previously mentioned, it was decided to determine the enantiomeric ratio at various stages along the route to find out if any epimerisation was occurring. However, due to the presence of diastereomers at this stage, it proved challenging to determine conditions to separate the four compounds using chiral HLPC analysis, and therefore the enantiomeric ratio was not determined at this stage. Having said this, later in the synthesis the methyoxy group would be removed, and consequently only enantiomers would be present; therefore, it was decided to reassess the enantiomeric ratio once this had occurred.



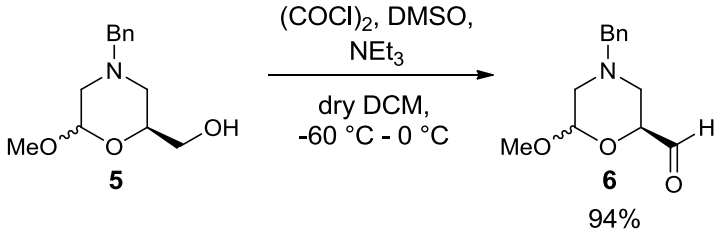
Scheme 6

The next stage in the synthesis was the removal of the TIPS group, and this was effected using TBAF, as shown in **Scheme 7**, to produce the free alcohol in good yield.



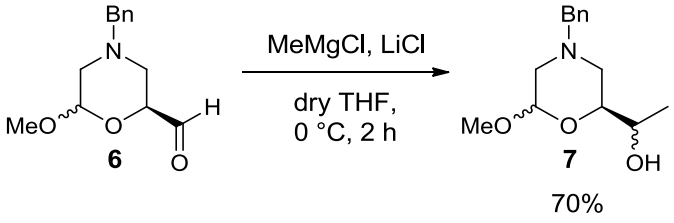
Scheme 7

The primary alcohol was then converted to the corresponding aldehyde *via* the use of standard Swern conditions,[2] with the aldehyde isolated in an excellent yield, as shown in **Scheme 8**. Due to the sensitive nature of the aldehyde functionality, it was necessary to synthesise and react the aldehyde in the subsequent step within the same day.



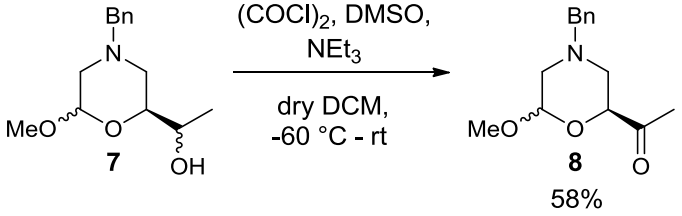
Scheme 8

Following the oxidation, the aldehyde was then reacted with methylmagnesium chloride to produce the secondary alcohol **7** in a 70% yield (**Scheme 9**).



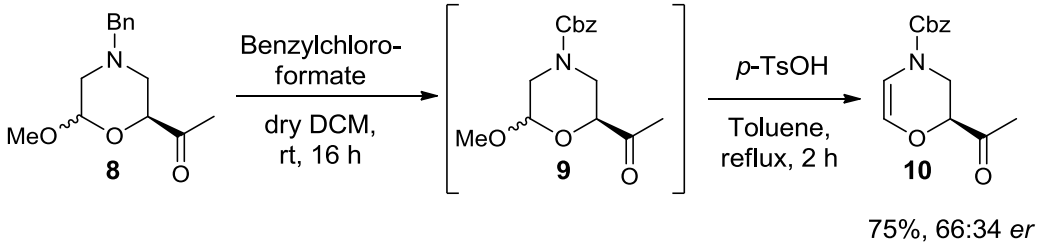
Scheme 9

With the secondary alcohol in hand, a second oxidation using Swern conditions was performed to synthesise ketone **8** in a moderate yield, as illustrated in **Scheme 10**.



Scheme 10

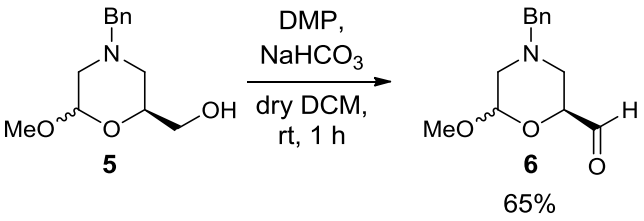
The next step in the synthesis involved the removal of the methoxy group to install a double bond. This was achieved by carrying out the initial protecting group switch on ketone **8**, followed by an elimination reaction to install the double bond. Ketone **10** was successfully isolated in a good yield over two steps (**Scheme 11**). Due to diastereomers no longer being present, the *er* of ketone **10** was determined using chiral HPLC analysis. Disappointingly, it was found on analysing ketone **10** that, at some stage during the synthesis, significant epimerisation had occurred, as an *er* of 66:34 was obtained (compared with >99:1 *er* for the amine alkyl chain **3**).



Scheme 11

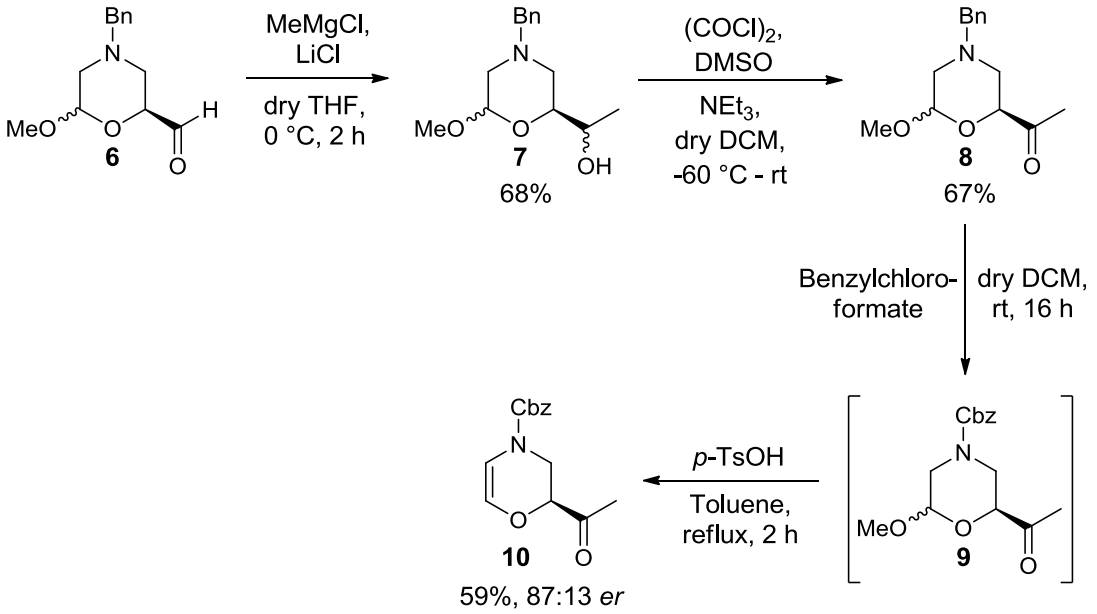
During the route both an aldehyde (**6**), and a ketone (**8**) were synthesised, both of which contain a readily epimerisable centre. Indeed, it was at these stages it was envisaged that erosion of the enatiomeric purity was most likely to be occurring, therefore alternative conditions for their synthesis were investigated. In order to probe where the epimerisation was occurring, it was firstly decided to use an alternative oxidation procedure to form aldehyde **6**. Due to Dess-Martin periodinane

(DMP) being a milder oxidant, which can be buffered to allow the reaction to occur under near neutral conditions,[3-5] it was decided to investigate this reagent in the first instance. It was pleasing to find that DMP (in addition to sodium hydrogen carbonate) was able to oxidise alcohol **5**, albeit in a comparatively yield compared to the previously employed Swern conditions (65% vs 94%) (**Scheme 12**).[3]



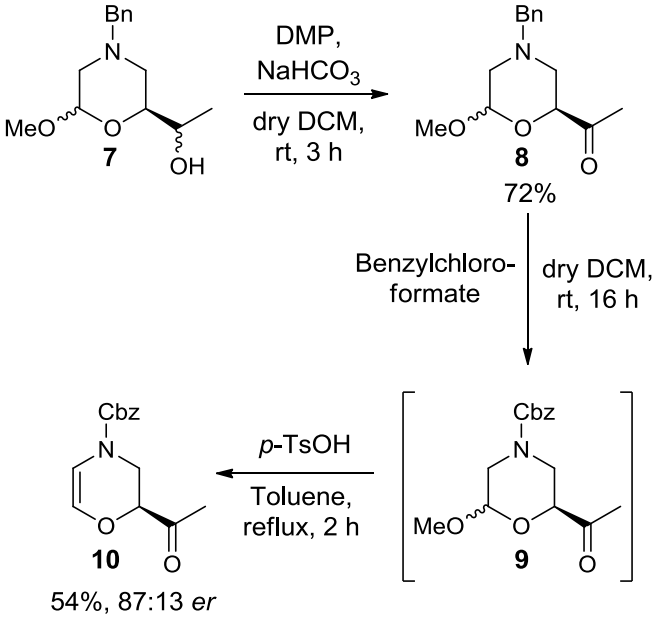
Scheme 12

The resultant aldehyde was then reacted though the subsequent steps as previously described to produce ketone **10**, as illustrated in **Scheme 13**. It was only at this stage that the enantiomeric ratio could accurately be measured. When the enantiomeric purity of ketone **10** was checked, it was very pleasing to find that epimerisation had occurred to a much lesser extent under these alternative oxidation conditions (87:13 *er*). This finding showed that the Swern conditions were, indeed, causing the chiral centre to epimerise significantly.



Scheme 13

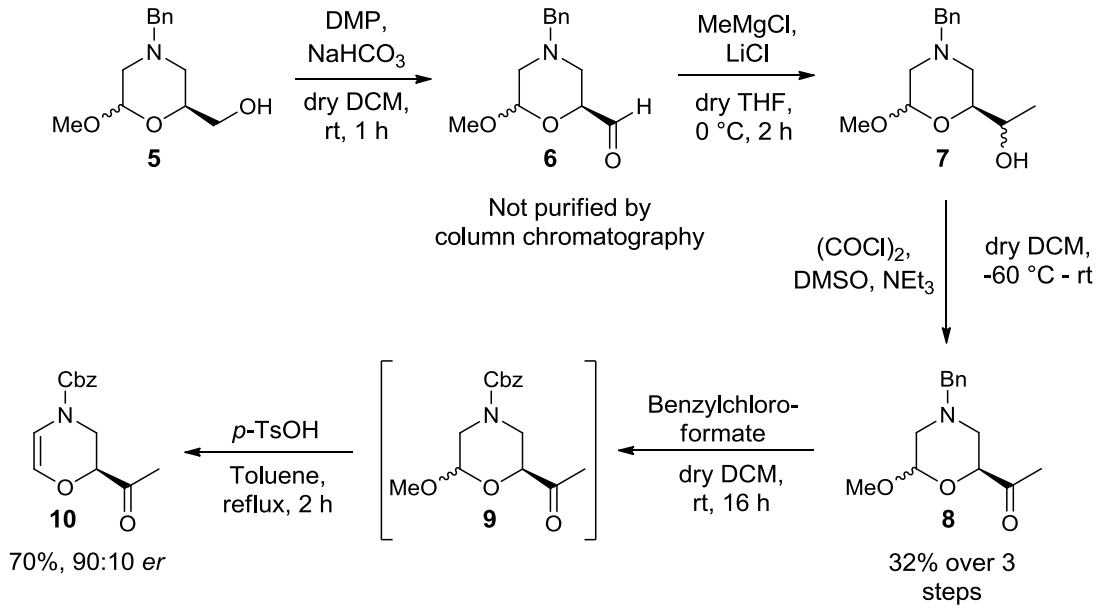
To investigate whether the Swern conditions to produce ketone **8** were also causing slight epimerisation, alcohol **7** was also subjected to the buffered DMP conditions. Alcohol **7** successfully underwent an oxidation reaction to produce ketone **10** in a high 72% yield. Following the protecting group switch and subsequent elimination, the desired ketone **10** was obtained (**Scheme 14**). On analysing the ketone by chiral HPLC, it was found to have the same *er* of 87:13 as to when Swern conditions were employed during the ketone synthesis. This suggested that if any epimerisation was occurring during the oxidation step to form ketone **8**, Swern conditions would not have any more of a detrimental effect on the enantiomeric ratio than the buffered DMP conditions.



Scheme 14

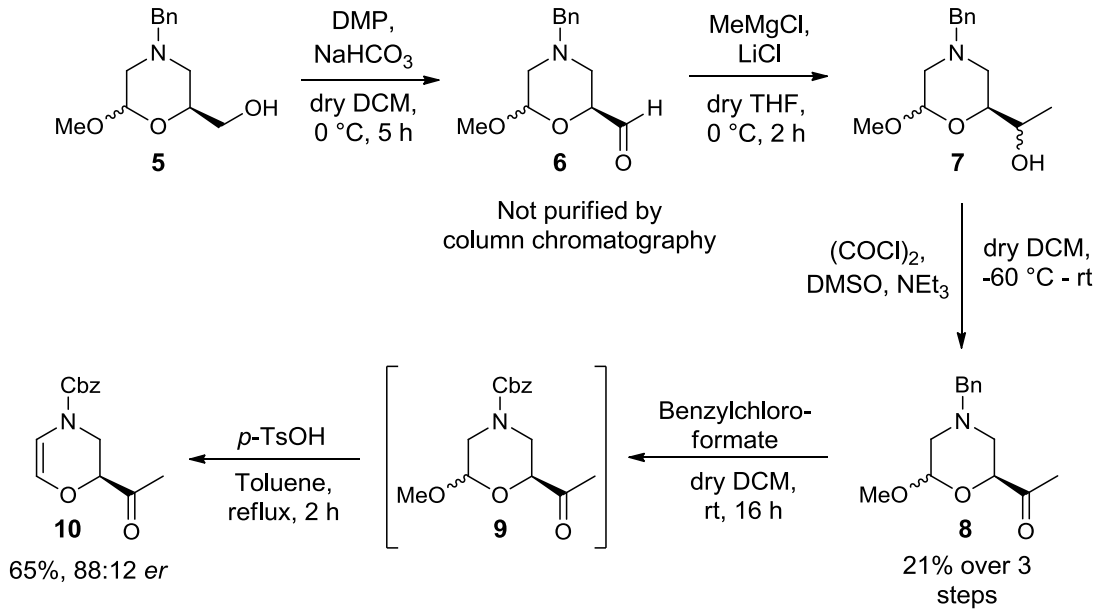
In an attempt to improve the enantiomeric ratio further, the same DMP buffered oxidation reaction was performed to generate aldehyde **6**, however, this product was not purified by column chromatography. After performing the work-up, the aldehyde was not obtained in a pure enough form to determine an accurate yield. It was also found that the downstream secondary alcohol **7** could not be obtained in a pure form, even after column chromatography. However, the subsequent oxidation yielded ketone **8** without any impurities, therefore the yield was calculated over the three

steps (**Scheme 15**). Following final protecting group switch and elimination, chiral HPLC analysis revealed a very slight improvement in the enantiomeric ratio (90:10), indicating that aldehyde **6**, indeed, should not be purified *via* column chromatography.



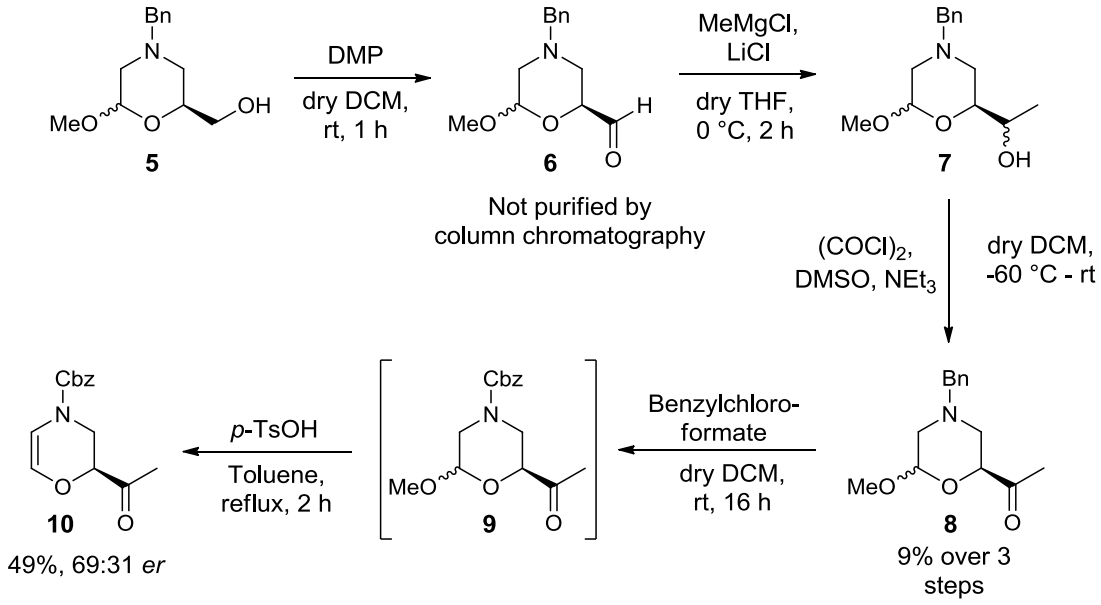
Scheme 15

In an attempt to improve the *er* further, the aldehyde oxidation step was performed at 0 °C. It was found that when performing the reaction at 0 °C the reaction took 5 h to proceed to completion, and a total of 2.5 eq. of DMP was required (at ambient temperature 1.1 eq. of DMP was required). The aldehyde was then taken through the subsequent steps to ketone **8** and, as the aldehyde was not purified by column chromatography, the yield was calculated over the three steps, with a lower overall yield of 21% obtained. Following the usual protecting group switch and elimination reaction, the desired ketone was obtained (**Scheme 16**). On checking the enantiomeric ratio of ketone **10**, it was found that performing the oxidation reaction at 0 °C had very little effect, as an *er* of 88:12 was obtained.



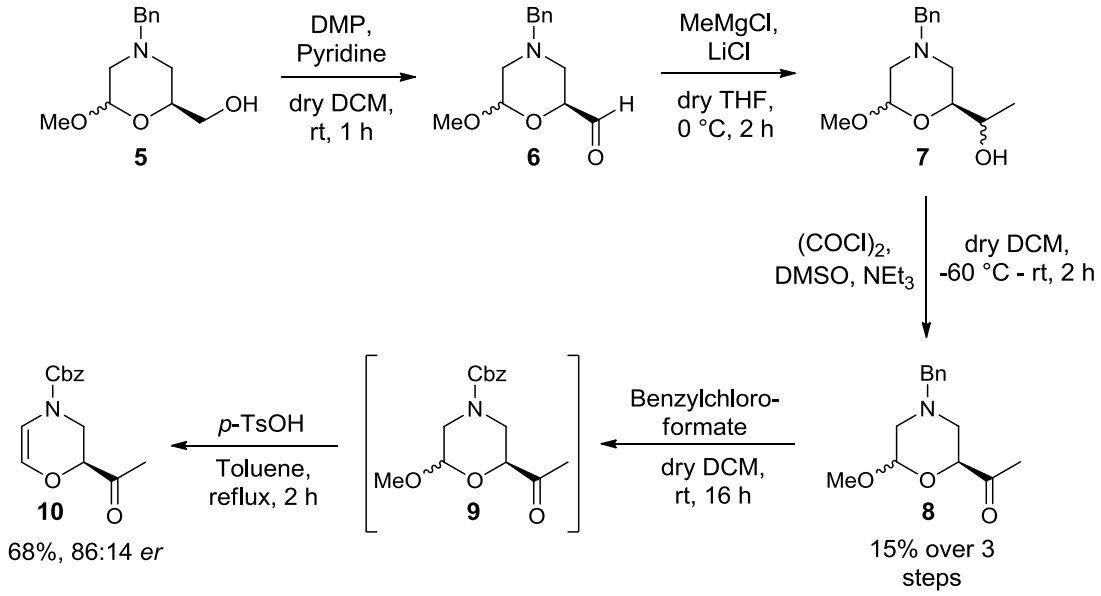
Scheme 16

In order to deduce whether the sodium hydrogen carbonate was in fact needed to buffer the aldehyde oxidation, the reaction was performed in the absence of the base. As performing the oxidation at 0 °C did not improve the *er*, and required a prolonged reaction time, it was decided to perform the non-buffered oxidation at ambient temperature. The oxidation without sodium hydrogen carbonate successfully produced aldehyde **6**, and as with the previous reaction sequences, the aldehyde was taken through the two subsequent steps and the yield calculated over the three steps (**Scheme 17**). A lower yield of 9% was obtained under the alternative reaction conditions. Following the protecting group switch and elimination, ketone **10** was successfully isolated and chiral HPLC analysis revealed that the base was needed to buffer the reaction, as a much reduced *er* of 69:31 was obtained.



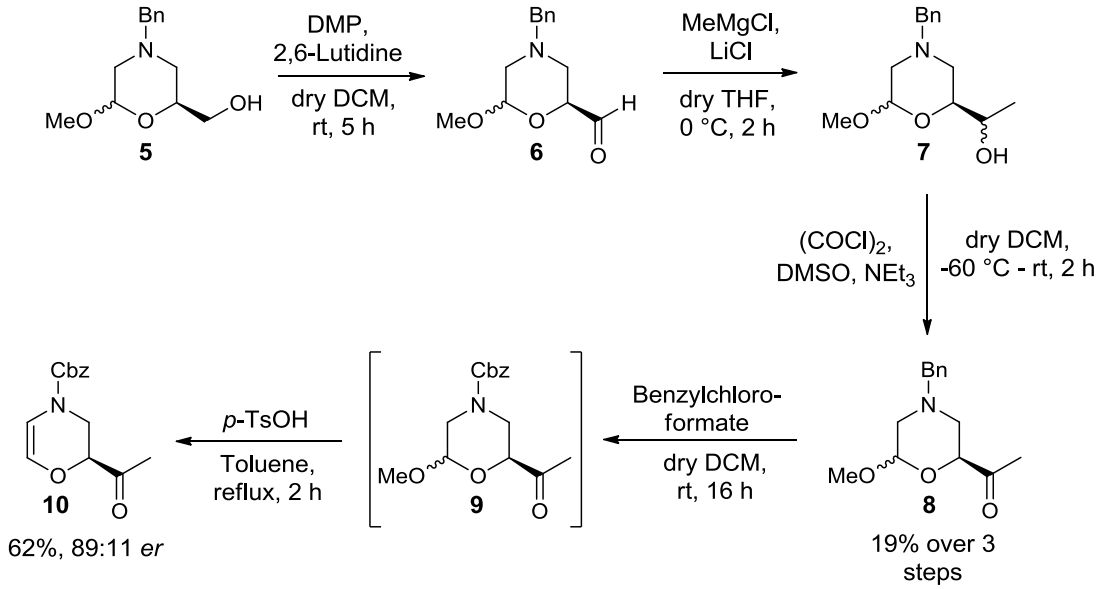
Scheme 17

As sodium hydrogen carbonate was found to be crucial for controlling the epimerisation of aldehyde **6**, alternative bases were investigated in an attempt to improve the enantiomeric ratio further. Since pyridine has been shown to be successful in DMP oxidations, it was initially investigated (**Scheme 18**).[4] The aldehyde was found to be successfully oxidised when incorporating pyridine into the reaction protocol, however, due to the large excess of the organic base being utilised, the aldehyde had to undergo column chromatography to remove the excess base present. Unfortunately, even after column chromatography, pyridine was still present, and due to the sensitivity of aldehyde **6**, it was decided not to re-purify the aldehyde and take through the subsequent step with the slight excess of pyridine. Successful alkylation was achieved, followed by oxidation to ketone **8** (**Scheme 18**). Due to the excess of pyridine in the aldehyde, the yield was calculated over the three steps, with an overall yield of 15% being obtained. Following the protecting group switch and subsequent elimination, it was discovered, following chiral HPLC analysis, that a slightly poorer *er* of 86:14 was obtained when using pyridine as the base in the oxidation of alcohol **5**.



Scheme 18

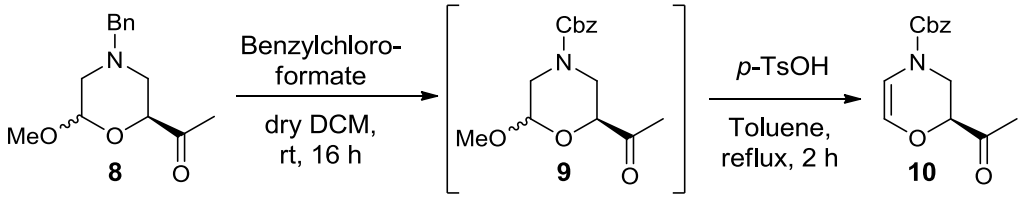
In addition to pyridine, using 2,6-lutidine as the base in the initial oxidation reaction was also investigated.[5] As with pyridine, even after purification, 2,6-lutidine was still present, therefore the aldehyde was taken through in crude form. Following successful alkylation and subsequent oxidation, ketone **8** was obtained in a 19% yield over the three steps. After performing a successful protecting group switch, followed by the elimination reaction, ketone **10** was obtained in a 62% yield. After analysing the ketone by chiral HPLC analysis, the ketone was found to have an *er* of 89:11. Both 2,6-lutidine and sodium hydrogen carbonate gave comparable enantiomeric ratios, however, due to the sodium hydrogen bicarbonate buffered reaction not requiring column chromatography purification, it was decided that for all other reactions this would be the base utilised.



Scheme 19

With regards to the practicality of this series of optimisation studies, the final elimination step was being performed on a very small scale. As such, this required the dilution to be increased in comparison to the level employed in the established racemic process, due to Dean Stark apparatus being employed. Indeed, it was now questioned if this was a significant factor in the optimisation results. It was found that when the reaction sequence was performed on a larger scale, and the elimination reaction was carried out under the optimal concentration used during the development of the racemic synthesis (0.06 M), a drop in the enantiomeric ratio from 90:10 to 81:19 was observed (**Scheme 20**, **Table 1**, **Entry 1**). To prove that this decrease in *er* was occurring as a consequence of the elimination reaction concentration, a concentration study was performed. Ketone **8**, which had been synthesised *via* the DMP/$NaHCO_3$ oxidation protocol, was split and used in two reactions with different concentrations. The more concentrated (0.04 M) elimination reaction produced the requisite ketone with an *er* of 85:15 (**Entry 2**). In contrast, when using the ketone in the more dilute reaction (0.025 M), **10** was obtained with an *er* of 90:10 (**Entry 3**), thus proving that the concentration of the elimination reaction plays a crucial role in the epimerisation occurring. In an effort to establish whether a higher *er* could be obtained, the concentration of the reaction was further

lowered. However, when the reaction was carried out with a concentration of 0.01 M, the *er* remained the same (90:10) (**Entry 4**), and thus for any further reactions performed, a concentration of 0.025 M would be employed.

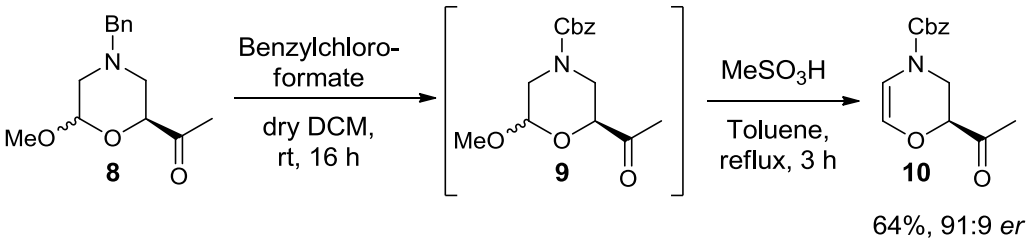


Scheme 20

Entry	*Concentration (M)*	*Yield (%)*	*er*
1	0.06	60	81:19
2	0.04	68	85:15
3	0.025	59	90:10
4	0.01	61	90:10

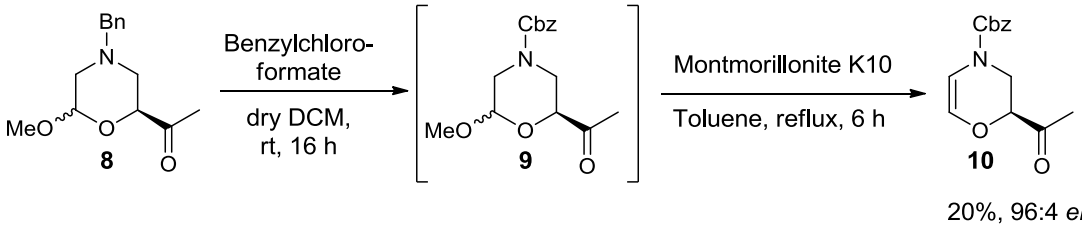
Table 1

It had now been shown that by changing the initial oxidation conditions and carefully controlling the concentration of the elimination reaction, the ketone could be obtained with an *er* of 90:10. Since the initial starting epoxide was obtained with an *er* of >99:1, it was clear that a step, or steps, was or were still causing epimerisation to occur. Since the elimination reaction concentration influenced the *er*, a more extensive investigation into this reaction was initiated to determine if the loss of chirality was within this step, or if it was more likely to be during the aldehyde formation. In this regard, it was decided to investigate the effect the acid had on the elimination. Therefore, the acid catalyst was changed from *p*-toluenesulfonic acid to the milder methanesulfonic acid, whilst keeping the concentration at 0.025 M. The reaction proved to be successful when using methanesulfonic acid, as the ketone **10** was obtained in a 64% yield (**Scheme 21**). On analysing the enantiomeric ratio of ketone **10**, it was found that when using the milder acid a very slight improvement in the *er* was obtained (91:9).



Scheme 21

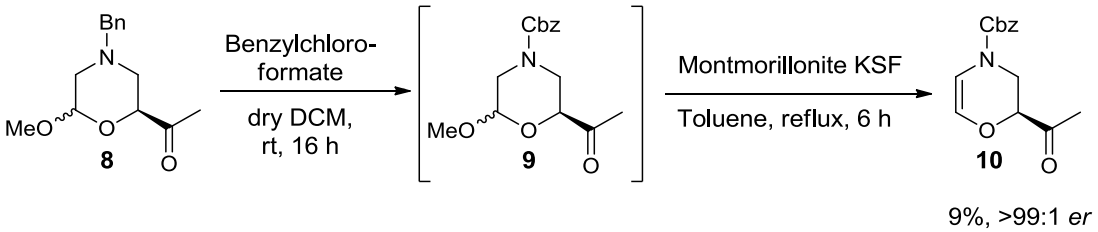
To further probe whether the acid was having an effect on the epimerisation, the acid clay Montmorillonite K10 was utilised (**Scheme 22**).[6] After 2 h, the desired ketone was observed *via* TLC analysis, however, the carboxybenzyl intermediate was also still present. After a further 4 h at reflux the intermediate was still present, however, the reaction was stopped to allow the *er* to be deduced. It was found that a 20% yield of the desired product was obtained with 25% of **9** being recovered. On analysing **10** by chiral HPLC, it was extremely pleasing to find an improved *er* of 96:4. This result showed that not only was the concentration of the elimination reaction extremely important, but also that the acid was playing a key role in the epimerisation of the key stereogenic centre.



Scheme 22

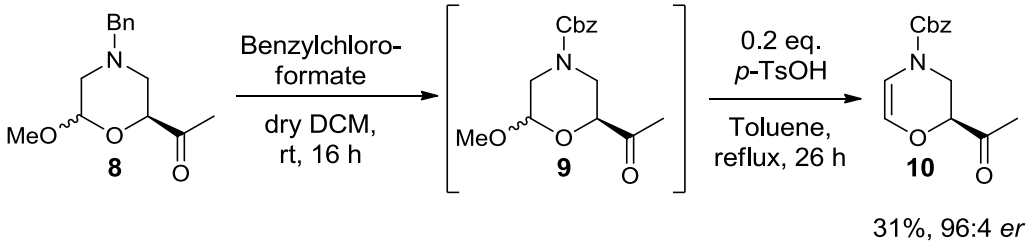
Having now discovered that the acid does cause epimerisation to occur, and the acid clay Montmorillonite K10 improved the *er*, it was decided to trial a reaction using the alternative acid clay, Montmorillonite KSF. Under these conditions it was found that although a poor yield of the elimination product was obtained (9%), the ketone had now been synthesised with an *er* of >99:1. This was a key result at this point in the research, as up until this point it was not known whether the oxidation to the

aldehyde with DMP/sodium hydrogen carbonate was completely stopping the epimerisation from occurring. Having now synthesised ketone **10** with an *er* of >99:1, this showed that no loss in chirality was occurring during the oxidation process, and any loss which was observed was solely coming from the elimination step.



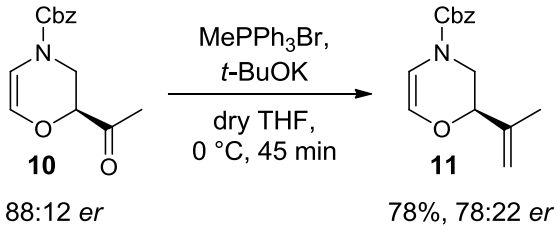
Scheme 23

Although Montmorillonite KSF caused no epimerisation to occur, a less than acceptable yield was obtained. It was therefore decided to investigate the original reaction conditions using *p*-toluenesulfonic acid, but lowering the equivalents to determine if this would improve the *er*. The original reaction involved the use of 0.4 eq., therefore, a reaction was performed with 0.2 eq. (**Scheme 24**). It was discovered that after 26 h the carboxybenzyl ketone **9** was still present in the reaction mixture. However, to deduce whether the acid equivalents had an effect on the *er* the reaction was stopped. It was pleasing to find that the ketone was now obtained with an *er* of 96:4, however, the ketone was only obtained in a 31% yield.



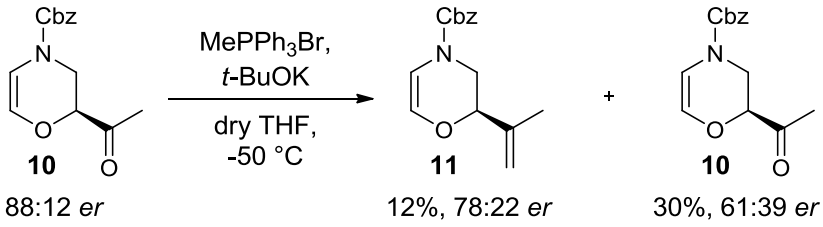
Scheme 24

Simultaneous to the investigation into the elimination reaction, research was also being carried out on the subsequent Wittig reaction. It was found that when using the Wittig conditions that were performed during the racemic synthesis, epimerisation was, once again, occurring (**Scheme 25**). The ketone starting material for this reaction had an *er* of 88:12, however, the alkene product was obtained with an *er* of 78:22. This disappointing result led to an investigation into different olefination conditions in an effort to prohibit the epimerisation from occurring at this stage in the synthesis.



Scheme 25

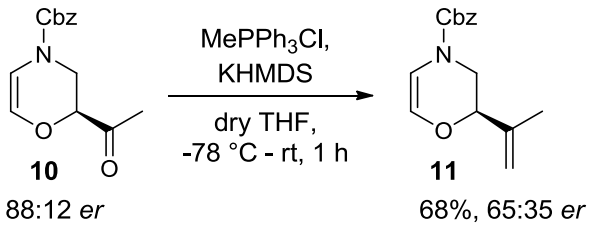
In this regard, a reaction was performed whereby the ketone was added to the preformed ylide at -50 °C instead of 0 °C. When the reaction was performed under these conditions, not only had significant epimerisation occurred (ketone **10**, 88:12; alkene **11**, 78:22) but the reaction failed to go to completion, even after being warmed to ambient temperature. When the *er* of the recovered ketone was checked, it was found that it now had an *er* of 61:39.



Scheme 26

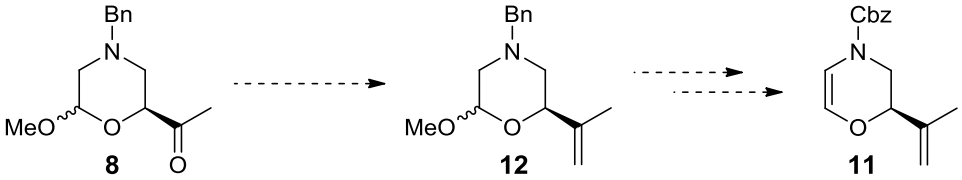
In an effort to supress the epimerisation from occurring, a reaction was carried out with the alternative base, KHMDS, to check whether the base influenced the

outcome. When this alternative reaction was performed, it was again disappointing to see that significant epimerisation had occurred (ketone **10**, 88:12; alkene **11**, 65:35).



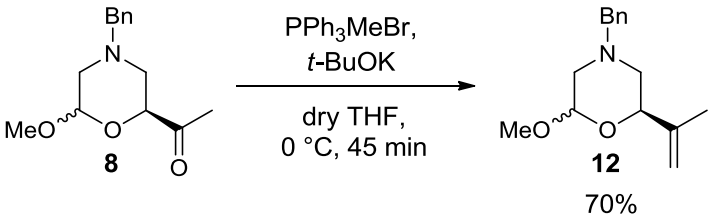
Scheme 27

Since both the elimination reaction and the Wittig reaction caused the key stereogenic centre to epimerise, it was decided that an alternative approach was required. In this regard, it was decided to carry out the elimination reaction and Wittig reaction in a different order. It was thought that the Wittig reaction could be carried out on ketone **8**, after which the elimination reaction would be performed (**Scheme 28**). It was envisaged that the different electronic and steric effects of ketone **8**, compared to **10**, could have an effect on the epimerisation. In addition to this, there would no longer be a readily epimerisable centre present during the elimination reaction.



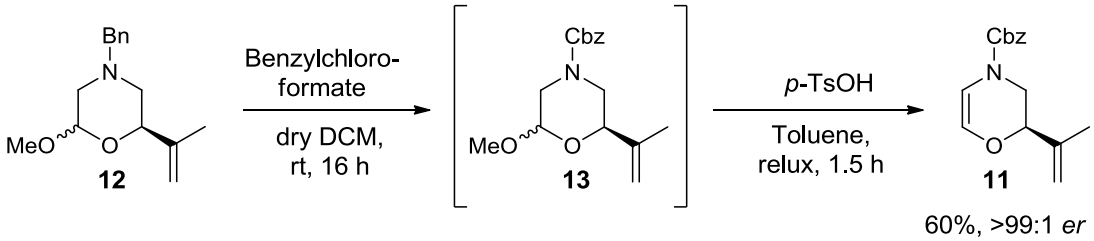
Scheme 28

This alternative approach began with performing the Wittig reaction on substrate **8**. It was pleasing to find that the Wittig reaction was successful, with the olefinated product being obtained in a 70% yield (**Scheme 29**).



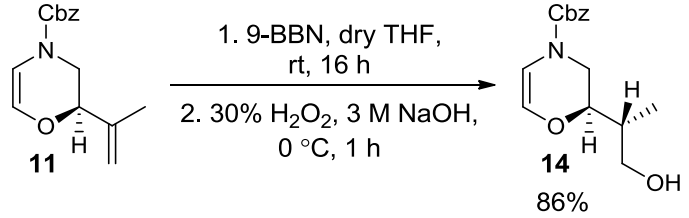
Scheme 29

With alkene **12** now in hand, the protecting group switch and elimination sequence could be performed. It was found that the protecting group switch occurred smoothly with the olefin in place, and when the elimination reaction was performed the desired product was obtained in a 60% yield (**Scheme 30**). It was extremely pleasing to find that no step in this new reaction sequence caused the stereogenic centre to epimerise, as compound **11** was obtained with an *er* of >99:1.



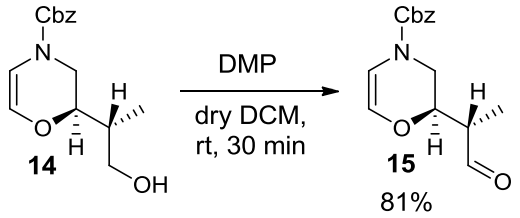
Scheme 30

Consequently, through these extensive optimisation studies, a route had now been developed which allowed compound **11** to be synthesised in an enantiomerically pure form. What remained was to perform the final few steps and reassess the *er* of the targeted bridged morpholine product. In this regard, **11** was transformed to alcohol **14** *via* a hydroboration oxidation sequence as shown in **Scheme 31**.[7]



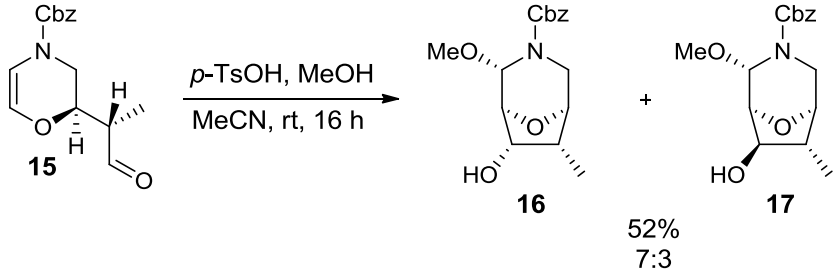
Scheme 31

With the primary alcohol in hand, the oxidation to synthesise the bridged morpholine precursor was performed. Utilising DMP as the oxidant, the aldehyde was synthesised in an 81% yield (**Scheme 32**).



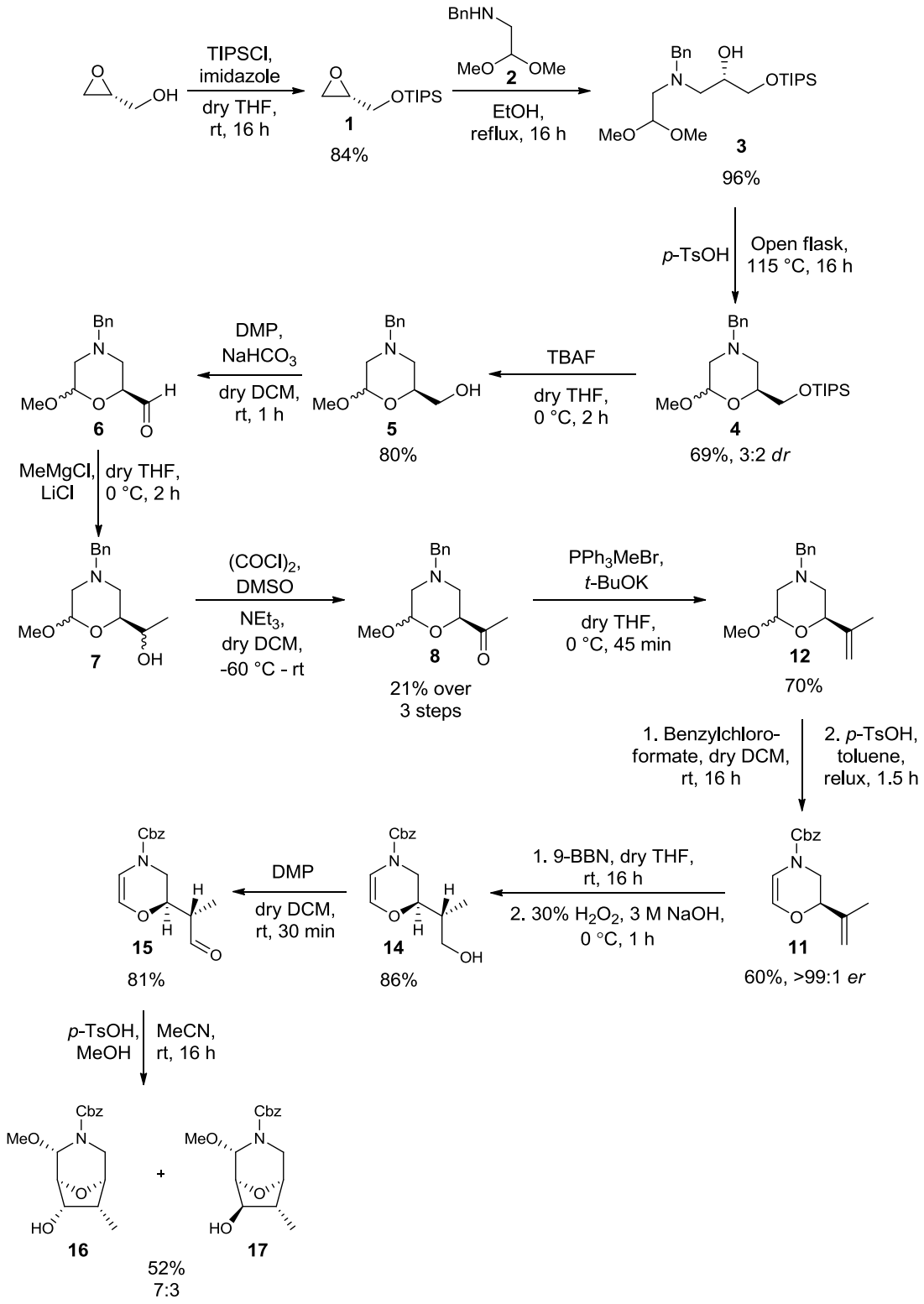
Scheme 32

Finally, aldehyde **15** successfully cyclised under acidic conditions to produce a 7:3 mixture of the desired bridged morpholine diastereomers (**Scheme 33**). The major diastereomer (**16**) was isolated from the mixture and the *er* of this compound was assessed. It was to great delight that it was established that during the final steps no epimerisation had occurred, as an *er* of >99:1 was observed by chiral HPLC analysis.



Scheme 33

The original racemic route failed to deliver a key intermediate with the chirality remaining intact. However, by changing the order that two of the reactions were performed, as well as optimising key oxidation and elimination protocols, a route had now been developed, which allows bridged morpholines **16** and **17** to be synthesised in enantiomerically enriched form (**Scheme 34**).


TIPSCl, imidazole, dry THF, rt, 16 h
1
84%
2
EtOH, reflux, 16 h
3
96%
p-TsOH
Open flask, 115 °C, 16 h
4
69%, 3:2 dr
TBAF
dry THF, 0 °C, 2 h
5
80%
DMP, NaHCO3
dry DCM, rt, 1 h
6
MeMgCl, LiCl
dry THF, 0 °C, 2 h
7
(COCl)2, DMSO
NEt3, dry DCM, -60 °C - rt
8
21% over 3 steps
PPh3MeBr, t-BuOK
dry THF, 0 °C, 45 min
12
70%
1. Benzylchloroformate, dry DCM, rt, 16 h
2. p-TsOH, toluene, relux, 1.5 h
11
60%, >99:1 er
1. 9-BBN, dry THF, rt, 16 h
2. 30% H2O2, 3 M NaOH, 0 °C, 1 h
14
86%
DMP
dry DCM, rt, 30 min
15
81%
p-TsOH, MeOH
MeCN, rt, 16 h
16
17
52%
7:3

Scheme 34

Having successfully completed the first route, investigation of the alternative route for the non-methylated bridged morpholine **18** began.

2.2 Non-Methylated Bridged Morpholine

The synthesis toward bridged morpholine **18** involved aldehyde **6**, which was described in the previous synthesis. Having found Swern conditions to be detrimental to the key stereogenic centre in **6**, and that DMP, in conjunction with sodium hydrogen carbonate, prohibited the epimerisation from occurring, it was decided to carry out the synthesis of the non-methylated bridged morpholine **18** (**Figure 1**) utilising aldehyde **6**, which had been synthesised under those conditions.

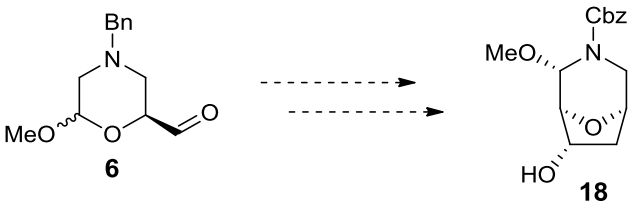
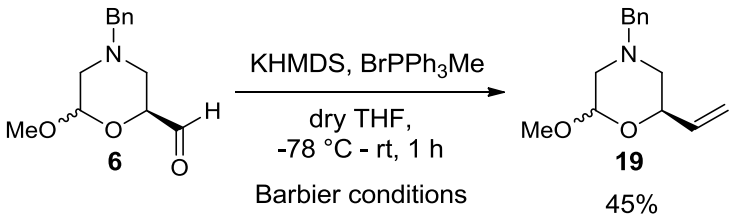


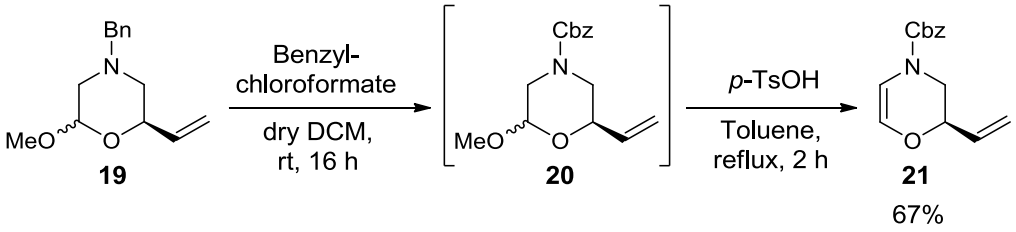
Figure 1

The racemic synthesis to bridged morpholine **18** utilised the Wittig reaction to install the olefin in compound **19**. It was found during the optimisation of this reaction that Barbier conditions with KHMDS produced the desired product in the highest yield (59%), therefore these conditions were employed for the asymmetric synthesis. When the aldehyde underwent the Wittig reaction, the morpholine derivative **19** was obtained in a moderate 45% yield (**Scheme 35**). As with the alternative route the enantiomeric ratio was not checked until the methoxy group was removed, and diastereomers were no longer present.



Scheme 35

With the olefin in hand, the required protecting group switch and elimination sequence was performed. Following the successful protecting group switch, the elimination reaction to install the double bond produced **21** in a moderate yield of 67% (**Scheme 36**).



Scheme 36

With the second stereogenic centre having now being removed, it was decided that the enantiomeric ratio would be checked at this stage. Unfortunately, with the chiral columns available, no conditions were found which enabled the enantiomers to be separated using chiral HPLC analysis. It was therefore hoped that alcohol **22** (**Figure 2**), which is produced in the subsequent step, could be separated.

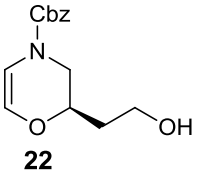
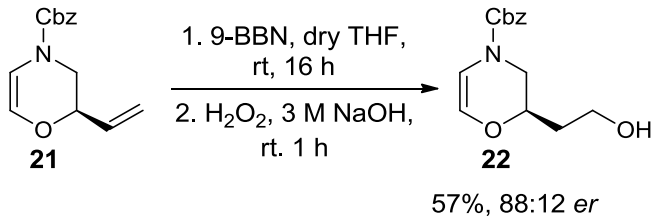


Figure 2

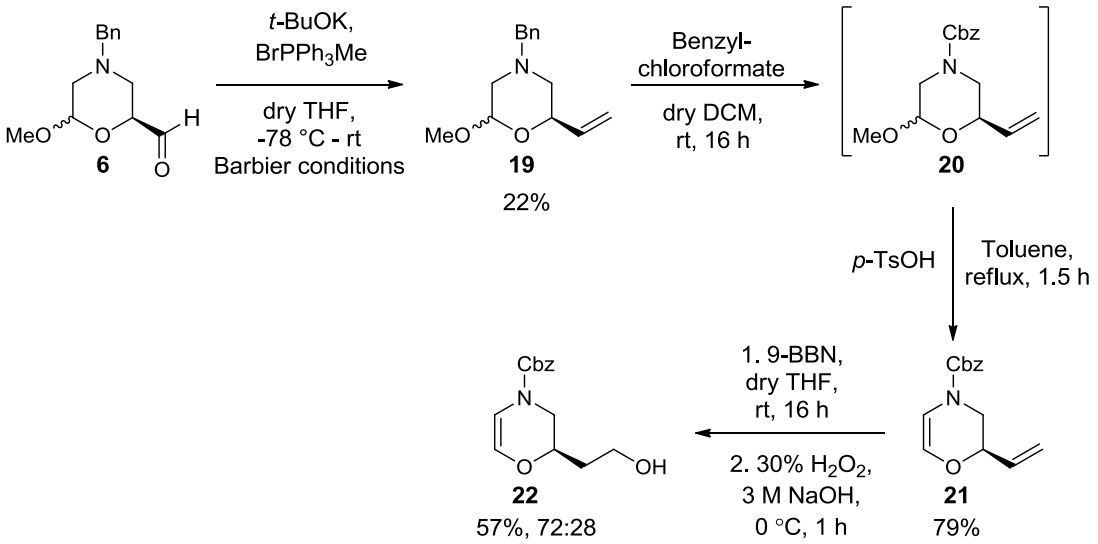
Following the elimination reaction, oxazine **21** underwent a hydroboration-oxidation sequence to produce alcohol **22** in a 57% yield (**Scheme 37**).[7] It was pleasing to find that the racemic alcohol could be separated using chiral HPLC, however, when the *er* of **22** was determined, it was disappointing to find that the *er* was 88:12. Knowing that the starting aldehyde had an *er* of >99:1, and that the aldehyde was the most

likely substrate to epimerise, it was proposed that the loss in *er* was taking place during the Wittig reaction.



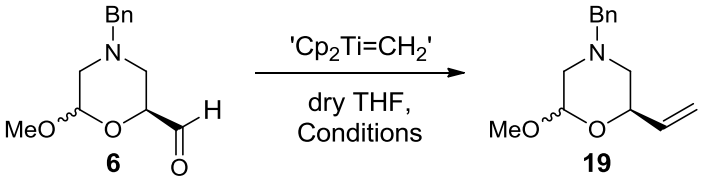
Scheme 37

During the racemic synthesis it was found that any other Wittig conditions apart from Barbier conditions failed to provide a yield higher than 8%, meaning that optimising the *er* with the Wittig reaction would be a challenge. KHMDS gave the highest yield of 59%, however, having discovered that these conditions caused epimerisation, they could not be utilised. When Barbier conditions were utilised with *t*-BuOK during the racemic synthesis, a yield of 32% was obtained. Although a poor yield, these conditions should give enough material to take through the subsequent steps and assess the *er* when this alternative base was used. When these conditions were applied to aldehyde **6** a poor yield of only 22% was obtained, however, sufficient material was obtained for the subsequent steps. Following the same reaction sequence described previously, alcohol **22** was obtained and the *er* was assessed (**Scheme 38**). It was disappointing to discover that signification epimerisation had occurred with *t*-BuOK as the base, as an *er* of 72:28 was obtained.



Scheme 38

As only a limited number of Wittig conditions could be performed on aldehyde **6**, it was decided that an alternative olefination reaction should be investigated. Due to the mildness of the Tebbe olefination, it was decided to perform this reaction with aldehyde **6** (**Scheme 39**).[8] It was decided to synthesise the Tebbe reagent and use it *in situ* (see **Experimental Section** for full details). The first attempt involved cooling the reagent to -78 °C, and then adding in the aldehyde dropwise and leaving the reaction to stir at -78 °C for 1 h (**Table 2**, **Entry 1**). After this time aldehyde **6** was observed by TLC analysis, therefore, the reaction mixture was warmed to ambient temperature and stirred until no aldehyde was observed by TLC analysis (3 h). On performing the reaction under these conditions, it was pleasing to find that the reaction was successful, although a poor yield of 25% was obtained. In an attempt to improve this yield, once the aldehyde was added at -78 °C, the reaction temperature was increased to only -50 °C, and stirred at this temperature for 3 h (**Entry 2**). After this time, aldehyde still appeared to be present in the reaction mixture, therefore the reaction was warmed to ambient temperature. After a further 2 h at ambient temperature, it was difficult to determine if aldehyde was still present, as the TLC plate showed a streak, therefore the reaction was stopped. It was discovered that a lower yield of 18% was obtained, in addition to a 27% recovery of the starting aldehyde.

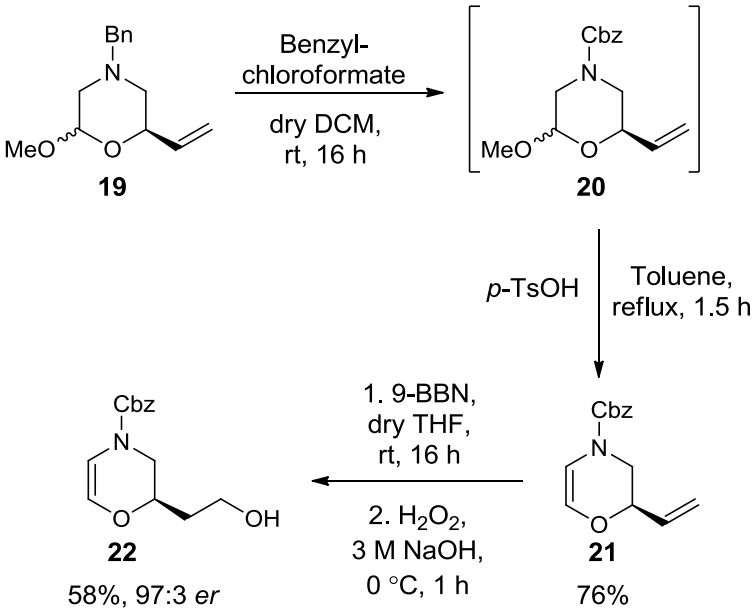


Scheme 39

Entry	*Conditions*	*Yield (%)*	*6 (% recovery)*
1	-78 °C for 1 h then rt for 3 h	25	0
2	-50 °C for 3 h then rt for 2 h	18	27

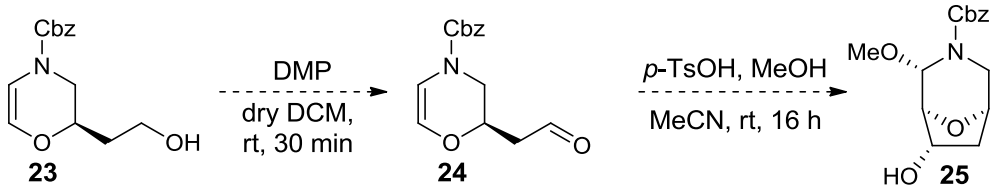
Table 2

To determine if Tebbe conditions controlled the epimerisation, the material obtained from **Table 2**, **Entry 1** was taken through the subsequent steps as shown in **Scheme 40**. On analysis of alcohol **22** it was discovered that under Tebbe olefination conditions only slight epimerisation had occurred, as **22** was obtained with an *er* of 97:3.



Scheme 40

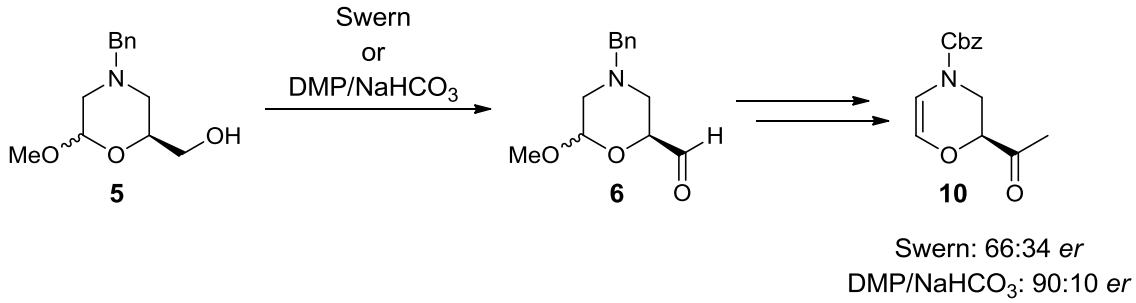
It was pleasing to have synthesised a key intermediate towards the synthesis of the non-methylated bridged morpholine with an *er* of 97:3. Furthermore, it was envisaged from the work carried out towards the synthesis of morpholines **16** and **17** that the remaining two steps (**Scheme 41**) should not cause any epimerisation to occur. However, due to insufficient material and time constraints, this part of the project was terminated at this stage.



Scheme 41

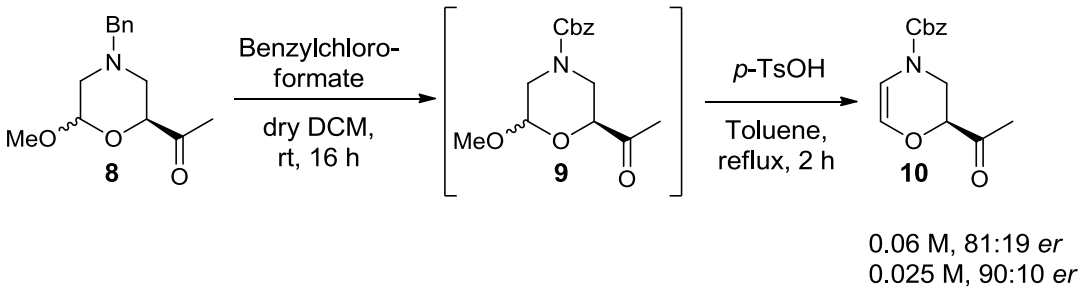
3. Conclusions and Future Work

Having developed a racemic synthesis into a range of bridged morpholines (**Chapter 1**), the potential for performing this route asymmetrically was investigated. The route began with (*R*)-glycidol, which was obtained commercially with a >99:1 *er*, however, it was found that when the Swern conditions were employed for the synthesis of aldehyde **6**, they caused the key stereogenic centre to significantly epimerise (**Scheme 42**). On changing the oxidant to DMP, in conjunction with sodium hydrogen carbonate, this epimerisation occurred to a much lesser extent.



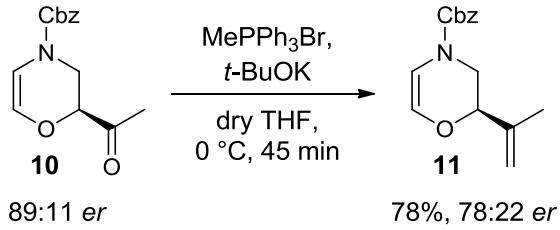
Scheme 42

It was also found that the concentration of the elimination reaction to produce ketone **10** proved to be crucial for controlling the epimerisation. After optimisation studies, it was discovered that a more dilute concentration to that utilised during the racemic synthesis was required in order to obtain ketone **10** with an *er* of 90:10 (**Scheme 43**). In addition to this, it was also found that the use of the acid clay Montmorillonite KSF produced the ketone with an *er* of >99:1, indicating that the decrease in the enantiomeric ratio was occurring as a consequence of the acid used in the elimination reaction. Having said this, when employing Montmorillonite KSF, although no epimerisation occurred, a very poor yield of only 9% was achieved.



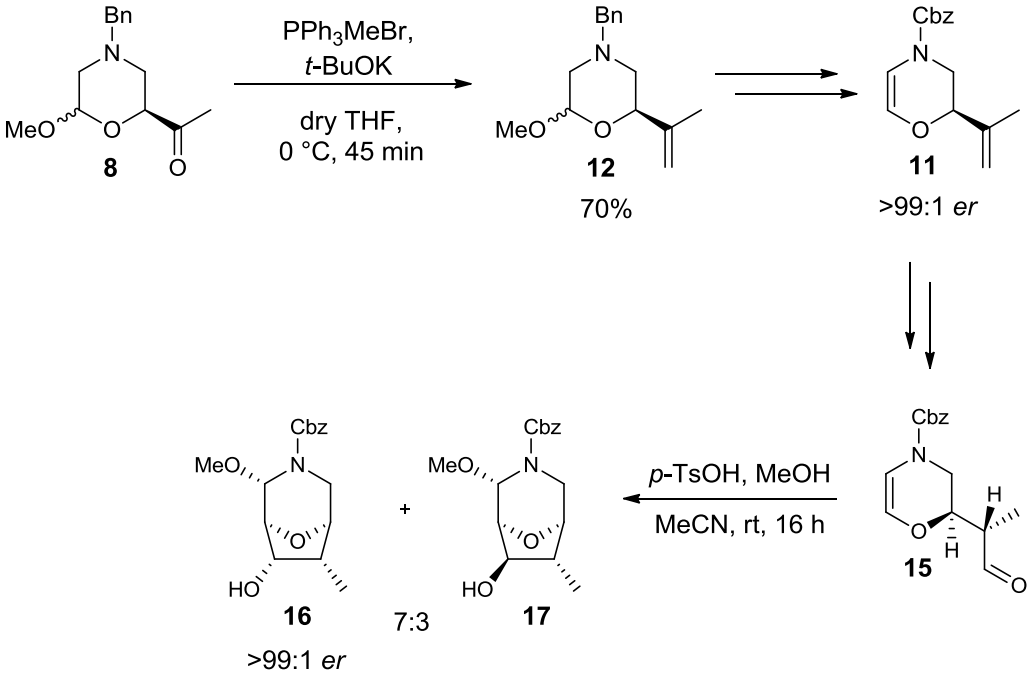
Scheme 43

As well as the elimination reaction causing epimerisation, the subsequent Wittig reaction also caused signification epimerisation (**Scheme 44**). Altering the Wittig reaction by performing the reaction at a lower temperature, or employing an alternative base, did not improve the *er*.



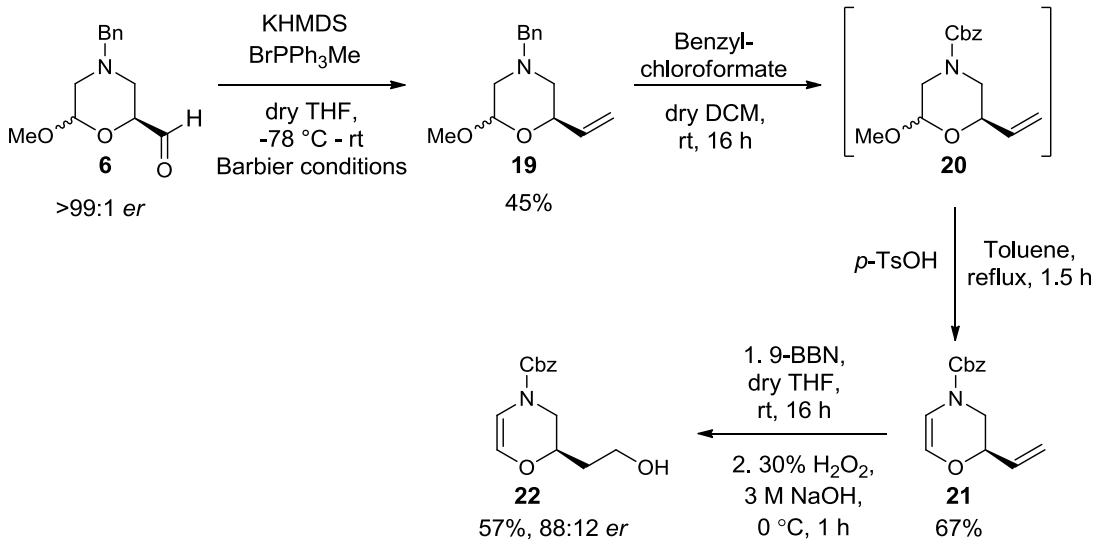
Scheme 44

It was found that by changing the order in which the reactions were performed (Wittig followed by the elimination reaction), that intermediate **11** could now be synthesised without any loss in chirality (**Scheme 45**). It was also pleasing to find that upon completing the synthesis, the final bridged morpholine **16** was obtained with an *er* of >99:1.



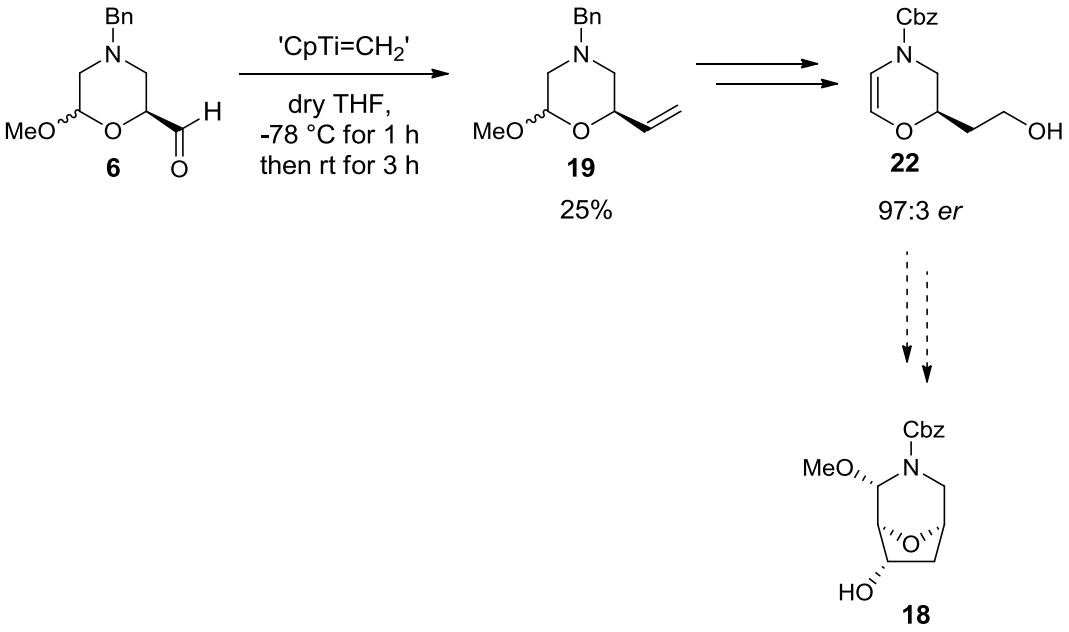
Scheme 45

With regards to the alternative route to synthesise bridged morpholine **18**, it was found that on synthesising oxazine **19**, utilising the Wittig conditions developed during the racemic synthesis, a drop in the *er* was observed (88:12 *er*) (**Scheme 46**).



Scheme 46

In due course, it was found that on utilising the Tebbe reagent in the olefination reaction, only slight epimerisation had occurred (97:3 *er*) (**Scheme 47**).



Scheme 47

Therefore, future work in this area would be to confirm that the final two steps to bridged morpholine **18** do not cause any loss in the *er*. Indeed, it is envisaged from the work carried out towards the synthesis of morpholines **16** and **17** that the remaining two steps should not cause any epimerisation. Future work would also involve the optimisation of the Tebbe olefination, as at this stage, a yield of only 25% was obtained. This could be achieved *via* the use of the Tebbe reagent in combination with pyridine, as the addition of a Lewis base has been shown to enhance the overall effectiveness of such transformations.[9]

4. Experimental

4.1 General

All reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. All reactions were carried out under an inert, dry, nitrogen atmosphere unless otherwise stated. All glassware was flame dried and cooled under a blanket of nitrogen.

- Dichloromethane and THF were obtained from Innovatic Technology, Pure Solv, SPS-400-5 drying columns.
- Methanol was distilled over calcium hydride before use.
- Benzaldehyde was distilled under nitrogen before use.
- Petrol refers to petroleum ether boiling point range 40-60 °C.
- MeMgCl was obtained as a 3 M solution in THF.
- 9-BBN was obtained as a 0.5 M solution in THF.
- KHMDS was obtained as a 0.5 M solution in toluene.
- Trimethylaluminium was obtained as a 2 M solution in toluene.
- Tetra-*n*-butylammonium fluoride was obtained as a 1 M solution in THF

Thin layer chromatography was carried out using silica gel 60 F_{254} plates. This was analysed using a Mineralight UVG-25 lamp or developed using vanillin solution.

Flash chromatography was carried out using Zeo Chem silica gel (40-63 μm).

IR spectra were recorded on a Perkin Elmer Spectrometer 1 machine.

^{1}H and ^{13}C spectra were recorded on a Bruker DPX 400 Spectrometer at 400 MHz and 100 MHz, respectively, or a Bruker 500 Spectrometer at 500 MHz and 125 MHz, respectively. Analysis for compounds **16** and **17** were recorded on a Bruker DPX 600

Spectrometer at 600 MHz. Chemical shifts are reported in ppm and coupling constants are reported in Hz and refer to $^{3}J_{\text{H-H}}$ interactions unless otherwise specified.

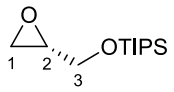
KHMDS and MeMgCl were standardised using salicylaldehyde phenylhydrazone as an indicator.[10]

High resolution mass spectra were recorded on a Finnigan MAT 90XLT instrument at the EPSRC Mass Spectrometry facility at the University of Swansea, Wales.

High performance liquid chromatography was carried out using a Chiralcel OD-H or Chiralcel OJ column using a Waters 501 HPLC pump, a Waters 484 tuneable absorbance detector (set at 254 nm), and processed using a Waters 746 data module.

Optical rotations were obtained on Perkin Elmer 341 polarimeter using a cell with a path length of 1 dm and concentration is expressed in g/100 cm^3.

(S)-Triisopropyl(oxiran-2-ylmethoxy)silane, ***1***[11]



Chemical Formula: $C_{12}H_{26}O_2Si$
Molecular Weight: 230.42

Scheme 3

Imidazole (9.5 g, 0.14 mol) was added to a stirred solution of (*R*)-glycidol (10.0 g, 0.13 mol) in dry THF (250 mL). Triisopropylsilyl chloride (32.0 mL, 0.14 mol) was then added during which a white precipitate formed. The reaction mixture was stirred at ambient temperature for 16 h. The precipitate was filtered through a bed of celite and washed with diethyl ether. The filtrate was concentrated *in vacuo* and purified by column chromatography (0-5% diethyl ether in petrol) to yield **1** as a colourless oil (26.9 g, 84%).

FTIR (CH_2Cl_2): 1260, 1266, 3050, 3061 cm^{-1}.

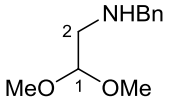
^{1}H NMR (400 MHz, $CDCl_3$): 1.06-1.13 (m, 21H, $Si(CH(CH_3)_2)_3$), 2.69 (dd, ^2J = 5.2 Hz, J = 2.8 Hz, 1H, H1), 2.80 (dd, ^2J = 5.3 Hz, J = 4.2 Hz, 1H, H1), 3.12-3.15 (m, 1H, H2), 3.78 (dd, ^2J = 11.7 Hz, J = 4.6 Hz, 1H, H3), 3.93 ppm (dd, ^2J = 11.6 Hz, J = 3.3 Hz, 1H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): 11.5, 17.4, 44.0, 52.1, 63.4 ppm.

HRMS *m/z* (ESI) calc for $C_{12}H_{27}O_2Si$ (M^++H): 231.1775. Found: 231.1777.

$[\alpha]_D^{25}$ = -3.7 (c=1.0, $CHCl_3$). Lit: $[\alpha]_D^{25}$ = -3.7 (c=1.0, $CHCl_3$).[11]

N-Benzyl-2,2-dimethoxyethanamine, ***2***



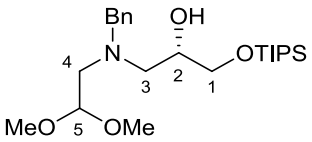
Chemical Formula: $C_{11}H_{17}NO_2$
Molecular Weight: 195.26

Scheme 4

Benzaldehyde (33 mL, 0.32 mol) was added to a stirred solution of 2,2-dimethoxyethylamine (35 mL, 0.32 mol) in methanol (670 mL) at ambient temperature and stirred for 16 h. The mixture was then cooled to 0 °C and sodium borohydride (18.2 g, 0.48 mol) was added portionwise. After stirring the mixture for 16 h at ambient temperature, the resultant solution was acidified to pH~9 with 2 M HCl. The methanol was then removed *in vacuo* and water was added. The pH was corrected again to pH~9 and the product was then extracted with ethyl acetate (x 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield **2** as a colourless oil (60.0 g, 96%).

FTIR (CH_2Cl_2): 2837, 3030 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 2.77 (d, J = 5.5 Hz, 2H, H2), 3.39 (s, 6H, OCH_3), 3.83 (s, 2H, benzylic CH_2), 4.51 (t, J = 5.5 Hz, 1H, H1), 7.28-7.35 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 50.6, 53.9, 54.0, 104.0, 127.0, 128.1, 128.4, 140.1 ppm.
HRMS *m/z* (ESI) calc for $C_{11}H_{18}NO_2$ (M^++H): 196.1332. Found: 196.1327.

(S)-5-Benzyl-10,10-diisopropyl-3-methoxy-11-methyl-2,9-dioxa-5-aza-10-siladodecan-7-ol, ***3***



Chemical Formula: $C_{23}H_{43}NO_4Si$
Molecular Weight: 425.68

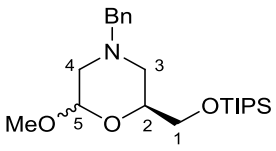
Scheme 5

Epoxide **1** (26.9 g, 0.12 mol) was added to a stirred solution of amine **2** (22.8 g, 0.12 mol) in ethanol (887 mL) at ambient temperature. The mixture was heated to reflux and stirred at this temperature for 16 h. The mixture was then cooled and concentrated *in vacuo* to yield **3** (49.2 g, 96%, >99:1 *er*) as a colourless oil.

FTIR (CH_2Cl_2): 1267, 2867, 3031, 3452 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.04-1.10 (m, 21H, $Si(CH(CH_3)_2)_3$), 2.60-2.70 (m, 2H, H3, H4), 2.73-2.81 (m, 2H, H3, H4), 3.29 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 3.48 (s, 1H, OH), 3.64-3.78 (m, 4H, H1, benzylic CH_2), 3.80-3.86 (m, 1H, H2), 4.38 (t, *J* = 5.5 Hz, 1H, H5), 7.31-7.36 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 11.4, 17.5, 52.7, 53.4, 55.6, 57.8, 60.0, 65.3, 68.7, 102.9, 126.7, 127.8, 128.6, 138.4 ppm.
HRMS *m/z* (ESI) calc for $C_{23}H_{44}NO_4Si$ (M^++H): 426.3034. Found: 426.3033.
$[\alpha]_D^{22}$ = -37.5 (c=1.0, $CHCl_3$).

Chiral HPLC analyisis: Chiracel OD-H column, 1% IPA in *n*-hexane, 1 mL/min flow rate, 254 nm detector, t_R (*R*) = 8.4 min and t_R (*S*) = 9.1 min.

(6S)-4-Benzyl-2-methoxy-6-(((triisopropylsilyl)oxy)methyl)morpholine, ***4***



Chemical Formula: $C_{22}H_{39}NO_3Si$
Molecular Weight: 393.64

Scheme 6

Substrate **3** (49.2 g, 116 mmol) was added to a one necked round bottom flask, and *p*-toluenesulfonic acid (8.8 g, 46 mmol) was added. A plug of cotton wool was placed in the neck of the flask and the flask was placed into an oil bath which had been pre-heated to 115 °C. The reaction mixture was left to stir at this temperature for 16 h. The mixture was then dissolved in DCM and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-20% diethyl ether in petrol) to yield **4** as a pale yellow oil (31.6 g, 69%, 3:2 *dr*).

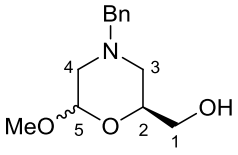
FTIR (CH_2Cl_2): 1270, 2867 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 1.02-1.09 (m, 21H, $Si(CH(CH_3)_2)_3$), 1.87-2.01 (m, 1.6H, H3, H4), 2.23 (dd, ^2J = 11.7 Hz, J = 2.8 Hz, 0.4H, H4), 2.84-2.97 (m, 2H, H3, H4), 3.42 (s, 1.2H, OCH_3), 3.50 (s, 1.8H, OCH_3), 3.53-3.90 (m, 4.6H, H1, H2, benzylic CH_2), 4.05-4.12 (m, 0.4H, H2), 4.51 (dd, J = 8.5 Hz, J = 2.5 Hz, 0.6H, H5), 4.68 (bd, J = 2.4 Hz, 0.4H, H5), 7.29-7.39 ppm (m, 5H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): 11.9, 17.9, 55.0, 55.1, 55.2, 55.7, 56.2, 56.8, 62.8, 63.4, 64.7, 65.0, 74.5, 97.3, 100.4, 127.2, 128.2, 129.2, 129.5, 136.7, 137.5 ppm.

HRMS *m/z* (ESI) calc for $C_{22}H_{40}NO_3Si$ (M^++H): 394.2772. Found: 394.2771.

((2S)-4-Benzyl-6-methoxymorpholin-2-yl)methanol, ***5***



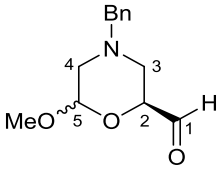
Chemical Formula: $C_{13}H_{19}NO_3$
Molecular Weight: 237.29

Scheme 7

Tetra-*n*-butylammonium fluoride (80.0 mL, 80.3 mmol, 1 M THF) was added to a stirred solution of **4** (31.6 g, 80.3 mmol) in dry THF (600 mL) at 0 °C. The solution was then allowed to stir at 0 °C for a further 2 h. The reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The alcohol was then purified by column chromatography (80% diethyl ether in petrol) to yield **5** as a colourless oil (15.2 g, 80%, 3:2 *dr*).

FTIR (CH_2Cl_2): 2883, 3031, 3598 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.93-2.03 (m, 1.6H, H3, H4), 2.27 (dd, ^2J = 11.7 Hz, J = 2.9 Hz, 0.4H, H4), 2.72-2.74 (m, 0.6H, H3), 2.75-2.77 (m, 0.4H, H3), 2.85-2.92 (m, 1H, H4), 3.44 (s, 1.2H, OCH_3), 3.49-3.75 (m, 5.8H, OCH_3, H1, benzylic CH_2), 3.76-3.83 (m, 0.6H, H2), 4.06-4.14 (m, 0.4H, H2), 4.57 (dd, J = 8.4 Hz, J = 2.4 Hz, 0.6H, H5), 4.74 (bs, 0.4H, H5), 7.28-7.35 ppm (m, 5H, ArH).
^{13}C NMR (125 MHz, $CDCl_3$): 53.4, 53.6, 55.2, 55.7, 56.5, 56.7, 62.7, 63.3, 63.8, 64.2, 69.0, 74.3, 97.4, 100.6, 127.3, 128.3, 128.4, 129.2, 129.5, 136.7, 137.4 ppm.
HRMS *m/z* (ESI) calc for $C_{13}H_{20}NO_3$ (M^++H): 238.1438. Found: 238.1440.

(2S)-4-Benzyl-6-methoxymorpholine-2-carbaldehyde, ***6***



Chemical Formula: $C_{13}H_{17}NO_3$
Molecular Weight: 235.28

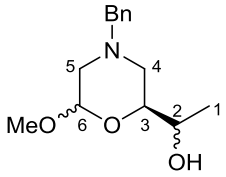
Scheme 8

DMSO (248 µL, 3.50 mmol) was added slowly to a stirred solution of oxalyl chloride (169 µL, 1.98 mmol) in dry DCM (3.3 mL) at -60 ºC. The mixture was stirred at this temperature for 10 minutes and then **5** (361 mg, 1.52 mmol), as a solution in dry DCM (1.1 mL), was slowly added. The reaction mixture was stirred for a further 15 min before triethylamine (1.1 mL, 7.60 mmol) was added. The mixture was then warmed to 0 °C and toluene (3 mL) was added. The slurry was concentrated *in vacuo* to remove only the DCM. The slurry was purified by column chromatography (80% diethyl ether in petrol) to yield **6** as a pale yellow oil (338 mg, 94%, 1:1 *dr*).

FTIR (CH_2Cl_2): 1737 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 2.18-2.33 (m, 1.5H, H3, H4), 2.40 (dd, ^2J = 11.7 Hz, J = 3.1 Hz, 0.5H, H4), 2.76-2.83 (m, 1.5H, H3, H4), 2.93-2.98 (m, 0.5H, H4), 3.47-3.60 (m, 5H, OCH_3, benzylic CH_2), 4.09 (dd, J = 8.7 Hz, J = 3.3 Hz, 0.5H, H2), 4.47 (dd, J = 9.7 Hz, J = 3.2 Hz, 0.5H, H2), 4.64 (dd, J = 6.8 Hz, J = 2.5 Hz, 0.5H, H5), 4.82 (apparent t, J = 2.5 Hz, 0.5H, H5), 7.26-7.37 (m, 5H, ArH), 9.65 (s, 0.5H, H1), 9.74 ppm (s, 0.5, H1).
^{13}C NMR (125 MHz, $CDCl_3$): 51.0, 51.1, 55.1, 55.2, 55.9, 56.1, 62.1, 62.4, 73.7, 77.5, 97.1, 99.6, 127.0, 127.9, 128.6, 128.8, 135.8, 136.3, 199.8, 200.2 ppm.

Due to the sensitive nature of the substrate accurate mass spectral details could not be obtained.

*1-((2S)-4-Benzyl-6-methoxymorpholin-2-yl)ethanol, **7***



Chemical Formula: $C_{14}H_{21}NO_3$
Molecular Weight: 251.32

General Procedure A

Lithium chloride was placed in a three necked round bottom flask which was flame dried under vacuum and allowed to cool under a blanket of nitrogen. Methylmagnesium chloride was added and the resultant mixture was cooled to 0 °C. Aldehyde **6**, as a dry THF solution, was slowly added and the mixture was stirred at 0 °C for a further 2 h. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride and the organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant alcohol was purified by column chromatography (60-80% diethyl ether in petrol) to yield **7** as a colourless oil.

Scheme 9

The following experiment was carried out using ***General Procedure A***. Data are reported as: (a) amount of lithium chloride, (b) amount of methylmagnesium chloride, (c) amount of substrate **6**, (d) volume of dry THF (e) amount of **7**, and (f) yield.

(a) 122 mg, 2.87 mmol, (b) 0.96 mL, 2.87 mmol, 3 M in THF, (c) 338 mg, 1.44 mmol, (d) 3.3 mL, (e) 251 mg, and (f) 70%.

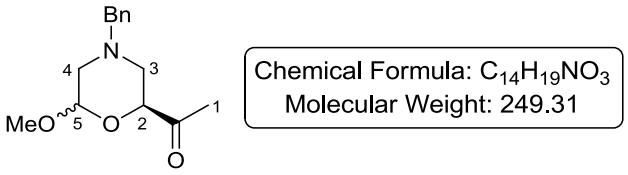
FTIR (CH_2Cl_2): 3032, 3599 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.17-1.24 (m, 3H, H1), 1.86-2.31 (m, 2H, H4, H5), 2.75-2.91 (m, 2H, H4, H5), 3.40-3.63 (m, 6H, benzylic CH_2, H2, OCH_3), 3.84-3.97

(m, 1H, H3), 4.52-4.57 (m 0.5H, H6), 4.70-4.77 (m, 0.5H, H6), 7.30-7.37 ppm (m, 5H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$):18.4, 18.5, 52.2, 55.1, 55.6, 56.4, 56.7, 62.9, 63.4, 68.4, 68.5, 71.9, 97.5, 100.6, 127.3, 128.3, 129.2, 129.5, 136.7, 137.5 ppm.

HRMS *m/z* (ESI) calc for $C_{14}H_{22}NO_3$ (M^++H): 252.1594. Found: 252.1595.

1-((2S)-4-Benzyl-6-methoxymorpholin-2-yl)ethanone, ***8***



General Procedure B

DMSO was added slowly to a stirred solution of oxalyl chloride in dry DCM at -60 ºC. The mixture was stirred at this temperature for 10 minutes and then **7**, as a solution in dry DCM, was slowly added. The reaction mixture was stirred for a further 15 minutes before triethylamine was added. The mixture was warmed to ambient temperature and allowed to stir for 1 h. The reaction mixture was quenched with saturated aqueous solution of ammonium chloride, and the organic layer was separated. After washing with water (x 2) and brine, the organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-50% diethyl ether in petrol) to yield **8** as an off yellow oil.

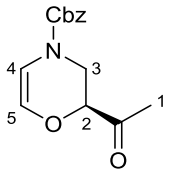
Scheme 10

The following experiment was carried out using ***General Procedure B***. Data are reported as: (a) amount of DMSO, (b) amount of oxalyl chloride, (c) volume of dry DCM, (d) amount of substrate **7**, (e) volume of dry DCM, (f) amount of triethylamine, (g) amount of **8**, (h) yield, and (g) *dr*.

(a) 85 µL, 1.19 mmol, (b) 58µL, 0.68 mmol, (c) 1.2 mL, (d) 131 mg, 0.52 mmol, (e) 0.4 mL, (f) 362 µL, 2.60 mmol, (g) 75 mg, (h) 58%, and (g) 3:2.

FTIR (CH_2Cl_2): 1718, 2828, 3031 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.91-2.04 (m, 1.2H, H3, H4), 2.08-2.15 (m, 0.4H, H4), 2.22-2.29 (m, 3.4H, H1, H3), 2.83-2.92 (m, 1H, H3), 3.00-3.14 (m, 1H, H4), 3.48 (s, 1.2H, OCH_3), 3.50-3.62 (m, 3.8H, benzylic CH_2, OCH_3), 4.09 (dd, *J* = 10.5 Hz, *J* = 2.9 Hz, 0.6H, H2), 4.45 (dd, *J* = 10.4 Hz, *J* = 2.9 Hz, 0.4H, H2), 4.56 (dd, *J* = 8.5 Hz, *J* = 2.4 Hz, 0.6H, H5), 4.80 (bs, 0.4H, H5), 7.29-7.56 ppm (m, 5H, ArH).
^{13}C NMR (125 MHz, $CDCl_3$): 26.3, 53.0, 53.1, 55.3, 55.5, 56.2, 56.5, 62.5, 63.0, 74.3, 79.2, 97.5, 100.7, 127.4, 128.3, 128.4, 129.1, 129.4, 136.4, 137.0, 207.1, 207.2 ppm.
HRMS *m/z* (ESI) calc for $C_{14}H_{20}NO_3$ (M^++H): 250.1438. Found: 250.1440.

(S)-Benzyl 2-acetyl-2H-1,4-oxazine-4(3H)-carboxylate, ***10***



Chemical Formula: $C_{14}H_{15}NO_4$
Molecular Weight: 261.27

General Procedure C

Benzylchloroformate was added to a stirred solution of **8** in dry DCM. The mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The resultant oil was dissolved in toluene and *p*-toluenesulfonic acid was added. The reaction mixture was then stirred at reflux for 2 h using Dean-Stark apparatus. The solution was then cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The oil was then purified by column chromatography (0-40% diethyl ether in petrol) to yield **10** as a pale yellow oil.

Scheme 11

The following experiment was carried out using ***General Procedure C***. Data are reported as: (a) amount of benzylchloroformate, (b) amount of substrate **8**, (c) volume of dry DCM, (d) volume of toluene, (e) amount of *p*-toluenesulfonic acid, (f) amount of **10**, (g) yield, and (h) *er*.

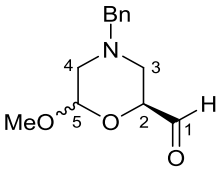
(a) 96 µL, 0.60 mmol, (b) 75 mg, 0.30 mmol, (c) 1.9 mL, (d) 12 mL, (e) 23 mg, 0.12 mmol, (f) 59 mg, (g) 75%, and (h) 66:34.

FTIR (CH_2Cl_2): 1666, 1710 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 2.30 (s, 3H, H1), 3.71 (dd, ^2J = 13.2 Hz, J = 6.5 Hz, 0.5H, H3), 3.80 (dd, ^2J = 13.4 Hz, J = 6.3 Hz, 0.5H, H3), 3.95 (bd, ^2J = 13.4 Hz, 0.5H, H3), 4.05 (bd, ^2J = 13.0 Hz, 0.5H, H3), 4.37-4.43 (m, 1H, H2), 5.17-5.26 (m, 2H, benzylic CH_2), 6.01 (d, J = 4.8 Hz, 0.5H, H4), 6.13 (d, J = 4.8 Hz, 0.5H, H4), 6.29 (d, J = 4.8 Hz, 0.5H, H5), 6.43 (d, J = 4.8 Hz, 0.5H, H5), 7.30-7.46 ppm (m, 5H, ArH).
^{13}C NMR (125 MHz, $CDCl_3$): 26.2, 41.7, 42.2, 67.9, 78.1, 78.5, 106.5, 107.1, 127.6, 128.2, 128.4, 128.6, 135.7, 135.9, 148.0, 206.4 ppm.
HRMS *m/z* (ESI) calc for $C_{14}H_{16}NO_4$ (M^++H): 262.1074. Found: 262.1079.

A 1:1 ratio of rotamers were observed in the ^{1}H NMR.

Chiral HPLC analyisis: Chiracel OD-H column, 40% IPA in *n*-hexane, 1 mL/min flow rate, 254 nm detector, t_R (*S*) = 26.0 min and t_R (*R*) = 31.0 min.

(2S)-4-Benzyl-6-methoxymorpholine-2-carbaldehyde, ***6***



Chemical Formula: $C_{13}H_{17}NO_3$
Molecular Weight: 235.28

Scheme 12

DMP (826 mg, 1.95 mmol) was added to a stirred solution of alcohol **5** (419 mg, 1.77 mmol) and sodium hydrogen carbonate (428 mg, 5.10 mmol) in dry DCM (11 mL). The reaction mixture was stirred at ambient temperature for 1 h during which time a white precipitate formed. The reaction mixture was diluted with diethyl ether and DCM was removed *in vacuo*. The mixture was further diluted with diethyl ether and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate and saturated aqueous solution of sodium bicarbonate was added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography, (80% diethyl ether in petrol) to yield **6** (269 mg, 65%, 3:2 *dr*) as a colourless oil.

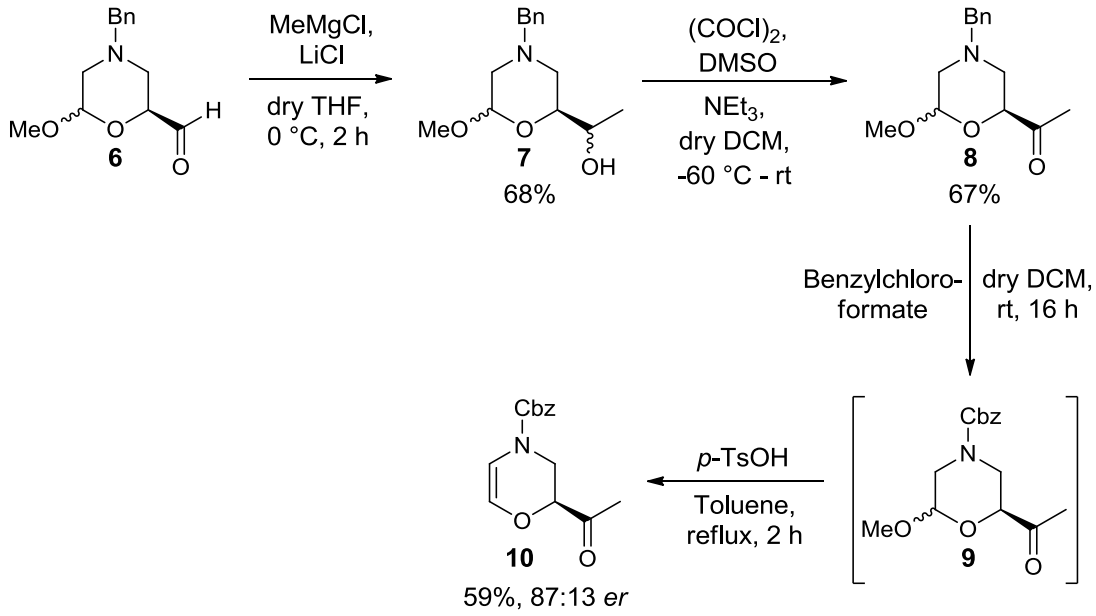
FTIR (CH_2Cl_2): 1737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 2.18-2.33 (m, 1.6H, H3, H4), 2.40 (dd, ^2J = 11.7 Hz, J = 3.1 Hz, 0.4H, H4), 2.76-2.83 (m, 1.6H, H3, H4), 2.93-2.98 (m, 0.4H, H4), 3.47-3.60 (m, 5H, OCH_3, benzylic CH_2), 4.09 (dd, J = 8.7 Hz, J = 3.3 Hz, 0.6H, H2), 4.47 (dd, J = 9.7 Hz, J = 3.2 Hz, 0.4H, H2), 4.64 (dd, J = 6.8 Hz, J = 2.5 Hz, 0.6H, H5), 4.82 (apparent t, J = 2.5 Hz, 0.4H, H5), 7.26-7.37 (m, 5H, ArH), 9.65 (s, 0.4H, H1), 9.74 ppm (s, 0.6, H1).

^{13}C NMR (125 MHz, $CDCl_3$): 51.0, 51.1, 55.1, 55.2, 55.9, 56.1, 62.1, 62.4, 73.7, 77.5, 97.1, 99.6, 127.0, 127.9, 128.6, 128.8, 135.8, 136.3, 199.8, 200.2 ppm.

Due to the sensitive nature of the substrate accurate mass spectral details could not be obtained.

Scheme 13



Synthesis of compound 7

The following experiment was carried out using ***General Procedure A (page 306)***. Data are reported as: (a) amount of lithium chloride, (b) amount of methylmagnesium chloride, (c) amount of substrate **6**, (d) volume of dry THF, (e) amount of **7**, and (f) yield.

(a) 97 mg, 2.29 mmol, (b) 0.76 mL, 2.29 mmol, 3 M in THF, (c) 269 mg, 1.14 mmol, (d) 2.4 mL, (e) 202 mg, and (f) 68%.

*The data for compound **7** is shown on **page 306**.*

Synthesis of compound 8

The following experiment was carried out using ***General Procedure B (page 307)***. Data are reported as: (a) amount of DMSO, (b) amount of oxalyl chloride, (c) volume of dry DCM, (d) amount of substrate **7**, (e) volume of dry DCM, (f) amount of triethylamine, (g) amount of **8**, and (h) yield.

(a) 64 µL, 0.89 mmol, (b) 44 µL, 0.51 mmol, (c) 1 mL, (d) 89 mg, 0.39 mmol, (e) 0.3 mL, (f) 272 µL, 1.95 mmol, (g) 65 mg, and (h) 67%.

*The data for compound **8** is shown on **page 308**.*

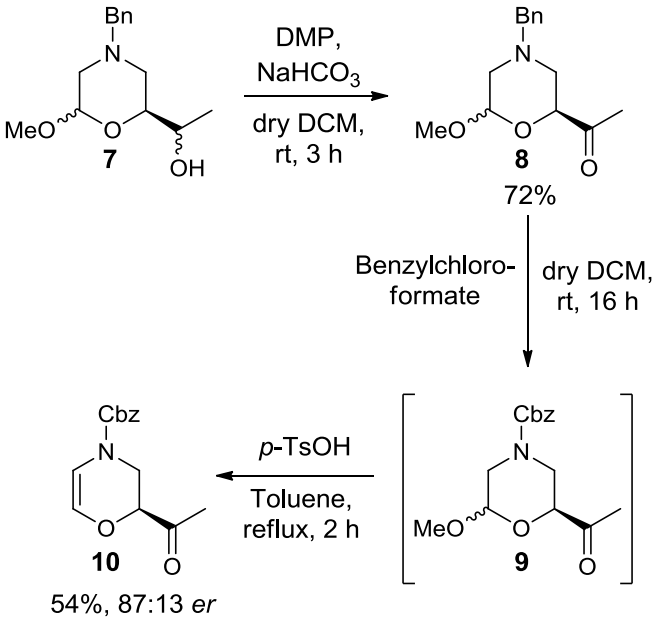
Synthesis of compound 10

The following experiment was carried out using ***General Procedure C (page 308)***. Data are reported as: (a) amount of benzylchloroformate, (b) amount of substrate **8**, (c) volume of dry DCM, (d) volume of toluene, (e) amount of *p*-toluenesulfonic acid, (f) amount of **10**, (g) yield, and (h) *er*.

(a) 63 µL, 0.44 mmol, (b) 65 mg, 0.26 mmol, (c) 1.7 mL, (d) 10.4 mL, (e) 20 mg, 0.10 mmol, (f) 40 mg, (g) 59%, and (h) 87:13.

*The data for compound **10** is shown on **page 309**.*

Scheme 14



Synthesis of compound 8

DMP (211 mg, 0.50 mmol) was added to a stirred solution of alcohol **7** (104 mg, 0.41 mmol) and sodium hydrogen carbonate (105 mg, 1.23 mmol) in dry DCM (2.6 mL). The reaction mixture was stirred at ambient temperature for 3 h during which time a white precipitate formed. The reaction mixture was diluted with diethyl ether and DCM was removed *in vacuo*. The mixture was further diluted with diethyl ether and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate and saturated aqueous solution of sodium bicarbonate was added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography, (60% diethyl ether in petrol) to yield **8** (74 mg, 72%, 7:3 *dr*) as a colourless oil.

*The data for compound **8** is shown on **page 308**.*

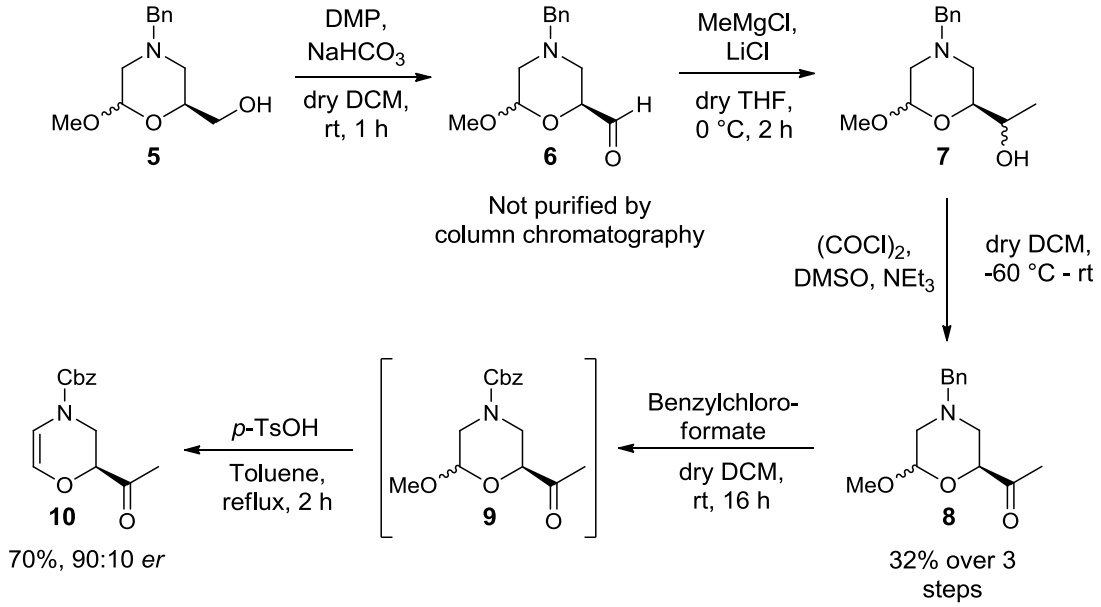
Synthesis of compound 10

The following experiment was carried out using ***General Procedure C (page 308)***. Data are reported as: (a) amount of benzylchloroformate, (b) amount of substrate **8**, (c) volume of dry DCM, (d) volume of toluene, (e) amount of *p*-toluenesulfonic acid, (f) amount of **10**, (g) yield, and (h) *er*.

(a) 85 µL, 0.59 mmol, (b) 74 mg, 0.30 mmol, (c) 1.9 mL, (d) 12 mL, (e) 23 mg, 0.12 mmol, (f) 40 mg, (g) 54%, and (h) 87:13.

*The data for compound **10** is shown on **page 309**.*

Scheme 15



Synthesis of compound 6

DMP (554 mg, 1.31 mmol) was added to a stirred solution of alcohol **5** (282 mg, 1.19 mmol) and sodium hydrogen carbonate (300 mg, 3.57 mmol) in dry DCM (7.4 mL). The reaction mixture was stirred at ambient temperature for 1 h during which time a white precipitate formed. The reaction mixture was diluted with diethyl ether and DCM was removed *in vacuo*. The mixture was further diluted with diethyl ether and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate and saturated aqueous solution of sodium bicarbonate was added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield **6**, which was used directly in the next step (244 mg).

*The data for compound **6** is shown on **page 310**.*

Synthesis of compound 7

The following experiment was carried out using ***General Procedure A (page 306)***. Data are reported as: (a) amount of lithium chloride, (b) amount of

methylmagnesium chloride, (c) amount of substrate **6**, (d) volume of dry THF, and (e) amount of **7**.

(a) 88 mg, 2.07 mmol, (b) 0.69 mL, 2.07 mmol, 3 M in THF, (c) 244 mg, (d) 2.3 mL, and (e) 163 mg.

*The data for compound **7** is shown on **page 306**.*

Synthesis of compound 8

The following experiment was carried out using ***General Procedure B (page 307)***. Data are reported as: (a) amount of DMSO, (b) amount of oxalyl chloride, (c) volume of dry DCM, (d) amount of substrate **7**, (e) volume of dry DCM, (f) amount of triethylamine, (g) amount of **8**, and (h) yield.

(a) 106 µL, 1.49 mmol, (b) 72 µL, 0.85 mmol, (c) 1.4 mL, (d) 163 mg, (e) 0.5 mL, (f) 452 µL, 3.24 mmol, (g) 64 mg, and (h) 32% over the three steps.

*The data for compound **8** is shown on **page 308**.*

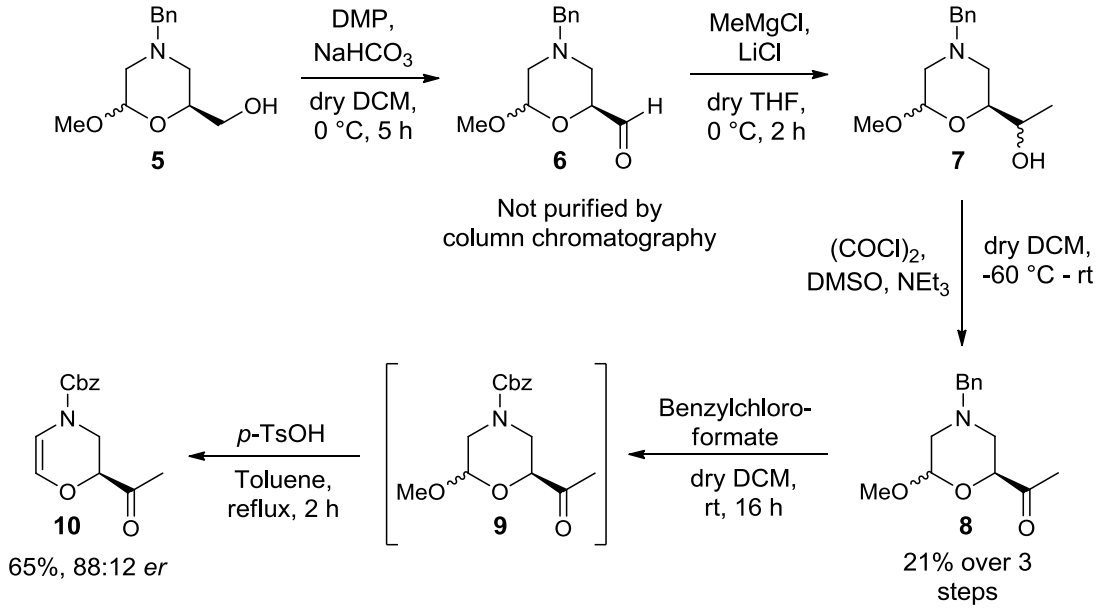
Synthesis of compound 10

The following experiment was carried out using ***General Procedure C (page 308)***. Data are reported as: (a) amount of benzylchloroformate, (b) amount of substrate **8**, (c) volume of dry DCM, (d) volume of toluene, (e) amount of *p*-toluenesulfonic acid, (f) amount of **10**, (g) yield, and (h) *er*.

(a) 73 µL, 0.51 mmol, (b) 64 mg, 0.26 mmol, (c) 1.6 mL, (d) 10.4 mL, (e) 20 mg, 0.10 mmol, (f) 47 mg, (g) 70%, and (h) 90:10.

*The data for compound **10** is shown on **page 309**.*

Scheme 16



Synthesis of compound 6

DMP (1.5 g, 3.67 mmol) was added to a stirred solution of alcohol **5** (348 mg, 1.47 mmol) and sodium hydrogen carbonate (494 mg, 5.88 mmol) in dry DCM (9 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 h during which time a white precipitate formed. The reaction mixture was diluted with diethyl ether and DCM was removed *in vacuo*. The mixture was further diluted with diethyl ether and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate and saturated aqueous solution of sodium bicarbonate was added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield **6** which was used directly in the next step (281 mg).

Synthesis of compound 7

The following experiment was carried out using ***General Procedure A (page 306)***. Data are reported as: (a) amount of lithium chloride, (b) amount of methylmagnesium chloride, (c) amount of substrate **6**, (d) volume of dry THF, and (e) amount of **7**.

(a) 101 mg, 2.39 mmol, (b) 0.79 mL, 2.36 mmol, 3 M in THF, (c) 284 mg, (d) 2.7 mL, and (e) 202 mg.

*The data for compound **7** is shown on **page 306**.*

Synthesis of compound 8

The following experiment was carried out using ***General Procedure B (page 307)***. Data are reported as: (a) amount of DMSO, (b) amount of oxalyl chloride, (c) volume of dry DCM, (d) amount of substrate **7**, (e) volume of dry DCM, (f) amount of triethylamine, (g) amount of **8**, and (h) yield.

(a) 119 µL, 1.84 mmol, (b) 90 µL, 1.04 mmol, (c) 1.8 mL, (d) 202 mg, (e) 0.6 mL, (f) 558 µL, 4.00 mmol, (g) 77 mg, and (h) 21% over the three steps.

*The data for compound **8** is shown on **page 308**.*

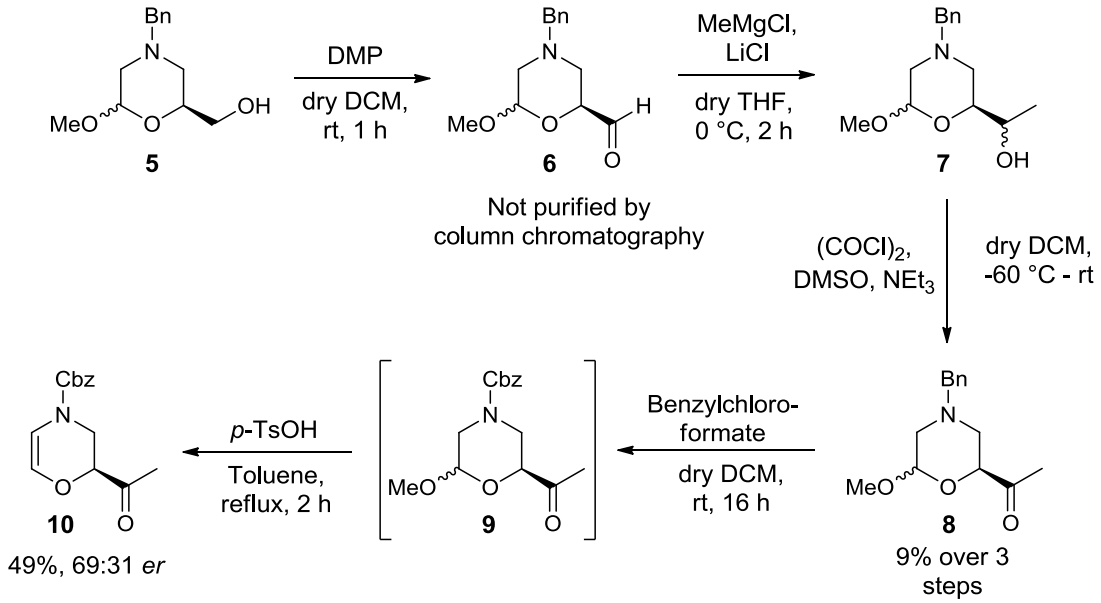
Synthesis of compound 10

The following experiment was carried out using ***General Procedure C (page 308)***. Data are reported as: (a) amount of benzylchloroformate, (b) amount of substrate **8**, (c) volume of dry DCM, (d) volume of toluene, (e) amount of *p*-toluenesulfonic acid, (f) amount of **10**, (g) yield, and (h) *er*.

(a) 88 µL, 0.62 mmol, (b) 77 mg, 0.31 mmol, (c) 1.9 mL, (d) 12.4 mL, (e) 24 mg, 0.12 mmol, (f) 53 mg, (g) 65%, and (h) 88:12.

*The data for compound **10** is shown on **page 309**.*

Scheme 17



Synthesis of compound 6

DMP (688 mg, 1.62 mmol) was added to a stirred solution of alcohol **5** (350 mg, 1.47 mmol) in dry DCM (9 mL) at ambient temperature. The reaction mixture was stirred for 1 h during which time a white precipitate formed. The reaction mixture was diluted with diethyl ether and DCM was removed *in vacuo*. The mixture was further diluted with diethyl ether and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate and saturated aqueous solution of sodium bicarbonate was added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield **6** which was used directly in the next step (345 mg).

*The data for compound **6** is shown on **page 310**.*

Synthesis of compound 7

The following experiment was carried out using ***General Procedure A (page 306)***. Data are reported as: (a) amount of lithium chloride, (b) amount of

methylmagnesium chloride, (c) amount of substrate **6**, (d) volume of dry THF, and (e) amount of **7**.

(a) 124 mg, 2.93 mmol, (b) 0.98 mL, 2.93 mmol, 3 M in THF, (c) 345 mg, (d) 3.3 mL, and (e) 115 mg.

*The data for compound **7** is shown on **page 306**.*

Synthesis of compound 8

The following experiment was carried out using ***General Procedure B (page 307)***. Data are reported as: (a) amount of DMSO, (b) amount of oxalyl chloride, (c) volume of dry DCM, (d) amount of substrate **7**, (e) volume of dry DCM, (f) amount of triethylamine, (g) amount of **8**, and (h) yield.

(a) 75 µL, 1.06 mmol, (b) 51 µL, 0.59 mmol, (c) 1 mL, (d) 115 mg, (e) 0.3 mL, (f) 321 µL, 2.30 mmol, (g) 35 mg, and (h) 9% over the three steps.

*The data for compound **8** is shown on **page 308**.*

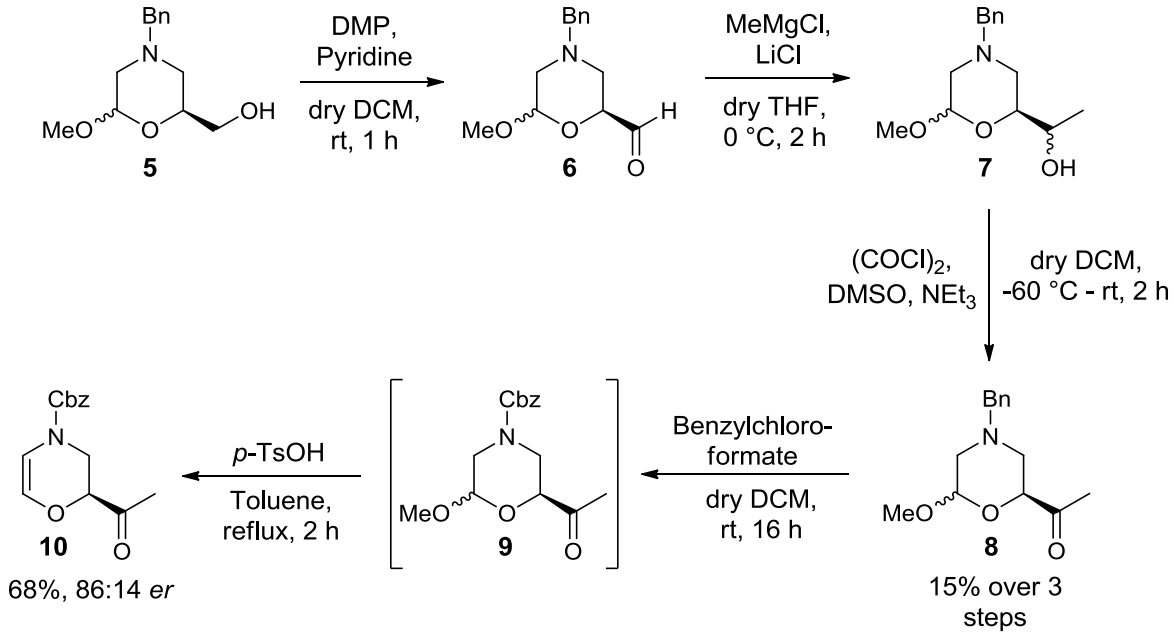
Synthesis of compound 10

The following experiment was carried out using ***General Procedure C (page 308)***. Data are reported as: (a) amount of benzylchloroformate, (b) amount of substrate **8**, (c) volume of dry DCM, (d) volume of toluene, (e) amount of *p*-toluenesulfonic acid, (f) amount of **10**, (g) yield, and (h) *er*.

(a) 40 µL, 0.28 mmol, (b) 35 mg, 0.14 mmol, (c) 1 mL, (d) 10 mL, (e) 11 mg, 0.06 mmol, (f) 18 mg, (g) 49%, and (h) 69:31.

*The data for compound **10** is shown on **page 309**.*

Scheme 18



Synthesis of compound 6

DMP (818 mg, 1.93 mmol) was added to a stirred solution of pyridine (567 µL, 7.01 mmol) alcohol **5** (416 mg, 1.75 mmol) in dry DCM (11 mL) at ambient temperature. The reaction mixture was then stirred for 1 h during which time a white precipitate formed. The reaction mixture was diluted with diethyl ether and DCM was removed *in vacuo*. The mixture was further diluted with diethyl ether and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate and saturated aqueous solution of sodium bicarbonate was added. The organic layer was separated, washed with brine, dried over sodium Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography, (60% diethyl ether in petrol) to yield **6** (266 mg) as a colourless oil with traces of pyridine present.

*The data for compound **6** is shown on **page 310**.*

Synthesis of compound 7

The following experiment was carried out using ***General Procedure A (page 306)***. Data are reported as: (a) amount of lithium chloride, (b) amount of methylmagnesium chloride, (c) amount of substrate **6**, (d) volume of dry THF, and (e) amount of **7**.

(a) 96 mg, 2.26 mmol, (b) 754 µL, 2.26 mmol, 3 M in THF, (c) 266 mg, (d) 2.8 mL, and (e) 154 mg.

*The data for compound **7** is shown on **page 306**.*

Synthesis of compound 8

The following experiment was carried out using ***General Procedure B (page 307)***. Data are reported as: (a) amount of DMSO, (b) amount of oxalyl chloride, (c) volume of dry DCM, (d) amount of substrate **7**, (e) volume of dry DCM, (f) amount of triethylamine, (g) amount of **8**, and (h) yield.

(a) 100 µL, 1.41 mmol, (b) 68 µL, 0.79 mmol, (c) 1.4 mL, (d) 154 mg, (e) 0.5 mL, (f) 425 µL, 3.05 mmol, (g) 64 mg, and (h) 15% over the three steps.

*The data for compound **8** is shown on **page 308**.*

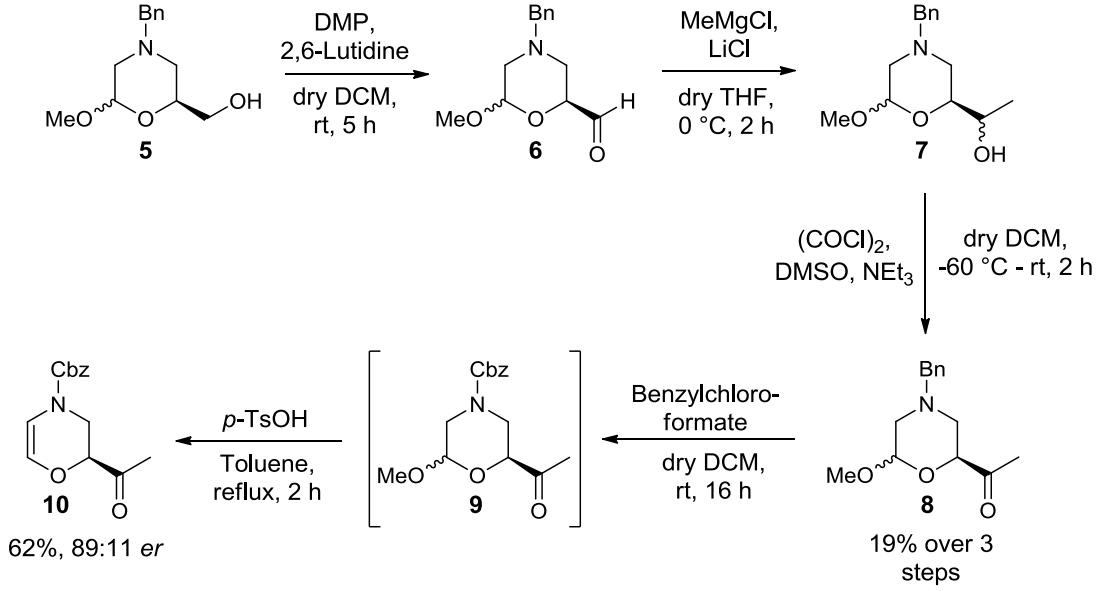
Synthesis of compound 10

The following experiment was carried out using ***General Procedure C (page 308)***. Data are reported as: (a) amount of benzylchloroformate, (b) amount of substrate **8**, (c) volume of dry DCM, (d) volume of toluene, (e) amount of *p*-toluenesulfonic acid, (f) amount of **10**, (g) yield, and (h) *er*.

(a) 76 µL, 0.53 mmol, (b) 66 mg, 0.27 mmol, (c) 1.6 mL, (d) 10.8 mL, (e) 20 mg, 0.11 mmol, (f) 47 mg, (g) 68%, and (h) 86:14.

*The data for compound **10** is shown on **page 309**.*

Scheme 19



Synthesis of compound 6

DMP (871 mg, 2.05 mmol) was added to a stirred solution of 2,6-lutidine (866 µL, 7.48 mmol) alcohol **5** (443 mg, 1.87 mmol) in dry DCM (12 mL) at ambient temperature. The reaction mixture was stirred for 5 h during which time a white precipitate formed. The reaction mixture was diluted with diethyl ether and DCM was removed *in vacuo*. The mixture was further diluted with diethyl ether and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate and saturated aqueous solution of sodium bicarbonate was added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography, (60% diethyl ether in petrol) to yield **6** (397 mg) as a colourless oil with traces of 2,6-lutidine.

*The data for compound **6** is shown on **page 310**.*

Synthesis of compound 7

The following experiment was carried out using ***General Procedure A (page 306)***. Data are reported as: (a) amount of lithium chloride, (b) amount of methylmagnesium chloride, (c) amount of substrate **6**, (d) volume of dry THF, and (e) amount of **7**.

(a) 143 mg, 3.37 mmol, (b) 1.1 mL, 3.37 mmol, 3 M in THF, (c) 397 mg, (d) 4.2 mL, and (e) 241 mg.

*The data for compound **7** is shown on **page 306**.*

Synthesis of compound 8

The following experiment was carried out using ***General Procedure B (page 307)***. Data are reported as: (a) amount of DMSO, (b) amount of oxalyl chloride, (c) volume of dry DCM, (d) amount of substrate **7**, (e) volume of dry DCM, (f) amount of triethylamine, (g) amount of **8**, and (h) yield.

(a) 157 µL, 2.21 mmol, (b) 107 µL, 1.25 mmol, (c) 2.1 mL, (d) 241 mg, (e) 0.7 mL, (f) 669 µL, 4.80 mmol, (g) 88 mg, and (h) 19% over the three steps.

*The data for compound **8** is shown on **page 308**.*

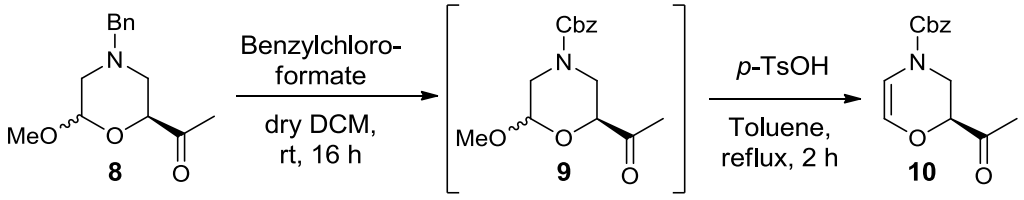
Synthesis of compound 10

The following experiment was carried out using ***General Procedure C (page 308)***. Data are reported as: (a) amount of benzylchloroformate, (b) amount of substrate **8**, (c) volume of dry DCM, (d) volume of toluene, (e) amount of *p*-toluenesulfonic acid, (f) amount of **10**, (g) yield, and (h) *er*.

(a) 101 µL, 0.71 mmol, (b) 88 mg, 0.35 mmol, (c) 2.2 mL, (d) 14 mL, (e) 27 mg, 0.14 mmol, (f) 57 mg, (g) 62%, and (h) 89:11.

*The data for compound **10** is shown on **page 309**.*

Scheme 20**, **Table 1



The following experiment was carried out using ***General Procedure C (page 308)***. Data are reported as: (a) amount of benzylchloroformate, (b) amount of substrate **8**, (c) volume of dry DCM, (d) volume of toluene, (e) amount of *p*-toluenesulfonic acid, (f) amount of **10**, (g) yield, and (h) *er*.

Entry 1: (a) 398 µL, 2.80 mmol, (b) 349 mg, 1.40 mmol, (c) 8.7 mL, (d) 23.3 mL, (e) 106 mg, 0.56 mmol, (f) 220 mg, (g) 60%, and (h) 81:19.

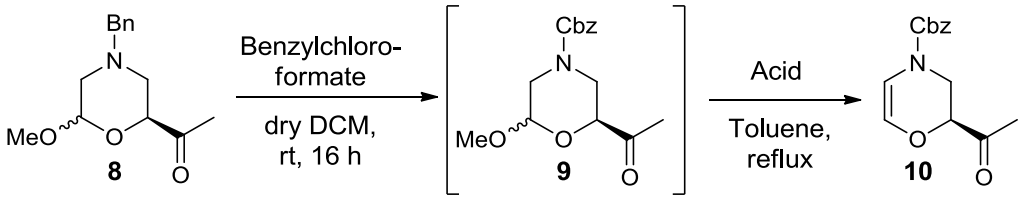
Entry 2: (a) 128 µL, 0.90 mmol, (b) 112 mg, 0.45 mmol, (c) 2.8 mL, (d) 11.3 mL, (e) 34 mg, 0.18 mmol, (f) 79 mg, (g) 68%, and (h) 85:15.

Entry 3: (a) 127 µL, 0.89 mmol, (b) 111 mg, 0.45 mmol, (c) 2.8 mL, (d) 18 mL, (e) 34 mg, 0.18 mmol, (f) 69 mg, (g) 59%, and (h) 90:10.

Entry 4: (a) 56 µL, 0.39 mmol, (b) 49 mg, 0.19 mmol, (c) 1.2 mL, (d) 20 mL, (e) 15 mg, 0.08 mmol, (f) 31 mg, (g) 61%, and (h) 90:10.

*The data for compound **10** is shown on **page 309**.*

Synthesis of compound 10 using different acids:



General Procedure D

Benzylchloroformate was added to a stirred solution of **8** in dry DCM. The mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The resultant oil was then dissolved in toluene and the acid was added to the mixture. The mixture was then stirred at reflux for the required time using Dean-Stark apparatus. The solution was then cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The oil was then purified by column chromatography (0-40% diethyl ether in petrol) to yield **10** as a pale yellow oil.

The following experiments were carried out using ***General Procedure D***. Data are reported as: (a) amount of benzylchloroformate, (b) amount of substrate **8**, (c) volume of dry DCM, (d) volume of toluene, (e) acid utilised, (f) amount of acid, (g) time, (h) amount of **10**, (i) yield, and (j) *er*.

Scheme 21

(a) 118 µL, 0.83 mmol, (b) 103 mg, 0.41 mmol, (c) 2.5 mL, (d) 16.4 mL, (e) methanesulfonic acid, (f) 16 mg, 0.17 mmol, (g) 3 h, (h) 69 mg, (i) 64%, and (j) 91:9.

Scheme 22

Benzylchloroformate (112 µL, 0.79 mmol) was added to a stirred solution of **8** (98 mg, 0.39 mmol) in dry DCM (2.5 mL). The mixture was stirred at ambient

temperature for 16 h before being concentrated *in vacuo*. The resultant oil was then dissolved in toluene (15.6 mL) and Montmorillonite K10 (400 mg) was added the mixture. The mixture was then stirred at reflux for 6 h using Dean-Stark apparatus. The slurry was then cooled to ambient temperature, filtered, and the clay was washed with methanol. The filtrate was concentrated *in vacuo* and the resultant oil was purified by column chromatography (0-40% diethyl ether in petrol) to yield **10** as a pale yellow oil (21 mg, 20%, 94:6 *er*) as well as **9** (30 mg, 25% recovery).

Scheme 23

Benzylchloroformate (77 µL, 0.54 mmol) was added to a stirred solution of **8** (67 mg, 0.27 mmol) in dry DCM (1.7 mL). The mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The resultant oil was then dissolved in toluene (11 mL) and Montmorillonite KSF (400 mg) was added the mixture. The mixture was then stirred at reflux for 3 h using Dean-Stark apparatus. After this time a further quantity of Montmorillonite KSF (200 mg) was added and the reaction mixture was stirred at reflux for a further 3 h. The slurry was then cooled to ambient temperature, filtered, and the clay was washed with methanol. The filtrate was concentrated *in vacuo* and the resultant oil was purified by column chromatography (0-40% diethyl ether in petrol) to yield **10** as a pale yellow oil (6 mg, 9%, >99:1 *er*) as well as **9** (19 mg, 24% recovery).

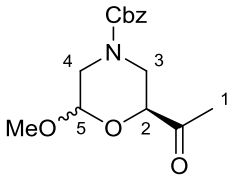
Scheme 24

The following experiments were carried out using ***General Procedure D***. Data are reported as: (a) amount of benzylchloroformate, (b) amount of substrate **8**, (c) volume of dry DCM, (d) volume of toluene, (e) acid utilised, (f) amount of acid, (g) time, (h) amount of **10**, (i) yield, and (j) *er*.

(a) 84 µL, 0.59 mmol, (b) 73 mg, 0.29 mmol, (c) 1.9 mL, (d) 12 mL, (e) *p*-toluenesulfonic acid, (f) 11 mg, 0.058 mmol, (g) 26 h, (h) 24 mg, (i) 31%, and (j) 96:4. Also obtained 40 mg (47% recovery) of **9**.

*The data for compound **10** is shown on **page 309**.*

*(2S)-Benzyl 2-acetyl-6-methoxymorpholine-4-carboxylate, **9***



Chemical Formula: $C_{15}H_{19}NO_5$
Molecular Weight: 293.32

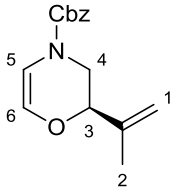
FTIR (CH_2Cl_2): 1705 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 2.26 (s, 2.1H, H1), 2.30 (s, 0.9H, H1), 2.66-3.01 (m, 1.3H, H3, H4), 3.01-3.04 (m, 0.7H, H4), 3.44 (s, 2.1H, OCH_3), 3.58 (s, 0.9H, OCH_3), 3.94-4.45 (m, 3H, H3, H4, H2), 4.46-4.53 (m, 0.3H, H5), 4.72-4.85 (m, 0.7H, H5), 5.11-5.22 (m, 2H, benzylic CH_2), 7.30-7.42 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 25.9, 43.5, 45.6, 46.2, 54.6, 56.0, 67.0, 67.2, 71.8, 77.9, 95.6, 96.0, 99.3, 127.3, 127.6, 127.8, 128.0, 128.1, 135.6, 135.9, 154.7, 155.1 ppm.

HRMS *m/z* (ESI) calc for $C_{15}H_{20}NO_5$ (M^++H): 294.1336. Found: 294.1337.

*(R)-Benzyl 2-(prop-1-en-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, **11***



Chemical Formula: $C_{15}H_{17}NO_3$
Molecular Weight: 259.30

Scheme 25

Potassium *tert*-butoxide (241 mg, 2.15 mmol) was added portionwise to a stirred slurry of methyltriphenylphosphonium bromide (768 mg, 2.15 mmol) in dry THF (13 mL) at 0 ºC. The resultant yellow slurry was stirred at this temperature for 30 min. A solution of **10** (432 mg, 1.65 mmol, 88:12 *er*) in dry THF (4 mL) was added dropwise and the resultant slurry was stirred at 0 ºC for a further 45 min. The mixture

was then warmed to ambient temperature before being quenched with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-20% diethyl ether in petrol) to yield **11** as a pale yellow oil (335 mg, 78%, 78:22 *er*).

Scheme 26

Potassium *tert*-butoxide (33 mg, 0.30 mmol) was added portionwise to a stirred slurry of methyltriphenylphosphonium bromide (124 mg, 0.35 mmol) in dry THF (4 mL) at 0 ºC. The resultant yellow slurry was stirred at this temperature for 30 min before being cooled to – 50 °C. A solution of **10** (70 mg, 0.27 mmol, 88:12 *er*) in dry THF (1 mL) was added dropwise and the resultant slurry was stirred at -50 ºC for a further 45 min before being warmed slowly to ambient temperature. The mixture was then quenched with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-20% diethyl ether in petrol) to yield **11** as a pale yellow oil (8 mg, 12%, 78:22 *er*) as well as recovered ketone **10** (21 mg, 30%, 61:39 *er*).

*The data for compound **10** in shown on **page 309***

Scheme 27

KHMDS (1 mL, 0.50 mmol, 0.5 M in toluene) was added dropwise to a stirred slurry of methyltriphenylphosphonium bromide (211 mg, 0.59 mmol) in dry THF (6 mL) at -78 ºC. The resultant slurry was stirred warmed to 0 °C and stirred at this temperature for 30 min before being cooled to -78 °C. A solution of **10** (110 mg, 0.42 mmol, 88:12 *er*) in dry THF (1.6 mL) was added dropwise and the resultant slurry was stirred at -78 ºC for a further 1 h before being warmed slowly to ambient temperautre. The mixture was then quenched with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was

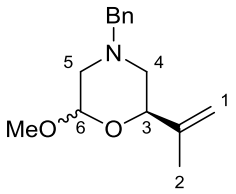
separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-40% diethyl ether in petrol) to yield **11** as a pale yellow oil (73 mg, 68%, 65:35 *er*)

FTIR (CH_2Cl_2): 1665, 1703 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.79-1.82 (m, 3H, H2), 3.17 (dd, ^2J = 13.0 Hz, J = 8.7 Hz, 0.6H, H4), 3.27 (dd, ^2J = 12.8 Hz, J = 8.7 Hz, 0.4H, H4), 4.08 (bd, ^2J = 12.3 Hz, 0.4H, H4), 4.18-4.28 (m, 1.6H, H3, H4), 5.04 (bs, 1H, H1), 5.09 (d, ^2J = 5.6 Hz, 1H, H1), 5.18-5.27 (m, 2H, benzylic CH_2), 6.10 (d, J = 5.0 Hz, 0.6H, H5), 6.12 (d, J = 5.0 Hz, 0.4H, H5), 6.25 (d, J = 4.8 Hz, 0.6H, H6), 6.37 (d, J = 4.8 Hz, 0.4H, H6), 7.32-7.49 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 18.2, 18.3, 44.3, 44.9, 67.2, 75.7, 76.1, 104.7, 105.2, 112.9, 113.2, 127.6, 127.7, 127.8, 128.1, 128.5, 129.6, 135.6, 140.5, 151.4, 151.7 ppm.
HRMS *m/z* (ESI) calc for $C_{15}H_{18}NO_3$ (M^++H): 260.1281. Found: 260.1286.

A 2:3 ratio of rotamers were observed in the ^{1}H NMR.

Chiral HPLC analyisis: Chiracel OD-H column, 10% IPA in *n*-hexane, 0.7 mL/min flow rate, 254 nm detector, t_R (*S*) = 26.3 min and t_R (*R*) = 28.3 min.

(6R)-4-Benzyl-2-methoxy-6-(prop-1-en-2-yl)morpholine, ***12***



Chemical Formula: $C_{15}H_{21}NO_2$
Molecular Weight: 247.33

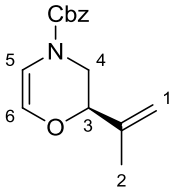
Scheme 29

Potassium *tert*-butoxide (189 mg, 1.68 mmol) was added portionwise to a stirred slurry of methyltriphenylphosphonium bromide (700 mg, 1.96 mmol) in dry THF

(10.5 mL) at 0 ºC. The resultant yellow slurry was stirred at this temperature for 30 min. A solution of **8** (349 mg, 1.40 mmol) in dry THF (3.5 mL) was added dropwise and the resultant slurry was stirred at 0 ºC for a further 45 min. The mixture was then warmed to ambient temperature before being quenched with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-20% diethyl ether in petrol) to yield **12** as a pale yellow oil (241 mg, 70%, 7:3 *dr*).

FTIR (CH_2Cl_2): 1656 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.75-1.77 (m, 3H, H2), 1.89-2.09 (m, 1.6H, H4, H5), 2.23 (d, *J* = 11.9 Hz, 0.4H, H5), 2.77-2.92 (m, 2H, H4, H5), 3.41 (s, 1.2H, OCH_3), 3.47-3.62 (m, 3.8H, OCH_3, benzylic CH_2), 4.06 (d, *J* = 10.4 Hz, 0.6H, H3), 4.41 (d, *J* = 8.1 Hz, 0.4H, H3), 4.55 (d, *J* = 2.5 Hz, 0.6H, H6), 4.72 (bs, 0.4H, H6), 4.99 (s, 1H, H1), 5.01 (s, 0.4H, H1), 5.04 (s, 0.6H, H1), 7.23-7.39 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 19.2, 19.3, 55.1, 55.4, 56.3, 56.6, 62.7, 63.3, 71.2, 97.4, 100.4, 111.7, 111.9, 127.2, 128.2, 128.3, 129.2, 129.5, 136.8, 137.3, 142.8, 143.4 ppm.
HRMS *m/z* (ESI) calc for $C_{15}H_{22}NO_2$ (M^++H): 248.1645. Found: 248.1648.

(R)-Benzyl 2-(prop-1-en-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, ***11***



Chemical Formula: $C_{15}H_{17}NO_3$
Molecular Weight: 259.30

Scheme 30

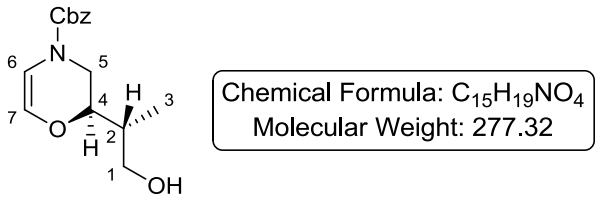
Benzylchloroformate (278 µL, 1.95 mmol) was added to a stirred solution of **12** (241 mg, 0.97 mmol) in dry DCM (6.1 mL). The mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The resultant oil was then

dissolved in toluene (39 mL) and the *p*-toluenesulfonic acid (74 mg, 0.39 mmol) was added the mixture. The mixture was then stirred at reflux for the 1.5 h using Dean-Stark apparatus. The solution was then cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The oil was then purified by column chromatography (0-20% diethyl ether in petrol) to yield **11** as a pale yellow oil (151 mg, 60%, *er* >99:1).

$[\alpha]_D^{24}$ = -41.5 (c=1.0, $CHCl_3$).

*The data for compound **11** is shown on **page 329**.*

*(R)-Benzyl 2-((R)-1-hydroxypropan-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, **14***



Scheme 31

9-BBN (1.9 mL, 0.93 mmol, 0.5 M solution in toluene) was added to a stirred solution of **11** (151 mg, 0.58 mmol) in dry THF (5.8 mL) and the resultant solution was stirred at ambient temperature for 16 h. The reaction mixture was then cooled to 0 °C and water (0.5 mL), followed by 3 M NaOH (1.6 mL) and 30% hydrogen peroxide (1.1 mL) were added. The reaction mixture was stirred for a further 1 h before being diluted with diethyl ether and the organics separated. The aqueous was extracted (x 2) with diethyl ether. The extracts were combined and a saturated aqueous solution of sodium metabisulfite was added and the mixture stirred vigorously for 10 min. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (40-80% diethyl ether in petrol) to yield **14** as a colourless oil (138 mg, 86%).

FTIR (CH_2Cl_2): 1665, 1694, 3477 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 0.99-1.04 (m, 3H, H3), 1.89-2.01 (m, 2H, H2, OH), 3.22 (dd, ^2J = 13.1 Hz, J = 8.7 Hz, 0.7H, H5), 3.35 (dd, ^2J = 12.7 Hz, J = 8.7 Hz, 0.3H, H5), 3.69-3.76 (m, 2H, H1), 3.81-3.88 (m, 1H, H4), 3.97-4.06 (m, 0.3H, H5), 4.13-4.20 (m, 0.7H, H5), 5.16-5.27 (m, 2H, benzylic CH_2), 5.92-5.95 (m, 0.7H, H6), 6.04-6.06 (m, 0.3H, H6), 6.24-6.26 (m, 0.7H, H7), 6.36-6.38 (m, 0.3H, H7), 7.31-7.45 ppm (m, 5H, ArH).

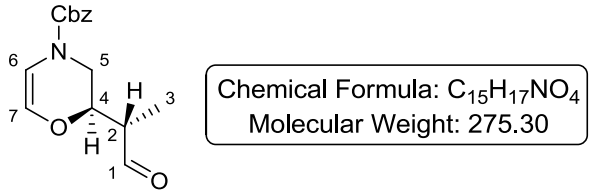
^{13}C NMR (125 MHz, $CDCl_3$): 13.2, 13.3, 37.2, 37.5, 44.0, 44.5, 65.5, 67.7, 67.8, 76.7, 105.7, 106.2, 128.1, 128.3, 128.6, 128.9, 129.3, 136.1, 152.2 ppm.

HRMS *m/z* (ESI) calc for $C_{15}H_{19}NO_4Na$ (M^++Na): 300.1206. Found: 300.1211.

$[\alpha]^{21}_D$= -10.2 (c=0.5, $CHCl_3$).

A ratio of 7:3 of rotamers was observed in the ^{1}H NMR.

(R)-Benzyl 2-((S)-1-oxopropan-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, ***15***



Scheme 32

DMP (232 mg, 0.55 mmol) was added to a stirred solution of alcohol **14** (138 mg, 0.49 mmol) in dry DCM (3.1 mL). The reaction mixture was stirred at ambient temperature for 30 min, during which time a white precipitate formed. The reaction mixture was diluted with diethyl ether and DCM was removed *in vacuo*. The mixture was further diluted with diethyl ether and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate and saturated aqueous solution of sodium bicarbonate was added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography, (20-60% diethyl ether in petrol) to yield **15** as a colourless oil (112 mg, 81%).

FTIR (CH_2Cl_2): 1662, 1699 cm^{-1}.

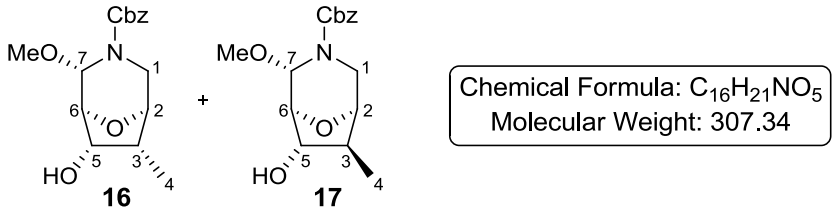
^{1}H NMR (400 MHz, $CDCl_3$): 1.14-1.26 (m, 3H, H3), 2.60-2.72 (m, 1H, H2), 3.34 (dd, ^2J = 12.7 Hz, J = 7.7 Hz, 0.6H, H5), 3.42 (dd, ^2J = 13.0 Hz, J = 7.9 Hz, 0.4H, H5), 3.95-4.20 (m, 2H, H4, H5), 5.17-5.26 (m, 2H, benzylic CH_2), 5.91 (d, J = 5.0 Hz, 0.6H, H6), 6.05 (d, J = 4.8 Hz, 0.4H, H6), 6.27 (d, J = 5.0 Hz, 0.6H, H7), 6.39 (d, J = 4.9 Hz, 0.4H, H7), 7.33-7.44 (m, 5H, ArH), 9.71-9.80 ppm (m, 1H, H1).

^{13}C NMR (100 MHz, $CDCl_3$): 9.68, 42.7, 43.2, 47.1, 47.3, 67.4, 73.2, 73.7, 105.2, 105.8, 127.6, 127.7, 127.8, 127.9, 128.1, 128.8, 135.4, 201.4, 201.6 ppm.

$[\alpha]_D^{23}$ = +1.3 (c=0.5, $CHCl_3$).

Due to the sensitive nature of the substrate accurate mass spectral details could not be obtained.

(1S,2S,5R,6R,7S)-Benzyl 7-hydroxy-2-methoxy-6-methyl-8-oxa-3-azabicyclo[3.2.1] octane-3-carboxylate ***16*** *and (1S,2S,5R,6S,7S)-benzyl 7-hydroxy-2-methoxy-6-methyl-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate* ***17***



Scheme 33

Methanol (33 µL, 0.82 mmol) followed by *p*-toluenesulfonic acid (8 mg, 0.04 mmol) were added to a stirred solution of **15** (112 mg, 0.41 mmol) in acetonitrile (4.1 mL) at ambient temperature. The reaction mixture was stirred for 16 h before being quenched with a saturated aqueous solution of sodium bicarbonate. The solution was diluted with diethyl ether and the organics were separated. The aqueous layer was extracted with diethyl ether (x 2) and the combined organic extracts were dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column

chromatography (100% diethyl ether) to yield **16**/**17** as a colourless oil (65 mg, 52%, 7:3 *dr*).

FTIR (CH_2Cl_2): 1679, 3488 cm^{-1}.

16/17 Mixture

^{1}H NMR (400 MHz, $CDCl_3$): 1.10-1.27 (m, 3H, H4), 1.82-2.13 (m, 1.3H, OH, H3), 2.12-2.37 (m, 0.7H, H3), 3.27-4.30 (m, 8H, H1, H2, H5, H6, OCH_3), 4.96-5.27 (m, 3H, H7, benzylic CH_2), 7.30-7.45 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 12.6, 12.7, 14.8, 19.1, 19.2, 29.8, 39.2, 39.4, 43.4, 44.6, 45.2, 45.3, 53.0, 54.8, 55.0, 55.5, 65.4, 67.1, 67.4, 73.2, 73.5, 77.5, 78.0, 79.0, 79.8, 80.0, 80.1, 80.5, 81.1, 81.5, 82.0, 83.8, 84.2, 127.4, 127.5, 127.6, 127.7, 127.8, 128.0, 128.1, 128.2, 135.4, 135.5, 155.3, 155.8 ppm.

***Compound 16** (major diastereomer)*

^{1}H NMR (400 MHz, $CDCl_3$): 1.10 (d, J = 2.2 Hz, 1.5H, H4), 1.12 (d, J = 2.2 Hz, 1.5H, H4), 1.82 (bs, 1H, OH), 2.23-2.37 (m, 1H, H3), 3.29 (s, 1.5H, OCH_3), 3.34 (dd, ^2J = 13.0 Hz, J = 2.3 Hz, 0.5H, H1), 3.40-3.45 (m, 2H, H1, OCH_3), 3.55 (bd, ^2J = 12.1 Hz, 0.5H, H1), 3.63 (bd, ^2J = 12.9 Hz, 0.5H, H1), 3.97 (s, 0.5H, H2), 4.04 (s, 0.5H, H2), 4.14 (d, J = 0.9 Hz, 0.5H, H6), 4.17 (d, J = 7.7 Hz, 0.5H, H5), 4.21-4.25 (m, 1H, H5, H6), 4.98 (d, J = 1.3 Hz, 0.5H, H7), 5.10 (d, J = 1.2 Hz, 0.5H, H7), 5.13-5.27 (m, 2H, carbamate CH_2), 7.31-7.45 ppm (m, 5H, ArH).

A 1:1 ratio of rotamers were observed in the ^{1}H NMR.

***Compound 17** (minor diastereomer)*

^{1}H NMR (600 MHz, $CDCl_3$): 1.19-1.23 (m, 3H, H4), 1.80-1.85 (m, 0.4H, H3), 1.87-1.92 (m, 0.6H, H3), 3.30 (s, 1.2H, OCH_3), 3.39-3.42 (m, 2.4H, OCH_3, H1), 3.47-3.51 (0.4H, H1), 3.63-3.67 (m, 0.4H, H1), 3.74-3.76 (m, 1H, H1, H2), 3.83 (bs, 0.6H, H2), 3.94-3.98 (m, 1H, H5), 4.15-4.18 (m, 0.6H, H6), 4.23-4.26 (m, 0.4H, H6), 5.14-5.21 (m, 2H, benzylic CH_2), 5.21 (bs, 0.6H, H7), 5.29 (bs, 0.4H, H7), 7.29-7.38 ppm (m, 5H, ArH).

A 3:2 ratio of rotamers were observed in the ^1H NMR.

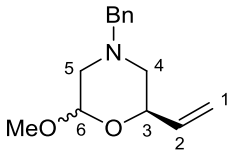
HRMS *m/z* (ESI) calc for $C_{16}H_{21}NO_5Na$ (M^++Na): 330.1312. Found: 330.1316.

Compound 16: $[\alpha]_D^{23}$= + 18.5 (c=1, $CHCl_3$). (Major) (>99:1 *er*)

Compound 17: $[\alpha]_D^{23}$= +16.5 (c=0.65, $CHCl_3$). (Minor)

Major diastereomer: chiral HPLC analysis: C2 (ID 2) column, 30% ethanol in *n*-hexane, 2 mL/min flow rate, 254 nm detector, t_R (minor) = 7.8 min and t_R (major) = 9.4 min.

(6R)-4-Benzyl-2-methoxy-6-vinylmorpholine, ***19***



Chemical Formula: $C_{14}H_{19}NO_2$
Molecular Weight: 233.31

Scheme 35

KHMDS (2.3 mL, 1.15 mmol, 0.5 M in toluene) was slowly added to a stirred mixture of aldehyde **6** (246 g, 1.05 mmol) and methyltriphenylphosphonium bromide (410 mg, 1.15 mmol) in dry THF (12 mL) at -78 ºC. The resultant mixture was then warmed to -50 °C and stirred at this temperature for 50 min during which time the reaction mixture turned bright yellow in colour. The reaction was then warmed to ambient temperature and quenched with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-30% diethyl ether in petrol) to yield **19** as a pale yellow oil (110 mg, 45%, 2:3 *dr*).

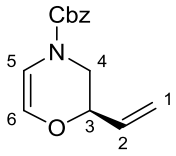
FTIR (CH_2Cl_2): 1649 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 1.89-2.04 (m, 1.6H, H4, H5), 2.26 (dd, ^2J = 11.6 Hz, J = 2.8, 0.4H, H5), 2.70-2.93 (m, 2H, H4, H5), 3.43 (s, 1.2H, OCH_3), 3.53-3.56 (m, 3.8H, OCH_3, benzylic CH_2), 4.12-4.18 (m, 0.6H, H3), 4.46-4.52 (m, 0.4H, H3), 4.52 (dd, J = 8.5 Hz, J = 2.4, 0.6H, H6), 4.73 (bd, J = 2.4 Hz, 0.4H, H6), 5.16-5.21 (m, 1H, H1), 5.30-5.38 (m, 0.4H, H1), 5.61 (dt, J = 7.3 Hz, ^4J = 1.5 Hz, 0.6H, H1), 5.76-5.91 (m, 1H, H2), 7.28-7.36 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 54.6, 54.9, 55.9, 56.0, 56.6, 56.8, 62.1, 62.7, 74.0, 96.9, 99.9, 115.9, 116.2, 126.7, 126.8, 127.7, 127.8, 128.7, 128.9, 135.1, 135.7, 136.3, 136.9 ppm.

HRMS *m/z* (ESI) calc for $C_{14}H_{20}NO_2$ (M^++H): 234.1489. Found: 234.1483.

(R)-Benzyl 2-vinyl-2H-1,4-oxazine-4(3H)-carboxylate, ***21***



Chemical Formula: $C_{14}H_{15}NO_3$
Molecular Weight: 245.27

General Procedure E

Benzylchloroformate was added to a stirred solution of **19** in dry DCM. The mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The resultant oil was then dissolved in toluene and *p*-toluenesulfonic acid was added to the mixture. The mixture was then stirred at reflux for 2 h using Dean-Stark apparatus. The solution was then cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The oil was then purified by column chromatography (0-30% diethyl ether in petrol) to yield **21** as a pale yellow oil.

Scheme 36

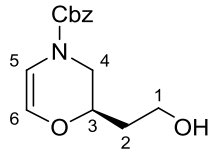
The following experiments were carried out using ***General Procedure E***. Data are reported as: (a) amount of benzylchloroformate, (b) amount of substrate **19**, (c) volume of dry DCM, (d) volume of toluene, (e) amount of *p*-toluenesulfonic acid, (f) amount of **21**, and (g) yield.

(a), 107 µL, 0.75 mmol, (b) 110 mg, 0.47 mmol, (c) 3 mL, (d) 18.8 mL, (e) 36 mg, 0.19 mmol, (f) 77 mg, and (g) 67%.

FTIR (CH_2Cl_2): 1701, 1662 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 3.20-3.33 (m, 1H, H4), 3.97-4.02 (m, 0.4H, H4), 4.08-4.13 (m, 0.6H, H4), 4.35-4.45 (m, 1H, H3), 5.22 (s, 2H, benzylic CH_2), 5.30-5.36 (m, 1H, H1), 5.40-5.47 (m, 1H, H1), 5.82-5.94 (m, 1H, H2), 5.97 (d, *J* = 5.0 Hz, 0.6H, H5), 6.10 (d, *J* = 5.0 Hz, 0.4H, H5), 6.24 (d, *J* = 5.0 Hz, 0.6H, H6), 6.37 (d, *J* = 5.0 Hz, 0.4H, H6), 7.32-7.45 ppm (m, 5H ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 45.8, 45.5, 67.2, 71.4, 73.1, 73.6, 104.8, 105.3, 117.7, 117.9, 127.5, 127.6, 127.7, 127.8, 128.1, 128.2, 129.1, 129.3, 133.1, 135.6 ppm.
HRMS *m/z* (ESI) calc for $C_{14}H_{19}N_2O_3$ (M^++NH_4): 246.1125. Found: 246.1128.

A 2:3 ratio of rotamers were observed in the ^{1}H NMR.

(R)-Benzyl 2-(2-hydroxyethyl)-2H-1,4-oxazine-4(3H)-carboxylate, ***22***



Chemical Formula: $C_{14}H_{17}NO_4$
Molecular Weight: 263.29

General Procedure F

9-BBN was added to a stirred solution of **21** in dry THF and the resultant solution was stirred at ambient temperature for 16 h. The reaction mixture was then cooled to

0 °C and water, followed by 3 M NaOH and 30% hydrogen peroxide, were added. The reaction mixture was then stirred for a further 1 h before being diluted with diethyl ether and the organics separated. The aqueous layer was extracted (x 2) with diethyl ether. The extracts were combined and a saturated aqueous solution of sodium metabisulfite was added and the mixture stirred vigorously for 10 min. The organic layer were separated, dried over Na_2SO_4, and concentrated *in vacuo*. The oil was then purified by column chromatography (40-80% diethyl ether in petrol) to yield **22** as a colourless oil.

Scheme 37

The following experiment was carried out using the ***General Procedure F***. Data are reported as: (a) amount of 9-BBN, (b) amount of substrate **21**, (c) volume of dry THF, (d) amount of water, (e) amount of 3 M NaOH, (f) amount of 30% hydrogen peroxide, (g) amount of **22**, (h) yield, and (i) *er*.

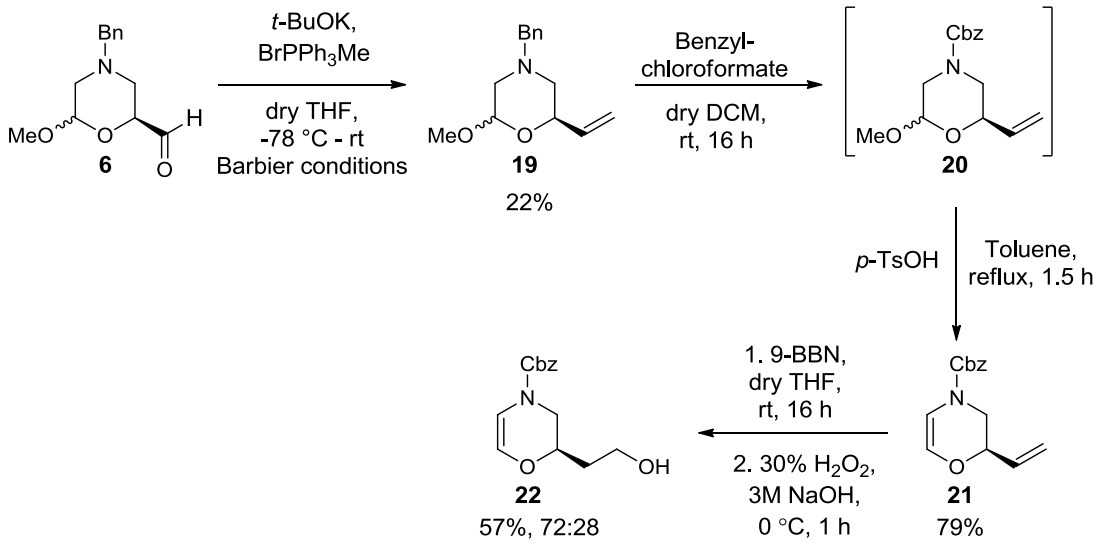
(a) 1.6 mL, 0.80 mmol, 0.5 M in THF, (b) 100 mg, 0.40 mmol, (c) 4 mL, (d) 0.4 mL, (e) 1.1 mL, (f) 0.8 mL, (g) 60 mg, (h) 57%, and (i) 88:12.

FTIR (CH_2Cl_2): 1662, 1697, 3414 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 1.81-1.92 (m, 3H, H2, OH), 3.18 (dd, ^2J = 12.8 Hz, J = 8.3 Hz, 0.6H, H4), 3.26 (dd, ^2J = 13.1 Hz, J = 8.4 Hz, 0.4H, H4), 3.80-3.87 (m, 2H, H1) 4.05-4.16 (m, 2H, H3, H4), 5.20 (s, 2H, benzylic CH_2), 5.88 (d, J = 5.0 Hz, 0.6H, H5), 6.02 (d, J = 5.0 Hz, 0.4H, H5), 6.23 (d, J = 5.0 Hz, 0.6H, H6), 6.36 (d, J = 5.0 Hz, 0.4H, H6), 7.31-7.43 ppm (m, 5H, ArH).
^{13}C NMR (125 MHz, $CDCl_3$): 34.6, 34.7, 45.6, 46.3, 59.4, 67.7, 67.7, 71.7, 72.3, 105.5, 106.0, 128.1, 128.3, 128.6, 129.3, 136.1, 151.9, 152.2 ppm.
HRMS *m/z* (ESI) calc for $C_{14}H_{18}NO_4$ (M^++H): 264.1230. Found: 264.1223.

A 2:3 ratio of rotamers were observed in the ^{1}H NMR.

Chiral HPLC analyisis: Chiracel OD-H column, 1% IPA in *n*-hexane, 1 mL/min flow rate, 254 nm detector, t_R (*S*) = 24.1 min and t_R (*R*) = 26.8 min.

Scheme 38



Synthesis of compound 19

t-BuOK (129 mg, 1.15 mmol) was slowly added to a stirred mixture of aldehyde **6** (270 mg, 1.15 mmol) and methyltriphenylphosphonium bromide (615 mg, 1.72 mmol) in dry THF (12 mL) at -78 ºC. The resultant mixture was then warmed to -50 °C and stirred at this temperature for 50 min during which time the reaction mixture turned bright yellow in colour. The reaction was then warmed to ambient temperature and quenched with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-30% diethyl ether in petrol) to yield **19** as a pale yellow oil (60 mg, 22%).

*The data for compound **19** is shown on **page 336**.*

Synthesis of compound 21

The following experiments were carried out using ***General Procedure E (page 336)***. Data are reported as: (a) amount of benzylchloroformate, (b) amount of substrate **19**, (c) volume of dry DCM, (d) volume of toluene, (e) amount of *p*-toluenesulfonic acid, (f) amount of **21**, and (g) yield.

(a) 73 µL, 0.51 mmol, (b) 60 mg, 0.26 mmol, (c) 1.6 mL, (d) 10.4 mL, (e) 20 mg, 0.10 mmol, (f) 50 mg, and (g) 79%.

*The data for compound **21** is shown on **page 337**.*

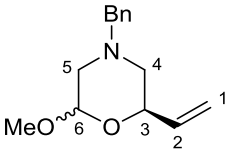
Synthesis of compound 22

The following experiment was carried out using the ***General Procedure F (page 337)***. Data are reported as: (a) amount of 9-BBN, (b) amount of substrate **21**, (c) volume of dry THF, (d) amount of water, (e) amount of 3 M NaOH, (f) amount of 30% hydrogen peroxide, (g) amount of **22**, (h) yield, and (i) *er*.

(a) 0.8 mL, 0.4 mmol, 0.5 M in THF, (b) 50 mg, 0.20 mmol, (c) 2 mL, (d) 0.2 mL, (e) 0.6 mL, (f) 0.4 mL, (g) 31 mg, (h) 57%, and (i) 72:28.

*The data for compound **22** is shown on **page 338**.*

(6R)-4-Benzyl-2-methoxy-6-vinylmorpholine, ***19***



Chemical Formula: $C_{14}H_{19}NO_2$
Molecular Weight: 233.31

Scheme 39, Table 2

Entry 1:

Trimethylaluminium (0.85 mL, 1.70 mmol) was added a flask containing titanocene dichloride (212 mg, 0.85 mmol) at ambient temperature and the resultant red solution was stirred for 3 days. After the 3 days, the red solution was cooled to -78 °C and aldehyde **6** (200 mg, 0.85 mmol) as a dry THF solution (1 mL) was added dropwise. The resultant solution was then stirred at -78 °C for 1 h before being warmed to ambient temperature and stirred for a further 3 h. After this time 5 drops of 1 M sodium hydroxide was then added over 10 min. Stirring was continued until gas evolution ceased, and then sodium sulfate was added to the resultant orange solution. The mixture was then filtered through a bed of celite and the celite washed with diethyl ether. The filtrate was then concentrated *in vacuo*, and the resultant oil purified by column chromatography (0-30% diethyl ether in petrol) to yield **19** as a pale yellow oil (50 mg, 25%, 7:3 *dr*).

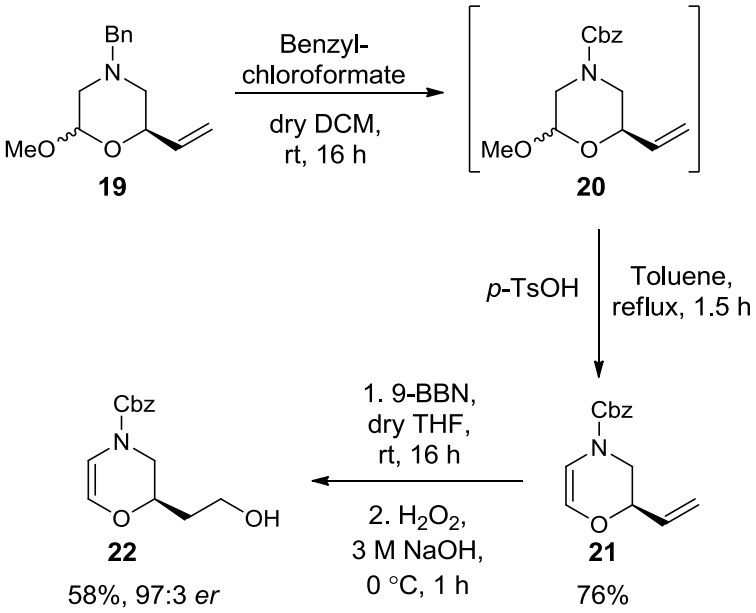
Entry 2:

Trimethylaluminium (0.85 mL, 1.70 mmol) was added a flask containing titanocene dichloride (212 mg, 0.85 mmol) at ambient temperature and the resultant red solution was stirred for 3 days. After the 3 days the red solution was cooled to -78 °C and aldehyde **6** (200 mg, 0.85 mmol) as a dry THF solution (1 mL) was added dropwise. The resultant solution was then stirred at -50 °C for 3 h before being warmed to ambient temperature and stirred for a further 2 h. After this time 5 drops of 1 M sodium hydroxide was then added over 10 min. Stirring was continued until gas

evolution ceased, and then sodium sulfate was added to the resultant orange solution. The mixture was then filtered through a bed of celite and the celite washed with diethyl ether. The filtrate was then concentrated *in vacuo*, and the resultant oil purified by column chromatography (0-30% diethyl ether in petrol) to yield **19** as a pale yellow oil (35 mg, 18%, 7:3 *dr*) as well as **6** (54 mg, 27% recovery).

*The data for compound **19** is shown on **page 336** and the data for compound **6** is shown on **page 310**.*

Scheme 40



Synthesis of compound 21

The following experiments were carried out using ***General Procedure E (page 336)***. Data are reported as: (a) amount of benzylchloroformate, (b) amount of substrate **19**, (c) volume of dry DCM, (d) volume of toluene, (e) amount of *p*-toluenesulfonic acid, (f) amount of **21**, and (g) yield.

(a) 61 µL, 0.43 mmol, (b) 50 mg, 0.21 mmol, (c) 1.3 mL, (d) 8.4 mL, (e) 16 mg, 0.08 mmol, (f) 40 mg, (g) 76%.

$[\alpha]_D^{22}$= -19.7 (c=1.0, $CHCl_3$). (94% *ee*).

*The data for compound **21** is shown on **page 337**.*

Synthesis of compound 22

The following experiment was carried out using the ***General Procedure F (page 337)***. Data are reported as: (a) amount of 9-BBN, (b) amount of substrate **21**, (c) volume of dry THF, (d) amount of water, (e) amount of 3 M NaOH, (f) amount of 30% hydrogen peroxide, (g) amount of **22**, (h) yield, and (i) *er*.

(a) 0.7 mL, 0.33 mmol, 0.5 M in THF, (b) 40 mg, 0.16 mmol, (c) 1.6 mL, (d) 0.2 mL, (e) 0.5 mL, (f) 0.3 mL, (g) 25 mg, (h) 58%, and (i) 97:3.

$[\alpha]_D^{25}$= -12.7 (c=1.0, $CHCl_3$). (94% *ee*).

*The data for compound **22** is shown on **page 338**.*

5. References

1. R. Bogacki, D. M. Gill, W. J. Kerr, S. Lamont, J. A. Parkinson and L. C. Paterson, *Chem. Commun.*, 2013, **49**, 8931.
2. A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165.
3. I. C. Gonzalez and C. J. Forsyth, *J. Am. Chem. Soc.*, 2000, **122**, 9099.
4. V. Caprio, M. A. Brimble and D. P. Ruhmann, *Tetrahedron*, 2001, **57**, 4023.
5. U. Reiser, J. Jauch and E. Herdtweek, *Tetrahedron: Asymmetry*, 2000, **11**, 3345.
6. G. Nagendrappa, *Resonance*, 2002, **7(1)**, 64.
7. C. H. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 1959, **81**, 247.
8. F. N. Tebbe, G. W. Parshall and G. S. Reddy, *J. Am. Chem. Soc.*, 1979, **100**, 3611.
9. R. H. Grubbs, S. H. Pine, In *Comprehensive Organic Synthesis*; B. M. Trost, Ed.; Pergamon Press: New York, 1991, **5**, 1115.
10. B. E. Love and E. G. Jones, *J. Org. Chem.*, 1999, **64**, 3755.
11. S. Hoppen, S. Baurle and U. Koert, *Chem. Eur. J.*, 2000, **6**, 2382.

Chapter Three:

Bridged Piperazines

Table of Contents

1. Proposed Work

As discussed in the introductory section, bridged heterocycles have emerged as desirable targets within the pharmaceutical industry. More specifically, AstraZeneca have become interested in exploring the bioactivity of bridged piperazines (**Figure 1**), and as previously illustrated, there are a lack of routes into these types of scaffolds which allow for diversification.

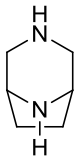
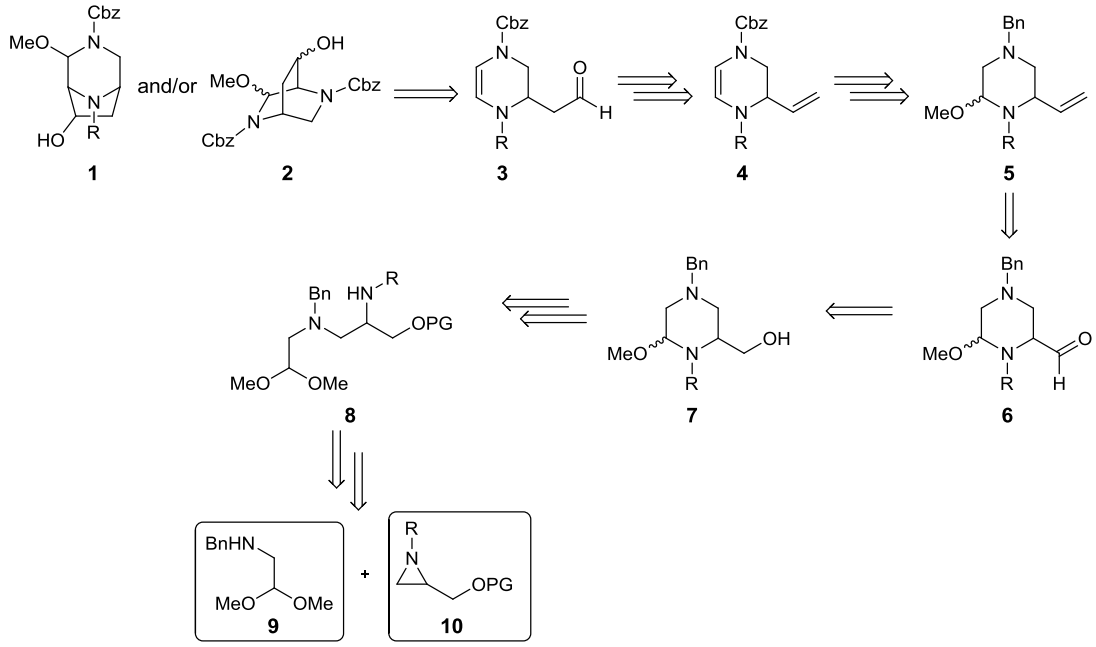


Figure 1

Having disclosed a preparatively flexible strategy to access a series of novel bridged morpholines (**Chapter 1**),[1] it was proposed that this methodology could be used to access alternative bridged heterocycles, such as bridged piperazines. It was proposed that the synthesis of bridged piperazines could be accessed using an aziridine (such as **10**) in combination with amine acetal **9** (**Scheme 1**).



Scheme 1

The route would employ similar synthetic steps which were utilised during the bridged morpholine synthesis, however, within the bridged piperazine route, it was envisaged that aldehyde **3** could cyclise by two different pathways to give different products (**1** or **2**) (**Figure 2**). One possibility would be for **3** to cyclise by the same pathway which constructed the bridged morpholines. This pathway would involve the "top" nitrogen reacting initially, leading to the synthesis of bridged piperazine **1**. The second possible pathway would involve the cyclisation initiating from the "bottom" nitrogen, and this would lead to the [2.2.2] system (**2**) being synthesised.

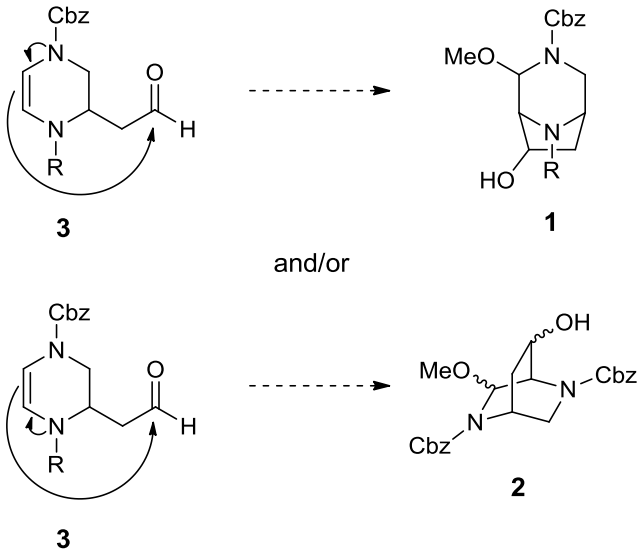


Figure 2

Within the bridged morpholine synthesis, glycidol was used as the starting epoxide, which was commercially available. However, the corresponding requisite aziridine for the bridged piperazine synthesis was unfortunately not commercially available (**Figure 3**).

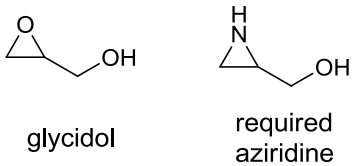
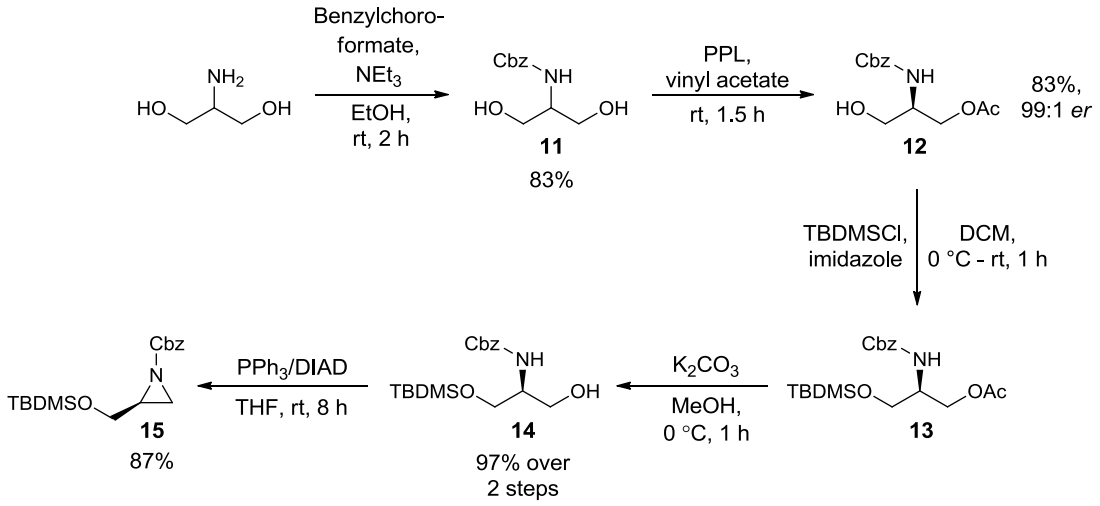


Figure 3

In this regard, a literature indicated that Choi and Borch had disclosed a paper in which they had synthesised aziridine **15**, an intermediate it was anticipated could be utilised in the synthesis of the bridged piperazines.[2] Furthermore, they had been able to synthesise the aziridine with extremely high levels of enantioselectivity by employing an enzyme-mediated desymmetrisation reaction of diol **11** (**Scheme 2**). Their synthetic route began with commercially available serinol, which was initially carboxybenzyl protected. The diol (**11**) was then subjected to the enzyme-mediated desymmetrisation reaction, which utilised a pig pancreatic lipase in combination with vinyl acetate, to produce intermediate **12** with high levels of enantioselectivity (99:1 *er*). The free hydroxyl group in **12** was then silyl protected, and the acetate functionality was subsequently removed to produce **14** in an excellent yield over the two steps. Finally, **14** was subjected to Mitsunobu conditions to synthesise the desired aziridine **15** in high yield.[2]



Borch et al.

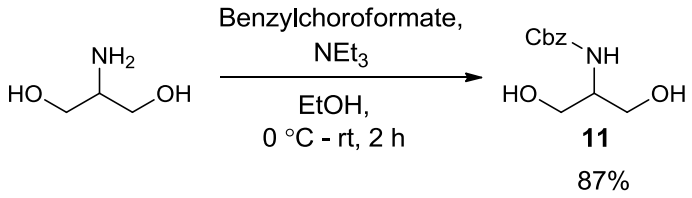
Scheme 2

In order to investigate the proposed synthetic pathway to create a novel route into a range of differentially functionalised bridged piperazines, the aziridine synthesis developed by Choi and Borch would initially have to be performed.

2. Results and Discussion

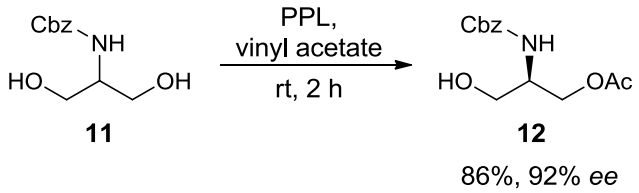
*2.1 Synthesis of Aziridine **15***

In order to investigate the synthesis of these novel bridged piperazine motifs, the aziridine had to be synthesised. As previously mentioned, the initial step in the synthesis was the protection of the primary amine in serinol with benzylchloroformate. The reaction was found to be successful with diol **11** being obtained in an 87% yield (**Scheme 3**).



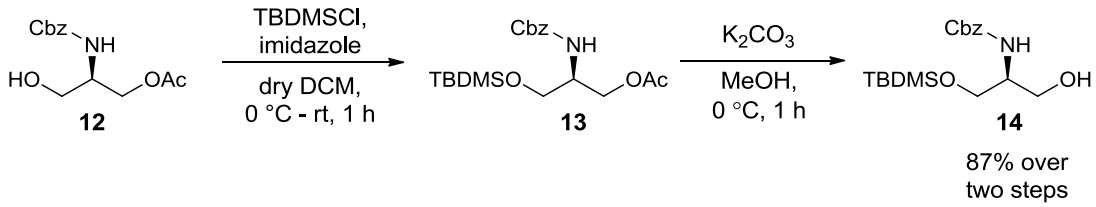
Scheme 3

Diol **11** was then subjected to the enzyme-mediated desymmetrisation conditions, which produced **12** in an excellent yield of 86%, with an *ee* of 92% (**Scheme 4**).



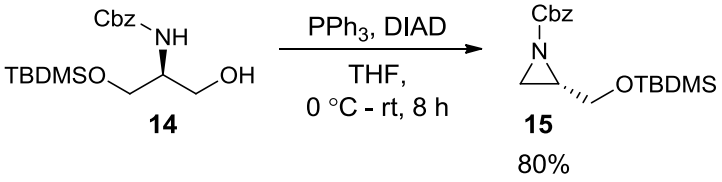
Scheme 4

Following the successful desymmetrisation reaction, silyl protection of the free alcohol unit, and subsequent cleavage of the ester group was performed. This two-step process worked successfully with alcohol **14** being obtained in a high 87% yield over the two steps (**Scheme 5**).



Scheme 5

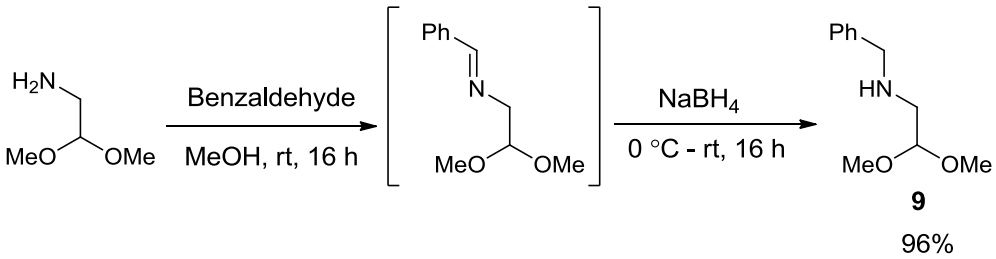
Utilising the Mitsunobu reaction,[3] alcohol **14** successfully cyclised to produce the desired aziridine in high overall yield (**Scheme 6**).



Scheme 6

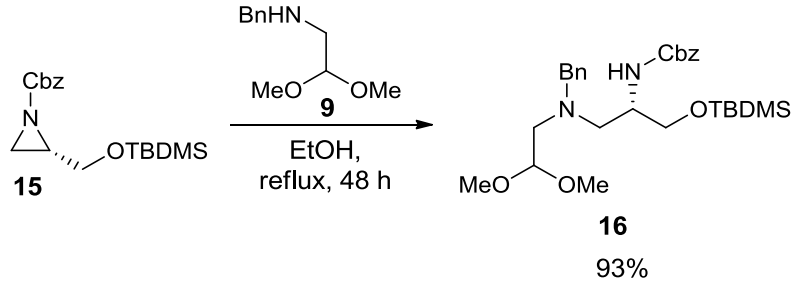
2.2 Synthesis of Bridged Piperazines

The next stage in the synthesis involved opening aziridine **15** with the benzyl protected amine acetal **9**. Before this reaction could be investigated, the amine itself required protection. The primary amine, which is commercially available, was benzyl protected *via* a reductive amination reaction to produce **9** in near quantitative yield (**Scheme 7**).



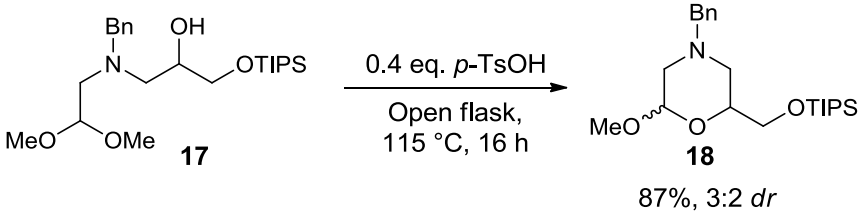
Scheme 7

With the desired aziridine and protected amine acetal now in hand, an investigation into the synthesis of the bridged piperazines could be initiated. This investigation began with the ring opening of the aziridine using the amine acetal. This regioselective ring opening reaction took 48 h to proceed to completion, however, an excellent yield of 93% of amine alkyl chain **16** was obtained (**Scheme 8**).



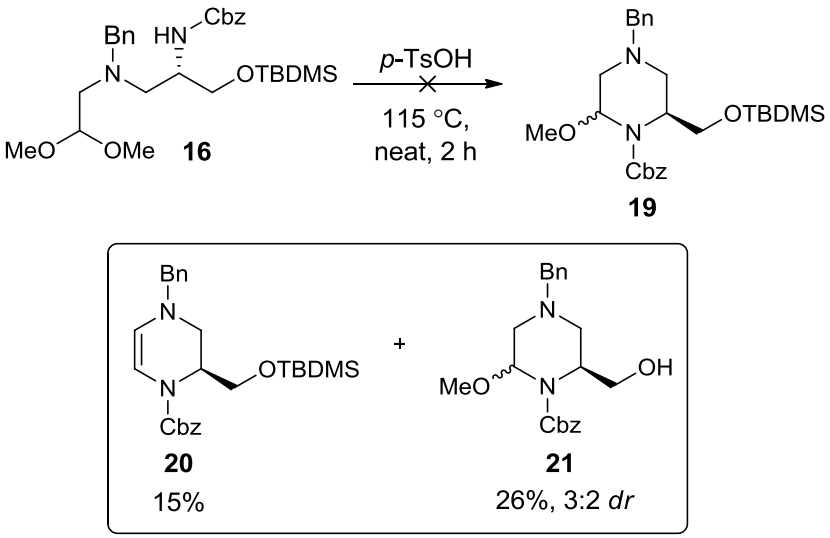
Scheme 8

The next step in the synthesis involved the ring closure of **16** to form the piperazine core. The initial attempt at this cyclisation reaction involved utilising the conditions that were used during the bridged morpholine synthesis to construct the morpholine moiety **18** (**Scheme 9**) (see **Chapter 1**).



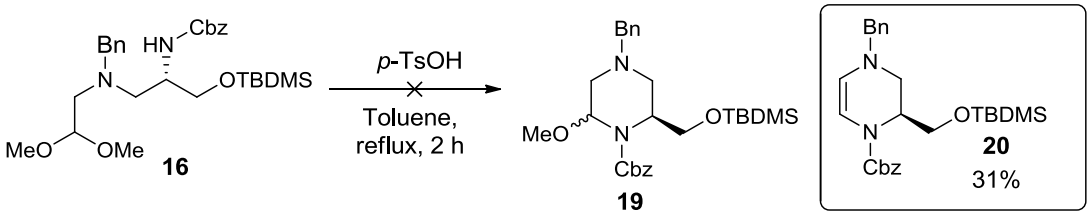
Scheme 9

Under the above conditions, it was found that after only 2 h no starting material was observed by TLC analysis (**Scheme 10**). Unfortunately, none of the desired product was obtained from the reaction, and instead, 15% of the eliminated compound **20** was obtained, in addition to 26% of piperazine **21**, whereby the alcohol had been deprotected. It should be noted that the cyclisation to compound **21** produced a 3:2 mixture of the two diastereomers.



Scheme 10

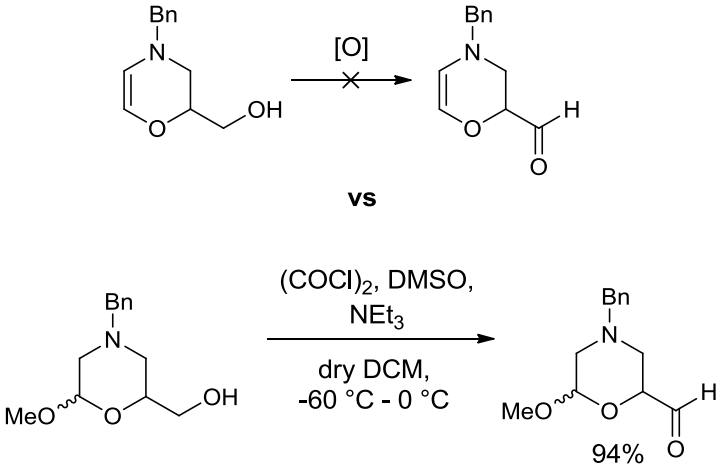
It was thought that the neat reaction conditions were possibly too harsh, therefore a reaction diluted with toluene was performed (**Scheme 11**). After 2 h, no starting material was observed by TLC analysis, however, none of the desired product was obtained, and instead a 31% yield of the eliminated product (**20**) was again isolated. It should also be noted that under these conditions none of the deprotected compound **21** was isolated from this reaction.



Scheme 11

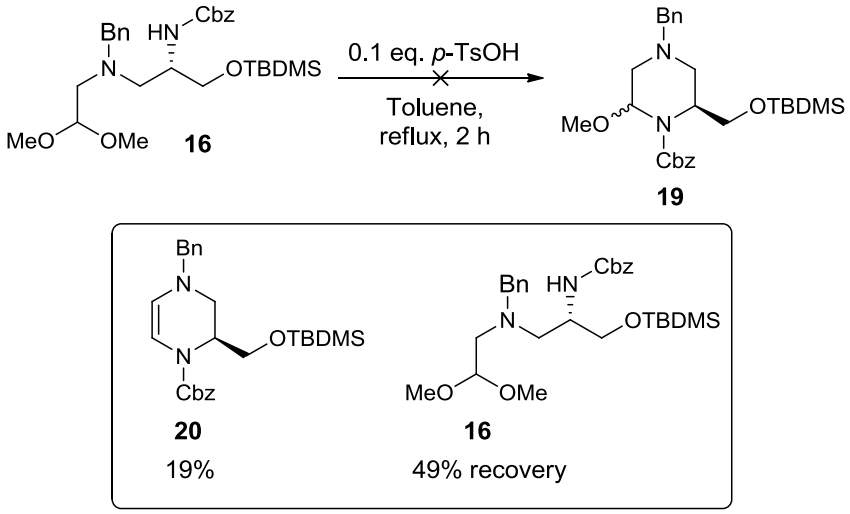
Although the eliminated product could be an alternative intermediate in the synthesis towards the bridged piperazines, there was a concern as to whether, once deprotected, the free alcohol would successfully undergo an oxidation reaction to form the required aldehyde. This concern was due a similar compound synthesised during the bridged morpholine series, which did not undergo an oxidation reaction

with the double bond present, with only decomposition product obtained. In contrast, when the double bond was not present, the oxidation to the aldehyde occurred in high yield (**Scheme 12**).



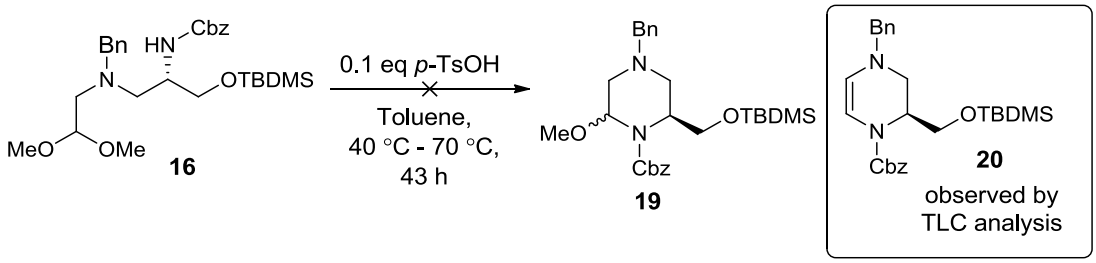
Scheme 12

It was for this reason that the synthesis of the non-eliminated product was further investigated. The next reaction performed involved using only 0.1 eq. of acid (compared to 0.4 eq.) with toluene as the solvent. After only 2 h, the eliminated product was again observed by TLC analysis, with none of the desired product being observed (**Scheme 13**).



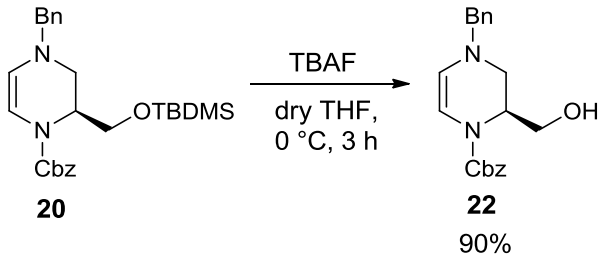
Scheme 13

In an attempt to supress the elimination reaction, a temperature study was carried out (**Scheme 14**). When performing the reaction at 40 °C, after 4 h only starting material was observed by TLC analysis, therefore the reaction temperature was increased to 50 °C. After a further 3 h, again only the amine alkyl chain was present in the reaction mixture. The temperature was further increased to 60 °C, however, after a further 16 h no reaction appeared to have occurred. After increasing the temperature to 70 °C and stirring at this temperature for 4 h, it was frustrating to observe the undesired eliminated product by TLC analysis. Unfortunately, when the reaction was left at this temperature for a further 16 h, only the eliminated product was present.



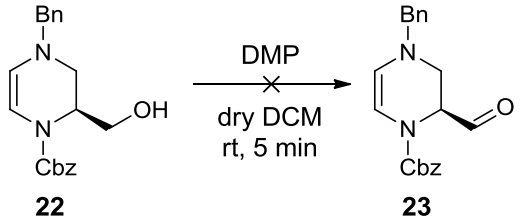
Scheme 14

Since the non-eliminated product was proving a challenge to synthesise, and the eliminated moiety **20** had been obtained in every case, it was decided to investigate the oxidation of the free alcohol **22**. In this regard, **20** was initially deprotected using TBAF, with the free alcohol being obtained in a 90% yield (**Scheme 15**).



Scheme 15

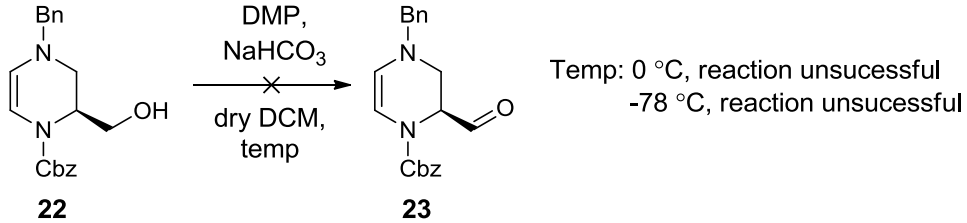
In the first instance, it was decided to employ the mild oxidant Dess-Martin periodinane in an attempt to oxidise alcohol **22** to the corresponding aldehyde (**Scheme 16**). Unfortunately, after only 5 min the reaction had turned dark brown in colour, therefore the reaction was stopped. Upon analysis of the crude ^{1}H NMR spectrum, no aldehyde peak was observed and, in fact, the spectrum was extremely complex with no starting material peaks identifiable.



22 **23**

Scheme 16

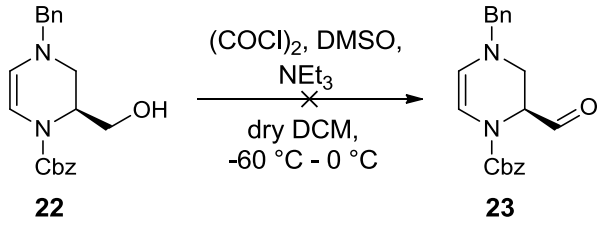
The subsequent reaction performed involved adding sodium hydrogen carbonate into the reaction mixture to ensure that the reaction was being performed under near neutral conditions. In addition, the reaction was cooled to 0 °C before the oxidant was added. After the reaction had been stirring for only 10 min, the reaction mixture was brown in colour. Subsequently, on working up the reaction and analysing the crude ^{1}H NMR spectrum, no aldehyde peak was observed, as well as no starting material peaks being identified. A final attempt to perform this oxidation with DMP involved repeating the reaction with the addition of the base, as well as cooling the reaction to -78 °C before the oxidant was added. After 20 min the TLC plate showed a streak, therefore the reaction was quenched at -78 °C. Unfortunately, as with the previous DMP attempts, analysis of the crude ^{1}H NMR spectrum revealed only degradation products.



22 **23**

Scheme 17

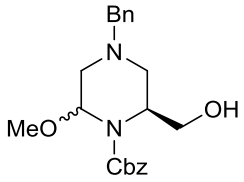
The final attempt to oxidise alcohol **22** involved the use of standard Swern conditions (**Scheme 18**).[4] It was observed that on addition of the alcohol to the reaction mixture, the colour of the reaction turned brown in colour. Disappointingly, on warming the reaction to 0 °C and working the reaction up, only degradation products were observed by ^{1}H NMR analysis.



22 **23**

Scheme 18

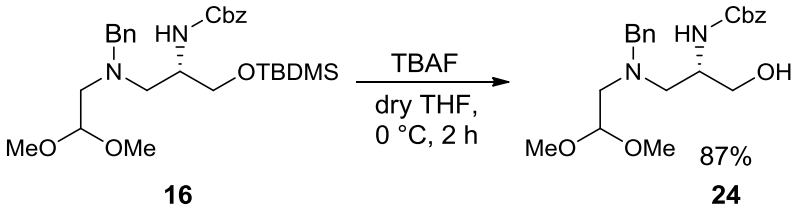
Since the oxidation of the alcohol functionality proved to be unsuccessful with the olefin in place, an alternative strategy was sought. Whilst attempting to cyclise intermediate **16** (see **Scheme 10**), the non-eliminated deprotected compound **21** was isolated (**Figure 4**), in addition to eliminated compound **20**. As such, it was decided to oxidise this substrate in an attempt to push on towards the desired piperazine targets.



21

Figure 4

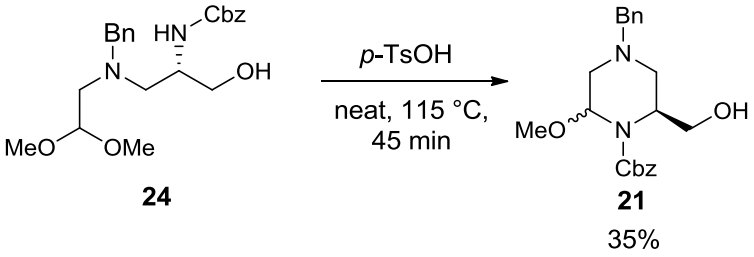
In an attempt to solely form **21**, the silyl group was initially removed from the amine alkyl chain **16**. This deprotection was successfully performed under TBAF conditions to produce the free alcohol in an 87% yield (**Scheme 19**).



16 **24**

Scheme 19

With the deprotected chain in hand, attention turned to the cyclisation reaction. The initial attempt at the cyclisation was performed using neat conditions with catalytic *p*-toluenesulfonic acid (**Scheme 20**). The reaction was complete after only 45 min, however, only a poor yield of 35% of the desired cyclised non-eliminated product was obtained.



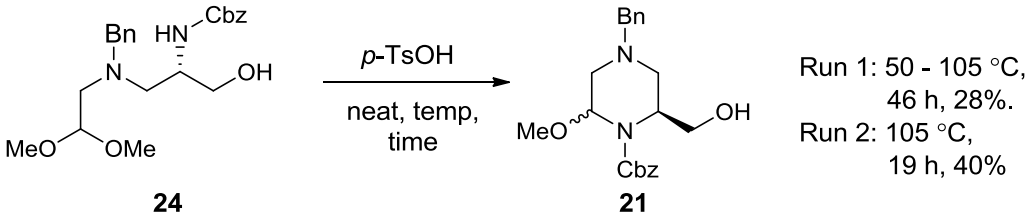
24 **21**

35%

Scheme 20

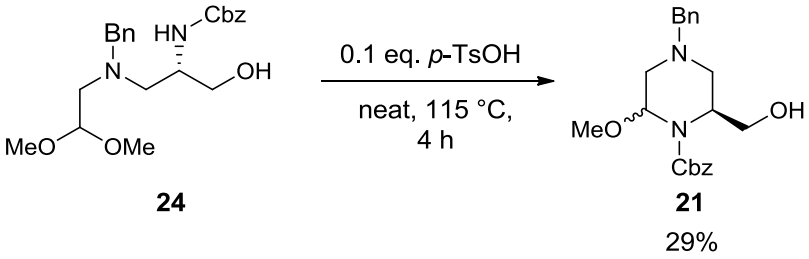
To optimise this reaction a temperature study was performed (**Scheme 21**). The oil bath was initially set to 50 °C and the neat reaction was placed into the pre-heated oil bath. After 4 h it was shown by TLC analysis that no reaction had taken place, as only the starting amine alkyl chain was observed. The oil bath was therefore heated to 70 °C, and the reaction was left stirring for 16 h. After this time, it was again shown by TLC analysis that no reaction had taken place. To try and initiate the reaction, the oil bath temperature was increased to 105 °C. After 2 h TLC analysis revealed that the cyclisation reaction was beginning to take place, therefore the reaction was left stirring at 105 °C until no starting material was observed. After a further 24 h the reaction appeared to have gone to completion, however, a disappointing yield of 28% of the desired product was obtained (**Scheme 21**, **Run 1**). Due to the reaction being heated for 20 h prior to being heated at 105 °C for 26 h the

reaction was repeated with the initial temperature being set to 105 °C. This reaction took 19 h to go to completion with a slightly improved yield of 40% being obtained (**Scheme 21**, **Run 2**).



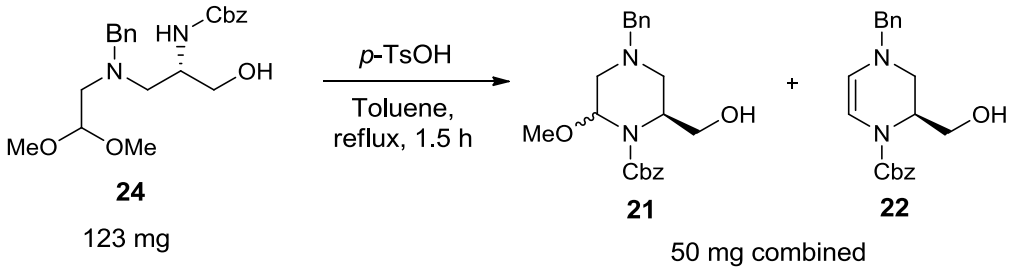
Scheme 21

All previous reactions to cyclise amine alkyl chain **24**, utilised 0.3 eq. of acid, therefore it was decided to trial a reaction whereby only 0.1 eq. of the acid was used. When this reaction was performed the reaction took only 4 h to go to completion, however, a lower yield of 29% of the desired product was obtained.



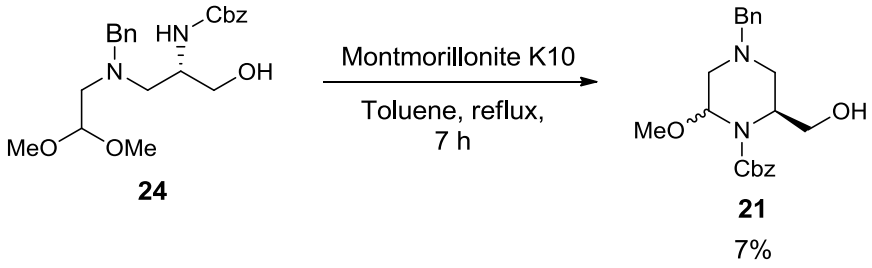
Scheme 22

In an attempt to improve the yield, it was decided to use less harsh conditions by using toluene as a solvent rather than performing the reaction neat (**Scheme 23**). After 1.5 h, no starting material was observed by TLC analysis, however, upon inspection of the ^{1}H NMR spectrum it was found that not only had the desired product formed, but the eliminated product had also been synthesised. In addition, the mass balance for this reaction was poor, as only 50 mg of the combined products (inseparable by column chromatography) was obtained from 123 mg of the starting alcohol.



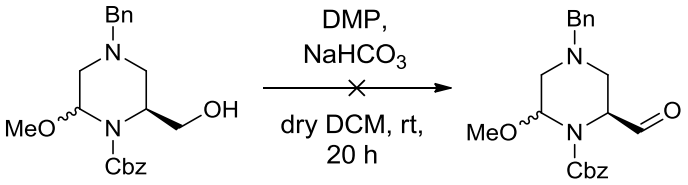
Scheme 23

With the above reactions, utilising *p*-toluenesulfonic acid, seemingly proving to be too harsh, the focus turned to the use of an acid clay, Montmorillonite K10.[5] It was pleasing to find that the amine alkyl chain did cyclise, however, the desired product was only obtained in a 7% yield.



Scheme 24

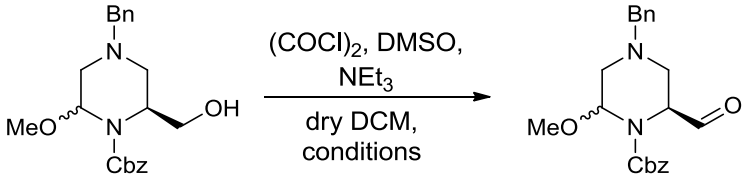
Before attempting to optimise this reaction any further, it was decided to determine if the oxidation of **21** would take place at all. The initial reaction that was performed utilised DMP as the oxidant with the addition of sodium hydrogen carbonate (**Scheme 25**). The reaction was performed at ambient temperature using 1.4 eq. of DMP, however, after 4 h none of the desired aldehyde was observed by TLC analysis, with only the starting alcohol present. A further 0.6 eq. of DMP was therefore added and the reaction was stirred for a further 16 h. After this time, no aldehyde was present, with only the alcohol being observed by TLC analysis. In order to check that it was indeed the alcohol that was being observed by TLC analysis, the reaction was stopped. The crude ^{1}H NMR spectrum revealed only the starting alcohol to be present, and on purifying the mixture by column chromatography the alcohol was recovered in an 80% yield.



21 **25**

Scheme 25

As DMP was not successful in oxidising alcohol **21** to its corresponding aldehyde **25**, attention turned to utilising the Swern reaction (**Scheme 26**, **Table 1**). The reaction was performed at -60 °C, and after addition of the triethylamine the reaction was warmed to ambient temperature and quenched (**Entry 1**). It was again discovered that the oxidation had not taken place, with 81% of the alcohol being recovered (no aldehyde peak was observed in the crude ^{1}H NMR spectrum). In an attempt to promote this reaction, following addition of the alcohol, the reaction was stirred at -50 °C for 5 h prior the addition of triethylamine and warming to ambient temperature (**Entry 2**). The reaction was performed this way as the "activated" DMSO species formed in the reaction mixture becomes unstable and decomposes at temperatures above -20 °C, therefore, if the alcohol has not reacted with the "activated" DMSO species by the time the reaction reaches -20 °C, no reaction will take place.[6] Despite this, it was found that when performing the reaction in this fashion no reaction had taken place, as again no aldehyde peak was observed in the crude ^{1}H NMR spectrum, and 83% of the alcohol was recovered.



21 **25**

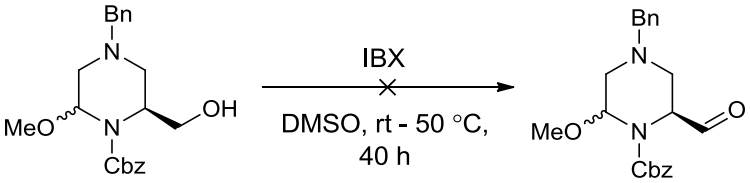
Scheme 26

Entry	*Conditions*	*Yield (%)*	*Recovered 21 (%)*
1	-60 °C → rt	-	81
2[a]	-60 °C → -50 °C → rt	-	83

[a] Reaction held at -50 °C for 5 h

Table 1

Due to the Swern reaction proving to be unsuccessful, alternative oxidation conditions were sought. The next reaction performed utilised the oxidant IBX. The reaction was performed at ambient temperature, and after leaving the reaction to stir for 20 h only the alcohol was observed by TLC analysis. The reaction was therefore heated to 40 °C, however, after 4 h at this temperature only starting material was present. The temperature was further increased to 50 °C for a further 16 h, however, after this time none of the desired product or the starting alcohol were observed in the crude ^{1}H NMR spectrum.



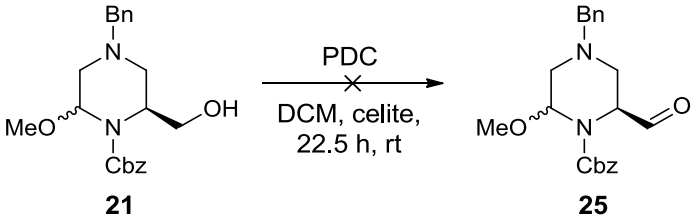
21 **25**

Scheme 27

At this stage, and on further analysis of the IR spectrum of alcohol **21**, it was noted that the hydroxyl unit was hydrogen bonding to, presumably, the carbonyl group of the carbamate unit (OH stretch was 3335 cm^{-1}), which could be prohibiting the oxidation reaction from taking place.

With the hydrogen bond in mind, it was decided to use the stronger chromium-based oxidant, PDC (**Scheme 28**). After a 4.5 h reaction time, it was shown by TLC analysis that only the starting alcohol was present in the reaction mixture, therefore a further quantity of PDC was added. The reaction was left stirring for further 18 h, however, it was disappointing to observe only starting material after this time. As

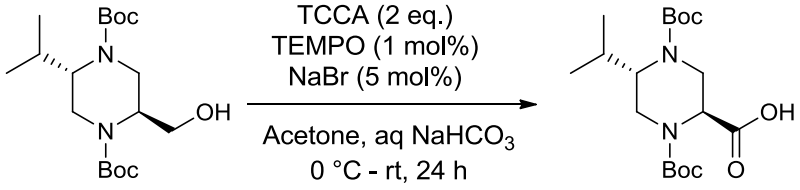
such, the reaction was stopped at this point, and it was discovered that although the alcohol was being observed by TLC analysis, only a 12% recovery was obtained, showing that the alcohol was not stable to these oxidation conditions.



21 **25**

Scheme 28

At this stage, an attempt was then made to synthesise the carboxylic acid derivative instead of the aldehyde to check if the stability of the aldehyde was also a problem. This was trialled using a procedure developed by Giacomelli *et al*., which involved the use of catalytic TEMPO, in addition to TCCA (**Scheme 29**).[7]

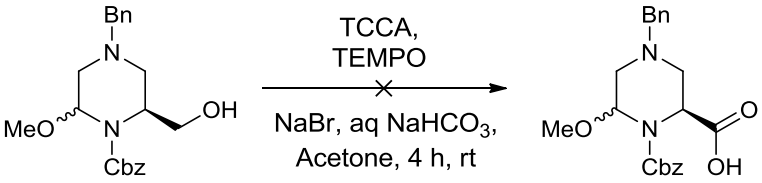


100% Conversion

Giacomelli et al.

Scheme 29

When applying these oxidation conditions to alcohol **21**, it was found that after 4 h the carboxylic acid had not formed, with only degradation products being observed (**Scheme 30**).



21 **26**

Scheme 30

Having attempted various unsuccessful oxidation conditions on alcohol **21**, with a high recovery of the alcohol being obtained from several of the reaction protocols, it was decided to synthesise a protected piperazine which would not be able to form a hydrogen bond with the alcohol, since this was assumed to be prohibiting the oxidation from occurring (**Figure 5**).

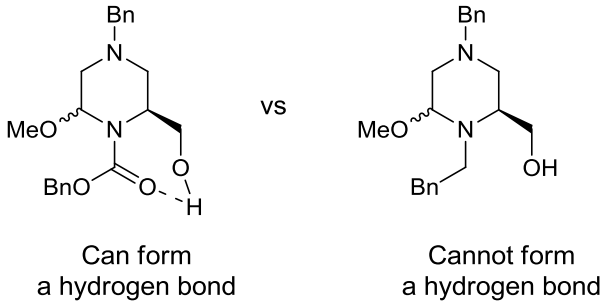
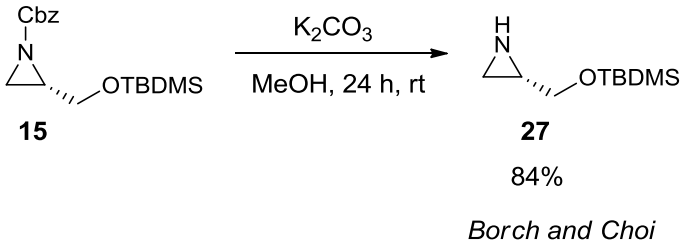


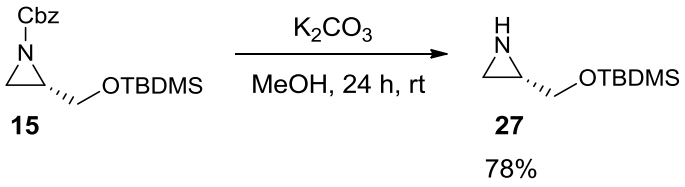
Figure 5

In this regard, due to the challenges of removing the carbamate group, whilst leaving the aminal functionality in place, as well as the other nitrogen benzyl protected, it was decided to access the required substrate by synthesising the benzyl protected aziridine. In addition to this, Choi and Borch had shown that the carboxybenzyl protected aziridine could be deprotected simply by using potassium carbonate in conjunction with methanol to produce the deprotected aziridine **27** in an 84% yield (**Scheme 31**).[2] It was therefore proposed that this free aziridine would be synthesised and, subsequently, benzyl protected.



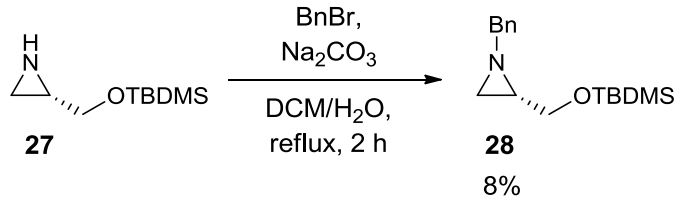
Scheme 31

In this regard, the deprotection of the aziridine was performed, and the free aziridine was obtained in a 78% yield (**Scheme 32**).



Scheme 32

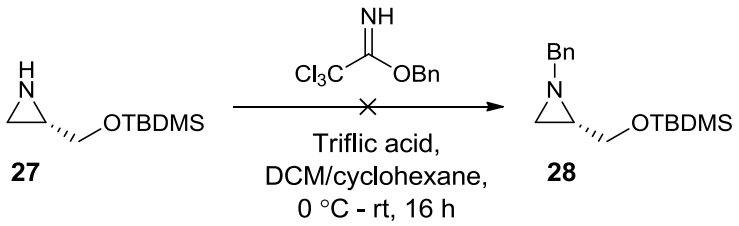
With the unprotected aziridine in hand, an investigation into the benzyl protection could now be initiated. The first reaction to be performed involved the use of benzyl bromide in addition to sodium carbonate, with the reaction going to completion after refluxing for 2 h. Although the desired benzyl protected aziridine had been synthesised, a poor yield of only 8% was obtained (**Scheme 33**).



Scheme 33

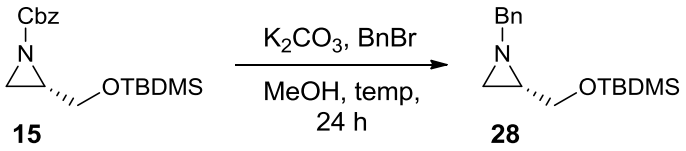
In an effort to improve this yield, alternative conditions were utilised. These conditions involved the use of benzyl 2,2,2-trichloroacetimidate in conjunction with

catalytic acid (**Scheme 34**). Unfortunately, under these conditions none of the desired product was obtained, with only degradation products being observed.



Scheme 34

It was thought that the unprotected aziridine was relatively unstable, therefore, it was decided to perform a one pot process in order to avoid isolating the free aziridine. Potassium carbonate was required for the deprotection step, and a base is also needed when utilising benzyl bromide, therefore it was anticipated that by adding benzyl bromide into the deprotection reaction mixture at the start, a one pot process could be achieved. It was pleasing to find that under these alternative conditions the benzyl protected aziridine was produced in a 48% yield over two steps (**Scheme 35**, **Table 2**, **Entry 1**). In an attempt to improve this yield further, the reaction was performed at 0 °C rather than ambient temperature. By performing the reaction at a lower temperature, the desired product was still obtained, however, the yield did not improve (**Entry 2**).

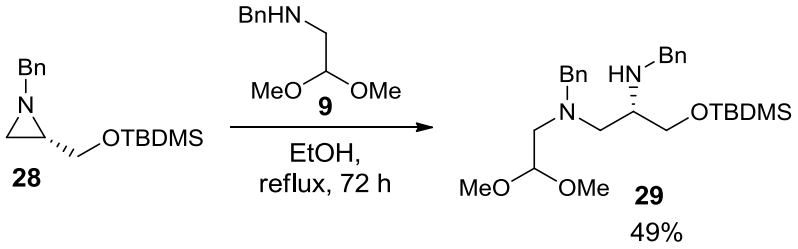


Scheme 35

Entry	*Temperature*	*Yield (%)*
1	Ambient temperature	48
2	0 °C	48

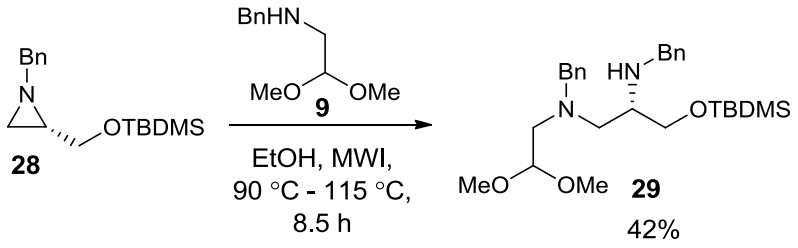
Table 2

Having now synthesised the benzyl protected aziridine, research into the ring opening with the benzyl protected amine acetal **9** could commence. When the aziridine was heated to reflux in ethanol with amine acetal **9**, it was found that 72 h were required in order for the reaction to go to completion. After this time, only a moderate yield of 49% was obtained (**Scheme 36**).



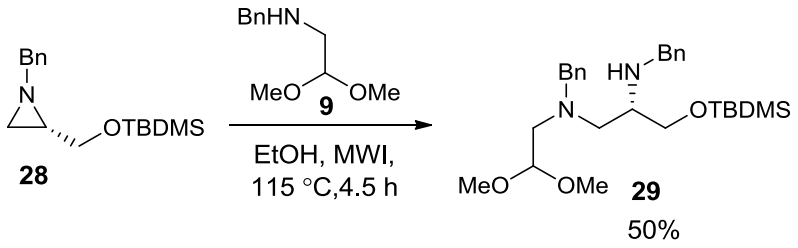
Scheme 36

In attempts to reduce the reaction time from 72 h, microwave irradiation was employed. The reaction was initially heated to 90 °C with the cooling function on. After 3.5 h at this temperature the aziridine was still observed by TLC analysis, therefore the temperature was increased to 115 °C. The reaction required a further 5 h in order for all the aziridine to react, with the desired product being obtained in a moderate 42% yield (**Scheme 37**).



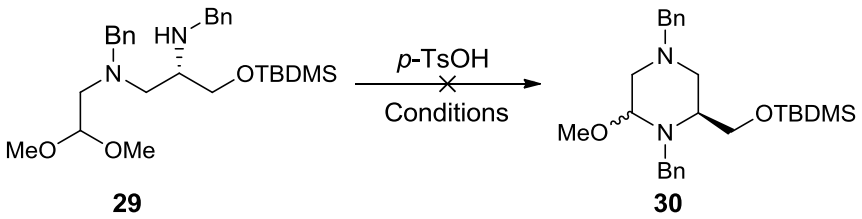
Scheme 37

When the reaction was repeated using the microwave, and starting the reaction temperature at 115 °C, it was found that using a slightly larger excess of the amine acetal allowed the reaction to proceed to completion in only 4.5 h, with a slightly improved yield of 50% being obtained (**Scheme 38**).



Scheme 38

The next step in the synthesis to the bridged piperazines involved the ring closure of the amine alkyl chain **29**. The initial reaction carried out involved performing the reaction neat with a catalytic amount of *p*-toluenesulfonic acid, and placing the reaction mixture into a pre-heated oil bath at 115 °C. When performing this reaction it was found that after 4 h no reaction appeared to have occurred, and after a further 16 h, decomposition products were obtained. It was proposed that under such conditions the secondary amine moiety was becoming protonated, therefore, prohibiting the desired protonation of the methoxy group, and ultimately preventing the cyclisation from occurring. A reaction was therefore carried out using 1.2 eq. of acid, however, within 1 h the starting material had decomposed.

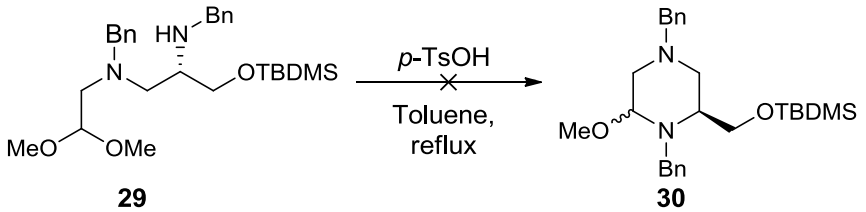


Scheme 39

Entry	*Conditions*	*Yield (%)*	*Recovered 29 (%)*
1	0.4 eq. acid, neat, 115 °C, 20 h	-	-
2	1.2 eq. acid, neat, 115 °C, 1 h	-	-

Table 3

In further efforts to try and promote the cyclisation reaction, milder reaction conditions were utilised. It was initially decided to use toluene as the solvent with super-stoichiometric amounts of acid (**Scheme 40**, **Table 4**). When trialling the reaction with toluene it was also decided to start the reaction at a lower temperature, therefore the reaction was initially performed at 50 °C. After stirring the reaction at this temperature for 4 h, only the amine alkyl chain was observed by TLC analysis. The reaction temperature was therefore increased to 60 °C, from which it was found that after a further 16 h stirring only the starting material was observed by TLC analysis. As no reaction had taken place, the reaction temperature was further increased to 70 °C. It was found that after a further 4 h at this temperature a streak was observed on the TLC plate, therefore the reaction was stopped. Disappointingly, only degradation products were obtained from this reaction. A final attempt at using *p*-toluenesulfonic acid was performed in toluene using sub-stoichiometric amounts of the acid. The reaction was initially performed at 80 °C, however, after 16 h only starting material was observed by TLC analysis. In an attempt to promote the reaction, the temperature was increased to 100 °C. However, after a further 16 h it was disappointing to see by TLC analysis that only the amine alkyl chain was present, therefore, the reaction temperature was further increased to reflux. On monitoring the reaction it was found that after 6 h the material had unfortunately decomposed.

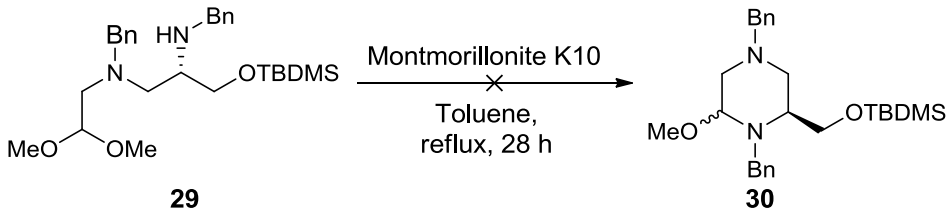


Scheme 40

Entry	***Conditions***	***Yield (%)***	***Recovered 29 (%)***
1	1.2 eq. acid, toluene, 50 - 70 °C, 24 h	-	-
2	0.4 eq. acid, toluene, 80 °C – reflux, 38 h	-	-

Table 4

A final attempt to cyclise **29** utilised the acid clay, Montmorillonite K10 (**Scheme 41**). The reaction was initially performed in refluxing toluene, however, after 6 h TLC analysis revealed that only the starting material was present in the reaction mixture, therefore another portion of the acid clay was added. After stirring the reaction for a further 16 h at reflux, it was disappointing to again only see the starting material by TLC analysis. In an attempt to promote the reaction, another portion of the acid clay was added, however, within the next 6 h only the starting material was observed on the TLC plate, which then became increasingly faint, until nothing was observed. On filtering off the clay, and washing the clay with methanol, nothing was retrieved from the reaction. It was therefore presumed that **29** was absorbing onto the clay as the reaction progressed.



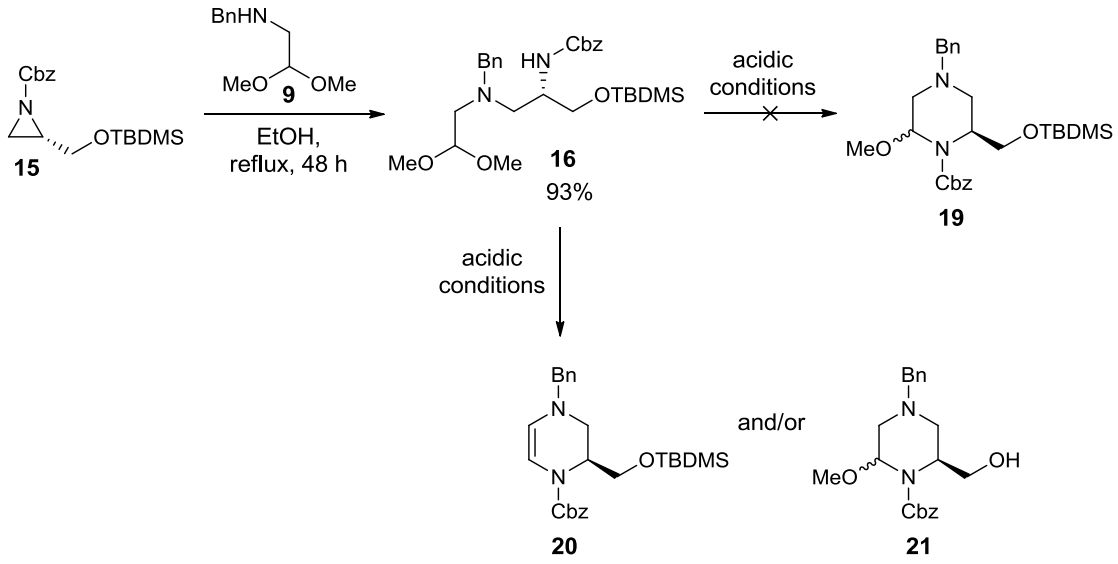
29 **30**

Scheme 41

At the outset of this project it was anticipated that a similar approach to that used to synthesise the bridged morpholines could be employed for the synthesis of a range of bridged piperazines. However, many unexpected challenges were faced, and due to time constraints, further research into this route was halted at this stage.

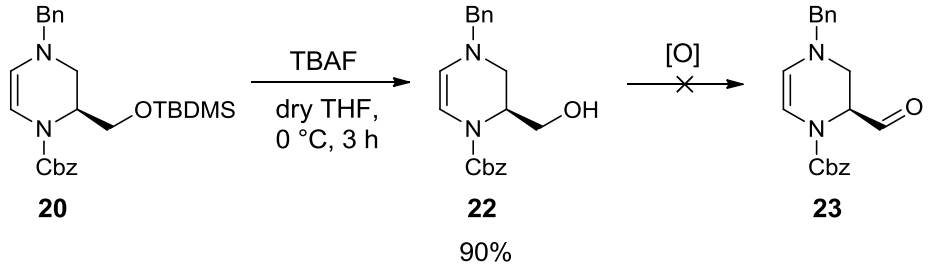
3. Conclusions and Future Work

Following a very successful project in which a range of bridged morpholine products were delivered in both a racemic and asymmetric form, it was anticipated that this research could be extended towards the preparation of bridged piperazine targets. In this regard, aziridine **15** was successfully obtained using a procedure developed by Borch and Choi,[2] and was regioselectively opened with the benzyl protected amine acetal **9** to produce amine alkyl chain **16** in an excellent yield. Efforts where then made to cyclise **16** to obtain the piperazine derivative **19**. However, it was realised that under a variety of conditions **19** was not obtained, with eliminated product **20** and/or the free alcohol compound **21** isolated instead (**Scheme 42**).



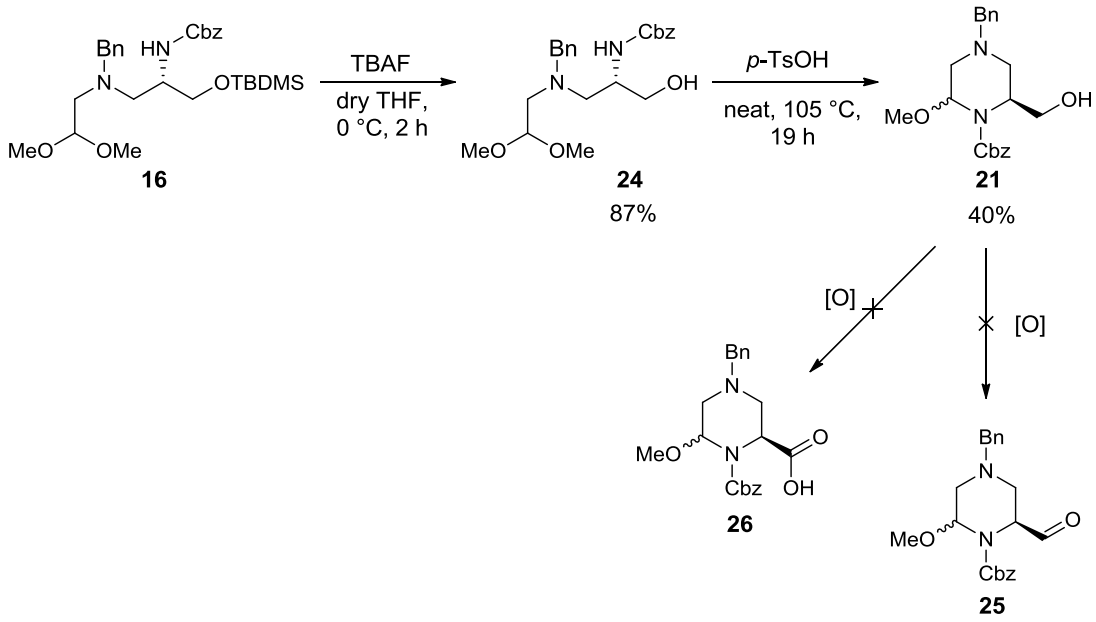
Scheme 42

Due to the isolation of **20**, efforts where then made to oxidise the free primary alcohol to its corresponding aldehyde, which would have provided the requisite handle for subsequent chain elongation. As such, the alcohol was subjected to a variety of oxidation conditions which proved to be unsuccessful, with neither the starting substrate, nor the aldehyde being recovered from the reaction mixtures (**Scheme 43**).



Scheme 43

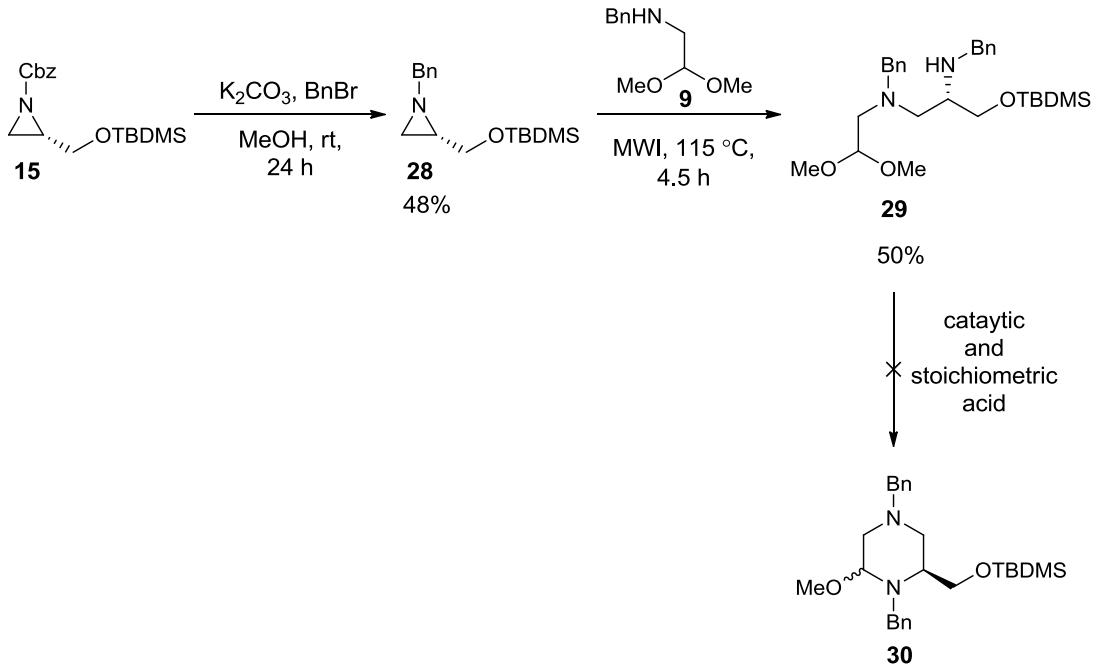
Since alcohol **21** had also been isolated, it was decided to selectively synthesise this compound and then perform the oxidation at this stage. Although **21** could be selectively formed, all oxidations to either the corresponding aldehyde or the carboxylic acid proved to be unsuccessful (**Scheme 44**). It was hypothesised that the hydroxyl unit present in **21** was forming a strong hydrogen bond with the carbonyl portion of the carbamate, which was prohibiting the hydroxyl group from reacting.



Scheme 44

In an attempt to prevent the hydrogen bond from forming, it was decided to synthesise a piperazine ring which did not have a carbamate protected nitrogen. In this regard, it was thought that it would be easier to synthesise the benzyl protected

aziridine rather than removing the carbamate unit of **21** selectively. Choi and Borch showed that the carboxybenzyl nitrogen could be deprotected using potassium carbonate,[2] and it was found that by incorporating benzyl bromide into the deprotection reaction mixture, the desired benzyl aziridine could be synthesised in a moderate yield (**Scheme 45**). The aziridine was then regioselectively opened to form **29**. However, it was found that under acidic conditions the desired dibenzyl protected piperazine could not be accessed. It was proposed that under the acidic conditions the secondary amine was becoming protonated, and therefore prohibiting the protonation of the desired methoxy group, and ultimately preventing the cyclisation from occurring.

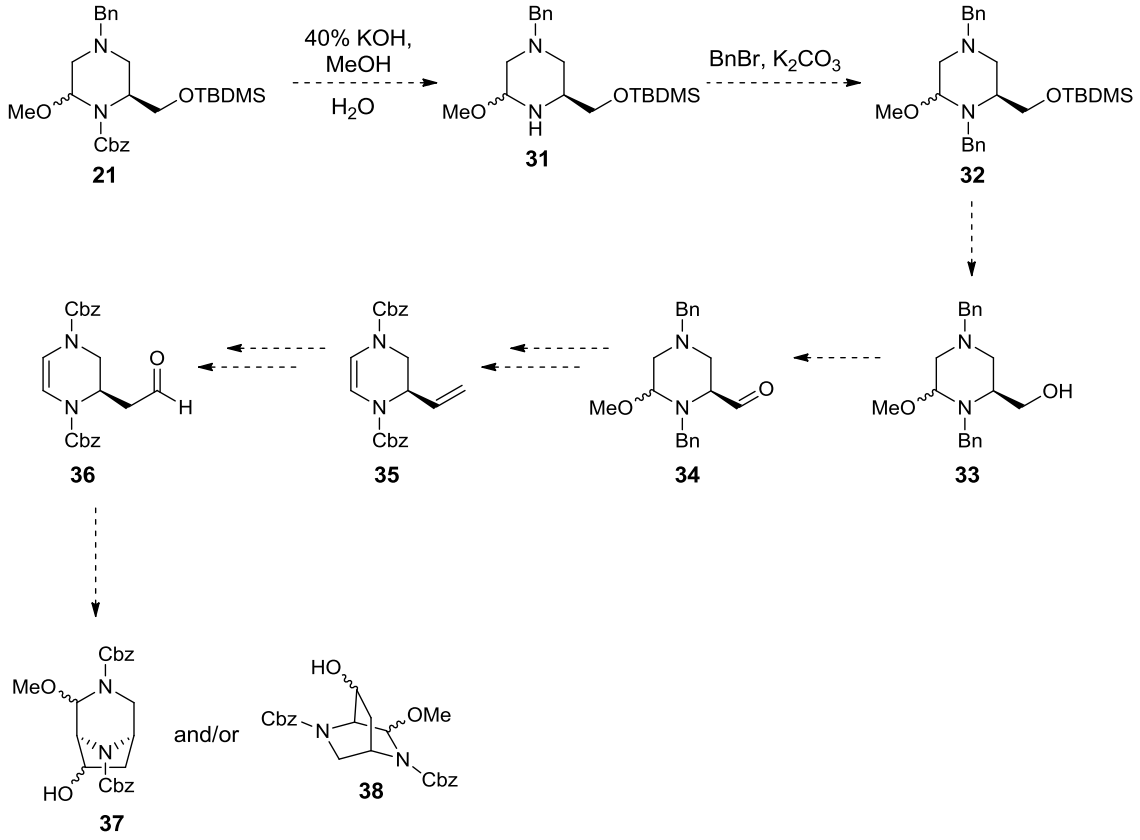


Scheme 45

Many unexpected challenges were met along the route development towards the bridged piperazine scaffolds, and unfortunately due to time constraints, further research into this route was halted at this stage.

Future work in this area of research would involve attempting to remove the carboxybenzyl group from compound **21**, and then protecting the nitrogen with the

benzyl group. This would have to occur under conditions that would leave the other nitrogen benzyl protected, as well as leaving the aminal portion intact. Therefore, acidic and reductive conditions could not be utilised. A possibility would be to remove the carboxybenzyl group under basic conditions, as shown in **Scheme 46**.[8] Once the carboxybenzyl nitrogen has been transformed into the benzyl protected nitrogen, and the alcohol has been deprotected, an investigation into the oxidation could occur. If the oxidation of this piperazine compound proved to be successful, the remainder of the proposed synthesis would remain as initially proposed (**Scheme 46**).



Scheme 46

4. Experimental

4.1 General

All reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. All reactions were carried out under an inert, dry, nitrogen atmosphere unless otherwise stated. All glassware was flame dried and cooled under a blanket of nitrogen.

- Dichloromethane, THF, diethyl ether and toluene were obtained from Innovatic Technology, Pure Solv, SPS-400-5 drying columns.
- Petrol refers to petroleum ether boiling point range 40-60 °C.

Thin layer chromatography was carried out using silica gel 60 F_{254} plates. This was analysed using a Mineralight UVG-25 lamp or developed using vanillin solution.

Flash chromatography was carried out using Zeo Chem silica gel (40-63 μm).

IR spectra were recorded on a Perkin Elmer Spectrometer 1 machine.

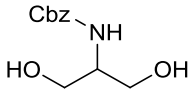
Optical rotations were obtained on Perkin Elmer 341 polarimeter using a cell with a path length of 1 dm and concentration is expressed in g/100 cm^3.

^1H and ^{13}C spectra were recorded on a Bruker DPX 400 Spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz and refer to $^3J_{H\text{-}H}$ interactions unless otherwise specified.

High resolution mass spectra were recorded on a Finnigan MAT 90XLT instrument at the EPSRC Mass Spectrometry facility at the University of Swansea, Wales.

Melting points were obtained on a Gallenkamp Griffin melting point apparatus.

Benzyl (1,3-dihydroxypropan-2-yl)carbamate, ***11*** [2]



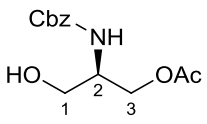
Chemical Formula: $C_{11}H_{15}NO_4$
Molecular Weight: 225.24

Scheme 3

Triethylamine (8.4 mL, 60.4 mmol) followed by benzylchloroformate (7.8 mL, 54.9 mmol) were added to a stirred solution of serinol (5 g, 54.9 mmol) in ethanol (183 mL) at 0 °C. The resultant solution was allowed to warm to ambient temperature and stirred for a further 2 h. Ethanol was then removed *in vacuo*. Acetone (300 mL) was added to the residue and the resulting white precipitate was filtered, and the filtrate was concentrated *in vacuo*. The resultant solid was purified by column chromatography (10% methanol in dichloromethane) to give the **11** as a white solid (10.8 g, 87%).

Mp: 104 – 106 °C. Lit value: 107 °C.[2]
FTIR: 1684, 3295 cm^{-1}.
^{1}H NMR (400 MHz, DMSO-*d*6): 3.34-3.52 (m, 5H, OCH_2, NCH), 4.56 (t, *J* = 5.5 Hz, 2H, OH), 5.01 (bs, 2H, benzylic CH_2), 6.84 (d, *J* = 7.6 Hz, 1H, NH), 7.29-7.41 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, DMSO-*d*6): 55.0, 60.4, 65.1, 127.7, 128.3, 137.2, 155.9 ppm.

(R)-2-(((Benzyloxy)carbonyl)amino)-3-hydroxypropyl acetate, ***12*** [2]



Chemical Formula: $C_{13}H_{17}NO_5$
Molecular Weight: 267.28

Scheme 4

PPL (1.34 g) was added to a solution of **11** (1.05 g, 4.46 mmol) in vinyl acetate (89 mL) at ambient temperature and the mixture was stirred for 2 h. PPL was then

removed *via* filtration and the filtrate was concentrated *in vacuo*. The resultant oil was purified by column chromatography (70% EtOAc in petrol) to yield **12** as a colourless oil (1.07 g, 86%, 92% *ee*).

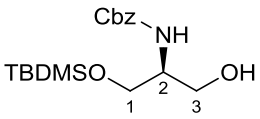
FTIR: 1704, 3340 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 2.10 (s, 3H, CH_3), 3.63-3.78 (m, 2H, H1), 3.93-4.03 (m, 1H, H2), 4.25 (d, *J* = 5.7 Hz, 2H, H3), 5.10-5.25 (m, 3H, benzylic CH_2, NH), 7.32-7.42 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 20.3, 51.1, 61.3, 62.3, 66.6, 127.7, 127.8, 128.1, 135.7, 155.9, 170.9 ppm.

$[\alpha]^{20}_{D}$= -6.8 (c=1.0, EtOAc). Lit: $[\alpha]^{20}_{D}$= -7.4 (c=1.0, EtOAc).[2]

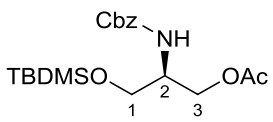
(S)-Benzyl (1-((tert-butyldimethylsilyl)oxy)-3-hydroxypropan-2-yl)carbamate, ***14*** [2]



Chemical Formula: $C_{17}H_{29}NO_4Si$
Molecular Weight: 339.50

Scheme 5

Imidazole (5.06 g, 74.3 mmol) was added to a stirred solution of **12** (7.95 g, 29.7 mmol) in dry DCM (149 mL) at 0 °C. *Tert*-butyldimethylsilyl chloride (4.92 g, 32.7 mmol) was then added at 0 °C, during which a white precipitate formed. The reaction mixture was stirred at ambient temperature for 1 h. The reaction mixture was diluted with DCM and washed with a saturated aqueous solution of ammonium chloride. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*.



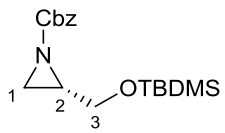
Chemical Formula: $C_{19}H_{31}NO_5Si$
Molecular Weight: 381.54

^{1}H NMR (400 MHz, $CDCl_3$): 0.07 (s, 6H, $Si(CH_3)_2$), 0.91 (s, 9H, $SiC(CH_3)_3$), 2.06 (s, 3H, OAc), 3.63-3.69 (m, 1H, H1), 3.74-3.80 (m, 1H, H1), 4.00 (bs, 1H, NH), 4.09-4.16 (m, 1H, H3), 4.18-4.25 (m, 1H, H3), 5.06-5.18 (m, 3H, benzylic CH_2, H2), 7.33-7.41 ppm (m, 5H, ArH).

The resultant oil was dissolved in methanol (150 mL) and cooled to 0 °C. K_2CO_3 powder (4.10 g, 29.7 mmol) was added to the solution at 0 °C, and stirred at this temperature for 1 h. The reaction mixture was diluted with EtOAc and quenched with a saturated aqueous solution of ammonium chloride. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (30% EtOAc in petrol) to yield **14** as a colourless oil (8.83 g, 87%).

FTIR: 1701, 3441 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 0.09 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 3.70-3.91 (m, 5H, H1, H2, H3), 5.14 (s, 2H, benzylic CH_2), 5.39 (s, 1H, NH), 7.32-7.41 ppm (m, 5H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): 6.10, 17.7, 25.3, 52.5, 63.4, 63.5, 66.4, 127.6, 127.7, 128.0, 135.9, 155.9 ppm.
$[\alpha]_D^{20}$= -12.3 (c=1.0, EtOAc). Lit: $[\alpha]_D^{20}$= -13.5 (c=1.0, EtOAc). [2]

(S)-Benzyl 2-(((tert-butyldimethylsilyl)oxy)methyl)aziridine-1-carboxylate, ***15*** [2]



Chemical Formula: $C_{17}H_{27}NO_3Si$
Molecular Weight: 321.49

Scheme 6

DIAD (7.2 mL, 36.4 mmol) was added dropwise to a stirred solution of **14** (8.83 g, 26.0 mmol) and PPh_3 (10.22 g, 39.0 mmol) in dry THF at 0 °C. The reaction mixture was then warmed to ambient temperature and stirred for a further 8 h. The solution

was then concentrated *in vacuo* and the resultant oil was purified by column chromatography (20% diethyl ether in petrol) to yield **15** as a colourless oil (6.69 g, 80%).

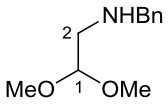
FTIR: 1724 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 0.07 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 2.25 (d, J = 3.8 Hz, 1H, H1), 2.33 (d, J = 5.9 Hz, 1H, H1), 2.64-2.69 (m, 1H, H2), 3.77 (dd, ^{2}J = 11.4 Hz, J = 4.0 Hz, 1H, H3), 3.85 (dd, ^{2}J = 11.4 Hz, J = 4.0 Hz, 1H, H3), 5.14 (d, ^{4}J = 1.4 Hz, 2H, benzylic CH_2), 7.34-7.41 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): -5.93, -5.85, 17.8, 25.3, 28.1, 36.0, 61.5, 67.5, 127.6, 127.7, 128.0, 135.4, 162.3 ppm.

$[\alpha]_D^{20}$ = -43.4 (c=2.5, EtOAc). Lit: $[\alpha]_D^{20}$ = -47.3 (c=2.5, EtOAc). [2]

N-Benzyl-2,2-dimethoxyethanamine, ***9***



Chemical Formula: $C_{11}H_{17}NO_2$
Molecular Weight: 195.26

Scheme 7

Benzaldehyde (33 mL, 0.32 mol) was added to a stirred solution of 2,2-dimethoxyethylamine (35 mL, 0.32 mol) in methanol (670 mL) at ambient temperature and stirred for 16 h. The mixture was then cooled to 0 °C and sodium borohydride (18.2 g, 0.48 mol) was added portionwise. After stirring the mixture for 16 h at ambient temperature, the resultant solution was acidified to pH~9 with 2 M HCl. The methanol was then removed *in vacuo* and water was added. The pH was corrected again to pH~9 and the product was then extracted with ethyl acetate (x 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield **9** as a colourless oil (60.0 g, 96%).

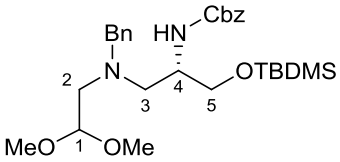
FTIR (CH_2Cl_2): 2837, 3030 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 2.77 (d, *J* = 5.5 Hz, 2H, H2), 3.39 (s, 6H, OCH_3), 3.83 (s, 2H, benzylic CH_2), 4.51 (t, *J* = 5.5 Hz, 1H, H1), 7.28-7.35 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 50.6, 53.9, 54.0, 104.0, 127.0, 128.1, 128.4, 140.1 ppm.

HRMS *m/z* (ESI) calc for $C_{11}H_{18}NO_2$ (M^++H): 196.1332. Found: 196.1327.

(S)-Benzyl (5-benzyl-3-methoxy-10,10,11,11-tetramethyl-2,9-dioxa-5-aza-10-siladodecan-7-yl)carbamate, ***16***



Chemical Formula: $C_{28}H_{44}N_2O_5Si$
Molecular Weight: 516.74

Scheme 8

Aziridine **15** (759 mg, 2.36 mmol) was added to a stirred solution of amine **9** (461 mg, 2.36 mmol) in ethanol (18 mL) at ambient temperature. The mixture was heated to reflux and stirred at this temperature for 48 h. The mixture was then cooled, concentrated *in vacuo*, and the resultant oil was purified by column chromatography (30% diethyl ether in petrol) to yield **16** as a colourless oil (1.13 g, 93%).

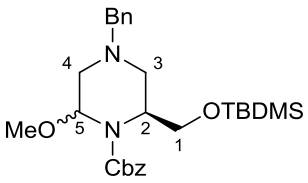
FTIR: 1722, 3342 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 0.05 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 2.64-2.79 (m, 4H, H2, H3), 3.26 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 3.63-3.82 (m, 5H, benzylic CH_2, H4, H5), 4.37 (t, *J* = 5.4 Hz, 1H, H1), 5.09-5.22 (m, 2H carbamate CH_2), 5.42 (s, 1H, NH), 7.22-7.43 ppm (m, 10H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): -6.0, -5.9, 17.7, 25.4, 50.7, 52.6, 53.2, 59.9, 55.5, 59.6, 62.3, 65.9, 103.2, 126.6, 127.4, 127.7, 127.8, 127.9, 128.0, 128.5, 138.7, 155.8 ppm.

HRMS *m/z* (ESI) calc for $C_{28}H_{45}N_2O_5Si$ (M^++H): 517.3092. Found: 517.3084.

Attempted synthesis of (2S)-benzyl 4-benzyl-2-(((tert-butyldimethylsilyl)oxy)methyl)-6-methoxypiperazine-1-carboxylate, ***19***



Chemical Formula: $C_{27}H_{40}N_2O_4Si$
Molecular Weight: 484.70

Scheme 10

Substrate **16** (188 mg, 0.36 mmol) was added to a one necked round bottom flask and *p*-toluenesulfonic acid (21 mg, 0.11 mmol) was added. A plug of cotton wool was placed in the neck of the flask, and the flask was placed into an oil bath which had been pre-heated to 115 °C. The reaction mixture was left to stir at this temperature for 2 h. The mixture was then dissolved in DCM and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-40% diethyl ether in petrol) to yield **20** (24 mg, 15%) and **21** (35 mg, 26%, 3:2 *dr*).

Scheme 11

p-Toluenesulfonic acid (17 mg, 0.09 mmol) was added to a stirred solution of **16** (152 mg, 0.29 mmol) in toluene (1.5 mL). The resultant mixture was heated to reflux and stirred at this temperature for 2 h. The reaction mixture was cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-20% diethyl ether in petrol) to yield **20** (41 mg, 31%).

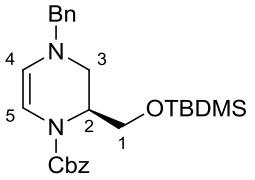
Scheme 13

p-Toluenesulfonic acid (5.2 mg, 0.027 mmol) was added to a stirred solution of **16** (142 mg, 0.27 mmol) in toluene (1.4 mL). The resultant mixture was heated to reflux and stirred at this temperature for 2 h. The reaction mixture was cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-20% diethyl ether in petrol) to yield **20** (25 mg, 19%), as well as recovered starting material (70 mg, 49%).

Scheme 14

p-Toluenesulfonic acid (4.7 mg, 0.025 mmol) was added to a stirred solution of **16** (127 mg, 0.25 mmol) in toluene (1.3 mL). The resultant mixture was heated to 40 °C and stirred at this temperature for 4 h. The reaction mixture was then heated 50 °C for a further 3 h. After this time the reaction mixture temperature was increased to 60 °C and stirred at this temperature for 16 h. The temperature was then further increased to 70 °C for 4 h, during which time **20** was observed by TLC analysis. The reaction mixture was left to stir at this temperature for a further 16 h after which time only **20** was observed by TLC analysis, and, therefore, the reaction was terminated.

(S)-Benzyl-4-benzyl-2-(((tert-butyldimethylsilyl)oxy)methyl)-3,4-dihydropyrazine-1(2H)-carboxylate, ***20***



Chemical Formula: $C_{26}H_{36}N_2O_3Si$
Molecular Weight: 452.66

FTIR: 1662, 1701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): -0.03-0.16 (m, 6H, $Si(CH_3)_2$), 0.79-0.97 (m, 9H, $SiC(CH_3)_3$), 2.73-2.84 (m, 1H, H3), 3.29 (d, ^2J = 11.4 Hz, 0.4H, H3), 3.39 (d, ^2J = 11.4 Hz, 0.6H, H3), 3.74-3.74 (m, 2H, H1, H2), 3.97-4.09 (m, 2H, benzylic CH_2),

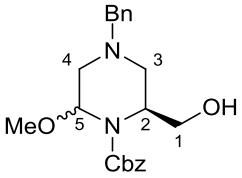
4.22-4.30 (m, 0.4H, H1), 4.34-4.42 (m, 0.6H, H1), 5.14-5.26 (m, 2H, carbamate CH_2), 5.43 (dd, J = 6.7 Hz, ^4J = 1.0 Hz, 0.6H, H4), 5.55 (dd, J = 6.7 Hz, ^4J = 1.0 Hz, 0.4H, H4), 5.89 (dd, J = 6.6 Hz, ^4J = 1.1 Hz, 0.6H, H5), 6.02 (dd, J = 6.6 Hz, ^4J = 1.1 Hz, 0.4H, H5), 7.26-7.44 ppm (m, 10H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): -6.0, -5.8, 17.7, 25.3, 44.6, 44.7, 51.7, 52.4, 58.5, 59.5, 60.2, 66.8, 100.1, 100.9, 119.4, 120.3, 126.9, 127.5, 127.5, 127.7, 128.0, 128.1, 135.9, 136.0, 137.7, 151.6, 151.8 ppm.

HRMS *m/z* (ESI) calc for $C_{26}H_{37}N_2O_3Si$ (M^++H): 453.2567. Found: 453.2568.

A ratio of 3:2 of rotamers was observed in the ^1H NMR.

(2S)-Benzyl 4-benzyl-2-(hydroxymethyl)-6-methoxypiperazine-1-carboxylate, ***21***



Chemical Formula: $C_{21}H_{26}N_2O_4$
Molecular Weight: 370.44

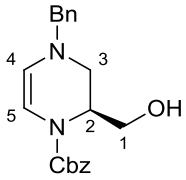
FTIR: 1717, 3335 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 2.40 (dd, ^2J = 14.7 Hz, J = 8.9 Hz, 0.6H, H3), 2.50-2.74 (m, 1.4H, H3, H4), 2.90-3.11 (m, 2H, H3, H4), 3.33 (s, 1.8H, OCH_3), 3.39 (s, 1.2H, OCH_3), 3.56-4.05 (m, 5H, H1, H2, benzylic CH_2), 4.57 (dd, J = 7.4 Hz, J = 4.3 Hz, 1H, H5), 5.06-5.13 (m, 2H, carbamate CH_2), 5.84 (2 overlapping singlets, 1H, OH), 7.24-7.43 ppm (m, 10H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 25.4, 49.7, 49.9, 54.3, 54.9, 59.2, 61.1, 62.0, 62.7, 63.0, 66.1, 66.2, 100.7, 102.4, 126.8, 127.5, 127.6, 127.9, 128.0, 128.2, 128.3, 136.0, 136.2, 138.2, 138.4, 155.1, 155.3 ppm.

HRMS *m/z* (ESI) calc for $C_{21}H_{27}N_2O_4$ (M^++H): 371.1965. Found: 371.1967.

(S)-Benzyl 4-benzyl-2-(hydroxymethyl)-3,4-dihydropyrazine-1(2H)-carboxylate, ***22***



Chemical Formula: $C_{20}H_{22}N_2O_3$
Molecular Weight: 338.40

Scheme 15

Tetrabutylammonium fluoride (1 mL, 1.04 mmol, 1 M in THF) was added to a stirred solution of **20** (335 mg, 0.74 mmol) in dry THF (6.2 mL) at 0 °C. The solution was then allowed to stir at 0 °C for a further 3 h. The reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The alcohol was then purified by column chromatography (0-50% diethyl ether in petrol) to yield **22** as a colourless oil (225 mg, 90%).

FTIR: 1695, 3447 cm^{-1}.

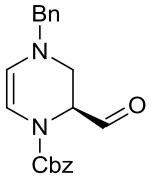
^{1}H NMR (400 MHz, $CDCl_3$): 2.80-2.88 (m, 1H, H3), 3.14-3.22 (m, 1H, H3), 3.69-3.82 (m, 2H, H1), 3.99-4.02 (m, 2H benzylic CH_2), 4.30 (bs, 0.4H, H2), 4.44 (bs, 0.6H, H2), 5.18-5.22 (m, 2H, carbamate CH_2), 5.44 (d, *J* = 6.4 Hz, 0.6H, H4), 5.57 (d, *J* = 6.5 Hz, 0.4H, H4), 6.00 (d, *J* = 6.4 Hz, 0.6H, H5), 6.11 (d, *J* = 6.3 Hz, 0.4H, H5), 7.27-7.44 ppm (m, 10H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 45.8, 46.2, 52.0, 52.1, 58.6, 62.0, 62.6, 67.0, 67.2, 101.2, 102.1, 119.2, 120.2, 127.2, 127.5, 127.6, 127.7, 127.8, 128.0, 128.1, 135.8, 136.8, 151.6, 152.6 ppm.

HRMS *m/z* (ESI) calc for $C_{20}H_{23}N_2O_3$ (M^++H): 339.1703. Found: 339.1704.

A ratio of 3:2 of rotamers was observed in the ^{1}H NMR.

Attempted synthesis of (S)-benzyl 4-benzyl-2-formyl-3,4-dihydropyrazine-1(2H)-carboxylate, ***23***



Chemical Formula: $C_{20}H_{20}N_2O_3$
Molecular Weight: 336.38

Scheme 16

DMP (97 mg, 0.23 mmol) was added to a stirred solution of alcohol **22** (70 mg, 0.21 mmol) in dry DCM (1.3 mL) at ambient temperature. After 5 min the reaction mixture turned dark brown, therefore it was diluted with ether and DCM was removed *in vacuo*. The mixture was further diluted with ether and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate and saturated aqueous solution of sodium bicarbonate was added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Only decomposition products were observed in the ^{1}H NMR spectrum.

Scheme 17

Temperature 0 °C:

DMP (91 mg, 0.21 mmol) was added to a stirred solution of alcohol **22** (66 mg, 0.91 mmol) and sodium hydrogen carbonate (64 mg, 0.76 mmol) in dry DCM (1.2 mL) at 0 °C. After 10 min the reaction mixture turned dark brown, therefore it was diluted with diethyl ether and DCM was removed *in vacuo*. The mixture was further diluted with diethyl ether and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate and saturated aqueous solution of sodium bicarbonate was added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Only decomposition products were observed in the ^{1}H NMR.

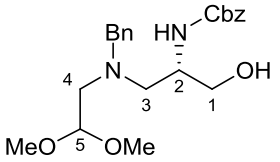
Temperature -78 °C:

DMP (77 mg, 0.18 mmol) was added to a stirred solution of alcohol **22** (56 mg, 0.17 mmol) and sodium hydrogen carbonate (57 mg, 0.68 mmol) in dry DCM (1.1 mL) at -78 °C. After 20 min the reaction mixture turned dark brown, therefore it was diluted with diethyl ether and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate and saturated aqueous solution of sodium bicarbonate was added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Only decomposition products were observed in the ^1H NMR spectrum.

Scheme 18

DMSO (28 µL, 0.39 mmol) was slowly added to a stirred solution of oxalyl chloride (19 µL, 0.23 mmol) in dry DCM (1 mL) at -60 ºC. The mixture was stirred at this temperature for 10 min and then **22** (59 mg, 0.17 mmol), as a solution in dry DCM (0.5 mL), was added during which time the reaction turned brown in colour. The reaction mixture was stirred for a further 15 min before triethylamine (119 µL, 0.85 mmol) was added and the mixture being warmed to 0 °C. The mixture then quenched with saturated aqueous solution of ammonium chloride, and the organic layer was separated. After washing with water (x 2) and brine, the organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. Only decomposition products were observed in the ^1H NMR spectrum.

(S)-Benzyl (1-(benzyl(2,2-dimethoxyethyl)amino)-3-hydroxypropan-2-yl)carbamate, ***24***



Chemical Formula: $C_{22}H_{30}N_2O_5$
Molecular Weight: 402.48

Scheme 19

Tetrabutylammonium fluoride (5 mL, 5.03 mmol, 1 M in THF) was added to a stirred solution of **16** (2 g, 3.87 mmol) in dry THF (32 mL) at 0 °C. The solution was then allowed to stir at 0 °C for a further 2 h. The reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The alcohol was then purified by column chromatography (0-50% diethyl ether in petrol) to yield **24** as a colourless oil (1.36 g, 87%).

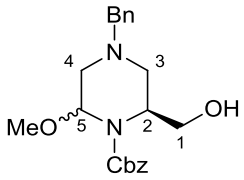
FTIR: 1715, 3331 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 2.56-2.78 (m, 4H, H3, H4), 3.25 (s, 3H, OCH_3), 3.29 (s, 3H, OCH_3), 3.56-3.92 (m, 6H, H1, H2, benzylic CH_2, NH), 4.38 (bs, 1H, H5), 5.09-5.18 (m, 2H, carbamate CH_2), 5.60 (bs, 1H, OH), 7.26-7.42 ppm (m, 10H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 50.6, 52.5, 53.2, 55.1, 59.8, 63.7, 66.2, 102.5, 127.0, 127.4, 127.5, 127.6, 128.0, 128.7, 136.1, 156.4 ppm.

HRMS *m/z* (ESI) calc for $C_{22}H_{31}N_2O_5$ (M^++H): 403.2227. Found: 403.2227.

(2S)-Benzyl 4-benzyl-2-(hydroxymethyl)-6-methoxypiperazine-1-carboxylate, ***21***



Chemical Formula: $C_{21}H_{26}N_2O_4$
Molecular Weight: 370.44

Scheme 20

Substrate **24** (169 mg, 0.42 mmol) was added to a one necked round bottom flask and *p*-toluenesulfonic acid (24 mg, 0.13 mmol) was added. A plug of cotton wool was placed in the neck of the flask and the flask was placed into an oil bath which had been pre-heated to 115 °C. The reaction mixture was left to stir at this temperature for 45 min. The mixture was then cooled to ambient temperature, dissolved in DCM, and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-40% diethyl ether in petrol) to yield **21** as a colourless oil (54 mg, 35%).

Scheme 21

Run 1:

Substrate **24** (123 mg, 0.31 mmol) was added to a one necked round bottom flask and *p*-toluenesulfonic acid (18 mg, 0.09 mmol) was added. A plug of cotton wool was placed in the neck of the flask and the flask was placed into an oil bath which had been pre-heated to 50 °C. The reaction mixture was left to stir at this temperature for 4 h, after which time only **24** was observed by TLC analysis. The oil bath was then heated to 70 °C and stirred for a further 16 h, after which time, again, only **24** was observed by TLC analysis. The oil bath was therefore heated to 105 °C and after 26 h the reaction mixture was cooled to ambient temperature, dissolved in DCM and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was

purified by column chromatography (0-40% diethyl ether in petrol) to yield **21** as a colourless oil (32 mg, 28%).

Run 2:

Substrate **24** (121 mg, 0.31 mmol) was added to a one necked round bottom flask and *p*-toluenesulfonic acid (18 mg, 0.09 mmol) was added. A plug of cotton wool was placed in the neck of the flask and the flask was placed into an oil bath which had been pre-heated to 105 °C. The reaction mixture was left to stir at this temperature for 19 h. The mixture was then cooled to ambient temperature, dissolved in DCM, and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-40% diethyl ether in petrol) to yield **21** as a colourless oil (44 mg, 40%).

Scheme 22

Substrate **24** (118 mg, 0.29 mmol) was added to a one necked round bottom flask and *p*-toluenesulfonic acid (6 mg, 0.029 mmol) was added. A plug of cotton wool was placed in the neck of the flask and the flask was placed into an oil bath which had been pre-heated to 115 °C. The reaction mixture was left to stir at this temperature for 4 h. The mixture was then cooled to ambient temperature, dissolved in DCM, and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-40% diethyl ether in petrol) to yield **21** as a colourless oil (32 mg, 29%).

Scheme 23

p-Toluenesulfonic acid (17 mg, 0.09 mmol) was added to a stirred solution of **24** (123 mg, 0.31 mmol) in toluene (3.1 mL). The resultant mixture was then heated to reflux and stirred at this temperature for 1.5 h. The reaction mixture was cooled to

ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-40% diethyl ether in petrol) to yield a mixture of **21** and **22** as a colourless oil (50 mg).

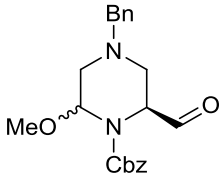
*Data for compound **21** is shown on page **384** and data for compound **22** is shown on page **385**.*

Scheme 24

Montmorillonite K10 (300 mg) was added to a stirred solution of **24** (97 mg, 0.24 mmol) in toluene (2.4 mL). The resultant mixture was then heated to reflux and stirred at this temperature for 7 h. The reaction mixture was cooled to ambient temperature, filtered, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-40% diethyl ether in petrol) to yield a **21** as a colourless oil (6 mg, 7%)

*Data for compound **21** is shown on page **384**.*

*Attempted synthesis of (2S)-benzyl 4-benzyl-2-formyl-6-methoxypiperazine-1-carboxylate, **25***



Chemical Formula: $C_{21}H_{24}N_2O_4$
Molecular Weight: 368.43

Scheme 25

DMP (94 mg, 0.23 mmol) was added to a stirred solution of alcohol **21** (54 mg, 0.16 mmol) and sodium hydrogen carbonate (50 mg, 0.60 mmol) in dry DCM (1 mL). The reaction mixture was stirred at ambient temperature for 4 h. TLC showed only **21** to be present, therefore a further quantity of DMP (42 mg, 0.10 mmol) was then added

to the reaction mixture, and it was stirred for a further 16 h. The reaction mixture was diluted with diethyl ether and DCM was removed *in vacuo*. The mixture was further diluted with diethyl ether and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate and saturated aqueous solution of sodium bicarbonate was added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography, (40% diethyl ether in petrol) to yield **21** (43 mg, 80% recovery).

Scheme 26, ***Table 1***

Entry 1:

DMSO (47 µL, 0.66 mmol) was slowly added to a stirred solution of oxalyl chloride (30 µL, 0.34 mmol) in dry DCM (0.6 mL) at -60 ºC. The mixture was stirred at this temperature for 10 min and then **21** (106 mg, 0.29 mmol), as a solution in dry DCM (0.3 mL), was slowly added. The reaction mixture was stirred for a further 15 min before triethylamine (199 µL, 1.43 mmol) was added. The mixture was warmed to ambient temperature and quenched with saturated aqueous solution of ammonium chloride, and the organic layer was separated. After washing with water (x 2) and brine, the organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (40% diethyl ether in petrol) to yield **21** as a pale yellow oil (86 mg, 81% recovery).

Entry 2:

DMSO (38 µL, 0.53 mmol) was slowly added to a stirred solution of oxalyl chloride (26 µL, 0.30 mmol) in dry DCM (0.6 mL) at -60 ºC. The mixture was stirred at this temperature for 10 min and then **21** (86 mg, 0.23 mmol), as a solution in dry DCM (0.3 mL), was slowly added. The reaction mixture was stirred for a further 5 h at -50 °C before triethylamine (160 µL, 1.15 mmol) was added. The mixture was warmed to ambient temperature and quenched with saturated aqueous solution of ammonium chloride, and the organic layer was separated. After washing with water (x 2) and

brine, the organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The oil was purified by column chromatography (40% diethyl ether in petrol) to yield **21** as a pale yellow oil (71 mg, 83% recovery).

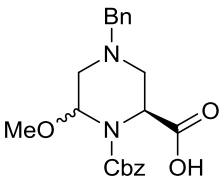
Scheme 27

IBX (66 mg, 0.23 mmol) was added to a stirred solution of alcohol **21** (58 mg, 0.16 mmol) in DMSO (1.6 mL). The reaction mixture was stirred at ambient temperature for 20 h. The reaction mixture was then heated to 40 °C for a further 4 h. After this time the reaction mixture was heated to 50 °C for a further 16 h. Water was then added to precipitate the insoluble hypervalent iodine compounds. The reaction mixture reagent was then filtered and washed with water. The filtrate was extracted with DCM, the organic phase separated, dried over Na_2SO_4, and concentrated *in vacuo*. The reaction was unsuccessful as no product was formed and none of the alcohol was recovered.

Scheme 28

PDC (104 mg, 0.29 mmol) was added to a stirred slurry of alcohol **21** (79 mg, 0.21 mmol) and celite (84 mg) in dry DCM (1 mL). The reaction mixture was stirred at ambient temperature for 4.5 h, after which time only **21** was observed by TLC analysis, therefore a further quantity of PDC (38 mg, 0.17 mmol) was added. The resultant mixture was then stirred for a further 18 h after which time the reaction mixture was filtered and concentrated *in vacuo*. The oil was purified by column chromatography (40% diethyl ether in petrol) to yield **21** as a pale yellow oil (9 mg, 12% recovery).

Attempted synthesis of (2S)-4-benzyl-1-((benzyloxy)carbonyl)-6-methoxypiperazine-2-carboxylic acid, ***26***

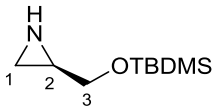


Chemical Formula: $C_{21}H_{24}N_2O_5$
Molecular Weight: 384.43

Scheme 30

Alcohol **21** (70 mg, 0.19 mmol) was dissolved in acetone (2 mL) and the solution was cooled to 0 °C. 15% aqueous $NaHCO_3$ (0.6 mL) was added followed by NaBr (2 mg, 0.019 mmol) and TEMPO (1 mg, 0.006 mmol). TCCA (89 mg, 0.38 mmol) was then added in 2 portions over 20 min. The reaction mixture was warmed to ambient temperature and stirred at this temperature for 4 h. Isopropyl alcohol (0.5 mL) was then added and the mixture was filtered through a bed of celite and washed with diethyl ether. The filtrate was then concentrated *in vacuo*. The reaction was unsuccessful as no product was formed and none of the starting alcohol was recovered.

(R)-2-(((tert-Butyldimethylsilyl)oxy)methyl)aziridine, ***27*** [2,9]



Chemical Formula: $C_9H_{21}NOSi$
Molecular Weight: 187.35

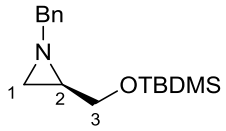
Scheme 32

Potassium carbonate (123 mg, 0.89 mmol) was added to a stirred solution of aziridine **15** (285 mg, 0.89 mmol) in methanol (4.4 mL). The resultant mixture was stirred for 24 h at ambient temperature. After 24 h the reaction mixture was filtered and concentrated *in vacuo*. The resultant oil was subsequently purified by column

chromatography (0-80% ethylacetate in petrol) to yield **27** as a colourless oil (131 mg, 78%).

FTIR (CH_2Cl_2): 1464 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 0.09 (s, 6H, $Si(CH_3)_2$), 0.91 (m, 9H, $SiC(CH_3)_3$), 1.57 (bs, 1H, H1), 1.67 (bs, 1H, H1), 2.13 (bs, 1H, H2), 3.78 ppm (bs, 2H, H3).
^{13}C NMR (100 MHz, $CDCl_3$): -5.9 -5.8, 17.8, 21.4, 25.4, 30.6, 62.7 ppm.
$[\alpha]^{20}_D$= -3.7 (c=1.0, EtOAc). Lit: $[\alpha]^{20}_D$= -4.2 (c=1.0, EtOAc).[2]

(R)-1-Benzyl-2-(((tert-butyldimethylsilyl)oxy)methyl)aziridine, ***28***



Chemical Formula: $C_{16}H_{27}NOSi$
Molecular Weight: 277.48

Scheme 33

Sodium carbonate (146 mg, 1.38 mmol), as a solution in water (1.1 mL), followed by benzyl bromide (91 µL, 0.77 mmol) was added to a stirred solution of aziridine **27** (131 mg, 0.69 mmol) in DCM (2.2 mL). The resultant reaction mixture was heated to reflux and stirred for 2 h. The reaction mixture was cooled to ambient temperature and the organic phase separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-15% diethyl ether in petrol) to yield **28** as a colourless oil (16 mg, 8%).

Scheme 34

Benzyl 2,2,2-trichloroacetimidate (134 µL, 0.72 mmol) followed by triflic acid (5 µL, 0.062 mmol) was added to a stirred solution of aziridine **27** (117 mg, 0.62 mmol) in dry DCM (0.8 mL) and cyclohexane (1.7 mL) at 0 °C. The reaction mixture was then warmed to ambient temperature and stirred for 16 h. The reaction mixture was

then diluted with DCM and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography to yield only decomposed products.

Scheme 35, ***Table 2***

Entry 1:

Potassium carbonate (309 mg, 1.51 mmol) followed by benzyl bromide (136 µL, 1.14 mmol) was added to a stirred solution of aziridine **15** (243 mg, 0.76 mmol) in methanol (3.8 mL). The reaction mixture was then stirred at ambient temperature for 24 h. The mixture was then quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-15% diethyl ether in petrol) to yield **28** as a colourless oil (101 mg, 48%).

Entry 2:

Potassium carbonate (445 mg, 3.22 mmol) followed by benzyl bromide (287 µL, 2.42 mmol) was added to a stirred solution of aziridine **15** (534 mg, 1.66 mmol) in methanol (8.1 mL) at 0 °C. The reaction mixture was then stirred at 0 °C for 24 h. The mixture was then quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-15% diethyl ether in petrol) to yield **28** as a colourless oil (221 mg, 48%).

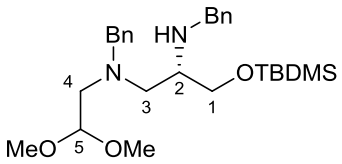
FTIR (CH_2Cl_2): 1083, 1252 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 0.06 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 1.47 (d, J = 6.4 Hz, 1H, H1), 1.71 (d, J = 3.5 Hz, 1H, H1), 1.75-1.87 (m,

1H, H2), 3.43, 3.53 (ABq, J_{AB} = 13.5 Hz, 2H, benzylic CH_2), 3.59 (dd, ^2J = 11.0 Hz, J = 5.3 Hz, 1H, H3), 3.64 (dd, ^2J = 11.0 Hz, J = 3.6 Hz, 1H, H3), 7.24-7.42 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): -5.8, -5.7, 17.9, 25.4, 31.4, 40.5, 63.9, 65.5, 126.4, 127.5, 127.8, 138.7 ppm.

HRMS *m/z* (ESI) calc for $C_{16}H_{28}NOSi$ (M^++H): 278.1935. Found: 278.1933.

(S)-N1,N2-dibenzyl-3-((tert-butyldimethylsilyl)oxy)-N1-(2,2-dimethoxyethyl)propane-1,2-diamine, ***29***



Chemical Formula: $C_{27}H_{44}N_2O_3Si$
Molecular Weight: 472.74

Scheme 36

Aziridine **28** (168 mg, 0.61 mmol) was added to a stirred solution of amine **9** (130 mg, 0.67 mmol) in ethanol (4.6 mL) at ambient temperature. The mixture was heated to reflux and stirred at this temperature for 72 h. The mixture was then cooled, concentrated *in vacuo*, and the resultant oil was purified by column chromatography (40% diethyl ether in petrol) to yield **29** as a colourless oil (147 mg, 49%).

Scheme 37

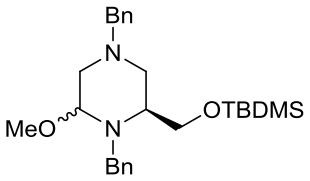
Aziridine **28** (62 mg, 0.22 mmol) was added to a solution of amine **9** (47 mg, 0.24 mmol) in ethanol (2.2 mL) in a microwave vial. The vial was sealed, placed in the microwave and the temperature set to 90 °C for 3.5 h with the cooling function on. After this time the temperature was increased to 115 °C and stirred at this temperautre for 5 h. The reaction mixture was then cooled, concentrated *in vacuo*, and the resultant oil was purified by column chromatography (40% diethyl ether in petrol) to yield **29** as a colourless oil (45 mg, 42%).

Scheme 38

Aziridine **28** (71 mg, 0.26 mmol) was added to a solution of amine **9** (65 mg, 0.33 mmol) in ethanol (1.3 mL) in a microwave vial. The vial was sealed, placed in the microwave and the temperature set to 115 °C for 4.5 h with cooling function on. The reaction mixture was then cooled, concentrated *in vacuo*, and the resultant oil was purified by column chromatography (40% diethyl ether in petrol) to yield **29** as a colourless oil (61 mg, 50%).

FTIR: 1251, 2854 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 0.06 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 2.44 (m, 2H, H3), 2.63-2.72 (m, 2H, H4), 2.75-2.84 (m, 1H, H2), 3.23 (s, 3H, OCH_3), 3.28 (s, 3H, OCH_3), 3.51-3.91 (m, 6H, H1, 2 x benzylic CH_2), 4.38 (t, *J* = 5.2 Hz, 1H, H5), 7.20-7.40 ppm (m, 10H, ArH).
^{13}C NMR (100 MHz, $CDCl_3$): -5.9, 17.8, 25.4, 51.9, 52.8, 53.1, 55.7, 56.6, 57.0, 59.7, 64.2, 102.9, 126.3, 126.5, 127.7, 127.7, 127.9, 128.6, 138.8 ppm.
HRMS *m/z* (ESI) calc for $C_{27}H_{45}N_2O_3Si$ (M^++H): 473.3194. Found: 473.3186.

Attempted synthesis of 1,4-dibenzyl-2-(((tert-butyldimethylsilyl)oxy)methyl)-6-methoxypiperazine, ***30***



Chemical Formula: $C_{26}H_{40}N_2O_2Si$
Molecular Weight: 440.69

Scheme 39, Table 3

Entry 1:

Substrate **29** (136 mg, 0.29 mmol) was added to a one necked round bottom flask and *p*-toluenesulfonic acid (22 mg, 0.12 mmol) was added. A plug of cotton wool was placed in the neck of the flask and the flask was placed into an oil bath which had

been pre-heated to 115 °C. The reaction mixture was left to stir at this temperature for 20 h. The mixture was then cooled to ambient temperature, dissolved in DCM, and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-100% diethyl ether in petrol) to yield only degradation products.

Entry 2:

Substrate **29** (112 mg, 0.24 mmol) was added to a one necked round bottom flask and *p*-toluenesulfonic acid (55 mg, 0.29 mmol) was added. A plug of cotton wool was placed in the neck of the flask and the flask was placed into an oil bath which had been pre-heated to 115 °C. The reaction mixture was left to stir at this temperature for 1 h. The mixture was then cooled to ambient temperature, dissolved in DCM, and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-100% diethyl ether in petrol) to yield only degradation products.

Scheme 40, ***Table 4***

Entry 1:

p-Toluenesulfonic acid (36 mg, 0.19 mmol) was added to a stirred solution of **29** (74 mg, 0.16 mmol) in toluene (1.6 mL). The resultant mixture was then heated to 50 °C and stirred at this temperature for 4 h, during which time the reaction turned dark brown in colour. The reaction mixture was then heated to 60 °C and stirred at this temperature for a further 16 h. After this time the reaction temperature was further increased to 70 °C, and after 4 h the reaction mixture was cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The

resultant oil was purified by column chromatography (0-100% diethyl ether in petrol) to yield only degradation products.

Entry 2:

p-Toluenesulfonic acid (10 mg, 0.05 mmol) was added to a stirred solution of **29** (60 mg, 0.13 mmol) in toluene (1.3 mL). The resultant mixture was heated to 80 °C and stirred at this temperature for 16 h, during which time the reaction turned dark brown in colour. The reaction mixture was then heated to 100 °C, and stirred at this temperautre for a further 16 h. After this time the reaction temperature was further increased to reflux, and after 6 h the reaction mixture was cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-100% diethyl ether in petrol) to yield only degradation products.

Scheme 41

Montmorillonite K10 (100 mg) was added to a stirred solution of **29** (69 mg, 0.15 mmol) in toluene (1.5 mL). The resultant mixture was then heated to reflux and stirred at this temperature for 6 h, after which time only **29** was observed by TLC analysis, therefore a further quantity of Montmorillonite K10 (100 mg) was added, and the reaction was stirred at reflux for an additional 16 h. After this time only **29** was observed by TLC analysis, therefore a further portion of Montmorillonite K10 (100 mg) was added and the reaction stirred at reflux for a further 6 h. The reaction mixture was cooled to ambient temperature, filtered, the clay washed with methanol, and the filtrate concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-100% diethyl ether in petrol), however, nothing was obtained.

5. References

1. R. Bogacki, D. M. Gill, W. J. Kerr, S. Lamont, J. A. Parkinson and L. C. Paterson, *Chem. Commun.*, 2013, **49**, 8931.
2. J. Y. Choi and R. F. Borch, *Org. Lett.*, 2007, **9**, 215.
3. O. Mitsunobu and Y. Yamada, *Bull. Chem. Soc. Jpn.*, 1967, **40**, 2380.
4. A. J. Mancuso and D. Swern, *Synthesis*, 1985, 165.
5. G. Nagendrappa, *Resonance*, 2002, **7(1)**, 64.
6. A. J. Mancuso, D. S. Brownfain and D. Swern, *J. Org. Chem.*, 1979, **44**, 4148.
7. L. D. Luca, G. Giacomelli, S. Masala and A. Porcheddu, *J. Org. Chem.*, 2003, **68**, 4999.
8. S. R. Angle and D. O. Arnaiz, *Tetrahedron Lett.*, 1989, **30**, 515.
9. S. C. Bergmeier and P. P. Seth, *Tetrahedron Lett.* 1999, **40**, 6181.